SYNTHETIC STUDIES ON NITROGEN HETEROCYCLES

A thesis presented in part fulfilment of the requirements for the Degree of Doctor of Philosophy

by

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To

My parents, whose sacrifices

half a century ago, made

possible my First Degree

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Several chlorohydrin alkyl ethers, 2-benzoyl-4-chloro-1-cyano-3-ethoxy-1,2,3,4-tetrahydroisoquinoline (27), and the corresponding 3-methoxy compound (28) were prepared from Reissert compound, 2-benzoyl-1-cyano-1,2-dihydroisoquinoline (2). The stereochemistry of these ethers was investigated. With triethylamine there was a 1,4-elimination of hydrogen chloride to give reactive intermediates (29) and (30), respectively, which were trapped as Diels-Alder adducts (83) and (84) with N-phenylmaleimide. The stereochemistry of these adducts was determined using ^{1}H n.m.r. nuclear Overhauser enhancement spectra.

Other Reissert compounds, and their derivatives, have been studied briefly.

Part 2

Oxidation of benzyl N-hydroxycarbamate, $PhCH_2OCONHOH$ (55a), with sodium periodate in the presence of cyclopentadiene gave the cycloadduct (87a) of the transient dienophile, benzyl C-nitrosoformate, $PhCH_2OCONO$ (56a), and the diene. The cycloadduct (87b) of tert-butyl C-nitrosoformate, Bu^tOCONO (56b) was prepared similarly. Both cycloadducts dissociated reversibly in benzene at 80 °C. When heated in this solvent in the presence of triphenylphosphine, the cycloadducts gave triphenylphosphine oxide and N-alkoxycarbonylazepines (85a) and (85b) arising, apparently, from attack of alkoxycarbonyl nitrenes on the solvent. The cycloadduct of tert-butyl C-nitrosoformate also gave small amounts of 5,5-dimethyloxazolidin-2-one (86).

The cycloadduct (92a) of 3-methylbut-2-enyl C-nitrosoformate (91a) and cyclopentadiene was heated in benzene at 80°C to liberate the nitroso compound which underwent an intramolecular 'ene' reaction. The structure (93) of the 'ene' reaction product, 3-hydroxy-4-isopropenyloxazolidin-2-one, was established by synthesis of the corresponding dihydro compound from (±)-valine.

Oxidation of hydroxyurea in the presence of cyclopentadiene gave the cycloadduct (130a) of the transient dienophile C-nitrosoformamide (129a). N-methyl-, N-phenyl-, N,N-dimethyl-, and N,N-diphenyl-C-nitrosoformamide (129b-e) were likewise trapped as their cycloadducts (130b-e) with cyclopentadiene.

These cyclopentadiene adducts dissociated at 80°C in the presence of 2,3-dimethylbuta-1,3-diene to give the corresponding cycloadducts (131) of the nitrosoformamides and dimethylbutadiene. Unexpectedly, the dimethylbutadiene adducts (131) were accompanied by substantial amounts of hydroxamic acids (135) arising from 'ene' reactions of the nitrosoformamides (129) and dimethylbutadiene. The cyclopentadiene adducts of N,N-dimethyl- and N,N-diphenyl-C-nitrosoformamide, when heated alone, decomposed to give the carbamic anhydrides (132d) and (132e).

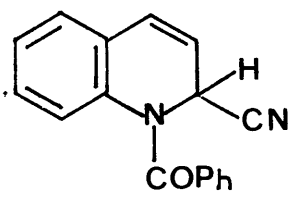
PART ONE

CHLOROHYDRINS

OF

ISOQUINOLINE

REISSERT COMPOUNDS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N
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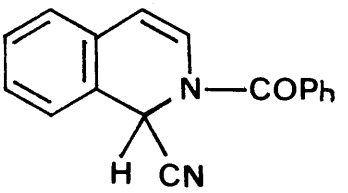
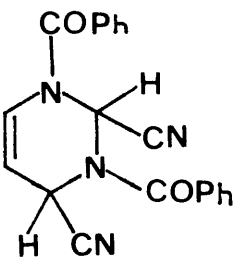
(1)


N—COPh
H CN

(2)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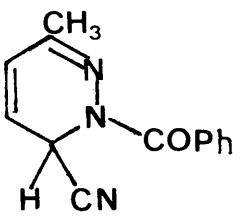
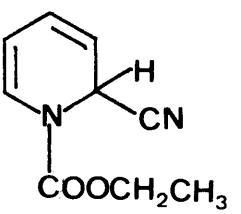
N
H
CN
N
COPh
H CN

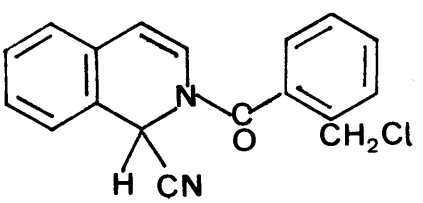
(3)


CH3
N
N
COPh
H CN

(4)


H
N
CN
COOCH2CH3

(5)


N
C
O
CH2Cl
H CN

(6)

1. INTRODUCTION

1.1 Reissert Compounds

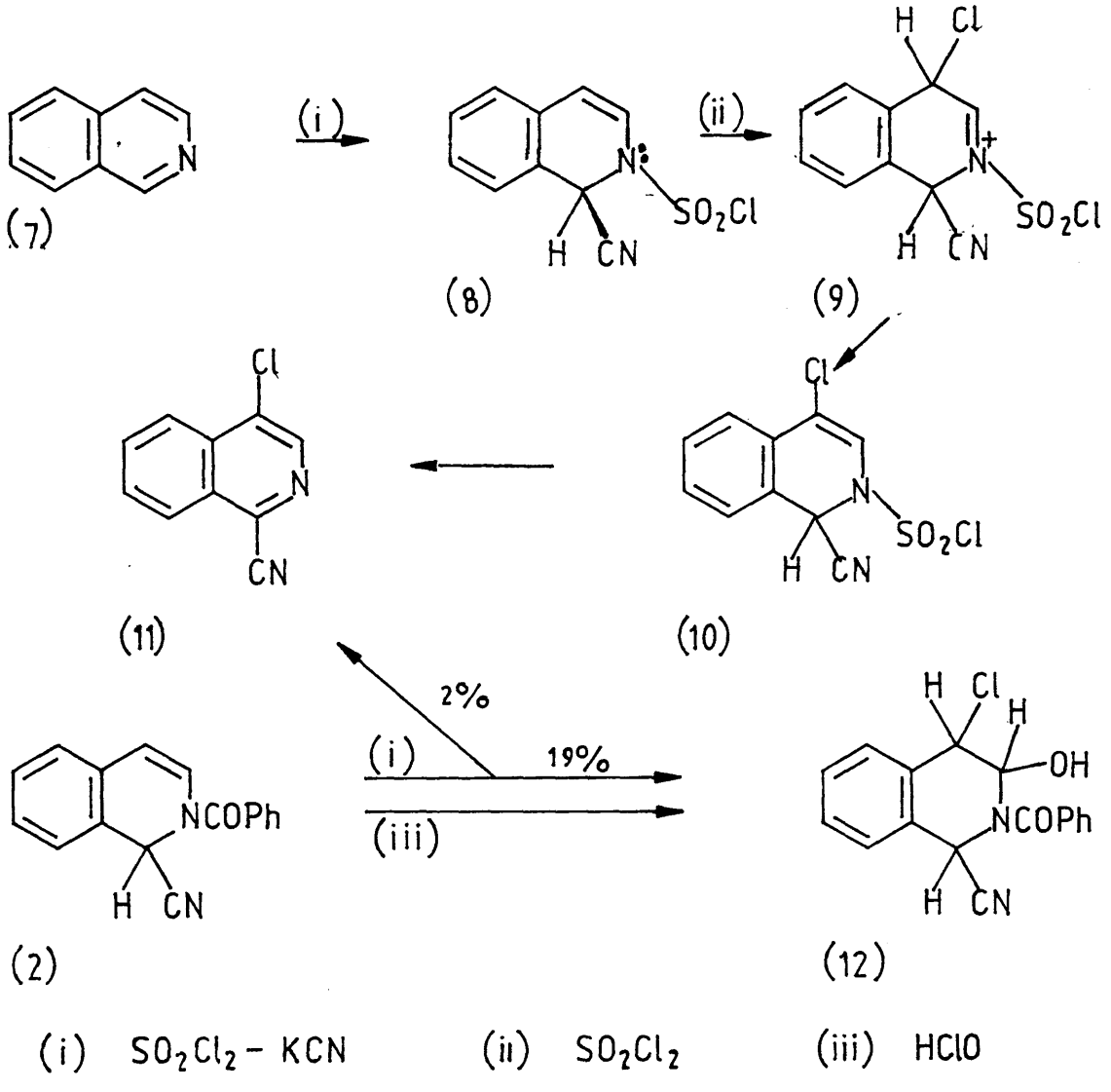
In 1905 A. Reissert reported [1] that quinoline and isoquinoline reacted with benzoyl chloride and aqueous potassium cyanide to give compounds (1) and (2) respectively, the first examples of the class of compounds now bearing his name. As part of his study, Reissert hydrolysed the quinaldonitrile (1) with concentrated hydrochloric acid and obtained benzaldehyde as one of the products. This early experiment was important as it provided a general method for the preparation of aldehydes in a pure state.

Numerous Reissert compounds have been prepared, [3, 4, 5] and many have proved to be valuable intermediates in synthesis. Indeed, Cooney[4] has estimated that, from the time McEwen and Cobb published the first Review (1955) up to 1983, more than 300 papers concerned with Reissert compounds have appeared. One example of the interest in this field, and its fruitfulness, is the fact that in 1963 Popp and Soto in one paper [6] listed about 40 Reissert compounds in their evaluation of the various preparative methods. Although much of the original work involved the use of quinoline as the tertiary amine, the study of isoquinoline Reissert compounds has been expanding steadily because of the pharmacologically useful nature of the isoquinoline alkaloids.

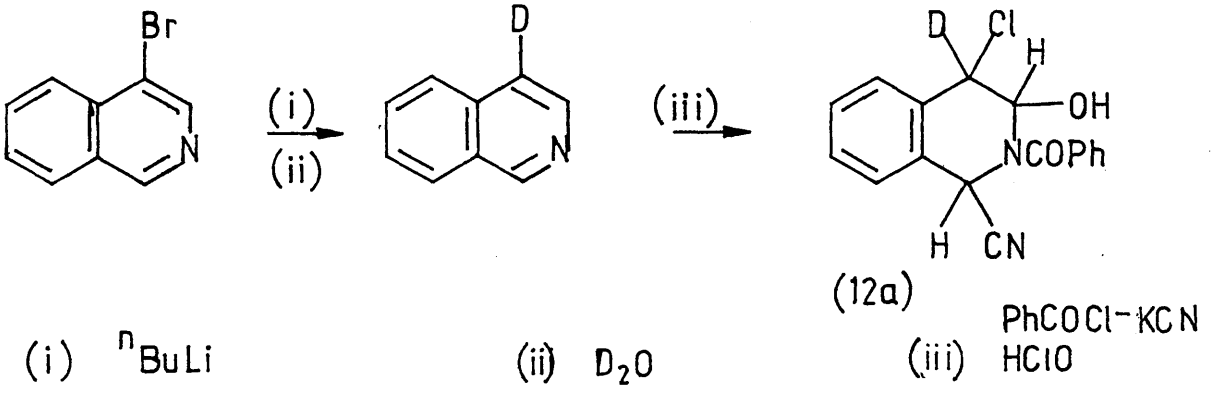
Nowadays the name 'Reissert Compound' is applied to derivatives of a variety of heterocyclic bases. Their characteristic features are a) a tertiary amide group in which the nitrogen is part of a heterocyclic ring, and

b) a hydrogen atom and a cyano group bonded to a ring carbon atom adjacent to the ring nitrogen. As a class, they are simple to prepare and are easily handled, yet quite reactive when subjected to acidic or basic conditions. To date, Reissert compounds have not been synthesised from pyridine, acridine, or 1,10-phenanthroline although there has been success with pyrimidine and 3-methylpyridazine [7] to give the compounds (3) and (4), and a pyridine Reissert compound analogue (5), a urethane rather than an amide, has been prepared.

Reissert's method for the preparation of his compounds has several drawbacks. Both the bases and the products are likely to be insoluble in water, and so the products tend to appear as gums. Another problem is the hydrolysis of reactive acid halides; although this can be minimised by using cold saturated aqueous potassium cyanide. Many non-aqueous solvents have now been investigated. According to Cooney [4], probably the most general non-aqueous medium for Reissert compound synthesis is anhydrous benzene with anhydrous hydrogen cyanide, but he states that a newer system employing trimethylsilyl cyanide in anhydrous dichloromethane is becoming more common. For the formation of Reissert compounds involving acid chlorides of intermediate reactivity towards water, a mixed solvent system often provides the most convenient alternative. Generally, the acid chloride is added neat, or in dichloromethane, to a mixture of the nitrogen heterocycle, dichloromethane, potassium



Scheme 1



Scheme 2

cyanide, and a minimum amount of water. This was the preferred method used in the present study. Tyrell and McEwen [9] report that when catalytic amounts of benzyltrialkylammonium chlorides were employed as phase transfer reagents they increased the yield of product (6) from 20% to 80%.

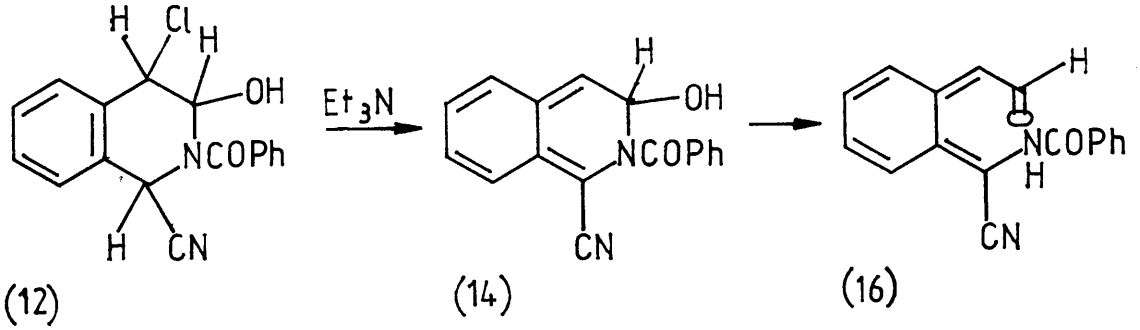
As the chemistry of Reissert compounds has been surveyed regularly, and there are excellent reviews [2,3,4,5], earlier work will not be included here, unless it is of direct relevance to our own investigations.

1.2. Rearrangement Reactions of a Reissert Compound Chlorohydrin

The enamine nature of Reissert compounds seems to have been neglected prior to the work of Kirby *et al.* [10]. They treated isoquinoline with sulphuryl chloride and potassium cyanide using the two-phase system (water - dichloromethane) and obtained 4-chloro-1-cyanoisoquinoline (11) as the main product (Scheme 1). This was considered to arise by electrophilic attack on the intermediate (8) at C(4).

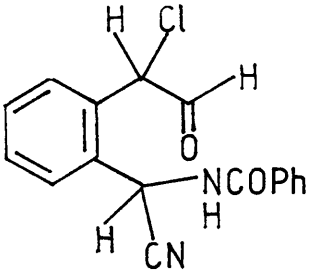
Further insight into the proposed mechanism was obtained from the reaction of the isoquinoline Reissert compound (2) with the above reagents in the same solvent system, and under the same conditions. Two crystalline products were isolated from the complex reaction mixture. The minor product (2%) was the expected chloro-derivative (11) and the major (19%) was a novel chlorohydrin (12). The same chlorohydrin was prepared by treatment of the Reissert

compound (2) with hypochlorous acid in dioxan (50% yield), or N-chlorosuccinimide in aqueous dioxan (39% yield). The i.r. spectrum of (12) showed bands for hydroxy (3 303 cm^{-1}), cyano (2 248 cm^{-1}), and amide (1 638 cm^{-1}) groups. In the ^1H n.m.r. spectrum [in $(CD_3)_2SO$] signals were observed at δ 4.35 (4-H) and 5.65 (3-H) for vicinally coupled (J 4.3 Hz) protons, the latter being further split (J 4.3 Hz) by the hydroxy proton (δ 6.76). The proton at C(1) gave a singlet in the expected region, (δ 6.32) of the spectrum. The chlorohydrin (12) appeared from its sharp melting point, 176-178°C, and n.m.r. spectrum to be a single isomer, but the relative configuration of the substituents was not determined. One would expect that addition of hypochlorous acid to the 3,4-double bond of the Reissert compound would have occurred as shown (12), or in the opposite sense, with the attachment of chlorine at C(3) and hydroxy at C(4). This point was settled in favour of (12), by deuterium labelling. 4-Bromoisoquinoline was treated with n-butyl-lithium at -35°C, and the reaction mixture quenched with deuterium oxide (Scheme 2). The resulting 4-deuterioisoquinoline was converted into the 4-deuterio-analogue of (12). The n.m.r. spectrum of this product (12a) showed *inter alia*, an AB quartet, δ 6.75 and 5.60 (J 4.5 Hz) for the protons at C(3) and in the hydroxy-group. The signals at δ 6.75 disappeared when the sample was treated with deuterium oxide and, as expected, the signal at δ 5.60 then collapsed to a singlet: thus the hydroxy group was attached to C(3) and not C(4).



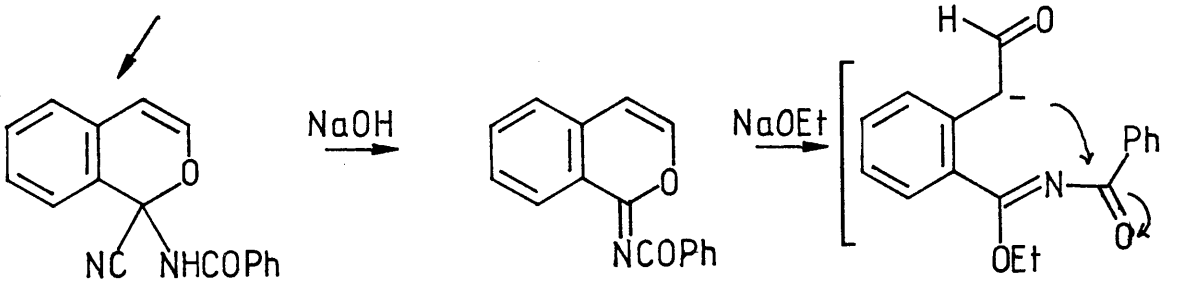
(12) (14) (16)

or

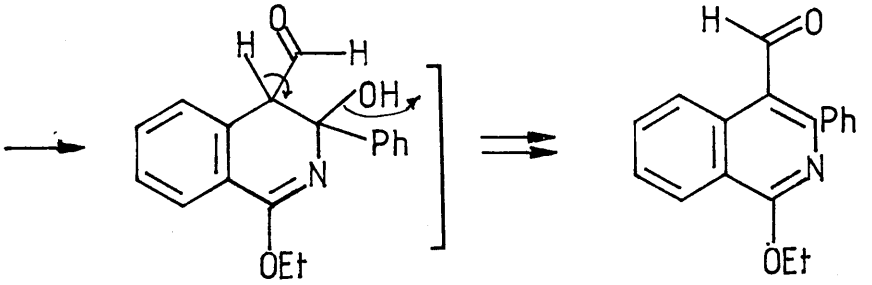


(15)

(16)

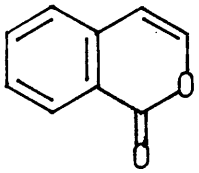


(17) (18)



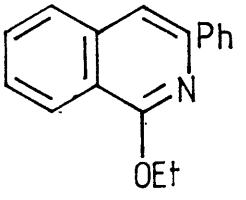
(19) (20)

Scheme 3



(21)

(22)

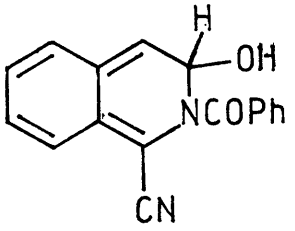


Treatment of the chlorohydrin (12) with triethylamine (1 equiv.) in dioxan at room temperature produced a yellow colour which faded slowly with concurrent precipitation of triethylamine hydrochloride. The major reaction product (40%) was assigned the isochromene structure (17) on the following grounds. The ^{1}H n.m.r. spectrum [$(CD_3)_2SO$] showed signals for the olefinic protons, δ 6.25 and 6.80 (AB quartet $J_{3,4}$ 5.9 Hz) and for the NH proton δ 10.14 (broad singlet), which disappeared upon addition of deuterium oxide. The i.r. spectrum of (17) showed no detectable cyano-absorption but this is to be expected when the cyano-group is attached to carbon carrying oxygen and nitrogen substituents. (The nitrile absorption in Reissert compounds and cyanohydrins is always very weak and sometimes unobservable [2]). Treatment of (17) with sodium hydroxide in aqueous dioxan caused elimination of hydrogen cyanide with the formation of (18), which was the major (43%) product obtained directly from (12) with the same reagent. The compound (18) showed ^{1}H n.m.r. signals δ 6.30 and 6.98 (AB quartet, $J_{3,4}$ 5.8 Hz) for two olefinic protons, and an i.r. absorption between 1 683 and 1 633 cm^{-1}; no ^{1}H n.m.r. or i.r. bands corresponding to NH or OH groups were observed. Hydrolysis of (18) with dilute hydrochloric acid afforded, virtually quantitatively, isocoumarin (21) and benzamide. In contrast (18) reacted with ethanolic sodium hydroxide at room temperature to yield the isoquinoline derivative (20) as the major product (53%). This was accompanied by the

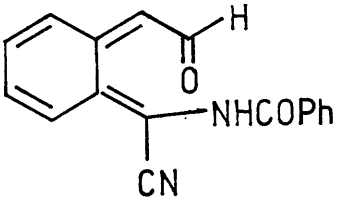
known [11] compound (22) which was identified by its melting point and that of the derived 3-phenylisoquinolone [11,12]. A mixture of (20) and (22), together with a small amount of benzamide, was also formed directly from (12) by reaction with ethanolic sodium hydroxide. The presence of an aldehyde group in (20) was revealed spectroscopically ($\nu_{max.}$ 1 671 cm^{-1}; δ10.14(s)) and confirmed by reduction with sodium borohydride to yield a primary alcohol [δ 1.8(1H, br s , exchangeable with D_2O), 4.90(s, CH_2)]. Decarbonylation [13] of (20) with palladium-charcoal (5%) at 220°C gave (22).

A possible reaction path to account for the formation of the products (17), (18), (19) and (20) from the chlorohydrin (12) is presented in Scheme (3). The product (22) could arise from attack of ethoxide on the formyl group of the intermediate (19) followed by elimination of ethyl formate and hydroxide with concurrent aromatisation. The proposed conversion (12) to (16), may involve 1,4-conjugated elimination of hydrogen chloride before or after opening of the carbinolamide ring, and the subsequent electrocyclic ring closure, (16) ⟶ (17), has ample precedent [14]. The remarkable base induced reactions of (12) thus provide simple preparative routes from isoquinoline to isocoumarin and the highly substituted system (20).

During his study of the base mediated reactions of the chlorohydrin (12), Tan [15] noted that the reaction mixtures turned yellow almost immediately and, when the base was triethylamine, there was a concomitant precipitation of



(14)



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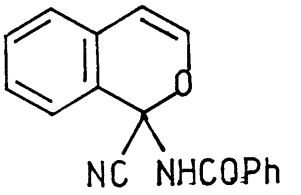

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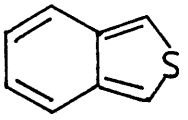

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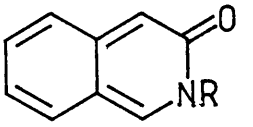

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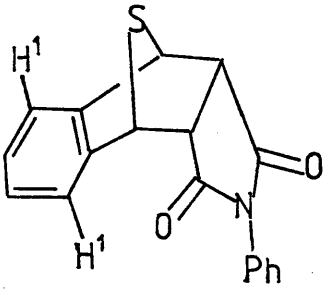

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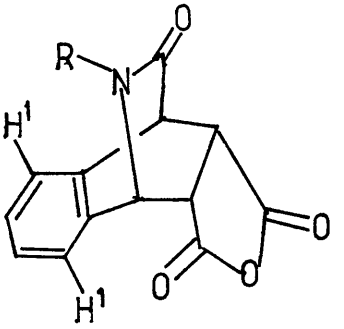

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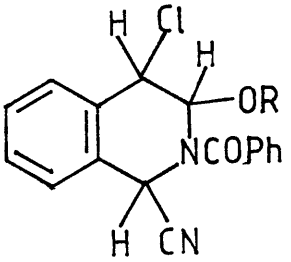
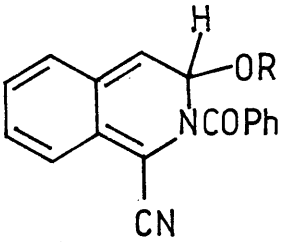


(27); R = Et
(28); R = Me



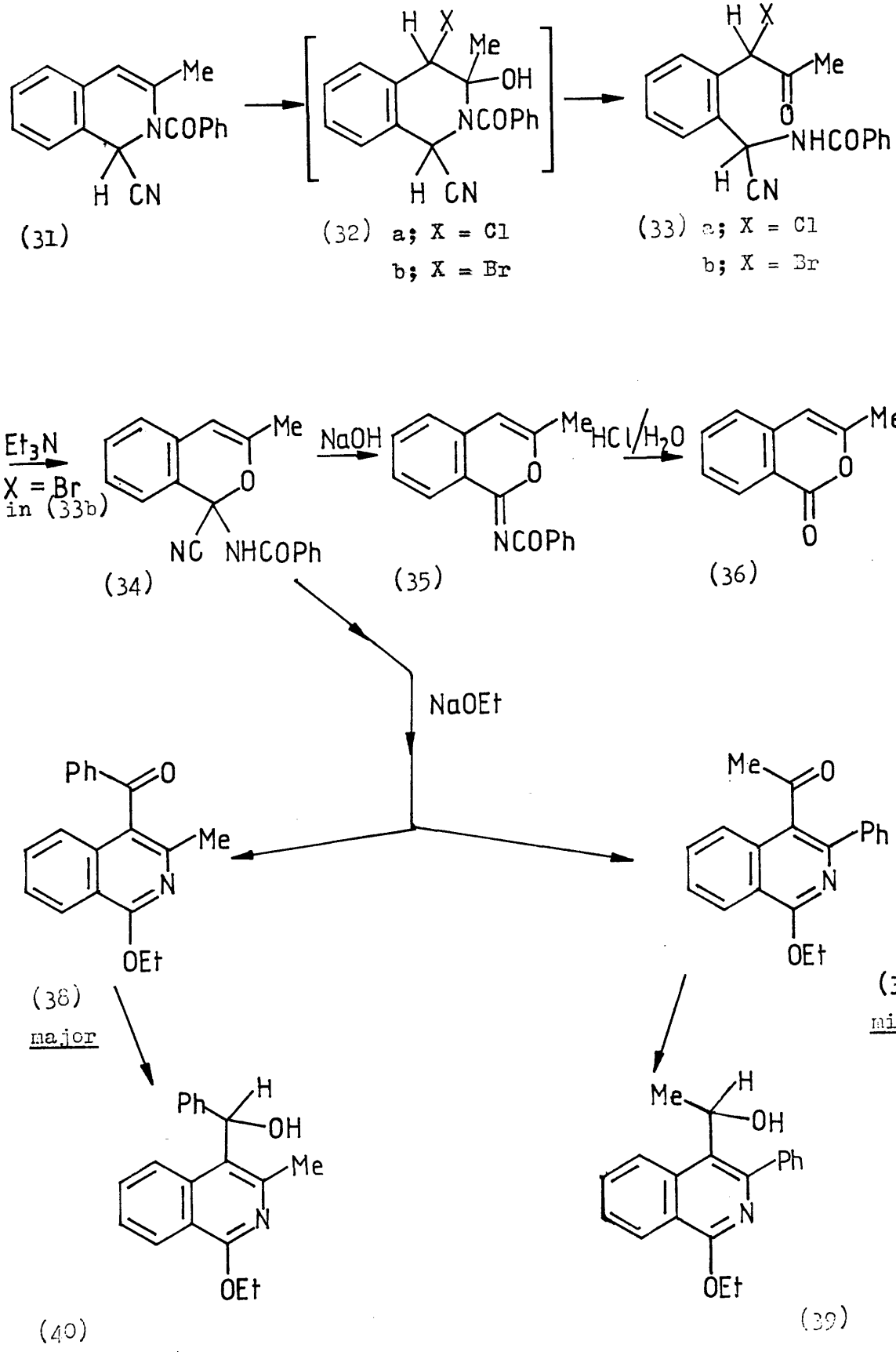
(29); R = Et
(30); R = Me

triethylamine hydrochloride. He postulated that this demonstrated the formation of a highly conjugated intermediate (e.g. 14) resulting from the 1,4-elimination of hydrogen chloride (Scheme 3). He cited [16,17,18a] benzothiophene (23) and 3-isoquinolinones (25) as similar conjugated systems, and pointed out that they react with N-phenylmaleimide or maleic anhydride to give adducts like (24) and (26). Of further interest was the fact that 2-methylisoquinoline-3-one (25; R = Me) was described as a viscous orange gum which deteriorates rapidly on standing [18]. Consequently, Tan treated a solution of the chlorohydrin (12) and N-phenyl-maleimide in dioxan with triethylamine in the hope of trapping either, or both, of the intermediates (14) and (16) as their Diels-Alder adducts. However no adduct was obtained, the only identified product being (17). Tan suggested that this failure of the dienophile to trap either intermediate was because both the carbinolamide ring opening [(14)→(16)] and cyclisation reaction [(16)→(17)] were very rapid. A study using an equimolecular mixture of the chlorohydrin (12) in ethanol and aqueous sodium hydroxide at 25°C supported this view by showing that the isochromene (18) had formed as the major product within one minute, with consumption of 97.5% of the base.

It was decided therefore to seek evidence for 1,4-conjugated elimination of hydrogen chloride by studying the action of base on the chlorohydrin ether (27). The elimination product (29) would be unable to undergo carbinol

amide ring opening and might therefore survive long enough to be trapped. Accordingly, Tan [15] treated the Reissert compound (2) with N-chlorosuccinimide in ethanolic dioxan, rather than aqueous dioxan, and obtained two products, in yields of 58% and 6%. He concluded that these products were isomeric chlorohydrin ethyl ethers (27). The ^{1}H n.m.r. of each isomer in deuteriochloroform resembled that of the chlorohydrin (12) except that the signal of the hydroxy group was replaced by those of an ethoxy group. The methylene protons of the ethoxy groups in both isomers gave complex multiplets rather than 1:3:3:1 quartets. This was not due to long range coupling with 3-H, since the signal for the latter was a doublet. The signals were temperature dependent, markedly so in the case of the major isomer. When this was heated to 100°C in deuteriochloroform the multiplet collapsed to a quartet. The temperature effect for the minor isomer was less apparent. Tan considered that the magnetic non-equivalence of the methylene protons could well be a result of steric hindrance, particularly by the amide phenyl ring. His alternative hypothesis was that the effect might be due to the inherent diasteriotopicity of the methylene protons in a chiral environment, although he pointed out that changes in temperature normally do not affect the isochronism and coupling constants of such magnetic non-equivalent diasteriotopic nuclei [19].

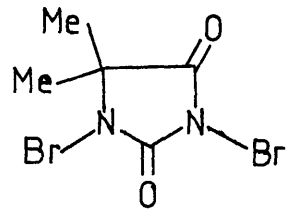
Unfortunately, circumstances prevented Tan from continuing with this work.


Me
NCOPh
H CN
(31)
H X
Me
OH
NCOPh
H CN
(32) a; X = Cl
b; X = Br
H X
Me
O
NHCOPh
H CN
(33) a; X = Cl
b; X = Br
Et3N
X = Br
in (33b)
Me
O
NC NHCOPh
(34)
NaOH
Me
O
NCOPh
(35)
HCl/H2O
Me
O
O
(36)
NaOEt
Ph
O
Me
N
OEt
(38)
major
Me
O
Ph
N
OEt
(37)
minor
Ph
H
OH
Me
N
OEt
(40)
Me
H
OH
Ph
N
OEt
(39)

Scheme 4

1.3. Some Other Reissert Compound Chlorohydrins

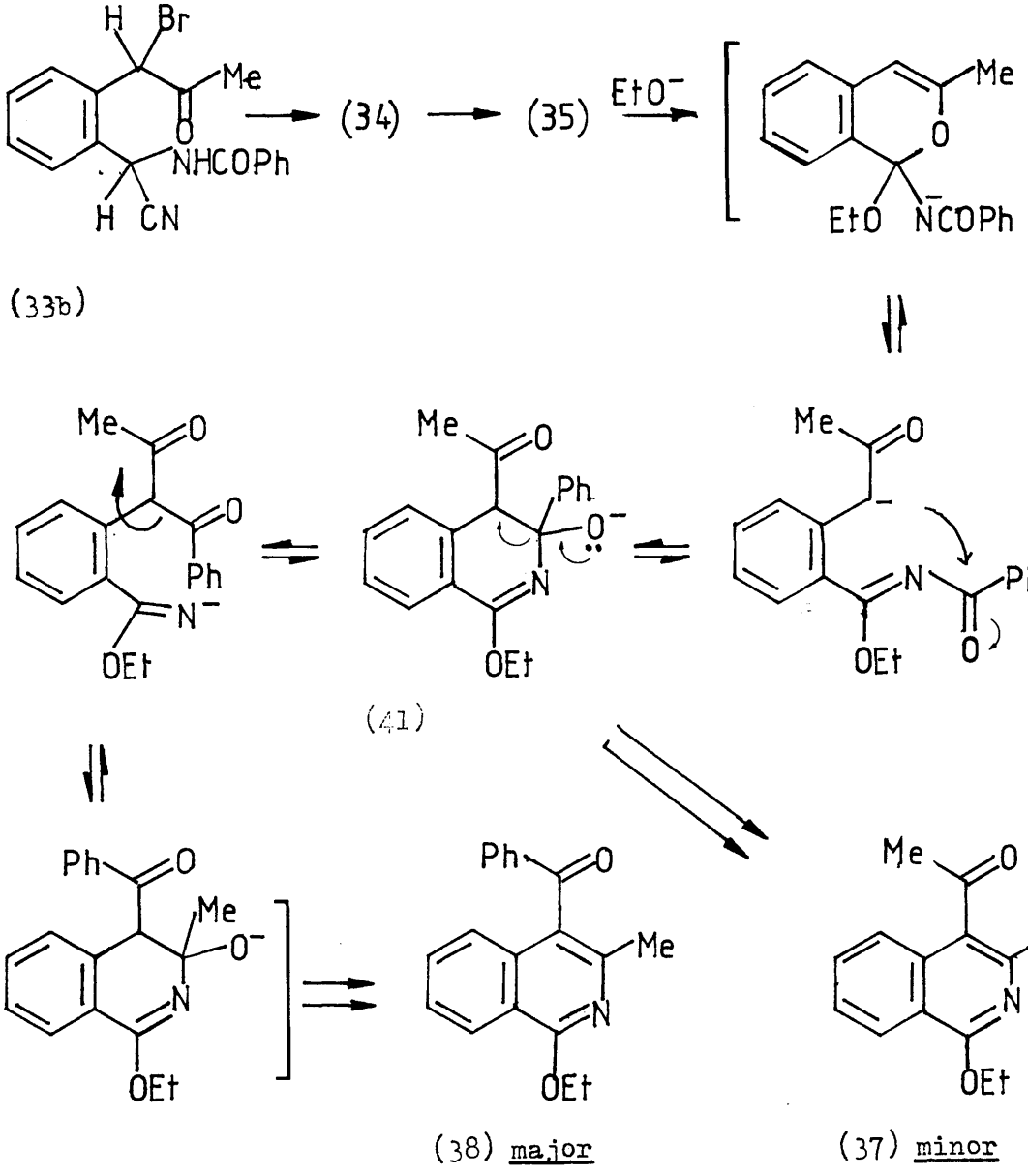
As an extension of their work on the chlorohydrins of Reissert compounds, Kirby *et al.* [20] treated the 3-methyl Reissert compounds (31, Scheme 4) with hypochlorous acid. Instead of the expected chlorohydrin (32a) they obtained the tautomeric chloroketone (33a). This product showed i.r. absorption, $\nu_{max.}$ (KBr) 1 728 cm^{-1} (ketonic carbonyl group), and at 1 650 cm^{-1} (amide carbonyl). Proton n.m.r. signals, for freshly made solutions, were δ $[(CD_3)_2SO]$ 2.15 (s, Me), 6.30 (s, CH), 6.69 (d, J 7 Hz, CH, collapsed to a singlet on addition of D_2O), and 9.87 (d, J 7 Hz, NH, disappeared on addition of D_2O). This indicated a ring-opened structure. However the n.m.r. spectrum changed with time. A new set of signals, δ $[(CD_3)_2SO]$ 2.22(s), 6.15(s), 6.74(d, J 7 Hz collapsed on addition of D_2O), and 9.76(d, J 7 Hz, disappeared on addition of D_2O), gradually appeared and, after 24 h, attained an intensity approximately equal to that of the original set. This apparent isomerisation did not involve exchange of hydrogen α to either the cyano- or keto-groups since no replacement of CH by CD was observed when (33a) was kept in $(CD_3)_2SO$ containing D_2O. The n.m.r. changes were provisionally attributed to either interconversion of amide rotamers or reversible elimination of hydrogen cyanide with consequent epimerisation of the chiral centre α to the cyano group. Unfortunately the authors [20] were unable to reproduce the preparation of (33a) and further investigation was abandoned. Instead (31) was treated in



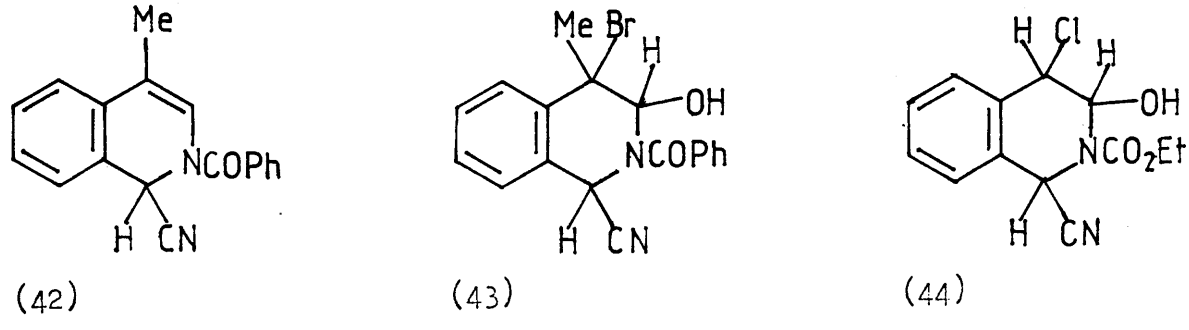
1,3-dibromo-5,5-dimethylhydantoin

aqueous dioxan with 1,3-dibromo-5,5-dimethylhydantoin [21] to afford, consistently, the bromoketone (33b), $\nu_{max.}$ 1 719 cm^{-1}. This product formed well-defined crystals, but the n.m.r. spectra of even freshly prepared solutions showed two sets of closely-spaced signals. It appears likely that the bromoketone exists in a single stereochemical form in the crystalline state, but forms a mixture of stereoisomers in solution, more quickly than does the chloroketone (33a).

Treatment of (33b) with triethylamine in dioxan gave, as expected, (cf. 17), the isochromene (2-benzopyran) (34) which was converted by sodium hydroxide into (35). The structure of (35) was confirmed by hydrolysis with dilute hydrochloric acid to yield the known [22] 3-methylisocoumarin (36). Treatment of (34) with ethanolic sodium hydroxide, under the usual conditions, gave an oily, ketonic product which was judged initially, from its spectroscopic properties, to be the expected methyl ketone (37) (cf. 20, Scheme 3). However, this product did not crystallise, and its ^1H n.m.r. spectrum consistently showed a weak signal (δ 2.07, s) attributed to an impurity which was not removed by chromatography. Further, reduction of the impure ketone with sodium borohydride gave, as the major product, a crystalline alcohol which clearly did not have the expected structure. The n.m.r. spectrum of this alcohol showed a singlet (δ 2.49), rather than a doublet, for the methyl protons and, after exchange with D_2O, a singlet (δ 6.41) rather than a quartet


H Br
Me
O
NHCOPh
H CN
(34)
(35)
EtO⁻
Me
O
EtO NCOPh
(33b)
Me O
Ph
N⁻
OEt
Me O
Ph
O⁻
N
OEt
(41)
Me O
N Ph
O
OEt
Ph O
Me
O⁻
N
OEt
Ph O
Me
N
OEt
(38) major
Me O
Ph
N
OEt
(37) minor

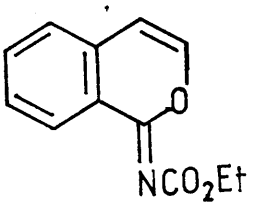
Scheme 5


Me
NCOPh
H CN
(42)
Me Br
H
OH
NCOPh
H CN
(43)
H Cl
H
OH
NCO₂Et
H CN
(44)

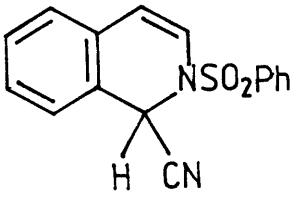
for the methine (-CHOD) proton. The alternative structure (40) for this alcohol was therefore considered and then established by unambiguous syntheses of each of the two isomers (39) and (40).

It appeared, therefore, that the reaction of (34) with sodium ethoxide had taken place with rearrangement to give the ketone (38) as the major product. Also, it seemed likely that the minor product, detected by n.m.r. spectroscopy, was the isomeric ketone (37). This view was supported by the following observations. Reduction of the impure ketone with sodium borohydride and separation of the products by thin layer chromatography gave (40) and (39) in the ratio ca.5:1. Further the n.m.r. spectrum of the impure ketone corresponded with that expected for a mixture (ca. 7:1) of the isomers (38) and (37); reference samples of each ketone were prepared by oxidation of (40) and (39) with chromium trioxide-pyridine in dichloromethane. A possible mechanism for the formation of the ketones (37) and (38) is outlined in Scheme 5. The route to (37) parallels that proposed in Scheme 3 for the parent halohydrin (12), while the formation of (38) is attributed to ring opening of the intermediate (41) followed by closure in the alternative sense.

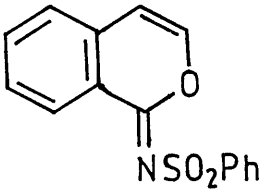
The analogous reactions of other Reissert compounds were referred to in the same paper by Kirby et al.[20]. Particular attention had been paid to the formation of halohydrins, since these polyfunctional derivatives are potentially valuable for the elaboration of a variety of heterocyclic systems. For example, the compound (42) formed a bromohydrin



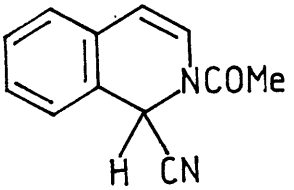
(45)



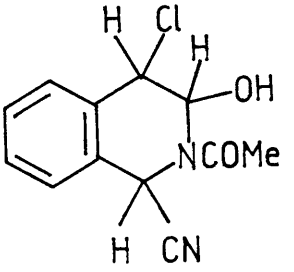
(46)



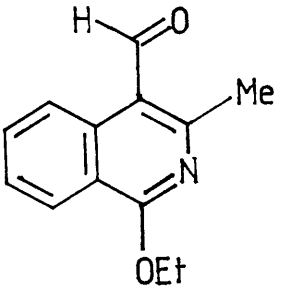
(47)



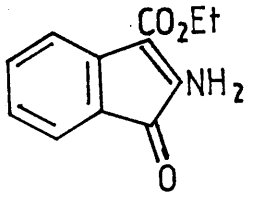
(48)



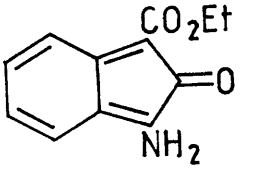
(49)



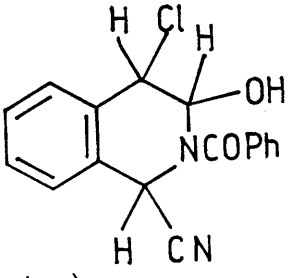
(50)



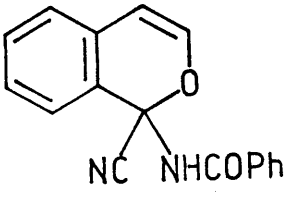
(51)



(52)



(12)



(17)

(43) and this was then converted under the usual conditions, via the isochromene, into 4-methylisocoumarin. Similarly, the chlorohydrin (44) was obtained from the corresponding Reissert compound and converted into the isochromene (45). Treatment of the sulphonyl derivative (46) with hypochlorous acid and chromatography of the crude reaction mixture on alumina gave directly the isochromene (47).

Kirby *et al.*, in the same paper, also reported some reactions of another new chlorohydrin (49) prepared from the N-acetyl derivative (48). When (49) was treated with ethanolic sodium hydroxide the expected aldehyde (50) was obtained in 54% yield (*cf.* 20 and 37).

2. DISCUSSION

2.1 Objectives of the Present Study

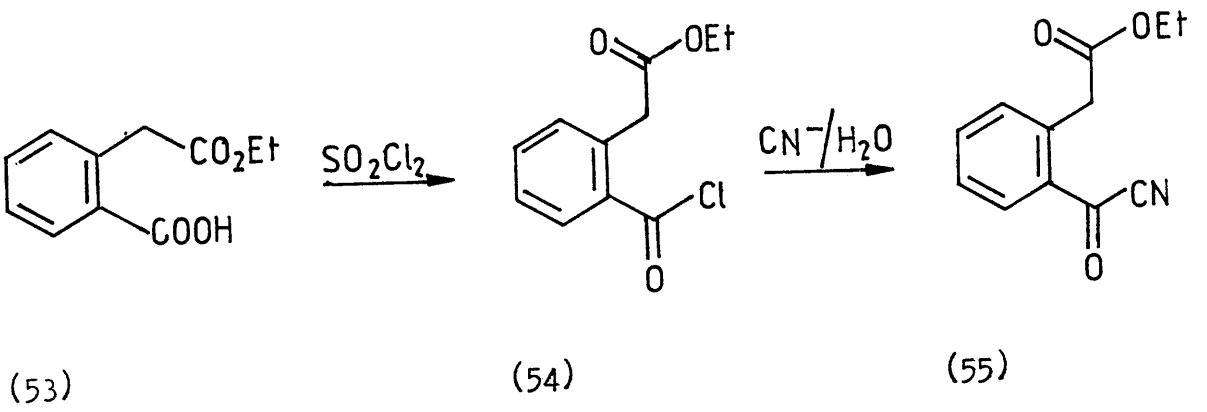
When the chlorohydrin (49) was treated with ethanolic sodium hydroxide to form the aldehyde (50), the crude reaction mixture was deeply coloured. Similar colours were observed when other halohydrins of isoquinoline Reissert compounds were treated with strong base. Thin layer chromatograms of the crude reaction mixtures revealed small amounts of orange or purple by-products. J.W.M. Mackinnon (Chemistry Department, University of Glasgow; unpublished work) was able to isolate a purple crystalline by-product from the reaction of the chlorohydrin (49) with ethanolic sodium hydroxide, but the quantities were too small to permit structural elucidation. The present study had two major aims, (i) to elucidate the structure of the purple compound derived from the chlorohydrin (49), and (ii) to test the mechanism (Scheme 3) proposed [10a] for the transformation of the chlorohydrin (12) into the isochromene (17).

2.2 The Purple Compound Derived from 2-Acetyl-4-chloro-1-cyano-3-hydroxy-1,2,3,4-tetrahydroisoquinoline (49)

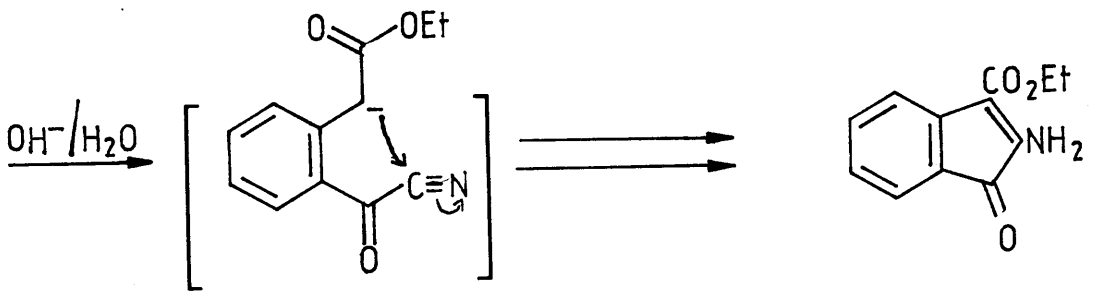
The chlorohydrin (49) was treated with ethanolic sodium hydroxide in the usual way. Most of the aldehyde (50) was removed from the reaction mixture by crystallisation and the mother liquors were subjected to repeated column and layer chromatography. In this way the by-product was obtained as deep purple needles (ca. 5%). We concluded that it did not

originate from impurities in the chlorohydrin because approximately the same yield was obtained from a sample of the chlorohydrin (49) which had been subjected to further rigorous purification by crystallisation (ethyl acetate) followed by t.l.c. on silica (chloroform-acetone, 9:1, $\underline{R}_f$ 0.15). The molecular formula, $C_{12}H_{11}NO_3$ of the by-product was deduced from microanalysis and accurate mass measurement of the molecular ion. The electronic spectrum, $\lambda_{max.}$ 263(ε 42 300) and 535 nm (ε 654), like the deep colour, indicated a highly conjugated chromophore. The i.r. spectrum (KBr) suggested the presence of two carbonyl groups ($\nu_{max.}$ 1733 and 1 760 cm^{-1}), and possibly a primary amino group (3 300 and 3 445 cm^{-1}). The ^1H n.m.r. spectrum confirmed the presence of two protons. exchangeable with D_2O [δ *ca.* 6 (2H, br s)], and showed signals for an ethoxy group [δ 1.36 (3H, t, *J* 8 Hz) and 4.33(2H, q, *J* 8 Hz)], and four olefinic or aromatic protons [δ 6.87(1H, d.t, *J* 8 and 2 Hz), and *ca.* 7.5 - 7.7 (3H, m)].

These data could be accommodated by either of the two structures (51) and (52). Although isoindenones are known only as transient species, a molecule with structure (52) might be stabilised by electron donation from the nitrogen of the amino group. However the purple compound was stable even above its melting point (127 - 131°C), and its mass spectrum showed fragmentation with loss of ethanol rather than of an ethoxy group. The latter observation is accommodated by the 2-aminoindenone structure (51) which has adjacent ethoxy and amino groups.



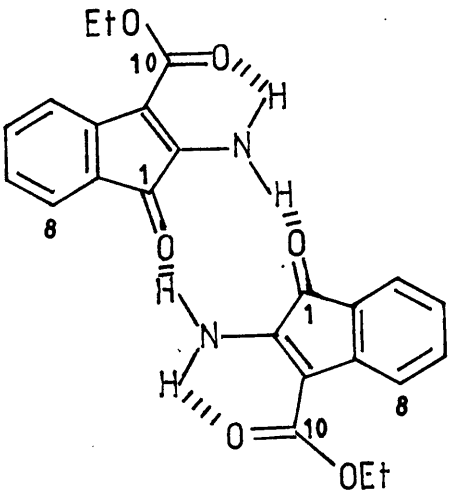
(53) (54) (55)



(56) (51)

purple product

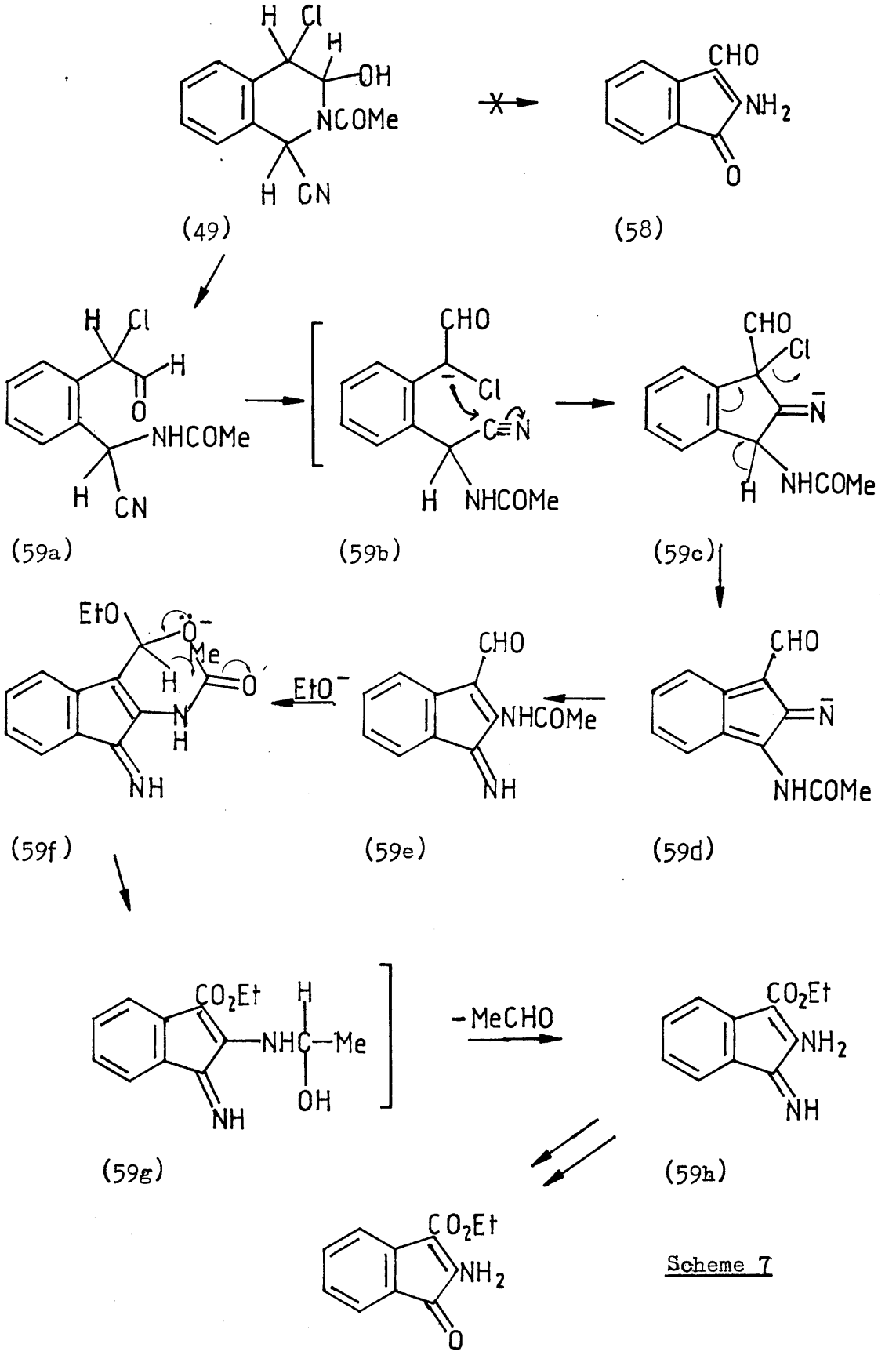
Scheme 6



(57)

Structure (51) seemed to be the more likely, and so it was decided to prepare the aminoindenone by syntheses. Homophthalic [23] ester (53) (Scheme 6) was treated with thionyl chloride in dichloromethane containing a catalytic amount of N,N-dimethylformamide, and the mixture was stirred with aqueous ethanolic potassium cyanide. The purple organic layer yielded, after chromatography, a purple compound, presumably resulting from the base catalysed cyclisation of an intermediate acyl cyanide (55). This synthetic ethyl 2-amino-1-oxo-inden-3-carboxylate (51) was identical in all respects to the purple by-product. The yield, however, was very small (5%).

In the meantime, a crystal of the original purple compound was subjected to X-ray analysis by Dr P.R. Mallison [24] (University of Glasgow) who proved that it had the strongly hydrogen-bonded structure (57). The four molecules in the unit cell are arranged in pairs, each pair consisting of centrosymmetrically related molecules. The ring carbonyl group of one is hydrogen bonded to the amino group of the other, and vice-versa, so that there is an eight-membered ring (X-ray crystallographers notation) in which two sides are formed by hydrogen bonds. There is also an intramolecular hydrogen bond between the amino group and the ester carbonyl group. Atoms 8(C), 10(C), 1-O, and 10-O deviate significantly from the plane of the other non-hydrogen atoms. The amino and aromatic hydrogen atoms lie in the plane within experimental error. Thus this X-ray analysis supports the

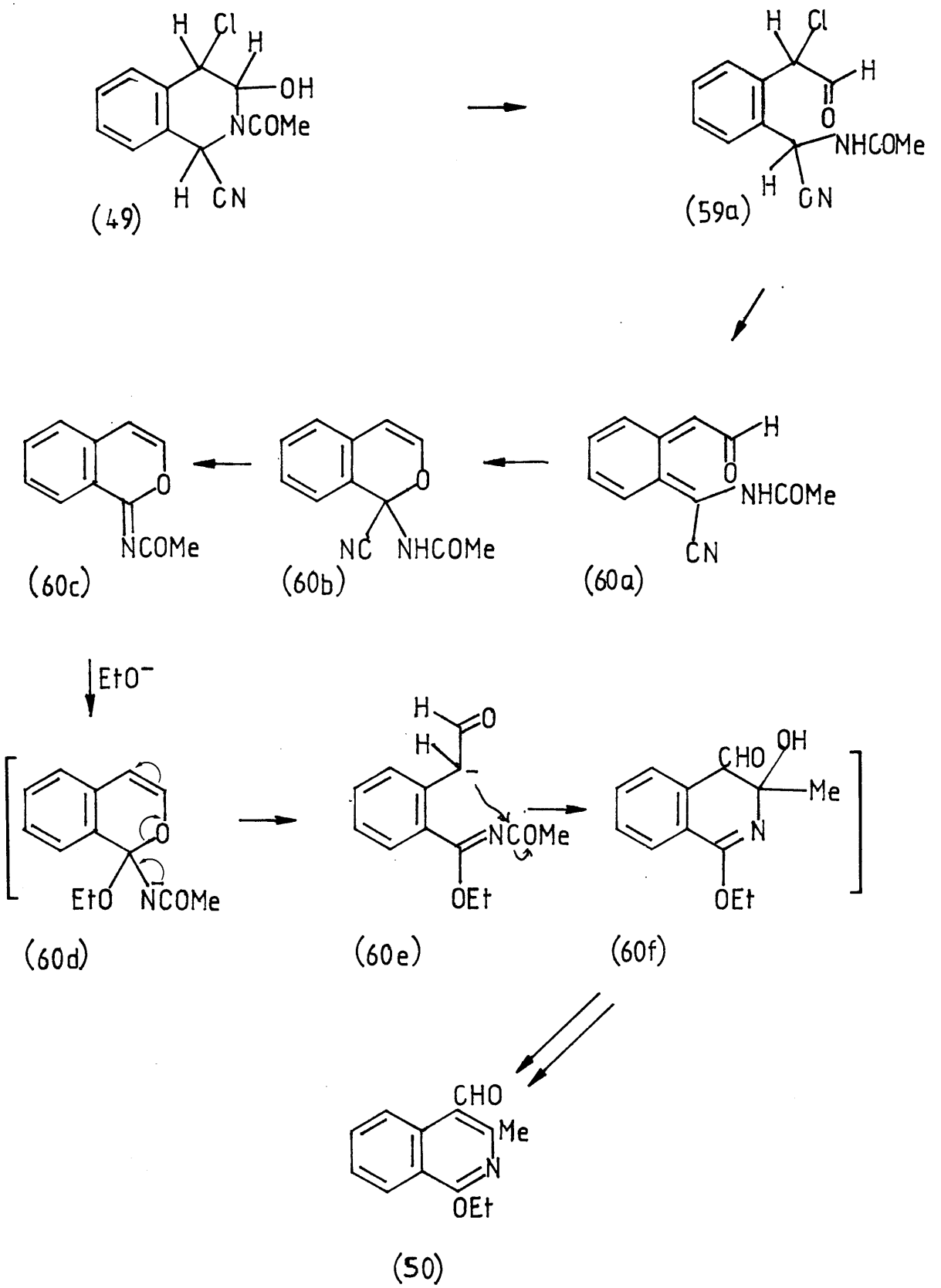

H Cl
H
OH
NCOMe
H CN
(49)
X
CHO
NH2
O
(58)
NHCOMe
(59a)
(59b)
(59c)
EtO
Me
EtO⁻
(59f)
(59e)
(59d)
CO2Et
NH
-MeCHO
(59g)
(59h)
NH2
(51) purple product

Scheme 7

data obtained by other means. The amino group is part of a vinylogous amide system and, consequently, resists attack by electrophiles. Indeed, the purple compound was not acetylated by lithium diisopropylamide in combination with acetyl chloride, nor even by heating under reflux in acetic anhydride containing sodium acetate.

A possible mechanistic route for the formation of the purple indenone (51) is shown in Scheme 7. A priori one would expect a product of this type to be an aldehyde (58) derived, for example, from an intermediate (59e) rather than an ester. One possible explanation is that an intramolecular hydride shift (59f), reminiscent of a Cannizzaro reaction, occurs to produce a carbinolamide (59g) which then loses acetaldehyde. It is interesting to compare this route with the one which is believed to lead to the major product (50, Scheme 8). According to Scheme 7, ring opening is followed by loss of a proton from C(4), the chlorine atom being retained (59b). This leads to a ring closure involving the cyano group. Only then does a 1,4-elimination of hydrogen chloride take place leaving a 5-membered ring as part of a highly conjugated system which rearranges with migration of an acetyl group to give (59e).

The route leading to the formation of the major product (50) involves the same type of transformations, but the stages at which they take place are different. Scheme 8 suggests that ring opening is followed by 1,4-elimination of hydrogen chloride to give a highly conjugated aldehyde (60a).



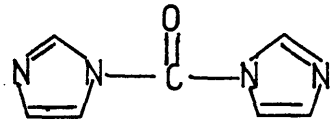
major product

Scheme 8

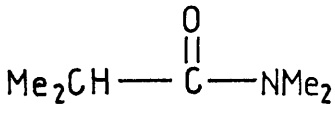
Ring closure and elimination of hydrogen cyanide leads to the isochromene (60c). Following attack by the ethoxy ion at C(1) the hetero ring opens, and recloses with loss of a molecule of water to give the major product (50).

In both of the above mechanisms it is postulated that the elimination of hydrogen chloride results in the formation of highly conjugated systems, viz. (59d) and (60a). A later section (2.4) describes an investigation of the elimination of hydrogen chloride from the chlorohydrin of the N-benzoyl Reissert compound (2).

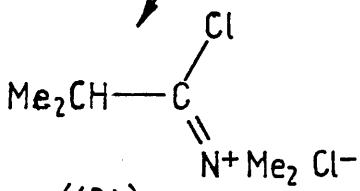
It was not unexpected that the yield of purple compound (51) from the homophthalic ester (53) was very low (5%). Fieser and Pechet [25] had already reported that the monomethyl ester of homophthalic acid reacts with phosphorus pentachloride, alone or in benzene solution, or with thionyl chloride in ether, to give 3-chloroisocoumarin rather than the expected acyl chloride. Our synthesis (Scheme 6) of the aminoindenone (51) involved the formation of the acid chloride (54) as a preliminary to the formation of the acyl cyanide (55). Thus the unsatisfactory link in the synthetic route to compound (51) was almost certainly that step involving formation of the acid chloride (54). Other reagents were tried as "activators" of the carboxyl group in the ester (53), for example, 1,1-carbonyldiimidazole [26] (61), and the chloroenamine [27] (62c). The results obtained using these and other "activators" are listed in the Experimental Section. Unfortunately, none of these reagents



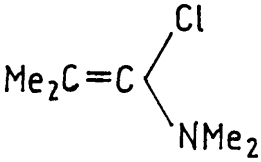
(61)



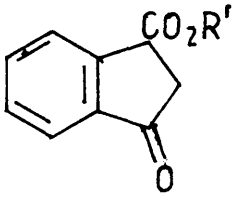
(62a)



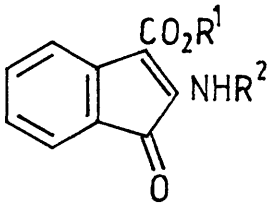
(62b)



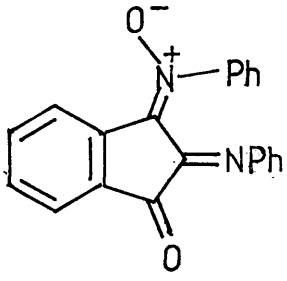
(62c)



(64) a; R^1 = Et
b; R^1 = H

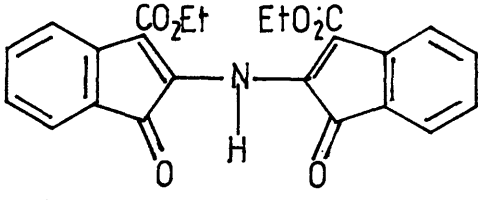


(65) a; R^1 = Et, R^2 = Bu^t
b; R^1 = Et, R^2 = Ph
c; R^1 = H, R^2 = Ph



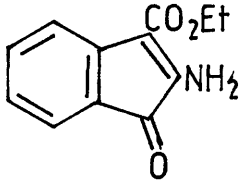
(66)

(65a)
CF_3COOH



(67)

CF_3COOH



(51)

Scheme 9

Formula (63); vid.p. 79a

gave a better yield than that obtained using our original thionyl chloride method.

A more satisfactory synthesis of the aminoindenone (51) was desired. The chosen alternative route required the preparation of 2-methyl-2-nitrosopropane and ethyl 1-oxo-indan-3-carboxylate (64a). It was hoped that the product (65a) formed by the condensation of these two substances in alkaline solution could be cleaved with acid to give the purple aminoindenone (51). In order to develop a suitable procedure for the condensation process, experiments were carried out using nitrosobenzene in place of the tert-butyl nitroso compound. The nitrosobenzene (1.25 equiv.) condensed with (64a) to give blue crystals. The molecular formula of this substance was deduced, from microanalysis and mass spectroscopy, to be $C_{18}H_{15}NO_3$. The electronic spectrum, [$\lambda_{max.}$ 205.5 (ε 26 100), 265(ε 29 700) and 566 nm (ε 2 040)] like the deep colour, indicated a highly conjugated chromophone. These data combined with that obtained from the i.r., ^1H and ^{13}C n.m.r. spectra confirmed the structure of the compound (65b). A trace of a dull-red material occurred as a by-product. This was possibly the nitrone (66), originating from a small quantity of hydrolysed ester (64b): nitrones are discussed in Section 2.3.

The procedure was then repeated using 2-methyl-2-nitrosopropane. The molecular formula of the resulting blue-black compound was deduced, from microanalysis and mass spectroscopy to be $C_{16}H_{19}NO_3$. The electronic spectrum,

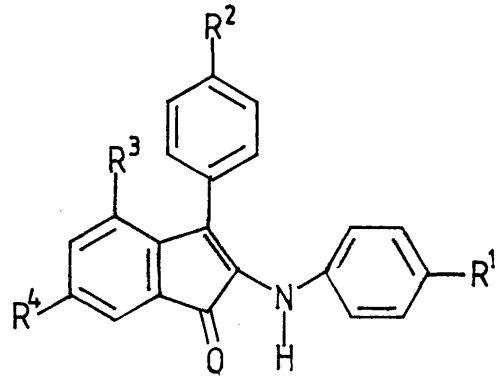
$\lambda_{max.}$ 221 (ε 1.25 x 10^3), 266 (ε 2.9 x 10^4) and 584 nm (ε 920)), like the deep colour, indicated a highly conjugated chromophore. These data combined with that obtained from the i.r. and ^{1}H n.m.r. confirmed the structure of the compound (65a). All attempts to remove the tert-butyl group by cleavage with acid failed to give the aminoindenone (51). The acidic reagents employed included concentrated sulphuric acid, which had been used by Lacey [28] to cleave N-tert-butyl aromatic amides. With one of the reagents, trifluoroacetic acid, (65a) did give products worthy of further consideration. Analytical t.l.c. on silica developed with chloroform, showed that the crude reaction mixture contained two coloured compounds. There was a tiny purple spot which had the same (R_f 0.1) as the aminoindenone (51). It seemed likely that this was the target molecule (51), but it was present in such small amounts that it was not considered profitable to devote more effort to its isolation. The other (R_f 0.4) had a striking light-blue colour and was suspected of being a product formed by a secondary reaction of the molecule (51) with the trifluoroacetic acid.

Obviously, the reaction of the tert-butylaminoindenone (65a) with trifluorocetic acid was not an efficient route to (51), but the possibility that the light-blue product (R_f 0.4) resulted from an attack of the acid on (51) had to be investigated. Accordingly, some of the aminoindenone (51) was dissolved in trifluoroacetic acid and left at room temperature for 0.75 h. After work-up, a blue crystalline product was obtained in low yield. The molecular formula, $C_{24}H_{19}NO_6$, of the product was deduced from microanalysis

and the mass spectrum. The electronic spectrum (λ 577 nm (ε 8 360)), and the light blue colour suggested the indanone chromophone. The i.r. and n.m.r. spectra supported (67) as the structure of the compound. From this structure one can see that it consists of two indanone moieties connected by a nitrogen bridge, and that it had been formed from two molecules of the purple compound (51) following the elimination of one molecule of ammonia. This little series of experiments, involving the tert-butyl nitroso compound, provided more confirmation of the structure of the amino-indenone (51).

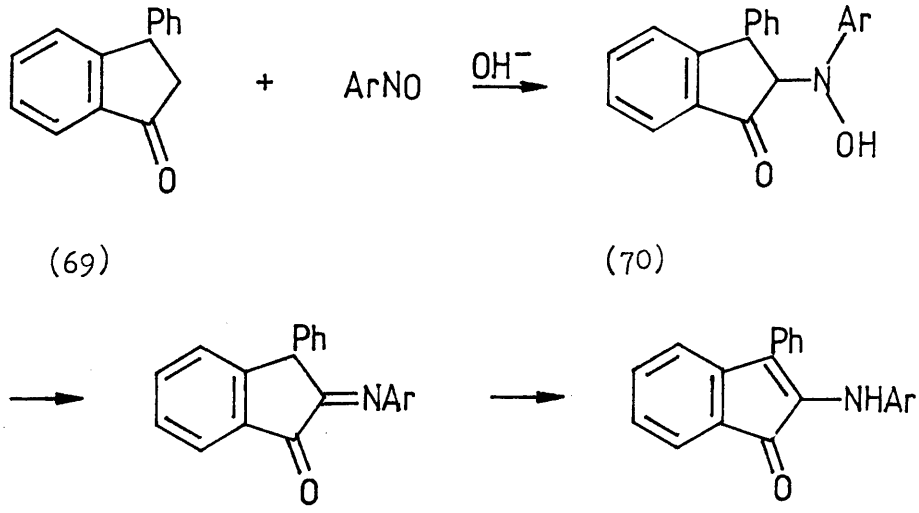
2.3. Reactions of Indanones with C-Nitroso Compounds

Pfeiffer et al. [29] described a number of purple compounds which they had prepared by condensing indanones with nitroso arenes in the presence of alkali. In their earlier papers, these products were described as "anils", but in 1937 Schonberg and Michaelis [31a] reported evidence that these anils were the substituted aminoindenones (68). Pfeiffer accepted these corrections. A suggested mechanism for the formation of compounds like (68) is shown in Scheme 10.
In the present study, similar compounds, which were characterised using n.m.r. and i.r. spectroscopy, support the structures assigned by Schonberg and Michaelis. Thus the purple compound (51) gave a broad two proton singlet at ca. 6, and compounds (65a), (65b) and (67) gave one proton singlets at ca. 8.7, 9.18 and 10.0 respectively. The i.r. spectra of these



(68)

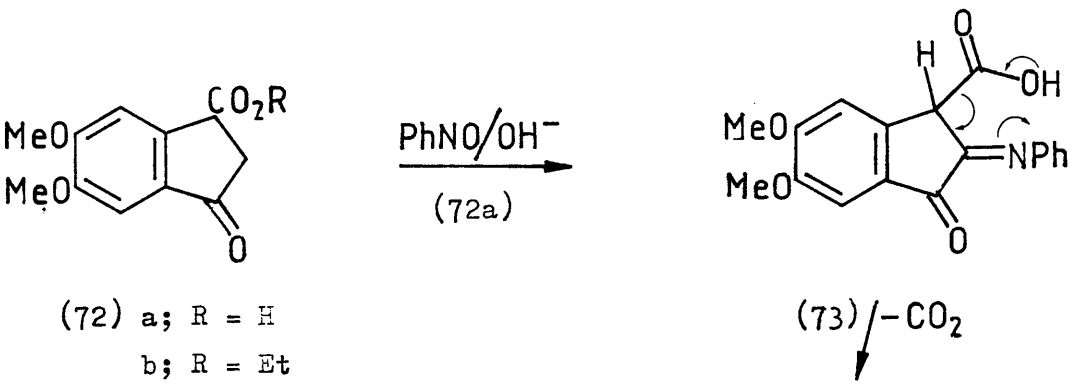
	R^1	R^2	R^3	R^4
a)	H	H	H	H
b)	OMe	H	H	H
c)	NMe_2	H	H	H
d)	NMe_2	H	H	Me
e)	NMe_2	H	Me	Me
f)	NMe_2	H	H	Et
g)	NMe_2	Br	H	Br



(69) (70)

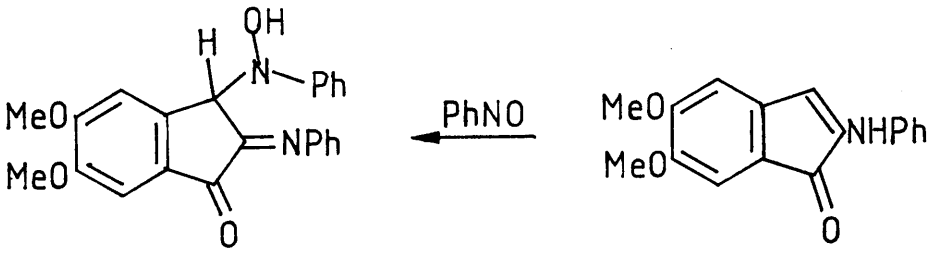
(71) anil (68a)

Scheme 10



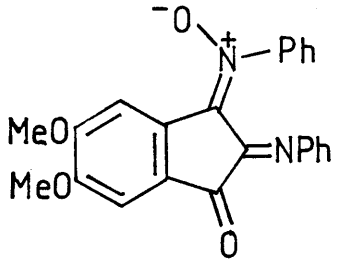
(72) a; R = H
b; R = Et

(73) /−CO2

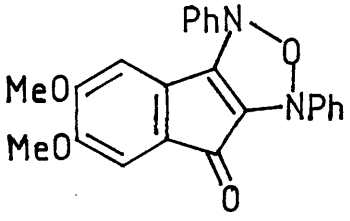


(75) (74)

PhNO



(76) + PhNHOH (77)



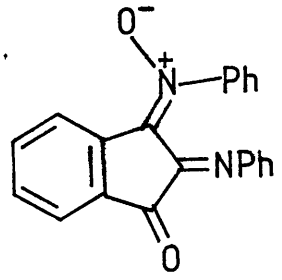
(78)

Scheme 11

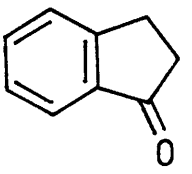
compounds showed the following absorptions (cm^{-1}) which could be due to N-H stretching: compound (51), 3 330 and 3 445; (65a), 3 255; (65b), 3 290; (67), 3 270. It is to be noted that the structures of compounds (68), as amended by Schonberg and Michaelis, all show the presence of the 2-aminoindenone chromophore.

By chance, it was discovered that Dr A.J. Baker (University of Glasgow) had a sample of 5,6-dimethoxy-3-oxoindan-1-carboxylic acid (72a), a derivative of that carboxylic acid (64b) which had been esterified in the present study, and then condensed with 2-methyl-2-nitrosopropane in the search for an alternative route to the aminoindenone (51). A convenient source of more compounds with the indenone structure seemed to have become available. The acid (72a) was esterified, (72b), and attempts were then made to condense this with nitrosobenzene. The reaction mixture became brown, and analytical t.l.c. gave yellow, orange and turquoise spots, but there was no constituent present in sufficient quantity to justify the continuation of these experiments.

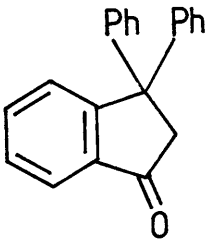
Then the carboxylic acid itself (72a) was treated with the nitrosobenzene. Instead of the expected blue product, that is, one with the aminoindenone chromophore, (*cf.* 65), red crystals were obtained. The molecular formula, $C_{23}H_{18}N_2O_4$ was deduced from microanalysis and mass spectroscopy. The proposed structure (76) is supported by the data from ^1H n.m.r. A possible route to this nitrone is shown in Scheme 11. According to this, anil (73) formation is followed by



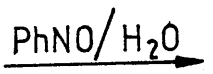
(66)

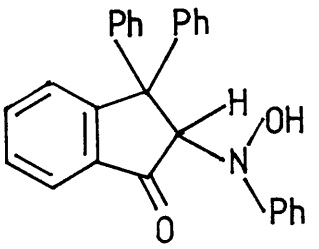


(79)

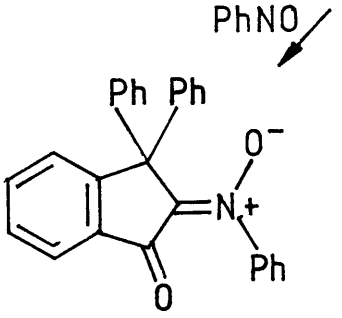


(80)





(81)



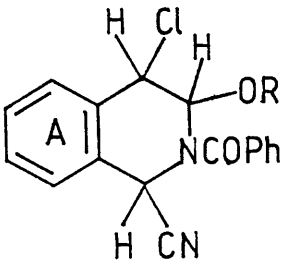
(82)

Scheme 12

decarboxylation to give the aminoindenone (74). Then further attack by the nitroso compound leads to (75). The residual nitrosobenzene in the reaction mixture then acts as an oxidising agent (see below), and this leads to the formation of the nitrone (76) and phenylhydroxylamine (77). Obviously three equivalents of the nitroso compound are required for each equivalent of the oxoindan-1-carboxylic acid (72a). An alternate structure for the product shown as the nitrone (76) might be (78). However, this possibility was not investigated.

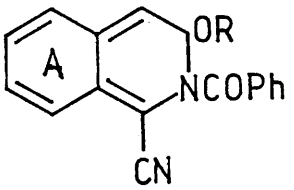
Pfeiffer and Milz [30] obtained a nitrone (66) when they treated indan-1-one (79) with nitrosobenzene. Schonberg and Michaelis [31] reported that 3,3-diphenylindan-1-one (80) and two equivalents of nitrosobenzene, in the presence of alkali, gave a reddish compound to which they assigned the nitrone structure (82, Scheme 12). They postulated that nitrosobenzene, as well as taking part in the condensation, acted as an oxidising agent. They did not isolate any phenylhydroxylamine, but they did find a little azoxybenzene, a known [32] product of the reaction of phenylhydroxylamine with nitrosobenzene.

Work involving the dimethoxy compounds (72) was halted because it required investigation of problems too far removed from the original aims of the study.



(27) R = Et

(28) R = Me



(29) R = Et

(30) R = Me

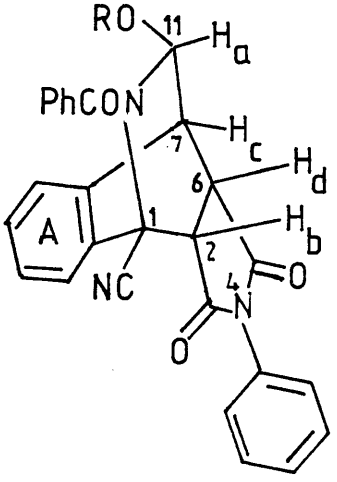
2.4. 1,4-Elimination of Hydrogen Chloride from Chlorohydrin Alkyl Ethers

a. Use of N-Phenylmaleimide as a Trapping Agent for Intermediates (29) and (30)

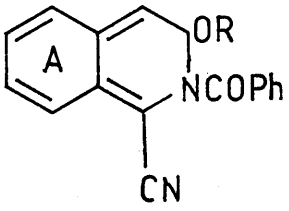
In Section 1.2 we reported work by S.L. Tan [15] involving the isomeric chlorohydrin ethyl ethers (27), and his suggestion that evidence for a base-induced 1,4-conjugated elimination of hydrogen chloride would be obtained if the postulated highly conjugated reactive intermediate (29) could be trapped.

With this end in view, the preparation of the chlorohydrin ethyl ethers (27) was repeated by the present author. The ^{1}H n.m.r. spectrum of the major isomer showed a complex quartet for the diastereotopic methylene protons, whereas that of the minor isomer showed two complex quartets [δ 3.23 and 3.73 ($\underline{J}$ 7 Hz, C$\underline{H}_2$Me)]. The chlorohydrin methyl ethers (28) were also prepared for the present studies. A major isomer constituted 95% of the isolated methyl ethers. The ^{1}H n.m.r. spectrum of each of these isomers resembled that of the corresponding chlorohydrin ethyl ether except, of course, that the ethyl signals were replaced by a single methyl signal.

A study of the elimination of hydrogen chloride from the ethers (27) and (28) was then undertaken as follows. The major isomer of the chlorohydrin ethyl ether (27) and N-phenylmaleimide (5 mol equiv.) in dioxan were treated at room temperature with triethylamine (1.1 mol equiv.). The



(83a) R = Et
(84a) R = Me



(29) R = Et
(30) R = Me

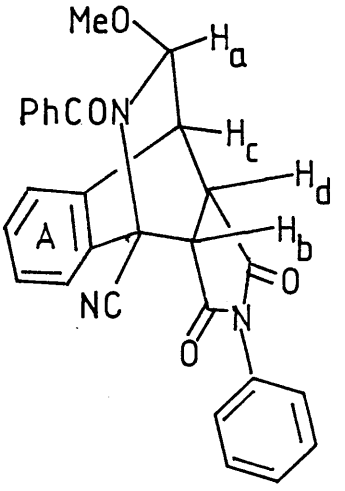
usual yellow colour developed. Very slowly, crystals appeared. The reaction mixture was left for 45 h. Then the crystals were filtered off, washed with dioxan, and finally with water to remove triethylamine hydrochloride. The product had a greenish tinge before recrystallisation from acetone. Microanalysis showed that it had the composition expected for a N-phenylmaleimide adduct (83a). The minor isomer of the ethyl ether (27) gave the same adduct, although its yield was less (45% instead of 75%). When the reaction with the major isomer, was repeated at 75-80°C it was faster than at room temperature, but the yield was 50% rather than 75%. The fact that both chlorohydrin ethyl ethers gave the same N-phenylmaleimide adduct confirms Tan's view that they were stereoisomers, not structural isomers. The structure (83a) for the adduct, and thereby the structure (27) for the ethers, was established, as follows, by ^{1}H n.m.r. spectroscopy. Protons attached to saturated carbon atoms in the adduct have been assigned letters in structure (83a) for ease of reference. The ^{1}H n.m.r. signals from these protons were observed at δ 3.66(d d, J 3 and 8.5 Hz, H_d) 4.11(br t, J 3 and 4 Hz, H_c), 4.36(d, J 8.5 Hz, H_b), and 4.98(br d, J 4 Hz, H_a). The various signals could be assigned unambiguously from the observed chemical shifts, multiplicities, and coupling constants.

The N-phenylmaleimide adduct of the elimination product of the chlorohydrin methyl ether (28) was prepared in the

same way in 64% yield, except that the amount of the dienophile was reduced to 1 mol. equiv. When the reaction time was reduced to 2.5 h by maintaining the temperature at 75°C the yield was 43%. This adduct was assigned the structure (84a). On the basis of the ^{1}H n.m.r. spectrum, the relevant signals were observed at δ 3.68(d d, J 3 and 8.5 Hz, H_d), 4.21(br t, J 3 and 3.7 Hz, H_c), 4.35(d, J 8.5 Hz, H_b), and 4.94(d, J 4 Hz, H_a). The similarity between these signals and those given by the ethoxy adduct (83a) is very marked.

The structures (83a) and (84a) would arise from the intermediates (29) and (30) by endo addition of N-phenylmaleimide anti to the alkoxy group. The alternative modes of addition would be endo-syn, exo-anti, and exo-syn. The issue was settled unambiguously, in favour of endo-anti addition, by Nuclear Overhauser Effect (N.O.E) experiments, using the "N.O.E. difference" technique on the methoxy adduct (84a). These experiments were carried out by Dr D.S. Rycroft (University of Glasgow).

The methoxy protons and H_a were irradiated in turn, and their effect on each other, and on other protons, was measured by subtracting the original signal intensities from the intensities observed upon irradiation. The results are given in Table 1.



(84a)

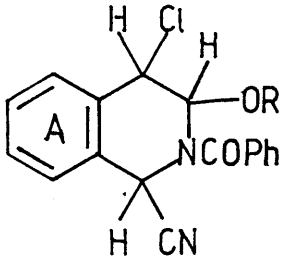
Table 1

N.O.E. Experiment

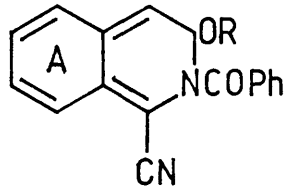
Methoxy-N-phenylmaleimide adduct (84a). Enhancements (%) upon irradiation of methyl and H_a

Methoxy protons	o-benzoyl protons	H_a	H_b	H_c	H_d
irradiated	2.73	9.57	Nil	6.39	Nil
10.09	3.99	irradiated	Nil	8.49	9.74

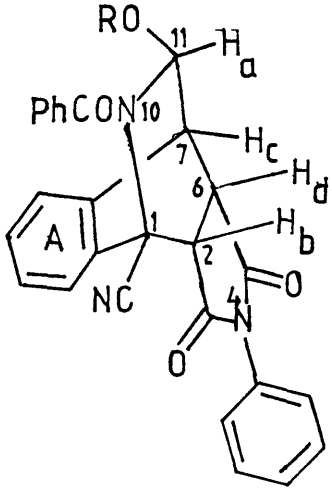
When using these enhancement values to make decisions concerning the stereochemistry of the molecule, it is assumed that the irradiation of a particular proton acts through space in such a way that the resonances of geometrically close protons are increased. The nearer a particular proton is to the one being irradiated, the greater is the enhancement of its signal. The effect falls off very sharply with distance. The present state of the art is not sufficiently advanced to permit accurate assessments of interatomic distances. Thus, as will be illustrated in Section 2.5 where the problems relating to the stereochemistry of the chlorohydrin ethers (27) and (28) are more difficult, N.O.E. experiments must be supported by other chemical facts about a particular compound before an accurate stereochemistry can be deduced. However, although the method lacks the precision and impartiality



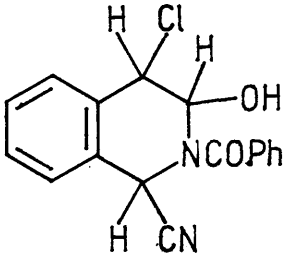
(27) R = Et
(28) R = Me



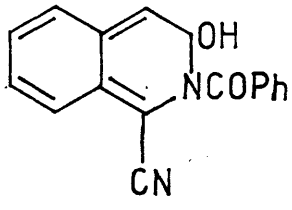
(29) R = Et
(30) R = Me



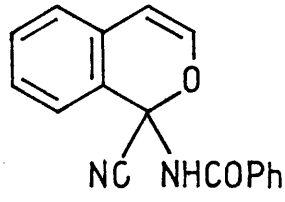
(83a) R = Et
(84a) R = Me



(12)



(14)



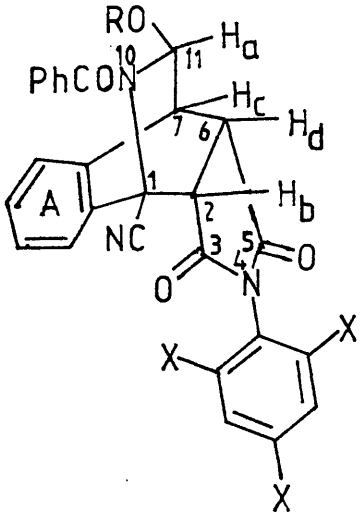
(17)

of X-ray analysis, the results were unambiguous in the case of the adduct (84a).

Table 1 shows that there is a close spacial relationship between the methyl protons (10.09%) and H_a (9.57%); this, of course, merely serves to confirm the assignment of the H_a signal. The methyl protons and H_a are sufficiently close to have some influence on the ortho-benzoyl protons, suggesting that the favoured amide rotamer is the one having the phenyl group orientated away from the carbon framework. The methyl group is quite close to H_c (6.39%) but is distant from H_b and H_d. H_a is a little closer to H_d (9.74%) than to H_c (8.49%), but is distant from H_b. The strong H_a-H_d enhancement, taken alone, establishes the relative stereochemistry of all centres in the adduct. Thus, the stereochemistry of the methoxy N-phenylmaleimide adduct is that shown as (84a). By analogy, that of the corresponding ethoxy adduct is (83a).

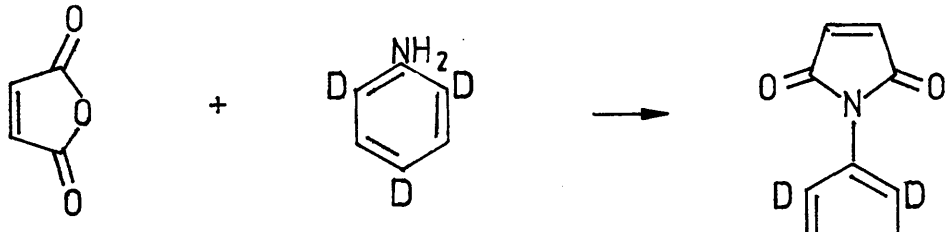
The fact that such adducts can be obtained proves that the intermediates (29) and (30) are formed by the action of base on the chlorohydrin ethers (27) and (28), under the conditions used to effect rearrangement of the chlorohydrin (12, Scheme 3). This lends support to the suggestion that (12) also undergoes 1,4-elimination of hydrogen chloride with the formation of the reactive conjugated intermediate (14) as a preliminary reaction leading to the isochromene (17).

The N-phenylmaleimide adducts showed additional spectroscopic properties of interest. The expanded ^1H n.m.r. spectrum



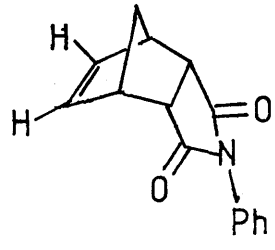
(83) a; R = Et, X = H
b; R = Et, X = D

(84) a; R = Me, X = H
b; R = Me, X = D



(85) (86) (87)

Scheme 13



(88)

of the methoxy adduct (84a) showed certain weak signals which may have arisen from a similar compound, present in relatively small concentration. These signals were at δ 3.34(s), 4.14(br t, J 3 Hz and 3.6 Hz), and 5.25(d, J 3.6 Hz), and accompanied, and were visually similar to, those given by the methyl group, H_c and H_a of the cycloadduct. Possibly they show the presence of a minor rotamer of (84a) resulting from slow rotation around the N-benzoyl bond. However such an interpretation would require signals corresponding to those for H_a and H_d in compound (84a). Although the missing signals might have been isochronous with those for H_b and H_d, there does not seem to be enough proof that a rotamer was present.

When the problem of the stereoisomerism of the N-phenylmaleimide adducts (83a) and (84a) was first investigated it was noted that the ^{1}H n.m.r. spectra of these compounds showed 2-proton multiplets at δ ca. 6.4-6.5, clearly separated from the aromatic proton signals in the range δ 7-8. However integration indicated that the 2-proton multiplets, also, arose from aromatic protons. Having confirmed the endo configuration of the adducts, it was decided to investigate the relationship between benzo ring A [(83a) and (84a)] and the ortho-protons of the N-phenylmaleimide residue. For this purpose N-(2,4,6-trideuteriophenyl)maleimide (87) of purity greater than 80% was prepared and used to obtain the adducts (83b) and (84b). These new adducts gave ^{1}H n.m.r.

spectra from which the anomalous signals were missing. This proved that the signals at δ ca. 6.4-6.5 had arisen from the ortho-protons of the N-phenylmaleimide residue. In each of the spectra there were weak doublets at δ ca. 6.42 - 6.53 (83b), and ca. 6.35 - 6.51 (84b). These signals were likely due to traces of N-(2,4-dideuteriophenyl)maleimide adducts arising from incomplete deuteriation of the aniline.

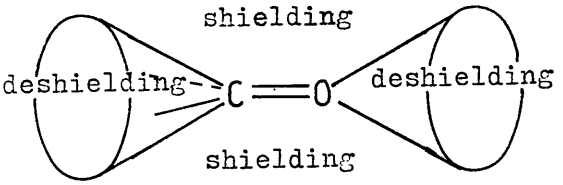
Finally, the N-phenylmalimide adduct (88) of cyclopentadiene was prepared. This is structurally similar to (83a) and (84a), but lacks the benzo ring A. The ^{1}H n.m.r. spectrum of this compound showed that none of its protons resonated outwith the normal proton range. Therefore, in the absence of ring A, there is no possibility of up-field resonance arising from the ortho-protons of the N-phenyl group.

Conclusions concerning the up-field 2-proton multiplets (δ ca. 6.4 - 6.5), which appear in the ^{1}H n.m.r. spectra of compounds (83a) and (84a), can be summarised as follows:-

i) the protons from which these signals arise are the ortho-protons on the N-phenyl group, and not those in the benzo ring A,

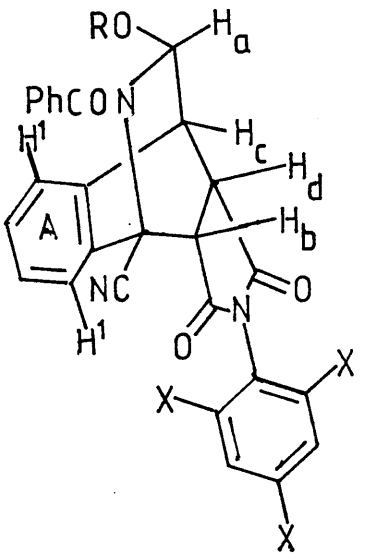
ii) These ortho-protons are shielded due to a secondary field associated with the benzo ring A [33].

Other workers have noted the presence of a 2-proton multiplet at δ ca. 6.4-6.5 in the ^{1}H n.m.r. spectra of Diels-Alder adducts, and have used this high-field resonance in their assignments of configuration to the adducts. As



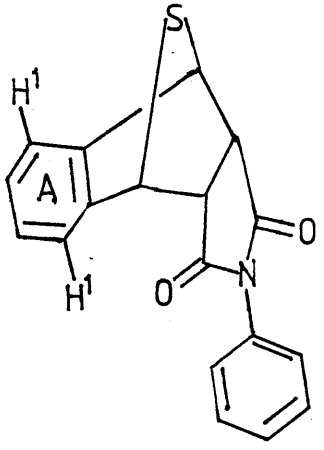
(89)

The anistrophy of the carbonyl group



(83) a; R = Et, X = H
b; R = Et, X = D

(84) a; R = Me, X = H
b; R = Me, X = D



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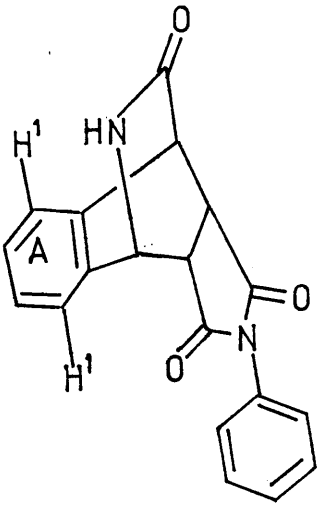

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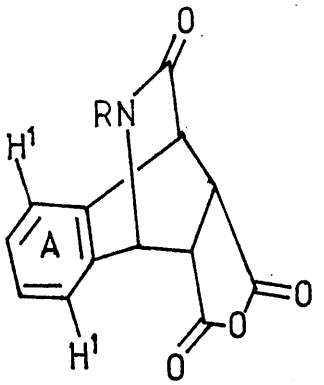
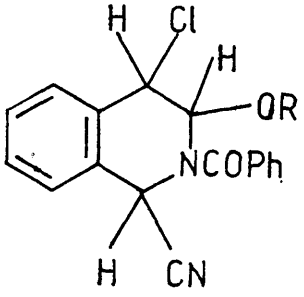
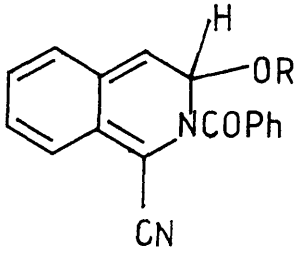


(26)

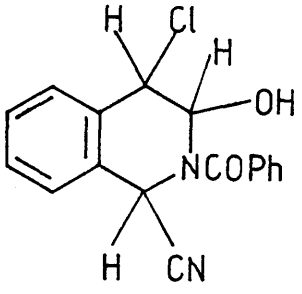
a result of work with the N-phenylmaleimide adducts (83) and (84), it can now be stated that their assignments were based on a faulty assumption. Earlier in this study reference has been made to an adduct of benzoisothiophene with N-phenylmaleimide (24) prepared by Cava and Pollack [16]. Like (83a) and (84a) the ^{1}H n.m.r. spectrum of this adduct showed a 2-proton aromatic multiplet at δ 6.43. The authors assigned this to the two protons (H^1) in the benzo ring A. They believed that these two protons fell within the shielding zone (89) of the maleimide carbonyl groups. If this were the case, then it follows that the adduct had the endo configuration. Jones [17] used the same argument when he assigned an endo configuration to an adduct (90) he had prepared from the isoquinolinone (25; R=H) and N-phenylmaleimide. Later Mruk and Tieckelmann [18a] prepared an adduct (26) from 2-methyl-3-isoquinolinone (25; R = Me) and maleic anhydride. They assigned an exo-structure to (26) (R=Me) because all four of the aromatic protons, including those designated H^1, absorb downfield. They assumed that, if the geometry of these adducts had been endo, the protons H^1 would have been shielded by the carbonyl groups of the anhydride system, and would have absorbed further upfield. As support for their argument they quoted the above authors (Cava and Pollack [16] and Jones [17]). Of course, it has now been shown here that neither the endo or exo configurations of adduct (26; R = Me) could give rise to a 2-proton multiplet at δ ca. 6.5, because the protons necessary for a resonance at such a high field



(27); R = Et
(28); R = Me



(29); R = Et
(30); R = Me



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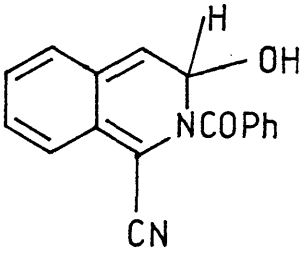

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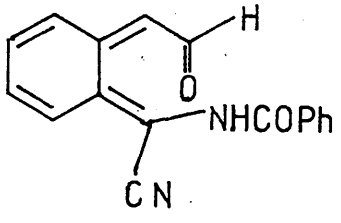
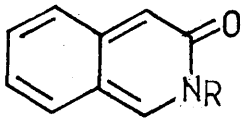


(16)



(25)

are not present in a maleic anhydride residue. Whether the compound (26; R = Me) is the endo or exo isomer is still not settled, although preferential formation of an endo adduct would be expected.

b) Use of Visible Spectroscopy in the Search for Intermediates (29) and (30)

Tan [15] observed that when the chlorohydrin (12) in dioxan was treated with triethylamine, the reaction mixture became yellow almost immediately and there was a concomitant precipitation of triethylamine hydrochloride. The yellow colour increased in intensity for a while, but had usually disappeared by the time that the reaction was worked-up. Tan associated the yellow colour with the presence of a reactive intermediate such as (14) or (16). This postulate was supported by the description of the unstable orange isoquinolinone (25; R = Me) prepared by Mruk and Tieckelman [18a]. Crystallisation did not provide a pure substance but left an orange gum. According to Evans et al. [18b] this difficulty was caused by auto-oxidation taking place during the purification process. Later Mruk and Tieckelman found that, when its solution in benzene was boiled in the presence of air, auto-oxidation did take place, with the formation of N-methyhomophthalimide derivatives. A solution of the gum in ethanol lost its yellow colour in 2-3 h. The orange gum rapidly became covered with a film of white product which seemed to be photodimerised material. The parent isoquinolinone (25; R = H) was obtained by Jones [17] as light yellow needles.

This compound readily photodimerised.

Proof as to the existence of the reactive intermediates (29) and (30) has already been provided. However in a preliminary part of this study an attempt was made to obtain evidence for (29) and (30) without resorting to trapping experiments. For example, a solution of the chlorohydrin ethyl ether (27) in dioxan was treated with one equivalent of triethylamine. Even after 20 h at room temperature the yellow colour of the reaction mixture still persisted and, on work-up, some of the starting material (27) was recovered. The precipitated triethylamine hydrochloride proved that 60% of the possible weight of hydrogen chloride had been eliminated. There was a mixture of other products, none of which was identified. Attention was then directed to the use of visible spectroscopy using the Unicam S.P. 800 machine. In order to obtain a suitable display it was necessary to reduce the concentration of the reactants in dioxan by a factor of about 10 compared to that used in the trapping experiments. Thus a comparison of the different types of experiments presents difficulties in interpretation.

Accordingly, a fresh solution of the major isomer of the chlorohydrin ethyl ether (27) and triethylamine in dioxan (4 mM in respect of each constituent) was continuously monitored. Dioxan was used as the reference solvent. The yellow colour appeared and increased in intensity. Absorption maxima developed at 422 and 443 nm. At the end of 5.5 h the absorbances were 0.73 (420 nm) and 0.61 (442 nm). By this time it was possible to identify a broad maximum at

373 nm with an absorbance of 0.80. Below 320 nm, the absorbance was greater than 1.0. The reaction mixture was stored overnight at room temperature, When the same solution was examined the next day, the absorption had spread from the U.V. region to beyond 500 nm leaving only 'a vestige' of the maxima at 443 nm. A further experiment involved the use of a more concentrated solution (5 mM, instead of 4 mM, in respect of each constituent). This time the reference liquid was a dioxan solution of the ether (27) (5 mM). The maxima at 420 and 442 nm developed as expected, but started to decrease 4 h later with little trace of a maximum at 373 nm. The absorbances, obtained as a function of time from the above experiments, could not be fitted to any simple kinetic equation. However, the maxima at 420 and 442 nm seemed to have arisen from the same substance as indicated by their almost parallel growth rates.

A reaction mixture of the ethyl ether (27) and triethylamine in dioxan (4 mM) was monitored for 10 minutes in a 5 mm spectrometer cell. A few small crystals of N-phenylmaleimide were then added. The absorption, all along the display, from 410 nm into the U.V. region, fell leaving the maxima at 420 and 442 nm reduced, but still visible above a general absorption. A second similar addition of N-phenylmaleimide one hour later, had a similar effect, but the two peaks could still be identified. It had been expected that the amount of N-phenylmaleimide was sufficient to cause the complete, and fast, removal of these maxima,

assuming that they arose from the presence of the reactive intermediate (29). Of course the dilution may have slowed considerably the trapping of (29).

In order to obtain some evidence for the persistence of the reactive intermediate, tests were carried out using more concentrated reaction mixtures. Thus the ether (27) (110 mg) along with one equivalent each of triethylamine and N-phenylmaleimide were dissolved in dioxan (7 ml). After 15 minutes, the mixture was worked up. No adduct was isolated. Our spectroscopic experiments had shown that the absorbances of the two maxima at 420 and 442 nm increased for about 5.5 h, and our earlier experiment had shown that some (27) could be recovered from a dioxan solution containing triethylamine at the end of a contact time of 20 h. These results were tested by allowing a solution of the ether (27) (110 mg) and triethylamine (1.2 equivalents) in dioxan (2 ml) to stand at room temperature for 5 h. N-phenylmaleimide (5.0 equivalents) was then added. Eight days later a few milligrams of adduct (83a) were obtained on work-up.

The reaction between the major isomer of the methyl ether (28) and triethylamine in dioxan (4 mM) was also examined spectroscopically. The spectrum looked remarkably like that obtained from the ethyl ether, with maxima at 422 and 443 nm. In this case the reaction was much faster, and the absorbances were 0.83 and 0.76, respectively, at the end of 40 minutes. Within 1 h, however, the absorbances had fallen to approximately half these values.

All the above results indicate the complex nature of the reactions of the ethers (27) and (28) under basic conditions, and the need for a more comprehensive spectroscopic study is obvious. Of course, the n.m.r. spectroscopic examinations of the N-phenylmaleimide adducts (83) and (84) have already shown that (29) and (30) are formed by the action of base on the ethers (27) and (28). Now an explanation of the associated visible phenomena can be suggested.

1. The slow formation of the yellow intermediates (29) and (30) was accompanied by their marginally slower decomposition, or re-arrangement, resulting in compounds with no chromophores in the visible region. Thus the yellow colour increased slowly in intensity until all starting material had been consumed. Thereafter the colour decreased in intensity because no fresh intermediate was being formed, and that which remained was changing. This explains why the observed absorbances were relatively small: only small concentrations of intermediates were present at any time.

2. Work-up shortly after all the reactants had been mixed produced no measurable yield of adduct (83a) because the yellow reactive intermediate had not formed in sufficient quantity.

3. When the trapping agent was added 5 h after basification of the ethyl ether, most of the latter had already reacted and most of the reactive intermediate had sufficient time to change. The residual ether was still

reacting with base, and the resulting small amount of intermediate was trapped to give a few milligrams of adduct.

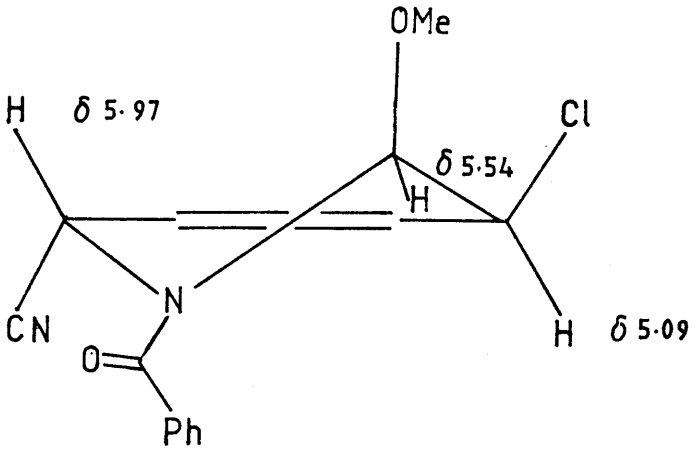
Of course, the results obtained from the experiments involving the addition of a few crystals of N-phenylmaleimide to the basified ether (27) in the spectroscope cell casts some doubt on the above explanations. But as stated above, the discrepancy may be ascribed to a dilution effect.

The recommended method for the preparation of the adducts (83) and (84) requires that the N-phenylmaleimide be present in the basic solutions of the ethers from the beginning. In this way the optimum amounts of the intermediates are trapped.

2.5. The Stereochemistry of the Chlorohydrin Alkyl Ethers

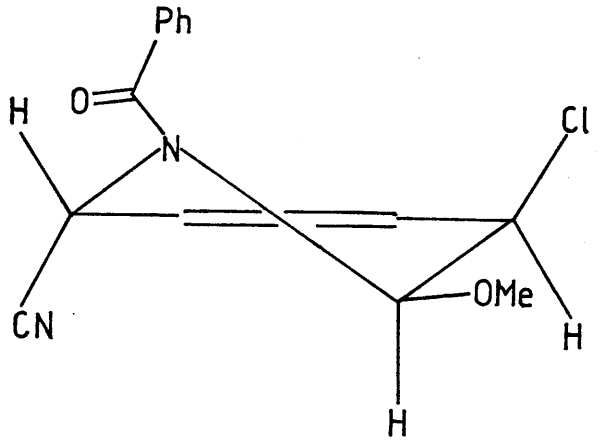
The formation of the N-phenylmaleimide adduct (84a) shows that the chlorohydrin methyl ether must have the constitution (28), with chlorine attached at C(4) and the methoxy group at C(3) rather than *vice versa*. Thus, as assumed earlier by Tan [15], the chlorohydrin ethers must have structures analagous to that of the chlorohydrin (12). However, nothing was known about the stereochemistry of either the chlorohydrin or the ethers.

Nuclear Overhauser Enhancement (difference) spectroscopy was employed by Dr D.S. Rycroft in an attempt to determine the stereochemistry of the chlorohydrin methyl ether (28). The relevant proton shifts, and Dr Rycroft's results, are shown in Tables 2 to 7. As for similar experiments involving

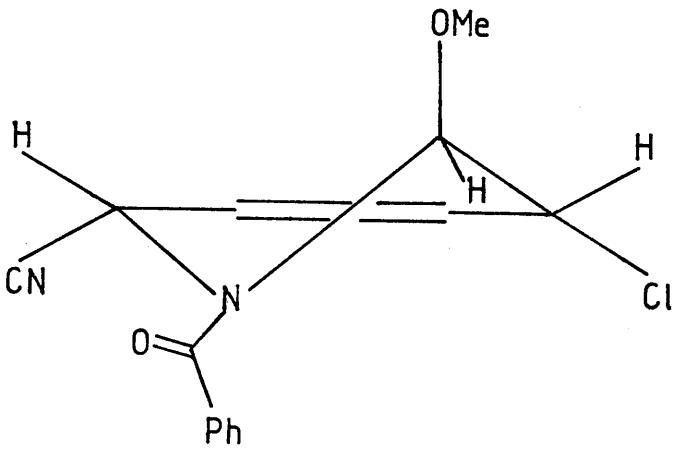


No deshielding of 1-H (δ 5.97) by carbonyl group [cf.(96)]

(92)



(93)



(94)

Chlorohydrin Methyl Ether (28), Major Isomer

Table 2

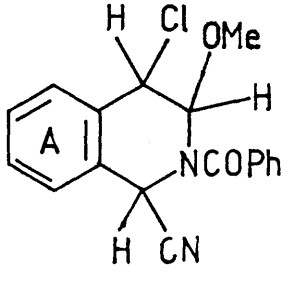
^{1}H n.m.r. spectrum

Protons	o-Benzoyl	Other Aryl	1-H	3-H	4-H	Me
δ_H at 297 K ($J_{3,4}$= 3.1 Hz)	Ca. 7.37-7.8	Ca. 7.28-7.60	5.97(s)	5.54 (br s)	5.09 (d)	3.01

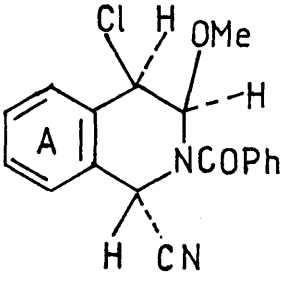
Table 3

Nuclear Overhauser enhancement (difference) spectra

	N.O.E. ENHANCEMENT (%)					
Irradiated protons (below)	o-benzoyl -H	Benzo-H (Ring A)	1-H	3-H	4-H	Me
1-H	0.92	10.24	-100	0.01	0.26	1.25
3-H	10.65	0.32	0.32	-100	9.25	6.77
4-H	-0.15	11.87	0.32	9.01	-100	1.43
Me	3.45	1.65	2.51	8.77	2.06	-300



(28)



(91)

the N-phenylmaleimide adduct (84a), it was assumed that, when a particular proton was irradiated, the greater the enhancement of the signals of other protons, the closer these are to the one being irradiated.

The results using the major isomer of (28) are shown in Tables 2 and 3. Thus the signal for 3-H (δ 5.54) can be identified from the enhancements of the methyl and o-benzoyl signals. In confirmation, the doublet, δ 5.09, may be assigned to 4-H from the enhancement of the benzo-H (ring A) signals. Although near to the benzo ring A, 1-H seems to be rather far from the o-benzoyl group. Later we will present evidence that 1-H (δ 6.36) in the minor isomer of (28) is deshielded by the carbonyl group, (see 96). However, 1-H (δ 5.97) of the major isomer is not so deshielded. Thus, according to our interpretation of the results from the N.O.E. experiment, the stereochemistry of the major isomer is that shown as (91) and (92) with the chloro and methoxy constituents cis to one another. Tan [15] had already proved that chlorination of the Reissert compound (2) had taken place at C(4). The N.O.E. experiments show that the attack had occurred on the less hindered side, that is, on the face trans to the cyano. Instead of attacking trans to the chloro substituent, the methanol must have found an easy approach to C(3) which was still exposed due to the half-chair conformation of the intermediate carbonium ion.

The conformation (92) is preferred to (93) because, in the latter, the benzoyl and methoxy groups would be on the same face of the molecule. Deshielding of 1-H, (5.97) (*cf.* 96) could also be expected. An alternative stereochemistry represented by (94) has been rejected because the enhancements involving 3-H and 4-H were large, (9.01 and 9.25%), suggesting that these two protons had a *cis* arrangement, and those involving 4-H and methyl were small, (2.06 and 1.43%), suggesting a *trans* arrangement.

Firm conclusions concerning the stereochemistry of the major isomer of the chlorohydrin (28) are not claimed. In fact as the study progressed, one became even more aware of the difficulties. For example, there is the problem of deciding between the two conformations, (92) and (93), and it is also not possible to distinguish between a strong N.O.E. from a minor (disfavoured) conformation and a weak N.O.E. from a major conformation. The magnitude of the N.O.E. may, therefore, be misleading and may even appear contradictory.

The lack of certainty in the assignment of stereochemistry to the major isomer also applies to the minor. Tables 4 and 5 show the results obtained from the latter. From these data it has been deduced that 1-H is relatively close to the other hetero protons, the *o*-benzoyl protons and benzo ring A. As could be expected 3-H is very close to 4-H and to the methoxy group. The 4-H is distant from the methoxy group. The stereochemistry proposed for the minor isomer (28), shown as (95) and (96), suggests that in this conformation

Chlorohydrin Methyl Ether (28), Minor Isomer

Table 4

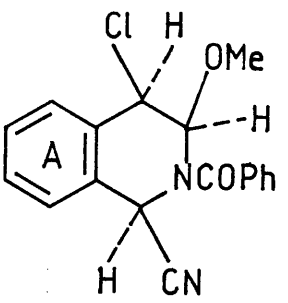
H^1 n.m.r. spectrum

Protons	o-benzoyl	Other Aryl	1-H	3-H	4-H	Me
δ_H(253 K) ($J_{3,4}$ 2.1 Hz	Ca. 7.63-7.83	Ca. 7.28-7.63	6.36 (br s)	5.45 (br s)	5.14 (d)	3.26

Table 5

Nuclear Overhauser enhancement (difference) Spectra

	N.O.E. Enhancement (%)					
Irradiated protons tabulated below	o-Benzoyl -H	Benzo-H (Ring A)	1-H	3-H	4-H	Me
1-H	4.01	10.28	-100	-35.0	4.78	4.33
3-H	9.03	2.83	-4.34	-100	11.96	8.72
4-H	Nil	11.28	0.95	9.56	-100	0.10
Me	4.74	3.88	1.62	11.63	0.35	-300



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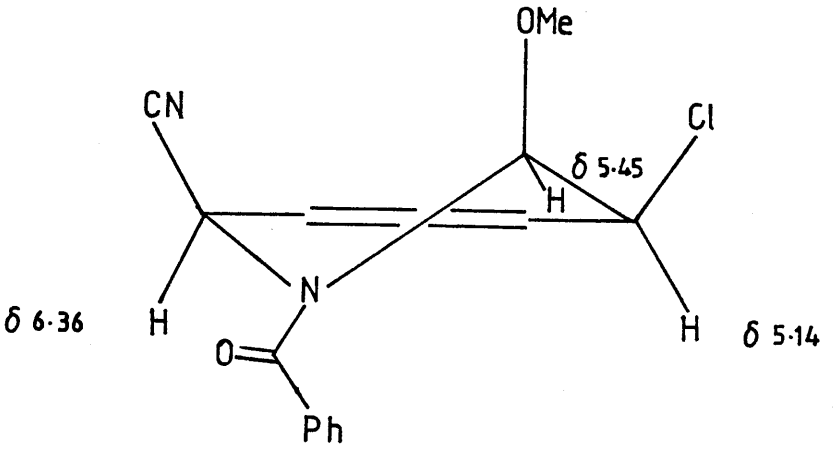
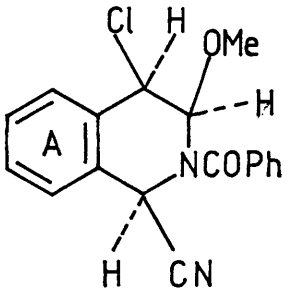


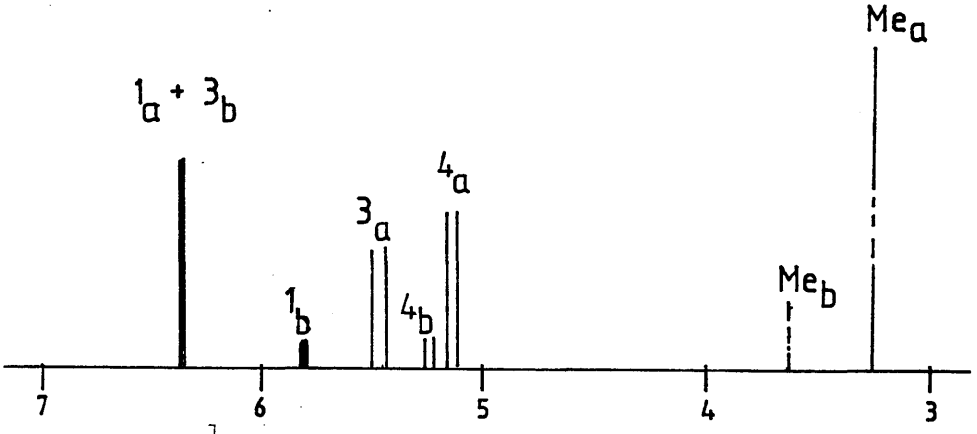
(96)

1-H (δ 6.36) is deshielded by the carbonyl group (cf. (92) 1-H, (δ 5.97)). The negative enhancements for 1-H (-4.34%) and 3-H (-35.0 %) is due to "saturation transfer" and suggests the presence of a rotamer of the minor isomer (see below). The difference in the two isomers (92) and (96) is determined by the face to which the cyano group is attached at C(1). The minor isomer results from slower chlorination at C(4) cis to the cyano group. We have already postulated that the major isomer is formed by chlorination at C(4) trans to the cyano group.

It had been noted that the ^{1}H n.m.r. spectrum, at 253 K, of the minor isomer was accompanied by a number of small signals which, taken as a set, (Table 6), showed the presence of a compound closely related to its more abundant companion. There also seemed to be a link between this compound, believed to be a minor rotamer, and the negative enhancements noted in Table 5. In order to make it easier to present the argument, the hetero ring protons in rotamer (96) are labelled with the letter "a", and those in the minor rotamer with the letter "b". When the ^{1}H n.m.r. spectrum was run at 213 K it showed that a small doublet at δ 6.33 was now separate from the original broad singlet at δ 6.36, (vid. 97). The 1-H_a signal had sharpened considerably. Near the doublet at δ 5.45 (3-H_a), there was a tiny singlet at δ 5.80. The presence of two singlets and two doublets, as well as other related resonance was an important factor in showing that the minor isomer (95) really did consist of

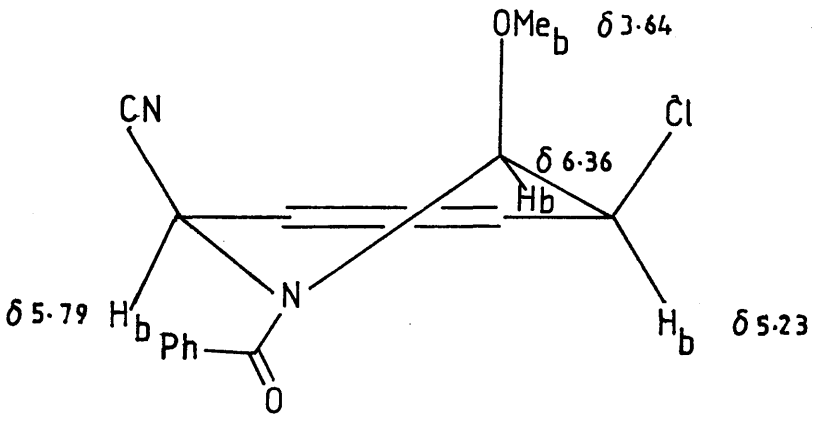


(95)



^{1}H N.M.R. at 253 K (not to scale)

(97)



(98)

Chlorohydrin Methyl Ether (28). Rotamers of Minor Isomer.

Table 6

^{1}H n.m.r. spectra

More abundant rotamer	1-H_a	3-H_a	4-H_a	Me_a
(253 K)	6.36(s)	5.45(d)	5.14(d)	3.26(s)
Less abundant rotamer	1-H_b	3-H_b	4-H_b	Me_b
(253 K)	5.79(s)	6.36(d)	5.23(d)	3.64(s)

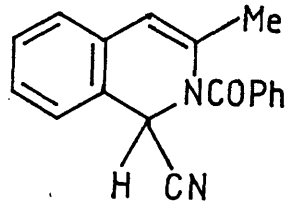
Table 7

Nuclear Overhauser Enhancement (difference) spectra.
Saturation transfer from major to minor rotamer.

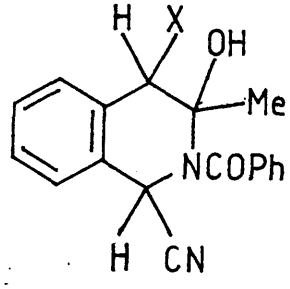
Signals decoupled (δ)	Irradiated protons	Other signals effected (δ)	Saturation transfer (%)	Protons receiving transfer
6.36 (brs)	1-H_a	5.79 (s)	-4.92	1-H_b
" "	3-H_b	5.45 (d)	-35.0	3-H_a
5.45 (d)	3-H_a	6.36 (d)	-4.34	3-H_b
5.14 (d)	4-H_a	5.23 (d)	slight	4-H_b
3.26 (s)	Me_a	3.64 (s)	-14.49	Me_b

a pair of rotamers, (Tables 6 and 7): one of the rotamers being in low abundance. The N.O.E. experiment was carried out at 253 K, and at that temperature the signal arising from 1-H_a (δ 6.36) covered the small doublet arising from 3-H_b (at 253 K it had moved to δ 6.36). Obviously the 100% saturation by the applied signal at δ 6.36 would saturate both the singlet and the small hidden doublet. Thus the less abundant rotamer with its signal for 3-H_b resonating at δ 6.36 was continuously interconverting into its more abundant rotamer containing 3-H_a resonating at δ 5.45. The saturation imposed on 3-H_b, now in its new environment as a proton of the major isomer, persisted long enough to have an effect on the signal arising from the non-irradiated 3-H_a. Consequently, there is considerable saturation transfer to 3-H_a (-35.0%). In the same way, some of the saturation on 1-H_a (δ 6.36) was simultaneously transferred to 1-H_b (δ 5.79). Thus the 1-H_b singlet was downfield in comparison to 1-H_a. In the case of the 3-H doublet, the reverse had happened resulting in 3-H_a (δ 5.45) being upfield in comparison to 3-H_b (δ 6.36): the latter was now deshielded by the carbonyl group, (*cf.* 92 and 96). Saturation transfer was also observed when the resonances arising from 4-H_a and Me_a were irradiated. The signals from 4-H_b and Me_b were downfield in comparison.

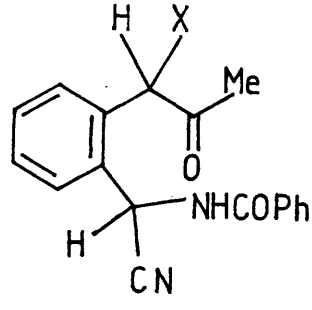
Almost certainly an examination of the chlorohydrin ethyl ethers (27) would have provided results similar to those



(31)



(32) a; X = Cl
b; X = Br



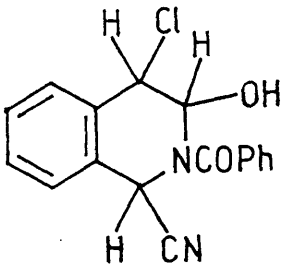
(33) a; X = Cl
b; X = Br

reported above for (28). The existence of the rotamers is attributed to the possibility of rotation around the C-N bond.

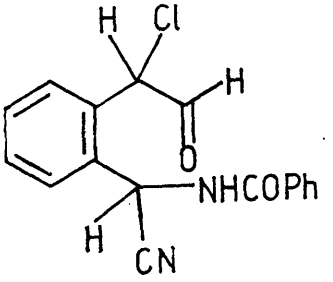
Finally it must be reiterated that these stereochemical assignments are not wholly convincing. It would seem that X-ray analysis of the chlorohydrin ethers would be the only method by which definite proof could be established.

2.6. Some Reactions of a 3-Methyl Reissert Compound

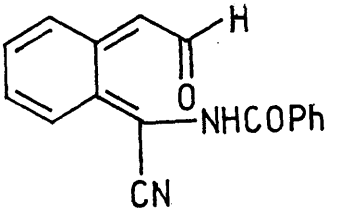
Earlier, it has been mentioned that Kirby *et al.*[20] were unable to repeat their preparation of the chloroketone (33a). Their method also failed when it was used in this study. Further investigation showed that the sodium hypochlorite solution, which had been used by us, was of indeterminate age and quality. Its original sodium chloride content, combined with that formed during the ageing process was, possibly, the cause of the observed, and surprising, non-mixing of the aqueous hypochlorous acid with the dioxan solution of the Reissert compound (31). Thus, effective contact between the reagents was reduced. When a freshly supplied solution was acquired, and the derived hypochlorous acid used at half the recommended concentration the chloroketone (33a) was obtained, reproducibly, in 34% yield. Kirby *et al.*[20] found the ^{1}H n.m.r. signals of the chloroketone changed with time. The product obtained in the present study gave similar spectra. The principal signals, δ_H [$(CD_3)_2SO$ 2.14(s, Me), 6.25(s,CH), 6.69(br s, CH), *ca.* 7.15-8.20(4H, m,



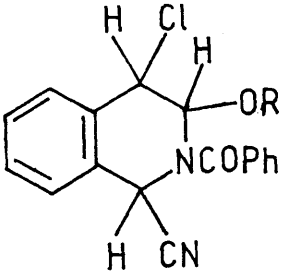
(12)



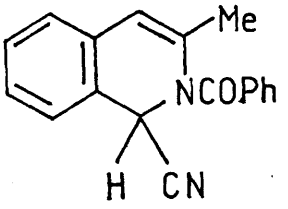
(15)



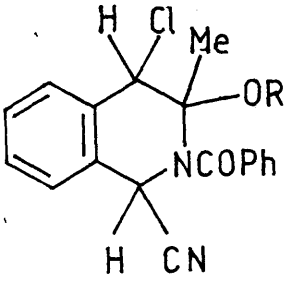
(16)



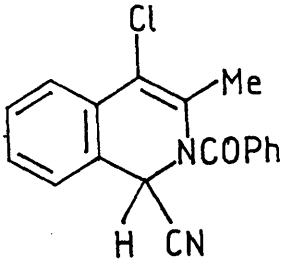
(27) R = Et
(28) R = Me



(31)



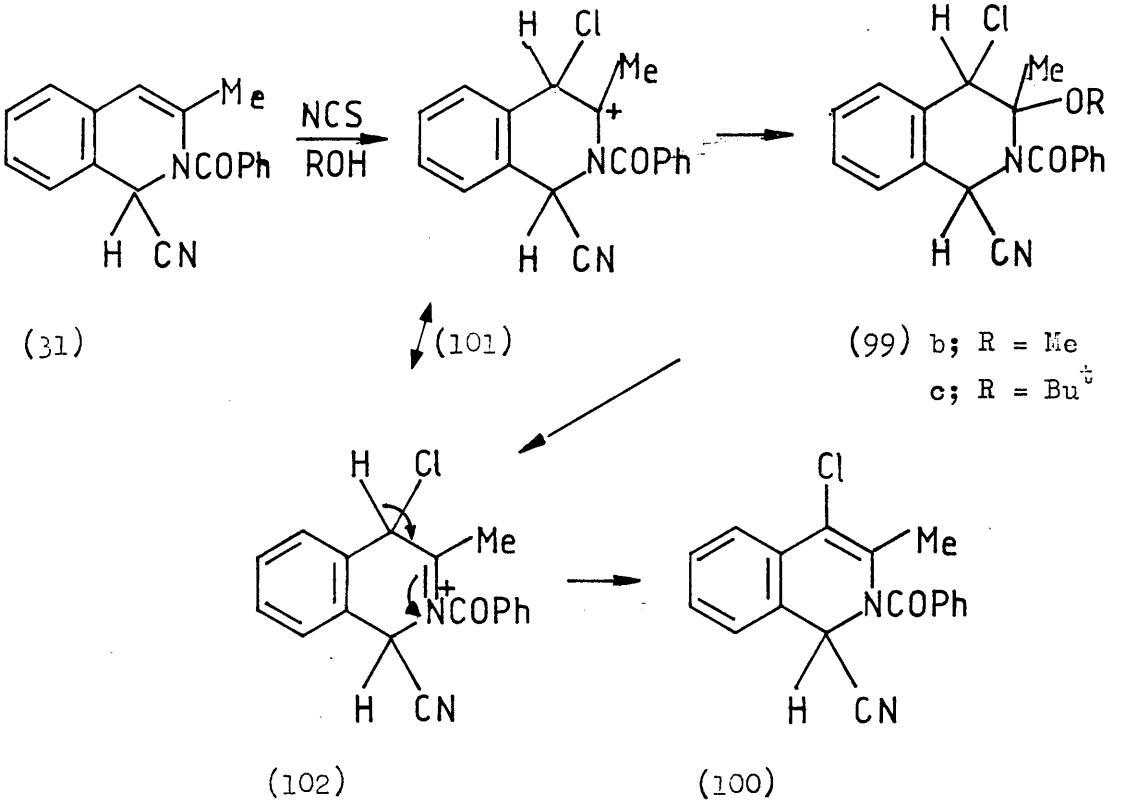
(99) a; R = Et
b; R = Me
c; R = Bu^t



(100)

aryl-H), and 9.84(br s, NH, exch. with D_2O), indicated a ring-opened structure. At the end of 24 h, a second set of signals, having an intensity approximately equal to that of the first set had appeared, δ 2.2, 6.15, 6.74(d, J 7 Hz, CH, collapsed to a signal on addition of D_2O) and 9.76(d, NH, exch. with D_2O). The formation of the haloketones (33) can be attributed to the presence of a hydroxy group in the hypothetical halohydrins (32). Deprotonation of the hydroxy group by the water present in the solvent mixture seems to be a facile process. Hetero ring opening follows to give (33). Already, in Section 1.2, we have discussed a similar process when we dealt with the properties of the chlorohydrin (12). The possibility of (15) as an intermediate on the route to (16) was suggested by Kirby et al. [10].

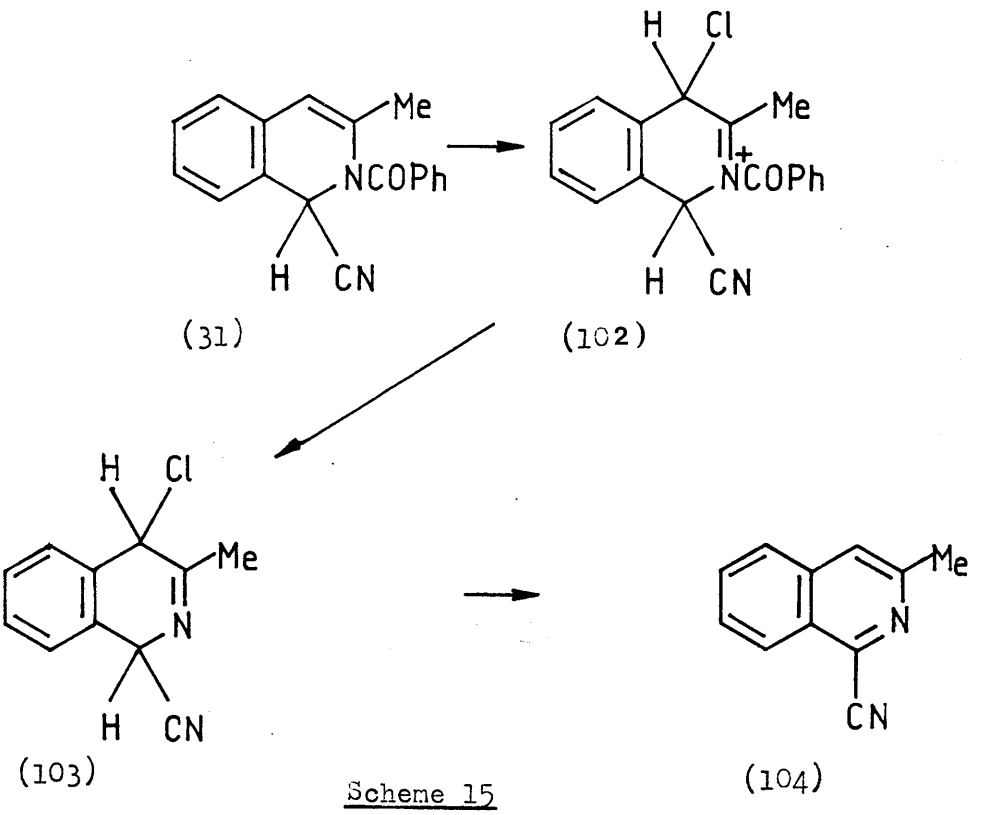
As reported in Section 2.4 the work of S.L. Tan [15] relating to the chlorohydrin alkyl ethers (27) and (28) has been extended. It was hoped that the homologous ethers (99) could be obtained from the 3-methyl Reissert compound (31). However, when (31) was treated with N-chlorosuccinimide in methanol-dioxan at room temperature, the product was not the expected methyl ether (99b) but the 4-chloro-3-methyl Reissert compound (100) instead, in a 25% yield. In the ^1H n.m.r. of the crude reaction mixture there was some indication that a small amount of the methyl ether (99b) had also been formed. An improved yield (61%) of (100) was obtained when tert-butanol was substituted for methanol in the reaction



NCS = N-chlorosuccinimide

ROH = MeOH or Bu^tOH

Scheme 14



Scheme 15

mixture, and the reaction temperature was raised to 83°C. This time, the reaction mixture also contained a little 1-cyano-3-methylisoquinoline (104), (2.4% yield).

A pathway leading to the formation of the Reissert compound (100) is suggested in Scheme 14. It starts with the assumption that chlorination takes place much faster at C(4) than nucleophilic addition at C(3). That attack at C(3) was more successful for methanol than for the more bulky tert-butanol is supported to some degree by the meagre evidence, reported above, that a trace of the target methyl ether (99b) was identified in the reaction mixture. If the pathway included the ethers (99b) and (99c) then these ethers must have ionised rapidly to give the intermediates (101) and (102). The latter being then deprotonated at C(4) to give the Reissert compound (100). The much improved yield of this Reissert compound, when tert-butanol was used as solvent, may reflect the failure of the bulky molecule to react at C(3) and so forcing the reaction directly to (102) via (101). More support for the postulated pathway, via (102), was provided by the formation of the isoquinoline (104) when tert-butanol was used as a solvent (see Scheme 15).

3. Experimental

3.1. Services and Special Reagents

Melting points were measured on a Köfler hot-stage apparatus, and were corrected. Microanalysis was performed by Ms. Harkness and her staff. Infrared spectra were obtained from Perkin-Elmer 257 or 580 infrared spectrometers by Ms. F. Lawrie and her staff. Ultraviolet spectra were obtained on a Pye-Unicam S.P. 800 spectrometer. Mass spectra were recorded on a G.E.C. - A.E.I. M12 spectrometer and accurate mass measurements on a MS 902S spectrometer by Mr A. Ritchie and his staff. Proton nuclear magnetic resonance spectra were recorded on a Varian T-60A (60 MHz) and a Perkin Elmer R32 (90 MHz). Certain n.m.r. spectra were recorded by Dr D.S. Rycroft using a Varian XL100 (100 MHz), or a Bruker (200 MHz).

Unless reported otherwise, the term "light petroleum" refers to that fraction b.p. 60-80°C.

Suppliers of Special Reagents

Alumina, Camag M.F.C., Alkaline, Activity 111, Hopkins and and Williams, Chadwell Heath, London.

Alumina, Camag M.F.C., Neutral, Activity 111, Hopkins and Williams.

1,1'-carbonyldiimidazole, Aldrich Chemical Co. Ltd., Gillingham, England.

18-Crown-6, Aldrich.

Ethyl Chloroformate, Aldrich.

Homophthalic Acid, Aldrich.

Isobutyric Acid, Aldrich.

3-Methylisoquinoline, Koch-Light Laboratories Co., Ltd., Coinbrook, England.

Oxalyl Chloride, Aldrich.

Phenylsuccinic Acid, Aldrich.

Silica GF 254 and 254E, Fluka A.G., Buchs, Switzerland.

Silica HF 254, Fluka A.G.

Tetraethylammonium Chloride, B.D.H. Chemicals Co. Ltd., Poole, England.

Tetraethylammonium Cyanide, Fluka A.G.

3.2. Isolation and Synthesis of Ethyl 2-Amino-1-oxo-inden-3-carboxylate

2-Acetyl-1-cyano-1,2-dihydroisoquinoline (48)

A general method described by Popp and Soto[34] was used. Acetyl chloride (24.3 g, 0.31 mol) was added over a period of 1.25 h to a cooled and stirred two-phase mixture of isoquinoline (20.1 g, 0.16 mol) in dichloromethane (200 ml) and potassium cyanide (31.2 g, 0.48 mol) in water (80 ml). The mixture, which tended to heat up, turned brown. It was left stirring for seven hours. Contamination with tarry material made it difficult to separate off the organic solvent layer, and so it was found necessary to filter the mixture in order to accomplish this. The dichloromethane solution was washed with water, 5% hydrochloric acid, 5% sodium hydroxide and finally water. After drying ($MgSO_4$) and evaporation, the residue was crystallised from 95% ethanol to give the Reissert compound (48) (72%, lit. 87%), m.p.

120°C; ν_{max}(KBr) 1 630 and 1 680 cm^{-1} (CO).

2-Acetyl-4-chloro-1-cyano-3-hydroxy-1,2,3,4-tetrahydroisoquinoline (49)

This preparation is a modification of one reported by Kirby *et al.* [20]. The sodium hypochlorite solution (12% wt./vol. available chlorine) must be fresh.

To the Reissert compound (48) (5 g, 0.025 mol) in dioxan (25 ml) at 0°C was added, dropwise, a hypochlorous acid solution (70 ml), which had been prepared at 0°C from sodium hypochlorite solution (16 ml) and 0.7M nitric acid (54 ml). The reaction mixture was agitated vigorously. At first there were two liquid phases, but towards the end of the addition, these suddenly merged. This solution was left overnight at 5°C. The crystals which formed were washed with water and recrystallised from ethyl acetate to give the chlorohydrin (49) m.p. 174°C (lit. 182-183°C); δ_H $(CD_3)_2SO$ 2.34(s, Me), 5.36(d, *J* 3 Hz, 4-H), 5.85 t, *J* 3 Hz and 5 Hz(d, *J* 3 Hz after D_2O exchange) 3-H , 6.05(s, 1-H), 6.75(d, *J* 5 Hz, exchanged with D_2O, OH), and *ca.* 7.3-7.8(4H, m, aryl-H), (lit. 2.35, 5.40, 5.90, 6.09 and 7.4-7.8).

Reaction of the N-Acetyl Chlorohydrin (49) with Ethanolic Sodium Hydroxide

When Kirby *et al.* [20] prepared 1-ethoxy-3-methylisoquinoline-4-carbaldehyde (50) from (49), they noted the deep red colour

of the mother liquors, and from these they isolated a deep purple compound melting at 125-127°C; (m/z 217.0738). This was repeated thus:- the chlorohydrin (49), (2.0 g, 8 mmol), in ethanol (250 ml) was treated with 10% aqueous sodium hydroxide (640 mg, 16 mmol), dropwise, with stirring, at room temperature. Stirring was continued for another 3 h. Most of the water was removed ($MgSO_4$), and the filtered solution was evaporated to small bulk. A further filtration removed most of the major product, the aldehyde (50). Analytical t.l.c. of the coloured filtrate showed the presence of about 14 different coloured bands. A purple one proved to be most easily recognisable, and so it was decided to isolate and identify its contents. All the concentrated mother liquors were subjected to column chromatography on "Camag" neutral alumina, Activity 111. Benzene was used as the elutant. The fastest moving purple band was collected. This impure material was chromatographed on Silica, G.F. 254, and developed with toluene-ethyl acetate (9:1). A diffuse purple band, R_f 0.5, was removed and extracted with ether. The purple solid residue was still contaminated by a clear crystalline substance. Further chromatography on alumina (Merck GF 254E), developed with toluene-diethyl ether (9:1), provided a black solid which, on crystallisation from diethyl ether, melted at 131°C (some softening at 127°C). When the molten purple liquid was allowed to cool, it resolidified to give black crystals with the same long needle structure and had the same melting point (131°C). Physical examination and its subsequent synthesis (see later)

proved it to be ethyl 2-amino-1-oxo-indene-3-carboxylate (51) m.p. and mixed m.p. 131°C (Found: C, 66.4; H, 6.6; N, 5.2; M^+ 217.0737. $C_{12}H_{11}NO_3$ requires C, 66.4; H, 6.5; N, 5.1%; M^+ 217.0739); ν_{max}(KBr) 3 445, 3 330, 1 733, and 1 676 cm^{-1}; λ_{max}(Et OH) 263(ε 42 300) and 535 nm (654); $\delta_H(CDCl_3)$ 1.36 (t, J 8 Hz, Me), 4.33(q, J 8 Hz, CH_2), ca. 6(br s, exch. with D_2O, NH_2), 6.87(2H, dt, J 8 Hz and 2 Hz, ar.), and ca. 7.5-7.7(3H, m, aryl-H).

Origin of the 2-Aminoindenone (51)

There was always the possibility that the trace purple compound (51) was formed from impurity in the chlorohydrin (49).

a) Some already purified chlorohydrin was chromatographed on silica (GF 254). Development with chloroform-acetone (9:1) gave a band at R_f 0.15. Elution with acetone provided pure chlorohydrin, m.p. 174°C. This substance, on treatment with alcoholic sodium hydroxide, gave the expected coloured compounds.

b) Next, the pure chlorohydrin (0.5 g) in dioxan (15 ml) was treated with a large excess of dilute hypochlorous acid (5 ml sodium hypochlorite solution and 17 ml 0.7M nitric acid). However there was no indication that a double halohydrin had been formed and the crude glue-like product gave no increased yield of (51).

c) When solutions of the non-coloured products of the reaction between the chlorohydrin and ethanolic sodium hydroxide were allowed to stand in contact with active silica, and also with active alumina, there was no formation of coloured compounds.

Along with other considerations, the above experiments left no doubt as to the origin of (51).

Synthesis of the 2-Aminoindenone (51) from Homophthalic Acid

a) Homophthalic Anhydride [35]. Homophthalic acid (10 g, 0.056 mol) and acetyl chloride (40 g, 0.51 mol) were heated together under reflux conditions for 0.5 h. A new type of crystal appeared on cooling the reaction mixture. Light petroleum was added to aid crystallisation. The crystals were filtered off under suction and washed with the same solvent. The anhydride melted at 146°C (lit. 141-142°C); (8.9 g, 90%).

b) ortho-(Carbethoxymethyl) benzoic Acid (53). The anhydride (0.8 g) in ethanol (1 ml) was heated under reflux for 0.5 h. When the ethanol was evaporated, a glassy solid remained. Crystallisation from water gave (53) (1 g, 100%), m.p. 109°C (lit. [23a] 109°C); $\delta_H(CDCl_3)$ 1.28(t, Me), 4.08(s, CH_2), 4.20(q, $CH_3\underline{CH_2}$), ca. 7.1-7.8 (3H, m, aryl-H), ca. 8-8.3 (1H, m, ar.), and 9.65(1H, br , exchangeable with D_2O, OH); [lit. [23b] 1.28, 4.08, 4.20, 8.2-9.2(?), 9.2].

c) The 2-Aminoindenone (51)

1. From Ester (53) using Thionyl Chloride. The half ester (53) (260 mg, 1.25 mmol) in dichloromethane (1.5 ml), containing N,N-dimethylformamide (27 mg, 0.37 mmol) as catalyst, was treated with thionyl chloride (0.1 ml, 1.37 mmol). The mixture was kept at room temperature for 25 minutes, diluted with dichloromethane (2.5 ml), and then poured into a stirred aqueous solution of potassium cyanide (2.5 ml). Ethanol (2.5 ml) was added immediately and stirring was continued at room temperature for 2 h. The additional dichloromethane prevented an appreciable rise in temperature when the strongly acid solution mixed with the aqueous potassium cyanide. To facilitate the separation of the two phases additional water (10 ml) and dichloromethane (10 ml) were added. The dichloromethane layer was washed with water, then with water containing a few drops of dilute sulphuric acid, and finally with water once more. It was dried ($MgSO_4$), filtered and reduced to small bulk. Chromatography on silica plates developed with chloroform-ethyl acetate (95:5) was used to isolate the 2-aminoindenone (51) (15 mg) which had the physical properties of the purple indenone produced as a by-product in the preparation of the carbaldehyde (50).

2. From Ester (53) using the Chloroenamine (62c).

The description of the preparation of the chloroenamine (62c) follows this report. A sealed ampoule of the chloroenamine (62c) was opened. One gram of it was quickly abstracted and dissolved in dry dichloromethane (5 ml).

This solution was added to the half-ester (53) (1.5 g, 1 equivalent) in dichloromethane (5 ml). All operations were carried out under a blanket of nitrogen. The flask was then stoppered and allowed to stand at room temperature for 1 hour before the contents were emptied into saturated aqueous potassium cyanide (10 ml) and ethanol (10 ml). The resulting purple-coloured organic layer was separated, washed, dried ($MgSO_4$), and evaporated to small bulk. Chromatography on alumina (Camag M.F.C. alkaline, activity III), developed with chloroform-ethyl acetate (93:3), and eluted with diethyl ether gave a rather impure sample of the purple compound (51) (200 mg, 13%).

1-Chloro-N,N,2-trimethylprop-1-en-1-amine (62c)

a) Isobutyryl Chloride [36]. Isobutyric acid (1.5 mol) was added to thionyl chloride (1.65 mol) at 0°C. The solution was heated at 80°C for 0.5 h. Distillation provided the acid chloride, (bp. 90-92°C) yield 90%.

b) N,N-Dimethylisobutyramide [37] (62a). Dimethylamine (0.2 mol), which had been cooled in ether-solid carbon dioxide mixture, was dissolved in dry diethyl ether (100 ml), and added to isobutryl chloride (0.1 mol) in dry diethyl ether (400 ml) at 10°C, with vigorous stirring. The precipitated dimethylamine hydrochloride was filtered off, and the ether evaporated. Distillation of the residue gave the amide (7.22 g, 63%; lit. 85%), b.p. 175-176°C.

c) 1-Chloro-N,N,2-trimethylpropylideniminium Chloride (62b)

The method described by Ghosez [27] was used. Liquid phosgene (33 ml, 0.5 mol) was added to dry dichloromethane (70 ml) and this solution was cooled in an ice-sodium chloride mixture. Freshly distilled N,N-dimethylisobutyramide (38.3 g, 0.33 mol), in dry dichloromethane (50 ml), was added dropwise. The temperature of the reaction mixture was maintained at 0°C during this addition. It was then allowed to rise slowly to that of the surroundings. Gas evolution became vigorous, and the liquid was allowed to boil under reflux conditions. The reaction mixture was left overnight. Next day, the excess phosgene and solvent were distilled off under slightly reduced pressure. A white solid, 1-chloro-N,N,2-trimethylpropylideniminium chloride (62b) remained in the flask. It could have been stored under argon, but, instead, it was used directly.

d) The Chloroenamine (62c). In this preparation the main difficulty resulted from the highly hydroscopic nature of the product. The simple method adopted by Ghosez et al. [27] proved inadequate. In this study the product was quickly added to a sintered glass funnel, which was immediately stoppered and supplied with a stream of nitrogen to force the mother liquors through the filter.

The iminium salt (62b) was suspended in dry dichloromethane (70 ml), and triethylamine (46.7 g, 0.47 mol) was added slowly to the mixture from a dropping funnel, with

vigorous stirring over a period of 1 h. Two hours later dry petroleum (50 ml) was added. The mixture was filtered under nitrogen and the solvent was removed by distillation under nitrogen. A second distillation using a Vigreux fractionating column gave 1-chloro-*N*,*N*,2-trimethylprop-1-en-1-amine, (62c) (26189-59-3), contained in a fraction boiling in the range 115-134°C, (26.2 g); $\delta_H(CDCl_3)$ 1.77(s, allylic Me) and 1.79(s, allylic Me) and 2.37(s, N Me_2); δ (CCl_4) 1.73(s, allylic Me) 1.79(s, allylic Me) and 2.37(s, N Me_2). The product was not further purified. Ghosez *et al.* obtained a yield of 36 g, boiling range 125-134°C. The reported ^1H n.m.r. agreed with that given above, using $^C Cl_4$.

Summary of Attempts to Prepare Ethyl 2-Amino-1-exo-inden-3-carboxylate (51) from o-(Carbethoxymethyl) benzoic acid (53)

Reagents used for suitable carboxyl group attack	Reagents used for cyanide formation and ring closure	Amount of (51) formed
$ClCO_2Et$ + Et_3N in CH_2Cl_2	KCN + 18-crown-6	Nil
$ClCO_2Et$ + Et_3N in CH_2Cl_2	$KCN_{(aq)}$ + EtOH	trace
$(COOCl)_2$ in C_6H_6	"	trace
$(COOCl)_2$ + Pyridine in C_6H_6	"	trace
α-Chloroenamine (62c) in CH_2Cl_2	"	13%(impure)
$POCl_3$ + Et_3N in CH_2Cl_2	"	trace
$SOCl_2$	"	nil
$SOCl_2$ + DMF* in CH_2Cl_2	$Cu(CN)_2$ + $NaOH_{(aq)}$	nil
$SOCl_2$ + DMF in CH_2Cl_2	$Cu(CN)_2$ + t-BuOH	nil
" " "	$KCN_{(aq)}$ + EtOH	5.5% (pure)
" " "	$KCN_{(aq)}$ + Et_4NOH	trace
" " "	$KCN_{(aq)}$ + t-BuOH	trace
" " "	$KCN_{(aq)}$ + Bu_4NOH	trace
" " "	Et_4NCN + $NaOH_{(aq)}$	trace
" " "	Et_4NCl + $NaOH_{(aq)}$	trace
1,1'-Carbonyldiimidazole in THF* [26] (61)	All the above reagents were tested	nil

*DMF = N,N-dimethylformamide

THF = tetrahydrofuran

Attempted Acylation of the 2-Aminoindenone (51).

a) Acetic Anhydride with Sodium Acetate. A sample of the aminoindenone (51) in acetic anhydride mixed with anhydrous sodium acetate was heated on a steam bath for 2 h. The acetic anhydride was evaporated on a rotary evaporator and the residue was extracted with diethyl ether. The ^{1}H n.m.r. spectrum of the product showed that it was unchanged starting material.

b) Acetyl Chloride with Lithium Diisopropylamide. A solution of lithium diisopropylamide was prepared from 1.6 M butyl lithium in hexanes (1 ml), diisopropylamine (0.22 ml) and dry tetrahydrofuran (5 ml). The aminoindenone (51) (50.7 mg, 0.23 mmol) in tetrahydrofuran (5 ml) was stirred under argon at -78°C in a flask sealed with a rubber septum. Using a hypodermic needle, lithium diisopropylamide solution (1 ml, 0.25 mmol) was added, followed 10 minutes later by acetyl chloride (0.28 mmol) in tetrahydrofuran (1 ml). The solution, which had now become indigo blue, was stirred for 2 h at -78°C, after which the temperature was allowed to rise to that of the surroundings. As the solution was found to be alkaline, sufficient acetyl chloride for acidification was added. The product contained unchanged aminoindenone but no acetyl derivative.

c) Acetyl Chloride with Butyl Lithium in conditions similar to the above (b) also failed, as did Benzoyl Chloride with Lithium Diisopropylamide.

d) Sodium Hydride with Acetyl Chloride. A few milligrams of the aminoindenone (51) were dissolved in N,N-dimethylformamide, and excess sodium hydride was added, with stirring, at room temperature. The purple colour changed to prussian blue. The mixture was filtered through glass wool, and excess acetyl chloride was added, whereupon the colour changed to a dirty red. Water was used to destroy the reagents, and ethyl acetate was used to extract soluble material. Analytical t.l.c. on silica (chloroform) gave several yellow spots and some of the indenone, but no acetyl compound.

Similar experiments using tetrahydrofuran and toluene as solvent were equally unsuccessful.

Reaction of the Aminoindenone (51) with Trifluoroacetic Acid

The indenone (51) (210 mg) was kept in trifluoroacetic acid (2 ml) at room temperature for 45 minutes. This mixture was evaporated to dryness and the residue dissolved in a little ethanol which was then evaporated. The residue was partitioned between dichloromethane and water containing a little hydrogen carbonate. Chromatography on silica plates developed with chloroform gave a blue band at R_f 0.4 and a purple band at R_f 0.1. After a second development with chloroform, the purple band was removed and found to contain the starting material (51) mixed with a substance more reddish in colour. The blue band, now at R_f 0.63, was eluted with ether to give diethyl 1,1'-dioxo-2,2'-iminodi-indene-3-carboxylate (67) (26 mg), m.p. 212-214°C (from chloroform-

ethanol) (Found: C, 69.0; H, 4.8; N, 3.15. $C_{24}H_{19}NO_6$ requires C, 69.1; H, 4.6; N, 3.4%); $\lambda_{max.}(CCl_4)$ 577 nm (ε8 360); ν_{max}(KBr) 3 270(NH), 1 723 and 1 675 cm^{-1}(CO); $\delta_H(CDCl_3)$ 1.42(t, 2 x Me), 4.42(q, 2 x CH_2), ca. 6.94-7.73 (8H, m, aryl-H), and 10.0(1H, br s, exch. with D_2O, NH); m/z 417(M^+) and 371.

3.3 The Reactions of Indanones with 2-Methyl-2-nitrosopropane: a Search for an Alternative Route to the Aminoindenone.

3-Oxo-2-phenylamino-1-carboxylic acid (65c)

a) 3-Oxo-indan-1-carboxylic acid (64b). A mixture of phenylsuccinic acid [38] (10 g, 50 mmol) and thionyl chloride (10 g, 84 mmol) was heated on the water bath for 0.5 h.[39] After evaporation, the residue was dissolved in dry nitrobenzene (20 ml). Anhydrous aluminium chloride (10 g, 75 mmol) was added, and all was heated at 80°C for 1.5 h. When cold, the reaction mixture was added to water (250 ml). After work-up and crystallisation from benzene, the acid (64b) was obtained, m.p. 118°C (lit. 120°C). The authors claimed a yield of 5.6 g. In this study 3.9 g were obtained from the first crystallisation.

b) Attempted Preparation of 3-Oxo-2-phenylamino-inden-1-carboxylic acid (65c). A series of twelve experiments were performed in attempts to obtain a satisfactory sample of (65c). It was found that the products, and their yields, were greatly affected by small differences in conditions. The most promising routine was the following in which the experiment was carried out at 0°C in alkaline conditions and under nitrogen. All wash water used during this phase was "oxygen-free".

The carboxylic acid (64b) (528 mg, 3 mmol) in ethanol (6 ml) was mixed with 10% sodium hydroxide (6 ml, 15 mmol). To this was added 6 ml of an ethanol solution of nitrosobenzene (321 mg, 3 mmol). Five minutes after mixing, the ethanol was removed on a rotary evaporator at room temperature. Water (75 ml) was then added, and the alkali was neutralised

with dilute sulphuric acid. Cooling was supplied during this operation; a dark blue precipitate formed in the water. On the addition of diethyl ether (200 ml), this solid moved into the organic layer. The aqueous layer was red. The ether was removed and washed several times with oxygen-free water. Previous experience had shown that the usual drying agents adsorbed the blue substance strongly, so none was used. Instead, the ether was evaporated without initial drying. The residue was suspended in benzene, filtered, and washed with more benzene. It was dissolved in ethanol and chromatographed on silica using chloroform-acetone (9:1). The blue band at $\underline{R}_f$ 0.06 - 0.8 was eluted with ether to give blue crystals. These crystals were washed with benzene and recrystallised several times from ethanol. The beautiful needle-shaped dark-blue crystals seemed homogenous, but on recrystallisation some reddish crystals were obtained from the mother liquor. At different stages in the purification process the crystals had melting points 132°C and 154°C. Finally a product, m.p. 171°C, was obtained: the next day it melted at 140-146°C (1). This product was likely 3-Oxo-2-phenylamino-inden-1-carboxylic acid (65c) (120 mg), m/z 265($\underline{M}^+$) with important peaks at 247, 221 (base peak), 205, 193, 165 and 89; Exact mass: 265.07389; $C_{16}H_{12}NO_3$ requires 265.073887; $\nu_{max}(CHCl_3)$ 564 cm^{-1}, λ_{max}(EtOH) 541 nm δ [$(CD_3)_2SO$] ca. 6.7-7.7; other signals at 6.48(s, 0.5H) and 8.30(br s, 0.5H); the shift of 8.30 ppm was rather uncertain. The microanalysis did not support the above data; (Found:

C, 69.51 and 69.34; H, 3.76 and 3.79; N, 4.76 and 4.88; $C_{16}H_{12}NO_3$ requires C, 72.45 ; H, 4.15; N, 5.28%).

Ethyl 1-Oxo-2-phenylamino-indene-3-carboxylate (65b)

a) Esterification of the Indane Carboxylic Acid (64b). Baker and Lees [39] state that "the ethyl ester was formed in the usual way. It crystallised from petroleum ether (60-80°C) in small thin nacreous rectangular plates, m.p. 49-50°C".

To the indanone carboxylic acid (64b) (7.8 g, 44 mmol) in ethanol (26 ml), was added concentrated sulphuric acid (2 ml). This solution was boiled under reflux conditions for 4 h. The ethanol was evaporated and replaced with water. The resulting solution was extracted with chloroform. This extract was treated with sodium hydrogen carbonate, washed twice with water, dried ($MgSO_4$), and evaporated to dryness. The residue was crystallised twice from light petroleum (b.p. 40-60°C) to give (64a) (80%), m.p. 45°C.

b) Reaction of the Indane Carboxylate (64a) with Nitrosobenzene

To a solution of the carboxylate (64a) (510 mg, 2 mmol), nitrosobenzene (268 mg, 2.5 mmol) and one crystal of 18-crown-6 in dichloromethane (20 ml) was added solid potassium hydroxide (140 mg, 2.5 mmol). The mixture was stirred for 1 h under a static atmosphere of nitrogen. Oxygen-free water was then added (50 ml), followed by sufficient dilute sulphuric acid for neutralisation. The dichloromethane layer was washed with water, dried ($MgSO_4$), filtered, and evaporated to dryness. The residue was dissolved in a minimum volume of carbon tetrachloride and chromatographed on a column of silica

(HF 254). Development with chloroform-toluene (75:25) separated the expected blue band from an orange material. The blue solid was extracted with chloroform and proved to be ethyl 1-oxo-2-phenylaminoinden-3-carboxylate (65b) (158 mg, 27%), m.p. 100.5°C; (Found: C, 73.8; H, 4.9; N, 4.6. $C_{18}H_{15}NO_3$ requires C, 73.7; H, 5.1; N, 4.8%); z/m 293(M^+); ν_{max}(KBr) 3 290(NH), 1 663 and 1 732 cm^{-1} (CO); λ_{max}(MeOH) 205.5 nm (ε 26 100), 265(ε 29 700) and 566 nm(ε 2 040); $\delta_H(CDCl_3)$ 1.35(3H, t, Me), 4.33(2H, q, CH_2), ca. 6.8-7.55(9H, m, ar.) and ca. 9.18(1H, br s, exchangeable with D_2O, NH); $\delta_C(CDCl_3)$ 16.4(q), 60.3(t), 107.8(s), 121.1(s), 123.1(d), 124.1(d), 124.8(d), 125.2(d), 127.1(s), 128.8(d), 136.0(d), 138.1(s), 145.4(s), 147.2(s), 166.9(s) and 190.6(s).

The tert-Butyl Nitroso Compound

a) 2-Methyl-2-Nitropropane [40]. tert-Butylamine (100 g, 1.37 mol) was oxidised using potassium permanganate (650 g, 4.11 mol) in water (3 ℓ) at 55°C for 4 h. After steam distillation the less dense nitro compound was separated, diluted with diethyl ether (250 ml) and washed with dilute hydrochloric acid and then water. The ethereal solution was dried ($MgSO_4$) and then distilled. Removal of the ether gave 100 g crude nitro compound, which was used in the next step. Distillation of a sample of this product gave 2-methyl-2-nitropropane, b.p. 127-128°C; $\delta_H(CCl_4)$ 1.58(s).

b) N-tert-Butylhydroxylamine. Aluminium foil (30.1 g, 1.1 mol) was amalgamated by dipping the strips into mercuric chloride solution (8 g in 400 ml water) for 15s. After drying the

amalgam was put into a mixture of ether (1.5 ℓ) and water (15 ml). 2-Methyl-2-nitropropane (60 g, 0.58 mol) was added dropwise with vigorous stirring. One half hour later, the gelatinous mass was allowed to settle, and was then filtered through glass wool. After washing with sodium hydroxide, and then water, the solvent was removed. The crude product (36 g) was crystallised from pentane as white platelets, m.p. 64-65°C; $\delta_H(CCl_4)$ 5.86(2H, br, NH and OH) and 1.09(9H, s, C-Me_3). Separating the gelatinous aluminium material from the ethereal solution was not as simple as suggested in the literature. The hydroxylamine is readily oxidised in air, so all manipulations had to be performed rapidly.

c) 2-Methyl-2-nitrosopropane. A solution of sodium hypobromite was prepared by adding bromine (57.5 g, 18.5 ml, 0.36 mol), with stirring, to a solution of sodium hydroxide (36 g, 0.9 mol) in water (225 ml). The resulting yellow solution was cooled to -20°C. Without allowing the temperature to rise above 0°C, a suspension of N-tert-butylhydroxylamine (26.7 g, 0.3 mol) in water (50 ml) was added as rapidly as possible. This procedure is almost exactly that given by Calder et al.[40]. However, if the sodium hypobromite solution is at -20°C when the aqueous hydroxylamine is added, the latter solidifies when it enters the flask. Here the temperature was allowed to rise sufficiently to keep everything liquid (-10°C). The reaction mixture was again cooled to -20°C and then slowly allowed to rise to room temperature. At the end of 4 h, the solid product was filtered off,

pulverised, and washed with water (1 ℓ) to remove all traces of alkali. 2-Methyl-2-nitrosopropane (ca. 20 g, 80%), was obtained as a light blue solid, m.p. 80-81°C; $\nu_{max}(CCl_4)$ 1 560 cm^{-1}(NO); $\delta_H(CCl_4)$ 1.24(monomer) and 1.57 (dimer); $\delta_H(C_6D_6)$ 0.97 (monomer) and 1.49 (dimer); at about 40°C these solutions contained 80% monomer.

Ethyl 2-(tert-Butylamino)-1-oxo-inden-3-carboxylate (65a)

Ethyl 1-oxo-indan-3-carboxylate (64a) (204 mg, 1 mmol), 2-methyl-2-nitrosopropane (261 mg, 3 mmol) and one large crystal of 18-crown-6 were dissolved in dichloromethane (10 ml). Two pellets of potassium hydroxide (0.2 g) were added, and the reaction mixture was stirred for 40 minutes. The solution was orange in colour. Oxygen-free water (20 ml) was added, followed by enough dilute sulphuric acid to make the aqueous layer neutral. After several washings with water the dichloromethane layer was dried ($MgSO_4$), and evaporated. The residue was dissolved in carbon tetrachloride and chromatographed on a column of silica (GF 254), developed with chloroform. An intense blue band moved down the column behind a vague turquoise band. The blue band was collected and eluted with diethyl ether to give a deep blue solution. Overnight this changed to purple and yielded a dark brown solid on evaporation. Recrystallisation from ethanol and then methanol provided a product which on micro-analysis gave the results expected, except that the figure for the nitrogen content was low. Therefore the substance was chromatographed on silica plates developed with benzene.

The blue band, R_f 0.56 was removed and eluted with ether. Crystallisation from methanol gave beautiful tiny black needles of ethyl 2-(tert-butylamino)-1-oxo-inden-3-carboxylate (65a) (about 30 mg, but much was lost during the vigorous process of purification), m.p. 104°C; (Found: C, 68.91; H, 7.4; N, 5.0. $C_{16}H_{19}NO_3$ requires C, 70.31; H, 7.01; N 5.1%); z/m 273.1362; $C_{16}H_{19}NO_3$ requires 273.1364; ν_{max}(KBr) 1 646 and 1 725 cm^{-1} (CO), 3 255 cm^{-1}(NH); λ_{max}(EtOH) 221(ε1 250), 266 (ε29 000) and 584(ε 920); δ_H(XL 100 Hz) ($CDCl_3$) 1.41(t, J 7.2 Hz, CH_2-Me), 1.49(9H, s Bu^t), 4.31(2H, q, J 7.1 Hz, CH_2-Me), ca. 7.26-7.32(4H, m, aryl-H), and ca. 8.7(1H, br s, exch. with D_2O, NH).

Attempted Cleavage of Ethyl 2-(tert Butylamino)-1-oxo-inden-3-carboxylate (65a) under Acidic Conditions.

It was suggested that the tert-butyl group in (65a) might yield to cleavage under acidic conditions and so provide an alternative route to the purple aminoindenone (51).

However, with ethanolic hydrogen chloride, the blue colour of (65a) was lost within 1 h at room temperature. Acetyl chloride in ethanol, and dilute mineral acid had the same effect. Concentrated sulphuric acid discharged the colour almost immediately. When (65a) was added to dichloromethane containing hydrogen chloride at -78°C the solution immediately became yellow. Although t.l.c. monitoring demonstrated that new products were being formed, there was little indication that one of these products had a purple

colour. Two hours later, at a temperature of -78°C, the reaction was complete, and no (65a) remained. There was no purple coloured product.

Use of Trifluoroacetic Acid. The indenone (65a) was added to trifluoroacetic acid at room temperature. Tiny gas bubbles formed around the crystals as they dissolved. Initially the solution was purple, but soon it turned blue. At the end of 35 minutes the acid was evaporated at ambient temperature and under reduced pressure (water vacuum pump). Some ethanol was added, and immediately this, also, was removed by the same means. Water and dichloromethane used together, brought everything into solution. All was neutralised with sodium hydrogen carbonate, and the organic layer was washed until neutral, dried ($MgSO_4$), and tested on a silica t.l.c. plate developed with chloroform. Many substances were present. The most striking were two spots: a blue one at $\underline{R}_f$ 0.4, which was likely compound (67), m.p. 214-216°C, and another, at $\underline{R}_f$ 0.1, was purple in colour - perhaps, the target aminoindenone (51).

Reaction of 5,6-Dimethoxy-3-oxoindan-1-carboxylic Acid (72a) with Nitrosobenzene

The oxoindane [41] carboxylic acid (72a) (249 mg, 1.06 mmol) and nitrosobenzene (270 mg, 2.5 mmol) in ethanol (50 ml) were stirred at 0°C, and 10% aqueous sodium hydroxide (1 ml, 2.5 mmol) was added dropwise. A red precipitate appeared. One hour later the precipitate was filtered off, and washed with ethanol. The solid was placed in a soxhlet thimble and

extracted with toluene. This was a very slow operation. Orange-red crystals were obtained. They were not the expected condensation product. Instead this was likely 5,6-dimethoxy-2-phenylimino-3-(phenylimino oxide)-indan-1-one (76), or an isomer, (202 mg, 55%); m.p. 231°C; (Found: C, 71.36; H, 4.6; N, 7.0. $C_{23}H_{18}N_2O_4$ requires C, 71.49; H, 4.7; N, 7.25%); δ_H [$(CD_3)_2CO$] 3.96(3H, s, OMe), 4.12(3H, s, OMe), and ca. 6.6-7.7(12H, m, aryl-H); z/m 386(M^+), 270. The product was insoluble in chloroform, benzene, and only slightly soluble in toluene. On an analytical silica t.l.c. plate, an amusing phenomenon was observed - a spot of the red product (76) applied to the plate and developed with acetone left a red spot at the base line and an orange one had moved to the top. When the plate was dried, and inverted in the solvent the orange spot left a red spot at the new base-line, and a new orange spot appeared at what was now the top of the plate.

Reaction of Ethyl 5,6-Dimethoxy-1-oxo-indan-3-carboxylate (72b) with Nitrosobenzene

a) The Ester (72b). The oxindane carboxylic acid (72a) (0.59 g, 2.5 mmol) in ethanol (15 ml) was heated under reflux for 4 h with concentrated sulphuric acid (0.2 ml). The ethanol was evaporated on a rotary evaporator. Water and chloroform were added to the residue. The chloroform layer was washed with sodium hydrogen carbonate solution, and then with water. After drying ($MgSO_4$) it was filtered and evaporated. The

residue was first crystallised from methanol (0.56 g), and then redissolved in ethyl acetate, treated with active charcoal, and filtered. Addition of light petroleum gave crystals of ethyl 5,6-dimethoxy-1-oxo-indan-3-carboxylate (72b) (0.5 g, 76%), m.p. 82°C; (Found: C, 63.75; H, 6.1. $C_{14}H_{16}O_5$ requires C, 63.64; H, 6.1%); ν(KBr) 1 697 and 1 730 cm^{-1}(CO); δ_H($CDCl_3$) 1.28(t, Me, J 7 Hz), 2.82(1H, dd, J 20 Hz and 8 Hz, 2-H), 3.05(1H, dd, J 20 Hz and 4 Hz, 2-H) 3.9(3H, s, OMe), 3.95(3H, s, OMe), ca. 4.08-4.43 (dq, 7 Hz and 3 Hz, CH_2 and 1-H), 7.07(1H, m, aryl-H) and 7.17(1H, aryl-H); m/z 264(M^+).

b) Reaction between the Ester (72b) and Nitrosobenzene. The ester (72b), (53 mg, 0.2 mmol), nitrosobenzene (21.4 mg, 0.2 mmol), and a crystal of 18-crown-6 were dissolved in dichloromethane. Solid potassium hydroxide (11 mg, 0.2 mmol) was added and all was shaken at room temperature for 20 minutes. The mixture became brown in colour, and t.l.c. on silica developed with chloroform, gave yellow, orange, and turquoise spots, but there was no constituent present in sufficient quantity to justify its separation. Work on this reaction was halted.

2-Phenylimino-3-(phenylimino oxide)-indan-1-one (66)

Indanone (1 g, 7.6 mmol) and nitrosobenzene (3 g, 28 mmol) in ethanol (10 ml) were kept at 10°C while 4 drops of 20% potassium hydroxide in methanol were being added. The colour of the solution changed from green to violet. Within about

five minutes a red precipitate formed and this was filtered off two hours later [30]. Recrystallisation from methanol gave the red 2-phenylimino-3-(phenylimino oxide)-indan-1-one (66) (1.2 g, 50%), m.p. 163°C (lit. 165°C); m/z 326(M^+).

3.4. The Chlorohydrin Alkyl Ethers and their Diels-Alder Adducts with N-Phenylmaleimide

The Chlorohydrin Ethyl Ethers (27)

The method described by Tan [15] was employed. Reissert compound [42], 2-benzoyl-1-cyano-1,2-dihydroisoquinoline (2) (6.5 g, 25 mmol) in ethanol (100 ml) was added to N-chlorosuccinimide (3.9 g, 30 mmol) in dioxan (5 ml). The mixture was heated slowly to 80-90°C and stirred at this temperature for 2 h until chlorosuccinimide was absent, as shown by the use of starch-iodide paper. Some solid, which separated, was filtered off and washed with ethanol. The combined filtrates were evaporated to dryness and the residue was extracted with chloroform. This extract was washed with water, dried (Na_2SO_4), and evaporated to give a solid which, on crystallisation from ethyl acetate, yielded 2-benzoyl-4-chloro-1-cyano-3-ethoxy-1,2,3,4-tetrahydroisoquinoline (27) (4.95, 58%), m.p. 196-200°C (Tan 193-196°C); $\delta_H(CDCl_3)$ 0.84(t, J 7 Hz, Me), 2.95-3.45(m, J 7 Hz, O-CH_2 - CH_3), 5.05(d, J 3 Hz, 4-H), 5.62(d, J 3 Hz, 3-H), 5.94(s, 1-H), and ca. 7.30-7.90(9H, m, aryl-H); (Tan 0.85, 2.95-3.44, 5.09, 5.65, 5.98, and 7.40-7.90); m/z 340 and 342 (M^+).

When the ethyl acetate mother liquor was concentrated,

a minor stereoisomer (27) was obtained (0.5 g, 6%); m.p. 151-152°C; $\delta_H(CDCl_3)$ 1.03(t, J 7 Hz, Me), 3.10-3.90(2 x m.q. J 7 Hz and 3 Hz, CH_2 Me), 5.11(d, J 3 Hz, 4-H), 5.63(br s, 3-H), 6.33(s, 1-H), and 7.30-7.80(9H, m, ar-H). (Tan 1.03, 3.1-3.9, 5.11, 5.58, 6.33 and 7.2-7.8); m/z 340 and 342(M^+).

Deuteriated N-Phenylmaleimide (87)

a) Deuteriated Aniline [43]. Aniline hydrochloride (5.16 g) in deuterium oxide (7 ml) was heated under reflux conditions for 72 h. Twice during this period, some of the solvent was removed by evaporation, and the volume was made up to the original with fresh deuterium oxide. When the reaction was stopped sodium carbonate was used to neutralise the reaction mixture. The deuteriated aniline was extracted with ether. Drying (Na_2CO_3), and evaporation of the solvent gave a specimen of 2,4,6-trideuterio-aniline (3 g) of more than 70% purity (n.m.r. spectrometric assay); $\delta_H(CDCl_3)$ 3.5(s, NH_2) and ca. 6.57-7.40(m, ar-H; 84% of this signal appeared as a broad singlet at 7.15); m/z 96(M^+), and m/z 95($M^+ - 1$): this latter peak was 30% of the height of the (M^+) peak. In the non-deuteriated aniline the peak of the ($M^+ - 1$) signal was 26% of the height of the (M^+) peak.

b) Deuteriated N-Maleanilic Acid [44]. Maleic anhydride (85) (3.0 g, 31 mmol) in anhydrous diethyl ether (40 ml) was placed in a flask fitted with a condenser and stirrer. A solution of the deuteriated aniline (2.95 g, 31 mmol) was

added. The resulting thick suspension was stirred for 1 h at room temperature and then filtered under suction. The solid was the deuteriated N-maleanilic acid (98% yield), m.p. 201-202°C and was used without further purification.

c) N-(2,4,6-trideuteriophenyl)maleimide (87). Anhydrous sodium acetate (1 g) and acetic anhydride (10.5 ml, 110 mmol) were mixed with the deuteriated maleanilic acid (5 g, 25 mmol). The resulting suspension was heated, with stirring, on a steam bath for 0.5 h. Some of the sodium acetate remained undissolved. The cooled reaction mixture was poured into ice-water (20 ml), and then filtered. The resulting crystals were washed three times with water, and then with light petroleum (b.p. 40-60°C) to give N-(2,4,6-trideuteriophenyl) maleimide (87) 2.5 g, 57% (of more than 80% purity, n.m.r. spectrometric assay) ; m.p. 90°C (from cyclohexane); $\delta_H(CDCl_3)$ 6.85(s, CH=CH), 7.50(br s, ar-H). There was a tiny signal at δ 7.33, likely due to di-deuteriated N-phenylmaleimide.

The Cycloadduct of the Chlorohydrin Ethyl Ether (27) with N-Phenylmaleimide

a) Major Stereoisomer (27). (m.p. 193-196°C). To the chlorohydrin ether, (340 mg, 1 mmol) in dry dioxan (20 ml) was added N-phenylmaleimide (865 mg, 5 mmol). Heat was supplied to speed up solution. The solution was cooled to room temperature, and triethylamine (110 mg, 1.1 mmol) was added to the yellow solution (N-phenylmaleimide is yellow). The reaction mixture was kept at room temperature for 45 h,

by which time greenish-looking crystals had formed. These crystals were washed with dioxan to remove triethylamine and any unchanged (27), and then with water to dissolve out triethylamine hydrochloride. The residue was almost pure adduct (83a) (360 mg, 75%). Because of the relative insolubility of the solid, it was purified by extraction with acetone using a Soxhlet apparatus. Recrystallisation from the same solvent gave the cycloadduct (83a) (210 g, 45%), m.p. 316°C; (Found: C, 72.8; H, 4.9; N, 8.5. $C_{29}H_{23}N_3O_4$ requires C, 72.9; H, 4.9; N, 8.8%); ν_{max}(KBr) 1 663 and 1 785 cm^{-1}(N-CO-Ph), 1716 cm^{-1}(CO-N-CO), and 2 250 cm^{-1}(CN, w); δ_H [$(CD_3)_2CO$ + $(CD_3)_2SO$] 0.85(t, J 7 Hz, Me), 3.04(dq, J 7 Hz and 2 Hz, Me-C-H), 3.40(dq, J 7 Hz and 3 Hz, Me-C-H), 3.66(dd, J 3 Hz and 8.5 Hz, 6-H_d), 4.11(br t, J 3 Hz and 4 Hz, 7-H_c), 4.36(d, J 9 Hz, 2-H_b), 4.98(br d, J 4 Hz, 11-H_a), ca. 6.44 (2H, br t, aryl-H), and ca. 7.05-8.0(12H, m, aryl-H).

b) Minor Stereoisomer (27) (m.p. 151-152°C). This chlorohydrin ether reacted with N-phenylmaleimide to give an adduct which was identical to that described above (83a). The yield, however, was smaller (45% before recrystallisation).

c) Alternative Preparation of Adduct (83a). Later, adduct formation was speeded up by carrying out the preparation at 70-75°C under reflux conditions for a period of 0.5 h. The proportion of triethylamine had been increased from 1.1 equivalents to 3 equivalents. The yield was 50%.

d) Deuteriated Adduct (83b). The adduct was prepared in the same way as its non-deuteriated analogue except that 2 equivalents of the deuteriated N-phenylmaleimide were employed. The adduct (83b) was obtained in 75% yield, m.p. 309-312°C (acetone); $\delta_H[(CD_3)_2CO + (CD_3)_2SO]$ 1.91(t, J 7 Hz, Me), 3.61(dd, J 9 Hz and 3 Hz, 6-H_d) 4.13(dd, J 3 Hz and 4 Hz, 7-H_c), 4.44(d, J 9 Hz, 2-H_b), and 4.94(br d, J 4 Hz, 11-H_a), and ca. 7.1-8.1(14H, m, aryl-H). There was a signal at ca. 6.42-6.53, barely distinguishable from the noise level. This signal was possibly due to the presence of a little dideuterio-N-phenylmaleimide adduct.

The Chlorohydrin Methyl Ether (28)

The N-benzoyl Reissert compound (2), (6.5 g, 25 mmol) in methanol (100 ml) and N-chlorosuccinimide (3.9 g, 30 mmol) in dioxan (10 ml) were used in the preparation of the methyl ether (cf. preparation of 27). Even after heating under reflux conditions for 25 h, the mixture still gave a positive test for the presence of chlorine. The reaction product was recrystallised from ethanol to give 2-benzoyl-4-chloro-1-cyano-3-methoxy-1,2,3,4-tetrahydroisoquinoline (28) (4.9 g, 60%), m.p. 194-196°C; (Found: C, 65.9; H, 4.8; Cl, 10.9; N, 8.6. $C_{18}H_{15}ClN_2O_2$ requires C, 66.1; H, 4.6; Cl, 10.9; N, 8.6%); ν_{max}(KBr) 1 658 cm^{-1} (CO) and 2 245 cm^{-1} (CN w); δ_H (Bruker 200 M Hz at 26°C) ($CHCl_3$) 3.01(s, Me), 5.09(d, J 3.1 Hz, 4-H), 5.54(d, J 3.1 Hz, 3-H), 5.97(s, 1-H), and ca. 7.37-7.80(9H, m, aryl-H). At 229 K the signal, originally at δ 5.97 had changed to δ 6.12; z/m 326 and 328 (M^+).

While the above compound was being freed from the ethanolic mother liquor by vacuum filtration, another small batch of crystals formed. These were filtered off and provided a minor isomer of (28) (250 mg, 3%), m.p. 168°C; ν_{max}(KBr) 1 660 cm^{-1}(CO) and 2 235 cm^{-1} (CN w); δ_H(Bruker 200 MHz at 21°C)($CHCl_3$) 3.31(s, Me), 5.14(d, J 2.1 Hz, 4-H), 5.50(br s 3-H), 6.33(br s, 1-H), and ca. 7.42-7.53(9H, m, aryl-H); δ_H(200 MHz at -44°C) ($CHCl_3$) 5.19(1H, d, J 2.2 Hz, 4-H), 5.50(1H, d, J 2.1 Hz, 3-H), and 6.38(1H, s, 1-H); m/z 326 and 328 (M^+).

Closer inspection of the n.m.r. spectrum of this minor isomer carried out at a temperature of 213 K revealed the presence of a very small proportion of a rotamer. In comparison with the spectrum of its companion, the chemical shifts of this rotamer were found to be inverted for 1-H and 3-H. δ ($CHCl_3$) 3.64(s, Me), 5.23(d, J 2.1 Hz, 4-H), 5.79(br s, 1-H), 6.36(d, J 2 Hz, 3-H).

The filtrate, from which the minor stereoisomers had crystallised, was evaporated and the residue (800 mg) proved to be a mixture of both major and minor isomers.

Thus, this preparation gave a conversion from Reissert compound to the chlorohydrin ethers in yields totalling 73%.

The Cycloadduct of the Chlorohydrin Methyl Ether (28) with N-Phenylmaleimide

a) Major Stereoisomer (28), (m.p. 196-200°C). To the chlorohydrin ether (28) (110 mg, 0.33 mmol) in dioxan (5.15 mmol) were added N-phenylmaleimide (60 mg, 0.33 mmol) and

triethylamine (37 mg, 0.37 mmol). The reaction mixture was left for 4 days at room temperature. Triethylamine hydrochloride, which had separated out, was filtered off, and washed with a little dioxan. The solvent was evaporated, and the residue was washed with water, air-dried, and then extracted with acetone using a Soxhlet apparatus. Recrystallisation from the same solvent gave the cycloadduct (84a) (100 mg, 64%), m.p. 286-288°C; (Found: C, 72.6; H, 4.5; N, 9.1. $C_{28}H_{21}N_3O_4$ requires C, 72.5; H, 4.6, N 9.1%); ν(KBr) 1 657 and 1 716 cm^{-1} (CO), and 2 240 cm^{-1} (CN w); δ_H(Bruker 200 MHz) (DMSO-d_5) 2.94(s, Me), 3.68(dd, J 8.5 and 3 Hz, 6-H_d), 4.21(br t, 3 and 3.7 Hz, 7-H_c), 4.35(d, J 8.5 Hz, 2-H_b), 4.94(d, J 3.7 Hz, 11-H_a), ca. 6.4-6.5(2H, m, benzoyl-H), and ca. 7.2-7.9(12H, m, aryl-H).

The Bruker n.m.r. spectrum of the above compound was accompanied by a spectrum of what seemed to be a similar substance in relatively small amounts. These weak signals were δ 3.34(s), 4.14(br t, J 3 and 3.6 Hz), and 5.25(d, J 3.6 Hz).

b) Cycloadduct (84a). Alternative Preparation. As in the case of the preparation of the ethoxy adduct (83a), it was later found that the *methoxy* adduct (84a), also, could be obtained by carrying out the reaction at 75°C using the same concentration of reactants enumerated above, but with a reaction time of 2.5 h; yield 43%.

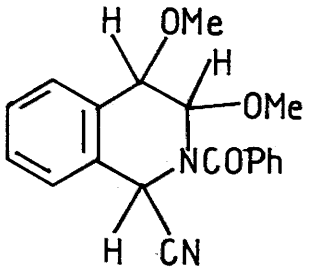
c) Deuteriated adduct (84b). The deuteriated adduct was prepared in the same way as the non-deuteriated form using the deuteriated N-phenylmaleimide. The reaction mixture was kept at room temperature for 4 days. After the usual work-up and recrystallisation, the adduct (84b) was obtained, m.p. 284-286°C; δ_H [$(CD_3)_2SO$] 2.93(s, Me), 3.67(dd, J 3 Hz and 9 Hz, 6-H), 4.19(br t, J 3 Hz and 4 Hz, 7-H), 4.38(d, J 9 Hz, 2-H), 4.93(d, J 4 Hz, 11-H), and ca. 7.23-7.88(12H, m, aryl-H); there was a signal at ca. 6.35-6.51 just above the "noise" level which was possibly due to the presence of a little di-deuteriophenylmaleimide adduct.

Cycloadduct of Cyclopentadiene with N-Phenylmaleimide

N-Phenylmaleimide (800 mg, 4.6 mmol) and cyclopentadiene (300 mg, 0.41 ml, 4.6 mmol) in dichloromethane (20 ml) were allowed to stand at room temperature for 0.5 h. The solvent was then removed, and the residue was crystallised from ethanol to give large crystals of the cycloadduct (88) m.p. 142°C; $\delta_H(CDCl_3)$ 1.51 and 1.7(2 x br d, bridgehead CH_2), 3.36 and 3.42(br d, 4 x CH), 6.23(2H, br s, CH = CH), and ca. 6.9-7.15(5H, m, ar-H).

Reaction of the Chlorohydrin Methyl Ether (28) with Methanolic Sodium Hydroxide

A solution of the major isomer (28) (330 mg, 1 mmol) and 5 M sodium hydroxide (0.2 ml, 2 mmol) in methanol (25 ml) was allowed to stand at room temperature for 1.5 h. The precipitate, which formed, was washed with water and the filtrate was evaporated. The resulting solid was extracted



(63)

with chloroform. 2-Benzoyl-1-cyano-3,4-dimethoxy-1,2,3,4-tetrahydroisoquinoline (63) was crystallised from ethanol (45 mg, 14%), m.p. 205°C; (Found: C, 70.93; H, 5.75; N, 8.83; $C_{19}H_{18}N_2O_3$ requires C, 70.77; H, 5.63; N, 8.70%); ν_{max}(KBr) 1 648 cm^{-1}(CO), 2 240 cm^{-1} (CN w). $\delta_H(CDCl_3)$ 3.29(s, OMe), 3.40(s, OMe), 4.26 (d, J 3 Hz, 4-H), 5.37(br s at 35°C: d. at -50°C J 3 Hz, 3-H), 6.29(s, 1-H) and ca. 7.26-7.80 (9H, m, aryl-H); z/m 307(M^+ - Me), 291, 259, and 217.

3.5 Some Reactions of a 3-Methylisoquinoline Reissert Compound.

2-Benzoyl-1-cyano-3-methyl-1,2-dihydroisoquinoline (31)

The Reissert compound (31) was prepared by the 2-phase method[42] from 3-methylisoquinoline; yield 60%; m.p. 139°C. (lit.[45] 139 °C); (Found: C, 78.6; H, 5.3; N, 10.3. $C_{18}H_{14}N_2O$ requires C, 78.8; H, 5.1; N, 10.2%); $\delta_H(CDCl_3)$ 1.80(s, Me), 6.23(s, 4-H), 6.48(s, 1-H), and ca. 7.25-7.73(9H, m, aryl-H).

Reaction of the 3-Methylisoquinoline Reissert Compound (31) with Hypochlorous Acid

a) Dilute hypochlorous acid was prepared as described by Kirby et al.[10b] Sodium hypochlorite (12% wt./vol. available chlorine) (10 ml) was mixed with 2 M nitric acid (12 ml). A solution of the Reissert compound (31) (0.5 g, 1.8 mmol) in dioxan (4 ml) was added dropwise with vigorous shaking. When the reaction mixture was allowed to settle two distinct layers appeared. After work-up, compound (31) was recovered unchanged.

b) It was decided that the difficulty arose due to a high concentration of sodium chloride in a rather old sample of hypochlorous acid. When the solution, prepared as described above (22 ml), was diluted with water (22 ml), and the Reissert compound (31) was added, dropwise with vigorous shaking, oily crystals formed. These were washed copiously with water, and successively with sodium hydrogen carbonate solution, sodium thiosulphate solution and water. The solid was recrystallised from methanol.

A little methanol was used to wash the crystals of the chloroketone, 2-benzoylamino-2-[2'-(1"-chloro-2"-oxopropyl) phenyl] acetonitrile (33a) (34%), m.p. 148°C (lit. 148-150°C). Kirby *et al.*[10b] reported that the ^{1}H n.m.r. spectrum changed with time. A new set of signals appeared and after 24 h the two sets were of approximately equal intensity. In our study, the spectrum of a freshly prepared solution consisted of a major set of signals along with a minor set. At the end of 24 h they, also, had become of approximately equal intensity; δ_H[$(CD_3)_2SO$] 2.14(s, Me), 6.25(s, CH), 6.69(br s, CH), *ca.* 7.15-8.20(4H, m, aryl-H) and 9.84(br s, exchangeable with D_2O, NH). The less intense signals were δ_H[$(CD_3)_2SO$] 2.22(s, Me), 6.11(1H, s, CH), 6.59(br s, CH), *ca.* 7.15-8.20(4H, m, aryl-H), and 9.76(1H, br s, exchangeable with D_2O, NH). The values reported by Kirby *et al.* were 2.15, 6.3, 6.69(d), 9.87 for the freshly prepared sample, and 2.22, 6.15, 6.74(d) and 9.76 for the new set of signals.

2-Benzoyl-4-chloro-1-cyano-3-methyl-1,2-dihydroisoquinoline (100)

Method (a), Solvent: Methanol and Dioxan. The 3-Methylisoquinoline Reissert compound (31), (690 mg, 2.5 mmol) in methanol (10 ml) was mixed with N-chlorosuccimide (390 mg, 2.9 mmol) in dioxan (2 ml) and allowed to stand at room temperature. At the end of 0.5 h, the starch-potassium iodide test for chlorosuccimide was negative. Twenty minutes later, the solution, now yellow in colour, was evaporated. The coffee-coloured residue, which consisted of large needle-shaped crystals, was chromatographed on silica developed with benzene-ethyl acetate (4:1). The main band at R_f 0.75 was eluted with ether and crystallised from ethanol to give 2-benzoyl-4-chloro-1-cyano-3-methyl-1,2-dihydroisoquinoline (100) (260 mg, 34%), m.p. 144°C, (Found: C, 69.60; H, 4.1; Cl, 11.8; N, 8.7. $C_{18}H_{13}ClN_2O$ requires C, 70.00; H, 4.3; Cl, 11.5; N, 9.1%); ν_{max} 1 666 cm^{-1}(CO) and 2 246 cm^{-1} (CN, w); $\delta_H(CDCl_3)$ 1.91(s, Me), 6.53(s, 1-H), and ca. 7.17-7.80(9H, aryl-H); m/z 308 and 310(M^+). The spectrum of the crude product showed tiny signals which could be ascribed to the presence of the cyanoisoquinoline (104) described in method (b).

Method (b), Solvent: tert-Butanol. The 3-methylisoquinoline Reissert compound (31) (4.08 g, 15 mmol) and N-chlorosuccimide (2.20 g, 16.5 mmol) in tert-butanol (200 ml) were heated

under reflux for 20 minutes. The solvent was evaporated and the yellowish product was dissolved in chloroform (50 ml). This solution was washed with water, dried (Na_2SO_4) and filtered, and the chloroform was evaporated. On treatment with ethanol (20 ml) the residue crystallised. Recrystallisation gave 2-benzoyl-4-chloro-1-cyano-3-methyl-1,2-dihydroisoquinoline (100), (2.52 g, 54%), m.p. 144°C.

The ethanol mother liquors were evaporated and crystals appeared which on recrystallisation from ethanol-water (7:3) proved to be 1-cyano-3-methylisoquinoline[10b] (104) (60 mg, 2.4%), m.p. 105-106°C. (Found: C, 78.43; H, 4.5; N, 16.3. $C_{11}H_8N_2$ requires C, 78.5; H, 4.8; N, 16.7%); ν_{max}(KBr) 2 236 cm^{-1}(CN); $\delta_H(CDCl_3)$ 2.70(s, Me), ca. 7.35-7.95(4H, m, aryl-H), and ca. 8.13-8.40(1H, m, 4-H); m/z 168(M^+)

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Reference 33a

1,4-Elimination Reactions of Chlorohydrin Ethers derived from an Isoquinoline Reissert Compound

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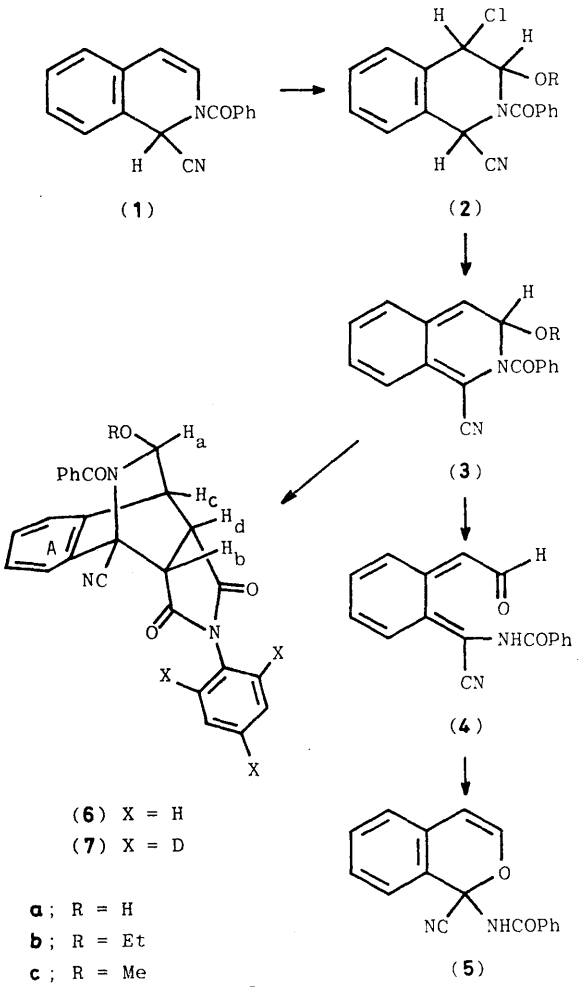
We report that the chlorohydrin ethyl (**2b**) and methyl (**2c**) ethers, derived from the isoquinoline Reissert compound (**1**), undergo 1,4-conjugated elimination of hydrogen chloride to give the 2,3-dihydroisoquinoline derivatives (**3b**) and (**3c**), which were trapped *in situ* as Diels–Alder adducts with *N*-phenylmaleimide.

The halogenohydrins derived from isoquinoline Reissert compounds undergo a series of base-induced rearrangements.[1,2] For example,[1] the chlorohydrin (**2a**) reacted with triethylamine at room temperature to give the isochromene (**5**). We proposed,[1] as one possibility, the reaction sequence presented in the Scheme, involving the transient intermediates (**3a**) and (**4**). The following experiments were carried out to test this proposal.

The chlorohydrin[1] (**2a**) was treated with triethylamine in the presence of *N*-phenylmaleimide in the hope that either or both of the intermediates (**3a**) and (**4**) would be trapped as Diels–Alder adducts [*e.g.* (**6a**)]. However, the reaction proceeded as before[1] to give the isochromene (**5**) and the related benzoylimino derivative. Attention was then turned to the chlorohydrin ethers (**2b**) and (**2c**), as the corresponding intermediates (**3b**) and (**3c**) would be unable to undergo the carbinolamide ring opening possible for the intermediate (**3a**), and might, therefore, persist long enough to be trapped.



Scheme

The Reissert compound (**1**) reacted with *N*-chlorosuccinimide in ethanolic or methanolic dioxane to give, respectively, the chlorohydrin ethyl (**2b**) and methyl (**2c**) ethers, which were both obtained as pairs of stereoisomers. Treatment of either the major or minor stereoisomer (**2b**) with triethylamine in the presence of *N*-phenylmaleimide gave the same cycloadduct (**6b**), derived from the postulated intermediate (**3b**). The major stereoisomer (**2c**) similarly gave the corresponding cycloadduct (**6c**). Thus, 1,4-conjugated elimination of hydrogen chloride from the chlorohydrin ethers (**2b**) and (**2c**) occurs under the conditions used to transform the chlorohydrin (**2a**) into the isochromene (**5**). These observations support the mechanistic ideas proposed earlier.[1]

The stereochemistry of the cycloadducts (**6b**) and (**6c**) was deduced from the ^{1}H n.m.r. spectra with the aid of the nuclear Overhauser enhancements arising from the irradiation of H_a and the methoxy protons of the cycloadduct (**6c**). Both cycloadducts gave 2-proton multiplets, δ 6.44, which were absent from the spectra of the trideuterio derivatives (**7b**) and (**7c**). These high-field multiplets must arise therefore from the protons *ortho* to nitrogen in the *N*-phenyl groups, which, presumably, are shielded by the benzene rings A. Similar multiplets had been observed earlier in the spectra of cycloadducts of *N*-phenylmaleimide and isobenzothiophene and certain 3-isoquinolone derivatives[3,4] (see also ref. 5). However, they were assigned to *peri* protons in the benzo rings, which were thought to be shielded by the carbonyl groups of the maleimide units.

We thank Dr D. S. Rycroft (University of Glasgow) for nuclear Overhauser difference spectra.

Techniques used: N.m.r., mass spec., i.r.

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Reference 33b

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Appendix Table 8 cont'd.

Compound (12)

OBSERVED AND CALCULATED STRUCTURE FACTORS FOR L195 C29H35NO8 P21(C) Z=8 PAGE 21

H K L 10FO 10FC	H K L 10FO 10FC	H K L 10FO 10FC	H K L 10FO 10FC	H K L 10FO 10FC
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

Appendix Table 8 cont'd.

Compound (12)

OBSERVED AND CALCULATED STRUCTURE FACTORS FOR L195 C29H35NO8 P21(C) Z=8 PAGE 22

H K L 10FO 10FC	H K L 10FO 10FC	H K L 10FO 10FC	H K L 10FO 10FC	H K L 10FO 10FC
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

Appendix Table 8 cont'd.

Compound (12)

OBSERVED AND CALCULATED STRUCTURE FACTORS FOR L195 C29H35NO8 P21(C) Z=8 PAGE 23

H K L 10FO 10FC	H K L 10FO 10FC	H K L 10FO 10FC	H K L 10FO 10FC	H K L 10FO 10FC
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

Appendix Table 8 cont'd.

Compound (12)

OBSERVED AND CALCULATED STRUCTURE FACTORS FOR L195 C29H35NO8 P21(C) Z=8 PAGE 24

H K L 10FO 10FC	H K L 10FO 10FC	H K L 10FO 10FC	H K L 10FO 10FC	H K L 10FO 10FC
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

Appendix Table 8 cont'd.

Compound (12)

OBSERVED AND CALCULATED STRUCTURE FACTORS FOR L195 C29H35NO8 P21(C) Z=8 PAGE 25

H K L 10FO 10FC	H K L 10FO 10FC	H K L 10FO 10FC	H K L 10FO 10FC	H K L 10FO 10FC
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

Appendix Table 8 cont'd.

Compound (12)

OBSERVED AND CALCULATED STRUCTURE FACTORS FOR L195 C29H35NO8 P21(C) Z=8 PAGE 26

H K L 10FO 10FC	H K L 10FO 10FC	H K L 10FO 10FC	H K L 10FO 10FC	H K L 10FO 10FC
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

Appendix

Table 9. Anisotropic thermal parameters* ($\AA^2 \times 10^3$) for compound (12).

Molecule I

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
N	50(3)	49(3)	43(3)	-3(2)	14(2)	-10(2)
O(1)	63(3)	82(4)	144(5)	-30(3)	-32(3)	21(3)
O(2)	62(3)	41(3)	70(3)	-1(2)	-4(2)	5(2)
O(3)	56(3)	77(3)	87(4)	-12(3)	22(3)	-20(2)
O(4)	54(3)	77(3)	91(4)	2(3)	1(3)	10(3)
O(5)	77(3)	84(3)	73(3)	32(3)	-9(3)	-10(3)
O(6)	70(3)	67(3)	63(3)	7(2)	-17(2)	-24(2)
O(7)	83(4)	93(4)	151(5)	-69(4)	-18(4)	16(3)
O(8)	60(3)	77(3)	116(4)	-7(3)	15(3)	13(3)
C(17)	81(5)	72(5)	61(5)	18(4)	28(4)	-15(4)
C(23)	107(6)	34(4)	86(5)	2(4)	14(5)	34(4)
C(25)	32(5)	183(11)	204(11)	-4(9)	26(6)	27(6)
C(27)	77(6)	145(8)	103(7)	14(6)	-50(5)	-32(6)
C(29)	115(7)	82(6)	137(8)	-14(6)	41(6)	46(5)

Molecule II

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
N	61(3)	49(3)	57(3)	-9(3)	13(3)	6(3)
O(1)	89(4)	97(4)	178(7)	48(4)	-54(4)	-45(4)
O(2)	105(4)	38(3)	84(4)	4(2)	-28(3)	-13(3)
O(3)	61(3)	90(4)	96(4)	-16(3)	18(3)	10(3)
O(4)	58(3)	81(3)	98(4)	-21(3)	4(3)	-20(3)
O(5)	93(4)	120(5)	84(4)	-42(3)	-14(3)	6(4)
O(6)	84(4)	88(4)	84(4)	-7(3)	-25(3)	29(3)
O(7)	114(5)	80(4)	102(4)	25(3)	24(4)	-8(3)
O(8)	89(4)	78(4)	196(7)	-47(4)	58(4)	-26(3)
C(17)	106(6)	82(5)	70(5)	-17(4)	34(5)	27(5)
C(23)	180(10)	48(5)	116(7)	18(5)	-36(7)	-58(6)
C(25)	39(5)	165(9)	171(10)	-31(8)	20(5)	-29(5)
C(27)	128(9)	175(11)	153(10)	-26(8)	-91(8)	71(8)
C(29)	176(10)	71(6)	200(12)	-31(7)	102(9)	-64(7)

* The exponent takes the form: $-2\pi^2\Sigma\Sigma U_{ij}h_ih_ja_i^*\cdot a_j^*$.

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1,4-Elimination Reactions of Chlorohydrin Ethers Derived from an Isoquinoline Reissert Compound.

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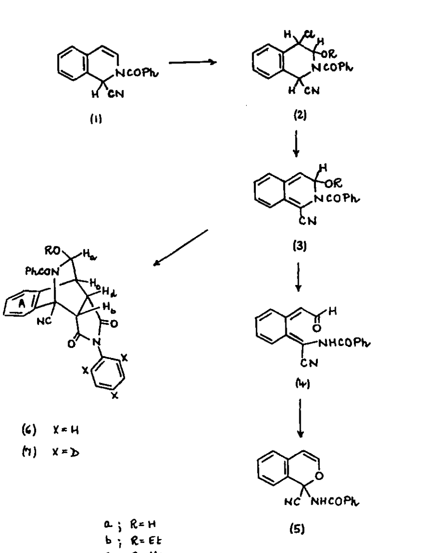
The chlorohydrin ethyl (2b) and methyl (2c) ethers derived from the isoquinoline Reissert compound (1), when treated with triethylamine, underwent 1,4-conjugated elimination of hydrogen chloride to give the corresponding 3-alkoxy-2-benzoyl-1-cyano-2,3-dihydroisoquinolines (3b) and (3c), which were trapped *in situ* with *N*-phenylmaleimide to form the cycloadducts (6b) and (6c). The 2-proton multiplets, δ 6.44, observed in the ^{1}H n.m.r. spectra of the cycloadducts (6b) and (6c) were shown, using the trideuterio-derivatives (7b) and (7c), to arise from protons *ortho* to nitrogen in the *N*-phenyl groups; the spectra of other cycloadducts of *N*-phenylmaleimide, reported earlier in the literature, are reinterpreted.

The halohydrins derived from isoquinoline Reissert compounds undergo a series of base-induced rearrangements.[1,2] For example,[1] the chlorohydrin (2a) reacted with triethylamine at room temperature to give the isochromene (5). We proposed,[1] as one possibility, the reaction sequence presented in the Scheme, involving the transient intermediates (3a) and (4). The following experiments were carried out to test this proposal.

References: see frame 3097.



a ; R = H
b ; R = Et
c ; R = Me

Scheme

The chlorohydrin[1] (2a) was treated with triethylamine in the presence of N-phenylmaleimide in the hope that either or both of the intermediates (3a) and (4) would be trapped as Diels-Alder adducts [e.g. (6a)]. However, no adduct was detected, the reaction proceeding as before[1] to give the isochromene (5) and the related benzoylimino-derivative. Thus it appeared that the intermediates, if formed, had been transformed into the product (5) too rapidly to be captured by N-phenylmaleimide. We therefore turned our attention to the chlorohydrin ethers (2b) and (2c), recognising that the corresponding intermediates (3b) and (3c), unlike the carbinolamide (3a), would be unable to undergo ring opening and might persist long enough to be trapped.

The Reissert compound (1) reacted with N-chlorosuccinimide in ethanolic dioxan to give two stereoisomeric ethers (2b) in yields of 58 and 6%. Treatment of the major isomer (2b) with triethylamine in the presence of N-phenylmaleimide gave the cycloadduct (6b) (45% yield after purification) derived from the postulated intermediate (3b). Moreover, the minor isomer (2b) gave the same cycloadduct (6b). The Reissert compound (1) was converted similarly into two, stereoisomeric, methyl ethers (2c), and the major isomer, when treated with triethylamine in the presence of N-phenylmaleimide, gave the cycloadduct (6c) (64%). Thus, 1,4-conjugated elimination of hydrogen chloride from the chloro ethers (2b) and (2c) occurs under the conditions used to transform the chlorohydrin (2a) into the isochromene (5). These observations support the mechanistic ideas proposed earlier.[1]

The stereochemistry of the cycloadducts (6b) and (6c) was deduced, as follows, from the ^{1}H n.m.r. spectra. Signals for H_a, H_b, H_c, and H_d in the cycloadduct (6c) were readily identified by their multiplicity and the magnitude of the vicinal

References: see frame 3097.

coupling constants $J_{b,d}$ 8.5, $J_{c,d}$ 3.3, and $J_{a,c}$ 3.3 Hz. Irradiation of H_a gave nuclear Overhauser enhancements of the signals arising from H_c, H_d, the methoxy-group, and the ortho protons of the benzoyl group, but not from H_b. Again, irradiation of the methoxy-protons enhanced signals from H_a, H_c, and the ortho, benzoyl protons, but not from H_b or H_d. Moreover, the methyl ether (6c) gave a singlet for the methoxy-protons at abnormally high field, δ 2.94, indicating that the methoxy-group is cis to, and shielded by, the benzene ring A. The corresponding stereochemistry (6b) was assigned to the ethyl ether, since the signals for H_a, H_b, H_c, and H_d were almost superimposable on those of the methyl ether (6c).

We conclude, therefore, that N-phenylmaleimide traps the transient intermediates (3b) and (3c) predominantly by endo addition anti to the alkoxy-groups. Endo addition of N-phenylmaleimide to the labile isoquinol-3-ones (8; R^1 = R^2 = H) and (8; R^1 = Me, R^2 = H) had been observed earlier.[3] The stereochemistry of the adducts was deduced from a high-field, δ 6.5, multiplet assigned to 5-H and 8-H of the isoquinolones (8) which, in the adducts, were believed to be shielded by the carbonyl groups of the maleimide units. The multiplet, δ 6.43, given by the endo adduct of N-phenylmaleimide and isobenzothiophene (9) had earlier[4] been interpreted similarly. The cycloadducts (6b) and (6c) likewise gave high-field, δ 6.44, 2-proton multiplets. However, these multiplets were absent from the spectra of the trideuterio-derivatives (7b) and (7c), which were prepared in the usual way using N-(2,4,6-trideuteriophenyl)maleimide. The multiplets must arise, therefore, from the protons ortho to nitrogen in the N-phenyl group, which are, presumably, shielded by the benzene ring A. Our findings strongly support the

References: see frame 3097.

(8)

(9)

earlier[3,4] stereochemical conclusions, but indicate that a reinterpretation of the spectra is necessary. In a later study,[5] the cycloadduct of N-methylisoquinol-3-one (8; R^1 = H, R^2 = Me) and maleic anhydride was assigned an exo configuration on the grounds that the n.m.r. spectrum showed no high-field, aromatic multiplet. Our results suggest that neither the endo nor exo adducts would have highly shielded, aromatic protons and that the stereochemistry of this adduct must, for the present, be open to question.

Experimental

M.p.s. were determined with a Kofler hot-stage apparatus. N.m.r. spectra were recorded using tetramethylsilane as internal standard. Mass spectra were obtained by electron impact with an ionising voltage of 70eV.

Preparation of the Chlorohydrin Ethyl Ethers (2b).- 2-Benzoyl-1-cyano-1,2-dihydroisoquinoline (1) (6.5 g, 25 mmol) in ethanol (100 ml) was added to N-chlorosuccinimide (4.0 g, 30 mmol) in dioxan (5 ml). The mixture was heated slowly with stirring to 80-90 °C and kept at this temperature until, after ca. 2 h, all the N-chlorosuccinimide had been consumed (starch-iodide test). The mixture was cooled and filtered and the filtrate was evaporated. The residue was extracted with chloroform and the extracts were washed with water, dried (Na_2SO_4), and evaporated. The oily product was crystallised from ethyl acetate to give 2-benzoyl-4-chloro-1-cyano-3-ethoxy-1,2,3,4-tetrahydroisoquinoline (major stereoisomer) (2b) (4.95 g, 58%) as rhombs, m.p. 193-196 °C (Found: C, 66.9; C, 5.0; Cl, 10.5; N, 8.3. $C_{19}H_{17}ClN_2O_2$ requires C, 67.0; H, 5.0; Cl, 10.4; N, 8.2%); $\nu_{max.}$ (KBr) 2 243 w and 1 658 cm^{-1}; δ_H (90 MHz, $CDCl_3$) 0.84 (t, J 7 Hz, Me), 2.95-3.45

References: see frame 3097.

(m, OCH_2CH_3), 5.08 (d, J 3.0 Hz, 4-H), 5.64 (d, J 3.0 Hz, 3-H), 5.97 (s, 1-H), 7.3-7.6 (7H, m, aryl-H), and 7.75 (2H, m, o-benzoyl-H); m/z 340 and 342 (M^+). The mother liquors were concentrated to give the minor stereoisomer (2b) (0.5 g, 6%) as plates, m.p. 151-152 °C (from ethanol) (Found: C, 66.7%; H, 5.1; Cl, 10.5; N, 8.2%); $\nu_{max.}$ (KBr) 2 243 and 1 658 cm^{-1}; δ_H (90 MHz, $CDCl_3$, 30 °C) 1.03 (t, J 7 Hz, Me), 3.0-3.5 and 3.5-4.0 (2 x m, OCH_2CH_3), 5.11 (d, J 3.0 Hz, 4-H), 5.60 (br s, 3-H), 6.33 (br s, 1-H), 7.3-7.6 (7H, m, aryl-H), and 7.70 (2H, m, o-benzoyl-H) (the spectrum was temperature dependent); m/z 340 and 342 (M^+).

Preparation of the Chlorohydrin Methyl Ethers (2c).- The Reissert compound (1) (6.5 g) in methanol (100 ml) was treated with N-chlorosuccinimide (4.0 g) in dioxan (10 ml), as described for the preparation of the ethyl ethers (2b). Crystallisation of the product mixture from ethanol gave 2-benzoyl-4-chloro-1-cyano-3-methoxy-1,2,3,4-tetrahydroisoquinoline (major stereoisomer) (2c) (4.9 g, 60%), m.p. 194-196 °C (Found: C, 65.9; H, 4.7; Cl, 10.9; N, 8.6. $C_{18}H_{15}ClN_2O_2$ requires C, 66.1; H, 4.6; Cl, 10.85; N, 8.6%); $\nu_{max.}$ (KBr) 2 245 w and 1 658 cm^{-1}; δ_H (90 MHz, $CDCl_3$) 3.01 (s, OMe), 5.09 (d, J 3.1 Hz, 4-H), 5.54 (d, J 3.1 Hz, 3-H), 5.97 (s, 1-H), 7.35-7.65 (7H, m, aryl-H), and 7.75 (2H, m, o-benzoyl-H); m/z 326 and 328 (M^+). Concentration of the mother liquors gave the minor stereoisomer (2c) (250 mg, 3%), m.p. 168 °C; $\nu_{max.}$ (KBr) 2 239 w and 1 660 cm^{-1}; δ_H (90 MHz, $CDCl_3$, 30 °C) 3.31 (s, OMe), 5.14 (d, J 2 Hz, 4-H), 5.50 (br s, 3-H), 6.33 (br s, 1-H), 7.30-7.60 (7H, m, aryl-H), and 7.67 (2H, m, o-benzoyl-H) (the spectrum was temperature dependent); m/z 326 and 328 (M^+).

Cycloadducts (6b), (6c), (7b), and (7c) of the Intermediates (3b) and (3c).- The major stereoisomer of the ethyl ether (2b) (340 mg, 1 mmol) and N-phenylmaleimide (865 mg, 5 mmol) were

warmed in dioxan (20 ml) until dissolution was complete. The mixture was cooled to room temperature and triethylamine (110 mg, 1.1 mmol) was added. A crystalline product gradually separated out and, after 45 h, was collected and washed successively with dioxan and water and then dried. The ^{1}H n.m.r. spectrum of this material (360 mg) showed it to be substantially pure cycloadduct (6b). Recrystallisation from acetone (Soxhlet extraction) gave the cycloadduct (6b) (210 mg, 45%), m.p. 316 °C (Found: C, 72.7; H, 4.9; N, 8.5. $C_{29}H_{23}N_3O_4$ requires C, 72.9; H, 4.9; N, 8.8%); $\nu_{max.}$ (KBr) 2 250 w, 1 785, 1 716 s, and 1 663 cm^{-1}; δ_H (90 MHz, $(CD_3)_2SO$) 0.84 (t, J 7 Hz, Me), 2.6-3.1 and 3.2-3.7 (2 x m, OCH_2CH_3), 3.66 (dd, J 8.3 and 3 Hz, H_d), 4.11 (br t, J 3 Hz, H_c), 4.35 (d, J 8.5 Hz, H_b), 4.98 (d, J 3.7 Hz, H_a), 6.44 (2H, m, o-H_x), 7.20-7.65 (10H, m, aryl-H), and 7.73 (2H, m, o-benzoyl-H). Similarly, the major stereoisomer of the methyl ether (2c) (0.33 mmol) and N-phenylmaleimide (0.37 mmol) were treated with triethylamine (0.37 mmol) in dioxan (5.15 ml) at room temperature for 4 d to give the cycloadduct (6c) (64%), m.p. 286-288 °C (from acetone) (Found: C, 72.6; H, 4.5; N, 9.1. $C_{28}H_{21}N_3O_4$ requires C, 72.5; H, 4.6; N, 9.1%); $\nu_{max.}$ (KBr) 2 240 w, 1 781, 1 716 s, and 1 657 cm^{-1}; δ_H (220 MHz, $(CD_3)_2SO$) 2.94 (s, OMe), 3.68 (dd, J 8.5 and 3.0 Hz, H_d), 4.21 (br t, J 3.3 Hz, H_c), 4.35 (d, J 8.5 Hz, H_b), 4.95 (d, J 3.7 Hz, H_a), 6.44 (2H, m, o-H_x), 7.25-7.70 (10H, m, aryl-H), and 7.76 (2H, m, o-benzoyl-H); nuclear Overhauser effects were observed, as follows, from difference spectra [200 MHz, $(CD_3)_2SO$]: irradiation of H_a enhanced signals for the o-benzoyl-protons (4.0), H_c (8.5), H_d (9.7), and the methoxy-protons (3.4%), and irradiation of the methoxy-protons enhanced signals for the o-benzoyl-protons (2.7), H_a (10.2), and H_c (6.4%). The trideuterio-cycloadducts (7b) and

(7c) were obtained similarly using N-(2,4,6-trideuteriophenyl)-maleimide, which was prepared by standard methods[6] from 2,4,6-trideuterioaniline.[7] The ^{1}H n.m.r. spectra of the adducts (7b) and (7c) both lacked the 2-proton multiplet, δ 6.44 given by (6b) and (6c), but showed instead a weak doublet, δ 6.44 (J 8 Hz), arising from 2,4-dideuteriated material.

Acknowledgements

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REF. 24

Formation and *X*-Ray Crystal Structure of Ethyl 2-Amino-1-oxo-inden-3-carboxylate

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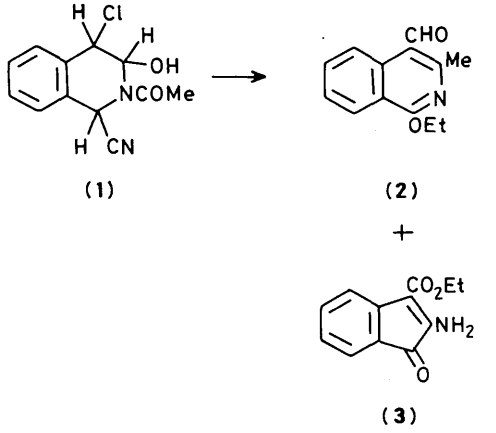
Treatment of 2-acetyl-4-chloro-1-cyano-1,2,3,4-tetrahydro-3-hydroxyisoquinoline (**1**) with ethanolic sodium hydroxide gave 1-ethoxy-3-methylisoquinoline-4-carbaldehyde (**2**) accompanied by a purple by-product identified as ethyl 2-amino-1-oxoindene-3-carboxylate (**3**). The structure of compound (**3**), the first example of a simple 1-aminoindenone, was confirmed by synthesis from the homophthalic ester (**5**) and by an *X*-ray crystallographic analysis. The mechanism of the conversion, (**1**)→(**3**), is briefly discussed.

The chlorohydrin (**1**) reacts with sodium hydroxide in ethanol to give the aldehyde (**2**) as a major product.[1] The chloro-and bromo-hydrins derived from other isoquinoline Reissert compounds behave similarly.[2] Characteristically, the crude mixtures from these reactions are deeply coloured and are seen, by thin layer chromatography (t.l.c.), to contain small amounts of orange or purple substances. We report here the isolation of a purple by-product from the transformation of compound (**1**) into the isoquinoline (**2**) and its identification as ethyl 2-amino-1-oxoindene-3-carboxylate (**3**).

The chlorohydrin (**1**) was treated with ethanolic sodium hydroxide at room temperature in the usual way.[1] Most of the aldehyde (**2**) was removed from the reaction mixture by crystallisation and the mother-liquors were subjected to repeated column and layer chromatography. The by-product (**3**), $C_{12}H_{11}NO_3$, was obtained as deep-purple needles, $\lambda_{max.}$ 263 (ε 42 300) and 535 nm (654). The i.r. spectrum (KBr) suggested the presence of two carbonyl groups ($\nu_{max.}$ 1 676 and 1 739 cm^{-1}) and possibly an amino group (3 330 and 3 445 cm^{-1}). The ^1H n.m.r. spectrum confirmed the presence of two protons exchangeable with D_2O and showed signals for an ethoxy group and four olefinic or aromatic protons. Two alternative structures, (**3**) and (**4**), were considered for the by-product. Although isoindenones are known only as transient species,[3] it was possible that the amino group in the 2-ketone (**4**) would stabilise the structure by electron donation. However, the by-product was stable even above its melting point (127—131 °C) and its mass spectrum showed fragmentation with loss of ethanol rather than an ethoxy group. This latter observation is accommodated by the structure (**3**), which contains adjacent ester and amino groups.

The structure (**3**) was confirmed by a short, though inefficient, synthesis. The homophthalic ester (**5**)[4] was treated with thionyl chloride[5] in dichloromethane containing a catalytic amount of dimethylformamide and the mixture was stirred with aqueous ethanolic potassium cyanide. The purple organic layer yielded, after chromatography, a sample of compound (**3**) identical with the foregoing by-product. The indenone (**3**) was presumably formed, as planned, by base-catalysed cyclisation of an intermediate acyl cyanide. However, despite many variations of reagents and reaction conditions,[5] the yield of pure product did not exceed 6%. Nevertheless the structure (**3**) was established unambiguously by the *X*-ray analysis described below.

2-Aminoindenones unsubstituted on nitrogen [as in (**3**)] have apparently not been prepared previously. 2-Arylamino derivatives, *e.g.* (**6**), are, however, readily formed by condensation of indanones with nitrosoarenes and have been described as deep blue-violet substances.[6] It appears then that



(**1**) (**2**) + (**3**)

the striking colour of these compounds may be attributed to the parent, 2-aminoindenone chromophore. Compound (**3**), a vinylogous amide, was not acetylated even in refluxing acetic anhydride containing sodium acetate. It decomposed slowly in trifluoroacetic acid at room temperature with the formation of a blue product assigned the structure (**7**) on the basis of its spectroscopic properties (see Experimental section).

The transformation, (**1**)→(**3**), would appear to involve the cyclisation of an anion derived from the ring-opened tautomer of compound (**1**) either before [as (**8**)] or after [as (**9**)] 1,4-elimination of hydrogen chloride. The acetamido group could then be detached hydrolytically. The formation of the ester (**3**) rather than the corresponding aldehyde is surprising, although reminiscent of a Cannizzaro reaction. One possible explanation is that acetyl group migration occurs, following the cyclisation, to give initially 2-acetamido-1-oxoindene-3-carbaldehyde. Intramolecular hydride transfer *via* the ethoxide adduct (**10**) would then yield a carbinolamine able to collapse to the ketone (**3**) and acetaldehyde.

X-*Ray Crystal Structure of Compound* (**3**).—The four molecules in the unit cell are arranged in pairs, each pair consisting of centrosymmetrically related molecules (Figure). The ring carbonyl group of one is hydrogen-bonded to the amino group of the other, and *vice-versa*, so that there is an eight-membered ring in which two sides are formed by hydrogen bonds. The relevant distances are O(1)···· N^I 2.96(1), O(1)···· H(N^Ib) 2.14(7) Å. There is also an intramolecular hydrogen bond between the amino group and ester carbonyl group, the distances here being O(3)···· N 2.82(1), O(3)···· H(Na) 1.83(16) Å. The location of the amino

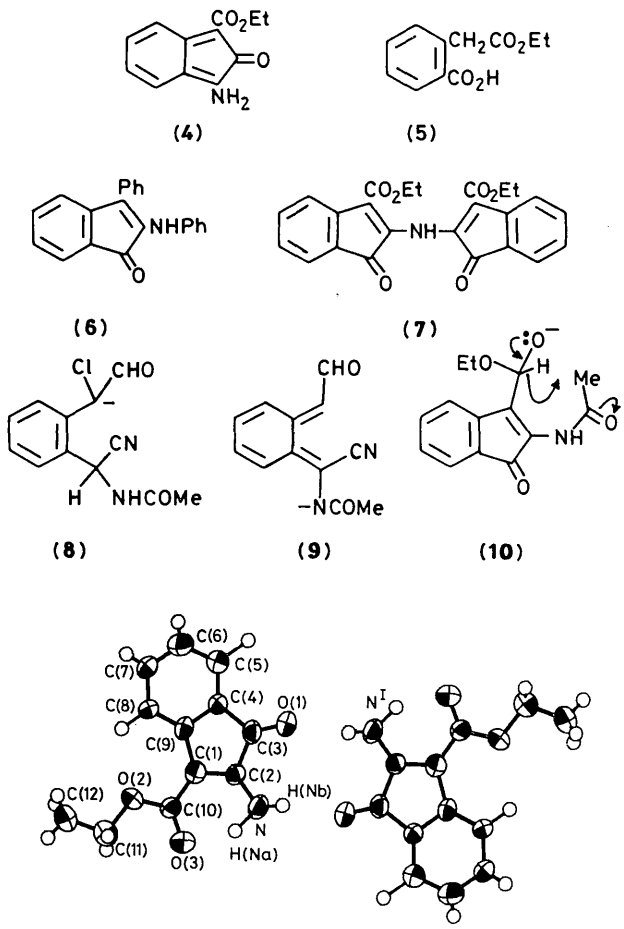


Figure. The centrosymmetric hydrogen-bonded dimeric unit. Atoms other than hydrogen are shown as 50% probability vibration ellipsoids. Hydrogen atoms are shown as spheres of arbitrary size, and have the same numbers as the atoms to which they are attached. The Roman numeral refers to the equivalent position $-x, 2-y, -z$ with respect to the asymmetric unit at x, y, z

hydrogen atoms confirms the atom type assignments of the five-membered ring substituents.

Atoms C(6), C(10), O(1), and O(3) deviate significantly from the plane of the other non-hydrogen atoms, the distances being 0.05(1), 0.08(1), −0.12(1), and 0.19(1) Å respectively. The amino and aromatic hydrogen atoms lie in the plane within experimental error.

The shortest distances between atoms in different molecules are C(aryl)···C(aryl) 3.47(1), C(aryl)···C(carboxy) 3.82(1), C(aryl)···C(ethyl) 3.74(2), C(aryl)···N 3.53(1), C(aryl)···O 3.24(1), C(ethyl)···C(ethyl) 3.68(2), C(ethyl)···O 3.66(2), N···O 2.96(1) (H-bond), 3.93(1), and O···O 3.57(1) Å.

Experimental

Preparation of Ethyl 2-Amino-1-oxoindene-3-carboxylate (**3**) *from 2-Acetyl-4-chloro-1-cyano-1,2,3,4-tetrahydro-3-hydroxyisoquinoline* (**1**).—The chlorohydrin [1] (**1**) (2.0 g) in ethanol (250 ml) was treated with 10% aqueous sodium hydroxide (2 mol equiv.) with stirring at room temperature for 3 h. The resulting, deep red solution was dried ($MgSO_4$) and evaporated to a small volume. The precipitated aldehyde (**2**) was filtered off and the mother-liquors were chromatographed on grade III, neutral alumina. Elution with benzene gave a purple fraction which was purified further by chromatography successively on silica GF_{254} plates developed with toluene–ethyl acetate (9:1) and alumina GF_{254} type E plates developed with toluene–diethyl ether (9:1). *Ethyl 2-amino-1-oxoindene-3-carboxylate* (**3**) formed deep purple needles (8 mg), m.p. 131 °C (sintering from 127 °C) (from diethyl ether) (Found: C, 66.4; H, 6.6; N, 5.2%; M^+, 217.0737. $C_{12}H_{11}NO_3$ requires C, 66.4; H, 6.45; N, 5.1%; M^+, 217.0739); $\nu_{max.}$(KBr) 3 445, 3 330, 1 733, and 1 676 cm^{-1}; $\lambda_{max.}$(EtOH) 263 (ε 42 300) and 535nm (654); δ($CDCl_3$) 7.7—7.5 (m, 3 H), 6.87 (dt, *J* 8 and 2 Hz, 1 H), *ca.* 6 (br s, 2 H, exchangeable with D_2O), 4.33 (q, *J* 8 Hz, 2 H), and 1.36 (t, *J* 8 Hz, 3 H).

Preparation of Ethyl 2-Amino-1-oxoindene-3-carboxylate from the Ethyl Homophthalate (**5**).—The ester [4] (**5**) (260 mg) in dichloromethane (1.5 ml) containing *N,N*-dimethylformamide (27 mg) was treated with thionyl chloride (0.1 ml). The mixture was kept at room temperature for 35 min, diluted with dichloromethane (2.5 ml), then poured into a stirred, saturated aqueous solution of potassium cyanide (2.5 ml). Ethanol (2.5 ml) was added immediately to the mixture which was then stirred for 2 h. The dichloromethane layer was washed with water and dilute sulphuric acid, then dried ($MgSO_4$) and evaporated. The indenone (**3**) (15 mg), isolated by chromatography on silica GF_{254} plates, developed with chloroform–ethyl acetate (95:5), had spectroscopic properties identical with those of the foregoing material.

Decomposition of Ethyl 2-Amino-1-oxoindene-3-carboxylate (**3**) *in Trifluoroacetic Acid.*—The indenone (**3**) (210 mg) was kept in trifluoroacetic acid (2 ml) at room temperature for 45 min. The mixture was evaporated to dryness and the residue dissolved in a little ethanol which was then evaporated. The residue was partitioned between dichloromethane and water containing a little sodium hydrogen carbonate. The organic products were separated on silica GF_{254} plates developed twice with chloroform. A fast-running blue component (26 mg) was identified as *diethyl 1,1′-dioxo-2,2′-iminodi-indene-3,3′-dicarboxylate* (**7**), m.p. 212—214 °C (from chloroform–ethanol) (Found: C, 69.0; H, 4.8; N, 3.15. $C_{24}H_{19}NO_6$ requires C, 69.1; H, 4.6; N, 3.4%); $\lambda_{max.}$(CCl_4) 577 nm (ε 8 360); $\nu_{max.}$(KBr) 1 723 and 1 675 cm^{-1}; δ($CDCl_3$) 10.0 (br s, 1 H, exchangeable with D_2O), 6.94—7.73 (m, 8 H), 4.42 (q, 4 H), and 1.42 (t, 6 H); *m/z* 417 and 371.

Crystal Structure Analysis of the Indenone (**3**).—*Crystal data.* $C_{12}H_{11}NO_3$, M = 217.2. Monoclinic, a = 14.988(1), b = 5.133(1), c = 15.192(3) Å, β = 112.73(1)°, U = 1 078.0 Å^3, Z = 4, D_c = 1.34 g cm^{-3}. F(000) = 456. Space group $P2_1/a$. μ = 7.2 cm^{-1} for Cu-K_α radiation, λ = 1.542 Å (1Å ≡ 10^{-10}m).

Deep purple, very thin plate-like crystals were obtained by the crystallisation of compound (**3**) from ether. A square plate measuring 0.1 mm along the edge was used for the measurement at room temperature (20 °C) of 2 048 independent *X*-ray intensities by a θ–ω scan on a Nonius CAD4 diffractometer, by use of graphite-monochromated Cu-K_α radiation. These comprised all possible reflections with sin θ/λ < 0.61 Å^{-1}. 976 Reflections having $F^2 > 2\sigma(F^2)$ were considered observed, where $\sigma(F^2) = [C + 4(B_1 + B_2) + 0.0009I^2]^{1/2}/(t_c Lp)$, where C is the total integrated count in time t_c; B_1 and B_2 are background counts; $I = C - 2(B_1 + B_2)$, Lp is the correction factor for Lorentz and polarisation effects, and $F^2 = I/(t_c Lp)$. Intensities were not corrected for absorption. Counting-coincidence errors were avoided by use of an attenuator on high intensities. Unit cell parameters were determined by least-squares refinement of diffractometer setting angles for 25 reflections. The sample crystal was twinned on [001] such that overlap of reflections from the two parts of the twin occurred

Table 1. Fractional atomic co-ordinates, with e.s.d.s in the least significant digits in parentheses. Hydrogen atoms have the suffixes of the atoms to which they are attached

	x/a	*y/b*	*z/c*
C(1)	0.399 5(6)	0.530 2(17)	0.263 5(6)
C(2)	0.437 4(5)	0.695 9(17)	0.339 4(6)
C(3)	0.389 6(6)	0.647 5(17)	0.408 4(7)
C(4)	0.318 4(6)	0.438 3(18)	0.365 6(6)
C(5)	0.252 6(7)	0.330 2(20)	0.399 3(7)
C(6)	0.193 3(8)	0.138 8(24)	0.341 9(8)
C(7)	0.200 8(7)	0.057 1(21)	0.259 6(7)
C(8)	0.266 4(6)	0.171 1(18)	0.227 6(6)
C(9)	0.325 3(6)	0.364 6(17)	0.280 2(6)
C(10)	0.428 1(6)	0.530 8(19)	0.183 8(6)
C(11)	0.416 2(10)	0.321 4(30)	0.040 2(8)
C(12)	0.356 8(11)	0.127 3(32)	−0.025 2(10)
N	0.505 0(5)	0.875 1(17)	0.355 5(7)
O(1)	0.411 5(5)	0.752 4(14)	0.485 2(5)
O(2)	0.385 7(4)	0.343 1(12)	0.120 0(4)
O(3)	0.484 6(4)	0.686 0(14)	0.174 1(4)
H(5)	0.244(9)	0.405(23)	0.475(8)
H(6)	0.165(5)	0.049(14)	0.361(5)
H(7)	0.155(6)	−0.036(18)	0.224(6)
H(8)	0.272(4)	0.117(13)	0.159(5)
H(11A)	0.474(6)	0.201(17)	0.078(6)
H(11B)	0.402(8)	0.475(22)	0.000(7)
H(12A)	0.341(9)	−0.033(28)	−0.005(8)
H(12B)	0.388(7)	0.062(20)	−0.064(7)
H(12C)	0.287(8)	0.155(20)	−0.061(7)
H(NA)	0.507(11)	0.882(31)	0.281(11)
H(NB)	0.525(5)	0.964(14)	0.405(5)

Table 2. Bond lengths (Å) in compound (**3**), with e.s.d.s in the least significant digits in parentheses

C(1)–C(2)	1.367(13)	C(1)–C(9)	1.497(12)
C(1)–C(10)	1.432(13)	C(2)–C(3)	1.500(13)
C(2)–N	1.320(12)	C(3)–C(4)	1.476(13)
C(3)–O(1)	1.210(12)	C(4)–C(5)	1.391(13)
C(4)–C(9)	1.393(12)	C(5)–C(6)	1.385(16)
C(5)–H(5)	1.26(12)	C(6)–C(7)	1.363(16)
C(6)–H(6)	0.76(8)	C(7)–C(8)	1.384(13)
C(7)–H(7)	0.84(10)	C(8)–C(9)	1.364(13)
C(8)–H(8)	1.11(7)	C(10)–O(2)	1.341(11)
C(10)–O(3)	1.213(12)	C(11)–C(12)	1.45(3)
C(11)–O(2)	1.456(14)	C(11)–H(11A)	1.04(9)
C(11)–H(11B)	0.97(12)	C(12)–H(12A)	0.94(14)
C(12)–H(12B)	0.95(10)	C(12)–H(12C)	0.99(12)
N–H(NA)	1.14(16)	N–H(NB)	0.83(8)

whenever h = O. A correction factor for the ($0kl$) intensities was determined by measuring a number of non-overlapping intensities from both parts of the twin. Computations were carried out on I.C.L. 2976 and Gould S.E.L. 32/27 computers at Glasgow University; the principal computer programs used are listed in ref. 7. Atomic scattering factors were taken from ref. 8.

Structure determination. The formula corresponds to the asymmetric unit, so that the molecule has no crystallographic symmetry, and all atoms are in general positions. The structure was solved by the MULTAN program, the hydrogen atoms being located in difference-Fourier maps calculated during the anisotropic least-squares refinement, which reduced R to a final value of 0.089 for the observed reflections, with R' 0.137 [$R' = (\Sigma w\Delta^2/\Sigma w|F_o|^2)^{1/2}$]. All isotropic hydrogen parameters were included in the refinement. The function minimised was $\Sigma w\Delta^2$, where $w = 1/\sigma^2(F_o)$, $\Delta = ||F_o| - |F_c||$. A difference-Fourier map computed from the final structure factors for the observed reflections showed no peaks or holes of magnitude > 0.4 e A^{-3}.

Table 3. Selected bond angles (°) in compound (**3**)

C(2)–C(1)–C(9)	107.7(8)	C(2)–C(1)–C(10)	123.3(8)
C(9)–C(1)–C(10)	129.0(8)	C(1)–C(2)–C(3)	109.3(8)
C(1)–C(2)–N	129.0(9)	C(3)–C(2)–N	121.7(9)
C(2)–C(3)–C(4)	105.8(8)	C(2)–C(3)–O(1)	125.1(9)
C(4)–C(3)–O(1)	129.0(9)	C(3)–C(4)–C(5)	128.5(8)
C(3)–C(4)–C(9)	107.9(8)	C(5)–C(4)–C(9)	123.6(9)
C(4)–C(5)–C(6)	115.1(9)	C(5)–C(6)–C(7)	122.5(11)
C(6)–C(7)–C(8)	120.9(10)	C(7)–C(8)–C(9)	119.3(9)
C(1)–C(9)–C(4)	109.3(8)	C(1)–C(9)–C(8)	132.0(8)
C(4)–C(9)–C(8)	118.7(8)	C(1)–C(10)–O(2)	113.4(8)
C(1)–C(10)–O(3)	123.7(9)	O(2)–C(10)–O(3)	122.9(8)
C(12)–C(11)–O(2)	108.5(12)	C(2)–N–H(NA)	98.7(79)
C(2)–N–H(NB)	122.2(48)	H(NA)–N–H(NB)	137.8(93)
C(10)–O(2)–C(11)	116.3(9)		

Table 4. Some torsion angles (°) in compound (**3**)

C(9)–C(1)–C(2)–C(3)	−0.3(7)
C(2)–C(1)–C(9)–C(8)	179.8(14)
C(10)–C(1)–C(2)–C(3)	178.5(12)
C(2)–C(1)–C(10)–O(2)	176.6(13)
C(10)–C(1)–C(9)–C(4)	−177.4(13)
C(9)–C(1)–C(10)–O(2)	−4.9(8)
C(1)–C(2)–C(3)–C(4)	−0.7(8)
N–C(2)–C(3)–C(4)	179.3(12)
C(2)–C(3)–C(4)–C(5)	−177.0(13)
O(1)–C(3)–C(4)–C(5)	7.2(10)
C(3)–C(4)–C(5)–C(6)	178.7(15)
C(3)–C(4)–C(9)–C(8)	179.6(12)
C(9)–C(4)–C(5)–C(6)	0.5(10)
C(4)–C(5)–C(6)–C(7)	1.8(10)
C(6)–C(7)–C(8)–C(9)	1.1(10)
C(7)–C(8)–C(9)–C(4)	1.1(9)
O(3)–C(10)–O(2)–C(11)	4.3(10)
C(2)–C(1)–C(9)–C(4)	1.3(8)
C(9)–C(1)–C(2)–N	179.7(13)
C(10)–C(1)–C(2)–N	−1.5(9)
C(2)–C(1)–C(10)–O(3)	−3.8(9)
C(10)–C(1)–C(9)–C(8)	1.1(10)
C(9)–C(1)–C(10)–O(3)	174.7(15)
C(1)–C(2)–C(3)–O(1)	175.4(13)
N–C(2)–C(3)–O(1)	−4.6(10)
C(2)–C(3)–C(4)–C(9)	1.4(8)
O(1)–C(3)–C(4)–C(9)	−174.4(14)
C(3)–C(4)–C(9)–C(1)	−1.7(7)
C(5)–C(4)–C(9)–C(1)	176.9(12)
C(5)–C(4)–C(9)–C(8)	−1.9(9)
C(5)–C(6)–C(7)–C(8)	−2.6(10)
C(7)–C(8)–C(9)–C(1)	−177.3(15)
C(1)–C(10)–O(2)–C(11)	−176.1(12)
C(12)–C(11)–O(2)–C(10)	−174.6(14)

Results

Atomic co-ordinates and their estimated standard deviations are in Table 1. Temperature factors and bond angles are available as a Supplementary Publication (SUP. No. 56120, 3pp.).* Structure factors are available from the editorial office on request. Tables 2—4 show the bond lengths, selected bond angles, and selected torsion angles. The labelling of the atoms is shown in the Figure.

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* For details of the Supplementary Publications Scheme see Instructions for Authors (1985) in *J. Chem. Soc., Perkin Trans. 1*, 1985, Issue 1.

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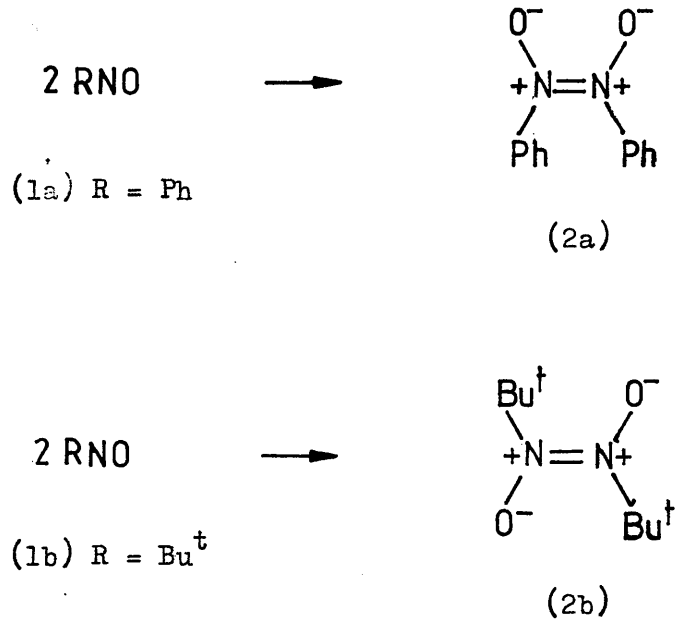
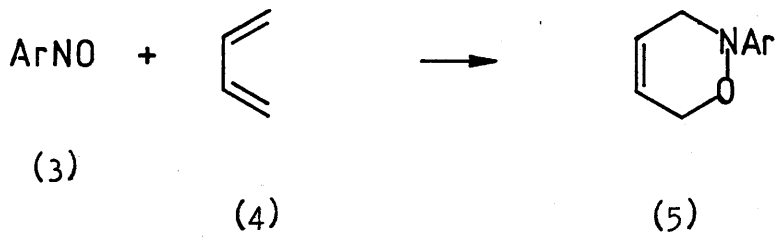
PART TWO

TRANSIENT

C-NITROSOCARBONYL COMPOUNDS



Scheme 1



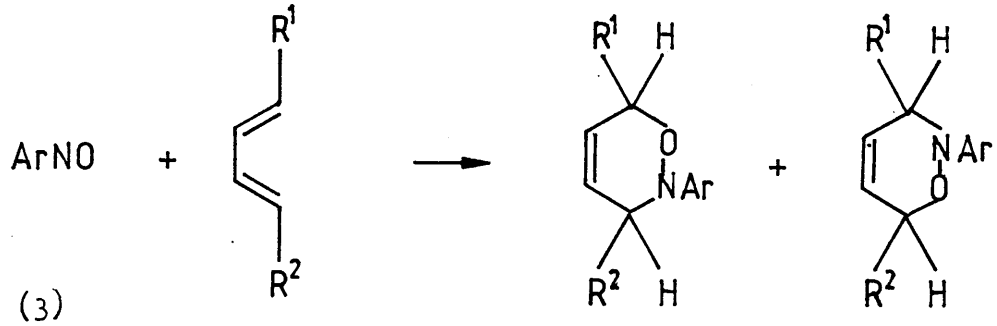
Scheme 2

1. Introduction

1.1. Electrophilic C-Nitroso Compounds

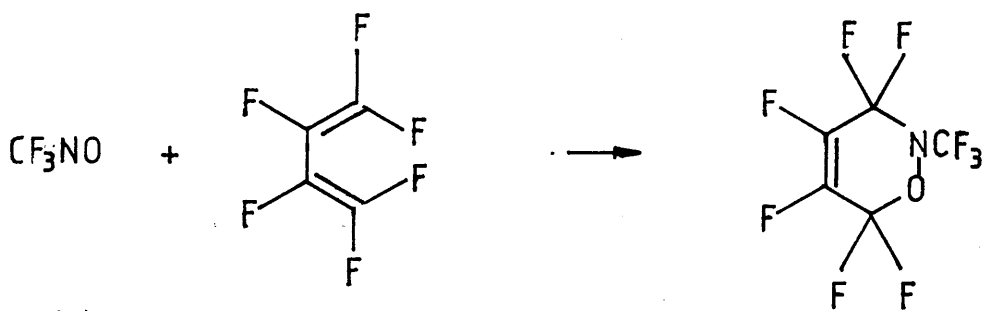
Our earlier work with Reissert compounds required the use of nitrosobenzene and 2-methyl-2-nitrosopropane for the preparation of several aminoindenones. Such nitroso compounds (1) (Scheme 1) are isolated as almost colourless solid dimers (2), which dissociate freely and reversibly in solution. Nitrosobenzene is greenish in solution, and the dimer occurs in the cis form (2a). 2-Methyl-2-nitrosopropane is blue in solution, and the dimer occurs in the trans form (2b). This difference between the two dimers has been investigated by Gowenlock and Luettke[2]. These well-known compounds served as a bridge to the present work in which newer types of nitroso-compounds were studied.

That C-nitroso-compounds can form Diels-Alder adducts with conjugated dienes was first reported by Wichterle[3] in 1947, and later by Arbuzov[4] in 1948. Hamer and Ahmad[5], by 1967, had made great progress in this field. Their findings, and those of Kresze et al.[6], showed that nitroso-arenes (3) can react with simple dienes, like butadiene (4), to give 1,2-oxazines (5) (Scheme 2) in good yield. Kresze et al.[6] studied the effect of various dienes, with substituents (R^1 and R^2) (Scheme 3), on the structure of the resulting oxazines (7a and 7b). A selection of their results is given overleaf. This demonstrates the manner in which an electron-withdrawing group on the diene can influence the regio-chemistry of the product.



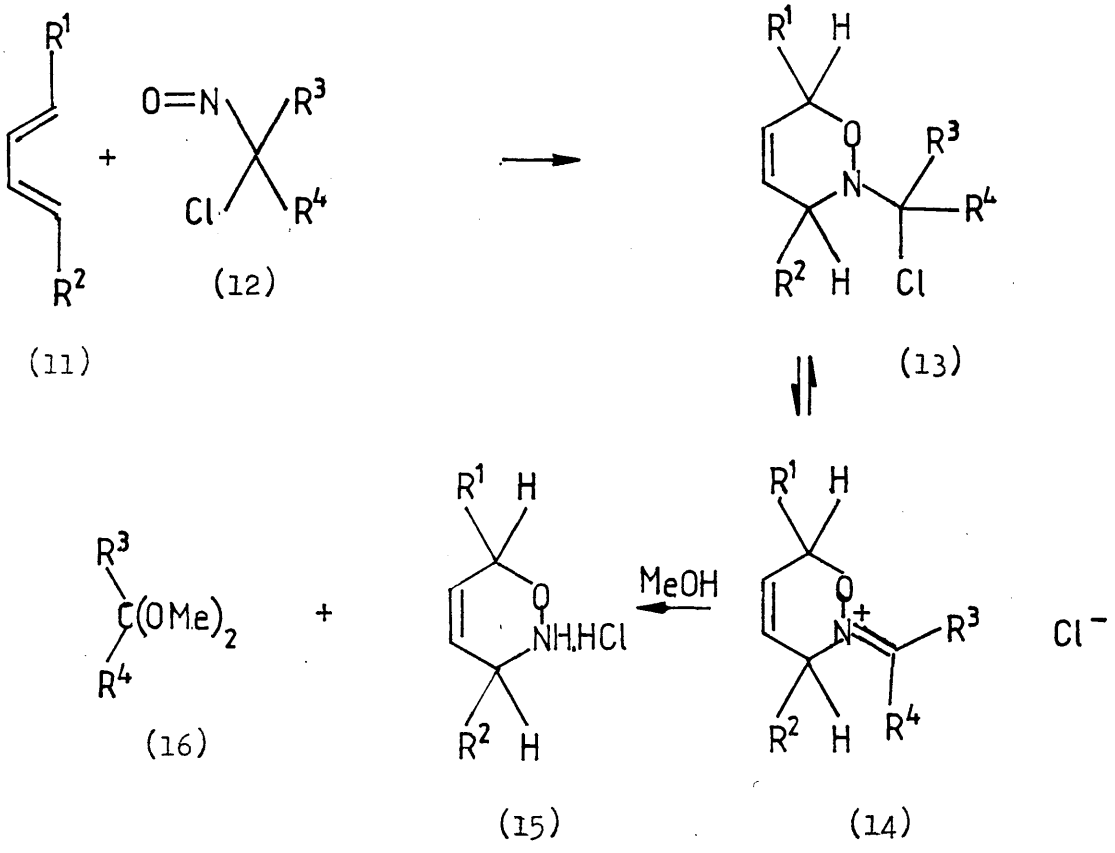
(3) (6) (7a) (7b)

Scheme 3

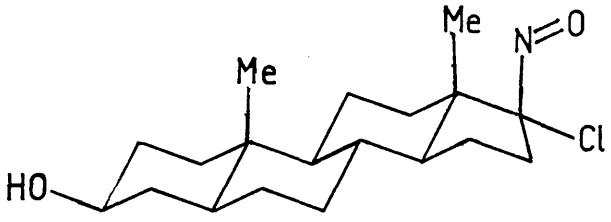


(8) (9) (10)

Scheme 4

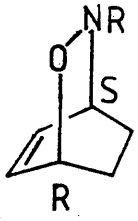


Above Outline of research study. The actual development is given below. For an earlier report of a related study see reference 8.

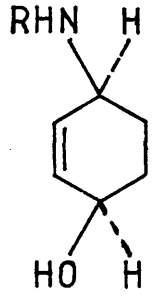


(17)

(18)



(19) a; R = H.HCl
b; R = COPh



(20) a; R = H
b; R = COPh

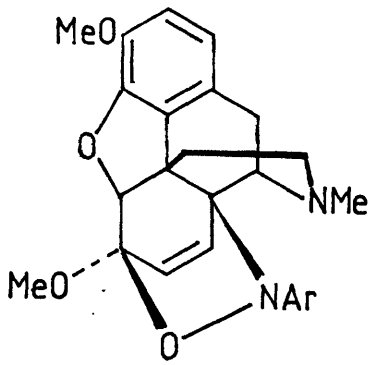
Scheme 5

C-NO bond may be suppressed due to a rigid molecular framework, and bulky groups in the vicinity of the C(Cl)NO moiety (vid. 17, Scheme 5). The chosen diene, in its least hindered orientation, then attacks, preferentially, one side of the nitroso group. In the case of an enantiomerically pure nitroso derivative, this results in diasterioselectivity, if the 1,3-diene is substituted in 1-, or 1,4-position.

One of the chiral nitroso compounds, chosen as models, was 17-chloro-17-nitroso-3β-hydroxy-5α-androstane (17) in the 17α-chloro-17β-nitroso configuration. Cyclohexa-1,3-diene (18) was the model diene. The reaction was performed in chloroform solution in the presence of methanol. An optically active adduct (19a) was isolated from the reaction mixture in 69% yield, with an enantiomeric excess of at least 95%. The parent adduct (19a) was benzoylated to give (19b). Reductive cleavage of the N-O bond gave (20a) and (20b). Sabuni *et al.* suggested that it might be possible to extend this type of Diels-Alder reaction to the use of 1,3-cyclohexadienes already containing heteroatom substituents in positions 5 and 6.

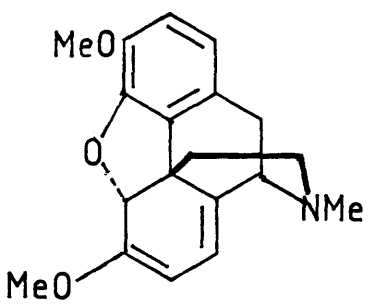
The adduct (19b) of nitrosocarbonylbenzene (PhCONO) has been prepared by Kirby and his co-workers[9], who oxidised benzohydroxamic acid (PhCONHOH) in the presence of cyclohexa-1,3-diene. Other adducts of nitrosocarbonylbenzene, prepared similarly, are discussed later.

In 1979, Kirby *et al.*[10] prepared adducts (22) of thebaine (21) with nitrosoarenes (3) (Scheme 6). They observed that a



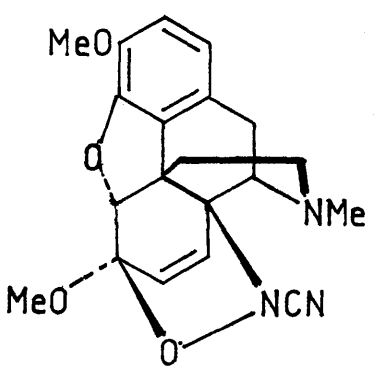
ArNO
(3)

(22)



thebaine (21)

nitrosyl cyanide
NCNO (23)



(24)

Scheme 6

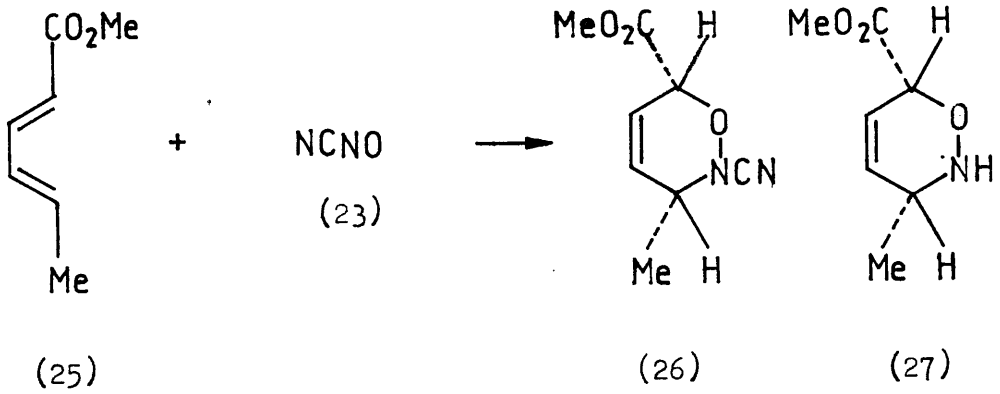
solution of the colourless nitrosobenzene adduct, after a short period at room temperature, acquired a green tint. They demonstrated that this colour was due to the presence of some of the nitrosobenzene monomer, and so proved that the reaction of the nitroso compound with the diene is reversible. The dissociation is diminished by electron-withdrawing groups, such as nitro, and enhanced by electron-donating groups, such as dimethylamino. The following approximate percentage dissociations (0.5 M solutions in deuteriochloroform at 35 °C) were reported.

Table 2

Dissociation of adducts of thebaine with p-Substituted Nitrosobenzenes

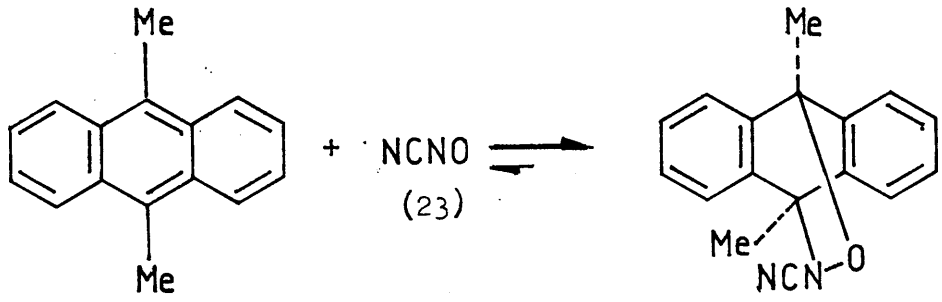
p-Substituent on Nitrosobenzene	Dissociation (%)
NO_2	0
Cl	0
Nil	10
Me	35
NMe_2	100

Nitrosyl cyanide is a dienophile with a strong electron-withdrawing group. How this compound can be transferred from its adduct with 9,10-dimethylanthracene to other dienes, is reported in the next section.



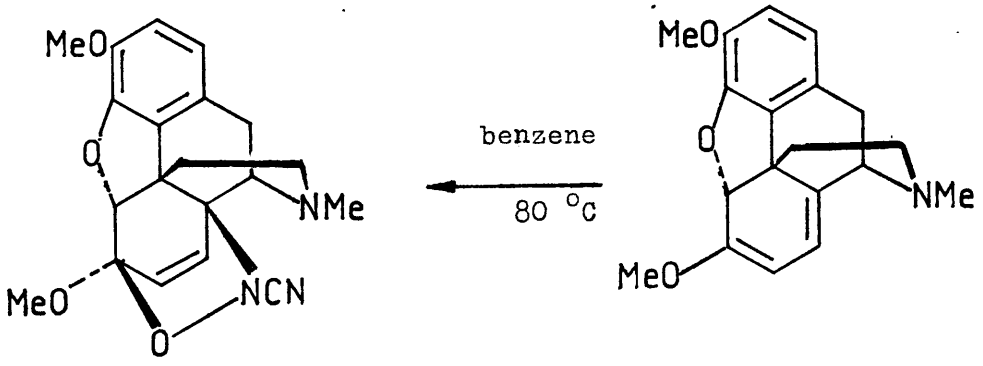
(25) (26) (27)

Scheme 7



(28) (29)

+



\+ DMA (28)

(24) thebaine (21)

Scheme 8

1.2. Nitrosyl Cyanide

Horsewood and Kirby[11a] reported in 1971 the reactions of the blue-green gas, nitrosyl cyanide (NCNO) (23). This reactive dienophile and the conjugated diene thebaine (21) (Scheme 6) gave the adduct (24). Similar cycloadditions were observed[11b] with other dienes. The identities of some of these adducts were confirmed by their synthesis *via* other routes. One such adduct (26) was prepared in 70% yield from methyl *trans*-*trans*-sorbate (25) (Scheme 7). This was important because the product was identical with that obtained from the parent oxazine (27) of known[12] structure and stereochemistry. Thus nitrosyl cyanide behaved like other *C*-nitroso-compounds, at least in this case, and added *cis* to the diene system with the preferred orientation shown.

Nitrosyl cyanide reacted[11c] with 9,10-dimethylanthracene (DMA) (28) to form the stable crystalline adduct (29). When this was heated with thebaine in benzene at 80°C, rapid and quantitative intermolecular transfer of the nitroso compound to thebaine was observed (Scheme 8) with the formation of the thebaine adduct (24) and liberation of DMA. This transfer reaction was followed kinetically in benzene at 40°C by observing the formation of DMA (absorption at 385 nm). First-order kinetics were observed with a rate constant, $k = 6.8 \times 10^{-5}\ s^{-1}$, using a 4 mM concentration of thebaine. The rate was not particularly sensitive to the initial concentration of thebaine. It appears that, under these

conditions, the DMA adduct dissociates (the rate determining step) into DMA and nitrosyl cyanide, and the latter is captured rapidly, and effectively irreversibly, by the reactive diene, thebaine.

1.3. C-Nitrosocarbonyl Compounds

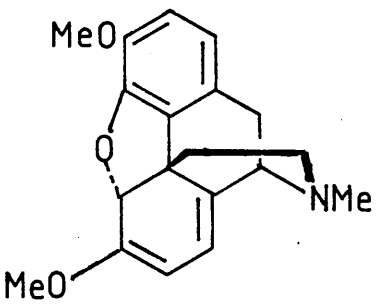
The highly dienophilic character of nitrosyl cyanide suggested to Kirby *et al.*[13] that nitrosocarbonyl compounds, RCONO, would be reactive dienophiles, which might form cycloadducts with various conjugated dienes. They were aware that nitroso compounds, RCONO and ROCONO, had been proposed[14] as reactive intermediates in reactions involving the oxidation of hydroxamic acids, RCONHOH and ROCONHOH. It had been assumed, that, if such nitroso compounds really did exist, they were too unstable to be isolated, or even detected. In all these experiments, product formation involved cleavage of the CO-N bond. For example, Prosser *et al.*[15] studied the thermal decomposition of octadecyl azidoformate in dimethyl sulphoxide (DMSO) at 120°C and postulated the following reaction scheme to account for the formation of Me_2S, CO_2, and NO.

$$ROCON_3 \longrightarrow ROCON + N_2$$

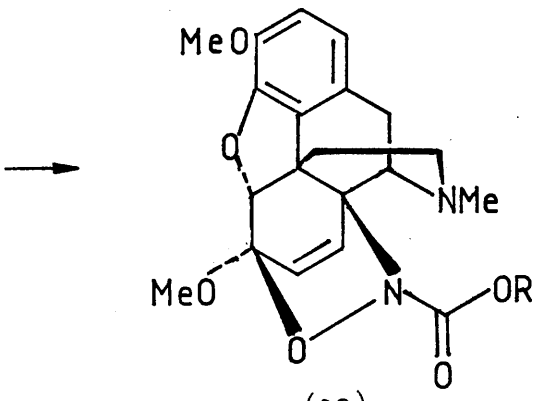
$$ROCON + Me_2SO \longrightarrow ROCONO + Me_2S$$

$$ROCONO \longrightarrow R^{\bullet} + CO_2 + NO$$

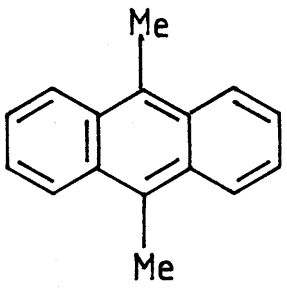
RCONHOH (30) ⟶ RCONO (31) ⟶ Nitrosocarbonyl Adducts



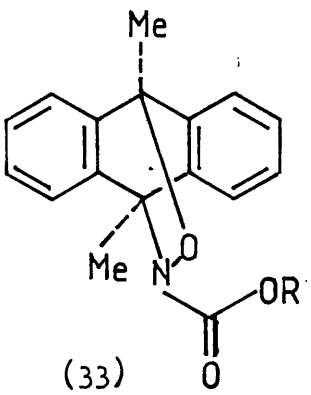
(21)



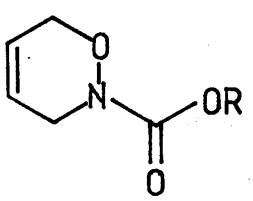
(32)



(28)



(33)



a; R = Me
b; R = Ph

(34)

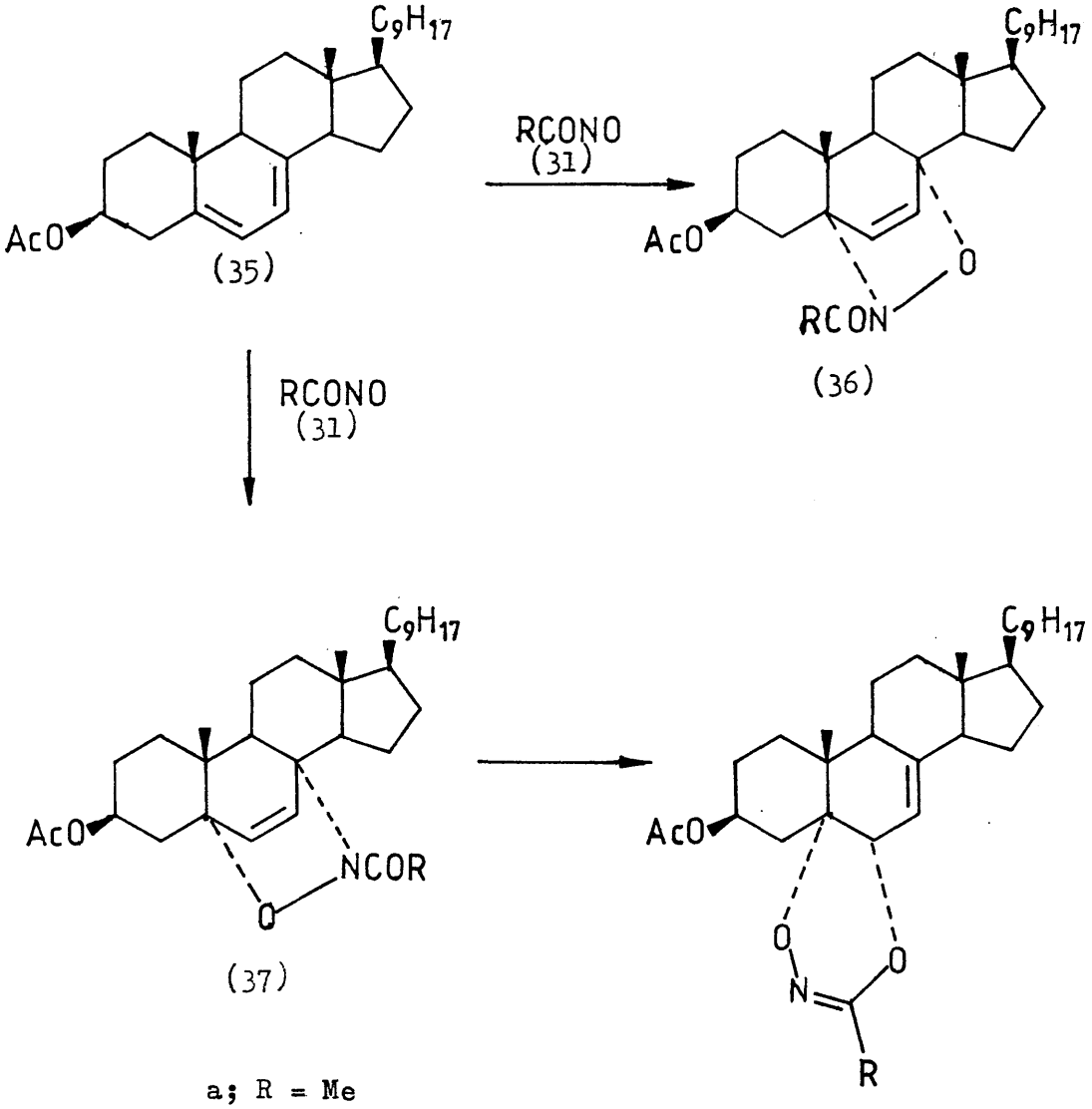
Scheme 9

Nevertheless, Kirby *et al.*[13] decided on the oxidation of hydroxamic acids with the intention of trapping any fugitive nitroso compounds with suitable dienes. Hydroxamic acids are readily prepared, and may be oxidised under mild conditions with a variety of reagents[16]. Tetraethylammonium periodate[17], which is freely soluble in both water and organic solvents, was chosen as a convenient mild oxidant. For the initial experiment, the alkaloid thebaine (21) was selected as the conjugated diene, since the spectroscopic and chemical properties of its adducts with C-nitroso compounds were well understood[1,10,11].

The method adopted by Kirby *et al.* involved the addition of the hydroxamic acid, e.g. (30a) to a solvent system of ethyl acetate and aqueous buffer (pH 6) at 0 °C, containing tetraethylammonium periodate and thebaine. One hour later, the reaction mixture was basified. When the solvent was removed, the cycloadduct (32a) was obtained in 96% yield, suggesting a remarkably efficient capture of the putative intermediate, nitrosocarbonylmethane (31a). Other adducts (33a) and (34a) were prepared using DMA and 1,3-butadiene. The formation of these three adducts did not necessarily imply the involvement of nitrosocarbonylmethane as a discrete intermediate. Confirmatory evidence was obtained by transferring, in benzene under reflux conditions, nitrosocarbonylmethane from the DMA adduct (33a) to thebaine, resulting in the formation of the original adduct (32a). Benzohydroxamic acid (30b) gave a similar set of adducts (32b, 33b, 34b).

hydroxamic acids (RCONHOH)
(30)

ergosteryl acetate (35) + nitrosocarbonyl compounds (31) ⟶ adducts

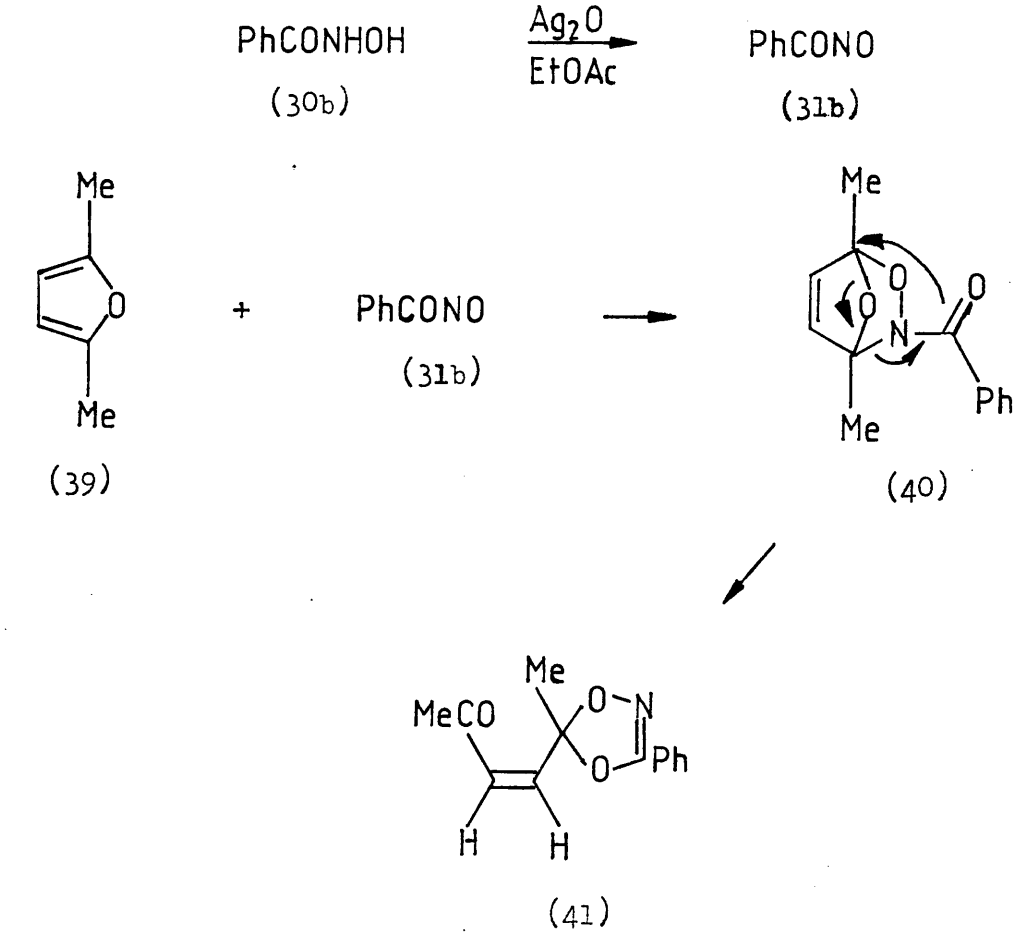


a; R = Me
b; R = Ph
c: R = 4-BrC_6H_4
d; R = 4-$MeOC_6H_4$
e; R = 4-$NO_2C_6H_4$

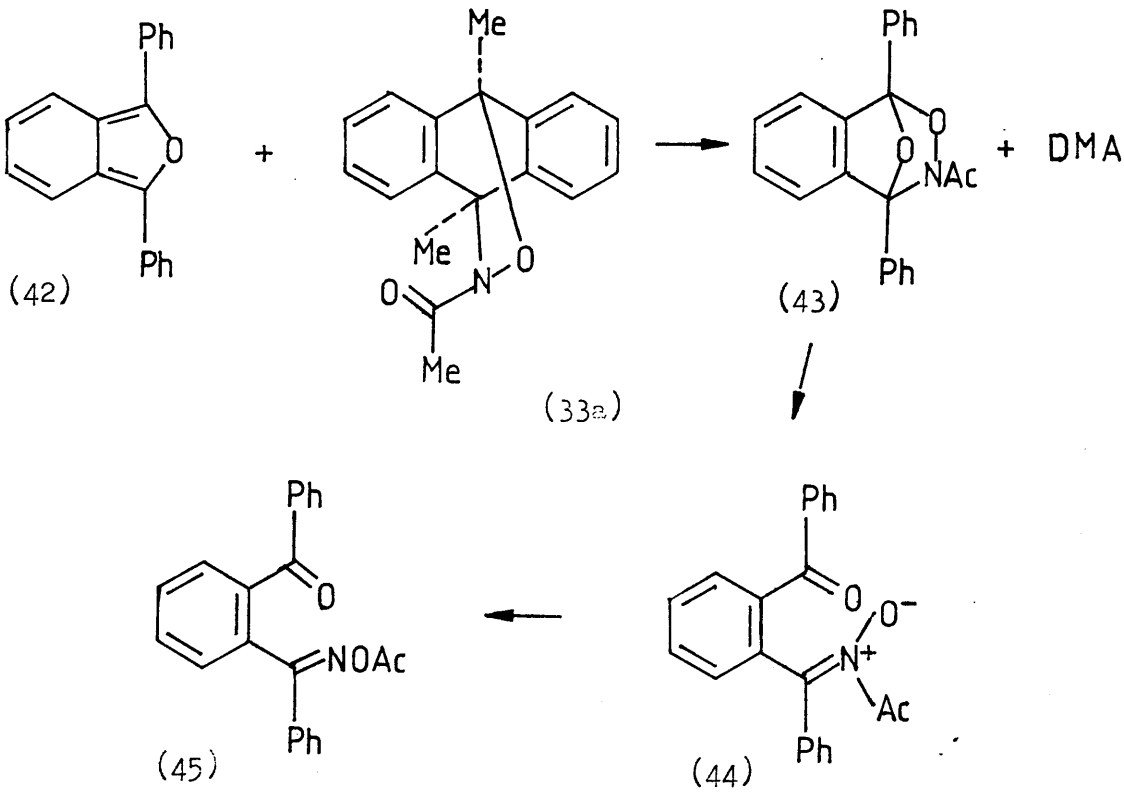
Scheme 10

Here, also, the nitroso compound could be transferred from its DMA adduct (33b) to thebaine. These transfer reactions were followed kinetically. The DMA adducts (33a) and (33b) dissociated at 60 °C in benzene with first-order kinetics, $k = 4.4 \times 10^{-5}$ s^{-1} and $k = 5.4 \times 10^{-5}$ s^{-1} respectively. Dissociation was much slower than for the nitrosyl cyanide adduct (29), since the latter showed $k = 6.8 \times 10^{-5}$ s^{-1} at 40 °C rather than 60 °C. However the DMA adduct (29) of nitrosyl cyanide was stable to prolonged heating in benzene in the absence of any trapping agent, whereas the adducts (33a) and (33b) decomposed slowly. The decomposition of the benzoyl adduct (33b) in benzene at 80 °C resulted in the formation of benzoic anhydride (73% yield) accompanied by the evolution of N_2O (detected mass spectrometrically)[18]. The mechanism of this reaction is still not clear.

The unsymmetrical diene, ergosteryl acetate (35), can form two types of adducts[18], as exemplified by (36) and (37). The adducts of type (37) can rearrange to form dioxazines (38) (Scheme 10). However, adducts (37a), (38a), and (37c) were not isolated as products in this series of experiments. The fact that several types of adducts could be prepared, with ergosteryl acetate as the diene, provided another powerful argument for the existence of carbonylnitroso compounds. An outline of the argument is as follows. a) Benzohydroxamic acid (30b) was oxidised in the presence of ergosteryl acetate to yield, under kinetic control, the two adducts (36b) and



Scheme 11

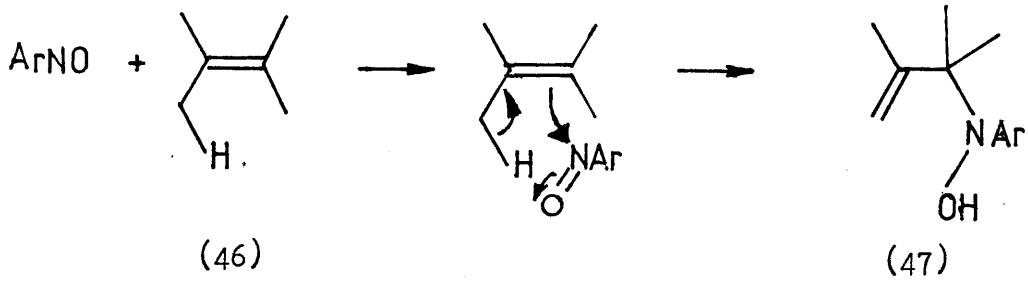


Scheme 12

and (38b) in the yield ratio 1:1.7. b) Ergosteryl acetate was heated with the DMA adduct (33b) in benzene at 60 °C. This time the isomeric adducts (36b) and (38b) were obtained in the yield ratio 1:1.6. Such close agreement in the product ratios is evidence that a common intermediate, nitrosocarbonylbenzene (31b) is involved.

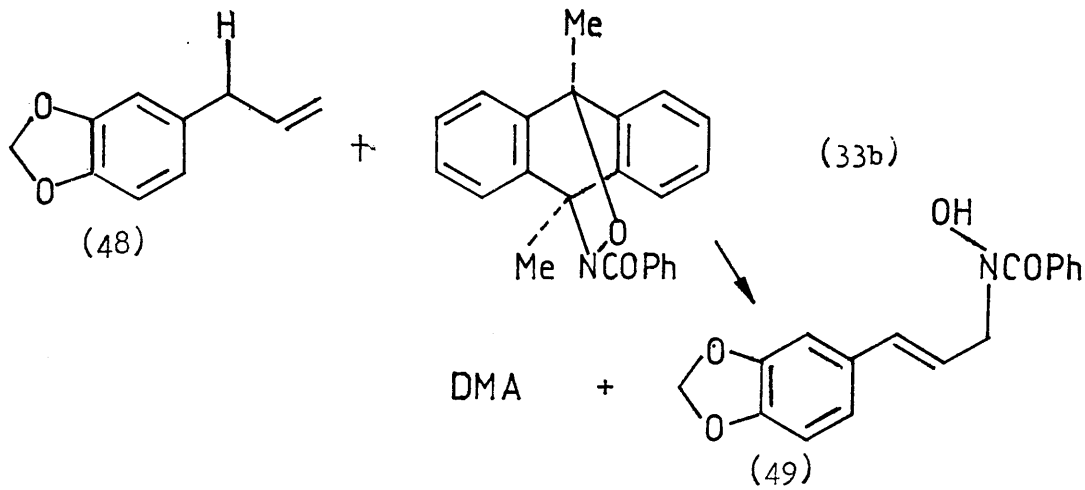
Another example of a reaction which gave rise to an unexpected product[19] is provided by the oxidation of benzohydroxamic acid (30b) using silver oxide in an ethyl acetate solution of the diene, 2,5-dimethylfuran (39). A nearly quantitative yield of (41) was obtained instead of the 1,4-cycloadduct (40). Almost certainly, the latter was an intermediate (Scheme 11).

Cycloadducts of nitrosocarbonyl compounds and DMA are especially useful for studies with co-reactants sensitive to the oxidising conditions in which nitroso compounds are generated directly from hydroxamic acids. Undesirable oxidation is avoided by transferring the 'pre-formed' nitroso compound from the appropriate DMA adduct to the sensitive co-reactant by simply heating the two substances in an inert solvent. For example[20], 1,3-diphenylisobenzofuran (42) and the DMA adduct (33a) of nitrosocarbonylmethane were heated in benzene under nitrogen. The oxime acetate (45), presumably from the expected cycloadduct, was obtained along with the liberated DMA, Scheme 12.



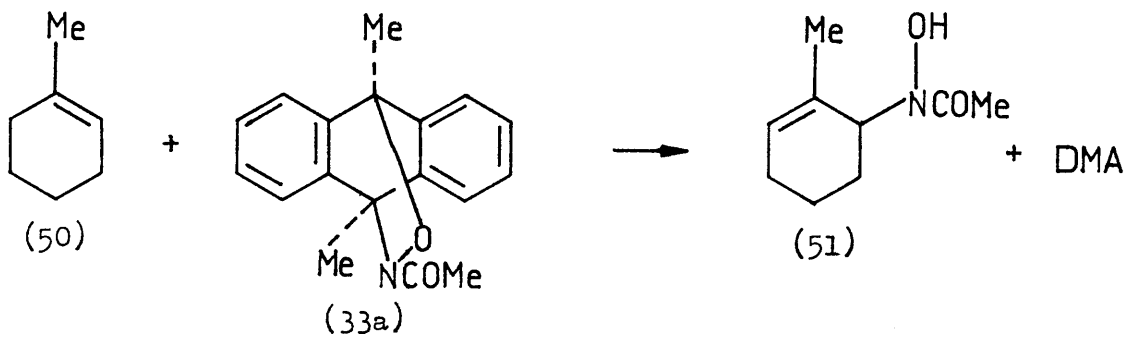
(46) (47)

Scheme 13



(48) (49)

Scheme 14



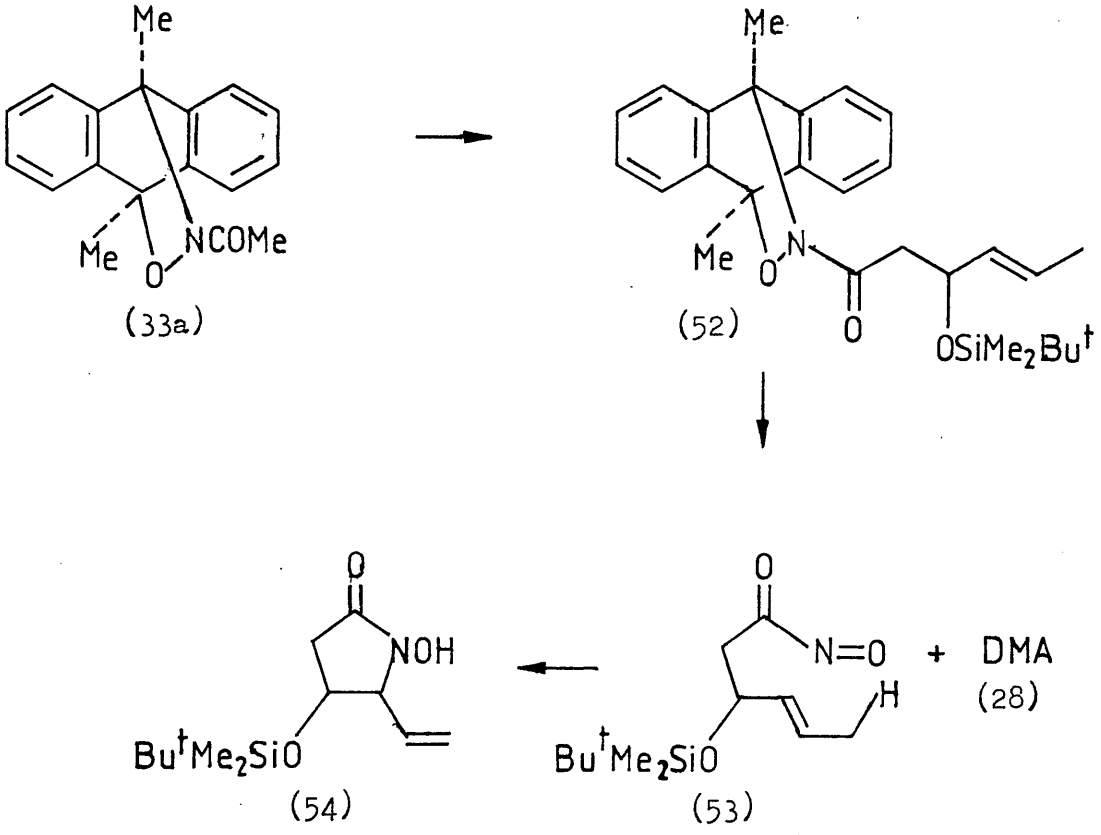
(50) (33a) (51)

Scheme 15

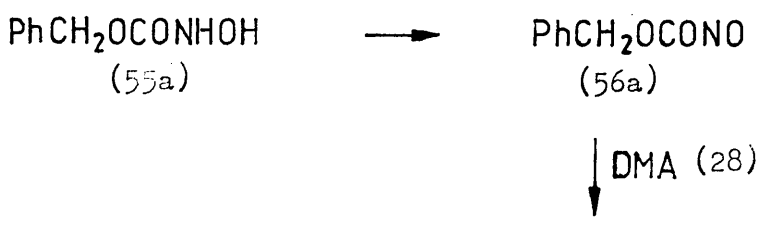
1.4. 'Ene' Reactions of C-Nitrosocarbonyl Compounds

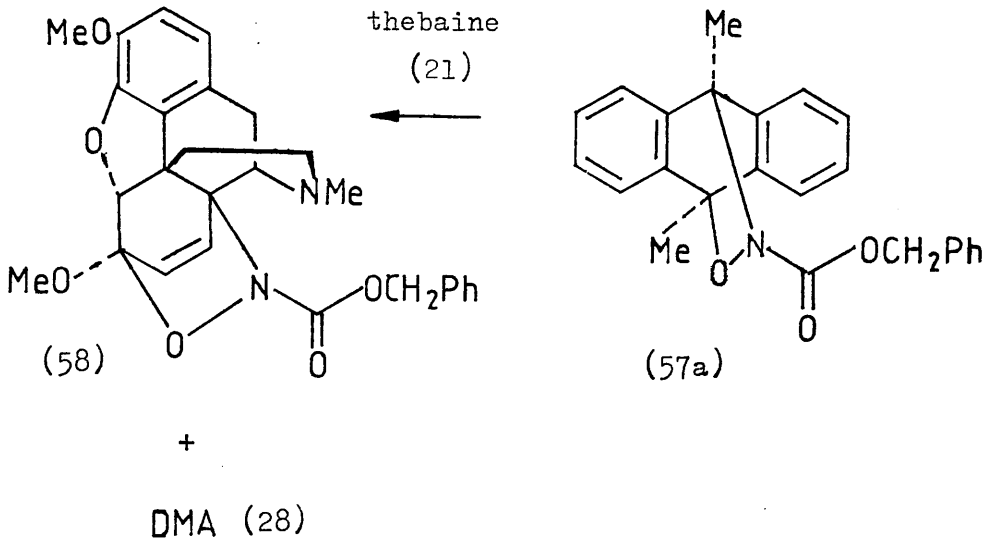
Nitrosoarenes can react with certain mono-olefins by an 'ene' process[21]. This is the addition of a compound with a double or triple bond, the enophile, to an olefin possessing an allylic hydrogen, the 'ene', and involves an allylic shift of one double bond, transfer of the allylic hydrogen to the enophile and bonding between the two unsaturated termini. Sullivan[22] and also Knight and Pepper[23] reported that various substituted nitrosobenzenes undergo such a reaction with 2-methylpent-2-ene and 2,3-dimethylbut-2-ene (46) to yield in the latter case, the unsaturated hydroxylamine intermediate (47) (Scheme 13). Corrie et al.[9] found that C-nitrosocarbonyl compounds, released thermally from their DMA adducts, react likewise with mono-olefins to form N-allyl hydroxamic acids, e.g., safrole (48) reacts with nitrosocarbonylbenzene to give (49) (Scheme 14). Keck et al.[24] attempted a series of intermolecular 'ene' reactions with olefins using the DMA adduct of nitrosocarbonylmethane (33a) for the thermal release of the nitroso compound (31a). Except in the case of simple olefins, these reactions gave complex mixtures of products. With 1-methylcyclohexene (50), the reaction proceeded as shown (Scheme 15). The 'ene' reactions of C-nitrosocarbonyl compounds are generally slow relative to their Diels-Alder addition to conjugated dienes.

Keck et al.[24] had become interested in the intramolecular 'ene' process as a possible methodology in the context of natural product synthesis. They pointed out that a large



Scheme 16



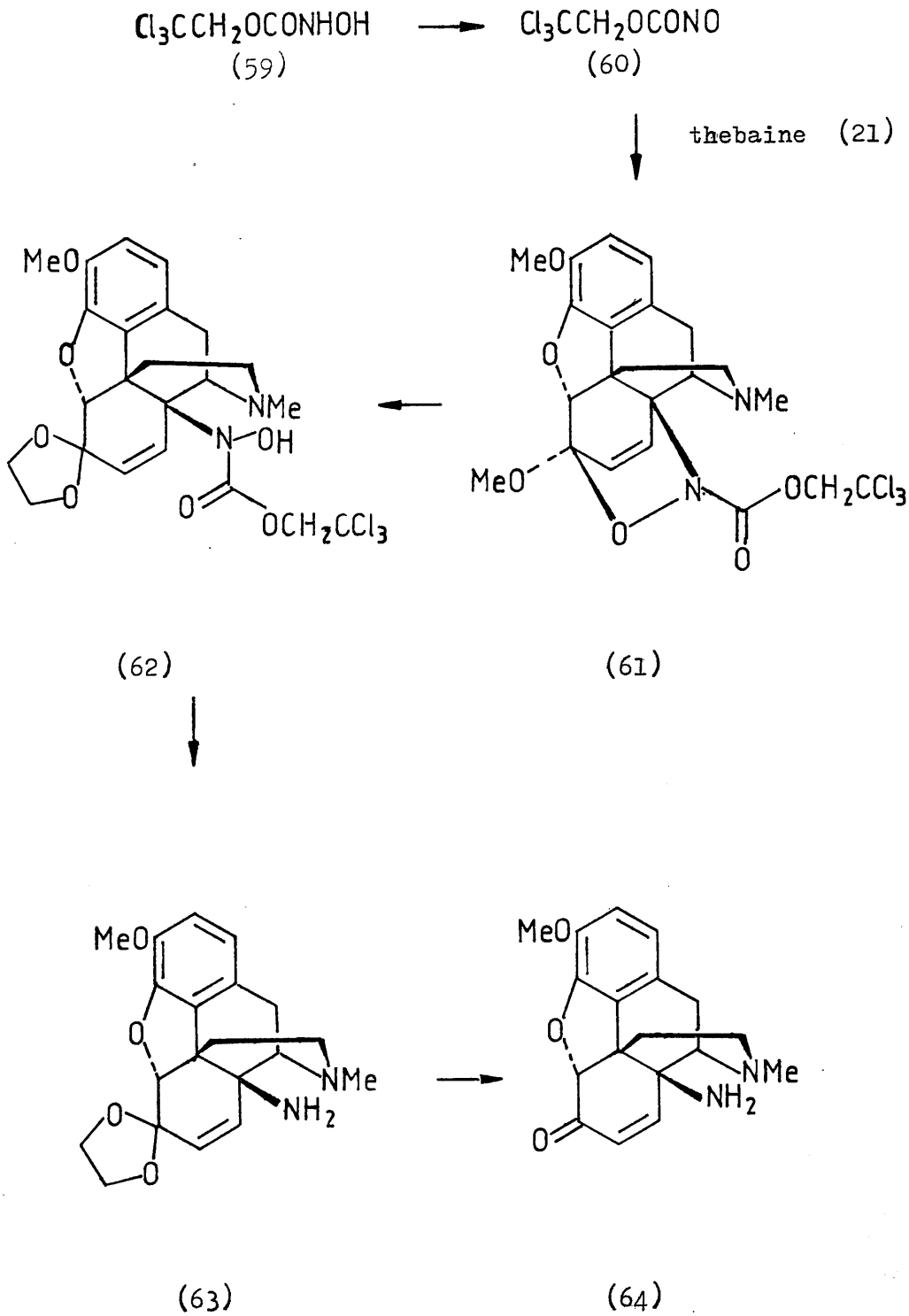


Scheme 17

number of alkaloids can be regarded as a carbocycle onto which a nitrogen-containing ring has been annulated. Their intramolecular 'ene' reactions afford a two-step path to the construction of such ring systems, the first step being the introduction of a protected acylnitroso group into a carbocyclic substrate, followed by a second step of thermal liberation of the enophile with concomitant 'ene' reaction. In all their syntheses they used the nitrosocarbonylmethane-DMA adduct (33a) in the form of its lithium enolate and condensed this with various aldehydes and ketones, silylating the resulting alkoxides. One example of their work, relevant to the present study is shown in Scheme 16.

1.5. C-Nitrosoformate Esters

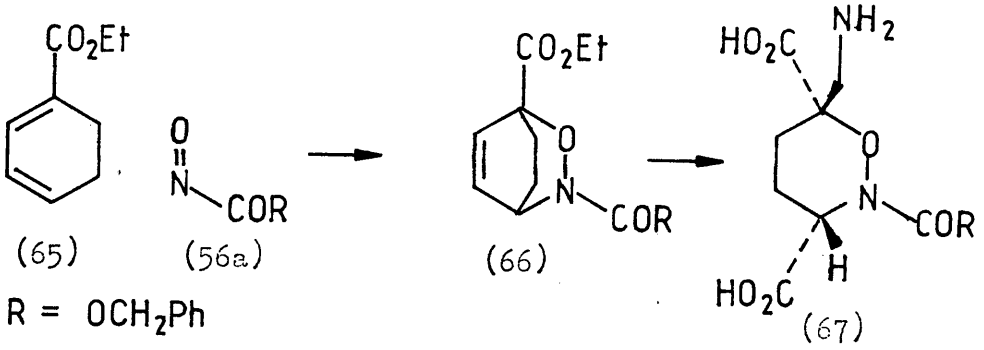
Kirby et al.[25] investigated the C-nitrosoformate esters, ROCONO, with the expectation that they, too, would behave as reactive dienophiles. Accordingly, N-hydroxycarbamic ester (55a) was oxidised with periodate in the presence of DMA to give the expected adduct (57a). Again, the expected transient nitrosoformate ($PhCH_2OCONO$) was transferred to thebaine when the DMA adduct was heated with the alkaloid. Dissociation of the DMA adduct was observed, as before, with a first-order rate constant k (60 °C in benzene) = $4.3 \times 10^{-4} s^{-1}$ for the release of DMA. This is about ten times that measured for the dissociation of the DMA adduct (33a) of nitrosocarbonylmethane[13]. However, once again, the authors found it impossible to detect any free nitroso compound by direct physical means.

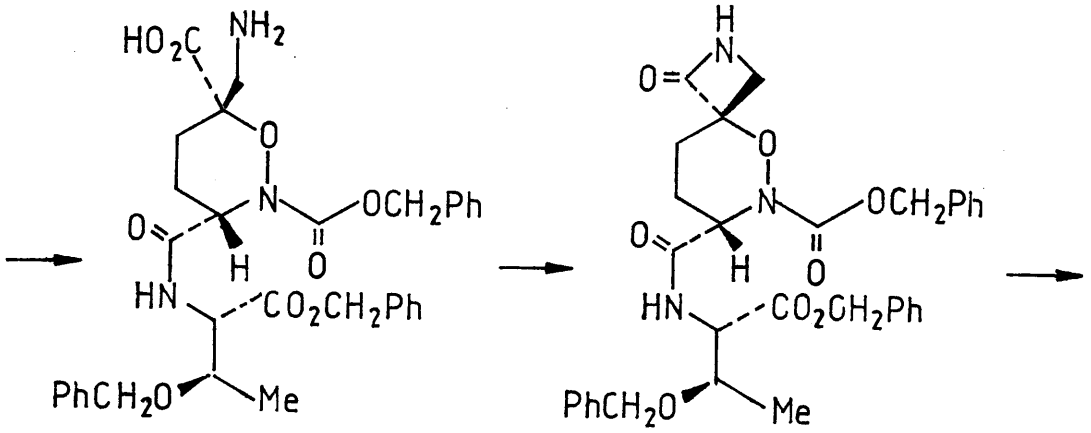

Cl3CCH2OCONHOH
(59)
Cl3CCH2OCONO
(60)
thebaine (21)
MeO
NMe
N-OH
OCH2CCl3
(62)
(61)
(63)
(64)

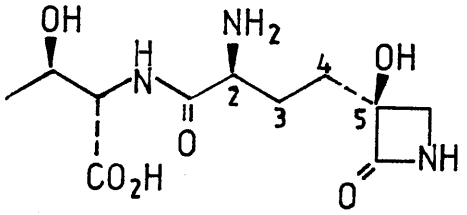
Scheme 18

In his review[1], Kirby forecast that C-nitrosoformate esters would prove to be well-suited to the synthesis of 4-aminoalcohols since they are readily prepared, and with the appropriate choice of alkoxy group, the derived cyclo-adducts (N-alkoxycarbonyloxazines) are readily de-acylated. One early, and important, illustration of his idea was presented by an improved synthesis of 14β-aminocodeinone[26]. The new route to the important precursor avoided the use of tetranitromethane, and there was an improvement in the overall yield. N-(2,2,2-Trichloroethoxycarbonyl)hydroxylamine (59) (Scheme 18), in aqueous sodium acetate, was oxidised by sodium periodate in the presence of thebaine to give the expected adduct (61). This was converted, at room temperature, by dry ethylene glycol containing hydrogen chloride, into the ethylene acetal (62). Thereafter, reduction ($Zn-NH_4Cl$), followed by acid hydrolysis gave the desired analgesic precursor (64).

Another application of nitrosoformate chemistry was employed by Baldwin *et al.*[27] in their synthesis of tabtoxin (70) (Scheme 19). In this work, the crucial stereochemical relationship between C(2) and C(5) in tabtoxin was achieved by the simultaneous formation of the C(2)-N, and C(5)-O bonds *via* a Diels-Alder reaction of benzyl nitrosoformate with ethyl cyclohexa-1,3-dienecarboxylate. This adduct (66) was obtained as a single regioisomer in 93% yield.







(70)

tabtoxin

Scheme 19

1.6. Carbonylnitrenes

A brief survey of the chemistry of nitrenes is given here as background to the study, described later, in which the possibility that nitrenes might be obtained by the deoxygenation of nitrosoformate esters was investigated.

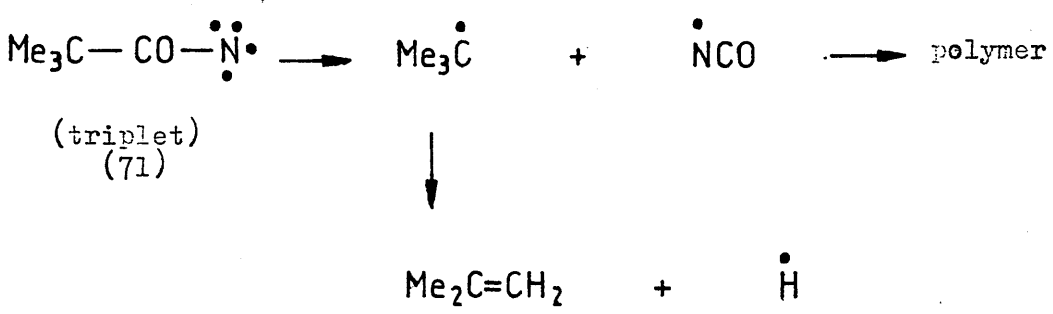
The use of nitrenes is one of the few ways in which a functional group can be introduced into an unactivated carbon centre, and, as such, it is potentially important as a method of forming heterocyclic systems by intramolecular insertion, for binding substrates to receptor sites in biological systems, and for functionalizing remote centres in steroids[28,29].

Nitrenes are the nitrogen analogues of carbenes. The most common method for their generation is the photolytic or thermal decomposition of azides, e.g.

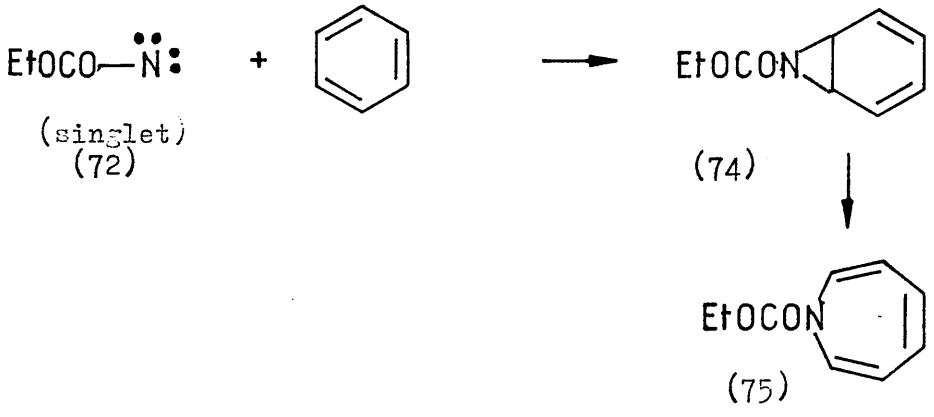
$$EtO\text{-}CO\text{-}N_3 \longrightarrow EtO\text{-}CO\text{-}N$$

Alkyl nitrenes have been isolated by trapping them in matrices at 4K, and aryl nitrenes, which are less reactive, can be trapped at 77K. Ultraviolet irradiation of ethyl azidoformate in a rigid matrix, at 4K, gave a product which was identified as the carbethoxy nitrene by its E.S.R. spectrum[30]. Nitrenes are usually formed in a singlet state, in which the electrons are spin coupled, and the ground state is a triplet, in which two electrons in separate orbitals have the same spin,

$$\underset{\text{(72), singlet (s)}}{R\ddot{C}O\ddot{N}:} \quad \text{and} \quad \underset{\text{(73), triplet (t)}}{R\ddot{C}O\ddot{N}\cdot}$$



Scheme 20

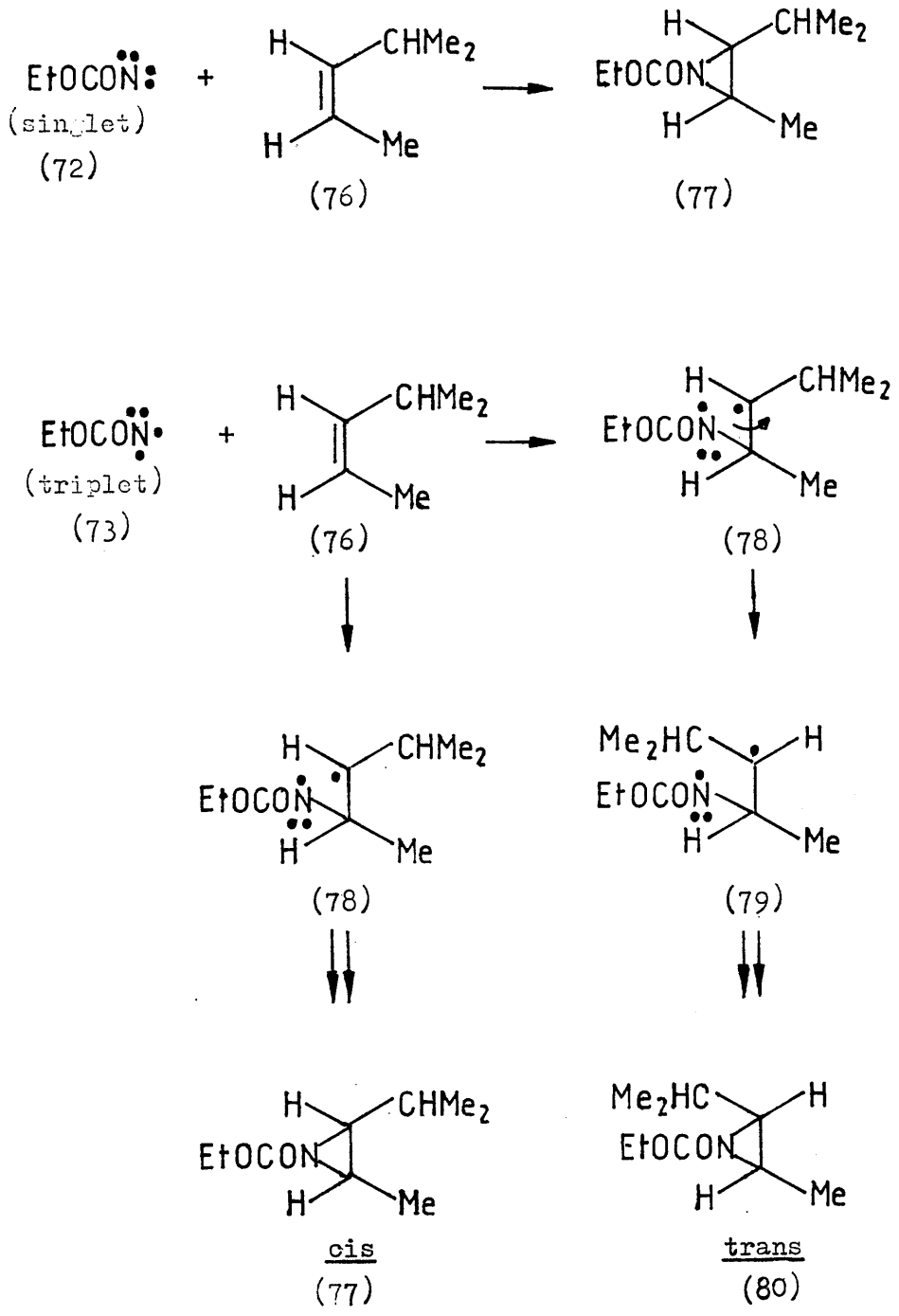


Scheme 21

The usual life of a nitrene is between 10^{-7} and 10^{-5} s but there are some which have lives of up to 1 s. Little is known about the ultimate fate of nitrenes which have not been consumed in intra- or intermolecular reactions. However, the fate of pivaloylnitrene (71) has been investigated. This, when generated in unreactive solvents (dichloromethane, neopentane), decomposes to give isobutene[31] and a gum. The latter seems to be a polymer of HCNO and isobutene, formed, perhaps, as shown in Scheme 20. In the absence of a suitable reactant, singlet carbethoxy nitrene, Et OCON, crosses to the triplet state and then, at least in the gas phase, seems to dissociate into ethoxy and cyanato radicals[32].

Dehydrogenation Reactions Dehydrogenations by carbonyl nitrenes have been reported[33] for a variety of systems. For example, cyclohexane gives cyclohexene, and it seems that both hydrogens at the adjacent carbons are removed simultaneously. Triplet nitrene seems to be primarily responsible.

Insertion into C-H Bonds This is typical of singlet nitrenes. The yields depend on the activity of the C-H bonds of the substrate. The lower this activity, the more of the nitrene crosses over to the triplet state and becomes lost to the insertion reaction. An example of an insertion reaction is given by n-octadecyl azidoformate, $C_{18}H_{37}OCON_3$, which, when heated in a cyclohexane substrate[34], gave a 52% yield of the cyclohexylurethane, $C_{18}H_{37}OCONHC_6H_{11}$.


EtOCON:
(singlet)
(72)
+
H
CHMe2
H
Me
(76)
H
CHMe2
EtOCON
H
Me
(77)
EtOCON•
(triplet)
(73)
+
H
CHMe2
H
Me
(76)
H
CHMe2
EtOCON
H
Me
(78)
H
CHMe2
EtOCON
H
Me
(78)
Me2HC
H
EtOCON
H
Me
(79)
H
CHMe2
EtOCON
H
Me
cis
(77)
Me2HC
H
EtOCON
H
Me
trans
(80)

Scheme 22

Reactions with Benzene Carbethoxynitrene (72) generated in benzene solution by thermolysis[35], expands the benzene ring to give N-carbethoxyazepine (75). This reaction is ascribed to singlet nitrene (Scheme 21).

Reactions with Olefins Carbethoxy nitrene (72) in solution adds readily to carbon-carbon double bonds[36] to give N-carbethoxyaziridines (77) and (80) (Scheme 22). The addition is stereospecific for the singlet and nonstereospecific for the triplet. A singlet nitrene takes part in a concerted reaction and yields a cis-aziridine (77). On the other hand, a triplet nitrene gives a mixture of the cis and trans compounds, because there is time for rotation about the C-C bond (78) before the ring is formed.

Phosphinimide Formation C-Nitroso compounds are known to react with phosphines to yield phosphinimides[20,37,38], derived, at least formally, from the corresponding nitrenes

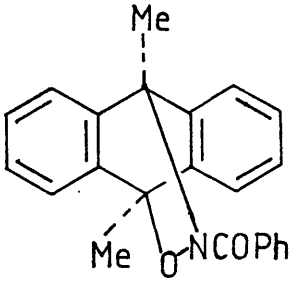
$$Ph_3P + O{=}NCN \longrightarrow Ph_3P^{+}O\text{-}\bar{N}\text{-}CN$$

$$\longrightarrow Ph_3PO + \ddot{:}NCN$$

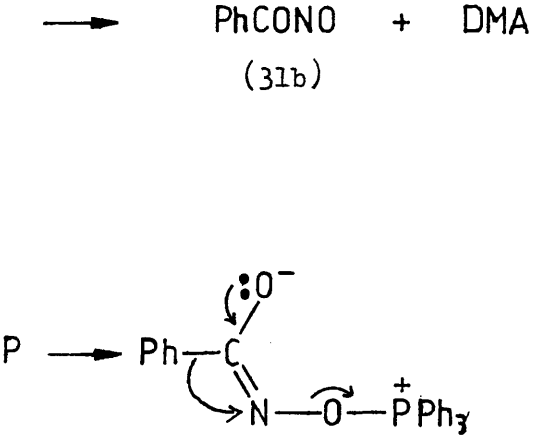
$$Ph_3P + \ddot{:}NCN \longrightarrow Ph_3P{=}N\text{-}CN$$

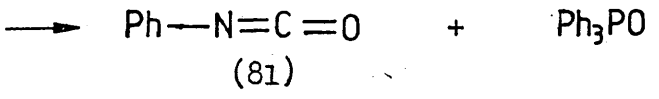
Nitrenes and Isocyanates

The thermolysis of carbonyl azides, $RCON_3$, involves a Curtius rearrangement giving exclusively isocyanates, R-N = C = O, (Scheme 23). According to Lwowski[28], all attempts to trap nitrene intermediates in such experiments have failed. However, azidoformates ($ROCON_3$) do give nitrenes on thermolysis. As early as 1890, Curtius[39] reported that,



(33b)

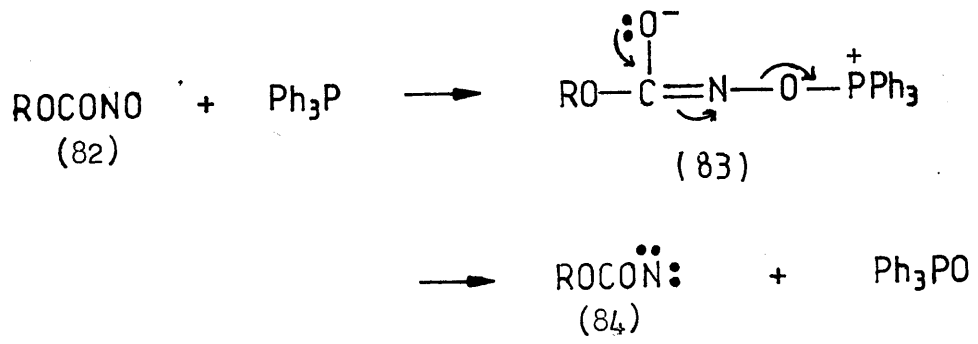




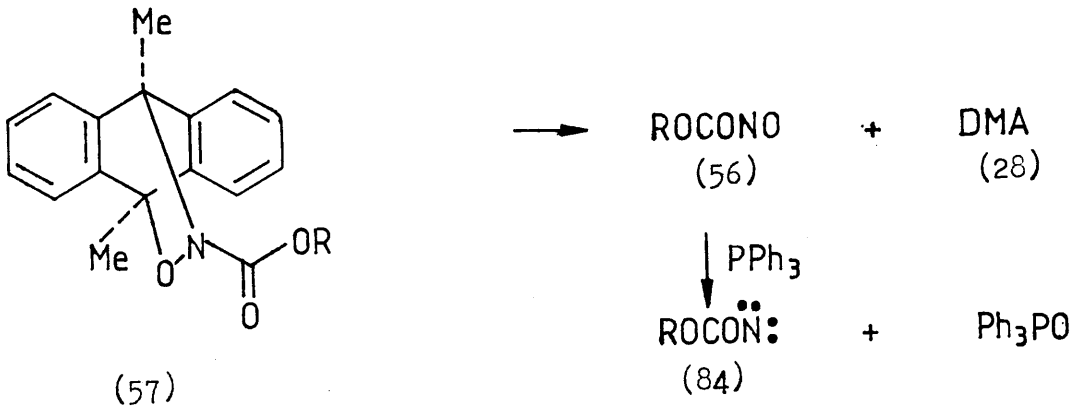
Scheme 23

whereas carbonyl azides (and the related species in the Hoffman and Lossen rearrangements), readily undergo 1,2 shifts via assumed nitrene intermediates, carboxy and sulphonyl azides give nitrenes which do not rearrange during the reaction process. These latter types of azides were classified by Curtius as 'fixed' (starre).

The possibility of nitrene formation resulting from the deoxygenation of nitrosoformates is discussed in Section 2.2.

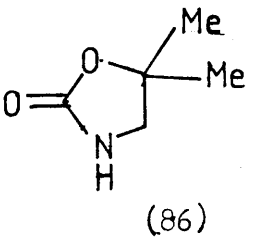


Scheme 24



a; R = $PhCH_2$

b; R = Bu^t



Scheme 25

2. Discussion

2.1. Objectives of the Present Study

The study concerned the synthesis and chemistry of a number of C-nitrosocarbonyl compounds. The practicability of using C-nitrosoformate esters as nitrene precursors was to be examined. Work on a series of intramolecular 'ene' reactions of transient, allylic and homoallylic C-nitrosoformate esters was to be completed. Finally, representatives of a new class of transient dienophiles, the C-nitrosoformamides, formed by the oxidation of N-hydroxyureas, were to be prepared, and their properties investigated.

2.2. Nitrene Formation from Transient C-Nitrosoformate Esters

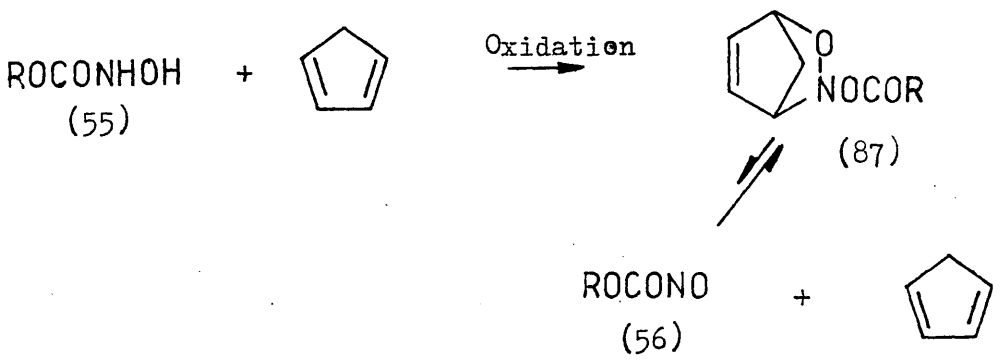
Lwowski's[28] contribution to the chemistry of nitrenes, formed by the pyrolysis of acyl azides, has already been indicated. Meth-Cohn,[41] and his co-workers, are involved in this field and part of their research has resulted in compounds which are similar to some obtained in this study.

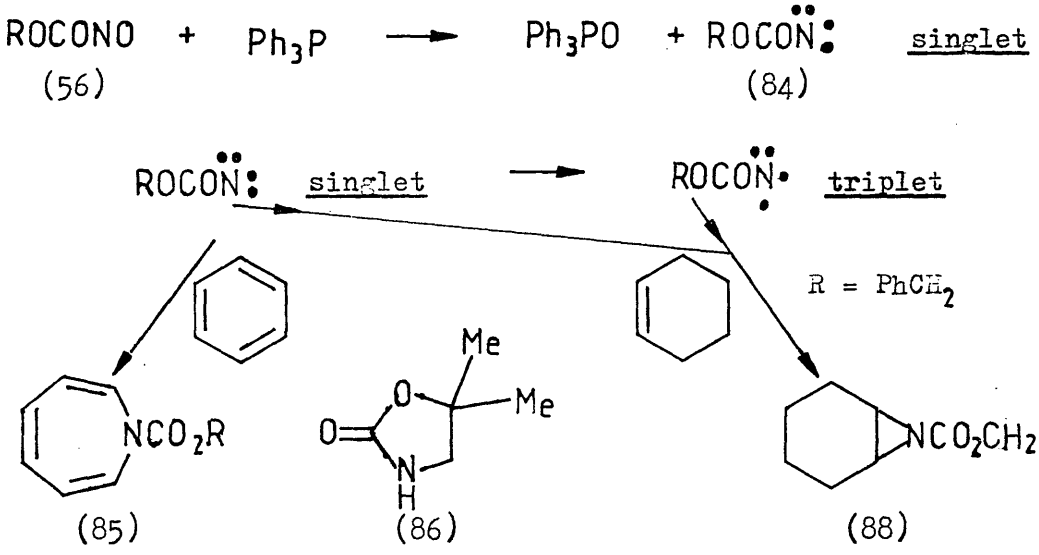
Corrie et al.[40] found that the C-nitrosocarbonyl compound (31b), generated by dissociation of its DMA adduct (33b), was deoxygenated by triphenylphosphine with the formation of the isocyanate (81) (Scheme 23). The DMA adducts of other transitory acyl nitroso compounds behaved likewise. They then turned their attention to the DMA adducts of the nitrosoformate esters to find out if such nitroso compounds would behave as the equivalents of Curtius's 'starre' azides and serve as sources of nitrene intermediates (Scheme 24). The adduct (57a) of DMA and benzyl nitrosoformate was prepared

and found to be largely unchanged after prolonged (24 h) heating in benzene at 80 °C. Such conditions had led to the complete decomposition of the corresponding adducts of nitrosocarbonylmethane (33a) and nitrosocarbonylbenzene (33b). However, when the benzyl nitrosoformate adduct (57a) was heated in benzene at 60 °C, in the presence of triphenylphosphine (1 mol. equivalent), decomposition ensued with the formation of triphenyl phosphine oxide and DMA. First-order kinetics were observed for the release of DMA, and the rate constant, $k = 4.5 \times 10^{-4}\ s^{-1}$, was similar to that measured for the reaction of the adduct with thebaine. Chromatographic separation of the reaction products from the DMA adduct (57a) gave the yellow N-benzyloxycarbonylazepine (85a) (22-32% yield from several experiments). Another set of similar experiments, using the DMA adduct (57b) of tert-butyl nitrosoformate (56b), gave N-t-butoxycarbonylazepine (85b) (6.6%). This was accompanied by 5,5-dimethyloxazolidin - 2-one (86) (4%).

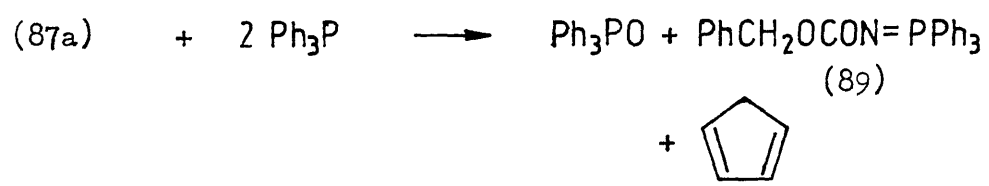
That part of the present study, which was concerned with the search for nitrenes from carbonylnitroso compounds now follows. With cyclopentadiene as the diene, adducts were prepared by the oxidation of the hydroxamic acids (55a) and (55b). The adducts (87a) and (87b) were then deoxygenated using triphenylphosphine[25] under various conditions, and the products were examined for compounds, the presence of which, would suggest the possibility of nitrenes as intermediates.

Deoxygenation of transient C- nitrosoformate esters using cyclopentadiene adducts.





Scheme 26



Scheme 27

Insertion into C-H Bonds. Kreher and Bockhorn[42] obtained 5,5-dimethyloxazolidin-2-one (86) from tert-butyl azidoformate via the corresponding nitrene (84b). With triphenylphosphine (1 equivalent) in benzene at 80°C, and in dichloromethane at 82 °C, the adduct (87b) of tert-butyl nitrosoformate gave the above oxazolidinone (86), but in low yield (4%), (Scheme 26). Both transient nitrosocompounds gave azepines: N-tert-butoxycarbonylazepine[42d] (85b), and benzyloxycarbonylazepine (85a) in yields of 6.6 and 19% respectively. These yellow liquids were identified by mass spectrometry, and by their n.m.r. spectra. A group of three multiplets in their ^{1}H n.m.r. spectra was easily recognisable, even when the crude reaction mixtures were examined: there was a rounded multiplet at δ ca. 5.5(3- and 6-H), a double of multiplets at ca. 5.8-5.9 (2- and 7-H), and a triplet of multiplets at ca. 6(4- and 5-H).

Reaction with Cyclohexene. When heated under reflux in cyclohexene containing triphenylphosphine, benzyl nitrosoformate gave what was probably the aziridine (88), in 12% yield (Scheme 26). However, this product was not fully characterised.

Phosphinimide Formation. The cyclopentadiene adduct of benzyl nitrosoformate (87a) (Scheme 27) was heated in dichloromethane at 80 °C in a sealed tube with two equivalents of triphenylphosphine. A small amount of triphenylphosphine benzyloxycarbonylimide (89) (2%) was isolated together with some starting material (87a) (5%).

Although, in this set of experiments, small quantities of products were isolated, it cannot be concluded that a

minor proportion of each nitroso compound had been deoxygenated. In fact, it was only in the phosphinimide experiment that any cyclopentadiene adduct survived. Always, the isolated products were accompanied by many other substances, too meagre in quantity to justify their isolation in the present circumstances. The yields of triphenylphosphine oxide proved that deoxygenation of the nitroso compounds had been achieved.

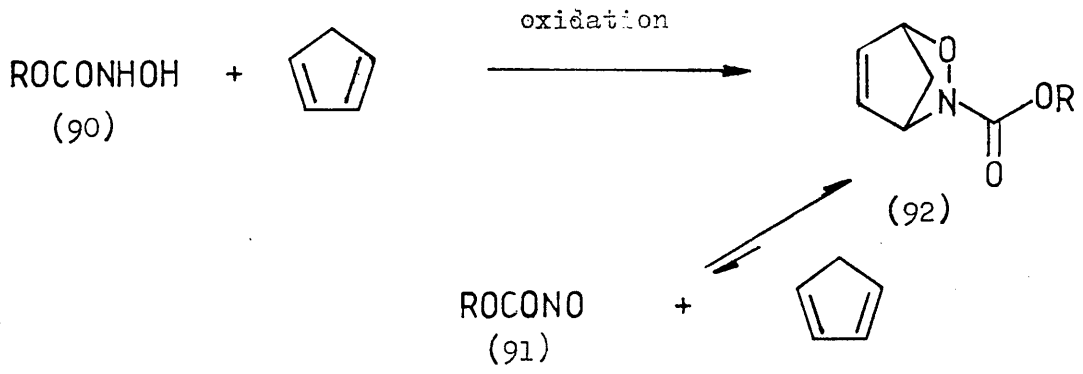
Without exception, the observed products can be accounted for by the nitrene mechanisms outlined in Section 1.6, and so one cannot discount, completely, nitrene formation. If nitrenes were not intermediates in these reactions, then certainly closely related entities had been present. From such a limited study it would be too much to expect that the presence of nitrenes would be established absolutely, when one realises that in other fields, in which nitrene formation is taken for granted (cf. acyl azides[43]), alternative mechanisms have been suggested. At present, the cyclopentadiene adducts of C-nitrosoformate esters do not appear to offer any advantage over those traditional precursors of alkoxycarbonylnitrenes, the acyl azides.

However these experiments did provide additional evidence that transient nitrosocompounds do exist, and that they react in the manner which would be expected of such a species.

2.3. Intramolecular 'Ene' Reactions of Transient Allylic and Homoallylic C-Nitrosoformate Esters

I. Open-Chain Esters

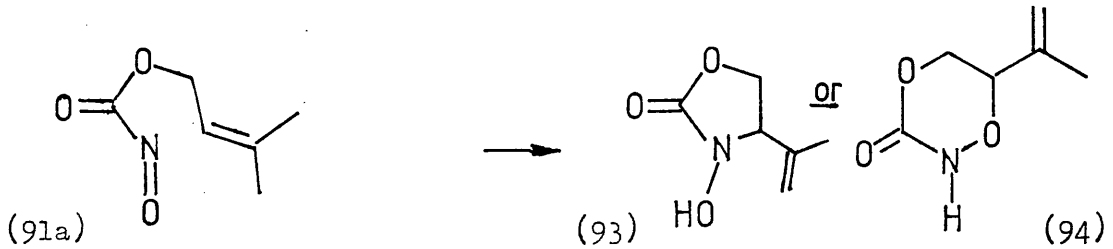
In order that the work carried out as part of the present study of the intramolecular 'ene' reactions of C-nitrosoformate

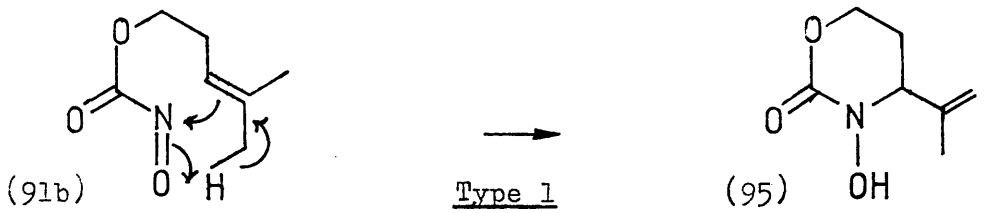


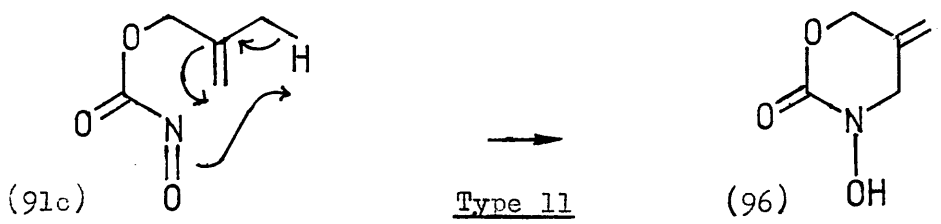
a; R = $Me_2C{=}CHCH_2$ c; R = $CH_2{=}C(Me)CH_2$

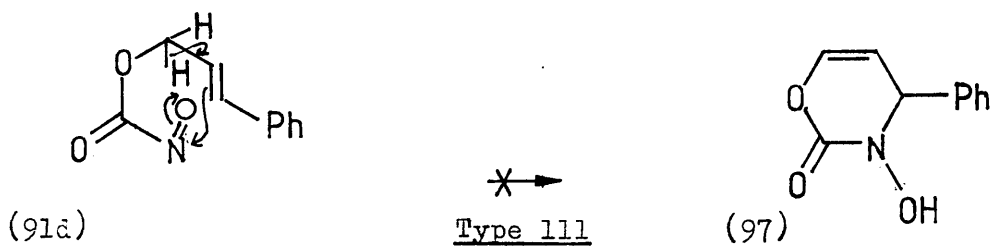
b; R = $Me_2C{=}CHCH_2CH_2$ d; R = $PhCH{=}CHCH_2$

Transient C-Nitrosoformate Esters — Products







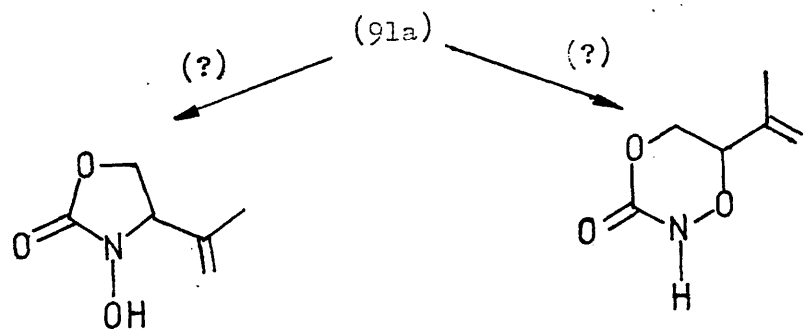


Scheme 28

esters, and the results obtained earlier by D. McLean[26a] can be seen as parts of the same project, there follows an outline in which, for the sake of completeness, the new facts are included. The discussion of the experiments which revealed these facts will follow shortly.

A number of transient allylic and homoallylic nitrosoformate esters were considered by McLean as possible illustrations of the three types of thermally induced concerted cyclisations recognised by Oppolzer and Snieckus[44] in which the enophilic part of the molecule would become linked by a bridge, either to the olefinic terminal (Type 1), the central atom (Type 11), or the allylic terminal (Type 111). McLean prepared the appropriate transient nitrosoformate esters (91a-c) by the periodate oxidation of the corresponding hydroxamic acids, and using cyclopentadiene, trapped them as adducts (92a-c). Cyclopentadiene had replaced the DMA used for trapping in previous studies, because the former is more readily available, and its volatility permits its easy removal from reaction mixtures. The reaction of (91b) proceeded, as expected, according to a Type 1 mechanism, but in the case of (91a) there were doubts as to the structure of the product. The available data supported both (93) and (94). During the present study, the true structure was found to be (93). Thus, here also, the predicted Type 1 mechanism had been revealed. The reaction mechanism involving (91c) was the expected Type 11. A Type 111 mechanism was sought by McLean using adduct (92d) of (E)-cinnamyl nitrosoformate (91d).

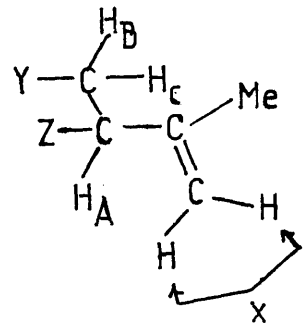
(92a) (91a)



(93) (94)

EtO—CO—NHOEt

(98)



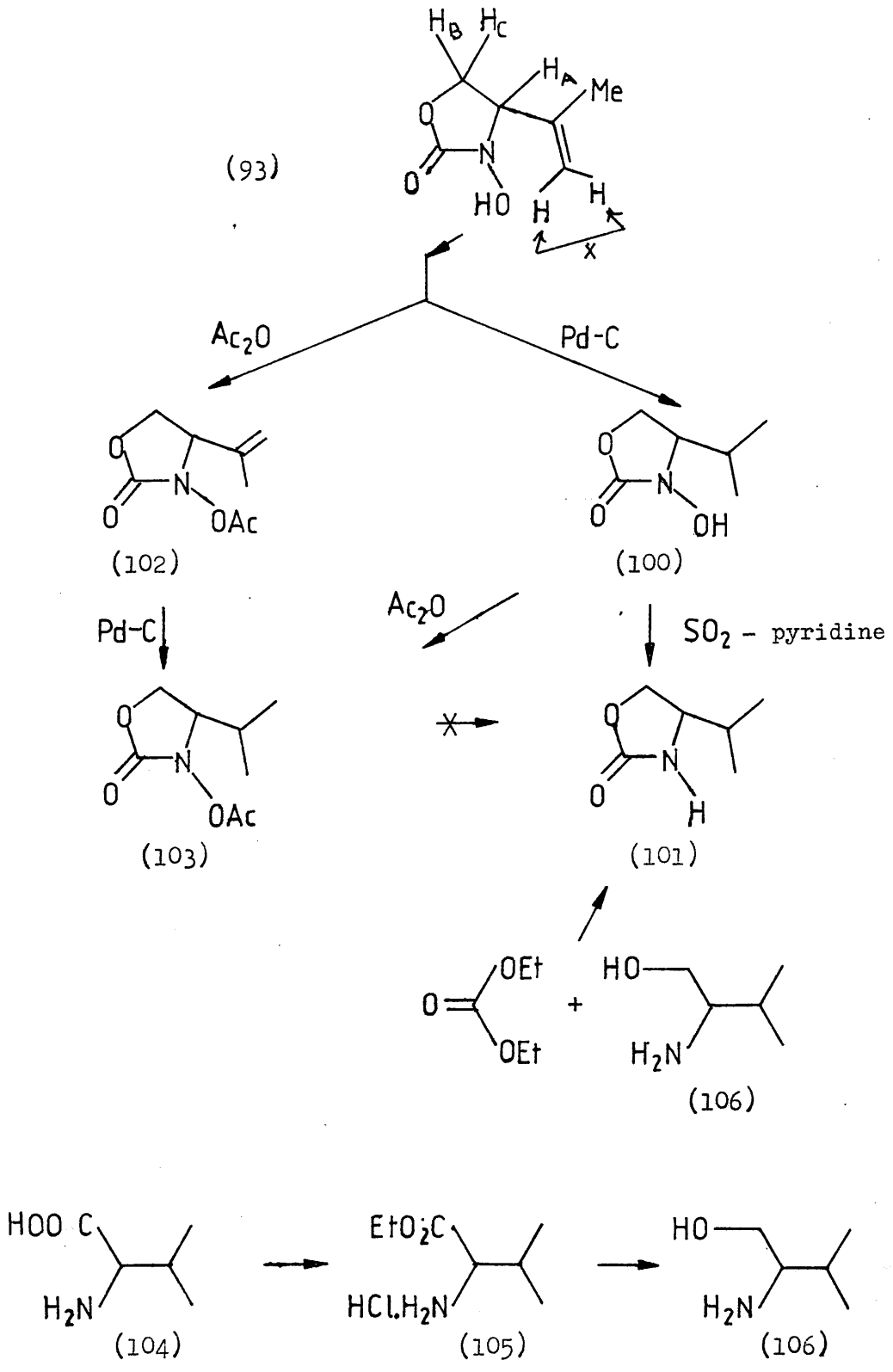
(99)

Scheme 29

However the adduct was stable in benzene under reflux, and decomposed in toluene at 111 °C to give an intractable mixture of products. Thus no classification was possible.

Identification of the Product Formed by the Thermolysis of Adduct (92a)

The adduct (92a) when heated in benzene at 80 °C gave a single product m.p. 74.5 - 75 °C (Scheme 29). Microanalysis showed that it had the empirical formula $C_6H_9NO_3$, and the mass spectrum gave an ion at 143 confirming this. Two possible structures were considered, (93) and (94). The i.r. spectrum gave a high frequency carbonyl band, ν_{max}^{1} 775 cm^{-1}, which suggested a 5-membered ring. However, the model straight chain compound (98) gave a band at 1 765 cm^{-1} and it was expected that a 6-membered ring compound such as (94) might give a higher frequency. Thus the size of the ring was still in doubt. The compound represented by (93) is a hydroxamic acid. But unlike the other hydroxamic acids he had prepared, McLean[26a] was unable to obtain, with this new compound, the characteristic purple colouration on the addition of ethanolic ferric chloride. The ^{1}H and ^{13}C n.m.r. spectra were δ_H 1.77 (br s, Me), 3.88-4.55(3H, m), 5.05-5.20(2H, m, vinyl H) and 8.45(br s, exch. with D_2O); δ_c 29.7(Me), 64.8, 65.8, 117.0 ($\underline{C}H_2$ = CMe), 139.1(CH_2 = $\underline{C}$Me) and 161.1. The protons attached to the heterocyclic ring gave an ABC n.m.r. pattern with additional, fine coupling to an olefinic proton, H_x. This part structure is shown as structure (99). Approximate δ and $\underline{J}$ values were obtained from the 360 MHz spectrum by Dr I.H. Sadler (University of Edinburgh). Refined values were obtained


(93)
H_B H_C
H_A
Me
O
N
HO
H
H
X
Ac_2O
Pd-C
O
N
OAc
(102)
O
N
OH
(100)
Pd-C
Ac_2O
SO_2 - pyridine
O
N
OAc
(103)
O
N
H
(101)
OEt
O
OEt
+
HO
H_2N
(106)
HOO C
H_2N
(104)
EtO_2C
$HCl.H_2N$
(105)
HO
H_2N
(106)

Scheme 30

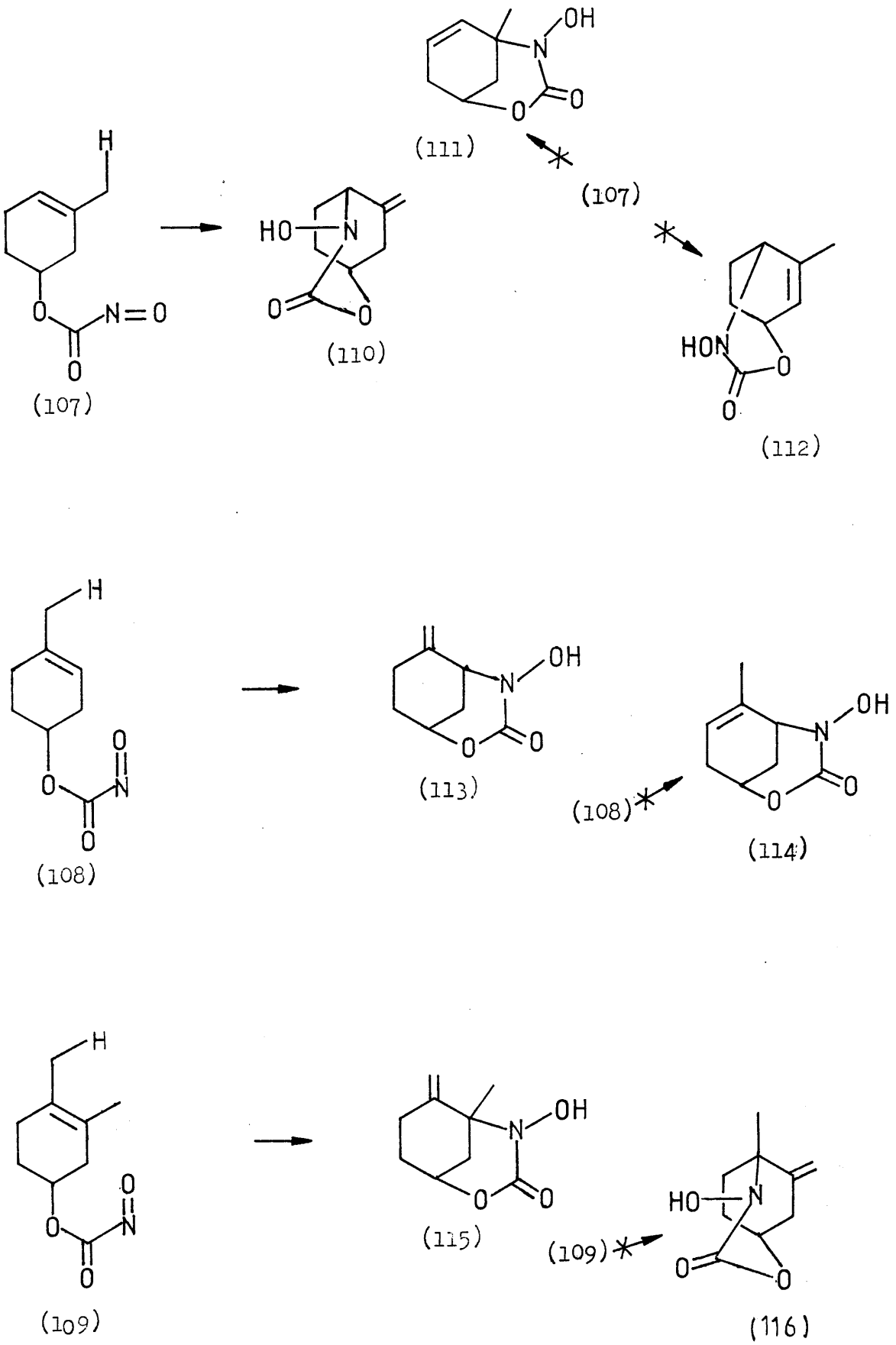
from the 100 MHz spectrum by Dr D.S. Rycroft (University of Glasgow) using a spin simulation programme[45]; δ 4.43(H_A), 4.41(H_B), 4.02(H_C), and 5.14(H_x); $\underline{J}_{AB}$ + 8.5; $\underline{J}_{AC}$ + 8.6; $\underline{J}_{BC}$ 8.7 and J_{AX} 0.5 Hz.

The important ethanolic ferric chloride test for a hydroxamic acid was investigated as part of the present study and it was found that when a freshly neutralised solution of alcoholic ferric chloride was used, the product gave a transient blue colour. Almost certainly the product had the oxazolidinone structure (93). This was confirmed[46] by chemical correlation with a derivative of (±)-valinol (106) (Scheme 30). The available starting material, (±)-valine (104) was converted into the hydrochloride of its ethyl ester (105). The free ester was reduced with lithium aluminium chloride to give (±)-valinol (106) which reacted with diethyl carbonate to yield the target molecule 4-isopropyloxazolidin-2-one (101). However to achieve a correlation with this molecule, a dual reduction of the putative hydroxyoxazolidinone (93) was necessary. The reduction of the olefinic bond was easily accomplished using hydrogen with a palladium carbon catalyst. The reduction product, possibly 3-hydroxy-4-isopropyloxazolidin-2-one (100), gave a faint blue colour with ethanolic ferric chloride. However, a spot of the same solution on a silica t.l.c. plate immediately turned purple when sprayed with ethanolic ferric chloride. Reductive cleavage of the N-O bond in hydroxamic acids had been accomplished by Keck *et al.*[47], who treated the corresponding O-acetyl derivatives, either

with sodium amalgam in ethanol containing disodium hydrogen phosphate, or with aluminium amalgam in tetrahydrofuran. Accordingly compounds (93) and (100) were acetylated, but the reductive methods used by Keck et al. failed. Keck et al.[24], in a later publication, reported similar difficulties with their sodium amalgam procedure, the outcome of which is apparently highly dependent on the batch of sodium employed. They recommended, instead reductive cleavage of hydroxamic acids with titanium trichloride - a method used by Mattingly and Miller[48]. Instead, a method devised in this laboratory by R.I. Gourlay[49] had already been adopted with success. He had discovered that the ethylene acetals of 14β-(N-acyl-hydroxyamino)codeinones could be reductively cleaved to give the corresponding amides, using sulphur dioxide in refluxing pyridine. Using this novel reagent, the hydroxamic acid (100) was converted into the oxazolidone (101), confirming that the nitroso compound (91a) had undergone an intramolecular 'ene' reaction to give the oxazolidone (93) instead of the dioxazinone (94).

II. Cyclic Homoallylic Esters

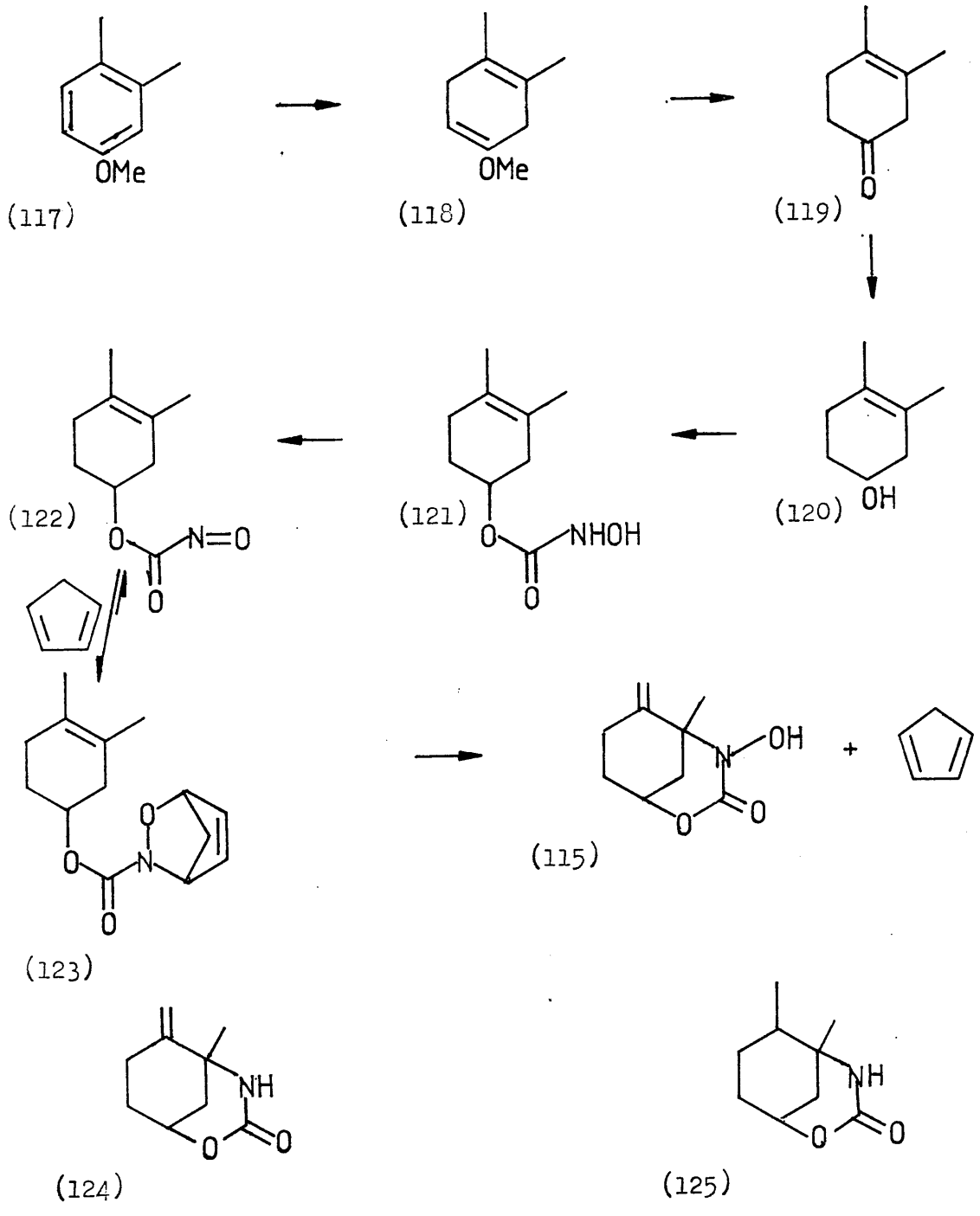
Two cyclic, homoallylic nitrosoformates (107) and (108) were used by McLean[26a, 46] as other subjects in his study of intramolecular 'ene' reactions. Thermolysis of the cyclopentadiene adduct of the nitrosoformate (107) gave the bridged hydroxamic acid (110), a new 7-membered ring with an exocyclic olefin having been formed. The adduct of the nitroformate


H
O
N=O
O
(107)
HO
N
O
O
(110)
OH
N
O
O
(111)
(107)
HON
O
O
(112)
H
O
N
O
O
(108)
OH
N
O
O
(113)
(108)
OH
N
O
O
(114)
H
O
N
O
O
(109)
OH
N
O
O
(115)
(109)
HO
N
O
O
(116)

Scheme 31

(108) also gave a hydroxamic acid with an exocyclic olefin, but this time the new ring was 6-membered (113). This series of experiments was completed as part of the present study in which a third cyclic homoallylic nitrosoformate (109) was prepared and trapped with cyclopentadiene. The two methyl substituents in this nitrosocompound combined in one molecule those features present in compounds (107) and (108). The 'ene' product from compound (109) proved to be (115): again a hydroxamic acid. The new ring was 6-membered, and like the other two products this, also, had an exocyclic olefin. The preparation and identification of 'ene' product (115) will be described shortly.

All three 'ene' reactions illustrated a Type 1 mechanism as defined by Oppolzer and Snieckus[44]. It is, however, puzzling why nitrosocompounds (108) and (109) both gave 6-membered rings but that compound (107) gave a 7-membered ring. The following is a quote from the relevant paper by Kirby et al.[46] - the compound numbers used in the present discussion have been substituted for those employed by Kirby et al. "It is possible that electronic effects play a role in controlling cyclisation of the nitrosoformate (107). If C-N bond formation leads to hydrogen abstraction, then, in the polarised transition state, the electrophilic nitroso group would carry a partial negative, and the olefinic group a partial positive charge. Attack at the less substituted end of the olefinic double bond would then be favoured. In principle, this would lead to either of the oxazepinones (110) or (112). However, molecular models indicate that the transition state leading



(117) (118) (119) (120) (121) (122) (123) (115) (124) (125)

Scheme 32

(126) (127)

to (112) would be significantly strained". Other products which might have been formed in these reactions, and which were considered as possible candidates, are given in Scheme 31.

III. The Bridged Oxazinone (115).

The bridged oxazinone (115), obtained by the pyrolysis of the cyclopentadiene adduct (123) has already been included in the discussion of the series of 'ene' reactions which involved it, and the other two bridged hydroxamic acids (110) and (113). There follows an outline of the synthesis of (115), and its reduction (Scheme 32). 3,4-Dimethylphenol was converted into the anisole (117), which was then reduced (Birch) to compound (118). From this the ketone (119) was obtained using the traditional aqueous bisulphite method. Operationally, this proved to be the most frustrating part of the synthesis because it was very difficult to decide when the hydrolysis of the enol ether was complete, and then how best to separate the bisulphite addition compound from the excess sodium bisulphite and the unchanged anisole. The ketone was reduced to the alcohol (120) and this was treated with phosgene, followed by hydroxylamine, to give the carbamate (121). Oxidation and adduct formation (123) and then its pyrolysis in benzene at 80 °C, yielded the bridged oxazinone (115). The progress of the pyrolysis was followed using chromatography. It seemed to require 18.5 h to convert all the starting material (123) into (115). Later, kinetic studies (see Table 1) proved that t.l.c. was too demanding a test for completeness, and that a 75% conversion could be achieved with a heating period of 1 h.

An even faster conversion was attained by azeotroping off the liberated cyclopentadiene with the benzene solvent, and then resuming the heating following an addition of fresh benzene. The reason for the efficacy of this procedure is discussed in the kinetic study which follows shortly.

The product, formed by pyrolysis, had the following physical properties. Microanalysis gave the empirical formula as $C_9H_{13}NO_3$; m/z 183(M^+); δ_H 1.53(s, Me), 1.5-2.5(m, 3 x CH_2), 4.5-4.7(m, 1-H), 4.98 and 5.04(2 x br s, vinyl-H) and 8.25 (br s, OH, exch with D_2O); δ_C 21.3(Me), 27.0, 32.5, and 39.6(8-, 7-, and 9-C, not necessarily in this order), 61.0(5-C), 73.3(1-C), 110.8 $\underline{C}H_2$ = C(6) , 147.0(6-C), and 156.4(3-C). It gave a purple colour with ethanolic ferric chloride. The carbonyl absorption at 1 686 cm^{-1} resembled that of the oxazinone (113) (Scheme 31) at 1 680 cm^{-1}, rather than of the oxazepinone (110), 1 640 cm^{-1}. This was sufficient to fix its structure as (115). The yield from this experiment was quoted as 39%, but kinetic experiments demonstrated that more than 75% could be expected, even after a thermolysis period of 1 h. The low yield of product actually isolated, is a reflection of the difficulties of purification.

Double reduction to the bridged oxazolidinone (125) was achieved using the novel sulphur dioxide-pyridine system[49] for the cleavage of the N-O bond, followed by hydrogenation of the olefinic double bond using palladium carbon catalyst. Alternatively, the same end-product (125) could be obtained by using the reducing agents in the reverse order. Both

successful routes to (125) demonstrated the efficacy of the sulphur dioxide - pyridine procedure for the reductive cleavage of the N-O bond.

Decomposition of the Cyclopentadiene adduct (123). A Kinetic Study.

Cookson's reagent[50], 4-phenyl-1,2,4-triazolinedione (126), in the form of a standard solution, was used to measure the concentration of cyclopentadiene in benzene. The brick-red colour of the reagent is discharged by the diene due to the formation of adduct (127). Although the life of the reagent in solution seemed to be only a few hours, it was sufficiently long for demonstrating that a solution of cyclopentadiene in benzene, originally 0.01 M, could be heated under reflux for 21.9 h, in an open system, and still retain 44% of the diene. It was unlikely that this retained compound was cyclopentadiene dimer, because simple experiments, in which volume contractions were noted, showed that it requires a period of weeks for the major part of a fresh neat sample of cyclopentadiene to change into the denser dimer. It was also noted that the diene formed an azeotropic mixture with benzene. Thus, during a period of heating under reflux conditions, a condensate containing cyclopentadiene is constantly being returned to the reaction mixture. These simple experiments showed that, when a cyclopentadiene adduct of a nitroso compound dissociates in refluxing benzene, cyclopentadiene monomer is largely retained, and so remains available for the reverse reaction.

It has already been reported that, when analytical t.l.c. was used to follow the decomposition of the adduct (123) it seemed to require 18.5 h to complete the reaction. That such

a long time is not the optimum for a preparation of (115) was proven when the decomposition was monitored using ^{1}H n.m.r. analysis. The experiment was carried out using three different concentrations of adducts. Aliquots were removed at intervals, and analysed. Because the aliquots were relatively small (10 ml) and dilute (as required for rapid decomposition), their analysis strained the capabilities of the 90 MHz n.m.r. machine used to monitor the reaction. Consequently no great accuracy can be claimed for the following results.

Table 1

Decomposition of adduct (123) and formation of hydroxyoxazinone (115)

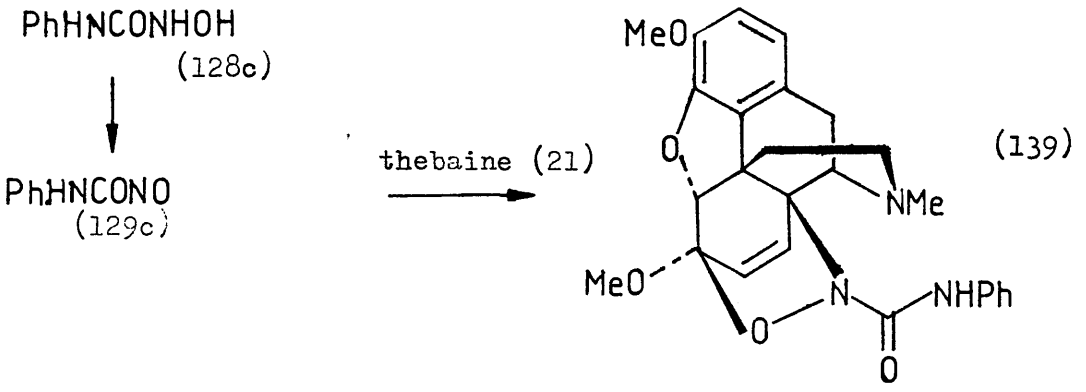
	Molar fraction (%) of hydroxyoxazinone (115) present in reaction mixture at end of period							
	Time (h)	0.25	0.5	1	2	3	4	6	11.4
Conc. of solns.	0.03 M	52	55	70	70	-	-	-	-
	0.01 M	47	52	63	68	70	71	71	92
	0.004M	-	67	75	75	77	-	76	-

The results show that the 'ene' reaction was fastest in the most dilute solution. Within a period of one hour, the adduct content was reduced to one quarter of the original. In each case, the increase in the concentration of free cyclopentadiene resulted in the reverse reaction (addition of the nitroso compound to cyclopentadiene) becoming an increasingly important alternative to oxazinone formation. It required a period of more than 11 h to bring the reaction

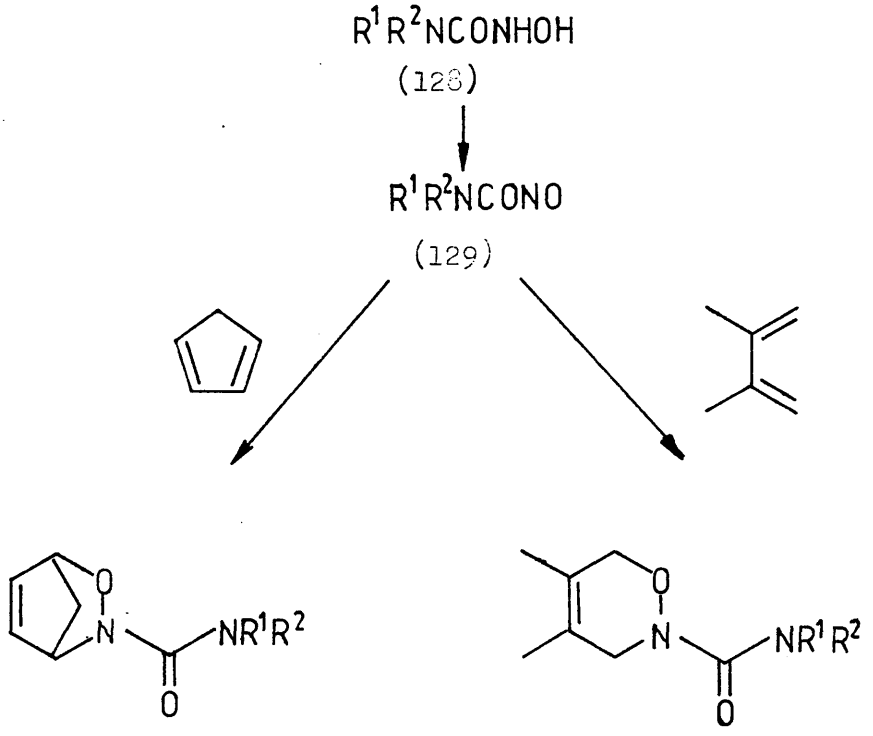
to near completion (0.01 M solution). After all the aliquots required for n.m.r. analysis had been withdrawn from the most dilute solution (0.004 M), there still remained sufficient for an assay of the benzene distillate using Cookson's reagent (126). This showed that, even after 6 h, about 85% of the original cyclopentadiene was present in the reaction mixture. These experiments also explain the difficulty experienced using analytical t.l.c. to monitor the progress of the decomposition: the reaction mixture always contained a considerable proportion of starting material. The results obtained with a reaction time of one hour were used to make an estimate of the rate of decomposition of the adduct. Assuming the reaction to be first-order, the values for $k(80\ ^{o}C)$ were $2.6 \times 10^{-4}\ s^{-1}$ (0.004 M), and $1.6 \times 10^{-4}\ s^{-1}$ (0.01 M).

When more dilute solutions of the adduct (123) were used, the second-order reverse reaction is slowed down because the freed nitroso compound has less chance of being recaptured by the more widely spaced cyclopentadiene molecules before it has reacted intramolecularily.

The above conclusions are in agreement with the observation made by Kirby *et al.*[46] that adducts of allylic and homoallylic nitrosoformate esters decompose at rates dependent upon their initial concentration in benzene, decomposition being faster the more dilute the solution.



(139)



(130)

(131)

a; R^1 = H, R^2 = H
b; R^1 = Me, R^2 = H
c; R^1 = Ph, R^2 = H
d; R^1 = Me, R^2 = Me
e; R^1 = Ph, R^2 = Ph

$(R^1R^2NCO)_2O$
(132)

Scheme 33

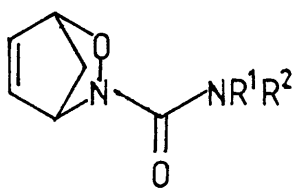
2.4. C-Nitrosoformamides

Within the last decade, progress in the field of transient nitroso compounds has been so considerable, that already chemists have integrated them into their armoury of synthetic intermediates. In the original study of such compounds, the nitroso moiety was attached directly to the carbon of an alkyl or aryl group, RNO. The next advance was the insertion of a carbonyl group, RCONO, and then followed the further insertion of an oxygen atom to give the nitrosoformate esters, ROCONO. One further extension of this strategy was to replace the alkoxy group by an amino group, R^1R^2N. This idea materialised as a study of the nitrosoformamides, R^1R^2NCONO, obtained by the oxidation of hydroxyureas. The smaller electronegativity of nitrogen compared with that of oxygen, and the accompanying increased delocalization of nitrogen electrons, could be expected to influence the properties of the resulting transient nitroso compounds. The first nitroso formamide, PhNHCONO, was reported by Mackinnon[37] in 1976. He had oxidised N-phenyl-N^1-hydroxyurea in the presence of thebaine (21) and had trapped the nitroso compound as an adduct. The present study involved an exploration of the formation and reactivity of this new class of transient dienophiles formed by the oxidation of N-hydroxyureas[51].

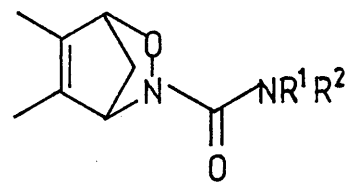
Hydroxyurea (128a), and its derivatives (128b-e) were each oxidised in the presence of cyclopentadiene to give the corresponding adducts (130a-e) (Scheme 33). Similarly, oxidation of these hydroxyureas in the presence of 2,3-dimethylbuta-1,3-diene gave another set of cycloadducts (131a-e).

The oxidations were carried out at 0 °C using sodium periodate or tetraethylammonium periodate. The use of tetraethylammonium periodate was generally more convenient. Earlier, sodium acetate-acetic acid buffer solution was used in conjunction with sodium periodate for the oxidations, but it was found that the buffer could be omitted without reduction in the yields of the cycloadducts and, at the same time, avoided the need to remove acetic acid from the products. The structures of the two sets of adducts (130) and (131) were established readily by comparison of their spectra with those of the adducts of the C-nitrosocarbonyl compounds and C-nitrosoformate esters discussed above.

A summary of the reaction times is given in Table 2. Later kinetic studies suggested that the time taken to add the oxidising agents to the hydroxyureas, based on decisions made quite arbitrarily, could be shortened to about 10 minutes. The low yields reported for some preparations reflect the difficulties encountered during purification, and not necessarily the inefficiency of the desired chemical transformation. The time required for the actual reaction was monitored by a simple t.l.c. method which was sensitive to very small concentrations of hydroxamic acid, but, as had been found when preparing the oxazinone (115), this simple monitoring is really unsatisfactory when one wishes to find the minimum reaction time for optimum yield. Nevertheless, the reaction times, as determined in this way, do give some idea of reaction rates. All the adducts were crystalline



(130)



(131)

a; R^1 = H, R^2 = H
b; R^1 = Me, R^2 = H
c; R^1 = Ph, R^2 = H
d; R^1 = Me, R^2 = Me
e; R^1 = Ph, R^2 = Ph

$(R^1R^2NCO)_2O$

(132)

solids, except that of dimethylnitrosoformamide with dimethylbutadiene (131d) which was a liquid. The corresponding cyclopentadiene adduct (130d) melted at 30 °C, and became dark on storage.

Table 2

Cycloadducts prepared from hydroxyureas ($R^1R^2NCONHOH$)

R^1R^2N	Cyclopentadiene Adducts (130)			Dimethylbutadiene Adducts (131)		
	Addition time (h)	Reaction time after addition (h)	Yield (%)	Addition time (h)	Reaction time after addition (h)	Yield (%)
H_2N	0.5	0.5	47	0.75	0.75	40
MeHN	1.3	1.0	50	0.75	0.75	42
PhHN	0.7	0.5	67	0.7	0.5	68
Me_2N	0.5	0.5	47	0.5	0.7	60
Ph_2N	0.1*	1.3	60	0.1*	2.0	24

Footnote:

*Sodium periodate was the oxidising agent; otherwise tetraethylammonium periodate was used.

Attempted Thermolysis of the Cyclopentadiene Adducts of the C-Nitrosoformamides. The five nitrosoformamide adducts (130a-e) were heated in Nujol oil on a microscope stage at above 130 °C, that is, above their melting points, in order to see if dissociation accompanied by gas evolution would occur. In the

case of the parent adduct (130a), there was a copious evolution of gas, one of the constituents of which was probably ammonia (see below). Only the diphenylnitrosoformamide adduct (130e) gave a comparable evolution of gas. The other three adducts did not show this phenomenon to any extent. Corrie *et al.*[52] described a similar gas evolution from the DMA adduct of nitrosocarbonylmethane, and investigated it using differential scanning calorimetry. They reported that an initial endothermic process (melting) occurred near 130°C, and inverted rapidly to an exothermic decomposition over the range 136-141 °C. The gaseous products evolved at 130 °C were investigated by microwave spectroscopy. They did not identify free nitroso-carbonylmethane in the products, but did detect nitrous oxide, acetic acid, and ketene. When the parent nitrosoformamide adduct (130a), obtained in the present study, was subjected to similar treatment it was found that the proportion of ammonia in the gaseous product was so great that the presence of other products was masked in the microwave spectrum.

The thermolysis of the cyclopentadiene adducts (130a-e) in a solvent was next investigated. Because it was insoluble in benzene, the cyclopentadiene adduct of the nitrosoformamide (129a) was tested as a solution in ethyl acetate at 77°C. The other adducts (130b-e) were heated in benzene at 80 °C. The only new products isolated, and purified, were the carbamic anhydrides (132d) and (132e). The liquid dimethyl-carbamic anhydride (132d) was identified from its i.r. and ^{1}H n.m.r. spectrum, and by comparison with an authentic sample[53].

The solid diphenylcarbamic anhydride (132e) was fully characterised (microanalysis, ^{1}H n.m.r. spectrum, etc.), and compared with its literature description[54]. From all these experiments, some adduct was recovered along with oily or tarry material. When the diphenylnitrosoformamide adduct (130e) was thermolysed, 19% of it was recovered unchanged.

Table 3

Attempted thermolysis, in solution, of cyclopentadiene adducts of R^1R^2NCONO

Adduct	(130a)	(130b)	(130c)	(130d)	(130e)
R^1R^2N	H_2N	MeHN	PhHN	Me_2N	Ph_2N
Heating time at 80 °C (h)	5 (at 77°C)	4.5	5.5	2	9
Anhydride $(R^1R^2NCO)_2O$ (yield)	Nil	Nil	Nil	132d (30%)	132e (70%)

The pyrolysis of the dimethylnitrosoformamide adduct (130d) was repeated at three different dilutions, but this time the reaction was followed using ^{1}H n.m.r. analysis. The integral of the signal arising from the carbamic anhydride (132d) was measured and compared with that arising from the residual adduct. The percentages appearing in Table 4, refer to the ratio of carbamic anhydride to carbamic anhydride plus adduct. The products were not isolated.

Table 4

Pyrolysis of N,N-dimethyl adduct (130d) in benzene at 80 °C. Conversion (%) into anhydride (132d), as determined by ^{1}H n.m.r. spectroscopy.

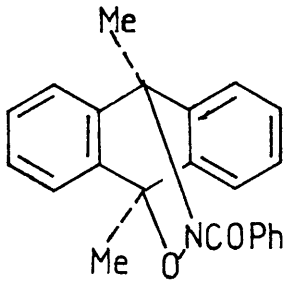
Molarity of Solutions	Heating time at 80 °C (h)				
	1.5	2.0	2.5	3.0	3.5
0.01	89	100	new peaks	-	-
0.02	70	93	100	-	-
0.03	-	-	-	80	100

The isolated yield of the anhydride (132d), given as 30% in Table 3, was obtained using a benzene solution of molarity 0.006. From Table 4 it can be seen that the experiment carried out at almost the same dilution (0.01 M), and for the same length of time (2 h), suggests that an almost theoretical yield is a possibility. However, with reference to the data given in Table 3, it must be pointed out that, on the t.l.c. plates used in the purification, the position of the anhydride was difficult to discern, and reliance had to be placed on a comparison with sample plates stained with iodine. At the time, it was not considered worthwhile to repeat the experiment, and to introduce some other mode of purification as, for example, column chromatography. Another factor, which boosts the yields, as measured using ^{1}H n.m.r. spectroscopy, is that the results reported in Table 4 were obtained by comparing the amount of anhydride with the amount of surviving adduct:

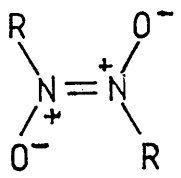
this ignored any by-products in the reaction mixture.

Earlier, it has been described how, when the adduct (130e) was heated on the hot stage of a microscope, there was a copious evolution of gas (nitrous oxide?). Also, the mass spectrum of the adduct showed peaks at m/z 292 (the adduct), and at m/z 408, the anhydride (132e) . It seemed, therefore, that it might not have been necessary to use a solvent, under reflux, to obtain the anhydride. Thus, the adduct (130e) was heated in a glass tube oven at 170 °C under vacuum (1 cm Hg). This was successful, but the yield of anhydride (132e) was lower than that obtained by pyrolysis in benzene (36% as against 70%). The product from one of these 'non-solvent' experiments melted at 110 °C instead of at 132 °C, the melting point given by the product of another similar experiment. Pyrolysis in benzene solution had given a product melting at 132 °C. The latter was also the melting point of the anhydride reported by Schroder and Wilcox[54]. Surprisingly, when a sample, prepared by the solvent pyrolysis method, which had originally melted at 132 °C was re-examined, it, also, melted at 110 °C. The difference in melting points was ascribed to a difference in crystalline structure. When the N,N-dimethylnitrosoformamide adduct (130d) was heated in a glass tube oven under vacuum, the products were gaseous and were not trapped in the cooled receiver. Thus the corresponding anhydride (132d) was not obtained by this method.

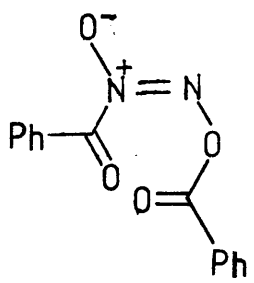
Anhydride production is not a reaction peculiar to these nitrosoformamides, or their adducts with cyclopentadiene.



(33b)



(133)



(134)

a; R = PhCO

b; R = C_4H_9

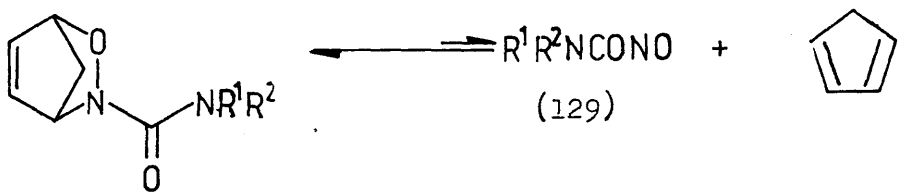
Corrie et al. reported[9] that the DMA adduct of nitrosocarbonylbenzene (33b) decomposed in benzene at 80 °C to give benzoic anhydride in 73% yield along with DMA. When the experiment was conducted in an evacuated sealed tube, nitrous oxide was detected by mass spectrometry in the evolved gases. This suggested that nitrosocarbonylbenzene had decomposed according to the following equation

$$2PhCONO \longrightarrow (PhCO)_2O + N_2O$$

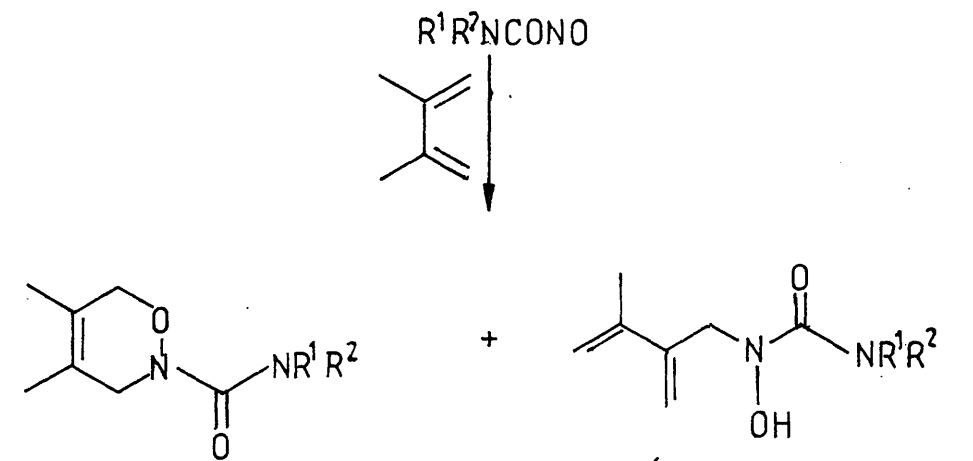
These authors considered that a dimer (133) of the nitroso compound might behave like an acylnitrone[55] and rearrange to the O-benzoyl derivative (134), which could collapse to give benzoic anhydride and nitrous oxide. However, they did not exclude a radical chain process, initiated by a homolysis of nitrosocarbonylbenzene to give a benzoyl radical and nitric oxide.

Transfer of N-Nitrosoformamides from their Cyclopentadiene Adducts to 2,3-Dimethylbuta-1,3-diene

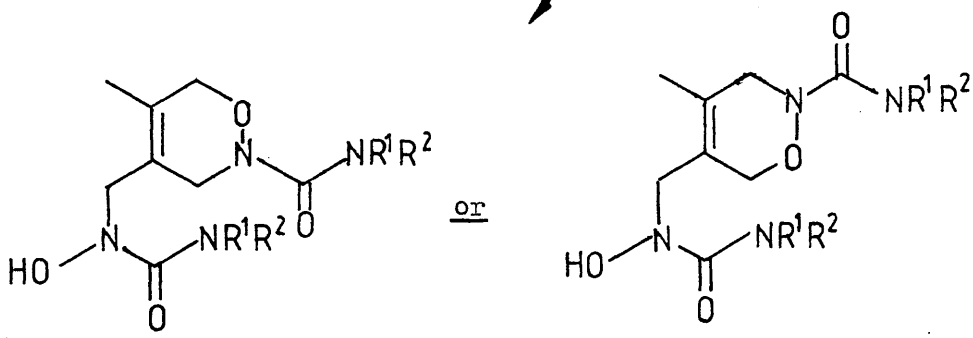
The cyclopentadiene adducts (130a-e) dissociate at 80 °C in benzene, and so can serve as convenient auxiliary sources of the transient nitrosoformamides (129a-e) for reactions with suitable dienes. In this study, 2,3-dimethylbuta-1,3-diene was chosen as the receptive model diene. Adducts of this diene with these transient nitroso compounds had already been prepared in this study, and it had been found that these, dihydro-oxazines (131a-e), did not dissociate. However the transfer experiments did not give merely the expected adducts. 'Ene' products accompanied the dihydro-oxazines. A summary



(130) (129)



(131) (135)
'ene' product



(136)
dihydroxazines

$(R^1R^2NCO)_2O$

(132)

a; R^1 = H, R^2 = H
b; R^1 = Me, R^2 = H
c; R^1 = Ph, R^2 = H
d; R^1 = Me, R^2 = Me
e; R^1 = Ph, R^2 = Ph

Scheme 34

of the results is given below. In order to simplify comparison, all the yields of products are quoted as fractions of 1 mmol arising from 1 mmol of the cyclopentadiene adducts (130a-e).

Table 5

Transfer of N-nitrosoformamides, R^1R^2NCONO, from their cyclopentadiene adducts, to 2,3-dimethylbutadiene (DMBD) in benzene at 80 °C.

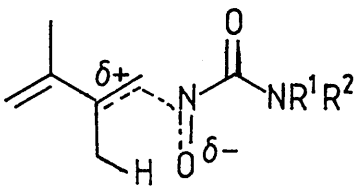
Yields of products are reported as fractions of 1 mmol of starting material.

R^1R^2NCONO	129a	129b	129c	129d	129e	
R^1R^2N	H_2N	MeHN	PhHN	Me_2N	Ph_2N	
Molarity of adduct solutions	0.025	0.04	0.04	0.04	0.04	0.04
Equivalents of DMBD used	5	10	10	1.1	10	10
Reaction times (h)	5.5	2	2	3	3	1.5
Dihydro-oxazines (131)	0.50	0.71	0.75	0.35	0.66	0.56
'Ene' products (135)	0.17	0.22	0.20	0.08	0.19	0.14
'Ene' products Dihydro-oxazines (136)	Nil	Nil	Nil	Nil	0.19	0.11
Anhydrides (132)	Nil	Nil	Nil	0.26	Nil	Nil

It was sometimes difficult to be sure that the transfer was complete, and this problem underlies the difference in reaction times. The experiment involving the transfer of the parent nitrosoformamide (129a) was especially awkward in this respect.

Earlier, it has been reported that the oxidation of the hydroxyureas (128a-e) in the presence of 2,3-dimethylbuta-1,3-diene gave the expected adducts (131a-e), but no 'ene' products. As the 'ene' products are themselves hydroxamic acids, they would be oxidised in the same way as the parent hydroxamic acids to give products which were not detected. On the other hand, when the oxidising agent was absent, the hydroxamic acids resulting from the 'ene' reactions persisted and were isolated.

It is clear from the earlier studies of carbonylnitroso compounds, and from those by Keck *et al.*[24], that these compounds react much more rapidly with conjugated dienes to give 1,4-cycloadducts, than with mono-olefins to give 'ene' reaction products. However, in the case of the *C*-nitrosoformamides (129a-c), 1,4-cycloaddition was only 3-4 times as fast as the 'ene' reaction. When one takes into account the dihydro-oxazines (136d) and (136e), which had 'ene' intermediates, cycloaddition was only about twice as fast as the 'ene' reaction. These results, which are surprising, might be explained according to Kirby and his co-workers[51] if the transition state for a concerted 'ene' reaction is polarised as shown in (137), with C-N bond formation leading hydrogen



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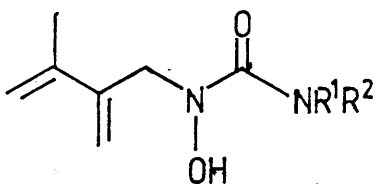

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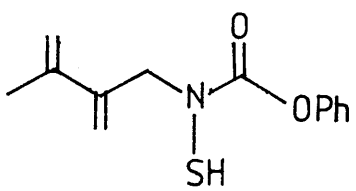
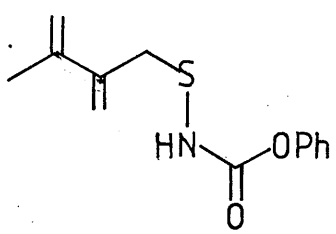


(138)

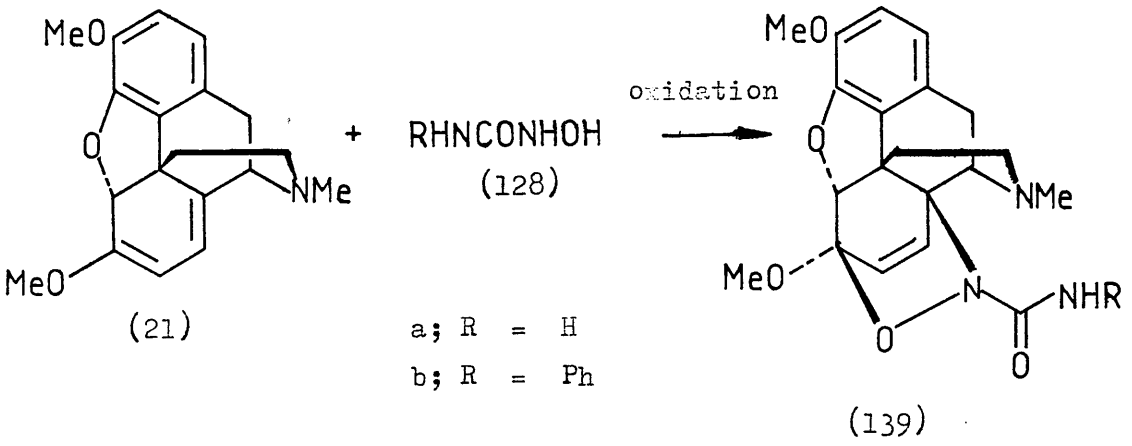


(138a)

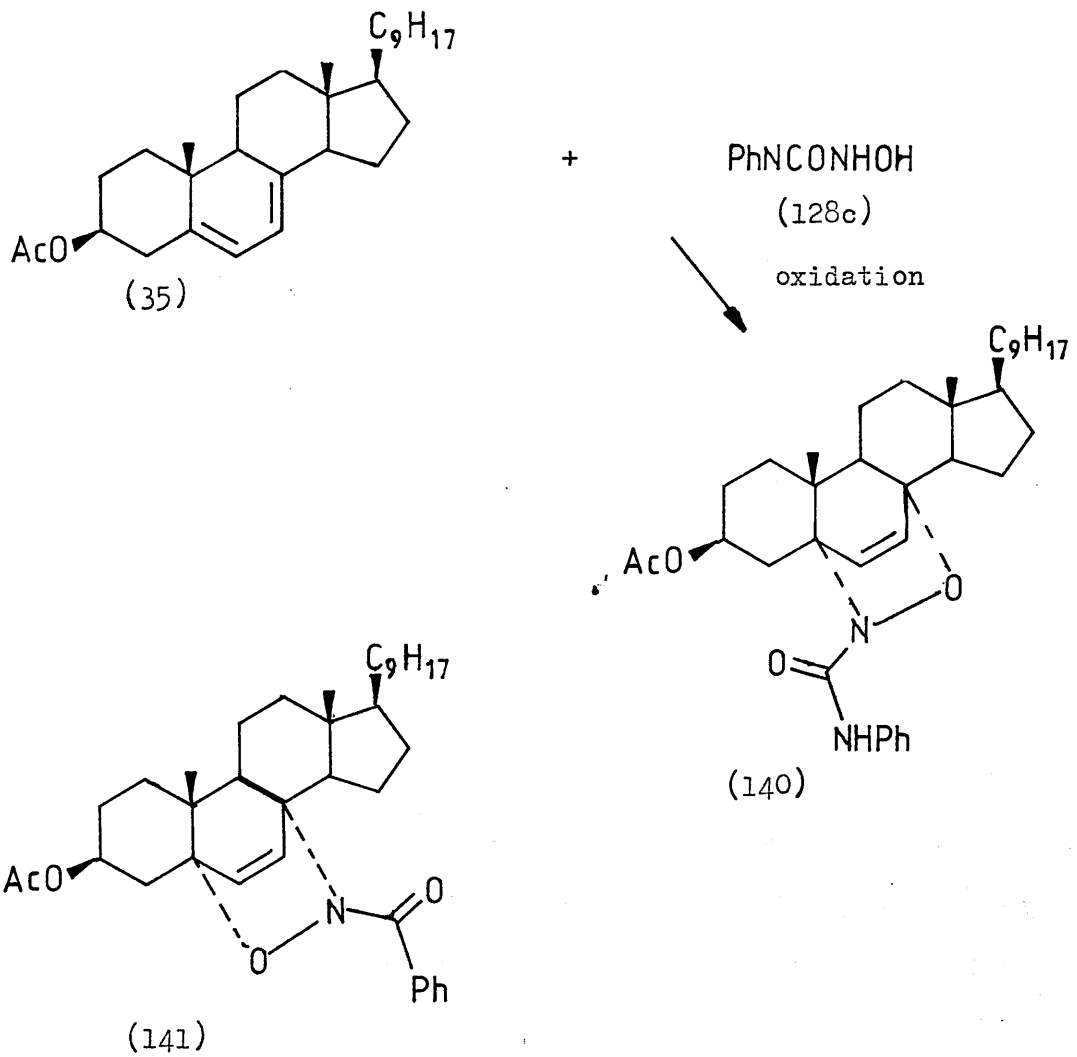
transfer. Then the positive charge developing on the 'ene' component will be stabilised by the other double bond, and the 'ene' reaction will be correspondingly favoured, resulting in the formation of compounds of the type (135). The latter compounds are substituted buta-1,3-dienes, but only the di-substituted nitrosoformamides seem to be sufficiently activated to give 1,4-cycloadducts (136d) and (136e). The rates for the 'ene' reactions of the nitroso compounds (129d) and (129e) approach those reported by Meth-Cohn and van Vuuren[56] who found that, for example, when phenyl thionitrosoformate, PhOCONS, reacted with 2,3-dimethylbuta-1,3-diene, approximately equal amounts of a 1,4-adduct and an 'ene' product were formed. In this case the 'ene' reaction occurred with C-S[(138a)] rather than C-N bond formation (138).

In the one experiment, in which a modest excess (1.1 equivalents) of 2,3-dimethylbuta-1,3-diene was used, some anhydride, $(Me_2NCO)_2O$ (132d) was formed. This is not surprising because the conditions had much in common with the thermolysis of the same adduct (130d) in benzene, which gave the same anhydride as product. However, the yield of anhydride obtained in the transfer experiment using dimethylbutadiene (Table 5) is remarkably high, and it would seem that the rate of anhydride formation was about three-quarters that of the dihydro-oxazine (131d).

When the present author's work on the C-nitrosoformamides was finished, the study was taken up by C.C. Christie[51]. He carried out some experiments using the unsymmetrical diene,



Scheme 35



Scheme 36

thebaine (21), for the purpose of comparing the regio-selectivity of the C-nitrosoformamides with that of other C-nitroso compounds. C-Nitrosoformamide (129a), and N-phenyl-C-nitrosoformamide (129c) both form adducts with thebaine in which the nitrogen of the nitroso group is attached at C(14). That the structures are as shown in (139a) and (139c) is in agreement with the findings of other workers[11,26,40], who prepared adducts of nitroso compounds with thebaine. It would seem that the stereochemistry of this diene forces it to discriminate strongly between the possible orientations of the attacking transient nitroso compounds. When Christie oxidised N-hydroxy-N'-phenylurea (128c) in the presence of ergosteryl acetate (35) the one product he was able to isolate was adduct (140c) (Scheme 36). Kirby and Mackinnon[18] had established that ergosteryl acetate forms two well-characterised series of 1,4-adducts with C-nitroso compounds, e.g. (140; NHR = Ph) and (141). That the nitrosoformamide (129c) gave only one type of adduct is puzzling, because there seems to be no structural feature in ergosteryl acetate which would favour, overwhelmingly, one particular type. However, the fact that Christie obtained a single ergosteryl adduct (140) is not without precedent as Kirby *et al.*[25] have reported the isolation of only one adduct with benzylnitrosoformate, $PhCH_2OCONO$ and 2,2,2-trichloroethylnitrosoformate, CCl_3CH_2OCONO. Christie also prepared the cycloadduct of C-nitrosoformamide (129a) with dimethylanthracene, and was able to transfer the nitroso compound from that adduct to thebaine (*vid.* Scheme

17; $OCH_2Ph = NH_2$). The release of DMA during this transfer was monitored spectrometrically by absorption at 378 nm. First-order kinetics were observed ($k = 9.1 \times 10^{-5}$ s^{-1}, at 40 °C), corresponding to rate-determining dissociation of the adduct, followed by rapid capture of C-nitrosoformamide by the thebaine. Thus this DMA adduct dissociates more rapidly at 40 °C than does the corresponding adduct of nitrosocarbonylmethane[20], (33a) (Scheme 9) at 60 °C, $k = 4.7 \times 10^{-5}$ s^{-1}. Therefore the DMA adduct of C-nitrosoformamide provides an even more facile method for the transference of C-nitrosoformamide (and, presumably, the other nitrosoformamides studied) than does the corresponding adduct with nitrosocarbonylmethane.

2.5. The Persistence of Transient Nitrosocarbonyl Compounds in Solution: a Kinetic Study

When adducts were being prepared, the progress of the reaction was usually monitored using thin layer chromatography. A spot of the reaction mixture was applied to an analytical silica plate, and after development, the plate was examined under U.V. light, and then sprayed with ethanolic ferric chloride to detect the presence of any residual hydroxamic acid. It has already been reported here several times, that this system was often so lacking in precision that one had to decide on a purely arbitrary time to allow the reaction to take place. Towards the end of the present study, it was decided to examine the matter of reaction times more closely.

A simple procedure using analytical t.l.c. showed that hydroxyurea (128a), in ethanolic solution, reacted with the oxidising agent, tetraethylammonium periodate within five seconds of mixing.

In a second series of tests at room temperature, a solution of hydroxyurea in ethanol (10 ml, 0.1 M) was mixed with the above oxidising agent, also in ethanol, (15 ml, 0.1 M), Both solutions were almost saturated. A predetermined 'delay' was employed before cyclopentadiene (2 mmol) was added. Then there was a period (1 to 31s) to permit adduct formation. Immediately this period had elapsed, the reaction was quenched by pouring the mixture into excess sodium thiosulphate solution. The results are shown below.

Table 6

Formation of cyclopentadiene adduct of H_2NCONO from 1 mmol hydroxyurea at room temperature. Gravimetric method of assay.

Experiment	1	2	3	4	5
Delay time (s). (oxidation in absence of diene)	0	0	5	60	600
Time(s) for reaction with diene	1	5	5	5	30
Dichloromethane extract (mg)	80.5	108	96.7	84.8	not weighed
Colour of extract	faint yellow	faint yellow	yellow	yellow	brown
Extract after water-wash to remove colour (mg)	not required	31.9	28.3	0	13
Yield of adduct (130a) isolated (mmol)	0.57	0.23	0.20	0	0

It would seem that water-washing removed much of the adduct. Best results were obtained by mixing all the reagents (hydroxyurea, diene, and oxidising agent) at the start of the preparation, and then allowing not more than 5s for the reactions to take place before destroying the excess oxidising agent with sodium thiosulphate (cf. experiments 1 and 2). Experiments 3 and 4 suggested that some nitrosoformamide persisted at least for 5s, and, maybe, even for 60s at room temperature. The following set of experiments proved that this period, 60s, was too low an estimate.

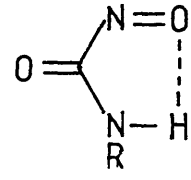
In this third series of experiments, representation of two different classes of nitrosocarbonyl compounds were involved, and proton n.m.r. spectrometry was used to follow changes in their concentration. The starting materials were hydroxyurea, $NH_2CONHOH$ (128a) and acetohydroxamic acid, $CH_3CONHOH$ (30a). As in the last experiments, oxidation was allowed to continue at room temperature for a given period in order that the nitroso compounds might have time to form (and decay) before the addition of the trapping diene. Using the experience gained in the last experiments, the water washing step was eliminated. The amount of adduct present in the residue was assayed by dissolving it in deuteriochloroform, and adding a known weight of anisole. The resulting solution was subjected to ^1H n.m.r. spectroscopy. Examination of the spectrum of the mixture enabled one to calculate the weight of the adduct. In order to calculate the rate at which the transient nitroso compounds decomposed, some measure of their

concentration at 'zero time' was required. This, of course, was not available. However, in order to obtain an estimate of the rates, it was assumed that the concentration at 'zero time' was represented by the mmols of adduct recovered when there was no delay in mixing all the reactants and this reaction mixture was left for 60s before quenching. This gave 'zero time' concentration of 0.61 mmol for C-nitrosoformamide, and 0.57 mmol for C-nitrosocarbonylmethane.

Table 7

Formation of cyclopentadiene adducts of H_2NCONO and CH_3CONO at room temperature. ^1H n.m.r. method of assay, using anisole as concentration standard.

Hydroxamic acids oxidised (1 mmol)	Hydroxyurea (128a)			Acetohydroxamic acid (30a)			
Delay time (s) (oxidation in absence of diene)	0	60	300	0	0	60	120
Time(s) allowed for reaction with diene	60	60	60	6	60	60	60
Yield of adduct (mmol)	0.61	0.40	0.12	0.21	0.57	0.11	0.04
Amount of nitroso compound trapped(mmol)	0.61	0.40	0.12	0.21	0.57	0.11	0.04
Rate of decomposition of carbonylnitroso compound (averaged) k at 20°C (s^{-1})	6×10^{-3}			2.5×10^{-2}			
Half-life of carbonyl-nitroso compound	115			29			

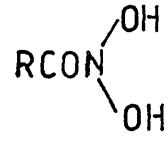


(142)

a; R = H

b; R = Me

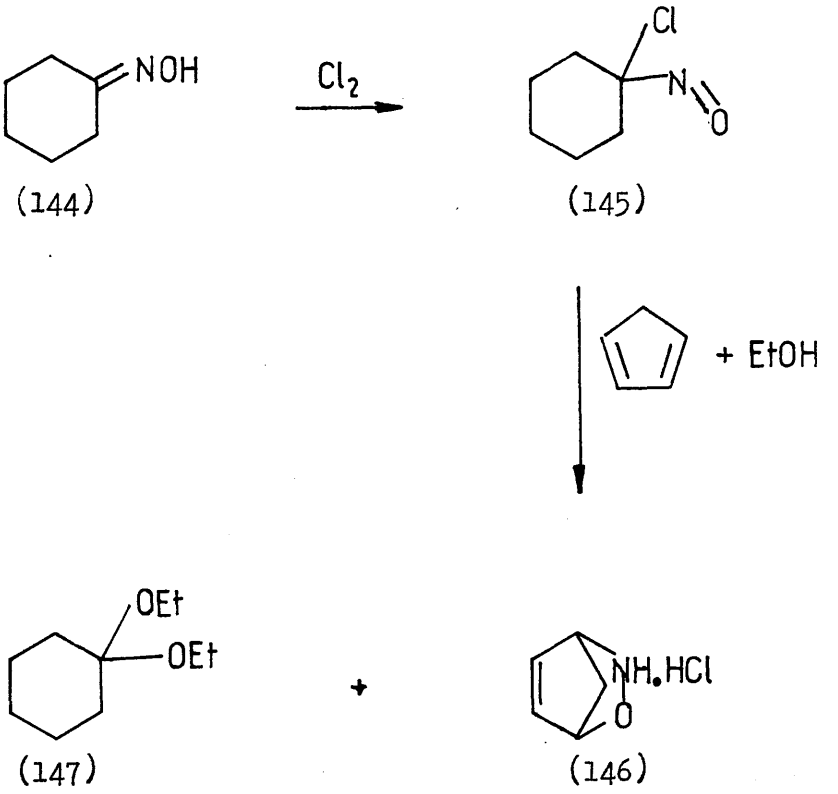
c; R = Ph



(143)

Once again it has been demonstrated that it is best to initiate the preparation of adducts by mixing all the reactants in one solution. Sixty seconds later a reasonable yield of adduct can be obtained by addition of cyclopentadiene. The omission of water-washing increased the yield of the nitrosoformamide adduct (130a). Most important is the discovery that even 300s after oxidation of hydroxyurea, some C-nitroso-formamide still persisted in the reaction mixture. This remarkably long life may partly be due to stabilisation of the compound by hydrogen bonding (142a). Hydrogen bonding may also play a part in the reactions of the other two mono-substituted nitrosoformamides (vid. 142b and 142c). Nitroso-carbonylmethane (31a) is not quite so persistent: nevertheless there remained a considerable amount - 60s, and even 120s, after oxidation of the acetohydroxamic acid. Although the values for 'k' and 'half-life' given above must be treated with reserve, they do show that the nitrosoformamide is considerably more persistent than nitrosocarbonylmethane.

Throughout this study, the transient compounds under consideration have been referred to as 'nitroso compounds', and given the general formula, RCONO. The justification for the use of this concept has largely been based on a study of adduct formation in solution, and a transfer of the entity from one diene to another. However, no evidence has been uncovered which identifies them as monomers, or dimers $(RCONO)_2$, or as solvated compounds like (143). Now that it has been demonstrated that the persistence of some of



(144) (145) (147) (146)

Scheme 37

the reactive species is much longer than hitherto expected, it would be worthwhile to make a spectrometric search for evidence to confirm their identity.

2.6. Attempted Preparation of Cycloadduct of Nitrosyl Hydride and Cyclopentadiene

One disappointment in this work was the failure to repeat, in satisfactory yield, the preparation of what might have been a suitable starting material for some of the cyclopentadiene adducts used in this study. Ranganathan *et al.*[57] reported preparation of a bridged oxazine (146) (Scheme 37) from 1-chloro-1-nitrosocyclohexane and cyclopentadiene in ether-ethanol. The potential of such an adduct can be considered as great as that of the related adduct (19) (Scheme 5) of 1,3-cyclohexadiene. In a private communication Dr D. Ranganathan elaborated on the precautions which ought to be taken, and recommended an increase in the reported amount of cyclopentadiene from 10 to 20 equivalents, but such additional quantities had already been tried without obtaining the expected yield of adduct. Only the source of chlorine was different. In this laboratory, the gas had been obtained from a reliable supplier, and in a cylinder. Ranganathan *et al.* had prepared the gas *in situ* by the traditional method of oxidising concentrated hydrochloric acid using potassium permanganate, followed by drying with concentrated sulphuric acid.

It is interesting to note that Just and Cutrone[58] reported that, using 1-chloro-1-nitrosocyclohexane as a dienophile, a low temperature reaction with cyclopentadiene gave a product which decomposed at -30°C with formation of a black tar.

3. Experimental

3.1. Services and Special Reagents

The services and special equipment described in the Experimental Section of Part 1 were employed also in Part 2. A Gallenkamp melting point apparatus (Cat. No. MFB, 595, 010M) was used to confirm the corrected melting points obtained with the Köfler hot stage apparatus.

Suppliers of Special Reagents

Benzyl chloroformate, Aldrich Chemical Co. Ltd., Gillingham, Kent.

Dimethylcarbamoyl chloride, Aldrich.

3,4-Dimethylphenol, Aldrich.

Dimethyl sulphate, Aldrich.

tert-Butyl N-hydroxycarbamate, Lancaster Synthesis Co. Ltd., Lancaster, England.

Hydroxyurea, Aldrich.

N'-Hydroxy-N,N-diphenylurea, Professor Kirby supplied a sample prepared earlier in this laboratory.

3-Methylbut-2-en-1-ol, Aldrich; Air Products and Chemicals Inc.

Methyl isocyanate, Aldrich.

Palladium - carbon catalyst, Aldrich.

Phenyl isocyanate, Aldrich.

Phosgene in toluene, B.D.H. Chemicals Co. Ltd., Poole, England.

Phosgene gas, B.D.H. Chemicals.

Silica (Flash Chromatography), 'Kieselgel 60', Merck, Darmstadt, Germany.

(±)-Valine, Sigma Chemical Co. Ltd., Poole, England.

3.2. General Preparative Methods

Hydroxylamine

Hydroxylamine[59] was prepared by the treatment of hydroxylamine hydrochloride with ethanolic sodium ethoxide, moisture being excluded. All was cooled in an acetone-solid carbon dioxide bath to induce crystallisation of the hydroxylamine, which was filtered off under dry argon.

Tetraethylammonium Periodate[17]

Paraperiodic acid (7.72 g, 0.034 mol) in water (20 ml) was added in portions to 25% tetraethylammonium hydroxide (20 ml, 0.034 mol). The mixture was evaporated under reduced pressure (using a safety screen) and the residue was extracted with hot tert-butanol. The combined extracts were diluted with di-isopropyl ether to precipitate tetraethylammonium periodate. Recrystallised from tert-butanol, the product (8.5 g) had m.p. 176 °C (lit. 176-177 °C); $\delta_H(CDCl_3)$ 1.38 (mt, J 7 Hz, 4 x Me), and 3.33(m q, 7 Hz, 4 x CH_2).

Oxidation of Hydroxamic acids

The oxidation of hydroxamic acids was accomplished using, either sodium periodate, or tetraethylammonium periodate in an organic solvent. A sodium acetate-acetic acid buffer (pH 6) is recommended for use in conjunction with the former oxidising agent, but for some preparations it was found to be unnecessary. Tetraethylammonium periodate is the more convenient oxidising agent.

Cycloadducts of C-Nitrosocarbonyl Compounds

System A: Aqueous Sodium Periodate as Oxidising Agent

A solution of the hydroxamic acid, or the hydroxyurea, was added, dropwise, to a two-phase mixture of an aqueous solution of sodium periodate, and an ethyl acetate solution of the diene. The mixture was stirred vigorously at 0 °C for about 2 h. At the end of this period the organic layer was separated off, and the aqueous layer was extracted with ethyl acetate. The combined organic solutions were washed three times with brine: the first wash contained sodium thiosulphate to remove any free iodine, and the second contained sodium hydrogen carbonate. After the solution had been dried ($MgSO_4$), and the solvent evaporated, the adduct was obtained from the residue. From this point onwards, the procedure varied, because the purification of the products demanded individual methods.

System B: Tetraethylammonium Periodate as Oxidising Agent

Both the hydroxyurea and the diene were added to ethanol, and the resulting solution was stirred vigorously at 0 °C. A solution of tetraethylammonium periodate in ethanol was added over a period of 0.5 h. Stirring and cooling were continued for another 0.5 h. The ethanol was removed using the rotary evaporator, with the bath temperature below 45 °C. Dichloromethane was added to the residue and the resulting solution was filtered. This solution, usually quite brown in colour, was washed three times with brine. A little sodium

thiosulphate was included in the first wash. After drying (Na_2SO_4), the solvent was evaporated. From this point onwards the procedure varied, because the purification of the products demanded individual methods.

Kinetic experiments, carried out at a later date, indicated that it might have been possible to reduce the reaction times used in this series of preparations.

3.3. Nitrene Studies Using C-Nitroso Formates.

Cycloadduct of tert-Butyl C-Nitrosoformate and Cyclopentadiene

System A

tert-Butyl N-hydroxycarbamate (55b, Scheme 26) (2.66 g, 20 mmol) in ethyl acetate (25 ml), cyclopentadiene (5 ml, 60 mmol) in ethyl acetate (200 ml), and sodium periodate (6.42 g, 30 mmol) in 0.5 M sodium acetate-acetic acid buffer solution (pH 6, 300 ml) were used. The reaction time was 2.5 h. The crude product was dissolved in chloroform and this solution was filtered through cotton wool. Brownish yellow crystals of the relatively pure adduct were obtained (3.18 g, 81%). In order to complete the purification, the solid was dissolved in chloroform, and passed through a column of silica (5.5 cm x 3 cm), using suction. Some chloroform appeared first (10 ml), and this was followed by a solution of the adduct, still slightly coloured. On recrystallisation from light petroleum (b.p. 40-60 °C), long needles of 3-tert-butoxycarbonyl-2-oxa-3-azabicyclo[2.2.1]hept-5-ene (87b) were obtained (2.86 g, 73%), m.p. 45.5 °C; mass spectrometry gave no molecular ion, but

important peaks were m/z 141(loss of tert-butane), 66.1(loss of C_5H_6), 57.2 base peak, $(Me)_3C^+$ (Found: C, 61.0; H, 7.7; N, 7.2. $C_{10}H_{15}NO_3$ requires C, 60.9; H, 7.6; N, 7.1%); ν_{max}(KBr) 1 743 cm^{-1} (CO); $\delta_H(CDCl_3)$ 1.45(s, 3 x Me), 1.69 and 1.95 (2 x br d, J 9 Hz, bridgehead-CH_2), 4.97 and 5.20(br s, 2H, O-C-H and N-C-H), and 6.39(m, CH = CH). A spot of this adduct on an analytical t.l.c. silica plate gave a purple colour when sprayed with alcoholic ferric chloride.

Deoxygenation of tert-Butyl C-Nitrosoformate with Triphenylphosphine

a) Benzene as solvent. The tert-butyl nitrosoformate adduct (87b) (197 mg, 1 mmol) and triphenylphosphine (262 mg, 1 mmol) were heated in benzene (50 ml) under reflux for 1.5 h. Within three minutes, the solution had turned straw yellow (azepine?). The solution was concentrated, and dry ether was used to cause most of the triphenylphosphine oxide to crystallise out. These crystals melted at 159.5 °C (mixed m.p. 159.5 °C); $\delta_H(CDCl_3)$ 7.48(br s, 3 x Ph). A total of 253 mg of relatively pure oxide was collected from this crystallisation, and as a result of the later chromatographic operations. This recovery, combined with that of unchanged triphenylphosphine (35 mg approx.) is a measure of the efficacy of the latter as a de-oxygenating agent in this reaction. The ether-soluble portion of the reaction mixture was chromatographed on a column of 'Florisil' (t.l.c. grade). Elution with ether provided a very early yellow fraction. This fraction, chromatographed again on 'Florisil', and eluted with chloroform-

ethyl acetate (97:3), gave a first colourless fraction containing triphenylphosphine (35 mg), $\delta_H(CDCl_3)$ 7.28(d, J 4 Hz, 3 x Ph). The yellow band, which followed, contained N-tert-butoxycarbonylazepine[60](85b) (6%) as a yellow oil; Found: (accurate mass spectrometry) 193.1103(M^+); required for $C_{11}H_{15}NO_2$, 193.1102 ; $\delta_H(CDCl_3)$ 1.45(s, Bu^t), ca. 5.3-5.65 (br m, 3- and 6-H), 5.80(d m, J 8 Hz, 2- and 7-H), and 5.97 (t m, J 3 Hz, 4- and 5-H).

After the azepine and the excess triphenylphosphine had been eluted with ether from the first 'Florisil' column, some more products, mainly triphenylphosphine, were obtained: the accompanying products were present in small amounts, and were not identified. About 150 ml of ether were used as the elutant. The 'Florisil' was then extracted with chloroform and this extract gave 5,5-dimethyloxazolidin-2-one (86) (5 mg, 4%), m.p. 75-80 °C (lit.[42] 80 °C); $\nu_{max}(CHCl_3)$ 1 757 cm^{-1} (CO) and 3 478 cm^{-1}(NH), (lit. ν_{max}(KBr) 1 724 and 3 268 cm^{-1}); $\delta_H(CDCl_3)$ 1.46(s, 2 x Me), 3.34(s, CH_2), and 6.14(br s, NH, exch. with D_2O), (lit. 1.45, 3.35, 6.87); m/z 115(M^+).

b) Dichloromethane as Solvent. The tert-butyl nitrosoformate adduct (87b) (394 mg, 2 mmol), and triphenylphosphine (576 mg, 2.2 mmol) in dry dichloromethane (6 ml) were heated at 82 °C for 1 h in a sealed 'Carius' tube - the volume of solvent was limited by the capacity of the tube. The resulting yellow solution was concentrated, and then treated with diethyl ether in order to precipitate most of the triphenylphosphine oxide produced in the reaction. The filtered solution

was chromatographed on silica plates, with ether as the developer, and methanol as the elutant. A band, approximately R_f 0.1, was removed, and chromatographed once more on silica plates, but this time the developing solvent was chloroform-methanol (96:4). A band, R_f 0.3, bounded by two fine yellow bands, was eluted with methanol to give the oxazolidinone (86) (10 mg, 4%). The triphenylphosphine oxide and the oxazolidonone were the only two products identified.

Benzyl N-Hydroxycarbamate (55a)

A method described by Boyland and Nevy[16] was used in this preparation. The available sample of benzylchloroformate was old stock of a 'technical grade' (78% purity). It was used without initial purification. This chloroformate (68 g, ca. 0.4 mmol) was added, dropwise, to a stirred solution of hydroxylamine hydrochloride (31 g, 0.45 mol) and sodium hydroxide (36 g, 0.9 mol) in water (500 ml) at 0°C. Three hours later the acidity was adjusted to pH 2 using 6 N hydrochloric acid. The solid, which separated out, was collected, and recrystallised from benzene-light petroleum. Additional product was obtained by extracting the aqueous layer with ether. Benzyl N-hydroxycarbamate (55a) was obtained as colourless plates (32.5 g), m.p. 66-69 °C (lit. 71 °C); $\delta_H(CDCl_3)$ 5.08(s, CH_2), 7.26(s, Ph), ca. 7.00-8.00(br s, NH and OH). This hydroxamic acid on an analytical t.l.c. silica plate, developed with acetone-light petroleum (3:7), appeared as a purple spot when sprayed with ethanolic ferric chloride.

Cycloadduct of Benzyl C-Nitrosoformate and Cyclopentadiene

System A

Benzyl N-hydroxycarbamate (55a, Scheme 26) (167 mg, 1 mmol) in ethyl acetate (5 ml), cyclopentadiene (0.15 ml, 1.8 mmol) in ethyl acetate (20 ml) and sodium periodate (214 mg, 1 mmol) in 0.5 M sodium acetate-acetic acid buffer solution (10 ml) were used. The reaction time was 2 h. A clear liquid remained when the ethyl acetate was evaporated, but after being left overnight in the refrigerator, it crystallised (210 mg, 91%). When recrystallised from light petroleum 3-benzyloxycarbonyl-2-oxa-3-azabicyclo[2,2,1]hept-5-ene (87a) (71%), m.p. 33-36 °C, was obtained. This product was described as an oil by Mackinnon[37]. The analytical results are:-(Found: C, 67.45; H, 5.83; N, 6.04; m/z 231.0897, $C_{13}H_{13}NO_3$ requires C, 67.53; H, 5.63; N, 6.06; M^+ 231.0895); ν_{max}(KBr) 1 706 and 1 742 cm^{-1}(CO); δ($CDCl_3$) 1.67 and 1.93 (2 x d m, J 9 Hz, 7-CH_2), 5.00 and 5.20(2 x m,1- and 4-H), 5.11(s, $PhCH_2$) 6.33(m, 5- and 6-H) and 7.30(s, Ph). A sample of this adduct, when chromatographed on silica using acetone-light petroleum (3:7) as the developer, gave a spot at R_f 0.56, which turned purple a few minutes after being sprayed with ethanolic ferric chloride.

Attempted Thermolysis of the Cycloadduct of Benzyl C-Nitroso-formate and Cyclopentadiene

a) Benzene Solution. The benzyl nitrosoformate adduct (87a) (210 mg, 0.9 mmol) in dry benzene (160 ml, 5.6×10^{-3}M solution), even when heated under reflux conditions for 24 h, was recovered unchanged (164 mg). No other product was isolated.

b) Toluene Solution. The adduct (164 mg, 0.71 mg) was heated

in dry toluene (160 ml, 4.4 x 10^{-3}M solution) for 18 h. The solution was, by this time, saffron in colour. Evaporation of the solvent left an oily residue, which was mainly unchanged adduct (87a).

Deoxygenation of Benzyl C-Nitrosoformate using Triphenylphosphine

(a) Benzene as solvent: Formation of Azepine. The benzyl nitrosoformate adduct (87a) (506 mg, 2.19 mmol) and triphenylphosphine (631 mg, 2.41 mmol) were heated under reflux in dry benzene (100 ml, 2.4 x 10^{-2}M with reference to the adduct) for 1.75 h. The solvent was evaporated, and the brown residue, dissolved in hexane-ethyl acetate (9:1), was filtered, under vacuum, through a column of silica (3 cm x 3 cm). This retained a brown material, and the first fraction of elutant (10 ml) contained the excess triphenylphosphine (72 mg, 0.27 mmol) (identified as described earlier). The next fraction (10 ml), yellow in colour, was rechromatographed on a column of silica (25 cm x 1 cm) with the original elutant. The distinctive yellow band provided N-benzyloxycarbonylazepine[37,51] (85a), (95 mg, 19%); (Found: m/z 227.0944. $C_{14}H_{13}NO_2$ requires M^+, 227.0946); ν_{max}(liquid film) 1 715 cm^{-1}(CO);δ($CDCl_3$) 5.22 (s, CH_2), ca. 5.3-5.65(br m, 3- and 6-H), 5.88(dm, J 7 Hz, 2- and 7-H), 6.08(t m, J 3 Hz, 4- and 5-H), and 7.36(s, Ph). The azepine seemed sufficiently stable to permit distillation under reduced pressure. Distillation was attempted, but the azepine decomposed. The experiment was not repeated, and so a sample, pure enough for analysis, was not obtained. The azepine and the excess triphenylphosphine were the only products recovered.

b) Dichloromethane as solvent: Phosphine Benzyloxycarbonylimide formation. The benzyl nitrosoformate adduct (87a) (152 mg, 0.66 mmol) and triphenylphosphine (350 mg, 1.32 mmol) in dichloromethane (5 ml) were heated in a sealed 'Carius' tube at 80 °C for 1 h. The reaction mixture was separated by preparative t.l.c. on silica, developed with chloroform-ethyl acetate (97:3). Four main bands had formed. Those at R_f 0.8-0.9 and R_f 0.1-0.15 contained triphenylphosphine and triphenylphosphine oxide respectively (identified as described earlier). However the band R_f 0.1-0.15 was not homogeneous and so was subjected to preparative t.l.c. on silica with chloroform-methanol (95:5) as developing agent. The triphenylphosphine oxide was in the band at R_f 0.46 and some residual adduct (87a) (8 mg) was in the one at R_f 0.5. A band at R_f 0.6, on elution with methanol, yielded triphenylphosphine benzyloxycarbonylimide (89) (5 mg, 2%), identical with an authentic specimen supplied by Professor G.W. Kirby, which had been prepared by adding benzyl azidoformate (1 mmol) in light petroleum to triphenylphosphine (1 mmol) in light petroleum (5 ml). After 0.5 h at room temperature, this solution was evaporated to give triphenylphosphine benzyloxycarbonylimide (89) 100%; m.p. 108-109 °C; (Found: 75.6; H, 5.3; N, 3.4. $C_{26}H_{22}NO_2P$ requires C, 75.9; H, 5.4; N, 3.4%); ν_{max}(KBr) 1 692 cm^{-1}; $\delta_H(CDCl_3)$ 5.05(s, $C\underline{H}_2$), 7.25(s, Ph), and 7.30-7.90(m, Ph_3P); m/z 411($\underline{M}^+$).

c) Cyclohexene as Solvent. Aziridine Formation. The benzyl nitrosoformate adduct (87a) (258 mg, 1.12 mmol) and triphenylphosphine (506 mg, 1.93 mmol) in cyclohexene (25 ml) were heated under reflux for 1 h. A few brown crystals (20 mg), quite insoluble in acetone and chloroform, separated on cooling (20 mg). When the solvent had been evaporated, the residue was redissolved in the minimum of chloroform and chromatographed on a column of silica (3 cm x 2 cm), eluting with chloroform. The first fraction (60 ml) contained the excess triphenylphosphine. A second fraction (20 ml), which proved to be of most interest, provided a white crystalline solid, and a third fraction (20 ml) contained a mixture of several substances including triphenylphosphine oxide. More of the latter was obtained by removing the silica from the column, and eluting it with chloroform.

The interesting second fraction, referred to above, was chromatographed on silica plates developed with chloroform.

A barely visible band, R_f 0.2, was eluted with ether, and the extract gave a waxy solid, m.p. 60-69 °C. This was chromatographed once more on silica plates which were developed with chloroform-ethyl acetate (97:3). The band, R_f 0.5, was eluted with ether to give a product, m.p. 60-80 °C, containing the aziridine, 7-benzyloxycarbonyl-7-azabicyclo [4,1,0]heptane (88a)(32 mg, 12%); $\delta_H(CDCl_3)$ 1.08-2.22(10H, br m, $C_6\underline{H}_8$ and CH-N-CH), 4.84(s, CH_2O), and 7.35(s, Ph); $\delta_C(CDCl_3)$ 23.7(t, 3- and 4-C), 31.8(t, 2- and 5-C, 74.6(d,1- and 6-C), 78.6(t, O-CH_2), 128.6(d, 2'-, 6'-, and 4'-C, Ph), 129.1(d, 3'-, 5'-C, Ph), 135.7(O-CH_2), and 157.3(s, C=O). There was

no molecular ion. However there were important peaks at m/z 173($M^+ - C_4H_{10}$), 107(Ph CH_2O^+), and 91(base peak, $C_6H_5CH_2^+$).

3.4. C-Nitrosoformates: Intramolecular 'Ene' Reactions

I. 3-Hydroxy-4-isopropenyloxazolidin-2-one.

Preparation of 3-Methylbut-2-en-oxycarbonyl-N-hydroxycarbamate (90a).

3-Methylbut-2-en-1-ol (3.3 ml, 30 mmol) was added, dropwise to a 12.5% solution of phosgene in toluene (52.5 ml, 60 mmol) at -40 °C. This reaction mixture was stirred for 3 h at -40 °C, and then poured slowly into a stirred ice-cold solution of hydroxylamine hydrochloride (10.5 g, 150 mmol) and sodium hydroxide (8.4 g, 210 mmol) in water (150 ml). The mixture was stirred at room temperature for 1 h. After acidification (5% hydrochloric acid), all was extracted with diethyl ether. The extract was washed with brine, dried ($MgSO_4$), and the solvent was evaporated to give a yellow oil. Elution of this through a 'Florisil' column, using chloroform-methanol (95:5) gave the N-hydroxycarbamate[26a,46] (90a, Scheme 28) as an oil (1.76 g, 40%, McLean 45%); ν_{max}(Thin film) 3 300 (NH and OH) and 1 715 cm^{-1}(CO); $\delta_H(CDCl_3)$ 1.70(br s, 2 x Me), 4.61(d, J 8 Hz, O-CH_2), 5.39(t m, J 8 Hz and allylic coupling, olefinic H), 7.60(br s, exch. with D_2O, NH and OH); m/z 145(M^+).

Cycloadduct of 3-Methylbut-2-enyl C-Nitrosoformate and Cyclopentadiene

System A

3-Methylbut-2-en-oxycarbonyl-N-hydroxycarbamate (90a)

(290 mg, 2 mmol) in ethyl acetate (5 ml), cyclopentadiene (0.33 ml, 4 mmol) in ethyl acetate (70 ml), and sodium periodate (428 mg, 2 mmol) in 0.5 M sodium acetate-acetic acid buffer solution (pH 6, 35 ml) were used. The reaction time was 1.2 h. On evaporation of the ethyl acetate solution, 3-(3'-methylbut-2'-enoxycarbonyl)-2-oxa-3-azabicyclo[2,2,1] hept-5-ene (92a) (51%, McLean[26a] 83%); $\nu_{max}(CCl_4)$ 1 750, 1 705 cm^{-1}; $\delta_H(CDCl_3)$ 1.68(br s, Me), 1.72(br s, Me), 1.99 (d m, J 9 Hz, bridge-methylene-H), 4.62(br d, J 8 Hz, OCH_2), 5.04 and 5.24(2 x m, NCH and OCH), 5.35(br t, J 8 Hz CH_2 $CH = CMe_2$), and 6.41(2H, br s, CH = CH).

Thermolysis of the Cycloadduct of 3-Methylbut-2-enyl C-Nitrosoformate and Cyclopentadiene

The adduct (92a) (50 mg, 0.24 mmol) in anhydrous benzene (40 ml) was heated under reflux for 3.5 h in an atmosphere of nitrogen. Evaporation of the solvent left an oil. This, crystallised from hexane, was 3-hydroxy-4-isopropenyloxazolidin-2-one (93) (24 mg), m.p. 74.5-75 °C; (Found: C, 50.4; H, 6.3; N, 9.7. $C_6H_9NO_3$ requires C, 50.4; H, 6.3; N, 9.8%); ν_{max}(KBr) 3 250 and 1 775 cm^{-1}; $\delta_H(CDCl_3)$ 1.77(br s, Me) 3.88-4.55(3H, m, 4- and 5-H), 5.05-5.20(2H, m, vinyl-H), and 8.45(br s, OH, exch. with D_2O); δ_C 29.7(Me), 64.8(C-4), 65.8(C-5), 117.0(CH_2 = CMe), 139.1(CH_2 = C Me), and 161.1(C-2); m/z 143(M^+), 127, and 112. The protons attached to the heterocyclic ring gave an ABC n.m.r. pattern with additional, fine coupling to an olefinic proton, H_x vid. structure (99), Scheme 29 . Approximate

δ and J values were obtained from the 360 MHz spectrum; refined values were obtained from the 100 MHz spectrum using a spin simulation programme[45]; δ 4.43(H_A), 4.41(H_B), 4.02(H_C), and 5.14(H_X), J_{AB} + 8.5, J_{AC} + 8.6, J_{BC} -8.7, and J_{AX} 0.5 Hz.

3-Acetoxy-4-isopropenyloxazolidin-2-one (102)

The N-hydroxyoxazolidinone (93) was treated with an excess of acetic anhydride in pyridine at room temperature overnight. The solution was evaporated and the residue crystallised from light petroleum (b.p. 40-60°C) to give 3-acetoxy-4-isopropenyloxazolidin-2-one (102) (150 mg, 81%); (Found: C, 51.8; H, 6.3; N, 7.8. $C_8H_{11}NO_4$ requires C, 51.9; H, 6.0; N, 7.6%); $\nu_{max}(CCl_4)$ 1 782 cm^{-1}; $\delta_H(CDCl_3)$ 1.79 (br s, vinyl Me), 2.13(s, Ac), 3.88-4.60(3H, m, 4- and 5-H), and 4.99-5.15(2H, m, vinyl-H); m/z 185(M^+). Analysis of the ABCX spin system as for compound (93), gave δ 4.56(H_A), 4.49(H_B), 4.13(H_C), and 5.06(H_X); J_{AB} + 8.5, J_{AC} + 8.6, J_{BC} - 8.7, and J_{AX} 0.5 Hz. δ and J values for the ^1H ABCX system were obtained by computer simulation[45] of the 100 M Hz spectrum. When a sample of this product was applied to an analytical t.l.c. silica plate, and this was developed with dichloromethane-ethyl acetate (97:3), a spot at R_f 0.5 became visible in iodine vapour.

Attempted Reductive Cleavage of the N-O Bond in 3-Acetoxy-4-isopropenyloxazolidin-2-one (102) using Sodium Amalgam. Keck and Webb[47] reported sodium amalgam reduction of an acylated cyclic hydroxamic acid similar to (102). It seemed a convenient method for the reduction of the current oxazolidinone

Sodium amalgam was prepared as described by Fieser and Fieser[61].

The acetylated oxazolidinone (102) (100 mg, 0.54 mmol) was dissolved in dry ethanol [6.4 ml, distilled over $Mg(OEt)_2$] and cooled to 0 °C in an atmosphere of argon. Anhydrous disodium hydrogen phosphate (309 mg, 2.18 mmol) and sodium amalgam (6%, 1.5 g) were added. Under a static argon atmosphere, the mixture at 0 °C was stirred for 4 h, and then filtered through a pad of 'Celite' on filter paper. The residue on the filter pad was washed with ethanol, and the solution was evaporated. Carbon tetrachloride was added to the residue. After another filtration, an extract containing at least 5 different products was obtained. Other modifications of the suggested procedure were equally unsuccessful.

An alternative procedure involving the dilution of the reaction mixture with tetrahydrofuran followed by filtration (a method used by Keck and Webb), also failed to give easily identifiable products. In a later paper Keck *et al.*[24] state on p.4013. "However, since our initial report, we have found that results here are highly dependent on the batch of sodium amalgam employed for the reduction".

Hydrogenation of 3-Acetoxy-4-isopropenyloxazolidin-2-one (102)

The oxazolidinone (102) (42.9 mg) in ethanol (7 ml), and palladium-carbon catalyst (17.5 mg) were stirred together at room temperature in an atmosphere of hydrogen for 44 h.

The reaction mixture was filtered through 'Celite', and the residue on the pad was washed with ethanol. After the solvent had been evaporated, the oily product was evacuated for 1.5 h on a mechanical vacuum pump. 3-Acetoxy-4-isopropyloxazolidin-2-one (103) was obtained, [49.4 mg (?), theory 43.4 mg] $\nu_{max}(CCl_4)$ 1 788 cm^{-1} (CO); $\delta_H(CDCl_3)$ 0.92(3H, d, J 3 Hz, Me), 0.99(3H, d, J 3 Hz, Me), 1.64-2.15(1H, m, C<u>H</u>-Me_2), 2.20(3H, s, Ac); 3.7-4.6(3H, m, C<u>H</u>$_2$ and N-C-H).

This crude product was subjected to hydrogenolysis, using the sodium amalgam method described earlier. To a solution of product (103) (34.8 mg, 0.19 mmol) in ethanol(2.1 ml) [distilled from $Mg(OEt)_2$] was added disodium hydrogen phosphate (103 mg, 0.73 mmol) and 6% sodium amalgam (500 mg). The mixture was stirred 3 h at 0 °C. Tetrahydrofuran (1 ml) was added, and all was filtered through 'Celite'. This was washed with more tetrahydrofuran. Evaporation left an oil from which no identifiable product was isolated.

Hydrogenation of 3-Hydroxy-4-isopropenyloxazolidin-2-one (93)

The oxazolidinone (93) (438 mg) in ethanol (10 ml), and 10% palladium-carbon catalyst (104 mg) were stirred together at room temperature in an atmosphere of hydrogen for 44 h. The reaction mixture was filtered through 'Celite' which was then washed with ethanol (5 ml). After evaporation the residue was dissolved in chloroform. Analytical t.l.c. on silica (chloroform) showed one main product, R_f 0.2. This spot immediately turned purple when sprayed with ferric chloride-ethanol solution. The chloroform solution was passed through

a column of 'Florisil' (t.l.c.) to remove base-line impurity. A clear liquid was obtained when the solvent was evaporated. 3-Hydroxy-4-isopropyloxazolidinone-2-one (100) (282 mg, 64%), m/z 145.0738(M^+); $C_6H_{11}NO_3$ requires 145.0738; $\nu_{max.}$(CCl_4) 3 250(N-OH) and 1 772 cm^{-1} (CO); δ_H($CDCl_3$) 0.93(d, J 7 Hz, Me), 0.98(d, J 7 Hz, Me), 1.9-2.34(m, HC-Me_2), 3.64-4.47(3H, m, CH_2 and N-C-H), and 7.72(1H, m, exch. with D_2O, N-O-H).

Acetylation of 3-Hydroxy-4-isopropyloxazolidin-2-one

The product (100) (approx. 100 mg) was dissolved in pyridine, and three drops of acetic anhydride were added. Two hours later the volatile liquids were evaporated. The crude 3-acetoxy-4-isopropyloxazolidinone (103) was not recrystallised. The ^1H n.m.r. spectrum of this product proved that it was identical to the oxazolidinone prepared earlier by the alternative route of acetylation followed by palladium-carbon reduction.

Attempted Reductive Cleavage of the N-O Bond in 3-Acetoxy-4-isopropyloxazolidin-2-one (103)

a) Attempted Al(Hg) Reduction[47] A solution of the oxazolidinone (103) (60 mg, 0.32 mmol) in aqueous tetrahydrofuran (THF and H_2O, 10:1) was cooled to 0 °C with stirring. Aluminium amalgam (from aluminium, 300 mg, 11.1 mmol) prepared by sequential exposure (10-25 s each) of small strips to 1 M KOH, water, mercuric chloride (aq. 0.5%), distilled water, and dry THF, was then added to the solution of the adduct, and stirring was continued at 0 °C. The mouth of the reaction vessel was stoppered by a tube fitted with a deflated balloon. At the

end of 2 h all the aluminium had reacted, and the balloon contained some gas (hydrogen ?). Additional amalgam was added (200 mg, 7.4 mmol) and stirring and cooling were continued for another 4 h.

The mixture was filtered through 'Celite' and washed with tetrahydrofuran followed by evaporation of the solvent. The residue was dissolved in water, the solution was acidified (aqueous sulphuric acid), and extracted with chloroform. After drying (Na_2SO_4), and solvent evaporation, a solid remained. It was impure starting material (103).

b) Attempted Na(Hg) Reduction. An attempt was made to use this method to bring about the cleavage of the N-O bond in compound (103). As before, it failed. No identifiable new products resulted.

Sulphur Dioxide-Pyridine Reduction[49] of 3-Hydroxy-4-isopropyloxazolidin-2-one (100)

The oxazolidone (100)(127 mg) in dry pyridine (10 ml) was contained in a 3-holed round-bottomed flask (100 ml) sitting in an electric heating mantle. The central neck of the flask was fitted with a Liebig condenser ending in a trap containing solid potassium hydroxide. One of the side necks carried an adapter with a thermometer, the bulb of which was immersed in the liquid. Between the sulphur dioxide cylinder and a bubbler connected through the third neck of the flask, a liquid trap (10 ml) was inserted as a precaution. The gas was bubbled through the pyridine. Without the application of any external heat, the liquid became hot (ca.

60 °C) and turned yellow. The gas injection was suspended, and the solution was heated under reflux for a total of 1.5 h. Four times during this period, sulphur dioxide was injected for about 2 minutes, great care being taken to prevent the "suck-back" of pyridine into the gas cylinder. At the end of the heating period, the pyridine was evaporated to leave a jelly which crystallised as needles (oxazolidinone-SO_2-pyridine complex ?). This material was strongly acidic, and so it was neutralised with aqueous sodium bicarbonate. Pyridine was liberated during the neutralisation, and was removed as an azeotrope with toluene (2 x 10 ml). The residue was extracted with ether and the extract was dried (Na_2SO_4), filtered, and the solvent evaporated. The new residue was washed with light petroleum (bp. 40-60 °C) before being crystallised from a mixture of that solvent and an equal volume of carbon tetrachloride to give 4-isopropyloxazolidin-2-one (101) (55 mg, 49%), m.p. 75 °C (mixed with authentic sample, 75 °C). Analytical t.l.c. on silica using chloroform-methanol (96:4) gave a spot of the compound at $\underline{R}_f$ 0.44 (made visible with iodine). Other properties were as reported for the authentic sample (<u>vid.</u> later).

Preparation of (±)-Valine Ethyl Ester Hydrochloride (105)

A method reported by Schwyzer *et al.*[62] was employed. Thionyl chloride (3.6 ml, 40 mmol) was added, dropwise, to ethanol (100 ml) at -10 °C in a 250 ml flask. This was followed by (±)-valine (104) (Scheme 30) and all was heated under reflux for 12 h (later tests suggested that heating for 3 h at 50 °C would have sufficed). The reactants were again cooled to -10 °C, and more thionyl chloride (1 ml, 11 mmol) in ethanol (10 ml) was added. Heating under reflux was resumed for another 1 h. The ethanol was evaporated, replaced with more ethanol (100 ml), and this was evaporated in turn. The solid, (±)-valine ethyl ester hydrochloride (105), after washing with dry ether, weighed 7.07 g (97%). It was crystallised from an ethanol-ether mixture (5.16 g, 71%). The crystals seemed to melt below 98 °C at which temperature another type of crystal had formed: these melted at 110 °C; $\delta_H(D_2O)$ 0.95(d, J 8 Hz, 2 x Me). 1.22(t, J 9 Hz, $C\underline{H}_3CH_2$), 1.13-2.60(m, 1 H, $C\underline{H}CMe_2$) 4.04(d, $C\underline{H}\ NH_2$), and 4.36(q, 9 Hz, $CH_3\ C\underline{H}_2$).

Preparation of (±)-Valinol (106)

(±)-Valine ethyl ester hydrochloride (105) (2.1 g, 11.6 mmol) in ether (150 ml) was treated with sufficient aqueous sodium bicarbonate to provide the free ethyl ester. The ether solution was dried (Na_2SO_4), and filtered into a dropping funnel. Meantime lithium aluminium hydride (882 mg, 23.2 mmol), in dry ether (100 ml), was placed in a 3-necked R.B. flask (500 ml), fitted with a reflux condenser. The second neck

carried the dropping funnel, and the remaining neck was stoppered. The ether solution was added to the liquid in the flask over a period of 0.5 h with stirring. Stirring was continued for another 0.25 h. Water (10 ml) was then added to destroy the excess reducing agent. The organic solvent layer was separated off, and the aqueous layer was extracted 5 times with ether. All the ether solutions were combined and dried (Na_2SO_4). When the solvent was evaporated there remained (±)-valinol[63] (106) (78.1 mg, 66%); $\delta_H(CDCl_3)$ 0.9(6H, d, J 7 Hz, 2 x Me), 1.60(1H, m, C<u>H</u>Me_2), 2.62(3H, br s, exch. with D_2O, N<u>H</u>$_2$ and O<u>H</u>), 2.50-2.70(1H, m, C-<u>H</u>-NH_2), 3.29(1H, t, J 10 Hz, C<u>H</u>OH), and 3.65(1H, dd, J 10 Hz and 5 Hz, C<u>H</u>OH). For the purpose of identification, the hydrochloride was prepared by passing dry hydrogen chloride gas into a concentrated solution of (±)-valinol. After filtration and evaporation, followed by crystallisation from acetone, plates m.p. 124 °C were obtained. The melting point determination was checked using both a Kofler hot-stage apparatus and a Gallenkamp apparatus employing a thermocouple. Karrer *et al.*[63] reported the melting point as 120 °C.

<u>4-Isopropyloxazolidin-2-one (101). Synthesis from (±)-Valinol</u>

A procedure reported by Homeyer[63] was employed. Diethyl carbonate (100 ml, b.p. 123-127 °C) was distilled, the first 20 ml distillate was rejected. This provided the anhydrous ester used in the preparation.

(±)-Valinol (0.23 g, 2.2 mmol) was added to anhydrous diethyl carbonate (10 ml) contained in a distilling flask

(25 ml), connected in the usual way to a Liebig condenser with receiver. The flask was heated in an oil bath. Some ester (2 ml) was distilled to ensure that the system was completely anhydrous. The solution was cooled, and 250 microlitres of a solution of sodium methoxide in methanol were added: this contained 4.24% of sodium methoxide (with reference to the valinol). Heating was resumed, and the temperature of the water bath was arranged so that the ester just failed to distil. At the end of 0.5 h the ester was evaporated leaving a residue which was then dissolved in ether. The solution was washed, first with a little dilute hydrochloric acid, and then with water. After drying (Na_2SO_4) and filtering, the ether was evaporated. The residue consisted of almost pure 4-isopropyloxazolidin-2-one (101), (yield 1.69 mg, 59% with reference to valinol). When recrystallised from carbon tetrachloride-light petroleum (b.p. 50-52 °C), it melted at 75 °C; (found: C, 55.7; H, 8.6; N, 10.7. $C_6H_{11}NO_2$ requires C, 55.8; H, 8.5; N, 10.85%); ν_{max}(KBr) 3 248 cm^{-1}(NH) and 1 745 cm^{-1}(CO); $\delta_H(CDCl_3)$ 0.89 and 0.95(2 x d, J 7 Hz, 2 x Me), 1.5-1.93(m, Me_2CH), 3.63 (distorted q, J 8 Hz, 4-H), 4.00-4.60(m, 2H, 5-H); and 6.93(br s, NH, exch. with D_2O); m/z 129(M^+).

II - The Bridged Oxazinone Derived from 3,4-Dimethylcyclohex-3-enyl Nitrosoformate

3,4-Dimethylanisole (117)

A method described by Vogel for anisole was used[64]. 3,4-Dimethylphenol (45.9 g, 0.376 mol) and sodium hydroxide

(15.8 g, 0.395 mol) in water (150 ml) were contained in a three-necked R.B. flask fitted with a dropping funnel, condenser, and mechanical stirrer. Dimethyl sulphate (35.3 ml, 0.373 mol) was added over a period of 1 h with stirring. After heating under reflux for 2 h, the reaction mixture was cooled. Water (150 ml) was added, and all was transferred to a separating funnel. The organic layer was separated off, and the aqueous layer was extracted twice with water. The combined organic extracts were washed once with water, twice with dilute sulphuric acid, and finally with water until neutral. When dry (Na_2SO_4), the ether was evaporated leaving a residue which was distilled at atmospheric pressure. The liquid b.p. 200-201 ^{o}C, was collected. This was 3,4-dimethylanisole[65] (117), (48.5 g, 95%), $\delta_H(CDCl_3)$ 2.18, (s, C-Me), 2.22(s, C-Me), 3.76(s, O-Me), 6.50-6.80(1H, br d, J 9 Hz, Aryl), and 6.89-7.14(2H, br d, 9 Hz, Aryl). These values are in accord with measurements taken from the relevant spectrum (1.843A) in the 'Aldrich Library[66] of N.M.R. Spectra'.

1-Methoxy-4,5-dimethylcyclohexa-1,4-diene[67] (118)

Freshly distilled ammonia (500 ml) was kept in liquid form in a three-necked R.B. flask, immersed in an acetone-carbon dioxide bath. Vigorous agitation was provided by a magnetic stirrer. The central neck of the flask carried a condenser tube designed for acetone-carbon dioxide cooling. This condenser tube ended in a drying tube containing potassium hydroxide. One of the side-necks of the flask was closed by a stopper, and the other carried a dropping

funnel. 3,4-Dimethylanisole (6 g, 44 mmol) in ethanol (13 ml, 313 mmol) was added to the ammonia. The anisole proved difficult to disperse in the solid. Sodium (6 g, 261 mmol) was added in small portions over 0.5 h. Meantime, a dark-blue sludge, with orange patches had formed. Stirring and cooling were continued for another 1.5 h. The apparatus was left open overnight in order to allow the ammonia to evaporate. A minimum of ice, necessary to destroy the sodium residues was added, and when that operation was complete, the reaction mixture was extracted with ether. After the extract had been dried (K_2CO_3), it was distilled using a fractionating column under atmospheric pressure. When the ether had evaporated, a fraction b.p. 183 ^{o}C was collected (3.96 g). The residue in the flask (0.77 g) also contained the desired product, but it was contaminated with the anisole. The distilled product was 1-methoxy-4,5-dimethylcyclohex-1,4-diene (118), $\delta_H(CDCl_3)$ 1.62(s, 2 x Me), 2.66(4H, br s, $C\underline{H}_2$-C-C-CH_2), 2.52(s, OMe), and 4.57(1H, m, $C\underline{H}$-C-OMe).

3,4-Dimethylcyclohex-3-en-1-one[68] (119)

A non-distilled product from a similar Birch reduction, and consisting mainly of 1-methoxy-4,5-dimethylcyclohex-1,4-diene (118) (7 g) was shaken with a saturated solution of sodium hydrogen sulphite in water (20 ml). When the amount of crystalline bisulphite compound seemed to have depleted considerably the concentration of the inorganic salt, more of the latter, in a solid form, was added. At the end of 21 h, the mixture was filtered, and the solid was washed,

first with methanol, and then with ether. The resulting material (10 g) was treated with sodium hydrogen carbonate solution. At first the solid reacted quickly: experience had proved that this was largely the excess sodium hydrogen sulphite. The material remaining as residue reacted very slowly, and, in fact, had to be heated gently with the bicarbonate solution in order to make it react. All the resulting alkaline solution was extracted with ether. The extract was dried ($MgSO_4$), and the ether was evaporated through a fractionating column, leaving a residue of 3,4-dimethylcyclohex-3-en-1-one (119) (1.15 g).

In subsequent preparations of the bisulphite addition compound, a purer sample of the diene (118) was used.

The n.m.r. spectrum of the ketone (119) showed the following signals, $\delta_H(CDCl_3)$ 1.68(br s, 2 x Me), 2.42(4H, m, C-C$\underline{H}_2$-C$\underline{H}_2$-C), 2.77(2H, m, C-C$\underline{H}_2$-CO), (lit.[68] 1.68, 2.36, 2.62).

3,4-Dimethylcyclohex-3-en-1-ol (120)

Method (a). A three-necked R.B. flask with a magnetic stirrer contained lithium aluminium hydride (0.8 g, 21 mmol) in dry ether (100 ml). The central neck of the flask was fitted with a dropping funnel, and a water condenser, ending in a silica gel trap, was in one side neck. The other neck was stoppered. The dropping funnel contained 3,4-dimethyl-cyclohex-3-en-1-one (119) (1.1 g, 8.9 mmol) in dry ether (50 ml), which was added to the solution in the flask over a period of 0.5 h. When the reaction mixture had been stirred

for another 0.5 h, saturated aqueous sodium sulphate (15 ml) was added to liberate the alcohol and to destroy excess lithium aluminium hydride. The solid was filtered and washed with ether. The combined ethereal solutions were dried (Na_2SO_4). When the ether was evaporated 3,4-dimethylcyclohex-3-en-1-ol (120) remained (0.94 g, 84%). This apparently high yield must be balanced against the low yield of the ketone (119) from the crude bisulphite addition compound. Method (b). In this preparation, a relatively pure sample of 1-methoxy-4,5-dimethylcyclohex-1,4-diene (118) was the starting material and no attempt was made to isolate the ketone (119). As before, the bisulphite compound was prepared, and a sample of it (3.8 g, 16.7 mmol) was added to a stirred mixture of ether (100 ml) and water (5 ml). Sodium carbonate was added in sufficient quantity to react with the addition compound. After filtration, the ether layer was separated off, and this solution was augmented by ether extracts of the aqueous layer. When the combined organic solution was dry (Na_2SO_4), it was reduced in bulk to 100 ml. Lithium aluminium hydride (0.8 g, 22 mmol) was added to the stirred ethereal solution over a period of 0.5 h and the reaction mixture was stirred for another 1.5 h. The rest of the operation was as described in Method (a) above. 3,4-Dimethylcyclohex-3-en-1-ol (120) was obtained (1.15 g, 55%, based on the bisulphite compound, which was assumed to be pure); $\delta_H(CDCl_3)$ 1.58(br s, 2 x Me), 1.4-1.8(2H, m, $C\underline{H}_2$, 5-H), 1.9-2.2(4H, m, 2 x CH_2, 2- and 6-H), 3.10(br s, O-H, exch.

with D_2O), and 3.7-4.1(m, 1-H). The spectrum reported[68] for the compound is δ_H 1.57(br s, 6H, 2 x Me), 1.4-1.8(2H, m), 1.8-2.2(4H, m), 2.8(shift dependent on concentration, 1H, s, OH), and 3.76(1H, m, HOH).

3,4-Dimethylcyclohex-3-enyl N-hydroxycarbamate (121)

The cyclohexenol (120) used in this preparation was that obtained, by the lithium aluminium hydride reduction of the ketone described above, and was not subjected to any additional purification.

A three-necked R.B. flask (100 ml) containing a magnetic stirrer, and fitted with a Liebig condenser and dropping funnel (10 ml), was immersed in an ice-salt cooling mixture. Phosgene solution in toluene (12 ml, 12.5%, 15 mmol) was run into the flask, and 3,4-dimethylcyclohex-3-en-1-ol (120) (0.94 g, 7.5 mmol) in toluene (5 ml) was added dropwise from the dropping funnel. After continuous stirring and cooling for a period of 3 h, the resulting chlorocarbonate solution was added to an aqueous solution (90 ml water) at 0 °C consisting of hydroxylamine hydrochloride (2.6 g, 37.4 mmol) and sodium hydroxide (2.9 g, 52.2 mmol). Stirring at 0 °C was continued for 2 h. The solution was neutralised, using dilute hydrochloric acid, and extracted with ether. The extract was washed with brine, dried, and the solvent was evaporated; (1.22 g; theoretical yield, based on the alcohol, 1.38 g). It was crystallised by dissolving in ethyl acetate, and adding light petroleum (b.p. 40-60 °C) to the solution, to give 0.45 g (33%) of the pure product

3,4-dimethylcyclohex-3-enyl N-hydroxycarbamate (121) as beautiful platelets, m.p. 108-110 °C, obscured by gas evolution; (Found: C, 58.5; H, 8.0; N, 7.5. $C_9H_{15}NO_3$ requires C, 58.4; H, 8.2; N, 7.6); ν_{max}(KBr) 3 330 cm^{-1}(NH and OH) and 1 684 cm^{-1} (CO); δ_H($CDCl_3$) 1.59(s, 2 x Me), 1.3-2.6(6H, br m, C-C$\underline{H}_2$-C$\underline{H}_2$-CO, and C-C$\underline{H}_2$-C-O), 4.8-5.2(1H, m, O-C-$\underline{H}$), and 6.5 and 7.2(2 x m, exch. with D_2O, N$\underline{H}$ and O$\underline{H}$). Mass spectroscopy gave no molecular ion. The base peak was at $\underline{m/z}$ 108; other important peaks were $\underline{m/z}$ 124 and 93. A sample of this hydroxamic acid on an analytical t.l.c. silica plate developed with chloroform-methanol (9:1) appeared at $\underline{R_f}$ 0.64 as a purple spot, when sprayed with ethanolic ferric chloride.

Cycloadduct of 3,4-Dimethylcyclohex-3-enyl nitrosoformate and cyclopentadiene

System A

3,4-Dimethylcyclohex-3-enyl carbamate (121) (310 mg, 1.7 mmol) in ethyl acetate (10 ml), cyclopentadiene (220 mg, 0.28 ml, 3.4 mmol) in ethyl acetate (60 ml), and sodium periodate (395 mg, 1.9 mmol) in 0.5 M sodium acetate-acetic acid buffer solution (pH 6, 33 ml) were used. The reaction time was 2 h.

A liquid residue was obtained when the solid was evaporated (440 mg, theoretical yield 418 mg). Further purification involved t.l.c., the plates being developed with chloroform-methanol (98:2). A wide band between $\underline{R_f}$ 0.3 and 0.5 was removed and eluted with ether. The recovered material was insufficiently pure, so it was subjected to a

second purification by preparative t.l.c. using the same developing solvent mixture. The single important band, that at $\underline{R}_f$ 0.6-0.65 was collected and eluted with ether. Attempts to crystallise the product failed. It was 3-(3,4-dimethylcyclohex-3-enyloxycarbonyl)-2-oxa-3-azabicyclo [2.2.1]hept-5-ene (123) (330 mg, 79%), $\nu_{max}(CHCl_3)$ 1 730 br cm^{-1}, (CO); $\delta_H(CDCl_3)$ 1.58(s, 2 x Me), 1.5-2.6(8H, m, 4 x CH_2), 4.90(m, cyclohex-1-yl-H), 5.02 and 5.24(2 x br s, OCH and NCH), and 6.40(2H, m, CH = CH); δ_C(multiplicities in parenthesis were obtained by off-resonance decoupling) 18.6(q), 19.9(q), 28.1(t), 29.6(t), 36.7(t), 48.1(t), 65.0(d), 72.7(d), 83.6(d), 122.3(s), 125.2(s), 132.9(d), 134.3d, and 159.3(s).

Thermolysis of the Cycloadduct of 3,4-Dimethylcyclohex-3-enyl Nitrosoformate and Cyclopentadiene

The adduct (123) (200 mg, 0.8 mmol) in benzene (180 ml) was heated under reflux in a static atmosphere of nitrogen. It required 18.5 h heating before the amount of (123) was reduced to an inappreciable level (n.m.r. monitoring). When the solvent was evaporated the solid residue weighed 154 mg (theoretical weight 147 mg). This residue was washed four times with benzene (4 x 1 ml). After each wash, the benzene was removed using a fine-tipped Pascal pipette. The remaining solid was dissolved in hot benzene and the product was obtained as crystals when light petroleum (b.p. 40-60 °C) was added to the cold solution. Alternatively, the crude product from another similar experiment was purified by preparative t.l.c. on silica, using chloroform-methanol (9:1) as the developing solvent. This method had the disadvantage

that a sample side-strip of each plate had to be sprayed with ethanolic ferric chloride. A slow-developing purple-coloured zone identified the position (R_f 0.6) of the desired product. Ethyl acetate was used as elutant. The product was 4-hydroxy-5-methyl-6-methylene-2-oxa-4-azabicyclo[3.3.1]nonan-3-one (115) (60 mg, 39%), m.p. 174 °C (small hexagonal crystals separated out at about 150 °C), (Found: C, 59.2; H, 7.2; N, 7.5. $C_9H_{13}NO_3$ requires C, 59.0; H, 7.2; N, 7.65%); ν_{max}(KBr) 3 190 cm^{-1}(OH) and 1 686 cm^{-1}(CO); δ_H($CDCl_3$) 1.53(3H, s, Me), 1.5-2.5(m, 3 x CH_2); 4.5-4.7(m, 1H), 4.98 and 5.04(2 x br s, vinyl-H), and 8.25(br s, OH, exch. with D_2O); δ_C 21.3(Me), 27.0, 32.5, and 39.6(8-, 7-, and 9-C, not necessarily in this order), 61.0(5-C), 73.3(1-C), 110.8 [$\underline{C}H_2$ = C(6)], 147.0(6-C), and 156.4(3-C); m/z 183(M^+). The yield from this experiment (39%), contrasts with the results of later kinetic experiments, which suggested that 75% could be expected, even after a thermolysis period as short as 1 h. Ignoring other considerations, the low yield actually obtained is a reflection of the difficulties of purification.

Sulphur Dioxide-Pyridine Reduction of 4-Hydroxy-5-methyl-6-methylene-2-oxa-4-azabicyclo[3.3.1]nonan-3-one (115)

Dry pyridine (10 ml) was saturated with sulphur dioxide as described for the preparation of the oxazolidone (100). The hydroxyoxazinone (115) (30 mg, 16.4 mmol) in dry pyridine (4 ml) was added. Some more sulphur dioxide was injected. The solution was heated for 8 h under reflux conditions, more gas being injected at 2 h intervals. Long needles

separated on cooling, (a pyridine-sulphur dioxide-product complex?). After the solvent had been evaporated, a little sodium hydrogen carbonate was added to neutralise the acid. The resulting solution was extracted with ether and dried ($MgSO_4$). When the ether has been evaporated, the product still smelled of pyridine, and so toluene (5 ml) was added and the pyridine was removed as an azeotropic mixture. This operation was repeated with another 5 ml of toluene. The crude product was dissolved in ethyl acetate, and the solution was filtered. Most of the solvent was evaporated and light petroleum (b.p. 40-60 °C) was added until crystals formed. These crystals were washed twice with a few drops of light petroleum; 5-methyl-6-methylene-2-oxa-4-azabicyclo[3.3.1] nonan-3-one (124) (12 mg, 43%), m.p. 148 °C (small rectangular crystals appeared at about 140 °C); (Found: C, 64.6; H,7.6; N, 8.1. $C_9H_{13}NO_2$ requires C, 64.65; H, 7.8; N, 8.4%); ν_{max}(KBr) 3 220 and 3 100 cm^{-1}(NH) and 1 698 cm^{-1}(CO); ν_{max}($CHCl_3$) 3 440 cm^{-1}(NH) and 1 697(CO); δ_H($CDCl_3$) 1.41(s, Me), 1.4-2.9(6H, m, 3 x $C\underline{H}_2$), 4.72(m, 1-H), 4.83(2H, br s, vinyl H), and 5.83(br s, NH, exch. slowly with D_2O). Analytical t.l.c. on silica using chloroform-methanol (98:2) as developing agent, gave a spot at $\underline{R}_f$ 0.25 which became visible when exposed to iodine vapour. There was no purple colouration when the developed plate was sprayed with ethanolic ferric chloride.

The following three experiments were exploratory and the products were not purified. Nevertheless, they showed that

a double reduction of the bicyclo-oxazinone (115) was relatively simple.

a) Palladium-Carbon Reduction of 5-Methyl-6-methylene-2-oxa-4-azabicyclo[3.3.1]nonan-3-one (124)

Compound (124) (18 mg, 0.11 mmol) was mixed with palladium-carbon (5.4 mg) in ethanol (5 ml), and stirred in an atmosphere of hydrogen for 3.75 h. After filtration through Celite, and evaporation of the ethanol, small needles were obtained. These crystals showed signs of melting at 147 °C but they did not really melt until 177-178 °C. The n.m.r. spectrum of the product was $\delta_H(CDCl_3)$ ca. 1.0-2.25 (12 or 13 H, m, this multiplet included one methyl singlet at 1.28), 4.65(m, H-CO), and 6.27(m, NH, exch. slowly with D_2O). It likely contained some isomer of 5,6-dimethyl-2-oxa-4-azabicyclo[3.3.1]nonan-3-one (125).

b) Palladium-Carbon Reduction of 4-Hydroxy-5-methyl-6-methylene 2-oxa-4-azabicyclo[3.3.1]nonan-3-one (115)

The bicyclooxazinone (115) (40 mg, 0.22 mmol) in ethanol (5 ml) was mixed with palladium-carbon (10 mg) and hydrogenated (4.7 h) as described above. The product (32.5 mg) was a liquid: $\delta_H(CDCl_3)$ 1.0-2.6(12 or 13H, m, this multiplet included one methyl singlet at 1.45), 4.54(m, H-C-O), and 6.8-8.0(br s, exchangeable with D_2O, N-OH). This product was likely 4-hydroxy-5,6-dimethyl-2-oxa-4-azabicyclo[3.3.1] nonan-3-one.

c) Sulphur dioxide-Pyridine Reduction of 4-Hydroxy-5,6-dimethyl-2-oxa-4-azabicyclo[3.3.1]nonan-3-one

The product from experiment (b) (above) (32.5 mg) was

heated under reflux in pyridine (5 ml) which had been saturated with sulphur dioxide. The heating was continued for 8 h with injections of sulphur dioxide on six occasions. After filtration and solvent evaporation, needle-like crystals were obtained as residue. These softened at 145 °C, but did not actually melt until about 185 °C. The n.m.r. spectrum contained the following signals; $\delta_H(CDCl_3)$ ca. 1.0-2.23 (12 or 13H, m; this multiplet included 2 methyl signals at 1.19 and 1.25), 4.64(m, H-C-O), and 5.25-6.10(br s, exch. slowly with D_2O, NH). The product likely contained some isomer of 5,6-dimethyl-2-oxa-4-azabicyclo[3.3.1]nonan-3-one (125)

Kinetic Study: The Formation of the Hydroxyoxazinone (115)

(a) Cyclopentadiene in Benzene Solution. Cookson's Reagent[50] 4-phenyl-1,2,4-triazolinedione (126) in benzene (approx. 0.01 M) was used to measure the cyclopentadiene content of benzene solutions by titration. The 'end-point' was indicated by the discharge of the brick-red colour of the reagent. The solution must be fresh because it decomposes appreciably even within a few hours. The change in composition is reflected as an obvious loss of colour.

Freshly distilled cyclopentadiene in dry benzene (0.01 M) was heated under reflux using a condenser terminating in a drying tube. Aliquots were removed periodically and titrated against Cookson's reagent. Even after 21.9 h, the solution still contained 44% of the original cyclopentadiene: a half-life of about 18 h.

(b) Thermolysis of the Cycloadduct of 3,4-Dimethylcyclohex-3-enyl Nitrosoformate and Cyclopentadiene. The adduct (123) (176 mg) in benzene (176 ml, 0.004 M) was heated under reflux in a static atmosphere of nitrogen at atmospheric pressure. Aliquots (10 ml) were removed at intervals and these were evaporated, and then assayed using proton n.m.r. spectrometry. When the last aliquot had been abstracted, the remaining solution (ca. 100 ml) was distilled, and the benzene was collected, and assayed for cyclopentadiene using Cookson's reagent. It contained 22.6 mg cyclopentadiene. This is to be compared with the 26.4 mg cyclopentadiene moiety present in 100 ml of the original adduct solution. The above procedures were repeated, using adduct solutions of molarity 0.03 and 0.01. A selection of the results have already appeared in Table 1, Section 2.3. Most of the material from these experiments was re-united, the solvent was evaporated, and the residue (149 mg) was redissolved in benzene (60 ml). The resulting solution was heated under reflux for 1 h. The product was 93% hydroxyoxazinone.

3.5. C-Nitrosoformamides

Cycloadduct of C-Nitrosoformamide and Cyclopentadiene

System B

Hydroxyurea (128a) (0.76 g, 10 mmol) and cyclopentadiene (1.65 ml, 20 mmol) in ethanol (150 ml) was used with tetraethylammonium periodate (3.53 g, 11 mmol). The volume of dichloromethane used for extraction was 300 ml.

Almost from the start, the reaction mixture turned straw yellow. The solid residue (0.86 g) was dissolved in a chloroform-methanol mixture (9:1), and passed through a column of silica. This was not completely successful, so a solution of the eluted material was dissolved in ethyl acetate and passed through another column of silica (4 cm x 2 cm). The first 10 ml of solvent removed a fast-running yellow impurity. Continued development with the same solvent, brought out the desired adduct, leaving behind a slow moving yellow impurity. 3-carbamoyl-2-oxa-3-azabicyclo[2.2.1]hept-5-ene (130a) (yield 47%) m.p. 137 °C (decomp)(from ethyl acetate). Some crystals of the adduct were mixed with 'nujol' and heated on a microscope stage. Between 130-139 °C there was a profuse evolution of gas. No bubbles appeared after the substance had melted. Other data were (Found: C, 51.2; H, 5.9; N, 20.0. $C_6H_8N_2O_2$ requires C, 51.4; H, 5.75; N, 20.0%); ν_{max} 3 435, 3 295, 3 250, 3 182, 1 660 and 1 625 cm^{-1}; δ_H 1.80 and 2.00 (ABq, J 9 Hz with fine splitting, 7-CH_2), 5.20(m, 1- and 4-H), 5.50(br s, NH_2 exch. with D_2O), 6.38 and 6.42(2 x m, 5- and 6-H); m/z 140(M^+).

Attempted Thermolysis of the Cycloadduct (130a) of C-Nitrosoformamide and Cyclopentadiene

a) Disregarding the fact that the cyclopentadiene adduct (130a) is insoluble in benzene, 12 mg of it, in 20 ml of that solvent, were heated under reflux for 2 h. No recognisable products were obtained.

b) The adduct (6.3 mg) was dissolved in ethyl acetate (5 ml, 0.009 M) and heated under reflux for 5 h. At the end of this period 5.1 mg of material were recovered. It consisted of the original adduct (130a) and some tarry material.

c) A more concentrated solution of the adduct in ethyl acetate (0.025 M) remained unchanged when heated under reflux for 2 h.

Cycloadduct (131a) of C-Nitrosoformamide and 2,3-Dimethylbuta-1,3-diene

System B

Hydroxyurea (76 mg, 1 mmol) and 2,3-dimethylbut-1,3-diene (1.13 ml, 10 mmol) in ethanol (20 ml) were used with tetraethylammonium periodate (353 mg, 1.1 mmol) in ethanol (15 ml).

The dichloromethane solution of the reaction mixture was evaporated to small bulk, and then applied to a column of t.l.c. grade silica (6 cm x 2 cm. dia.), which was eluted under suction, using acetone-light petroleum (35:65). After 30 ml of solvent had been passed through the column, the following 30 ml of solvent contained 2-carbamoyl-3,6-dihydro-4,5-dimethyl-2H-1,2-oxazine (131a) (yield 63 mg, 40%), m.p. 106 °C (from ethyl acetate); (Found: C, 53.7; H, 7.8; N, 18.0. $C_7H_{12}N_2O_2$ requires C, 53.8; H, 7.75; N, 17.9%); ν_{max}(KBr) 1 654 cm^{-1}(CO), 3 210(s), 3 285 and 3 410(N-H); $\delta_H(CDCl_3)$ 1.59 and 1.70(2 x s, 2 x Me), 3.94 and 4.23(2 x br s, 2 x Me), and 5.67 (br s, NH_2 exch. with D_2O); m/z 156 (M^+).

Thermal Transfer of C-Nitrosoformamide from the Cyclopentadiene Adduct (130a) to 2,3-Dimethylbuta-1,3-diene

The cyclopentadiene adduct (130a) (70 mg) (0.5 mmol) and the dimethylbutadiene (0.285 ml, 2.5 mmol) were dissolved in ethyl acetate (20 ml), and heated under reflux for 5.5 h. The molarity of the adduct (130a) was 0.025 at the start of the experiment. At the end of the reaction, the liquids were evaporated, and the residue, which remained, weighed 70 mg. Preparative t.l.c. on silica, using chloroform-methanol (92:8) as the developing solvent, followed. Because the position of the dimethylbutadiene adduct on the plates was difficult to detect, the portions between limits set by two dark bands, R_f 0.3 and 0.45, were removed and eluted with methanol. About 40 mg (50%) of the cycloadduct (131a) of nitrosoformamide and 2,3-dimethylbuta-1,3-diene were isolated.

Another band at R_f 0.2 was eluted with acetone to yield about 10 mg of a product, which gave a purple colour with ethanolic ferric chloride. Almost certainly, it had resulted from an 'ene' reaction, and was N-hydroxy-N-(3-methyl-2-methylenebut-3-enyl)urea (135a), $\delta_H(CDCl_3)$ 1.93(s, Me), 4.39(s, CH_2N), and 5.05, 5.24, 5.32, 5.40 (4 x br s, 4 x vinyl H).

Table 7

Transfer of C-nitrosoformamide from 0.5 mmol of cyclopentadiene adduct (130a) to dimethylbutadiene (DMBD)

DMBD adduct	Weight of DMBD adduct (mg)	Nitroso compound transferred (mmol)
(131a)	40	0.25
(135a)	10	0.06

N^1-Hydroxy-N-methylurea (128b)

Method (a). A flask (50 ml capacity) containing benzene (10 ml) was tared. Some hydroxylamine base[59] was added, and the flask with contents were weighed. The weight of base was 1.8 g (55 mmol). Some more benzene was added (15 ml). Methylisocyanate (1.74 g, 2.5 ml, 42 mmol) was added, dropwise, with stirring at 0 °C. The volume of the reaction mixture was reduced to 15 ml, and crystals of N^1-hydroxy-N-methylurea (128b) separated. The crystals were filtered off, and dried on filter paper; (2.8 g, 73% based on methylisocyanate). Three crystallisations from ethyl acetate gave a product, m.p. 133-134 °C, (lit.[69] 130-132 °C - no other details given); (Found: C, 26.7; H, 6.7; N, 31.2, $C_2H_6N_2O_2$ requires C, 26.7; H, 6.7; N, 31.1%); ν_{max}(KBr) 3 395 cm^{-1}(NH), 3 210(NH and OH), and 1 643(CO); $\delta_H[(CD_3)_2CO]$ 2.8(d, J 6 Hz, Me), 6.32(1H, br s, NHMe), and 7.57 and 7.94(2 x s, HONH); m/z 90(M^+).

Method (b). This avoided the preparation of hydroxylamine base. Sodium (230 mg, 10 mmol) was dissolved in ethanol (20 ml) containing a trace of phenolphthalein. A solution of powdered hydroxylamine hydrochloride (695 mg, 10 mmol) in ethanol (40 ml) was added, with stirring, at 0 °C. The indicator was employed to ensure that the hydroxylamine hydrochloride was present in slight excess. Methyl isocyanate (533 mg, 0.55 ml, 9.3 mmol) in ethanol (10 ml) was added over a period of a few minutes. Cooling (0 °C) and stirring were continued for 1 h. The sodium chloride was filtered off, and washed with ethanol (10 ml). 'Flash chromatography' using

ethyl acetate-ethanol (9:1) as the eluting solvent gave $\underline{N}^1$-hydroxy-$\underline{N}$-methylurea (128b) (590 mg, 70% based on the methyl isocyanate).

Cycloadduct of N-Methyl-C-nitrosoformamide and Cyclopentadiene System B

$\underline{N}^1$-Hydroxy-$\underline{N}$-methylurea (128b) (0.67 g, 7.4 mmol), cyclopentadiene (6.08 ml, 74 mmol) in ethanol (200 ml), and tetraethylammonium periodate (2.62 g, 8.16 mmol) in ethanol (60 ml) were used. The reaction time was 1.3 h for the addition of the oxidising agent, and then all was left one more hour.

Instead of using dichloromethane, the brown residue was extracted with chloroform (100 ml), and the resulting solution was washed with water, rather than with brine. 'Flash chromatography'[70] with ethyl acetate-light petroleum (9:1) as the eluting agent, was used to purify the solid reaction product. Crystallisation from ethyl acetate-light petroleum, b.p. 40-60 °C, gave 3-(N-methylcarbamoyl)-2-oxa-3-azabicyclo [2.2.1]hept-5-ene (130b), (0.57 g, 50%); m.p. 83 °C (decomp.); (Found: C, 54.3; H, 6.6; N, 18.2. $C_7H_{10}N_2O_2$ requires C, 54.5; H, 6.5; N, 18.2%); $\nu_{max}^{(KBr)}$ 3 375 and 1 658 cm^{-1}; δ_H 1.73 and 1.95(ABq, $\underline{J}$ 9 Hz, with fine splitting, 7-CH_2), 2.71(d, $\underline{J}$ 6 Hz, NMe), 5.16(br s, 1- and 4-H), 5.62(br s, NH, exch. with D_2O), and 6.36(m, 5- and 6-H), $\underline{m/z}$ 154($\underline{M}^+$). A few minutes after having been sprayed with ethanolic ferric chloride, a spot of this compound on an analytical t.l.c. silica plate turned purple.

Attempted Thermolysis of the Cycloadduct of N-Methyl-C nitrosoformamide and Cyclopentadiene

(a) Adduct (130b) (51 mg, 0.33 mmol) in dry benzene (33.3 ml), an approximately 0.01 molar solution, was heated under reflux conditions for 4.5 h. The solvent was evaporated, and the residue was analysed using t.l.c., and n.m.r. spectroscopy. The product was unchanged adduct, but obviously depleted in amount. When the original volume of benzene was added, and the resulting solution heated under reflux for an additional 7.5 h, no product was found on "work-up".

(b) The experiment was repeated with an adduct solution of molarity 0.4. Thus the adduct (130b) (122 mg) in benzene (20 ml) was heated under reflux conditions. After 5.5 h some adduct remained. It was accompanied by insoluble material (40 mg). Even 9.5 h was not long enough to decompose all the adduct. This time there was a residue of 35 mg, in the form of a yellowish brown intractable solid.

(c) Experiment (a) was repeated, with toluene being used in place of benzene (0.01 molar solution). Heating under reflux conditions for 1 h was sufficient to destroy all the adduct. The residue was insoluble in chloroform, acetone, and benzene.

Cycloadduct of N-Methyl-C-nitrosoformamide and 2,3-Dimethylbuta-1,3-diene

System B

N^1-Hydroxy-N-methylurea (128b) (237 mg, 2.6 mmol), 2,3-dimethylbut-1,3-diene in ethanol (130 ml) and tetra-ethylammonium periodate (930 mg, 2.9 mmol) in ethanol (40 ml)

were used. The reaction time was 0.75 h for the addition of the oxidising agent followed by an additional 0.75 h. Chloroform (150 ml), instead of dichloromethane, was used in the work up. The recovered solid (250 mg) was further purified using 'Flash chromatography'[70]. Elution was with ethyl acetate-light petroleum (4:1). Crystallisation, from ethyl acetate-light petroleum (b.p. 40-60 °C) gave 3,6-dihydro-4,5-dimethyl-2-(N-methylcarbamoyl)-2H-1,2-oxazine (131b), 190 mg, 42% based on (128b), long needles, m.p. 71 °C; (Found: C, 56.4; H, 8.45; N, 16.4. $C_8H_{14}N_2O_2$ requires C, 56.5; H, 8.3; N, 16.5%); ν_{max}(KBr) 3 358 and 1 658 cm^{-1}; δ_H 1.57 and 1.66(2 x br s, 2 x Me), 2.83(d, J 6 Hz, NMe), 3.86 and 4.18(2 x br s, 2 x CH_2), and 5.84(br s, NH, exch. with D_2O): m/z 170(M^+).

Thermal Transfer of N-Methyl-C-nitrosoformamide from the Cyclopentadiene Adduct (130b) to 2,3-Dimethylbuta-1,3-diene

The cyclopentadiene adduct (130b) (63.3 mg, 0.41 mmol) was dissolved in ethyl acetate (10.3 ml) to give a solution of approximate molarity 0.04. Dimethylbutadiene (0.47 ml, 4.1 mmol) was added. The solution was heated, under reflux, for 2 h, at the end of which time, no cyclopentadiene adduct could be detected by analytical t.l.c. (ethyl acetate). Now a new spot had appeared on the t.l.c. plate at R_f 0.6. This gave a purple colour with alcoholic ferric chloride. 'Flash chromatography'[70], eluting with ethyl acetate-light petroleum (4:1), provided aliquots (3 x 10 ml) containing the dimethylbutadiene adduct (131b) (50 mg approx.). The next aliquot

(10 ml) was rejected, but the following 50 ml of solvent yielded rather oily crystals, which, when subjected to preparative t.l.c. on silica, developed with chloroform-ethyl acetate (4:1), gave a main band at $\underline{R}_f$ 0.15. When this was eluted with ethyl acetate, long needle-shaped crystals of N-hydroxy-N'-methyl-N-(3-methyl-2-methylenebut-3-enyl)urea (135b) were obtained, yield 15 mg; m.p. 105 °C; (Found: 56.2; H, 8.2; N, 16.2; m/z 170.1056. $C_8H_{14}N_2O_2$ requires C, 56.5; H, 8.3; N, 16.5%; M 170.1055); $\nu_{max}^{(KBr)}$ 3 365, 3 160, 1 625, and 1 650 cm^{-1}; λ_{max}(EtOH) 239 nm(ε 4 390); $\delta_H(CDCl_3)$ 1.89(s, vinyl-Me); 2.76(d, J 6 Hz, NMe), 4.31(s, NCH_2), 4.97, 5.13, 5.17, 5.23(4 x br s, 4 x vinyl-H), 5.92(br s, NH, exch. with D_2O), and 7.15(br s, OH, exch. with D_2O). Adduct (135b) immediately gave a purple colour with ethanolic ferric chloride.

Table 8

Transfer of N-methyl-C-nitrosoformamide from the cyclopentadiene adduct (130b) (0.41 mmol) to dimethylbutadiene (DMBD).

DMBD adduct	Weight of DMBD adduct (mg; approx.)	Nitroso compound transferred (mmol)
(131b)	50	0.29 (72%)
(135b)	15	0.09 (21%)

Approximately 90% of the nitrosoformamide had been transferred.

N'-Hydroxy-N-phenylurea (128c)

The method described by Von der Kall[71] was employed. A solution prepared from hydroxylamine hydrochloride (27.8 g, 0.4 mol) and sodium hydroxide (15 g, 0.38 mol) in water (200 ml) was stirred vigorously at 0 °C. Phenyl isocyanate (11.9 g, 10.87 ml, 0.1 mol) was added dropwise. White crystals appeared. Stirring and cooling were continued for 3 h. The solid material was filtered off, and washed with a little ether to remove a yellow colouration, and was then dissolved in ether (3 litres). When the ether was evaporated to small bulk, N'-hydroxy-N-phenylurea (128c) was obtained (8.7 g, 57%). Further crystallisation from ethyl acetate gave a product which melted at 146 °C, with decomposition (lit. 140 °C, uncorrected); $\delta_H[(CD_3)_2CO]$ 6.87-7.0(m, Ph), 8.10 and 8.37(3H, 2 x br s, 2 x NH and OH, exch. with D_2O). The product gave a purple colour with ethanolic ferric chloride.

Cycloadduct of N-Phenyl-C-nitrosoformamide and Cyclopentadiene System B

N'-Hydroxy-N-phenylurea (128c) (254 mg, 1.67 mmol) and cyclopentadiene (1.52 ml, 1.84 mmol) in ethanol (62.5 ml) with tetraethylammonium periodate (0.59 g, 1.84 mmol) in ethanol (12.5 ml) were used.

Water, rather than brine, was employed during the washing procedure. A n.m.r. spectrum of the residue showed that it was reasonably pure adduct (82%). The use of a column of silica under vacuum, with chloroform as elutant, provided a purer sample (67% yield). For the purpose of microanalysis,

further purification involved the use of 'Flash Chromatography'[70] using chloroform as the elutant. A persistent trace of yellow colour was finally removed by solution in a minimum of ethyl acetate followed by the addition of light petroleum (b.p. 40-60 °C) to induce crystallisation. The product was 3-(N-phenylcarbamoyl)-2-oxa-3-azabicyclo[2.2.1]hept-5-ene (130c), m.p. 103 °C; (Found: C, 66.7; H, 5.5; N, 13.05. $C_{12}H_{12}N_2O_2$ requires C, 66.7; H, 5.6; N, 12.95%); ν_{max}(KBr) 1 663 cm^{-1}(CO) and 3 368 cm^{-1}(NH); δ_H($CDCl_3$) 1.79 and 2.00(ABq, J 9 Hz with fine splitting, 7-CH_2), 5.23(br s, 1- and 4-H), 6.39 and 6.48 (2 x m, 5- and 6-H), and 6.9-7.6(m, Ph); m/z 216(M^+). Several minutes after having been sprayed with ethanolic ferric chloride, a sample of this compound on an analytical silica plate turned purple.

Attempted Thermolysis of the Cycloadduct of N-Phenyl-C-nitrosoformamide and Cyclopentadiene

a) The adduct (130c) (34 mg, 0.17 mmol) was dissolved in dry benzene (34 ml) to give a solution of approximate molarity 0.0046. This was heated under reflux conditions for 5.5 h. When the solvent was evaporated, the oily residue was found to be a complex mixture containing some of the adduct.

b) The concentration of the adduct in benzene was increased to 0.04 M - that concentration used for the transfer of the nitroso compound from adduct (130c) to dimethylbutadiene (see later). Two hours under reflux did not yield any identifiable new products.

c) Even the use of boiling toluene (0.0046 M and 0.02 M) proved inadequate as a medium for producing recognizable

products. In each case, some of the adduct was recovered.

Cycloadduct of N-Phenyl-C-nitrosoformamide and 2,3-Dimethylbuta-1,3-diene

System B

N'-Hydroxy-N-phenylurea (0.51 g, 3.33 mmol) and 2,3-dimethylbuta-1,3-diene (0.76 ml, 6.67 mmol) in ethanol (150 ml), with tetraethylammonium periodate (1.07 g, 3.33 mmol) in ethanol (40 ml) were used.

A brown solid remained when the dichloromethane was evaporated. Examination of the n.m.r. spectrum showed that it was quite pure adduct (131c). When subjected to 'Flash Chromatography'[70] using a column of silica, 25 cm x 2 cm dia., with chloroform as the eluting solvent, the first 150 ml of chloroform carried out most of the brown impurity. The following 300 ml of solvent contained almost-colourless adduct (131c) (160 mg, 0.69 mmol, 21% yield). For the purposes of microanalysis, a purer sample was obtained using preparative t.l.c. on silica, with benzene as the developing agent, and acetone as the elutant of a band, R_f 0.5. A slight yellow contamination was removed by washing the crystals with light petroleum. Recrystallisation from ethyl acetate gave 3,6-dihydro-4,5-dimethyl-2-(N-phenylcarbamoyl)-2H-1,2-oxazine (131c), m.p. 101.5 °C; (Found: C, 67.4; H, 7.2; N, 11.9. $C_{13}H_{16}N_2O_2$ requires C, 67.2; H, 6.9; N, 12.0%); ν_{max}(KBr) 3 280 cm^{-1}(NH) and 1 652 cm^{-1}(CO); $\delta_H(CDCl_3)$ 1.58 and 1.68(2 x br s, 2 x Me), 3.98 and 4.30(2 x br s, 2 x CH_2), 6.90-7.60(m, Ph), and 7.65(br s, NH, exch. with D_2O); m/z 232(M^+).

Thermal Transfer of N-Phenyl-C-nitrosoformamide from the Cyclopentadiene Adduct (130c) to 2,3-Dimethylbuta-1,3-diene

The adduct (130c) (86 mg, 0.4 mmol) and dimethylbutadiene (0.455 ml, 4 mmol) were dissolved in benzene (10 ml), and heated under reflux conditions for 2 h. Although monitoring, using t.l.c., suggested that the reaction was complete in 2 h, heating was continued for another hour. When the solid was evaporated, the resulting residue was subjected to preparative t.l.c. on silica, developing with light petroleum-acetone (65:35). There were two main bands, and these were eluted with acetone. One band, R_f 0.6, gave the expected adduct (131c) in 74% yield based on (130c) . The other band, R_f 0.55, gave a solid which was crystallised by adding light petroleum to its solution in ethyl acetate. This compound was N-hydroxy-N-(3-methyl-2-methylenebut-3-enyl)-N'-phenylurea (135c), 18 mg, 20% based on the cyclopentadiene adduct (130c) , m.p. 133 °C; (Found: m/z 232.1204. $C_{13}H_{16}N_2O_2$ requires M, 232.1211); $\delta_H[(CD_3)_2CO]$ 1.89(s, vinyl-Me), 4.41(s, NCH_2), 5.01(br s, vinyl-H), 5.28(br s, 3 x vinyl-H) 6.85-7.45(m, 3H, m- and p-phenyl-H), 7.55-7.75(2H, m, o-phenyl-H), 8.53(br s, NH, exch. with D_2O), and 8.73(br s, OH, exch. with D_2O).

Table 9

Transfer of C-phenylnitrosoformamide from 0.4 mmol cyclopentadiene adduct (130c) to dimethylbutadiene (DMBD)

DMBD adduct	Weight of DMBD adduct (mg)	Nitroso compound transferred (mmol)
(131c)	64	0.30
(135c)	18	0.08

More than 90% of the N-phenyl-C-nitrosoformamide had been transferred.

N'-Hydroxy-N,N-dimethylurea (128d)

Hydroxylamine (3.4 g, 0.103 mmol) and triethylamine (7.16 ml, 0.052 mmol) were dissolved in dry dioxan (200 ml), and to this a solution of N,N-dimethylcarbamoyl chloride (4.75 ml, 5.56 g, 0.052 mmol) in dry dioxan (20 ml) was added, dropwise, with constant rapid stirring. One hour later, triethylamine hydrochloride was filtered off, and the dioxan was evaporated. The residue was dissolved in a minimum of methanol and the solution was filtered. Addition of diethyl ether to this solution gave crystals of N'-hydroxy-N,N-dimethylurea (128d) in 93% yield, m.p. 113 °C (lit.[72a] m.p. 107-109 °C; lit.[72c] 109-110 °C, "almost pure"); (Found: C, 34.7; H, 7.7; N, 26.9. $C_3H_8N_2O_2$ requires C, 34.6; H, 7.8; N, 26.9%) ν_{max}(KBr) 1 650 cm^{-1} (CO) and 3 320 cm^{-1} (NH); $\delta_H(CDCl_3)$ 2.92(s, 2 x Me), and 7.00(br s, NH and OH, exch. with D_2O).

A British patent, in the names of Laridon *et al.*[73], suggested a preparation which would have avoided the use of the very hydroscopic hydroxylamine base. However, the method proved to have other disadvantages. Nevertheless it gave a 75% yield.

Cycloadduct of N,N-Dimethyl-C-nitrosoformamide and Cyclopentadiene

System A

N'-Hydroxy-N,N-dimethylurea (0.104 g, 1 mmol) in water (10 ml) and cyclopentadiene (1.5 ml, 1.23 g, 18.6 mmol) in ethyl acetate (20 ml) were used. Test preparations, with varying amounts of cyclopentadiene, were tried. Best results were obtained with a large excess of the diene. The oxidising agent was sodium periodate (0.214 g, 1 mmol) in tap water (30 ml).

The urea was added, dropwise, over a period of 1 h. After the usual work up, the solvent was evaporated, leaving crystals. Further purification was required in order to remove a brown contamination. This was carried out using t.l.c., with acetone-light petroleum (3:7) as the developing agent. The wide band, R_f 3.5-6, was eluted with acetone, and gave a straw-yellow product 3-(N,N-dimethylcarbamoyl)-2-oxa-3-azabicyclo[2.2.1]hept-5-ene (130d) (47%), m.p. ca. 30 °C; (Found: m/z 168.0904, $C_8H_{12}N_2O_2$ requires M 168.0898); ν_{max} ($CHCl_3$) 1 650 cm^{-1} (CO). δ_H 1.74 and 1.94 (ABq, J 9 Hz with fine splitting, 7-CH_2), 2.93 (s, NMe_2), 4.93 and 5.08 (2 x br s, 1- and 4-H), and 6.38 and 6.52 (2 x m, 5- and 6-H). One minute

after having been sprayed with ethanolic ferric chloride, a sample of this compound, on an analytical t.l.c. plate, turned purple. The adduct darkened considerably on prolonged storage. In fact, a proton n.m.r. spectrum taken at the end of a seven-week storage period exhibited a tiny peak at δ 2.98 which could have arisen from a trace of the anhydride (132d) described in the next experiment, and appearing here as a decomposition product.

Thermolysis of the Cycloadduct of N,N-Dimethyl-C-nitroso-formamide and Cyclopentadiene

a) A solution of the adduct (130d) in dry benzene (40 mg adduct in 40 ml solvent, 0.006 M) was heated under reflux for 2 h. After the solvent had been removed, the residue was chromatographed on silica plates developed with acetone-light petroleum (1:1). Because it was difficult to identify the positions of the bands containing products, decisions as to their whereabouts were made according to information obtained by iodine-staining a sample plate. Sections of the plates between $\underline{R}_f$ 0.6 and $\underline{R}_f$ 0.85 were removed and eluted with ethanol to give a viscous liquid, N,N-dimethyl-carbamic anhydride (132d), 5-10 mg, which was identical to an authentic sample[74] (see following experiment); $\nu_{max}(CHCl_3)$ 1 758 and 1 716; $\delta_H(CDCl_3)$ 2.98(s, 4 x Me); $\delta_H[CDCl_3-C_6D_6$ (1:1)][75] 2.60(s, 2 x Me), and 2.70(s, 2 x Me); $\delta_C(CDCl_3)$ 36.5(2 x Me), 36.7(2 x Me), and 151.0(2 x CO). The clear liquid did not darken, even on prolonged storage at room temperature.

b) The adduct (130d) was heated in a glass tube oven (Büche Kügelrohr GKR50) under a vacuum (1.0 cm Hg) provided by a water pump. The experiment was repeated several times at various temperatures between 140 and 170 °C. The adduct gasified and nothing was trapped in the cooled receiver; cf. the similar experiment with adduct (130e) .

Authentic N,N-Dimethylcarbamic Anhydride[74] (132d)

N,N-Dimethylcarbamoyl chloride (3.23 g, 2.97 ml, 0.03 mmol) in a mixed solvent system consisting of dry benzene (13.5 ml) and dry toluene (1.5 ml) was stirred with silver oxide (4.17 g, 0.18 mmol) at 0 °C for 4 h. The mixture was then stored at 5 °C for 10 days. Filtration removed the silver residues. After the solvent was evaporated in the usual way, the last traces of it, and of some byproducts, were removed using a mechanical vacuum pump (0.1 - 0.2 mbar.). The residue was a solid. As soon as the flask was opened to the atmosphere, the solid changed to a viscous liquid. According to the literature[74], this phenomenon is the result of a reaction between water vapour and the anhydride. The authentic N,N-dimethylcarbamic anhydride (132d) was obtained in 30% yield; $\lambda_{max}(CHCl_3)$ 1 758 and 1 716 cm^{-1}(CO). This i.r. spectrum was identical to that given by the thermolysis product from the adduct (130d). The ^1H n.m.r. spectrum was the same as that given by our earlier product when the concentrations of the products from the two experiments were approximately equal. The ^{13}C n.m.r. spectrum of the authentic sample in concentrated solution gave $\delta_C(CDCl_3)$ 36.54 and 36.69(dq, 4 x Me) and 151.02(s, 2 x CO). For

purposes of comparison with the product obtained by thermolysis, a more dilute solution was used. Then δ_C was 36.83(s, 4 x Me) and 151.12(s, 2 x CO) in both cases.

Effect of Dilution on the Formation of N,N-Dimethylcarbamic Anhydride from the Cycloadduct (130d)

The adduct (130d) (90 mg) was dissolved in benzene (26.8 ml) to provide an 0.02 M solution for use in this series of tests. An aliquot of this solution (10 ml) was heated under reflux, and the pyrolysis was followed using analytical silica t.l.c. plates, developed with acetone-light petroleum (1:1). The spot of the cyclopentadiene adduct (130d) was visible under U.V. light and when sprayed with ethanolic ferric chloride it became purple within one minute. Iodine stained all the spots. The progress of the reaction was also followed using ^1H n.m.r. spectroscopy.

At the end of each 30 minute period the solvent was evaporated, the residue was dissolved in deuterochloroform, and a sample was used for n.m.r. spectrometric assay. Then the deuterochloroform was evaporated, and the total residue was dissolved in benzene (10 ml), and heating under reflux conditions was resumed.

Benzene solutions of the adduct (130d) of molarities 0.01 M and 0.04 M were treated in the same manner.

The percentage anhydride (132d) in the reaction mixture was evaluated, using the n.m.r. spectra, by comparing the intensity of the methyl signal at δ 2.98 (anhydride) with that at δ 2.93 (adduct). The most dilute solution was 89%

anhydride after 1 h: the most concentrated solution was only 80% anhydride after 3 h; see Table 4, Section 2.4, p.36.

Cycloadduct of N,N-Dimethylnitrosoformamide and 2,3-Dimethylbuta-1,3-diene

System B

N'-Hydroxy-N,N-dimethylurea (420 mg, 4 mmol) as a suspension with 2,3-dimethylbutadiene (2.28 ml, 20 mmol) in dichloromethane (60 ml), and tetraethylammonium periodate (2.56 g, 8 mmol) in dichloromethane (20 ml) were used. Evaporation of the solvent left a yellow oil, which was shown by n.m.r. spectroscopy to be essentially pure adduct (131d) (0.643, 88% yield). Nevertheless, it was chromatographed on silica plates developed with acetone-light petroleum (3:7). A band, centering on R_f 0.52, was removed and eluted with acetone to give the 3,6-dihydro-4,5-dimethyl-2-(N,N-dimethylcarbamoyl)-2H-1,2-oxazine (131d) (60% yield), b.p. 110 °C (0.04 mbar. Kügelrohr distillation); (Found: C, 58.5; H, 9.0; N, 15.2; m/z 184.1210. $C_9H_{16}N_2O_2$ requires C, 58.7; H, 8.8; N, 15.2%; M 184.1212); $\nu_{max}(CHCl_3)$ 1 654 cm^{-1}; δ_H 1.59 and 1.67(2 x br s, 2 x Me), 2.95(s, NMe_2), and 3.71 and 4.15(2 x br s, 2 x CH_2).

Thermal Transfer of N,N-Dimethyl-C-nitrosoformamide from the Cyclopentadiene Adduct to 2,3-Dimethylbuta-1,3-diene

Experiment (a). Dimethylbutadiene (61 mg, 0.54 mmol) in benzene (1 ml) was added to the cyclopentadiene adduct (130d) (81.7 mg, 0.45 mmol) in benzene (10 ml). The combined reactants,

0.04 M with respect to the adduct (130d) were heated under reflux for 3 h. The solvent was evaporated and the residue was chromatographed on silica plates which were developed with acetone-light petroleum (3:7). A band, $\underline{R}_f$ 0.55, was eluted with acetone to give the dimethybutadiene adduct (131d), [32.1 mg, 36% based on the cyclopentadiene adduct (130d)].

A band, $\underline{R}_f$ 0.25, was also eluted with acetone, and gave N,N-dimethylcarbamoyl anhydride (132d) as identified by spectrometric analysis (^1H and ^{13}C n.m.r., and i.r.). The yield of this compound was 13 mg [39% based on (130d)].

A third band $\underline{R}_f$ 0.08-2.00 was eluted with acetone to give a solid (14 mg). Further purification made use of t.l.c. on silica, developing with chloroform-methanol (9:1) and eluting a band, $\underline{R}_f$ 0.6, with methanol. With the aid of n.m.r. spectroscopy this product [6 mg, 4% based on the adduct (130d)] was tentatively assigned the structure 3,6-dihydro-2-(N,N-dimethylcarbamoyl)-4-methyl-5-[N'-(N",N"-dimethylcarbamoyl)-N'-hydroxyaminomethyl] -2H-1,2-oxazine (136d) or an isomer (see below). The above three products accounted for 56% of the cyclopentadiene adduct (130d).

Experiment (b). In this experiment the conditions were the same as in experiment (a), except that the proportion of dimethylbutadiene was increased from 1.1 equivalents to 10 equivalents.

The cyclopentadiene adduct (130d) (81.4 mg, 0.48 mmol) and dimethybutadiene (0.55 ml, 4.9 mmol) were dissolved in

sufficient benzene to give a solution of molarity 0.04 with respect to the adduct. At the end of a heating period, under reflux, of 3 h, the solvent was evaporated, and the residue was chromatographed on silica as in experiment (a). This time 66% of the products was the adduct (131d). No anhydride was isolated. A band, $\underline{R}_f$ 0.3, was eluted with acetone and provided N',N' dimethyl-N-hydroxy-N-(3-methyl-2-methylenebut-3-enyl)urea (135d), 16.4 mg[18.5% based on adduct (130d)]; $\delta_H(CDCl_3)$ 1.95(br s, Me), 2.93(s, NMe_2), 4.00(s, NCH_2), 4.99(br s, 2H, C = CH_2), and 5.38 and 5.51 (2 x br s, C = CH_2).

In conformity with the method employed in Experiment (a) the band at $\underline{R}_f$ 0.08-0.20 was eluted with methanol, and this gave the oxazine (136d), or its isomer, 13 mg[9.5% based on adduct (130d)], m.p. 112 °C; $\nu_{max}(CHCl_3)$ 1 660 cm^{-1}(CO) and 3 310 cm^{-1}(OH); $\delta_H(CDCl_3)$ 1.75(br s, C-Me), 2.95 and 2.96(2 x br s, 2 x NMe_2), 3.74, 3.85 and 4.50(3 x br s, 3 x CH_2), $\underline{m/z}$ 286($\underline{M}^+$), the fragmentation pattern supported the suggested structure . The product gave a purple colour with ethanolic ferric chloride.

Table 10

a) Transfer of N,N-dimethyl-C-nitrosoformate from 0.49 mmol cyclopentadiene adduct (130d) to dimethylbutadiene (DMBD) (1.1 equivalents)

Anhydride	Weight of anhydride (mg)	DMBD adduct	Weight of DMBD adduct (mg)	Nitroso compound transferred (mmol)
		(131d)	32.1	0.17
		(135d)	6.0	0.04
(132d)	13		Total	0.21

Table 11

b) Transfer of N,N-dimethyl-C-nitrosoformamide from 0.48 mmol cyclopentadiene adduct (130d) to dimethylbutadiene (DMBD) (10 equivalents).

Anhydride	Weight of anhydride (mg)	DMBD adduct	Weight of DMBD adduct (mg)	Nitroso compound transferred (mmol)
		(131d)	58.4	0.32
		(135d)	16.4	0.09 (approx.
		(136d)	13.0	0.09 (approx.
(132d)	Nil		Total	0.50 (approx.

Cycloadduct of N,N-Diphenyl-C-nitrosoformamide and Cyclopentadiene

System A

N'-Hydroxy-N,N-diphenylurea (0.684 g, 3 mmol) in ethyl acetate (150 ml), cyclopentadiene (2.5 ml, 30 mmol) in ethyl

acetate (150 ml), and sodium periodate (0.705 g, 3.3 mmol) in water (75 ml) were used. The reaction time was 1.5 h.

Evaporation of the solvent left 3-(N,N-diphenylcarbamoyl-2-oxa-3-azabicyclo[2.2.1]hept-5-ene (130e) in almost pure crystalline form. Recrystallisation from ethyl acetate gave a 60% yield of the adduct as thick short needles, which showed signs of melting at 126 °C, but did not really melt until the temperature reached 134 °C. When observed under a drop of liquid paraffin (Nujol) over this temperature range, it was seen that there was decomposition, and that this was accompanied by gas evolution. Mass spectrometry gave the expected ion, m/z 292, corresponding to adduct (130e) but this ion was accompanied by an important one at m/z 408, which suggested the formula $C_{26}H_{20}N_2O_3$. A compound with this formula was obtained by the thermolysis of (130e) and identified as diphenylcarbamic anhydride (132e) (See next experiment). A repeat determination of the mass spectrum at a lower inlet temperature gave m/z 292(M^+) with no heavier ion. Other properties of adduct (130e) were (Found: C, 73.7; H, 5.3; N, 9.5. $C_{18}H_{16}N_2O_2$ requires C, 74.0; H, 5.5; N, 9.6%); ν_{max}(KBr)1 664 cm^{-1} (CO); $\delta_H(CDCl_3)$ 1.58 and 1.79(ABq, J 9 Hz with fine splitting, 7-CH_2), 4.82 and 5.00(2 x br s, 1- and 4-H); 6.40 and 6.55(2 x m, 5- and 6-H), and 6.97-7.47(m, NPh_2).

Thermolysis of the Cycloadduct of N,N-Diphenyl-C-nitroso-formamide and Cyclopentadiene

a) The cyclopentadiene adduct (130e) (58.5 mg, 0.2 mmol)

was heated under reflux in benzene (5 ml) (0.04 M solution). Five and a half hours later, about half of the adduct remained. Additional benzene was added to give a solution of molarity 0.01 M and heating was resumed for another 4 h. Preparative t.l.c. on silica, using acetone-light petroleum (35:65) as the developing agent, gave two bands in close proximity. In order to get a better separation, each plate was developed three times with the above solvent mixture. A band, $\underline{R}_f$ 0.70, was eluted with acetone to give the cyclopentadiene adduct (130e) (19%). The other band, $\underline{R}_f$ 0.75, yielded N,N-diphenylcarbamic anhydride (132e) (28.2, 70%), m.p. 132 °C (from ethyl acetate-light petroleum; lit.[76] 128.5 - 132 °C); (Found: C, 76.3; H, 4.9; N, 6.7. $C_{26}H_{20}N_2O_3$ requires C, 76.45; H, 4.9; N, 6.9%); ν_{max}(KBr) 1 758 and 1 727 cm^{-1}(CO); $\delta_H(CDCl_3)$ 6.9-7.6(m, Ph); $\underline{m/z}$ 408($\underline{M}^+$).

b) It has already been stated that the mass spectrograph of the cyclopentadiene adduct (130e), in addition to yielding the expected molecular ion, also yielded an ion at $\underline{m/z}$ 408, which was ascribed to the diphenylcarbamic anhydride (132e), and seemed to have originated at the inlet to the ion chamber. This observation suggested an alternative to the procedure used in method (a).

The adduct (130e) (221 mg) was heated in a glass tube oven (Büchi Kügelrohr GKR50) under vacuum (1.0 cm. mercury), provided by a water pump. The crystals melted at 140 °C with gas evolution. The temperature was raised to 170 °C and maintained there for 20 minutes, by which time the gas

evolution had stopped. The residue (56 mg, 36%) was subjected to 'Flash chromatography'[70] using dichloromethane as eluting solvent. Crystallisation from ethyl acetate-light petroleum gave crystals melting at 110 °C. This was surprising because a similar experiment carried out at 150 °C gave a product, m.p. 132 °C, identical to that obtained by method (a). According to Schroder and Wilcox[76], the anhydride melts at 128.5-132 °C. It was even more surprising to find that a sample of the adduct, which had been prepared ten months earlier, and which had had a melting point of 132 °C, was now found to melt at 110 °C. The samples prepared in methods (a) and (b) gave identical n.m.r. and i.r. spectra.

Cycloadduct of N,N-Diphenyl-C-nitrosoformamide and 2,3-Dimethylbuta-1,3-diene

System A

N'-Hydroxy-N,N-diphenylurea (196 mg, 0.86 mmol) in ethyl acetate (45 ml), 2,3-dimethylbuta-1,3-diene (0.244 ml, 2.15 mmol) in ethyl acetate (45 ml), and sodium periodate (211 mg, 0.99 mmol) in water (22.5 ml) were used. The reaction time was 2 h.

When the reactants were first mixed, the ethyl acetate phase became slightly yellow. The colour soon disappeared. The reaction mixture was washed with water rather than with brine. Preparative t.l.c. on silica, using acetone-light petroleum (b.p. 40-60 °C) (35:65) as developing solvent, was used in order to isolate the product. Two developments were necessary to give a good separation. A band, centering at

R_f 0.75, was extracted with acetone, and yielded a solid (62.5 mg), which was recrystallised from the acetone-light petroleum mixture. This product was the expected 3,6-dihydro-4,5-dimethyl-2-(N,N-diphenylcarbamoyl)-2H-1,2-oxazine (131e). (24%), m.p. 134 °C (from acetone-light petroleum); (Found: C, 74.05; H, 6.5; N, 9.05. $C_{19}H_2N_2O_2$ requires C, 74.1; H, 6.5; N, 9.1%); ν_{max}(KBr) 1 668 cm^{-1}; $\delta_H(CDCl_3)$ 1.44 and 1.63(2 x br s, 2 x Me), 3.43 and 3.85(2 x br s, 2 x CH_2), and 7.00-7.45(m, NPh_2); m/z 308(M^+). No attempt was made to improve the yield by altering the experimental conditions.

Thermal Transfer of N.N-Diphenyl-C-nitrosoformate from the Cyclopentadiene Adduct to 2,3-Dimethylbuta-1,3-diene

The cyclopentadiene adduct (130e) (292.3 mg, 1 mmol) and dimethylbutadiene (1.14 ml, 10 mmol) were dissolved in benzene (25 ml, 0.04 M adduct solution), and heated under reflux for 1.5 h. The residue which was obtained on evaporation, was almost colourless, but proved to be a mixture. Preparative t.l.c. on silica, developed with acetone-light petroleum (35:65) gave three main bands. Acetone was used as the elutant.

a) The band, R_f 0.7, contained the dimethylbutadiene adduct (131e), the characteristics of which have already been reported. The yield was 171.8 mg, 56%, based on the cyclopentadiene adduct (130e).

b) A band, R_f 0.6, was not pure, and so its contents (70 mg) were subjected to a second chromatographic separation on silica: this time development was with chloroform-methanol (97:3). A dark band under U.V. light, R_f 0.45 was eluted

with acetone. The solid product crystallised from ethyl acetate-light petroleum as beautiful needles, N-hydroxy-N-(3-methyl-2-methylenebut-3-enyl)-N',N'-diphenylurea (135e) (4.3 mg, 18%), m.p. 101 °C; (Found: C, 74.1; H, 6.5; N, 9.1. $C_{19}H_{20}N_2O_2$ requires C, 74.0; H, 6.5; N, 9.1%); ν_{max}(KBr) 3 100, 1 616, 1 590 and 1 577 cm^{-1}; λ_{max}(EtOH) 239.4 nm, (ε 1.23 x 10^{-4}); δ_H($CDCl_3$) 1.89(s, vinyl-Me), 4.31(s, NCH_2), 5.03(br s, 2 x vinyl-H), 5.15 and 5.24 (2 x br s, 2 x vinyl-H), 5.66(br s, OH, exch. with D_2O), and 7.00-7.55(m, NPh_2), m/z 308(M^+). Several minutes after having been sprayed with ethanolic ferric chloride, a sample of this compound, on an analytical silica plate, turned purple.

c) The material from the band, R_f 0.4 was eluted with acetone and chromatographed for a second time on silica, this time developing with chloroform-methanol (96:4). A band, R_f 0.5 was eluted with methanol and gave plate-like crystals. This melted at about 86 °C. This product was likely impure 3,6-dihydro-2-(N,N-diphenylcarbamoyl)-4-methyl-5-[N'-(N", N"-diphenylcarbamoyl)-N'-hydroxyamino-methyl]-2H-1,2-oxazine (136e) or an isomer (21 mg), δ_H($CDCl_3$ 1.64(br s, Me), 3.43, 3.86 and 3.93 (3 x br s, 3 x CH_2), and ca. 6.80-7.60(m, 4 x Ph and OH).

Table 12

Transfer of N,N-diphenyl-C-nitrosoformamide from 1 mmol cyclopentadiene adduct (130e) to dimethylbutadiene (DMBD).

DMBD adduct	Weight of DMBD adduct (mg)	Nitroso compound transferred (mmol)
(131e)	172	0.56
(135e)	43	0.14
(136e)	21	0.11
	Total	0.81

Approximately 80% of the nitrosoformamide had been transferred from the cyclopentadiene adduct to dimethylbutadiene.

3.6. The Persistence of Carbonylnitroso Compounds. A Kinetic Study.

a) The Periodate Oxidation of Hydroxyurea (128a)

Attempts were made to find a simple method for monitoring progress in a reaction involving the oxidation of a carbamic acid with tetraethylammonium periodate. The use of the traditional sodium thiosulphate-potassium iodide method for the estimation of periodate failed. Another attempt, involving ethanolic ferric chloride as an external indicator for residual hydroxamic acid, met the same fate.

The employment of analytical t.l.c. plates was more successful. On development with chloroform-ethanol (6:4), a sample spot of tetraethylammonium periodate remained near

the base line, in contrast to one of hydroxyurea (128a), which moved to a position at $\underline{R}_f$ 0.4. When ethanolic solutions of these two reactants were mixed in the ratio of 1.5 moles of oxidising agent to 1.0 mole of hydroxamic acid, and applied to an analytical silica plate within about 5 seconds, and developed immediately, a diffuse spot could be detected under U.V. light. When the plate was sprayed with ethanolic ferric chloride, no purple colour developed. The hydroxamic acid was missing. On the other hand, when the hydroxyurea was in excess, in the ratio of 1 mole to 0.75 mole of the oxidising agent, and the action was again allowed to run for 5s, a spot due to the hydroxamic acid could be detected.

A period of 5s was found to be the minimum time required to perform the mixing of the reagents, and the application of the reaction mixture to the plate. Although the actual development of the t.l.c. plate required several minutes, it was assumed that the reaction would stop almost immediately after application, due to the separation of the reactants. The period of 5s is significant when considered in relation to the ^{1}H n.m.r. spectroscopic studies which follow.

b) <u>The Persistence of Transient Nitrosocompounds in Solution</u>

Two hydroxamic acids, hydroxyurea (128a) and acetohydroxamic acid (30a), representative of their classes, were oxidised to the putative nitroso compounds, which reacted with cyclopentadiene to yield the corresponding cycloadducts

(130a) and (34a). The cycloadduct of C-nitrosocarbonylmethane has been described by Mackinnon[25,37], who had prepared the acetohydroxamic acid used in these experiments.

The Persistence of C-Nitrosoformamide:Gravimetric Method

Tetraethylammonium periodate (482 mg, 1.5 mmol) in ethanol (15 ml), contained in a conical flask (25 ml), was added rapidly to hydroxyurea (76 mg, 1 mmol) in ethanol (10 ml). The mixture was stirred vigorously at room temperature. A minimum volume of solvent had been used, and so the two solutions were almost saturated. A pre-determined delay was employed before the cyclopentadiene (132 mg, 2 mmol) was introduced. This was followed by a short period to permit adduct formation. When this period had elapsed, the excess oxidising agent was destroyed by pouring the reaction mixture into water (30 ml) containing sodium thiosulphate (3 g). The solution was extracted with dichloromethane and this extract was washed twice with water (2 x 10 ml), and dried ($MgSO_4$). After the solvent had been evaporated, the residue was weighed. When there was no 'delay' in adding the diene to the transient nitrosoformamide, the procedure was altered slightly. In such cases, the cyclopentadiene was included in the periodate solution, and consequently these two reagents could be added together to the hydroxamic acid solution. When the 'delay' was small (ca. 5s), the crude product was practically pure adduct. In these experiments the solution of the crude adduct in dichloromethane was washed with water. This operation caused a considerable loss of adduct.

The results are recorded in Table 6, p. 44.

The Persistence of C-Nitrosoformamide and C-Nitrosocarbonylmethane: ^{1}H N.m.r. Spectrometric Assay. In this experiments the method was the same as that described above (b) up to the point when the dichloromethane extracts, containing the crude adduct, were obtained. In order to reduce loss of the adducts, the water-washing operation was omitted. The dry extracts (Na_2SO_4) were filtered, and the solvent was evaporated. After the residues had been weighed they were dissolved in chloroform, filtered again, and the filtrate was adjusted with sufficient chloroform to give an accurate volume of 25 ml. A suitable aliquot of each solution, found by trial runs on the n.m.r. spectrometer, was evaporated to dryness, and a known volume of anisole (e.g. 10 microlitres, 9.2×10^{-2} mmol) was added. The addition of sufficient deuteriochloroform to dissolve the mixture of adduct and anisole provided the sample for the assay. Comparison of the superimposed spectra (impure adduct and anisole) was used to calculate the amount of pure adduct in a particular sample. The results are given below in Tables 13 and 14. A summary of these results has already been presented in Table 7, p.46.

Table 13

Cyclopentadiene adduct formation from 1 mmol hydroxyurea

Experiment	1	2	3
Delay time (s)	0	60	300
Time allowed for reaction with diene (s)	60	60	60
Dichloromethane extract (mg)	95.7	80.4	47.7
Yield of adduct (mg) (n.m.r.)	86	57	17.2
Yield of adduct (mmol) (n.m.r.)	0.61	0.40	0.12
Rate Constant (k) (s^{-1})	-	7×10^{-3}	5×10^{-3}
Half-life (s)		100	130

Table 14

Cyclopentadiene adduct formation from 1 mmol acetohydroxamic acid

Experiment	1	2	3	4	5	6
Delay time (s)	0	0	60	90	120	300
Time allowed for reaction with diene (s)	6	60	60	60	60	60
Dichloromethane extract (mg)	43	102	37.7	32.1	27.1	14.7
Yield of adduct (mg) (n.m.r.)	29	79	16	9.1	5.7	0
Yield of adduct (mmol) (n.m.r.)	0.21	0.57	0.11	0.07	0.04	0
Rate Constant (k) (s^{-1})	-	-	2.7×10^{-2}	2.4×10^{-2}	2.2×10^{-2}	-
Half-life (s)	-	-	26	29	32	

3.7. Attempted Preparation of the Cycloadduct of Nitrosyl Hydride and Cyclopentadiene

1-Chloro-1-nitrosocyclohexane[77] Chlorine gas was passed into a stirred solution of cyclohexanone oxime (144) (20 g) in dry ether (166 ml) until a precipitate formed, and the blue solution had become tinged with green. The solution was washed twice with 2M sodium hydroxide, and then with water. It was dried (Na_2SO_4), and the solvent was evaporated. The residual blue liquid was distilled under reduced pressure, using a water pump to provide the vacuum. The first few millilitres of distillate were rejected. The remainder of the distillate boiling at 49 °C, 12 Torr, provided the nitroso compound; (lit. b.p. 51 °C at 12 Torr). 1-Chloro-1-nitroso-cyclohexane (145) was obtained as an unpleasant-smelling blue liquid.

The Cycloadduct (146). Ranganathan et al.[57] reported an 89% yield of this compound. They added freshly-cracked cyclo-pentadiene (25 g, 0.378 mmol) to a stirred, and ice-chilled solution of chloronitrosohexane (5.8 g, 0.039 mmol) in ethanol-dry ether (1:3, 100 ml). Stirring was continued for 3 h during which time the blue colour of the reagent dis-appeared completely. The white crystalline product, which crystallised, was collected, washed with ether, and dried.

When repeated here, it was found that this procedure gave very unsatisfactory results. In a search for an improvement, nine different experiments were performed. For example, a) the cyclopentadiene was distilled in a

stream of nitrogen, b) the preparation was completed under a blanket of that gas, c) the weight of diene was altered within wide limits, d) the temperature was reduced to -10 °C and then to -20 °C, and e) the volume of solvent, and the proportion of ethanol in it, were varied.

Generally, a white crystalline product soon appeared, but before the blue colour of the starting material had been discharged, the precipitate began to redissolve, and the solution became orange. Best results were obtained by working with a fifteen-fold excess of cyclopentadiene at -10 °C, and allowing the reaction to run until the precipitation seemed to have reached a maximum (2 h). At this point the solid was filtered off, and washed with diethyl ether. As a result, 0.36 g (7% yield) of 2-oxa-3-azabicyclo[2.2.1]hept-5-ene hydrochloride (146) was isolated, m.p. 81-83 °C (lit.[57] 83-55 °C); δ_H(D_2O, ref. tert-BuOH) 2.14(m, CH_2), 5.24(br, 4H), 5.64(br, 1-H), and 6.67, 6.83(2 x m, CH=CH); (lit. 2.35, 5.75, 6.75 and 6.95).

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