THESIS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY

entitled

SUBSTITUENT INTERACTIONS IN ortho-SUBSTITUTED NITROBENZENES

SUBMITTED TO THE UNIVERSITY OF GLASGOW

by

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Substituent Interactions in ortho-Substituted Nitrobenzenes.

Summary of Ph.D. Thesis submitted to the University of Glasgow by

Ian P. Sword B.Sc.

A review is given of relevant interactions published in the literature between 1964 and 1967.

Degradative studies show that the product obtained by treatment of 2,3-epoxy-3-(o-nitrophenyl)propiophenone with ethereal hydrogen chloride is 6-chloro-1,4-dihydro-1,3-dihydroxy-2-phenyl-4-oxoquinoline, and that the corresponding unhalogenated heterocycle is the product when quinol is present in the reaction mixture.

3-Carbamoylanthranil is the sole crystalline product from the reaction of o-nitrobenzyl cyanide with concentrated sulphuric acid, and evidence is presented that o-nitrophenylacetamide is not an intermediate in the cyclisation.

Whereas 5-hydroxy-2-nitrobenzaldehyde and phenol are shown to react in ethereal hydrogen chloride to give the expected halogenated product, namely 7-chloro-5-hydroxy-3-(p-hydroxyphenyl)anthranil, 5-methoxy-2-nitrobenzaldehyde gives, abnormally, the corresponding unhalogenated anthranil. The latter reaction is discussed in the light of a working hypothesis regarding possible mechanisms involved.

The scope of the reaction of o-nitrobenzylidene derivatives with aqueous ethanolic potassium cyanide is explored and extended. The plethora of products so obtained are shown by degradative, synthetic and

spectroscopic studies to be derivatives of quinoline N-oxide and of 1-hydroxyindole. Unexpectedly, in some instances a 4-cyano substituent in the quinoline-type products fails to survive the reaction without hydrolysis. This is discussed with reference to the isolation of 4-acetyl-5-methyl-3-(p-nitrophenyl)-2-aminofuran from reaction of p-nitrobenzylideneacetylacetone with aqueous ethanolic potassium cyanide.

The Michael addition product from o-nitrobenzyl cyanide and 1,2-dibenzoylethylene is synthesised; its reactions with sodium ethoxide and sodium carbonate are investigated and shown to give products comparable with those from the reactions of o-nitrobenzylidene derivatives described above.

Glasgow, June 1967.

ACKNOWLEDGMENTS

The writer would like to express his sincere thanks to Dr. J. D. Loudon whose encouragement, advice, and good humour have been unfailing during the three years' research which this Thesis represents.

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CONTENTS

PREFACE

In the field of heterocyclic syntheses, a nitro group is often utilised, after reduction, as a source of the heterocyclic aza atom. However, when a suitable side-chain and a nitro group are situated ortho to one another in a benzene ring, the nitro group as such can participate in an aldol-type condensation or in a redox interaction with its ortho-substituent.

Over the past decade, an active study in this Department of the latter two phenomena has given some understanding of the deep-seated changes involved, and the present work was undertaken with the object of investigating further the scope and limitations of these reactions.

Since the publication in 1964 of an excellent Review* assembling the scattered information on these less familiar aspects of nitro group behaviour, a number of novel and related interactions have been reported in the literature. An attempt has been made in Chapter 1 of this Thesis to review these recent publications and to interpret them, as far as possible, in the light of earlier examples. Material which is germane to the work described in the sequel is discussed in the preamble to appropriate chapters.

*J.D. Loudon and G. Tennant, Quart. Rev., 1964, 18, 389.

The interactions have been broadly classified according as they occur in an acid or an alkaline environment. While ionic mechanisms are assumed to operate throughout, the details of the complex mechanistic pathways of these interactions remain, as yet, obscure. Only working hypotheses can be entertained regarding the mechanism of the various reactions and the origin of structural differences found among the products. Indeed the strongly reducing nature of the media in which many of the reactions occur adds further complication, since it is possible that reaction intermediates suffer reduction by the medium and subsequently undergo further change.

Some results which are negative but perhaps significant have been accumulated and these are discussed where apposite.

CHAPTER 1

Chapter 1

A Review of Substituent Interactions in ortho-Substituted Nitrobenzenes Since 1964.

Aromatic nitro compounds are notorious for the facility with which they produce abnormal, uninviting products from seemingly straightforward reactions. Although often summarily dismissed as regrettable evidence of the nitro group's ease of reduction, a harvest of otherwise inaccessible products may be reaped from such aberrant processes.

Generally in this Thesis we shall be concerned only with those products arising from ortho nitro compounds. In the latter the nitro group's demand for electrons may be supplied from outwith the molecule or, if supplied from within, supply lines may run through the molecular framework or across space. Thus redox interactions, intramolecular condensations, and photochemical transformations between the nitro group and its ortho substituent may variously play a part in the formation of aza- or oxaza-heterocycles.

Such interactions have never been systematically studied, and in consequence, examples are widely scattered throughout the literature. Those interactions reported up until 1964 have been reviewed by Loudon and Tennant,[1] but since then several further examples have been published, and these form the subject matter of this brief Review. No attempt has been

made to be exhaustive, but it is to be hoped that no relevant examples from the major journals have been overlooked. Of examples to be discussed, those which occur in basic media are by far the most common.

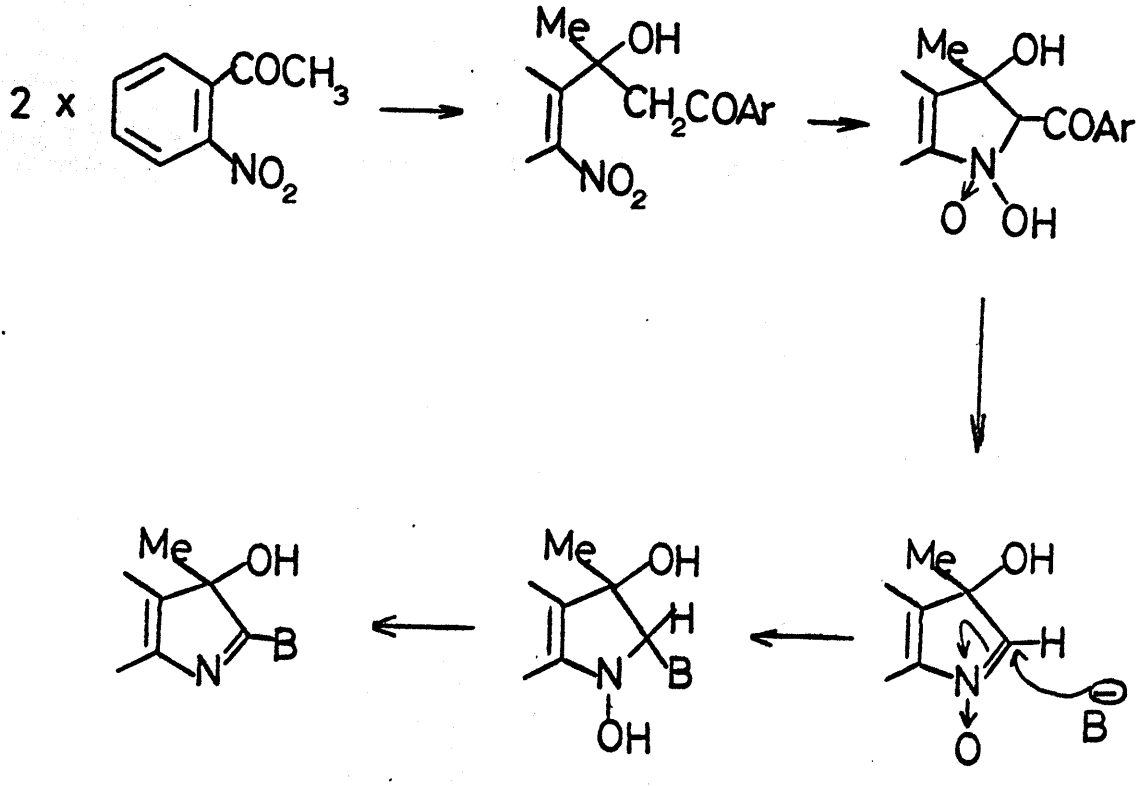
The proposition that the nitro group can act as an electrophilic site for intermolecular carbanion attack in an aldol-type condensation has never been unequivocally substantiated.[1] Recently however Hassner and Fitchmun[2] reported formation of the nitrone (1) and the acid (2) by base-catalysed condensation of 1-indanone with o-nitrobenzaldehyde. These workers claim that formation of (1) is direct evidence for initial condensation of the nitro group with the enolate anion of 1-indanone to give the intermediate nitrone (3). This, they claim, subsequently undergoes further aldol condensation to give (1). Their mechanism is open to challenge in view of the previously undisputed greater reactivity of an aldehyde over a nitro group as an electrophil. A mechanism compatible with the latter premise is formation of a normal aldol (4), followed by that of the spiro-condensate (5). Decomposition of (5) in alternative ways then accounts for the products observed.

Ahmad and Shamsi[3] have cyclised o-nitroveratrylidenesuccinic acid (6) to the carboxylic quinoline N-oxide (7) using aqueous

potassium hydroxide, and this is a good example of intramolecular carbanion attack at a nitro group. A further example, this time to produce a five-membered ring, is that reported by Petracek[4] who treated ethyl α-(o-nitrophenyl)-α-(o-nitrobenzyl) cyanoacetate (8) with methanolic potassium carbonate and obtained a derivative of 1-hydroxyindole (9).

Examples of cyclisations involving derivatives of o-nitroacetophenone often become complicated because the isatogens to be expected as products are highly sensitive and may be subject to modification in the reaction environment. This was undoubtedly the cause of wrongly assigned structures of products from reaction of the compounds (10) with cold potassium hydrogen carbonate.[5] Wibberley and Hooper[6] have now reinvestigated the reactions and have shown the respective products to be a mixture of an indogenide (11) and an isatogen (12). It is suggested[6] that the initially formed simpler isatogens (13) may act as oxidising agents in the production of (12).

A transformation which invites comparison with the above is reported in a series of papers by Sakan and his co-workers.[7] It involves the action of sodamide in liquid ammonia on o-nitroacetophenone, and, depending on the quantities of reagents used, two products (14) and (15) can be isolated.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An exposition of the mechanism promised by the above authors has not yet appeared in print, but a possible scheme to account for the products is shown opposite. Analogy for the final steps is provided by some work of Tennant.[8]

In a continuation of his studies on the action of alkali on derivatives of o-nitroaniline, Tennant[8] has shown that a by-product from reaction of α-acetyl-o-nitroacetanilide with aqueous sodium hydroxide has the structure (16), and may arise through substitution of the first-formed N-oxide (17) by a molecule of starting material, the N-oxide group being removed in the process. The same worker has also prepared C-alkylated derivatives of α-benzoyl-o-nitroacetanilide (18) and demonstrated their facile cyclisation in ethanolic sodium hydroxide to the quinoxaline N-oxides (19).

Tennant and Vaughan[9] have extended the scope of this type of direct interaction between a nucleophilic centre in the side-chain and the nitro group, by examining the action of base on N-substituted o-nitrobenzamides (20). Thus derivatives of 1,4-dihydro-1-hydroxy-4-oxoquinazoline (21) are formed by treatment of o-nitrobenzamidoacetonitrile with sodium alkoxides, the nature of group R depending on the alkoxide used. It is probable that displacement of the cyano substituent in (22) by OR^- is a stage in the overall reaction.

The next series of compounds comprises derivatives of 2'-substituted 2-nitrodiphenyls, and the examples are essentially extensions to the classic work of Muth and his colleagues;[10] these too provide compelling evidence for a simple aldol-type of interaction. In each case provision of an anion directly attached to the un-nitrated nucleus seems to be a factor essential to successful cyclisation. Poesche,[11] in the course of his studies in the N-oxidation of dibenzo-(c,h) cinnolines treated the amine (23) with Triton B and obtained a high yield of the cinnoline N-oxide (24). Barton and Thomas[12] have used the same catalyst to cyclise 2-amino-5,2'-dinitrodiphenyl (25) to the benzocinnoline N-oxide (26).

Taylor et al.[13] have obtained 6-cyanophenanthridine (27) from the extremely rapid reaction of the diphenyl derivative (28) with sodium ethoxide, and the same product is obtained under photolytic conditions. It is proposed that both processes proceed via the nitroso intermediate (29) and the oxadiazetidine (30).

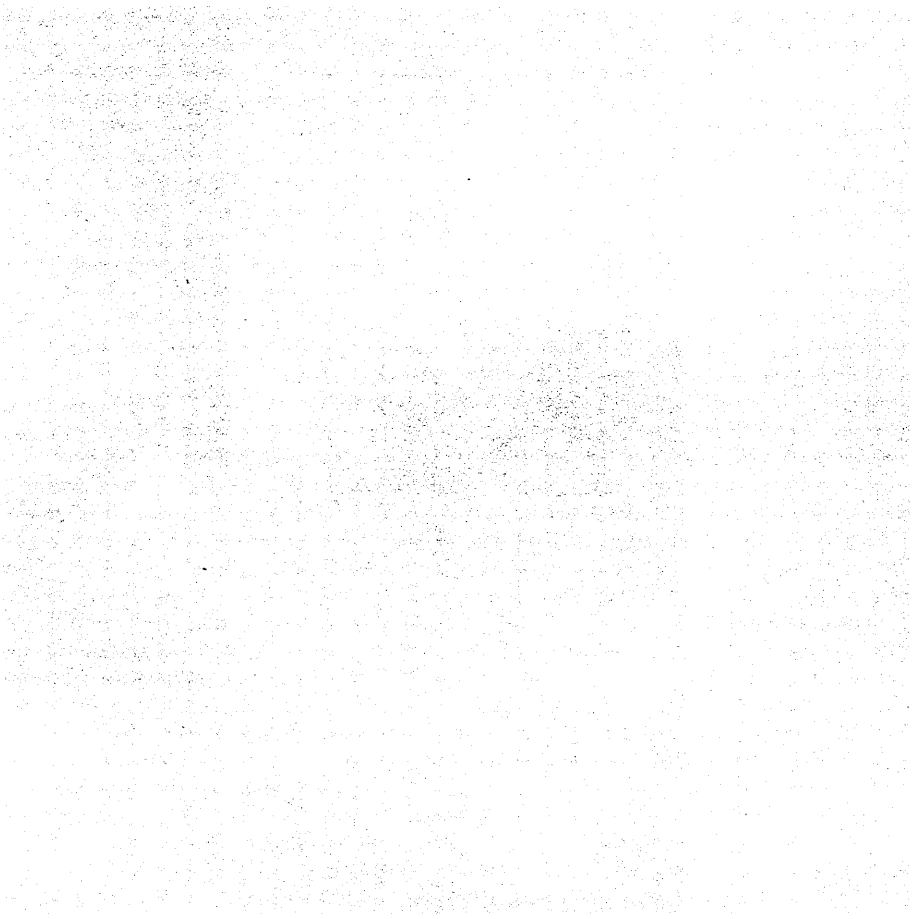
Luetzow and his co-workers[14] have shown that methyl α-(2,4-dinitrophenylamino)acrylate (31) prepared in situ rapidly reacts with methanolic sodium methoxide to give the sodium salt of the benzimidazole (32;R=CO_2Me) or the corresponding amide (32;R=$CONH_2$) when the reaction is

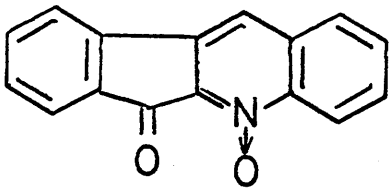
conducted in methanolic ammonia. Pollit[15] and later Russell[16] prepared the related benzimidazoles (32;R=H,Me,Ph etc.) by photolysis of C-alkyl- or -aryl-glycine derivatives (33;R=H,Me, etc.) in acidic media. These reactions may proceed via 4-nitro-2-nitrosoaniline (34) but this awaits confirmation. These appear to be the only recent examples of interactions occurring in an acid environment.

Barltrop and his collaborators[17] have developed a photosensitive protecting group, using in the deprotection step the oxygen transfer (35) → (35a) photochemically induced in aromatic nitro compounds which have a C - H substituent in the ortho position.[18] By this process carboxylic acids can be recovered from their o-nitrodiphenylmethyl esters (35), and amines from N-(o-nitrodiphenylmethyloxycarbonyl) derivatives (36). Nitrosobenzoyl compounds are by-products from the photochemical decomposition. The indogenide (37) is reported by Capuano[19] to arise by exposure to sunlight of the product (38) obtained by treating o-nitrobenzaldehyde with ethereal diazomethane.

Moll, Musso, and Schroder[20] previously reported an intriguing example of an ortho interaction during catalytic hydrogenation of o-nitrobenzonitrile. The product is o-aminobenzamide and it was shown by labelling studies that

the oxygen atom of the amide function ultimately arose from the nitro group. Musso and Schroder[21] have now shown that oxygen transfer proceeds intramolecularly at the o-hydroxylaminobenzonitrile stage, 3-aminoanthranil (39) being the next formed intermediate which is finally reduced to the product.





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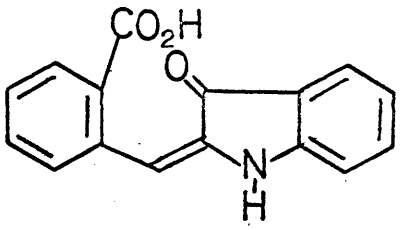

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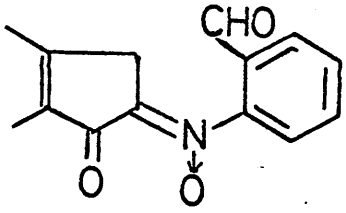

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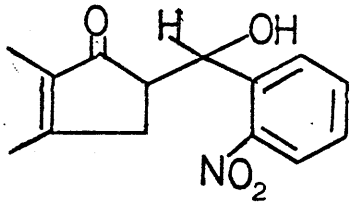

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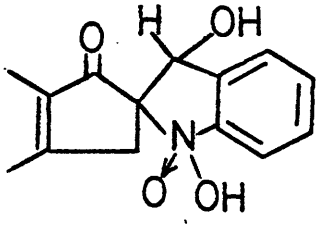

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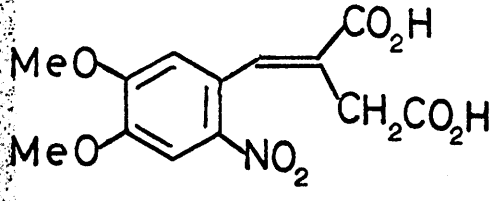

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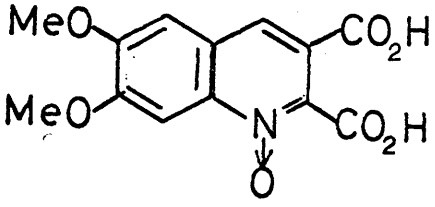

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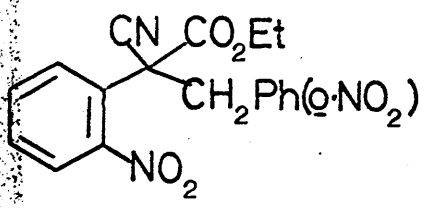

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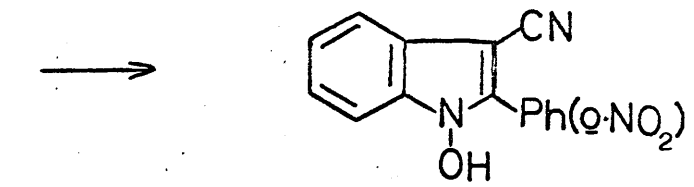

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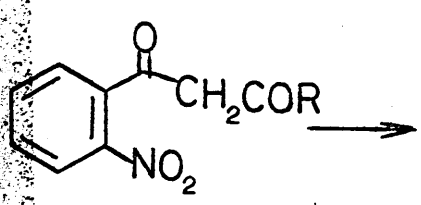
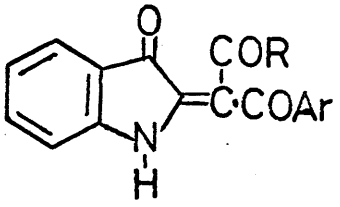


(10;R=OMe, OEt, Me)



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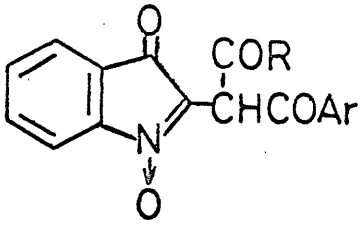

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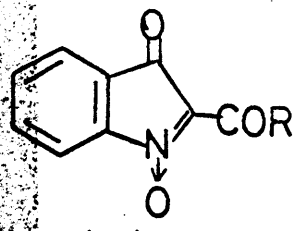

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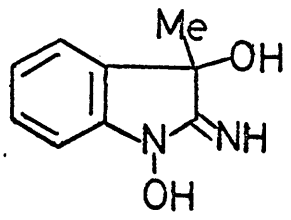

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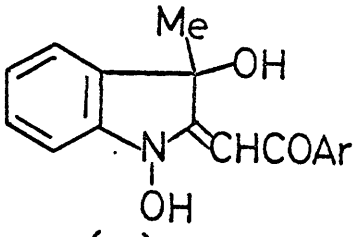

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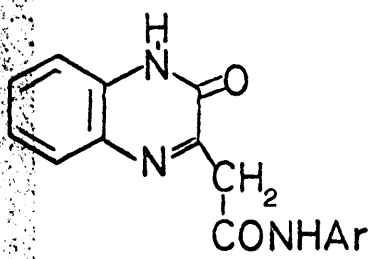

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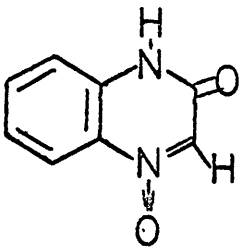

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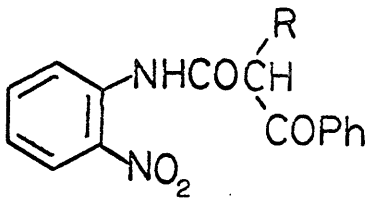
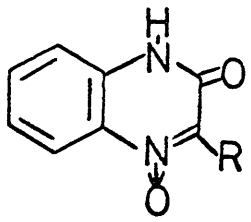


(18;R=n-alkyl)



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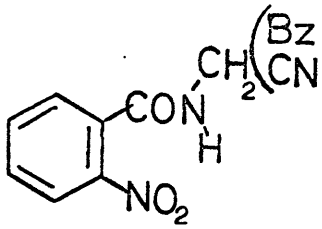

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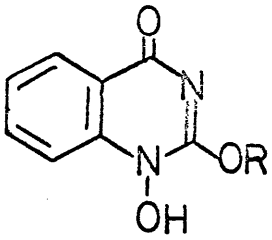

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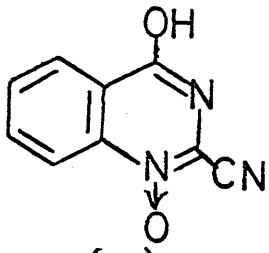

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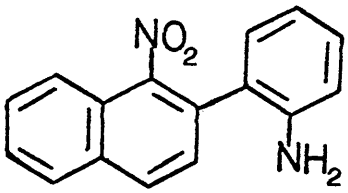

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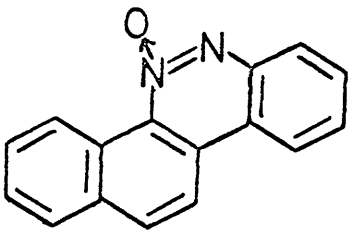

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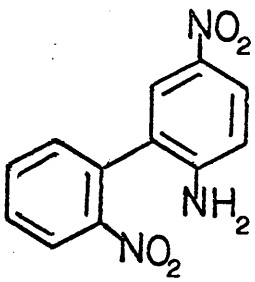

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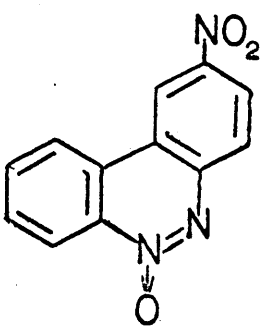

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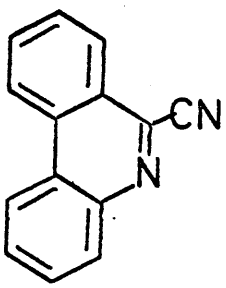

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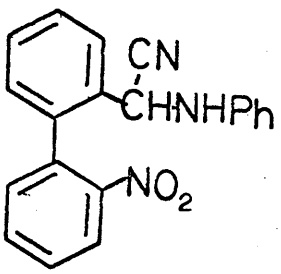

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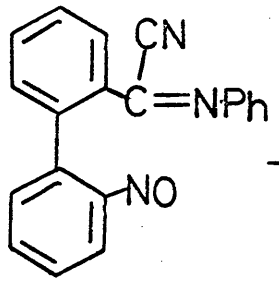

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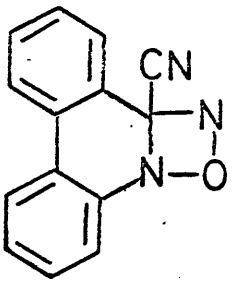

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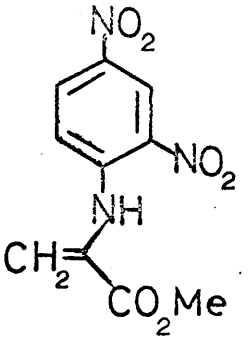

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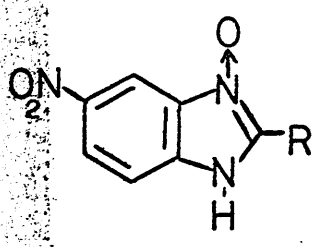
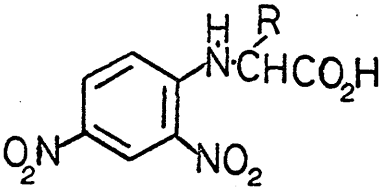


(32)



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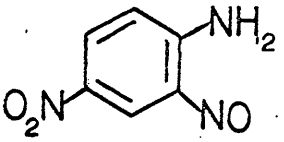
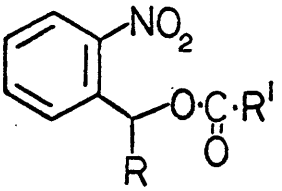


(34)



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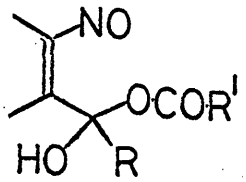

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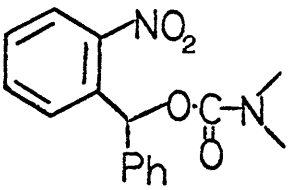
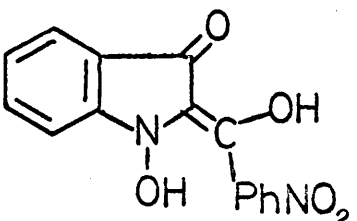
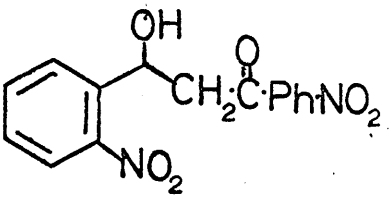


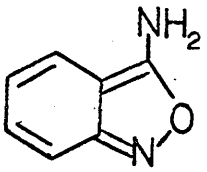
(36)



(37)



(38)



(39)

CHAPTER 2

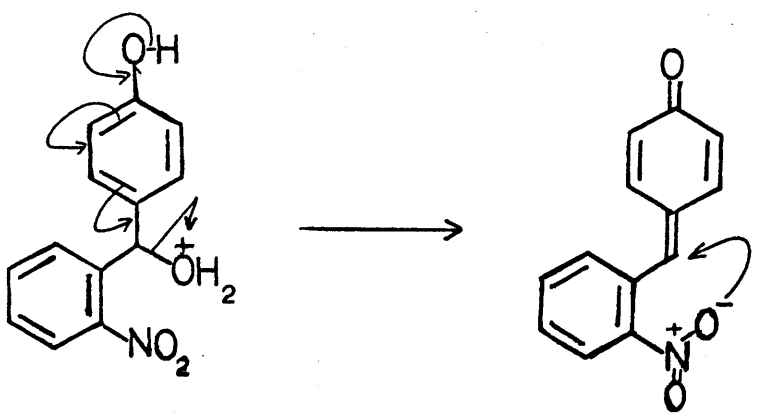
Chapter 2

Acid-Catalysed Interactions.

Introduction

Acid-catalysed nitro group/substituent interactions are by no means as common as their base-catalysed counterparts, and a large number of the products from the acid-catalysed series are anthranils. Anthranil derivatives are almost exclusively the heterocyclic products from the acid-catalysed condensation of o-nitrobenzaldehyde with reactive aromatic reagents, and the first reported anthranil synthesis by means other than deliberate reduction was an example of this type of reaction. This was accomplished by Zincke and Prenntzell[1] who condensed o-nitrobenzaldehyde with dimethylaniline in concentrated hydrochloric acid to give 5-chloro-3-(p-dimethylaminophenyl)anthranil (1). Similar condensation of o-nitrobenzaldehyde with phenol and ethereal hydrogen chloride gave the 5-chloroanthranil (2;X=Cl,Y=H) (the Zincke-Siebert reaction[2]).

In the course of his research at Glasgow, Tennant[3] extended the scope of the Zincke-Siebert reaction and showed that with hydrogen bromide, o-nitrobenzaldehyde and phenol condensed to give a mixture of 3-p-hydroxyphenylanthranil (2;X=Y=H) and its 5-bromo derivative (2;X=Br,Y=H). A more


OH
OH2
NO2
O
N
O
O

complete contrast in the behaviour of the two hydrogen halides in these reactions was also noted by Tennant,[3] for, in the reactions of phenol with 5-bromo- or 5-chloro-2-nitrobenzaldehyde, hydrogen chloride afforded 5,7-dihalogeno anthranils (2;X=Br,Y=Cl and 2;X=Y=Cl), whereas hydrogen bromide gave only 5-halogeno anthranils (2;X=Br,Y=H and 2;X=Cl,Y=H). In other words, hydrogen bromide appeared able to effect cyclisation without substitution by bromine, while hydrogen chloride could cause cyclisation only with concomitant entry of chloride ion. When quinol was used instead of phenol, even hydrogen chloride effected the condensation with o-nitrobenzaldehyde without chloride entering the nucleus, and the product in this case was shown to be 3-(2,5-dihydroxyphenyl)anthranil (3).[3]

Carbinols of the type (4) are potential intermediates in these reactions, and this postulate was confirmed when the pre-formed carbinol (4;R=p-C_6H_4.OH) yielded the anthranil (2;X=Cl,Y=H) on treatment with hydrogen chloride.[4] It is worth noting that this reaction is much more facile than that of (4;R=Ph), because, in the former, there is a possibility of assistance from the para hydroxyl group for elimination of water from the intermediate carbinol, as shown schematically opposite. The oxidation product from the carbinol (4;R=Ph) is 2-nitrobenzophenone, and, together with triarylmethanes,[5] is often a by-product of reactions which lead to anthranils.[6,7]

This suggests but does not prove that carbinols of the type (4;R=p-C_6H_4.OH) could act as requisite reducing agents.

From the work of Wellings[8] and later of Tennant[3] on the acid-catalysed formation of 1-hydroxy-4-quinolones from o-nitrobenzaldehydes and reactive methylene compounds, it soon became clear that a close relationship existed between this reaction and the formation of anthranils. For example hydrogen chloride was shown to react with o-nitrobenzaldehyde and ethyl acetoacetate via ethyl o-nitrobenzylideneacetoacetate (5) to yield the 6-chloro-1-hydroxy-4-quinolone (6).[8] As with anthranils, hydrogen bromide provided a contrast by giving a halogen-free product (6;H for Cl) and correspondingly, the pre-formed benzylidene derivative (5) gave, on treatment with hydrogen chloride in presence of quinol, the same halogen-free compound (6;H for Cl).[3]

A number of reactive methylene compounds have been treated with o-nitrobenzaldehyde and hydrogen chloride in this fashion, and many cyclise to give quinolones, but there are some notable exceptions e.g. ethyl benzoylacetate and acetone, which give only mono- and di-benzylidene derivatives respectively.[8,9]

The anthranils and quinolones which are generally formed in these reactions can be formally derived from o-hydroxylaminophenyl ketones e.g. (9) by cyclodehydration. Since the latter

are at a lower oxidation level than their o-nitrobenzylidene progenitors (which correspond in oxidation level to o-nitrosophenyl ketones), a reduction step must be invoked in these transformations. From the experimental facts it appears that hydrogen bromide or quinol can act as external reducing agents, supplying the requisite pair of electrons directly, whereas hydrogen chloride can only do so by insertion of a chloride ion into the (original) nitrophenyl nucleus. It is worth noting that when quinol and hydrogen chloride operate together, reduction by the former appears to be preferred to chloride insertion by the latter.

Reactions leading to Anthranils

Discussion

Earlier, Smith[9] showed that the ease of 4-quinolone formation from a 2-nitrobenzaldehyde and a reactive methylene compound was greatly enhanced when an electron-donating substituent was situated ortho or para to the nitro group of the aldehyde moiety. For example, as mentioned earlier, Wellings[8] noted that in the presence of hydrogen chloride, o-nitrobenzaldehyde condensed with ethyl benzoylacetate to give only the benzylidene derivative (5;COPh for $COCH_3$), whereas Smith[9] showed that 5-hydroxy-2-nitrobenzaldehyde and ethyl benzoylacetate reacted under the same conditions to give the 4-quinolone (7). Similar ease of 4-quinolone formation was noted with 5-methoxy-2-nitrobenzaldehyde and also with 3-hydroxy-2-nitrobenzaldehyde and its methyl ether.[9]

Prompted by analogy with quinolone formation, we looked for evidence of facilitated anthranil formation in the reactions of 5-hydroxy- and 5-methoxy-2-nitrobenzaldehyde with phenols. As events showed, the true situation is less simple than expected, and our efforts were, in a measure, frustrated by an abnormal but interesting reaction.

From the practical point of view, the general procedure

adopted for the preparation of 3-arylanthranils was to saturate, in a suitable solvent, a mixture of one mole of the aldehyde and two moles of phenol with dry hydrogen chloride. A steady temperature was maintained by using a water-bath to cool the reaction vessel. The sealed flask was then allowed to stand at room temperature for a time, whereafter the product was collected by filtration or by solvent extraction. In cases where it was desirable to use hydrogen bromide as condensing agent, this was very easily achieved by treating the mixed reactants with a commercially available solution of hydrogen bromide in glacial acetic acid. In a pilot control reaction it was shown that the small amount of water present in the commercial material did not affect the quantity, quality, or nature of the products. The obvious advantages of this technique are discussed in the Experimental section.

The structure of products was assigned on the basis of their analyses and spectral properties, and on those of their methoxy- or acetoxy-derivatives, and also by analogy with the proved structure of products from the reaction of 5-chloro-2-nitrobenzaldehyde with phenol in presence of hydrogen chloride.[3]

Turning now to the detailed results of the present work, both 5-hydroxy-2-nitrobenzaldehyde and its methyl ether

were prepared by published methods.[10,11] We have found that only the hydroxynitroaldehyde reacts with phenol and hydrogen chloride in the normal way affording the chlorinated anthranil (2;X=OH,Y=Cl). With phenol and ethereal hydrogen chloride the methoxyaldehyde failed to react, while with phenol and hydrogen chloride in acetic acid it gave a very dark mixture from which was recovered a dark unattractive looking product. The latter was purified with difficulty by chromatography, and shown to be the unhalogenated anthranil (2;X=OMe,Y=H). Much decomposition product was in evidence, and this together with the formation of dark, poor quality material is exceptional in these circumstances.

With hydrogen bromide in acetic acid, both aldehydes behaved normally, giving the expected unhalogenated anthranils (2;X=OH,Y=H) and (2;X=OMe,Y=H) which both gave the same dimethyl ether (8) on treatment with ethereal diazomethane. While the free anthranil (2;X=OH,Y=H) was rather difficult to handle because of its tendency to decompose, it was readily characterised as its diacetyl derivative.

Disappointingly, the attempted condensation of the methoxyaldehyde with quinol in place of phenol led only to a black tar from which no sensibly crystalline material could be recovered.

The behaviour of the methoxy-aldehyde is thus exceptional in that with phenol and hydrogen chloride it either fails to react, or having reacted with abnormal side effects, gives the unchlorinated anthranil (2;X=OMe,Y=H) in poor yield. The abnormality is more pronounced in view of the normal reaction by which the same methoxy-aldehyde yields (i) the anthranil in presence of hydrogen bromide and (ii) the expected chlorinated quinolone with acetylacetone and hydrogen chloride.[9] This abnormal behaviour might be trivial or significant in its origin, but on the premise of its significance it is here considered mechanistically in terms of a working hypothesis. It is emphasised that neither the order of events, nor the extent to which they are concerted, is known.

For the moment we shall set aside the anomalous methoxy-aldehyde reaction and discuss postulated mechanisms for normal formation of anthranils and quinolones. Reactions of a substituted o-nitroaldehyde with phenol and acetylacetone are representative examples, and in (10a,b) the group Z represents that part of the side-chain variously derived from the initial reactants (cf. p. 10). Two allied reaction mechanisms are possible, one concerted (A), the other stepwise (B).

In both mechanisms cyclisation is initiated by protonation

of a carbonyl group in Z. The resultant electron deficiency at the carbon atom α to the nitrophenyl nucleus attracts and shares an electron pair from an oxygen atom of the nitro group. In scheme (A) electron flow from the nitro group is compensated either by supply of electrons from an external reducing agent (hydrogen bromide or quinol) or by entry of chloride ion into the nitrophenyl nucleus. The net result is formation of the species (11) (equivalent to an hydroxylaminophenyl ketone). From the latter, depending on the nature of Z, two major pathways can be followed: with ($Z=p\text{-}C_6H_4O$..) direct elimination of the elements of water leads immediately to the 3-arylanthranil (12). With ($Z=C(COMe)_2$) isomerisation to an hydroxylaminophenyl ketone (13) permits the possibility of cyclodehydration between a carbonyl group of the acetylacetone residue and the hydroxylamino group, leading to formation of a six-membered heterocyclic ring.*

In scheme (B) reorganisation of electrons in (10b) leads to a nitrosophenyl ketone (14) (or its equivalent) which then yields an hydroxylaminophenyl ketone (13) either directly

* It has not been overlooked that anthranils could be the precursors of quinolones. The known conversion of 3-phenylanthranils into acridones[13]. offers a somewhat distant analogy.

by reduction or indirectly by entry of halide ion. A part-analogy for the latter step is the known conversion of nitrosobenzene to p-chlorophenylhydroxylamine in presence of hydrogen chloride.[12] Depending on the nature of Z cyclodehydration of the hydroxylaminophenyl ketone leads either to a five- or six-membered heterocycle as before.

In any event an hydroxylaminophenyl ketone e.g. (13) (or its equivalent) can be regarded as a common intermediate to the various reactions.

Turning now to the abnormal reaction of the methoxy-aldehyde with phenol and hydrogen chloride, we must focus our problem as " what potentialities are lost to the anthranil, but not to the quinolone, synthesis when the mobile hydroxylic hydrogen of the hydroxyaldehyde is replaced by methyl?"

For the sake of clarity, the mechanisms of reactions of the hydroxy- and methoxy-aldehydes will be considered only as concerted processes (C). Again Z represents an acetylacetone or phenolic residue in the variously derived intermediates (15;R=H,Me). As before protonation of a carbonyl group in Z causes a flow of electrons from the nitro group across space to the carbon atom α to the nitrophenyl nucleus. However, in this instance the flow can be compensated by internal supply of electrons from hydroxyl or methoxyl

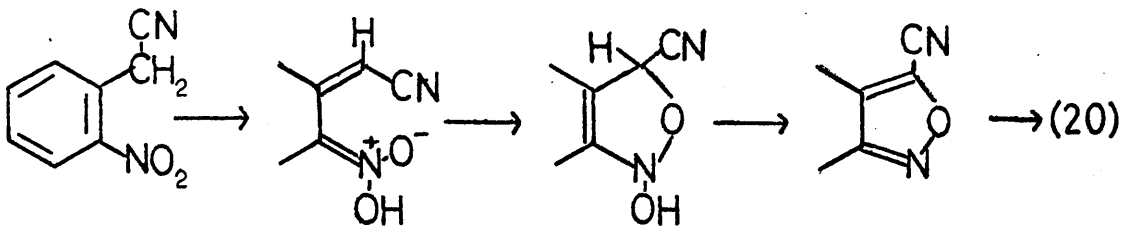
acting as donor substituents. Thus p-quinonoid species (16;R=H,Me) can assist the early stages of reaction. (Such species can not be invoked to any appreciable extent with H or Cl for OR, and normal reactions are observed in these instances). With the hydroxyaldehyde, the species (16;R=H), can be restored to neutrality of charge by loss of R (=H). Addition of hydrogen chloride to the resultant quinonoid intermediate should then be possible. Now, as before, an anthranil or quinolone can be obtained by suitable reorganisation of electrons followed by cyclodehydration.

In contrast, for the methoxyaldehyde, the species (16;R=Me) can best alleviate its positive charge by loss of a proton from the carbon atom attached to the original nitrophenyl nucleus. Now the intermediate is (17;R=Me) and subsequent change will be dominated by the mobility of H*. When Z is an acetylacetone residue, removal of H* is facilitated by the driving force to return of aromaticity in the methoxylated ring. Subsequent reaction of the resultant nitrosophenyl ketone then proceeds normally.

However, in (17;R=Me) when Z is an hydroxyphenyl group, prototropic change to restore aromaticity in the methoxylated ring destroys the aromatic ring in Z. Conceivably, therefore, this could create a barrier to the intermediate formation of a nitrosophenyl ketone and so cause the reaction to miscarry.

Anthranils are also isolated from acid-catalysed cyclodehydrations of o-nitrobenzyl compounds; for example, 2,4-dinitrophenyl-acetone[14] or -acetic acid[15] yield 6-nitroanthranil with hot concentrated sulphuric acid, and 3-carbamoylanthranil derivatives are obtained[16] by treating the corresponding o-nitrophenylacetamides with phosphorus pentachloride. However the ease of anthranil formation varies enormously, for, while o-nitrophenylacetic acid (18) reacts with acetic anhydride to give the benzoxazone (19), presumably as shown (18) → (19), neither o-nitrobenzyl cyanide nor esters of o-nitrophenylacetic acid are affected by the same reaction conditions.[17]

In an attempt to hydrolyse o-nitrobenzyl cyanide to o-nitrophenylacetamide, the former was added to cold concentrated sulphuric acid.[cf.18] The ensuing reaction was rather violent and resulted in severe charring of the material. When however the nitrile was brushed slowly into ice-cold concentrated sulphuric acid, the violence of the reaction was somewhat modified, and, after diluting the mixture with water, collecting the dark product and chromatographing it, a small amount of 3-carbamoylanthranil (20) was isolated. It was identified by its elemental analysis and by a direct comparison of its melting point and infrared spectrum with an


CN
CH2
NO2
H
CN
N
O
OH
H
CN
O
N
OH
CN
O
N
(20)

authentic sample prepared by the method of Ardnt et al.[19]

Further elution of the column afforded an insoluble red acidic powder which could not be satisfactorily purified, but it was established that this material was not N-hydroxyisatin.

o-Nitrophenylacetamide does not appear to be an intermediate in the formation of (20) from o-nitrobenzyl cyanide, since it was recovered unchanged after treatment with warm concentrated sulphuric acid. If o-nitrophenylacetamide is not an intermediate in the above reaction, and we assume that the amide oxygen atom of (20) does not arise from the nitro group (for which postulate there is no evidence) then the reaction mechanism shown opposite becomes a possible one. Related reactions from the literature[14,15,16] have already been mentioned.

The limitations on the above reaction appear to be rather severe, since no comparable reactions were observed when o-nitrophenylacetic acid (18), its ethyl ester, or the N-benzylphthalimide (21)[20] were dissolved in concentrated sulphuric acid.

A Novel Synthesis of some Substituted 3,4-Dihydroxyquinolines.

In 1918 Bodforss[24] synthesised the epoxide (22) by the Darzens-type condensation of phenacyl bromide with o-nitrobenzaldehyde, and he noted that two distinct α and β isomers of the epoxide existed. He further demonstrated that the two isomers were interconvertible under suitable conditions, but little else of the chemistry of this potentially interesting epoxide has appeared in print. Cromwell and Seterquist[25] re-investigated the nature of both α and β forms, and concluded that the higher melting β form had cis stereochemistry, and the lower melting α form trans stereochemistry. These workers also effected reductive cyclisation of the epoxide to yield 3-hydroxy-2-phenylquinoline (23).

We have repeated and verified Bodforss's synthesis and have also prepared the epoxide by the action of alkaline hydrogen peroxide on a hot ethanolic solution of the benzylidene compound (24) (a modified version of the method used by Cromwell et al.[25]). Both the Darzens condensation and the epoxidation of the benzylidene compound (24) are known to give the lower melting trans epoxide (22).[25]

The potentiality of a side-chain epoxide for acid-catalysed nitro group/substituent interaction is virtually unknown.

Only two ortho-nitrophenyl epoxides have previously been examined for this type of reaction: thus o-nitrophenylglycidic acid (25;R=H) is known[26] to yield a mixture of anthranil and its aldehyde (26) when distilled in steam or heated in acetic acid, and o-nitrophenylethylene oxide (27) affords the rather unstable o-nitrosobenzoylmethanol (28) when treated with acid, or the acetate of this methanol when treated with acetic anhydride.[27] This shortage of data on the behaviour of the o-nitrophenyl epoxides in acidic media prompted us to examine the effect of ethereal hydrogen chloride on the readily available epoxide (22).

During the course of our work with a variety of o-nitrophenyl epoxides, we found that their n.m.r. spectra were especially interesting, since they could be used to verify the presence of the three-membered ring, a functional group not readily identifiable by other spectroscopic techniques.[28] The protons H_A and H_B of (22) and (25;R=H,Me etc.) showed a characteristic pair of doublets (J_{AB}ca.2-3c/s) with H_B resonating fairly constantly at ca. τ5.3. In the epoxide (29)[29] the corresponding H_A and H_B signals are at sufficiently different τ values to permit differentiation between (22) and (29). The relevant n.m.r. data are set out in Table 1. It should be pointed out that the epoxides examined have been assigned,

by virtue of their method of preparation[25] and J_{AB} values,[30] trans stereochemistry. Unfortunately it was found impracticable to prepare the cis epoxide (22) in sufficient quantity for its examination either spectroscopic or chemical, and in the present work only the trans isomer has been examined.

As will be discussed in the sequel, the reaction of the epoxide (22) with hydrogen chloride presented us with a facile synthesis of some substituted 3,4-dihydroxyquinolines - a group of compounds which are not readily accessible by other methods, and which, by comparison with their positional isomers, have been almost overlooked.[31]

Most of the effort in the 3,4-dihydroxyquinoline field has been directed towards their synthesis, and little energy seems to have been left over to expend on an investigation of their chemistry; this is rather disappointing since by analogy with the 4-quinolones,[32] the (increased) opportunities for tautomerism e.g. (30)→(31)→(32) etc., ought to make their thorough study an interesting and rewarding experience. Unfortunately a review of these compounds written by Musajo et al.[33] is not available in a readily accessible form, and an attempt to glean information about the tautomerism of the 3,4-dihydroxyquinolines by comparing them with the better known 3,4-dihydroxypyridines did not meet with any success,

since the latter do not appear to have been studied in any greater detail. The syntheses of 3,4-dihydroxypyridines have been adequately covered in a review.[34]

The first claim to the synthesis of a 3,4-dihydroxyquinoline was made in 1894 by Claus and Howitz[35] who prepared the parent compound (30;R=H) by heating the corresponding dibromoquinoline with concentrated hydrochloric acid in a sealed tube: little experimental detail was given in this paper.

The next synthesis of a 3,4-dihydroxyquinoline was reported in 1935 by Putokhin who claimed that treatment of the N-substituted isatin (33) with sodium methoxide led to the di-sodium salt of 2-carboxy-3,4-dihydroxyquinoline (30;R=CO_2H), from which the free quinoline carboxylic acid could be recovered on acidification.[36]

Later Coppini[37] approached the synthetic problem from a different angle by introducing a bromine atom at the 3-position of a variety of the more readily accessible 4-quinolones, finally replacing the halogen by a hydroxyl group, using potassium hydroxide solution in a sealed tube at high temperature. Recently Morgan et al.[38] have achieved neat syntheses of 3,4-dihydroxyquinoline (30;R=H) and 3,4-dihydroxy-2-methylquinoline (30;R=Me) by first formylating the corresponding 4-quinolones (34;R=H and 34;R=Me) in position 3, subsequently replacing

the aldehyde by a hydroxyl group using the Dakin reaction. However the same workers reported that the Dakin reaction with (35) gave an abnormal product (36), which was isolated as its di-sodium salt.[38]

Formally derivable from the 3,4-dihydroxyquinolines by oxidation, are the 3,4-quinolinequinones e.g. (37); because of their intrinsic interest, elusiveness, and their appearance in the course of our work, they also merit mention here, but again their reported chemistry is sketchy. As far as can be ascertained from the literature, there are only a very few claims that compounds of this type have been isolated. The first claim was made in 1931 by Passerini et al.[39] who noted the formation of the dianil of 3,4-quinolinequinone (38) as a result of the curious trimerisation of phenyl isonitrile in presence of nitrosobenzene. The free quinone (37;R=H) obtained by hydrolysis of the dianil, reportedly could not be purified because of its instability. Recently Morgan et al.[38] have prepared and characterised the same compound, preparing it in good yield by mild oxidation of 3,4-dihydroxyquinoline. The same workers reported however that 2-methyl-3,4-quinoline-quinone (37;R=Me) prepared in an analogous way, was too unstable to be purified for analysis.[38] Kruber et al.[40] oxidised 7-methylcarbostyril (39) with chromium trioxide and

assigned the product the quinone structure (40). The latter formed a quinoxaline, and when fused with potassium hydroxide afforded p-toluic acid.

A variety of nuclear-substituted derivatives of 3,4-quinolinequinones in which the carbonyl functions are masked have also been prepared, but in these cases the free quinones were not isolated.[41]

Discussion

When a suspension of the trans epoxide (22) in sodium dried ether was saturated at room temperature with dry hydrogen chloride, the material slowly dissolved, and after standing overnight a colourless precipitate of a rather unstable hydrochloride had separated. When the latter was treated with aqueous methanol it readily liberated the golden yellow parent compound which contained covalently bound chlorine and gave an elemental analysis corresponding to the empirical formula $C_{15}H_{10}NO_3Cl$; that the latter was also the molecular formula was confirmed by a molecular weight determination. The parent compound (which was designated Q1) was both acidic and feebly basic, and it imparted a deep blue-green colour to methanolic ferric chloride. Q1 dissolved readily in dilute sodium hydroxide to give a yellow solution with a green fluorescence, and it could be recovered unchanged when this solution was acidified with dilute mineral acid. Its infrared spectrum revealed no absorption corresponding to a nitro group, but showed a weak band at ca. 1595cm.$^{-1}$ and considerable hydrogen bonding in a broad peak from 2300 - 3450cm.$^{-1}$ Its n.m.r. spectrum (trifluoracetic acid) was rather featureless, showing only a complex aromatic multiplet signal in the region τ1.3-τ2.3. When Q1 was treated with acetic anhydride it gave

a deep red solution from which no sensibly crystalline acetate could be recovered, but when treated with benzoyl chloride in alkaline solution it formed a colourless, highly crystalline dibenzoate which displayed carbonyl absorption in the infrared at 1740cm.$^{-1}$

On the basis of this data in conjunction with rational mechanistic postulates (which are discussed later) we were able to narrow considerably the possibilities for the structure of Q1, and the two most likely structures appeared to be the anthranil (41) and the 4-quinolone (42a), tautomeric with the 3,4-dihydroxyquinoline N-oxide (42b). That Q1 did not have the anthranil structure (41) was indicated by the following evidence: anthranils are not generally sufficiently basic to permit hydrohalide formation,[42] whereas Q1 forms a crystalline hydrochloride, albeit a rather unstable one. Further, 4-quinolones are well known to form unstable salts with mineral acids,[3] and the alkali solubility of Q1 makes the anthranil structure (41) seem even more unlikely, since in that molecule there is no site of appreciable acidity, whereas quinolinols are known to behave like phenols by being alkali soluble.[37]

Spectroscopically too the anthranil structure (41) is disfavoured, since the ultraviolet spectrum of Q1 bears resemblance to that of the known N-hydroxy-4-quinolone (6)[8]

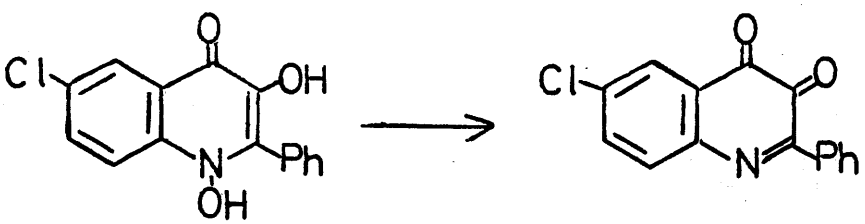
and moreover the spectrum of Q1 does not show the broad, long wavelength band at ca. 350mμ which is characteristic of 3-substituted anthranils.[43] The infrared evidence suggests that the low intensity band at 1595cm.$^{-1}$ could be attributed to the carbonyl stretching frequency of a 4-quinolone in which there are possibilities of hydrogen bonding to the carbonyl group.[44] On the other hand it could be argued that the 1595cm.$^{-1}$ peak corresponds to an aromatic absorption, and that in the solid state at least, Q1 exists in the di-hydroxy quinoline N-oxide form (42b). The acyloin group of (41) would be expected to show carbonyl absorption around 1670cm.$^{-1}$ [45] Finally the n.m.r. spectrum shows only aromatic proton resonances, and no signal corresponding to the methine proton required by the anthranil structure (41) was observed.

The evidence so far has been rather negative, and to show that Q1 was in fact the 4-quinolone (42a,b) we resorted to chemical degradation. Q1 was particularly susceptible to oxidation, and a variety of products were isolated depending on the rigour of the conditions used. Thus oxidation with sodium dichromate in a refluxing mixture of acetic and sulphuric acids afforded the known 4,4'-dichloroazoxybenzene-2,2'-dicarboxylic acid (43) which was identified by a comparison of its melting point, mixed melting point and

infrared spectrum with that of an authentic sample.[8] Thus the substitution pattern in the halogenated ring is established.

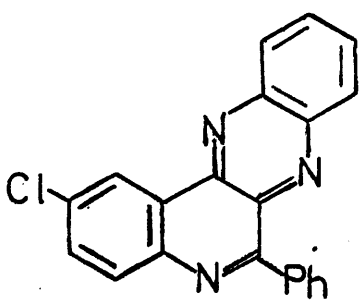
On the other hand oxidation with potassium permanganate or hydrogen peroxide in an alkaline environment followed by acidification, led, surprisingly, to benzoic acid as the sole isolable product. Although this confirmed the presence of a C-phenyl group in Ql, it was disappointing, for even prolonged extraction of the essentially neutralised reaction mixture did not yield the other (presumably amphoteric) fragment of the molecule.

More positive results were obtained when the permanganate oxidation was repeated in acetic acid at room temperature: the product, an essentially neutral colourless crystalline compound $C_{14}H_8NO_3Cl$, displayed carbonyl absorption in the infrared at 1680 and 1780cm.$^{-1}$ A comparison of its spectral properties with those of a known unchlorinated benzisoxazolone[46] (44;H for Cl) which was isolated later from an analogous reaction led us to propose the N-benzoylbenzisoxazolone structure (44) for the compound $C_{14}H_8NO_3Cl$. An attempt to synthesise the latter was thwarted when it was found impossible to prepare the key hydroxylamine (45) by reduction of the corresponding 5-chloro-2-nitrobenzoic acid. Since the N-benzoylbenzisoxazolone (44) is obviously the cyclodehydration product of the N-hydroxy



(Q1)

(50)



(51)

carboxylic acid (46) it is reasonable to assume the partial structure (47) for Q1; confirmation of this was obtained when the latter on oxidation with warm concentrated nitric acid yielded N-benzoyl-5-chloroanthranilic acid (48), a sample of which was readily prepared by shaking together 5-chloroanthranilic acid and benzoyl chloride in presence of dilute alkali. This synthetic sample and the material from the degradation were identical in melting point, mixed melting point and infrared spectrum, and both yielded the known[47] internal anhydride (49) when treated with hot acetic anhydride.

To locate the positions of the remaining atoms in Q1, and to demonstrate that two oxygen functions were situated ortho to one another in the heterocyclic ring, use was made of the fact that Q1 was structurally suited for a 1,4 elimination of water to give the 3,4-quinolinequinone (50) as shown opposite. Although attempts to isolate this quinone met with no success, it was trapped and characterised as its quinoxaline derivative (51) when a solution of Q1 in pyridine was treated first with toluene-p-sulphonyl chloride (affording a deep red solution), followed rapidly by the addition of o-phenylenediamine.

Having thus established the gross structure of Q1 we sought to confirm it by reduction and this is discussed later

in the chapter. At this stage more fundamental information regarding the nature of the cyclisation of the epoxide (22) seemed necessary, and we were led to re-examine the original reaction with hydrogen chloride having quinol present in the solution as a readily available reducing agent.

The product from this reaction was again a colourless unstable hydrochloride from which, as before, a yellow parent compound (Q2) could be liberated by treatment with aqueous methanol. The parent compound in this instance had the distinction of being halogen-free, and its elemental analysis and mass spectrum confirmed the molecular formula $C_{15}H_{11}NO_3$. In physical and spectral properties it was very similar to Q1, a similarity which extended to its behaviour on oxidation, whereby, under the appropriate conditions, the corresponding de-chloro compounds (44,48;H for Cl) were isolated, and since the latter are known substances they were rigidly identified by direct comparison of their melting points, mixed melting points and infrared spectra with authentic specimens.

When a solution of Q2 in pyridine was treated with toluene-p-sulphonyl chloride, a deep red solution resulted and, as before, it was found impossible to isolate quinonoid material. However two pieces of evidence pointed to the fact that an o-quinone was present in the reaction mixture. When the red

solution was treated with a saturated aqueous solution of sodium dithionite, the colour was rapidly discharged. The product, the 3,4-dihydroxyquinoline, (30;R=Ph ⇌ 31;R=Ph) was a pale yellow amphoteric solid which showed absorption in the infrared at 1630 (w) $cm.^{-1}$ (CO of 4-quinolone[44]) and 2500-3350 (broad) $cm.^{-1}$ (NH and OH stretch). Material identical to this in all respects was obtained from the hydrogenations of Q1 and Q2, both of which were reduced sluggishly in presence respectively of $Pd/CaCO_3$ and Pd/C as catalysts, some starting material being recovered in each case. The 3,4-dihydroxyquinoline (30;R=Ph) has not previously been synthesised; as noted earlier, Morgan et al.[38] failed to obtain this compound. The molecular weight, elemental analysis and spectral properties of our material are consistent with the proposed structure, and on mild oxidation with aqueous potassium permanganate in acetic acid (30;R=Ph) readily gave N-benzoylanthranilic acid (48;H for Cl). When warmed with acetic anhydride (30;R=Ph) formed a highly crystalline monoacetate which also had elemental analysis and infrared spectrum consistent[48] with its proposed formulation as the O-acetyl derivative of (31;R=Ph) (ν CO 1758 and 1635$cm.^{-1}$). The formation of monoacetyl derivatives from dihydroxyquinolines is unusual, but by no means unknown.[49]

The second indication that an o-quinone was present in the pyridine/toluene-p-sulphonyl chloride reaction of Q2 came again from the apparent formation of a quinoxaline, but while this had the predicted molecular weight and absorption spectra, a satisfactory analysis was unfortunately not obtained. On the above evidence Q2 was assigned the structure (42a,b;H for Cl).

Our next objective was to attempt to extend the scope of the synthesis of 3,4-dihydroxyquinolines by selecting a different o-nitrophenyl epoxide, and to this end the recently prepared[50] nitrophenylglycidic ester (25;R=Et) was chosen. On treatment with ethereal hydrogen chloride it afforded a viscous dark oil which could not be purified by distillation or chromatography: the crude product showed nitro group absorption in its infrared spectrum and gave a positive Beilstein test. A sample of this oil when shaken overnight with dilute sodium hydroxide gave, on acidification, the known o-nitrophenylglycidic acid[51] (25;R=H) which was identified by its elemental analysis, n.m.r. spectrum, and by direct comparison of its melting point, mixed melting point and infrared spectrum with a specimen prepared by careful alkaline hydrolysis of the nitrophenylglycidic ester (25;R=Et). With diazomethane the glycidic acid (25;R=H) afforded the corresponding methyl ester (25;R=Me) which also had satisfactory analytical and spectral properties, but

its m.p. (95°) differed appreciably from that of the published value (65°).[51]

No evidence for cyclisation of the ester (25;R=Et) was obtained even when the reaction time, temperature and solvent were varied. It was concluded that in this case the product from the epoxide was a mixture of the halohydrins (52) and (53).

Mechanism of the reaction

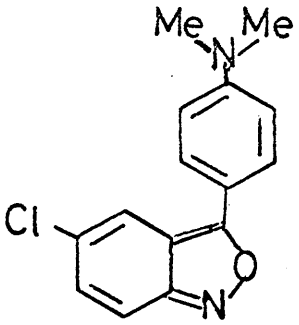
Any attempt to formulate a mechanism for the conversion of the epoxide (22) to the cyclised product (42a,b) can, at this juncture, be based purely on conjecture, but a plausible mechanism can be written to explain the experimental facts.

In the acidic environment it is reasonable to assume that the initial step in our reaction as with other epoxides will be protonation of the epoxide oxygen atom.[52] Bodforss[53] and House[54] respectively have shown that under similar conditions, the epoxides (22;m-NO_2 for o-NO_2) and (22;H for NO_2) subsequently suffer anionic attack at the benzylic carbon atom, presumably because this is potentially the more stable carbonium ion site. However a full or partial positive charge centred on the benzylic position of a suitably substituted ortho-nitro compound appears to be a prerequisite or at least a facilitating factor for the acid-catalysed formation of 3-substituted anthranils and 1-hydroxy-4-quinolones.[55] The ortho-nitro

group in our reaction can reasonably be envisaged attacking the benzylic carbon atom in a nucleophilic manner either in a stepwise or concerted fashion as discussed earlier in this Chapter. The net result once more is formation of an hydroxylaminophenyl ketone (54) which can cyclodehydrate in either of two ways - to afford the anthranil (41) or the quinoline N-oxide (42a,b), and the latter appears to be the more favoured process. Again quinol provides a contrast by supplying the necessary reducing power directly for the formation of the hydroxylaminophenyl ketone, and the product in this case (Q2) is halogen-free.

The failure of o-nitrophenylglycidic ester (25;R=Et) to undergo cyclisation is rather interesting, and it can not be ascribed to any difference in stereochemistry between this compound and the epoxide (22). The true situation may be related to the inability of the benzylidene compound (5;CO_2Et for COMe) to undergo cyclisation in presence of hydrogen chloride. The latter fact has been attributed to insufficient polarisation of the carbon atom α to the nitrophenyl nucleus when a feebly activating di-ester group is the side-chain substituent.

Because of the known ability of ethyl o-nitrobenzylacetoacetate (55)[56] and the 2,4-dinitrophenylacetoacetic ester (56;R=Ph)[57] to undergo ortho-substituent interactions, and the apparent inability of the related acetoacetic ester (56;R=Me) to do so, we were interested to note a report by Morley et al.[58] that the acetoacetic ester (57) gave an unidentified product when treated with boiling acetic anhydride. We have re-examined this reaction and found that the product, which analysed for $C_{13}H_{10}N_2O_8$, could readily be hydrolysed back to the starting ester (57) with warm dilute sodium hydroxide followed by acidification with dilute mineral acid. These facts together with the absence in the infrared spectrum of bands corresponding to a carboxyl group, and the appearance of a peak at 1620cm.$^{-1}$ corresponding to a double bond led us to assign the enol-lactone structure (58) to the product. This was confirmed by the n.m.r. spectrum which in addition to signals corresponding to an ethyl ester, showed a singlet (3H) at τ7.25 attributable to a methyl group on a double bond and adjacent to oxygen.



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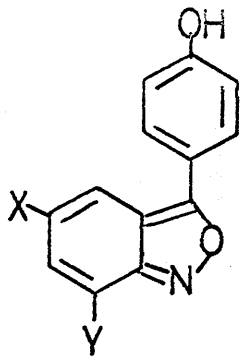

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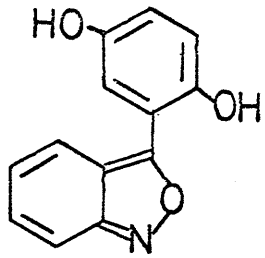

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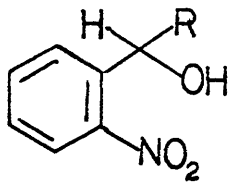

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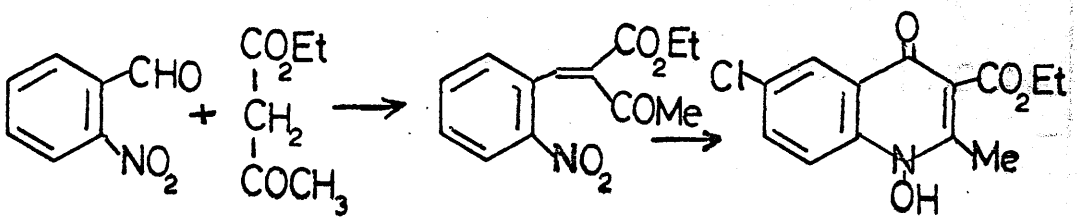

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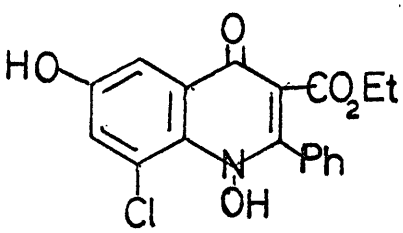

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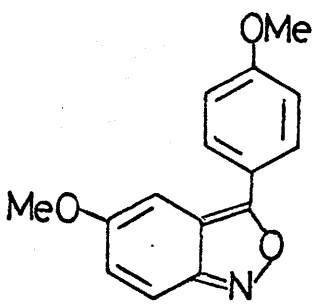

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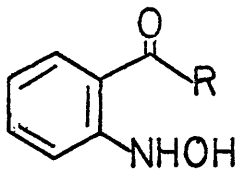

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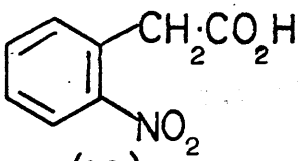

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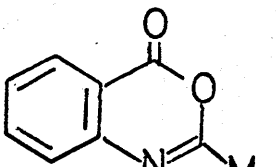

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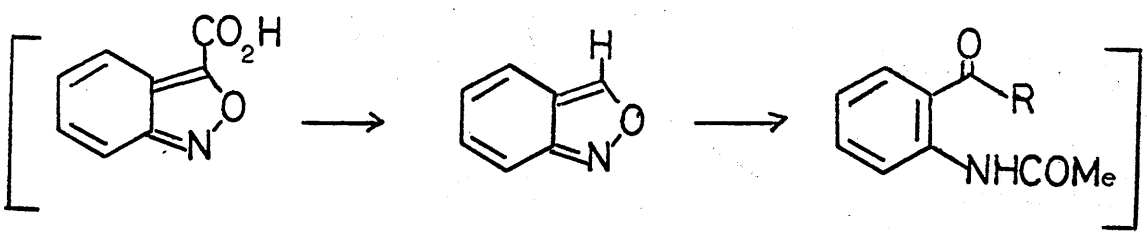

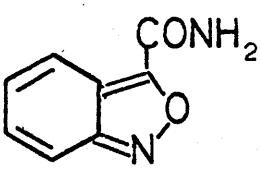

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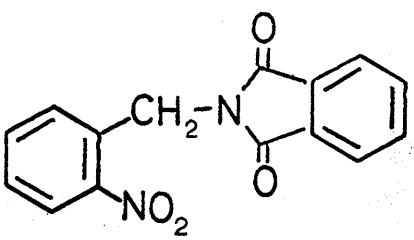

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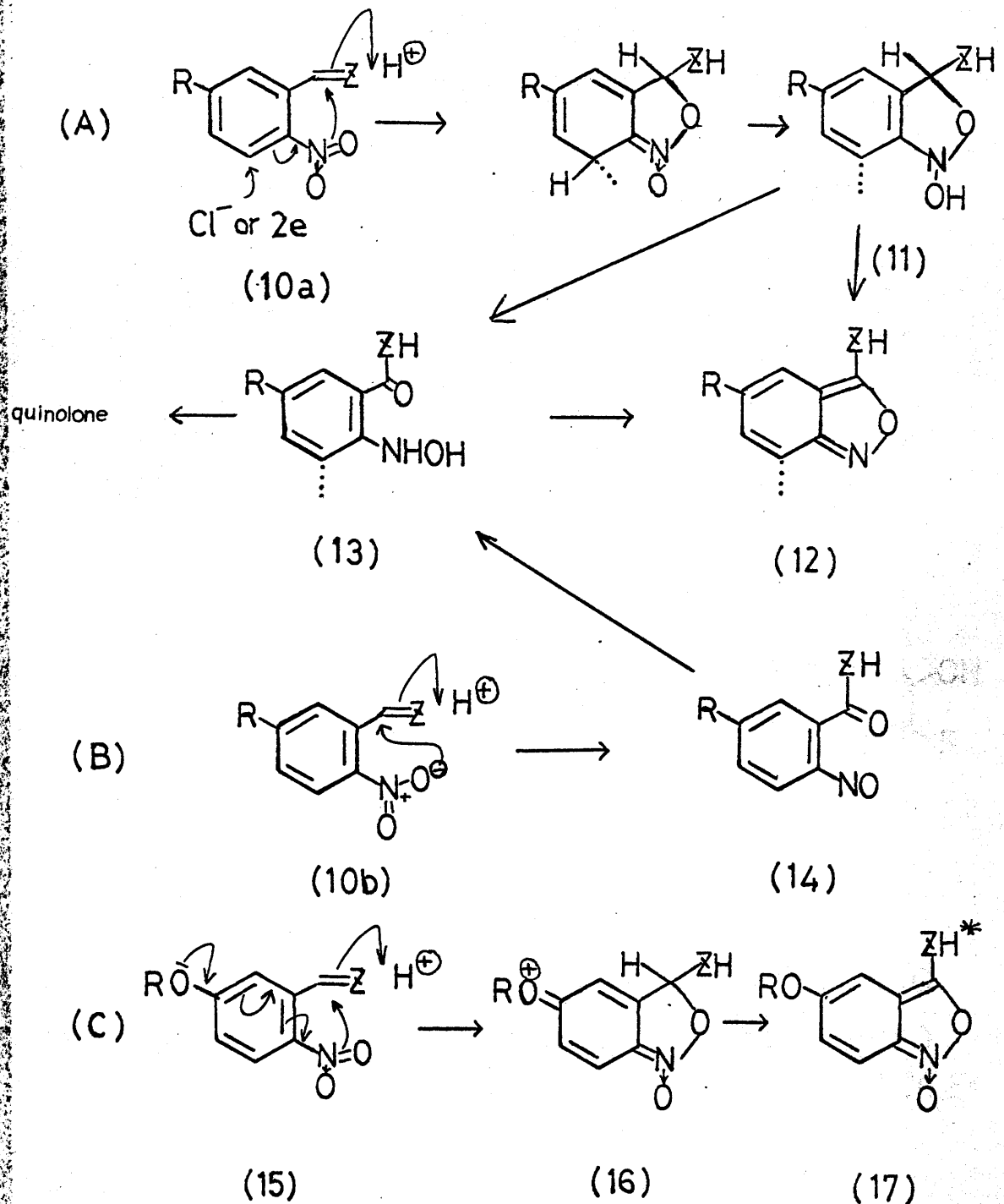
(A)
Cl⁻ or 2e
(10a)
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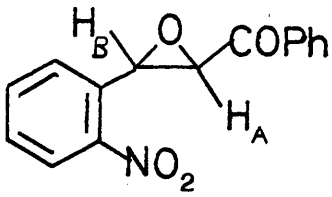

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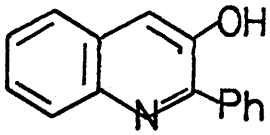

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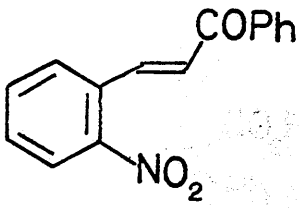

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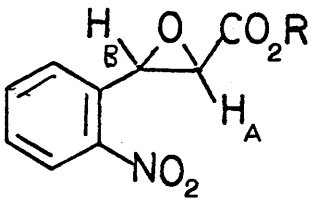

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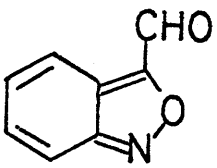

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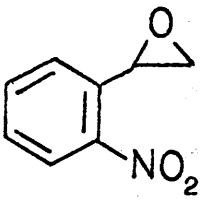

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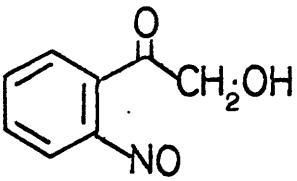

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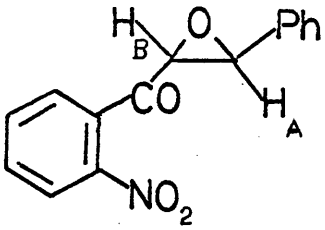

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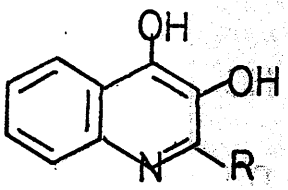

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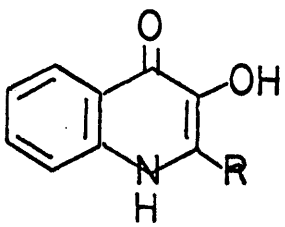

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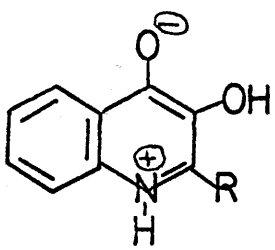

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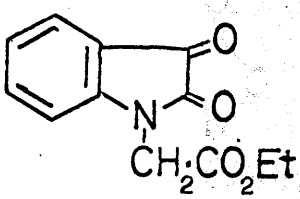

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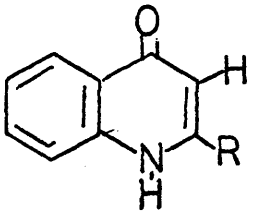

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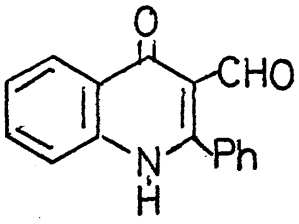

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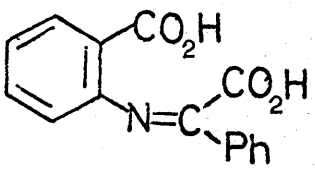

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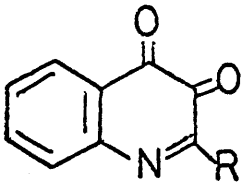

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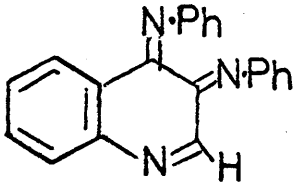

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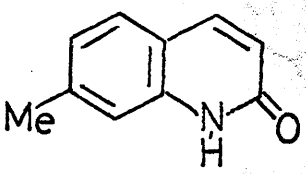

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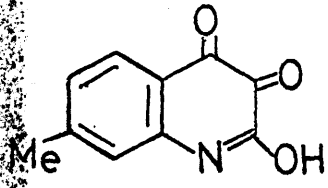

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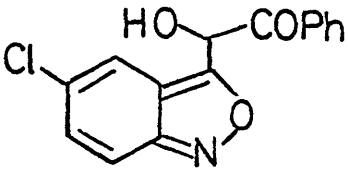

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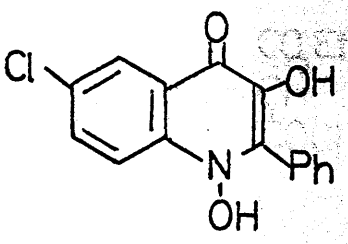

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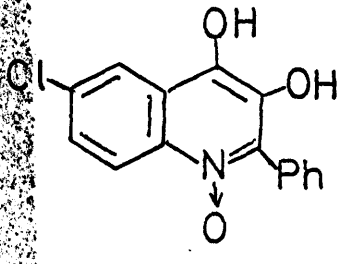

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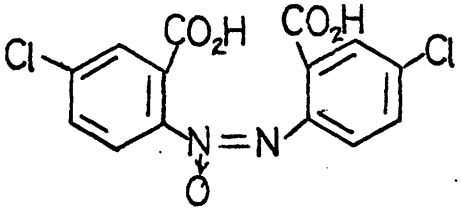

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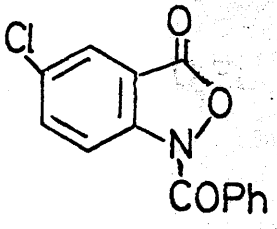

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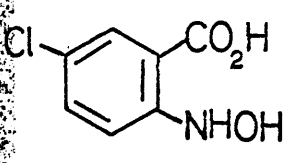

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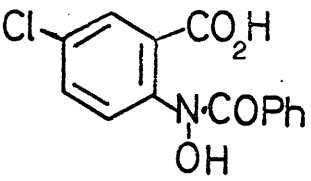

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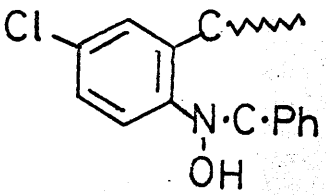

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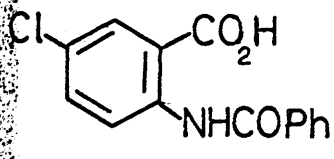

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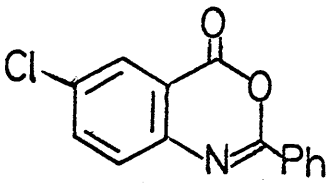

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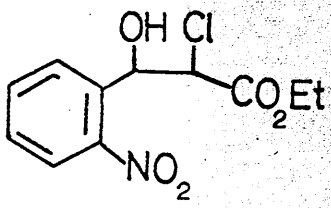

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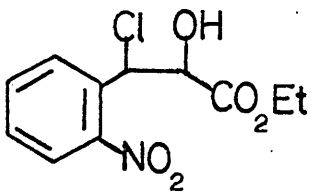

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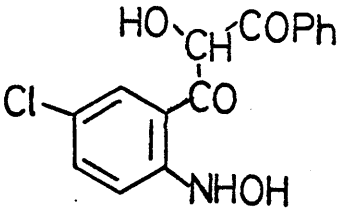

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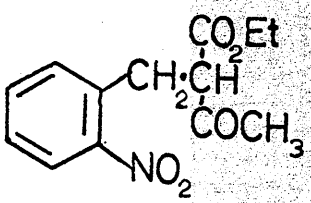

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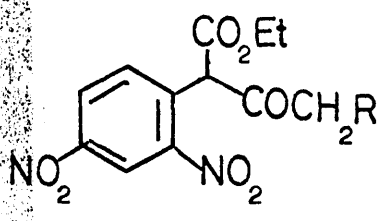

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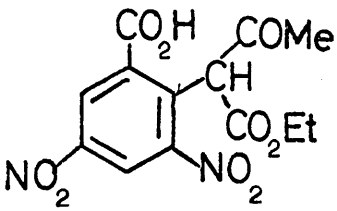

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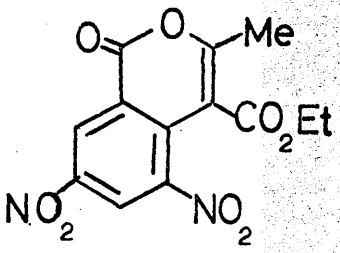


(58)

TABLE 1

N.m.r. spectral data in $CDCl_3$ at 60Mc/s.

Compound number	Multiplicity	Centred at τ	No. of H's	J cps	Assignment
22	doublet	5.35	1	3	H_B
	"	5.73	1	3	H_A
	multiplet	ca.2.2	4	-	aromatic H's
25;R=Et	doublet	5.30	1	2	H_B
	doublet	6.60	1	2	H_A
	triplet	8.65	3	7	ester CH_3
	quartet	5.65	2	7	ester CH_2
	multiplet	ca.2.1	4	-	aromatic H's
25;R=Me	doublet	5.29	1	2.5	H_B
	doublet	6.59	1	2.5	H_A
	singlet	6.10	3	-	ester CH_3
	multiplet	ca.2	4	-	aromatic H's
25;R=H	doublet	5.21	1	2	H_B
	doublet	6.54	1	2	H_A
	multiplet	ca.2.1	4	-	aromatic H's
29	doublet	6.14	1	3	H_B
	doublet	6.28	1	3	H_A
	multiplet	ca.2.3	4	-	aromatic H's
58 (trifluoroacetic)	singlet	7.25	3	-	CH_3-C(=O)-C=
	triplet	8.58	3	7	ester CH_3
	quartet	5.50	2	7	ester CH_2
	multiplet	0.65	2	-	aromatic H's

CHAPTER 3

Chapter 3

The Action of Potassium Cyanide on Various o-Nitrobenzylidene Compounds.

Introduction

In this chapter we shall concern ourselves only with those base-catalysed cyclisations which lead to heterocycles containing a new carbon-nitrogen bond, and, in general, the examples discussed involve reaction of aqueous ethanolic potassium cyanide with an o-nitrobenzylidene derivative e.g. (1a,b,c etc.).

This work was initiated by Wellings,[1] who, in an attempt to prepare ethyl β-cyano-β-o-nitrophenylpropionate (2) from diethyl o-nitrobenzylidenemalonate (1e) with ethanolic potassium cyanide, obtained only the quinoline N-oxide derivative (3;R=CN, X=CO_2Et, Z=OH). Using carefully controlled conditions the same worker found it possible to isolate the adduct (4a) which is potentially an intermediate in the above cyclisation. On renewed treatment with potassium cyanide, the nitrile (4a) was indeed converted to the same quinoline N-oxide (3;R=CN, X=CO_2Et, Z=OH).[1]

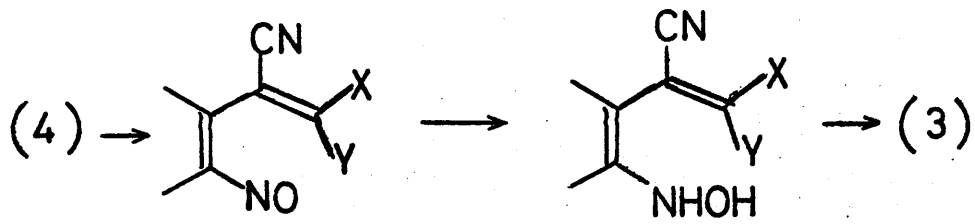
When the adduct (4a) or its derived amide ($CONH_2$ for CN) were treated under more mildly alkaline conditions (aqueous sodium carbonate), the reaction took a different course and derivatives of 1-hydroxyindole (5;X=CO_2Et) and (5;X=CO_2Et, $CONH_2$ for CN) respectively were obtained.[1]

In an extension of this work, Tennant[2] demonstrated the conversion of either benzylidene compound (6) or (1f) with ethanolic potassium cyanide to a mixture of a 1-hydroxyindole (5;X=Ph) and a quinoline N-oxide (3;R=CN,X=Ph,Z=NH_2). A reaction comparable with the latter has also been noted with o-nitrobenzylideneacetophenone.[3]

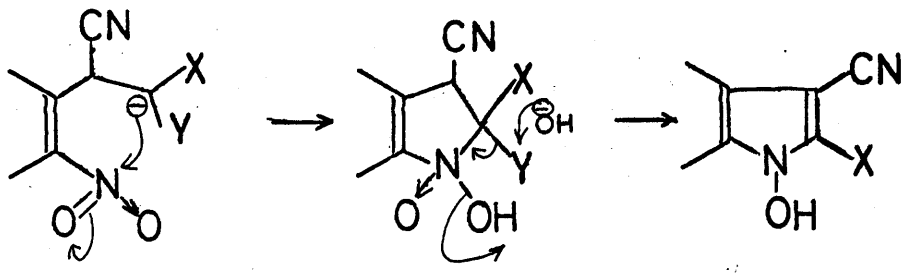
Generally, quinoline formation seems to be favoured by strongly alkaline reaction conditions and demands that from (1) (or 4) one of the groups X or Y furnish both a carbon atom and a substituent Z to complete the heterocycle. Indole formation is generally favoured by more weakly alkaline conditions and requires eventual elimination of one of the groups X or Y.

It is not usually possible to isolate intermediates from these reactions, but the above experimental evidence points to the adducts (4) being the first-formed products which subsequently suffer change. In (4) each of the α and β carbon atoms in the ortho side-chain carries a reactive hydrogen, and this is a common feature of successful cyclisations. However, feeble reactivity at (say) the α carbon can apparently be compensated for by increased acidity at the β centre, and vice versa. For example, cyclisation of o-nitrobenzylmalonic acid[4] and of ethyl o-nitrobenzylacetoacetate (7)[5] occurs in

A



B



(4) (5)

aqueous alkali to form 1-hydroxyindole-2-carboxylic acid, the reaction of (7) occurring so readily that ester (8) is also isolated. On the other hand, even with feeble activation at the β methylene centre of the side-chain, as in α-benzyl-5-methoxy-2-nitrobenzyl cyanide (9), cyclisation occurs in ethanolic alkali to yield 3-cyano-1-hydroxy-5-methoxy-2-phenylindole (10).[2]

With the present lack of information about mechanisms in such interactions, it is not possible to state categorically how or when the many and variable factors operate. However plausible mechanisms can be written to explain formation of the various heterocyclic products.

Quinoline N-oxide formation requires a reduction step at some stage, and it is conceivable that the necessary reducing power is provided by the strongly alkaline environments in which quinoline production is favoured. A possible mechanism (A) is illustrated opposite. Therein alkali promoted dehydration between the acidic α and β protons in the saturated side-chain and the nitro group leads to a nitroso intermediate. The latter can now suffer reduction to a hydroxylamine which on cyclodehydration yields a quinoline-type product.

Indole formation, generally in media of lower alkalinity and reducing power, can be regarded as a type of aldol

condensation between the nitro group acting as electrophil, and a carbanion generated at the β centre of the ortho side-chain of (4). Decomposition of the intermediate condensate then yields the product. This process (B) is also illustrated on the previous facing page.

Work to be described in the sequel was undertaken as an examination of the scope of the above cyclisations.

Discussion

In the following series of reactions between an o-nitrobenzylidene derivative and potassium cyanide, it was found necessary to adjust the time and temperature of the reaction according to the degree of reactivity of the double bond. In every case however, unless stated otherwise, an approximately four molar excess of potassium cyanide was used. The general work-up procedure was to cool the reaction mixture, dilute it with water and extract with an organic solvent to remove non-acidic material. Acidification of the alkaline aqueous phase with mineral acid followed by solvent extraction then gave acidic material which was further separated into bicarbonate-soluble and -insoluble portions.

2-Nitrobenzylideneacetylacetone

This compound (1a) has previously been prepared from o-nitrobenzaldehyde and acetylacetone under both acidic[6] and basic[7] catalysis. The method adopted for its bulk preparation during the course of the present work was that of Loudon and Marshall,[8] who obtained the product in excellent yield by condensing the reagents in presence of piperidine/piperidine acetate as catalyst.

Attempts under a wide variety of conditions to prepare the corresponding hydrogen cyanide adduct (4c) from the benzylidene compound (1a) and potassium cyanide were uniformly unsuccessful. When an effort was made to control the pH of the reaction environment by introducing a phosphate (pH 7) or borate (pH 8) buffer solution, or by using carefully calculated quantities of reagents,[1] the reaction led either to a dark gum which could not be crystallised, or to returned starting material. Similar results were noted when the reaction was conducted in presence of magnesium chloride or of acetone cyanohydrin with triethylamine.[cf. 9]

When no effort was made to control the pH of the reaction environment, the course of events differed markedly. Addition of excess aqueous potassium cyanide to 2-nitrobenzylidene-acetylacetone in ethanol at room temperature caused rapid

darkening of the solution, and a spontaneous, vigorously exothermic reaction set in almost immediately. In our hands the only crystalline material obtainable from this reaction was the 4-carbamoylquinoline N-oxide (11;R=NH_2) which was isolated along with some dark tarry gum. The latter showed no evidence of yielding solid material on attempted crystallisation, and on treatment with warm acetic anhydride showed no apparent tendency to react. The amide (11;R=NH_2) was also the sole isolable product when potassium hydrogen carbonate was present in the original reaction mixture, and it was found that formation of the same product (11;R=NH_2) was not seriously impeded when ethanol was absent from the reaction environment.

The structure of the 4-carbamoylquinoline N-oxide (11;R=NH_2) was confirmed by the following experimental evidence. Elemental analysis of the highly insoluble high-melting cream coloured solid corresponded to the molecular formula $C_{13}H_{12}N_2O_3$, and its molecular weight (244) determined by mass spectrometry confirmed this. Its infrared spectrum revealed no absorption corresponding to a nitro group, but showed bands corresponding to an amide NH_2 (3100 and 3180cm.$^{-1}$) together with a broad carbonyl peak (1700cm.$^{-1}$ shouldered at 1690 and 1675 (w) cm.$^{-1}$) which is attributable to both COMe and amide carbonyl groups.

Although unaffected by boiling acetic anhydride, the

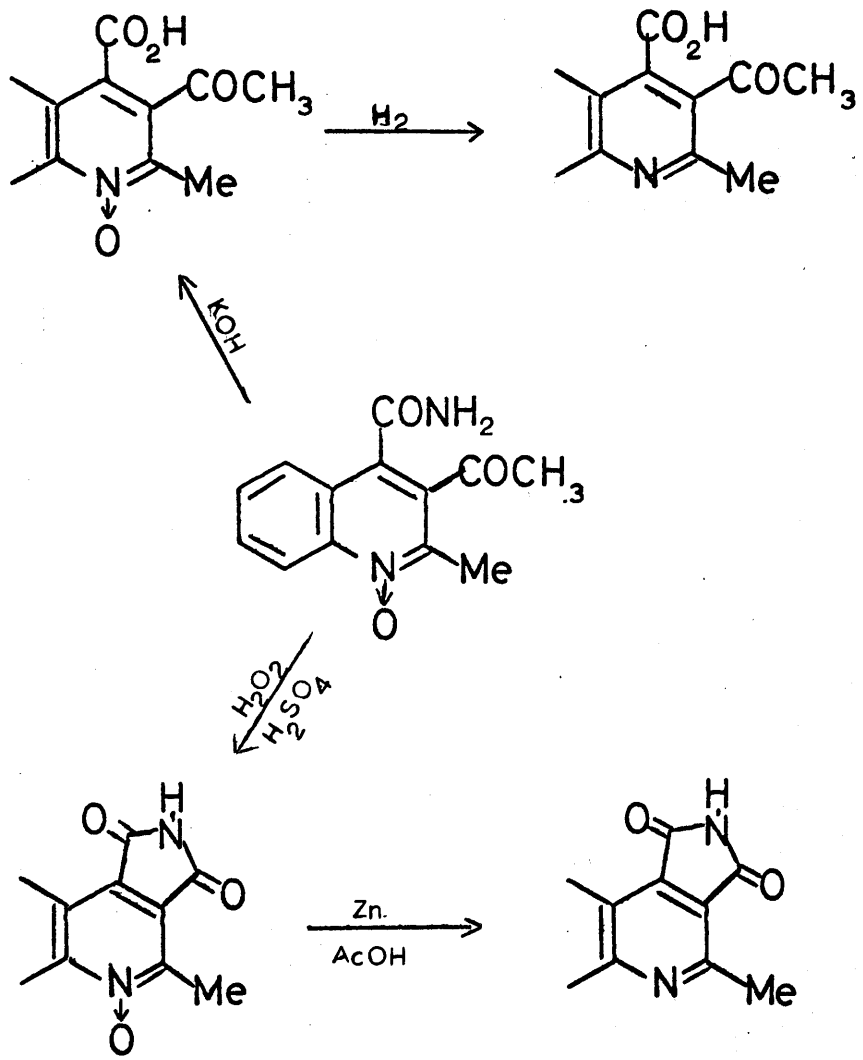
amide readily suffered hydrolysis to the corresponding carboxylic acid (11;R=OH) by refluxing it with aqueous methanolic potassium hydroxide, ammonia being evolved in the process. The acid (11;R=OH) because of its greater solubility in organic solvents was more easily workable than the amide (11;R=NH_2). On treatment with ethereal diazomethane the acid (11;R=OH) gave a colourless highly crystalline methyl ester (11;R=OMe).

The presence of an N-oxide group in these compounds was established by hydrogenation. Thus a solution of the acid (11;R=OH) was readily hydrogenated in a mixture of acetic acid, acetic anhydride and concentrated hydrochloric acid in presence of a palladium-charcoal catalyst. Concentration of the filtered reaction mixture afforded the acetyl cinchoninic acid (12) as its hydrochloride, from which the free cinchoninic acid was liberated by careful addition of dilute sodium hydroxide. The acid (12) was identical in melting point, mixed melting point and infrared spectrum with a sample prepared from potassium isatate and acetylacetone by the method of Stephanovic and his collaborators.[10]

Further confirmation of the structure of the amide (11;R=NH_2) was obtained when it readily yielded the N-oxido quinoline-3,4-dicarbonimide (13;R=Me) on treatment with hydrogen peroxide in cold concentrated sulphuric acid. This

imide was in turn reduced to the corresponding deoxy imide (14;R=Me) by boiling it briefly with a slight excess of zinc dust in glacial acetic acid. The deoxy compound (14;R=Me) was identical in all respects with an authentic specimen prepared by fusing together urea and 3-carboxy-2-methyl-cinchoninic acid according to the method of Lawson et al.[11]

Worthy of comment at this stage is the rather surprising solubility of the amide (11;R=NH_2) in warm aqueous ethanolic alkali: whereas the amide is insoluble in water, most organic solvents, and both warm and cold aqueous alkali, it readily dissolves in warm ethanolic sodium hydroxide. It is not reprecipitated from the latter either by cooling or diluting with water, but, provided the length of its exposure to the alkaline medium is not prolonged, it can be recovered unchanged on addition of dilute mineral acid. Since the amide (11;R=NH_2) contains no sites of appreciable acidity, a literature search for comparable behaviour in model systems seemed in order. Perhaps because of the reported difficulty in its synthesis[12] or its alleged instability[13] the most closely related compound 2-acetylbenzamide does not appear to have been examined for anomalous behaviour. However, 2-benzoylbenzamides have been studied in some detail and are reported[14] to be capable of existing in tautomeric 3-hydroxyphthalimidine forms e.g. (15) → (16;R=Ph), of which the parent member (16;R=H) is said


CO2H
COCH3
Me
N
O
H2
KOH
CONH2
H2O2
H2SO4
Zn.
AcOH
H

to be readily soluble in alkali.[15] It is possible that ring-chain tautomerism of this type plays a part in the alkali solubility of the 4-carbamoylquinoline N-oxide (11;R=NH_2).*

On the basis of the above evidence the product from the reaction of potassium cyanide and 2-nitrobenzylideneacetylacetone was assigned the structure of the amide (11;R=NH_2) and the main degradation scheme can be set down as shown opposite.

Ethyl α-2-nitrobenzylideneacetoacetate

This compound (1b) was prepared both by the published method[17] and also from its formative mixture of o-nitrobenzaldehyde and ethyl acetoacetate in presence of a piperidine/piperidine acetate catalyst.

The reaction of this benzylidene compound with potassium cyanide was not so vigorous as that of the previous example, and required gentle warming to initiate an exothermic process. After subsidence of the reaction, the mixture was diluted with water and separated into acidic and non-acidic fractions, of which acidic material was in preponderance. Chromatography of the latter on silica afforded a yellow solid which was identified by its melting point, mixed melting point and infrared spectrum as the previously isolated imide (13;R=Me).

* The ability of related carboxylic acids and their derivatives to undergo tautomerism of this type is also well documented.[16]

The non-acidic fraction yielded a small amount of gum which on trituration with methanol afforded a pale yellow highly crystalline neutral compound: on the basis of its elemental analysis it had the molecular formula $C_{14}H_{12}N_2O_3$. Absorptions in its infrared spectrum at 2250 and 1725cm.$^{-1}$ were assigned respectively to the presence of -CN and -CO_2Et groups. An indication that these substituents were juxtaposed was derived from the facile conversion of the compound $C_{14}H_{12}N_2O_3$ into the ubiquitous imide (13;R=Me) by treatment with hot concentrated sulphuric acid. On this evidence, and by analogy with the proved structure of products isolated from related cyclisations,[1,2] the compound $C_{14}H_{12}N_2O_3$ was assigned the 4-cyanoquinoline N-oxide structure (17;R=Me).

2-Nitrobenzylidenedibenzoylmethane

The compound (1c) crystallised as long colourless silky needles from a mixture of o-nitrobenzaldehyde, dibenzoylmethane, acetic acid and piperidine which was allowed to stand for several days at room temperature. Elemental analysis and its infrared spectrum were in accord with the expected structure.

This benzylidene compound was not affected by cold aqueous ethanolic potassium cyanide, but when refluxed briefly in the same medium, the mixture darkened rapidly, and, after cooling and diluting with water, it was separated into acidic and

non-acidic portions. The acidic fraction was totally soluble in aqueous sodium bicarbonate, and from its physical appearance it was obviously a mixture. Separation into its components was effected by boiling with water and filtering the hot solution containing suspended solid. Benzoic acid crystallised from the filtrate and was identified by its melting point and infrared spectrum. The water insoluble component analysed for $C_{16}H_{13}NO_5$ and showed absorption in the infrared at 1350, 1525 (NO_2), 1665 (COPh), 1700 (CO of CO_2H) and a broad band at 2500-3300cm.$^{-1}$ (OH of CO_2H). Solely on this evidence this compound was assigned the benzoyl-propionic acid structure (18).

The non-acidic fraction was worked up to afford a rather insoluble colourless high melting compound which analysed for $C_{23}H_{16}N_2O_3$. That this material was in fact the amide (19;R=NH_2) was confirmed by the following experimental evidence. Its infrared spectrum showed significant absorptions at 1700cm.$^{-1}$ (shouldered) (COPh and CO of amide), 3200 and 3475cm.$^{-1}$ (amide NH_2), and there were no bands corresponding to a nitro group. This compound was readily hydrolysed by aqueous methanolic potassium hydroxide to the corresponding carboxylic acid (19;R=OH) which was a colourless highly crystalline solid, more readily soluble in organic solvents than the parent amide. When treated with ethereal diazomethane the acid formed a

methyl ester. On hydrogenation in presence of acetic anhydride and concentrated hydrochloric acid (19;R=OH) was readily reduced to the deoxy acid viz. the cinchoninic acid derivative (20) obtained initially as its hydrochloride from the filtered concentrated reaction mixture. This deoxy acid (20) was identical in melting point, mixed melting point and infrared spectrum with an authentic sample prepared by heating together potassium isatate and dibenzoyl methane according to the method of Stephanovic et al.[10]

As with its methyl analogue (11;R=NH_2), the amide (19;R=NH_2) was soluble in warm ethanolic alkali, and could be recovered unchanged if the solution was promptly acidified with dilute mineral acid.

Thus when treated with potassium cyanide, 2-nitrobenzylidene-dibenzoylmethane afforded a mixture of benzoic acid, the propionic acid (18) and the 4-carbamoylquinoline N-oxide (19;R=NH_2).

Ethyl α-2-nitrobenzylidenebenzoylacetate

The benzylidene-ester (1d) was prepared according to the published method by saturating an ethereal solution of o-nitrobenzaldehyde and ethyl benzoylacetate with dry hydrogen chloride.[6]

When refluxed briefly with an aqueous ethanolic solution

of potassium cyanide this benzylidene compound gave a deep red solution which was worked up in the usual manner. The acidic fraction was purified by chromatography on silica to afford a golden yellow solid. Elemental analysis indicated the molecular formula $C_{17}H_{10}N_2O_3$ and this was confirmed by a determination of its molecular weight. It was noted that the carbonyl region of its infrared spectrum was almost identical with that of the 1-oxido quinoline -3,4-dicarbonimide (13;R=Me) and further the region above 3000cm.$^{-1}$ of both materials showed close correspondence. The identity of compound $C_{17}H_{10}N_2O_3$ as the imide (13;R=Ph) was established by refluxing it briefly with zinc dust in acetic acid. Thereby a deoxy compound $C_{17}H_{10}N_2O_2$ was obtained and this also showed characteristic imide absorption in the infrared.[18] The deoxy imide (14;R=Ph) was synthesised by an independent route: 3,4-dicarboxy-2-phenylquinoline was prepared from isatin and ethyl benzoylacetate by the published method,[19] ground into an intimate mixture with urea and fused carefully until no further gas was evolved.[cf.11] Extraction of the reaction mass with boiling acetic acid afforded 2-phenylquinoline-3,4-dicarbonimide (14;R=Ph) as beautiful yellow plates. The latter was identical in melting point, mixed melting point and infrared spectrum with the deoxy imide from the zinc/acetic

acid reduction.

The non-acidic fraction from the cyanide reaction yielded pale yellow needles of a neutral compound $C_{19}H_{14}N_2O_3$ which displayed significant absorption in the infrared at 1725cm.$^{-1}$ (ester CO) and 2225cm.$^{-1}$(CN). Treatment of this compound with hot concentrated sulphuric acid readily converted it to the previously isolated imide (13;R=Ph) with which it was identical in melting point, mixed melting point and infrared spectrum. By analogy with its methyl analogue (17;R=Me) the neutral material $C_{19}H_{14}N_2O_3$ was assigned the cyano-ester structure (17;R=Ph).

Thus ethyl α-2-nitrobenzylidenebenzoylacetate on treatment with potassium cyanide afforded two quinoline-type products - the imide (13;R=Ph) and the cyano-ester (17;R=Ph).

β-(2-Nitrobenzylidene)propiophenone.

The benzylidene compound (1i) was obtained in good yield when a solution of o-nitrobenzaldehyde in propiophenone was saturated at room temperature with dry hydrogen chloride. The resultant pale yellow reaction mass afforded the product when crystallised from methanol.

It became apparent after several runs of the reaction of β-(2-nitrobenzylidene)propiophenone with aqueous ethanolic potassium cyanide that the nature of the products was not

materially affected either by concentration of cyanide used or by the length of the reflux period. When the reaction mixture was worked up, only some unreacted starting material was present in the non-acidic fraction, whereas the bicarbonate-soluble portion was identified as benzoic acid. The interesting material lay in the alkali-soluble bicarbonate-insoluble fraction and this was obtained in a colourless crystalline form after treatment with charcoal.

This moderately acidic compound analysed for $C_{10}H_8N_2O$ and it was apparent from the infrared spectrum that it contained a cyano group (2200cm.$^{-1}$) and a hydroxyl group (3150cm.$^{-1}$). Analogy with a related reaction[2] suggested that this material was the cyano-indole (5;X=Me). With warm acetic anhydride it formed an acetate whose infrared spectrum contained a strong absorption band at 1800cm.$^{-1}$ which is indicative of a cyclic N-OAc grouping[1] and, consistently, hydrogenolysis of this acetate yielded a non-acidic deoxy-compound (5;X=Me, H for OH).

The gross structure of the cyano-indole (5;X=Me) was shown by forceful alkaline hydrolysis which apparently occurred with decarboxylation and reduction.[cf.2] The product obtained was 2-methylindole, identified by t.l.c. comparison with an authentic sample, by its pungent smell, and also by a t.l.c. comparison of its dark brown picrate with an authentic specimen.

The deoxy compound (5;X=Me,H for OH) has been reported several times in the literature but most of the published preparations are hazardous.[20,21,22] Since it was essential that a synthetic sample of this compound be obtained to establish without doubt the identity of (5;X=Me,H for OH), an alternative method of synthesis was sought. The preparation adopted involved formylation of 2-methylindole under Vilsmeier conditions[cf. 23] to afford the known[24] 3-formyl-2-methylindole in excellent yield. The oxime[25] of this aldehyde was then smoothly dehydrated in presence of acetic anhydride to give the desired 3-cyano-2-methylindole. This synthetic sample and the product obtained by hydrogenolysis of the acetate of (5;X=Me) were identical in melting point, mixed melting point and infrared spectrum.

It is worth noting that the cyano-indole (5;X=Me) does not affect the colour of methanolic ferric chloride. Similar behaviour has been noted for the related cyano-indole (5;X=Ph),[2] whereas 1-hydroxy-2-phenylindole is known to impart a deep red-brown colour to the same reagent.[2]

3-(2-Nitrobenzylidene)butan-2-one.

The methyl ketone (1h) was prepared by the method of Heller et al.[26] This involved dissolving o-nitrobenzaldehyde and ethyl methyl ketone in cold concentrated sulphuric acid.

The crude product obtained from the reaction was very dark and unattractive, but treatment with charcoal readily improved the colour of the material and after two crystallisations from ethanol it was obtained as pale yellow needles.

When refluxed with aqueous ethanolic potassium cyanide the benzylidene derivative (1h) afforded a mixture of starting material and the cyano-indole (5;X=Me); the latter was identical in melting point, mixed melting point and infrared spectrum with a sample isolated as described earlier. No effort was made to isolate the acetic acid generated in this cyclisation. Increasing the concentration of cyanide in the reaction mixture did not affect the nature of the products.

2-(2-Nitrobenzylidene)cyclohexanone.

We appreciated from the outset that the synthesis of 2-(2-nitrobenzylidene)cyclohexanone (21) might involve difficulty, since it is known that under acid catalysis cyclohexanone forms a di-o-nitrobenzylidene derivative,[27] whereas it forms a mono-benzylidene derivative with benzaldehyde under carefully controlled conditions.[28] The first method attempted for preparation of the benzylidene compound (21) involved shaking an excess of cyclohexanone with a dispersion of o-nitrobenzaldehyde in very dilute alkali. The product obtained in poor yield showed nitro group absorption in the

infrared but no bands corresponding to a double bond. Instead it showed a strong absorption at 3450cm.$^{-1}$ indicating the presence of a hydroxyl group. From its elemental analysis, ready formation of a highly crystalline tosylate and its absorption spectra this compound was deduced to be the aldol (22). Surprisingly, the aldol (22) was formed in good yield when o-nitrobenzaldehyde was allowed to react with the morpholine enamine of cyclohexanone either in the cold, in boiling benzene, or in the presence of toluene-p-sulphonic acid. The remarkable stability of the aldol under these conditions must derive wholly or in part from the formation of a strong intramolecular hydrogen bond e.g. as shown in (22).

(The direct condensation of an enamine with the carbonyl group of an aldehyde is a potentially useful synthetic reaction which has been reported recently by two schools,[29, 30] but has apparently escaped attention of reviewers in the enamine field.[31,32])

Treatment of the aldol (22) with dry ethereal hydrogen chloride led smoothly to its dehydration with formation of the desired benzylidene derivative (21). The same product was obtained when a solution of the tosylate (22;OTs for OH) was heated with potassium cyanide in dimethylformamide.[cf.33] The benzylidene derivative showed a tendency to form a ketal

or hemiketal on crystallisation from methanol especially when no effort was made to keep the solution rigorously free from traces of acid.

An attempt to condense o-nitrobenzaldehyde with cyclohexanone in the presence of acetic anhydride and potassium bicarbonate resulted in formation of o-nitrocinnamic acid as the sole isolable product.

When the o-nitrobenzylidene derivative (21) was refluxed briefly with aqueous ethanolic potassium cyanide, it dissolved to give a deep red solution. Separation of the mixture into its components afforded only unchanged starting material in the non-acidic fraction, and a yellow gum in the alkali-soluble portion. On cooling and scratching, the gum solidified to yield a light brown solid which analysed for $C_{14}H_{14}N_2O_3$ and of which the absorption spectra were rather revealing. In the infrared it showed a carboxyl group (3300-2500 (broad), and 1710cm.$^{-1}$) and a cyano group (2225cm.$^{-1}$), while the ultraviolet spectrum was almost superimposable on that of 3-cyano-1-hydroxy-2-methylindole. The presence of an N-hydroxy group in the molecule was again demonstrated by its ready reaction with acetic anhydride to form an acetate which showed infrared absorption at 1800cm.$^{-1}$ When this acetate was treated with ethereal diazomethane it formed a gummy ester which showed

absorption at 2260cm.$^{-1}$ (CN), 1805cm.$^{-1}$ (N-OAc) and 1730cm.$^{-1}$ (CO_2Me).

This evidence was the basis of our assignment of the hydroxyindole structure (23) to the product formed by treating 2-(2-nitrobenzylidene)cyclohexanone with aqueous ethanolic potassium cyanide.

3,4-Dibenzoyl-2-(2-nitrophenyl)butyronitrile.

The adduct (4b) was smoothly prepared in a Michael-type addition of 2-nitrobenzyl cyanide to 1,2-dibenzoylethylene, catalysed by dilute sodium hydroxide. This reaction was self-indicating, since 2-nitrobenzyl cyanide gives a bright blue solution in alkali, and when further addition of alkali caused no further development of colour, reaction was assumed to be over. The adduct showed expected infrared absorptions at 1345, 1530cm.$^{-1}$ (NO_2), 1675cm.$^{-1}$ (COPh) and 2270cm.$^{-1}$(CN), and a satisfactory elemental analysis was obtained. Significant differences were found in its behaviour with different bases.

When a suspension of (4b) was shaken overnight with cold sodium ethoxide in ethanol, a dark solution with suspended solid resulted. After dilution of the mixture with water it was separated into acidic and non-acidic fractions. Washing the non-acidic fraction with ethanol removed some ethyl

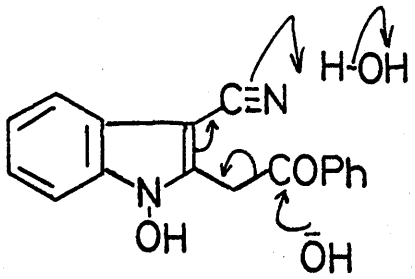
benzoate, and left an almost colourless, neutral, high-melting solid. From its elemental analysis the latter had the molecular formula $C_{24}H_{18}N_2O_3$ and from its infrared spectrum it clearly contained a primary amide function (3450, 3270, 1665cm.$^{-1}$) and a carbonyl group (1700cm.$^{-1}$). No absorption corresponding to a nitro group was observed.

By analogy with formation of the amides (11;R=NH_2) and (19;R=NH_2) the present compound was assigned the 4-carbamoylquinoline N-oxide structure (24;R=NH_2). An unsuccessful attempt was made to transform it into the imide (13;R=Ph) by oxidation-dehydration with hydrogen peroxide in concentrated sulphuric acid. A t.l.c. examination of the product from this reaction showed it to be a mixture of several components, and no attempt was made to separate these. More satisfactory results were obtained with hot concentrated sulphuric acid alone, for with this reagent a very smooth cyclodehydration occurred between the juxtaposed carbamoyl and phenacyl groups. The product was the lactam (25), which showed expected cyclic amide absorptions in the infrared (3250, 1695 shouldered at 1670cm.$^{-1}$). (Very recently Boyce and Levine[34] have demonstrated that the related isocarbostyrils (e.g. 26) arise from treatment of 2-phenacylcyanobenzenes (e.g. 27) with acid, the corresponding amides being possible intermediates.)

The amide (24;R=NH_2) was also readily hydrolysed by alkali to the corresponding carboxylic acid, (24;R=OH) which formed a colourless highly crystalline ester (24;R=OMe) on treatment with diazomethane. Again the presence of an N-oxide grouping in this series of compounds was demonstrated by reduction: the parent amide (24;R=NH_2) gave the corresponding deoxy compound (28) when treated with iron powder in boiling glacial acetic acid.

The acidic fraction from the original ethoxide reaction was washed with sodium bicarbonate to remove some benzoic acid; the remaining portion was dissolved in warm methanol and filtered to remove a very small amount of a rather insoluble colourless compound which was never obtained in easily workable quantity; nor were reproducible analyses or infrared spectra obtained. This material was not further examined.

The remainder of the acidic portion comprised a colourless solid whose ultraviolet spectrum was almost superimposable on that of 3-cyano-1-hydroxy-2-methylindole. Elemental analysis indicated the molecular formula $C_{17}H_{12}N_2O_2$ and the infrared spectrum revealed the presence of a carbonyl group (1685cm.$^{-1}$), an intact (and very intense) cyano group (2250cm.$^{-1}$), and a hydroxyl group (3100cm.$^{-1}$). The presence of an N-OH group was again revealed by the ready formation of an acetate which


H-OH
C≡N
COPh
N
OH
OH

showed characteristic absorption at 1795cm.$^{-1}$ in the infrared. The acidic product $C_{17}H_{12}N_2O_2$ was clearly the N-hydroxyindole (5;X=CH_2COPh) and this was confirmed by its rather remarkable hydrolysis with refluxing sodium hydroxide to give a mixture of benzoic acid and 3-cyano-1-hydroxy-2-methylindole (5;X=Me). Presumably this occurs by a mechanism akin to that shown opposite. Both hydrolysis products were identified by comparison with authentic materials.

This facile hydrolysis of the 3-cyano-2-phenacylindole (5;X=CH_2COPh) prompted an investigation of the ease of base-catalysed hydrolysis of the model system, 2-phenacylcyanobenzene (27). Under a variety of alkaline conditions the only product isolated was the known 3-phenylisocarbostyril (26)[34] which was identified by analysis, melting point, mixed melting point and infrared spectrum, all of which were comparable with those of authentic material. This underlines the marked differences in reactivity of substituents in the ring systems of (5) and (27).

When the Michael addition product (4b) was refluxed with aqueous ethanolic sodium carbonate, the relative amounts of the major products differed significantly from those of the ethoxide-catalysed reaction. Under the more mildly alkaline conditions only three products were obtained - benzoic acid,

the 4-carbamoylquinoline N-oxide (24;R=NH_2) and the 1-hydroxyindole (5;X=CH_2COPh). Whereas with the strongly alkaline ethoxide reaction the quinoline predominated in the mole ratio 3.3:1, in the carbonate reaction the ratio dropped sharply to 0.9:1.

If the mother-liquors from the crystallisation of the hydroxyindole (5;X=CH_2COPh) were allowed to stand at room temperature for several days, a basic, bright yellow product slowly deposited. This material was much less soluble and stable than the hydroxyindole (5;X=CH_2COPh). The same product was formed (t.l.c. analysis) when ethanolic solutions of the indole (5;X=CH_2COPh) were allowed to stand for several days at room temperature, either with or without a trace of mineral acid being present. The base proved difficult to crystallise by conventional methods since it decomposed in solvents at whose boiling point it was appreciably soluble. The most satisfactory method found was to crystallise the material first from acetic acid, which afforded the base as its colourless unstable hydroacetate; the latter on treatment with boiling ethanol liberated the free-base as its ethanolate. Efforts to remove the solvent by application of heat in vacuo resulted in severe decomposition of the material, but after allowance for this molecule of ethanol, analysis indicated the

base to be isomeric with the hydroxyindole (5;X=CH_2COPh).

The outstanding features of this base were first its infrared spectrum which showed no peaks corresponding to CN, CO, or OH absorptions, but showed instead peaks at 1610cm.$^{-1}$(w) (C=C?), 1640cm.$^{-1}$(broad) (C=N?) and a poorly defined band from 2500-3300cm.$^{-1}$ Secondly the base was notable for its reaction with alkali, for when dissolved in sodium hydroxide and reprecipitated with acetic acid, the cyano-indole (5;X=CH_2COPh) was regenerated. On the other hand when the base was refluxed with aqueous alkali a mixture of benzoic acid and 3-cyano-1-hydroxy-2-methylindole (5;X=Me) was obtained.

The ease of interconversion of the hydroxyindole (5;X=CH_2COPh) and the base implied their very close relationship, and suggested that the phenacyl and cyano groups might be participating in a ring-chain tautomerism. With this in mind the base was provisionally assigned the imino-lactone structure (29a) or its amino tautomer (29b).

Again the 2-phenacylcyanobenzene (27) was used as a model compound, this time to determine if ring-chain tautomerism (29a) $\rightleftharpoons$ (29b) is a general feature of this particular pair of ortho-substituents. However this cannot be the case, for in our hands the nitrile (27) appeared stable on prolonged

exposure to a cold acidic environment. On the other hand it was smoothly converted to the isocarbostyril (26) by refluxing it with ethanolic sulphuric acid.[cf. 34] Again the explanation of differences in reactivity between (5;X=CH_2COPh) and (27) must be accounted for by the greater reactivity of substituents in the heterocyclic ring of (5;X=CH_2COPh) compared with substituents in (27).

Although our work on the proof of the structure (29a,b) is incomplete, the novelty of the (apparent) tautomerism (5;X=CH_2COPh) $\rightleftharpoons$ (29a,b) led us to seek analogies in the literature. The present example can be regarded as a type of intramolecular Pinner reaction[35] in which the alcoholic group is provided by enolisation of the carbonyl function. The most closely related example is one which has only recently been resolved by Kuhn and Weiser[36] and concerns the true structure of the product obtained by condensing o-hydroxybenzaldehyde with benzyl cyanide. Borshe and Streitberger[37] originally performed the condensation and assigned the product the structure (30). Houben and Pfankuch[38] repeated the work and noted that the compound (30) formed a hydrochloride which they regarded as being the hydrochloride of (31). Critical repetition of both reactions by Kuhn and Weiser[36] has revealed that the material (30) does not exist as such, but as the

imino-lactone (31). In this instance the enolic hydroxyl group for an internal Pinner-type reaction is "preformed".

In an effort to obtain information about the apparent ease of amide formation in the foregoing reactions, we were prompted to examine comparable ease of hydrolysis in para nitro compounds. Although the results of our preliminary investigations are interesting in themselves, it is not yet clear whether they bear any direct relation to the facile formation of amides during cyclisation of ortho nitro compounds.

p-Nitrobenzylideneacetylacetone (32) was selected as a suitable test-case and was prepared by the same method as its ortho-isomer. When treated with cold aqueous ethanolic potassium cyanide it afforded from the acidified alkaline phase, an excellent yield of a deep red highly crystalline solid. While elemental analysis and molecular weight determination confirmed the red material to be isomeric with the expected product (33) its infrared spectrum was incompatible with its formulation as such. No absorption corresponding to a nitrile was present and in Nujol suspension a series of three peaks appeared above 3100cm.$^{-1}$ On dilution studies ($CHCl_3$) the latter resolved into two absorptions at 3403 and 3523cm.$^{-1}$ respectively, indicating the presence of a primary amino group. This was consistent with formation of

a colourless unstable salt when the red compound was treated with concentrated hydrochloric acid, and also with the n.m.r. spectrum (in acetone) which showed a singlet corresponding to two protons (τ 4.7) which disappeared on D_2O exchange. The n.m.r. spectrum (in pyridine) showed two singlet methyl signals at τ7.57 and τ7.77.

The 2-aminofuran structure (34;R=H) for the red compound is consistent with the above experimental evidence, and is substantiated by formation of a colourless secondary amide on treatment of the red material with acetic anhydride in benzene. This secondary amide had elemental analysis and absorption spectra compatible with its formulation as (34;R=$COCH_3$).

Solutions of the aminofuran (34; R=H) are not stable and fairly quickly deposit a pale yellow solid which may be the amide (35). The latter was unaffected by acetic anhydride.

Oxidation of the aminofuran with sodium dichromate in acetic and sulphuric acids gave p-nitrobenzoic acid.

2-Aminofurans are not a particularly well known class of compounds but recently they have been investigated by the Scandanavian[39] and German[40] schools who have generally prepared them by "alkylating" a reactive β-dicarbonyl compound with a halogenated acetonitrile. Tautomerism of the intermediate to the 2-aminofuran occurs spontaneously during the course of the reaction.

Results from the present series of base-catalysed cyclisations are tabulated together with related examples from the literature (Table 2).

In view of the large number of variables which may operate to affect the nature of products, protracted discussion of individual cyclisations is unwarranted, but certain salient features of the Table deserve special mention.

Clearly, the scope of the reaction makes it potentially useful synthetically, but there is a drawback in the unpredictability of the nature of the products in certain instances. For example, in a few cyclisations only indolic products are obtained, in others exclusively quinolinic, while the remainder yield a mixture of both types.

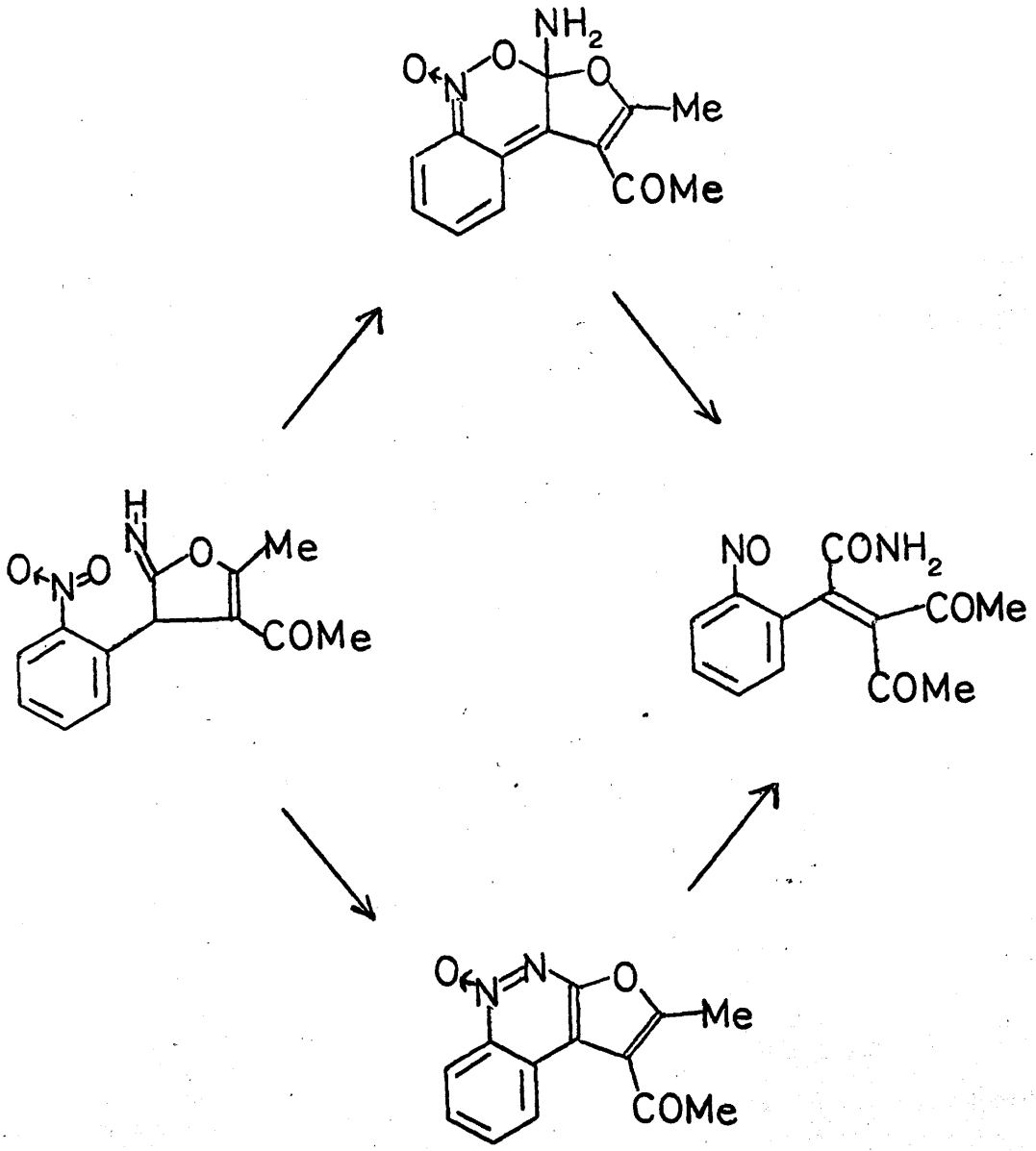
Several factors play a part in determining the type of product (indolic or quinolinic), or the proportion of these products in a mixture. One of these factors is alkalinity of the reaction environment. Compounds (1e), (4a) and (4b) provide cogent evidence for this. Thus under strongly alkaline conditions both (1e) and (4a) give only a quinoline-derived product, whereas (4a) on treatment with aqueous sodium carbonate yields only a derivative of 1-hydroxyindole. Relatedly, (4b) gives a much higher ratio of indolic to quinolinic product when treated under mildly alkaline

conditions than it does in a strongly alkaline environment (e.g. in sodium ethoxide). Reactivity at both α and β centres in the side-chain is another product-determining factor.

Formation of both types of product appears to be facilitated by the presence of an α cyano substituent in the (assumed) intermediates (e.g. 4), and its presence is a necessity for quinoline formation; in its absence e.g. (7), the product from treatment with alkali is exclusively indolic.[5] No less important is reactivity at the β centre of the side-chain.

In all cases, development of a β carbanion provides opportunity for indole formation (cf. scheme B facing p.40). However, diminution of this opportunity will result from resonance between this carbanion and the corresponding enolate (or equivalent) anion. The latter may be regarded as the major contributing structure in, for example, the anion from (1a), and indeed it is now found that such a situation with the <u>para</u> nitro isomer leads to cyclisation (32) → (34) to a 2-aminofuran. Intermediacy of a 2-aminofuran has not yet been substantiated in the <u>ortho</u> nitro series but analogy suggests several ways (scheme A opposite) by which an <u>ortho</u> nitro group and side-chain may combine a redox interaction with nitrile group hydrolysis. Thereby a nitroso intermediate

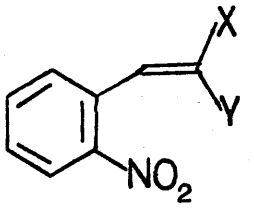
Scheme A


NH2
O
N
O
O
Me
COMe
NH
O
N
O
O
Me
COMe
NO
CONH2
COMe
COMe
O
N
N
O
Me
COMe

- which is presumably subject to reduction - becomes the precursor of a phenylhydroxylamine, and thus sets the course to a quinolinic product. Although this mechanism is purely conjecture, it does serve to illustrate another feature of the Table, namely that only in certain quinolinic products does the nitrile function fail to survive as such.

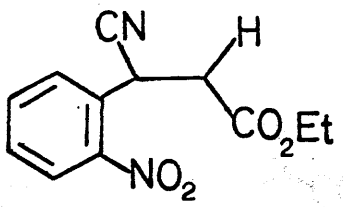
It is also apparent from the Table that nitrile hydrolysis does not invariably accompany quinolinic closure which then often appears in competition with indolic closure. Again formation of a nitroso intermediate - this time by transfer of two protons from side-chain to nitro group - leads ultimately to the quinoline-type product and is likely to be facilitated by both the α cyano substituent and high pH.

In certain instances we have invoked stabilisation of the β carbanion as a factor in the exclusive formation of quinoline-type products. On the other hand, by virtue of their bearing alkyl substituents, the β anions from (1h), (1i), and (21) will be of lower stability, and this may be a factor in their exclusive formation of indoles. Stabilisation of these anions by resonance to the corresponding enolate anions is limited through absence of a second β carbonyl group, and their fruitful contribution results from relatively rapid attack on the (sterically favourable) nitro group.



(1)

	X	Y
a	COMe	COMe
b	COMe	CO_2Et
c	COPh	COPh
d	COPh	CO_2Et
e	CO_2Et	CO_2Et
f	Ph	CN
g	COPh	H
h	COMe	Me
i	COPh	Me



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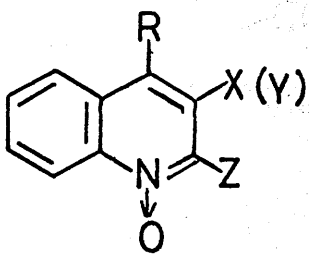

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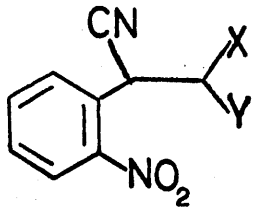
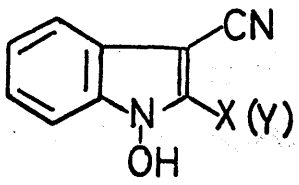


(4)

	X	Y
a	CO_2Et	CO_2Et
b	COPh	CH_2COPh
c	COMe	COMe



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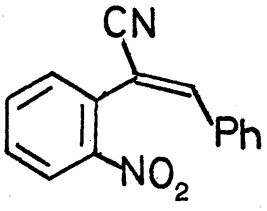

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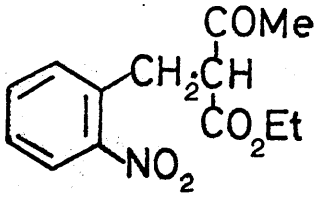

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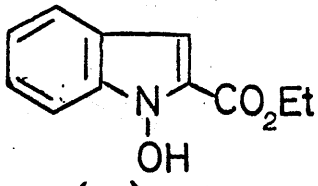

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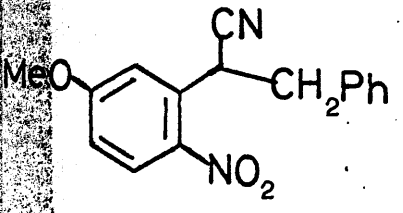

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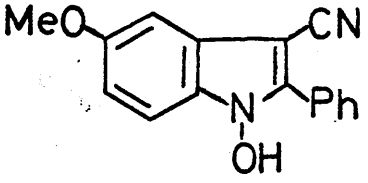

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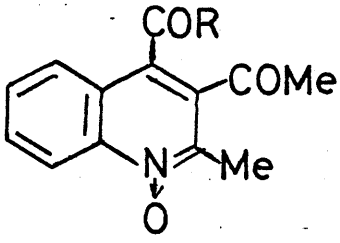

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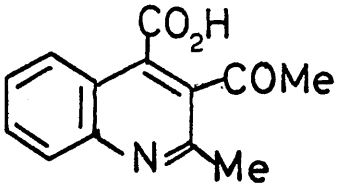

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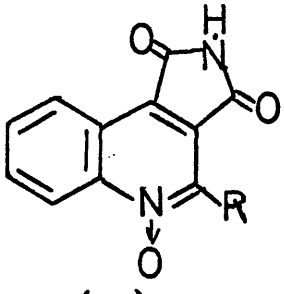

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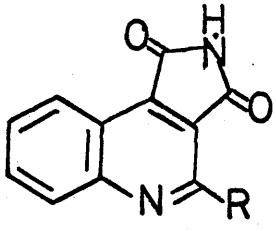

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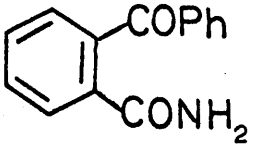

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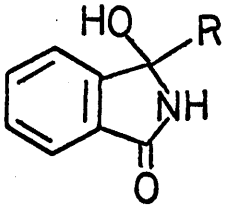

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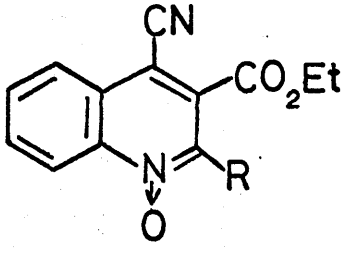

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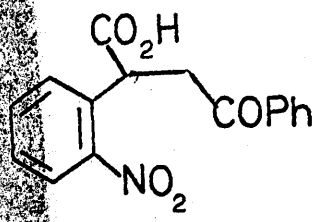

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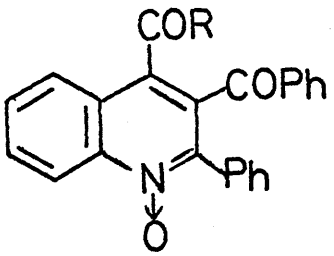

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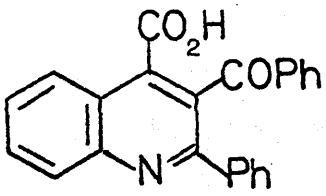

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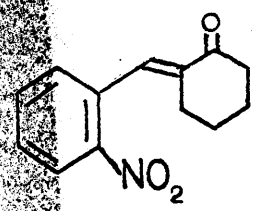

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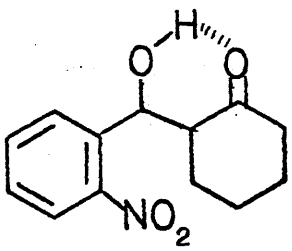

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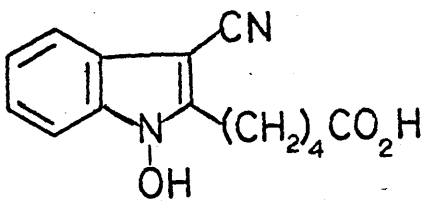

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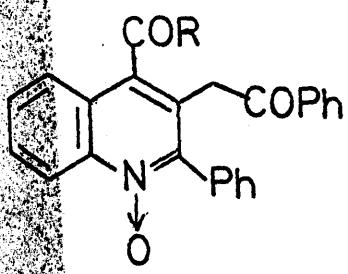

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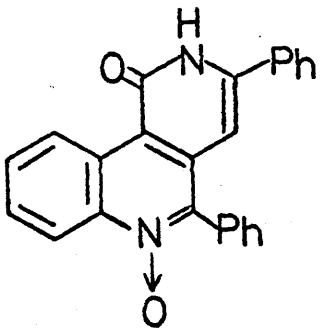

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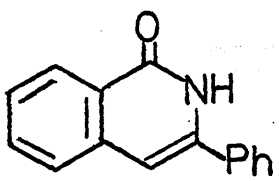

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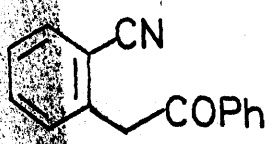

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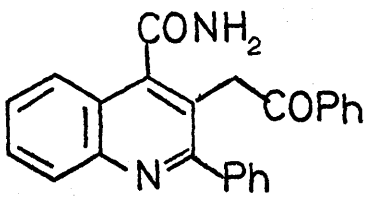

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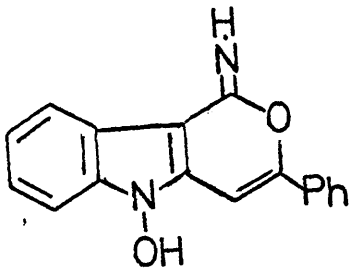

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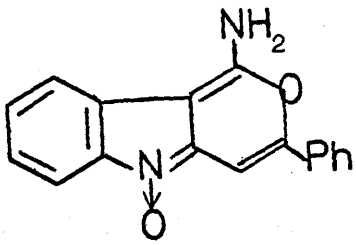

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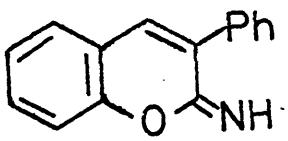

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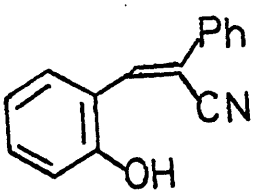

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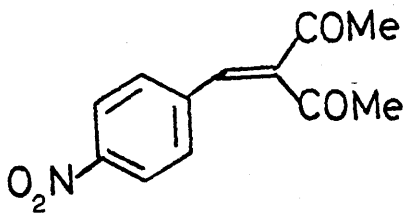

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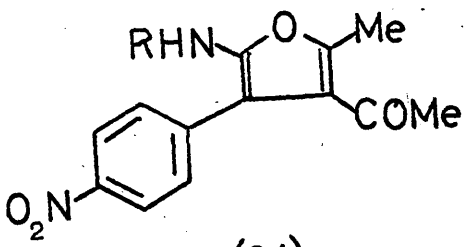

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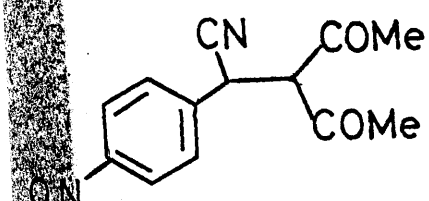

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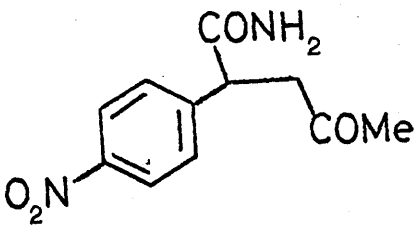

(35)

TABLE 2.

No.	Starting Material X	Starting Material Y	Quinolinic Product (3) R	Quinolinic Product (3) X	Quinolinic Product (3) Z	Indolic Product (5) X	By-products
1a	* COMe	COMe	$CONH_2$	COMe	Me	-------	--------
1b	* COMe	CO_2Et	-CONHCO- (CN, CO_2Et)		Me	-------	--------
1c	* COPh	COPh	$CONH_2$	COPh	Ph	-------	$PhCO_2H$ + (18)
1d	* COPh	CO_2Et	-CONHCO- (CN, CO_2Et)		Ph	-------	--------
1e	CO_2Et	CO_2Et	CN	CO_2Et	OH	-------	--------
1f	Ph	CN	CN	Ph	NH_2	Ph	--------
1g	COPh	H	CN	H	Ph	COPh	--------
1h	* COMe	Me	----------			Me	(CH_3CO_2H)
1i	* COPh	Me	----------			Me	$PhCO_2H$
2l	* 1-substituted cyclohexanone		----------			$(CH_2)_4CO_2H$	--------
4a	** CO_2Et	CO_2Et	CN	CO_2Et	OH	CO_2Et	--------
4b	*, ** COPh	CH_2COPh	$CONH_2$	CH_2COPh	Ph	CH_2COPh	$PhCO_2H$

* Reactions investigated in course of present work.

** For clarity in tabulation these are treated as benzylidene derivatives.

EXPERIMENTAL

SECTION.

Experimental

Melting points (m.p.) were taken on a Kofler microscope hot-stage. Infrared spectra were taken in Nujol mulls on a Unicam S.P. 200 infrared spectrometer unless otherwise stated and bands noted are either strong or medium in intensity unless denoted as weak (w). Ultraviolet spectra were measured for solutions in 95% ethanol. Nuclear magnetic resonance (n.m.r.) spectra were recorded on a Perkin Elmer R10 60Mc/s machine with tetramethylsilane as internal reference. Molecular weights (M) were measured on an A.E.I. M.S.9 mass spectrometer. Light petroleum refers to the fraction of b.p. 60-80°.

Experimental - Chapter 2

5-Hydroxy-2-nitrobenzaldehyde was prepared by the method of Hornig.[10] The crude nitration product was purified by washing it with hot benzene then crystallising it from water to m.p. 167-169°. Lit.[10] m.p. 167-168°.
The corresponding methyl ether was prepared by the method of Smith[11] et al. and had m.p. 81-83° (from ethanol). Lit.[11] m.p. 83-83.5°.

7-Chloro-5-hydroxy-3-p-hydroxyphenylanthranil (2;X=OH,Y=Cl).

A solution of 5-hydroxy-2-nitrobenzaldehyde (1.34g.) and phenol (1.56g.) in dry ether (ca 40ml.) was saturated with dry hydrogen chloride. A water-bath was used to maintain a steady temperature. The sealed flask was allowed to stand for 24hr. at room temperature, after which the yellow crystalline precipitate of the anthranil (2;X=OH,Y=Cl) (1.06g.) was collected, washed with ether and dried. It melted with decomposition above 350° (from methanol). A further 0.51g. of product was obtained by resaturation of the mother-liquors with hydrogen chloride. (Found: C,59.2; H,2.9; N,5.25. $C_{13}H_8NO_3Cl$ requires C,59.5; H,3.1; N,5.35%). (M found 262; calculated 261.7), λ max. 262,280, 358 mμ (ε 30,000, 2500, 30,500). $\lambda_{max.}^{NaOH}$ 308, 428 mμ.

The same product was obtained more smoothly when a solution of 5-hydroxy-2-nitrobenzaldehyde (1.2g.) and phenol (1.35g.) in glacial acetic acid (20ml.) was saturated at room temperature with dry hydrogen chloride. The resultant deep red solution precipitated yellow needles of the product (2;X=OH,Y=Cl) immediately the passage of gas was stopped. The reaction mass was filtered off after 2 hr. affording almost pure anthranil (2;X=OH, Y=Cl) (1.3g.). Resaturation of the mother-liquors with hydrogen chloride precipitated a further 0.2g. of product.

The corresponding dimethyl ether was obtained when a methanolic solution of (2;X=OH,Y=Cl) was treated with ethereal diazomethane. M.p. 151° (from ethyl acetate). (Found: C,62.3; H,4.4; N,5.1. $C_{15}H_{12}NO_3Cl$ requires C,62.2; H,4.15; N,4.8%).

Note on the use of hydrogen bromide as cyclising agent

Since the laboratory preparation of pure dry hydrogen bromide in bulk is rather troublesome,[21] we investigated the use of commercially available hydrogen bromide in acetic acid (50% w/v) as a suitable cyclising agent for reactions of the type described above.

In a test reaction, o-nitrobenzaldehyde (1.5g.) and phenol (1.8g.) were treated at room temperature with hydrogen

bromide in glacial acetic acid (50%, 10ml.). The mixture warmed up spontaneously, and after 2hr., deposition of a yellow solid began. After 4hr. the reaction mixture was filtered and the product (2.7g.) washed well with water and ethanol. Analytical thin layer chromatography (10% methanol/chloroform as eluant) showed that the products (2;X=Y=H) and (2;X=Br,Y=H) corresponded to those obtained when the reaction was conducted with ethereal hydrogen bromide.[3] No trace of any by-products resulting from the use of the commercial hydrogen bromide could be detected.

5-Hydroxy-3-p-hydroxyphenylanthranil (2;X=OH,Y=H)

To a well chilled mixture of 5-hydroxy-2-nitrobenzaldehyde (1.2g.) and phenol (1.3g.) in glacial acetic acid (4ml.) was added, slowly, hydrogen bromide in glacial acetic acid (50%, 4ml.). The resultant deep red solution warmed up spontaneously and was cooled intermittently in a water bath. The sealed reaction flask was allowed to stand 84hr. at room temperature, after which the deep yellow precipitate of the anthranil (2;X=OH,Y=H) was filtered off. Concentration of the mother-liquors in vacuo gave a further 0.5g. of product. Difficulty was encountered in purifying this material by crystallisation, since it tended to decompose to some extent on heating. The crude material decomposed above 250°.

When a suspension of this material in methanol was treated with ethereal diazomethane it formed the corresponding dimethyl ether (8), identical in m.p., mixed m.p. and infrared spectrum with the dimethyl ether from (2;X=OMe,Y=H) described below. With boiling acetic anhydride the anthranil (2;X=OH,Y=H) formed a diacetate which crystallised as large colourless plates m.p. 156° (from acetic anhydride, ethanol or acetic acid). (Found: C,65.7; H,4.1; N,4.8. $C_{17}H_{13}NO_5$ requires C,65.6; H,4.2; N,4.5%).

3-p-Hydroxyphenyl-5-methoxyanthranil (2;X=OMe,Y=H)

(a) 5-Methoxy-2-nitrobenzaldehyde (1 mole) and phenol (2 moles) failed to react in ethereal hydrogen chloride.

A solution of 5-methoxy-2-nitrobenzaldehyde (2.66g.) and phenol (2.8g.) in glacial acetic acid (12ml.) was saturated at room temperature with dry hydrogen chloride. A water bath was used to maintain a steady temperature. The sealed flask was set aside for 30hr. at room temperature, after which the reaction mixture was concentrated in vacuo to half bulk, diluted with ether and thoroughly extracted with 2N sodium hydroxide. The aqueous phase was acidified with dilute sulphuric acid and extracted with ether: the ethereal extract was washed with water and dried ($MgSO_4$). Concentration in vacuo afforded a dark gum which was chromatographed on silica

with 2% ether/benzene as eluant. The yellow solid (0.48g.) obtained by concentration of the eluate in vacuo was crystallised first from benzene then from methanol, yielding the pure anthranil (2;X=OMe,Y=H) as long yellow needles m.p. 197° (decomp.). The material showed a tendency to sublime before decomposing.

(b) The above material was identical in m.p., mixed m.p. and infrared spectrum with that obtained almost quantitatively when a mixture of 5-methoxy-2-nitrobenzaldehyde (1.17g.) and phenol (2.3g.) was treated directly at room temperature with hydrogen bromide in glacial acetic acid (50%, 6.5ml.). After the subsidence of the exothermic reaction, (ca. 15min.) the mixture was seeded and on standing it rapidly precipitated 3-p-hydroxyphenyl-5-methoxyanthranil (2;X=OMe,Y=H) (Found: C,69.7; H,4.55; N,6.1. $C_{14}H_{11}NO_3$ requires C,69.7; H,4.6; N,5.8%).

λmax. 265,370mμ (ε 17,500, 21,500).

$\lambda_{max.}^{NaOH}$ 275,410mμ.

Treatment of a methanolic suspension of this phenol with ethereal diazomethane gave the dimethyl ether (8) m.p. 107° (from ethanol). (Found: C,70.3; H,5.4; N,5.5. $C_{15}H_{13}NO_3$ requires C,70.6; H,5.1; N,5.5%).

2-Nitrobenzyl cyanide was prepared essentially by the method of Rousseau and Lindwall,[22] with the modification that o-nitrophenyl pyruvic acid oxime prepared in the penultimate stage of the synthesis was dehydrated to 2-nitrobenzyl cyanide by the method of Rinderknecht et al.[23] The nitrile had m.p. 84°. Lit.[23] m.p. 84°.

3-Carbamoylanthranil (20).

Finely powdered 2-nitrobenzyl cyanide (2.9g.) was added very cautiously to ice-cold concentrated sulphuric acid (10ml.). The resultant dark solution was allowed to stand 30 min. at room temperature, and was then poured on to ice. The dark precipitate (1.9g.) was filtered, washed well with water, dried and chromatographed on silica (150g.). Elution with 18% ether/benzene gave a pale yellow solid (0.04g.) which sublimed readily to give pale yellow needles of the anthranil (20) m.p. 211-213°. (Found: C,59.3; H,3.6; N,17.1. Cald. for $C_8H_6N_2O_2$: C,59.3; H,3.7; N,17.3%). This material was identical in infrared spectrum with an authentic sample prepared by the method of Ardnt et al.[19] Mixed m.p. 211-212°.

Subsequent elution of the column with ethyl acetate gave a red amorphous powder (0.34g.) which resisted further attempts at purification. It was established that this compound was not N-hydroxyisatin.

(The reaction of finely powdered 2-nitrobenzyl cyanide with concentrated sulphuric acid at room temperature was rather violent, and no crystalline material could be recovered from the resultant dark reaction mass).

The following o-nitrobenzyl-compounds were recovered unchanged when subjected to the above treatment: o-nitrophenylacetamide (also withstood concentrated sulphuric acid at 55-60° for 30 min.), o-nitrophenylacetic acid (18) and its ethyl ester, N-(o-nitrobenzyl)-phthalimide[20] (21).

2-Nitrobenzylideneacetophenone (24).

An ice-cold solution of o-nitrobenzaldehyde (3.62g.) in acetophenone (2.88g.) was saturated with dry hydrogen chloride and the sealed flask allowed to stand overnight at room temperature. The crystalline reaction mass was then crushed, washed with ethanol and filtered. Crystallisation (from ethanol) gave 4.8g. of product m.p. 123-124°. Lit.[59] m.p. 124°. (Found: C,71.0; H,4.3; N,5.5. Cald. for $C_{15}H_{11}NO_3$: C,71.1; H,4.4; N,5.5%).

Trans 2,3-epoxy-3-(o-nitrophenyl) propiophenone (22) was prepared by two methods -

(a) By the method of Bodforss[24] it had m.p. 111-112.5°. Lit. m.p. 110°.

(b) By epoxidation of 2-nitrobenzylideneacetophenone (24)

To a hot solution of the benzylidene compound (24) (1.25g.) in ethanol (15ml.) was added, all at once, a solution of potassium hydroxide (1.2g.) in water (7ml.) and hydrogen peroxide (30%, 3ml.). The mixture was then cooled in ice, and after 30 min. an excess of water was added. The precipitated epoxide (22) was collected and crystallised from ethanol to yield 1.18g. of colourless plates m.p. 108-109°. (Found: C,66.6; H,4.3; N,5.1. Cald. for $C_{15}H_{11}NO_4$: C,66.9; H,4.1; N,5.2%)

6-Chloro-1,4-dihydro-1,3-dihydroxy-2-phenyl-4-oxoquinoline (42a,b)

A suspension of the epoxide (22) (0.6g.) in dry ether (ca. 20ml.) was saturated at room temperature with dry hydrogen chloride. The epoxide slowly dissolved and precipitation of a colourless flocculent solid began. The sealed flask was allowed to stand at room temperature for 20 hr., after which the product (0.46g.), the rather unstable hydrochloride of the quinolone (42a,b) was filtered off. Resaturation of the mother-liquors with dry hydrogen chloride gave a further small amount of material. The hydrochloride crystallised as long colourless silky needles m.p. 264° (decomp.) (from hydrochloric acid). (Found: C,55.3; H,3.7; N,4.2. $C_{15}H_{11}NO_3Cl_2$ requires C,55.5; H,3.4; N,4.3%).

The free base (42a,b) was liberated by treating the hydrochloride with aqueous methanol. It crystallised as golden yellow needles m.p. 264° (decomp.) (from methanol/d m f) (Found: C,62.7; H,3.3; N,5.0. $C_{15}H_{10}NO_3Cl$ requires C,62.6; H,3.5; N,4.9%).

νmax. 1595, 2300-3450 (broad) $cm.^{-1}$

λmax. 222, 269, 378 mμ (ε 34,000, 55,000, 12,500).

$\lambda_{max.}^{NaOH}$ 288 mμ. (M found 287; calculated 287.7)

N.m.r. (trifluoracetic acid) - aromatic multiplet τ 1.3 - τ 2.3. This material gave a deep blue/green colour with

methanolic ferric chloride solution.

With benzoyl chloride in dilute sodium hydroxide it formed a dibenzoate which crystallised as colourless needles m.p. 181° (from methanol). (Found: C,70.2; H,3.75; N,3.4. $C_{29}H_{18}NO_5Cl$ requires C,70.2; H,3.7; N,2.8%).

νmax. 1740cm.$^{-1}$

Oxidative degradations of 6-chloro-1,4-dihydro-1,3-dihydroxy-2-phenyl-4-oxoquinoline (42a,b)

a) A solution of the quinolone (42a,b) (0.20g.) in acetic acid (4ml.), water (2.5ml.) and concentrated sulphuric acid (1ml.) was treated dropwise with a solution of sodium dichromate (1.20g.) in water (3ml.) and the solution then refluxed for 1 hr. On cooling, the green solution deposited fine yellow needles of 4,4'-dichloroazoxybenzene-2,2'-dicarboxylic acid (43) (0.072g.) m.p. 265° (decomp.) (from acetic acid) identical (mixed m.p. and infrared spectrum) with an authentic sample.[8]

b) To a cold solution of (42a,b) (0.24g.) in aqueous sodium hydroxide (2N, 2ml.) was added, dropwise, 30% hydrogen peroxide until the solution was pale yellow. Acidification with dilute sulphuric acid followed by continuous ether extraction of the solution for 24 hr. afforded benzoic acid (0.04g.) as the only isolable product from the concentrated ethereal extract.

c) Oxidation of (42a,b) (0.14g.) in sodium hydroxide (0.03g.) and water (4ml.) with an aqueous solution of potassium

permanganate (7ml.) (from 1.14g. potassium permanganate and 95ml. water) gave results as in (b) above.

d) A suspension of (42a,b) (0.23g.) in acetic acid (10ml.) was treated all at once with aqueous potassium permanganate (1%, 15ml.), and allowed to stand at room temperature for 4 hr. with occasional swirling. The solution was clarified by flushing it with sulphur dioxide, and the product (0.13g.) collected by filtration. Recrystallisation from aqueous ethanol afforded N-benzoyl-5-chlorobenzisoxazolone (44) as colourless silky needles m.p. 179°. (Found: C,61.0; H,2.8; N,5.0. $C_{14}H_8NO_3Cl$ requires C,61.4; H,2.9; N,5.1%).

νmax. 1680, 1780cm.$^{-1}$

e) Addition of cold concentrated nitric acid to the quinolone (42a,b) caused immediate development of a deep red colour which faded very rapidly when the mixture was warmed gently for a few moments on the steam-bath. The cooled solution was poured on to water and the (almost quantitative) precipitate of N-benzoyl-5-chloroanthranilic acid (48) was oollected by filtration. It crystallised as colourless needles m.p. 249° (decomp.) (from ethanol). (Found: C,60.7; H,3.9; N,5.1. $C_{14}H_{10}NO_3Cl$ requires C,61.0; H,3.7; N,5.1%).

νmax. 1615, 1670, 1690, 1705, 2800-3300 (broad) cm.$^{-1}$

This material was identical (mixed m.p. and infrared spectrum)

with a sample prepared by shaking 5-chloroanthranilic acid[60] with benzoyl chloride in the presence of aqueous sodium hydroxide.

A solution of N-benzoyl-5-chloroanthranilic acid in acetic anhydride was heated on the steam bath for 30 min. On cooling, the solution deposited 6-chloro-2-phenyl-4H-3,1-benzoxazin-4-one (49) as long colourless needles m.p. 197° (from benzene/ethanol). (Found: C,64.95; H,3.35; N,5.3. Cald. for $C_{14}H_8NO_2Cl$: C,65.25; H,3.1; N,5.4%). Legrand[47] prepared this compound by an alternative method and records m.p. 196°.

νmax. 1620, 1755cm.$^{-1}$

6-Chloro-2-phenylquino (3,4-b) quinoxaline (51)

A solution of the quinolone (42a,b) (0.085g.) in dry pyridine (0.5ml.) was treated with freshly prepared, finely ground toluene-p-sulphonyl chloride (0.060g.). The resultant deep red solution was then treated with finely ground o-phenylenediamine (0.33g.), whereupon the colour changed to very dark green. After 5 min. the precipitated quinoxaline (51) (0.03g.) was filtered and washed with cold ethanol to remove some dark impurities. The quinoxaline crystallised as long yellow needles m.p. 254° (decomp.) (from acetic acid). (Found: C,74.0; H,3.3; N,12.4. $C_{21}H_{12}N_3Cl$ requires C,73.8; H,3.5; N,12.3%). (M found 341; calculated 341.8)

λmax. 225, 253, 279, 305mμ (ε 50,000, 43,000, 47,000, 35,000).

1,4-Dihydro-1,3-dihydroxy-2-phenyl-4-oxoquinoline (42a,b;H for Cl).

A suspension of epoxide (22) (0.56g.) in dry ether (30ml.) containing quinol (0.20g.) was saturated with dry hydrogen chloride. A water bath was used to maintain a steady temperature. After 48 hr. the colourless crystalline mass of a rather unstable hydrochloride (0.21g.) was filtered off and washed with a little dry ether. Resaturation of the mother-liquor with hydrogen chloride afforded a further 0.12g. of the hydrochloride m.p. 180° (decomp.) (from hydrochloric acid). (Found: C,61.9; H,4.2; N,5.1. $C_{15}H_{12}NO_3Cl$ requires C,62.2; H,4.2; N,4.8%). Treatment of the hydrochloride with aqueous methanol liberated the free base (42a,b; H for Cl) which crystallised as bright yellow needles m.p. 180° (decomp.) (from aqueous acetic acid) (Found: C,71.0; H,4.35; N,5.8. $C_{15}H_{11}NO_3$ requires C,71.1; H,4.4; N,5.5%) (M found 253; calculated 253.2).

λmax. 218, 259, 376 mμ (ε 27,000, 40,000, 11,000).

$\lambda_{max.}^{NaOH}$ 280 mμ

N.m.r. (trifluoracetic acid) - aromatic multiplet τ1.3-2.3.

νmax. 1590, 2300 - 3450 (broad) cm.$^{-1}$

With methanolic ferric chloride solution the quinolone gave a deep blue colour. With benzoyl chloride in aqueous sodium hydroxide it formed a dibenzoate m.p. 163° (from ethanol) which crystallised as colourless needles. (Found: N,3.05. $C_{29}H_{19}NO_5$

requires N,3.0%).

νmax. 1740cm.$^{-1}$

Oxidative degradations of 1,4-dihydro-1,3-dihydroxy-2-phenyl-4-oxoquinoline

a) A suspension of the above quinolone (0.05g.) in glacial acetic acid was treated with an aqueous solution of potassium permanganate (1%, 3ml.). After standing 5 hr. at room temperature with occasional swirling, the solution was decolourised with sulphur dioxide and the product collected by filtration. It crystallised as colourless needles m.p. 153° (from ethanol) and was identical in infrared spectrum with an authentic specimen of N-benzoylbenzisoxazolone (44; H for Cl) prepared by the method of Bamberger et al.[43] The mixed m.p. was 153 - 154°.

b) The same product was obtained when a suspension of the quinolone (42a,b; H for Cl) (0.01g.) in acetic acid (0.5ml.) was treated at room temperature with 4 drops of a solution of sodium dichromate (1.5g.) in acetic acid (50ml.). After 2 min. the mixture was poured on to water and the product recovered by filtration.

c) N-Benzoylanthranilic acid (48; H for Cl) was formed almost quantitatively when the quinolone (42a,b; H for Cl) was warmed gently on the steam-bath for a few moments with a little concentrated nitric acid and the cooled mixture poured on to

water. After crystallisation (from benzene/petrol) it had m.p. 178-180°. The infrared spectrum was identical with that of a sample prepared by shaking anthranilic acid with benzoyl chloride in the presence of sodium hydroxide. Mixed m.p. 179-180°. Lit.[61] m.p. 181°.

3,4-Dihydroxy-2-phenylquinoline (30;R=Ph) was prepared in three ways:

a) A solution of 6-chloro-1,4-dihydro-1,3-dihydroxy-2-phenyl-4-oxoquinoline (42a,b) (0.25g.) in ethanol hydrogenated very sluggishly at room temperature and pressure with 10% $Pd/CaCO_3$ (0.1g.) as catalyst. The solid residue from the filtered, concentrated solution was washed with hot benzene to remove the product (30;R=Ph) (0.1g.) from unchanged starting material (0.1g.).

b) A solution of 1,4-dihydro-1,3-dihydroxy-2-phenyl-4-oxoquinoline (42a,b; H for Cl) (0.49g.) in acetic acid (50ml.) was hydrogenated at room temperature and pressure with 10% Pd/charcoal (0.15g.) as catalyst. The filtered solution was concentrated in vacuo to one third of its bulk and diluted with water. The precipitate of the quinoline (30;R=Ph) (0.15g.) was recovered from starting material (0.27g.) as in (a) above.

c) To a solution of 1,4-dihydro-1,3-dihydroxy-2-phenyl-4-oxoquinoline (42a,b; H for Cl) (0.25g.) in dry pyridine (2ml.)

was added finely powdered, freshly crystallised toluene-p-sulphonyl chloride (0.19g.). The resultant deep red solution was treated at room temperature with freshly prepared saturated aqueous sodium dithionite solution (0.3ml.). The deep red colour was instantly discharged; addition of an excess of water precipitated a pale yellow gum which solidified on being rubbed with methanol. The product (30;R=Ph) (0.10g.) was identical (mixed m.p. and infrared spectrum) with the materials isolated from (a) and (b) above. It crystallised as cream coloured hexagons m.p. 269° (decomp.) (with prior sublimation at 220°) (from aqueous d m f). (Found: C,75.9; H,4.8; N,5.9. $C_{15}H_{11}NO_2$ requires C,75.9; H,4.7; N,5.9%) (M found 237; calculated 237.25).

νmax. 1630, 2500 - 3350 (broad) $cm.^{-1}$

With methanolic ferric chloride it gave a deep blue colour, and with warm acetic anhydride it formed an acetate which crystallised as colourless needles m.p. 227° (decomp.) (from acetic anhydride). (Found: C,73.0; H,4.6; N,5.0. $C_{17}H_{13}NO_3$ requires C,73.1; H,4.7; N,5.0%).

νmax. 1635, 1758, 2600 - 3350 (broad) $cm.^{-1}$

A suspension of 3,4-dihydroxy-2-phenylquinoline (30;R=Ph) (0.05g.) in acetic acid (1.5ml.) was treated at room temperature with aqueous potassium permanganate (1%, 3ml.). After standing

overnight, the solution was decolourised with sulphur dioxide and the product (0.035g.) filtered, washed with water and crystallised from benzene/petrol to m.p. 178-180° and was identified (by mixed m.p. and infrared spectrum) as N-benzoylanthranilic acid (48; H for Cl).

2-Phenylquino (3,4-b) quinoxaline (51; H for Cl).

A solution of 1,4-dihydro-1,3-dihydroxy-2-phenyl-4-oxo-quinoline (42a,b; H for Cl) (0.25g.) in dry pyridine (2ml.) was treated with powdered, freshly crystallised toluene-p-sulphonyl chloride (0.19g.). To the resultant deep red solution was added freshly ground o-phenylenediamine (0.11g.). The dark green mixture rapidly deposited needles of the quinoxaline (51; H for Cl) (0.07g.) which were collected and washed with ethanol. Recrystallisation from acetic acid afforded the product as yellow needles m.p. 252-254° (decomp.).

λmax. 228, 256, 288 mμ (ε 45,000, 39,000, 53,000).

(M found 307; calculated 307.4)

A satisfactory analysis was not obtained for this compound. (Found: C,78.6; H,4.4; N,12.95. $C_{21}H_{13}N_3$ requires C,82.1; H,4.3; N,13.7%).

Reactions with ethyl o-nitrophenylglycidate (25;R=Et).

Ethyl o-nitrophenylglycidate was prepared essentially by the method of Martynov et al.[50] M.p. 60° (from aqueous ethanol). Lit. m.p. 62.5°.

All attempts to cause cyclisation of the ester (25;R=Et) with hydrogen chloride under a variety of times, temperatures and solvents were unsuccessful.

In a typical experiment, a solution of the ester (0.76g.) in dry ether (12ml.) was saturated at room temperature with dry hydrogen chloride; a water bath was used to maintain a steady temperature. The sealed flask was set aside overnight, after which volatile material was removed in vacuo, to leave a viscous dark oil which could not be distilled or purified by chromatography on silica gel or alumina. The crude oil gave a positive Beilstein test and gave no solid material when treated with warm acetic anhydride. The infrared spectrum of the crude material showed strong absorption characteristic of a nitro group.

The oil was shaken overnight with 2N sodium hydroxide, and the solution then acidified with dilute sulphuric acid and extracted with ether. The ethereal extract was washed with water, dried ($MgSO_4$) and concentrated in vacuo to yield o-nitrophenylglycidic acid (25;R=H) m.p. 124° (decomp.) (from

benzene). (Found: C,51.6; H,3.4; N,6.9. Cald. for $C_9H_7NO_5$: C,51.7; H,3.4; N,6.7%).

This material was identical (mixed m.p. and infrared spectrum) with a sample of o-nitrophenylglycidic acid prepared by careful alkaline hydrolysis of ethyl o-nitrophenylglycidate. Lit.[51] m.p. 124 - 125.5°.

With ethereal diazomethane the carboxylic acid formed the corresponding methyl ester (25;R=Me) m.p. 95° (from ethanol) (Found: C,53.9; H,4.0; N,6.6. Cald. for $C_{10}H_9NO_5$: C,53.8; H,4.1; N,6.3%). Lit.[51] m.p. 65°.

The n.m.r. spectra of the above epoxides are shown in Table 1.

Repetition of the work of Morley, Simpson and Stephenson[58]

Ethyl 2,4-dinitro-6-carboxyphenylacetoacetate (57) m.p. 142-143° (from benzene/petrol) was prepared by the method described by the above authors. Lit.[58] m.p. 142-143°.

The dark brown solution obtained by refluxing the acid-ester (57) (0.75g.) in acetic anhydride (3ml.) for 10 min. was concentrated in vacuo to small bulk and allowed to stand overnight. The crystalline product so obtained was washed with a little ether and recrystallised to m.p. 121°. (Lit.[58] m.p. 124°) from chloroform. (Found: C,48.4; H,2.9; N,8.9. $C_{13}H_{10}N_2O_8$ requires C,48.5; H,3.1; N,8.7%).

νmax. 1360, 1550, 1620, 1725, 1750cm.$^{-1}$

N.m.r.(Trifluoracetic acid). See Table 1.

When warmed with dilute sodium hydroxide the product dissolved slowly to give a deep red solution which on acidification with dilute sulphuric acid deposited crystals of the acid-ester (57), identified by its m.p., mixed m.p. and infrared spectrum , which were identical with those of authentic material.

On the basis of these data the product from Morley, Simpson and Stephenson's reaction was assigned the enol-lactone structure (58).

2'-Nitrochalcone epoxide (29)

To a hot solution of 2'-nitrochalcone (1.22g.) in ethanol (30ml.) was added, portionwise, a solution of potassium hydroxide (1g.) in water (5ml.) and hydrogen peroxide (30%,5ml.). The cooled solution was then treated with ice and the product (2.25g.) collected by filtration. It crystallised as colourless needles from ethanol m.p. 80°. (Found: C, 67.2; H,4.1; N,5.2. Cald. for $C_{15}H_{11}NO_4$: C,66.9; H,4.1; N,5.2%). Barnes[29] et al. report m.p. 79-80°. The n.m.r. spectrum is shown in Table 1.

Experimental- Chapter 3

2-Nitrobenzylideneacetylacetone (1a)

To a solution of piperidine (4.25g.) and glacial acetic acid (4g.) was added a solution of o-nitrobenzaldehyde (7.5g.) in acetylacetone (25g.). After being allowed to stand at room temperature for 2hr., the solution was poured on to water and the product collected by filtration. Recrystallisation from ethanol gave 9.0g. of colourless plates m.p. 74-76°. Lit.[6] m.p. 76°.

3-Acetyl-4-carbamoyl-2-methylquinoline 1-oxide (11;R=NH_2)

To 2-nitrobenzylideneacetylacetone (7.0g.) in ethanol (30ml.) was added a solution of potassium cyanide (7.0g.) in water (14ml.). A spontaneous reaction set in after a few seconds, and the solution was cooled intermittently in an ice-bath. When the reaction had subsided (ca. 20min.), water (15ml.) was added, and the solution extracted with chloroform (3x75ml.). The chloroform extract was washed with dilute sodium hydroxide (2x10ml.) then with water. The aqueous phase and aqueous washings were combined.

Chloroform layer was dried ($MgSO_4$) and concentrated in vacuo, but gave only trace amounts of solid.

Aqueous layer was acidified with dilute sulphuric acid, and the precipitate of the quinoline (11;R=NH_2) (3.0g.) was collected by filtration and washed with methanol to remove some dark tarry material (0.85g.). Extraction of the acidified

mother-liquors with chloroform (3x50ml.) gave, after washing (water), drying ($MgSO_4$), and concentrating in vacuo a further 1.3g. of dark tarry material which could not be solidified and which gave no solid material with warm acetic anhydride: the infrared spectrum of the crude material from this attempted acetylation showed no absorption in the region 1750-1810cm.$^{-1}$

(On one occasion, treatment of this dark tar with acetic anhydride caused precipitation of a small amount of the amide (11;R=NH_2)).

The quinoline N-oxide (11;R=NH_2) crystallised as cream coloured prisms m.p. 260°(decomp.) (from dmf). (Found: C,64.3; H,5.4; N,11.75. $C_{13}H_{12}N_2O_3$ requires C,63.95; H,5.0; N,11.5%). (M found 244. Calculated 244.2).

$\lambda_{max.}^{dmf}$ 270,350,367mμ (qualitative because of insolubility)

νmax. 3100, 3180, 1700(shouldered at 1690, 1675(w))cm.$^{-1}$

The same quinoline N-oxide was also the sole product from each of the following reactions:-

(a) A suspension of finely powdered 2-nitrobenzylideneacetylacetone (0.36g.) in ethanol (3ml.) was shaken overnight with a solution of potassium cyanide (0.16g.) in water (3ml.). The precipitate of the quinoline N-oxide was filtered and augmented by a further small amount obtained by acidifying the mother-liquor with dilute sulphuric acid.

(b) As in (a) above, but without ethanol. No material was precipitated from the acidified mother-liquor. Yield 0.2g.

(c) A suspension of 2-nitrobenzylideneacetylacetone (1.0g.) and crushed potassium hydrogen carbonate (1.0g.) in ethanol (12ml.) was treated over 15min. with a solution of potassium cyanide (1.0g.) in water (15ml.). The dark solution was allowed to stand at room temperature for several hours, and was worked up as before to afford the quinoline (0.6g.)

Notes on the solubility of 3-acetyl-4-carbamoyl-2-methylquinoline 1-oxide in alkali.

While the above compound is insoluble in both hot and cold dilute aqueous potassium hydroxide, it is soluble in warm aqueous ethanolic alkali, from which solution it can not be recovered by cooling or adding water, but can be reprecipitated unchanged on acidification with dilute hydrochloric acid. Prolonged heating in aqueous ethanolic alkali results in hydrolysis to the corresponding carboxylic acid (see below).

3-Acetyl-4-carboxy-2-methylquinoline 1-oxide (11;R=OH)

A solution of the amide (11;R=NH_2) (0.25g.) in potassium hydroxide (0.5g.), water (5ml.) and methanol (2ml.) was refluxed for 2hr. The cooled solution was acidified with dilute sulphuric acid, and the precipitate of the carboxylic acid (11;R=OH) (0.15g.) was collected and washed well with water. M.p. 219°(decomp.) (from ethanol with charcoal). (Found: C,63.9; H,4.75; N,6.1. $C_{13}H_{11}NO_4$ requires C,63.7; H,4.5; N,5.7%).

λmax. 250,342,356 mμ (ε 34,000, 11,500, 11,000).

νmax. 1710, 1755, 2600-3500(broad)cm.$^{-1}$

With ethereal diazomethane it gave the corresponding methyl ester (11;R=OMe) m.p. 152°(from methanol). (Found: C,64.6; H,4.9; N,5.7. $C_{14}H_{13}NO_4$ requires C,64.9; H,5.05; N,5.4%).

3-Acetyl-4-carboxy-2-methylquinoline (12)

A solution of 3-acetyl-4-carboxy-2-methylquinoline 1-oxide (11;R=OH) (0.2g.) in acetic acid (10ml.), acetic anhydride (10ml.) and concentrated hydrochloric acid (5 drops) was smoothly hydrogenated at room temperature and pressure with 10% Pd/C (0.12g.) as catalyst. The filtered solution was diluted with water and concentrated in vacuo, affording the product as its hydrochloride, which crystallised as colourless needles m.p. 200°(decomp.) (from hydrochloric acid). (Found: C,59.0; H,4.7; N,5.2. $C_{13}H_{12}NO_3Cl$ requires C,58.8; H,4.55; N,5.3%). This material was identical in infrared spectrum with a sample prepared by treating the authentic carboxylic acid[10] with concentrated hydrochloric acid. Treatment of the hydrochloride with a calculated amount of dilute sodium hydroxide gave the free quinoline carboxylic acid (12) m.p. 199°(decomp.) (from aqueous ethanol) identical (mixed m.p. and infrared spectrum) with a sample prepared by the method of Stephanovic et al.[10] who record m.p. 198° for the acid.

νmax. 1750(broad), 2500-3400(broad)cm.$^{-1}$

2-Methylquinoline-3,4-dicarbonimide 1-oxide (13;R=Me)

The red solution obtained by dissolving 3-acetyl-4-carbamoyl-2-methylquinoline 1-oxide (11;R=NH_2) (0.27g.) in ice cold concentrated sulphuric acid was treated slowly at 0° with hydrogen peroxide (30%, 2.5ml.), and allowed to stand overnight at room temperature. Addition of water precipitated the imide (13;R=Me) (0.17g.) as bright yellow platelets m.p. 257°(decomp.) (from dmf). (Found: C,63.6; H,4.1; N,12.4. $C_{12}H_8N_2O_3$ requires C,63.2; H,3.55; N,12.3%). (M found 228. Calculated 228.1).

νmax. 1720, 1760, 3250(broad)cm.$^{-1}$

2-Methylquinoline-3,4-dicarbonimide (14;R=Me)

A solution of the corresponding N-oxide (13;R=Me) (0.02g.) in boiling acetic acid (2ml.) was treated portionwise with a slight excess of zinc powder and the heating continued for several minutes. The filtered, concentrated solution deposited 0.01g. of the imide (14;R=Me) m.p. 256-257°(decomp.). This material was identical in infrared spectrum with an authentic sample prepared by the method of Lawson et al.[11] The mixed m.p. was 257°(decomp.) (with sublimation prior to melting).

Further attempts to prepare the adduct (4c).

(a) To a solution of potassium cyanide (0.7g.) in water (2.5ml.) and ethanol (20ml.) was added, with cooling, dilute acetic acid (from 4.5g. water and 0.5g. acetic acid) and then finely powdered 2-nitrobenzylideneacetylacetone (2.0g.). The suspension was shaken at room temperature and after 20min.

the solid had dissolved to give a pale yellow solution. After 2hr. the solution was cooled in ice and a portion of the solid which crystallised was collected. It was identified as starting material by its m.p. and infrared spectrum. When the reaction was allowed to continue for a further 1hr., the solution turned red and on addition of water there precipitated a red gum which could not be crystallised.

(b) A suspension of magnesium chloride (1.5g.), potassium cyanide (0.32g.) and 2-nitrobenzylideneacetylacetone (1.15g.) in dimethylformamide (3ml.) was shaken overnight at room temperature. The gelatinous mass was poured into a saturated solution of ammonium chloride. The product which precipitated was identified as starting material by its m.p. and infrared spectrum. Shaking for 36hr. after the further addition of potassium cyanide (0.15g.), water (0.75ml.) and ammonium chloride (0.3g.) also gave only starting material.

(c) When the benzylidene compound (1a) was shaken for different times and in different solvents with a variety of concentrations of potassium cyanide in presence of various amounts of phosphate (pH 7) or borate (pH 8) buffer, the product was invariably a dark gum which could not be crystallised.

Ethyl α-2-nitrobenzylideneacetoacetate (1b)

A solution of o-nitrobenzaldehyde (7.5g.) in ethyl acetoacetate (25ml.) was added to a mixture of piperidine (5ml.) and acetic acid (4ml.) and the solution allowed to stand at room temperature for 2hr. The mixture was then poured on to ice and extracted with ether. The ethereal phase was washed well with water, dried ($MgSO_4$) and concentrated in vacuo. The resultant yellow oil on cooling and seeding precipitated the product as colourless plates m.p. 68-69° (from ethanol). Lit.[17] m.p. 69°.

4-Cyano-3-ethoxycarbonyl-2-methylquinoline 1-oxide (17;R=Me)

To a solution of ethyl 2-nitrobenzylideneacetoacetate (5.0g.) in ethanol (35ml.) was added, portionwise, a solution of potassium cyanide (5.0g.) in water (25ml.). The solution was warmed gently until a spontaneous reaction had set in, and was then allowed to cool, poured on to water (75ml.) and extracted with chloroform (3x50ml.). The chloroform extract was washed with dilute sodium hydroxide then with water. The aqueous washings were combined with the aqueous phase from the extraction.

Chloroform layer on drying ($MgSO_4$) and concentrating in vacuo gave an oil which on trituration with methanol afforded the cyano-ester (17;R=Me) (0.15g.) as pale yellow needles m.p. 132° (from ethanol). (Found: C,65.5; H,4.55;

N,11.15. $C_{14}H_{12}N_2O_3$ requires C,65.6; H,4.7; N,10.9%).

λmax. 215,240,303 mμ (ε 21,000, 18,000, 5000).

νmax. 2250, 1725cm.$^{-1}$

Aqueous layer on acidification with dilute sulphuric acid yielded a yellow solid (2.65g.) which was purified by chromatography on silica with chloroform as eluant. This material was identical with the previously isolated imide (13;R=Me) (m.p. mixed m.p. and infrared spectrum).

A solution of the cyano-ester (17;R=Me) (0.012g.) in concentrated sulphuric acid (1.5ml.) was heated at 100° for 5min. The cooled solution was poured on to ice, affording the imide (13;R=Me) (0.004g.), identical (mixed m.p. and infrared spectrum) with the material previously isolated.

2-Nitrobenzylidenedibenzoylmethane (1c)

A solution of o-nitrobenzaldehyde (1.5g.) and a slight excess of dibenzoyl methane (ca.3g.) in acetic acid (20ml.) and piperidine (5ml.) was allowed to stand at room temperature for several days. The silky mass of the product (2.5g.) was washed well with water and a little ethanol. It crystallised as colourless silky needles m.p. 136-137°(from ethanol). (Found: C,73.9; H,4.1; N,3.9. $C_{22}H_{15}NO_4$ requires C,73.9; H,4.2; N,3.9%).

3-Benzoyl-4-carbamoyl-2-phenylquinoline 1-oxide (19;R=NH_2)

2-Nitrobenzylidenedibenzoylmethane (3g.) in ethanol (75ml.) was heated under reflux for 30min. with a solution of potassium

cyanide (3g.) in water (15ml.). The dark red solution was cooled, diluted with water (50ml.) and extracted with chloroform. The organic layer was washed first with dilute sodium hydroxide then with water. The aqueous washings and the aqueous phase were combined.

Chloroform layer was dried ($MgSO_4$) and concentrated in vacuo to yield 3-benzoyl-4-carbamoyl-2-phenylquinoline 1-oxide (0.7g.) as almost colourless needles m.p.270°(decomp.) (from dmf). (Found: C,74.7; H,4.4; N,7.3. $C_{23}H_{16}N_2O_3$ requires C,75.0; H,4.4; N,7.6%).

λmax. 247,356,370 mμ (ε 34,000, 8500, 8500).

νmax. 1700(shouldered), 3200, 3475cm.$^{-1}$

Aqueous phase was acidified with dilute sulphuric acid and extracted with chloroform. The organic layer was then washed with saturated aqueous sodium hydrogen carbonate and water. Only traces of gum were obtained from the dried and concentrated chloroform extract. The bicarbonate washings were worked up to yield a mixture of carboxylic acids (1.24g.) which were separated by boiling the mixture with water and filtering the hot solution. Benzoic acid (0.7g.) was recovered from the filtrate. The water insoluble acid (0.3g. from ethanol) is assumed to be 3-benzoyl-2-(o-nitrophenyl)propionic acid (18). It crystallised as colourless needles m.p. 182° (decomp.) (from aqueous acetic acid). (Found: C,64.1; H,4.1; N,4.7.

$C_{16}H_{13}NO_5$ requires C,64.2; H,4.4; N,4.7%).

νmax. 1350, 1525,1665, 1700, 2500-3300(broad)cm.$^{-1}$

3-Benzoyl-4-carboxy-2-phenylquinoline 1-oxide (19;R=OH)

A suspension of the amide (19;R=NH_2)(0.22g.) in methanol (1ml.) was heated at 100° for 2hr. with a solution of potassium hydroxide (0.5g.) in water (2ml.). The cooled solution was acidified with dilute sulphuric acid, and the crude hydrolysis product reprecipitated from its sodium hydrogen carbonate solution by the addition of acid. Crystallisation afforded the acid (0.12g.) as colourless hexagons m.p. 251° (decomp.) (from aqueous acetic acid). (Found: C,74.8; H,4.5; N,4.0. $C_{23}H_{15}NO_4$ requires C,74.8; H,4.1; N,3.8%). With ethereal diazomethane it gave the corresponding methyl ester (19;R=OMe) as colourless sturdy needles m.p. 169° (decomp.) (from methanol). (Found: C,75.5; H,4.6; N,4.0. $C_{24}H_{17}NO_4$ requires C,75.2; H,4.5; N,3.65%).

3-Benzoyl-4-carboxy-2-phenylquinoline (20)

A solution of the N-oxide (19;R=OH) (0.09g.) in acetic acid (2ml.), acetic anhydride (3ml.) and concentrated hydrochloric acid (5 drops) rapidly absorbed one mole of hydrogen when hydrogenated at room temperature and pressure with 10% Pd/C (0.05g.) as catalyst. The filtered solution was diluted with water and concentrated in vacuo, affording the quinoline carboxylic acid (20) as its hydrochloride. The

free product (0.65g.) was liberated by careful addition of dilute sodium hydroxide to the hydrochloride. The acid had m.p. 266° (decomp.) (from ethanol). Mixed m.p. with an authentic sample prepared essentially by the method of Stephanovic and his collaborators[10] 266-267°(decomp.): the infrared spectra were identical. Lit.[10] m.p. 257°.

Ethyl α-2-nitrobenzylidenebenzoylacetate (1d) was prepared by the method of Loudon and Wellings.[6]

4-Cyano-3-ethoxycarbonyl-2-phenylquinoline 1-oxide (17;R=Ph)

A solution of the benzylidene compound (1d) (1.32g.) in ethanol (24ml.) was refluxed for 30min. with a solution of potassium cyanide (1g.) in water (10ml.). The deep red solution was diluted with water and extracted with chloroform. The various extracts were worked up as described previously, the chloroform layer afforded the cyano-ester (17;R=Ph) (0.1g.) as long pale yellow needles m.p. 133-134° (decomp.) (from ethanol). (Found: C,71.7; H,4.75; N,9.1. $C_{19}H_{14}N_2O_3$ requires C,71.7; H,4.4; N,8.8%).

νmax. 1725, 2225cm.$^{-1}$

2-Phenylquinoline-3,4-dicarbonimide 1-oxide (13;R=Ph)

Acidification of the aqueous phase from the above reaction precipitated the imide (13;R=Ph) (0.65g.) which was purified by chromatography on silica using chloroform as eluant. It crystallised as golden yellow rods m.p. 248°

(decomp.) (from acetic acid). (Found: C,70.0; H,3.6; N,9.7. $C_{17}H_{10}N_2O_3$ requires C,70.3; H,3.5; N,9.65%). (M found 290. Calculated 290.3).

νmax. 1725, 1765, 3300(broad)cm.$^{-1}$

The same product (0.3g.) was obtained when a solution of the cyano-ester (17;R=Ph) (0.4g.) in concentrated sulphuric acid (5ml.) was heated at 100° for 5min. and the cooled solution then poured into water.

2-Phenylquinoline-3,4-dicarbonimide (14;R=Ph)

A solution of the imido N-oxide (13;R=Ph) (0.04g.) in boiling acetic acid (3ml.) was treated portionwise with a slight excess of zinc dust and heating continued for a few minutes. The filtered concentrated solution deposited the product (0.025g.) as glistening pale yellow plates m.p. 284° (decomp.) (from acetic acid). (Found C,74.6; H,3.7; N,10.2. $C_{17}H_{10}N_2O_2$ requires C,74.45; H,3.7; N,10.2%). This compound was identical in m.p. mixed m.p. and infrared spectrum with a sample prepared by the following method:-

An intimate mixture of 3,4-dicarboxy-2-phenylquinoline[19] (1g.) and urea (0.5g.) was fused at 150° with constant stirring . When no further gas was evolved (ca. 5min.) the solid yellow reaction mass was extracted with boiling acetic acid, leaving an insoluble residue (0.5g.). The cooled acetic acid solution deposited pale yellow needles of 2-phenylquinoline-

3,4-dicarbonimide (0.3g.) m.p. 284° (decomp.).

νmax. 1720, 1765, 3200(broad)cm.$^{-1}$

β-(2-Nitrobenzylidene)propiophenone (1i)

A solution of o-nitrobenzaldehyde (1.5g.) in propiophenone (3ml.) was saturated with dry hydrogen chloride at room temperature. After standing overnight the oil was poured into water, affording a pale yellow semi-solid which gave the product (1.7g.) when rubbed with methanol. It crystallised as colourless plates m.p. 81° (from ethanol). (Found: C,72.1; H,4.9; N,5.5. $C_{16}H_{13}NO_3$ requires C,71.9; H,4.9; N,5.2%).

3-Cyano-1-hydroxy-2-methylindole (5;X=Me)

A solution of β-(2-nitrobenzylidene)propiophenone (6.1g.) in ethanol (50ml.) was refluxed for 1.75hr. with a solution of potassium cyanide (5g.) in water (25ml.). The cooled solution was diluted with water and separated into acidic and non-acidic fractions as described earlier. The non-acidic fraction was worked up to give unchanged starting material (1.25g. from ethanol) which was identified by its m.p. and infrared spectrum.

The acidic fraction was dissolved in ether and washed with aqueous sodium bicarbonate. The bicarbonate washings were worked up to afford benzoic acid (0.79g.). The washed (water) and dried ($MgSO_4$) ethereal layer was concentrated in vacuo, affording the hydroxyindole (5;X=Me) (2.61g.) as colourless

needles m.p. 160° (decomp.) (from ethanol with charcoal). (Found: C,69.6; H,4.7; N,16.1. $C_{10}H_8N_2O$ requires C,69.8; H,4.7; N,16.3%). This material did not affect the colour of methanolic ferric chloride solution.

λmax. 229,290 mμ (ε 18,500, 10,500).

νmax. 2200, 3150cm.$^{-1}$

With warm acetic anhydride it readily formed the corresponding 1-acetoxy derivative m.p. 124° (from ethanol). (Found: C,67.7; H,4.7; N,13.3. $C_{12}H_{10}N_2O_2$ requires C,67.3; H,4.7; N,13.1%).

νmax. 1800, 2250cm.$^{-1}$

3-Cyano-2-methylindole (5;X=Me, H for OH) m.p. 213-214° (from ethanol) was obtained in two ways:-

(a) A solution of 1-acetoxy-3-cyano-2-methylindole (0.19g.) in ethanol (30ml.) rapidly absorbed one mole of hydrogen when hydrogenated at room temperature and pressure with 5% Pd/C (0.09g.) as catalyst. The product (0.15g.) was recovered from the filtered concentrated solution.

(b) Freshly distilled phosphorus oxychloride (1.0ml.) was added dropwise with cooling to dry dimethylformamide (3.5g.), the temperature being maintained at 10-20°. To this well stirred mixture was added slowly, a solution of 2-methylindole (1.3g.) in dimethylformamide (1.0g.), maintaining the temperature at 20-30°. After addition was complete the temperature was kept at 35-40° for 45min. (a light brown slurry formed after 15min.).

The mixture was then added to ice water and treated with a solution of sodium hydroxide (1.9g.) in water (10ml.), at such a rate that the solution was always acid. The mixture was boiled for 1.5min., cooled, and the precipitate of 3-formyl-2-methylindole (1.35g.) crystallised from ethanol to give long colourless needles m.p. 203-204° (with sublimation prior to melting). (Found: C,75.6; H,6,0; N,9.0. Cald. for $C_{10}H_9NO$: C,75.45; H,5.7; N,8.8%). Lit.[24] m.p.198-199°.

The oxime of this aldehyde was prepared by the method of Konig[25] and had m.p. 157° (decomp.) (from aqueous ethanol). Lit. m.p. 154°. A solution of the oxime (0.08g.) in acetic anhydride (2ml.) was refluxed 10min. The cooled solution on dilution with water gave 3-cyano-2-methylindole (0.04g.) m.p. 213-214° (from ethanol). (Found: C,76.5; H,5.3; N,18.3. Cald. for $C_{10}H_8N_2$: C,76.9; H,5.2; N,17.9%). Lit[24] m.p. 209-210°.

The infrared spectra of samples from (a) and (b) above were identical and the mixed m.p. was 213-214°.

2-Methylindole

3-Cyano-1-hydroxy-2-methylindole (0.075g.) was heated at reflux temperature for 30min. with potassium hydroxide (0.5g.) and ethylene glycol (1ml.). The cooled solution was diluted with water and extracted with ether. The ethereal extract was washed with water, dried ($MgSO_4$) and concentrated in

vacuo to afford a gum which was identified as 2-methylindole by its pungent smell and by t.l.c. comparison with an authentic specimen. The deep brown picrates formed by both samples also behaved identically on t.l.c.

When β-(2-nitrobenzylidene)propiophenone (1 mole) was refluxed in ethanol with aqueous potassium cyanide (10 moles) for 2hr., the only non-acidic product was unchanged starting material.

3-(2-Nitrobenzylidene)butan-2-one (1h) m.p. 61-62° (from ethanol) was prepared by the method of Heller et al.[26] who record m.p.62-63°.

3-Cyano-1-hydroxy-2-methylindole (5;X=Me)

A solution of 3-(2-nitrobenzylidene)butan-2-one (1.28g.) in ethanol (20ml.) was refluxed for 2hr. with a solution of potassium cyanide (1g.) in water (10ml.). The cooled mixture was diluted with water and separated into acidic and non-acidic fractions. The non-acidic portion yielded starting material (0.29g.), identified by its m.p. and infrared spectrum.

The acidic fraction was worked up to afford the indole (5;R=Me) (0.66g.) identical in m.p., mixed m.p. (160° decomp.) and infrared spectrum with the material previously isolated. No attempt was made to isolate the acetic acid generated in this reaction.

2-(α-Hydroxy-2-nitrobenzyl)cyclohexanone (22) m.p. 126-127° (from ethanol) was formed (a) when a suspension of o-nitrobenzaldehyde (3g.) in water (200ml.), cyclohexanone (4ml.) and sodium hydroxide solution (10%, 1.4ml.) was shaken at room temperature for 4 days (a further 1ml. of alkali was added after 2 days). The gummy solid which had formed was rubbed with methanol to give colourless crystals of the aldol (22) (0.82g.).

(b) A solution of o-nitrobenzaldehyde (1.5g.) in dry benzene (15ml.) was treated dropwise at room temperature with the morpholine enamine of cyclohexanone[41] (2ml.), and the mixture stirred overnight in an atmosphere of nitrogen. The reaction was worked up by adding cold dilute hydrochloric acid (10ml.), stirring for 45min., drawing off the benzene layer, washing it with water, drying ($MgSO_4$), and concentrating in vacuo to afford the aldol (22) (1.7g.). (Found: C,63.05; H,6.2; N,6.15. $C_{13}H_{15}NO_5$ requires C,62.6; H,6.1; N,5.6%).

νmax. 1695, 3450cm.$^{-1}$

With toluene-p-sulphonyl chloride in dry pyridine the aldol gave the corresponding tosylate m.p. 103-105° (from methanol). (Found: C,59.5; H,5.3; N,3.2. $C_{20}H_{21}NO_6S$ requires C,59.55; H,5.25; N,3.5%).

νmax. 1700cm.$^{-1}$

2-(2-Nitrobenzylidene)cyclohexanone (21)

A solution of the aldol (22) in dry ether was saturated at room temperature with dry hydrogen chloride. After standing overnight, volatile material was removed in vacuo and the residue washed well with water. Crystallisation from methanol gave an almost quantitative yield of the benzylidene compound (21) which crystallised as pale yellow plates m.p. 105°. (Found: C,67.6; H,5.7; N,6.2. $C_{13}H_{13}NO_3$ requires C,67.5; H,5.7; N,6.1%).

νmax. 1615, 1675cm.$^{-1}$

The same product was obtained when a solution of the tosylate of (22) (0.06g.) in dry dimethylformamide (1ml.) was heated at 100° for 30min. with potassium cyanide (0.02g.), and the cooled solution diluted with water and extracted with ether.

Direct preparation of the benzylidene compound (21) proved impossible. Reactions designed to yield it —e.g. by refluxing o-nitrobenzaldehyde with the morpholine enamine of cyclohexanone with or without p-toluene sulphonic acid— led only to the corresponding aldol. In another reaction o-nitrobenzaldehyde (1.5g.), cyclohexanone (2g.), potassium hydrogen carbonate (3.6g.) and acetic anhydride (3.6ml.) were heated together at 100° for 2hr. The sole isolable product was o-nitrocinnamic acid m.p. 229° (decomp.) (from methanol), identified by comparison

of its infrared spectrum with that of an authentic sample. (Found: C,56.2; H,3.9; N,7.15. Cald. for $C_9H_7NO_4$: C,56.0; H,3.65; N,7.25%). Lit.[42] m.p. 240°.

δ-(2-Cyano-1-hydroxyindol-2-yl)valeric acid (23)

A solution of 2-(2-nitrobenzylidene)cyclohexanone (21) (4.3g.) in ethanol (25ml.) was refluxed for 30min. with a solution of potassium cyanide (4.87g.) in water (20ml.). The cooled solution was diluted with water and extracted with ether. The ethereal extract was washed with dilute sodium hydroxide, then with water, dried ($MgSO_4$) and concentrated in vacuo to yield starting material (1.03g.) which was identified by m.p., infrared spectrum and t.l.c. comparison with authentic material.

The aqueous phase and aqueous washings were combined, acidified with dilute sulphuric acid and extracted with ether. The ethereal extract was washed (water), dried ($MgSO_4$) and concentrated in vacuo, affording the hydroxyindole (23) (3.6g.) as an oil which soon solidified when cooled and scratched. M.p. 128° (from ethanol/chloroform). (Found: C,65.4; H,5.6; N, 10.8. $C_{14}H_{14}N_2O_3$ requires C,65.1; H,5.5; N,10.85%).

λmax. 234,287 mμ (ε 10,700, 11,000).

νmax. 1710(broad), 2225, 2500-3300(broad)cm.$^{-1}$

With warm acetic anhydride it formed the corresponding 1-acetoxy derivative m.p. 120-123° (from benzene). (Found: C,64.3; H,5.1; N,9.0. $C_{16}H_{16}N_2O_4$ requires C, 64.0; H,5.4; N,9.3%).

νmax. 1710(broad), 1800, 2280, 2600-3500(broad)cm.$^{-1}$

The latter compound on treatment with diazomethane afforded a gummy methyl ester.

νmax. 2260, 1805, 1730cm.$^{-1}$

3,4-Dibenzoyl-2-(2-nitrophenyl)butyronitrile (4b)

To a well stirred suspension of 2-nitrobenzyl cyanide (8.5g.) and trans 1,2-dibenzoylethylene (12.0g.) in ethanol (75ml.) was added, dropwise, 0.1N sodium hydroxide until addition of alkali caused no further development of a blue colour. (Glass beads were added to prevent coagulation of the product). After the addition of alkali was complete, the mixture was stirred vigorously at room temperature for 30min. Water (20ml.) was added and the product collected, washed with water, cold ethanol then boiling ether. The adduct (16g.) crystallised as colourless prisms m.p. 158-160° (from acetic acid). (Found: C,72.6; H,4.8; N,7.25. $C_{24}H_{18}N_2O_4$ requires C,72.35; H,4.55; N,7.0%).

νmax. 1345, 1530, 1675, 2270(w)cm.$^{-1}$

Reactions with 3,4-dibenzoyl-2-(2-nitrophenyl)butyronitrile (4b)

(A) With sodium ethoxide.

A suspension of the nitrile (4b) (5.0g.) in dry ethanol (60ml.) was shaken at room temperature with sodium ethoxide (from 0.42g. sodium in 15ml. dry ethanol). The dark mixture was then diluted with water (150ml.) and extracted with ether

(3x100ml.). The ethereal layer was washed with a little dilute sodium hydroxide then with water. The aqueous phase and aqueous washings were combined.

Ethereal extract was dried ($MgSO_4$) and concentrated in vacuo to afford a mixture of ethyl benzoate (0.3g.) (which was removed by rubbing the concentrated extract with a little ethanol) and a neutral rather insoluble residue (2.7g.) which crystallised as small cream coloured prisms m.p. 224° (decomp.) (from acetic acid). (Found: C,75.4; H,4.6; N,7.3. $C_{24}H_{18}N_2O_3$ requires C,75.4; H,4.7; N,7.3%).

νmax. 3450, 3270, 1700,1665cm.$^{-1}$

This compound was identified as described later as 4-carbamoyl-3-phenacyl-2-phenylquinoline 1-oxide (24;R=NH_2).

Aqueous extract was carefully acidified at ca. 0° with dilute sulphuric acid, extracted with ether, and the ethereal extract washed with aqueous sodium bicarbonate, then with water.

The bicarbonate washings were worked up to afford benzoic acid (0.8g.) identified by its m.p. and infrared spectrum. The ether layer was dried ($MgSO_4$) and concentrated in vacuo. The residue so obtained was dissolved in warm methanol and filtered*. The filtrate afforded colourless needles of

* A small amount of an insoluble colourless compound m.p. ca. 230° (decomp.) was obtained at this stage. Its infrared spectrum and elemental analysis were not reproducible, and the compound was not further examined.

3-cyano-1-hydroxy-2-phenacylindole (5;X=CH_2COPh) (0.6g.), m.p. 147° (decomp.) (from aqueous ethanol). (Found: C,73.9; H, 4.3; N,10.0. $C_{17}H_{12}N_2O_2$ requires C,73.9; H,4.4; N,10.1%). This material did not affect the colour of methanolic ferric chloride solution.

λmax. 223,285 mμ (ε 19,000, 7000).

νmax. 1685, 2250, 3100cm.$^{-1}$

When warmed with a little acetic anhydride, this indole afforded an acetate which crystallised as fine colourless needles m.p. 227° (decomp.) (from ethanol). (Found C,71.7; H,4.3; N,9.1. $C_{19}H_{14}N_2O_3$ requires C,71.7; H,4.4; N,8.8%).

νmax. 1680,1795, 2250cm.$^{-1}$

(B) With sodium carbonate

A solution of the adduct (4b) (1.0g.) in ethanol (9ml.) was refluxed 1.25hr. with a solution of sodium carbonate (0.5g., AnalaR) in water (3ml.). The mixture was then concentrated to half bulk in vacuo, diluted with water, acidified with dilute sulphuric acid and thoroughly extracted with ether. The ethereal layer was washed successively with sodium bicarbonate, dilute sodium hydroxide, water and finally dried ($MgSO_4$). The various extracts were worked up as before to yield benzoic acid (0.13g.), the hydroxyindole (5;X=CH_2COPh) (0.28g.) and the quinoline N-oxide (24;R=NH_2) (0.35g.). These substances were identical in m.p. and infrared spectrum with the materials isolated as in (A) above.

Experiments with 4-carbamoyl-3-phenacyl-2-phenylquinoline (24;R=NH_2)

(a) A solution of the amide (24;R=NH_2) (0.3g.) in methanol (2ml.), water (2ml.) and potassium hydroxide (0.5g.) was refluxed for 2hr. The cooled, acidified solution deposited crystals of 4-carboxy-3-phenacyl-2-phenylquinoline 1-oxide (24;R=OH) (0.26g.) m.p. 266° (decomp.) (from dimethylformamide) (Found: C,75.5 H,4.7 N,3.9. $C_{24}H_{17}NO_4$ requires C, 75.2; H,4.5; N,3.65%).

A suspension of this acid in methanol was treated with ethereal diazomethane, affording a colourless methyl ester which crystallised as prisms m.p. 165° (from acetic acid) (Found: C,76.0; H,5.2; N,3.5. $C_{25}H_{19}NO_4$ requires C,75.55; H,4.8; N,3.5%).

(b) A solution of the amide (24;R=NH_2) (0.08g.) in concentrated sulphuric acid (2ml.) was treated in the cold with hydrogen peroxide (30%, 2ml.) and the mixture allowed to stand overnight. The product obtained by the addition of ice was shown by t.l.c. to be a mixture of about five components. This mixture was not further examined.

(c) A mixture of the amide (24;R=NH_2) (0.4g.), acetic acid (3ml.) and iron powder (0.2g.) was refluxed for 10min. The filtered solution was cooled and basified with ammonia. 4-Carbamoyl-3-phenacyl-2-phenylquinoline crystallised from the mixture as colourless needles m.p. 214° (decomp.) (from methanol).

(Found: N,7.5. $C_{24}H_{18}N_2O_2$ requires N,7.65.)

(d) A solution of the amide (24;R=NH_2) (0.5g.) in concentrated sulphuric acid (5ml.) was heated on the steam-bath for 5min. with exclusion of moisture. The deep red mixture was poured on to ice, and the precipitate of the lactam (25) collected. It crystallised as stout rods m.p. 260° (decomp.) (from acetic acid), the crystals were powdered before drying for analysis. (Found: C,79.3; H,4.2; N,7.7. $C_{24}H_{16}N_2O_2$ requires C, 79.1; H,4.4; N,7.7%).

νmax. 1600, 1695(shouldered), 3250cm.$^{-1}$

Experiments with 3-cyano-1-hydroxy-2-phenacylindole (5;X=CH_2COPh)

(a) A solution of the above indole (0.06g.) in sodium hydroxide (4N, 2ml.) was refluxed 1.5hr. The cooled solution was filtered, acidified with dilute sulphuric acid and extracted with ether (2x10ml.). The ethereal extract was washed with sodium bicarbonate solution then with water. The bicarbonate washings were worked up to afford benzoic acid (0.02g.) identified by its infrared spectrum. The dried ($MgSO_4$) ethereal extract gave on concentration, 3-cyano-1-hydroxy-2-methylindole (5;X=Me) (0.03g.) identified by its m.p. and a comparison of its mixed m.p. and infrared spectrum with an authentic sample.

(b) When the mother-liquors from crystallisation of the hydroxyindole (5;X=CH_2COPh) were allowed to stand at room temperature for several days, the yellow insoluble base (29a,b) was deposited. It was purified by crystallisation

from acetic acid to afford an unstable colourless hydroacetate which was subsequently decomposed with boiling ethanol to yield the base as its ethanolate , small bright yellow needles m.p. 165° (decomp.) (with prior softening at ca. 145°).

(Found: C,70.9; H,5.2; N,9.0. $C_{17}H_{12}N_2O_2.C_2H_6O$ requires C,70.8; H,5.6; N,8.7%).

νmax. 1610(w), 1640(broad), 2500-3300(broad)cm.$^{-1}$

λmax. 215,285,317,366mμ (ε 20,000, 34,000 21,000 15,000).

When the base (29a,b) was dissolved in dilute alkali and the solution acidified with dilute acetic acid, an almost quantitative yield of the hydroxyindole (5;X=CH_2COPh) was obtained; it was identical in all respects with authentic material.

A solution of the base (29a,b) (0.05g.) in sodium hydroxide (4N, 2ml.) was refluxed for 1.5hr. The cooled acidified solution was extracted with ether. The ethereal layer was washed with aqueous sodium bicarbonate to remove benzoic acid (7mg). and worked up to afford 3-cyano-1-hydroxy-2-methylindole (5;X=Me) (15mg.), identified by its m.p. and infrared spectrum.

(c) Two solutions of the 1-hydroxyindole (5;X=CH_2COPh) (20mg.) in ethanol (1ml.) were allowed to stand at room temperature for several days, one solution being acid-free, the other containing a trace of dilute sulphuric acid. Analytical t.l.c. comparison of both solutions against the starting material and the base (29a,b) showed that each test solution contained a high

concentration of a very polar compound which corresponded to the base (29a,b) in polarity.

2-Phenacylcyanobenzene (27) was prepared essentially by the method of Boyce et al.[34] with the modification that the black product was purified by washing it with ice cold ethanol followed by crystallisation from the same solvent. The material crystallised as long colourless needles m.p. 112-113°. Lit. m.p. 109.1-109.8°. This substance was not affected by dry or moist ethereal hydrogen chloride.

Hydrolysis of 2-phenacylcyanobenzene under basic conditions.

(a) A solution of the nitrile (27) (0.10g.) in ethanol (5ml.) was refluxed for 1hr. with a solution of sodium carbonate (AnalaR, 0.10g.) in water (2ml.). Starting material was quantitatively recovered.

(b) A solution of the nitrile (27) (0.085g.) in methanol (3ml.) and sodium hydroxide (4N, 2ml.) was heated for 1hr. on the steam-bath. The bright yellow solution was cooled, diluted with water (the solution turned colourless) and the colourless precipitate collected, dried, dissolved in chloroform and applied to a preparative chromatography plate (0.4cm.). Elution with benzene separated the mixture cleanly into its two components: the less polar band was identified as starting material. The more polar substance was identified by its m.p., mixed m.p., infrared spectrum and elemental analysis as

3-phenylisocarbostyril (26), identical with a sample prepared by the method of Boyce et al.[34] from 2-phenacylcyanobenzene under acidic conditions.

After crystallisation from ethanol the weight ratio of starting material:isocarbostyril was 4:1. 3-Phenylisocarbostyril crystallised as colourless needles m.p. 203-205° (from methanol). (Found: C,81.4; H,5.4; N,6.2. Cald. for $C_{15}H_{11}NO$: C,81.4; H,5.0; N,6.3%). Lit.[34] m.p. 198-199°.

(c) When the reaction (b) was repeated with the time of heating extended to 3hr., the starting material was completely converted to 3-phenylisocarbostyril.

(d) A solution of 2-phenacylcyanobenzene (0.06g.) in ethanol (3ml.) was refluxed for 2.25hr. with a solution of potassium cyanide (0.06g.) in water (2.5ml.). The reaction mixture was separated as before. The weight ratio of starting material: isocarbostyril was ca. 2:1.

4-Nitrobenzylideneacetylacetone (32)

To a solution of p-nitrobenzaldehyde (7.5g.) in acetylacetone (25ml.) was added, with cooling, piperidine (4ml.) and acetic acid (2ml.). After 1.5hr. the mixture was poured on to ice and the semi-solid product washed first with water then rubbed with ethanol to remove some yellow impurity. The product (8g.) crystallised as needles m.p. 90-91° (from ethanol). (Found: C,61.5; H,4.7; N,6.1. $C_{12}H_{11}NO_4$ requires C,61.8; H,4.75; N,6.0%).

νmax. 1345, 1520, 1620,1660, 1700cm.$^{-1}$

3-Acetyl-2-amino-4-methyl-3-(p-nitrophenyl)furan (34;R=H).

A suspension of the benzylidene compound (32) (3.5g.) in ethanol (15ml.) was treated at room temperature with a solution of potassium cyanide (3.5g.) in water (7.5ml.). The mixture immediately went deep red and a mildly exothermic reaction ensued, which had subsided completely after 5min. After a further 5min. the clear red solution was diluted with water and extracted with ether. This extract was washed (water), dried ($MgSO_4$) and concentrated in vacuo, but gave no appreciable amount of material. The aqueous phase was acidified with dilute hydrochloric acid and extracted with ether. This extract, after washing (water), drying ($MgSO_4$) and concentrating on a warm water bath in a well-ventilated fumecupboard afforded a beautiful deep red crystalline solid (3.0g.), which crystallised as needles m.p. 140° (decomp.) (from ethanol).

(Found:C,60.0; H,4.4; N,10.85. $C_{13}H_{12}N_2O_4$ requires C,60.0; H,4.65;
(60.2 4.5 10.6 N,10.8%)

(M found 260. Calculated 260.2). The colour of the material was not affected by charcoal, and it appeared as one spot on t.l.c. ($CHCl_3$ as eluant).

νmax. 1350, 1515, 1580 1600, 1650, 3250, 3370, 3470cm.$^{-1}$

$\nu_{max.}^{CHCl_3}$ 1698, 3403, 3523cm.$^{-1}$

N.m.r.(acetone) τ1.83,doublet(2H) (H_B of aromatic AB quartet); τ2.53,doublet(2H) (H_A of aromatic AB quartet J_{AB}=9c/s); τ4.7,broad singlet(ca.2H) (NH_2, disappears on D_2O exchange). N.m.r.(pyridine) τ7.57,singlet(3H); τ7.77,singlet(3H) (Me and COMe).

When warmed with acetic anhydride in benzene the red colour rapidly discharged and on addition of petroleum, the cooled solution deposited a pale yellow solid which recrystallised as completely colourless lustrous plates of the monoacetyl derivative (34;R=COMe) m.p. 153-154° (from benzene or ethanol) (Found: C, 59.7; H,4.55; N,9.1. $C_{15}H_{14}N_2O_5$ requires C,59.6; H,4.7; N,9.3%).

νmax. 1350, 1520, 1635(w), 1678, 3300cm.$^{-1}$

$\nu_{max.}^{CHCl_3}$ 1680, 1720, 3415cm.$^{-1}$

N.m.r.($CDCl_3$) τ8.0,singlet(3H) (MeCONH); τ7.87,singlet(3H) (MeCO); τ7.44,singlet(3H) (Me); τ2.57,doublet(2H) (H_A of aromatic AB quartet); τ1.81,doublet(2H) (H_B of aromatic AB quartet J_{AB}=8c/s); τ2.21,singlet(1H) (NH, disappears on D_2O exchange)

The aminofuran (34;R=H) does not appear stable in solution and gradually transforms to a pale yellow crystalline solid m.p. 188° (decomp.) (from ethanol) which may be the amide (35). (Found: C,56.4; H,4.7. $C_{11}H_{12}N_2O_4$ requires C,55.9; H,5.1%).

νmax. 1360, 1520, 1635(w), 1690, 3400(shouldered)cm.$^{-1}$

Oxidation of the 2-aminofuran (34;R=H)

2ml. of a solution of sodium dichromate (from 15g. sodium dichromate in 50ml. acetic acid) was added slowly to a refluxing solution of the amine (34;R=H) (0.1g.) in acetic acid (1ml.), water (1ml.) and concentrated sulphuric acid (0.5ml.). After refluxing 1.5hr. the cooled solution was diluted with water and allowed to stand overnight. The precipitate of p-nitrobenzoic acid (15mg.) was collected and crystallised from water. It was identified by its infrared spectrum.

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