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SUMMARY.

Part I. Synthetic Approaches to β-Vetivone

A stereoselective synthetic route to the β-vetivone structure (proposed by Pfau and Plattner) from a bicyclo[3,2,2]nonene derivative has been investigated.

Anti-3-exo-benzoyloxybicyclo[3,2,2]non-8-ene-6,7-endo-dicarboxylic acid anhydride, obtained after a detailed investigation of the Diels-Alder reaction of cyclohepta-3,5-dienol derivatives with maleic anhydride, has been elaborated in nine stages to 4-amino-3-cyano-9,9-ethylenedioxytricyclo[5,3,2,$0^{2,6}$]dodeca-3,11-diene (endo configuration) via 3,3-ethylenedioxy-6,7-endo-dicarbomethoxybicyclo[3,2,2]non-8-ene.

Appendix (with F.A. Cameron and G. Ferguson)

The major product from the Diels-Alder reaction of maleic anhydride with 1-p-bromobenzoyloxycyclohepta-3,5-diene is shown by an X-ray structure determination to be the anti-3-exo configuration.

Part II. N.M.R. Studies of some Bicyclo[3,2,2]nonene Derivatives

An N.M.R. comparative study of sixteen bicyclo[3,2,2]nonene derivatives (prepared in Part I) has indicated that the endo configuration of substituents

at C_6 and C_7 can be assigned unambiguously. Tentative proposals concerning the conformational stability of the three carbon bridge are put forward.

Part III. Synthetic Approaches to a Diterpene Intermediate

Two routes to 10-alkoxy-5-methyltricyclo [7,2,1,$0^{1,6}$]dodeca-4,12-dione as a precursor to tetracyclic diterpenes, have been investigated.

The synthesis of 9-carbethoxymethylene-5-methyl-$\Delta^{5,10}$-octalin-1,6-dione and the derived hydrogenation products are described.

The mechanism of a novel rearrangement of 2-carbethoxymethylene-2-(3'-ketopentyl)cyclohexane-1,3-dione and other 2,2-disubstituted cyclohexane-1,3-diones to substituted valerolactone derivatives is described.

CONTENTS

P A R T I.

SYNTHETIC APPROACHES TO β-VETIVONE

The Structure of α- and β-Vetivone

The essential oil of Vetiver (Vetiveria **zizanioides** Stapf.) owes its importance in the perfumery industry to the presence of two ketones called α- and β-vetivone, which could be isolated through their Girard or semicarbazone derivatives.

Pfau and Plattner,[1] restricting their investigation to β-vetivone, formulated it as (1) on the following evidence. Dehydrogenation of β-vetivone, and the hydrocarbons derived from it, afforded vetivazulene (2) together with small amounts of hydroxy eudalene (3). This indicated the bicyclic nature of the ketone as did the molecular refraction data which also indicated two double bonds, one of which was in conjugation with the ketone (later confirmed by its ultra-violet spectrum).

β-Vetivone was easily reduced to an optically inactive dihydro-β-vetivol (4) which afforded acetone and the hydroxyketone (6) on ozonolysis, confirming the presence of an isopropylidene group. Dehydration, reduction and oxidation of the hydroxy ketone (6) gave a diacid (7) which did not yield a ketone on acetic anhydride treatment indicating that the isopropylidene grouping was attached to a five membered ring.

The presence of a seven membered ring was based on the following evidence. Oxidation of tetrahydro-β-vetivone (8), on the other hand, furnished a diacid (9) which with acetic anhydride gave a ketone (10); dehydrogenation of this ketone gave 2-isopropyl-4,7-dimethyl indan-5-ol (11) identified by synthesis. The cis-fusion of the two rings was inferred from the fact that reduction of the double bond in conjugation with the ketone generated a plane of symmetry in the molecule. The structure (1) followed from the above evidence.

Naves and Perrottet,[2] in the following year, published their findings on the vetivones which indicated a close resemblance between the two ketones in their chemical and physical properties. They concluded that α- and β-vetivone were stereoisomeric modifications of (12) differing only in the configuration of the secondary methyl group .

The significant evidence on which the structure of α-vetivone was based was (a) the presence of an isopropylidene group, (b) the similarity of ultraviolet spectra, (c) a similar behaviour on hydrogenation and (d) the formation of vetivazulene on dehydrogenation.

Structures based on the vetivane skeleton have been assigned to the primary and tertiary bicyclo-

vetivenols[3,6](13), tricyclovetivene[4] (14), tricyclovetivenol[3] (15), the vetivenenes[5] (16) and others[6] on the basis of infra-red spectroscopy.

Recently Sorm[7] assigned the vetivane structure to hinesol (17) and this appeared to be confirmed by its conversion to (+)β-vetivone by Yosioka and Kimura.[8] The absolute configuration of the secondary methyl group in hinesol had been established as [S] by the degradation of hinesol to (+)α-methylglutaric acid.[7] Thus the secondary methyl in β-vetivone must be [R] configuration. The outstanding problem in the chemistry of β-vetivone was the relative stereorelationship of the secondary methyl group to the hydrogen at the ring junction.

In the present investigation, in order to clear up this problem, an unequivocal synthesis of β-vetivone was undertaken.

However, early in 1967, Endo and de Mayo[9] showed that α-vetivone was in fact the eremophiloid (18) by a study of its N.M.R. spectrum and by comparison of its oxidation product (19) with the optical enantiomer (20) derived from eremophilone (21). Marshall and Andersen[10] converted α-vetivone to (22), a transformation product of nootkatone (23), and arrived at the same conclusion as to the structure of α-vetivone.

A revised structure for β-vetivone followed rapidly. Marshall et al.[11] reported the syntheses of three 6,10-dimethyl-cis-decahydroazulen-8-ones (26),(27) and (28) (Scheme I), none of which corresponded to either of the epimeric desisopropylidenedihydro-β-vetivones (30) and (31), prepared from β-vetivone (Scheme II). This finding invalidated not only the structure of β-vetivone but also those of the entire class of bicyclic vetivone sesquiterpenes[3,4,5,6,7] as well. Compound (25) led to ketones (26) and (27) while isomer (24), through a similar pathway, yielded ketones (28) and (29). Structural assignment was obtained by the fact that ketones (26) and (29) were identical (by G.L.C., spectra) and therefore necessarily possess trans oriented methyl groups.

The structure (32) was proposed[11] and verified by the reaction sequence (Scheme III) starting from the meso dihydro-β-vetivone (33). Comparison of ketone (34) with the two isomers (37) and (38) obtained from the known spiro compound[12] (36), followed by comparison of their corresponding hydrocarbons led to the conclusion that (34) and (38) are epimeric at the spiro ring junction, since they afford the same hydrocarbon (35).

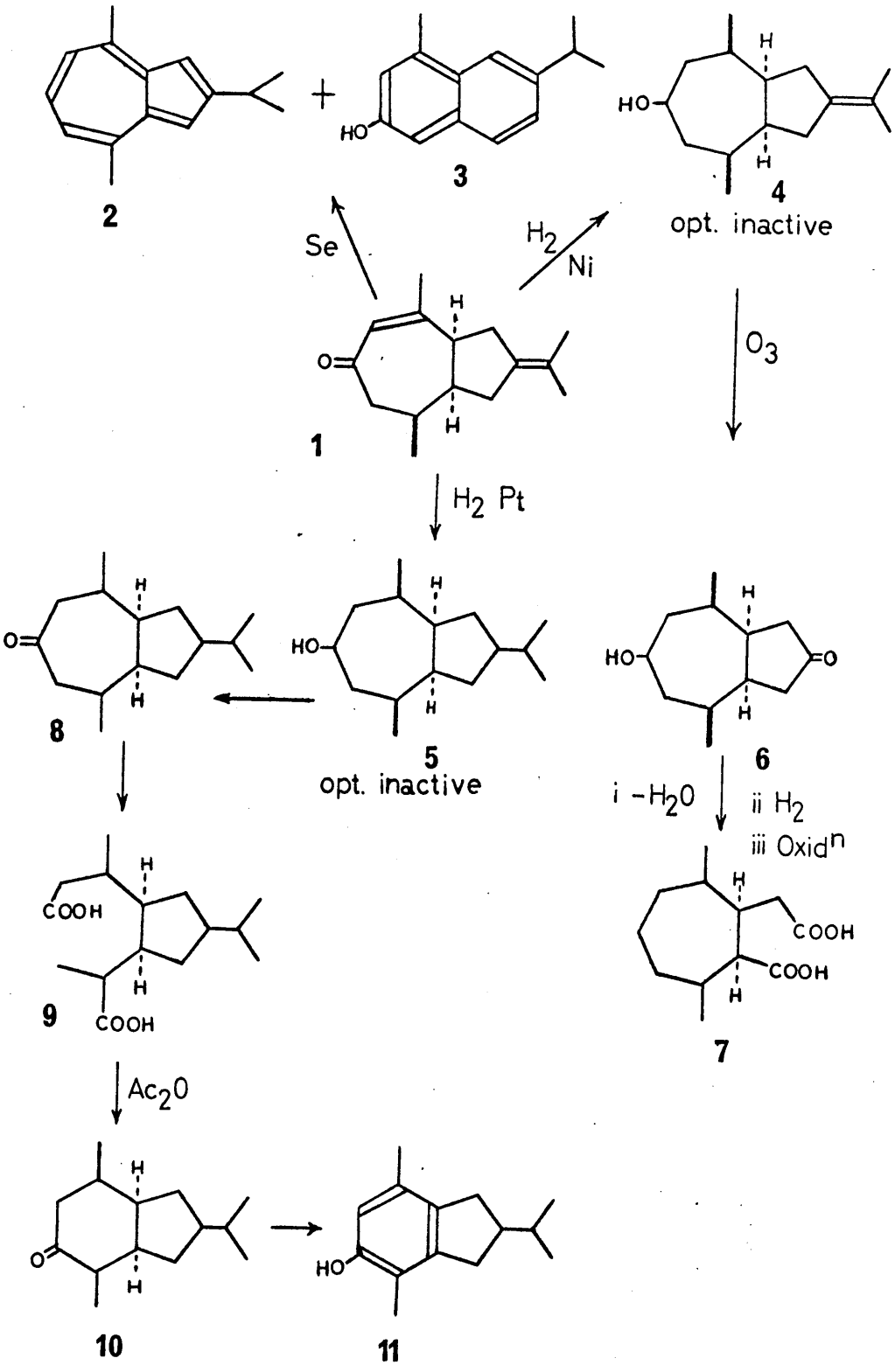
In view of the revised structure for β-vetivone, hinesol must be formulated as (40), a stereoisomer of agarospirol which has been tentatively assigned structure (41) by Bhattacharyya.[13] Additional evidence supporting the revised structure of β-vetivone has been obtained by Baker and Chalmers[14] from a study of the apoketone (44) derived from β-vetivone (Scheme IV). This ketone showed carbonyl absorption at 1743 $cm.^{-1}$ consistent with a cyclopentanone rather than a cyclohexanone derivative (46); an authentic synthetic sample of gross structure[15] (46) showed carbonyl absorption at 1714 $cm.^{-1}$. Moreover, the infra-red spectra of the derived and synthetic ketones were totally dissimilar. Both ketones, however, afforded the indanol (45) on dehydrogenation, these facts assigning a cyclohexenone rather than a cycloheptenone ring to β-vetivone.

β-Vetivone, therefore, belongs to the spirodecane group of sesquiterpenes which now includes hinesol, agarospirol and the acorones[16] (47).

The biogenesis of α- and β-vetivone could possibly proceed via the same carbonium ion intermediate (49) derived from dihydro-β-agarofuran[17] (48) (Scheme V), a cyclisation product from farnesyl pyrophosphate.

Migration of the bridgehead α-methyl group to the positive centre would give α-vetivone, whereas migration of the β C_9-C_{10} bond would afford β-vetivone.

In this investigation, the objective was to synthesise the previously accepted structure for β-vetivone by a completely stereoselective route, envisaging a cleavage of the type (50) → (51).


2
3
4
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Se
H2
Ni
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O3
H2 Pt
8
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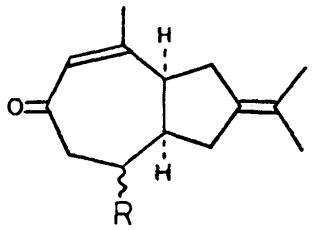
iii Oxidn
9
7
Ac2O
10
11



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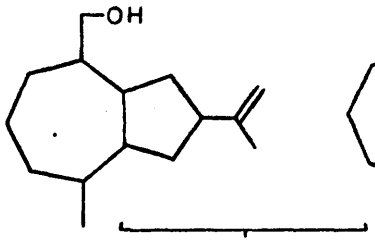
R= ∝Me , ∝-vetivone

R= βMe , β-vetivone



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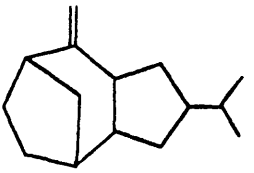

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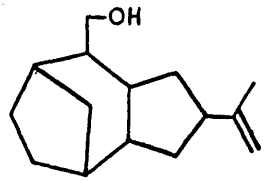

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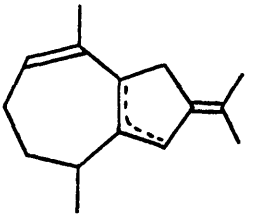

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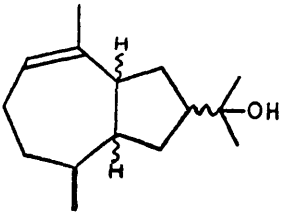

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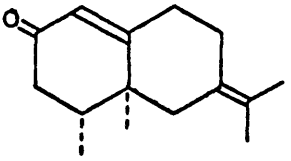

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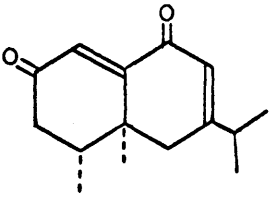

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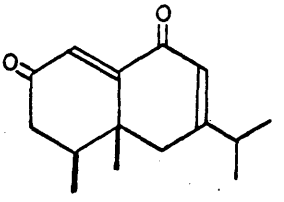

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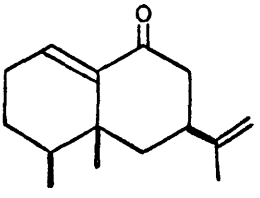

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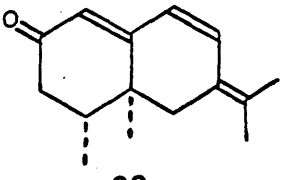

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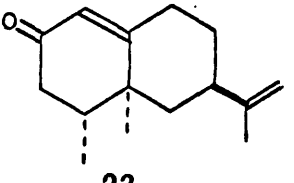

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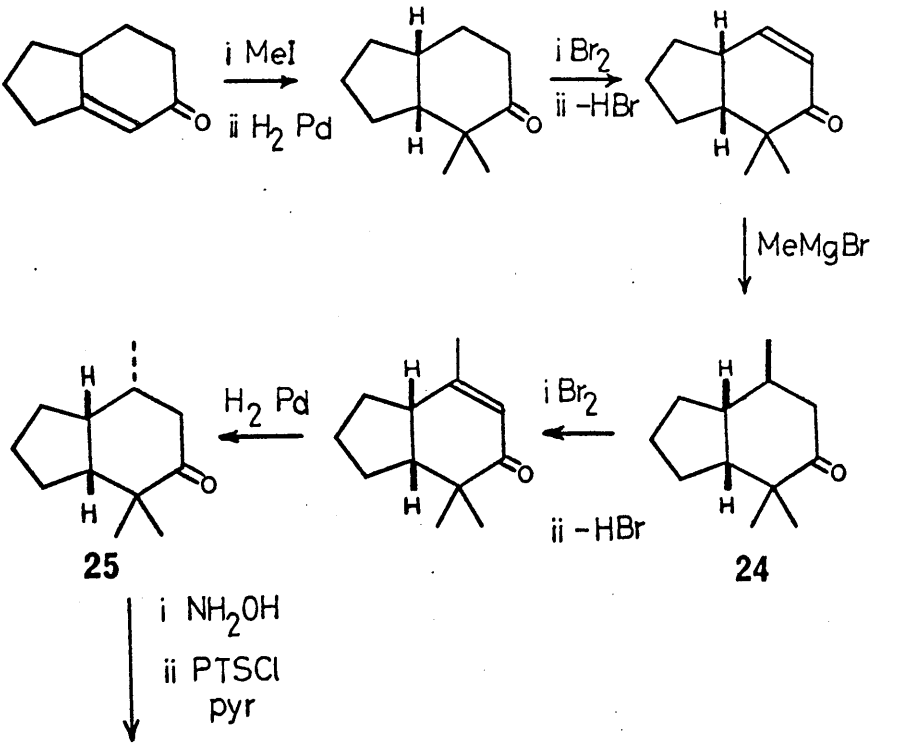
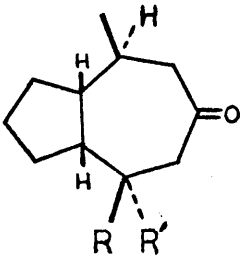
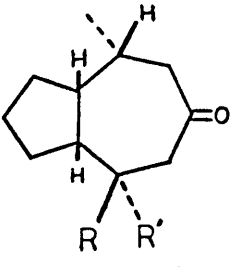


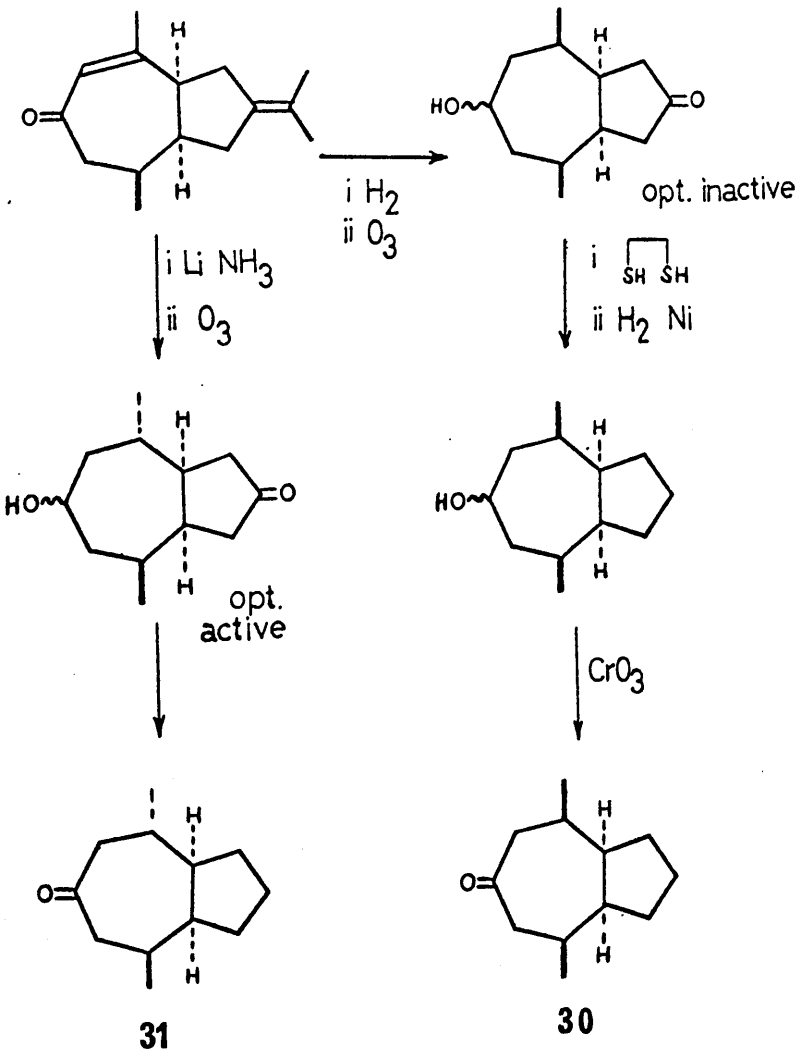
SCHEME **1**



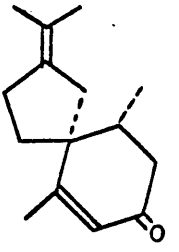
28 R=Me R'=H
29 R=H R'=Me



26 R=Me R'=H
27 R=H R'=Me


i H_2
ii O_3
opt. inactive
i Li NH_3
ii O_3
i SH SH
ii H_2 Ni
opt. active
CrO_3
31
30

SCHEME II



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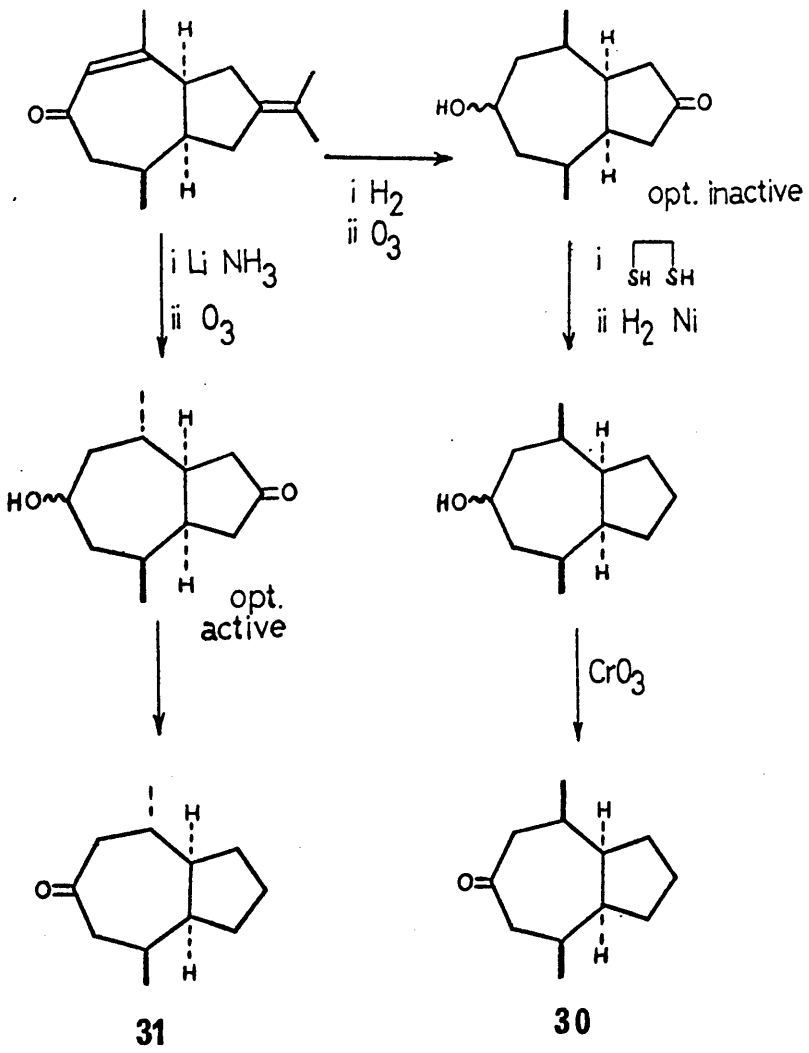

31 **30**

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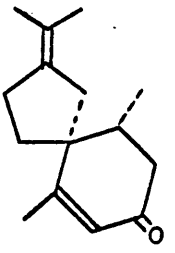

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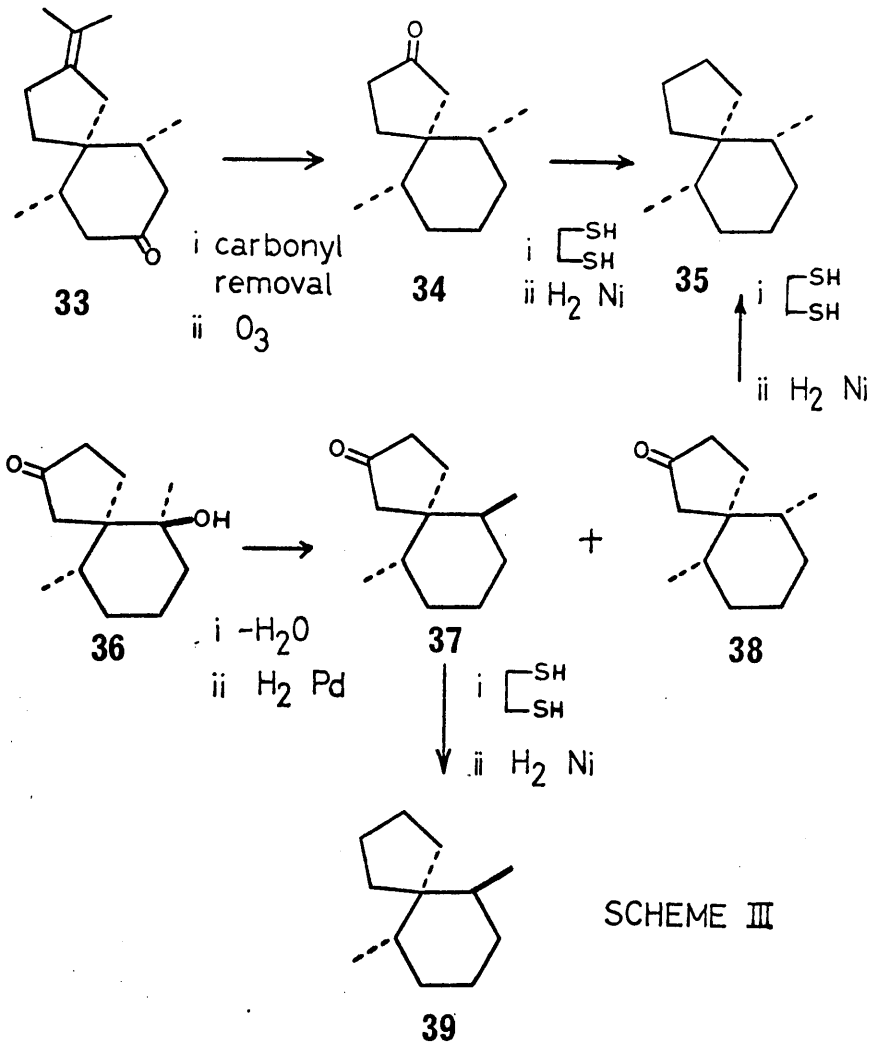

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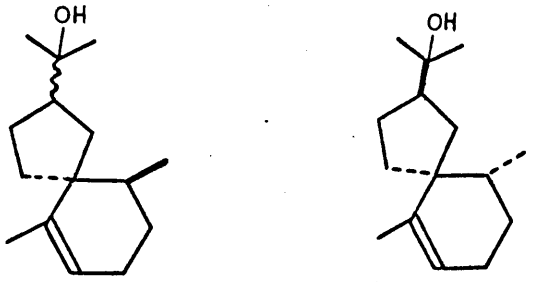

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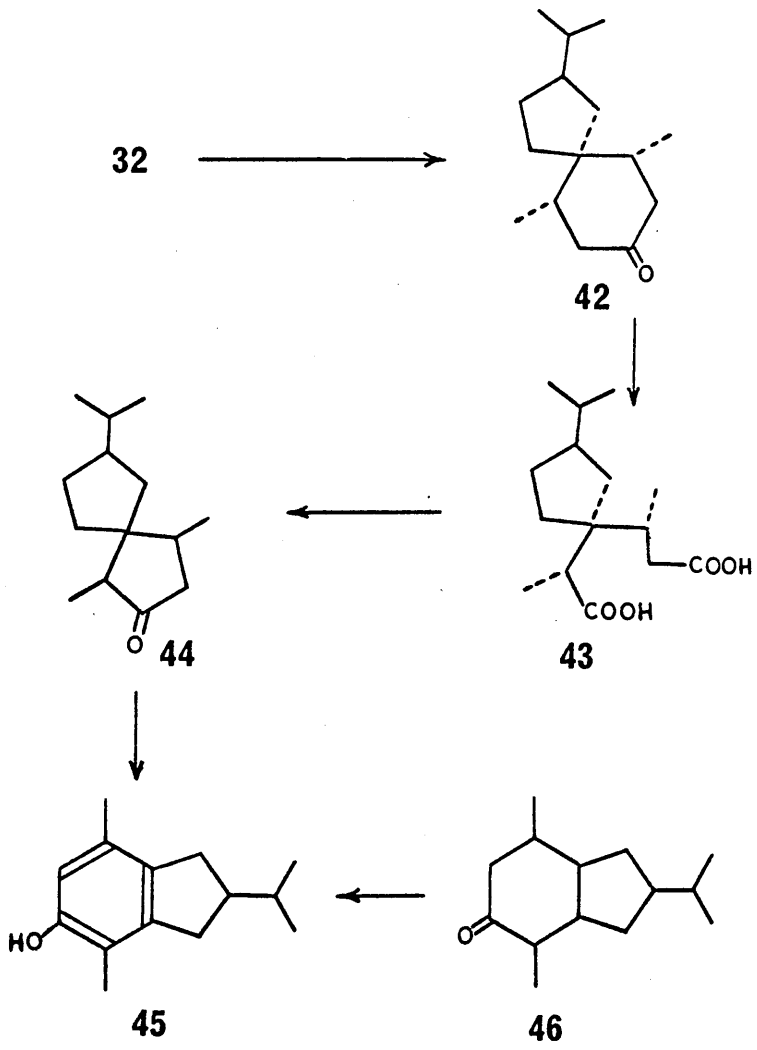

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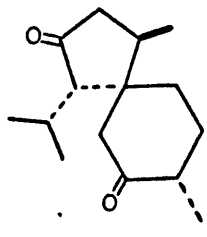

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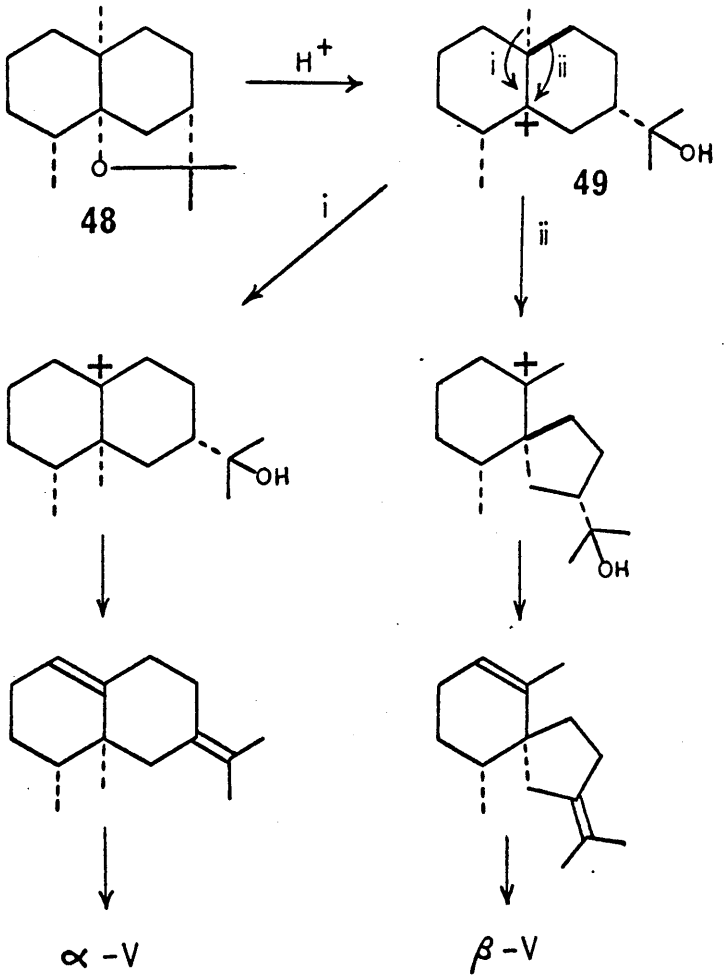

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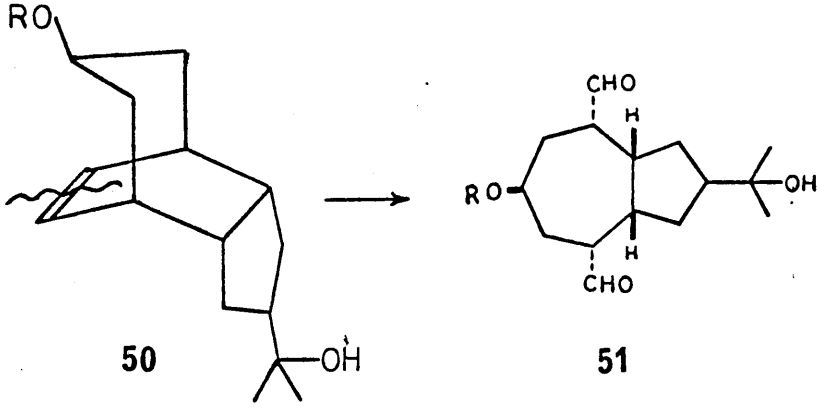

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DISCUSSION

The synthesis of β-vetivone* was undertaken in order to clear up the remaining problem regarding its stereochemistry, namely the relative configuration of the secondary methyl group to the bridgehead hydrogen atom.

From the synthetic viewpoint it offered the attractive problem of constructing the carbon skeleton with the correct functionality and at the same time maintaining stereochemical control at all stages in the synthesis.

The synthesis of β-vetivone has been the subject of at least two studies.

McGeachin[1] approached the problem of constructing the molecule by the route shown (Scheme 1) in which the stereochemistry was defined by the Diels-Alder reaction of hexa-2,4-diene with maleic anhydride. The seven membered ring was constructed by a carbene insertion reaction.

August,[2] on the other hand, used the cis fused tetrahydroindane(1) and generated the seven membered ring by cleavage of the bridgehead ketobicyclo[3,2,1] amine (2) as illustrated (Scheme 2).

* In this text, β-vetivone will refer to the structure proposed by Pfau and Plattner.

In our approach to the vetivone structure we envisaged starting with a cycloheptadiene in which the potential ketone was incorporated; the Diels-Alder reaction with maleic anhydride would be used to give

(a) the ring junction cis stereochemistry and hence the relative stereochemistry of the potential methyl groups (from the olefin bridge) to the ring junction hydrogens and

(b) the anhydride ring suitable for elaboration to a cyclopentane with the correct functionality.

The synthetic scheme is shown (Scheme 3).

The initial goal was the known meso-dihydro-β-vetivone which we considered could be used as a relay to β-vetivone itself.

The first hurdle was therefore to synthesise the anhydride (3) by a Diels-Alder reaction of an oxygenated cycloheptadiene (4) with maleic anhydride. The only known[3] bicyclic structure of this type was the adduct (5), the configuration of which had not been elucidated. Other adducts (6),[3,4] (7)[4] and (8)[5] have been synthesised and proved, chemically, to be in the endo configuration but all lacked the required functionality at carbon 3.

The hydroxy diene (9) studied by Meinwald had been obtained by base degradation of tropinone methiodide

followed by reduction (Scheme 4), and was therefore not readily available. Two methods of synthesis remained (Scheme 4), a tedious ring expansion[6] route via the dichloroethoxy compound (10) and a bromination/dehydrobromination sequence,[7] neither of which appeared particularly satisfactory for the initial stages of a synthetic scheme.

However Chapman[8] had shown that lithium aluminium hydride reduction of tropone (12) afforded in 67% yield a 2:3 mixture of cyclohepta-3,5-dione (13) and cyclohepta-3,5-dienol (9) and it was found that reduction of this mixture with sodium borohydride converted the remaining dienone to the dienol (9), the overall yield from tropone being 39%. Since tropone was readily prepared from cycloheptatriene, this latter method was used for preparation of the dienol.

Cyclohepta-3,5-dienol (9) and N-phenylmaleimide were reacted in refluxing benzene[3] for a period of seven days under a nitrogen atmosphere. The accepted mode of addition of a diene to the dienophile is stereospecifically <u>cis</u>, that configuration being adopted which has the maximum concentration of π electrons in the transition state i.e., the <u>endo</u> isomer as in (14) → (5). The initially formed adduct would therefore be expected to be

the kinetically more stable endo isomer with the thermodynamically more stable exo isomer predominant under equilibrating conditions over long heating periods or at high temperatures. Anti-3-exo-hydroxybicyclo[3,2,2]non-8-ene-6,7-endo-dicarboxylic acid N-phenylimide* (5) was shown by N.M.R. (Part II) to be of the endo configuration (despite a seven day heating period), confirmed later by comparison of the N.M.R. spectrum with that of an authentic endo adduct i.e., anti-3-exo-p-bromobenzoyloxybicyclo [3,2,2]non-8-ene-6,7-endo-dicarboxylic acid anhydride (15).

Attempted hydrolysis of the imide (5) by acidic and basic reagents proved unsuccessful, starting material being recovered in all cases; this was disappointing since a related hydrolysis[9] had been effected (16) → (17). As a result, another bicyclic derivative was sought, an anhydride species being attractive from the point of view of hydrolysis or reduction. The Diels-Alder reaction of cyclohepta-3,5-dienol (9) with maleic anhydride was conducted in an analogous manner, a product being isolated in 22% yield which proved to be tricyclo[3,2,2,$0^{2,4}$]non-8-ene-6,7-endo-dicarboxylic acid anhydride (6). An authentic sample of this adduct was prepared in high yield from cycloheptatriene and maleic anhydride;[4] comparison of spectra

* for notation p. 21.

showed the two compounds to be identical. It was assumed that trace amounts of maleic acid in the solution catalysed dehydration of the cyclohepta-3,5-dienol to bicycloheptatriene which reacted with maleic anhydride in the norcaradiene form (18). Repetition of the experiment with carefully purified maleic anhydride in benzene or xylene afforded only unidentified products and polymer, inferring instability of the oxygenated diene under the conditions.

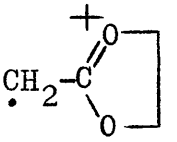
Two ways of overcoming these difficulties were either to use a dienophile more efficient than maleic anhydride[10] or to protect the alcohol function in order to avoid dehydration. Considering the former, it was well known[11] that tetracyanoethylene was an extremely powerful dienophile even at low temperatures and it was envisaged that hydrolysis of the resulting tetracyano adduct (19), followed by decarboxylation of two of the carboxylic functions might lead to the cis endo diacid (20) as in the case of tetracyanotetrahydrofuran[12] [(21) → (22)]. In the event, reaction of tetracyanoethylene with cyclohepta-3,5-dienol (9) in tetrahydrofuran at room temperature afforded the cyano alcohol (19) in 45% yield as a highly insoluble pale yellow solid. The spectral characteristics were in accord with the proposed structure which was

expected to adopt the anti configuration (19) as opposed to the sterically crowded syn form. Hydrolysis of the cyano adduct with concentrated hydrochloric acid[12] followed by continuous ether extraction gave an oil which by I. R. and T.L.C. indicated an acidic species. Diazomethane esterification gave a colourless solid, m.p. 270-275°, in 18% yield which analysed correctly for 3-hydroxy-6,7-dicyano-6,7-dicarbomethoxybicyclo[3,2,2]non-8-ene (23) ($C_{15}H_{16}O_5N_2$); the infra-red spectrum supported this structure [ν_{OH}^{KCl} : 3556 (s), 3436 (m) cm.$^{-1}$; ν_{COOR}^{KCl} : 1735 (s) cm.$^{-1}$] but did not indicate the presence of a cyano group. In view of the difficulties encountered in this hydrolysis and in those described in the literature,[12] rigorous investigation of (23) was not undertaken. Brief treatment of the tetracyano adduct (19) with cold sulphuric acid afforded a gum, its infra-red spectrum indicating it to be a complex mixture by the presence of acid, nitrile and imide absorption. Strong alkali treatment of (19), on the other hand, gave unidentified acidic products which displayed infra-red absorption at ν_{N-H}^{film} : 3300 cm.$^{-1}$ and $\nu_{C\equiv N}^{film}$: 2300 cm.$^{-1}$ No pure compound was isolated in either case.

Protection of the alcohol function of cyclohepta-3,5-dienol (9) was then investigated. Due to its ease of hydrolysis, the tetrahydropyranyloxy derivative seemed attractive. Treatment of the alcohol in ether with dihydropyran in the presence of a catalytic amount of mineral acid afforded the ether (24) in 94% yield as a colourless oil. Diels-Alder reaction of this ether with maleic anhydride in benzene (toluene or xylene) afforded no detectable amounts of adduct but reaction with N-phenylmaleimide resulted in a small yield of the required adduct (25) which showed imide absorption at 1705 $cm.^{-1}$ in the infra-red spectrum. The N.M.R. spectrum of this adduct was not well resolved but a singlet at 6·50 τ (<u>exo</u> protons H_6 and H_7) suggested the <u>endo</u> anhydride configuration (Part II). Repetition of this experiment at a higher reaction temperature, i.e. xylene 140°, gave unidentified products and polymer rather than increasing the yield.

The ketal diene (26) was the next compound to be tried as a suitable diene. Attempted preparation of the ketone (13) by oxidation of the dienol (9) with Jones reagent was unsuccessful, unidentified mixtures resulting. The dienone (13) has been shown[3] to undergo a Diels-Alder reaction with N-phenylmaleimide, but the product obtained has

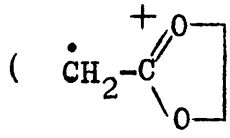
been proved to be the iso adduct (27). This is due to the fact that cyclohepta-3,5-dienone (13) was readily isomerised to the conjugated isomer cyclohepta-2,4-dienone (28) and reacted as such. The former dienone (13) was found to be an unstable compound[3] which decomposed on standing. In the light of this, it was not surprising that (13) could not be prepared by oxidation of the dienol. However, the dienone (13) has been prepared by the Garbisch method (Scheme 4) and this appeared a more acceptable route. This cycloheptanone was ketalised and carefully brominated in methanolic solution.[7] The crude product was directly dehydrobrominated with sodium methoxide in dimethyl sulphoxide to yield 1-methoxycyclohepta-1,3,5-triene (11) as an almost colourless liquid in 79% yield. It is noteworthy that by the same procedure carried out in ethylene glycol, the rate of bromination was much slower and dehydrobromination afforded cyclohept-2-enone ethylene ketal (29) in high yield [N.M.R.: 4·30 τ (2H, multiplet) (vinylic); 7·88 τ (2H, broad absorption) (allylic); 6·12 τ (4H, singlet) (ketal)]. This was in accord with Garbisch's finding that dibrominations in ethylene glycol are difficult to accomplish due to the insolubility of the mono bromoketals.

The triene ether (11) was hydrolysed to cyclohepta-3,5-dienone (13), ν_{CO}^{film} : 1715 cm.$^{-1}$, in 48% yield by sulphuric acid treatment. Immediate ketalisation of this product by the standard procedure resulted in a mixture of ketals which were separated by T.L.C. into a pure ketal A and an inseparable mixture of two ketals B. The structure of ketal A [$\lambda_{max.}^{EtOH}$: 239 mμ (ε, 5,980)] obtained in 34% yield, was proved mainly by examination of its N.M.R. spectrum which indicated the molecule to have the symmetrical structure (26) [4·03 τ (4H, multiplet) (vinylic); 7·47 τ (4H, doublet, J = 4) (allylic); 6·00 τ (4H, singlet) (ketal)] The mass spectrum displayed a base peak at m/e 86 corresponding to the ion fragment () as well as the molecular ion at m/e 152.

Ketals B, obtained in 5% yield, which had a boiling point similar to A but which decomposed on standing also lacked carbonyl absorption in the infra-red but showed ultraviolet maxima at $\lambda_{max.}^{EtOH}$: 289·5 mμ (ε, 3180) and 212 mμ (ε, 6680). This data plus the N.M.R. spectrum which showed two kinds of vinylic protons (3·59 τ and 4·55 τ), indicated the presence of a mixture of diene ketals (30) and (31).

A sharp doublet (J = 8) in the N.M.R. spectrum at 7·41 τ was good evidence for structure (31), in which the C_4 methylene protons would couple with the vinylic proton on C_3 but not with those on the adjacent methylene group due to symmetry. However, apart from the mentioned doublet, the N.M.R. spectrum was not well defined and the possibility of isomer (32) being present was not ruled out.

Diels-Alder reaction of the ketal diene (26) with maleic anhydride in refluxing toluene produced no adduct, but with N-phenylmaleimide a small yield of adduct (33) was obtained. The product was identified by its infra-red spectrum, ν_{CO}^{NUJ} : 1707 cm.$^{-1}$ (s) (phenylimide) and mass spectrum which gave the expected molecular weight, m/e 325, and a base peak at m/e 86 corresponding to the fragment



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It was thus evident from the lack of success of reaction of these dienophiles that a more stable form of diene was required. A more permanent type of protecting group seemed attractive, an acetate group being the obvious choice. Treatment of cyclohepta-3,5-dienol (9) in pyridine with acetic anhydride afforded the acetate (34) in

65% yield, the molecule showing typical acetate infra-red bands, 1735 $cm.^{-1}$ and 1240 $cm.^{-1}$ and a sharp singlet in the N.M.R. spectrum at 8·00 τ (methyl group). However, it was noticed that on some occasions, this preparation led to a mixture of acetate (34) and benzyl acetate [N.M.R.: 2·68 τ (singlet, aromatic protons); 4·92 τ (singlet, benzylic methylene); 7·93 τ (singlet, acetate methyl)]. This rearrangement is probably initiated by loss of an allylic proton to pyridine followed by formation of a cyclohexadiene derivative (Scheme 5) which then aromatised to benzyl acetate.

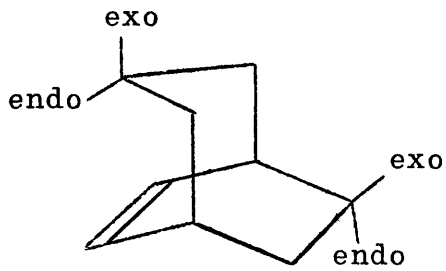
Diels-Alder reaction of (34) with maleic anhydride afforded a mixture of four isomers by G.L.C. (analysing for $C_{13}H_{14}O_5$), inseparable by preparative T.L.C. or by crystallisation. The N.M.R. of the mixture showed two singlets at 6·41 τ and 6·50 τ in the midst of other less well-defined signals. These singlets were assigned to the non-coupling exo H_6 and H_7 protons of epimers (35) and (36) by analogy with the benzoate epimers (Part II); the other two components were assumed to be the iso epimers (37) and (38), the exo protons of which would show coupling due to the asymmetry of the molecule and would not be easily observed among the other signals. The exo anhydride could not be

ruled out but, by analogy with the benzoate adducts following, a mixture of endo products appeared more likely.

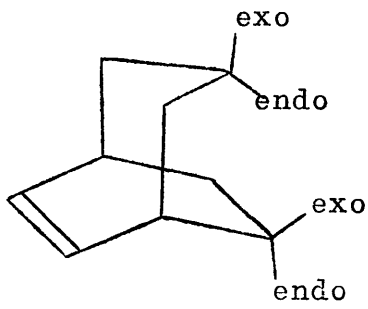
In view of the partial success with the acetate derivative, the benzoate diene (39) was prepared. Cyclohepta-3,5-dienol in cold pyridine on treatment with benzoyl chloride afforded an 88% yield of 1-benzoyloxycyclohepta-3,5-diene (39) as a pale yellow oil. The N.M.R. spectrum confirmed the symmetrical diene structure, the N.M.R. values for this diene and others being tabulated (Table I). It is to be noted that, whereas preparation of the acetoxy diene (34) gave, on occasions, amounts of benzyl acetate, none of the corresponding benzoate product was ever detected.

Reaction of 1-benzoyloxycyclohepta-3,5-diene (39) with maleic anhydride in refluxing xylene gave, after preparative T.L.C., a solid, m.p. 130-136°, which was shown by G.L.C. and analysis to consist of three isomers, 2-benzoyloxy and the epimeric 3-benzoyloxybicyclo[3,2,2]non-8-ene-6,7-endo-dicarboxylic acid anhydrides(40), (41) and (42). A singlet in the N.M.R. spectrum at 6·32 τ suggested the predominance in the mixture of one isomer having exo H_6 and H_7 protons. Variation of the reaction conditions (e.g., time of reaction, amount of solvent) led to an increased yield of the material and to the separation of

the isomers. After 24 hrs. heating at reflux temperature, cooling to room temperature afforded anti-3-exo-benzoyloxy-bicyclo[3,2,2]non-8-ene-6,7-endo-dicarboxylic acid anhydride (41) (endo A), m.p. 222-225°, in 33% yield (N.M.R.: Part II).



anti



syn

Chromatography of the residue from crystallisation on acid-washed alumina afforded first syn-3-exo-benzoyloxybicyclo [3,2,2]non-8-ene-6,7-endo-dicarboxylic acid anhydride (42) (endo B), m.p. 196-199°, followed by 2-benzoyloxybicyclo [3,2,2]non-8-ene-6,7-endo-dicarboxylic acid anhydride (40) (iso A), m.p. 152-155°. The structure of the latter compound (40) was identified as the unsymmetrical 2-benzoyloxy endo anhydride rather than the symmetrical 3-benzoyloxy exo anhydride (43) by a study of its N.M.R. spectrum which is fully discussed in Part II. The exo product (43), being symmetrical, would exhibit an A_2X_2 pattern (protons H_8,H_9,

H_1 and H_5) rather than the observed ABXY type for an unsymmetrical structure; neither the exo nor the iso adduct would exhibit a singlet for protons H_6 or H_7.

Alternatively, reduction of the filtrate (after separation from endo A) to smaller bulk and dilution with ether afforded batches of crystals, the comparison of which was estimated by G.L.C.

endo A 34%; endo B 11%; iso A 18%

The corresponding 2-epimer of iso A could not be detected.

Comparison of the infra-red and mass spectra (Tables II and III*) of each was undertaken but these alone offered no distinction between structures. The mass spectral breakdown pattern is illustrated in Scheme 6. The base peak, m/e 105 corresponded to fragment ion $(Ph\text{-}C{\equiv}O)^+$ which further fragmented to the aromatic ion $(C_6H_5)^+$ m/e 77 (metastable 56·5). A McLafferty rearrangement involving the ester led to loss of benzoic acid i.e., m/e 190 (M-122) which then lost CO followed by CO_2 to yield fragment ions m/e 162 and m/e 118. A retro Diels-Alder reaction of this fragment (m/e 190) afforded the stabilised tropylium ion m/e 91.

* Overleaf

Table II I.R. $\nu_{KCl}^{cm.^{-1}}$

Endo A	Endo B	Iso A
1868 m	1858 m	1859 m
1843 m	1840 w	
1832 m	1829 m	1833 m
1777 s	1773 s	1770 s
1713 s	1710 s	1704 s
1277 s	1277 s	1282 s
948 s	947 m	947 s
920 s	922 s	913 s
775 m	771 m	769 m
749 s	747 s	728 s
711 s	711 s	708 s

Table III M.S.

m/e	Endo A	Endo B	Iso A
77	30·5	32	24·5
91	18	15	6·5
92	10	7	1·8
105	100	100	100
117	15	11	2·2
118	22·5	15	2·9
123	4·8	3	1·1
134	1	L	L
162	1·7	1·3	1·8
190	29	19	4·3
207	0·7	L	L
286	L	L	L
294	0·5	L	L
312	L	1·3	L

L = less than 0·5% abundance.

The structure assigned to iso A (40) could possibly arise by two mechanisms, (a) thermal rearrangement in the reaction of the benzoyloxy diene (39) to the isomer (44), or (b) small amounts of dienol (45) present in the bulk preparation of the benzoate (39).

In confirmation of the above assigned structures, 1-p-bromobenzoyloxycyclohepta-3,5-diene (46), m.p. 57-59°, (ν_{COOR}^{melt} : 1715 cm.$^{-1}$) was prepared in an analogous fashion to the benzoyloxy diene. Its N.M.R. spectrum was in complete agreement with that of (39). Reaction with maleic anhydride under identical conditions to the benzoyloxy diene (39) yielded anti- 3-exo-p-bromobenzoyloxybicyclo [3,2,2]non-8-ene-6,7-endo-dicarboxylic acid anhydride (47) m.p. 116-117°, the N.M.R. of which showed an identical splitting pattern to that of endo A except, of course, for the aromatic region. An X-ray analysis of adduct (47) (Appendix) revealed the structure to be that expected from first principles with respect to non-bonded interactions i.e. as in endo A; assuming no distortions in the molecule, the anti form with the benzoate group exo would be expected to be preferred to the syn configuration (with the benzoate substituent exo) where there may be interaction of H_3 with the exo protons H_6 and H_7. The 3-endo epimers of both

syn and anti configurations would experience steric crowding.

With the success of the benzoyloxy diene as a suitable reactant for the Diels-Alder reaction, cyclopentene-3,5-dione, a less active dienophile, was tested for reactivity, the envisaged adduct (48) being attractive on account of the incorporated cyclopentanedione ring. In the event, however, the dienophile proved to be unreactive, starting materials being isolated with both xylene and benzene as solvent.

In view of previous endo anhydride structures (6), (8) being proved by chemical means e.g., bromolactonisation (49), this bromination technique was applied to the endo A and iso A anhydrides. The tropone-maleic anhydride adduct[5] (8) was prepared as a model compound; the residue from crystallisation was investigated for the presence of other isomers. However, only a small amount of the above adduct (8) plus starting materials were detected in the residue. Under identical conditions to that used in the benzoyloxy diene-maleic anhydride reaction, the adduct (8) m.p. 181-182° was obtained in 99% yield (N.M.R. Part II).

Bromination of (8) in water at 0^{o} afforded the described[5] bromolactone (49) or (50) as yellow crystals after 4 hrs. reaction, the product crystallising from the medium. The infra-red spectrum showed absorption at 3400-2500 $cm.^{-1}$ and 1735 $cm.^{-1}$ (assigned to the acid), 1770 $cm.^{-1}$ (γ-lactone) and 1675 $cm.^{-1}$ (enone). The infra-red values quoted[5,13] for this and other related compounds are tabulated (Table IV); it can be seen that there is a range of values for the acid group, the two different values quoted by Nozoe being attributed to the two different isomers (49) and (50). It is also noteworthy that there is often very little difference between corresponding ester and acid carbonyl frequencies.

Thus for chemical proof of the endo configuration, bromination of endo A (41) was undertaken. An identical reaction to that described above could not be effected due to the total insolubility in water of (41). A mixture of water and dioxane was therefore used for homogeneity and the product extracted with chloroform. The product contained bromine but was only slightly more polar than the starting material; only anhydride and benzoate peaks were observed in the infra-red spectrum; the product was considered to be the bromine addition compound (51).

Bromination in methanol/dioxane/water gave similar results while bromination in sodium carbonate solution afforded a benzoate diacid mixture assumed to be (52) and (53).

Using iso A in a dioxane/water mixture, a small amount of crystalline material believed to be (54) was obtained [ν_{OH}^{NUJ} : 3400 cm.$^{-1}$ (m), ν_{CO}^{NUJ} : 1775 cm.$^{-1}$, 1738 cm.$^{-1}$, 1705 cm.$^{-1}$] but attempts to purify it by basic extraction and acidification caused destruction of the molecule. Repetition of this experiment led to bromo diacids and complex mixtures, illustrating the importance of the solvent system. However, bromination in methanol/water/dioxane afforded a product m.p. 175·5-178·5°, the infra-red spectrum of which showed no acidic absorption but showed lactone (1780 (s) cm.$^{-1}$) and benzoate (1700 (s) cm.$^{-1}$) absorption as well as a band at 1735 cm.$^{-1}$. That this latter band was due to a methyl ester rather than to an acid group [despite the similarity in frequency with that of (54)] was further confirmed by T.L.C. on which the compound showed non-acidic character. Elemental analysis indicated the molecular formula ($C_{19}H_{18}O_6$) inferring an elimination of hydrogen bromide under the conditions used. As to the structure of this compound, a number of possibilities

exist if we consider that the bromolactone ester (55) or (56) was the initially formed product. Since elimination to give a double bond was impossible (anti-Bredt rule) unless a rearrangement had occurred, three possible structures could be derived viz., (57) (58) and (59) from (55). Since (56) would give rise to three similar products, the complexity of the problem seemed insurmountable.

It was felt that this intriguing reaction might be clarified by carrying out this bromination on a simpler molecule, namely bicyclo[3,2,2]non-8-ene-6,7-endo-dicarboxylic acid anhydride (7), the configuration of which had been proved by N.M.R. (Part II). Thus reaction of (7) in dioxane/water [due to the absence of the benzoate grouping, (7) was not so insoluble in water and therefore did not warrant the methanol/water/dioxane technique], followed by esterification of the crude lactonic acid with diazomethane afforded a crystalline compound, m.p. 96·5-97·5° which analysed for $C_{12}H_{14}O_4$. This compound showed lactone and ester absorption in the infra-red spectrum (1788 $cm.^{-1}$, 1740 $cm.^{-1}$) but no band at ca. 3070 $cm.^{-1}$ indicative of a cyclopropane ring (C-H). The ultraviolet spectrum showed no significant absorption above 200 mμ, the N.M.R. spectrum showed the following pattern:

5·39 τ (1H, quartet, J=6, J=3·5)

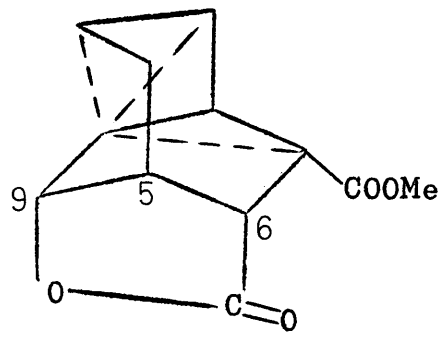
6·29 τ (3H, singlet)

7·20 τ (1H, doublet, J=5)

7·39 τ (1H, triplet, J=6)

7·66 τ (1H, broad absorption)

8·2-8·8 τ (6-7H, complex)



The quartet (5·39 τ) was assigned to H_9 (coupled to H_5, H_8) and the singlet at 6·29 τ to the ester methyl group. The fact that four signals, each for 1H, was seen excluded structure (63) since the latter should have two similar cyclopropane protons at higher field. Proton H_5 would be expected to be the signal at 7·66 τ (extensive coupling), with signals at 7·20 τ and 7·39 τ being assigned to H_7 and H_6 or vice versa. Since (61) and (62) are both highly strained systems, arguments based on the angular dependence of coupling constants are not strictly valid. However, the triplet at 7·39 τ could be due to an equal coupling with H_7 and H_5, whereas the doublet at 7·20 τ infers that H_7 subtends a dihedral angle of ca 90° with H_1, coupling only with H_6. Since there are no signals greater than 9·0 τ, the cyclopropane derivative seemed unlikely (in agreement with the lack of characteristic infra-red absorption) unless the strain in the system or conjugation with the ester shifted

the τ value to lower field [lit.[14] for ester (64), H_a, H_b 8·34 τ, d]. Certainly the 8·2 - 8·8 τ region (Fig. 1) had changed radically from the narrow absorption signal observed in the anhydride (7) for the three methylene groups but this could be explained by either the formation of a cyclobutane ring as in (61) or by the cyclopropane protons absorbing at lower field at or near the methylene value. However, the question of activation of the proton for elimination still remained, the most probable structure in this respect being (63), where the proton was adjacent to the carbethoxy group.

Despite the incompleteness of the structural elucidation of this compound, the formation of the lactone was good evidence for the endo configuration of the anhydride.

With the structure and chemistry of the benzoate adduct (41) elucidated, attention was again focussed on the initial aim viz., the synthesis of β-vetivone. Elaboration of the anhydride to the cyclopentane derivative (65) (Scheme 7) was then studied. Lithium aluminium hydride (L.A.H.) reduction of the anhydride function would yield the endo bis primary alcohol (66) (asymmetric centres adjacent to carbonyl groups do not undergo epimerisation on L.A.H. treatment),[15] further reactions having no effect on

the stereochemistry of these centres. Ditosylation of the bis alcohol (66), followed by ring closure with diethyl malonate and further elaboration, had been effected on simpler molecules by McGeachin[1] to afford as a final product, the isopropylidine derivative (65). However, in the case of endo A (41), there was the additional problem that the benzoate function, under these reduction conditions, would yield a secondary alcohol; the next step would therefore require to be a preferential tosylation of the two primary alcohol functions.

In the event, reduction of anti-3-exo-benzoyloxy bicyclo[3,2,2]non-8-ene-6,7-endo-dicarboxylic acid anhydride (41) with L.A.H. in tetrahydrofuran at reflux temperature resulted in the isolation of benzyl alcohol and 1,4-butanediol, b.p. $60^{\circ}/0{\cdot}05$ mm., as the major product, identified spectroscopically after acetylation and preparative T.L.C., ν_{COOR}^{film} : 1740-1720 $cm.^{-1}$ [N.M.R. 5·94 τ (4H, t, O-methylene), 7·99 τ (6H, s, acetate), 8·32 τ (4H, quintet, C-methylene)]. The mass spectrum showed no parent ion but displayed a large ion at m/e 131 ($M-CH_3CO$). The conditions must have effected a retro Diels-Alder reaction,[16] the resulting maleic anhydride being totally reduced to the diol. Room temperature

reduction generated a mixture of alcohols which could not be separated even after acetylation, although one component was identified as 1,4-diacetoxy butane. The N.M.R. of the crude mixture suggested the other component was either the bicyclic triacetate (67) or 1,4-diacetoxybut-2-ene.

To circumvent this problem it was thought that a derivative other than the anhydride might curtail the retro reaction during reduction. The anhydride (41) was therefore treated with warm sodium bicarbonate (20%), acidification yielding the endo diacid (**68**), m.p. 226·5-227·5°, in 89% yield, ν_{CO}^{KCl} 1717 (s) cm.$^{-1}$, 1708 (s) cm.$^{-1}$. Diazomethane esterification afforded the endo diester (69), m.p. 82-83°, in 93% yield, the N.M.R. spectra of both these compounds confirming that no epimerisation of the functions had taken place during the reaction. L.A.H. reduction of the diester (69) in refluxing ether for 4 hrs., afforded anti-3-exo-hydroxy-6,7-endo-dihydroxymethylbicyclo[3,2,2]non-8-ene (70) as a highly crystalline solid, m.p. 145-145·5° in 48% yield. Attempts to better this yield were unsuccessful. Examination of the residue from crystallisation showed it to be a mixture of the above mentioned butanediol, butenediol and benzyl alcohol indicating that the retro reaction was still in operation but to a lesser extent. Treatment of the triol

in pyridine with slightly in excess of a two molar quantity of p-toluenesulphonyl chloride afforded a mixture of about 5 components, the infra-red spectrum of which indicated both hydroxyl and carbonyl bands; none of the components could be obtained pure, although one was expected to be the hydroxy ether (71) by the intramolecular elimination (72) → (71). Preferential tosylation appeared therefore unfruitful since, in order to tosylate the primary functions, an excess of reagent would be required (as recommended by McGeachin[1]), which would also attack the less reactive secondary alcohol. In view of this difficulty, it was decided to convert the anhydride adduct (41) to a derivative that would have a function at the 3-position resistant to L.A.H. reduction. An attractive functionality was the ketal moiety. However, before discarding the benzoate diester (69), the latter was used as a model compound to study the cleavage of the C_8-C_9 double bond. This ester was chosen as a model essentially because material was available but also because it was considerably more stable than the anhydride, although it could be epimerised with base to lose its C_6, C_7 di-<u>endo</u> character.

Scheme 8 illustrated the proposed routes to the dimethyl cycloheptane derivative (73) of depicted stereochemistry, in each approach care being taken to avoid epimerisation of the aldehyde functions with acid or base. Ozonolysis was therefore the first step but, in the event, a mixture of acidic species was observed (I.R. and T.L.C.) (yellow stain with D.N.P. developer) as well as a small amount of minor less-polar materials; the main products were assumed to be the aldehydo acid (74) and the diacid (75). Osmium tetroxide treatment of the diester (69) in ether for 48 hrs., yielded the diol (76) in 43% yield as a heavy oil (M.W. 392), $\nu_{OH}^{CCl_4}$: 3640 (s), 3552 (s) cm.$^{-1}$. It is interesting to note that the two methyl esters appeared at different carbonyl frequencies in the infra-red spectrum, 1751 cm.$^{-1}$ and 1742 cm.$^{-1}$, which could be explained by the new flexibility incorporated in the structure with the removal of the double bond; the esters therefore had different environments in either of the two "flip" forms (77) and (78), although both still possessed the <u>endo</u> configuration. However, the N.M.R. (Part II) did not distinguish between these esters due to the much larger time interval of scanning, the time-averaged configuration resulting.

On attempted distillation of the diol (76), an interesting elimination took place, (79) → (80); benzoic acid (I.R., m.p.) sublimed first, followed by an oil, b.p. 150-160°/0·1 mm., which was shown by I.R. to be the hydroxy ether diester (80), showing no aromatic bands and a typical rigid-structure type fingerprint region. This elimination was also accomplished if the diol was allowed to stand in the atmosphere. However, information was gleaned from this elimination; the hydroxyl groups being cis from the osmylation, must also necessarily be in the exo configuration for such an interaction to occur, as well as having the three carbon bridge in the anti configuration. If the hydroxyls had been endo (81), it was expected that the dilactone (82) would have been generated under these conditions.

Confirmation of the structure of the cis diol (76) was obtained by the preparation of an acetonide (83), m.p. 140·5-142°, the mass spectrum of which showed a base peak at m/e 105 $(Ph-CO)^+$ [as did diol (76)] and, although no parent was observed, showed a large ion m/e 417 corresponding to $(M-CH_3)$.

The diol (76) on reaction with sodium periodate in aqueous methanol for 24 hrs., under an atmosphere of nitrogen afforded as the main product the dialdehyde (84)

showing no hydroxyl in the infra-red spectrum but instead a band at 2740 $cm.^{-1}$ (C-H of CHO). No starting diol was detected by T.L.C. and the dialdehyde stained yellow with D.N.P. developer. However, the compound darkened on standing and decomposed to acidic species (T.L.C.); attempts were made to characterise (84) as its D.N.P. and semicarbazone derivatives. Two D.N.P. derivatives, m.p. 145·5-148° and m.p. 153·5-156°, with almost identical infra-red spectra ν_{N-H}^{NUJ} : 3300, 1620 $cm.^{-1}$, were isolated. Neither could be obtained completely pure due to decomposition although the mass spectrum of the former showed, despite being involatile, a molecular ion m/e 745 ± 5 [(85) requires 750]. On this evidence, they were assumed to be the bis-dinitrophenylhydrazone (85) and one of its epimers (epimerisation caused by treatment with the acidic D.N.P. reagent). Attempts to prepare a semicarbazone were unsuccessful.

With the failure to isolate the bis-semicarbazone derivative, the Wolff-Kishner route to the dimethyl compound (73) (Scheme 8) was ruled out. The hydride reduction method seemed a more fruitful approach since L.A.H. reduction would also avoid epimerisation problems. However, the dialdehyde (84) was not a suitable model for this reaction, since the three ester functions would also

undergo reduction. Despite the knowledge that sodium borohydride reductions are conducted in a basic medium, a test run was undertaken and a yellow oil (T.L.C. one component) was isolated which showed lactone and benzoate absorption but no methyl ester absorption in the infra-red spectrum, ν_{CO}^{film} : 1790 (s), 1781 (s), 1718 (s) cm.$^{-1}$. This oil was believed to be a mixture of epimeric benzoate dilactones of the type (87 , 88 , 89) produced by the lactonisation of the generated alcohols with the neighbouring ester functions e.g., (86) → (87). Since epimerisation of a centre adjacent to an aldehyde, followed by lactonisation could lead to isomers (88) and (89) and since the oil itself decomposed on standing to acidic species, identification of the compound(s) could not be achieved.

In view of the unsuitability of the diester (69) as a model, thioacetalisation of the dialdehyde was not attempted; this reaction or the L.A.H. reduction could well be utilised at a later stage in the synthetic scheme e.g., (90) where there are no opportunities for additional reductions or intramolecular reactions.

In view of the results obtained at this stage, it was felt advisable to elaborate the anhydride to the cyclopentane ring moiety of β-vetivone before cleavage of

the C_8, C_9 double bond was considered. The initial step was to transform the benzoyloxy group to the ketal function, which would resist hydride reduction.

Thus hydrolysis of the benzoyloxy anhydride (41) was achieved with hot sodium carbonate solution over 3 hrs.,; the product on ether extraction consisted of benzoic acid, anti-3-exo-hydroxybicyclo[3,2,2]non-8-ene-6,7-endo-dicarboxylic acid anhydride (91) and anti-3-exo-hydroxybicyclo[3,2,2]non-8-ene-6,7-endo-dicarboxylic acid (92). The latter two were very soluble in water and required continuous ether extraction for their isolation. The mixture of the hydroxy diacid (92) and hydroxy anhydride (91) afforded anti-3-exo-acetoxybicyclo[3,2,2]non-8-ene-6,7-endo-dicarboxylic acid anhydride (93) as sole product on treatment with acetyl chloride at reflux temperature. This acetoxy anhydride (93) had similar characteristics (I.R., T.L.C.) to the mixture of isomeric acetoxy anhydrides (35 , 36 , 37 , and 38) obtained earlier. Oxidation of the hydroxy diacid mixture with Jones reagent followed by heating the product in acetyl chloride afforded the keto-anhydride (94), m.p. 199·5-200·5°, in 42% yield (from the benzoyloxy anhydride). The structure was confirmed in the usual manner, the N.M.R. spectrum illustrating the

endo configuration of the anhydride (Part II). Ketalisation of this compound with ethylene glycol and p-toluenesulphonic acid afforded the corresponding ketal (95), m.p. 225-226·5°, in 55% yield, the infra-red spectrum showing no trace of ketonic material. Warm aqueous sodium carbonate treatment of the ketal (95) afforded the diacid (96) which could not be isolated by precipitation but was esterified directly with diazomethane, since attempted isolation of the diacid yielded varying amounts of anhydride. The resulting diester (97), m.p. 89·5-91·5°, obtained in 49% yield from the anhydride (95), had the expected endo configuration (Part II). L.A.H. reduction of the diester in refluxing ether, afforded the diol (98), m.p. 137·5-138·5°, in 76% yield, which stained yellow with D.N.P. developer as a result of hydrolysis of the ketal by the reagent. Since protons H_6 and H_7 now couple with the adjacent methylenes in the N.M.R. spectrum, the endo configuration could not be confirmed; however L.A.H. reductions are known[15] to proceed without epimerisation of adjacent asymmetric centres and therefore the endo configuration could be safely assumed (later conversion to the cyclopentene system confirmed this assignment). The salient features in the N.M.R. of 3,3-ethylenedioxy-6,7-endo-dihydroxymethylbicyclo[3,2,2]non-8-ene (98) were: 6·13 τ (4H, s, ketal), 6·90 τ (2H, broad absorption, OH, D_2O exchange).

In order to work out conditions for the later stages of the synthesis, simultaneous work was started on a model compound lacking functionality at position 3. Bicyclo[3,2,2]non-8-ene-6,7-*endo*-dicarboxylic acid anhydride (7), whose preparation has been described earlier, on reduction afforded 6,7-*endo*-dihydroxymethylbicyclo[3,2,2]non-8-ene (99), m.p. 72-72·5° almost quantitatively. It would appear that functionality at position 3 was in some way responsible for the significant retro Diels-Alder reaction which occurred in the reduction of the benzoyloxy anhydride (41).

Bis-mesylation of (99) was then studied. It has been reported that attempts[17] to ditosylate diol (100) resulted in the formation of the cyclic ether (101) presumably via the cyclisation (72) → (71); the ether (102) has been reported[1] as a side-product in the ditosylation of (103). An analogy for using the *bis*-mesylate was afforded by Stork's synthesis of cantharidin in which the diol (104) was smoothly converted[18] to the *bis*-mesylate derivative. Thus slow addition of the diol (99) to excess methanesulphonyl chloride in pyridine at 0° resulted in a 96% yield of the *bis*-mesylate (105) as colourless needles, m.p. 96-97° [ν_{SO}^{NUJ} : 1175 (s) cm.$^{-1}$; *N.M.R.*: 7·00 τ (6H, singlet, *Me*-SO_2-)]. An analogous

reaction on the ketal diol (98) furnished the ketal bis-mesylate (106) in 77% yield, m.p. 106-107·5° [ν_{SO}^{NUJ} : 1180 (s) cm.$^{-1}$; N.M.R. : 7·02 τ (6H, singlet, Me-SO_2-)].

In the synthetic sequence, the next stage was the formation of the cyclopentane ring in such a way as to introduce a function suitable for elaboration to an isopropylidene grouping at a later stage. Two possibilities were available. Firstly, the dialkylation of malonic ester with a ditosylate has been reported e.g. ditosylate (107) → (108).[19] More pertinent to our problem was the work of McGeachin[1] who alkylated malonic ester with the ditosylate (103a). However, Bloomfield and Fennessey[20] reported an in situ replacement of the tosylate groups by cyanide with, on the addition of sodium hydride, concomitant Thorpe cyclisation to the β-cyano-enamine, (109) → (110); hydrolysis of β-cyanoenamines to cyclopentanones has been accomplished.[21] Thus treatment of the bis-mesylate (105) in dimethyl sulphoxide (D.M.S.O.) with potassium cyanide at 95°, followed by heating in sodium hydride gave in 68% yield the β-cyanoenamine (111), m.p. 188°. The colourless plates ($C_{13}H_{16}N_2$) showed infra-red absorption at ν_{N-H}^{NUJ} : 3460 (m), 3390 (m), 1645 (s) cm.$^{-1}$ and $\nu_{C\equiv N}^{NUJ}$: 2210cm^{-1} almost identical to that quoted for amino-2-cyanopent-1-ene (112); the ultraviolet maxima, $\lambda_{max.}^{EtOH}$ 263·5 mμ

(ε, 15,000) was also very similar to that quoted[22] [$\lambda_{max.}$ 263 mμ (ε, 13,000)]. Addition of hydrochloric acid to the solution caused a hypsochromic shift to $\lambda_{max.}$ 238 mμ (ε, 10,700) over a 1 hr. period. The wavelength shift was indicative of the β-cyanoenamine chromophore, since protonation of the amino group removed the availability of the electron pair of the nitrogen thus moving the maximum to lower wavelength. The N.M.R. also accounted for this structure (111), the amine protons absorbing at 5·76 τ (2H, broad, D_2O exchange). The C_{11}, C_{12} vinylic protons, being non-equivalent coupled and appeared as a multiplet at 2·97 τ; H_a, was a doublet, J = 8, coupling with H_a, the latter being observed as a multiplet due to coupling with the adjacent methylene group. The six methylene protons once again absorbed as an unresolved narrow absorption.

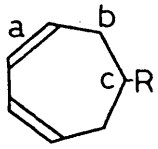
An analogous reaction, carried out on the ketal bis-mesylate (106), afforded an amber oil which was shown to consist essentially of one component. Preparative T.L.C. unfortunately resulted in only a small amount of material being recovered from the plate, i.e., 19%, as a pale yellow oil which could be crystallised as an amorphous solid, m.p. 149-151°. Owing to the small amount of material available (4·9 mg.,), this compound was identified

by infra-red and ultraviolet spectroscopy as the β-cyano-enamine ketal (113). The infra-red spectrum again showed N-H and C≡N absorption[ν_{NH}^{KBr} 3460 (m), 3345 (m), 1646 (m) cm.$^{-1}$ $\nu_{C\equiv N}^{KBr}$: 2175 (s) cm.$^{-1}$] and the ultraviolet spectrum showed a hypsochromic shift from $\lambda_{max.}^{EtOH}$ 263·5 mμ (ε, 12,700) to $\lambda_{max.}$ 238 mμ (ε, 8,870) on addition of 6N hydrochloric acid. The mass spectrum, however, showed (113) to be contaminated with a small amount of a compound, $C_{14}H_{17}O_3N$ which showed a base peak in the mass spectrum at m/e 95 [fragment (116)]. The base peak for the β-cyanoenamine (113) occurred at m/e 106 corresponding to fragment (117), suggesting that in both compounds a retro Diels-Alder reaction was the main fragmentation. Occurrence of a large ion at m/e 152 corresponding to the ketal diene (118) further substantiated this.

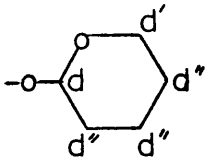
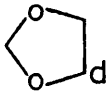
From this evidence and from a consideration of the reaction conditions employed the compound $C_{14}H_{17}O_3N$ was thought to be (114) formed by oxidation[23] of one mesylate group to the aldehyde (115), followed by cyanohydrin formation and nucleophilic displacement of the other mesylate function (Scheme 9).

In view of the fact that supplies of intermediates were now exhausted, the synthesis of β-vetivone was stopped at this stage. Completion of the synthesis would appear feasible but, because of the number of stages still remaining (Scheme 3) fairly large quantities of the cyanoenamine (113) would be required.

Table I.

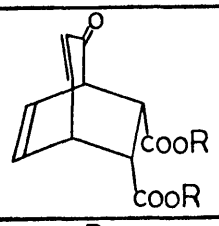


Solvent $CDCl_3$

R	H_a	H_b	H_c	H_d	$H_{d'}$	$H_{d''}$
H_2	4·26 bs	7·70 m	8·19 m			
OH[d]	4·16 m	7·47 q, J=4	5·78 q, J=5	7·70 s		
	4·21 m	7·47 m	6·00 m	5·27 bs	6·41 bt	8·38 bs
	4·03 m	7·47 d, J=4	-	6·00 s		
-OCOMe[d]	4·19 m	7·47 q, J=4	4·88 m	8·00 s		
-OCOPh[d]	3·94 m	7·24 q, J=4	4·44 m	2·26m 1·66m		
$-OCOC_6H_4$[d]-p-Br	4·16 m	7·36 q, J=4	4·66 m	2·3 m		

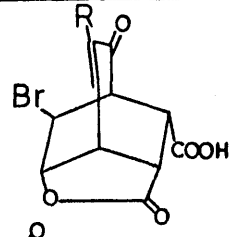
bs broad singlet bt broadened triplet

Table IV ($cm.^{-1}$) ν_{COOR}



R = H 1740, 1710

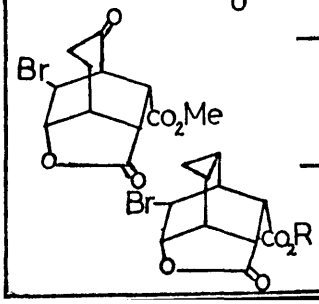
R = Me 1730



R = H 1730, 1745

R = Cl 1710

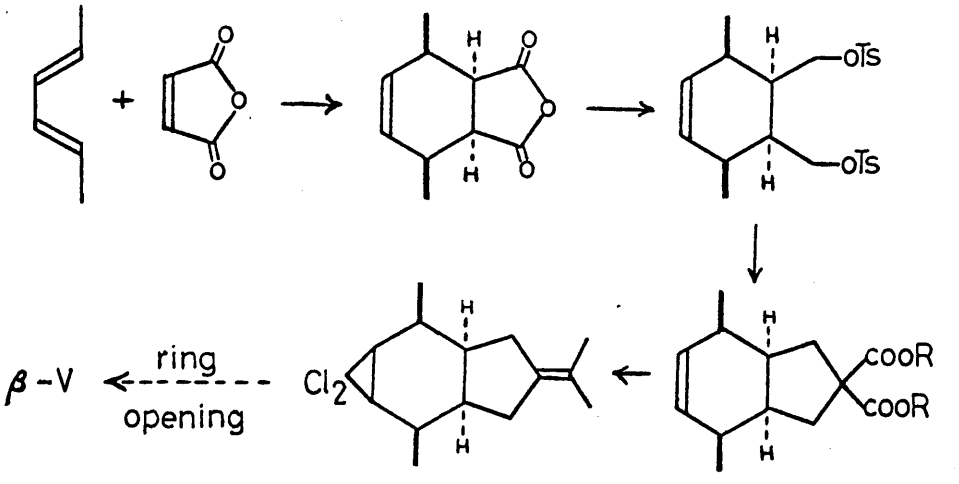
R = Br 1735



1726

R = H 1716

R = Me 1713



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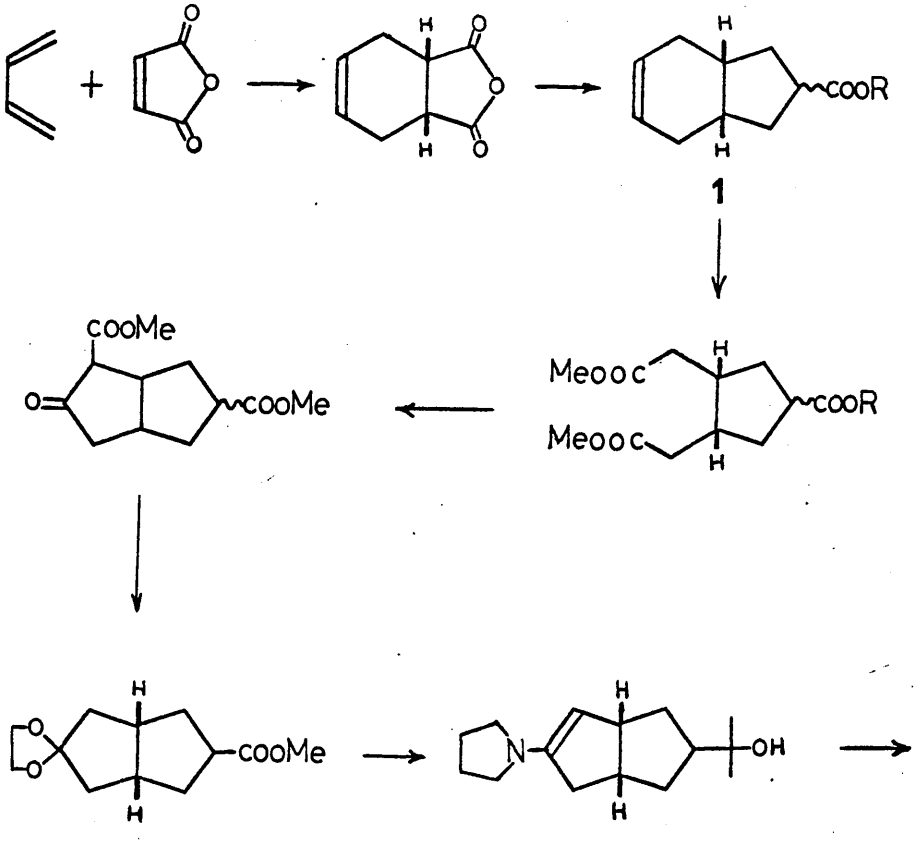

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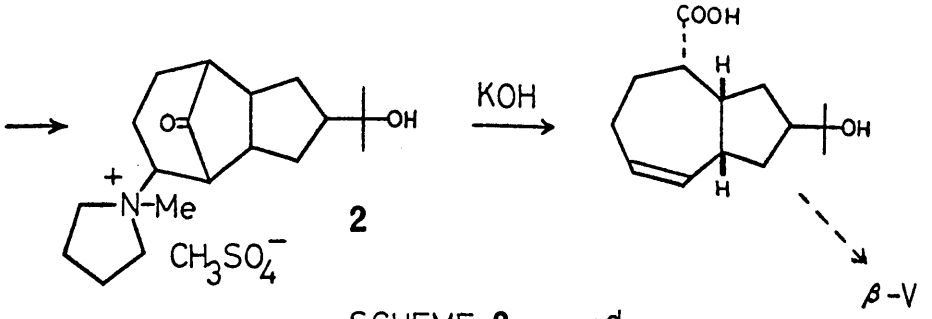

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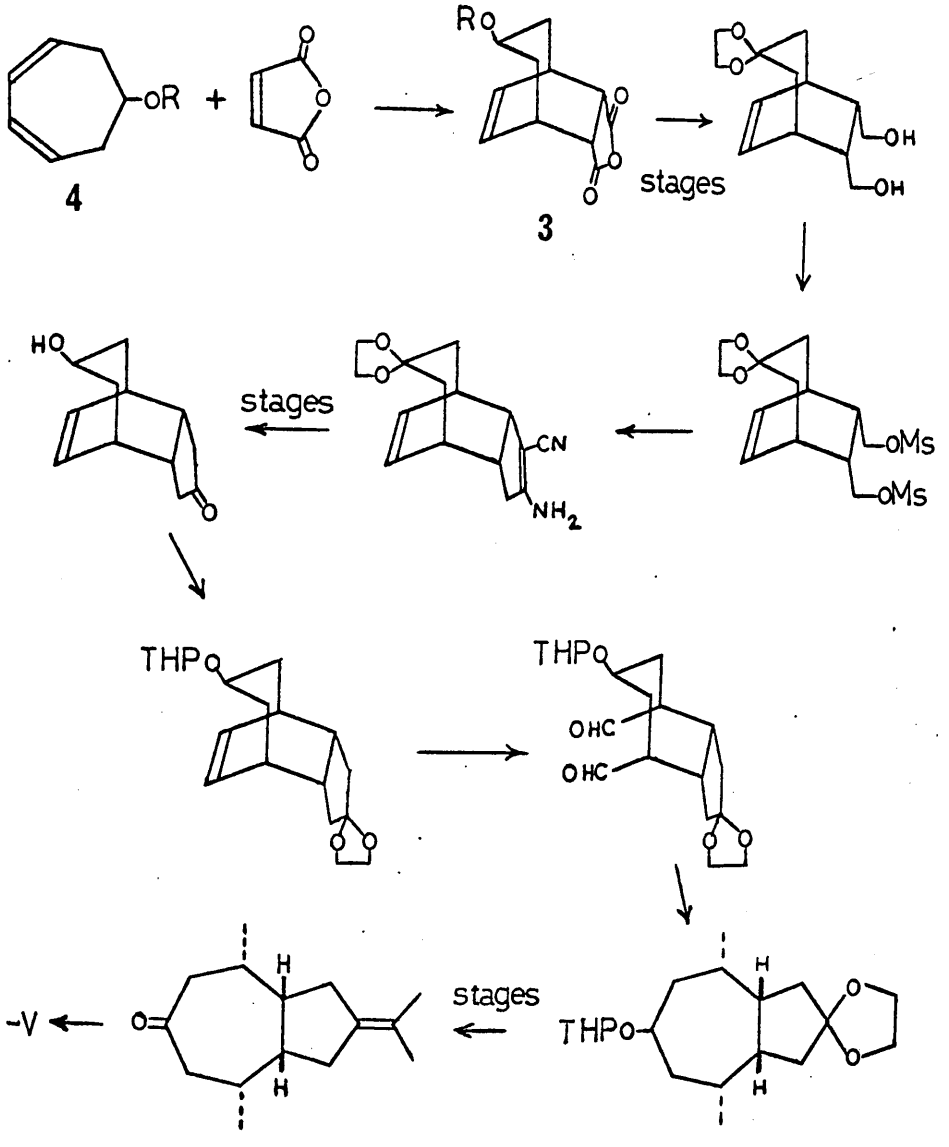

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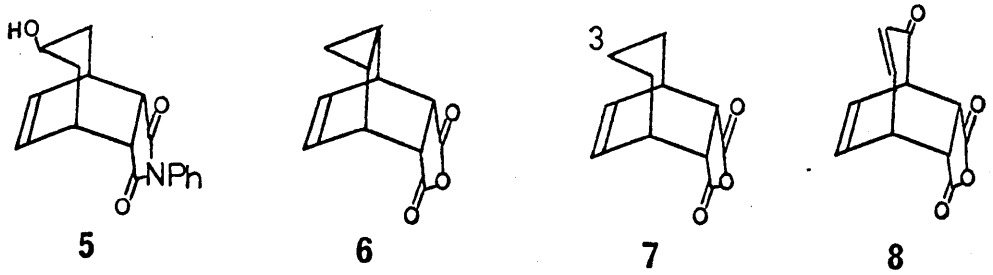

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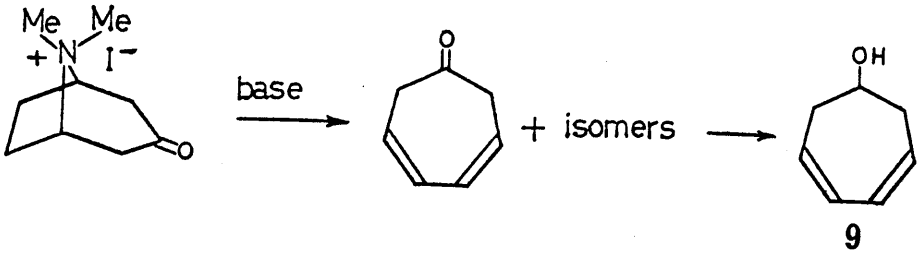

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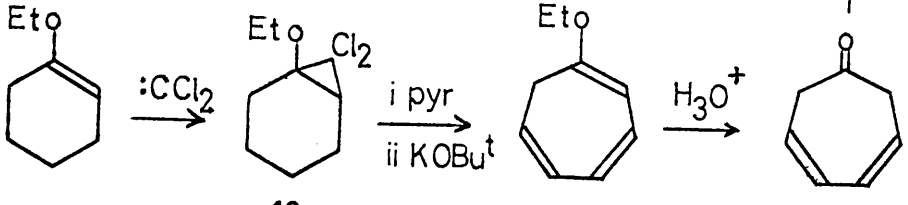

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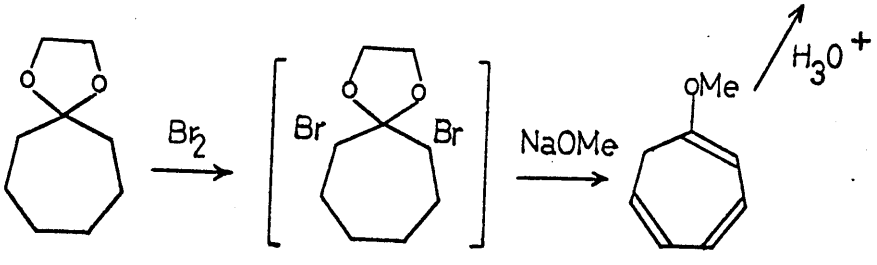

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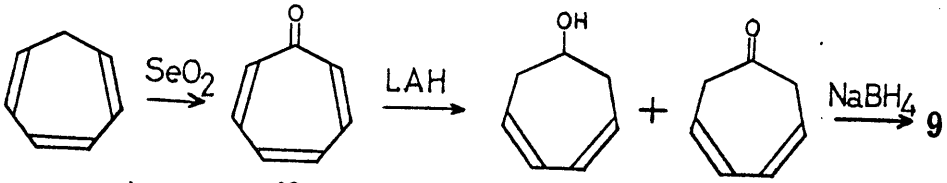

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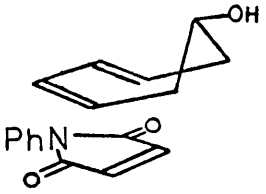

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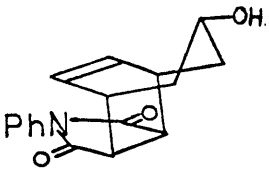

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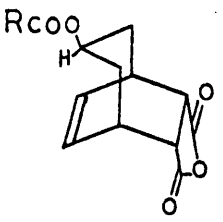
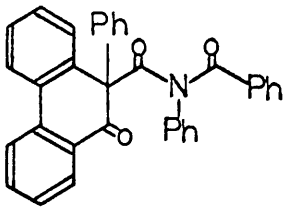


15 R= p-Br C_6H_4



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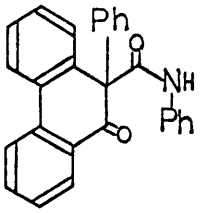

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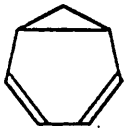

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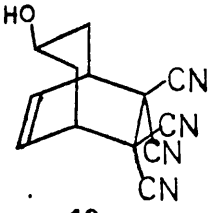

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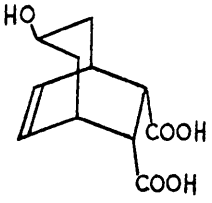

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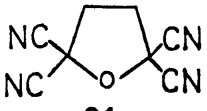

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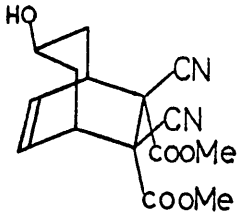

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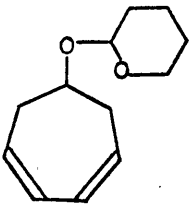

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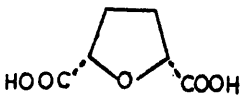

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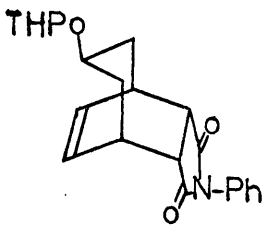

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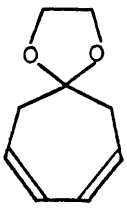

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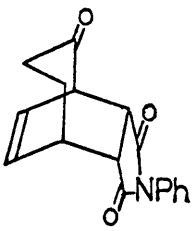

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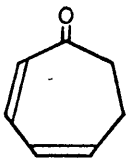

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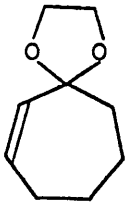

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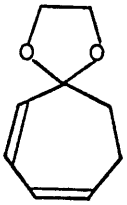
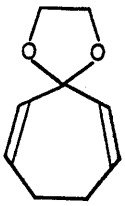
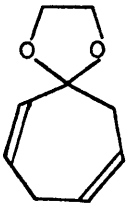


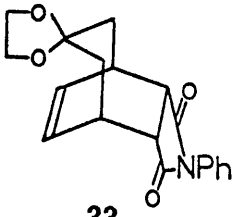
30



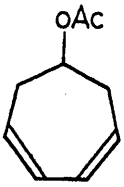
31



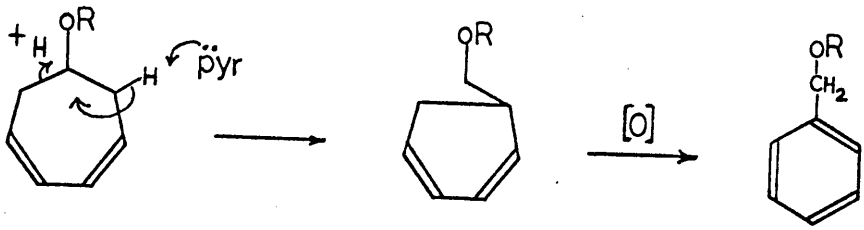
32



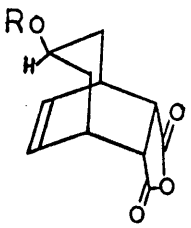
33



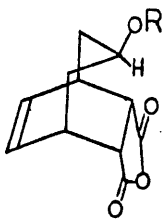
34



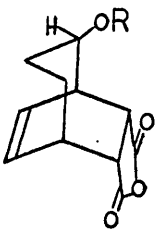
SCHEME 5



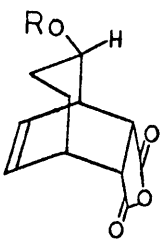
35 R=Meco
41 R=Phco



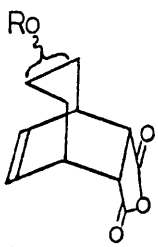
36 R=Meco
42 R=Phco



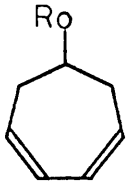
37 R=Meco



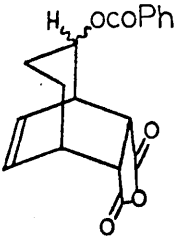
38 R=Meco



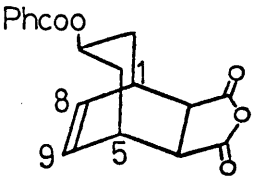
35a R=Meco
41a R=Phco



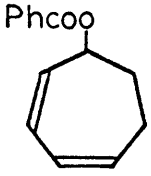
39 R=Phco
46 R=p-BrC_6H_4co



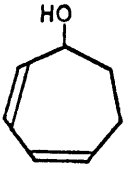
40



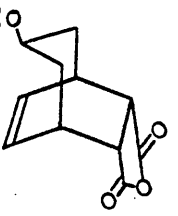
43



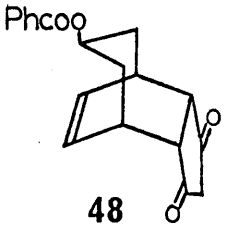
44



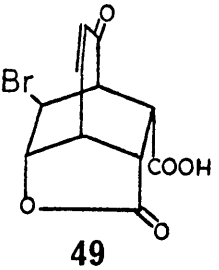
45



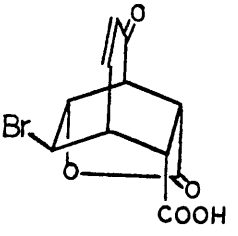
47 R=p-BrC_6H_4co



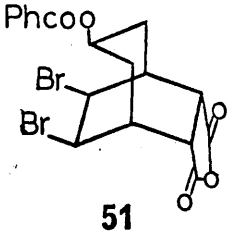
48



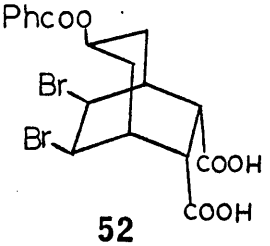
49



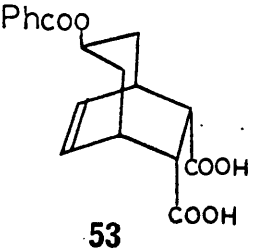
50



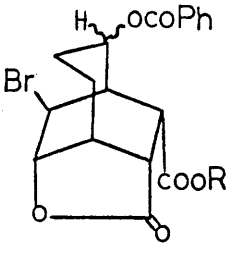
51



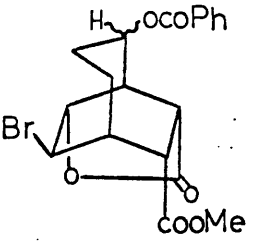
52



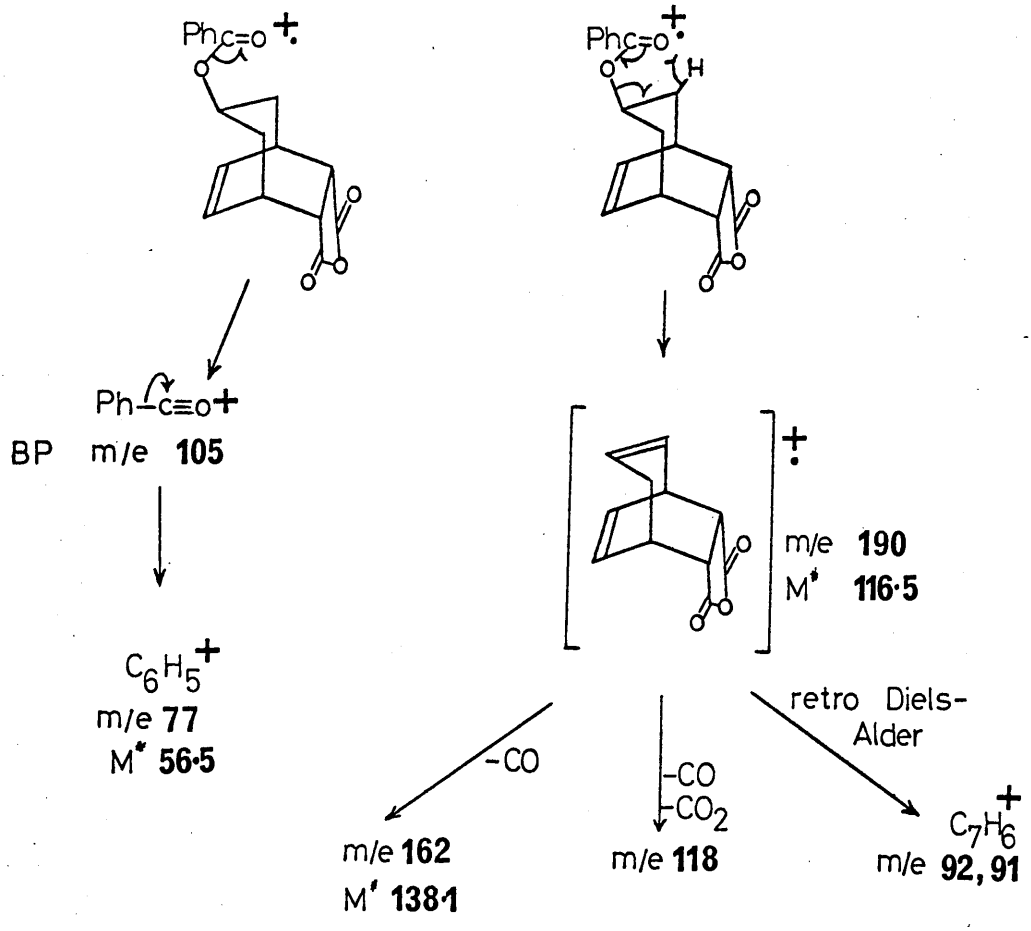
53



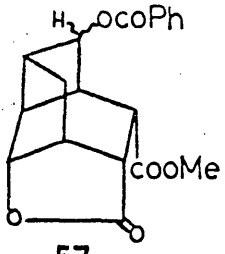
54 R=H
55 R=Me



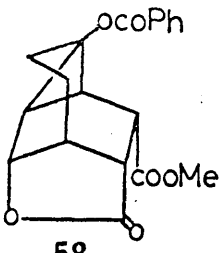
56


PhC≡O+·
Ph–C≡O+
BP m/e 105
C6H5+
m/e 77
M* 56·5
PhC≡O+·
H
m/e 190
M* 116·5
-CO
m/e 162
M* 138·1
-CO
-CO2
m/e 118
retro Diels-Alder
C7H6+
m/e 92, 91

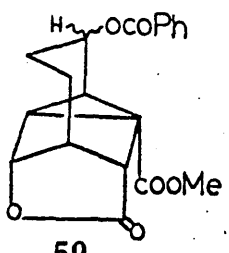
SCHEME 6



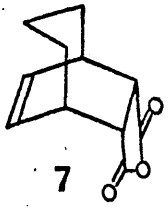
57



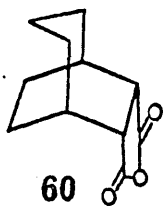
58



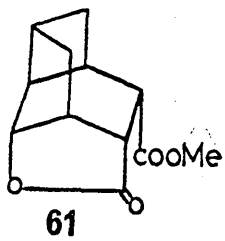
59



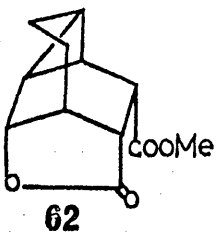
7



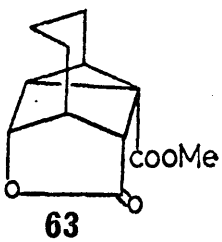
60



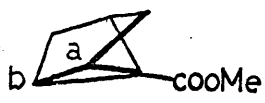
61



62



63



64

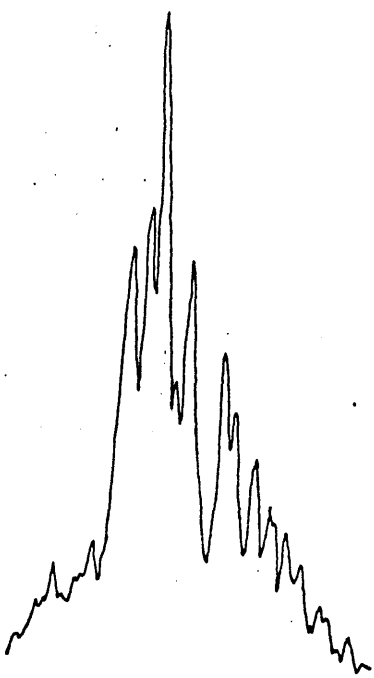
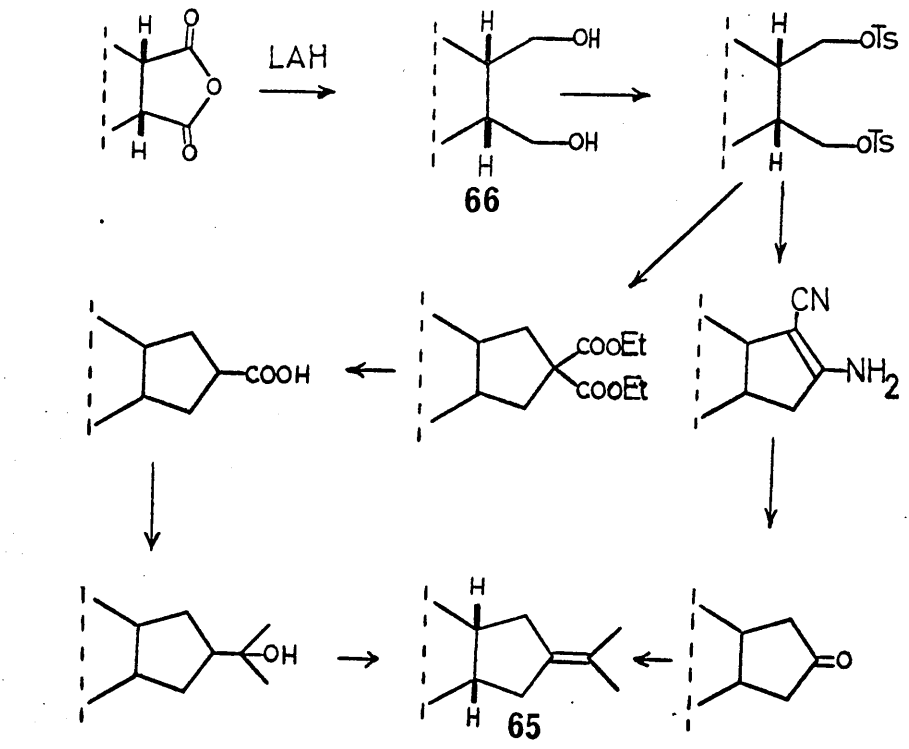
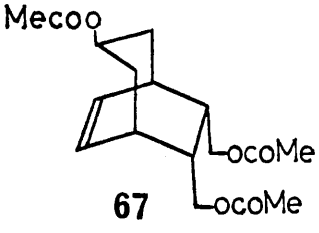


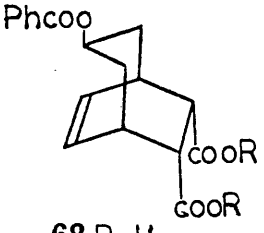
FIG I



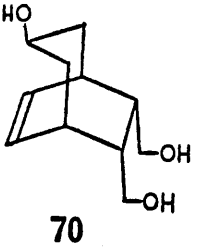
SCHEME 7



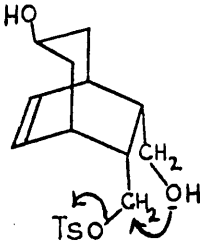
67



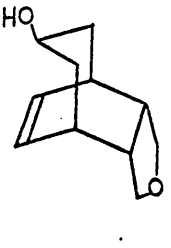
68 R=H
69 R=Me



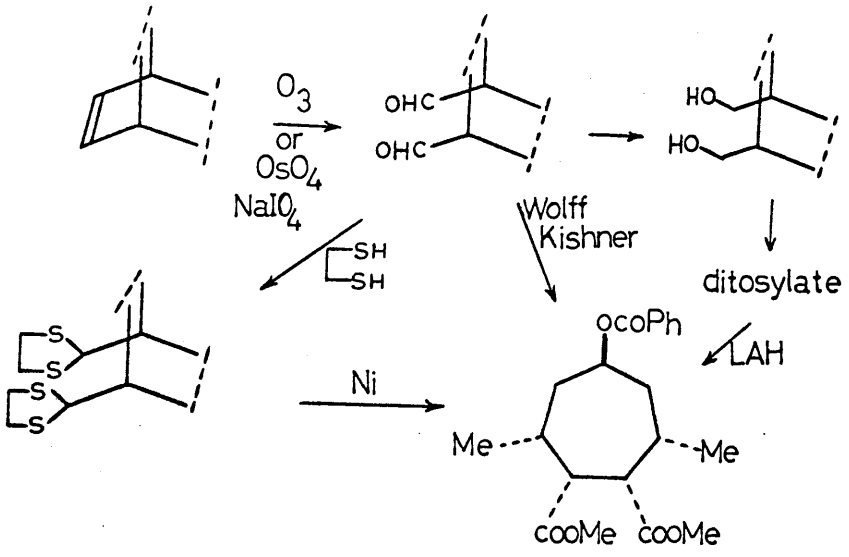
70



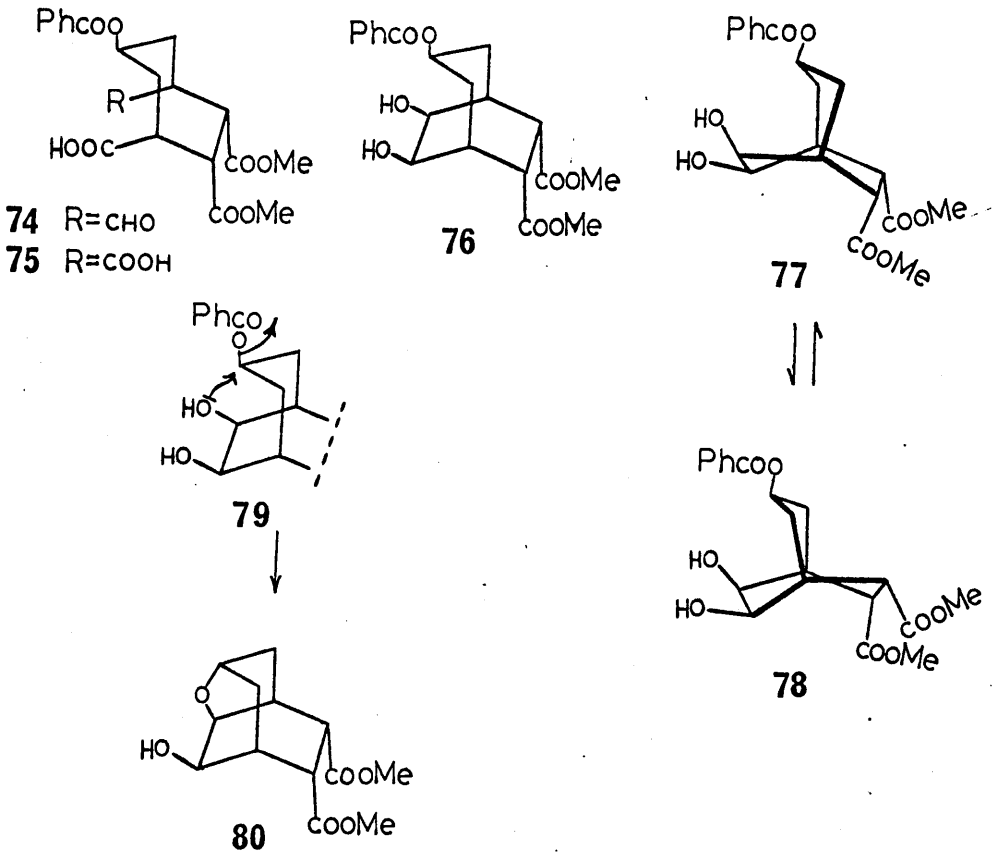
72

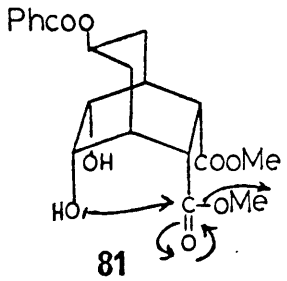


71

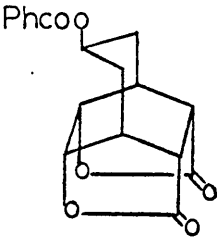

O3
or
OsO4
NaIO4
OHC
OHC
HO
HO
Wolff
Kishner
ditosylate
SH
SH
S
S
S
S
Ni
ocoPh
LAH
Me
Me
cooMe
cooMe
73

SCHEME **8**

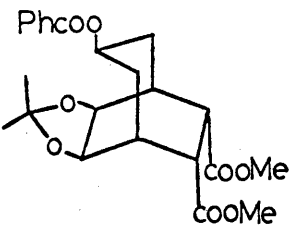

Phcoo
R
HOOC
cooMe
cooMe
74 R=CHO
75 R=COOH
Phcoo
HO
HO
cooMe
cooMe
76
Phcoo
HO
HO
cooMe
cooMe
77
Phco
O
HO
HO
79
Phcoo
HO
HO
cooMe
cooMe
78
O
HO
cooMe
cooMe
80



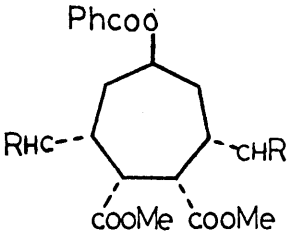
81



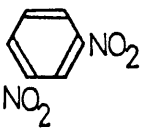
82

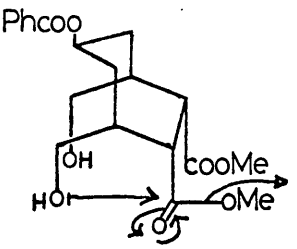


83

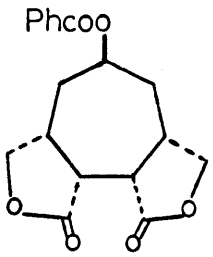


84 R=O

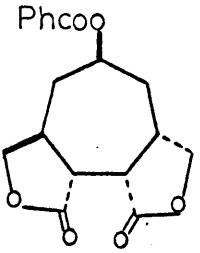
85 R= NNH 



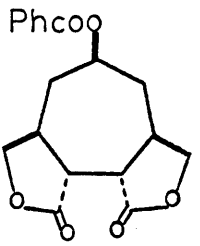
86



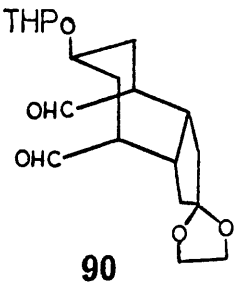
87



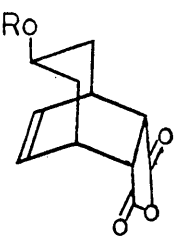
88



89

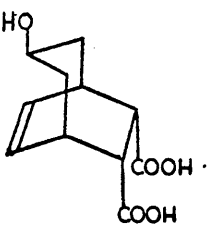


90



91 R=H

93 R=Meco



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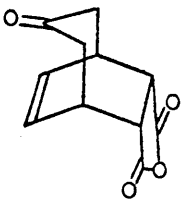

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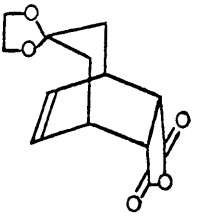

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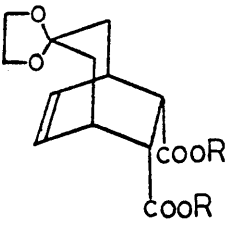
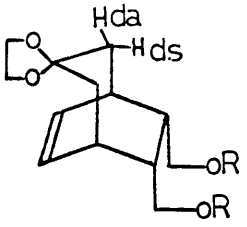
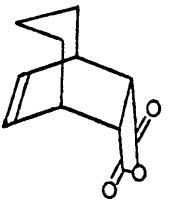


96 R=H
97 R=Me



98 R=H
106 R=Ms



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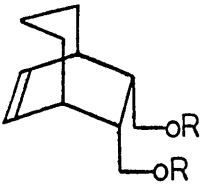
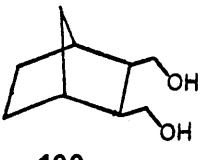


99 R=H
105 R=Ms



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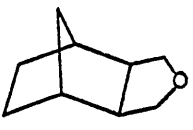

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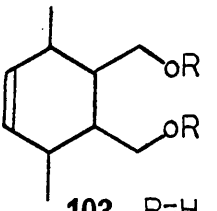
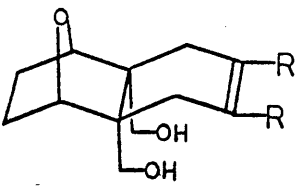


103 R=H
103a R= Ts



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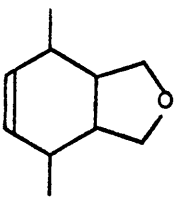

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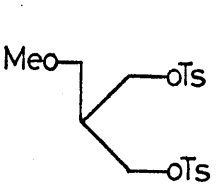

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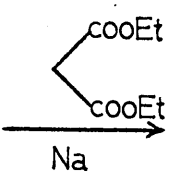

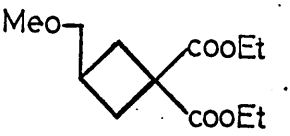

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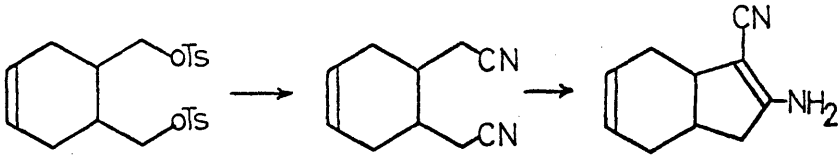

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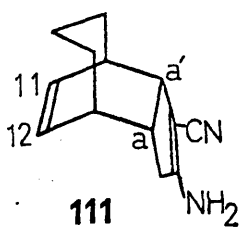

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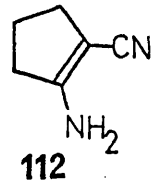

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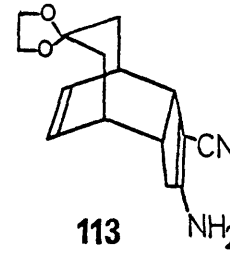

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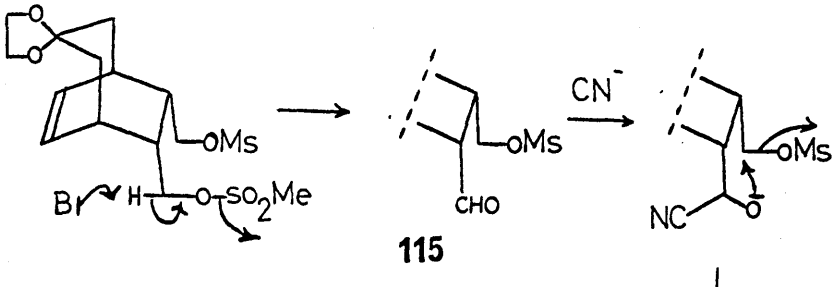

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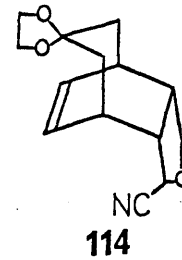
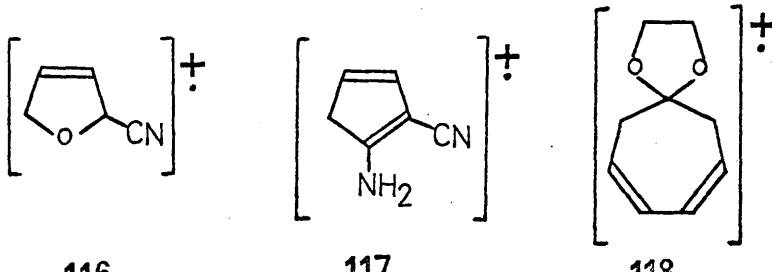


114

SCHEME 9



116 117 118

EXPERIMENTAL

Melting points were recorded on a Kofler microscope hot-stage and are uncorrected. Refractive indices were measured on an Abbe refractometer. Routine infra-red absorption spectra (liquid films and nujol mulls) were recorded on a Unicam S.P. 200 spectrophotometer and solution infra-red absorption spectra on a Unicam S.P. 100 double beam spectrophotometer, equipped with an S.P. 130 sodium chloride prism grating double monochromator operated under vacuum conditions.

Ultraviolet absorption spectra were recorded on a Unicam S.P. 800 spectrophotometer.

Nuclear magnetic resonance spectra (N.M.R.) were obtained on Perkin-Elmer R 10 and Varian HA 100 spectrometers, using approximately 0·3 molar solutions in deuterochloroform, unless otherwise stated, with tetramethyl silane as internal standard. Coupling constants (J) were measured in cycles per second (c.p.s.).

Gas liquid chromatography (G.L.C.) was carried out on a Pye Argon chromatograph equipped with a β-ionisation detector. Thin layer chromatography (T.L.C.) was carried out with silica [Kieselgel G (Merck) for analytical use, Kieselgel HF_{254} (Merck) for preparative purposes (prep.

T.L.C.)]. Retention factors (R_F) were those recorded using 35% ethyl acetate/benzene as eluant unless otherwise stated.

Mass spectra were recorded on an A.E.I. M.S. 9 spectrometer and coupled gas-chromatography - mass spectroscopy determinations (G.C.M.S.) were recorded on an L.K.B. 900 spectrometer. Figures quoted for molecular and other ions in the mass spectra refer to m/e values.

Petrol refers to light petroleum fraction, b.p. 40-60^{o} unless otherwise stated.

The seven-membered ring dienes used in the Diels-Alder reactions have been prepared as below.

(a) cyclohepta-1,3-diene

(b) cyclohepta-3,5-dienol (9)

(c) 1-tetrahydropyranyloxycyclohepta-3,5-diene (24)

(d) 1,1-ethylenedioxycyclohepta-3,5-diene (26)

(e) 1-acetoxycyclohepta-3,5-diene (34)

(f) 1-benzoyloxycyclohepta-3,5-diene (39)

(g) 1-p-bromobenzoyloxycyclohepta-3,5-diene (46)

Tropone (12).

Cycloheptatriene was oxidised with selenium dioxide as described in literature[24] to yield tropone (12), b.p. 58-60°/0·05 mm., 20% (lit. b.p. 91-92°/4 mm., 25%).

$\nu_{max.}^{cm.^{-1}}$ (film): 1735 (w), 1705 (s) (carbonyl);
1635 (s), 1585(s), 1522 (m), 1475 (m) (double bonds).

(a) Cyclohepta-1,3-diene

This was prepared as in literature[25] from cycloheptatriene by lithium-ammonia reduction at -60°. The colourless liquid distilled at b.p. 120-122° (lit. b.p. 121-122°/760 mm.,). The N.M.R. is shown in Table I.

(b) Cyclohepta-3,5-dienol (9).

Tropone (20 g., 0·188 mole) in dry ether (130 ml.,) was slowly added dropwise to a stirred suspension of lithium aluminium hydride (6·67 g., 0·175 mole) in dry ether (260 ml.,). The mixture was stirred at room temperature for a further 10 min., and then carefully quenched with hydrated sodium sulphate. The solution was diluted with ether, washed with brine and dried over sodium sulphate. Evaporation of the solvent in vacuo afforded an amber oil the infra-red spectrum of which showed absorption at 3500 $cm.^{-1}$ (hydroxyl), 1710 (s) $cm.^{-1}$ (ketone) and 1600 (w) $cm.^{-1}$ (double bond) which indicated the oil to be a mixture of cyclohepta-3,5-dienol (9) and cyclohepta-3,5-dienone (13) as reported.[8]

The oil, dissolved in AnalaR methanol (35 ml.,), was treated portionwise with sodium borohydride (30% excess) and allowed to stand for 4 hrs. After acidifying (H_2SO_4) the solution to pH7, the mixture was filtered. The filtrate

was poured into concentrated ammonium sulphate solution and the mixture extracted thoroughly with ether. The ethereal solution, after washing with brine, was dried over sodium sulphate and evaporated in vacuo. Distillation under reduced pressure yielded cyclohepta-3,5-dienol as an almost colourless oil (8·04 g., 39% from tropone) b.p. 86-90°/ 14 mm., n_D^{24} 1·5233, (lit. b.p. 45-52°/6 mm., n_D^{20} 1·5265). (Found: C, 76·22; H, 9·12. Calc. for $C_7H_{10}O$: C, 76·32; H, 9·15%).

$\nu_{max.}^{cm.^{-1}}$ (film): 3430 (s) (hydroxyl); 1615 (w) (double bond); 1060 (s), 1030 (s) (C-O); 695 (m) (cis db.)

$\lambda_{max.}^{EtOH}$ 244 mμ (ε, 5,770) [lit. 244 mμ (ε, 6,770)]

N.M.R. spectrum, Table I.

(c) 1-Tetrahydropyranyloxycyclohepta-3,5-diene (24).

Distilled dihydropyran (0·414 g., 0·0049 mole) in ether (1 ml.,) was added to cyclohept-3,5-dienol (9) (0·4624 g., 0·0042 mole) in ether (1 ml.,). The mixture was swirled and 1 small drop of concentrated hydrochloric acid added, after which the temperature rose by 3°. The solution was allowed to stand for 5 hrs., the excess dihydropyran removed in vacuo and the residue directly adsorbed on to preparative T.L.C. plates to yield the tetrahydro-

pyranyl ether (24) (0·766 g., 94%) as a colourless oil, b.p. 75-80°/0·1 mm., (sub. block).

(Found: C, 74·22; H, 8·75. $C_{12}H_{18}O_2$ requires: C, 74·19; H, 9·34%).

$\nu_{max.}^{cm.^{-1}}$ (film): 1615 (w) (double bond); 1130 (m), 1040 (s) (C-O); 700 (w) (cis d.b.).

$\lambda_{max.}^{EtOH}$ 243 mμ (ε, 5,900)

N.M.R. spectrum, Table I.

(d) Cycloheptanone ethylene ketal

Cycloheptanone (59·1 g., 0·528 mole), ethylene glycol (167·95 g., 2·71 mole) and p-toluenesulphonic acid (1·0 g.,) were refluxed in benzene with water separation for 1½ days. The product was isolated with ether and distilled under reduced pressure to yield a colourless liquid, b.p. 100-103°/20 mm., $n_D^{25·5}$ 1·4670, (63·43 g., 77%)

$\nu_{max.}^{cm.^{-1}}$ (film): 1125 (s), 1100 (s), 1075 (s), 960 (m) (C-O)

1-Methoxycyclohepta-1,3,5-triene (11).

This was prepared by the method of Garbisch[7] by dibromination in a hydroxylic solvent followed by dehydrobromination with sodium methoxide in dimethyl sulphoxide. The ketal (15·6 g., 0·10 mole) in methanol (250 ml.,) was

stirred and treated dropwise with bromine (32 g., 0·2 mole) without allowing the colour to vanish at any point. Towards the end of the second equivalent the colour became orange and when addition was complete, sodium methoxide (approx. 12·8 g.,) was added until the solution was neutral. The solution was poured on to water (600 ml.,) and extracted thoroughly with pentane, after which the organic layer was washed with brine and dried over sodium sulphate. Evaporation in vacuo yielded an opaque oil which was dissolved in pure dimethyl sulphoxide (100 ml.,) and sodium methoxide (13 g., 0·24 mole) added carefully with cooling in ice. The solution was left overnight at room temperature, poured into brine (400 ml.,) and extracted with pentane. After drying over sodium sulphate, the solvent was removed carefully at atmospheric pressure. The triene ether (11) obtained by distillation at reduced pressure was an almost colourless liquid, b.p. 84-88°/10 mm., (9·64 g., 79%) (lit. 54·5-55·5°/5·4 mm., 53%).

$\nu_{max.}^{cm.^{-1}}$ (film): 1617 (m) (double bond); 700 (m) (double bond)

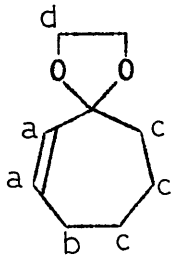
Using ethylene glycol as solvent instead of methanol, the ketal underwent only one bromination and therefore dehydro-

brominated to give 3,3-ethylenedioxycyclohept-1-ene (29) as a colourless liquid b.p. 81-83°/9 mm., $n_D^{20\cdot5}$ 1·4883, (yield 82%).

$\nu_{max.}^{cm.^{-1}}$ (film): 1660 (m) (double bond); 1110 (s), 1070 (s) 990 (m), 960 (m) (C-O); 700 (m) (cis d.b.)

N.M.R.

(CCl_4)



H_a 4·30 τ (2H, multiplet)

H_b 7·88 τ (2H, broad absorption)

H_c 8·24 τ (6H, multiplet)

H_d 6·12 τ (4H, singlet)

Cyclohepta-3,5-dienone (13).

Hydrolysis of the triene ether (11) was accomplished by the method of Garbisch,[7] using sulphuric acid (10%), stirring for 15 hrs., at room temperature. Distillation, under reduced pressure, of the isolated product gave cyclohepta-3,5-dienone (13) as a pale yellow oil, b.p. 69-71°/18 mm., (yield 48%) (lit. b.p. 54°/5·4 mm., 81%).

$\nu_{max.}^{cm.^{-1}}$ (film): 1715 (s) (ketone); 1600 (m) (double bond); 700 (s) (cis d.b.)

(Since the compound was rather unstable, it was not further characterised and was immediately ketalised.)

1,1-Ethylenedioxycyclohepta-3,5-diene (26).

Ethylene glycol (3·8 g., 0·061 mole), p-toluene-sulphonic acid (10 mg.,) and benzene (30 ml.,) were refluxed with water separation for 1 hr. The ketone (0·372 g., 0·0035 mole) was added in benzene (5 ml.,) and the reflux continued for 12 hrs. Evaporation in vacuo yielded an amber residue which was diluted with ether, washed with sodium bicarbonate (5%) and brine and dried over sodium sulphate. The infra-red spectrum of the residue showed no carbonyl absorption:

$\nu_{max.}^{cm.^{-1}}$ (film): 1610 (m) (double bond); 1110 (s), 1040 (s) (C-O).

T.L.C. of the oil showed it to consist of two main components A, R_F 0·7 and B, R_F 0·3 which were isolated by preparative T.L.C. The less polar component A, (179 mg., 34%) was shown to be the required diene ketal (26), b.p. 103-106°/ 10 mm., (sub. block).

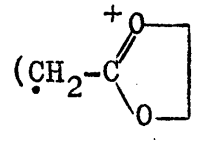
(Found: C, 70·96; H, 8·11. $C_9H_{12}O_2$ requires: C, 71·03; H, 7·95%).

$\nu_{max.}^{cm.^{-1}}$ (film): 1614 (m) (double bond); 1128 (s), 1107 (s), 1038 (s), 1028 (s), 944 (m) (C-O); 695 (s) (cis d.b.).

$\lambda_{max.}^{EtOH}$ 239 mμ (ε, 5,980).

N.M.R. spectrum, Table I.

Mass spectral determination showed a parent ion m/e 152 ($C_9H_{12}O_2$ requires 152) and a base peak m/e 86



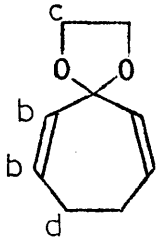
).

The second component B, (27·6 mg., 5%), b.p. 120-125°/10 mm., (sub. block) (with charring) was presumed to be a mixture of isomeric ketals (30) and (31) from the spectroscopic data given below:

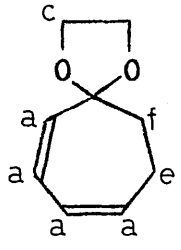
$\nu_{max.}^{cm.^{-1}}$ (film): 1620 (s) (double bond); 1160 (m), 1090 (m) (C-O).

$\lambda_{max.}^{EtOH}$ 212 mμ(ε, 6,680), 289·5 mμ (ε, 3,180)

N.M.R.



(31)



(30)

ratio ~ 1:1

H_a 3·59 τ (2H, multiplet)

H_b 4·55 τ (2H, multiplet)

H_c 6·10 τ (4H, singlet)

H_d 7·41 τ (2H, doublet, J = 8)

H_e 7·65-8·15 τ (ca 2H,

H_f broad multiplet)

(e) 1-Acetoxycyclohepta-3,5-diene (34).

To cyclohepta-3,5-dienol (1·1256 g., 0·0102 mole) in dry pyridine (15 ml.,), acetic anhydride (AnalaR, 15 ml.,) was added with swirling and the mixture allowed to stand overnight. After hydrolysing with water, the solution was diluted with ether and washed successively with sulphuric acid (3N), sat$^{d.}$ sodium bicarbonate and brine. After drying over sodium sulphate, evaporation in vacuo produced a sweet smelling brown oil which distilled under reduced pressure to yield the acetate (34) as a colourless, volatile liquid, b.p. 90-95°/1 mm., n_D^{26} 1·4891,(1·0779 g., 65%).

$\nu_{max.}^{cm.^{-1}}$ (film): 1735 (s) (ester); 1240 (s) (C-O); 705 (m) (cis d.b.)

$\lambda_{max.}^{EtOH}$ 242·5 mμ (ε, 6,160) N.M.R. Spectrum, Table I.

(Found: C, 71·17; H, 8·17. $C_9H_{12}O_2$ requires: C, 71·02; H, 7·95%).

It was noticed that on some occasions preparation of the compound led to mixtures of the acetate (34) and a re-arranged oxidation product, benzyl acetate. The mixture was illustrated by the N.M.R. spectrum which was compared with that of authentic benzyl acetate i.e. 2·68 τ (singlet, aromatic protons), 4·92 τ (singlet, benzylic methylene) and 7·93 τ (singlet, acetate).

(f) 1-Benzoyloxycyclohepta-3,5-diene (39).

Cyclohepta-3,5-dienol (9) (9·35 g., 0·085 mole) in dry pyridine (80 ml.,) was treated with redistilled benzoyl chloride (13·5 g., 0·096 mole), added slowly in portions with swirling and cooling in ice. After allowing to stand overnight, the excess acid chloride was hydrolysed with water and the solution extracted with excess ether. After washing the ethereal extract with sulphuric acid (3N), sodium bicarbonate ($sat^{d.}$) and brine, the solution was dried over sodium sulphate. Distillation under reduced pressure afforded the benzoate (39) (16·0 g., 88%) as a pale yellow oil, b.p. 99-103°/0·005 mm., $n_D^{23·5}$ 1·4802.

(Found: C, 78·20; H, 6·43. $C_{14}H_{14}O_2$ requires: C, 78·48; H, 6·59%).

$\nu_{max.}^{cm.^{-1}}$ (film): 1715 (s)(benzoate);1600(w), 1585(w)(aromatic); 1275 (s), 1115 (m) (C-O); 725 (s) (aromatic).

$\lambda_{max.}^{EtOH}$ 230·5 mμ (ε, 12,600), 208·5 mμ ($\varepsilon_{app.}$ 9,350).

N.M.R. Spectrum, Table I.

(g) 1-p-Bromobenzoyloxycyclohepta-3,5-diene (46).

This compound, obtained as pale yellow prisms, m.p. 57-59° from methanol, was prepared in a completely analogous manner and was purified by preparative T.L.C. (yield 44%).

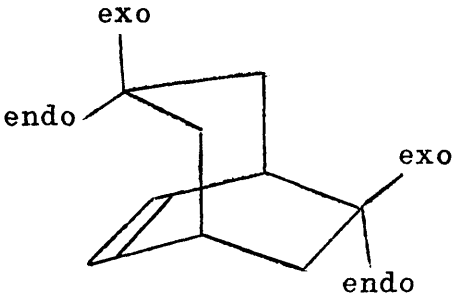
$\nu_{max.}^{cm.^{-1}}$ (melt): 1715 (s) (benzoate); 1590 (s) (aromatic); 1275 (s), 1125 (s), 1110 (s) (C-O); 863 (m), 770 (s), 695 (m) (aromatic and cis d.b.).

$\lambda_{max.}^{EtOH}$ 244·5 mμ (ε, 23,000), 206 mμ ($\varepsilon_{app.}$ 13,850).

(Found: C, 57·42; H, 4·49. $C_{14}H_{13}O_2Br$ requires: C, 57·33; H, 4·47%).

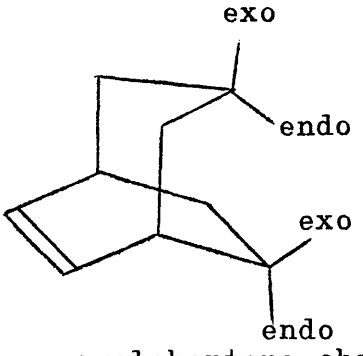
N.M.R. spectrum, Table I.

Diels-Alder reactions were carried out with the above diene derivatives using a variety of dienophiles i.e., N-phenylmaleimide, maleic anhydride, cyclopentenedione, tetracyanoethylene. The notation used to describe the bicyclic products is as follows:-



cycloheptene boat

anti



cycloheptene chair

syn

(a) Anti-3-exo-hydroxybicyclo[3,2,2]non-8-ene-6,7-endo-dicarboxylic acid N-phenylimide (5) (cyclohepta-3,5-dienol and N-phenylmaleimide)

Cyclohepta-3,5-dienol (9) (0·5021 g., 0·0046 mole) and N-phenylmaleimide (0·8233 g., 0·0048 mole) in benzene (15 ml.,) were refluxed[3] under an atmosphere of nitrogen for 7 days. On cooling, a light brown solid precipitated (0·5320 g., 41%) which was recrystallised from benzene to give the title compound (5) as colourless prisms, m.p. 186-188·5° (lit.[3] m.p. 185-188°, 33%). An analytical sample was obtained by repeated sublimation.

(Found: C, 72·30; H, 5·70; N, 5·04. Calc. for $C_{17}H_{17}O_3N$: C, 72·07; H, 6·05; N, 4·94%).

$\nu_{max.}^{cm.^{-1}}$ (CCl_4): 3620 (s) (hydroxyl); 1719 (s) (imide carbonyl).

The mass spectral determination showed a parent m/e 283 ($C_{17}H_{17}O_3N$ requires 283) and a base peak m/e 91.

N.M.R. is discussed in Part II.

Attempted preparation of anti-3-exo-hydroxybicyclo[3,2,2] non-8-ene-6,7-endo-dicarboxylic acid.

The adduct (5) was treated with both aqueous acidic and basic reagents under refluxing conditions for several hours. In every case, the starting adduct was isolated, the structure being obvious from T.L.C. and I.R.

(b) Anti-tricyclo[3,2,2,$0^{2,4}$]non-8-ene-6,7-endo-dicarboxylic acid anhydride (6); (Cyclohepta-3,5-dienol and maleic anhydride).

Cyclohepta-3,5-dienol (0·339 g., 0·0031 mole) in benzene (4 ml.,) was added to maleic anhydride (0·327 g., 0·0033 mole) in benzene (4 ml.,) and the resulting mixture refluxed under nitrogen for 7 days. Since cooling afforded no precipitate, the solvent was evaporated in vacuo and the

residual oil extracted with hot petrol. On cooling the petrol solution, an off-white solid (0·1257 g., 22%) was obtained which crystallised from diisopropyl ether as colourless platelets, m.p. 101-103°, and was identified as the cyclopropane derivative (6) (lit.[4] m.p. 102-104°) by I.R., T.L.C. and N.M.R. comparison with an authentic sample obtained in high yield by reaction of cycloheptatriene with maleic anhydride by the method of Kohler.[4]

(Found: C, 69·46; H, 5·30. Calc. for $C_{11}H_{10}O_3$: C, 68·92; H, 5·21%).

$\nu_{max.}^{cm.^{-1}}$ (NUJOL): 1850 (m), 1815 (m), 1770 (s) (anhydride); 750 (m), 740 (m) (cis d.b.)

N.M.R. spectrum is discussed in Part II.

(c) Anti-3-hydroxy-6,6,7,7-tetracyanobicyclo[3,2,2]non-8-ene (19). (Cyclohepta-3,5-dienol and tetracyanoethylene).

Tetracyanoethylene (0·289 g., 0·00226 mole) in tetrahydrofuran (dried over calcium hydride) (1·5 ml.,) was added to cyclohepta-3,5-dienol (0·248 g., 0·00226 mole) in tetrahydrofuran (1·5 ml.,). The resulting solution which became red immediately was left for 15 hrs. The solvent was removed in vacuo to yield a dark oil from which the tetracyano adduct (182·9 mg., 34%) could be obtained as a

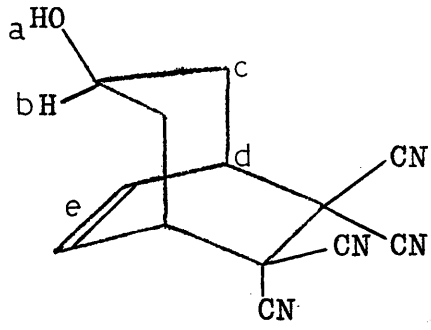
grey solid by crystallisation from ethyl acetate/petrol. Preparative T.L.C. of the mother liquor afforded further solid, R_F 0·2, to give a total yield of 45%. Recrystallisation from ethyl acetate/petrol afforded the tetracyano alcohol (19) as pale yellow platelets, m.p. 213·5-217·5°.

(Found: C, 65·43; H. 4·47; N. 23·84. $C_{13}H_{10}ON_4$ requires: C, 65·53; H, 4·23; N, 23·52%).

$\nu_{max.}^{cm.^{-1}}$ (KCl): 3380 (m), 3275, 3256 (hydroxyl); 2256 (w) (C≡N); 1674 (s) (double bond); 723 (s) (cis d.b.).

Mass spectral determination gave a parent ion m/e 238 $C_{13}H_{10}ON_4$ requires 238) and base peak m/e 41.

N.M.R.



CH_3CN

H_a 2·17 τ (broad absorption)

H_b 5·78 τ (multiplet)

H_e 3·85 τ (multiplet)

Pyridine

H_c 7·85 τ (multiplet)

H_d 6·40 τ (broad absorption)

Hydrolysis of Anti-3-hydroxy-6,6,7,7-tetracyanobicyclo [3,2,2]non-8-ene (19).

(i) Hydrochloric acid (concentrated).

The tetracyano alcohol (97·1 mg., 0·00041 mole) was dissolved in conc$^{d.}$ hydrochloric acid (2 ml.,) and the yellow solution refluxed for 16 hrs. After cooling, the aqueous solution was extracted continuously with ether for 12 hrs. Evaporation in vacuo afforded a heavy oil which had an acidic R_F value by T.L.C. This residue (in methanol) was directly esterified with diazomethane, affording, after filtration through celite, 3-hydroxy-6,7-dicyano-6,7-dicarbomethoxybicyclo[3,2,2]non-8-ene (23) as a pale yellow solid (22 mg., 18%). On recrystallisation from ether, colourless plates were obtained and an analytical sample was prepared by repeated sublimation, 220°/0·25 mm., m.p. 270-275°.

(Found: C, 59·70; H, 5·40; N, 9·38. $C_{15}H_{16}O_5N_2$ requires: C, 59·20; H, 5·30; N, 9·21%).

$\nu_{max.}^{cm.^{-1}}$ (KCl): 3556 (s), 3436 (m) (hydroxyl); 1735 (s) (ester); 723 (s) (cis d.b.) (no absorption attributable to a cyano group was observed).

Prolonged heating (3½ days) afforded the same product.

(ii) Sulphuric acid (conc$^{d.}$)

The tetracyano alcohol (17 mg.,) was treated with cold concentrated sulphuric acid (1 ml.,) and stirred for 5 min. The solution was poured on to ice and the product isolated with ether. The I.R. of the gum isolated showed hydrogen bonding, carbonyl absorption at 1755 cm.$^{-1}$ with a shoulder at 1710 cm.$^{-1}$ and weak absorption at 2300 cm.$^{-1}$ (C≡N).

(iii)

Refluxing the tetracyano alcohol (19) with potassium hydroxide (35%) for 2 days and isolation with chloroform led to unidentified acidic products showing I.R. absorption at 3300 cm.$^{-1}$ (N-H), a broad carbonyl region and cyano absorption (2300 cm.$^{-1}$).

(d) Attempted reaction of 1-tetrahydropyranyloxycyclohepta-3,5-diene (24) and maleic anhydride.

The diene (24) and maleic anhydride were heated at reflux temperature under an atmosphere of nitrogen in benzene, toluene and xylene for prolonged periods. In the cases of benzene and toluene, T.L.C. and I.R. showed

essentially starting materials together with unidentified acidic species. With xylene as solvent, much of the material polymerised and no well-defined product could be isolated.

(e) 3-Tetrahydropyranyloxybicyclo[3,2,2]non-8-ene-6,7-endo-dicarboxylic acid N-phenyl imide (25).

(1-tetrahydropyranyloxycyclohepta-3,5-diene (24) and N-phenyl maleimide).

The tetrahydropyran derivative (24) (0·193 g., 0·001 mole), N-phenylmaleimide (0·346 g., 0·002 mole) and hydroquinone (2 mg.) were refluxed in toluene (8 ml.,) under an atmosphere of nitrogen for 24 hrs. The solvent was evaporated in vacuo, the residue, on crystallisation from diisopropyl ether, affording a mixture of N-phenylmaleimide and the colourless adduct (25). However, careful recrystallisation of the mixture from diisopropyl ether/ ethyl acetate afforded the title compound (25) as a colourless solid, m.p. 140·5-143°, (34·5 mg., 10%).

(Found: C, 71·86; H, 7·04. $C_{22}H_{25}O_4N$ requires: C, 71·91; H, 6·86%).

$\nu_{max.}^{cm.^{-1}}$ (NUJOL): 1705 (s) (imide); 750 (s) (aromatic); 695 (w) (cis d.b.).

The mass spectrum showed a parent ion m/e 367 ($C_{22}H_{25}O_4N$ requires 367), a base peak m/e 91 and a large ion m/e 41.

N.M.R. : 3·83 τ (quartet, obs.splittings 5 and 4 cps)(vinylic HS)

6·50 τ (singlet) (exo H_6, H_7)

Due to neighbouring absorptions, the signal at 6·50 τ could not be rigorously determined as a singlet (indicative of exo protons)

The experiment, carried out using xylene as a solvent, resulted in mixtures of unidentifiable products and polymer, caused presumably by the higher reaction temperature .

(f) Attempted reaction of 1,1-ethylenedioxycyclohepta-3,5-diene and maleic anhydride.

The conditions of reaction were exactly those as in (g). By T.L.C., it was shown that the product was essentially starting ketal with other minor unidentifiable products.

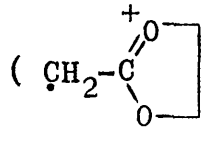
(g) 3,3-Ethylenedioxybicyclo[3,2,2]non-8-ene-6,7-endo-dicarboxylic acid N-phenyl imide (33).

(1,1-ethylenedioxycyclohepta-3,5-diene and N-phenylmaleimide)

The ketal (26) (52·6 mg., 0·00034 mole) and N-phenylmaleimide (118·5 mg., 0·00068 mole) in toluene (15 ml.) were refluxed under a nitrogen atmosphere in the presence of hydroquinone (2 mg.,) as a radical inhibitor. After evaporation of the solvent in vacuo, crystallisation from diisopropyl ether afforded a mixture of N-phenylmaleimide and the adduct (33). The N-phenylmaleimide was removed by dissolution in ethyl acetate, the adduct (2·5 mg.,) being completely insoluble. Preparative T.L.C. of the residue from the initial crystallisation afforded additional adduct (1·1 mg.,) (R_F 0·3, 10% ethyl acetate/benzene), thus giving a total yield of 3·6 mg., (3·2%). The combined product on recrystallisation from ether/diisopropyl ether afforded the title compound (3·1 mg.,) as colourless needles, m.p. 207-209°.

$\nu_{max.}^{cm.^{-1}}$ (NUJOL): 1707 (s) (imide); 1190 (s), 1095 (m), 1080 (m), 960 (w) (C-O); 760 (m), 735 (w), 700 (w) (aromatic and cis d.b.)

The mass spectrum, determined by G.C.M.S., showed a parent ion m/e 325 ($C_{19}H_{19}O_4N$ requires 325) and a base peak m/e 86



G.L.C.

Column 1% SE30, Temp. 200°, F.R. 34 ml./min.

R_t 20·1 min.

(h) Acetoxybicyclo[3,2,2]non-8-ene-6,7-endo-dicarboxylic acid anhydrides(35a)

(1-acetoxycycloheptа-3,5-diene and maleic anhydride)

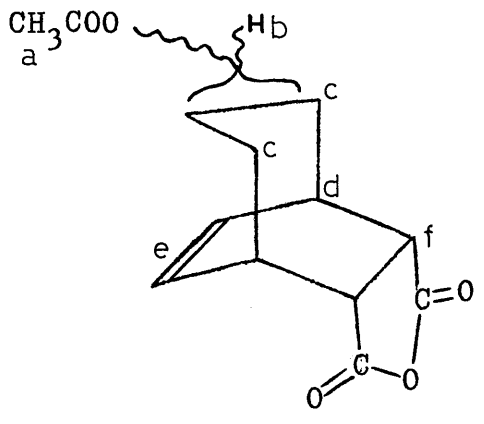
The diene (34) (0·4287 g., 0·00283 mole) and maleic anhydride (0·304 g., 0·0031 mole) were refluxed in xylene (20 ml.,) for 24 hrs., in an atmosphere of nitrogen. On cooling no solid appeared and the solvent was removed in vacuo, leaving an amber oil which could not be crystallised. Preparative T.L.C. of the mixture afforded the acetate adducts(35a), R_F 0·5, as a pale yellow oil (0·3428 g., 49%).

$\nu_{max.}^{cm.^{-1}}$ (film): 1865 (m), 1840 (m), 1780 (s) (anhydride); 1735 (s) (acetate).

The oil partially crystallised from chloroform/petrol but was still contaminated with starting diene acetate (34). Purification was finally effected by repeated distillation b.p. 140-145°/0·05 mm. (sub. block) and was analysed as an oil.

(Found: C, 62·05; H, 6·14. $C_{13}H_{14}O_5$ requires: C, 62·39; H, 5·64%).

N.M.R.



H_e 3·77 τ (2H, quartet, obs. splittings 5 and 3·5 cps)

H_b 5·10 τ (1H, multiplet)

H_f 6·41 τ, 6·50 τ (2H, singlets)

H_d 6·91 τ (broad absorption)

H_c 7·6–8·6 τ (multiplet)

H_a 7·97 τ, 7·94 τ (3H, singlets)

Additional small signals at 3·62 τ, 3·90 τ, 6·53 τ, 6·63 τ. This evidence suggested a mixture of acetate epimers but the spectrum was not well defined enough for confirmation. G.L.C. of the N.M.R. sample showed it to be a mixture of four components in approximately equal amounts, indicating a mixture of C_2 and C_3 stereoisomers [cf. (i) below].

Column. 1% QFI Temp. 175° F.R. 45 ml./min.

R_{ta} 15·1 min. R_{tb} 17·9 min. R_{tc} 20·5 min.

R_{td} 23·3 min.

Since these compounds could not be separated, this Diels-Alder reaction was not investigated further.

(i) 3-Benzoyloxybicyclo[3,2,2]non-8-ene-6,7-endo-dicarboxylic acid anhydride (41) and isomers.

(1-benzoyloxycyclohepta-3,5-diene and maleic anhydride)

The diene (39) (0·4116 g., 0·00192 mole) and maleic anhydride (0·2102 g., 0·00214 mole) were refluxed in xylene (10 ml.,) for 7 days under an atmosphere of nitrogen. Since no precipitate was obtained on cooling, the solvent was evaporated in vacuo. On addition of diisopropyl ether, a brown semisolid was obtained and an analytical sample (R_F 0·75) was prepared by preparative T.L.C. The adducts (41a) melted over a range, approximately 130-136°, but analysed correctly:

(Found: C, 69·23; H, 4·96. $C_{18}H_{16}O_5$ requires: C, 69·22; H, 5·16%).

$\nu_{max.}^{cm.^{-1}}$ (CCl_4): 1872 (m), 1834 (m), 1784 (s) (anhydride); 1723 (s) (benzoate).

The mass spectral determination gave a parent ion m/e 312 ($C_{18}H_{16}O_5$ requires 312). That the material obtained was a mixture of isomeric adducts was confirmed by G.L.C.

Column	Temp.	F.R. ml./min.	R_t min.
1% SE30	200°	53	7·65, 8·10 (shoulder), 9·35
1% DC-710	200°	47	26, 31, 33 (shoulder)

The N.M.R. of this sample indicated a mixture, although a large singlet at 6·32 τ suggested predominance of an isomer with C_6, C_7 exo protons (C_6, C_7 endo protons would be expected to show coupling with the bridgehead protons, Part II).

This reaction was further investigated varying the time and amount of solvent. The optimum conditions found were as below.

The benzoyloxydiene (39) (11·0 g., 0·057 mole) and maleic anhydride (6·01 g., 0·061 mole, purified) were stirred vigorously in dry xylene (40 ml.,) with hydroquinone as a radical inhibitor in an atmosphere of nitrogen. The solution was heated at reflux temperature for 24 hrs., and allowed to cool completely to room temperature by which time a white solid had precipitated. The solid was collected, washed with cold xylene and sucked dry on the water pump . After drying at 50° for several hours, the white powder (5·962 g.,) was recrystallised from chloroform/diisopropyl ether to yield a compound, endo A, the anti exo benzoate (41) as colourless platelets m.p. 222-225°, 5·30 g., (33%). The filtrate on evaporation afforded a gum which resisted crystallisation. It was chromatographed on an Alumina column (Woelm, acid-washed, 200 g.,). Elution with benzene,

followed by ether/benzene (4%) mixtures afforded only starting diene (39), but further elution with ether/benzene (8-16%) produced a compound, endo B, the syn exo benzoate (42) in low yield which recrystallised from chloroform/diisopropyl ether as platelets, m.p. 196-199°. Further elution [ether/benzene (32-100%)] afforded another isomer, iso A (40), in modest yield which crystallised also from chloroform/diisopropyl ether as platelets m.p. 152-155°. Continued elution with ether gave more of these materials but contaminated with acidic species. T.L.C. of these isomers showed iso A to be more polar than endo A and endo B (endo A, endo B, R_F 0·7; iso A, R_F 0·6). These isomers were characterised in addition by G.L.C.

Column: 1% QFI Temp: 210° F.R. 42 ml./min.

R_t in inches t = trace

endo A		endo B		iso A	
crude	rex.	crude	rex.	crude	rex.
3·94	3·94	3·91(t)			
3·25(t)		3·25	3·25		
				3·29(t)	
				4·00	4·01

Thus repeated crystallisation afforded an analytical sample of the three above isomers. The other component contaminating the originally eluted fractions of iso A i.e. R_t 3·29 may well be the epimer of iso A, namely iso B, but it could not be obtained free of iso A and appeared to be in trace amounts.

In another experiment, the filtrate of the initial crystallisation of endo A was evaporated in vacuo, diluted with ether and allowed to crystallise over a 2 hr. period. The filtrate was again diluted and the process repeated giving successive batches of crystals. The composition of the batches was followed by T.L.C. and G.L.C., endo A and endo B crystallising before the iso compound. Using the peak areas, the total amount of each isomer was calculated to be: endo A 34%, endo B 11%, iso A 18%; total yield 63%.

The infra-red spectra, N.M.R. spectra (Part II) and mass spectra of the isomers were compared, (Tables II and III).

(j) Anti-3-exo-p-bromobenzoyloxybicyclo[3,2,2]non-8-ene-6,7-endo-dicarboxylic acid anhydride (47).

(1-p-bromobenzoyloxycyclohepta-3,5-diene (46) and maleic anhydride).

The diene (46) (0·2538 g., 0·00087 mole) and maleic anhydride (0·110 g., 0·00112 mole) were treated

exactly as in the above case (i). An off-white solid (61·8 mg., 18%) crystallised from the medium on cooling. Repeated crystallisation from ethyl acetate/diisopropyl ether afforded the p-bromobenzoyloxy anhydride (47) as colourless prisms, m.p. 116-117°.

$\nu_{max.}^{cn.^{-1}}$ (KBr): 1860 (w), 1841 (w), 1830 (m), 1768 (s) (anhydride); 1706 (s)(benzoate); 1589 (s) (aromatic).

G.L.C.

Column: 1% QFI Temp. : 225° F.R. 46 ml./min.

R_t 27·85 min.

N.M.R. (Part II)

The spectrum was shown to display an identical splitting pattern to that of the corresponding epimer of the bromine-free adduct i.e., endo A (41).

(k) Attempted reaction of 1-benzoyloxycyclohepta-3,5-diene (39) and cyclopentene-3,5-dione.

Cyclopentene-3,5-dione[26] and the benzoate (39) were refluxed in benzene (or xylene) under conditions similar to above. In each case, starting materials accompanied by a polymeric species resulted, there being no adduct present in detectable amounts.

(ℓ) 2-Ketobicyclo[3,2,2]non-3,8-diene-6,7-endo-dicarboxylic acid anhydride (8)

(Tropone and maleic anhydride)

Tropone (1·325 g., 0·0125 mole) and maleic anhydride (2·51 g., 0·0255 mole) in xylene (10 ml.,) were stirred at reflux temperature for $4\frac{1}{2}$ hrs. in a stream of nitrogen. After allowing to cool completely, the resulting crystals were collected, dried and recrystallised several times from ethyl acetate/petrol to give colourless prisms, (2·264 g., 89%), m.p. 181-182° (lit. m.p. 181·5-182·5°).

$\nu_{max.}^{cm.^{-1}}$ (NUJ:) : 1860 (m), 1845 (m), 1770 (s) (anhydride); 1665 (s) (enone); 1625 (w) (double bond).

The N.M.R. spectrum is discussed in Part II.

The residue from crystallisation was placed on an alumina column (Woelm, acid-washed, 35 g.,) and eluted with benzene followed by ethyl acetate/benzene mixtures. Only a small amount of endo adduct plus starting materials could be detected. This showed that the endo molecule was the sole product.

Repeating the experiment under exactly the same conditions as for the benzoate adduct (41), resulted in a 99% yield of the endo isomer confirmed by N.M.R., I.R. and G.L.C.:

Column: 1% QFI, Temp. 150°, F.R. 30 ml./min.

R_t 21·95 min.

Bromolactonisation of the enone anhydride adduct (8). 5-bromo-3-oxa-2,7-diketotricyclo[4,4,1,$0^{4,10}$]undec-8-ene-11-endo-carboxylic acid (49).

The enone anhydride (66·8 mg.,) was dissolved in the minimum amount of water while stirred at 0°. Bromine was added dropwise until the colouration persisted and the temperature was maintained at 0° with occasional bromine addition for a further 4 hrs. Sodium bisulphite was added to destroy the excess bromine and the solution filtered to yield yellow crystals which, when dried over phosphorus pentoxide in a vacuum pistol, became pale yellow, crude m.p. 180°. Recrystallisation from ethyl acetate/petrol afforded prisms, m.p. 214-215° (lit. crude m.p. 185°, rex. m.p. 219°, from acetone)

$\nu_{max.}^{cm.^{-1}}$ (NUJOL): 3400-2500 (m) (acid); 1770 (s) (lactone); 1735 (s) (acid); 1675 (s) (enone).

Bromolactonisation of the benzoate anhydride adducts

(i) endo A.

The endo A adduct (70·6 mg.,) was found to be totally insoluble in water (13 ml.,) at 0°, dioxane being added to make the solution homogeneous. Bromine was added as above at 0° and, after 3 hrs., the excess bromine destroyed. The solution was extracted with chloroform which resulted in the isolation of a colourless oil. By T.L.C. this oil was shown to contain one main component, which was more polar than the starting material. This compound contained bromine (T.L.C., development silver nitrate: fluorescein) but the I.R. showed mainly anhydride peaks, indicating that the molecule was probably the bromine addition product (51)

$\nu_{max.}^{cm.^{-1}}$ (film): 1860 (w), 1830 (w), 1770 (s) (anhydride); 1710 (s) (benzoate); 725 (s) (aromatic)

Experiments using methanol/dioxane/water as a solvent system gave similar results.

Bromination in sodium carbonate solution (10%) afforded acidic species, showing no lactone absorption in the I.R.

$\nu_{max.}^{cm.^{-1}}$ (film): 3500-3000 (m) (acid); 1720-1710 (s) (acid, benzoate); 725 (s) (aromatic).

(ii) Iso A. : Dehydrolactonic diester (57) or isomer

Iso A adduct (18·5 mg.,) was dissolved in the minimum amount of dioxane at 0° and water (ca 2 ml.,) added without causing precipitation. The solution was treated with bromine at 0° as described above, an oil being isolated, which, on standing, yielded a small amount of crystalline material (2 mg.,), crude m.p. 190-198°.

$\nu_{max.}^{cm.^{-1}}$ (NUJOL): 3400 (m) (hydrogen bonding); 1775 (s) (lactone); 1738 (s) (acid); 1705 (s) (benzoate); 725 (s) (aromatic).

The residue was shown by T.L.C. to contain more of this acid, believed to be the bromolactone acid (54) but also contained less polar bromo compounds. Attempts to purify the crystalline acid by a basic extraction and acidification procedure caused destruction of the molecule. Repetition of the experiment unfortunately yielded only bromo diacids and unidentified products, illustrating the importance of the correct solvent system.

Bromination in a methanol/dioxane/water system afforded a pale yellow oil from which a colourless solid could be isolated by precipitation with petrol. Crystallisation from ethyl acetate/petrol afforded the title compound (57) as colourless plates, m.p. 175·5-178·5°

which showed neither acidic absorption in the I.R. nor an acidic R_F value (0·25).

$\nu_{max.}^{cm.^{-1}}$ (NUJOL): 1780 (s) (lactone); 1735 (s) (ester); 1700 (s) (benzoate).

(Found: C, 66·39; H, 5·32. $C_{19}H_{18}O_6$ requires: C, 66·66; H, 5·30%).

Bromination in aqueous sodium carbonate (20%) afforded a mixture of acid species and anhydride:

$\nu_{max.}^{cm.^{-1}}$ (film): 3500-3000 (m) (acid); 1860 (w), 1840 (w), 1775 (m) (anhydride); 1720-1710 (s) (acid, benzoate).

Bicyclo[3,2,2]non-8-ene-6,7-endo-dicarboxylic acid anhydride (7). (Cyclohepta-1,3-diene and maleic anhydride).

The adduct (7) was prepared by the method of Alder[4] as a colourless solid, m.p. 113-115° (lit. m.p. 114°).

$\nu_{max.}^{cm.^{-1}}$ (CCl_4): 1877 (w), 1865 (w), 1787 (s) (anhydride).

N.M.R. (Part II).

A small sample was hydrogenated[4] over PtO_2 in acetic acid to yield bicyclo[3,2,2]nonane-6,7-endo-dicarboxylic acid anhydride (60), m.p. 159° (lit. m.p. 156-157°) for N.M.R. purposes (Part II).

Bromination of bicyclo[3,2,2]non-8-ene-6,7-endo-dicarboxylic acid (7) : Dehydrolactonic ester (61) or isomer.

The anhydride adduct (7) (158·8 mg.,) in a solvent mixture of water and dioxane (2:1, 15 ml.,) was stirred at 0° and brominated as described above keeping the solution homogeneous with dioxane addition. After 3 hrs., at 0-5°, the excess bromine was destroyed and the solution extracted with ether. After washing and drying the ethereal solution, the solvent was removed in vacuo to afford a light brown oil (121·1 mg.,)

$\nu_{max.}^{cm.^{-1}}$ (film): 3500-2500 (m) (acid); 1765 (s) (lactone); 1695 (s) (acid).

Treatment of the oil with chloroform/petrol afforded a brown solid (56·8 mg.,) which was esterified with diazomethane in ether/methanol. The product (61) was a colourless solid which crystallised as prisms, m.p. 96·5-97·5°, from ether.

$\nu_{max.}^{cm.^{-1}}$ (CCl_4) : 1788 (s) (lactone); 1740 (s) (ester); 1199 (s) (C-O).

(Found: C, 65·01; H, 6·23. $C_{12}H_{14}O_4$ requires: C, 64·85; H, 6·35%).

N.M.R. ($CDCl_3$)

5·39 τ (1H, quartet, J = 6, J = 3·5)

6·29 τ (3H, singlet)

7·20 τ (1H, doublet, J = 5)

7·39 τ (1H, triplet, J = 6)

7·66 τ (1H, broad absorption)

8·2-8·8 τ (6-7H, complex)

The ultraviolet spectrum showed no maxima greater than 200 mμ (hexane).

Reduction of anti-3-exo-benzoyloxybicyclo[3,2,2]non-8-ene-6,7-endo-dicarboxylic acid anhydride (41) (endo A).

Benzoate anhydride (41) (58·7 mg., 0·00019 mole) in dry tetrahydrofuran (3 ml.,) was added dropwise to a stirred suspension of lithium aluminium hydride (17 mg., 0·00065 mole) in tetrahydrofuran (10 ml.,). After refluxing the solution for 2 hrs., the excess hydride was destroyed with sodium sulphate decahydrate, the ether-diluted solution being dried over anhydrous sodium sulphate. Evaporation in vacuo afforded a colourless oil (22 mg.,).

$\nu_{max.}^{cm.^{-1}}$ (film): 3450 (s) (hydroxyl); 1055-45 (s) (C-O); 770 (m), 710 (m) (aromatic).

T.L.C. of the oil showed a polar compound as well as several other minor species, one of which was identified by preparative T.L.C. as benzyl alcohol, R_F = 0·5 (20% ethyl acetate/benzene) [N.M.R. 2·66 τ (s, 5H, aromatic), 5·34 τ (s, 2H, methylene) 8·12 τ (s, 1H, hydroxyl)]. The polar component could not be crystallised nor purified by preparative T.L.C. (due to the low recovery from the plate). The oil, in pyridine (2 ml.,), was acetylated with acetic anhydride, the product being isolated with ether as a pale yellow liquid. Preparative T.L.C. afforded 1,4-diacetoxy-butane as a colourless liquid, b.p. 60°/0·05 mm. (sub. block).

$\nu_{max.}^{cm.^{-1}}$ (film): 1740-20 (s) (acetate); 1260-40 (s) (C-O).

N.M.R.

5·94 τ (t, 4H, O-methylene), 7·99 τ (s, 6H, acetate), 8·32 τ (quintet, 4H, C-methylene).

The mass spectrum showed no parent ion m/e 174 but displayed a base peak at m/e 43 $(CH_3CO)^+$ and ions at m/e 55 and 131 (M-43).

Repeating the experiment under milder conditions (stirring for 15 hrs., at room temperature) afforded an oil with a similar I.R. spectrum to that described above.

$\nu_{max.}^{cm.^{-1}}$ (film): 3450 (s) (hydroxyl); 1050-45 (s) (C-O).

Acetylation, followed by preparative T.L.C. afforded two main components (29·5 mg.,) which could not be separated, the less polar being identified as 1,4-diacetoxybutane. The ill-defined N.M.R. indicated that the more polar component could be either the bicyclic triacetate (67) or 1,4-diacetoxybut-2-ene:
3·85 τ (complex, vinylic), 5·90 τ (complex, O-methylene, O-methine), 7·53 τ (complex, allylic), 7·98 τ (singlet, acetate), 8·30 τ (complex, C-methylene).

Anti-3-exo-benzoyloxybicyclo[3,2,2]non-8-ene-6,7-endo-dicarboxylic acid (68).

Benzoate anhydride (endo A) (1·4418 g., 0·0045 mole) was dissolved in warm aqueous sodium carbonate (20%). After cooling, the solution was acidified with dilute hydrochloric acid, causing precipitation of a colourless solid, which was filtered and dried (1·3616 g., 89%). Recrystallisation afforded colourless prisms, m.p. 226·5-227·5° from methanol.

$\nu_{max.}^{cm.^{-1}}$ (KCl): 3000-2550 (m), 1717 (s)(acid); 1708 (s) (benzoate); 715 (s) (benzoate).

(Found: C, 65·16; H, 5·58. $C_{18}H_{18}O_6$ requires: C, 65·44; H, 5·49%).

N.M.R. (Part II).

Anti-3-exo-benzoyloxy-6,7-endo-dicarbomethoxybicyclo[3,3,2] non-8-ene (69).

The diacid (68) (0·2958 g., 0·00090 mole) as a slurry in methanol was esterified with diazomethane to yield the diester (69) (0·2998 g., 93%) as a colourless solid, m.p. 73-76°. Recrystallisation from ether afforded prisms, m.p. 82-83°.

$\nu_{max.}^{cm.^{-1}}$ (CCl_4): 1754 (s) (ester); 1720 (s) (benzoate).

(Found: C, 67·01; H, 6·23. $C_{20}H_{22}O_6$ requires: C, 67·02; H, 6·19%).

G.L.C.

Column: 1% QF 1 Temp. : 200° F.R. 40 ml./min.

R_t 19·00 min.

N.M.R. (Part II).

Anti-3-exo-hydroxy-6,7-endo-dihydroxymethylbicyclo[3,2,2] non-8-ene (70).

To a stirred solution of lithium aluminium hydride (100 mg.,) in ether (8 ml.,), the diester (69) (120·8 mg., 0·00034 mole) in ether (6 ml.,) was added dropwise. The solution was refluxed for 4 hrs., cooled and the excess hydride destroyed with sodium sulphate decahydrate. After dilution with ether and drying over sodium sulphate,

evaporation <u>in vacuo</u> afforded a colourless oil (89·1 mg.,), from which the title compound (70) was crystallised from methanol/ether as colourless needles, m.p. 145-145·5°, (32·3 mg., 48%).

$\nu_{max.}^{cm.^{-1}}$ (KCl): 3277 (m) (hydroxyl); 1033 (s) (C-O); 728 (m) (cis d.b.)

(Found: C, 66·42; H, 9·04. $C_{11}H_{18}O_3$ requires: C, 66·64; H, 9·15%).

The mass spectrum showed an ion m/e 199, (M+1) ($C_{11}H_{18}O_3$ requires 198), as well as ions at m/e 198, 180 ($M-H_2O$) and 92 (base peak).

<u>N.M.R.</u> (Part II).

The yields of triol (70) varied from 10% to 48% but could not be bettered even by a room temperature reaction. The residue in all cases was an amber, mobile liquid,

$\nu_{max.}^{cm.^{-1}}$ (film): 3350 (s) (hydroxyl); 1060 (s) (C-O), consistent with a mixture of butane-1,4-diol, but-2-ene-1,4-diol, and benzyl alcohol (which was isolated and identified in one case).

Preferential bis-tosylation of anti-3-exo-hydroxy-6,7-endo-dihydroxymethylbicyclo[3,2,2]non-8-ene (70).

To the triol (70) (16·2 mg., 0·0818 m mole), dissolved in a minimum amount of dry pyridine at 0°, p-toluenesulphonyl chloride (32·8 mg., 0·1725 m mole) in ice-cold pyridine (1 ml.,) was added with stirring during 15 min. The mixture was allowed to stand at 0° for 4 days after which time, crushed ice was added. Ether extraction followed by successive washing with dilute sulphuric acid (3N), sodium bicarbonate and brine afforded, after drying and evaporation in vacuo, a pale yellow oil (11·1 mg.,).

$\nu_{max.}^{cm.^{-1}}$ (film) : 3500 (s) (hydroxyl); 1705 (s) (carbonyl); 1600 (m) (double bond); 1160 (s) (S-O).

T.L.C. indicated that the oil consisted of at least 5 components, none of which were isolated.

Ozonolysis of anti-3-exo-benzoyloxy-6,7-endo-dicarbomethoxybicyclo[3,2,2]non-8-ene (69).

The benzoate diester (69) (85 mg., 0·00024 mole) in dry methanol (14 ml.,) was treated with ozonised oxygen for 1½ hrs., at a temperature of -30° which was lowered during the reaction to -60°. The system was flushed with nitrogen for 15 min., followed by addition of dimethyl

sulphide to the solution maintained at -30°. The mixture was stirred at -10° for 1 hr., followed by 1 hr., at room temperature. Evaporation of the solvent *in vacuo*, extraction of the residue with petrol (from an aqueous phase) afforded an almost colourless oil (97·5 mg.,) after drying and evaporation *in vacuo*.

$\nu_{max.}^{cm.^{-1}}$ (film): 3500-2500 (m) (acid); 1750-1710 (s) (carbonyls); 725 (s) (benzoate).

T.L.C. indicated the presence of at least one polar component as well as two less polar, minor components, neither of which was starting material. All the components stained yellow with D.N.P. developer but attempts to separate individual components of this complex mixture were unsuccessful.

Anti-3-*exo*-benzoyloxy-6,7-*endo*-dicarbethoxybicyclo[3,2,2] nonane-8,9-diol (76).

The benzoate diester (69) (152·6 mg., 0·00043 mole) in dry ether (4 ml.,) was treated with a solution (13 ml.,) of osmium tetroxide in ether (10 mg./ml.,) and the mixture allowed to stand for 48 hrs. Evaporation of the solvent *in vacuo* and addition of benzene (40 ml.,) afforded a solution which, when treated with a steam of hydrogen

sulphide, produced a black precipitate of osmium sulphide. After flushing with nitrogen, the solution was filtered through celite and the solvent removed *in vacuo*. Preparative T.L.C. of the resultant colourless oil (130·9 mg.) led to the isolation of starting material (26·4 mg., 17%) identified by I.R. and T.L.C. and a more polar component, the title compound (76) (71·9 mg., 43%) as a pale yellow syrup which resisted crystallisation.

$\nu_{max.}^{cm.^{-1}}$ (CCl_4): 3640 (s), 3553 (s) (hydroxyl); 1751 (s) (ester); 1742 (s) (ester); 1722 (s) (benzoate)

$\nu_{max.}^{cm.^{-1}}$ (film): 1290 (s), 1210 (s), 1080 (s), 728 (s).

N.M.R. (Part II).

The mass spectrum showed a parent ion m/e 392 ($C_{20}H_{24}O_8$ requires 392) and a base peak m/e 105.

On attempted short-path distillation of a sample of this oil (15·1 mg.,), a colourless solid was observed to sublime at b.p. 80°/0·1 mm., followed by a yellow oil, b.p. 150-160°/0·1 mm. The solid was shown to be benzoic acid, m.p. 122-123°, by a mixed melting point determination and I.R., [$\nu_{max.}^{cm.^{-1}}$ (NUJOL): 1687 (s) (acid)] : the oil (7·2 mg.,) proved to be the hydroxy ether diester (80).

$\nu_{max.}^{cm.^{-1}}$ (NUJOL): 3535 (s) (hydroxyl); 1727 (s) (ester);

1218 (s), 1155 (s), 1090 (s), 1020 (s),
970 (s), 940 (s), 845 (s), 825 (s);
no aromatic bands.

This elimination of benzoic acid also occurred if the diol was allowed to stand in the atmosphere for several days.

The diol (76) (20·3 mg.,) afforded an <u>acetonide</u> (83) (9·5 mg.,) on stirring with a mixture of dry acetone and anhydrous copper sulphate. The derivative was isolated by filtering the reaction mixture through celite, evaporating the filtrate <u>in vacuo</u> and crystallising the product from ethyl acetate as colourless plates, m.p. 140·5-142°.

$\nu_{max.}^{cm.^{-1}}$ ($CHCl_3$): 1735 (s) (ester); 1710 (s) (benzoate);
1600 (w), 1580 (w), 725 (w) (aromatic);
1290 (s), 1210 (s), 1075 (s), 1055 (s).

The mass spectrum showed <u>no</u> parent ion m/e 432 but instead a large ion m/e 417 ($M-CH_3$). A base peak m/e 55 and a large ion m/e 105 were observed.

Cleavage of anti-3-exo-benzoyloxy-6,7-endo-dicarbomethoxy-bicyclo[3,2,2]non-8,9-diol (76).

To a stirred solution of the diol (76) (38 mg., 0·0001 mole) in methanol (6 ml.,) under an atmosphere of nitrogen, sodium periodate (30 mg.,) in water (6 ml.,) was added in portions and the stirring continued for 24 hrs. The solution was extracted thoroughly with ether, the extracts being washed with brine, dried over sodium sulphate and evaporated in vacuo. The resultant pale yellow oil (30·1 mg.,) was essentially one component by T.L.C., the dialdehyde (84) R_F 0·6, contaminated with a more polar impurity, R_F 0·5. No starting material was detected and both components stained yellow with D.N.P. developer.

$\nu_{max.}^{cm.^{-1}}$ (film): 3480 (w) (carbonyl overtone); 2740 (w) (aldehyde C-H); 1735-1700 (s) (carbonyls); 1600 (w), 1580 (w), 730 (s) (aromatic)

Due to the fact that the dialdehyde decomposed to acidic species on standing, the crude material was not purified further but attempts were made to characterise it as its dinitrophenylhydrazone and semicarbazone, a freshly prepared sample being used in each case.

(i) Dinitrophenylhydrazone derivative

The oil (25·1 mg.,) was dissolved in methanol (10 ml.,) and treated with an ethanolic solution of dinitrophenylhydrazine in sulphuric acid in the usual manner. An orange solid was isolated which was shown to consist of three components by T.L.C., A (R_F 0·7), B (R_F 0·5) and C (R_F 0·35). Separation by preparative T.L.C. afforded B (9·5 mg.,) and C (11·1 mg.,) as the main products, A (2 mg.) being a minor unidentified component. Components B m.p. 145·5-148° and C m.p. 153·5-156° were both recrystallised from chloroform/ethanol and had very similar I.R. spectra. Neither compound could be obtained in a pure state due to gradual decomposition to acidic species (T.L.C.) and therefore further characterisation could not be effected.

B $\nu_{max.}^{cm.^{-1}}$ (NUJOL): 3300 (w) (N-H); 1620 (m), 1590 (m), 730 (s) (aromatic).

$\nu_{max.}^{cm.^{-1}}$ (CCl_4) : 1741 (s) (esters); 1727 (s) (benzoate).

C $\nu_{max.}^{cm.^{-1}}$ (NUJOL): 3300 (w) (N-H); 1620 (m), 1590 (m), 730 (s) (aromatic).

$\nu_{max.}^{cm.^{-1}}$ (CCl_4) ; 1752 (s) (esters); 1726 (s) (benzoate).

Despite being involatile, component B showed a molecular weight of 745 ± 5 by mass spectroscopy ($C_{32}H_{30}O_{14}N_8$ requires 750). This evidence suggested that B and C were epimeric bis-dinitrophenylhydrazone derivatives.

(ii) Semicarbazone derivative.

The dialdehyde (84) (27·2 mg.,) was treated with a semicarbazide solution in the standard manner. After 12 hrs. at 0°, the product was isolated with ether. The product proved to be a colourless syrup which resisted crystallisation and was shown to consist of several components by T.L.C., one of which R_F 0·1 was predominant.

$\nu_{max.}^{cm.^{-1}}$ ($CHCl_3$): 3500-3200 (m) (N-H); 1750 (m, shoulder); 1720-1700 (s) (carbonyls); 1670 (m, shoulder) (-NH-CO-NH_2); 725 (s) (benzoate).

This major component could not be separated satisfactorily from the other materials by chromatography and the investigation was continued no further.

Reduction of dialdehyde (84).

The dialdehyde (84) (48 mg.,), dissolved in methanol (7 ml.,), was treated with excess sodium borohydride and the mixture allowed to stand at room temperature for 15 hrs. The pH was lowered to 7, the solution filtered, poured into ammonium sulphate and isolated with ether. The product (31·1 mg.,), a pale yellow oil, proved to be essentially one component by T.L.C.(R_F 0·5). The I.R. spectrum showed no hydroxyl absorption but strong γ-lactone absorption.

$\nu_{max.}^{cm.^{-1}}$ ($CHCl_3$): 1790 (s), 1781 (s) (γ-lactones);
1718 (s) (benzoate)

The compound was thought to be the benzoate dilactone (87).

Hydrolysis of anti-3-exo-benzoyloxybicyclo[3,2,2]non-8-ene-6,7-endo-dicarboxylic acid anhydride (41) : (endo A).

The benzoate anhydride (41) (0·498 g., 0·0016 mole) was heated on a steam bath with dilute sodium carbonate (20%, 22 ml.,) for 3 hrs. The solution was filtered, cooled and acidified with dilute hydrochloric acid and evaporated to smaller bulk, at which time benzoic acid crystallised out of the solution. The filtrate was ether extracted continuously for 6 days affording a yellow, viscous oil which partially solidified.

$\nu_{max.}^{cm.^{-1}}$ (film): 3500 (s), 3440 (s) (hydroxyl); 3400-2500 (hydrogen bonding); 1855 (m), 1835 (m), 1770 (s) (anhydride); 1720 (s) (acid); 1690 (s) (benzoic acid); 1600 (w), 1580 (w), 720 (s) (aromatic).

This material was concluded to be a mixture of the hydroxy anhydride (91), the hydroxy diacid (92) and benzoic acid.

In one experiment, confirmation of the bicyclic structures was obtained by heating a sample of the mixture at reflux temperature with acetyl chloride for 2 hrs. The excess reagent was removed in vacuo and the product azeotroped with benzene to remove last traces. By preparative T.L.C., the main component was isolated, R_F 0·5, and was shown to be the acetoxy anhydride (93) by I.R. and T.L.C. comparison with acetoxy adducts obtained earlier.

$\nu_{max.}^{cm.^{-1}}$ (film): 1850 (m), 1830 (m), 1775 (s) (anhydride); 1730 (s) (methyl ester); 1250-1230 (s) (C-O acetate).

3-Ketobicyclo[3,2,2]non-8-ene-6,7-endo-dicarboxylic acid anhydride (94).

The mixture from above (330 mg.,) was stirred in acetone (10 ml.,), cooled in ice, and standard Jones reagent added dropwise. When the orange colour was maintained, methanol was added followed by ice, after a 15 min. interval. The mixture was extracted with ethyl acetate: ether (1:1), the organic extract washed with sodium bicarbonate (6%), brine and dried over sodium sulphate. Evaporation in vacuo afforded the keto anhydride (94) as a colourless solid (139·3 mg., 42% from benzoate anhydride)

m.p. 190-193°. The ketone was heated at reflux temperature with acetyl chloride for 3 hrs., the pure keto anhydride crystallising from the solution on cooling. Recrystallisation from acetone/diisopropyl ether afforded colourless plates, m.p. 199·5-200·5°.

$\nu_{max.}^{cm.^{-1}}$ (KBr): 1867 (m), 1834 (m), 1768 (s) (anhydride); 1697 (s) (ketone)

(Found: C, 64·30; H, 4·97. $C_{11}H_{10}O_4$ requires: C, 64·07; H, 4·89%).

G.L.C.

Column: 1% QF 1 Temp. : 175° F.R. 38 ml./min.

R_t 11·55 min.

The mass spectrum showed a parent ion m/e 206 ($C_{11}H_{10}O_4$ requires 206) and a base peak m/e 28.

N.M.R. (Part II).

3,3-Ethylenedioxybicyclo[3,2,2]non-8-ene-6,7-endo-dicarboxylic acid anhydride (95).

The ketone (94) (0·182 g., 0·00088 mole), ethylene glycol (0·637 g., 0·01025 mole) and p-toluenesulphonic acid (10 mg.,) in benzene (25 ml.,) were stirred at reflux with water separation using a Dean-Stark apparatus for 16 hrs. The solvent was removed in vacuo, ether added

and the ethereal solution washed successively with sodium bicarbonate (10%) and brine , and dried over sodium sulphate. Evaporation afforded the ketal (95) as a colourless solid (120·1 mg., 55%) which was crystallised from acetone to give needles, m.p. 225-226·5°.

$\nu_{max.}^{cm.^{-1}}$ (KBr): 1860 (m), 1829 (m), 1778 (s) (anhydride).

$\nu_{max.}^{cm.^{-1}}$ (NUJOL): 1100 (s), 965 (s), 945 (s), 765 (s)

(Found: C, 61·95; H, 5·74. $C_{13}H_{14}O_5$ requires: C, 62·39; H, 5·64%).

N.M.R. (Part II).

3,3-Ethylenedioxy-6,7-endo-dicarbomethoxybicyclo[3,2,2] non-8-ene (97).

The ketal anhydride (95) (103·7 mg., 0·0004 mole) was warmed in dilute sodium carbonate (20%, 15 ml.,) for 10 min., filtered and cooled to 0°. The pH was made just acid, the solution extracted thoroughly with ethyl acetate/ ether (1:1) and the organic phase dried over sodium sulphate. In one experiment, this solution was evaporated in vacuo to yield a pale yellow oil which soon solidified but was shown to be a mixture of the anhydride (95) and the corresponding diacid.

$\nu_{max.}^{cm.^{-1}}$ (NUJOL): 3500-2500 (m) (hydrogen bonding);
1830 (w), 1770 (m) (anhydride);
1710 (s) (acid).

This closure was avoided by carefully evaporating the organic solution (containing the diacid alone) to smaller bulk (80 ml.,) in vacuo and adding excess ethereal diazomethane. After evaporation of the excess diazomethane, followed by filtration through celite, the solvent was removed in vacuo to yield the diester (97) as an oil (60·5 mg., 49% from ketal anhydride), b.p. 180°/0·5 mm., which solidified slowly on standing. Crystallisation with difficulty from ether afforded colourless platelets, m.p. 89·5-91·5°.

$\nu_{max.}^{cm.^{-1}}$ ($CHCl_3$): 1745 (s) (ester)

$\nu_{max.}^{cm.^{-1}}$ (NUJOL): 1200 (s), 1170 (s), 1105 (s), 1065 (s).

(Found: C, 60·43; H, 6·88. $C_{15}H_{20}O_6$ requires C, 60·80; H, 6·80%).

N.M.R. (Part II).

3,3-Ethylenedioxy-6,7-endo-dihydroxymethylbicyclo[3,2,2] non-8-ene (98).

The ketal diester (97) (186·5 mg., 0·0006 mole) in ether (15 ml.,) was slowly added dropwise to a stirred suspension of lithium aluminium hydride (211·6 mg., excess) in ether (8 ml.,). The suspension was refluxed for 2 hrs., cooled and excess hydride destroyed. The ether-diluted solution was dried over sodium sulphate and evaporated in vacuo to yield the diol (98) as a colourless solid (107·4 mg., 76%). Recrystallisation from chloroform/ diisopropyl ether afforded plates, m.p. 137·5-138·5°.

$\nu_{max.}^{cm.^{-1}}$ (NUJOL): 3350 (s) (hydroxyl); 1110 (s), 1050 (s), 1035 (s) (C-O).

(Found: C, 64·59; H, 8·27. $C_{13}H_{20}O_4$ requires: C, 64·98; H, 8·39%).

Presence of the ketal function was also confirmed by yellow staining (T.L.C.) with D.N.P. developer indicating hydrolysis by acid.

N.M.R. 60 Mc.

3·85 τ (2H, quartet, obs. splitting 5,3 cps, vinylic)

6·13 τ (4H, singlet, ketal)

6·90 τ (2H, broad absorption, hydroxyl) D_2O exchange

7·95 τ (2H, quartet, obs. splitting 14,4 cps, H_{da}, A part of ABX)

8·22 τ (2H, quartet, obs. splitting 14,3 cps, H_{ds}, B part of ABX)

6,7-Endo-dihydroxymethylbicyclo[3,2,2]non-8-ene (99).

The olefinic anhydride (7) (0·605 g., 0·0032 mole), in ether (5 ml.,), was added dropwise to a stirred suspension of excess lithium aluminium hydride (700 mg.,) in ether (7 ml.,). The solution, after stirring for 2 hrs., was treated with sodium sulphate decahydrate and the ether-diluted solution dried. Evaporation of the solvent in vacuo afforded the diol (99) as a colourless solid, (0·5613 g., 97%) which was recrystallised from diisopropyl ether to give long needles, m.p. 72-72·5°.

$\nu_{max.}^{cm.^{-1}}$ (NUJOL): 3300 (s) (hydroxyl); 1040 (s), 1030 (s), 990 (m) (C-O); 710 (m) (double bond).

(Found: C, 72·23; H, 9·79. $C_{11}H_{18}O_2$ requires: C, 72·49; H, 9·96%).

N.M.R. : 4·01 τ (2H, quartet, obs. splitting 5,3 cps, vinylic).

8·47 τ (6H, broad singlet, bridge methylenes).

Bis-methanesulphonate (105) of 6,7-endo-dihydroxymethyl-bicyclo[3,2,2]non-8-ene (99).

To a stirred ice-cold solution of methanesulphonyl chloride (318 mg., 0·0028 mole) in dry pyridine (1 ml.,) a solution of diol (99) (104·7 mg., 0·00058 mole) in pyridine

(2 ml.,) was added dropwise. The contents were kept at 0° for 24 hrs., followed by another period of 24 hrs., at room temperature, after which time the deep amber mixture was treated with crushed ice. The mixture was thoroughly extracted with ether, the ethereal phase being washed successively with dilute hydrochloric acid, sodium bicarbonate (sat$^{d.}$) and brine. After drying, evaporation yielded a pale yellow oil, the bis-mesylate (105) (186·3 mg., 96%) which was easily crystallised from ethyl acetate/ether to yield colourless needles, m.p. 96-97°.

$\nu_{max.}^{cm.^{-1}}$ (NUJOL): 1175 (s) (S-O); 990 (s), 960 (s), 865 (m), 830 (m), 725 (m).

(Found: C, 46·13; H, 6·52. $C_{13}H_{22}O_6S_2$ requires: C, 46·13; H, 6·55%).

N.M.R. 3·92 τ (2H, quartet, obs. splitting 5,3 cps, vinylic)
7·00 τ (6H, singlet, mesylate)
8·43 τ (6H, broad singlet, bridge methylenes)

Bis-methanesulphonate (106) of 3,3-ethylenedioxy-6,7-endo-dihydroxymethylbicyclo[3,2,2]non-8-ene (98).

Ketal diol (98) (91·3 mg., 0·00038 mole), in pyridine (3 ml.,), was reacted as described above with methanesulphonyl chloride (0·273 mg., excess) in pyridine (4 ml).

On addition of crushed ice, a colourless solid was precipitated which was filtered and dried. The bis-mesylate (106) (116·1 mg., 77%) crystallised as colourless platelets, m.p. 106-107·5°, from methanol.

$\nu_{max.}^{cm.^{-1}}$ (NUJOL): 1180 (s) (S-O); 1110 (s), 1000 (s), 960 (s), 895 (s), 885 (s), 830 (s)

N.M.R. 60 Mc.

3·80 τ (2H, quartet, obs. splitting 5,3 cps, vinylic)

6·13 τ (4H, quartet, obs. splitting 4,3 cps, ketal)

7·02 τ (6H, singlet, mesylate)

7·98 τ (2H, quartet, obs. splitting 14,5 cps, H_{da}, A part of ABX)

8·28 τ (2H, quartet, obs. splitting 14,3 cps, H_{ds}, B part of ABX)

4-Amino-3-cyanotricyclo[5,3,2,$0^{2,6}$]dodeca-3,11-diene (111) (endo configuration).

The bis-mesylate (105) (128·7 mg., 0·00038 mole) in dimethyl sulphoxide (D.M.S.O.) (6 ml.,) was added to a stirred solution (at 90°) of potassium cyanide (AnalaR, 98·5 mg., 0·0015 mole) in D.M.S.O. (4·5 ml.,) under an atmosphere of nitrogen. After an hour at 95°, the solution

was cooled and a slurry of sodium hydride (49·9 mg., 50% dispersion in oil, 0·001 mole) in D.M.S.O. (4·5 ml.,) added dropwise. After heating at 95° for a further period of 1 hr., the solution was poured into ice/water, whereupon a light brown solid separated. Filtration and drying afforded the cyanoenamine (111) (52 mg., 68%) which was crystallised several times from benzene/petrol to give colourless platelets, m.p. 188°.

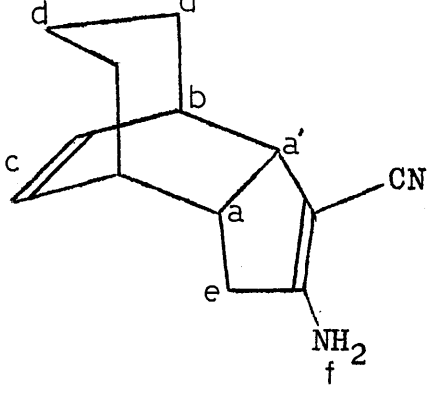
$\nu_{max.}^{cm.^{-1}}$ (NUJOL): 3460 (m), 3390 (m), 1645 (s) (N-H); 2210 (s) (C≡N); 1615 (m) (double bond).

(Found: C, 77·69; H, 7·85; N, 13·72. $C_{13}H_{16}N_2$ requires: C, 77·96; H, 8·05; N, 13·99%).

$\lambda_{max.}^{EtOH}$ 263·5 mμ (ε, 15,000).

After 1 drop HCl (6N), $\lambda_{max.}$ 238 mμ (ε, 10,700), after 1 hr. [lit. for 1-amino-2-cyanocyclopent-1-ene, $\lambda_{max.}$ 263 mμ (ε, 13,000)]

N.M.R.



H_a, 6·80 τ (1H, doublet, J = 8)

H_a ca 7·8 τ (ca 1H, complex)

H_b, H_e ca 7·3 τ (4H, complex)

H_c 2·97 τ (2H, multiplet)

H_d 8·56 τ (6H, broad singlet)

H_f 5·76 τ (2H, broad)

D_2O exchange

4-Amino-3-cyano-9,9-ethylenedioxytricyclo[5,3,2,$0^{2,6}$]dodeca-3,11-diene (113) (endo configuration.)

Under an atmosphere of nitrogen, the ketal mesylate (106) (37·2 mg., 0·09 m mole) in D.M.S.O. (1 ml.,) was reacted as described above with potassium cyanide (31·6 mg., 0·485 m mole) in D.M.S.O. (2 ml.,) at 90-95°. Treatmt. of the cooled solution with a slurry of sodium hydride (16·2 mg., 50% dispersion in oil, 0·34 m mole) in D.M.S.O. (1·5 ml.,), followed by a period of heating (1 hr.) afforded a solution which, on cooling, was treated with crushed ice. The product was isolated with ether, washed with brine and dried over sodium sulphate. Evaporation in vacuo afforded an amber oil (20·2 mg.,) which by T.L.C. was shown to consist of essentially one component, R_F 0·2 (20% ethyl acetate/benzene). However, isolation of pure material by preparative T.L.C. resulted in only a small amount of product being recovered from the plate, (4·9 mg., 19%) as a pale yellow oil. Crystallisation from benzene/petrol afforded (113) as an amorphous solid, m.p. 149-151°.

$\nu_{max.}^{cm.^{-1}}$ (KBr): 3460 (m), 3345 (m), 1646 (s) (N-H); 2175 (s) (C≡N); 1608 (m) (double bond)

$\lambda_{max.}^{EtOH}$ 263·5 mμ (ε, 12,700).

After 1 drop HCl (6N), $\lambda_{max.}$ 238 mμ (ε, 8,870) over 1 hr.

The mass spectrum showed a parent ion m/e 258·13762 ($C_{15}H_{18}O_2N_2$ requires 258·13682) but also contaminated with another parent ion m/e 247·12024 ($C_{14}H_{17}O_3N$ (114) requires 247·12083). Two large ions, assumed to be the base peaks for each molecule, were observed at m/e 106, 95 as well as a large ion at m/e 152.

APPENDIX

X-ray analysis of anti-3-exo-p-bromobenzoyloxybicyclo[3,2,2] non-8-ene-6,7-endo-dicarboxylic acid anhydride (47).

Undertaken by Dr. G. Ferguson and Mr. A.F. Cameron[27]

Rotation, oscillation, Weissenberg and precession photographs were taken with copper K-α (λ = 1·542 Å) and molybdenum K-α (λ = 0·710 Å) radiations. The cell dimensions were obtained from rotation and Weissenberg photographs, and the space group, P $2_{1/c}$, was determined uniquely from systematic absences.

Intensity data were obtained from equatorial and equi-inclination upper layer Weissenberg photographs, taken from crystals rotated about the needle axis (c crystal axis); the multiple film technique[28] was employed. Some 2,000 data were estimated visually by comparison with a calibrated strip, and were corrected for Lorentz polarisation and rotation factors appropriate to the upper layers.[29] Since small crystals were used, no corrections for absorption were applied. The various layers of data were placed on the same scale by comparison of the observed and calculated structure amplitudes obtained from the three dimensional Patterson synthesis.

The position of the bromine atom was found from the Patterson synthesis and the remainder of the structure elucidated by the heavy atom method,[30,31] although this was complicated slightly by the presence of initial pseudo-symmetry resulting from the "special" values of the bromine co-ordinates which were:-

$$x = 0{\cdot}2500$$

$$y = 0{\cdot}2073$$

$$z = 0{\cdot}0000$$

The structure was refined by least-squares procedures on the Glasgow KDF 9 computer. The value of R is now 19% and refinement of atomic parameters is continuing.

The structure and conformation of the molecule are shown in (47) and Figure II and a list of crystal data given below:-

CRYSTAL DATA

Molecular formula	$C_{18}H_{15}O_5Br$
Molecular weight	391·22
System	monoclinic
a	13·47 Å
b	12·31 Å
c	10·63 Å
β	117·45°

Unit cell volume	1564·14 $\mathring{A}^3$
No. of molecules/unit cell	4
absent spectra	h o l if l is odd
	o k o if k is odd
space group	$P2_{1/c}$
No. of electrons/unit cell	792
No. of intensities estimated	1977

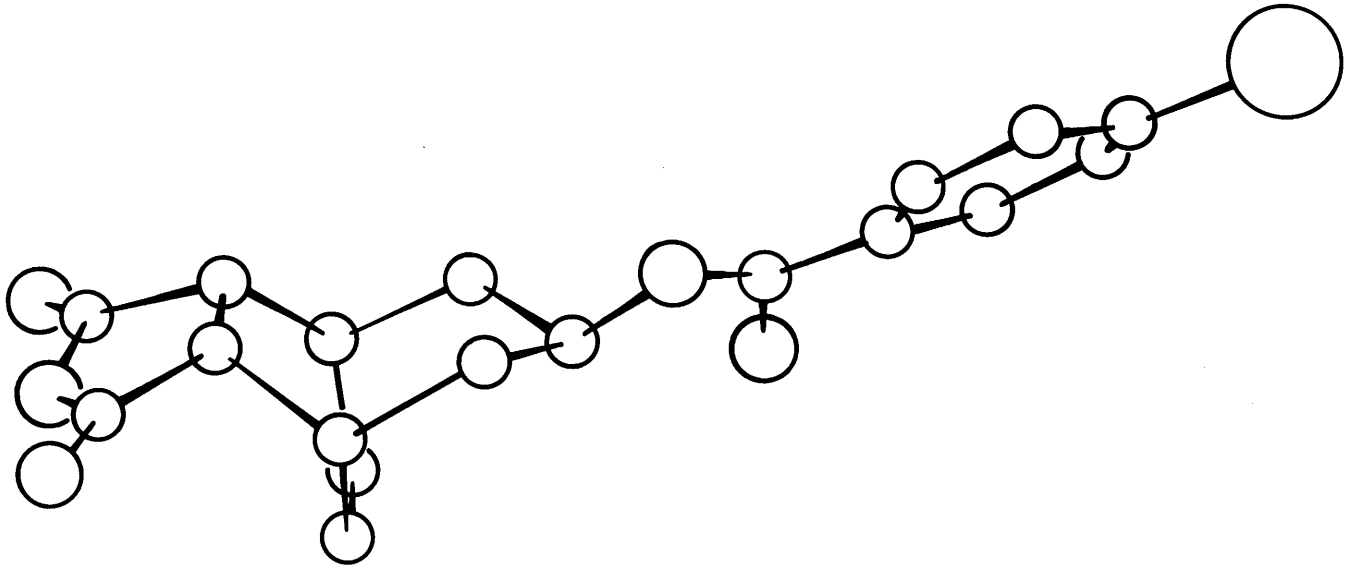


FIG II

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PART II.

N.M.R. Studies on 3-Substituted Bicyclo[3,2,2]non-8-ene-6,7-*endo*-dicarboxylic acid anhydrides and Related Compounds.

EXPERIMENTAL

Spectra were recorded on a Varian HA 100 spectrometer unless otherwise stated.

Deuterochloroform was used as solvent unless otherwise specified. Couplings constants were measured in c.p.s. and refer to $|J|$.

N.M.R. investigations of bicyclic structures, prepared by Diels-Alder reactions and by other means, have been the subject of numerous papers.[3,5,6] However, the most popular series by far has been the bicyclo[2,2,1] heptenes and heptanes as well as their heterocyclic counterparts. The larger proportion of these molecules have been synthesised by Diels-Alder reactions with cyclopentadiene[1] or furan[2] i.e. (115) and (116). Bicyclo[2,2,2]octenes have also been studied[3] but there has been no examination of the corresponding bicyclo[3,2,2]nonenes, probably due to the limited means of preparation.

The following discussion will be limited to comparison of aspects of bicyclic[2,2,1], [2,2,2] and [3,2,2]alkenes.

Karplus[4] has used a semi-empirical method to calculate coupling constants (J) between vicinal sp^3 hybridised carbons as a function of the dihedral angle ϕ:

$$J = 4{\cdot}22 - 0{\cdot}5 \cos \phi + 4{\cdot}5 \cos 2\phi$$

It has been shown that coupling constants depend on the following factors:

(i) electronegative substituents and also their configuration

(ii) the angles θ, θ' subtended by the carbon-carbon and the carbon-hydrogen bonds.

(iii) bond lengths.

Thus the N.M.R. spectra of bicyclo[2,2,1]heptenes (117) and (118) should illustrate configurational differences, since exo and endo protons on C_2 and C_3 subtend different angles with the bridgehead protons (numbering as in diagram (122) which will be continued throughout for comparison purposes). Anet,[2] comparing the endo and exo adducts (116) and (119), observed the endo protons in (116) as a singlet, showing no coupling with the bridgehead protons (ϕ = ca 80°) while a quartet was seen for the exo protons (ϕ = ca 45°) in (119). (This molecule was extremely useful for N.M.R. studies since the plane of symmetry made protons H_2 and H_3 equivalent.) Investigation[5] of the camphane diols (120) and (121) furnished the coupling constants, $J_{H_{3endo}-H_4} = 0$ ($\phi_{H_{3endo}-H_4}$ = ca 79°), $J_{H_{3exo}-H_4} = 4{\cdot}4$ ($\phi_{H_{3exo}-H_4}$ = ca 44°), which was in agreement with the Karplus theory. Mention was made, however, that bicyclo[2,2,1]heptenes were probably the limiting case as far as ring strain was concerned, smaller rings being expected to give anomolous splittings.

Lazlo and Schleyer[6] examined norbornene (122) and norbornane and assigned the following coupling constants:

	$J_{3x,2x}$	$J_{3n,2n}$	$J_{3x,2n}$	$J_{3n,4}$	$J_{3x,4}$	$J_{7s,4}$
norbornene	7·5–9·2	–	2·1–4·6	ca 0	3·2–4	1·5–2·0
norbornane	8·9–11·4	5·8–7·7	2·2–5·8	ca 0	3·0–6·0	$\leqslant$ 0·5

$J_{5,6}$ = 5–6, $J_{6,1}$ = 2·4–3·0, $J_{1,5}$ = 0·5–1·0

Investigating another member of this series, acid (123), Fraser[1] showed the exo H_2-H_1 coupling to be 3·8 cps, whereas endo H_2-H_1 coupling was in the range 0-1 cps. In addition to this, he noted that, due to the diamagnetic anisotropy of the double bond, endo protons (C_2) being below the plane of the double bond were shielded and appeared upfield from the expected value; exo protons, being in the plane, were consequently deshielded and found at lower field. Removal of this anisotropy by hydrogenation of the double bond, shifted the exo proton signal upfield, while the endo proton signal went to lower field. However, Wong and Lee[7] reported that in some cases (124, X = OH, OAc, OBs), the effect of the double bond was to shift both signals downfield, the endo proton to a lesser extent than the exo proton.

Other investigations[8] of the norbornene series have confirmed the above coupling constant values as well as showing that long range coupling involving the H_7 proton syn to the double bond and an endo H_3 proton was present (W-formation) (125). Unusual deshielding effects by the double bond have also been observed, the suggestion being that ring currents were involved.[9,10]

The bicyclo[2,2,2]octenes have been studied by Tori.[3] An examination of the geometry of the molecule (126) showed that both the exo and the endo protons (on C_2) subtended similar angles (ca 65°) with the C_1 bridgehead proton. As a result in structure (127) the coupling, $J_{H_{3exo}-H_4}$ had a value of 1·4 cps., while that for the saturated compound (128) was 1·6 cps. The isomeric exo anhydride was not quoted but comparison of the isomeric pair of bicyclo[2,2,2]octenols, (129) and (130) of very similar stereochemistry to bicyclo[2,2,2]oct-5-ene-2,3-endo-dicarboxylic acid anhydride (127), afforded couplings, $J_{H_{3exo}-H_4}$ = 2·7 and $J_{H_{3endo}-H_4}$ = 2·7. It could therefore safely be stated that exo and endo couplings to the bridgehead proton in the bicyclo[2,2,2]octene systems were similar to each other and usually small.

From the work reported on bicyclo[2,2,1]heptene and bicyclo[2,2,2]octene compounds, it can be seen that N.M.R. can be used unambiguously, in the former case, to assign exo and endo configurations, while in the latter case, no such assignment can be allocated.

In the bicyclo[3,2,2]nonene systems, (7) and (131), the dihedral angles were as follows: $\phi_{1,7endo}$ = ca 45°, J_{calc} = 4, $\phi_{1,7exo}$ = ca 75°, J_{calc} = 0. It would therefore be expected that the exo protons would

not couple (or couple weakly) with the bridgehead protons and, since both protons were equivalent due to the plane of symmetry, the signal would appear as a singlet. On the other hand, coupling would be expected for the endo proton in structure (131).

The coupling situation in the bicyclo[3,2,2] system should therefore be completely opposite to that in the bicyclo[2,2,1]case, since expansion of the one carbon bridge to a three carbon bridge has greatly altered the dihedral angles mentioned above.

It is also to be noted that structures (7) and (131) are not so highly strained as the bicyclo[2,2,1] heptenes, the three carbon bridge being capable of flipping from the anti form (7) into the alternative syn conformation (132) in the case of (7), whereas steric repulsions would inhibit an analogous flip in the case of exo anhydride (131). In addition, the opportunity for long-range couplings of the W-type between H_4 and H_6 (133) was not very great since their steric relationship was non-planar.[11]

The first molecule to be discussed is the cyclopropanyl adduct (6), the stereochemistry of which is more in accord with the bicyclo[2,2,2]octenes. (A summary of N.M.R. data for all the compounds is shown in Chart I.)

Tricyclo[3,2,2,$0^{2,4}$]non-8-ene-6,7-endo-dicarboxylic acid anhydride (6).

H_c 4·12 τ (2H, quartet, A part of A_2X_2 system, obs. splittings 5 and 4 c.p.s.)

H_b 6·55 τ (2H, multiplet)

H_a 6·72 τ (2H, doublet, J = 2)

H_d 8·86 τ (2H, complex)

H_e ca 9·7 τ (2H, complex)

Irradiation of the H_c signal caused a change in the multiplet at 6·55 τ (H_b) but did not appear to affect the doublet at 6·72 τ (H_a). Irradiation of the H_b absorption converted the vinylic quartet to a sharp singlet; this same irradiation collapsed the H_a doublet to a singlet and produced a quartet (J = 7, J = 4, A part of an A_2XY system) at 8·86 τ, assigned to the proton H_d coupling trans and cis with H_e, and H_e respectively. This molecule could be considered as a bicyclo[2,2,2]octene type illustrating again that the dihedral angle between H_a and H_b was such as to allow coupling.

2-Ketobicyclo[3,2,2]nona-3,8-diene-6,7-endo-dicarboxylic acid anhydride (8).

H_d 2·82 τ (1H, quartet, J = 11 and 8, A part of AMX system)

$H_{c'}$ 3·36 τ (1H, quartet, J = 8 and 8, A part of ABXY system)

H_c 3·72 τ (1H, quartet, J = 8 and 8, B part of ABXY system)

H_e 4·13 τ (1H, quartet, J = 11 and 2, M part of AMX)

H_a, $H_{a'}$, H_b, $H_{b'}$ 6·0–6·6 τ (4H, complex)

The complex region, 6·0–6·6 τ, is assigned to the protons H_a, $H_{a'}$ and H_b, $H_{b'}$. Thus, due to the asymmetry of the molecule, unidentifiable coupling of H_a in the region of H_b, was observed.

Bicyclo[3,2,2]non-8-ene-6,7-endo-dicarboxylic acid anhydride (7).

H_c 3·83 τ (2H, quartet, A part of A_2X_2, obs. splittings 6 and 4 c.p.s.)

H_a 6·60 τ (2H, singlet)

H_b 7·00 τ (2H, broad singlet)

H_d 8·31 τ (6H, ~ unresolved singlet)

Bicyclo[3,2,2]nonane-6,7-endo-dicarboxylic acid anhydride (60)

H_a 6·79 τ (2H, singlet)

H_b 7·49 τ (2H, broad singlet)

H_c 8·22 τ (4H, unresolved absorption)

H_d 8·34 τ (6H, unresolved absorption)

In both the saturated and unsaturated compounds, the exo protons (H_6, H_7) appeared as singlets, showing no coupling with H_b. The upfield shift (0·19 τ) of H_a on hydrogenation was in agreement with Fraser's theory[1] for an endo anhydride adduct. (It was assumed that the anomolous behaviour of compounds of type (124) (X = OH, OAc, OBs) was due to an effect of the oxygen attached to carbon 2.) The allylic proton H_b, due to couplings with the vinylic and / or methylene protons, appeared as a broad absorption.

The six methylene protons in the unsaturated compound (7) appeared as an almost unresolved singlet (half-band width, 8 c.p.s.); as a result, it could be postulated that the anti form (7) was equilibrating with the syn form (132) since the 3-endo proton in (7) would be expected to be shielded by the double bond and to appear therefore at higher field than the other five methylene protons. Thus, if the energy barrier between anti and syn forms was small, as was expected, the resultant N.M.R. absorption would be a time-averaged signal. However, in the syn form (132), interaction of the 3-endo proton with protons H_6 and H_7 would infer that the anti form would be the preferred conformation.

3-Benzoyloxybicyclo[3,2,2]non-8-ene-6,7-endo-dicarboxylic acid anhydride epimers, endo A (41) and endo B (42)

endo A

H_c 3·74 τ (2H, quartet, A part of A_2X_2, obs. splittings 5·5 and 3·5 c.p.s.)

H_e 4·72 τ (1H, quintet)

H_a 6·34 τ (2H, singlet)

H_b 6·82 τ (2H, unresolved absorption)

H_{da} 7·71 τ (2H, pair of triplets, obs. splittings 14·5 and 5·5 c.p.s.)

H_{ds} 8·11 τ (2H, pair of quartets, obs. splittings 14·5, 6 and 4 c.p.s.)

Irradiation of H_b gave the following changes:

H_{da} 7·71 τ (quartet, obs. splittings 15 and 6 c.p.s.)

H_{ds} 8·11 τ (quartet, obs. splittings 15 and 6 c.p.s.)

H_c 3·74 τ (singlet)

Irradiation of H_e gave the following changes:

H_{da} 7·71 τ (quartet, obs. splittings 15 and 5 c.p.s.)

H_{ds} 8·11 τ (quartet, obs. splittings 15 and 3·5 c.p.s.)

endo B

H_c 3·67 τ (2H, quartet, obs. splittings 5·5 and 3·5 c.p.s.)

H_e 4·69 τ (1H, heptet)

H_a 6·42 τ (2H, singlet)

H_b 6·79 τ (2H, unresolved signal)

H_{ds} 7·59 τ (2H, pair of triplets, J=13, J=6·5)

H_{da} 8·31 τ (2H, quartet, J=13·5, J=12)

As in the case of the unsubstituted anhydride (7), compounds endo A (41) and endo B (42) showed the same splitting pattern for protons H_a, H_b and H_c. This proved that both endo A and endo B had the anhydride group in the endo configuration, in agreement with the findings of an X-ray structure determination on an analogous bromobenzoate.

Since these compounds had large 3-substituents, they would be expected to adopt one of two conformations i.e., anti (41) and syn (42). In both these conformations, the 3-endo substituted compound would be unfavourable due to steric crowding; it therefore remained to differentiate between the 3-exo benzoates (41) and (42). On a first order basis, and assuming no distortions of the molecule, the protons H_d in either form would have the same splitting pattern, the result being that no differentiation would be observed by N.M.R. alone. However, from a study of non-bonding interactions, it was expected that, in the mixture of products formed in the Diels-Alder reaction, the anti-3-exo benzoate would be more stable than, and predominate over, the syn-3-exo isomer, in which the interaction of the 3-endo proton with the exo protons H_6 and H_7 would be

greater than the interaction of the 3-endo proton with the olefinic protons H_8 and H_9 in the former (anti) conformation. An X-ray structure analysis on the more abundant isomer showed it to be the anti-3-exo benzoate.

In fact (41) and (42) exhibited different splittings for the protons H_d. Examination of the pertinant dihedral angles (for H_d) showed that, whereas the endo B spectrum could be explained satisfactorally, that of endo A defied rationalisation on a first-order basis. Endo B (42) showed the expected quartet (H_{da}) i.e. a geminal coupling with H_{ds} ($J = 13{\cdot}5$) and a trans vicinal coupling with H_e ($J = 12$); since the angle between H_{da} and H_b in (42) is approx. 90°, no coupling was observed. It is worthy of note that, if endo B was in the anti form (43), the coupling constant of 12 c.p.s. would have been inconsistent with coupling to either of the H_d protons ($\phi \sim 65^\circ$). The other H_d proton of endo B (42), namely H_{ds}, also had a geminal coupling ($J = 13$) and two similar couplings with H_e and H_b (triplet), resulting in an overlapping pair of triplets as shown in Figure III.

On the other hand, the splittings for the H_d protons of endo A were more complex viz. a pair of triplets and a pair of quartets (Figure IV). Decoupling experiments indicated a splitting of 3·5 c.p.s. due to a

coupling between H_{ds} and H_b even although the dihedral angle was almost 90°. To explain this phenomenon, it was assumed that we were dealing with a perturbed system where the chemical shift difference between H_{da} and H_{ds} ($\Delta\delta_{H_{da}-H_{ds}}$ = 40 c.p.s.) was small. The chemical shift difference for the endo B H_d protons, which showed no perturbation, was, in contrast, much larger, $\Delta\delta_{H_{da}-H_{ds}}$ = 71 c.p.s.

Additional evidence for the perturbed H_d system of (41) was afforded by the fact that the diacid derivative (68) from endo A (41) displayed a simple splitting pattern (similar to endo B), the chemical shift difference being, as expected, larger ($\Delta_{H_{da}-H_{ds}}$ = 69 c.p.s.). Further justification for this theory was found in the observation that, when the spectrum of endo B was run at a frequency of 60 Mc, the originally unperturbed quartet for H_{da} showed additional splitting, due to a perturbation effect caused by the decrease in chemical shift difference on the instrument of lower field strength.

Thus, in view of these results, the multiplicity of the H_d protons was very much dependent on the chemical shifts of protons H_{da} and H_{ds}, which were characteristic of each compound. That the splittings were due to twisting effects of the three carbon bridge was excluded on the

grounds that conversion of the anhydride to the diacid, as above, should not alter the bridge conformation to any extent. It was worthy of note that, in conversion of the three carbon bridge from the anti to the syn form, the H_{ds} protons move outwards and horizontally; thus endo A, in an intermediate conformation e.g., (41a), would have H_{ds} protons which no longer subtended an angle of 90^{o} with H_b. However, the above diacid evidence appeared to exclude this theory.

2-Benzoyloxybicyclo[3,2,2]non-8-ene-6,7-endo-dicarboxylic acid anhydride (40).

H_c, $H_{c'}$ 3·75 τ (2H, quintet ≡ overlapping quartets, AB part of ABXY system)

H_e 4·91 τ (1H, multiplet)

H_a 6·40 τ (1H, quartet, J=8·5, J=2)

$H_{a'}$ 6·65 τ (1H, quartet, J=9, J=2)

H_b, $H_{b'}$ 6·78 τ (2H, unresolved signal)

H_d ca 8·2 τ (4H, complex)

Irradiation of H_e caused a slight change in the multiplet at ca 8·2 τ (H_d). Irradiation of H_b (or $H_{b'}$) gave a doublet at 3·67 τ (J = 9·5) and a quartet at 3·85 τ (J = 9·5, J = 6), illustrating the non-equivalence of H_c and $H_{c'}$. Irradiation of H_d reduced the broad multiplet at 4·91 τ to

a sharp doublet, J = 3·5 (coupling between H_e and H_b).

Due to the asymmetry of the molecule, H_a coupled with $H_{a'}$ (J = 9) and probably weakly with $H_{b'}$ (J = 2) giving rise to a pair of fine doublets. Owing to the proximity of the benzoyloxy group, the similar multiplicity for $H_{a'}$ appeared at a different chemical shift. H_c coupled with $H_{c'}$ (J = 9·5) and with H_b (J = 6) to give a quartet which overlapped with a similar quartet for $H_{c'}$.

Decoupling experiments showed that H_e coupled with H_b (J = 3·5) but due to the asymmetry of the molecule and perhaps distortion caused by the benzoate grouping, an assignment of the stereochemistry at C_2 could not be established.

Anti-3-exo-benzoyloxybicyclo[3,2,2]non-8-ene-6,7-endo-dicarboxylic acid (68).

H_e 4·80 τ (1H, complex)

H_a 6·31 τ (2H, singlet)

H_b 6·57 τ (2H, unresolved signal)

H_{da} 7·61 τ (2H, unidentified multiplet)

H_{ds} 8·29 τ (2H, quartet, J=13, J=10)

For solubility reasons, the spectrum of this compound was run in pyridine solution.

The singlet for the exo proton, H_a, was once again obvious and thus the diacid grouping could be assigned as endo. The multiplicity of the protons H_{da} and H_{ds} has been discussed when dealing with the corresponding anhydride (41), ($\Delta\delta_{H_{da-ds}}$ = 69 c.p.s.). Although the H_{ds} protons showed couplings dependent on the dihedral angles, the multiplicity of H_{da} could not be identified.

Anti-3-exo-benzoyloxy-6,7-endo-dicarbomethoxybicyclo[3,2,2] non-8-ene (69).

H_c 3·87 τ (2H, quartet, A_2 part of an A_2X_2 system obs. splittings 5·5 and 3·5 c.p.s.)

H_e 4·95 τ (1H, multiplet)

H_f 6·40 τ (6H, singlet)

H_a 6·63 τ (2H, singlet)

H_b 6·84 τ (2H, unresolved absorption)

H_{da} 7·60 τ (2H, pair of triplets, J=13·5, J≈7)

H_{ds} 8·38 τ (2H, quartet, J = 14, J=10)

The endo configuration of the ester groupings was similarly confirmed by the singlet at 6·63 τ. Although the H_d signals were not as well defined as in the anhydride cases, the difference in chemical shift ($\Delta_{H_{da}-H_{ds}}$ = 76 c.p.s.) was large enough for an approximate first order interpretation to be valid. Thus H_{ds} showed geminal coupling

(J = 14) and further splitting by H_e (J = 10) to afford a quartet although fine splitting was also observed (J < 1).

Anti-3-exo-p-bromobenzoyloxybicyclo[3,2,2]non-8-ene-6,7-endo-dicarboxylic acid anhydride (47)

H_f 2·13 τ (2H, doublet, J=9)

H_g 2·39 τ (2H, doublet, J=9)

H_c 3·75 τ (2H, quartet, obs. splittings 5·5 and 3·5 c.p.s.)

H_e 4·79 τ (1H, quintet)

H_a 6·42 τ (2H, singlet)

H_b 6·84 τ (2H, unresolved absorption)

H_{da} 7·71 τ (2H, pair of triplets, obs. splittings 14·5 and 5·5 c.p.s.)

H_{ds} 8·20 τ (2H, pair of quartets, obs. splittings 14·5, 6 and 3·5 c.p.s.)

The spectrum showed an identical splitting pattern to compound endo A (41), apart from the aromatic region. The endo configuration of the anhydride was once again noted. Since this structure was confirmed by X-ray analysis as (47), the perturbed multiplicity ($\Delta\delta_{H_{da}-H_{ds}}$ = 49 c.p.s.) for protons H_d was indicative of the 3-exo substituent in the anti form.

Anti-3-exo-hydroxybicyclo[3,2,2]non-8-ene-6,7-endo-dicarboxylic acid N-phenyl imide (5) (Recorded at 60 Mc)

H_c 3·91 τ (2H, quartet, obs. splittings 5 and 3 c.p.s.)

H_e 6·20 τ (1H, multiplet)

H_a 6·64 τ (2H, singlet)

H_b 6·81 τ (2H, unresolved absorption)

H_{da} 7·82 τ (2H, pair of triplets, obs. splittings 14·5 and 6 c.p.s.)

H_f 8·13 τ (1H, singlet) D_2O exchange

H_{ds} 8·49 τ (2H, pair of quartets, obs. splittings 14·5, 8 and 3 c.p.s.)

Since the splitting patterns were almost identical to that of endo A (41) and its bromo derivative (47), the endo configuration of the anhydride was confirmed as well as the anti-3-exo hydroxy conformation of the molecule. The chemical shift difference $\Delta\delta_{H_{da}-H_{ds}}$, in this case was 40 c.p.s.

3-exo-hydroxy-6,7-endo-dihydroxymethylbicyclo[3,2,2]non-8-ene (70). Solvent D_2O

H_c 4·00 τ (2H, quartet, obs. splittings 5·5 and 3·5 c.p.s.)

H_{ds} 8·74 τ (2H, quartet, J=13, J=10)

Due to additional absorption for the carbinol methylene group, individual splittings were not discernible and therefore stereochemical assignment of endo configuration for the hydroxymethyl group could not be made. However, the H_{ds} quartet was well separated from the other signals, and a first order interpretation was applicable.

Anti-3-exo-benzoyloxy-6,7-endo-dicarbomethoxybicyclo[3,2,2]nonane-7,8-diol (76).

H_f 2·04 τ, 2·51 τ (5H, complex)

H_e 4·28 τ (1H, multiplet)

H_c 5·74 τ (2H, unresolved signal)

H_g 6·38 τ (6H, singlet)

H_a 6·51 τ (2H, singlet)

H_b, H_{da} 7·26 τ (4H, multiplet)

H_{ds} 8·15 τ (2H, multiplet)

The hydroxyl protons were not obvious and appeared as a weak, broad absorption due to hydrogen bonding at ca 6·6 τ ($\sim$1·5 H), which disappeared on deuteration. Since the structure was saturated, much of the rigidity had gone thus allowing the molecule to adopt two possible twist conformations (77) and (78), the time-averaged configuration of which was seen by N.M.R. Thus H_6 and H_7 exo protons appeared as a singlet as in the previous cases.

The low value of H_e was consistent with the removal of the shielding effect of the double bond on hydroxylation. However, no information could be obtained from N.M.R. concerning the orientation of the hydroxyls although chemical evidence (Part I) suggested that they were in the exo configuration.

3,3-Ethylenedioxybicyclo[3,2,2]non-8-ene-6,7-endo-dicarboxylic acid anhydride (95).

H_c 3·85 τ (2H, quartet, obs. splittings 5 and 4 c.p.s.)

H_a 6·02 τ (2H, singlet)

H_e 6·20 τ (4H, quartet with small side bands A_2B_2 system)

H_b 7·98 τ (2H, unresolved signal)

H_{da} 8·01 τ (2H, quartet, J=14, J=7 A part of ABX system)

H_{ds} 8·33 τ (2H, doublet, J=14, B part of ABX system)

The anhydride configuration was again observed as endo; due to the asymmetric environment of the ketal grouping, an A_2B_2 pattern was seen for the two ketal methylenes. The splitting for the H_d protons is illustrated in Fig. V, the doublet at 8·33 τ being assigned to H_{ds}, i.e. coupling only with H_{da} (no coupling with H_b, $\phi \sim 90^\circ$). The quartet for H_{da} arose from coupling with H_{ds} and with H_b.

The further fine splitting (2 c.p.s.) of the described doublet at 8·33 τ on recording the spectrum at 60 Mc illustrated the sensitivity of these signals to field strength.

3-Ketobicyclo[3,2,2]non-8-ene-6,7-endo-dicarboxylic acid anhydride (94)

H_c 3·69 τ (2H, quartet, obs. splittings 5·5 and 3·5 c.p.s.)

H_a 6·04 τ (2H, singlet)

H_b 6·76 τ (2H, partially resolved signal)

H_{da} 7·14 τ (2H, quartet, J=18, J=4 A part of ABX system)

H_{ds} 7·43 τ (2H, quartet, J=18, J=4 B part of ABX system)

The singlet at 6·04 τ indicated once more the endo configuration of the anhydride; although the A B part (Fig.VI) of the ABX system was now symmetrical (in contrast to that of the corresponding ketal) conformational information could not be derived owing to the fact that this system was very sensitive to changes in operating frequency (100 Mc to 60 Mc), which caused splittings not readily explainable. It was interesting to note that, since carbon 3 was now trigonal, removal of the interactions, H_{3endo}-H_6, H_7, in the syn form, allowed the latter conformation to compete in stability with the anti form. However, it could not

be established from the sensitive H_d multiplicity whether an equilibrating system was present or not.

3,3-Ethylenedioxy-6,7-endo-dicarbomethoxybicyclo[3,2,2]non-8-ene (97).

H_c 3·72 τ (2H, quartet, obs. splittings 5·5 and 3·5 c.p.s.)

H_e 6·14 τ (4H, quartet, with side bands, A_2B_2 system)

H_a 6·24 τ (2H, singlet)

H_f 6·45 τ (6H, singlet)

H_b 7·14 τ (2H, broad absorption)

H_{da} 8·03 τ (2H, quartet, J=14, J=6, A part of ABX system)

H_{ds} 8·29 τ (2H, quartet, J=14, J=2, B part of ABX system)

Irradiation of H_b reduced the H_{da} , H_{ds} signals to a pair of doublets, J = 14 (AB quartet), as well as reducing H_c to a singlet.

The endo configuration for the diester was indicated by the singlet for H_a. The ketal absorption was again complex i.e., an A_2B_2 system due to asymmetry.

Thus from the splitting patterns, ABX and A_2B_2, in addition to the fact that there was likely to be steric compression in the syn form, the anti configuration was established.

However, comparison of this spectrum with that of the anhydride ketal (95), showed an additional splitting for H_{ds} in the former case (although small, J = 2). This splitting was also observed when the anhydride spectrum was recorded at 60 Mc. This illustrated that the H_d multiplets were indeed sensitive to the operating frequency.

From the above results and arguments, the following conclusions could be made regarding the stereochemistry of the bicyclo[3,2,2]nonene system.

The endo configuration of anhydride, diacid and diester groupings was readily deduced from a consideration of dihedral angles.

By analogy with Fraser's work[1] on bicyclo[2,2,1] heptene and heptane derivatives, the endo configuration of the anhydride was confirmed by the upfield shift of the C_6 and C_7 protons on hydrogenation of the C_8-C_9 double bond.

In the case of 3-substituted compounds, it could not be determined by N.M.R. alone (due to perturbation) whether the molecule adopted the anti or the syn conformation since the methylene protons H_d would afford

identical splitting patterns in both the syn and anti forms, on a first order basis. However, use of an X-ray analysis, in confirming the anti configuration of endo A (41), allowed the others to be defined.

Twisting and upward distortion of the three carbon bridge have not been overlooked.

In contrast to the 3-substituted compounds, the 3-methylene compound (7) and the 3-ketone (94) had more opportunity to flip from one form to the other (i.e. anti $\rightleftharpoons$ syn). In the case of the former, the N.M.R.was consistent with flipping but, owing to the sensitivity of the H_d protons to field strength, no similar conclusions could be derived from the N.M.R. of the latter. Low temperature N.M.R. studies on both molecules may well settle the issue.

Examination of N.M.R. spectra at both 100 Mc and 60 Mc illustrated the importance of not taking any one spectrum too literally.

Chart I.

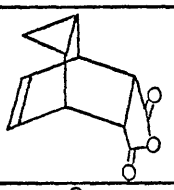
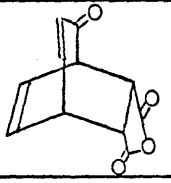
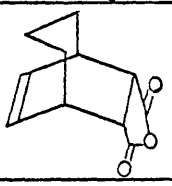
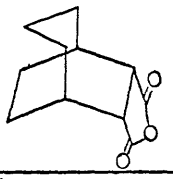
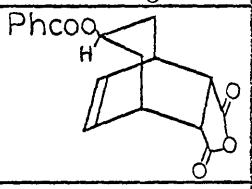
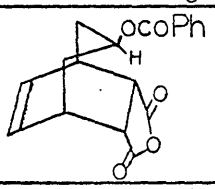
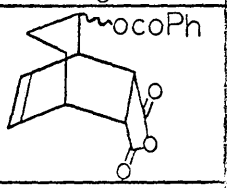
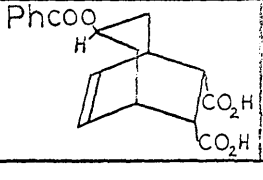
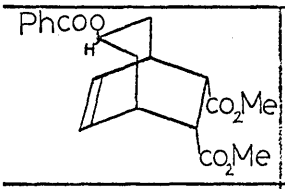
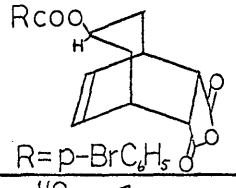
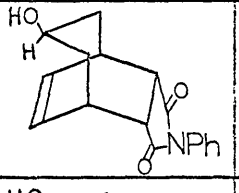
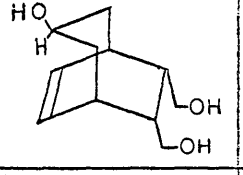
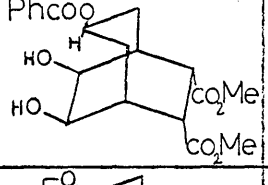
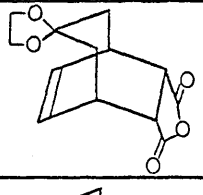
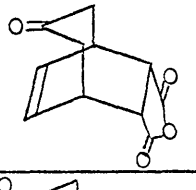
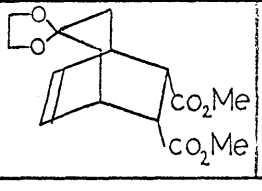
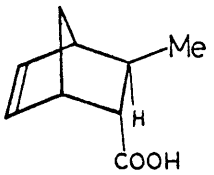
	H_a	H_b	H_c	H_d		H_e
	6·72 d J=2	6·55 m	4·12 q 5, 4	8·86 m		ca 9·7 m
	6·0–6·6 m		c'3·36 q, J=8,8 c 3·72 q, J=8,8	2·82 q J=11,8		4·13 q J=11, 2
	6·60 s	7·00 bs	3·83 q 6, 4	8·31 ~s		-
	6·79 s	7·49 bs	8·22 ~s	8·34 ~s		-
	6·34 s	6·82 bs	3·74 q 5·5, 3·5	H_{da} 7·71 d of t 14·5,5·5	H_{ds} 8·11 d of q 14·5, 6 and 4	4·72 quin.
	6·42 s	6·79 bs	3·67 q 5·5, 3·5	8·31 q J=13·5,12	7·59 d of t J=13,6·5	4·69 hept.
	a 6·40 q,J=8·5,2 a'6·65 q, J=9,2	6·78 bs	3·75 quin.	ca 8·2 m		4·91 m
	6·31 s	6·57 bs	-	7·61 m	8·29 q J=13, 10	4·8o m

Chart I contd.

	H_a	H_b	H_c	H_{da}	H_{ds}	H_e
	6·33 s	6·84 bs	3·87 q 5·5, 3·5	7·60 d of t J=13·5,7	8·38 q J=14, 10	4·95 m
	6·42 s	6·84 bs	3·75 q 5·5, 3·5	7·71 d of t 14·5,5·5	8·20 d of q 14·5, 6 and 3·5	4·79 quin.
	6·64 s	6·81 bs	3·91 q 5, 3	7·82 d of t 14·5, 6	8·49 d of q 14·5, 8 and 3	6·20 m
	–	–	4·00 q 5·5, 3·5	–	8·74 q J=13, 10	–
	6·51 s	7·26 m	5·74 bs	7·26 m	8·15 m	4·28 m
	6·02 s	7·98 bs	3·85 q 5, 4	8·01 q J=14, 7	8·33 d J=14	–
	6·04 s	6·76 m	3·69 q 5·5, 3·5	7·14 q J=18, 4	7·43 q J=18, 4	–
	6·24 s	7·14 bs	3·72 q 5·5, 3·5	8·03 q J=14, 6	8·29 q J=14, 2	–

bs = broadened singlet d of t = doublet of triplets



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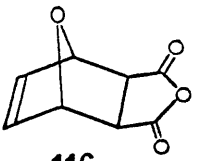

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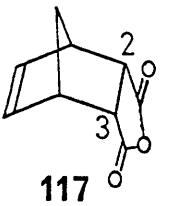

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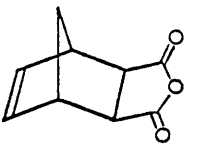

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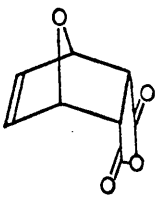

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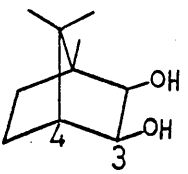

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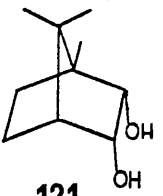

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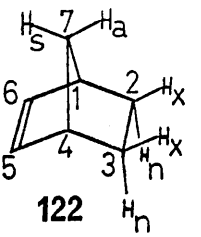

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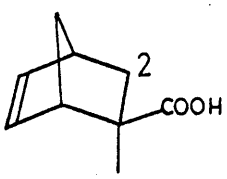

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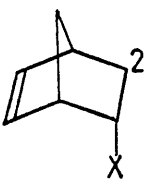

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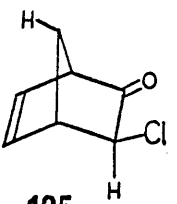

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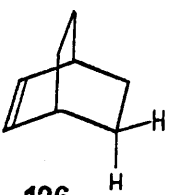

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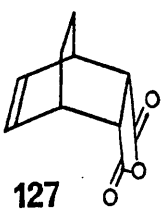

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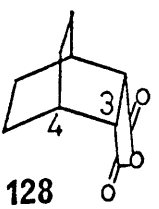

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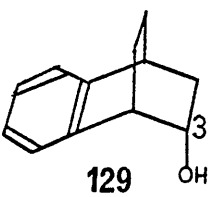

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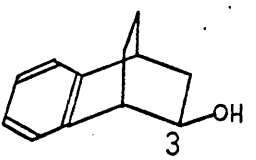

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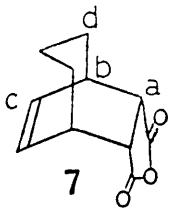

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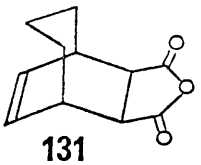

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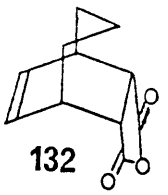

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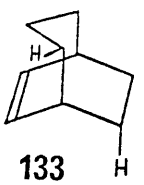

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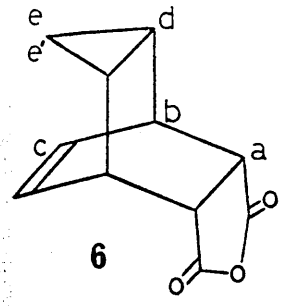

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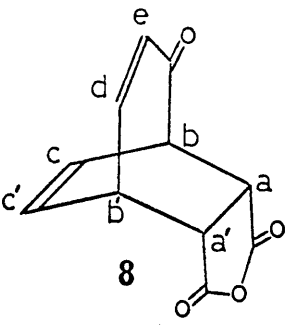

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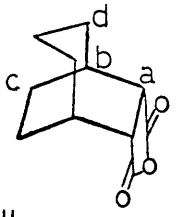

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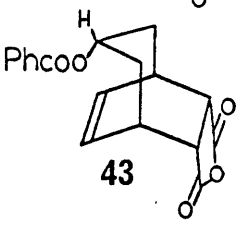

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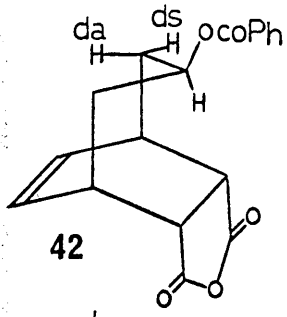

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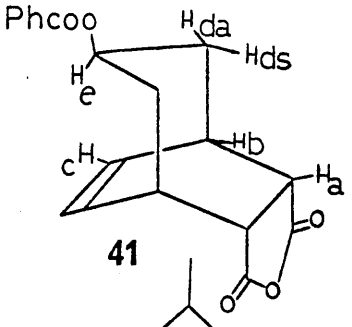

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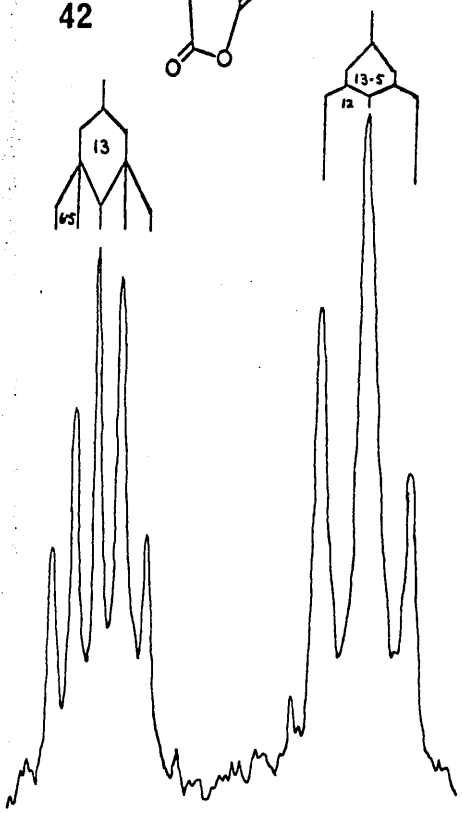


FIG III

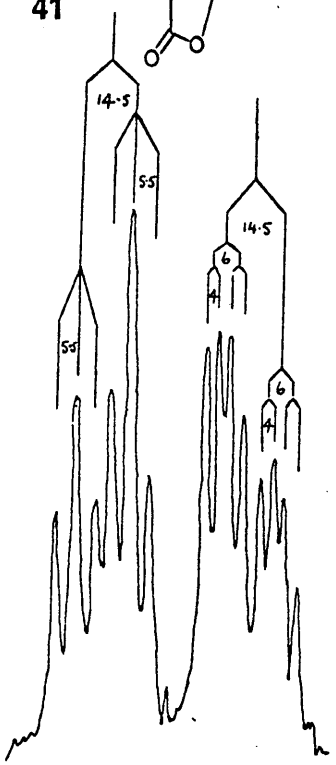
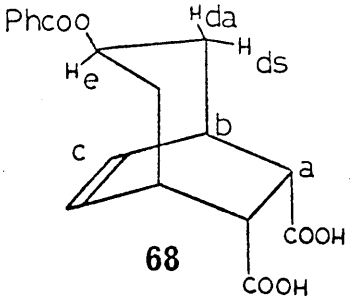


FIG IV



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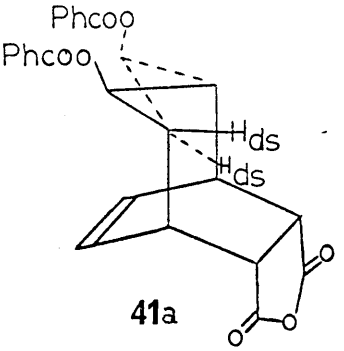

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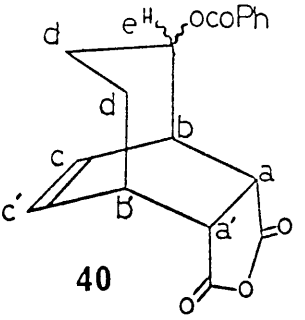

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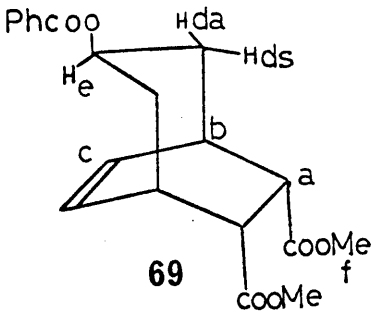

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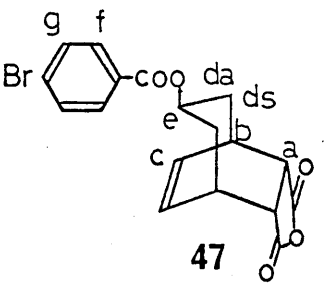

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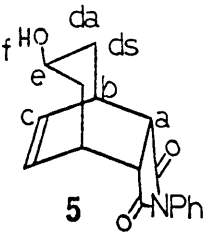

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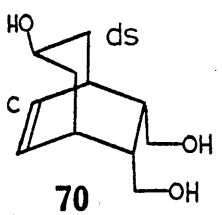

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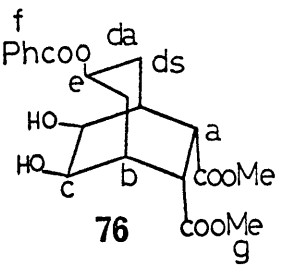

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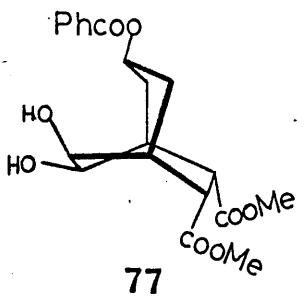

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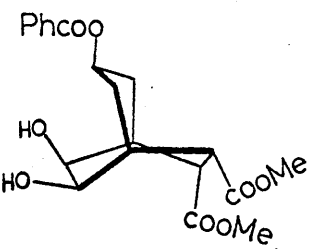

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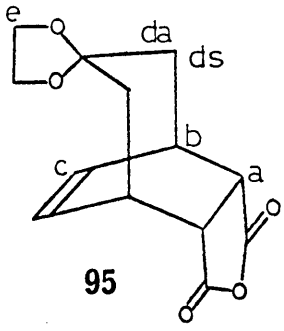

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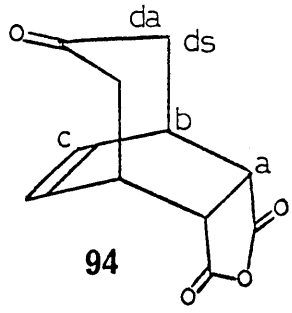

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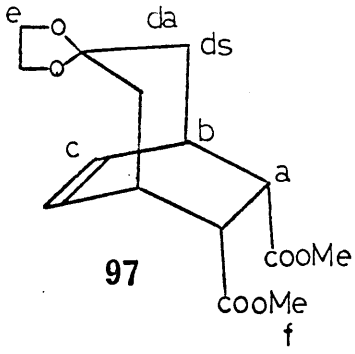

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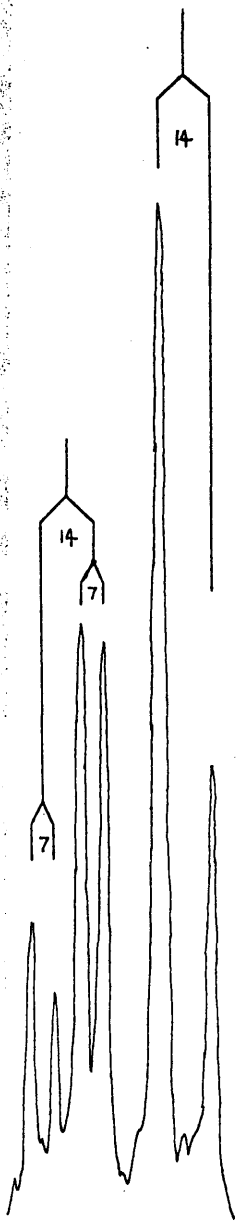

FIG V

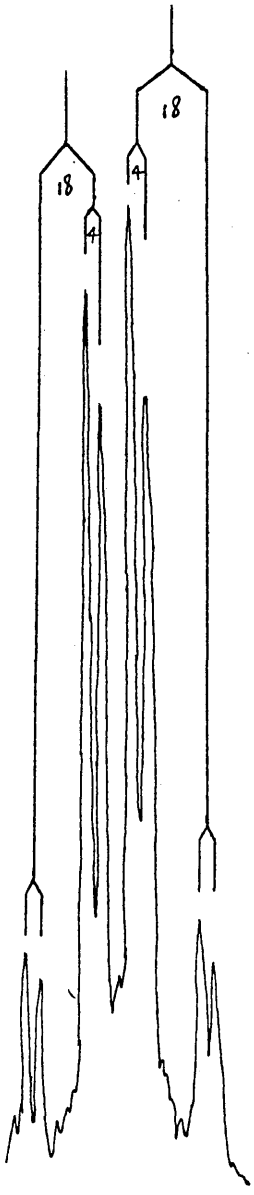

FIG VI

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P A R T III.

SYNTHETIC APPROACHES TO A DITERPENE INTERMEDIATE

SYNTHETIC APPROACHES TO DITERPENES

With the elucidation of the stereochemistry of many interesting diterpenes in the last decade, the synthesis of members of this group of natural products became a challenge.

The following review illustrates how this challenge has been dealt with in elaborating the carbon skeletons while excercising stereochemical control in the process. The notation e.g., A → B → C refers to the order of construction of the terpenoid rings.

1. Biogenetic Type
2. Tricyclic Diterpenes
   - (i) Aromatic type
     - (a) A → C → B
     - (b) B, C → A
     - (c) A, B → C
   - (ii) Non-aromatic type
     - (a) B, C → A
     - (b) A, B → C
3. Tetracyclic Diterpenes
   - (i) A, B, C → D
   - (ii) B, C → D → A
4. Ring Expanded and Contracted Diterpenes

1. Biogenetic Type

Since the biosynthesis of tricyclic diterpenoids appears to take place through the cyclisation of acyclic polyisoprenoid precursors, attempts have been made to parallel this behaviour *in vitro*. Caliezi and Schinz[1] successfully synthesised abietatriene (2) from the acyclic ketone (1) under acidic conditions, while others[2,3] using similar techniques isolated mixtures of A/B cis- and trans-isomers (4) from corresponding aromatic compounds (3). More recently van Tamelen[4] has shown interesting cyclisations of epoxides of the type (5) → (6) with boron trifluoride etherate, the resulting molecule displaying the natural product A/B ring configuration (6). However, although these workers have achieved a synthesis of triterpenes[5] of the β-onocerin type, there has been no assault on the diterpene skeleton.

2. Tricyclic Diterpenes

(i) Aromatic type

(a) A → C → B

Using 2,2,6-trimethylcyclohexanone (7) as the starting material, this route had the advantage of avoiding unspecific methylations and is the subject of numerous

papers.[6,7] A typical example of a satisfactory synthesis is totarol[8] (10) (Scheme 1) in which the ketone is treated with potassium m-methoxyphenylacetylide to give the acetylene alcohol (8) which, after hydrogenation, was cyclodehydrated to the tricyclic system (9). Further elaboration as shown afforded the diterpene (10). Use of the keto-ester (11) in a similar synthesis by King et al.[9] to give the ester of (±)-O-methyl podocarpic acid (12, R=Me) (not strictly diterpenoid) illustrated the potential of the route to the resin acids, although separation of stereoisomeric esters was required.

The conjugated enone (14) was of similar importance in the synthetic studies of Church et al.,[10] being the product of condensation of enone (13) with 1-diethylamino-3-pentanone methiodide. Hydrogenation, followed by reduction of the carbonyl to the alcohol and cyclisation with polyphosphoric acid, afforded the required skeleton (9).

In their elegant synthesis of dl-dehydroabietic acid (20), Ireland et al.[11] adopted an unusual approach to the tricyclic ring system (Scheme 2). Methylation in the 2-position of ketone (15) followed by condensation of the hydroxymethylene derivative with methyl vinyl ketone gave, on hydrolysis, a diketone (16) in which the ketone chain

was in the α-configuration. Methylation of the mono ketal and cyclisation of the regenerated diketone (17) afforded the trans ketone (18) on reduction of the double bond. Ozonolysis of the derived hydroxymethylene compound resulted in a diacid of known configuration. Polyphosphoric acid cyclisation and degradation of the acetic acid side chain concluded a completely unambiguous route to dl-dehydroabietic acid (20).

Keto-lactones of type (21) have been used[12] in synthetic schemes, the lactone acting as a precursor for the acid function of the resin acid, cyclisation being effected by polyphosphoric acid treatment to yield the enol-lactone (22). Depending on the manner of cleavage of this lactone, both the A/B cis- and trans- ring systems could be obtained.

(b) B, C → A

A stereospecific and widely used route to the desired tricyclic system made use of a β-tetralone as rings B and C. The synthesis of dehydroabietic acid (20) by Stork et al.[13] serves as a typical example (Scheme 3). Methylation of the β-tetralone followed by ring-extension using ethyl vinyl ketone yielded an enone (24), which, after

alkylation with bromoacetic ester on the less hindered side, was hydrogenated to give the ketoester (25) as shown. Removal of the carbonyl followed by a Barbier-Wieland degradation of the acetic ester finally gave (±)-dehydroabietic acid (20).

In a similar synthesis, Wenkert et al.[14] carboxylated the derived enone (26) with triphenylmethyl sodium and carbon dioxide; esterification gave a mixture of the ester (27) and the isomeric 2-carboxylic ester. Catalytic hydrogenation, then methylation afforded mainly the ketoester (28) which was converted by classical steps into podocarpic acid (12, R=H).

The synthesis[15] of nimbiol methyl ether (30) followed a similar pathway to the Stork route; methylation and hydrogenation of the methoxy enone (29), followed by carbonyl removal and oxidation afforded the product (30).

(c) A, B → C

Another well-studied approach to the diterpenoid skeleton is that of Spencer et al.[16] using the octalone (31) as the starting material. Using procedures similar to those already described, this enone was converted to the trans-fused hydroxy ester (32). Oxidation afforded a

moiety suitable for ring-extension, by the Robinson method, to the enone (33), ring C then being aromatised by standard methods to dehydrodesisopropylabietate (34).

Dutta et al.[17] also synthesised this molecule by essentially the same route, their ultimate step being an unusual A/B cis (35) → A/B trans (34) isomerisation effected by heating over palladium/charcoal.

(ii) Non-aromatic type

(a) B, C → A

In their synthesis of pimaradiene (41), Ireland et al.[18] (Scheme 5) hydrogenated the phenolic ring C and, after oxidation, converted the ketone to the enamine via the hydroxymethylene derivative. Reaction with methyl Grignard and subsequent methylation at C_{13} afforded separable epimers, which, after reduction to the alcohol and pyrolysis of the derived benzoate, afforded pimaradiene (41) and its C_{13} epimer, sandaracopimaradiene.

(b) A, B → C

The unsaturated aldehyde (42) was the building block for a synthesis of the unusual trans-syn-cis ring system (46) by Church and Ireland[19] (Scheme 6). The vinyl

ether (43) underwent a Claisen type rearrangement and the resulting aldehyde, protected as the acetal, was hydroborated and oxidised to yield compound (45) in which the side chains were α-*cis*. Acid cyclisation and hydrogenation afforded a ketone which was converted to the butylthiomethylene derivative (47) via the hydroxymethylene compound. Steam distillation of the derived alcohol furnished the unsaturated aldehyde (48) which finally afforded (Scheme 6) separable epimers (49), 9-isomers of the pimaradiene class.

Rimuene (55) is the product of a rearrangement on the biogenetic route, having a methyl group at the 9-position. Ireland *et al.*[20] made use of a β-tetralone as rings A and B (cf. 2(i)b.), ring-extending with methyl vinyl ketone (Scheme 7). Successive reductions of (51) yielded the saturated alcohol which, after Birch reduction and protection of the alcohol, afforded the enone (52). Dimethylation and carbonyl removal then left only the C ring to be elaborated. This was done via the ketone, the epoxide and the aldehyde as shown, further conversion to rimuene (55) being similar to that used in their synthesis of pimaradiene.

3. Tetracyclic Diterpenes

(i) A, B, C → D

In an approach to the bridged bicyclic C/D system of phyllocladene (67), it was required that there should be β-substitution at the ring junction carbon 8. Direct alkylation[21] of a C_{13} blocked derivative (56) with allyl bromide (Scheme 8) yielded the α-substituted product (57) but oxidative cleavage of ring C, followed by Dieckmann cyclisation of the derived triester (58) afforded, on hydrolysis and decarboxylation, dl-8β-carbomethoxy-13-oxopodocarpane (59), a degradation product of phyllocladene. Church et al.[22] also achieved the synthesis of (59), firstly by conversion of the enol ether (60) to the aldehyde (61) by a Claisen rearrangement (Scheme 9), then by cleavage of the double bond, followed by Dieckmann condensation of the derived anhydride ester (62).

Phyllocladene (67) has been obtained[23] from the keto ester (59) by a Reformatsky reaction with bromoacetic ester to yield the lactonic ester (63) (Scheme 10). Lactone ring opening, hydrogenation and hydrolysis afforded the diacid (64) which was pyrolised as the barium salt to form the D ring system. The acetal of the derived hydroxy-methylene compound was reduced and mineral acid treatment

afforded the unsaturated aldehyde (66). Wolff-Kishner reduction completed the synthesis of phyllocladene (67).

One of the intermediates used above, the olefinic aldehyde (61) had the steric requirements for a synthesis[24] of the kaurene skeleton. The acetal of (61) was hydroborated and oxidised to yield a separable mixture of the C_{13} and the C_{14} ketones (Scheme 11), the latter cyclising to ketol (70) on treatment with aqueous acid followed by alkoxide ion. Protection of the alcohol with dihydropyran, carbonyl removal and oxidation of the regenerated alcohol afforded the 16-ketone which, after condensation with methylenetriphenylphosphorane, yielded kaurene (72). It is noteworthy that the isomeric C_{13} ketone (73) obtained above can be transformed by an identical pathway into atisirine (74), a diterpene of the bicyclo[2,2,2]type.

The availability of the keto-acetal (73) allowed Bell et al.[25] to achieve a total synthesis of hibaene (79) in a masterly fashion (Scheme 12). Hydroboration and oxidation of the ethylidene derivative gave the 13-α-acetyl compound (75) which, after epimerisation with base, was cyclised to (76). After Beckmann rearrangement of the derived oxime, replacement of the acetamido group by acetate via rearrangement of the N-nitroso derivative

yielded the diacetate. After hydrolysis and oxidation, the hydroxy olefin (78) was obtained by condensation with methylenetriphenylphosphorane. Rearrangement of this type of compound to hibaene (79) followed a known pathway[26] thus concluding the synthesis.

(ii) B, C → D → A

A completely different approach to the synthesis of diterpenes of the kaurene type was undertaken by Masamune[27] who elected to construct rings B, C and D from the tetralin derivative (80) (Scheme 13). On base treatment cyclisation was effected producing the dienone (81) in high yield. The derived benzoate on hydrogenation afforded two isomeric ketones (82), the predominant cis-fused one then being carbomethoxylated and ring-extended with ethyl vinyl ketone to give enone (83) which by classical but tedious steps was converted into kaurene (72).

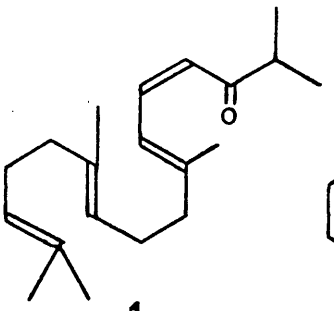
4. Ring Extended and Contracted Diterpenes

Tetracyclic diterpenes are not restricted to the six-membered ring variety as exemplified by gibberellic acid (84) and grayanotoxin-I (85).

As yet there have been no syntheses of such molecules, although model compounds have been studied. Gibberic acid[28] (86) and gibberone[29] (88) have been synthesised by way of the cyclisation step (87) → (88a) using boron trifluoride in acetic acid/acetic anhydride. Stork[30] has also accomplished an interesting cyclisation in this field, using the ethynyl ketone (89). Chemical reduction with potassium in an ammonia/tetrahydrofuran solution afforded a mixture from which the olefin alcohol (90) could be isolated. It is interesting to note that steviol (91), a diterpenoid acid, has the same C/D ring stereochemistry and could presumably be synthesised in the same way from a suitable precursor.

The synthesis of the grayanotoxins on the other hand, has received practically no attention although a probable route to the A/B skeleton is by a photochemical reaction of the type[31] (92) → (93). Yoshikoshi and coworkers[32] have shown in their interconversion between hibaene and kaurene that hibaene epoxide (94) can be rearranged to the glycol (95) which has the same relative configurations of the B/C/D ring functions and of the substituents in the C and D rings as the grayanotoxins (85), illustrating at the same time a possible biogenetic pathway.

In the present investigation it was envisaged that a bridged bicyclic molecule of the type (96) would prove to be suitable as an intermediate in the synthesis of diterpenes of the grayanotoxin series.



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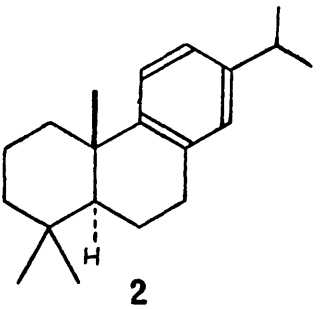

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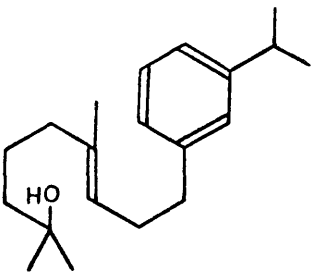

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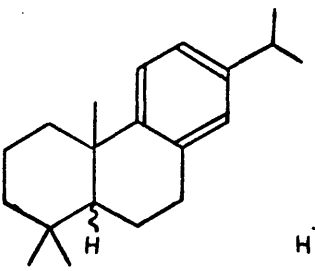

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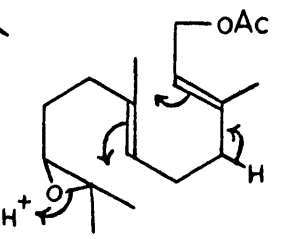

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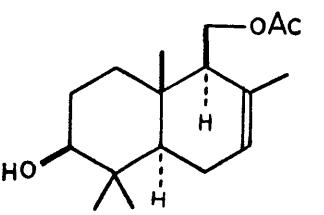

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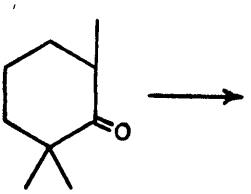

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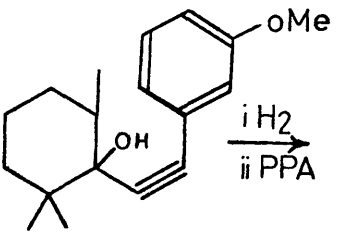

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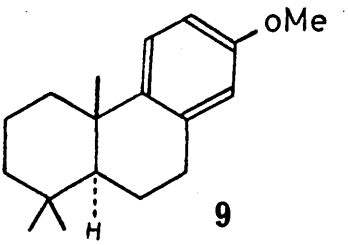

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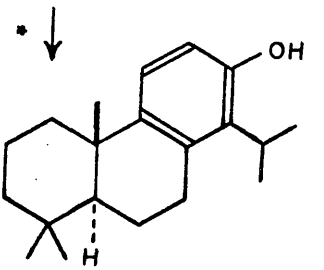

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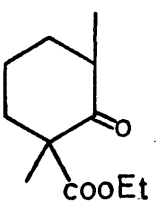
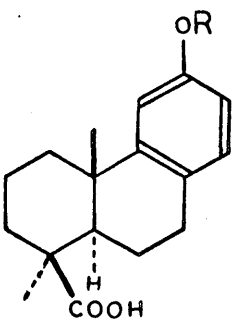


11

* i Birch Red^{n}
ii Alk^{n}
iii Dehydrog^{n}

SCHEME 1



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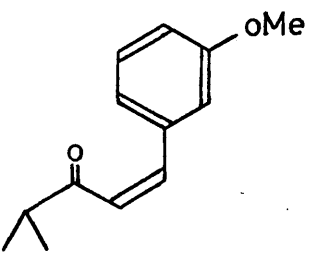

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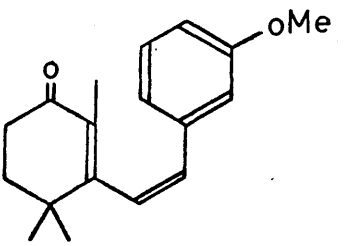

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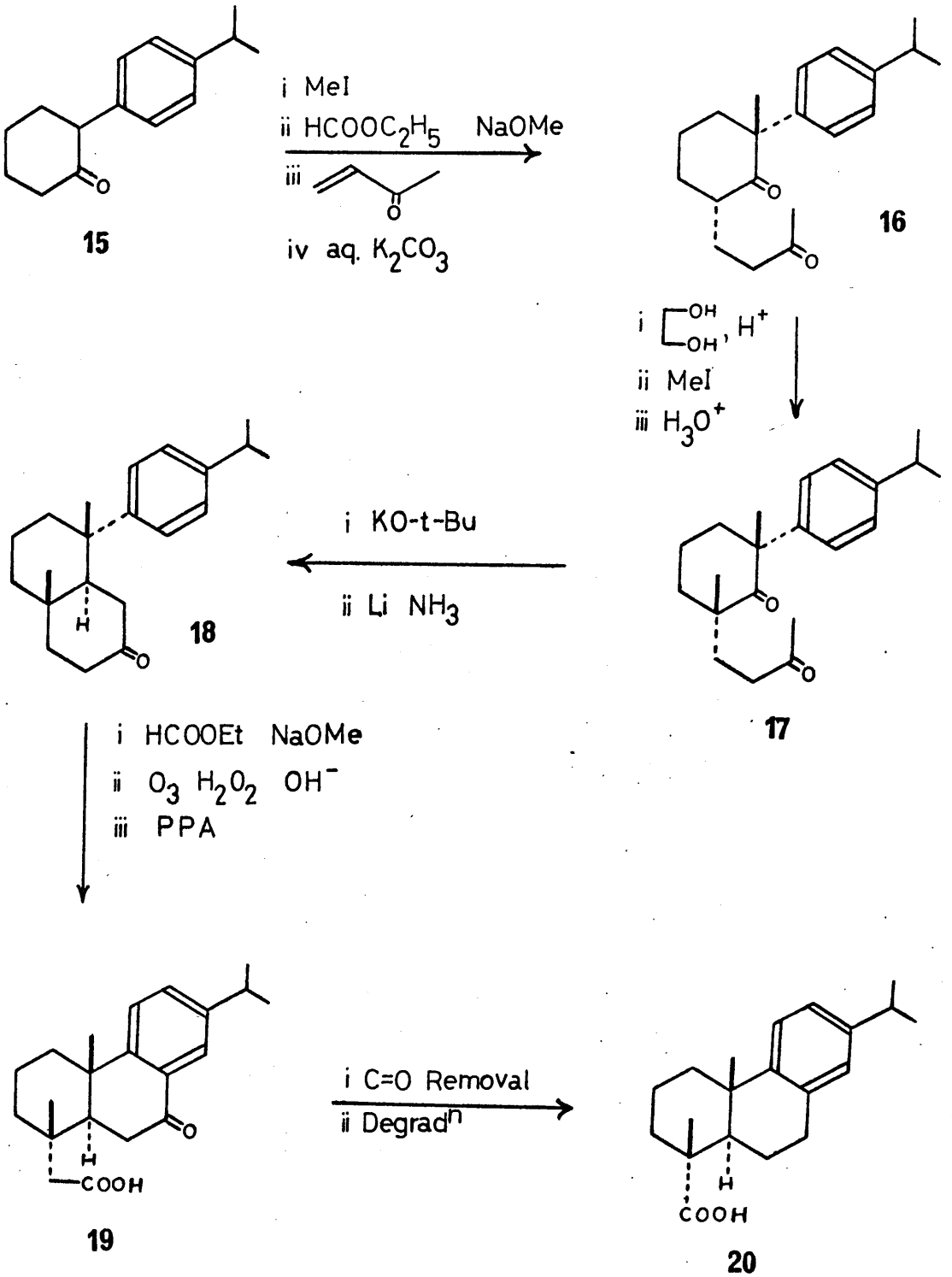
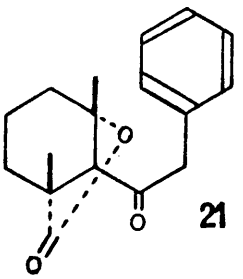

i MeI
ii HCOOC2H5 NaOMe
iii
iv aq. K2CO3
15
16
i OH, OH, H+
ii MeI
iii H3O+
17
i KO-t-Bu
ii Li NH3
18
i HCOOEt NaOMe
ii O3 H2O2 OH−
iii PPA
19
i C=O Removal
ii Degradn
20

SCHEME 2



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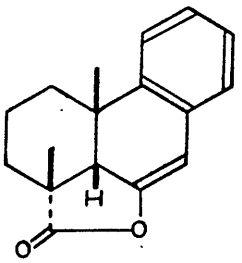

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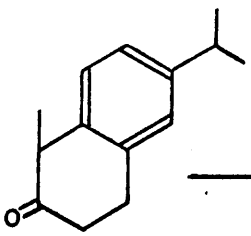

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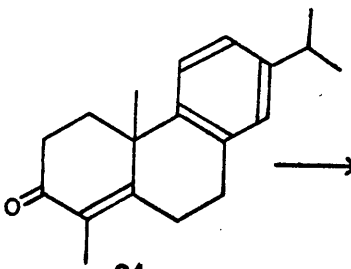

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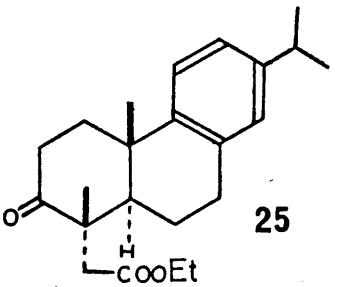

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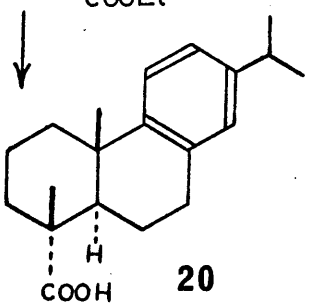
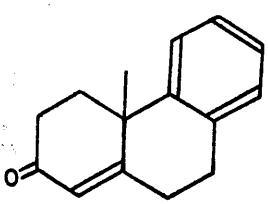


20

SCHEME 3



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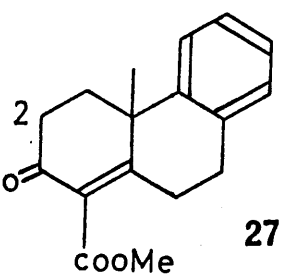

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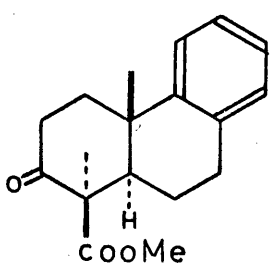

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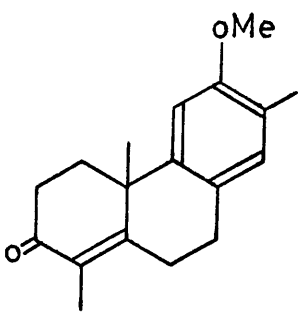

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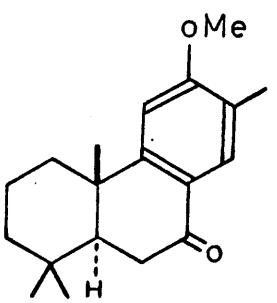

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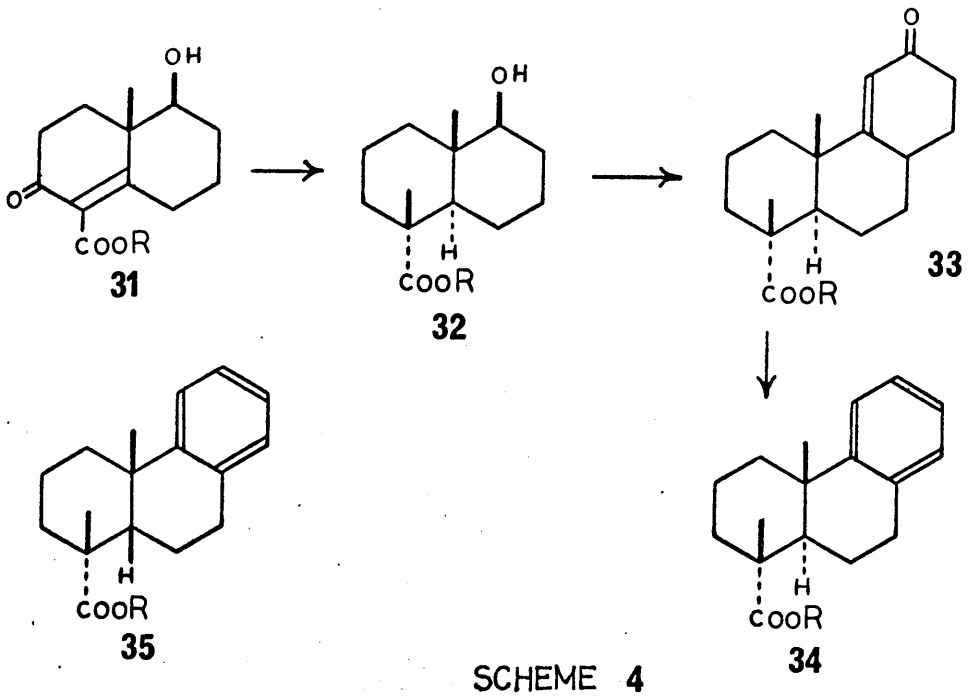

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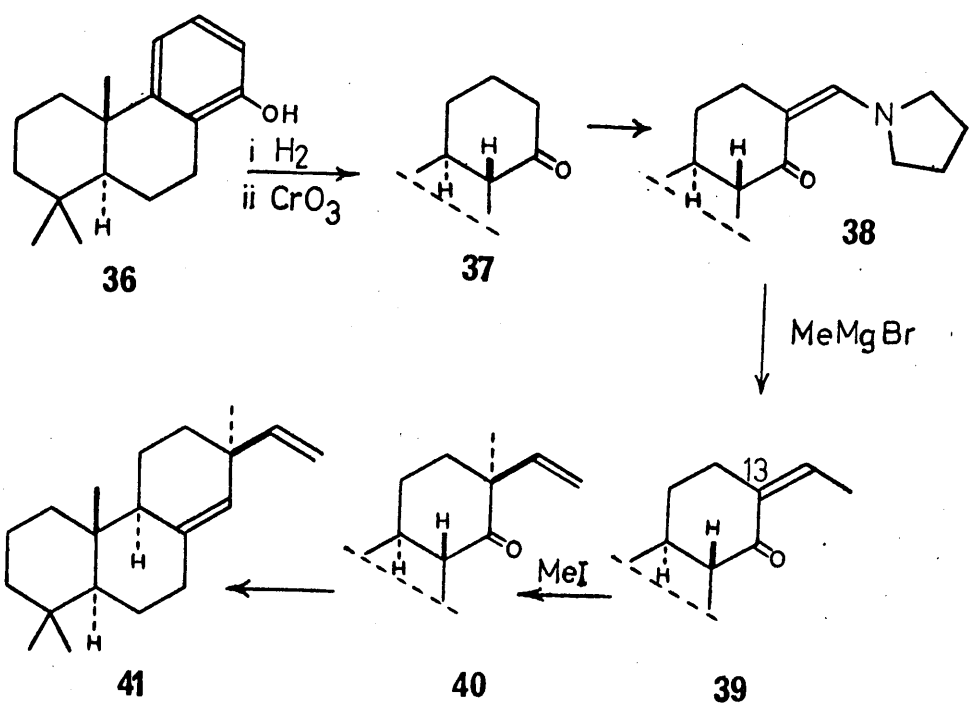
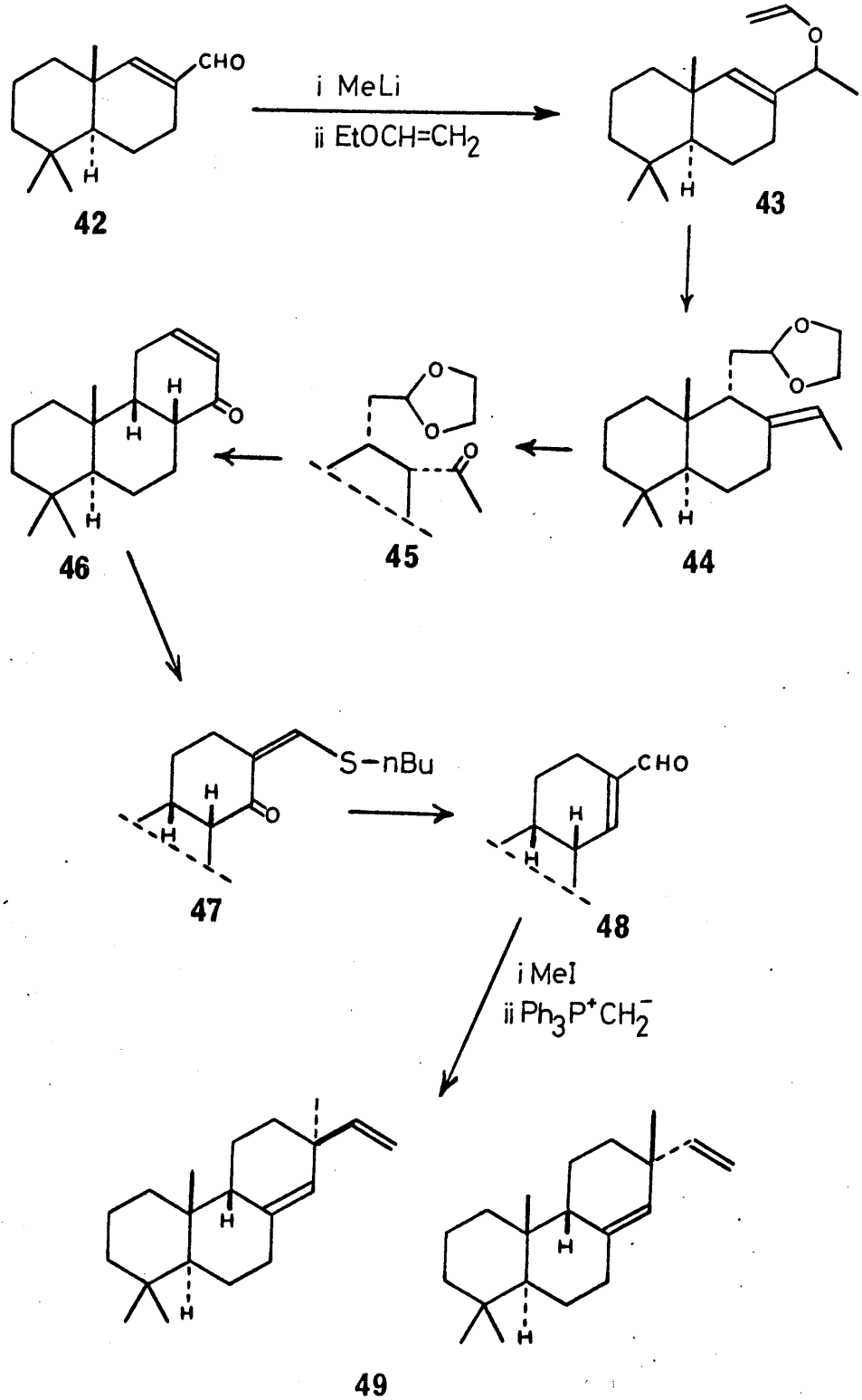
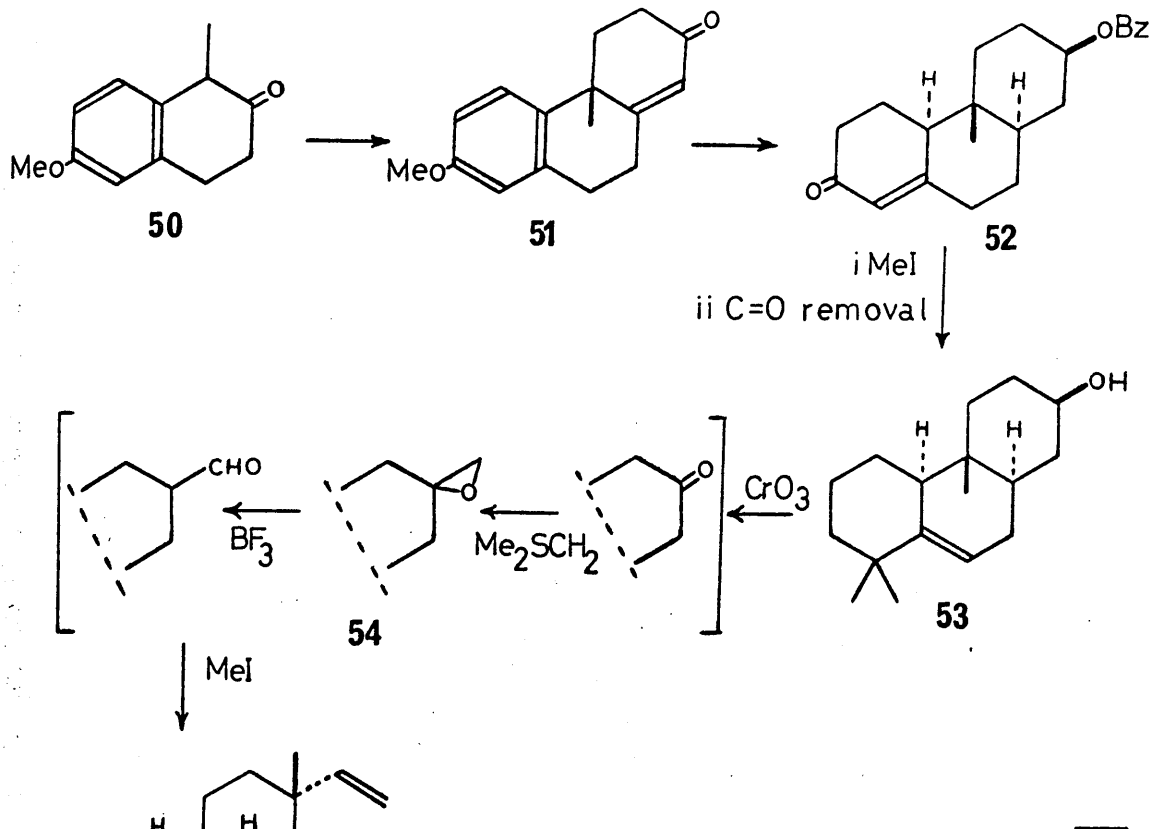


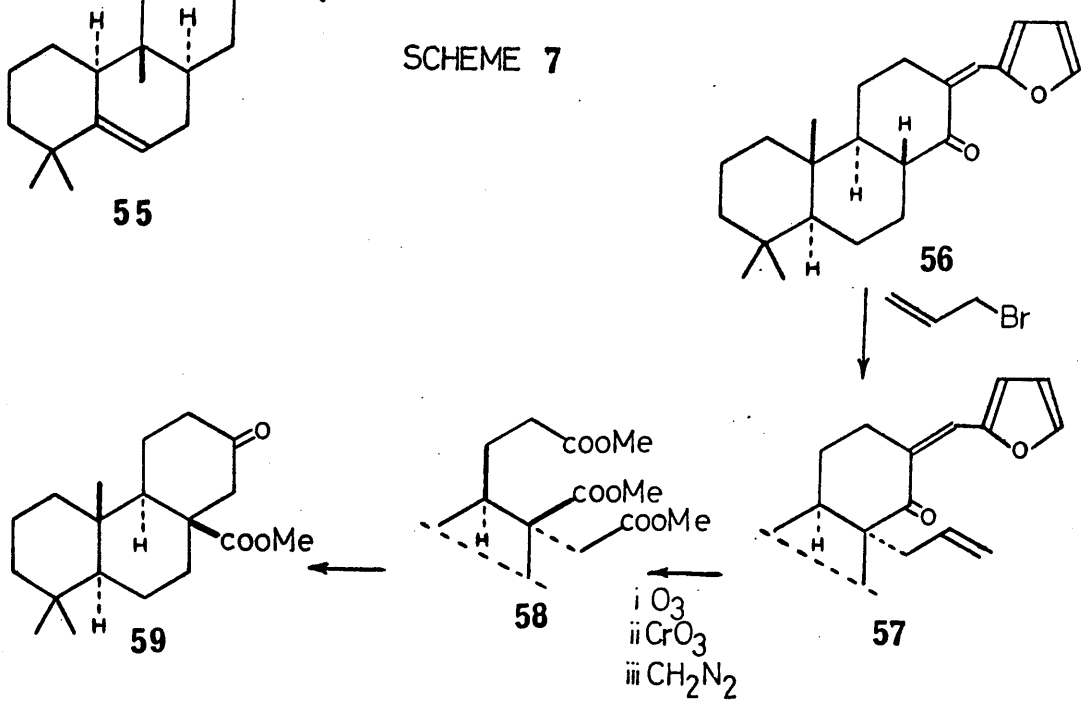
SCHEME 5


CHO
i MeLi
ii EtOCH=CH2
42
43
44
45
46
S-nBu
47
CHO
48
i MeI
ii Ph3P+CH2−
49

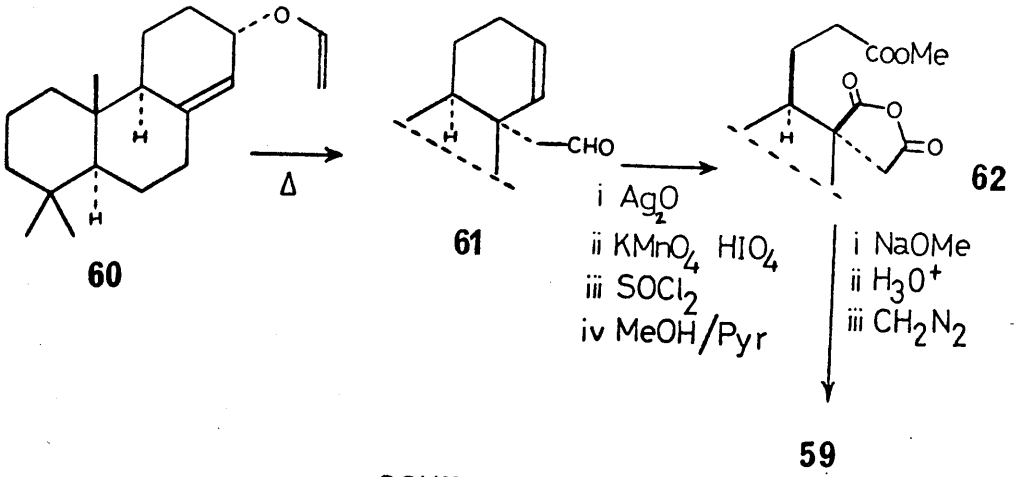
SCHEME 6



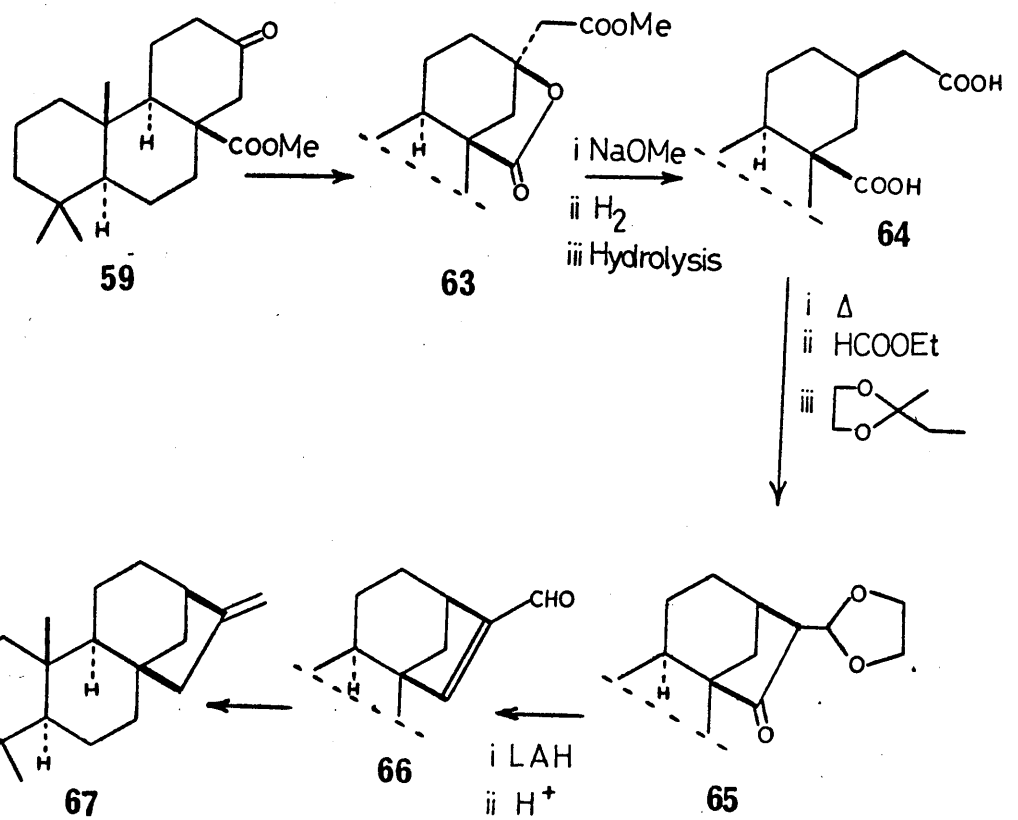
SCHEME 7



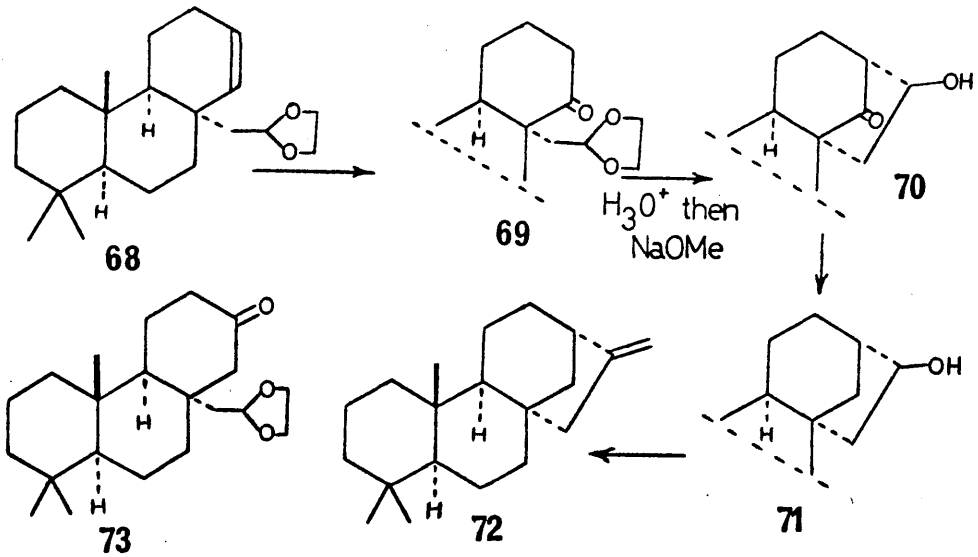
SCHEME 8



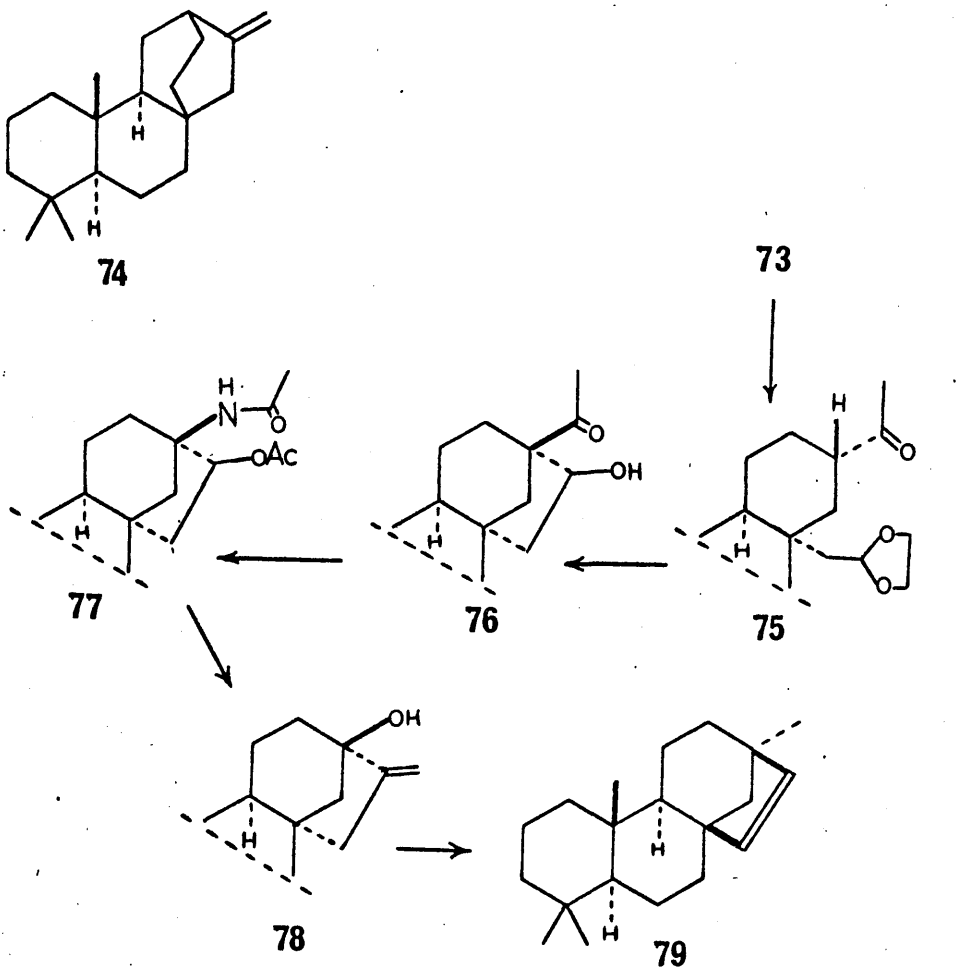
SCHEME 9



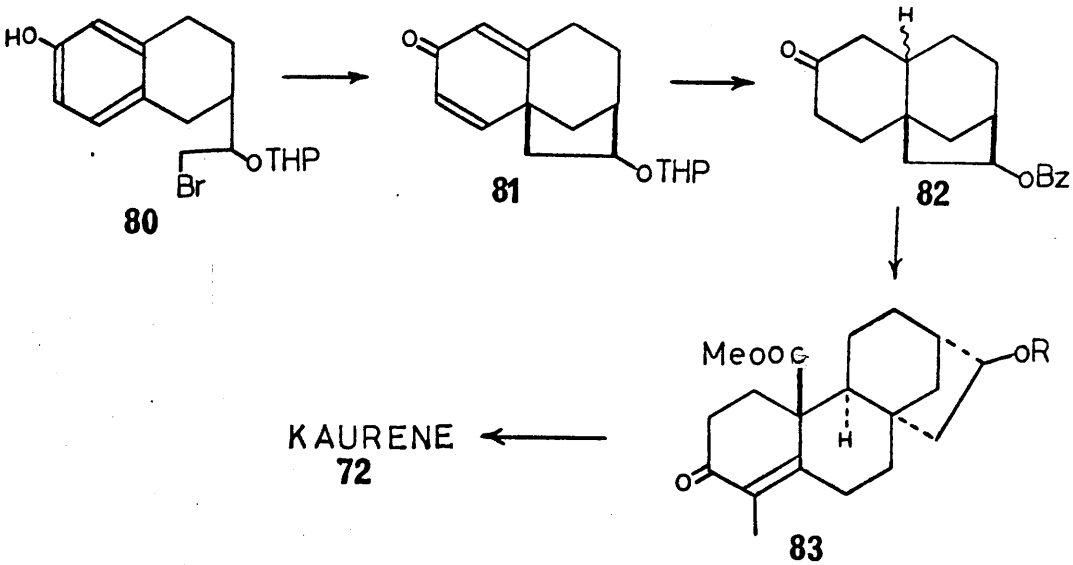
SCHEME 10



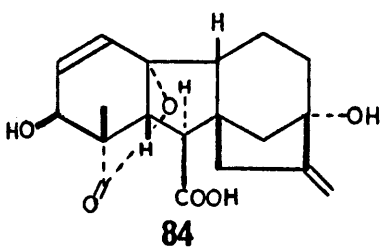
SCHEME 11

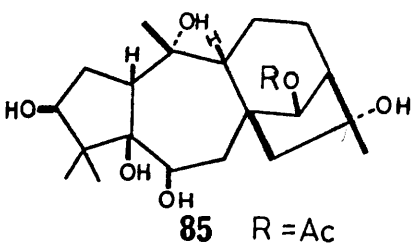


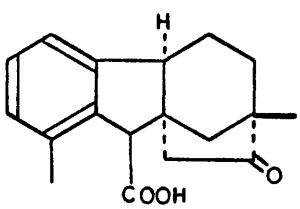
SCHEME 12

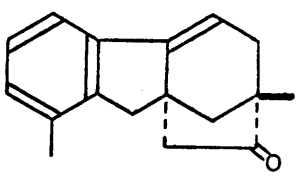

HO
OTHP
Br
80
O
OTHP
81
H
O
OBz
82
MeooC
OR
H
O
83
KAURENE
72

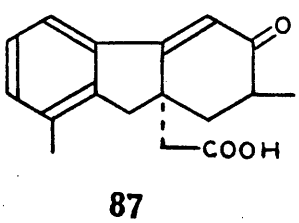
SCHEME 13

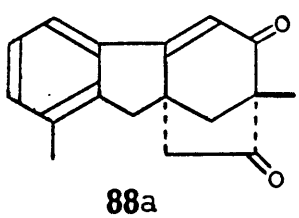

H
HO
OH
COOH
84

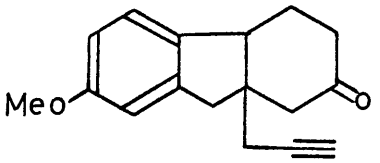

OH
H
Ro
HO
OH
OH
OH
85
R = Ac


H
COOH
O
86

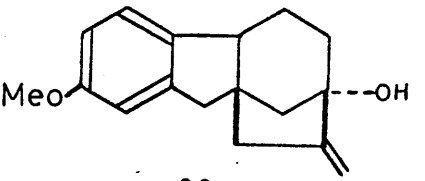

O
88


O
COOH
87

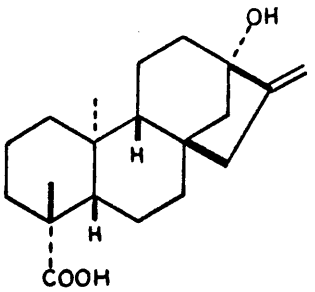

O
O
88a



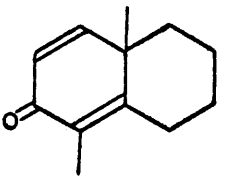
89



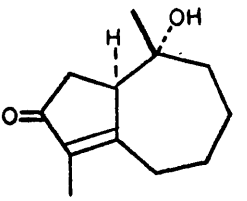
90



91



92



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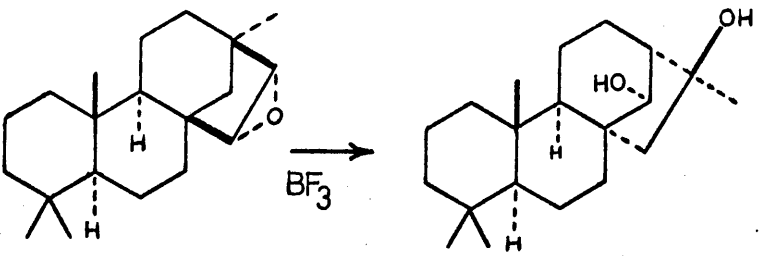
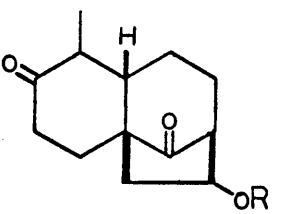


94 95



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DISCUSSION

Although the ultimate aim was the synthesis of the hydroazulenoid diterpene grayanotoxin-II (2) via a suitable kaurane derivative as shown (Scheme 1), it was realised that the synthesis of this derivative would be an extremely lengthy and difficult task. Attention was therefore initially directed towards the synthesis of a suitable tricyclic system (3) containing rings B, C and D of the kaurane skeleton, oxygenated at the 1 and 12 positions in such a way that the molecule could be elaborated to the desired kaurane precursor (1).

The B,C → D,A approach to the synthesis of tetracyclic diterpenoids has been the subject of several reports[1,2,3] which are outlined in Schemes 2, 3 and 4. Only the route devised by Masamune (see introduction) has been carried through to a diterpene.

With regard to the synthesis of a 14-oxygenated kaurene, there was the added complication of incorporating an oxygen function at position 1 in the tricyclic structure (3). This feature was present at a late stage in Ireland's synthesis[4] of kaurene and also in the product formed in the rearrangement of hibaene to kaurene[5] (see introduction).

The route chosen is shown in Scheme 5. 2-Carbethoxymethylenecyclohexane-1,3-dione (4) was prepared as described.[6] Preliminary attempts to prepare the acetal analogue (4a) by alkylation of cyclohexane-1,3-dione with bromoacetal were unrewarding.

While ring extension of a cyclic ketone by the Robinson-Mannich reaction has been widely used, it appeared to be sensitive to steric factors. The first stage was envisaged as a Michael addition of an alkyl vinyl ketone to give compound (9), followed by an aldol closure to the ketol (10) which could be dehydrated to the required enone system (11). Johnson et al.[7] showed by an N.M.R. study that although the final product was an octalone the intermediate ketol could be the bridged bicyclic ketol (8) in some cases. For (8) to be converted to the enone system, the equilibrium (Scheme 6) was postulated,[7] formation of the enone being irreversible.

Ketones (12) and (13) gave rise[8] to the normal ketols (14) and (15), these isomers being the sole ketols formed, although in the latter case, the yield was small. The yields in such reactions were determined by the insolubility of the ketols in the reaction media and by their ease of formation. Evidently, compounds such as

(13) and (16) prefer to condense with more vinyl ketone rather than to react intramolecularly. The stereoselective formation of (14) and (15) was not due to an equilibrium process but resulted from kinetic control in the aldol cyclisation. Spencer[9] attributed this selectivity to the favourability of the transition state i.e., if a 9-substituent is bulky, then the butanone side chain has to approach from the α-side. The case quoted by Spencer was ketol (17) which was shown to have the acetoxy and hydroxyl groups β-cis oriented; in the absence of a 9-substituent, the α-hydroxy ketol (15) would be expected.

Although Marshall[8] has shown that stepwise preparation of the enone via the ketol is often preferable, direct condensation using a vinyl ketone derivative and a basic catalyst has also been utilised.[10,11,12] Both simple enones[8,11,13,14] (18) (R = H, Me) and vinylogous β-diketones of the Wieland-Miescher type (19)[15,16,17,19] have been prepared by these methods. Closure of the Michael addition product of type (9) to the ketol has usually been effected by pyrrolidine; dehydrations of the ketol have been achieved using a variety of reagents including pyrrolidine in refluxing benzene with water-separation, ethanolic hydrochloric acid, and steam distillation from

potassium hydroxide solution. An example of the sensitivity of the reaction is illustrated by the fact that, although ketone (20) could not be converted[18] to the corresponding enone by p-toluenesulphonic acid in refluxing benzene, the same treatment effected the preparation of the five-membered ring analogue (22); however, using aluminium tri-t-butoxide, (20) smoothly underwent conversion[19] to (21).

From these results, it would appear that the annelation reaction is a very sensitive one[19] and conditions have to be established for individual cases.

The Robinson-Mannich annelation of 2-carbethoxymethylenecyclohexane-1,3-dione (4) with 1-diethylamino-pentan-3-one (23) was then investigated. The first procedure tried was that of Newman,[10] whereby the diketoester (4) was heated in refluxing benzene with triethylamine and the amino ketone (23) with water separation for 18 hrs. Further heating after addition of pyrrolidine afforded an amber oil which was shown to be a mixture of the required product, 9-carbethoxymethylene-5-methyl-$\Delta^{5,10}$-octalin-1,6-dione (5) and the triketoester (24) in a 6:1 ratio (23% yield) by G.L.C. Separation could not be effected by preparative T.L.C. but column chromatography afforded a pure sample of the enone (5) (in addition to impure samples),

b.p. 110°/0·05 mm. (sub.) [$\nu_{CO}^{CCl_4}$: 1738 (s), 1722 (s), 1674 (s) cm.$^{-1}$]. The N.M.R. spectrum showed a vinylic methyl at 8·16τ (3H, singlet) and a doublet at 7·13 τ (2H, J = 4 cps), in addition to the obvious ethyl ester signals. The doublet was assigned to the methylene of the side chain, the splitting being due to the slight non-equivalence of the protons caused by restricted rotation of the side chain (later examples of this methylene in non-rigid structures displayed a singlet). The mass spectrum of the enone showed, in addition to a parent ion at m/e 264, a base peak at m/e 176 corresponding to a loss of (CH_2=C(OH)-OEt) by a McLafferty rearrangement. The ultraviolet spectrum was fully consistent with this enone structure showing absorption at 254·5 mμ (ε, 10,080) and an inflexion at 292 mμ (ε, 742).

Attempts to increase the yield of the enone by this method were unsuccessful, presumably due to degradation of the product(s) to acidic species shown to be present by T.L.C. and I.R.

In a further attempt to increase the yield, the reaction was carried out in two stages. 2-Carbethoxy-methylene-2-(3'-ketopentyl) cyclohexane-1,3-dione (24) was therefore prepared as the intermediate by the method of

Wieland,[16] (4) being heated at 80° with the aminoketone (23) in t-butanol containing triethylamine for 15 min. The triketoester (24), m.p. 55·5-56·5°, was isolated in 40% yield. The N.M.R. spectrum was consistent with the structure, showing a triplet at 9·01 τ (3H, ethyl ketone) and a singlet at 7·06 τ (2H, methylene adjacent to ester). The singlet was indicative of the flexibility of the system. In addition to a parent ion at m/e 282, the mass spectrum showed a base peak at m/e 57 $(CH_3CH_2CO)^+$ and a large ion at m/e 236 $(M-CH_3CH_2OH)$. Although an ester and three ketone groups were present, the infra-red spectrum (in four solvents) showed only two absorption bands.

A series of experiments was then carried out using a variety of catalysts to effect cyclisation. The bases pyrrolidine, morpholine and triethylamine were used (Table Ia)* with water separation but with no success. Thus neither amine catalysis[20] (Scheme 7) (secondary amines) nor general base catalysis (tertiary amine) effected cyclisation.

Organic salts such as triethylamine/benzoic acid to effect cyclisation have been used.[9] Use of this salt in refluxing benzene or xylene with water separation was unsuccessful, starting material being recovered in each case (Table Ib). Although pyrrolidine/acetic acid was

* Overleaf

Table Ia

Base	Solvent	Type	Time	Temp.	Product
pyrrolidine	benzene	W.S.	1 hr.	80°	S.M.
pyrrolidine	benzene	W.S.	60 hrs.	80°	UNIDENTIFIED PRODUCTS
morpholine	benzene	W.S.	18 hrs.	80°	S.M.
triethylamine/ t-butanol	xylene	W.S.	60 hrs.	140°	S.M.

Table Ib

Salt	Solvent	Type	Time	Temp.	Product
triethylamine/ benzoic acid	benzene	W.S.	36 hrs.	80°	S.M.
triethylamine/ benzoic acid	xylene	W.S.	36 hrs.	140°	S.M.
pyrrolidine/ acetic acid	ether	-	2 hrs.	0°	S.M.
pyrrolidine/ acetic acid	benzene	-	72 hrs.	25°	ketol
pyrrolidine/ acetic acid	benzene	-	72 hrs.	80°/25°	enone/ketol
pyrrolidine/ acetic acid	-	-	5 hrs.	118°	enone

W.S. = water separation S.M. = starting material

ineffective in ether at 0^{o}, prolonged treatment (72 hrs.,) in benzene at room temperature afforded a pale yellow oil which was shown to be mainly one component more polar than either the starting triketoester (24) or the enone (5). Preparative T.L.C. afforded the ketol (26) in 35% yield as a colourless oil, $\nu_{OH}^{CCl_4}$: 3600 (s), 3426 (s) $cm.^{-1}$, $\nu_{CO}^{CCl_4}$: 1734 (s), 1711 (s) $cm.^{-1}$. The N.M.R. spectrum showed the ester pattern clearly together with a hydroxyl proton signal at 7·65 τ (D_2O exchange) and a doublet at 7·21 τ (J = 2), this latter signal being again attributed to the non-equivalence of the side chain methylene protons. A triplet at 9·05 τ (J = 8, $-CH_2-\underline{CH_3}$) indicated that the ketol has the bicyclo [3,3,1] (26) rather than the bicyclo[4,4,0] structure (25) which would display a doublet for the methyl signal. The methylene of this ethyl group could not be detected among the other methylene signals. The stereochemistry of 1-carbethoxymethylene-6-ethyl-6-hydroxybicyclo[3,3,1]nonane-2,9-dione (26) at C_6 was unable to be defined. Attempted purification of (26) by distillation afforded a clear oil which readily solidified and was shown to be identical with the triketoester (24) by infra-red comparison and a mixed melting point determination. The ketol also reverted to the triketoester on standing for several hours. Thus the

retro-aldol step occurred very readily, indicating a rather unstable molecule. This phenomenon has also been observed by Spencer et al.[9] with compound (27), which underwent ring opening on heating above its melting point or on attempted dehydration. Attempts to dehydrate the ketol (26) with acetic anhydride or with phosphorus oxychloride in pyridine similarly gave no dehydration product, starting material or unidentified products being obtained. Efforts to make the acetate of the ketol also effected the retro-aldol reaction; however, benzoylation afforded a new compound which was not the expected product but instead ethyl(6-keto-2-benzoyloxy-cyclohex-1-enyl)acetate (28). Proof of this structure was obtained by analysis, the infra-red spectrum ($\nu_{max.}^{CCl_4}$ 1743 (s), 1683 (s) and 1668 (m) $cm.^{-1}$) and the ultraviolet spectrum, 239·5 mμ (ε, 21,400). The N.M.R. spectrum was also consistent with the structure, displaying in addition to aromatic and ethyl signals, a sharp singlet at 6·66 τ (2H) assigned to the methylene adjacent to the ester. Ester (28) was shown to be identical with an authentic sample prepared by enol benzoylation of 1-carbethoxymethylenecyclohexane-1,3-dione (4). The degradation of molecule (26) reflected the instability of the system, the loss of the ketone side chain being a retro-Michael reaction.

It was envisaged that more forcing conditions (organic salt with heat) might effect dehydration to the enone (5). However, heating a solution of triketoester (24), pyrrolidine and acetic acid in benzene for 5 min., followed by a prolonged stirring period, afforded a mixture of triketoester, desired enone (5) (16%) and two ketols which were isolated by column chromatography. One ketol was shown to be the one described above (26), the other, which was obtained in small yield, decomposed rapidly and was assumed to be either the epimeric ketol (at C_6) or a decalin ketol (25).

Refluxing a similar solution for 5 hrs., appeared too drastic, affording enone (12%) and a mixture of acidic species.

Since cyclisations to octalones using acid catalysts e.g., p-toluenesulphonic acid in benzene have been reported,[18] the cyclisation of the triketoester (24) to the enone (5) was investigated utilising mineral as well as organic acid catalysts (Table II). Concentrated sulphuric

Table II.

Catalyst	Solvent	Time	Temp.	Product
conc. H_2SO_4	-	35 min.	90°	unid. prod.
conc. H_2SO_4	-	1 hr.	25°	S.M.
NaOAc/Ac_2O	Ac_2O	3½ hrs.	140°	S.M.
HCl/HOAc	HOAc	3½ hrs.	118°	unid. prod.
p.T.S.A.	benzene	24 hrs.	80°	S.M.
P.P.A.	-	45 min.	90°	lactone (29)
$BF_3.Et_2O$	HOAc	2½ hrs.	118°	lactone (29)
$BF_3.Et_2O$	Ac_2O	2½ hrs.	140°	unid. prod.

acid treatment at 90° afforded a mixture of compounds, spectral data on which inferred the presence of a lactone (ν_{CO}^{film} 1810 cm.$^{-1}$) and a conjugated system, ($\lambda_{max.}^{EtOH}$ 299 mμ). Recovery of starting material was experienced on room temperature reaction. Enol-lactonisation conditions (sodium acetate/acetic anhydride and hydrochloric acid/acetic acid) afforded no identifiable product; p-toluenesulphonic acid treatment in refluxing benzene resulted in cleavage of the β-diketone system, generating mixtures of acids and starting material.

Treatment of the triketoester (24) with the mild acid, polyphosphoric acid, and with boron trifluoride etherate afforded the same new crystalline product (29) by a complex

rearrangement which will be discussed at a later stage.

Thus ring closure could not be effected successfully in better yields than from direct condensation of the diketo-ester (4) with 1-diethylaminopentan-3-one. The reason could well be due to steric congestion in the aldol transition state since Spencer[21] noted that cyclisation of the ethyl ketone (30) was much slower than the methyl analogue; the increased bulk of the 9-substituent over an acetoxy or methyl group may also play an important part.

With 9-carbethoxymethylene-5-methyl-$\Delta^{5,10}$-octalin-1,6-dione (5) available, albeit in low yield, the next stage in the programme was to study its hydrogenation in an attempt to prepare the cis-fused 9-carbethoxymethylene-5-methyldecalin-1,6-dione (31).

The catalytic hydrogenation of octalones has given a variety of results using the recommended procedure[22] employing palladium in ethanolic potassium hydroxide at room temperature and atmospheric pressure. It has been shown that the ring junction substituent markedly influenced the product stereochemistry;[22] (32, R=H) gave cis- and trans-mixtures, (32, R=COOEt) gave predominantly the trans-fused isomer whereas with R=Me, $CHCl_2$ and CH_2OH the cis isomer was formed. Nazarov[23] has reduced (21) to

the cis isomer (33) using palladium/calcium carbonate in methanol, while lithium-ammonia[24] reduction has, under extremely careful conditions afforded the expected trans isomer. However, the latter workers have also reported that the hydrogenation of (34) over palladium/strontium carbonate in ethanol furnished the cis-fused isomer.

Since hydrogenation of a tetrasubstituted double bond as in enone (5) offered four possible isomers (without consideration of the stereochemical implications), it was necessary to have a method of identification of the product(s). Although from a synthetic point of view the cis decalone was alone required, a mixture of all four compounds would be useful for characterisation of each by G.C.M.S.

Isomers could be assigned by reasoning similar to that used in the hydrogenation of 4-methyl steroid enones.[25,26] Mazur and Sondheimer found that hydrogenation of the steroidal enone (35) with palladium/charcoal in ethanol afforded a mixture of three isomers (36), (37), and (38); the fourth isomer (39) could not be isolated, the reason being the large interaction between the 4-α methyl and the axial C_7 and C_9 protons (39). It was also found that ethanolic sulphuric acid treatment of trans isomer (37) produced the epimer (36), the driving force being the

removal of a large 4-β-,10-β-dimethyl interaction present in (37). The three isomers could therefore be identified.

In considering the case of hydrogenation of enone (5), all four isomers were theoretically possible since the analogous "missing" isomer, could adopt the non-steroid conformation[27] (43) thus avoiding steric crowding. However, since trans fused isomers cannot flip their conformations, it was expected that epimerising conditions would convert (41) into (40) to relieve the 1,3-diaxial interaction.

Hydrogenation of enone (5) was carried out over palladium/charcoal in a variety of solvents in an attempt to generate a cis-fused decalone; potassium hydroxide could not be used due to the instability of the enone. Triketoester (24) (K), to an extent of 14%, was used as a standard and the G.L.C. results on three columns are shown in Tables III, IV and V (see overleaf). A sample containing all four isomers (ethanol solvent) was treated with warm ethanolic sulphuric acid for epimerisation purposes. It was found that:

(i) only a 1% SE 30 column would separate pairs of epimers, C_1 and C_2 and T_1 and T_2, the other columns giving superposible peaks labelled C and T.

G.L.C. of Products of Hydrogenation of Enone (5)

Table III

Column: 1% SE 30 ; Temp. 140° ; F.R. 33 ml./min.

M.W.,	Enone (5) & triketo-ester (24)	Hydrogenation solvents				Epimer-isation conditions
		EtOH	CH_3COOH	Dioxane	EtOH/HCl	
266 C_2		19·50(w)	19·30		19·40	19·15
282 K	20·55			20·10		
266 C_1		21·00	20·85		21·00	20·90
266 T_1		23·75	22·95		22·90	22·75
264 E	24·60			24·70		
266 T_2		25·40				
328, K_1						35·05(w)

Table IV

Column : 2% P.E.G. 20M; Temp. 200°C ; F.R. 40 ml./min.

	Enone (5) & triketo-ester (24)	Hydrogenation solvent				Epimer-isation Conditions
		EtOH	CH_3COOH	Dioxane	EtOH/HCl	
C		19·35	19·40	20·00(w)	19·75	19·55
K	21·25	ca20·9*(w)	ca 20·9*(w)	21·30	21·40(w)	
T		24·60	24·65		25·05	24·95
E	25·60			25·55		
K_1		38·05(w)				37·85

R_t in minutes w = weak * could also be C_1 or C_2

Table V

Column : 1% CHDMS ; Temp. 200° ; F.R. 40 ml./min.

	Enone (5) & triketo-ester (24)	Hydrogenation solvents				Epimerisation conditions
		EtOH	CH_3COOH	Dioxane	EtOH/HCl	
C		13·40	13·30		13·20	13·15
K	13·65	ca15·1*(w)	ca 15·1*(w)	13·70		
E	16·10			16·15		
T		17·15	17·25		17·20	17·25
K_1		22·65(w)				22·75

* could also be C_1 or C_2

(ii) acetic acid and acidic ethanol gave similar hydrogenation products, while dioxane gave mainly starting materials.

(iii) alcoholic sulphuric acid epimerised only one epimer (T_2).

(iv) another component K_1 was observed in small amounts in some cases.

G.C.M.S. of the products was undertaken using the 1% SE 30 column Figures (i) (ii) (iii) and (iv) , the molecular weights being shown in Table III.

The isomers were identified by the above reasoning.[26] Thus, since epimer T_2 disappeared in epimerisation it was designated as (41) and, due to the fact that T_1 and T_2 had the same retention times on other columns, T_1 was assigned structure (40). The cis forms C_1 and C_2, corresponding to the steroidal ketone (42) and the non-steroidal ketone (43), appeared to equilibrate under epimeric conditions since their ratio varied but neither disappeared. It could not be determined whether the two cis components were (42) or (43) or vice versa.

Component K_1 (m.w. 328) was observed (in small yield) only when ethanol was present and was believed to be the ethanol addition product (44) of the triketoester (24) present in small amounts.

The mass spectrum of each decalone, being both of the α- and β-decalone type, was extremely complex and distinction between isomers was not possible.

Owing to the mixture of isomers formed in the hydrogenation of the enone and to the impossibility of separating them preparatively, this approach to the tricyclic triketone (7) was abandoned.

The following discussion stems from attempts to cyclise the triketoester (24) with polyphosphoric acid, as mentioned earlier. Treatment of the triketoester at 90° for 45 min., with vigorous stirring resulted in the isolation of an off-white crystalline compound (34% yield), m.p. 131-132°, which, by T.L.C. and infra-red spectroscopy, was shown to be non-acidic. On observing that the infra-red spectrum showed no absorption due to an ester carbonyl but absorption at 1823 $cm.^{-1}$, 1656 $cm.^{-1}$ and a shoulder at 1677 $cm.^{-1}$, it was hoped that the triketoester had not only cyclised to the enone (5) but had further ring closed at the 2-position to give the desired tricyclic diketoenone (45). However, the fact that only one carbonyl frequency (in addition to the enone frequency) was observed was not compatible with structure (45), the value being much too high despite the possibility of a strained molecule. The analysis ($C_{13}H_{14}O_3$) and mass spectrum [parent ion (also base peak) m/e 218, ions at m/e 91 (tropylium) and m/e 28 (C=O)] appeared to further substantiate structure (45), but the ultraviolet spectrum, $\lambda_{max.}^{EtOH}$ 306·5 mμ(ε, 20,150) was totally inconsistent, suggesting a highly conjugated chromophore. The N.M.R. spectrum showed no vinylic protons but a sharp singlet at 8·16 τ (3H) indicated a vinylic methyl

group; a broadened singlet at 8·30 τ (2H) inferred the presence of a normal hydrocarbon methylene, whereas all other signals 6·8 - 7·9 τ (complex) were attributed to allylic protons or protons adjacent to carbonyl functions. The proposed structure, therefore, compatible with this data was the lactone (29) [ultraviolet maxima calculated for the closely related lactone (46), $\lambda_{max.}$ = 314 mμ], the only critical comment being the assignment of the 1823 $cm.^{-1}$ band in the infra-red to the lactone frequency (lit. for γ, δ-unsaturated δ-lactone, 1795 $cm.^{-1}$). The structure (47) would be more consistent with this frequency but additional strain in the case of (29) due to the five membered ring may have caused the increase in frequency to 1823 $cm.^{-1}$. From a consideration of the N.M.R. spectrum, two reasons excluded the γ-lactone structure (47):

(1) four protons, at carbons a and b, should have been at higher field rather than the observed two.

(2) the methylene at carbon c, being both allylic and adjacent to the lactone carbonyl should have appeared at lower field than 6·8 τ.

Hydrogenation of (29) over palladium/charcoal in ethanol afforded an acidic species, indicating hydrogenolysis of a lactone; esterification gave essentially one product which, by G.C.M.S. was shown to consist mainly of stereo-isomers of (48), m/e 238 plus a small amount of enone (49), m/e 234. This illustrated the presence of two double bonds and a lactone grouping. Alkali treatment of the enone lactone resulted in fragmentation of the molecule.

The residue from the initial crystallisation of lactone (29) was acidic and was esterified to yield, by preparative T.L.C., a main component as an amber oil, the infra-red spectrum of which exhibited absorption for an ester and possibly a cyclopentanone (1740-30 $cm.^{-1}$), an enone (1660 $cm.^{-1}$), and a cyclohexanone (and possibly a cyclopentenone) (1705 $cm.^{-1}$); this indicated the oil to be an inseparable mixture of ketoenone esters (50) and (51).

Lawson has reported[28] that polyphosphoric acid or boron trifluoride treatment of diketo diester (52) resulted in the formation of a mixture of lactones (53) and (54) and postulated compound (55) as an intermediate. The mechanism of the rearrangement in our case could be envisaged as proceeding through a similar type of intermediate (Scheme 8).

In the light of the present work, the equally acceptable structure (56) could be written for the compound reported by Lawson.

It is noteworthy that compound (47) cannot be derived by the mechanism outlined in Scheme 8 .

In an attempt to verify this mechanism, especially the existence of the intermediate (57), other 2,2-disubstituted cyclohexane-1,3-diones were synthesised and subjected to reaction with polyphosphoric acid. Thus 2-methylcyclohexane-1,3-dione (58) was prepared[6] and C-methylated by the method of Nazarov[29] to yield 2,2-dimethylcyclohexane-1,3-dione (59), m.p. 33-36° in 65% yield. The monomethylated compound (58) also afforded 2-carbethoxymethylene-2-methylcyclohexane-1,3-dione (60) by alkylation[30] with ethyl bromoacetate.

Polyphosphoric acid treatment of dione (59) under exactly the same conditions as described above resulted in only starting material being recovered in 90% yield illustrating total unreactivity.

Polyphosphoric acid treatment of the ester dione (60), however, afforded a new compound, in 48% yield, purified by preparative T.L.C., as well as an acidic component in low yield which was not obtained pure.

The infra-red spectrum of the main product, G.L.C. pure, showed the presence of a lactone (1768 $cm.^{-1}$), an ester (1734 $cm.^{-1}$) and a double bond [1647 (w)], whereas the ultraviolet spectrum showed a high intensity absorption at $\lambda_{max.}^{EtOH}$ 209 mμ (ε_{app}12,900). The structure was shown to be the lactone ester (61) by the following data, although an unsaturated ester would be expected to show infra-red absorption at a slightly lower frequency. The analysis ($C_{11}H_{16}O_4$) and the mass spectrum [parent ion m/e 212, base peak m/e 41, large ion m/e 166 ($M-CH_3CH_2OH$)] were in agreement with (61) but the complete structural elucidation was accomplished by a study of the N.M.R. spectrum. The ethyl ester signals were observed at 5·94 τ (2H, q, J = 7) and 8·77 τ (3H, t, J = 7) while a singlet at 7·97 τ (3H) was indicative of a vinylic methyl group; vinylic proton H_f was observed as a fine quartet or triplet (J = 1·5) at 4·28 τ (1H) and was shown to couple with H_d, by irradiation at the H_d frequency, which caused the H_f signal to change to a singlet. The H_d proton at 5·21 τ (1H, broad), in addition to a small coupling with H_f, coupled with H_c; this was shown by irradiation in the region of the methylene H_c, causing a sharpening of the absorption at 5·21 τ (H_d). Methylenes **b** and c appeared together in the region 8 - 8·5 τ

as a multiplet, while methylene a was seen as an unsymmetrical triplet at 7·68 τ.

When the sample was run at an operating frequency of 60 Mc., the singlet at 7·97 τ (H_e) was observed as a fine quartet, J = 1 suggesting long-range coupling with the vinylic proton H_f and with H_d.

The acidic component showed a broad carbonyl region in the infra-red spectrum as well as absorption at 1647 $cm.^{-1}$ (double bond) similar to lactone (61). On account of the similar fingerprint region, it was assumed to be the lactonic acid (62).

Thus the conversion of diketoester (60) to the lactone (61) indicated a good case for the enol-lactone intermediate (63), since (61) was merely a double bond isomer; this latter transformation was easily explained since, in a medium such as polyphosphoric acid or phosphoric acid (as was generated in the work-up), isomerisation to the conjugated ester would be expected. That the reaction produced the conjugated ester (61) and not the expected enone (64) by analogy with the previous case remained unexplained.

For further insight into this reaction, 2,2-dicarbethoxymethylenecyclohexane-1,3-dione (65), a hitherto unknown dione, was prepared in 37% yield from the monoester

dione (4) using ethyl bromoacetate. The O-alkylated product (66) was also obtained in a similar yield (preparative T.L.C.) and a comparison undertaken for identification purposes. The O-alkylated compound (66), was more polar and showed two ester carbonyl frequencies in the infra-red spectrum (1763 $cm.^{-1}$, 1741 $cm.^{-1}$) as well as an enone band at 1665 $cm.^{-1}$; on the other hand, the dione (65) displayed only one ester band, 1740 (s) $cm.^{-1}$, in addition to two other carbonyl bands at 1707 (s) $cm.^{-1}$ and 1699 (s) $cm.^{-1}$. The lower band, together with a Fermi resonance shoulder at 1729 $cm.^{-1}$, was assigned to the ketone groups but the 1707 $cm.^{-1}$ band has not been assigned. The N.M.R. spectra of (65) and (66) were conclusive evidence; the O-alkylated compound (66) showed a singlet at 5·41 τ (2H) (ether methylene) and two sets of quartets and triplets corresponding to two different ester groupings, 5·77 τ, 5·92 τ and 8·83 τ, 8·88 τ respectively. In contrast, (65) displayed a singlet at 7·18 τ (4H) for two C-methylenes and ester signals at 5·97 τ(q) and 8·83 τ(t).

Polyphosphoric acid treatment of the dione (65) in the usual manner, afforded a highly crystalline, colourless solid, m.p. 134·5-135°, in 64% yield. The infra-red showed three carbonyl bands, $\nu_{CO}^{CCl_4}$ 1829 (s), 1813 (s) and 1729 (s)

$cm.^{-1}$, assigned to lactones and a ketone respectively. The analysis ($C_{10}H_{10}O_5$) and the mass spectrum (parent ion, m/e 210) were fully consistent with either of three structures, (67), (68) and (69). Since absorption for a 6-ring anhydride in the infra-red spectrum would be expected to appear about 1760 $cm.^{-1}$, structures (67) and (68) seemed unlikely. That (69) was indeed the correct structure was proved by the N.M.R. spectrum; the integration alone, ratio (1:1:1:1:1), was evidence for the dismissal of structures (67) and (68). Triplets at 7·42 τ (2H, J = 6) and 7·70 τ (2H, J = 6) were assigned to protons a and c respectively, a multiplet at 8·09 τ (2H) being observed for the b methylene protons. Irradiation of the H_b proton converted these triplets to broad singlets; irradiation of H_a caused the H_b signal to collapse to an ill-defined absorption. The two lactone methylene groups each had two non-equivalent geminal protons, the result being an AB quartet (6·85 τ, J = 18; 7·17 τ, J = 18); attempts to decouple these protons failed.

The mechanism of this reaction was not clear and did not appear to proceed via the expected enol-lactone intermediate (70). To account for the above structure, it had to be postulated that, due to the entropy effect of

having two similar esters in the proximity of the ketone, the mechanism operated as shown (Scheme 9) where decomposition with water afforded the final product.

Thus the reaction of dione (65) threw no light on the mechanism postulated above.

However, the rearrangement (Scheme 8) has been shown to be general for Lewis acids since boron trifluoride etherate treatment of (24) in acetic acid afforded a low yield of the same product (29). With acetic anhydride as solvent, similar treatment gave unidentified products.

The rearrangement was investigated no further.

In a second approach (Scheme 10) to the tricyclic intermediate (3) we hoped to adopt the method devised by Masamune[31] in his synthesis of kaurene. However, our scheme had to incorporate an oxygen function at the potential bridgehead position. Inspection of models indicated that a ketal group at position 1 of the bicyclo precursor (73) should not affect the course of cyclisation.

Whereas Masamune, following the method of Jacques and Horeau,[32] prepared the acidic ether(75) as in Scheme 11 via the methoxy acid (74) followed by ether cleavage and benzylation, it was found that 6-benzyloxy-1-tetralone (71) could be prepared in 72% yield by direct Jones oxidation of ar-2-tetralol benzyl ether. No trace of 6-benzoyloxy-tetralone was detected. Ethoxycarbonylation of 6-benzyloxy-1-tetralone with diethyl carbonate and sodium hydride in tetrahydrofuran gave 6-benzyloxy-2-carbethoxy-1-tetralone (72), m.p. 61-62·5°, isolated as its ether and water insoluble sodium salt in 46% yield. The β-keto ester (72) showed infra-red absorption at 1732 $cm.^{-1}$ and 1676 $cm.^{-1}$ and displayed a typical bathochromic shift in the ultra-violet spectrum on base addition. [$\lambda_{max.}^{EtOH}$ 278 mμ (ε, 19,900) to 337 mμ (ε,16,000)]. The N.M.R. spectrum showed the expected triplet and quartet (8·82 τ and 5·82 τ) for an ethyl ester, other absorptions being consistent with the structure.

Attention was then focussed on the ketalisation of the ketone function at carbon 1. Masamune had reported that in the solvolysis step, use of an α-keto-β-bromo ethyl group or its ethylene ketal derivative at the 2-position inhibited[31] the cyclisation. However, a ketal function

at the 1-position was not expected to exert a steric effect on this process.

In the event, attempts to ketalise the molecule failed under a variety of conditions, starting material being recovered in all but one experiment. In this latter case, strong heating in ethylene glycol/p-toluenesulphonic acid/benzene afforded the diester of ethylene glycol (76), m.p. 128-130°. This compound gave a green colouration with ferric chloride as did ketoester (72) and showed a bathochromic shift in the ultraviolet spectrum, [$\lambda_{max.}$ 279·5 mμ (ε, 34,900) to 340 mμ (ε, 33,100)]. Comparison of intensity values (ε) indicated two chromophores per molecule. The infra-red spectrum showed a ketone (1676 cm.$^{-1}$) and an ester (1741 cm.$^{-1}$) carbonyl, while the N.M.R. spectrum displayed a very similar pattern to the β-ketoester (72) with an additional fine doublet (4H) at 5·55 τ (J = 2) attributed to the glycol methylenes which appeared to be slightly non-equivalent. The mass spectrum was conclusive evidence for (76), showing in addition to a molecular ion at m/e 618, a large ion at m/e 322 corresponding to the fragment (77). Thus it would appear that ethylene glycol preferred to form the dimeric structure (76) by trans esterification than to ketalise the hindered ketone in the

1-position. This was in accord with the fact that the only known α-tetralone ketal was the ester (78) which was reported[33] to be unstable.

In an effort to find out how difficult ketalisation of an α-tetralone was, 6-benzyloxy-1-tetralone (71) was treated with ethylene glycol as described above. Two components were isolated which could not be separated completely; they were the starting ketone and the desired ketal (79). Preparative T.L.C. did not effect separation but chromatographic separation of the mixture resulted in a 16% yield of almost pure ketal (79), m.p. 62·5-64°. The analysis was almost satisfactory and no carbonyl was observed in the infra-red spectrum. The N.M.R. spectrum confirmed the structure, the salient features being the shift to higher field of protons which were deshielded by the carbonyl in ketone (71);

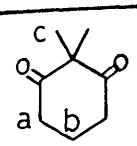
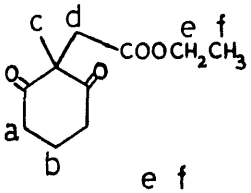
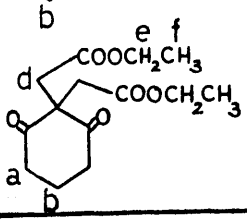
	ketone		ketal
H_f	2·05 τ d	→	ca 2·7 (masked doublet)
H_a	7·14 τ t	→	8·13 (complex)

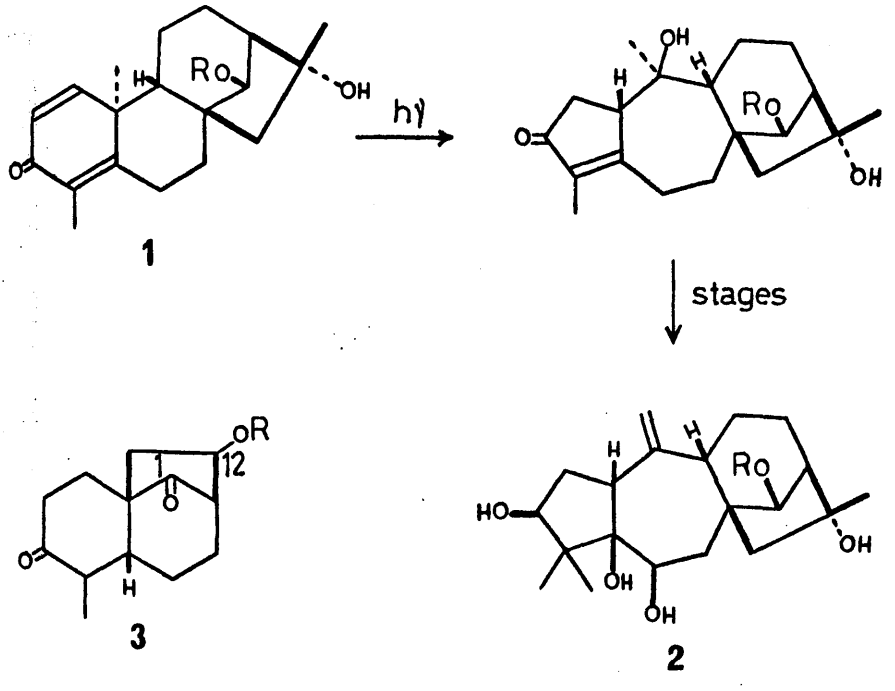
The ketal protons were observed at 5·98 τ (4H, singlet). G.L.C. of the isolated mixture showed the ratio of ketal to ketone to be 11/9.

After removal of free ketone with Girard Reagent P a mixture of ketal and ketone was again obtained indicating that the ketal hydrolysed readily in the work-up.

In view of the inability to ketalise the aromatic ketones, investigation of this route had to be abandoned. Use of the tetrahydropyranyl ether as a protecting group was excluded since difficulties would arise, firstly in elaborating the β-ketoester to the tetrahydropyranyl ether of the β-hydroxy ether and secondly, in attempts to separate the numerous stereoisomers present with the introduction of a second tetrahydropyranyl group as in (80).

Table VI.

	τ values					
	H_a	H_b	H_c	H_d	H_e	H_f
	7·30 t, J=6	8·00 q, J=6	8·71 s	-	-	-
	7·26 t, J=6	7·86 q, J=6	8·75 s	6·97 s	5·95 q, J=8	8·80 t, J=8
	7·23 t, J=6	7·83 q, J=6	-	7·18 s	5·97 q, J=8	8·83 t, J=8



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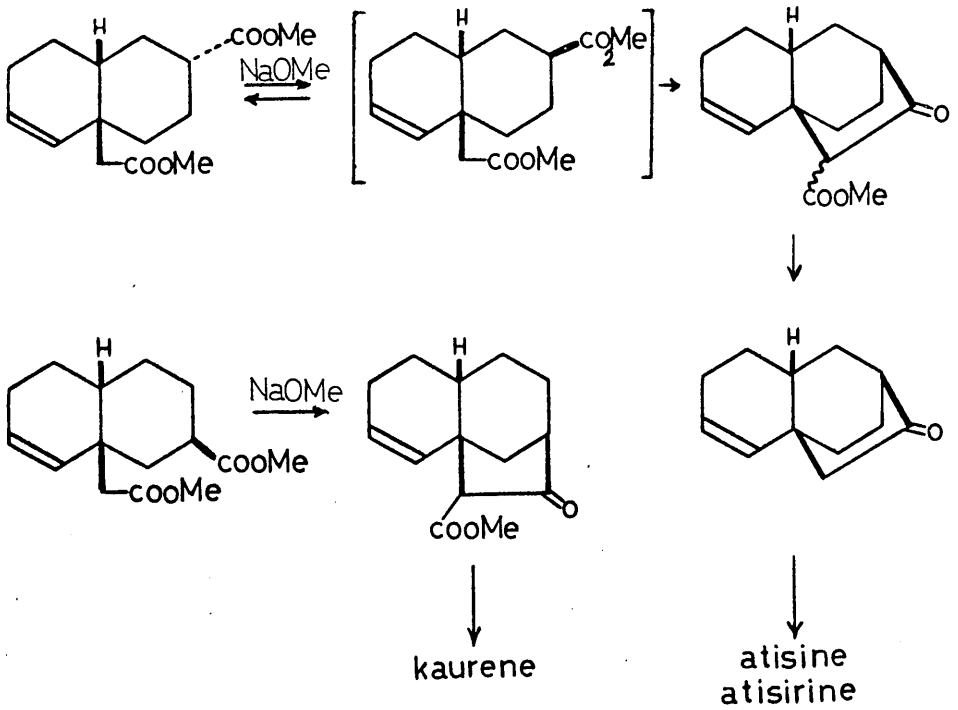

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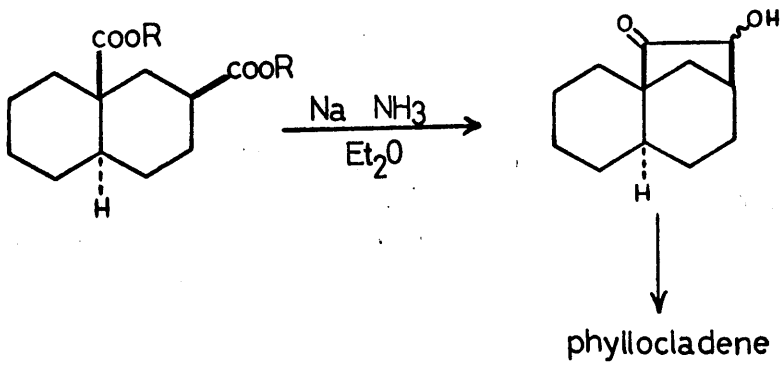

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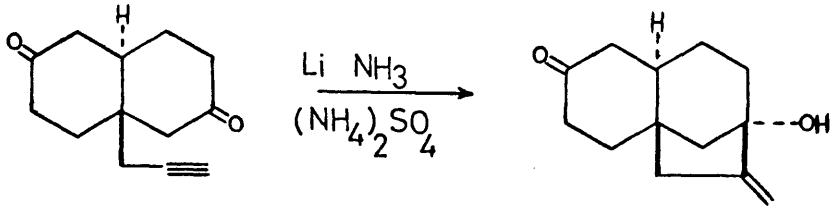
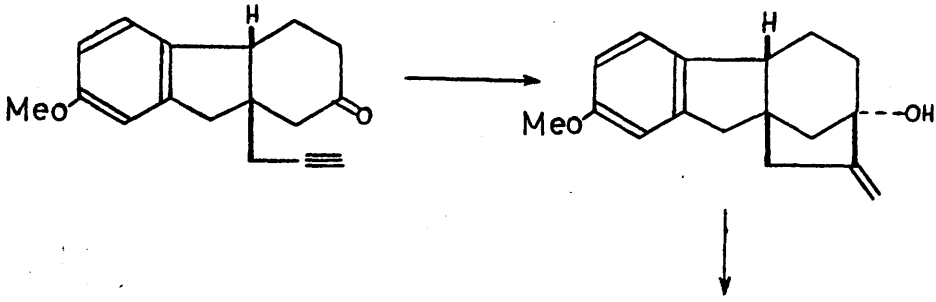
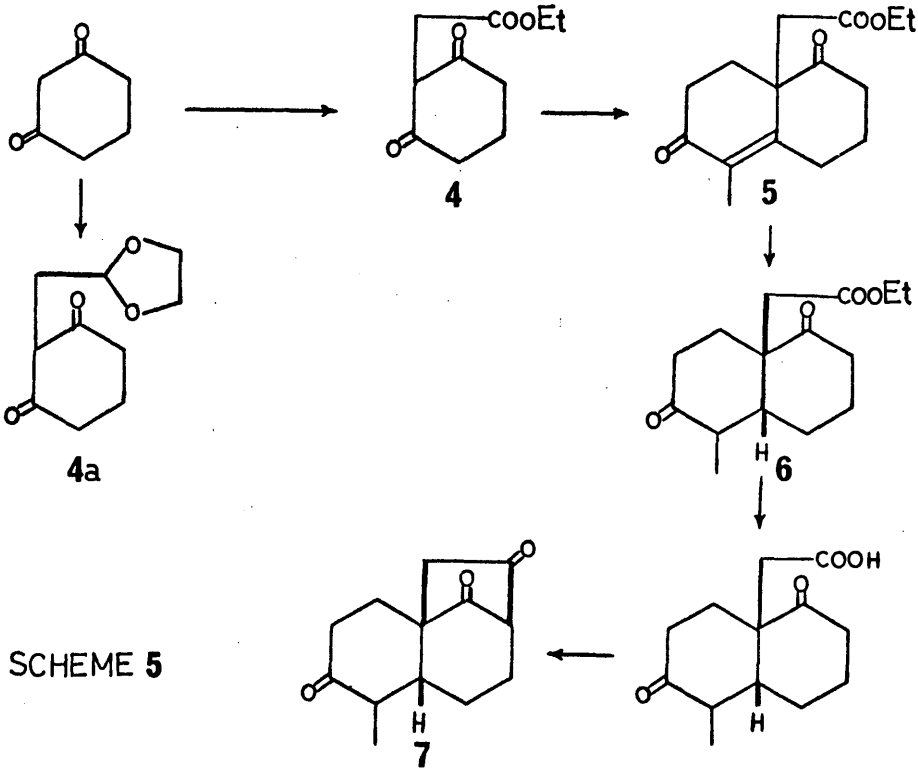




SCHEME **4** gibberellic acid



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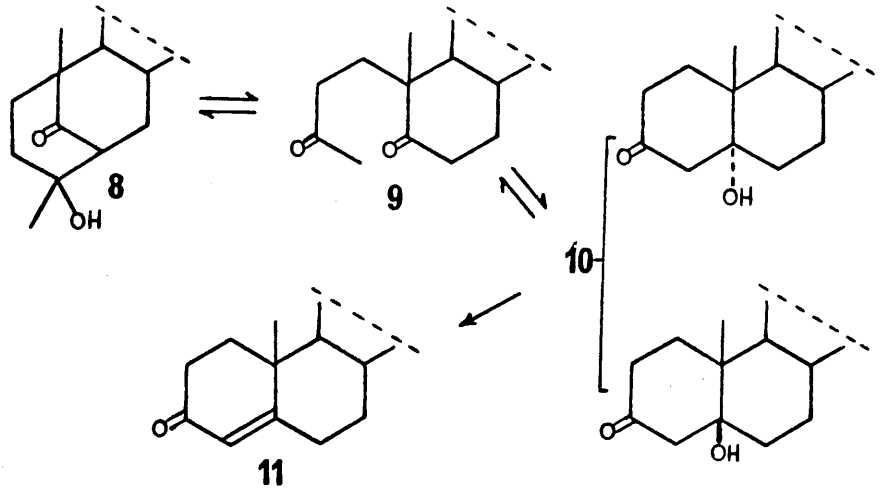

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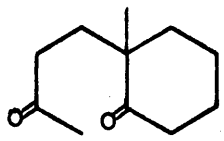
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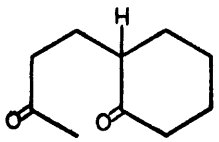

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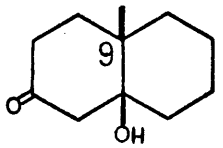

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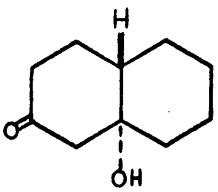

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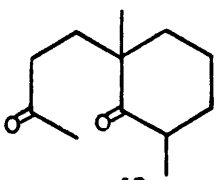
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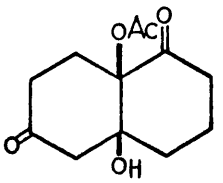

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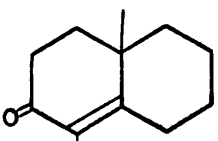

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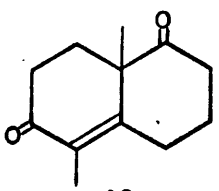

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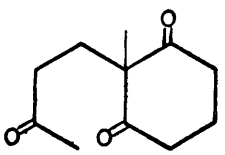

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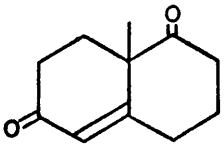

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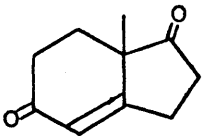

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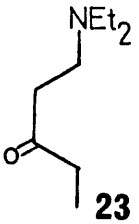

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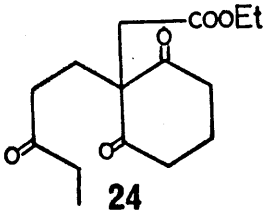

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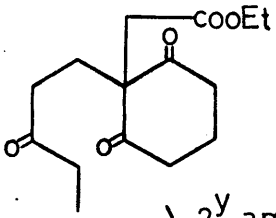
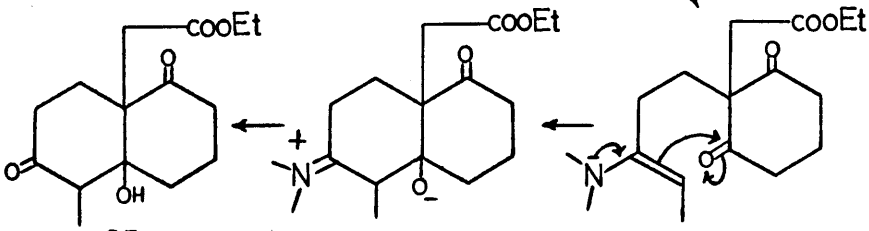


2^y amine



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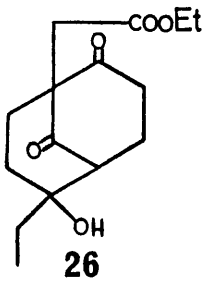
SCHEME 7



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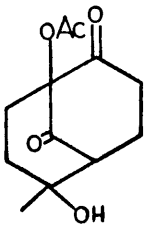

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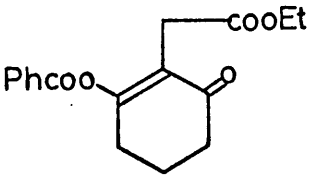

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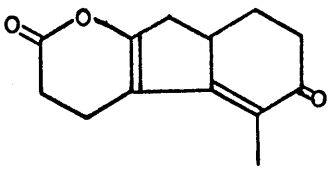

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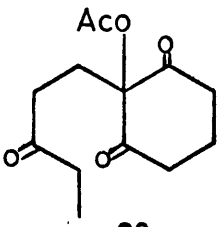

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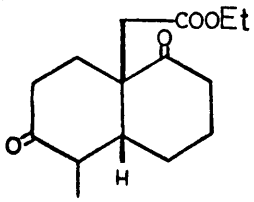

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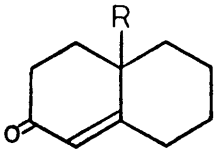

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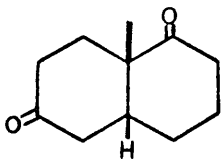

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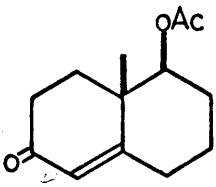

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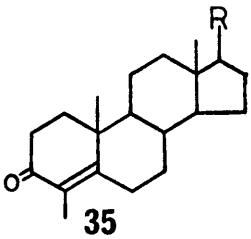

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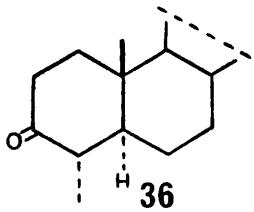

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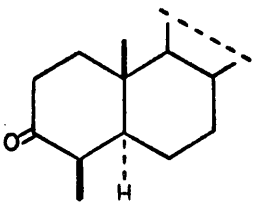

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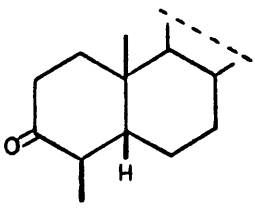

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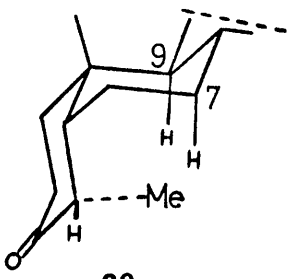

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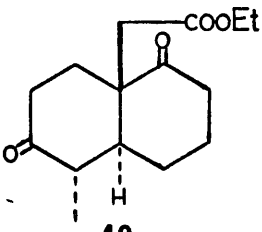

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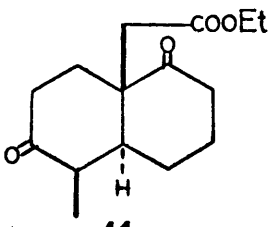

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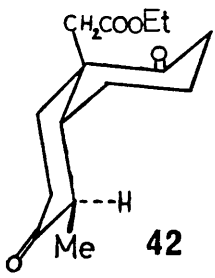

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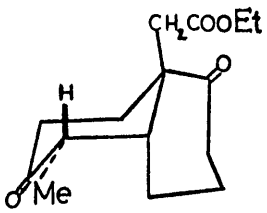

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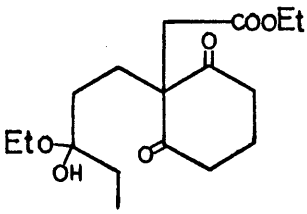

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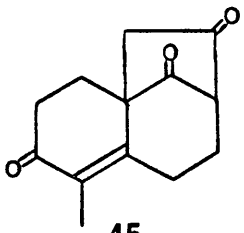

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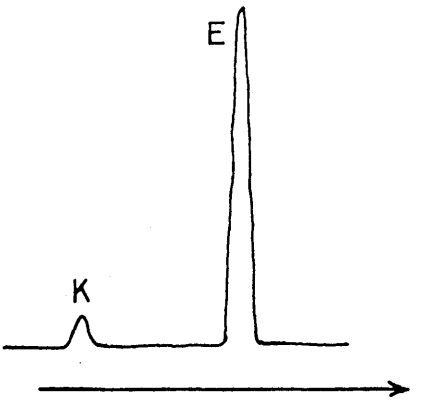
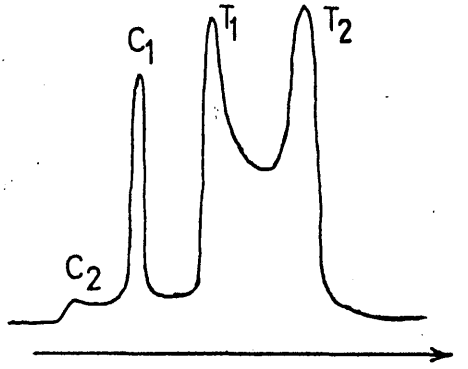
FIG i



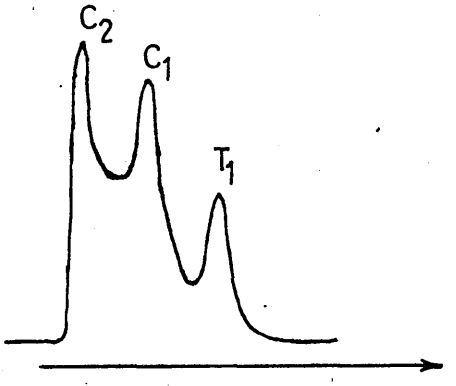
Enone
&
triketoester

FIG ii



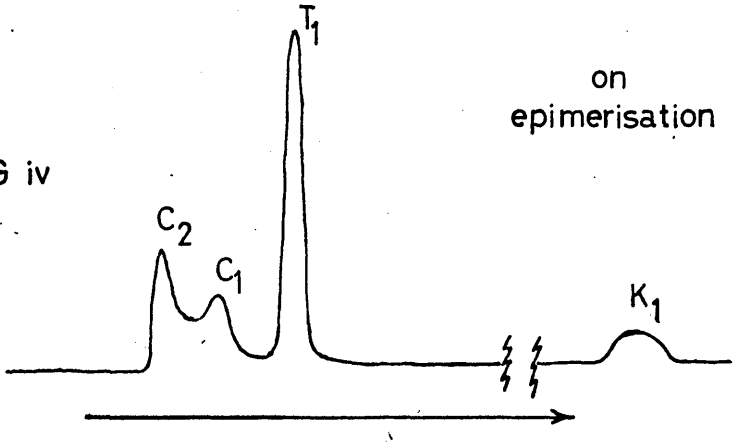
solvent
Etoh

FIG iii

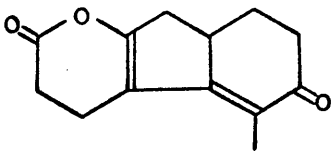


solvent
acetic acid

FIG iv



on
epimerisation



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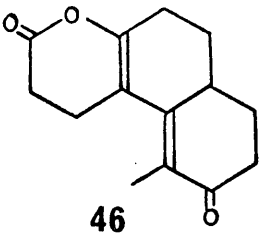

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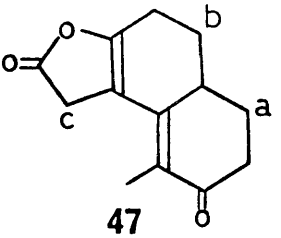

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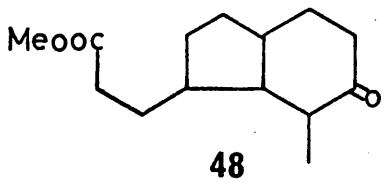

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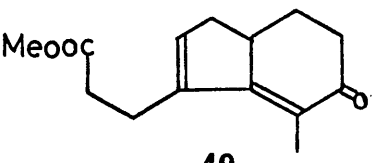

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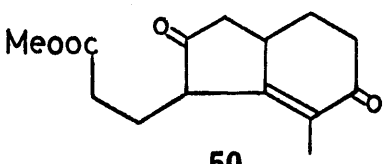

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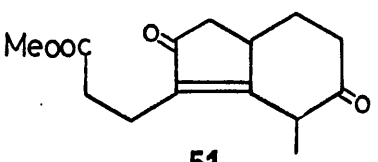

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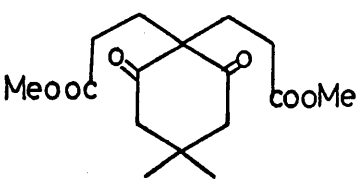

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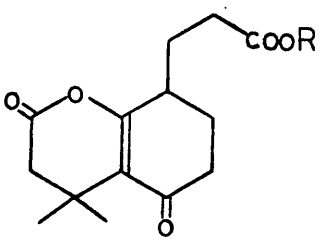
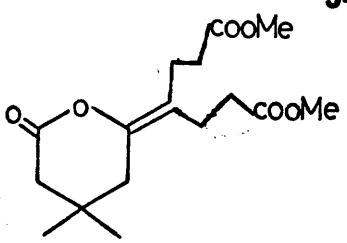


53 R=H
54 R=Me



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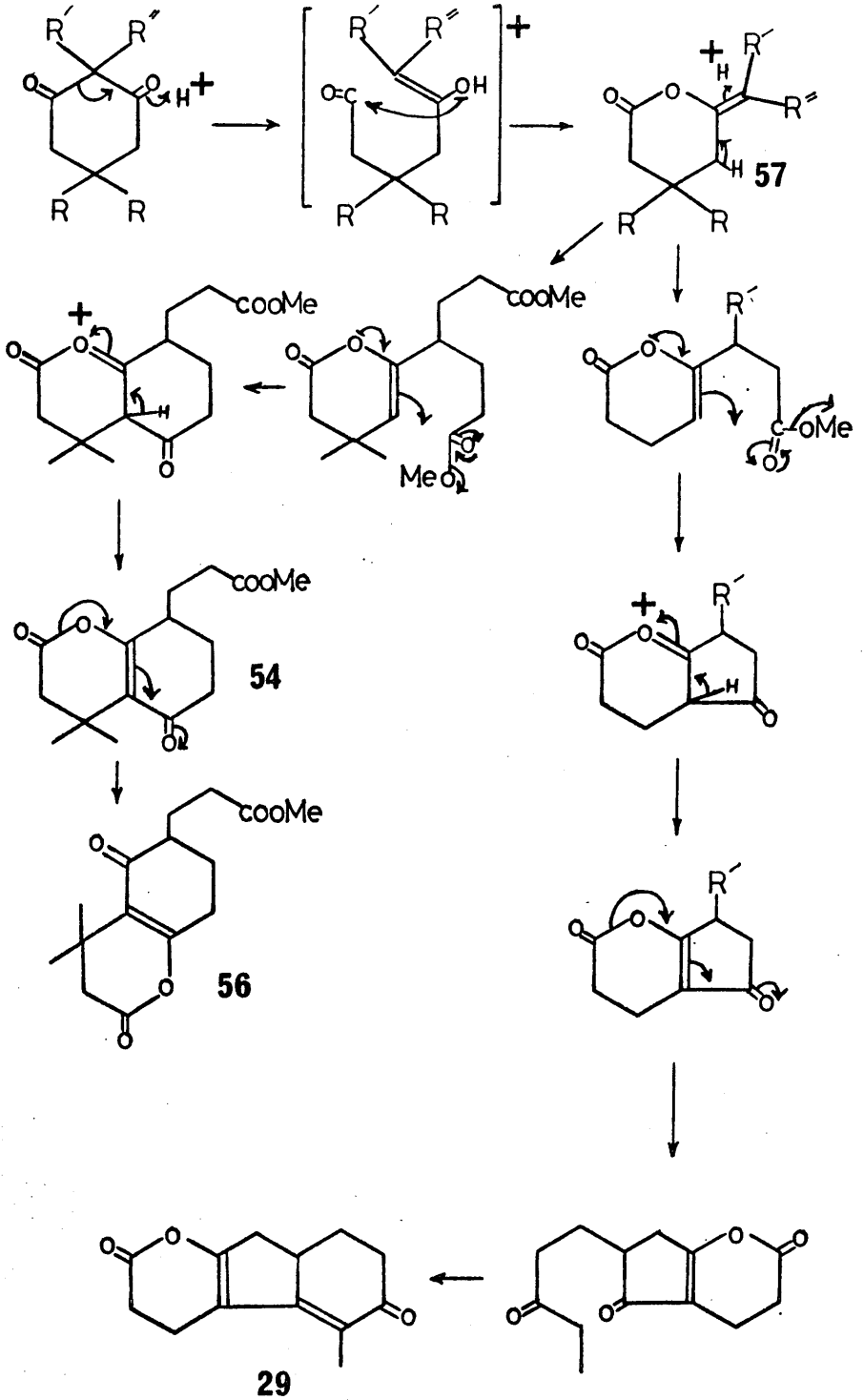

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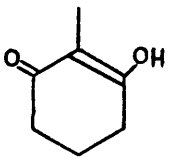

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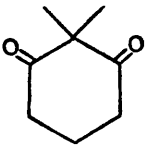

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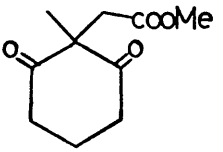

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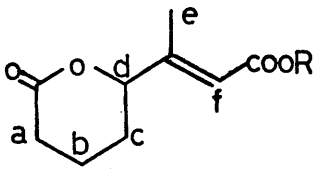
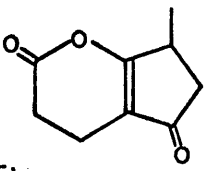


61 R=Et
62 R=H



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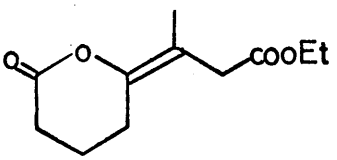

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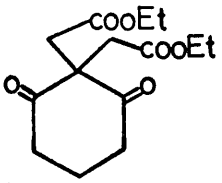

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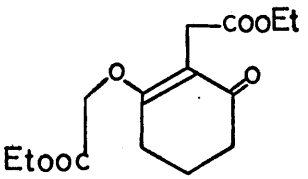

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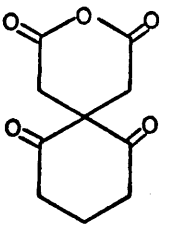

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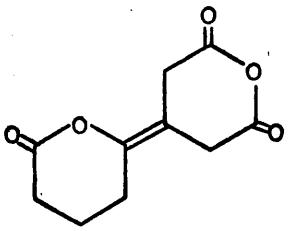

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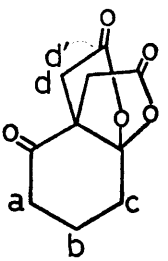

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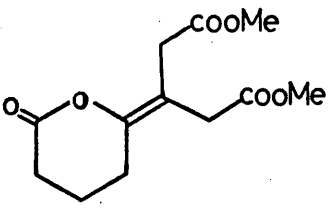

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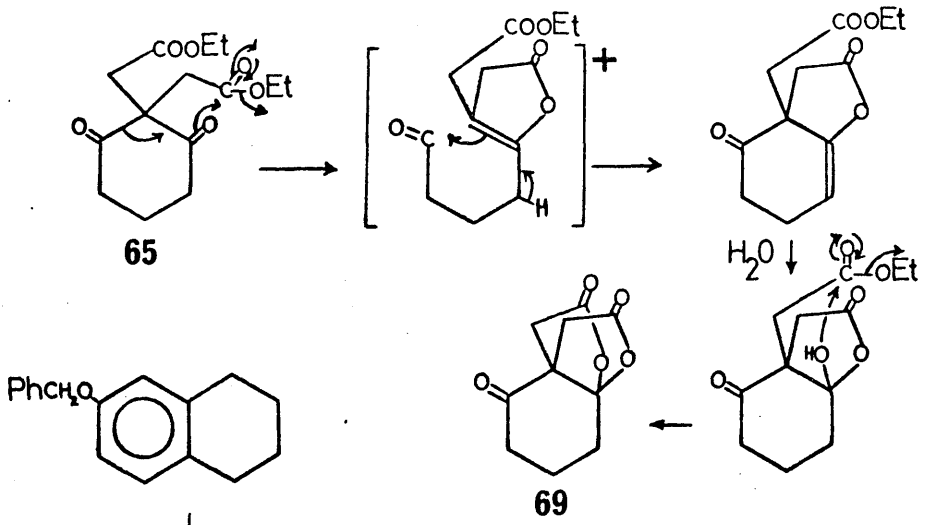

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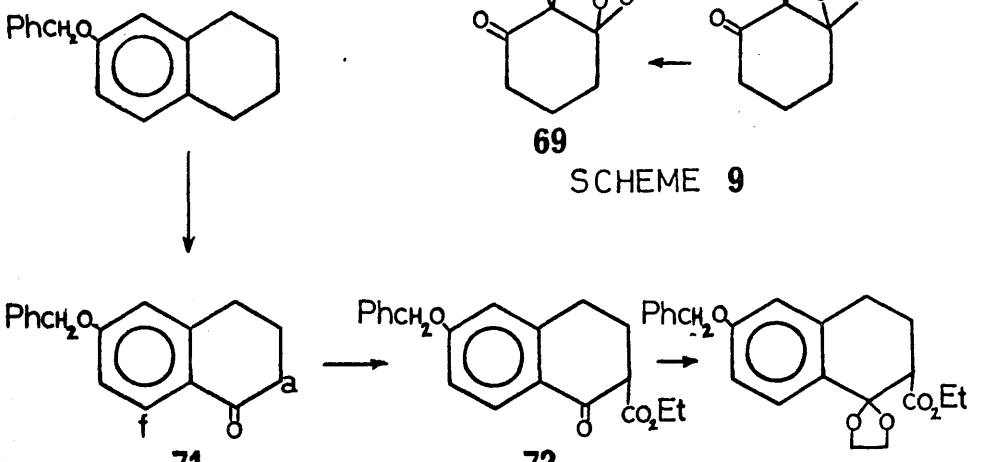

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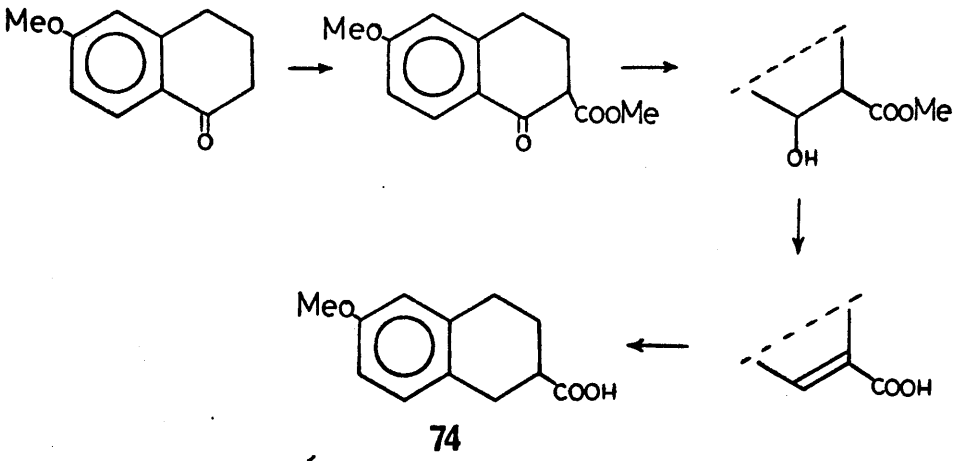

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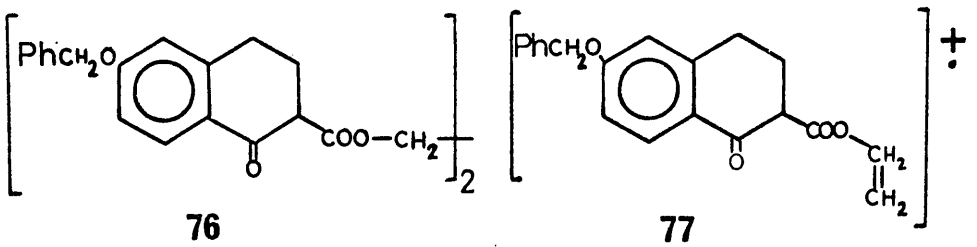
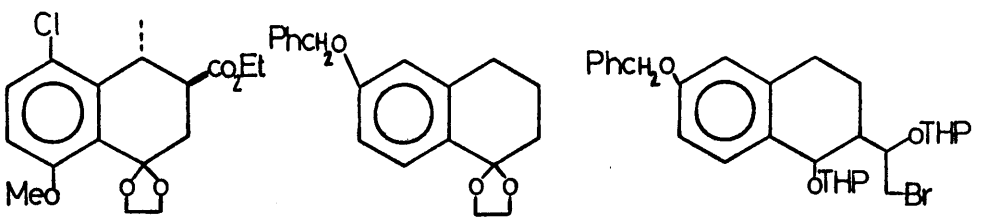


76 **77**



78 **79** **80**

EXPERIMENTAL

2-Carbethoxymethylenecyclohexane-1,3-dione (4)

This compound was prepared by Stetter's method[6] using ethyl bromoacetate and potassium ethoxide. The product was obtained as off-white plates, m.p. 85·5-86°, from water, 44% (lit. m.p. 85°, 51%)

$\nu_{max.}^{cm.^{-1}}$ (CCl_4): 3616 (w) (hydroxyl), 3137 (w) (bonded hydroxyl), 1729 (s) (ester), 1713 (s) (carbonyl), 1690 (s) (enone carbonyl), 1655 (s) (double bond).

N.M.R. 5·84 τ (2H, q, J = 8); 6·61 τ (2H, s); 8·76 τ (3H, t, J = 8).

1-Chloropentan-3-one

This was prepared by the literature procedure[34] using chloroform as solvent. The almost colourless liquid was distilled under reduced pressure, b.p. 47-49°/3 mm., n_D^{24} 1·4345 (lit. b.p. 32·3-33·3°/2·5 mm., n_D^{20} 1·4361).

1-Diethylaminopentan-3-one (23)

This was prepared by the method of Adamson *et al.*[35] The pale yellow product distilled at b.p. 76°/10 mm., n_D^{17} 1·4370 (lit b.p. 84°/13 mm., n_D^{15} 1·4368).

9-Carbethoxymethylene-5-methyl-$\Delta^{5,10}$-octalin-1,6-dione (5)

The diketoester (4) (0·5 g., 0·00255 mole), 1-diethylaminopentan-3-one (23) (0·49 g., 0·00315 mole) and triethylamine (0·1 g., 0·001 mole) were stirred in refluxing benzene using a water separator for 18 hrs. After this period, pyrrolidine (2 ml.) was added and the heating continued for 2 hrs., after which time the bulk of the solvent was evaporated in vacuo. The residual solution was diluted with ether, washed with dilute hydrochloric acid (1·5%) and brine. The aqueous solutions were re-extracted thoroughly with ether, the organic extracts combined and washed with brine. After drying over sodium sulphate, the solvent was removed in vacuo to yield an amber coloured oil (0·280 g.). Preparative T.L.C. of this oil (35% ethyl acetate/benzene) yielded the enone (5) (115·5 mg., 23%) R_F 0·55, as a pale yellow oil which was shown by T.L.C. to be contaminated with another compound, R_F ca. 0·55, which was later shown to be the triketoester (24) by G.L.C. comparison with an authentic sample. [T.L.C. : D.N.P. developer, enone (5) red; triketoester (24) yellow.]

G.L.C. analysis of the crude enone showed it to be a 6:1 mixture of enone : triketoester.

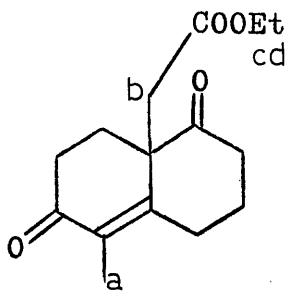
[Column: P.E.G. 20 M (2%), Temp. 200°, F.R. 51 ml./min., enone R_t = 23·85 min., triketoester R_t = 19·50 min.]

The impure enone (61 mg.) was adsorbed on to Woelm alumina (Grade I, acid-washed, 5 g.,) and eluted with benzene followed by gradient elution with ethyl acetate/benzene mixtures (x 25 ml.,). Pure enone (20·1 mg.,) was eluted with 4-8% mixtures (later fractions again yielding enone:triketoester mixtures) and was distilled under reduced pressure, b.p. 110°/0·05 mm., (sub. block).

(Found: C, 68·05; H, 7·64. $C_{15}H_{20}O_4$ requires: C, 68·16; H, 7·63%).

$\nu_{max.}^{cm.^{-1}}$ (CCl_4): 1738 (s) (ester), 1722 (s) (ketone), 1674 (s) (enone).

N.M.R.



H_a 8·16 τ (3H, singlet)

H_b 7·13 τ (2H, fine doublet, J = 4)

H_c 5·86 τ (2H, quartet, J = 8)

H_d 8·77 τ (3H, triplet, J = 8)

The mass spectrum showed a parent ion at m/e 264 ($C_{15}H_{20}O_4$ requires 264) and also a base peak at m/e 176, corresponding to loss of ($CH_2=\underset{\underset{OH}{|}}{C}-OEt$).

$\lambda_{max.}^{CHCl_3}$ 254·5 mμ (ε, 10,080), $\lambda_{INFLEX.}^{CHCl_3}$ 292 mμ (ε, 742) (calc. $\lambda_{max.}$ 254 mμ)

2-Carbethoxymethylene-2-(3'-ketopentyl) cyclohexane-1,3-dione (24)

To a vigorously stirred solution of diketoester (4) (2·1 g., 0·0106 mole) and 1-diethylaminopentan-3-one (23) (1·7 g., 0·0108 mole) in t-butanol (1·25 ml.,), triethylamine (1·25 ml.,) was added in small portions over 15 min. The mixture was warmed to an oil bath temperature of 80° and maintained thus for 10 min. The cooled solution was diluted with excess ether and washed successively with dilute sodium bicarbonate (2%), dilute sulphuric acid (2N) and brine . After drying over sodium sulphate the solvent was removed in vacuo yielding a pale yellow oil which was extracted thoroughly with hot petrol. Concentration in vacuo of the petrol solution, followed by cooling in carbon dioxide/acetone solution afforded the triketoester (24) (0·854 g., 40%) as a colourless solid, m.p. 54-55°.

The triketoester was purified by prep. T.L.C. and recrystallised from petrol or diisopropyl ether and had m.p. 55·5-56·5°.

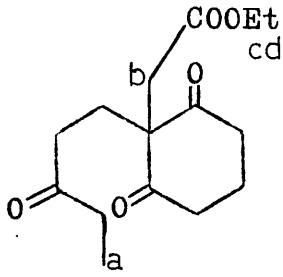
(Found: C, 63·69; H, 7·96. $C_{15}H_{22}O_5$ requires: C, 63·81; H, 7·85%).

The infra-red spectrum in several solvents showed only two maxima in the carbonyl region:

Solvent	ester C=O	ketone C=O
	cm.$^{-1}$	cm.$^{-1}$
cyclohexane	1728	1702
carbon tetrachloride	1725·5	1697·5
chloroform	1718	1694
acetonitrile	1722	1696

Mass Spectrum: Parent ion m/e 282, base peak m/e 57 $(CH_3CH_2CO)^+$ other ions m/e 236, 123.

N.M.R. Spectrum:



H_a 9·01 τ (3H, triplet, J = 8)

H_b 7·06 τ (2H, singlet)

H_c 5·96 τ (2H, quartet, J = 8)

H_d 8·82 τ (3H, triplet, J = 8)

G.L.C.

Column: P.E.G. 20 M (2%), Temp. 200°, F.R. 51 ml./min., R_t = 19·50 min.

Attempted synthesis of 9-carbethoxymethylene-5-methyl-$\Delta^{5,10}$-octalin-1,6-dione (5) by cyclisation of 2-carbethoxymethylene-2-(3'-ketopentyl) cyclohexane-1,3-dione (24)

Cyclisations were carried out using three general approaches:

(a) Using organic bases.

(b) Using organic salts.

(c) Using acidic catalysts.

(a) Using organic bases (Table Ia)

The triketoester (24), the base (10% molar excess) and solvent were heated at reflux in a Dean-Stark water-separator for a given time. The cooled solution was diluted with ether, washed with dilute sulphuric acid (2N) and then brine. After drying over sodium sulphate, the solution was evaporated in vacuo and the product identified using I.R. and T.L.C. As shown in Table Ia, variation in temperature, solvent and time of reaction afforded starting material (S.M.) or unidentified products.

(b) Using organic salts

(Table Ib).

(i) Triethylamine/benzoic acid[16]

The triketoester (24) (0·5 g., 0·00177 mole), benzoic acid (0·226 g., 0·00185 mole) and triethylamine (0·144 g., 0·00142 mole) in benzene (xylene) (10 ml.,) were refluxed with water-separation. Products were isolated as in (a), washing successively with sodium bicarbonate (2%), sulphuric acid (2N) and brine. In both cases, triketoester was recovered unchanged.

(ii) Pyrrolidine/acetic acid/ether.

The triketoester (24) (0·20 g., 0·00071 mole) was stirred in ether (10 ml.,) at 0^{o}. Pyrrolidine (49·7 mg., 0·0007 mole) was added and stirring continued for 5 min., after which time acetic acid (42 mg., 0·0007 mole) was added dropwise. After stirring for a further 2 hrs. at room temperature, the solvent was evaporated *in vacuo* and traces of residual acetic acid removed by azeotroping with benzene. A pale yellow solid remained which by I.R. and T.L.C. was shown to be entirely starting material.

(iii) Pyrrolidine/acetic acid/benzene. 1-Carbethoxy-methylene-6-ethyl-6-hydroxybicyclo[3,3,1]nonane-2,9-dione (26)

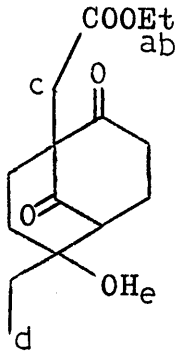
The triketoester (24) (0·2015 g., 0·00072 mole) and pyrrolidine (0·1295 g., 0·00183 mole) were stirred in benzene (8 ml.,) at room temperature. Acetic acid (0·1156 g., 0·00195 mole) in benzene (4 ml.,) was added dropwise over 15 min., and stirring continued for 72 hrs. The solution was diluted with ether and washed thoroughly with brine. Drying over sodium sulphate and evaporation in vacuo afforded a pale yellow oil, which was shown by T.L.C. to consist of a new compound, R_F 0·4, which was more polar than either the enone (5) or the triketoester (24). Preparative T.L.C. of the oil yielded the pure ketol (26) (71 mg., 35%) as a colourless oil.

$\nu_{max.}^{cm.^{-1}}$ (CCl_4): 3600 (s) (free hydroxyl), 3426 (m) (bonded hydroxyl), 1734 (s) (ester), 1711 (s) (ketone).

On distillation under reduced pressure (0·01 mm.,), the ketol yielded a clear oil which soon solidified and was shown by infra-red comparison and mixed melting point to be the triketoester (24). On standing for several hours, (26) became semi-solid and was shown by T.L.C. to be a mixture of triketoester and ketol. The pure ketol was not

subjected to analysis owing to its ready reversion to the isomeric triketoester.

The N.M.R. of the ketol showed it to be the bicyclo[3,3,1]nonane derivative:



H_a 5·92 τ (2H, quartet, J = 8)
H_b 8·78 τ (3H, triplet, J = 8)
H_c 7·21 τ (2H, doublet, J = 2)
H_d 9·05 τ (3H, triplet, J = 8)
H_e 7·65 τ (1H, singlet).

D_2O exchange confirmed the hydroxyl signal.

Attempts to dehydrate the bicyclic ketol (26)

(1) Pure ketol (18·2 mg.,) in acetic anhydride (10 ml.,) was refluxed for 3 hrs., after which time the solution was cooled, water added and, after 1 hr., extracted thoroughly with ether. The ether extracts were washed with brine, dried over sodium sulphate and, after azeotroping with benzene to remove the last traces of acetic acid, evaporated in vacuo. A pale yellow solid (12·7 mg.,), m.p. 54-55° identified as the triketoester (24) by I.R. and T.L.C. was obtained.

(2) Phosphorus oxychloride (6 drops) was added slowly to a solution of pure ketol (15·1 mg.,) in pyridine (3 ml.,), after which time the solution was allowed to stand for 24 hrs. The mixture was poured on to ice, extracted thoroughly with ether and the ether extracts washed with brine. After drying, removal of the solvent in vacuo yielded a brown oil (11·6 mg.,) which by T.L.C. appeared to consist of several acidic species. No bicyclic olefin could be detected by T.L.C. or infra-red analysis.

Attempts to synthesise an ester derivative of ketol (26)

(1) Acetate

Pure ketol (18·4 mg.,) and p-toluenesulphonic acid (8 mg.,) in acetic anhydride (12 ml.,) were heated for 1 hr. on a steam bath. The work-up was as in (1) above, the only product isolated being the triketoester (24) (15·2 mg.,).

(2) Benzoate

To a solution of pure ketol (30 mg., 0·00010 mole) in pyridine (2 ml.,), benzoyl chloride (31 mg., 0·00022 mole) was added dropwise. White crystals of pyridine hydrochloride soon appeared and, after 5 hrs., the excess acid

chloride was hydrolysed with water. The aqueous solution was then extracted with ether which was washed with brine and dried over sodium sulphate. The solvent was evaporated <u>in vacuo</u> affording a pale brown oil which by T.L.C. was shown to consist of mainly one component which was less polar (R_F 0·4, 10% ethyl acetate/benzene) than either the ketol (26) or the triketoester (24). An analytical sample was obtained by preparative T.L.C. and distilled under reduced pressure, b.p. 155-160°/0·05 mm.

(Found: C, 67·07; H, 6·10. $C_{17}H_{18}O_5$ requires: C, 67·54; H, 6·00%).

$\nu_{max.}^{cm.^{-1}}$ (CCl_4): 1743 (s) (ester), 1683 (s) (benzoate)

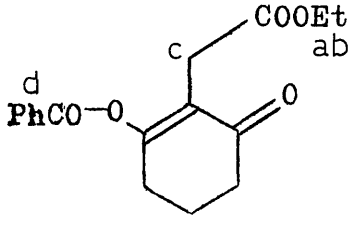
$\nu_{shoulder}^{cm.^{-1}}$: 1668 (m) (enone)

$\lambda_{max.}^{EtOH}$ 239·5 mμ (ε, 21,400)

$\lambda_{max.}^{EtOH}$ 239·5 mμ (ε, 21,400)

This compound was identified as ethyl (6-keto-2-benzoyloxy-[1] with an authentic sample made from the diketoester (4).

N.M.R..



H_a 5·91 τ (2H, quartet, J=7·5)

H_b 8·84 τ (3H, triplet, J=7·5)

H_c 6·66 τ (2H, singlet)

H_d ca 1·8, ca 2·3 (5H, complex)

(iv) Pyrrolidine/acetic acid/benzene with heat

To a solution of triketoester (24) (1·00 g., 0·00355 mole) and pyrrolidine (0·630 g., 0·00887 mole) in benzene (22 ml.,), acetic acid (0·57 g., 0·0095 mole) was added dropwise and the mixture heated at reflux for 5 min., cooled and stirred for 72 hrs. The solution was evaporated in vacuo and azeotroped with benzene to remove traces of acetic acid. Analysis of the residue by T.L.C. indicated the presence of starting triketoester, enone (5) and two more polar compounds which had retention factors (R_F 0·4, 0·35 for 35% ethyl acetate/benzene) similar to that of the ketol (26). The mixture was adsorbed on to Woelm alumina (Grade I, acid-washed, 40 g.,) and eluted with ethyl acetate/benzene mixtures affording a pure sample of triketoester (24) (161 mg.,) and an almost pure sample of enone (5) (again contaminated with triketoester) which was further purified by preparative T.L.C. (147·5 mg., 16%). The two polar components could not be separated by column chromatography but were partially separated by preparative T.L.C. The more polar of the two was obtained almost pure and showed an infra-red spectrum identical to that of the bicyclic ketol (26). The less polar compound, obtained in much smaller yield, readily decomposed to acidic species.

It was presumed to be either the epimeric ketol of the bicyclo[3,3,1]nonane series (26) or the decalin derivative (25) but could not be identified because of its instability.

(v) Pyrrolidine/acetic acid with heat

A mixture of triketoester (24) (100·8 mg., 0·00038 mole), pyrrolidine (61 mg., 0·00086 mole) and acetic acid (55 mg., 0·00092 mole) was heated at reflux for 5 hrs. The solution was cooled and azeotroped twice with benzene. Preparative T.L.C. afforded the enone (5) (11·3 mg., 12%) (which was characterised by I.R. and T.L.C.) and mixtures of acidic species indicating that the conditions had caused decomposition.

(C) Using acid catalysts (Table II)

(i) Concentrated sulphuric acid

A mixture of triketoester (24) (48·4 mg., 0·00017 mole) and conc. sulphuric acid (10 ml.,) was stirred on a steam bath for 35 min., cooled, poured on to ice and extracted thoroughly with chloroform. The organic solution was washed with brine, dried over sodium sulphate and evaporated in vacuo to give a brown oil which, by T.L.C., was shown to consist mainly of acidic materials. The

infra-red spectrum showed strong bonded absorption at 3500-3000 $cm.^{-1}$ as well as a strong band at 1810 $cm.^{-1}$ which was assigned to a lactone grouping. A conjugated system was inferred from the ultraviolet spectrum i.e., $\lambda_{max.}^{EtOH}$ 299 mμ but no pure compound could be isolated from the complex mixture.

Milder conditions (reaction at room temperature) resulted in the isolation of starting material as the only identifiable product.

(ii) Sodium acetate/acetic anhydride

Triketoester (109·5 mg., 0·00039 mole) and fused sodium acetate (14·4 mg.,) were dissolved in acetic anhydride (10 ml.,) and refluxed for $3\frac{1}{2}$ hrs. The cooled solution was diluted with excess water, extracted with ether and the organic layer washed thoroughly with brine. After drying over sodium sulphate, removal of solvent in vacuo yielded an amber oil which by T.L.C. and I.R. was shown to be starting triketoester.

(iii) Hydrochloric acid/acetic acid

Triketoester (101·4 mg.,), glacial acetic acid (5 ml.,) and conc. hydrochloric acid (5 ml.,) were refluxed

for $3\frac{1}{2}$ hrs., and the product isolated as in (ii) above. Analysis by T.L.C. of the brown oil showed about seven components which were not identified.

(iv) p-Toluenesulphonic acid/benzene

Triketoester (54 mg.,) and p-toluenesulphonic acid (10 mg.,) in benzene (20 ml.,) were heated at reflux in a Dean-Stark water separator for 24 hrs. The solvent was removed *in vacuo*, the residue diluted with ether, washed with brine and dried over sodium sulphate. Analysis by T.L.C. showed the presence of only acidic components and starting material.

(v) Polyphosphoric acid: 3,4,7,8,8a,9-hexahydro-2,6-diketo-5-methyl-1-oxafluorene (29).

Triketoester (0·4719 g., 0·00168 mole) was added in small portions to polyphosphoric acid (6·1 g.,) and stirred vigorously for 45 min., at an oil bath temperature of 90°. On cooling, the viscous, rust-coloured solution was poured on to ice and extracted thoroughly with chloroform (x4). The extracts were washed with brine, dried over sodium sulphate and evaporated *in vacuo* leaving an amber oil which afforded the crystalline title compound

(123·5 mg., 34%) on trituration with ether. An analytical sample, off-white platelets, m.p. 131-132°, was obtained by preparative T.L.C. (R_F 0·6) and recrystallisation from ether. (Found: C, 71·61; H, 6·48. $C_{13}H_{14}O_3$ requires: C, 71·54; H, 6·47%).

$\nu_{max.}^{cm.^{-1}}$ (CCl_4): 1823 (s) (enol-lactone), 1656 (s) (double bond)

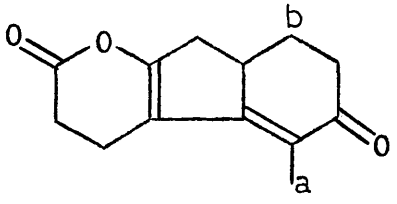
$\nu_{shoulder}^{cm.^{-1}}$ (CCl_4): 1677 (m) (enone)

$\lambda_{max.}^{EtOH}$ 306·5 mμ (ε, 20,150), 231 mμ (ε, 5,450), 213 mμ ($\varepsilon_{app.}$ 6,480)

$\lambda_{shoulder}^{EtOH}$ 238 mμ (ε, 5,120)

The analytical sample was shown to be homogeneous by G.L.C. Column: 5% QFI, Temp.: 200°, F.R. 37 ml./min., R_t = 43 min.

N.M.R.



H_a 8·16 τ (3 protons, singlet)

H_b 8·30 τ (2 protons, broad singlet)

The other protons appeared as a complex region 6·8 - 7·9 τ. The mass spectrum showed a parent ion at m/e 218 ($C_{13}H_{14}O_3$ requires 218) which is also the base peak. There were

large ions at m/e 28 and m/e 91.

The residue from crystallisation was shown by T.L.C. to be a mixture of acidic species and was esterified with diazomethane directly. T.L.C. of the ester mixture indicated an apparent main component, R_F 0·6, which was isolated as an amber oil by preparative T.L.C. The oil was thought to be a mixture of ketoenone esters (50 and 51) by the infra-red spectrum.

$\nu_{max.}^{cm.^{-1}}$ (film): 1740-30 (s) (ester, cyclopentanone), 1660 (s) (enone), 1625 (s) (double bond).

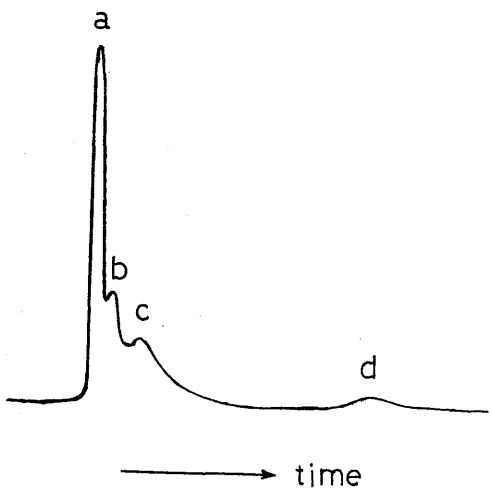
$\nu_{shoulder}^{cm.^{-1}}$ (film): 1705 (cyclohexanone, cyclopentenone)

These compounds were unstable and inseparable and were not further investigated.

Hydrogenation of 3,4,7,8,8a,9-hexahydro-2,6-diketo-5-methyl-1-oxafluorene (29).

The enone lactone (9·6 mg.,) was hydrogenated in ethanol (AnalaR, 2·5 ml.,) over palladium charcoal (10%, 6 mg.,), total uptake of hydrogen being complete after 12 min. The solution was filtered through celite and evaporated in vacuo to yield a yellow oil which by I.R. and T.L.C. indicated an acidic species. The oil in ether was esterified with diazomethane and the products purified by

preparative T.L.C. (15% ethyl acetate/benzene). The main component [a mixture of stereoisomers (48)] showed the following G.L.C. trace:



Column: 1% SE30

Temp. : 150°

F.R. : 46 ml./min.

R_t a 6·05 min.

R_t b 6·70 min.

R_t c 7·40 min.

R_t d 15·75 min.

The mass spectrum of each component was determined using G.C.M.S., the parent ion for components a, b and c being the same in each case, m/e 238 [$C_{14}H_{22}O_3$, the fully saturated compound (48), requires 238]. Component d (present in less than 5% yield) showed a parent m/e 234 confirming the unsaturated structure (49) which requires 234.

$\nu_{max.}^{cm.^{-1}}$ (CCl_4): 1742 (s) (ester), 1718 (s) (cyclohexanone)

The ultraviolet spectrum showed only weak end absorption.

Hydrogenation in ethyl acetate and in dioxane gave identical results, the latter case being a much slower reaction.

Attempts to separate any single stereoisomer were unsuccessful.

Action of dilute alkali on 3,4,7,8,8a,9-hexahydro-2,6-diketo-5-methyl-1-oxafluorene (29).

Several experiments were carried out stirring the enone lactone (29) in dilute sodium hydroxide at room temperature for 30 min. The aqueous solutions were washed with ether, acidified and extracted with ether continuously for 12 hrs. The resulting acidic species were esterified with diazomethane and the components examined by G.C.M.S. (1% SE30, Temp. 200° and 150°). Unfortunately the results were not reproducible, time for esterification being an important factor as well as disproportionation and aromatisation of the molecule. The experiment therefore threw no light on the original structure of the enone lactone and was discontinued.

2-Methylcyclohexane-1,3-dione (58)

Prepared by the method of Stetter[6] using potassium hydroxide and methyl iodide, this compound was obtained as pale yellow prisms, m.p. 185-186°, from methanol (lit. m.p. 204°, from methanol: water, 1:3).

$\nu_{max.}^{cm.^{-1}}$ (NUJOL): 2700 (m) (bonded hydroxyl), 1650 (w) (enone), 1580 (s) (double bond).

N.M.R. (CF_3COOH): 8·16 τ (3H, singlet).

2,2-Dimethylcyclohexane-1,3-dione (59)

Prepared by the Nazarov[29] method, this compound was obtained in 65% yield as plates, m.p. 33-36° from petrol (lit. m.p. 38-39°, 46%).

$\nu_{max.}^{cm.^{-1}}$ (CCl_4): 1734 (s), 1704 (s) (carbonyls). carbonyl interaction Δ = 30 $cm.^{-1}$.

The N.M.R. is shown in Table VI.

The O-alkylation product, 2-methyl-3-methoxy-cyclohex-2-ene-1-one was also obtained as a by-product in low yield.

$\nu_{max.}^{cm.^{-1}}$ (film): 1650 (s) (enone), 1615 (s) (double bond).

2-Carbethoxymethylene-2-methylcyclohexane-1,3-dione (60)

Prepared by the method of Stetter[30] from 2-methyl-cyclohexane-1,3-dione, the compound was obtained as colourless prisms, m.p. 62·5-63°, from petrol: diisopropyl ether, 6:1 (lit. m.p. 67°, from ligroin).

$\nu_{max.}^{cm.^{-1}}$ (CCl_4): 1728 (s) (ester, ketone), 1703 (s) (ketone).

The N.M.R. is shown in Table VI.

2,2-Di(carbethoxymethylene)cyclohexane-1,3-dione (65)

This was obtained from 2-carbethoxymethylene-cyclohexane-1,3-dione (4) (0·501 g., 0·0025 mole) by the above method[30] using ethyl bromoacetate. The product was a brown oil, which, by T.L.C., showed two main components which were separated by preparative T.L.C. The less polar component, R_F 0·7, (0·2653 g., 37%), b.p. 94°/0·025 mm., (sub.), was shown to be the diester (65).

$\nu_{max.}^{cm.^{-1}}$ (CCl_4): 1740 (s) (ester), 1729 (shoulder), 1707 (s), 1699 (s) (ketone).

(Found: C, 59·19; H, 7·37. $C_{14}H_{20}O_6$ requires: C, 59·14; H, 7·09%).

The N.M.R. is shown in Table VI.

The mass spectrum showed a parent ion m/e 284 ($C_{14}H_{20}O_6$ requires 284) and a base peak m/e 238 ($M-CH_3CH_2OH$), there being large fragment ions at m/e 123 and m/e 55.

The more polar component, R_F 0·35, the O-alkylated product (66) was obtained in 35% yield (0·2463 g.,) b.p. 130-135°/0·1 mm. (sub.).

$\nu_{max.}^{cm.^{-1}}$ (CCl_4): 1763 (s) (ester, β-oxygen); 1741 (s) (ester, β-carbon); 1665 (s) (enone); 1638 (s) (double bond).

The N.M.R. spectrum confirmed this by showing a singlet at 5·41 τ (2 protons) for the methylene adjacent to the oxygen and the ester group. Two different ester groups are identified by two quartets (5·77, 5·92 τ) and two triplets (8·83, 8·88 τ).

Action of polyphosphoric acid on 2,2-dimethylcyclohexane-1,3-dione (59)

The diketone (59) (0·224 g., 0·0016 mole) was added to a vigorously stirred syrup of polyphosphoric acid at an oil bath temperature of 90°. This temperature was maintained for 45 min., the solution cooled and ice added. The mixture was extracted thoroughly with chloroform, the extracts being washed with brine and dried over sodium sulphate. Evaporation afforded an amber oil (0·209 g., 90%) which by T.L.C. and I.R. was shown to be identical with the starting material.

Action of polyphosphoric acid on 2-carbethoxymethylene-2-methylcyclohexane-1,3-dione (60); ethyl β(2-keto-6-tetrahydropyranyl)crotonate.(61)

The diketoester (60) (0·2893 g., 0·00137 mole) was reacted as above. The product was a yellow oil which

showed one main component, R_F 0·6 by T.L.C. Separation by preparative T.L.C. afforded the lactone ester (61)(137·7 mg., 48%) b.p. 125°/ 0·25 mm., (sub.) and an acidic species (19·5 mg.,) which was not completely pure. Purity of the sample of lactone ester was shown by G.L.C. on various columns:

Column	Temp.	F.R.(ml./min.)	R_t(min)
5% QF1	175°	39	32·9
1% CHDMS 2% PVP	175°	39	10·0
10% APL	175°	38	20·65

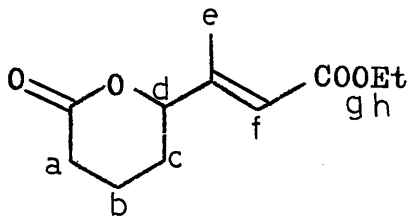
(Found: C, 62·24; H, 7·22. $C_{11}H_{16}O_4$ requires: C, 62·25; H, 7·60%).

$\nu_{max.}^{cm.^{-1}}$ (CCl_4): 1768 (s) (lactone); 1734 (s) (ester); 1647 (w) (double bond); 958 (m), 802 (w), 787 (w) (double bond).

$\lambda_{max.}^{EtOH}$ 209 mμ (ε_{app}12,900).

The mass spectrum showed a parent ion m/e 212 ($C_{11}H_{16}O_4$ requires 212) a base peak at m/e 41 and a large ion at m/e 166 ($M-CH_3CH_2OH$).

N.M.R. (100 Mc.)



H_a 7·68 τ (2H, triplet, J=6)

H_b 8–8·5 τ (4H, multiplet)
H_c

H_d 5·21 τ (1H, broad absorption)

H_e 7·97 τ (3H, singlet)

H_f 4·28 τ (1H, fine multiplet, J=1·5)

H_g 5·94 τ (2H, quartet, J=7)

H_h 8·77 τ (3H, triplet, J=7)

Irradiation at H_d converted the signal at 4·28 τ into a singlet, and also caused change in the methylene absorption around 8·3 τ. Irradiation at 8·3 τ produced a sharpening of the signal at 5·21 τ.

The singlet at 7·97 τ appeared as a fine quartet, J = 1, when the sample was run at 60 Mc.

The acidic component showed a broad carbonyl region in the infra-red spectrum as well as absorption at 1647 $cm.^{-1}$ (double bond), and was presumed to be the lactone acid (62).

Action of polyphosphoric acid on 2,2-di(carbethoxymethylene)-cyclohexane-1,3-dione (65); 7,12-dioxatricyclo[4,3,3,$0^{1,6}$] dodeca-2,8,11-trione (69).

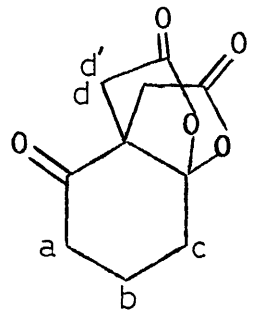
The diketodiester (65)(0·2428 g., 0·00086 mole) was treated with polyphosphoric acid exactly as above. A yellow oil (152 mg.,) was isolated which partially crystallised on standing. Separation of the crystals and recrystallisation from ethyl acetate/petrol afforded the keto dilactone (69)(114·8 mg., 64%) as colourless prisms, m.p. 134·5-135°.

(Found: C, 57·12; H, 4·68. $C_{10}H_{10}O_5$ requires: C, 57·14; H, 4·80%).

$\nu_{max.}^{cm.^{-1}}$ (CCl_4): 1829 (s) (γ-lactone); 1813 (s) (second γ-lactone); 1729 (s) (ketone).

The mass spectrum showed a parent ion m/e 210 ($C_{10}H_{10}O_5$ requires 210) and base peak m/e 110.

N.M.R.



H_a 7·42 τ (2H, triplet, J = 6)

H_b 8·09 τ (2H, multiplet.)

H_c 7·70 τ (2H, triplet, J = 6)

H_d 6·85 τ (2H, doublet, J = 18)

$H_{d'}$ 7·17 τ (2H, doublet, J = 18)

Irradiation at the H_b frequency converted the triplet at

7·70 τ and the triplet at 7·42 τ into broad singlets. Irradiation at the H_a frequency caused the multiplet at 8·09 τ to collapse to an ill-defined signal: attempts to decouple protons H_d and $H_{d'}$ failed due to the high coupling constant.

(vi) Boron Trifluoride/acetic acid

2-Carbethoxymethylene-2-(3'-ketopentyl)cyclohexane-1,3-dione (24) (0·201 g., 0·00071 mole) was added to a solution of freshly distilled boron trifluoride etherate (1 ml.,) and acetic acid (4 ml.,). The solution was refluxed for $2\frac{1}{2}$ hrs., cooled, poured into concentrated sodium acetate solution and thoroughly extracted with ether. The ether extracts were washed several times with brine, dried over sodium sulphate and azeotroped with benzene to remove traces of acetic acid. Preparative T.L.C. yielded the enone lactone (29) m.p. 131-132° (18·1 mg., 12%) as shown by I.R., T.L.C. and G.L.C.

(vii) Boron trifluoride/acetic anhydride

The ketoester (24) (0·1974 g., 0·00074 mole) after treatment with a solution of boron trifluoride etherate (1 ml.,) in acetic anhydride (4 ml.,) was refluxed for $2\frac{1}{2}$ hrs. The solution was extracted as above, the

resulting brown oil showing many components by T.L.C. The starting material had obviously fragmented and further investigation was abandoned.

Hydrogenation of 9-carbethoxymethylene-5-methyl-$\Delta^{5,10}$-octalin-1,6-dione (5).

The enone (5) with 14% triketoester (24) present as a standard was hydrogenated over palladium/charcoal (10%) using a variety of solvents,i.e., ethanol, acetic acid, dioxane, ethanol/hydrochloric acid. The hydrogenation products were identified by G.L.C. using a variety of columns and confirmed by examination using coupled mass spectroscopy and gas chromatography. Treatment of a sample of all four possible hydrogenated isomers (40, 41, 42 , 43,) with alcoholic sulphuric acid caused epimerisation of the epimer (41) with the methyl-methyl interaction as illustrated by G.L.C. and G.C.M.S. (Tables III, IV and V, discussion).

Ar-2-tetralol benzyl ether

This was prepared by the procedure of Lipovich.[36] The product distilled at b.p. 170-175°/0·03 mm., 85% yield n_D^{20} 1·5845 (lit. b.p. 169-171°/5-6 mm.).

6-Benzyloxy-1-tetralone (71)

Standard Jones reagent (8N) (264 ml., 0·7046 mole) was added dropwise over 3½ hrs., to a solution of ar-2-tetralol benzyl ether (83·85 g., 0·352 mole) in acetone (170 ml.,) at 5°. After complete addition, the cooling was removed and the mixture stirred for a further 12 hrs., at room temperature. Methanol (20 ml.,) was added to destroy excess reagent and stirring continued for a further 15 min., after which the mixture was poured on to ice. The aqueous solution was extracted thoroughly with an ethyl acetate/ether mixture (1:1), the organic layer then being washed (x4) with brine and evaporated in vacuo, after drying over sodium sulphate. Crystallisation of the resulting red oil from a small amount of methanol afforded the tetralone (71) as pale yellow plates, m.p. 97·5-98° (64·1 g., 72%).

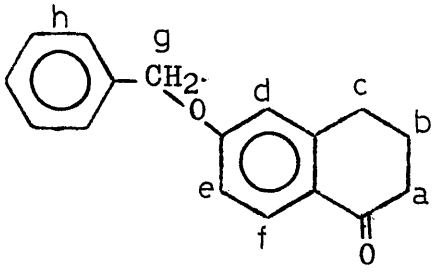
(Found: C, 80·91; H, 6·55. $C_{17}H_{16}O_2$ requires: C, 80·93; H, 6·39%).

$\nu_{max.}^{cm.^{-1}}$ (nujol): 1660 (s) (conj$^{d.}$ carbonyl)

$\lambda_{max.}^{EtOH}$ 275 mμ (ε, 16,120), 224 mμ (ε, 11,210),
208 mμ (ε, 18,390).

[Calc. $\lambda_{max.}$ 274 mμ]

N.M.R. (CCl_4)



H_a 7·14 τ (2H, triplet, J=6)

H_b 7·9 τ (2H, multiplet)

H_c 7·5 τ (2H, triplet, J=6)

H_d 3·25 τ (1H, broad singlet)

H_e 3·18 τ (1H, pair of doublets masked by H_d)

H_f 2·05 τ (1H, doublet, J=9)

H_g 4·93 τ (2H, singlet)

H_h 2·65 τ (5H, singlet)

The ketone yielded a dinitrophenylhydrazone derivative, dark red needles, m.p. 217-217·5°, from ethyl acetate. (Found: C, 63·90; H, 4·67; N, 12·91. $C_{23}H_{20}O_5N_4$ requires: C, 63·88; H, 4·66; N, 12·96%).

2-Carbethoxy-6-benzyloxy-1-tetralone (72)

A solution of the ketone (71) (4·0 g., 0·0158 mole) in dry tetrahydrofuran (25 ml.,) was added slowly to a mixture of sodium hydride (1·9 g., 50% suspension in oil, >0·033 mole) and diethyl carbonate (3·89 g., 0·033 mole)

in refluxing tetrahydrofuran (50 ml.,) under an atmosphere of nitrogen. Effervescence was observed and the heating continued for 3 hrs., after which time the mixture was allowed to cool and dilute acetic acid (100 ml.,) added to destroy excess sodium hydride. The solution was diluted with ether, the ether layer then being washed with dilute sodium hydroxide (4N). Examination of the alkaline phase afforded only a small amount of acidic species. The ether layer afforded, on standing, a pale purple solid, m.p. 150-155° (decomp.,). This solid gave a positive ferric chloride test and decolourised neutral potassium permanganate.

$\nu_{max.}^{cm.^{-1}}$ (nujol): 1650 (s) (conj$^{d.}$ ketone); 1625 (m) (double bond)

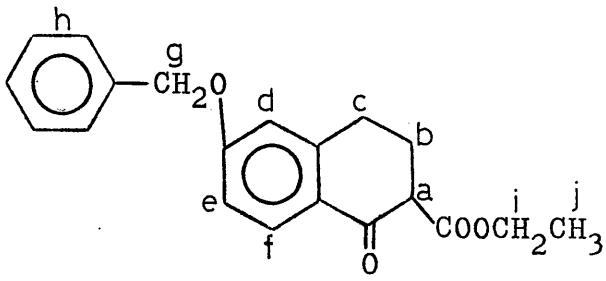
This sodium salt was dissolved in ice-cold dilute hydrochloric acid and thoroughly extracted with ether. The organic layer was washed with sodium bicarbonate (1%), then brine and dried over sodium sulphate. Evaporation <u>in vacuo</u> yielded the ketoester (72) as a pale yellow oil which crystallised from ethyl acetate as prisms, m.p. 61-62·5°, (2·36 g., 46%).

$\nu_{max.}^{cm.^{-1}}$ ($CHCl_3$): 1732 (s) (ester); 1676 (s) (conj$^{d.}$ ketone); 1597 (s) (aromatic).

$\lambda_{max.}^{EtOH}$ 278 mμ (ε, 19,900), 225 mμ (ε, 11,400), 211 mμ (ε, 16,600)

Addition of NaOH (6N) (4 drops) produced a bathochromic shift to $\lambda_{max.}^{EtOH/NaOH}$ 337 mμ (ε, 16,000), 253 mμ (ε, 10,650) (Found: C, 74·33; H, 6·46. $C_{20}H_{20}O_4$ requires: C, 74·06; H, 6·21%).

N.M.R.



H_a 6·6 τ (1H, multiplet)

H_b 7·67 τ (2H, multiplet)

H_c 7·07 τ (2H, triplet, J = 6)

H_d 3·27 τ (1H, broad singlet)

H_e 3·07 τ (1H, pair of doublets masked)

H_f 2·02 τ (1H, doublet, J = 9)

H_g 4·91 τ (2H, singlet)

H_h 2·62 τ (5H, singlet)

H_i 5·82 τ (2H, quartet, J = 7)

H_j 8·82 τ (3H, triplet, J = 7)

The ester gave a green colouration with ferric chloride.

Attempted Ketalisation of 2-carbethoxy-6-benzyloxy-1-tetralone (72)

(a) Ethyl orthoformate/ethanol/acetyl chloride

The ketoester (72) (0·25 g., 0·00077 mole), dissolved in anhydrous ethyl alcohol (0·35 g., 0·0077 mole), was treated with freshly distilled ethyl orthoformate (1·198 g., 0·0081 mole) and the mixture, after the addition of purified acetyl chloride (2 drops), was shaken for 15 minutes and left at room temperature for 24 hrs. The solution was heated at reflux for 1 hr., after which time excess orthoformate and alcohol were removed by evaporation *in vacuo*. The amber residue (0·201 g.,) consisted of only starting material as shown by T.L.C. and I.R.

(b) Ethylene glycol (10% excess)/p-toluenesulphonic acid/benzene.

The ketoester (72) (5·0 g., 0·0154 mole), ethylene glycol (1·057 g., 0·017 mole, 10% excess) and p-toluene-sulphonic acid (10 mg.,) in dry benzene (20 ml.,) were heated under reflux for 6 hrs., using a Dean-Stark water-separator. On concentration of the benzene solution *in vacuo*, a colourless solid (1·18 g., 25%) separated. The filtrate was further evaporated *in vacuo*, diluted with

ether and washed with water and dilute sodium bicarbonate (5%). The ethereal extract was washed with brine, dried over sodium sulphate and evaporated <u>in vacuo</u> to yield a pale brown oil which by T.L.C. and I.R. indicated starting material and phenolic products.

The solid material afforded colourless platelets, m.p. 128-130° from ether, and was shown to be the dimeric species (76).

(Found: C, 73·72; H, 5·48. $C_{38}H_{34}O_8$ requires: C, 73·77; H, 5·54%).

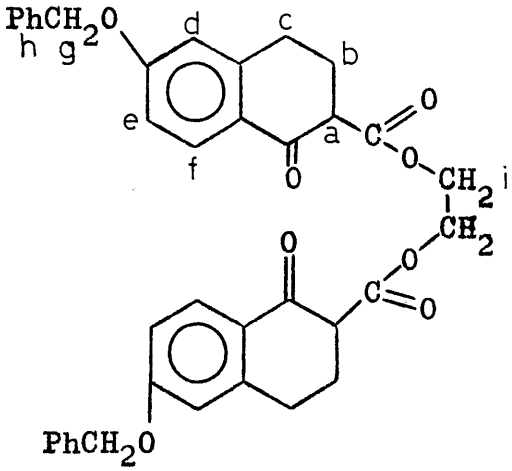
The dimer gave a green colouration with ferric chloride

$\nu_{max.}^{cm.^{-1}}$ ($CHCl_3$): 1741 (s) (ester); 1676 (s) (conj$^{d.}$ ketone); 1644 (w) (unsat$^{n.}$); 1597 (s) (aromatic).

$\lambda_{max.}^{75\%EtOH/CHCl_3}$: 279·5 mμ (ε, 34,900)

Base: $\lambda_{max.}$ 340 mμ (ε, 33,100), 254 mμ (ε, 24,550).

<u>N.M.R.</u>



H_a 6·39 τ (2H, multiplet)

H_b ca 7·6 τ (4H, multiplet)

H_c 7·02 τ (4H, triplet, J = 6)

H_d 3·16 τ (2H, broad singlet)

H_e 3·08 τ (2H, pair of doublets masked)

H_f 1·99 τ (2H, doublet, J = 9)

H_g 4·88 τ (4H, singlet)

H_h 2·57 τ (10H, singlet)

H_i 5·55 τ (4H, fine doublet, J = 2)

The mass spectrum gave a parent ion m/e 618 ($C_{38}H_{34}O_8$ requires 618), a base peak m/e 91 and a large ion m/e 322 corresponding to fragment (77).

(c) Ethylene glycol (10 molar excess)/p-toluenesulphonic acid/benzene.

Ethylene glycol (1·25 g., 0·02 mole) and p-toluenesulphonic acid (5 mg.,) in dry benzene (15 ml.,) were heated under reflux with vigorous stirring for 1½ hrs., using a Dean-Stark water-separator. The ketoester (72) (0·5 g., 0·0015 mole) was added and the heating continued for 48 hrs. The solution was evaporated in vacuo, diluted with ether, washed with dilute sodium bicarbonate (5%) then brine (x4) and dried over sodium sulphate. Evaporation in vacuo afforded an amber oil (1·12 g.,) which by T.L.C. and I.R. was shown to be the starting ketoester.

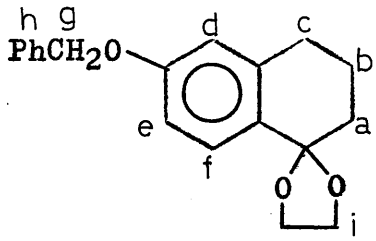
1,1-Ethylenedioxy-6-benzyloxytetralin (79).

Ethylene glycol (9·79 g., 0·158 mole) and p-toluenesulphonic acid (20 mg.,) in dry benzene (50 ml.,) were refluxed with vigorous stirring using a Dean-Stark apparatus for 1½ hrs. The ketone (71) (4·0 g., 0·0158 mole)

was added and water separation continued for 48 hrs. Using the procedure described above, a pale brown oil was isolated which by T.L.C. (20% ethyl acetate/ petrol) was shown to consist of starting ketone, R_F 0·6, plus a less polar component, R_F 0·7. A portion of this oil was placed on an alumina column (Woelm, Grade III, 70 g.,) from benzene (5 ml.,) and carefully eluted with benzene. By means of T.L.C. of the various fractions only one fraction contained relatively pure ketal (79) the others being contaminated with ketone (71). This pure fraction (0·7503 g., 16%) was crystallised from aqueous ethanol as prisms, m.p. 62·5-64° but completely pure material could not be obtained.

(Found: C, 77·43; H, 7·41. $C_{19}H_{20}O_3$ requires: C, 77·00; H, 6·80%).

$\nu_{max.}^{cm.^{-1}}$ (nujol): 1245 (s); 1165 (s); 1135 (s); 1070 (s); 1020 (s) (C-O); no carbonyl.



H_a 8·13 τ (4H, multiplet)
H_b
H_c 7·28 τ (2H, broad singlet)
H_d 3·40 τ (1H, broad singlet)
H_e ca 3·3 τ (1H, pair of doublets masked)
H_f ca 2·7 τ (1H, doublet masked)
H_g 5·01 τ (2H, singlet)
H_h 2·67 τ (5H, singlet)
H_i 5·98 T (4H, singlet)

Attempted separation of the ketone and the ketal by preparative T.L.C. could not be achieved. G.L.C. of the crude residue showed that the ratio of ketal to ketone was 11/9.

Column: 1% APL Temp. : 200° F.R. 40 ml.,/min.

R_t (ketone) 15·75 min. R_t. (ketal) 28·35 min.

Separation of the ketone and the ketal using Girard P Reagent also led to isolation of mixtures indicating a continual conversion of the ketal to the ketone.

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