SYNTHETIC APPROACHES TO LYCOPODINE

THESIS

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SUMMARY

The preparation of a series of substituted bicyclo-(3,3,1)nonane derivatives which possess the requisite functionality for rings B and D of lycopodine is described, culminating in the direct application of these results towards an attempt at a stereospecific synthesis of lycopodine.

The model compounds were prepared by treatment of a suitably substituted cyclohexyl-β-keto-ester with acrolein or methacrolein to furnish the corresponding substituted β-(1-ethoxycarbonyl-2-oxocyclohexyl)-propionaldehyde. These keto-aldehydes were then treated with either hydrochloric acid or triethylamine to furnish the corresponding ethyl-epimeric, hydroxybicyclo(3,3,1)nonan-9-one-1-carboxylates. Various unfruitful attempts to convert these ketols (and their derivatives) into the corresponding bicyclic-keto-olefin are described. In the event it was found that solvolysis of the axial p-toluenesulphonate esters in 10% aqueous acetic acid furnished the desired olefin in high yield.

The difficulties encountered in the preparation of 1-methoxycarbonyl-6-methoxy-2-tetralone* are described, together with a complete spectral and chemical proof of the proposed structure. A Michael reaction between this β-keto-ester and

methacrolein then furnished two diastereoisomeric keto-aldehydes which on treatment with hydrochloric acid afforded four epimeric ketols. Buffered acetolysis of the corresponding p-toluenesulphonates then gave methyl-7-methyl-3'-methoxy-2,3-benzobicyclo(3,3,1)non-2,6-diene-9-one-1-carboxylate in good yield. Catalytic hydrogenation of this olefin over 5% palladium on carbon resulted in the equatorial methyl dihydro derivative, and reduction over 5% rhodium on carbon furnished the axial methyl dihyro derivative. These stereochemical assignments were made with the aid of nuclear magnetic resonance spectroscopy. Insertion of the nitrogen atom and the attempts to construct ring A are then reported.

The reductive rearrangement of δ-enol-lactones to furnish the thermodynamically less stable axial bicyclic ketol, is discussed in the addendum. Further evidence in favour of the proposed mechanism* is presented.

*included publication.

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INTRODUCTION.

For many years the *Lycopodium* alkaloids have provided rich pastures for chemical investigation. As early as 1881, Bodeker[1] drew attention to the fact that *Lycopodium complantum* L., contained an alkaloid having the empirical formula $C_{16}H_{25}ON$ which he named lycopodine. Subsequently many other alkaloids have been isolated from a variety of *Lycopodium* species and it is of interest to note that lycopodine is present in all species native to the Northern Hemisphere. These alkaloids possess a diversity of biological activity[2,3] such as pressor effects, stimulation and contraction of the uterus and paralysis, but are moderately toxic and as yet have not been found useful in medicine.

So sparse was the chemical information relating to the *Lycopodium* species, that in the early stages the majority of the family were denoted merely by a letter and number. It was not until 1956 that the first positive steps were made in the structural elucidation of the alkaloids, when Wiesner and his group[4] proposed the structure (1) for annotinine. This structure was rejected by Marion *et al.*[5] on the basis of their own interpretation of the chemical evidence, but in 1957 the dichotomy was finally resolved when the structure (1) was corroborated by X-ray crystallography.[6] In the following years

many publications on the chemistry of the Lycopodium alkaloids have appeared, the field being dominated by Canadian researchers notably, Wiesner, Ayer, Harrison, MacLean and Anet.

Lycopodine and annotinine occur conjointly in Lycopodium annotinum. MacLean and Harrison[7] in 1960 deduced that the structure which best accommodated all the known reactions of lycopodine was that represented in formula (2), which like annotinine (1) contains a hexahydrojulolidine system (3). The interaction of lycopodine with cyanogen bromide gave rise to two isomeric cyano-bromolycopodines, α and β (4 and 5). In (4) the bromine may be exchanged for an acetoxy group, the latter saponified to a primary alcohol and the alcohol oxidised to a carboxylic acid without loss of carbon. Reduction of this keto-acid with sodium borohydride yielded a hydroxy-acid which failed to lactonise. Hydrolytic removal of the nitrile function in the keto-acid, and esterification of the resulting amino-acid with diazomethane furnished the compound (6), by spontaneous lactamisation ; the consequent lactam carbonyl absorption at 1635 $cm.^{-1}$ in the infrared indicated that this lactam was at least six-membered. Reduction of (6) with lithium aluminium hydride produced dihydrolycopodine, also obtainable by the action of the same reagent on lycopodine.

Treatment of (5) with silver acetate effected a displacement of the bromine by an acetoxy group, which on hydrolysis to

the corresponding primary alcohol gave, on oxidation, a keto-acid without loss of carbon. Reduction of the keto group in the latter compound by sodium borohydride yielded the lactone (7) which, according to its infrared carbonyl frequency (1734 $cm.^{-1}$), was probably six-membered.

Since the carbonyl frequency of lycopodine itself corresponds to a ketone in a six-membered ring, the above data are compatible with the part structure (8).

The compound selected for elucidation of the environment of the keto group in lycopodine was α-cyanolycopodine, obtained by hydrogenolysis of α-cyano-bromolycopodine (4) with palladium-calcium carbonate catalyst. Bromination of α-cyanolycopodine gave an uncharacterised dibromide which afforded (9) by mild alkaline hydrolysis. The ultraviolet ($\lambda_{max.}$ 280 nm.; $\log \varepsilon = 4$) and infrared (strong bands at 1660 and 1640 $cm.^{-1}$) spectra of the compound supported its formulation as an enolised α-diketone. α-Cyanolycopodine also yielded a benzylidine derivative which, by treatment with selenium dioxide, gave a mixture of two products, viz., the hydroxy compound (10) and the unsaturated compound (11). Ozonolysis of the benzylidine α-cyanolycopodine furnished the enolic diketone (9) whereas the hydroxy-benzylidine derivative (10) yielded on ozonolysis the hydroxy-dione (12). This latter derivative had ultraviolet ($\lambda_{max.}$ 420 nm.; $\log \varepsilon = 2.5$) and infrared (strong band at 1724 $cm.^{-1}$) spectra ; i.e. no enolic

properties. Hydrogenolysis using platinum oxide as the catalyst readily converted the non-enolic compound (12) into the fully enolised derivative (9).

Thus the only enolisible hydrogen in the diketone (9) is replaced by hydroxyl in the diketone (12), and so the arrowed carbon in (12) must either be quaternary or represent a bridge-head position towards which enolisation is impossible. This conclusion, coupled with the fact that lycopodine analysed for one C-methyl group in the Kuhn-Roth determination, was the foundation for the extension of the part structure (8) into the complete structure (2). Formula (2) readily explains the formation of 7-methyl and 5,7-dimethyl quinoline on dehydrogenation, which must originate from rings A and D of lycopodine. The fact that no quinoline dehydrogenation product corresponding to rings B and C has been isolated can be explained in terms of the ABC perhydrojulolidine system being destroyed by a reverse Mannich reaction with the formation of the intermediate (13). This compound may cleave according to a.... by a retro-Michael reaction and give, after dehydrogenation, 7-methylquinoline ; or it may undergo pyrolytic scission according to b.... with the ultimate formation of 5,7-dimethylquinoline.

A further important corroboration of structure (2) was the finding that both α- and β-cyanodihydrolycopodine (i.e. 4 and 5, with bromine replaced by hydrogen and ketone reduced to alcohol)

possess an n-propyl side chain. Both compounds furnished a mixture of acetic, propionic and butyric acids in a modified Kuhn-Roth oxidation, while lycopodine itself yielded only acetic acid.

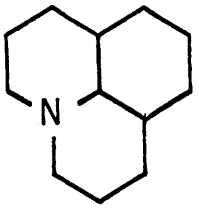
Since there does not appear to be an alternative structure for lycopodine which could readily explain all the above chemical information and at the same time be reasonably related to annotinine, it seems that structure (2) has been conclusively established.

Lycopodine (2) and annotinine (1) are the major Lycopodium alkaloids, but a large number of minor related alkaloids have been isolated. As was stated earlier, most of these were originally designated by number and letter, but now the majority have been assigned names and structures, mainly by the achievements of the various Canadian Schools and more recently by Japanese workers. This work allows the Lycopodium alkaloids to be conveniently divided skeletally into two distinct classes :- a) compounds with the hexahydrojulolidine framework and b) those containing a 6,10a-propanoperhydro-4,10-phenanthroline system (or some derivative thereof).

TABLE 1

Class (a) Hexahydrojulolidine unit.

Skeleton.....



Compound	Formula Number	Reference
Annotinine	1	4,6
Lycopodine	2	7
Dihyrolycopodine	14	8
Dihydrolycopodine acetate	15	9
Acrifoline	16	10
Lycofoline	17	11
Lycofoline di-acetate	18	12
Lycoclavine	19	13
Lycoclavine acetate	20	13
Clavolonine	21	14,15
Annofoline	22	16
Lycodoline	23	17
Flabelliformine	24	18

TABLE 1 ctd.

Compound	Formula Number	Reference
Flabelline	25	19
Fawcettiine	26	14,15
Fawcettiine acetate	27	14,15
Lofoline (C(12 epimer of 26)		20,21
Annotine	28	22
Lycofawcine	29	23,24
Lycofawcine acetate	30	12
Lyconnotine	31	25
Base L.20	32	26
*Serratinine	33	27,28
*Serratinidine	34	29
*Fawcettimine	35	23,30-32
**Cernuine	36	33-35
**Lycocernuine	37	33-35

*These alkaloids posses a considerably modified framework but are included here since they are believed to be biogenetically related to lycodoline.[28, 29]

**Thought to be biogenetically related to lycopodine.[33]

The majority of the alkaloids in Table 1 are not only structurally related by the hexahydrojulolidine skeleton but also contain a bicyclo(3,3,1)nonane framework and have simple variations of stereochemistry and oxygenation patterns. Almost all of the hexahydrojulolidine type alkaloids have been interrelated one with another. Lycoclavine (19) can be converted[13] to the α-dione (19a) by oxidation, hydrolysis of the acetate group and further oxidation, and the same α-diketone has been obtained from lycopodine (2) by the action of selenium dioxide. Clavolonine (21), an annofoline isomer, was oxidised[15] to a diketone which could also be obtained by oxidation of deacetylfawcettiine (26a), thus establishing oxygenation at C(5) and C(8). The structure (21) was finally confirmed by selective acetylation of deacetylfawcettiine (26a) at C(8) to afford compound (26b), an isomer of fawcettiine (26). Further acetylation of (26b) yielded acetylfawcettiine (27) and oxidation of (26b) to the corresponding C(5) ketone, followed by alkaline hydrolysis of the C(8) acetyl group gave clavolonine (21). Lycodoline (23),[17] on Wolff-Kishner reduction followed by dehydration afforded anhydrodehydrodesoxylycodoline (23a) which was reduced catalytically to dihydrodesoxylycopodine (23a, double bond saturated), identical to the Wolff-Kishner reduction product of lycopodine. Flabelliformine (24) afforded lycopodine (2) on reduction with hydroiodic

acid.[18] The acidic hydrolysis[19] of flabelline (25) produced lycopodine and the converse transformation has been effected by reducing a solution of lycopodine oxime in acetic anhydride under high pressure. Fawcettiine (26) has been oxidised[15] to a ketone which furnished annofoline (22) by mild alkaline hydrolysis. Lycofawcine (29) has been oxidised[24] to a keto-acetate which on dehydration afforded O-acetyl acrifoline (16, OH replaced by OAc). Catalytic hydrogenation[44] of acrifoline (16) yielded two dihydro derivatives, stereoisomeric at C(12), one of which proved to be identical with annofoline (22). Annofoline itself has been directly correlated with lycopodine (2)[44] as follows. Dehydration of deacetylfawcettiine (26a) afforded dehydro-deacetylfawcettiine (45) which on oxidation furnished the ketone (46) and subsequent Wolff-Kishner reduction then gave dihydro-anhydrolycopodine (47) which has been prepared from lycopodine (2) by reduction with lithium aluminium hydride followed by dehydration.

In an elegant conformational study, Anet[44] elucidated the stereochemistry of lycopodine (2), acrifoline (16) and annofoline (22) and consequently has correlated the stereo-chemistry of the majority of the hexahydrojulolidine class since in the above discussion it has been shown that nearly all the alkaloids of this type have been interconverted with either (2), (16) or (22). The reduction of annofoline (22) with sodium

borohydride gave a mixture of two isomeric diols, α- and β-dihydroannofoline (48,49) respectively. The β-dihydro compound was found to be identical with deacetylfawcettiine (26a). It has been shown that these two isomers are not merely epimeric at C(8) (as might be assumed) but also differ in the configuration of the C(15) methyl group. Reduction of annofoline (22) with sodium borohydride under neutral conditions gave only the α-isomer (48), whereas in alkaline medium up to 50% of the β-isomer (49) could be isolated. A rigorous proof that deacetylfawcettiine is not a primary reduction product of annofoline (22), but of its C(15) epimer was provided by the fact that 8-ketofawcettiine (50) and O-acetylannofoline (51, OH replaced by OAc) both give rise to annofoline on alkaline hydrolysis although in themselves are non-identical. Consequently, the latter compounds must differ in the configuration of the C(15) methyl group which is adjacent to the carbonyl group and hence may epimerise in the course of the alkaline treatment. It also follows from this experiment that annofoline represents the more stable of the two possible C(15) epimers.

The surprising finding that deacetylfawcettiine (49), a reduction product of the less stable C(15) epimer of annofoline, can be obtained from sodium borohydride reduction of annofoline in the presence of alkali, has been rationalised in terms of a rapidly established base-catalysed equilibrium between

annofoline (51) and its C(15) epimer, with the hydride reduction of the latter proceeding at a much faster rate than the reduction of annofoline. Annofoline (51) and acrifoline (16) exist both in the hemi-ketal and internally bonded hydroxy-ketone forms. This is only possible if ring D assumes a boat conformation. There is, in fact, a very strong replusion between the C(5) hydroxyl and C(15) methyl groups when ring D adopts a chair form. Since annofoline is the more stable of the two C(15) epimers, it must possess the methyl group equatorial to the D ring in boat form and is therefore represented by stereoformula (51).

In those alkaloids which do not possess a C(5) axial substituent, ring D will be more stable in the chair form, thus explaining the interconversion of dehydrodeacetylfawcettiine (45) and lycopodine (52) (see above).

The trans fusion of rings B and C in lycopodine follows from its stability to alkali. Rings A and B must be cis fused to explain the finding that α-cyanobromo-lycopodine (4), in the presence of base, undergoes an intramolecular alkylation at a position α to the ketone group (i.e., C(4) or C(6)).

The trans fusion of rings B and C in annofoline (51) and deacetylfawcettiine (49) follow from their ready dehydration to the same $\Delta^{4,5}$ olefin (47). Since the hydroxyl group at C(5) in both (51) and (49) is axially oriented, it follows that this facile dehydration must involve trans antiparallel elimination

involving the proton at C(4).

Anet has suggested that ring D in (49) must assume a chair conformation, since the C(15) methyl group would be forced into an extremely unfavourable flag-pole position if the boat form was adopted. The C(8) hydroxyl of (49) is taken as equatorial trans to the methyl group, since it resists dehydration and, in addition, hydride reduction of the corresponding ketone furnishes only (49). In this process both kinetic and thermodynamic control would result in the same configuration of the product, since an approach of hydride from the exo side of the bicyclo(3,3,1)nonane system results in the equatorial alcohol.

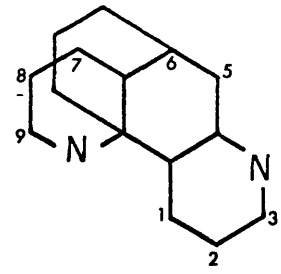
The absolute configuration of lycopodine and its related alkaloids follows from the application of the Octant Rule[45] to lycopodine as represented in formula (52). These deductions are in harmony with the chemical evidence cited above, and are also in agreement with the X-ray results obtained from annotinine bromohydrin.[6]

There are relatively few Lycopodium alkaloids possessing the propano-perhydrophenanthroline system (or some modification thereof), as Table 2 shows. Selagine (39) can be related to lycopodine biogenetically[39] but no chemical relationship has yet been established. If the structure of selagine is oriented as in (39), then it can be related to lycopodine by the following considerations :- ring A of lycopodine is opened ;

TABLE 2

Class (b) 6,10a-Propanoperhydro-4,10-phenanthroline unit.

Skeleton.....



Compound	Formula Number	Reference
Lycodine	38	36-38
Selagine	39	39
α-Obscurine	40	37
β-Obscurine	42	37
Sauroxine (C(12) epimer of 40)		34,35,40,41
Des-N-methyl-α-obscurine	41	42
Hydroxydes-N-methyl-α-obscurine	43	43
Flabellidine	44	43

the C(9) carbon is missing ; C(5) carries a nitrogen atom instead of an oxygen atom ; and C(1) in selagine is linked to this nitrogen atom (at C(5)) and not to the C(13) nitrogen. Exactly how these modifications can be accommodated into the general biogenetic scheme of the alkaloids will be discussed later.

The structures (40) and (42) were assigned to α- and β-obscurine respectively by Ayer and Iverach[37] on the basis of their probable biogenetic relationship to lycopodine. α-Obscurine can be converted into β-obscurine by treatment with N-bromosuccinimide, followed by chromatography on basic alumina.

Ayer and Iverach have also proposed the structure (38) for lycodine, which they later substantiated by a direct conversion of β-obscurine (42) into lycodine (38).

A direct correlation of lycodine (38) with lycopodine (2) was achieved by Anet and Rao.[38] β-Cyanobromo-lycopodine (4) was treated with sodium azide, the product hydrogenated and the resulting base which was partially cyclised was smoothly dehydrogenated to lycodine (38). In view of the previous direct correlation of the obscurines and of lycodine, and of the known stereochemistry of lycopodine (52), the three compounds (40), (42) and (38) possess the same stereochemistry and may be represented by the generalised stereoformula (53).

At the time when annotinine was the only structurally clarified Lycopodium base, Conroy[46] made the prophetic suggestion that the biogenesis of this alkaloid could be rationalised by an aldol condensation between two C_8 units (54) (each derived from four molecules of acetate), giving rise to (55). This hypothetical intermediate can now be manipulated to encompass all the known Lycopodium alkaloids. For example, the route to annotinine (1) involves oxidation of the C(8) methyl group to to a carboxyl group (56) with subsequent condensation between C(12) and C(15) to yield the cyclobutanone derivative (57). A Mannich reaction involving the C(13) carbonyl group, the C(4) methylene group and ammonia in this intermediate now furnishes (58) after lactamisation. Further steps to annotinine are uneventful.

The other alkaloids are considered to arise by the initial condensation of C(8) and C(15) in the intermediate (55) to afford (59). If C(4), C(13) and ammonia are now involved in a Mannich reaction, followed by lactamisation, compound (60), a plausible precursor of acrifoline (61=16) and lycopodine (62=2) is produced. If the above lactamisation did not occur, interaction of the carbonyl group at C(5) with ammonia, followed by dehydration would provide the intermediate (63). Pyridone ring formation and decarboxylation now gives selagine (64=39). The α- and β-obscurines (65=40) and (66=42) can also be related

biogenetically to the intermediate (63). The dibasic alkaloid lycodine (67=38) can also be evolved from the latter precursor, hence is related to β-obscurine and this fact has been corroborated in vitro, as mentioned above.

Serratinine (33) can be visualised as arising from lycodoline (23) or a close derivative thereof via the intermediates (68), (69) and (70). The fact that lycodoline and serratinine co-occur in the plant lends credence to the above postulates. Serratinidine (34)[29] and fawcettimine (35)[32] are considered to have similar biogeneses.

The structures and stereochemistry of two new alkaloids, cernuine (36) and lycocernuine (37) have recently been elucidated[33-35] and although they differ markedly from other known Lycopodium alkaloids, it is still possible to accommodate them into this biogenetic scheme. If the C-methyl group of cernuine (36) is derived from the terminal methyl of one of the polyketo-octanoic acid chains, then an aldol condensation between the C(7) carbonyl group of this chain with the methyl group of the other chain and condensation with two equivalents of ammonia (dashed lines in formula 72) can ultimately result in (36) and (37). If these alkaloids arise from a common biogenetic precursor only one carbon-carbon bond (C(8) to C(15)) is formed between the two polyketo-acid chains. This interesting consideration will be discussed below.

An alternative biogenetic path to these alkaloids stemming from lycopodine as the central intermediate has been considered by Anet,[47] in view of the ubiquitous distribution of this alkaloid in the Lycopodium species. However, if lycopodine is a central intermediate, then the isolation of cernuine and lycocernuine (36 and 37) could indicate that the C(8) - C(15) bond is the first carbon-carbon union in the condensation of the two C_8 units to afford (73) and hence condensation between C(12) and C(7) to furnish (59) must be effected at a later stage in the biogenetic pathway.

In order to correlate lycopodine (2) with annofoline (22) and annotinine (1), oxygenation at C(8) must be invoked and the conversion of lycopodine into annofoline (74=22) (in the hemiketal form to emphasise the similarity to annotinine) was the in vitro realisation of this step in this biogenetic scheme.[47] Anet converted lycopodine into the corresponding lactam (75) by oxidation with potassium permanganate in acetone. Sodium borohydride reduction of (75) afforded the dihydrolactam (76) which in turn was reduced with lithium aluminium hydride to furnish dihydrolycopodine (77), confirming the axial orientation of the hydroxyl group in (76). Oxidation of (76) with lead tetraacetate furnished the ether (78) which was converted to the acetoxyolefin (82) on treatment with boron trifluoride and acetic anhydride, and this olefin was transformed into the epoxide (83)

with m-chloroperbenzoic acid. All attempts to open the epoxide ring to introduce the desired C(8) group were unsuccessful, and so the epoxide (83) was treated with boron trifluoride-etherate to give the acetoxy-ether (79), which was then hydrolysed to the corresponding alcohol (80) and finally oxidised to the ketone (81). This same ketone could also be obtained by direct treatment of the epoxide(83) with aqueous hydrobromic acid, with subsequent oxidation. That the carbonyl was situated on C(8) was verified by the negative Cotton effect displayed by (81). All attempts to cleave the C(15) - oxygen bond α to the carbonyl function met with failure, and this route was abandonned when it was found that the reaction of the olefin (82) with excess diborane followed by treatment with alkaline hydrogen peroxide gave the alcohol (84), whose stereochemistry is based on the assumption that addition of diborane would occur from the less hindered side of the double bond.

Oxidation of the alcohol (84) with chromium trioxide-pyridine yielded O-acetylannofoline (85) which was hydrolysed to annofoline (22), identical in all respects with an authentic sample.

While all the biogenetic arguments can be moulded into a plausible general theory, they are purely speculative. The versatile intermediates (59) and (73) readily rationalise the skeletal similarity of the alkaloids and indeed they can encompass

the apparent anomalies such as selagine (39), serratinine (33), serratinidine (34), cernuine (36) and lycocernuine (37), but to date there have been no corroborative reports of either *in vivo* or *in vitro* experiments.

Although there has been much elegant degradative work done on the *Lycopodium* alkaloids, the number of documented synthetic approaches is relatively small. In 1964, Wiesner and his co-workers[48] reported a synthesis of the ketone (86), a degradation product of lyconnotine (31). The tricyclic phenol (87), readily available from the interaction of 1-bromo-3-chloropropane with m-anisidine, on catalytic hydrogenation over Raney nickel afforded tha vinylogous lactam (88) which was smoothly converted to the methiodide (89). This salt was then treated with iso-butyl lithium and acid hydrolysis of the resulting enol-ether gave, in 8% yield, the racemic ketone (90). This ketone was identical with a lyconnotine degradation product obtained in the following way. Lyconnotine (31), on reduction with lithium aluminium hydride, furnished a diene-diol (91) which was hydrogenated to the diol (92), converted to the corresponding diacetate (93), selectively hydrolysed to the monoacetate (94) with potassium carbonate and converted to the ketone (90) by an uneventful sequence.

A second synthetic approach[49] to the *Lycopodium* alkaloids was concerned with the development of stereospecific pathways.

By analogy with earlier work,[48] the methiodide (89) was treated with allyl magnesium bromide, and hydrolysis of the resulting enol-ether afforded the ketone (95) in 15% yield. That the stereochemistry of (95) is as illustrated, was deduced from the presence of Bohlmann bands[50,51] in the infrared spectrum,* and the fact that the axial alcohol formed from (95) by reduction with lithium aluminium hydride formed a cyclic bromoether on treatment with N-bromosuccinimide. In addition, prolonged adsorption of (95) on basic alumina converted it to a 1:1 mixture of (95) and (96), separable by preparative thin-layer chromatography. A recycling procedure thus afforded total epimerisation ; the product (96) showing no Bohlmann bands[50,51] in its infrared spectrum. With the stereochemistry thus rigorously established, a Prins reaction would now lead to the construction of a lycopodine-like ring system. This final cyclisation was achieved by treatment of (96) with boiling concentrated hydrobromic acid furnishing the alcohol (97) and the tertiary bromide (98). The latter compound on reduction with sodium amalgam gave the amine (99) which still has the required trans-cis stereochemistry because the ketones (95) and (96) do not epimerise under strongly acidic non-

* Bohlmann bands are generally observed when two or more C-H bonds are trans-diaxial to an adjacent nitrogen lone pair of electrons.

cyclising conditions, the necessary inversion at the nitrogen atom being inhibited by protonation.

In the same publication, Wiesner and his co-workers[49] have considered an alternate approach to similar ring systems. Dihydroorcinol (100) was converted to the monocyclic vinylogous lactam (101) with 3-aminopropanol. Treatment of (101) with an equal amount of pyridine hydroiodide then gave the bicyclic compound (102) which was readily converted to the N-methylated derivative (103). The immonium salt (104), obtained from (103) by the action of isopropyl iodide, was alkylated with allyl magnesium bromide to furnish (105) which on treatment with 75% sulphuric acid yielded the alcohol (106) and not as expected (107). In the course of the cyclisation, a transannular hydride shift had occurred, a phenomenon which has a number of analogies in the recent literature.[52-54]

The above publications reflect the importance of stereochemical control in any synthetic route to the Lycopodium alkaloids and with this in mind, Ayer[55] has developed an elegant cycle of reactions which provide a stereospecific method for elaborating the natural configuration at C(15) in these alkaloids. The unsaturated lactam (108) was reduced with lithium aluminium hydride to the alcohol (109) and then oxidised to the ketone (110), and subsequently reduced with sodium-ammonia-methanol to give the alcohol (111) which was quantitatively

converted into lycopodine (2) by the action of sulphuric acid. Under similar conditions the epimeric alcohol (109) only furnished the oxide (112). Since the ketone (110) can also be converted to dihydrodeoxyannofoline (113) by platinum catalysed reduction, stereo control of the C(15) centre is now complete, paving the way for the synthesis of lycopodine (2), annofoline (22) and their respective substituted derivatives.

A recent paper by Ayer[56] and his colleagues describes the construction of functionalised cis- and trans-hexahydrojulolidines of the type (114). When 9-methoxyjulolidine (115) was subjected to a Birch reduction , followed by dissolution of the product in ethylene glycol containing perchloric acid, the immonium salt (116) was obtained. This salt, on treatment with methallyl magnesium bromide, was converted to an amine (117) which, from the presence of Bohlmann bands[50,51] in its infrared spectrum, must possess either the cis-cis or the trans-trans stereochemistry at the ring junction. Theoretically, the Grignard addition is expected to occur from the least hindered side of (116) and since the product (117) reacted sluggishly with methyl iodide these two factors indicated that the stereochemistry of (117) was cis-cis.

Hydroboration of the exomethylene tricyclic amine (117) resulted in the formation of the racemic alcohol (118) which was deketalised to furnish the ketone (119). From the stereo-

formula (119) it is evident that the final cyclisation step is impossible unless the molecule adopted the highly strained inverted form which would not show the characteristic Bohlmann bands[50,51] in the infrared spectrum. In order to make this a feasible synthetic route to the Lycopodium alkaloids it was necessary to transform the cis-cis-hexahydrojulolidines into the cis-trans compounds such as (122). Using the model system (119), readily obtained from (117) by catalytic hydrogenation, the α,β-unsaturated ketone (123) was prepared by bromination to give (121) followed by dehydrobromination. The latter step proved difficult and was finally accomplished via the semicarbazone derivative of the bromo-ketone (121) which was exchanged with pyruvic acid-aqueous acetic acid. The resultant product did not show Bohlmann bands[50,51] in the infrared spectrum, indicating that it existed predominantly in conformation (123).

Because of conformational mobility at the nitrogen atom, it should be possible for the ketone (124) to assume the other conformation (123). This change involves an inversion of ring A at the nitrogen atom with subsequent transformation of the resultant boat into a new chair form and simultaneous conversion of the unsaturated ring from one half-chair form to the other half-chair. An examination of models indicates that (123) might, in fact, be favoured for the unsaturated ketone. Treatment of this ketone (123) with lithium-ammonia provided a ketone isomeric with

(124), showing no Bohlmann bands[50,51] in its infrared spectrum indicating the structure (123). By simple modification the above systems could be fruitful in achieving a total synthesis of lycopodine, since replacement of the hydroxyl function in (122) by tosylate or other good leaving group would permit an intramolecular ring forming alkylation step involving C(7) : cf. the conversion of (125) to (126) in 60% yield by the action of potassium t-butoxide.[57] However, in (122), base could readily abstract the proton situated at C(5) resulting in the alternative undesired ring closure.

Wiesner has also reported his synthetic approaches to annotinine (1), e.g., in 1965 the New Brunswick group[58] described the photochemical behaviour of the system (127). This bicyclic enone-lactam was prepared from the cyanoethyl derivative (128) by hydrolysis, lactamisation and methylation. Irradiation of (127) in the presence of allene furnished a mixture of the isomeric exomethylene cyclobutane derivatives (129) and (130). A stereospecific transformation of (130) to (131) was then accomplished by forming the corresponding ketal, catalytic hydrogenation and subsequent acid hydrolysis.

This synthetic sequence may very well represent the key steps in a total synthesis of annotinine (1) since, with suitable substitution, a system such as (132) may be induced to undergo a similar photoaddition with allene. Indeed, the tricyclic

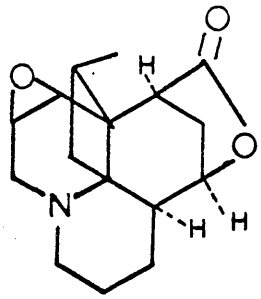
lactam (132) has very recently[59] been irradiated in the presence of allene to afford (133) as the sole adduct. Catalytic hydrogenation of the ethylene ketal of (133) furnished only the cyclobutane derivative (134) on regeneration of the ketone. Such stereospecificity must be due to the steric bulk of the ethylene ketal directing the delivery of hydrogen from the other, least hindered side of the double bond. The corresponding alcohol (135) was then converted to the mesylate (136) and treated with potassium cyanide in dimethylformamide to furnish a mixture of olefins (137) and (139). This mixture was then oxidised with selenium dioxide in acetic acid, the resultant acetates hydrolysed to the corresponding mixture of alcohols (138) and (140) and finally oxidised to give a separable mixture of the tetracyclic ketones (141) and (142). The infra-red spectrum of (141) was superimposable with that of the corresponding optically active product obtained previously[60] from annotinine (1). It is noteworthy that this synthetic procedure constitutes the first chemical proof of the configuration of the cyclobutyl methyl group in annotinine.

A later publication,[61] describes the construction of the lactam (143). Treatment of the keto-lactam (141) with potassium cyanide and ammonium chloride afforded the nitrile (144), which was then hydrolysed and esterified to give the racemic ester (145), identical to the optically active product of the same

structure.[60] Wiesner had previously described[60] both the conversion of (145) to (146) by selenium dioxide oxidation and the hydrogenation of (146) to (147). Compound (147), obtainable directly from (143), can be converted to the acid (148) by epimerisation and hydrolysis.[62] Treatment of (148) with p-toluenesulphonic acid furnished the lactone (143), identical with an authentic sample.

With the obtention of (143), Wiesner has brought the total synthesis of annotinine extremely close to completion, since by incorporating a substrate with an inherent double bond (asterisks in formula 143) into the synthetic scheme, the introduction of the oxirane moiety of annotinine (1) should be uneventful.

Thus, although the total synthesis of any one member of the Lycopodium family will be no mean task, the success of the stereoselective approaches detailed above suggest that this problem may soon be solved.



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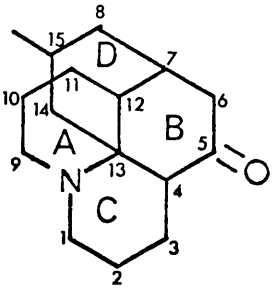

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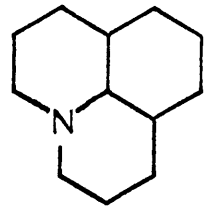

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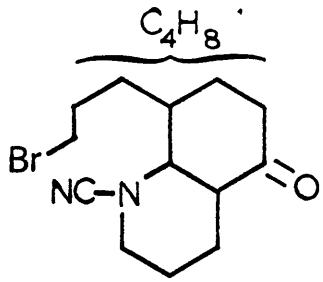

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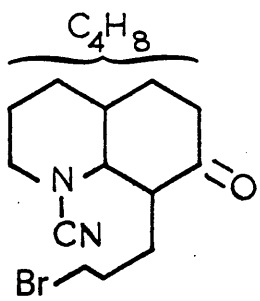

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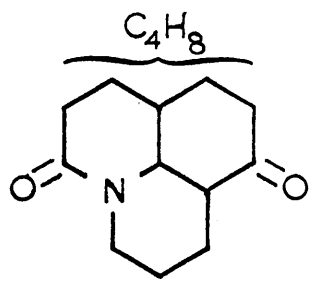

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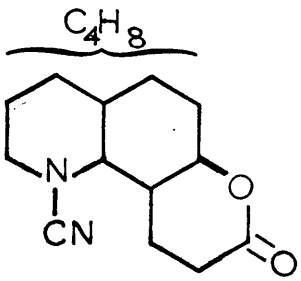

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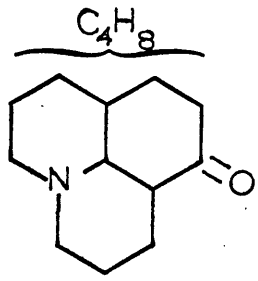

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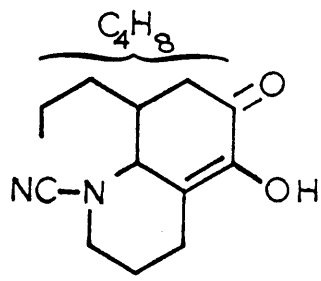

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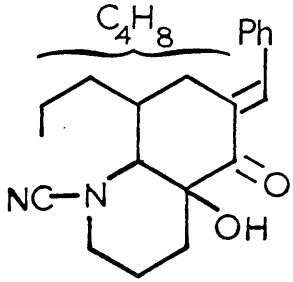

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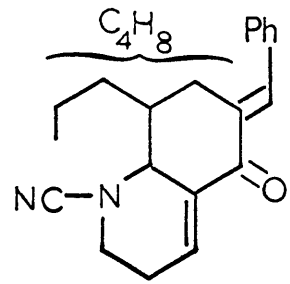

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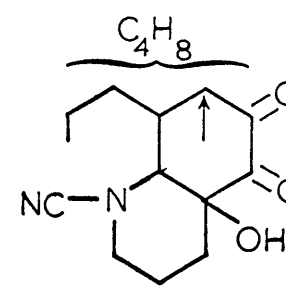

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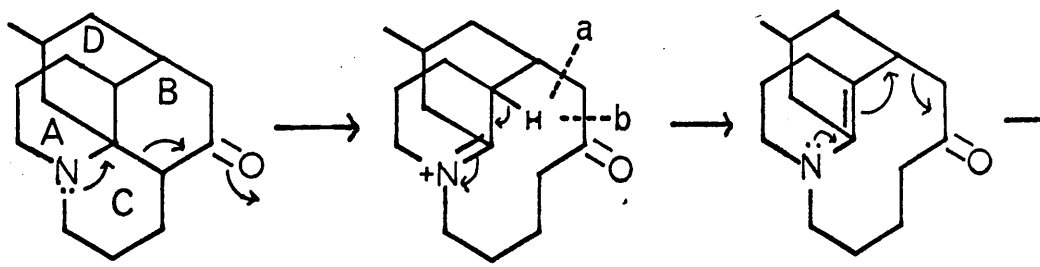

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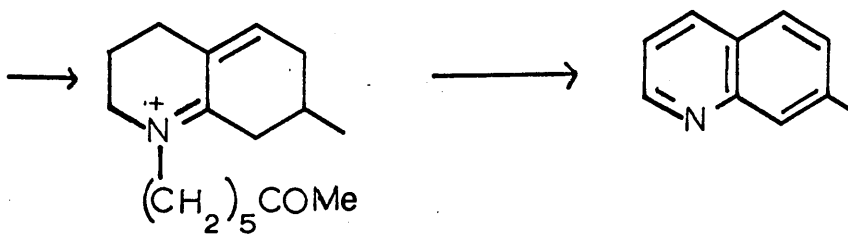

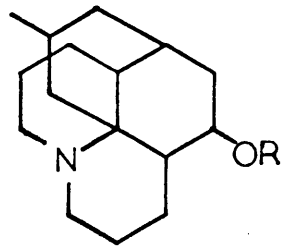

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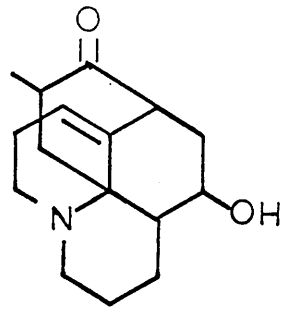

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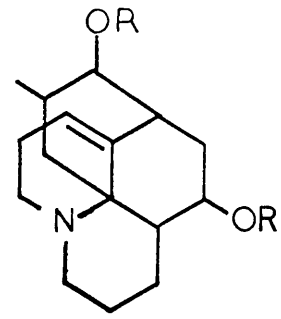

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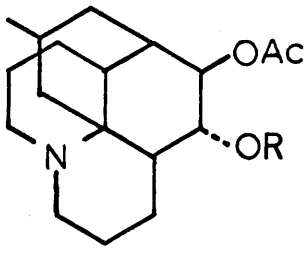

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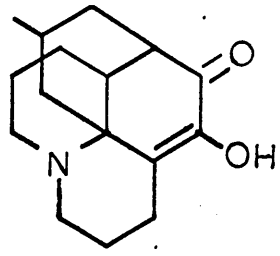

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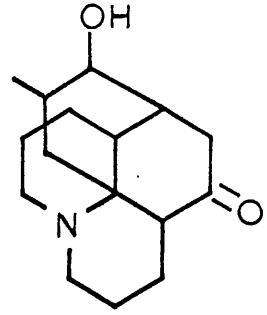

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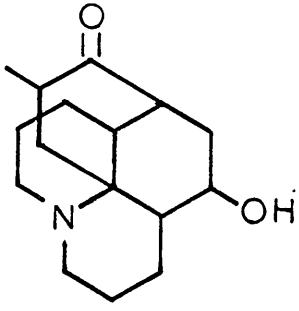

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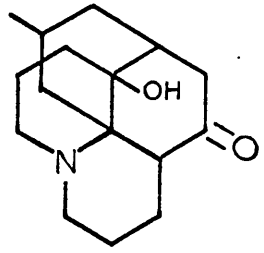

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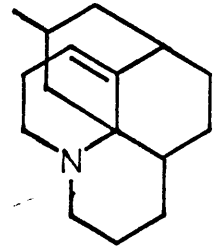

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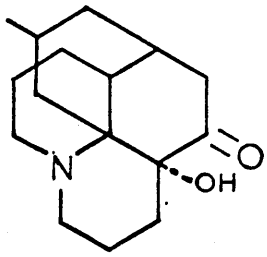

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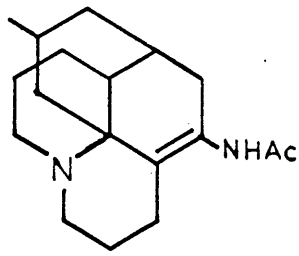

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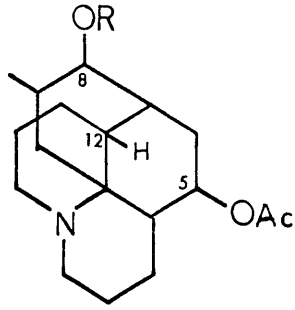

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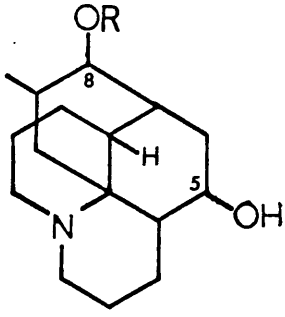

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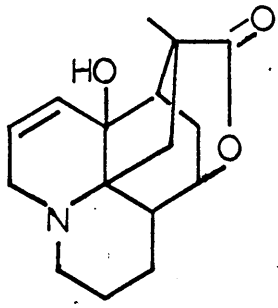

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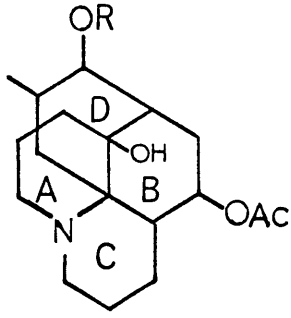

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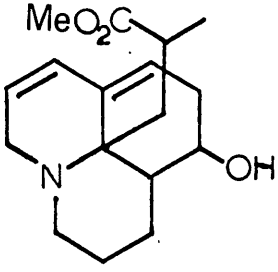

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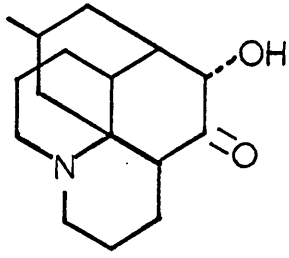

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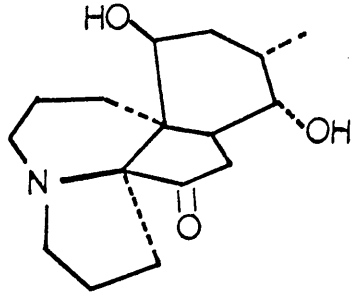

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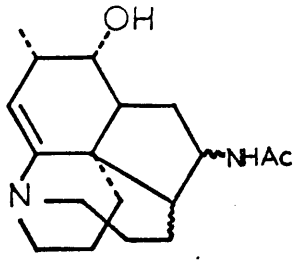

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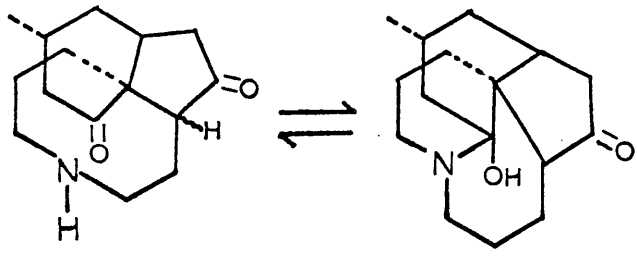

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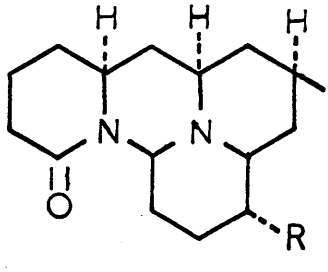

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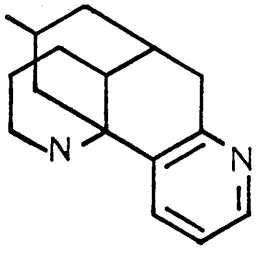

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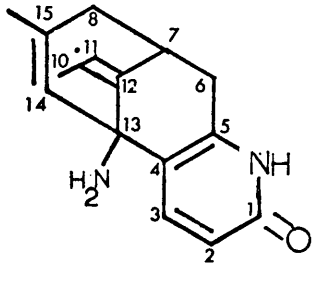

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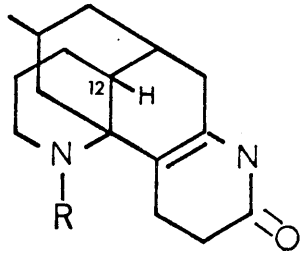

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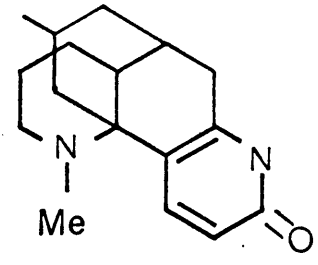

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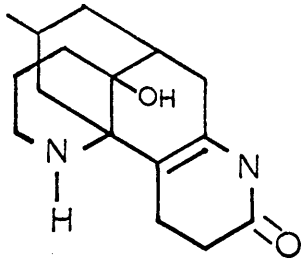

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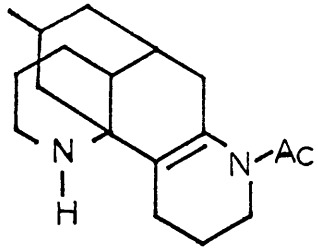

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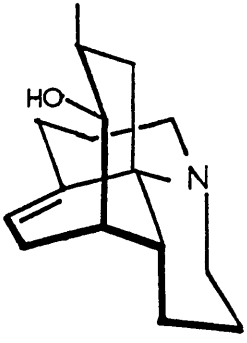

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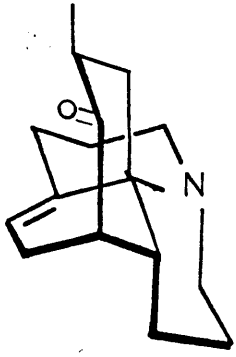

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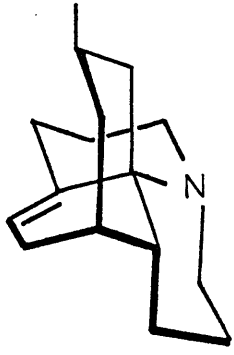

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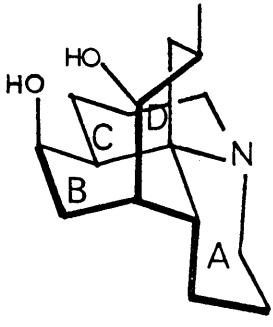

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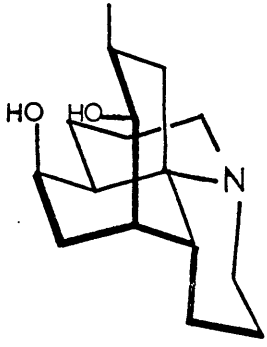

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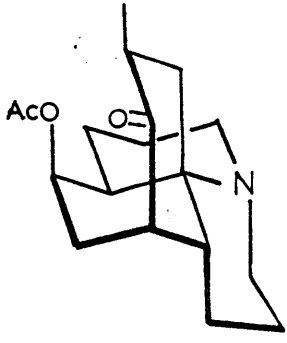

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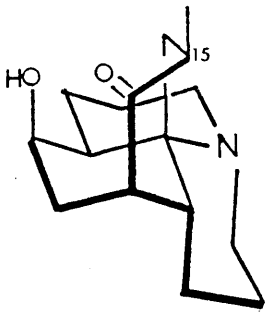

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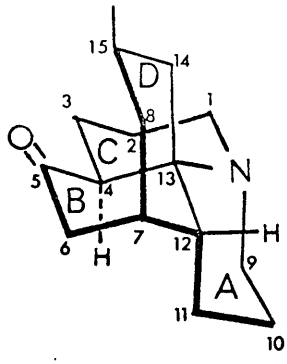

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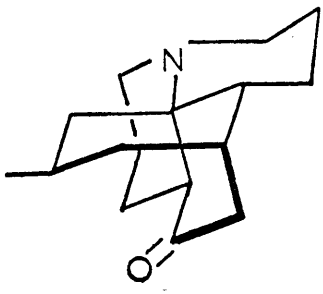

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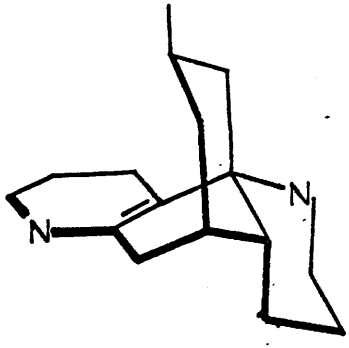

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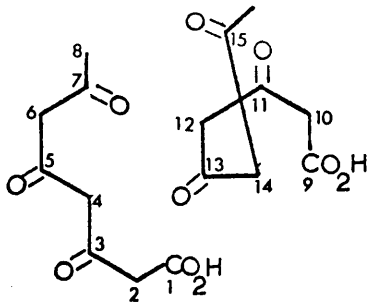

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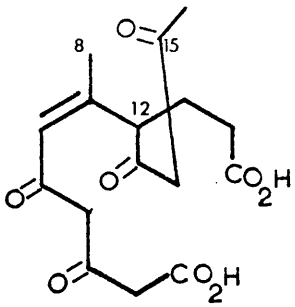

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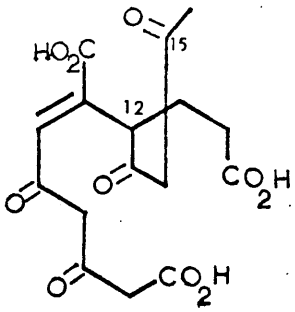

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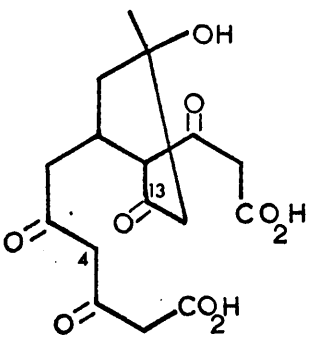

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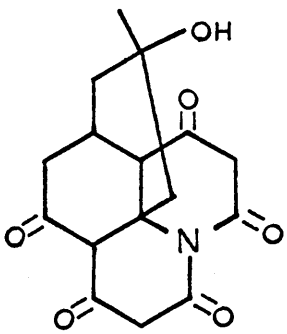

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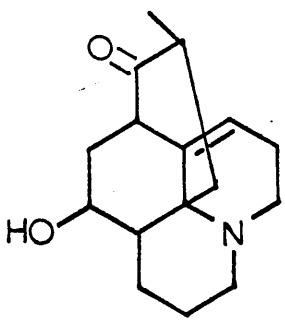

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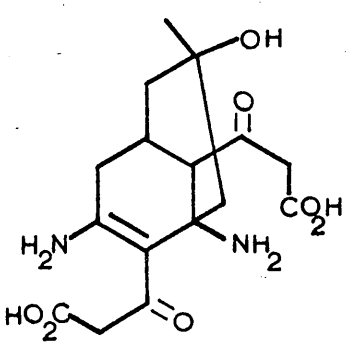

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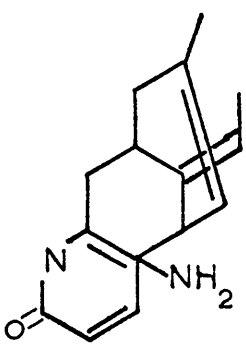

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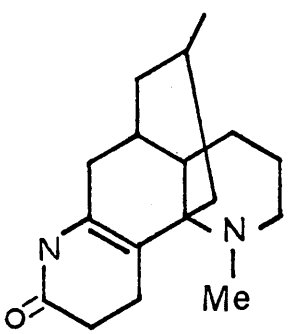

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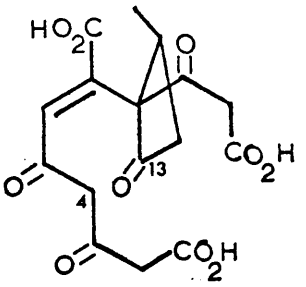

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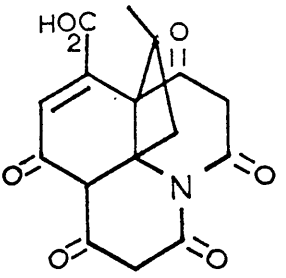

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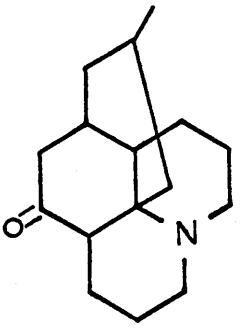

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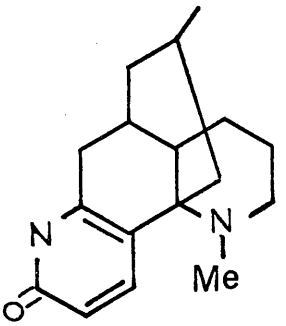

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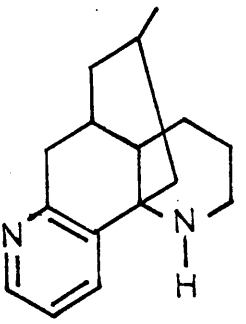

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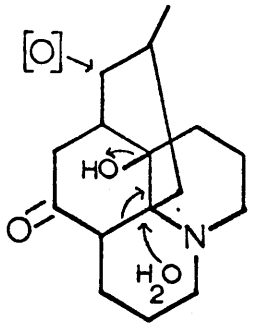

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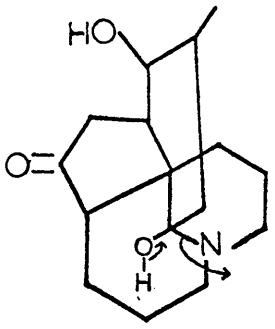

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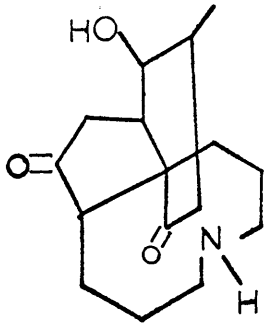

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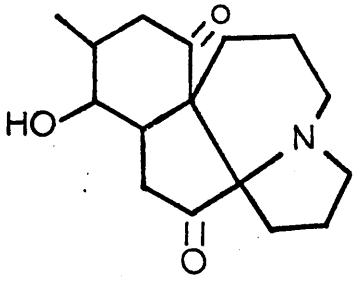

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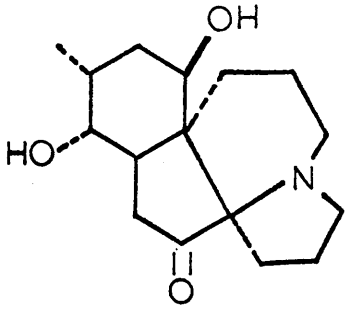
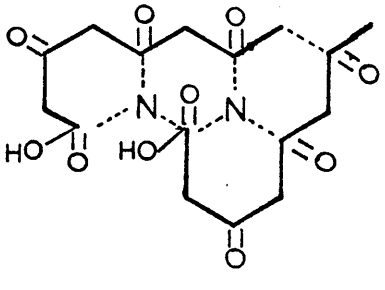


71 ≡ 33



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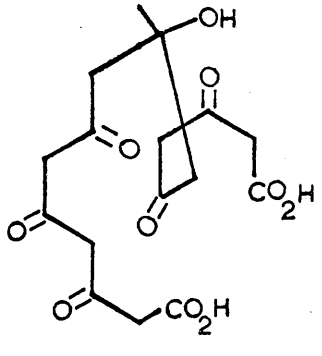

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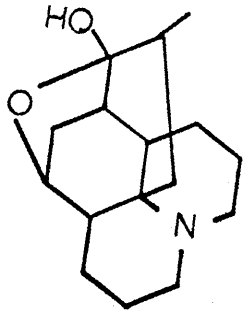

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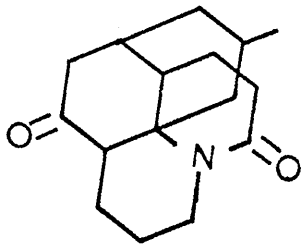

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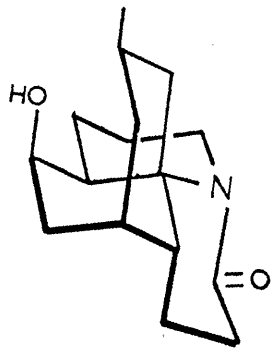

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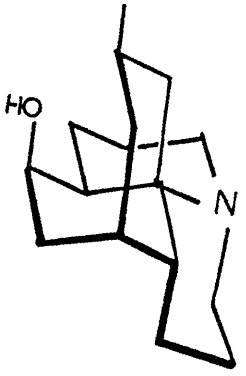

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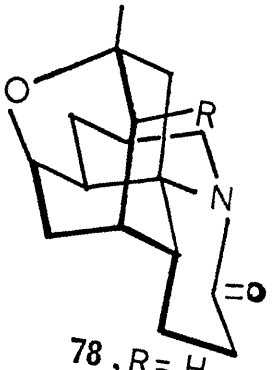
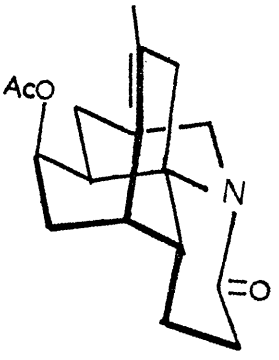
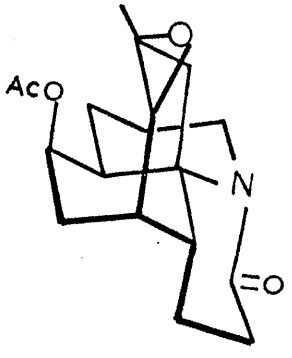


78, R = H
79, R = OAc
80, R = OH
81, R = >C=O



82



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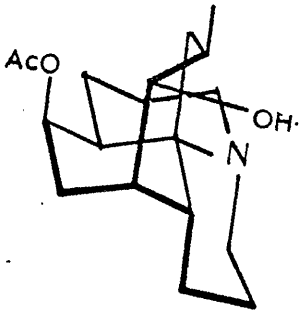

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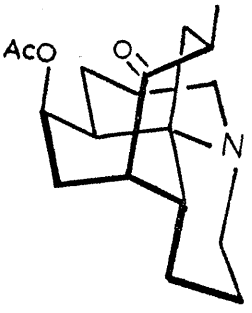

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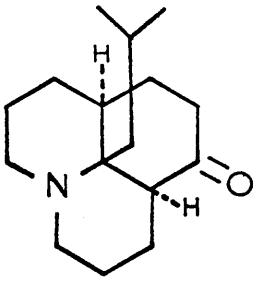

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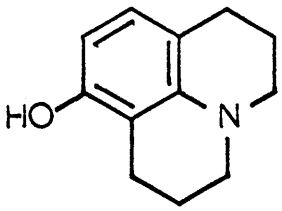

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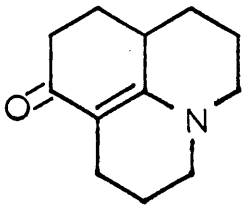

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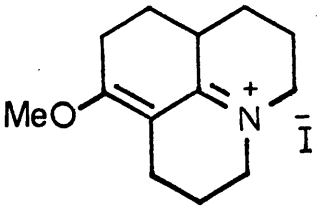

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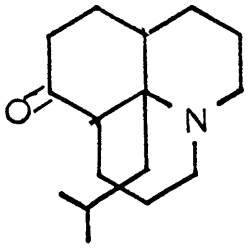

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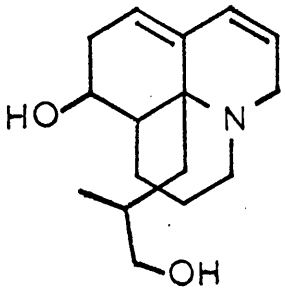

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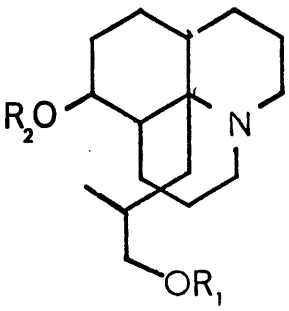
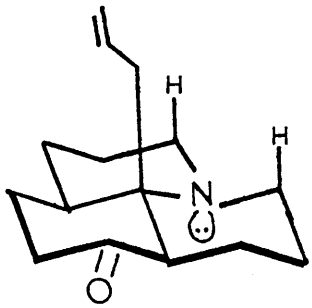


92 , $R_1=R_2=H$

93 , $R_1=R_2=Ac$

94 , $R_1=H$, $R_2=Ac$



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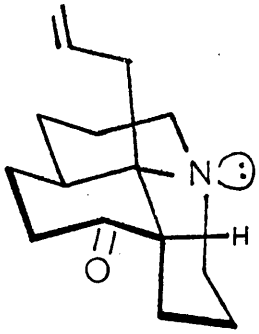

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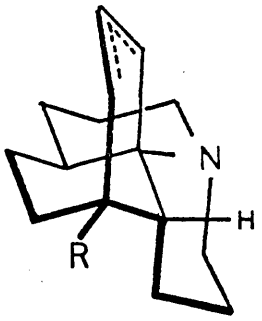
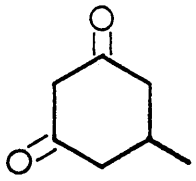


97, R =OH
98, R = Br
99, R =H



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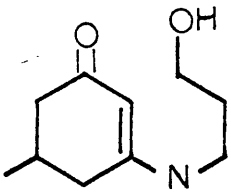

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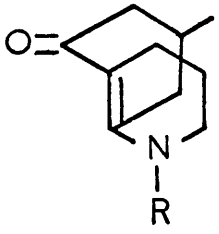
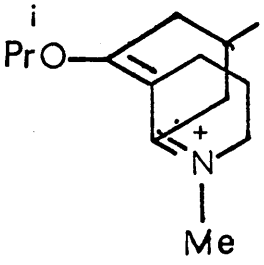


102, R =H
103, R =Me



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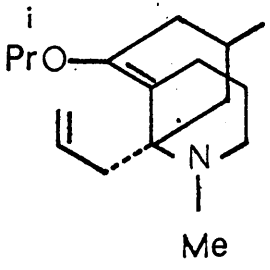

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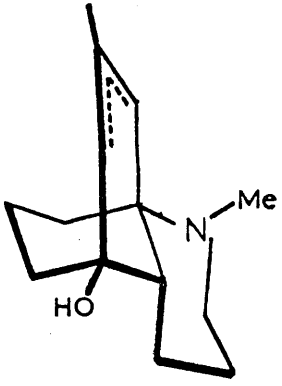

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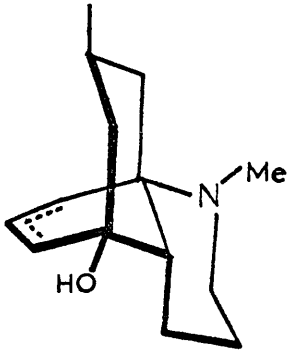

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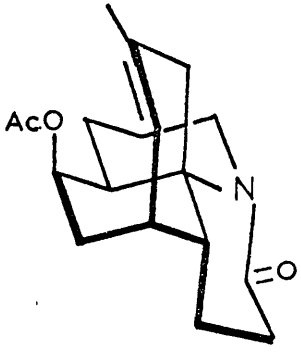

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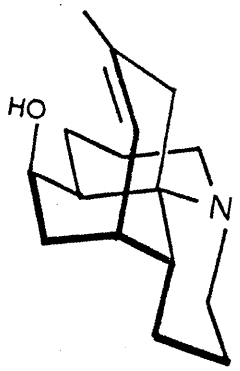

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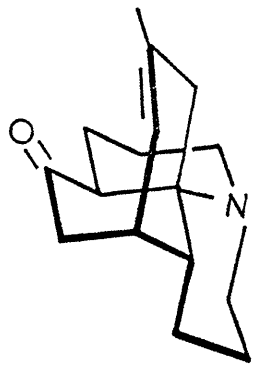

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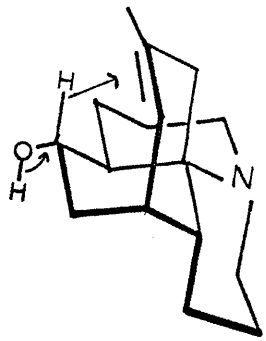

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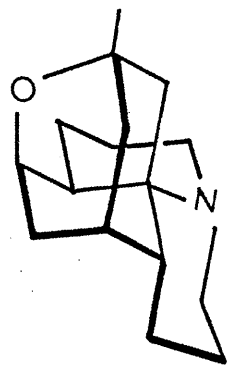

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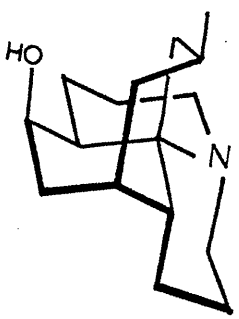

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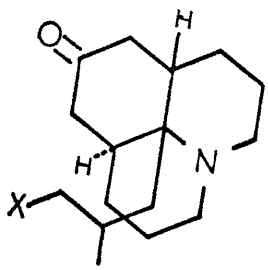

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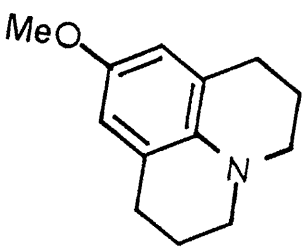

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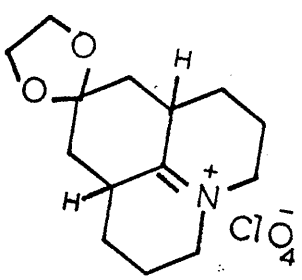

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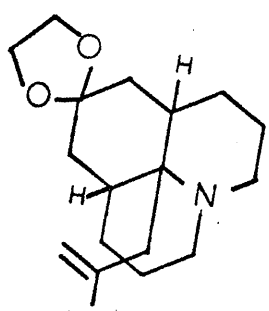

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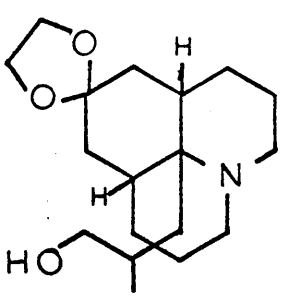

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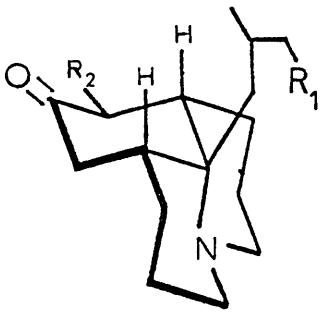
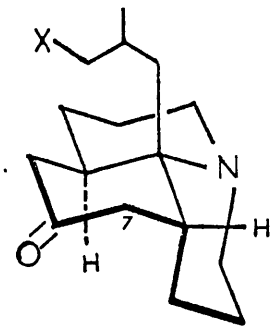


119, $R_1=R_2=H$
120, $R_1=OH, R_2=H$
121, $R_1=H, R_2=Br$



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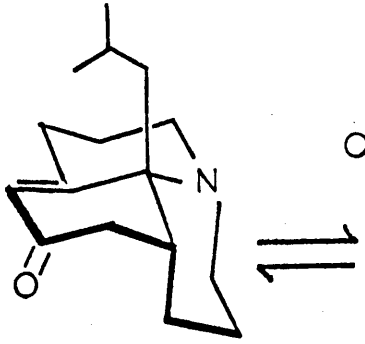

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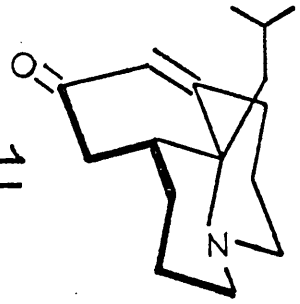

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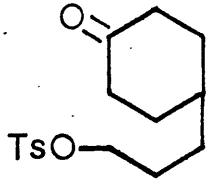

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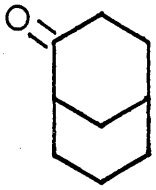

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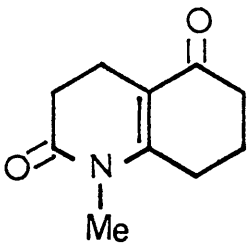

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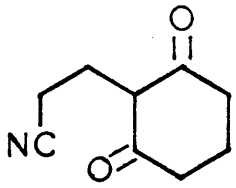

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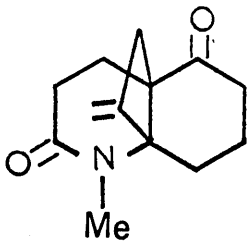

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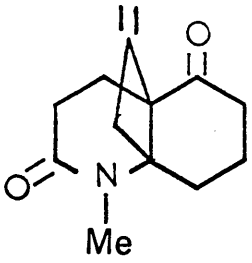

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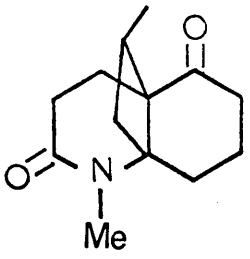

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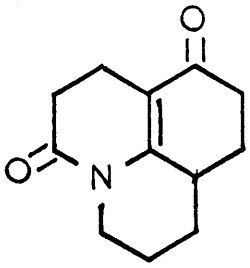

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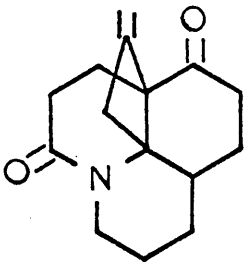

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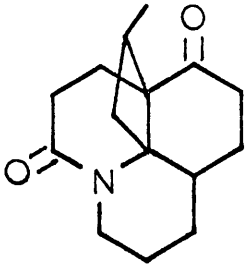

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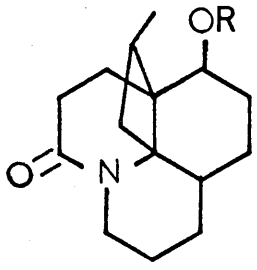
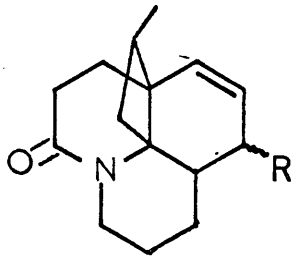
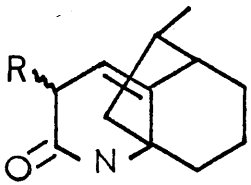


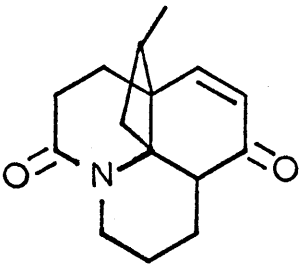
135, R=H
136, R=SO_2Me



137, R=H
138, R=OH



139, R=H
140, R=OH



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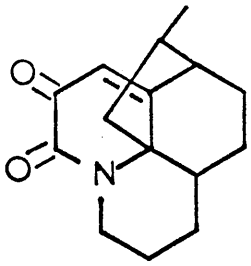

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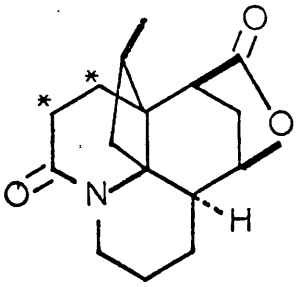

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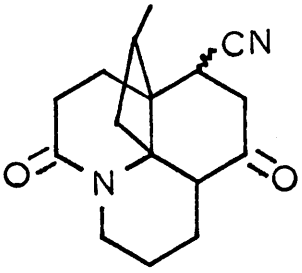

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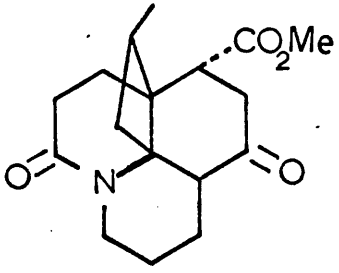

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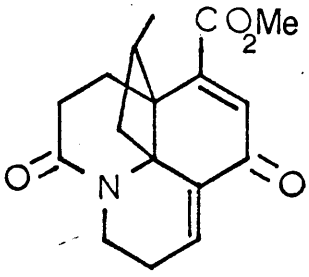

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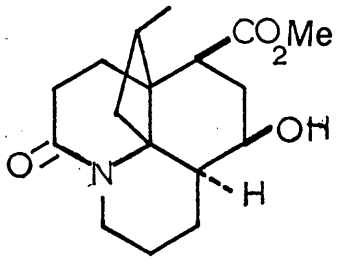

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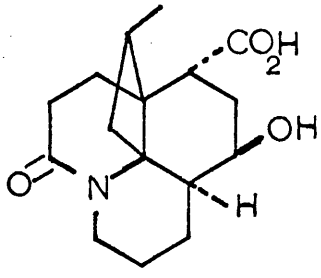


148

DISCUSSION.

All the synthetic approaches to the Lycopodium alkaloids described in the preceeding section involve the construction and subsequent elaboration of a hexahydrojulolidine unit. They all suffer from one major drawback, namely that they seemed to be designed to provide a specific member of the group.

It was felt that an entirely different, and still worthwhile, approach would be to attempt to devise a synthetic sequence which would be capable of simple modification, en route, to provide a large number of both the phenanthroline and hexahydrojulolidine classes. A predilection in these laboratories for the bicyclo(3,3,1)nonane system[53, 63-78] suggested the following ground plan for the synthesis of lycopodine (the simplest member of the family in terms of functionality) which for the present synthetic purposes has been re-numbered as illustrated in formula (149).

The 2,3-benzobicyclo(3,3,1)nonane derivative (150a) should be obtainable from a Michael condensation between the β-keto-ester (151) and methacrolein, followed by ring closure using the method described by Cope.[79] Dehydration of the ketols (150a) should afford the keto-olefin (152) which on catalytic reduction could furnish ring D (153) of lycopodine.

The positioning of a nitrogen atom at C(1) and subsequent construction of ring A were envisaged *via* a Curtius rearrangement of the acid azide corresponding to (153) followed by N-acylation with an activated pyruvoyl species,[80] to furnish the pyruvamide (154), which should possess the necessary activation of the terminal carbon atom to permit ring closure with the C(9) carbonyl group. The resultant enone-lactam (155) could then be converted to the tetracyclic derivative (156) by some sequence of reductive operations. The anisole moiety incorporated in (156) possesses the requisite potential to afford ring C, e.g., Birch reduction[81] should furnish a conjugated enone[82] (157) which on ozonolysis, decarboxylation and oxidation should produce the keto-acid (158). Lactam formation, lithium aluminium hydride reduction, and finally oxidation would then furnish the gross skeleton of lycopodine.

As mentioned earlier, the above route has the inherent potentiality to afford almost all of the *Lycopodium* alkaloids listed in tables 1 and 2, and the general nature of the synthetic plan will now be briefly discussed with reference to figure 1. Scheme A represents the pathway to those alkaloids possessing oxygen functionality at C(6); scheme B portrays the routes to desoxy derivatives at C(6); and scheme C accommodates selagine (39).

Scheme A

By the pathway described above the acetates (150b) could be converted to the enone-lactam (159), which on catalytic reduction of the $\Delta^{6,7}$ double bond, and subsequent Birch reduction of the anisole ring should then furnish the conjugated enone (160). Normal ozonolysis techniques could then afford the tetracyclic system (161), which can ultimately give rise to clavolonine (21), annofoline (22), fawcettiine (26) and its acetate (27). Alternatively, introduction of a hydroxyl group at C(9) in compound (159) followed by Birch reduction to the enone (162) and subsequent ring closure to (163) could lead to acrifoline (16), lycofoline (17) and its di-acetate (18), lycofawcine (29) and its acetate (30).

Scheme B

The route to lycopodine (149) has already been discussed and the step to dihydrolycopodine (14) would simply involve reduction of lycopodine with lithium aluminium hydride. In addition, enamine formation followed by N-acetylation would convert lycopodine into flabelline (25). Treatment of lycopodine (149) with selenium dioxide can give rise to two possible products; oxygenation at C(2) would provide flabelliformine (24) whereas oxygenation at C(4) could ultimately result in base L.20 (32) and lycoclavine (19).

The tricyclic keto-acid (158) in the presence of ammonia could furnish the enol-lactam (164) and this versatile intermediate would then furnish the alkaloids of the phenanthroline class, viz., lycodine (38), α-obscurine (40), β-obscurine (42), sauroxine, des N-methyl-α-obscurine (41) and flabellidine (44). Hydration of (155) followed by catalytic reduction and then Birch reduction, would furnish (165) which could then be converted into lycodoline (23).

Scheme C

Selagine (39) could be derived from the bicyclic system (150) by Birch reduction, ozonolysis, decarboxylation and oxidation, enol-lactamisation in the presence of ammonia to afford (165). Dehydration of the C(6) hydroxyl function (or pyrolysis of the corresponding acetates) followed by a Wittig reaction on the C(9) carbonyl group could lead to the unsaturated ester (167). A Curtius reaction on the acid azide corresponding to (167) and isomerisation of the $\Delta^{6,7}$ to the $\Delta^{7,8}$ olefin[72] would then yield selagine (39).

Any practicable synthesis in the Lycopodium series must be capable of stereochemical control since the gross lycopodine skeleton obtained from the above sequence would have three centres of undefined stereochemistry, viz., C(7), C(9) and C(2). The last centre should pose no problem

in this respect since the formation of ring C could be carried out under equilibrating conditions.

In lycopodine the configuration of the methyl group attached to C(7) is equatorial, as in the stereodiagram (149) and it is entirely possible that that both epimers (168) and (169) might be obtained by the catalytic reduction of the $\Delta^{6,7}$ double bond. Given that these isomers were separable their relative configurations could be determined from their respective nuclear magnetic resonance (n.m.r.) spectra e.g., the equatorial epimer (168) would be expected to show the protons of the C(7) methyl group at normal fields (ca τ, 9), whereas these same protons should be shielded in the axial epimer (169) since they lie in the shielding cone of the aromatic ring.[83] It is noteworthy that such an axial orientation of the C(7) methyl group is to be found in annofoline (22) and clavolonine (21) although the precise disposition is pseudo-equatorial since ring D undergoes ring inversion to the boat conformation in these alkaloids.[44] Even if the above sequence should eventually afford solely lycopodine with the wrong stereochemistry at C(7), Ayer[55] has made it possible to obtain the correct stereochemistry since a transannular hydride shift involving the unsaturated alcohol (111) affords lycopodine directly.

The second asymmetric centre of lycopodine lies at C(9), where the hydrogen atom can adopt two possible orientations, either syn or anti with respect to the carbonyl group. Stereoformula (170) shows that if the former is the case then the compound would be expected to show Bohlmann bands[50, 51] in its infrared spectrum; alternatively, these bands should be absent in the latter, desired, anti configuration (171a). Infrared spectroscopy could also differentiate between the two possible isomers in another way, viz., by comparison of the association constants[84] of the two amines in the presence of a phenol. The nitrogen lone-pair electrons in the anti case (171b) are slightly less sterically hindered than those of the syn epimer (170). Consequently the former case should favour stronger association with the phenol. A third possible means of identifying the stereochemistry at C(9) is based on the work of Hamlow and Okuda,[85] who suggest that in saturated cyclic nitrogen compounds in which the direction of the nitrogen lone-pair electrons is fixed, partial participation of the lone-pair with the σ^* C-$H_{ax.}$ orbital on the adjacent carbon takes place, thus generating more p-character between C(4) and **N** (also C(6) and **N**) in the amine (172). Consequently compound (172) exhibits an unusually large chemical shift difference in the n.m.r. spectrum,

between the equatorial and axial protons at C(4), as compared with cyclohexane. Other studies[86,87] confirm these findings. Considering compound (170), both axial hydrogen atoms adjacent to the nitrogen atom (i.e., situated on C(12) and C(13)) should demonstrate this phenomenon. In the anti configuration (171a) only the C(12) axial proton will be more shielded.

A fourth spectroscopic means of identifying the configuration at C(9) involves absorption in the ultraviolet region due to σ-coupled p-π electron systems.[88] Diaza-adamantanone (173) exhibits an ultraviolet maximum at 262 nm., (ε=3,600), due to σ-coupled p-π interaction between the nitrogen lone-pair electrons and the π electrons of the carbonyl group. An apparently analogous situation is present in the anti epimer (171c = 171a) in that the rigidity of the framework holds the nitrogen lone-pair (p) electron cloud parallel to the (π) electron cloud of the carbonyl group. That there should be no significant absorption with the syn epimer (170) (where the respective electron clouds are non-parallel) is borne out by the fact that the substituted 3,7-diaza-bicyclo(3,3,1)nonan-9-one (174) does not display this phenomenon. In fact, lycopodine does exhibit such an interaction in its ultraviolet spectrum.[89]

Catalytic hydrogenation of the intermediate (152) may or may not be stereospecific. One can speculate as to which part of the molecule will be bound to the catalyst's surface, thus influencing the direction of the hydrogen delivery at C(9), but in complex systems these conclusions can be misleading. In the event of the reduction resulting exclusively in the undesired syn epimer (170) an alternative stereospecific chemical sequence would be required. An S_N2' reaction of the hydroxy-tosylate (175a) or hydroxy-trichlorobenzoate[90] (as illustrated by the arrows 175c → 175e) could afford the desired stereochemistry at C(9) as in (171b). The diketone (176) on reduction with lithium aluminium hydride might furnish (175a) after selective tosylation. However, the synthesis of an intermediate such as (176) necessitates a deviation from the proposed synthetic scheme and would only be considered in the event of complete failure of the hydrogenation sequence.

One major question to be answered at an early stage in this synthetic plan was whether the envisaged cyclisation of (154) to (155) could be realised, and recently in these laboratories an elegant synthesis of the 5,8a-propanoperhydroquinoline system i.e. rings A,B and D of the lycopodine skeleton, has been completed.[74] The readily available olefin ketoester (177a)[91] was converted *via* the acid, acid azide and isocyanate into the benzyl carbamate (177b). Subsequent treatment with hydrogen bromide in acetic acid afforded an amino ketone which was isolated as the corresponding amine hydrobromide (177c) in order to avoid the facile dimerisation of the α-amino ketone. Treatment of (177c) with a mixture of phosphorus oxychloride and pyruvic acid in the presence of triethylamine proved to be an extremely efficient acylation procedure[80] and the resultant pyruvamide (177d) was then cyclised by means of sodium hydride in tetrahydrofuran to the tricyclic enone lactam (178). The corresponding lactim ether (179), obtained by treatment of the lactam (178) with triethyloxonium tetrafluoroborate[92] in methylene chloride, was then reduced with lithium aluminium hydride to furnish the stereochemically pure carbinolamine (180a) as the sole product. The corresponding diacetate (180b) was then catalytically reduced to the desired tricyclic system (181) using palladium on charcoal in ethanol containing perchloric acid.

It seemed a natural progression from these results to attempt a similar sequence starting with ethyl 7-methylbicyclo(3,3,1)-nonan-4-ene-9-one-1-carboxylate (182a), since a corresponding substitution pattern is to be found in ring D of lycopodine (149). The keto-aldehyde (183) was readily prepared by the method of Cope and Synerholm[91] from 2-ethoxycarbonyl-4-methylcyclohexanone (184), but subsequent treatment of this keto-aldehyde with concentrated sulphuric acid furnished an olefin in only 5% yield as a mixture of double bond isomers (182a) and (185).[93] Attempts to prepare the olefins (186),[69] (187)[65] and (188) by this sulphuric acid treatment have also been characterised by lower yields.

It was therefore decided to bring about the initial intramolecular aldol cyclisation of (183) under milder conditions and then to examine methods of carrying out a β-elimination to improve the yield of the olefin (182a). When the keto-aldehyde (183) was treated with either triethylamine in benzene or 6N aqueous hydrochloric acid in dioxan, two bicyclic ketols (189a) and (190a) were obtained in the ratio 2:1 as revealed by g.l.c. analysis of the mixture of corresponding acetates (189b) and (190b) (1% P.E.G.A., retention time, R_t, = 7.6 and 6.2 min. respectively). All attempts to separate this mixture by either column chromatography or preparative t.l.c. were unfruitful. Oxidation[94] of the mixture of ketols furnished the dione (191)

which on reduction with lithium hydridotri-t-butoxyaluminate furnished a single ketol in poor yield. G.l.c. analysis of the corresponding acetate (conditions as above, R_t = 7.6 min.) showed peak enhancement with the acetate corresponding to the more abundant isomer formed by acid- or base-induced ring closure of the keto-aldehyde (183). Since complex hydride reduction of the dione was expected to proceed from the least hindered side of the molecule, the derived ketol was expected to be the equatorial isomer (189a), and since the ring closure of the keto-aldehyde (183) was carried out under equilibrating conditions, one would expect the same equatorial ketol to be formed in preference.

When the keto-aldehyde (183) was oxidised to the keto-acid (192a) (characterised as the corresponding methyl ester (192b)*) and this acid treated with sodium acetate and acetic anhydride, the corresponding enol-lactone (193) was obtained. Reduction with lithium hydridotri-t-butoxyaluminate (see addendum) then gave the ketol (190a) which, on g.l.c. analysis of the corresponding acetate (190b), showed peak enhancement with the less predominant isomer formed in the cyclisation of the keto-aldehyde (183). Further treatment of this <u>axial</u> ketol with lithium hydridotri-t-butoxyaluminate furnished predominantly

* for fuller discussion, see addendum.

the syn diol (194), which exhibited concentration independent intramolecular hydrogen bonding in its infrared spectrum, and in addition was converted into a cyclic sulphite ester (195) on treatment with thionyl chloride and pyridine. In addition, the corresponding p-toluenesulphonate (190c) was prepared by the literature procedure[95] and its n.m.r. spectrum revealed the C(4) methine proton as a multiplet (1H) centred at τ, 4.9 ; width at half-height, 10 cps.[96] corroborating the axial stereochemistry. Hence the stereochemistry at C(4) of (189a) and (190a), the two ketols formed from the keto-aldehyde (183), has been established.

Since the acid-catalysed dehydration of the mixture of ketols (189a) and (190a) gives poor yields of olefin (see above), the possibility of achieving an E_2 elimination of p-toluenesulphonic acid from both tosylates (189c) and (190c) was then considered. However, it has been shown[97] that the equatorial tosylate (196) undergoes facile ring opening, as illustrated, to furnish (197), whereas the corresponding axial tosylate (198) on vigorous treatment with sodium ethoxide in ethanol is converted to the olefin (187). Treatment of the axial tosylate (190c) with sodium ethoxide in ethanol furnished the cyclooctene diester (199a) ($\nu_{max.}$ (CCl_4) 1735, 1709 and 1646 $cm.^{-1}$) as the sole product. The n.m.r. spectrum of this product showed the following signals :- doublet (3H)

centred at τ, 9.5 (J=6 c.p.s.) assigned to C(7) methyl protons ; two overlapping triplets (each 3H) centred at τ, 8.75 (J=6 c.p.s.) and two overlapping quartets (each 2H) centred at τ, 5.85 (J=6 c.p.s.) assigned to the ethyl ester resonances, the lower field set of signals being attributed to the ester group adjacent to the double bond (i.e. at C(5)) ; a quartet (1H) centred at τ, 3.02 (J=8 c.p.s.) assigned to the vinylic proton. This ring opening probably arises from a retro-Claisen reaction followed by β-elimination of p-toluenesulphonic acid as illustrated (200a 200b). Similar results have been obtained by other workers.[66] In an attempt to overcome the problem of this initial attack of alkoxide at the C(9) carbonyl group, the bulkier t-butoxide anion was used, but g.l.c. analysis of the product so obtained revealed the desired olefin (182a) as the minor component of a 20:1 mixture, the major component probably being the ethyl-t-butyl diester (199b).

It was therefore decided to overcome this difficulty by protecting the carbonyl group as the corresponding ethylene ketal. However, normal ketal preparative procedures, e.g. p-toluenesulphonic acid and ethylene glycol in refluxing benzene, afforded a small amount of the desired olefin (182a) as well as unreacted starting material.This result indicated that an acidic medium might be the means of carrying out the required β-elimination. Indeed, other results obtained in these laboratories

reflect this conclusion[98] in that the olefin (187) was obtained in 65% yield when the tosylate (198) was solvolysed in acetic acid. In the latter case besides the E_1 elimination process there is the possibility of Wagner-Meerwein rearrangements occurring by virtue of the C(5) tertiary methyl group being adjacent to the incipient secondary carbonium ion at C(4). In the present system, the C(5) position is secondary and so the tendency for similar rearrangements is reduced. Accordingly the tosylate (190c) was heated under reflux with 10% aqueous acetic acid to furnish in acceptable yield the olefin keto-acid (182b), which was converted to the corresponding methyl ester (182c) and found to be identical in all respects with an authentic sample.

Thus our prime objective had been accomplished in that 7-methylbicyclo(3,3,1)nonane derivatives could be prepared in reasonably good yields, but this same route neglected the stereochemical implications of the C(7) asymmetric centre. It was felt that if a bicyclo(3,3,1)nonane derivative having an oxygen function adjacent to the C(7) methyl group could be constructed, then such derivatives might represent the means of identifying the stereochemistry of the C(7) methyl group with the aid of n.m.r. spectroscopy. Accordingly, 1-carbethoxycyclohexanone (201)[99] was treated with methacrolein under the now normal Michael conditions to afford two keto-aldehydes (202). The n.m.r. spectrum

of this product revealed the aldehydic protons as two doublets (each 1H) centred at τ, 0.35 and 0.37 (J=3 c.p.s.), and g.l.c. analysis indicated two components in the ratio 1:1 (5% Q.F.1, R_t= 13.5 and 12 min.). Thus there now existed definite evidence for stereoisomerism about the methyl-bearing carbon atom. This was confirmed by the fact that treatment of the aldehydes (202) with 6N aqueous hydrochloric acid and dioxan furnished four isomeric ketols (203a) in the ratio 10:5:1:5, as estimated by g.l.c. examination of the corresponding acetates (203b) (5% Q.F.1, R_t= 24.75, 29.0, 30.0 and 44.5 min. respectively). Fractional crystallisation of the corresponding crude acetates furnished a single compound (g.l.c. R_t= 29 min.), whose n.m.r. spectrum revealed :- a multiplet (1H) at τ, 4.8 (width at half-height, 6 c.p.s.), which was assigned to the C(6) methine proton ; the ethyl ester resonances appeared as a sharp quartet (2H) centred at τ, 5.75 (J=6 c.p.s.) and a sharp triplet (3H) centred at τ, 8.75 (J=6 c.p.s.) ; the C(7) methyl protons appeared as a doublet (3H) centred at τ, 9.05 (J=6 c.p.s.). This crystalline acetate could be one of four possible compounds (204a→d). A conformational inspection suggests that in the case of (204c) and (204d) the severe C(3)-C(7) non-bonded hydrogen interaction would best be relieved by the cyclohexyl acetate ring undergoing ring inversion to give (204e) and (204f) respectively.

The chemical shift and half-band width of the carbinyl

C(6) proton suggest that the acetate grouping, in this crystalline derivative, is axial.[96] Hence it is possible to discount structures (204b) and (204e), but at this stage it is only possible to suggest that this single acetate is either (204a) or (204f).

The liquid fraction of these acetates was composed of three components as indicated by g.l.c. analysis, and the analytical and spectral data were compatible with the proposed gross structure. The only attempt made to elucidate the individual stereochemistry of the acetates (203b) involved equilibration of the ketols (203a) with triethylamine. The crude product on subsequent acetylation and g.l.c. analysis showed the same four components to be present in the ratio 12:6:1:9 ; this suggests that the first peak (R_t= 24.75, conditions as above) should correspond to the thermodynamically most stable epimer, namely (204b), in which both the C(6) and C(7) substituents have an equatorial environment. No further experiments were performed in this direction as it was sufficient for the present purpose to know that methacrolein would readily behave as a Michael acceptor and that C(7) methyl group isomers could be obtained.

Concurrent with these approaches a parallel investigation was initiated to examine the scope of the synthetic routes to substituted bicyclo(3,3,1)nonane derivatives containing a potential carbonyl function at C(3) since lycopodine (149) also

has a carbonyl group in this position. The selected starting material was the β-keto-ester (205) which was prepared in the following manner. β-2(Furyl)-acrylic acid (206) was treated with ethanolic hydrogen chloride to furnish 4-ketopimelic acid diethyl ester (207)[100] which was then transformed into the corresponding ethylene ketal (208).[101] Treatment of (208) with a suspension of solid sodium ethoxide in anhydrous ether effected a Dieckmann cyclisation to yield the β-keto-ester (205)[101] which in turn was reacted with acrolein in the presence of a catalytic amount of sodium ethoxide to furnish the keto-aldehyde (209). The presence of the additional ketal function in this molecule precluded the use of acid-promoted ring closure, but the keto-aldehyde was smoothly converted into a mixture of the epimeric ketols (210a) and (211a) by the action of triethylamine in refluxing benzene. G.l.c. analysis of the corresponding acetates (210b) and (211b) indicated the presence of two components in the ratio 2:1 (1% P.E.G.A., R_t= 7.4 and 5.6 min., respectively).

When the keto-aldehyde (209) was oxidised to the keto-acid (212) and then treated with sodium acetate and acetic anhydride, the corresponding enol-lactone (213) was obtained. Reduction of (213) with lithium hydridotri-t-butoxyaluminate* furnished a

* see addendum for discussion.

two component mixture in the ratio 1:5 as estimated by g.l.c. analysis of the corresponding acetates (R_t= 7.4 and 5.2 min. respectively, conditions as above). By direct analogy with the earlier studies the epimer having g.l.c. R_t= 5.2 min. was assigned the axial configuration for the C(6) substituent, (211a), the remaining acetate thus being the equatorial isomer (210a).

The earlier routes to the $\Delta^{6,7}$-olefin showed that base-induced E_2 processes were unfruitful and in this case 10% aqueous acetic acid would remove the ketal protecting group, thus thermal elimination reactions were now considered, since both the axial and equatorial epimers can give rise to a cis arrangement of a proton at C(7) and an ester at C(6) in the transition state. The corresponding carbonate esters (210c, 211c) were preferred over the acetates (210b, 211b) for a pyrolytic elimination since the acetic acid produced in the latter case might have served to remove the protecting ketal function.

In the event, pyrolysis provided no detectable quantities of olefin (214) but merely furnished starting material, carbonaceous product and appreciable quantities of the β-keto-ester (205) (identified by t.l.c. mobility and infrared spectrum). Even after several modifications of the reaction conditions no improvement on these results could be obtained.

Bearing the earlier solvolytic results in mind, it was thought that both the equatorial and axial tosylates (210d) and (211d) should furnish the same olefin (214) under strictly anhydrous buffered conditions. However, it was impossible to confirm this hypothesis since all attempts to isolate these esters were unsuccessful, the compounds being sensitive to air and moisture.

Although the formation of the olefin (214) was never realised, the above model series had at least indicated that bicyclo(3,3,1)-nonane derivatives possessing a potential C(3) carbonyl function could be prepared.

There now existed the inviting possibility of condensing the β-keto-ester (205) with methacrolein to derivatives of the type (215). The lycopodine skeleton could now be formed by first constructing ring A using the techniques of the early model series, to afford (216) and liberation of the C(3) carbonyl group would then produce a potential alkylation centre at C(2) in (216). This final ring construction, however, would present some severe synthetic problems, whereas the tetralone route as detailed earlier did not involve such difficulties. Therefore at this stage it was decided to focus attention on this main route since it was felt that sufficient experience had been gained in model systems to warrant an attempt at the total synthesis of lycopodine.

The required starting material was 6-methoxy-2-tetralone (217) but numerous attempts to prepare this compound by the literature procedure[102] involving the treatment of p-methoxyphenylacetic acid with ethylene, in the presence of aluminium chloride, met with no success despite elaborate precautions to exclude moisture. Other methods of synthesising the tetralone (217) have been reported[103,104] but they were initially considered less desirable due to low yields, impure products and laborious procedures. Fortunately, early in 1966, Kidwell and Darling[105,106] published an improved route to the desired tetralone, using the readily available 6-bromo-2-naphthol (218a)[107] as starting material. The Grignard reagent of the corresponding methyl ether (218b)[107] was prepared in dry tetrahydrofuran solution, filtered under nitrogen and then added to an ice-cold solution of trimethylborate[108] in anhydrous ether, and the resultant boronic ester (219a) hydrolysed to the corresponding aryl boronic acid (219b) by addition of water. Mild acidic oxidation of (219b) was achieved by adding a cold solution of 15% hydrogen peroxide containing ammonium chloride, to give the phenol (220) in 50% yield. Subsequent reduction with sodium in liquid ammonia[104] furnished the desired tetralone (217) in high yield.

A cursory consideration of the β-keto-ester (221) suggested that its formation should be a simple synthetic task since the tetralone (217) might have been expected to carboalkoxylate readily at C(1). The standard procedure involving dimethyloxylate and sodium methoxide[99] is reported[109] to give the aromatised tautomer (222) of the intermediate glyoxylic ester (223), which does not undergo decarbonylation. It has been shown that the enamines (224a), (224b) and (224c) possess a styrenoid double bond and that alkylation of these compounds results in substitution at C(1).[110] In addition, Stork[110] has described the carboethoxylation of enamines using ethyl chloroformate. When the enamine (224c) was treated with ethyl chloroformate using the recommended molar proportions of reactants no reaction occurred ; however, using a 2:1 ratio of ethyl chloroformate-benzene as solvent, this enamine (224c) was converted to a crystalline derivative $C_{17}H_{20}O_6$; mass spectral molecular weight 302 ; $\nu_{max.}$ (Nujol) 1740, 1675, 1640 and 1620 $cm.^{-1}$; $\lambda_{max.}$ 250 nm. (ε=19,400) shifting in base to 285 nm. (ε=30,400). The n.m.r. spectrum indicated the presence of two ethyl esters as two overlapping quartets (4H) centred at τ, 5.75 (J=6 c.p.s.) and two overlapping triplets (6H) centred at τ, 8.70 (J=6 c.p.s.). The compound gave a dark green coloration with ethanolic ferric chloride solution. On the basis of the above analytical and

spectroscopic data the product was identified as 1,3-bis-ethoxy-carbonyl-6-methoxy-2-tetralone (225).

Direct treatment of the tetralone (217) with diethyl carbonate[111] and sodium hydride (molar proportions 1:2:2 respectively) in refluxing tetrahydrofuran gave a disappointing mixture of products. However, a simple modification of this procedure[112] using dimethyl carbonate as both solvent and reactant led to a single product analysing for $C_{13}H_{14}O_4$ in high yield; mass spectral molecular weight 234 ; $\nu_{max.}$ (film) 1740, 1720, 1640 and 1620 cm.$^{-1}$; $\lambda_{max.}$ 250 nm. (ε=13,300) and 285 nm. (ε=6,200) shifting in base to 281 nm. (ε=18,200). The infrared spectrum and analytical data are compatible with an enolisable β-keto-ester (the compound also gave a pale green coloration with ethanolic ferric chloride solution), but do not distinguish per se between the obvious contenders (221) and (226). The ultraviolet spectrum, however, suggested that the enolic double bond is styrenoid (227) rather than unconjugated (228) (cf. the position and band shape of the ultraviolet maxima of 1,2-dihydronaphthalene (229) and 1,4-dihydronaphthalene (230)[113]).

In the n.m.r. spectrum (100 Mc./s.) of the β-keto-ester obtained above, the aromatic protons appear as illustrated in Figure 2. The following assignments were made with reference to the n.m.r. spectrum of 17α-ethynylestradiol (231).[114] The C(8)

proton signal occurs as a doublet centred at τ, 2.5 (J_{ortho}=8 c.p.s.) (the lines are somewhat broadened due to the small para coupling). The C(7) resonance is split by J_{ortho}=8 c.p.s. and J_{meta}=3 c.p.s.. One pair of the lines in the resulting quartet overlaps with the broad signal due to the C(5) hydrogen at τ, 3.42. Since the C(5) hydrogen is coupled to the other two aromatic protons with J values of 3 c.p.s. and 0-1 c.p.s., a total of six lines is predicted, but since they lie within three or four cycles, the observed spectrum shows the C(5) resonance as a broadened singlet. The remaining protons in (221) were assigned as follows :- ArO<u>Me</u> , singlet (3H) at τ, 6.20 ; CO<u>OMe</u> , singlet (3H) at τ, 6.31 ; the proton on C(1) appeared as a singlet (0.25H) at τ, 6.38 ; the hydroxylic proton, arising from the appreciable concentration of the enolic tautomer (227) was revealed as a sharp singlet (0.75H) at τ, -3.62, which disappeared on exchange with D_2O ; the protons on C(3) absorbed as a triplet (2H) centred at τ, 7.28 (J=6 c.p.s.) ; the protons on C(4) as a triplet (2H) at τ, 7.58 (J=6 c.p.s.).

These n.m.r. assignments were based on detailed comparison with related compounds, described below, and where possible checked by spin-decoupling experiments. For example, in the case of the above β-keto-ester, irradiation of the triplet centred at τ, 7.28 produced a sharp singlet at τ, 7.58, and irradiation at τ, 7.58

produced a singlet at τ, 7.28 ; these decouplings indicated the presence of two adjacent methylene groups.

In the n.m.r. spectrum (100 Mc./s.) of the tetralone (217) the aromatic protons appeared at τ, 2.5-3.5 (3H) ; ArOMe as a singlet (3H) at τ, 6.34 ; the protons on C(1) as a singlet (2H) at τ, 6.62 ; those on C(3) as a triplet (2H) centred at τ, 7.10 (J=6 c.p.s.) ; the protons on C(4) appeared as a triplet (2H) centred at τ, 7.58 (J=6 c.p.s.). Irradiation at the centre of the triplet centred at τ, 7.10 produced a singlet at τ, 7.58 and irradiation at τ, 7.58 resulted in a singlet at τ, 7.10. Thus, the β-keto-ester prepared as described above had, in all probability, the structure (221) since (a) the singlet at τ, 6.62 (2H) in the parent tetralone now appeared as a singlet at τ, 6.40 (0.25H) and (b) the two adjacent methylene groups were still present.

It has been shown that carboalkoxylation[115] using methyl magnesium carbonate, formylation[109] and alkylation[109,115] of 5-methoxy-2-tetralone all lead exclusively to C(3) substituted products while formylation of 2-tetralone itself occurs at both positions C(1) and C(3) in proportions which are solvent dependent.[116] In view of these results, unambiguous assignment of structure (221) to the mono-substituted product was required.

When the preparation of the pyrrolidine enamine (232a) of (221) was attempted using as little as two molar equivalents of organic base the only product isolated was the crystalline enamine-amide (232b) ; $\nu_{max.}$ (Nujol) 1610 cm.$^{-1}$ (superimposed C=N and amide carbonyl bands). In the n.m.r. spectrum of (232b) (100 Mc./s.) the sixteen protons of the pyrrolidine residues appeared as two multiplets (each 4H) centred at τ, 6.5 and 6.85 and a multiplet (8H) centred at τ, 8.21, all inter-related by decoupling experiments ; ArOMe , singlet (3H) at τ, 6.35 ; the protons on C(3) appeared as a triplet (2H) centred at τ, 7.32 (J=6 c.p.s.) ; and the protons on C(4) appeared as a triplet (2H) centred at τ, 7.60 (J=6 c.p.s.). That the protons on C(3) and C(4) were mutually coupled was verified by spin decoupling techniques. The absence of a signal due to the methoxycarbonyl function confirmed that aminolysis had occurred, and particularly important, the absence of any absorption due to a vinylic proton[115] excluded the structure (233a) for the enamine-amide. Structure (234) also possesses a tetrasubstituted double bond but since the product has two adjacent methylene groups the above enamine-amide cannot be represented by diagram (234).

As a chemical confirmation of the assigned structure, the β-keto-ester (221) was converted to 6-methoxy-1-naphthoic acid (235a) by the following reaction sequence. The β-keto-ester (221)

was reduced with sodium borohydride to the hydroxy-ester (236), $\nu_{max.}$ (Nujol) 3500 and 1720 cm.$^{-1}$, which was then dehydrated with phosphorus oxychloride and pyridine to furnish the 3,4-dihydro-naphthalene derivative (237a)[117] whose n.m.r. spectrum showed one vinyl proton as a triplet (1H) centred at τ, 2.81 (J=6 c.p.s.). Treatment of this ester with selenium dioxide afforded the fully aromatised system (235b) which, on alkaline hydrolysis, furnished 6-methoxy-1-naphthoic acid (235a), identical in all respects with an authentic sample prepared by the literature procedure.[118]

As final proof of the structure (221) and also for the sake of completeness, the reaction between the tetralone (217) and methyl magnesium carbonate was examined. By an exact duplication of the technique used by Pelletier[115] for the preparation of methyl 5-methoxy-2-tetralone-1-carboxylate, the β-keto-ester (226) was prepared in 30% yield. The spectral properties of (226) are compatible with an enolisable β-keto-ester ; $\nu_{max.}$ (CCl_4) 1740, 1720, 1699 and 1645 cm.$^{-1}$; $\lambda_{max.}$ 260 nm. (ε=5,800) and 280 nm. (ε=2,800) shifting in base to 281 nm. (ε=9,900) and 286 nm. (ε=10,000) (indicative of the system (230)). The n.m.r. spectrum (100 Mc./s.) revealed a singlet (1H) at τ, -2.81 which disappeared on exchange with D_2O. The β-keto-ester (223) was then treated with pyrrolidine to give the enamine (233b), $\nu_{max.}$ (film) 1730 and 1620 cm.$^{-1}$; and the n.m.r. spectrum of the product

revealed the vinylic proton as a singlet (1H) at τ, 5.04 ; ArOMe, a singlet (3H) at τ, 6.42 ; COOMe , a singlet (3H) at τ, 6.58 ;multiplets at τ, 6.84 (4H) and τ, 8.16 (4H) were assigned to the pyrrolidine protons ; the proton on C(3) appeared as a multiplet (1H) centred at τ, 6.19 ; and those on C(4) as a doublet (2H) centred at τ, 7.05 (J=4 c.p.s.). The above enamine, which could not be induced to crystallise, was extremely sensitive to air and moisture.

Now that the synthesis and structural elucidation of the β-keto-ester (221) had been completed, the next phase in the synthetic route involved the construction of the bicyclo(3,3,1)-nonane framework, incorporating a means of stereochemical control at C(7). A Michael condensation between the β-keto-ester (221) and methacrolein furnished a mixture of the diastereoisomeric keto-aldehydes (238) accompanied by the corresponding ketols (239a) as indicated by t.l.c. and infrared data, $\nu_{max.}$ (film) 3500, 2700 and 1740-1710 cm.$^{-1}$. The exact proportion of aldehyde to ketols could not be determined by g.l.c. analysis since a thermal retro-Michael reaction, which had been witnessed in the model series,appeared to be more facile in this case. However, 6N aqueous hydrochloric acid-dioxan treatment completely converted this mixture to the ketols (239a) and g.l.c. analysis of the corresponding acetates (239b) revealed the presence of

four components in the ratio 1:1:1.5:2.5 (5% Q.F.1., R_t= 17.5, 20.5, 22.5 and 26.0 min. respectively). At this stage no one peak could be assigned to any of the four possible isomers, but since the reaction was carried out under equilibrating conditions it was expected that the more abundant isomer would possess both the C(7) methyl and the C(6) oxygen functions in the thermodynamically more stable equatorial environments. The four ketols (239a) on oxidation with Jones reagent[94] furnished a mixture of the diones (240) which consisted of two components by analytical t.l.c. but which gave a single parent ion at the expected m/e value of 302 in its mass spectrum.

It is noteworthy that deacetylfawcettiine (26a) possesses both the C(7) methyl group and the C(6) oxygen function in equatorial environments in ring D. In any further schemes to deacetylfawcettiine using this route it was anticipated that normal base hydrolysis of the ketols (239a) would not afford the acids (241a), but instead would bring about fragmentation via a retro-aldol and a retro-Michael reaction. Consequently the acetates (239b) were subjected to a range of alkaline media in aqueous solvents, none of which produced the desired acetoxy-acid (241b). Eschenmoser et al.[119] have succeeded in selectively hydrolysing acetoxy methyl esters to the corresponding acetoxy-acids by means of lithium iodide and collidine. Accordingly, the

acetoxy-keto-esters (239b) (azeotropically dried with benzene prior to use) were heated under reflux with freshly distilled collidine and vacuum-dried lithium iodide in a nitrogen atmosphere for forty-five minutes. These optimum conditions afforded the acetoxy-keto-acids (241b) in 75% yield. A sample of this product was esterified with an ethereal solution of diazomethane and the methyl ester so obtained was found to be identical with the starting esters (239b). With the obtention of this keto-acid, elaboration of the C(1) carboxyl group to nitrogen was then attempted, using the same conditions which had been successful in the model series.[74] Pilot experiments were quite encouraging to the extent that infrared and t.l.c. evidence indicated that the desired transformations were occurring, but since the starting ester comprised four isomers and further necessary elaborations would create another asymmetric centre, it was decided temporarily to abandon this two-pronged approach in favour of the synthesis of lycopodine itself.

It was decided to dehydrate the four epimeric ketols (239a) to the single olefin (152), which, in turn, would provide the possibility of controlling the stereochemistry at the C(7) methyl group. Pyrolysis of the keto-acetates (239b) produced small amounts of the olefin (152), the bulk of the reaction mixture being starting material and carbonaceous matter. Even

after several modifications of the reaction conditions (e.g. varying the temperature ; presence or absence of solvent ; introduction of powdered glass or zinc oxide), decomposition was extensive. The pyrolytic decomposition of the corresponding carbonate esters (239c) was then studied since, in general, these derivatives undergo elimination at lower temperatures than their acetoxy analogues.

In order to determine the optimum conditions, a systematic investigation of the pyrolysis was undertaken. The recommended procedure[120] for the pyrolysis of high molecular weight carbonates involves heating the ester at 280° under reduced pressure, but using this procedure little or no reaction occurred. Increase of temperature did not enhance the yield but merely caused an increase in the amount of decomposition. Variation of the reaction time furnished similar results. Thus the optimum pyrolysis conditions would involve high temperatures, short reaction time and concomitant removal of the products. Accordingly, the carbonates (239c) were passed down a "Pyrex" tube containing glass beads, held at 400° using nitrogen as carrier gas and the volatiles collected in a cooled receiver. G.l.c. analysis of the product (1% Q.F.1.) indicated that almost complete decomposition had occurred. In view of the above divergency of results, it was decided to carry out a series of

g.l.c. monitored (1% Q.F.1.) pyrolyses over a range of reaction temperatures and times. During the pyrolysis, aliquots were withdrawn at intervals of five minutes. Table 3 summarises the results thus obtained and from these experiments it was concluded that the optimum yield of the olefin (152) was obtained when the carbonate esters were held at 350° for fifteen minutes at atmospheric pressure. However, it was found that when the above procedure was used in large scale experiments the results were irreproducible.

It was then apparent that milder conditions would be necessary to effect the desired elimination in acceptable and constant yields. In the light of the results in the model series it was decided to study the solvolytic behaviour of the four epimeric tosylates (239d). It has been shown that buffered acetolysis of the axial tosylate (198) and the corresponding equatorial epimer (196) gives rise to the olefins (187) and (244) respectively,[98] the latter arising from an acyl migration. Hence it was deemed prudent to examine the solvolytic behaviour of the two axial tosylates (242c) and two equatorial tosylates (243c) separately.

The preparation of the axial ketols (242a) was carried out by an exact duplication of the procedure described earlier, viz., lithium hydridotri-t-butoxyaluminate reduction of the enol-lactone

(245) of the keto-acid (246) obtained by oxidation of the keto-aldehydes (238).* G.l.c. analysis of the reduction product, performed on the corresponding acetates (242b) indicated two components in the ratio 1:1 (5% Q.F.1., R_t= 17.5 and 22.5 min.). These ketols were not readily converted to the corresponding tosylates using the conventional low temperature procedure,[95] but an extended reaction time of five days at room temperature produced the desired p-toluenesulphonic esters (242c) which were then heated under reflux for twelve hours in 10% aqueous acetic acid to furnish as sole product an acidic substance which, on treatment with diazomethane, gave the olefin (152) identical in all respects with an authentic sample obtained from the former pyrolysis route.

By analogy with the model series, the diones (240), on reduction with lithium hydridotri-t-butoxyaluminate, furnished two ketols ($\nu_{max.}$ (film) 3500, 1740-1720 $cm.^{-1}$) in the ratio 1:1 as estimated by g.l.c. analysis of the corresponding acetates (5% Q.F.1., R_t= 20.5 and 26 min.). Co-injection experiments established that the above ketols <u>did not</u> correspond to the pair of ketols formed in the reduction of the enol-lactone, but <u>did</u> give peak enhancement with the remaining two

* see addendum for fuller discussion.

peaks observed in the keto-aldehyde cyclisation product. Thus the structure (243a) (once again with undefined stereochemistry at C(7)) was assigned to the ketols derived from the diones (240).

The corresponding tosylates (243c), formed in two days at room temperature, were solvolysed under similar conditions as above to furnish a small amount of the olefin (152) and ketols (after treatment of the crude product with diazomethane). Acetylation of a portion of the crude reaction product followed by g.l.c. analysis indicated the presence of two components in the ratio 1:1 (column as above, R_t= 20.5 and 26 min.). It would, therefore, appear that under these conditions the equatorial tosylates (243b) were solvolysing with retention of configuration to produce the ketols (243a).

When a mixture of all four tosylates (239d) were subjected to the above solvolysis conditions, the olefin (152) (as the corresponding C(1) acid) was obtained in 30% yield, the major product being ketols which, on oxidation with Jones reagent, furnished the diones (240), identical with an authentic sample, thus indicating that no 2,8-transannular hydride shift had occurred to give the carbonium ion (247) and hence ketols of rearranged structure.

By carrying out the solvolyses in dry buffered conditions (dry acetic acid[121]-fused sodium acetate (1.1 molar equivalent)),

it was anticipated that proton elimination rather than counter ion capture would be the favoured process. Accordingly, the axial tosylates (242c) were solvolysed in refluxing acetic acid containing the requisite proportion of freshly-fused sodium acetate, and the olefin-ester (152) was the sole compound produced. The equatorial tosylates (243c), however, provided the olefin (152) in 70% yield together with a single acetate (5% Q.F.1., R_t= 22.5 min.) which gave peak enhancement with one of the two acetates (242b) on co-injection with an authentic sample. The fact that both the olefin (152) and all four acetates (239b) were stable to these solvolysis conditions indicated that the obtained acetate was a primary product. Hence it then seemed possible to by-pass the selective, but tedious, preparation of the axial and equatorial tosylates (242c and 243c) and to proceed directly to solvolysis of the four tosylates (239d) obtained from the four epimeric ketols (239a). As expected solvolysis of a mixture of all four tosylates reflected the individual results ; the yield of crystalline olefin after column chromatography being 65%. This was a most gratifying result in view of the irreproducible and consistently low yields encountered in the alternative pyrolytic procedure.

As mentioned above, the crystalline acetate obtained as the sole by-product from this solvolysis gave peak enhancement with

one of the acetates corresponding to the ketols (presumed axial) prepared by reduction of the enol-lactone (245) with lithium hydridotri-t-butoxyaluminate. Therefore this acetate could either have structure (248) or (249). The n.m.r. spectrum of the above acetate revealed :- the C(6) methine proton as a multiplet (1H) centred at τ, 4.75, width at half-height was 3 c.p.s. ; the C(7) methyl protons as a doublet (3H) at τ, 9.1 (J=6 c.p.s.) ; OCO<u>Me</u> , singlet (3H) at τ, 7.9 ; superimposed COO<u>Me</u> and ArO<u>Me</u> (6H) at τ, 6.18. The half-band width and chemical shift of the C(6) carbinyl proton are compatible with an axial acetate and, in addition, since the C(7) methyl protons appear as a doublet at τ, 9.1, the structure (248) is favoured because it would be expected that the methyl signal in (249) would be shielded by the aromatic ring current. Later work has revealed that this argument may be misleading for an example has been found where a C(7) methyl configuration similar to that of compound (249) shows <u>no</u> shielded methyl signal and, in fact, the methyl bearing cyclohexanone ring had undergone ring inversion to give the corresponding boat conformation of the ring. It was thought that if such were the case in this instance, then reduction of the C(9) carbonyl group with sodium borohydride should reverse this inversion due to severe bow-sprit (H) or (OH) and (H) interaction, and consequently reveal the methyl protons at a higher field.

In the event, reduction of the acetate furnished a sharp melting alcohol (250) whose n.m.r. spectrum showed the C(7) methyl signal as a doublet centred at τ, 9.1. Hence this by-product in all probability possesses structure (248).

With the obtention of the olefin (152) in good yield, catalytic hydrogenation was an obvious choice for stereochemical control at C(7). No reduction was observed when the olefin was exposed to hydrogen in the presence of a catalytic amount of 10% palladium on carbon, in ethyl acetate as solvent. However, using 95% ethanol as solvent, the crude hydrogenation product showed $\nu_{max.}$ (film) 3500, 1740 and 1720 $cm.^{-1}$; g.l.c. analysis indicated three components (1% Q.F.1., R_t= 8.5, 10.25 and 12 min.). The least polar compound was thought to be one of the saturated alcohols (251) by virtue of the infrared maximum at 3500 $cm.^{-1}$. Accordingly, the crude product was oxidised with Jones reagent to furnish a two component mixture in the ratio 1:1 as estimated by g.l.c. analysis (1% Q.F.1., R_t= 10.25 and 12 min.). This mixture, analysing for $C_{17}H_{20}O_4$ showed a single parent ion m/e, 288 in its mass spectrum and in the n.m.r. spectrum (100 Mc./s.) the C(7) methyl protons were revealed as a doublet (3H) centred at τ, 9.2 (J=6 c.p.s.). The above analytical and spectral evidence indicated that the reduction product consisted of the C(7) isomers (168) and (169). It was

considered that the C(7) substituent in (169) had adopted the pseudo-equatorial configuration as in (169a), since no abnormal methyl signal was observed in the n.m.r. spectrum, and accordingly the product was reduced with sodium borohydride to furnish the corresponding alcohols (252a) and (253a), which revealed two distinct doublets in the n.m.r. spectrum (100 Mc./s.) centred at τ, 9.2 and 9.6 (in each case, J=6 c.p.s.). Thus, the induced aromatic ring current was causing an upfield shift of the methyl doublet in compound (253a). The presence of saturated alcohols in the product from the catalytic hydrogenation step suggested that the molecule was bound to the metal surface by the $\Delta^{6,7}$-double bond and the C(9) carbonyl group resulting in the axial stereochemistry of (169). However, addition must also have occurred from the desired direction to explain the presence of the other isomer (168). The above postulate can also rationalise the experimental observations in the event of double bond isomerisation occurring. By protecting the C(9) carbonyl function as the corresponding ethylene ketal, this carbonyl-metal adsorption would be precluded ; prolonged reduction of (254), however, furnished only unreacted starting material.

Since rhodium on carbon is an efficient hydrogenation catalyst for aromatic rings[122] it was considered that the olefin (152) might be preferentially bound to the surface of rhodium by the

anisole ring and the $\Delta^{6,7}$-double bond. Accordingly, when the olefin (152) was catalytically reduced in the presence of 5% rhodium on carbon in ethyl acetate solution, a single ketone, homogeneous by g.l.c. (1% Q.F.1., R_t= 10.25 min.) was obtained. The n.m.r. spectrum (100 Mc./s.) of this product revealed the C(7) methyl protons as a doublet (3H) centred at τ, 9.2 (J=6 c.p.s.). The corresponding alcohols obtained by reduction of the product with sodium borohydride showed the C(7) methyl protons as a doublet (3H) centred at τ, 9.6 (J=6 c.p.s.), which, on irradiation at τ, 7.90, produced a singlet at τ, 9.6 ; indicating that this compound was the stereoisomer (253a) and hence the initial reduction product was (169a).

It was then necessary to study the hydrogenation of the olefin (152) with a series of palladium catalysts in an attempt to determine the optimum conditions for the production of the desired epimer (168). Accordingly, the olefin (152) was reduced over 1% and 5% palladium on carbon catalysts using absolute ethanol as the solvent. The former catalyst furnished small quantities of the saturated ketone (168) but the major component was unreacted starting material, even after prolonged reaction times. Reduction over the latter catalyst afforded the ketones (168) and (169a) in the ratio 10:1 after oxidation of the crude hydrogenation product with Jones reagent. Two successive

recrystallisations afforded the pure saturated ketone (168), homogeneous by g.l.c. (1% Q.F.1., R_t= 12 min.) ; $\nu_{max.}$ (CCl_4) 1730 and 1734 $cm.^{-1}$. In the n.m.r. spectrum (100 Mc./s.) the C(7) methyl protons were revealed as a doublet (3H) centred at τ, 9.2 (J=6 c.p.s.) which collapsed to a singlet at τ, 9.2 on irradiation at τ, 8.68. The C(7) methyl protons absorbed at similar fields in the n.m.r. spectrum of the corresponding alcohols (252a).

Both the epimers (168) and (169a) were sharp melting solids but the corresponding alcohols (252a) and (253a) could not be induced to crystallise. Since it was anticipated that these latter derivatives should have been crystalline solids, it was considered that these oily alcohols comprised a mixture of the C(9) epimers (i.e. the hydroxyl group syn or anti with respect to the anisole ring). Although g.l.c. analysis on several stationary phases (1% and 5% Q.F.1., 1% S.E.30) indicated the presence of one peak for the respective sodium borohydride reduction products, analytical t.l.c. displayed a marked 'tailing' of a diffuse spot. These alcohols were characterised as the corresponding carboxylic acids (252b and 253b). To summarise, catalytic hydrogenation of the keto-olefin (152) using 5% rhodium on carbon in ethyl acetate solution gives the stereoisomer (169a), whereas using 5% palladium on carbon in

absolute ethanol as solvent affords the stereoisomer (168), the latter compound possessing the required stereochemistry at C(7) for lycopodine (149).

At this point it seems pertinent to examine the state of our knowledge concerning the relative stereochemistry of the four keto-acetates (239b) (5% Q.F.1., R_t= 17.5, 20.5, 22.5 and 26 min.) obtained in the aldol cyclisation step, particularly in the light of their possible utility as precursors for synthetic approaches to other Lycopodium alkaloids, and also to aid in our understanding of the solvolytic behaviour of the corresponding p-toluenesulphonate esters (239d). Stereoformula (248) can be assigned to the acetate R_t= 22.5 min., both from spectral evidence and from the fact that it was one of the two compounds formed (as the corresponding ketols) by reduction of the enol-lactone (245) with lithium hydridotri-t-butoxyaluminate. On the reasonable assumption that these reductions are highly stereo-specific,* the stereoformula (249a) can be assigned to the other acetate (R_t = 17.5 min.), which is represented in the boat conformation of the methyl-bearing ring since the n.m.r. spectrum of a mixture of all four acetates (239b) showed no shielded C(7) methyl protons.

* see addendum for full discussion of the reductive rearrangement.

The remaining two acetates must therefore be equatorially disposed, and this postulate is confirmed by the fact that reduction of the diones (240) with lithium hydridotri-t-butoxyaluminate furnished two ketols whose acetates had g.l.c. R_t= 20.5 and 26 min., and which, on co-injection with the mixture of equilibrated keto-acetates (239b), gave peak enhancement of the remaining two peaks which were unaffected on co-injection with the "axial" acetates (242b). The predominant peak in the chromatogram of the mixed acetates (obtained under equilibrating cyclising conditions) would be expected to correspond to the stereoformula (255) since this is the thermodynamically most stable of the four acetates, and indeed, this is one of the two compounds formed in the reduction of the diones (240) with the complex hydride reagent. Thus the acetate with R_t= 26 min. is portrayed by formula (255) and so the remaining acetate with R_t= 22.5 min. must possess the stereoformula (256a) ((256) is not favoured for the same reason as (249) was eliminated).

It would, of course, be gratifying to confirm the above assignments by isolating each of the four epimers, but this could not be done by standard chromatographic procedures. Fortunately solvolysis has been a means of obtaining one of the isomers and, in the light of the earlier hydrogenation results, it was considered that (248) should be obtainable by catalytic reduction

of the enol-acetate (257) if 5% rhodium on carbon was the catalyst employed ; alternatively the enol-acetate should furnish (256 ⇌ 256a) when catalytically hydrogenated in the presence of 5% palladium on carbon. There are known cases[123] of catalytic reduction of enol-acetates using platinum oxide in dioxan as solvent ; moreover, in some instances these conditions can serve to hydrogenolyse the acetate group. Thus there may now exist another pathway to the saturated ketones (168) and (169a).

The enol-acetate (257) was prepared from the diones (240) using 1M acetic anhydride - 10^{-2}M perchloric acid in ethyl acetate solution.[124] The only reduction which has been attempted so far involved platinum oxide in dioxan as solvent, conditions which merely served to reduce the C(9) carbonyl group to the corresponding alcohol.

The earlier conformational discussion can now allow a brief consideration of the solvolytic behaviour of the four tosylates (239d). The "axial" tosylates (242c) both furnish the olefin (152), thus the obtained axial acetate must be derived from the equatorial derivatives (255 and 256a, acetate replaced by tosylate) and since evidence has already been presented for the stereochemistry of the acetate from solvolysis to be represented by formula (248) it seems most likely that the above acetate arises from the bis-equatorial isomer (255, acetate replaced by

tosylate).

With the obtention of the stereochemically pure keto-ester (168) in acceptable yield, the insertion of a nitrogen atom at C(1) was then considered. By direct analogy with the model series[74] the corresponding keto-acid (258a) was treated with sodium azide, ethylchloroformate and triethylamine but the derived acid-azide (258b) ($\nu_{max.}$ (film) 2400, 1720 and 1710 cm.$^{-1}$) was obtained in poor yield, the bulk of the reaction product being starting acid. This can be explained in terms of the azide anion attacking the more accessible carbonyl group of the intermediate mixed anhydride (259).

An alternate procedure which possibly involves the phosphite ester (258c) was then attempted. Treatment of a suspension of the keto-acid (258a) and activated sodium azide[125] in dry tetrahydrofuran, with phosphorus oxychloride and triethylamine in tetrahydrofuran resulted in complex mixtures, and, on subsequent changing of the solvent to benzene, the proportion of the desired azide formed still did not increase. The infrared spectrum of the neutral oil showed the expected azide bands[126] but, in addition, displayed intense absorption at 1800 and 1740-1720 cm.$^{-1}$, indicating that the sym anhydride or acid chloride (258d) was present. However, using an inverse addition of the acid (258a) to a suspension of phosphorus oxychloride,

triethylamine and activated sodium azide in benzene, a high yield of neutral non-crystalline material, whose infrared spectrum was fully compatible with the structure (258b), was obtained. This azide was then heated under reflux in dry toluene for twenty hours to afford a non-crystalline isocyanate (258e) in good yield ($\nu_{max.}$ (film) 2600 and 1720 $cm.^{-1}$), which was then heated with a solution of benzyl alcohol in toluene to furnish an oil in 65% yield whose infrared and mass spectra were in agreement with the structure (258f) for the benzyl carbamate.

Treatment of (258f) with reagent-grade hydrogen bromide - acetic acid solution met with failure since the desired product (i.e. the amine hydrobromide (258g)) was an extremely hygroscopic substance. However, when a solution of the benzyl carbamate (258f) in anhydrous ether was treated with dry hydrogen bromide[127] and the reaction mixture then heated in vacuo to remove the major volatile contaminant, benzyl bromide, the resulting amine hydrobromide (258g) was induced to solidify by trituration with anhydrous ether. The infrared spectrum of this solid was fully compatible with the structure (258g), but this product was very unstable, e.g. exposure of the white solid to air for a matter of one minute was sufficient to produce a purple oil. Nevertheless, treatment of the amine hydrobromide with acetic anhydride and pyridine gave a non-crystalline product whose infrared spectrum

was in complete agreement with the acetamide formulated as (258i).

With this result in hand several attempts were then made to convert the amine hydrobromide (258g) to the key intermediate pyruvamide (258j = 154). A mixture of pyruvic acid, triethylamine, the amine hydrobromide (258g) and dry tetrahydrofuran was treated with a solution of phosphorus oxychloride and triethylamine in dry tetrahydrofuran. This procedure gave a low yield of a neutral purple oil which was purified by preparative t.l.c. to furnish the pyruvamide (154) as an oil, $\nu_{max.}$ (film) 3400, 1720, 1680 and 1510 $cm.^{-1}$, whose mass spectrum showed the correct molecular weight and fragmentation pattern for the proposed structure. Figure 3 illustrates the major breakdown patterns exhibited by the pyruvamides (154) and (177d).[93]

In the model series, the ultraviolet spectrum of the pyruvamide (177d) showed $\lambda_{max.}$ 241 nm. shifting in base to 275 nm..[93] The product obtained from the above reaction sequence showed no such bathochromic shift, which might suggest that the ring closure from the pyruvamide (154) to the tetracyclic enone lactam (155) will not be as facile as in the model series. In addition, the low yields encountered here demanded an examination of alternative methods of obtaining the pyruvamide.

On the assumption that the major difficulty lay in the formation and reaction of the amine hydrobromide (258g), the isocyanate (258e) was heated with concentrated hydrochloric acid[128] and toluene, the aqueous layer separated after one hour, evaporated to dryness and then thoroughly dried by azeotropic distillation with toluene. The amine hydrochloride (258h) was obtained as a colourless glass, which on treatment with acetic anhydride and pyridine was converted in good yield to a non-crystalline product identical with the acetamide (258i) obtained above. However, sequential treatment of the amine hydrochloride with the pyruvoylating reagent once again resulted in a low overall conversion to the desired pyruvamide.

In order to overcome these difficulties, an attempt was then made to prepare the ketal-amine (260) since the use of this intermediate would obviate the necessity of handling the hygroscopic and extremely sensitive amine hydrobromide (258g). The ethylene ketal-ester (261a) was prepared by the standard procedure, but the C(1) ester function was completely inert to the alkaline hydrolysis conditions which had proved completely satisfactory in the case of the keto-ester (168). This conversion was finally achieved by treatment of the ketal-ester (261a) under the extremely forcing conditions of potassium hydroxide in refluxing ethylene glycol.[129]

Attempts to convert this acid (261b) to the corresponding azide (261c) by either the ethyl chloroformate or phosphorus oxychloride procedures resulted in complex product mixtures with very little infrared absorption due to an acid azide. In both cases, strong infrared maxima were evident at 1720 and 1230 $cm.^{-1}$. In an alternative attempt to prepare the acid azide (261c) via the acid chloride (261d), the acid (261b) was heated with oxalyl chloride in benzene, but the starting acid was recovered quantitatively.

It therefore appears that the model sequence for the construction of ring A is not entirely applicable to this synthetic route. Alternative procedures are under investigation e.g. a Beckmann rearrangement on the ketal oximino tosylate (262) might furnish the acetamide (261e) followed by transacylation with pyruvic acid. Alternatively, the isocyanate (263) on treatment with the newly investigated anion (264)[130] could furnish the pyruvamide (261f) directly after regeneration of the thioketal function in compound (265).

ADDENDUM

Reductive rearrangement of δ-enol-lactones*

In 1964, in these laboratories, it was discovered that the enol-lactone (266) on treatment with lithium hydrido-tri-t-butoxy aluminate in tetrahydrofuran solution followed by an acid work-up gave the thermodynamically less stable bicyclic ketol (267) in high yield.[65] This interesting result initiated the studies described below which were designed (a) to gain further insight into the reaction mechanism and (b) to investigate the possibility of using such reactions as viable synthetic methods.

In order to determine the role played by the position of the double bond in this rearrangement the two enol-lactones (268) and (269) were prepared as follows. The synthesis of the propionic ester (270a) and its subsequent hydrolysis to the corresponding acid (270b) was carried out using the literature procedures.[131, 132] It had been reported that when the above keto-acid was treated with sodium acetate and acetic anhydride, the tetrasubstituted

*The following work was done in collaboration with Dr. T.Stewart.

enol-lactone (268) was obtained as the sole product.[132] In our hands, however, this reaction furnished a two component mixture (268) and (269) in the ratio 4:1. Column chromatography on silica gel effected an efficient separation of these components; the less polar compound was assigned the structure (268) on the basis of the infrared spectrum, $\nu_{max.}$ (CCl_4) 1772 and 1709 $cm.^{-1}$; and the n.m.r. spectrum which did not show absorption in the vinylic region, indicating the presence of a tetrasubstituted double bond. The more polar compound was identified as the enol-lactone (269) on the following spectral grounds; $\nu_{max.}$ (CCl_4) 1766 and 1683 $cm.^{-1}$; and in its n.m.r. spectrum this compound revealed a narrow multiplet (1H) centred at τ, 4.73 assigned to the vinylic proton. Both compounds were unstable in air, hydrolysing rapidly to the keto-acid (270b).

Treatment of the enol-lactone (268) with one molar equivalent of lithium hydridotri-t-butoxy aluminate,[133] furnished only the keto-aldehyde (271), whereas under identical conditions the enol-lactone (269) afforded the ketols (272) and (273) in the ratio 19:1 (19% yield) (estimated as the corresponding acetates by g.l.c. analysis); accompanied by 1-hydroxy-2-oxabicyclo(4,4,0)decane (274) and the vinyl ether (275). The structural and stereochemical

assignments (272), (273), (274) and (275) have been documented elsewhere.[98] Several modification of the reaction conditions were then made, but no significant changes in yield or product distribution were observed.

Hence, initially it appeared that (a) the rearrangement process occurred only when the double bond was exocyclic to the lactone ring and (b) substituted derivatives afforded the derived axial ketols in much higher yield than in the unsubstituted case.

The preparation, reduction and product analysis of the enol-lactones (193), (213) and (245) have already been briefly described. In all these compounds the presence of the C(6) ester function forces the enolic double bond to adopt the exocyclic position.

The keto-aldehyde (183) was oxidised with Jones reagent to give an oily keto-acid (192a) and a neutral product. The acidic fraction was characterised as the corresponding methyl ester (192b) ($\nu_{max.}$ (film) 1740, 1720, 1710 and 1200 $cm.^{-1}$) homogeneous by g.l.c. analysis on several stationary phases. The neutral component proved to be the dione (191) indicating that the acidic oxidising medium had induced an aldol ring closure with subsequent oxidation of the formed ketols (189a) and (190a). Treatment of the above acid (192a) with

sodium acetate and acetic anhydride gave, in low yield, the enol-lactone (193) ($\nu_{max.}$ (CCl_4) 1780, 1740 and 1675 $cm.^{-1}$) whose n.m.r. spectrum revealed a broad quartet (1H) centred at τ, 4.5 (J= 3 c.p.s.). This enol-lactone was homogeneous on both g.l.c. and t.l.c. examinations and was extremely sensitive to moisture and air. Other methods of preparing this enol-lactone involving the acid chloride (192c) were investigated in an attempt to improve the yield, but these met with no greater success than the usual procedure.

Reduction of the enol-lactone (193) with lithium hydridotri-t-butoxyaluminate furnished an oil ($\nu_{max.}$ (film) 3,500, 1740-1720 $cm.^{-1}$) which afforded two main components on column chromatography. The less polar fraction consisted of a mobile neutral oil ($\nu_{max.}$ (CCl_4) 3,440, 1730 and 1680 $cm.^{-1}$) which could not be obtained in a pure state, but by analogy with the other studies was thought to be a mixture of the substituted 2-oxabicyclo(4,4,0)decane (276) and the vinyl ether (277). The second fraction proved to be the axial ketol (190a) ($\nu_{max.}$ (film) 3,500 and 1740-1720 $cm.^{-1}$) as indicated by g.l.c. analysis of the corresponding acetate (190b) (1% P.E.G.A., R_t= 6.2 min.) which, on co-injection with a sample of mixed acetates (189b) and (190b) (formed by the aldol-acetylation sequence on the keto-aldehyde (183))

gave peak enhancement with the minor acetate. The structural proof and stereochemical assignment (190a) have been discussed earlier.

The synthesis of the keto-acid (212) could not be accomplished using the standard Jones oxidation procedure. However, partial oxidation of the keto-aldehyde (209) was achieved using moist silver oxide, but the strongly alkaline medium also served to effect a retro-Michael reaction giving the β-keto-ester (205). In addition, when the keto-aldehyde (209) was treated with chromium trioxide and pyridine[134] only small quantities of the desired acid were produced, the major product after several attempts being starting material. Eventually, neutral conditions involving potassium permanganate and water, furnished the desired keto-acid (212) in acceptable yield. Treatment of this crystalline keto-acid with sodium acetate and acetic anhydride furnished the crystalline enol-lactone (213) ($\nu_{max.}$ (KCl disc) 1750, 1721 and 1680 $cm.^{-1}$) whose n.m.r. spectrum revealed a triplet (1H) centred at τ, 4.6 (J= 3 c.p.s.) assigned to the vinylic proton.

When this enol-lactone was treated with lithium hydrido-tri-t-butoxyaluminate in the usual manner and a portion of the crude product acetylated, g.l.c. examination of the

product revealed two components in the ratio 1:5 (1% P.E.G.A., R_t= 7.4 and 5.6 min. respectively). Co-injection of this product with a sample of the acetates derived from the base induced aldol cyclisation of the keto-aldehyde (209) gave enhancement with both peaks. The predominant epimer produced by this complex hydride reduction, was thought to be the axial ketol (211a) by analogy with the earlier studies. A complete separation of the epimers (210a) and (211a) was never achieved using either column chromatography or preparative t.l.c., the optimum purity in either case being in the order of 90%.

When the crude keto-aldehydes (238) were oxidised with Jones reagent, the corresponding keto-acids (246) and diones (240) were produced. Recrystallisation of the acidic product afforded a sharp-melting epimer, whereas an analytical sample of the solid dione, m.p. 163-7°, showed one peak on g.l.c. (Q.F.1) but revealed two spots on analytical t.l.c.. Obviously the mildly acidic oxidation conditions had caused partial ring closure of the keto-aldehyde (238) to give the ketols (239a) which in turn were oxidised to the diones (240). Treatment of the keto-acid (246) with acetic anhydride and sodium acetate gave not only a single crystalline enol-lactone (245) but also

the enol-acetate (257) in the ratio 1:1, which were separable by preparative t.l.c.. The enol-lactone (245) showed infra-red maxima at 1740, 1720 and 1680 $cm.^{-1}$; and its n.m.r. spectrum revealed the vinylic proton as a triplet (1H) centred at τ, 4.6 (J= 4 c.p.s.). The enol-acetate (257) showed $\nu_{max.}$ (KCl disc) 1746 and 1728 $cm.^{-1}$, and its n.m.r. spectrum revealed a singlet (3H) at τ, 8.56, assigned to C=C-Me. Formation of this enol-acetate can be rationalised in terms of the mixed anhydride (278) undergoing nucleophilic attack by the carbanion at C(5) as illustrated to furnish the diones (240) which would then be converted into the enol-acetate under the reaction conditions. Recently,[124] it has been shown that treatment of a δ-keto-acid with a solution of 1M acetic anhydride, 10^{-3}M perchloric acid in ethyl acetate solution, leads exclusively to the corresponding δ-enol-lactone, and indeed the keto-acid (246) was transformed into the enol-lactone (245) in high yield on treatment with the above reagent. Reduction of this enol-lactone with lithium hydridotri-t-butoxyaluminate, followed by acetylation of the product, furnished the axial acetates (242b) in the ratio 1:1 as estimated by g.l.c. analysis.

In general, it has been found that the yield of the axial ketol obtained by the reduction of these substituted enol-lactones was in the order of 60-80% The steroidal enol-lactone (279) on similar reduction has been shown to give similar yields of the corresponding bicyclo(3,3,1)-nonane axial ketol.[98]

As mentioned earlier, complex hydride reduction of the tricyclic enol-lactone (245) gave two ketols in the ratio 1:1 and in order to explain these results in terms of a single enol-lactone, the existance of the free keto-aldehyde at some stage during the reduction has to be invoked, since equilibration of the C(7) methyl function could readily be accommodated at this stage. The sharp melting point and the homogeneity of the enol-lactone by analytical t.l.c. and g.l.c. (several stationary phases) all suggest that this enol-lactone was stereochemically pure, but no definite assignment can be made with regard to the stereochemistry of the C(7) methyl group i.e., (280a) or (280b).

Initially,[75] it was considered that any mechanism for this reductive rearrangement of δ-enol-lactones would have to accommodate both the necessity for the double bond to be exocyclic with respect to the lactone ring and the

stereospecific formation of the thermodynamically less stable bicyclic ketol. One such scheme involves an initial intramolecular transfer of the trialkylaluminium residue from oxygen attached to the carbon atom initially attacked by the hydride ion, to the second (enolate) oxygen, as depicted in diagram (281). If this involved removal of R_3Al and re-entry to give (282), with the accompanying possibility of ketonisation and alternative enolisation of the ketonic carbonyl group in the interim, then one would expect to obtain a common intermediate, and hence a common product distribution from the lactones (268) and (269). This is not the case, and it therefore seems that the enolate structure is preserved throughout.

An alternative method of explaining the retention of enolate structure is to consider another representation of (281), viz., (283)-(284) in which the strong gegenion Li^+ is utilised as a means of retaining the enolate structure. Whether one considers (282) or (284), examination of models indicates that they are both capable of rearrangement by a cyclic process as shown, and moreover that this cyclic process must give rise exclusively to axial aluminate by the first mechanism or to axial lithium alkoxide by the second process described above. Minor amounts of equatorial epimers may

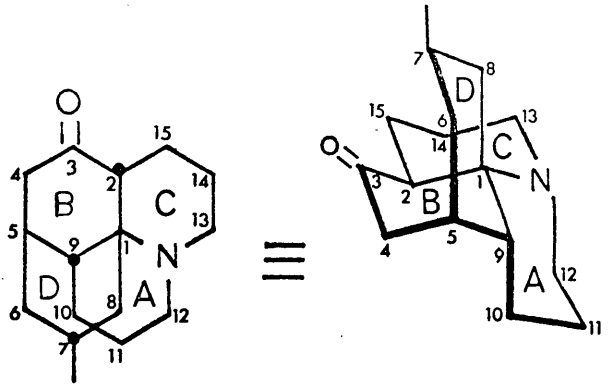
arise subsequently from the axial ketols by equilibration of the β-hydroxy-ketone system, when the reaction conditions are not strictly anhydrous, or before an excess of aqueous acid is present during work-up, since in either case free base could be liberated to effect such an equilibration.

That the aldehyde functionality in (282) is in fact formed gains support from the observation that the reduction of the sterically pure enol-lactone (245) gave rise to two ketols in the ratio 1:1, whose relative stereochemistries are formulated as (285) and (286). It would be advantageous to isolate the ketol (286) and to establish its relative stereochemistry about C(6) and C(7) as this would furnish more evidence in favour of the proposed mechanism to the extent that both the involved oxygen atoms must be cis with respect to each other.

These mechanisms can also rationalise the finding that the tetrasubstituted enol-lactone (268) gives rise only to the keto-aldehyde (271), since in the intermediate (287) there is no opportunity for a similar intramolecular rearrangement. Consequently in the presence of one molar equivalent of the hydride reagent the keto-aldehyde was the sole product. However, one can suggest that another type of intramolecular cyclic process might take place so

that the intermediate in this case (287) would lead to the spiro(5,3)nonane ketol (288) which would probably undergo a facile retro-aldol reaction on work-up, to furnish the observed product (271). Tamm[135] has recently carried out the reduction of the steroidal enol-lactone (289) using lithium aluminium hydride and the product isolated seems to be the cyclobutyl-diol (290). This result obviously demands a similar reduction of the enol-lactone (268) to be carried out, in order to clarify this point.

Although the above evidence does not constitute a rigorous proof of the proposed mechanism it has provided the impetus for a fuller investigation. Direction for further study can be delineated in terms of the role played by the lithium and aluminium species, and it is feasible to suggest that other moieties could participate with equal effectiveness. In these laboratories work is now in progress to substantiate these conclusions.



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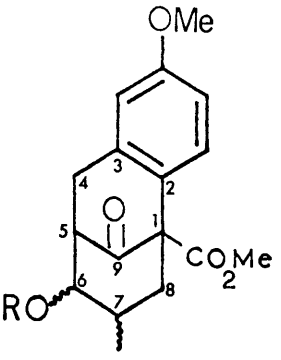
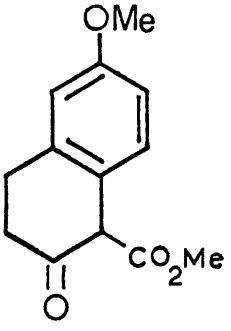


150 a, R=H
b, R=Ac



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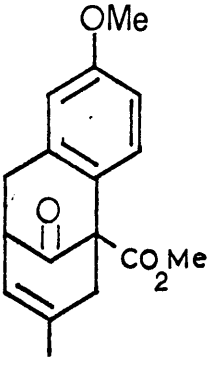

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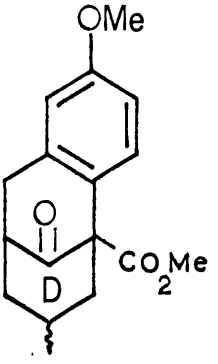

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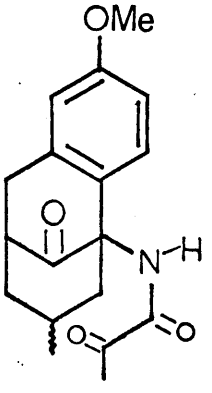

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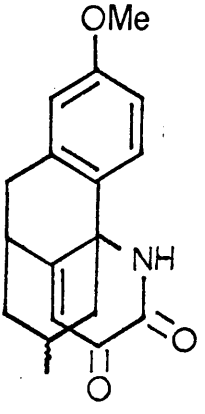

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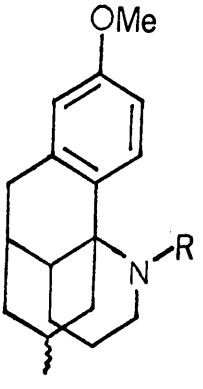

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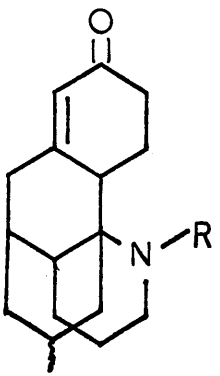

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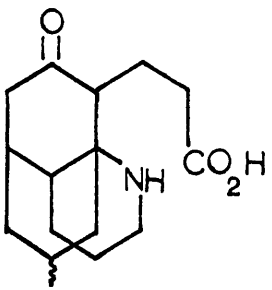

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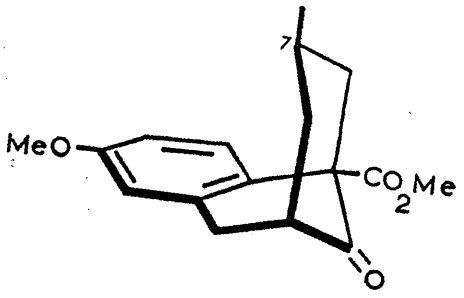

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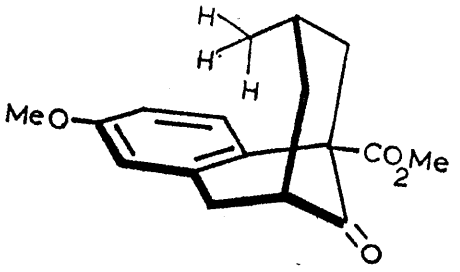

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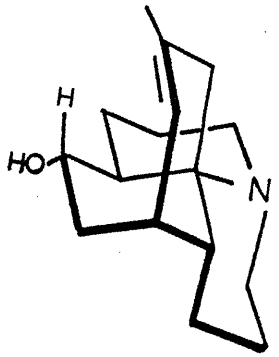

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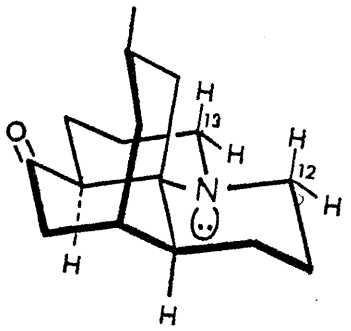

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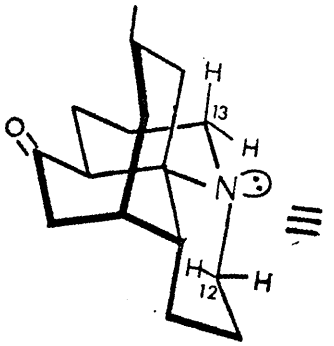

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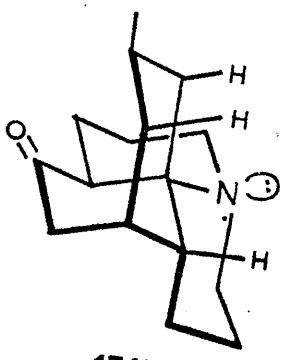

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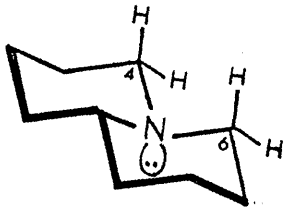

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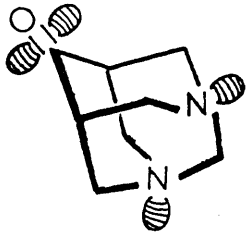

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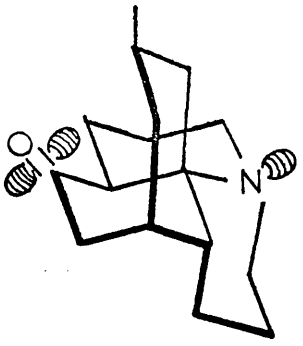

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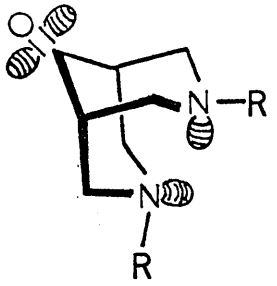

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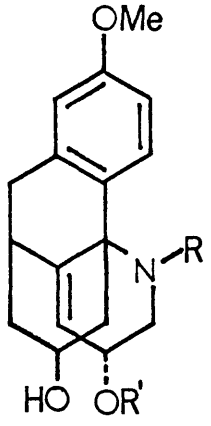
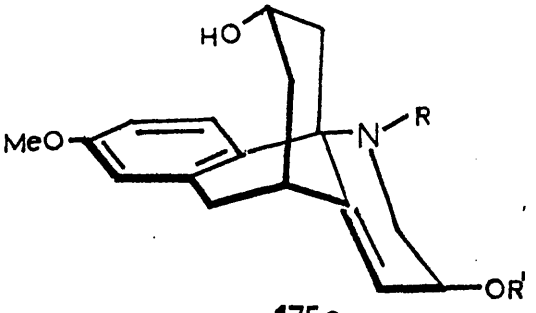


175 a, R' = Ts
b, R' = $COC_6H_2Cl_3$



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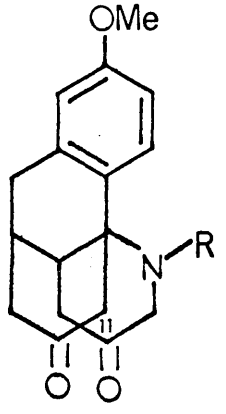

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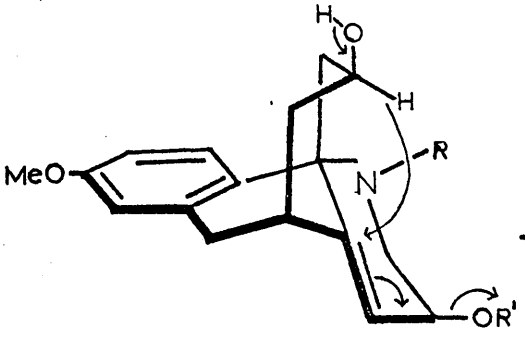

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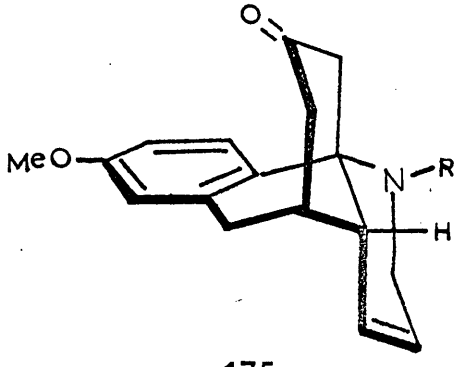

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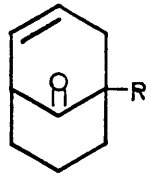
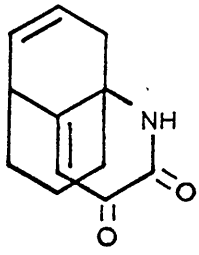


a, R = CO_2Et
b, R = $NHCO_2CH_2Ph$
177 c, R = NH_2·HBr
d, R = $NH_2COCOMe$



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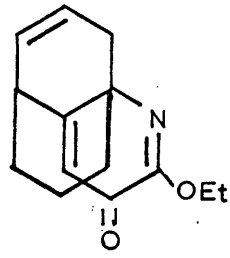

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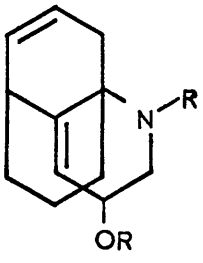

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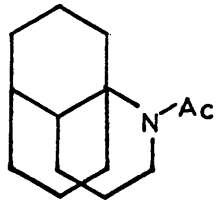
b, R = Ac



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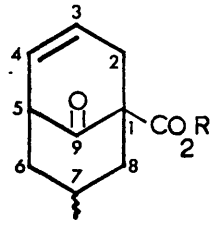
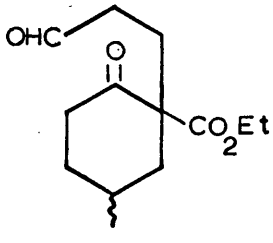


a, R = Et
182 b, R = H
c, R = Me



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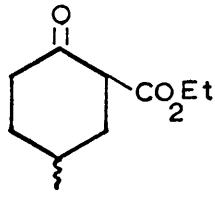

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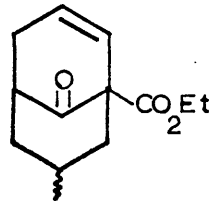

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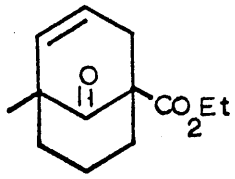

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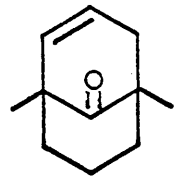

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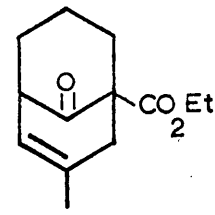

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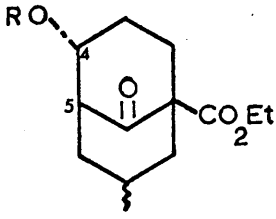

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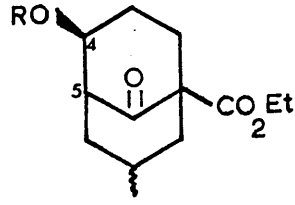
c,R=Ts



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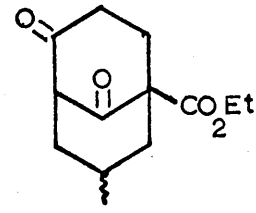

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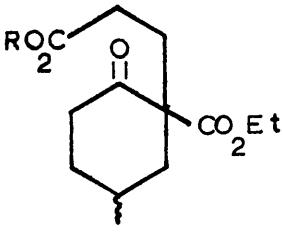

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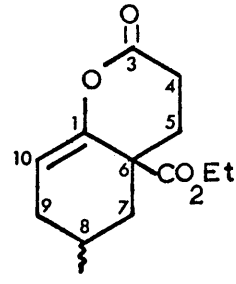
b,R=Me



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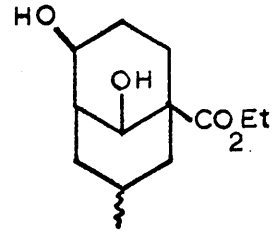

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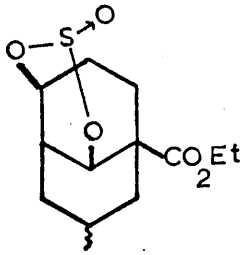

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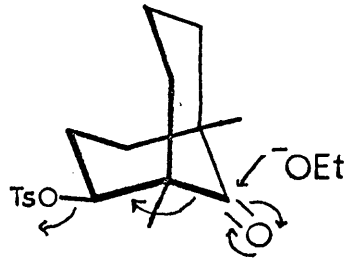

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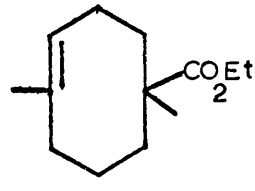

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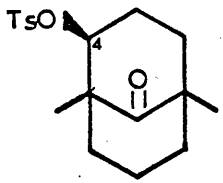

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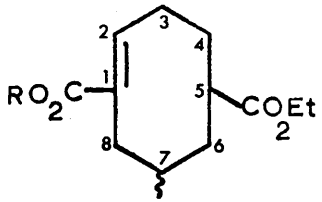
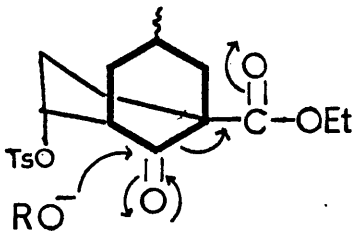
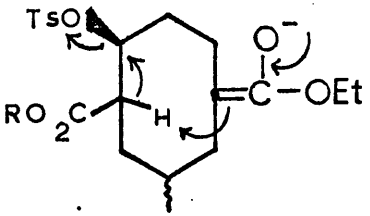


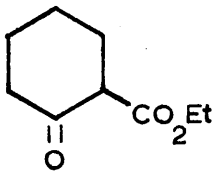
199 a, R=Et
b, R=^{t}Bu



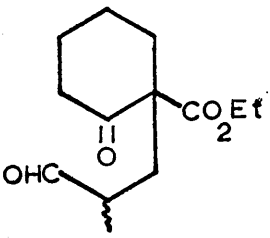
200a



200b



201



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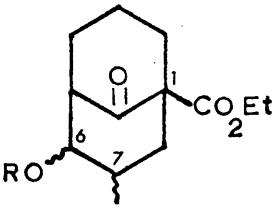
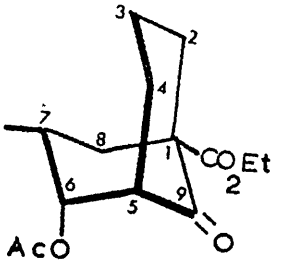
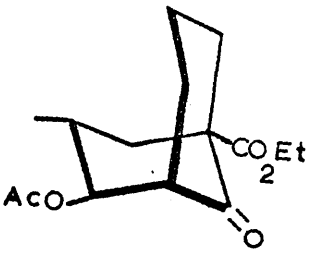


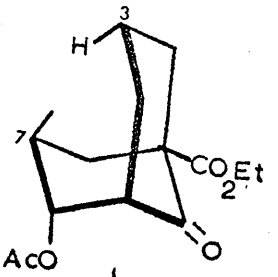
203 a, R=H
b, R=Ac



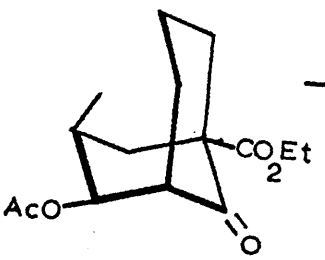
204a



204b



204c



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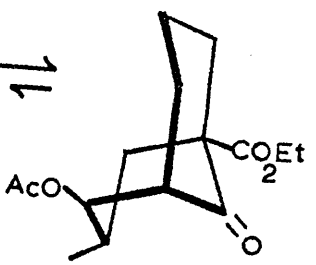

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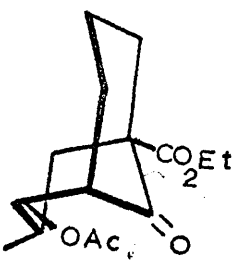

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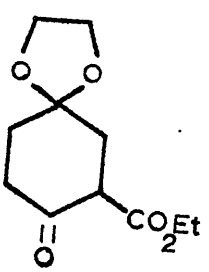
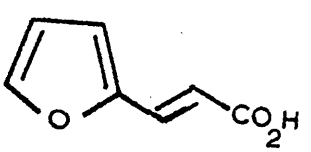


205



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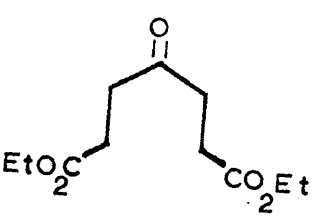
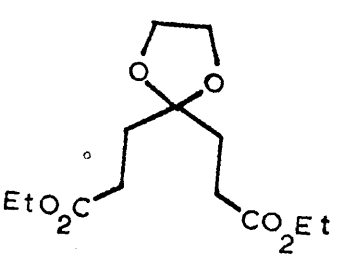
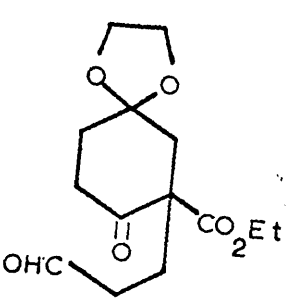


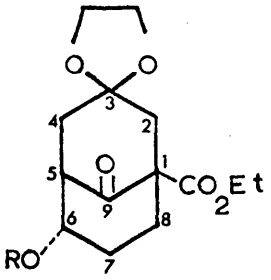
207



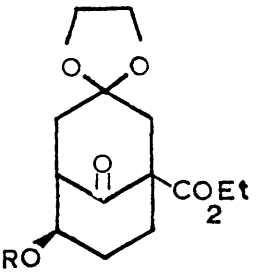
208



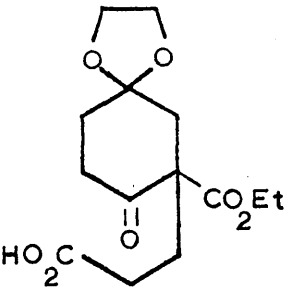
209



a R=H
b R=Ac
210 c R=CO_2Et
d R=Ts



a R=H
b R=Ac
211 c R=CO_2Et
d R=Ts



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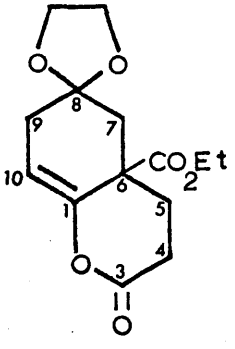

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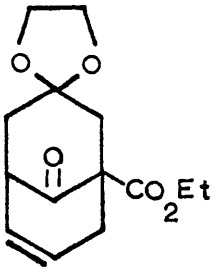
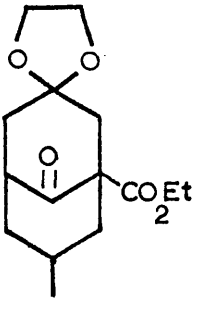
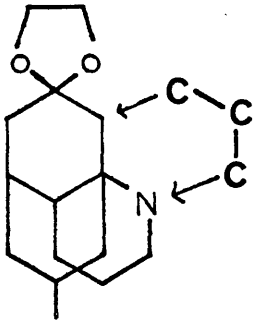


214



215



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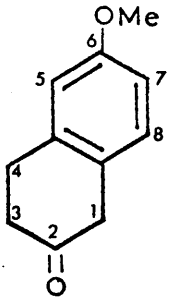

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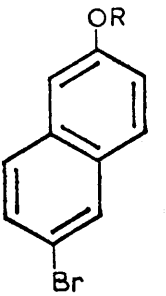
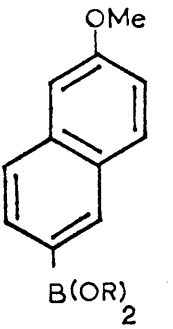
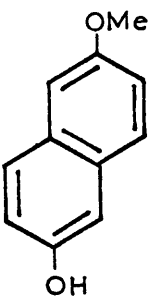


218 a,R=H b,R=Me



219 a,R=Me b,R=H



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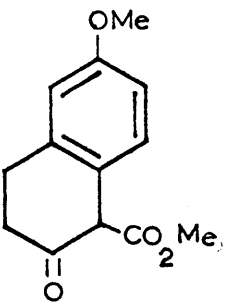

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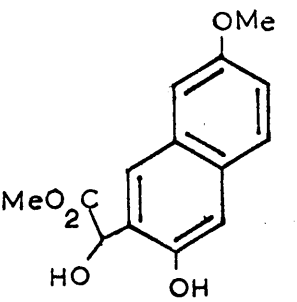

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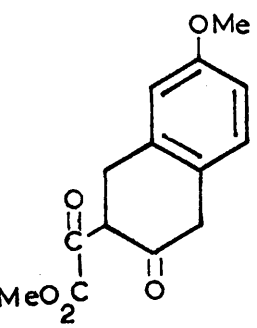
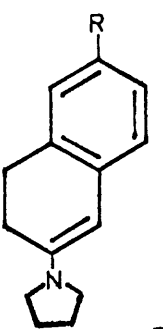
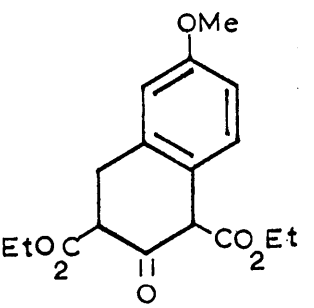


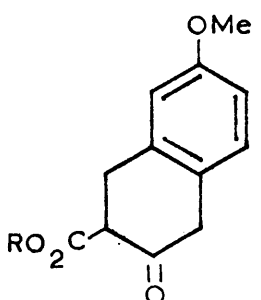
223



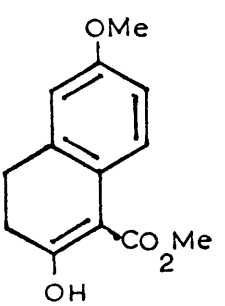
224 a,R=H b,R=^{i}Pr c,R=OMe



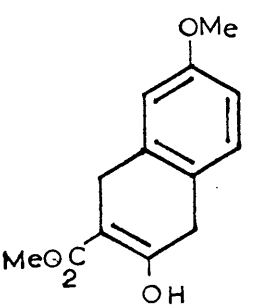
225



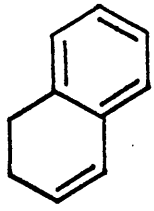
226 a,R=Me b,R=H



227



228



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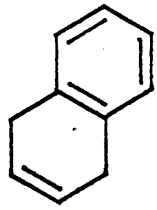

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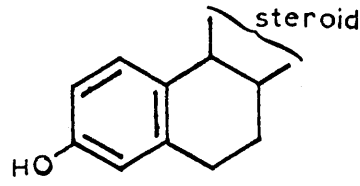
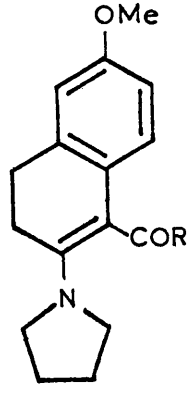
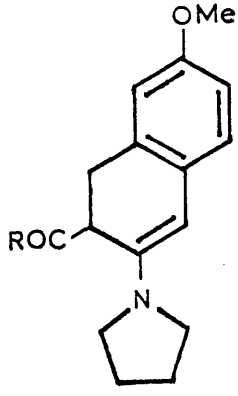


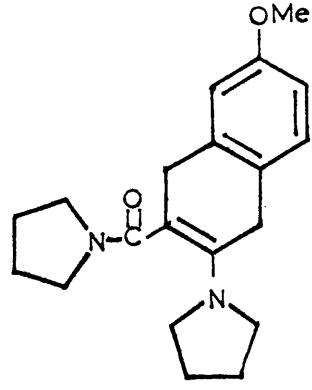
231



232 a, R = OMe
b, R = C_4H_8N



233 a, R = C_4H_8N
b, R = OMe



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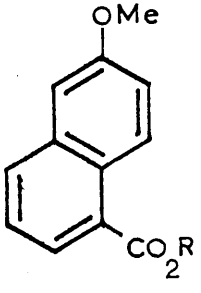
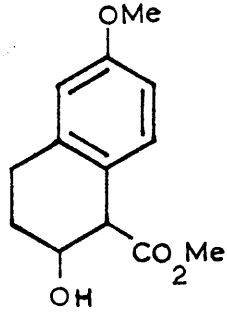
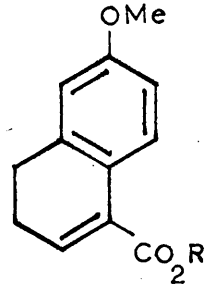


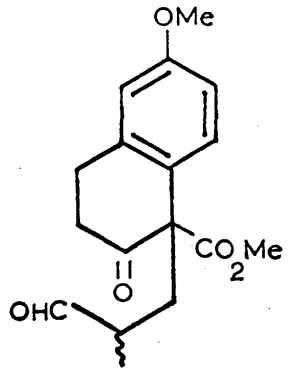
235 a, R = H
b, R = Me



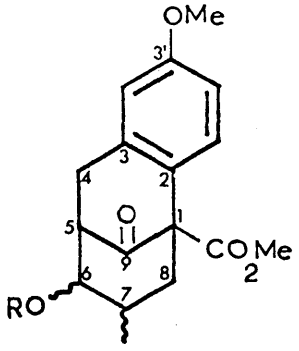
236



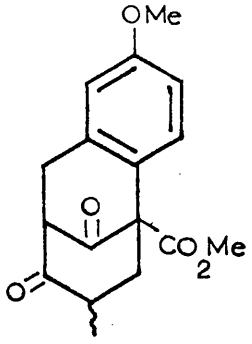
237 a, R = Me
b, R = H



238



a, R=H
b, R=Ac
239 c, R=CO Et
d, R=Ts 2



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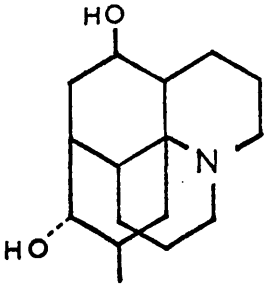
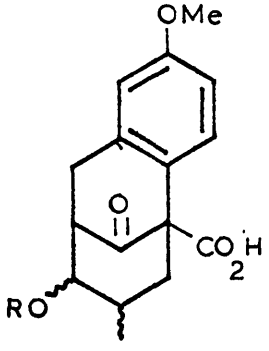
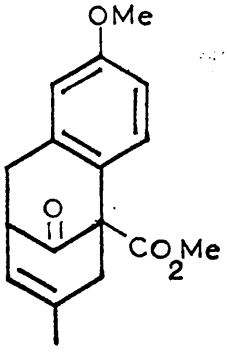


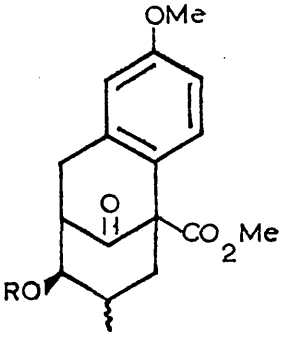
26a



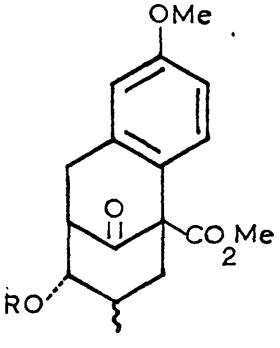
241 a, R=H
b, R=Ac



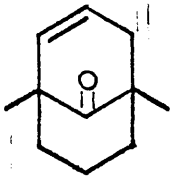
152



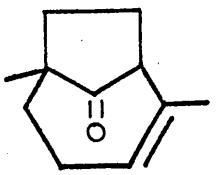
a, R=H
242 b, R=Ac
c, R=Ts



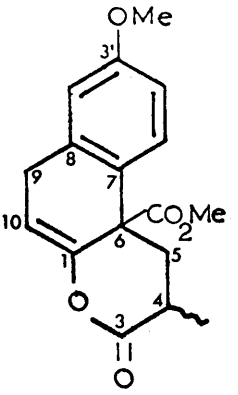
a, R=H
243 b, R=Ac
c, R=Ts



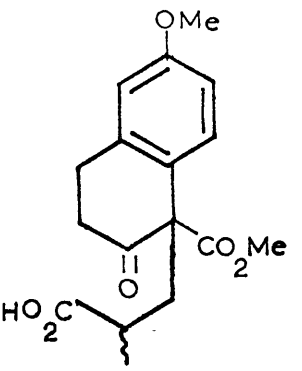
187



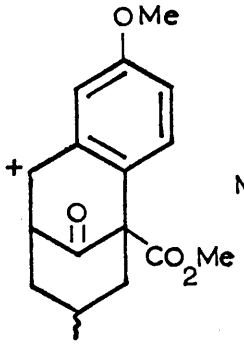
244



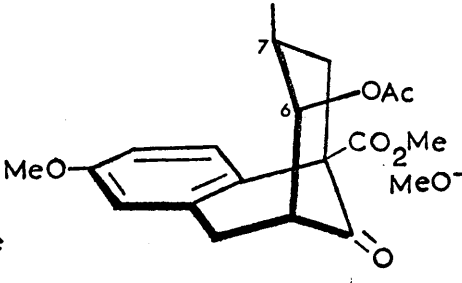
245



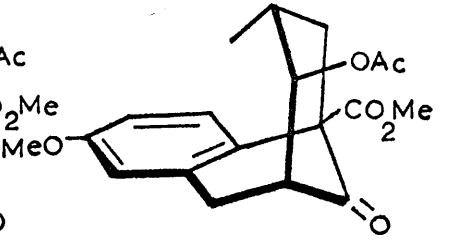
246



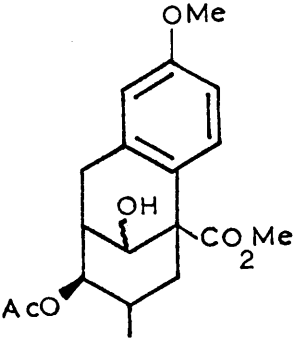
247



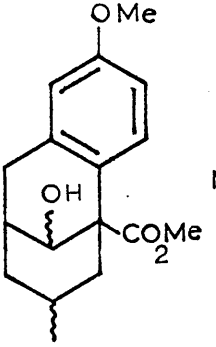
248



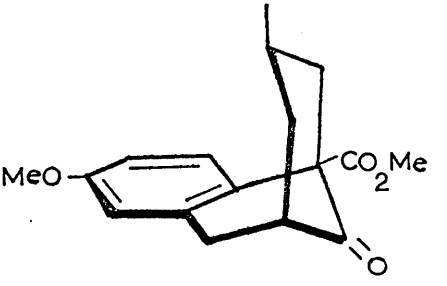
249



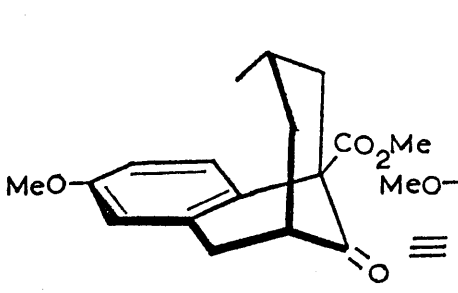
250



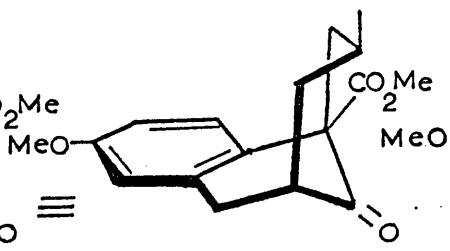
251



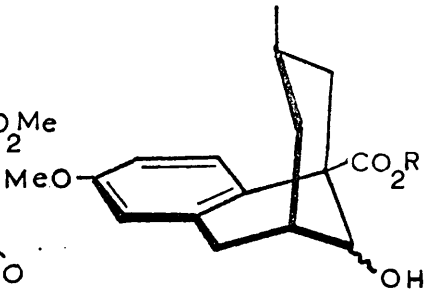
168



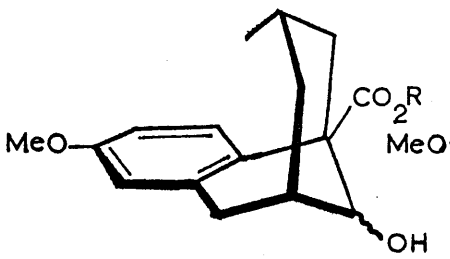
169



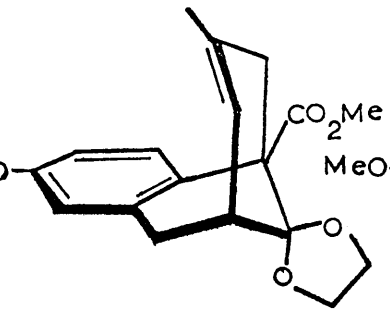
169a



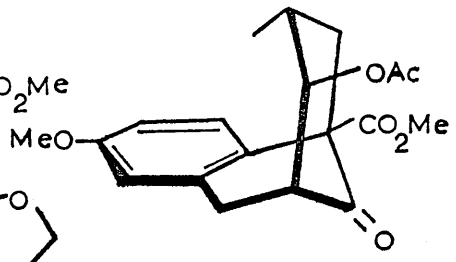
252 a, R=Me b, R=H



253 a, R=Me b, R=H



254



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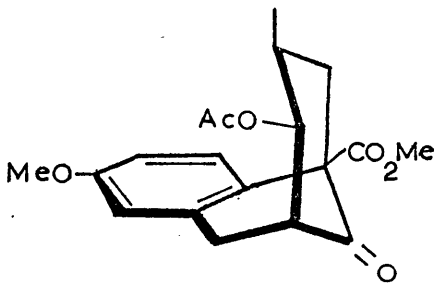
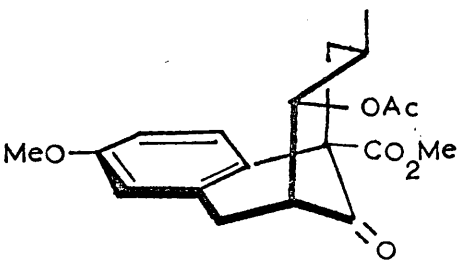
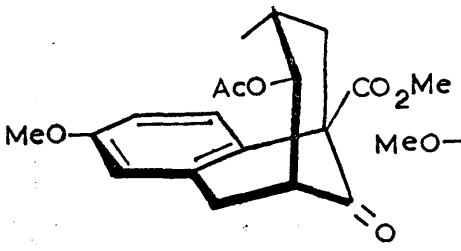
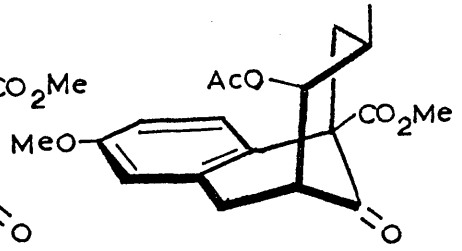


255

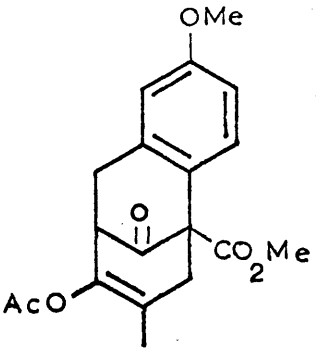


249a



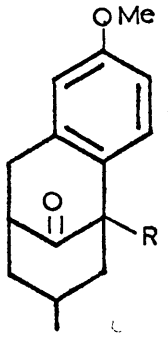


256 ≡ **256a**



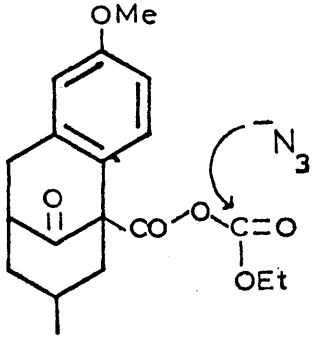
257

a, R = CO_2H
b, R = CON_3
c, R = $COPOCl_2$
d, R = COCl
e, R = NCO

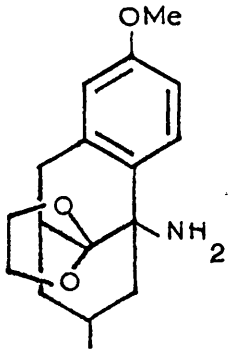


f R = $NHCO_2CH_2Ph$
g R = $NH_2 \cdot HBr$
h R = $NH_2 \cdot HCl$
i R = NHCOMe
j R = NHCOCOMe ≡ 154

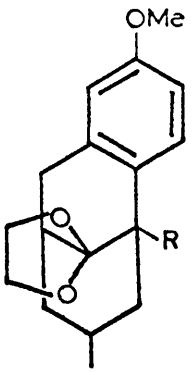
258



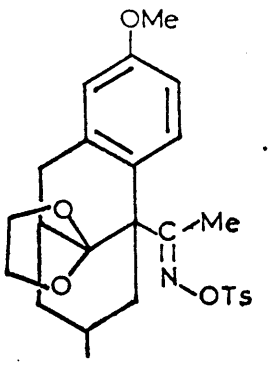
259



260



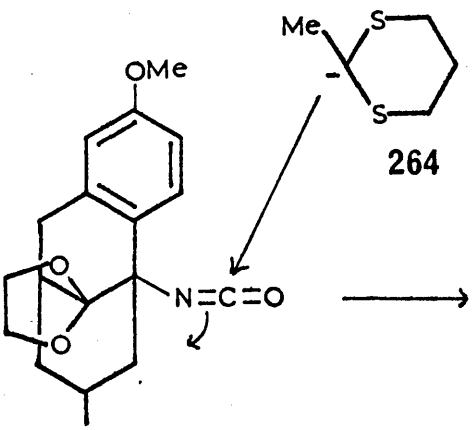
261



262

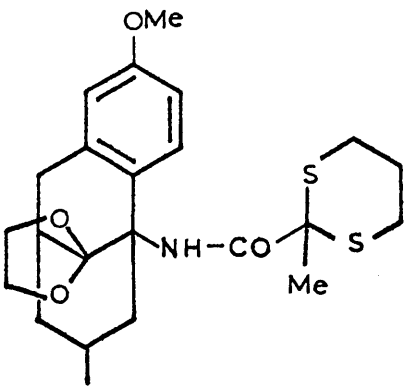
a, R = CO_2Me
b, R = CO_2H
c, R = CON_3
d, R = COCl
e, R = NHCOMe
f, R = NHCOCOMe

261e



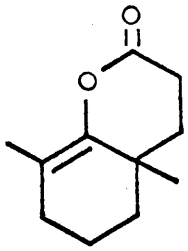
264

263

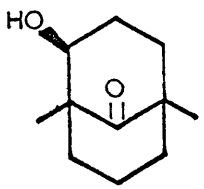


265

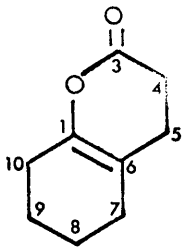
261f



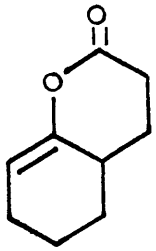
266



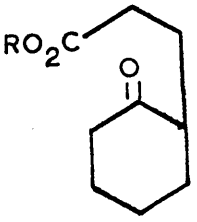
267



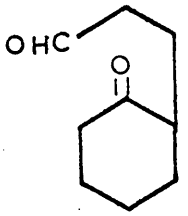
268



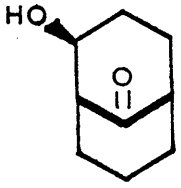
269



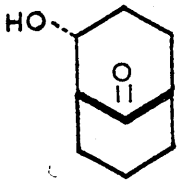
270 a,R=Et b,R=H



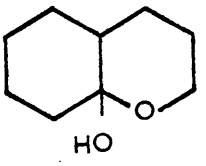
271



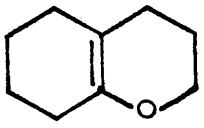
272



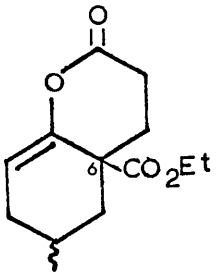
273



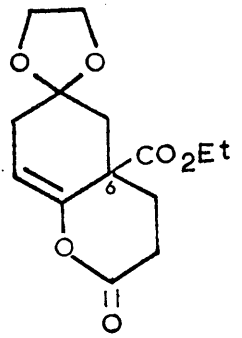
274



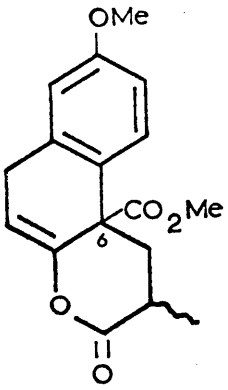
275



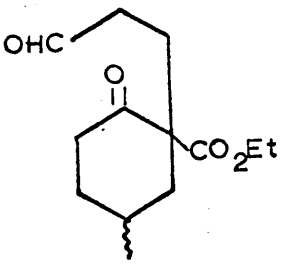
193



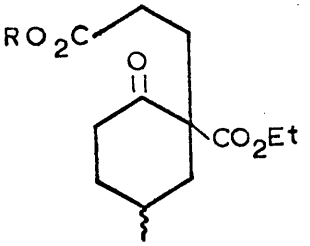
213



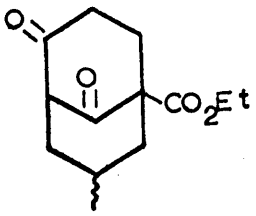
245



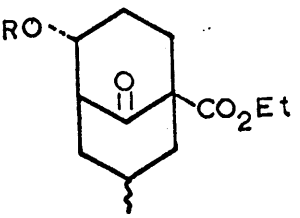
183



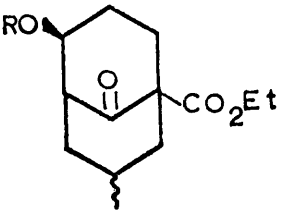
192 a, R = H
b, R = Me
c, R = Cl



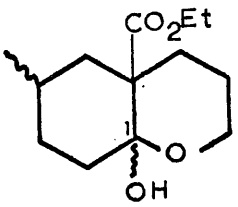
191



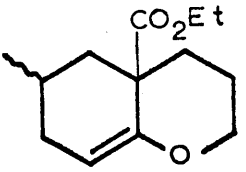
189 a R = H
b R = Ac



190 a R = H
b R = Ac



276



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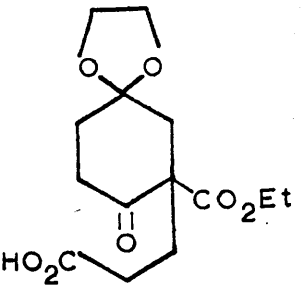

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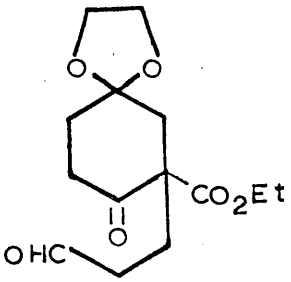
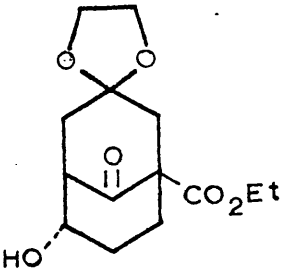
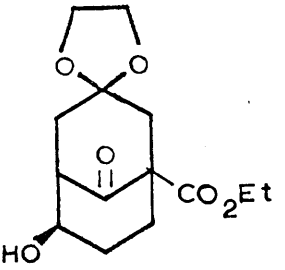


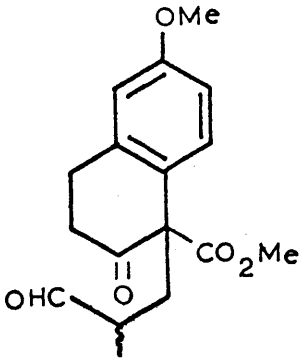
209



210a



211a



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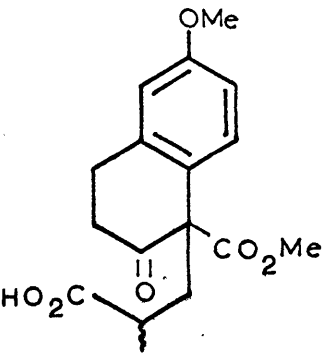

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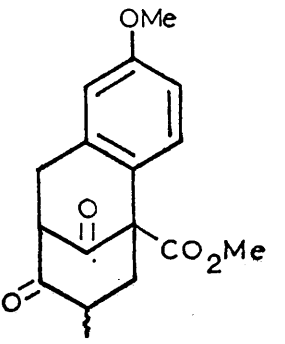

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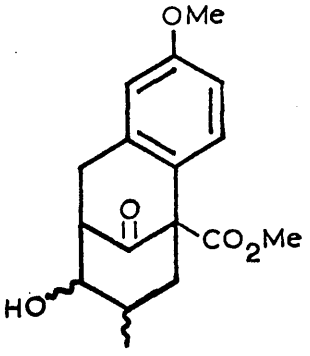

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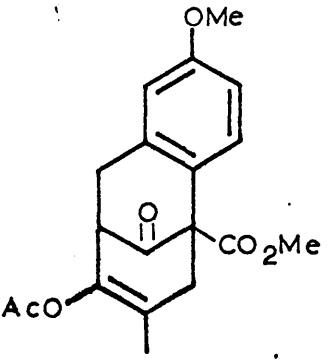

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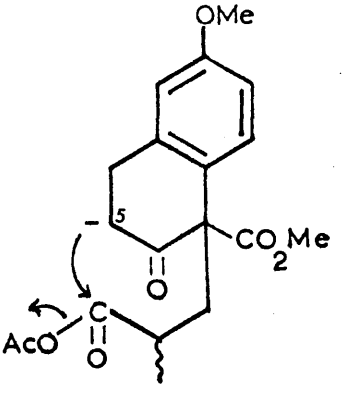

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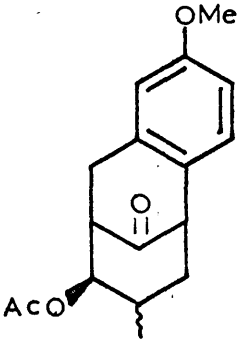

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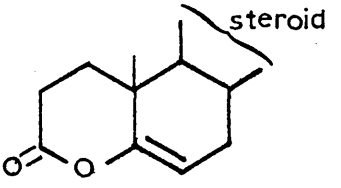

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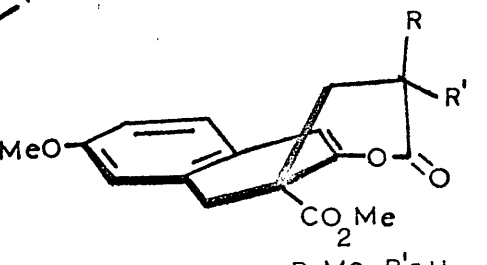
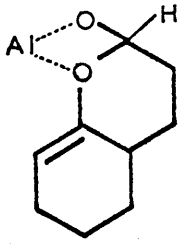


280 a, R=Me, R'=H
b, R=H, R'=Me



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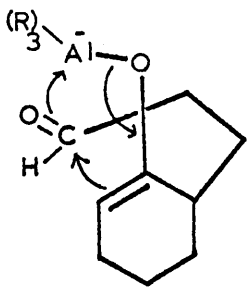

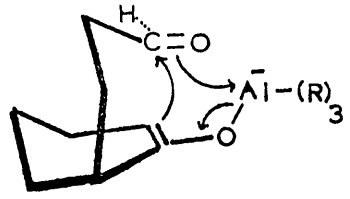

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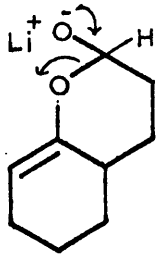

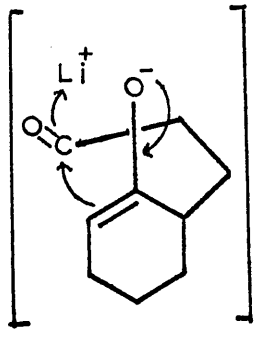

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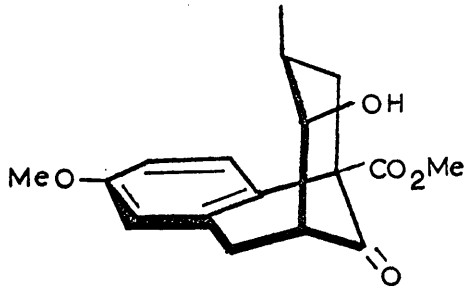

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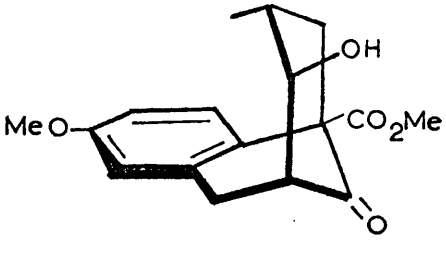

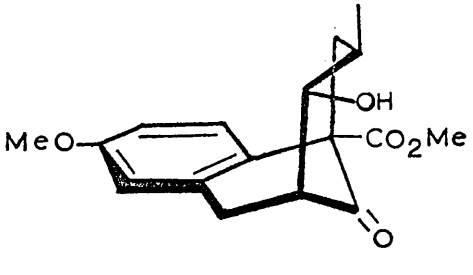

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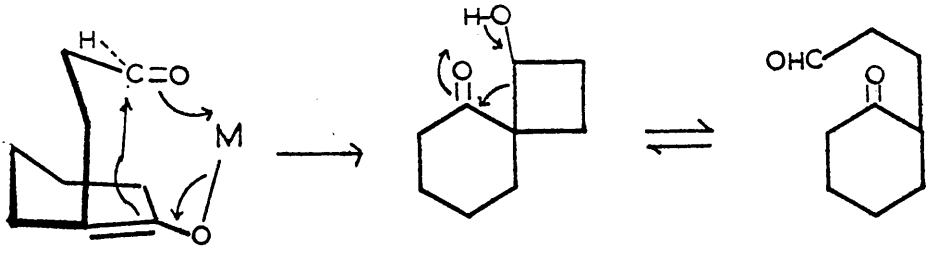

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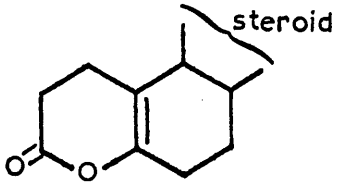

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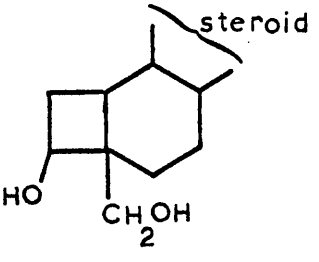

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TABLE 3

Pyrolysis Studies.

Temp. (°C)	Time (min.)	Olefin (%)	Starting material (%)	Decomposition (%)	Pressure (mm./Hg)
280	60	10	90	-	20
300	60	10	60	30	20
320	60	30	20	50	20
400	60	10	10	80	20
300	30	10	90	-	760
350	20	20	50	30	760
350	30	15	25	60	760
350	45	15	20	65	760
400	15	10	-	90	760

Scheme A

Scheme C

Scheme B

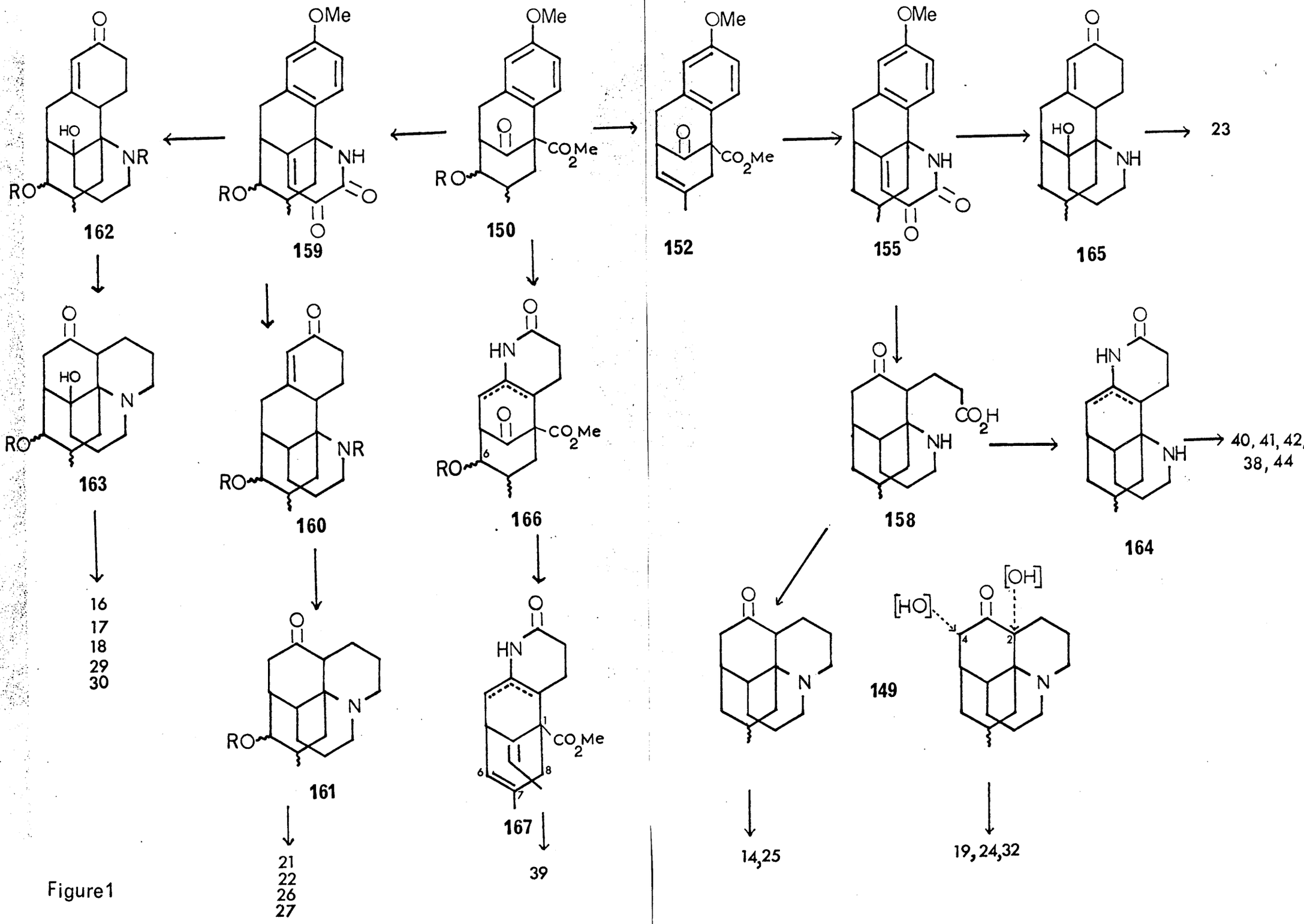
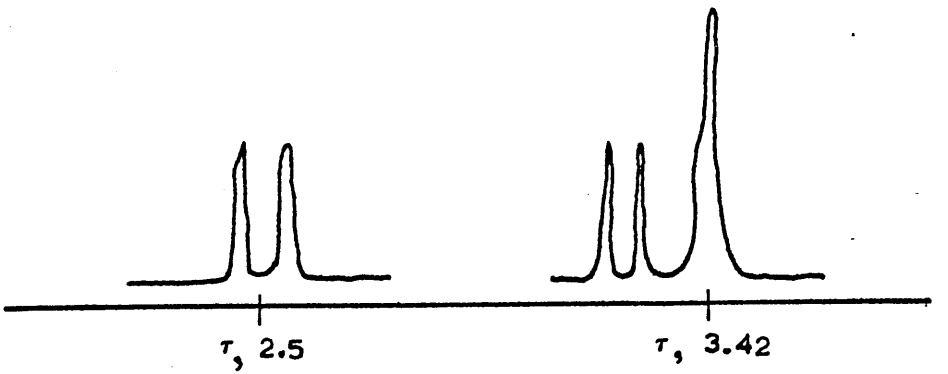
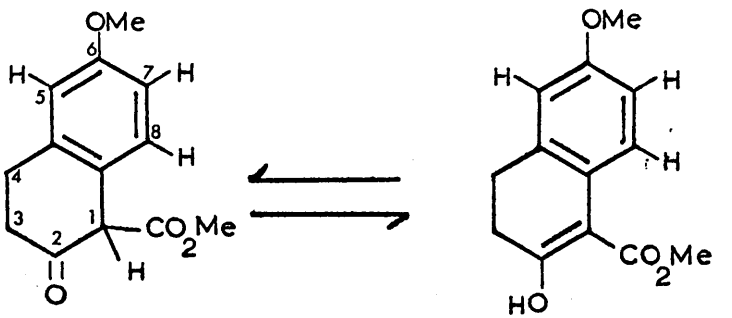


Figure1

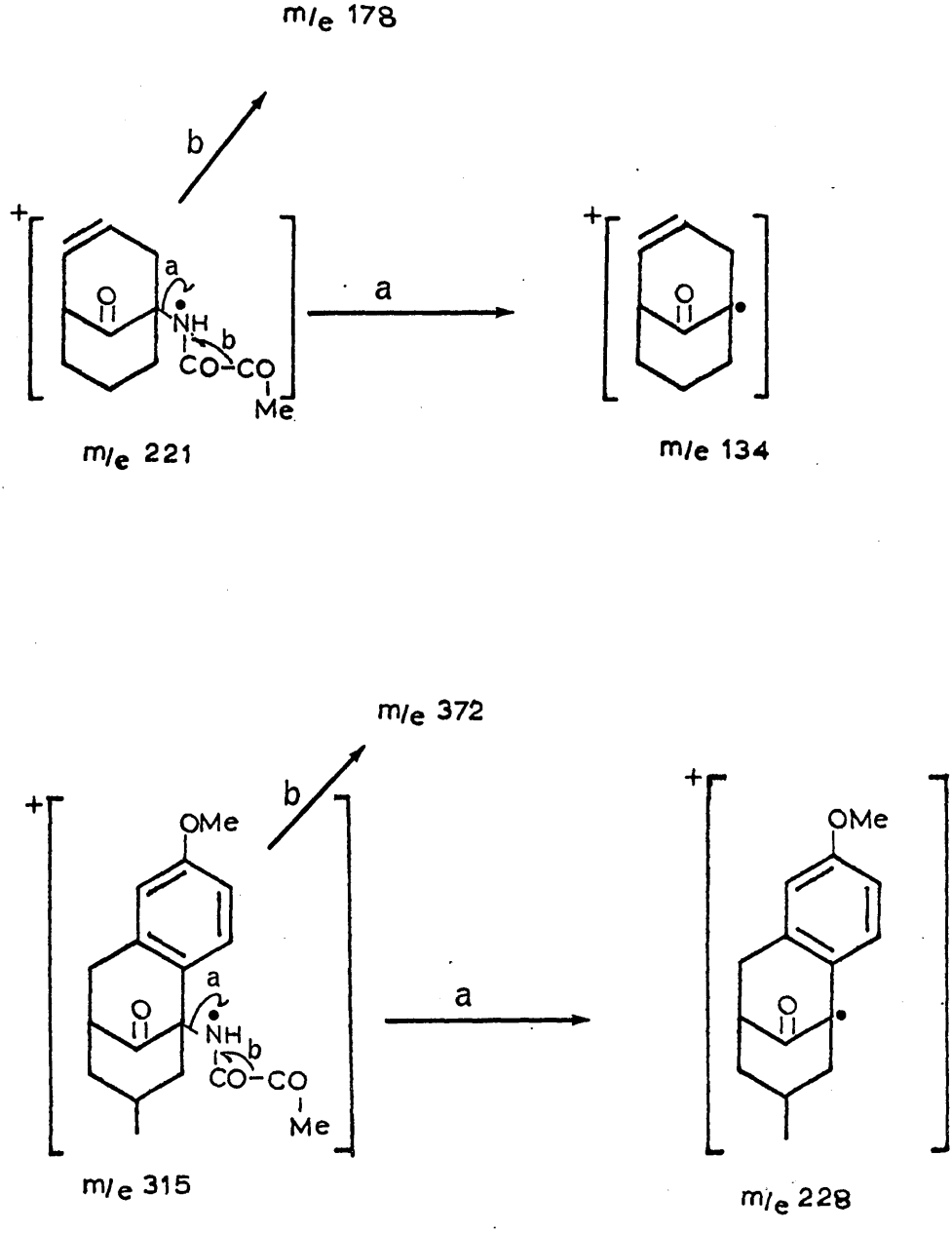




221 227

Figure 2

Figure 3


m/e 178
b
a
a
b
NH
CO-CO
Me
m/e 221
m/e 134
m/e 372
b
OMe
a
a
b
NH
CO-CO
Me
m/e 315
OMe
m/e 228

EXPERIMENTAL

Melting points were recorded on a Kofler block and are corrected; boiling points are uncorrected. Thin layer chromatoplates were prepared from "Kieselgel G" (Merck); preparative plates were 1 mm. thick. Light petroleum refers to the fraction of b.p. 60-80° unless otherwise stated. Analytical gas liquid chromatograms were run on a Pye Argon Chromatograph, using columns of length $52\frac{1}{2}$", under a pressure of 20 p.s.i..

Mass spectra were determined on an A.E.I. M.S.9 spectrometer. Ultraviolet absorption spectra refer to ethanol solutions and were measured with a Unicam S.P.800 instrument; base, refers to the addition of three drops of aqueous sodium hydroxide (4N) to both the sample and the reference cells. Routine infrared spectra were measured on a Unicam S.P.200 instrument and for high resolution spectra a Unicam S.P.100 double-beam infrared spectrophotometer equipped with an S.P.130 sodium chloride prism-grating double-monochromator, operated under vacuum. Proton magnetic resonance spectra were measured with tetramethylsilane as internal reference in deuterochloroform solution; routine spectra were measured on a Perkin Elmer 60 Mc./s. instrument equipped with an integrator, where spin decoupling

was required a Varian H.A.100 instrument was used and is referred to in the text where appropriate.

All solvents and liquid reagents were purified in the requisite manner; all solid reagents were recrystallised. All organic extracts were dried over anhydrous magnesium sulphate.

2-Ethoxycarbonyl-4-methylcyclohexanone (184)

This compound was prepared by analogy with the literature procedure for the preparation of 2-ethoxycarbonylcyclohexanone.[99] The β-keto-ester,184, was obtained in 49% yield; b.p. 126°/20 mm.; n_D^{24}= 1.4830; $\nu_{max.}$ (film) 1745, 1720, 1680 and 1620 $cm.^{-1}$; $\lambda_{max.}$ 257 nm. (ε=7,444) shifting in base to 284 nm. (ε =6,237). (Found: C, 66.10; H, 8.85. $C_{10}H_{16}O_3$ requires C, 66.20; H, 8.75%)

β-(1-Ethoxycarbonyl-2-oxo-4-methylcyclohexyl)-propionaldehyde,183, was prepared by analogy with the method described by Cope and Synerholm.[91]

Epimeric, ethyl-4-hydroxy-7-methylbicyclo(3,3,1)nonan-9-one-1-carboxylates. (189a) and (190a)

(a) Triethylamine procedure.

A solution of the keto-aldehyde, 183, (3.4 g.) in dry benzene (AnalaR 50 ml.) was heated under reflux with triethylamine (10 ml.) for forty-eight hr.. Removal of the solvent in vacuo, yielded a viscous oil (3.2 g.) which was adsorbed on silica gel (100 g.) from ether-light petroleum (1:2).

Elution with ether-benzene (2:1) afforded the epimeric ketols, 189a and 190a, (2.5 g.) as a pale yellow oil, consisting of two compounds as indicated by analytical t.l.c. using light petroleum-ethyl acetate (5:1) as developing solvent; $\nu_{max.}$ (film) 3,500, 1740-1710 $cm.^{-1}$. (Mass spectral molecular weight, 240. Calculated molecular weight 240)

A portion of the crude reaction product was treated with acetic anhydride and pyridine to furnish the corresponding acetates, which on g.l.c. analysis (1% P.E.G.A., 159°, 40 ml./min.) revealed the equatorial and axial acetates (189b) and (190b) respectively in the ratio 2:1, R_t=7.6 and 6.2 min..

(b) Hydrochloric acid procedure.

The keto-aldehyde,183, (2 g.) was slowly added with stirring to aqueous 6N hydrochloric acid (20 ml.) at 0° in a nitrogen atmosphere. The heterogeneous reaction mixture was stirred vigorously for twenty-four hours at room temperature, then diluted with saturated sodium carbonate solution and extracted with ether. The combined ethereal extracts were washed with brine, dried and the solvent removed under reduced pressure to furnish the ketols, 189a and 190a, as a viscous oil (1.8 g.)

A portion of the crude reaction product was acetylated in the usual manner and subsequent g.l.c. analysis (same conditions as above) showed two peaks in the ratio 2:1, R_t= 7.6 and 6.2 min. respectively. Co-injection of this product with that obtained by procedure (a) resulted in peak enhancement.

Attempts to separate these epimeric ketols by either column chromatography or preparative t.l.c. were only partially successful. The purest sample of the ketol whose acetate had R_t= 7.6 min. (i.e. equatorial) was still contaminated with 20% of the axial epimer.

Ethyl-7-methylbicyclo(3,3,1)nonan-2,9-dione-1-carboxylate (191)

Jones reagent (2 ml.) was slowly added to an ice-cold stirred solution of the ketols, 189a and 190a, (1 g.) in acetone (AnalaR, 10 ml.). The solution was then allowed to attain ambient temperature, stirring continued for thirty minutes and then methanol (2 ml.) added. Normal isolation procedure afforded a mobile yellow oil, which was distilled in vacuo, to furnish the pure dione, 191, (0.8 g.) b.p. 130-132°/0.6 mm.; n_D^{20}= 1.4792; $\nu_{max.}$ (CCl_4) 1740 and 1718 $cm.^{-1}$; the n.m.r. spectrum revealed: two overlapping quartets

(each 2H) centred at τ, 5.8 and 5.88 (J= 6 c.p.s.) assigned to $-COCH_2-Me$; two overlapping triplets (each 3H) centred at τ, 8.75 and 8.76 (J= 6 c.p.s.) assigned to $-COCH_2-Me$; the C(7) methyl protons appeared as a broad doublet (3H) at τ, 8.96 (J= 6 c.p.s.). (Found: C, 65.55; H, 7.80. $C_{13}H_{18}O_4$ requires C, 65.55; H, 7.60%)

β-(1-Ethoxycarbonyl-2-oxo-4-methylcyclohexyl)-propionic acid (192a)

Jones reagent (175 ml.) was slowly added to a stirred solution of the keto-aldehyde, 183, (150 g.) in acetone (AnalaR, 150 ml.) at 0° over one hour.. A further portion of Jones reagent (80 ml.) was then added and the solution stirred at room temperature for five hours. Methanol (50 ml.) was slowly introduced with cooling and stirring was then continued for a further ten minutes. The mixture was then poured into brine, extracted with ether and the combined ethereal extracts washed with brine, saturated sodium hydrogen carbonate solution and the layers separated.* The alkaline extract was then acidified with 6N sulphuric acid and extracted with ether. The combined ethereal extracts were washed with brine, dried and the solvent

*The organic layer furnished the dione, 191, (43 g.)

removed under reduced pressure to give β-(1-ethoxycarbonyl-2-oxo-4-methylcyclohexyl)-propionic acid, 192a, (98 g.) as a viscous oil $\nu_{max.}$ (film) 3,500-2,500 and 1730-1700 $cm.^{-1}$.

The corresponding methyl ester, 192b, was obtained by treatment of the above acid with an ethereal solution of diazomethane in the usual manner. Distillation under reduced pressure furnished an analytical sample, b.p. 158°/0.1 mm.; n_D^{25}= 1.4645; $\nu_{max.}$ (film) 1740-1720, 1710 and 1200 $cm.^{-1}$. (Found: C, 61.90; H, 8.00. $C_{14}H_{22}O_5$ requires C, 62.20; H, 8.20%)

$\Delta^{1,10}$-2-oxa-6-ethoxycarbonyl-8-methylbicyclo(4,4,0)-decen-3-one (193)

(a) A mixture of the keto-acid, 192a, (10 g.) and freshly fused sodium acetate (0.7 g.) was heated under reflux for seven hours with acetic anhydride (AnalaR, 30 ml.). Normal isolation procedure afforded a brown oil (8.8 g.) which was distilled under reduced pressure to give the enol-lactone, 193, as a pale yellow oil (6 g.) which was homogeneous by analytical t.l.c. using ethyl acetate-light petroleum (1:5) for development; b.p. 106-108°/0.07mm.; n_D^{24}= 1.4924; $\nu_{max.}$ (CCl_4) 1780, 1740 and 1675 $cm.^{-1}$.

The n.m.r. spectrum revealed the vinylic proton as a quartet (1H) centred at τ, 4.5 (J= 3 c.p.s.). (Found: C, 65.15; H, 7.50. $C_{13}H_{18}O_4$ requires C, 65.50; H, 7.60%)

(b) Acetyl chloride and pyridine procedure

A solution of the keto-acid, 192a, (2 g.) dry benzene (10 ml.) and acetyl chloride (AnalaR, 2 ml.) was heated under reflux for two hours. Dry pyridine (2 ml.) was then added and the solution heated on the steam bath for a further thirty minutes. The cooled solution was poured into brine and extracted with ether and the combined ethereal extracts* washed with brine, 0.5N hydrochloric acid, saturated sodium hydrogen carbonate solution, brine and finally dried. Removal of the solvent under reduced pressure furnished a brown oil (1.6 g.) which was adsorbed on silica gel (30 g.) from ether-light petroleum (1:3). Elution with ether-light petroleum (1:4) afforded the enol-lactone, 193, as a pale yellow oil (1.2 g.).

*The alkaline extracts on acidification with 6N hydrochloric acid, extraction with ether and normal isolation procedure gave the starting keto-acid (0.4 g.).

(c) Oxalyl chloride and pyridine procedure.

Oxalyl chloride (AnalaR, 5 ml.) was slowly added to a chilled solution of the keto-acid, 192a, (1 g.) in dry

benzene (10 ml.). The resultant yellow solution was stirred at room temperature for one hour, pyridine (1 ml.) added and the solution then stirred for a further thirty minutes. The solvent was then removed under reduced pressure and residual oxalyl chloride removed by azeotropic distillation with benzene (2x10 ml.). The brown residue was then dissolved in ether and normal isolation procedure furnished a neutral yellow oil (0.8 g.)* which was adsorbed on silica gel (24 g.) from ether-light petroleum (1:3). Elution with ether-light petroleum (1:4) afforded the enol-lactone, 193, as a pale yellow oil (0.65 g.).

*The alkaline extract afforded the keto-acid, 192a, (0.1 g.).

Reduction of the enol-lactone, 193, with lithium hydridotri-t-butoxyaluminate.

A suspension of lithium hydridotri-t-butoxyaluminate (13 g.) in dry tetrahydrofuran (50 ml.) was added to a stirred solution of the enol-lactone, 193, (8.8 g.) in dry tetrahydrofuran (100 ml.) at -70° in a nitrogen atmosphere. The reaction mixture was then allowed to reach room temperature, stirring continued for a further three hours, diluted with 6N hydrochloric acid and then thoroughly extracted with ether.

The combined ethereal extracts were washed with brine, saturated sodium hydrogen carbonate solution, brine and dried. Removal of the solvent *in vacuo*, furnished a yellow oil (7.4 g.) which was adsorbed on silica gel (250 g.) from ether-light petroleum (1:2). Elution with ether-light petroleum (1:5) furnished an uncharacterised oil (3 g.) $\nu_{max.}$ (film) 3,500, 1720, 1680 (sh) $cm.^{-1}$. Elution with ether-light petroleum (2:1) furnished the *axial ketol*, 190a, (4 g.) b.p. $150^{\circ}/0.1$ mm.; $n_D^{27} = 1.4882$; $\nu_{max.}$ (CCl_4 at high dilution) 3,608, 1738 and 1724 $cm.^{-1}$; the n.m.r. spectrum revealed the hydroxylic proton (1H) at τ, 6.7 which exchanged with D_2O.

The product was homogeneous by t.l.c. analysis (developing solvent light petroleum-ethyl acetate (5:1)) and by g.l.c. examination (conditions as above) of the corresponding *acetate*, 190b, $R_t = 6.2$ min..

The corresponding *toluene-p-sulphonate*, 190c, crystallised from ether as needles, m.p. $112-113^{\circ}$; $\nu_{max.}$ (CCl_4) 1741, 1726, 1184 and 1174 $cm.^{-1}$. The n.m.r. spectrum revealed the signal for the proton *gem* to the sulphonate ester group as a multiplet (1H) at τ, 4.9, with a width at half-height of 10 c.p.s.. (Found: C, 60.90; H, 6.40. $C_{20}H_{26}O_6S$ requires C, 60.90; H, 6.65%)

Reduction of the dione, 191, with lithium hydridotri-t-butoxyaluminate.

A suspension of lithium hydridotri-t-butoxyaluminate (0.12 g.) in dry tetrahydrofuran (5 ml.) was added with stirring to a solution of the dione, 191, (0.1 g.) in dry tetrahydrofuran (5 ml.) and the resulting suspension heated under reflux for two hours. 6N Hydrochloric acid was then added to the cooled reaction mixture and the suspension was then extracted with ether. The combined organic extracts were then washed with brine, saturated sodium hydrogen carbonate solution, brine and dried. Removal of the solvent in vacuo, furnished a yellow oil (0.09 g.) a portion of which was acetylated in the usual manner. Subsequent g.l.c. analysis (1% P.E.G.A.) indicated the presence of two components in the ratiom 8:1, the minor componentm corresponding to the equatorial acetate, 189b, and the major component being starting material. (These assignments were made by cross injection experiments.)

Ethyl-cis, 4,9-dihydroxy-7-methylbicyclo(3,3,1)nonane-1-carboxylate (194)

A suspension of lithium hydridotri-t-butoxyaluminate (0.17 g.) in dry tetrahydrofuran (5 ml.) was added to a stirred solution of the axial ketol, 190a, (0.12 g.) in dry tetrahydrofuran (5 ml.) and the resulting solution heated under reflux for eight hours. The cooled reaction mixture was then acidified with 6N hydrochloric acid, extracted with ether and the combined ethereal extracts washed with brine, saturated sodium hydrogen carbonate solution, brine and dried. Removal of the solvent under reduced pressure afforded a pale yellow oil (0.1 g.) which on vacuum distillation provided a sample of the cis diol, 194, b.p. 120°/0.1 mm.; $\nu_{max.}$ (CCl_4 at high dilution) 3512 $cm.^{-1}$. Analytical t.l.c. indicated that the product was homogeneous (developing solvent, light petroleum-ethyl acetate (2:3))

Cyclic sulphite ester of the above cis diol (195)

A solution of thionyl chloride (0.4 ml.) in dry ether (10 ml.) was added to an ice-cold stirred solution of the diol, 194, (0.5 g.) pyridine (2 ml.) and dry ether (10 ml.).

After thirty minutes at room temperature the reaction mixture was poured into brine, extracted with ether and the combined ethereal extracts washed with brine 6N hydrochloric acid, brine and dried. Removal of the solvent under reduced pressure furnished a yellow oil (0.64 g.) which was adsorbed on silica gel (10 g.) from ether-light petroleum (1:4). Elution with light petroleum-ethyl acetate (5:1) separated the sulphite ester, 195, as a colorless oil (o.5 g.) homogeneous by t.l.c.; $\nu_{max.}$ (film) 1200 and 1000 $cm.^{-1}$. Attempts to prepare an analytical sample of this compound by vacuum distillation resulted in decomposition. (Mass spectral molecular weight was 288. Calculated molecular weight 288.)

Diethyl-7-methylcyclooct-1-ene-1,5-dicarboxylate (199)

A solution of the axial tosylate, 190c, (0.48 g.) in dry ethanol (absolute, 10 ml.) was added to a solution of sodium ethoxide (prepared from sodium (0.3 g.) and dry ethanol (40 ml.)) and the resulting solution heated under reflux for twenty hours. The reaction mixture was then taken to dryness, extracted with ether, washed with brine, dried and the solvent removed in vacuo, to give a sweet-

smelling oil (0.27 g.). Vacuum distillation afforded the di-ester, 199, b.p. 100°/0.5 mm.; n_D^{18} = 1.4771; $\nu_{max.}$ (CCl_4) 1735, 1709 and 1646 $cm.^{-1}$; the n.m.r. spectrum revealed, a doublet (3H) at τ, 9.05 (J= 6 c.p.s.) assigned to the C(7) methyl protons; two overlapping triplets (each 3H) centred at τ, 8.8 and 8.7 (J= 6 c.p.s.) assigned to methyl protons of the ethyl esters; two overlapping quartets (each 2H) centred at τ, 5.85 (J= 6 c.p.s.) assigned to $-O-\underline{CH_2}-CH_3$; and a quartet (1H) centred at τ, 3.02 (J= 8 c.p.s.) assigned to the vinylic proton. (Found: C, 67.40; H, 8.75. $C_{15}H_{24}O_4$ requires C, 67.45; H, 9.00%)

Attempted ketalisation of the axial tosylate, 190c.

A solution of the axial tosylate, 190c, (0.2 g.) ethylene glycol (0.5 ml.) and ethyl orthoformate (1 ml.) containing p-toluenesulphonic acid (0.02 g.) was heated on the steam bath for two hr. with concomitant removal of ethanol. The solution was then taken to dryness to furnish a white solid (0.18 g.). Analytical t.l.c. (using ethyl acetate-light petroleum (1:2) for development) indicated that the product was a mixture of starting tosylate and a less polar component which had the same t.l.c. mobility as the keto-olefin (182a).

Ethyl-7-methylbicyclo(3,3,1)non-2 and -3 ene-9-one-1-carboxylate (182a) and (185)

(a) The keto-aldehyde, 183, (19 g.) was added in fine droplets with vigorous stirring, to concentrated sulphuric acid (38 ml.) cooled in an ice-salt bath. The mixture was left at room temperature for four hr., then poured into ice and extracted with ether. The combined ethereal extracts were washed with saturated sodium hydrogen carbonate solution, brine and dried. (Acidification of the alkaline washings afforded no ether soluble acidic material.) Removal of the solvent under reduced pressure furnished a brown oil (5.5 g.) which was adsorbed on alumina (Spence 'H', 150 g.) from light petroleum. Elution with ether afforded a white solid* (0.88 g.) which was purified by sublimation to give the pure keto-ester, 182a, m.p. 50-52°; $\nu_{max.}$ (Nujol) 3,100, 1740, 1715, 1660, 720 and 695 $cm.^{-1}$.

A solution of the above keto-ester, 182a, (0.099 g.) and hydrazine hydrate (100%, 0.1 ml.) in ethanol (5 ml.) was heated under reflux for twenty-four hr., and the solution then taken to dryness under reduced pressure to give the

*shown to be a mixture of the double bond isomers[93]

crude pyrazolone (0.074 g.). This was recrystallised from benzene to give the pure derivative as needles, m.p. 121-123°. (Found: C, 69.60 ; H, 7.70 ; N, 14.75. $C_{11}H_{14}N_2O_4$ requires C, 69.45 ; H, 7.40 ; N, 14.70%).

Hydrolysis of the above olefin-ester, 182a, with 2N aqueous sodium hydroxide solution in the usual manner, gave the corresponding olefin-acid, 182b, as a white solid. Sublimation in vacuo furnished an analytical sample, m.p. 110-113° ; $\nu_{max.}$ (KCl disc) 3400-2500, 1722, 1708, 1654, 734 and 706 $cm.^{-1}$. (Found: C, 67.70 ; H, 7.30. $C_{11}H_{14}O_3$ requires C, 68.00 ; H, 7.30%).

(b) A solution of the axial tosylate, 190c, (0.1 g.) in ethanol (absolute, 10 ml.) was treated with potassium-t-butoxide (from potassium (0.01 g.) and t-butanol (5 ml.)) and the solution heated under reflux for twenty hours. Normal isolation procedure afforded a colorless oil (0.05 g.) shown by g.l.c. analysis (10% P.E.G.A., 160°, 47 ml./min.) to consist of two components in the ratio 20:1, R_t= 8.9 and 21.5 min. respectively.

(c) A solution of the axial tosylate, 190c, (0.2 g.) in 10% aqueous acetic acid was heated under reflux for twelve hours. The cooled solution was poured into brine, extracted with ether and the combined ethereal extracts washed with

brine, dried and the solvent removed under reduced pressure to furnish a white solid (0.1 g.) which was recrystallised from light petroleum to furnish the pure olefin acid, 182b, (0.09 g.) as needles m.p. 109-113°, undepressed on admixture with an authentic sample.

The above acid was esterified with an ethereal solution of diazomethane in the usual manner to yield the corresponding methyl ester, 182c, whose infrared spectrum was superposible with that of an authentic sample and on g.l.c. analysis (10% P.E.G.A., 160°, 47 ml./min.) provided peak enhancement on co-injection with an authentic sample.

2-Ethoxycarbonylcyclohexanone (201)

This compound was prepared according to the method described in the literature.[99]

α-Methyl-β-(1-ethoxycarbonyl-2-oxocyclohexyl)-propionaldehydes (202)

An ice-cold mixture of the β-keto-ester, 201, (25 g.) and methacrolein (14 ml.) was added over one hour to a stirred solution of sodium ethoxide (from sodium (0.1 g.) and

dry ethanol (150 ml.)) containing hydroquinone (0.05 g.) held at -70° in a nitrogen atmosphere. This solution was allowed to reach room temperature, stirred for a further hour and the reaction mixture neutralised with glacial acetic acid (2 ml.). The solvent was then removed under reduced pressure, the residual oil dissolved in ether, washed with brine, saturated sodium hydrogen carbonate solution, brine and dried. Removal of the solvent *in vacuo* yielded a pale yellow oil (37 g.) which on distillation under reduced pressure furnished epimeric, α-*methyl*-β-(1-*ethoxycarbonyl*-2-*oxocyclohexyl*)-*propionaldehydes*, 202, (30.5 g.) b.p. 102-104°/0.2 mm.; n_D^{20} = 1.4719; $\nu_{max.}$ (CCl_4) 2790, 1730, 1720 and 1710 $cm.^{-1}$. The n.m.r. spectrum revealed the aldehydic protons as two separate doublets (each 1H) centred at τ, 0.35 and 0.37 (in each case J= 3 c.p.s.). G.l.c. examination of this product (5% Q.F.1., 175°, 35 ml./min.) showed two peaks in the ratio 1:1, R_t= 13.5 and 12 min.. (Found: C, 64.65; H, 8.20. $C_{13}H_{20}O_4$ requires C, 65.00; H, 8.40%)

Epimeric, ethyl-6-hydroxy-7-methylbicyclo(3,3,1)nonan-9-one-1-carboxylates (203a).

A solution of the keto-aldehydes, 202, (17.2 g.) in dioxan (AnalaR, 50 ml.) was added in a nitrogen atmosphere, to an ice-cold solution of 6N hydrochloric acid (100 ml.) in dioxan (AnalaR, 150 ml.) and the resulting solution stirred at room temperature for fifteen hours. The reaction mixture was then poured into brine and normal isolation procedure gave the epimeric ketols, 203a, as a yellow oil (15.3 g.) $\nu_{max.}$ (film) 3500, 1740-1710 $cm.^{-1}$.

A portion of the reaction mixture was acetylated by the normal procedure and subjected to g.l.c. analysis (5% Q.F.1., 175°, 35 ml./min.). These conditions allowed an efficient separation of three major components and one minor component which appeared as a shoulder, in the ratio 10:5:1:5, R_t= 24.75, 29.0, 30.0 (shoulder) and 44.5 min. respectively.

Large scale preparation of the acetates (203b).

Dry pyridine (1 ml.) was added to a solution of the epimeric ketols, 203a, (15 g.) in acetic anhydride (AnalaR, 30 ml.). The resultant solution was then heated on the steam bath for five hr. and then left at room temperature for twelve hr.. After removal of the solvent by azeotropic

distillation with xylene, the residual brown oil was dissolved in ether and washed successively with brine, 6N hydrochloric acid, brine, saturated sodium hydrogen carbonate solution, brine and finally dried. Removal of the solvent under reduced pressure furnished a pale yellow oil (16.2 g.) which was adsorbed on silica gel (320 g.) from light petroleum. Elution with light petroleum-ether (20:1) afforded the epimeric acetates, 203b, as a colorless oil (15.5 g.) which partially crystallised on standing. Fractional crystallisation from light petroleum* afforded the 'axial' acetate, 204a or 204f, as prisms, m.p. 133-133.5°; $\nu_{max.}$ (CCl_4) 1745, 1725, 1241 and 1233 $cm.^{-1}$. The n.m.r. spectrum revealed the C(6) methine proton as a multiplet (1H) centered at τ, 4.8 (J= 3 c.p.s.) with a width at half-height of 10 c.p.s.. Sublimation in vacuo afforded an analytical sample which on g.l.c. analysis (same conditions as above) showed one peak R_t= 29 min.. (Found: C, 63.65; H, 7.95. $C_{15}H_{22}O_5$ requires C, 63.80; H, 7.85%)

*Evaporation of the mother liquors furnished the remaining acetates having g.l.c. R_t= 24.75, 30 and 44.5 min.. Fractional distillation under reduced pressure afforded a sample, which was free from the minor component (R_t= 30 min.) by g.l.c. analysis, b.p. 126-130°/ 0.3 mm.; n_D^{20}= 1.4809;

$\nu_{max.}$ (CCl_4) 1735, 1720 and 1234 $cm.^{-1}$. The n.m.r. spectrum revealed the C(6) methine proton as a multiplet (1H) centred at τ, 5.4 with a width at half-height of 27 c.p.s.. (Found : C, 63.60 ; H, 7.70. $C_{15}H_{22}O_5$ requires C, 63.80 ; H, 7.85%).

Equilibration of the mixed ketols (203a).

Trimethylamine (1 ml.) was added to a solution of the epimeric ketols, 203a, (0.4 g.) in benzene (AnalaR, 20 ml.) and the solution heated under reflux for twenty-four hours. The solvent was then removed in vacuo and the residue (0.36 g.) was acetylated in the usual manner. G.l.c. analysis of this product (conditions as above) indicated the presence of four components in the ratio 12:6:1:9, R_t= 24.75, 29.0, 30.0 and 44.5 min. respectively.

Diethyl-4-oxopimelate (207).

This compound was prepared according to the literature method[100] using β-(2-furyl)-acrylic acid (206) as starting material.

Diethyl-4-ethylenedioxy-pimelate (208) and 2-ethoxy carbonyl-4-ethylenedioxy-pimelate (205) were prepared according to the published procedure.[101]

β-(1-Ethoxycarbonyl-2-oxo-4-ethylenedioxycyclohexyl)-propionaldehyde (209)

The β-keto-ester, 205, (2.9 g.) was treated with acrolein (1 g.) in the presence of a catalytic amount of sodium ethoxide as previously described. Removal of the solvent under reduced pressure gave a yellow oil (3.4 g.) which was adsorbed on alumina (grade V neutral, 100 g.) from light petroleum-benzene (2:1). Elution with ether-light petroleum (2:1) furnished the keto-aldehyde, 209, (3 g.) as a pale yellow oil, b.p. 128-130°/0.3 mm.; n_D^{22}= 1.4836; $\nu_{max.}$ (film) 2,800 and 1730-1710 $cm.^{-1}$.

Epimeric, 3-ethylenedioxy-6-hydroxybicyclo(3,3,1)nonan-9-one-1-carboxylates (210a) and (211a)

(a) Triethylamine (3 ml.) in benzene (AnalaR, 15 ml.) was added over ten min. to a stirred solution of the keto-aldehyde, 209, in benzene (AnalaR, 10 ml.) and the resultant

solution heated under reflux for forty-eight hours. The cooled reaction mixture was then diluted with 0.5N hydrochloric acid (10 ml.) and the benzene layer separated, washed with brine and dried. Removal of the solvent under reduced pressure gave a dark-brown oil (0.9 g.) which was adsorbed on alumina (grade V neutral, 30 g.) from light petroleum-benzene (2:1). Elution with benzene afforded a mixture of the ketols, 210a and 211a, as a pale yellow oil (0.7 g.) $\nu_{max.}$ (film) 3,550, 1730-1710 $cm.^{-1}$.

A portion of this ketol mixture was acetylated in the usual manner to furnish the corresponding acetates, 210b and 211b, as a viscous oil, b.p. 180°/0.05 mm. (bath temp.) $\nu_{max.}$ (film) 1740-1730 and 1710 $cm.^{-1}$. G.l.c. analysis of this mixture indicated the presence of two components in the ratio 2:1 (1% P.E.G.A., 200°, 60 ml./min., R_t = 7.4 and 5.6 min. respectively). (Found: C, 58.70; H, 6.55. $C_{16}H_{22}O_7$ requires C, 58.90; H, 6.80%)

β-(1-Ethoxycarbonyl-2-oxo-4-ethylenedioxycyclohexyl)-propionic acid (212)

(a) Moist silver oxide procedure.

The keto-aldehyde, 209, (0.2 g.) was shaken with

an aqueous suspension of silver oxide (prepared from saturated silver nitrate solution, 5 ml. and aqueous 4N sodium hydroxide solution, 10 ml.,) for thirty minutes. The precipitated silver was filtered off, the residue washed with hot water and the combined aqueous extracts were then cooled in ice, acidified with 0.5N hydrochloric acid, extracted with ether; then the organic layer was washed with brine and dried. Removal of the solvent <u>in vacuo</u> furnished a yellow oil (0.1 g.) $\nu_{max.}$ (film) 3,500-2,550, 1730-1700, 1620 and 1610 $cm.^{-1}$. This product gave a purple coloration with ethanolic ferric chloride solution.

(b) Chromium trioxide and pyridine procedure.

The keto-aldehyde, 209, (0.2 g.) in dry pyridine (3 ml.) was slowly added to a solution of chromium trioxide (0.16g.) in pyridine (10 ml.) held at 0°, and stirring continued for thirty-five minutes. The dark solution was then poured into ice/0.5 N hydrochloric acid and extracted with ether. The combined organic layers* were washed with saturated sodium hydrogen carbonate solution, and this alkaline extract acidified with 0.5N hydrochloric acid then extracted

*This ethereal extract was washed with brine, dried and the solvent removed to furnish starting material (0.1 g.).

with ether, washed with brine and dried. Evaporation of the solvent afforded a yellow oil (0.1 g.) $\nu_{max.}$ (film) 3,500-2,500, 1730-1700 $cm.^{-1}$.

(c) A solution of potassium permanganate (0.8 g.) in water (50 ml.) was added dropwise over twenty minutes to a stirred suspension of the keto-aldehyde, 209, (2 g.) in water (25 ml.). The reaction mixture was held at 70° for a further twenty min. and then set aside at room temperature for twelve hours in the dark. The precipitated manganese dioxide was filtered off and the residue washed with hot chloroform. The filtrate was then acidified (6N hydrochloric acid, 1 ml.) and extracted with chloroform. The combined organic layers were washed with brine, dried and the solvent removed under reduced pressure to give a viscous oil which solidified on trituration with ether. Recrystallisation from ether-chloroform (2:1) furnished the keto-acid, 212, (1.4 g.) as plates, m.p. 134-135°; $\nu_{max.}$ (KCl disc) 3,300-2,600, 1728, 1718 and 1700 $cm.^{-1}$. (Found: C, 55.90; H, 7.00. $C_{14}H_{20}O_7$ requires C, 56.00; H, 6.70%)

$\Delta^{1,10}$-2-Oxa-6-ethoxycarbonyl-8-ethylenedioxybicyclo(4,4,0) decen-3-one (213)

A mixture of the keto-acid, 212, (1 g.) and frshly fused sodium acetate (0.5 g.) was heated under reflux with acetic anhydride (AnalaR, 15 ml.) for four hours. After removal of the acetic anhydride by azeotropic distillation with xylene under reduced pressure, the residual brown oil was dissolved in ether, washed with brine, saturated sodium hydrogen carbonate solution and dried. Removal of the solvent *in vacuo* gave a white solid (0.85 g.) which was recrystallised from benzene-light petroleum (1:2) to furnish the enol-lactone, 213, (0.75 g.) as needles, m.p. 140-141°; $\nu_{max.}$ (KCl disc) 1750, 1721, 1680, 1083 and 1152 $cm.^{-1}$. In the n.m.r. spectrum the vinylic proton was revealed as a triplet (1H) centred at τ, 4.6 (J= 3 c.p.s.). (Found: C, 59.75; H, 6.55. $C_{14}H_{18}O_6$ requires C, 59.55; H, 6.45%)

Reduction of the enol-lactone (213)

A suspension of lithium hydridotri-t-butoxyaluminate (0.6 g.) in dry tetrahydrofuran (10 ml.) was added to a stirred solution of the enol-lactone, 213, (0.45 g.) in dry

tetrahydrofuran (10 ml.) in a nitrogen atmosphere. The reaction mixture was then allowed to come to room temperature and stirred for a further three hours. 0.5N hydrochloric acid was then added rapidly and the reaction mixture was then poured into brine and extracted with ether. The combined ethereal extracts were then washed with brine, saturated sodium hydrogen carbonate solution, brine and dried. Removal of the solvent *in vacuo* furnished a yellow oil (0.4 g.) which was adsorbed on alumina (grade V neutral, 120 g.) from light petroleum - benzene (2:1). Elution with ether-light petroleum (1:2) afforded the *ketols*, 210a and 211a, as a colorless oil (0.2 g.) which decomposed on distillation, $\nu_{max.}$ (film) 3500, 1740 and 1730 cm.$^{-1}$. G.l.c. analysis (1% P.E.G.A., 200°, 60 ml./min.) of the corresponding acetates, 210b and 211b, prepared in the usual manner showed two peaks in the ratio 1:5, R_t = 7.4 and 5.6 min. respectively. Co-injection with the acetates prepared according to the procedure described previously, indicated peak enhancement.

Preparation and pyrolysis of the carbonate esters (210c and 211c).

Redistilled ethyl chloroformate (2 ml.) was slowly added with stirring to an ice-cold solution of the epimeric ketols, 210a and 211a, (0.9 g.) in dry pyridine (2 ml.). The mixture was held at 0° for twenty-four hours, then poured into ice/0.5N hydrochloric acid and extracted with ether. The combined ethereal extracts were washed with brine, saturated sodium hydrogen carbonate solution, brine and dried. Removal of the solvent under reduced pressure gave a pink viscous oil (0.8 g.) which was adsorbed on alumina (grade V neutral, 24 g.) from light petroleum-ether (2:1). Elution with ether-light petroleum (1:2) separated the epimeric carbonate esters, 210c and 211c, as a viscous oil (0.7 g.) which on g.l.c. analysis (1% P.E.G.A., 200°, 60 ml./min.) showed two peaks in the ratio 2:1, R_t= 10.5 and 8.1 min. respectively. Micro distillation furnished an analytical sample, b.p. 200°/0.1 mm. (bath temp.) ; $\nu_{max.}$ (film) 1740-1720, 1260 and 800 cm.$^{-1}$. (Found: C, 56.95 ; H, 6.70. $C_{17}H_{24}O_8$ requires C, 57.30 ; H, 6.80%).

Pyrolysis procedures.

(a) The epimeric carbonate esters, 210c and 211c, (0.5 g.) were heated in a Woods alloy bath held at 350°, for ten min.. Distillation of the product under reduced pressure resulted in the recovery of starting material, identified by both t.l.c. and spectral evidence.

(b) A solution of the carbonate esters, 210c and 211c, (0.7 g.) and dinonyl phthalate (AnalaR, 10 ml.) was heated in a Woods alloy bath held at 350°, for ten min.. Distillation of the reaction product afforded phthalic anhydride, n-nonan-1-ol and starting material.

(c) A solution of the carbonate esters, 210c and 211c, in silicon fluid (M.S. 550, 5 ml.) was heated in a Woods alloy bath held at 350° for thirty min.. Attempts to remove the solvent by either column chromatography or vacuum distillation were unfruitful. Preparative t.l.c. developed in ether-hexane (3:4) furnished starting material and the β-keto-ester, 205.

(d) A solution of the carbonate esters, 210c and 211c, (0.3 g.) in ethanol (5 ml.) was slowly introduced into a distillation flask held at 350° (Woods alloy bath) and the volatile products concomitantly removed by applying water pump vacuum. The sole isolable products proved to be the β-keto-ester, 205, and starting material.

2-Bromo-6-methoxynaphthalene (218b) was prepared from β-naphthol by the literature procedure.[107]

6-Methoxy-β-naphthol (220).[105,106]

A solution of 6-methoxynaphthalene-2-magnesium bromide (from 2-bromo-6-methoxynaphthalene, 218a, (118.5 g.) and magnesium turnings (18 g.)) in dry tetrahydrofuran* (400 ml.) was slowly added to a cooled solution of trimethyl borate[108] (62.5 ml.) in ether (anhydrous, 200 ml.) with stirring, over forty-five minutes. Water (200 ml.) was then added and stirring continued as the bulk of the solvent was removed under reduced pressure (water pump). The reaction mixture was then cooled (-10°), a solution of ammonium chloride (100 g.) in water (350 ml.) added, followed by cold aqueous hydrogen peroxide solution (30% w/v, 200 ml.) which was added at such a rate so that the temperature of the vessel did not rise above 10°. The residual solvent was then removed under reduced pressure (water pump) and stirring continued for one hour. The resultant mixture was filtered under suction and the residue washed with water. This solid

* distilled from lithium aluminium hydride into the reaction vessel.

was then stirred with 1N aqueous sodium hydroxide solution (1 l.), filtered under suction and carbon dioxide bubbled through the filtrate. The resultant precipitate was filtered off and carbon dioxide bubbled through the filtrate. The combined residues were thoroughly washed with water and then dried at 50° for twenty-four hours to furnish 6-methoxy-β-naphthol, 220, as a grey powder (50 g.), m.p. 148-151° (lit.,[105] 150-151°).

6-Methoxy-2-tetralone (217).[104]

6-Methoxy-β-naphthol, 220, (50 g.) was slowly added to a stirred solution of dry t-butanol (50 ml.) in liquid ammonia (600 ml.). The reaction vessel was then equipped with an acetone-'Drikold' condenser and sodium (13 g.) added in small portions until a blue coloration was distributed throughout the solution. The condenser was then removed and the ammonia allowed to evaporate off under a stream of nitrogen. Ice-water was then added, followed by ether (300 ml.) and the product extracted under nitrogen. The combined ethereal extracts were washed with 6N hydrochloric acid, brine, dried and the solvent removed under reduced pressure to furnish a red oil (46 g.) Distillation under reduced

pressure furnished 6-methoxy-2-tetralone, 217, as a pale yellow oil (30 g.), b.p. 112-113°/0.5 mm., (lit.,[104] 111-114°/0.5 mm.). The n.m.r. spectrum (100 Mc./s.) revealed the aromatic protons as two multiplets (3H) at τ, 2.5-3.5 ; ArOMe, singlet (3H) at τ, 6.34 ; the protons at C(1) as a singlet (2H) at τ, 6.62 ; the protons at C(3) as a triplet (2H) centred at τ, 7.10 (J= 6 c.p.s.) ; the protons at C(4) as a triplet (2H) centred at τ, 7.58 (J= 6 c.p.s.).

1,3-Diethoxycarbonyl-6-methoxy-2-tetralone (225).

Under a nitrogen atmosphere, a solution of the tetralone, 217, (3 g.) in benzene (AnalaR, 20 ml.) was added slowly to a mixture of pyrrolidine (2.8 ml.) in benzene (AnalaR, 30 ml.) refluxing under a Soxhelet extractor containing calcium hydride. After a two hour reflux period, the reaction mixture was evaporated to dryness under reduced pressure and the dark-brown residue recrystallised from light petroleum (b.p. 40-60°) to give the pyrrolidine enamine, 224c, as steel-grey needles, m.p. 67-68.5° ; $\gamma_{max.}$ (Nujol) 1610 cm.$^{-1}$.

A solution of the above enamine (1 g.) and ethyl chloroformate (50 ml.) in benzene (AnalaR, 100 ml.) was heated

under reflux for twenty hours in a nitrogen atmosphere. The cooled solution was then stirred for forty-five minutes with 10% aqueous hydrochloric acid and the organic layer separated, washed with brine and dried. After removal of the solvent the resultant red oil (0.8 g.) was adsorbed on silica gel (24 g.) from ether-light petroleum (1:1). Elution with ethyl acetate-light petroleum (1:5) afforded the diester, 225, which crystallised from ether as pale yellow needles (0.34 g.) m.p. 68-70°; $\nu_{max.}$ (Nujol) 1740, 1675, 1640, 1620 and 1510 $cm.^{-1}$; $\lambda_{max.}$ 250 nm. (ε= 19,400) shifting in base to 285 nm. (ε= 30,040). The n.m.r. spectrum revealed the two ethyl esters as two overlapping quartets (each 2H) centred at τ, 5.75 (J= 6 c.p.s.) and two overlapping triplets (each 3H) centred at τ, 8.70 (J= 6 c.p.s.). (Found: C, 63.70 ; H, 6.50. $C_{17}H_{20}O_6$ requires C, 63.75 ; H, 6.30%. Mass spectral molecular weight was 320. Calculated molecular weight 320).

1-Methoxycarbonyl-6-methoxy-2-tetralone (221).

A solution of the tetralone, 217 (20 g.) in freshly distilled dimethyl carbonate (150 ml.) was added under a nitrogen atmosphere to a stirred suspension of sodium

hydride (50% dispersion in mineral oil, 7.1 g.) in dimethyl carbonate (250 ml.). Methanol (1 ml.) was then added and the suspension heated under reflux for three hours. The cooled reaction mixture was poured into ice-cold 6N sulphuric acid, extracted with ether and the combined organic extracts washed with brine, saturated sodium bisulphite solution, brine and dried. Removal of the solvents under reduced pressure gave a red oil (24 g.) which was adsorbed on silica gel (750 g.) from light petroleum. Elution with ether-light petroleum (1:10) furnished the β-keto-ester, 221, (22 g.) b.p. 144°/0.5 mm. ; $\nu_{max.}$ (film) 1740, 1720, 1640 and 1620-1600 cm.$^{-1}$; $\lambda_{max.}$ 250 nm. (ε= 13,300), 285 nm. (ε= 6,200) shifting in base to 281 nm. (ε= 18,200). The n.m.r. spectrum (100 Mc./s.) revealed, the aromatic protons (3H) at τ, 2.5-3.5 ; ArOMe singlet (3H) at τ, 6.20 ; COOMe singlet (3H) at τ, 6.31 ; proton at C(1) singlet (0.25H) at τ, 6.38 ; enolic proton, singlet (0.75H) at τ, -3.62 ; protons at C(3) triplet (2H) centred at τ, 7.26 (J= 6 c.p.s.) ; and the protons at C(4), triplet (2H) centred at τ, 7.58 (J= 6 c.p.s.). The above β-keto-ester gave an intense green coloration with ethanolic ferric chloride solution. (Found: C, 66.40 ; H, 5.65. $C_{13}H_{14}O_4$ requires C, 66.65 ; H, 6.00%. Mass spectral molecular weight was 234. Calculated molecular weight, 234).

Enamine-amide (232b).

The β-keto-ester, 221, (0.4 g.) was treated with pyrrolidine (0.8 g.) in refluxing benzene (AnalaR, 30 ml.) according to the literature procedure.[115] Removal of the solvent *in vacuo* gave a green oil (0.5 g.) which solidified on trituration with ether. Recrystallisation from acetone furnished the enamine-amide, 232b, as white prisms, m.p. 149-151°; $\nu_{max.}$ (Nujol) 1610 and 1580 cm.$^{-1}$; $\lambda_{max.}$ 314 nm. (ε= 22,760). (Found: C, 73.80 ; H, 8.15 ; N, 8.80. $C_{20}H_{26}N_2O_2$ requires C, 73.60 ; H, 8.05 ; N, 8.60%. Mass spectral molecular weight was 326. Calculated molecular weight 326).

1-Methoxycarbonyl-2-hydroxy-6-methoxy-1,2,3,4-tetrahydronaphthalene (236).

Sodium borohydride (0.12 g.) was added to an ice-cold stirred solution of the β-keto-ester, 221, (1 g.) in aqueous methanol (20 ml.). After three hr. stirring at room temperature the reaction mixture was poured into brine, extracted with ether and the combined extracts washed with brine and dried. Removal of the solvent *in vacuo* gave a white solid which was recrystallised from benzene - light petroleum (2:1)

to give the hydroxy-ester, 236, as small needles (0.9 g.) m.p. 108-109°; $\nu_{max.}$ (Nujol) 3,500 and 1720 $cm.^{-1}$. (Found: C, 65.95; H, 6.95. $C_{13}H_{16}O_4$ requires C, 66.10; H, 6.85% Mass spectral molecular weight was 236. Calculated molecular weight, 236.)

1-Methoxycarbonyl-6-methoxy-3,4-dihydronaphthalene (237a).

Phosphorus oxychloride (1.25 ml.) was added to an ice-cold solution of the hydroxy-ester, 236, (1.6 g.) in dry pyridine (15 ml.) over a period of ten minutes. The reaction mixture was then heated on the steam bath for one hr., poured into ice-cold 6N hydrochloric acid and then extracted with ether. The combined organic layers were washed with brine, saturated sodium hydrogen carbonate solution, brine and dried. Removal of the solvent afforded the olefin-ester, 237a, as a pale yellow oil (1.3 g.) $\nu_{max.}$ (film) 1720, 1610 and 1590 $cm.^{-1}$.

The corresponding olefin-acid, 237b, was obtained by alkaline hydrolysis of the olefin-ester, 237a,. This acid crystallised from benzene-light petroleum (2:1) as prisms m.p. 135-137° (lit.[117] 130-132°); $\nu_{max.}$ (Nujol) 3,300-2,700, 1680 and 1570 $cm.^{-1}$; $\lambda_{max.}$ (base) 284 nm. (ε = 14,320). The

n.m.r. spectrum (100 Mc./s.) revealed the vinylic proton as a triplet (1H) centred at τ, 2.6 (J= 3 c.p.s.). (Found: C, 70.45; H, 5.85. $C_{12}H_{12}O_3$ requires C, 70.60; H, 5.90%)

6-Methoxy-1-naphthoic acid (235a).

A solution of selenium dioxide (0.13 g.) and the above ester, 237a, (1 g.) in glacial acetic acid (AnalaR, 20 ml.) was heated under reflux in a nitrogen atmosphere for five min.. The cooled solution was then filtered through Celite 535, and the residue washed with two portions of acetic acid. The combined filtrates were evaporated to dryness under reduced pressure and the residual oil dissolved in ether, washed with brine, saturated sodium hydrogen carbonate solution, brine and dried. This dry extract was then shaken with silver powder to remove colloidal selenium, filtered and the solvent removed to give the crude ester, 235b, as a brown oil (0.9 g.) $\nu_{max.}$ (film) 1720, 1630, 1600 and 1570 $cm.^{-1}$.

Alkaline hydrolysis of the ester, 235b, furnished a white solid which was recrystallised from benzene-light petroleum (1:2) to give 6-methoxy-1-naphthoic acid, 235a, as needles, m.p. 180-181°, identified spectrally and which showed no depression on mixed melting point determination with

an authentic sample prepared by the literature method.[118] (Found: C, 70.95; H, 5.00. $C_{12}H_{10}O_3$ requires C, 71.30; H, 5.00%)

3-Methoxycarbonyl-6-methoxy-2-tetralone (226a)

Magnesium (4.8 g.) was added in two portions to dry methanol (80 ml.) containing two drops of carbon tetrachloride, and after all the magnesium had reacted most of the residual methanol was removed by distillation under reduced pressure. Redistilled, dry dimethyl formamide (80 ml.) was then added and dry carbon dioxide bubbled through the solution for two hours. The residual methanol was then removed by distillation and heating continued until the temperature of the distillate had reached 152°. The cooled solution was then stirred in an atmosphere of carbon dioxide for three hours.

A solution of the tetralone, 217, (2.8 g.) in dry dimethyl formamide (10 ml.) was added with stirring to the above solution of methyl magnesium carbonate, held in an atmosphere of nitrogen. The resultant red solution was then heated at 130° for four hours, with concomitant removal of methanol by distillation. The cooled (0°) reaction mixture was then poured into ice-cold 10% aqueous hydrochloric acid

extracted with ether and the combined organic extracts washed with saturated sodium hydrogen carbonate solution. This basic extract was then acidified with 6N sulphuric acid, thoroughly extracted with ether and the combined organic layers washed with water and dried. Removal of the solvent in vacuo gave a white solid (1 g.) which was recrystallised from ether to afford the keto-acid, 226b, as needles, m.p. 100-102°; $\nu_{max.}$ (CCl_4) 3,530-3,300, 2,700, 1723, 1680, 1662 and 1608 $cm.^{-1}$; $\lambda_{max.}$ 260 nm. (ε= 7,081). (Found: C, 65.70; H, 5.55. $C_{12}H_{12}O_4$ requires C, 65.45; H, 5.50%)

The keto-acid, 226b, was treated with an ethereal solution of diazomethane to give a pale yellow solid which was recrystallised from ether to furnish the pure keto-ester, 226a, as yellow needles, m.p. 108.5-109.5°; $\nu_{max.}$ (CCl_4) 1730, 1710, 1660 and 1630 $cm.^{-1}$; $\lambda_{max.}$ 260 nm. (ε= 5,812), 280 nm. (ε= 2,800) shifting in base to 281 nm. (ε= 9,888) and 286 nm. (ε= 10,130). The n.m.r. spectrum (100 Mc./s.) revealed the enolic proton as a singlet (1H) at τ, -2.81 which disappeared on shaking with D_2O. (Found: C, 66.60; H, 6.20. $C_{13}H_{14}O_4$ requires C, 66.65; H, 6.00%)

2-Pyrrolidino-3-methoxycarbonyl-6-methoxy-3,4-dihydronaphthalene (233b).

The β-keto-ester, 226a, (0.25 g.) was treated with pyrrolidine (0.4 ml.) in benzene solution according to the literature method.[115] Normal isolation procedure furnished a brown oil (0.27 g.) which could not be induced to solidify; $\nu_{max.}$ (film) 1730 and 1610 $cm.^{-1}$. The n.m.r. spectrum (100 Mc./s.) revealed, the aromatic protons (3H) at τ, 2.5-3.5; ArOMe as a singlet (3H) at τ, 6.42; COOMe as a singlet (3H) at τ, 6.58; multiplets (4H) centred at τ, 6.84 and 8.16 assigned to the pyrrolidino protons; proton at C(3) as a multiplet (1H) at τ, 6.19; protons at C(4) doublet (2H) centred at τ, 7.05 (J= 4 c.p.s.); vinylic proton, singlet (1H) at τ, 5.04.

Epimeric, α-methyl-β-(1-methoxycarbonyl-6-methoxy-2-tetralone)-propionaldehydes (238).

In a nitrogen atmosphere an ice-cold mixture of the β-keto-ester, 221,(20.5 g.) and methacrolein (12.5 g.) was added over one hour to a stirred solution of sodium methoxide (from sodium, 0.02 g., and methanol, 500 ml.)

containing hydroquinone (0.01 g.) held at -70°. The reaction mixture was allowed to reach room temperature, stirred for a further hour then neutalised with glacial acetic acid and the solvent removed under reduced pressure. The residual oil was dissolved in ether, washed with saturated sodium carbonate solution, brine and dried. Removal of the solvent *in vacuo* furnished the *keto-aldehydes*, 238, accompanied by a small ammount of the epimeric *ketols*, 239a. This mixture was obtained as a thick oil (31 g.); $\nu_{max.}$ (film) 3,500 (wk) 2,700, and 1740-1700 $cm.^{-1}$. (Mass spectral molecular weight was 304. Calculated molecular weight, 304.)

Epimeric, *methyl-6-hydroxy-7-methyl-3'-methoxy-2,3-benzo-bicyclo(3,3,1)non-2-ene-9-one-1-carboxylates* (239a).

A solution of the keto-aldehydes, 238, (31 g.) in dioxan (150 ml.) was added, in a nitrogen atmosphere, to a stirred ice-cold solution of 6N hydrochloric acid (100 ml.) and dioxan (150 ml.). The reaction mixture was then stirred at room temperature for twenty-four hours, poured into brine and thoroughly extracted with ether. The combined ethereal extracts were washed with brine, saturated sodium hydrogen carbonate solution, brine and dried. Removal of the solvent

afforded the epimeric ketols, 239a, as a viscous oil (27 g.) $\nu_{max.}$ (film) 3,600-3,400 and 1740-1720 $cm.^{-1}$.

Treatment of the above ketols with acetic anhydride and pyridine furnished a viscous oil which was adsorbed on silica gel from light petroleum-ethyl acetate (2:1). Elution with ethyl acetate-light petroleum (1:10) furnished the corresponding keto-acetates, 239b, as a colorless oil $\nu_{max.}$ (film) 1740 and 1720 $cm.^{-1}$. The n.m.r. spectrum revealed, the C(7) methyl protons as a doublet (3H) at τ, 9.1 (J= 6 c.p.s.); the acetate methyl protons as a singlet (3H) at τ, 7.9; ArOMe and COOMe as a singlet (6H) at τ, 6.2; axial proton on C(6) as a broad multiplet centred at τ, 5.2 with a width at half-height of 24 c.p.s.; equatorial proton at C(6) as a multiplet centred at τ, 4.8 with a width at half-height of 8 c.p.s.. The above mixture of acetates on g.l.c. analysis (5% Q.F.1., 225°, 35 ml./min.) indicated the presence of four peaks in the ratio 1:1:1.5:2.5, (R_t= 17.5, 20.5, 22.5 and 26 min. respectively). (Mass spectral molecular weight was 346. Calculated molecular weight, 346.)

The corresponding p-toluenesulphonate esters, 239d, were prepared by treatment of a solution of the ketols, 239a, (40 g.) in dry pyridine (50 ml.) with p-toluene-

sulphonyl chloride (32 g.) and the resulting solution set aside at room temperature for five days. Normal isolation procedure afforded a viscous oil (61 g.) which was adsorbed on silica gel (1.8 Kg.) from light petroleum-ethyl acetate (1:2). Elution with light petroleum-ethyl-acetate (5:1) furnished the mixed tosylates, 239d, (52 g.) as a viscous oil, $\nu_{max.}$ (film) 1740, 1720, 1200, 1190 and 700 $cm.^{-1}$.

Treatment of the ketols, 239a, (13 g.) with ethyl chloroformate (10 ml.) and pyridine (20 ml.) afforded a dark viscous oil (17 g.) which was adsorbed on silica gel (500 g.) from light petroleum-ethyl acetate (1:2). Elution with light petroleum-ethyl acetate (5:1) yielded the corresponding carbonate esters, 239c, (14 g.) as a pink viscous oil $\nu_{max.}$ (film) 1740-1720, 1260 and 800 $cm.^{-1}$. The above product on g.l.c. analysis (1% Q.F.1., 200°, 45 ml./min.) showed four peaks in the ratio 1:1:1.5:2.5, R_t= 15.6, 17.8, 19.6 and 23.4 min. respectively.

Epimeric, methyl-7-methyl-3'-methoxy-2,3-benzobicyclo(3,3,1) non-2-ene-6,9-dione-1-carboxylates (240).

Jones reagent (2 ml.) was slowly added to an ice-cold stirred solution of the ketols, 239a, (1.2 g.) in acetone

(AnalaR, 25 ml.) and stirring continued for thirty minutes. Methanol (1 ml.) was then added and after ten minutes the reaction mixture was poured into brine and extracted with ether. The combined ethereal extracts were washed with brine, saturated sodium hydrogen carbonate solution, brine dried and the solvent removed under reduced pressure to furnish a pale yellow solid. Two successive recrystallisations from benzene-light petroleum (2:1) afforded the diones, 240, (1.02 g.) as small needles, m.p. 163-167°; $\nu_{max.}$ (KCl disc) 1744, 1732 and 1710 $cm.^{-1}$. The analytical sample of this compound showed only one peak on g.l.c. analysis (1% O.F.1., 200°, 45 ml./min.) and (5% O.F.1., 225°, 40 ml./min.) whereas analytical t.l.c. showed two poorly resolved spots (using ethyl acetate-light petroleum (2:3) as developing solvent). These epimeric diones could not be separated by preparative t.l.c..

(Found: C, 67.75; H, 6.15. $C_{17}H_{18}O_5$ requires C, 67.55; H, 6.00% Mass spectral molecular weight was 302. Calculated molecular weight, 302.)

Methyl-6-acetoxy-7-methyl-3'-methoxy-2,3-benzobicyclo(3,3,1) non-2,6-diene-9-one-1-carboxylate (257).

A solution of the diones, 240, (1 g.) in 1M acetic anhydride-10^{-2}M perchloric acid-ethyl acetate (100 ml.) was set aside at room temperature for ten minutes. The reaction mixture was then washed with saturated sodium hydrogen carbonate solution, brine, dried and the solvent removed under reduced pressure to give a brown oil (1.1 g.) which was adsorbed on silica gel (30 g.) from ether-light petroleum (1:5). Elution with ethyl acetate-light petroleum (1:5) afforded a white solid (0.9 g.) which was recrystallised from ethyl acetate-light petroleum (1:2) to furnish the enol-acetate, 257, as prisms, m.p. 165-168°, $\nu_{max.}$ (KCl disc) 1746, 1728, 1262, 1230 and 1212 $cm.^{-1}$. The n.m.r. spectrum revealed, a singlet (3H) at τ, 8.56 assigned to C=C-Me; a singlet (3H) at τ, 7.86 assigned to OCOMe; a singlet (3H) at τ, 6.22 assigned to ArOMe; a singlet (3H) at τ, 6.25 assigned to COOMe. (Found: C, 66.35; H, 5.90. $C_{19}H_{20}O_6$ requires C, 66.30; H, 5.85%)

Epimeric, 6-acetoxy-7-methyl-3'-methoxy-2,3-benzobicyclo-(3,3,1)non-2-ene-9-one-1-carboxylates (241b).

Collidine (80 ml., freshly distilled from potassium hydroxide) was added to a mixture of the keto-acetates, 239b, (1 g., azeotropically dried with benzene, 2x20 ml.) and lithium iodide (3.6 g., dried at 170°/0.05 mm.) under a nitrogen atmosphere. The resultant solution was then heated under reflux for forty-five minutes, cooled and then partitioned between ether-methylene chloride (2:1)-6N hydrochloric acid (100 ml.). The combined organic extracts were washed with 6N hydrochloric acid, brine and saturated sodium hydrogen carbonate solution. The aqueous alkaline extracts were carefully acidified with 6N sulphuric acid, extracted with ether and the combined ethereal layers washed with brine and dried. Removal of the solvent in vacuo furnished the acetoxy-acids, 241b, as a yellow oil (0.825 g.) $\nu_{max.}$ (film) 3,300-2,300, 1730-1700 and 1230 $cm.^{-1}$.

A portion of the above acids was esterified with an ethereal solution of diazomethane in the normal way to furnish the keto-acetates, 239b, giving peak enhancement on g.l.c. analysis (5% Q.F.1., 225°, 35 ml./min.) when co-injected with an authentic sample.

α-Methyl-β-(1-methoxycarbonyl-6-methoxy-2-tetralone)-propionic acids (246).

Jones reagent (2 ml.) was added with stirring to an ice-cold solution of the keto-aldehydes, 238, (1 g.) in acetone (AnalaR, 10 ml.) and the reaction mixture stirred for one further hr. at room temperature. Methanol (2 ml.) was added and the reaction mixture poured into brine and extracted with ether. The combined organic extracts were washed with saturated sodium hydrogen carbonate solution and the alkaline extract* was then acidified with 6N sulphuric acid, extracted with ether and the separated organic phase washed with brine and dried. Removal of the solvent under reduced pressure afforded a yellow oil (0.7 g.) which partially solidified on trituration with ether. Fractional recrystallisation from light petroleum-ether (1:2) afforded a stereochemically pure ketoacid, 246, as needles, m.p. 118-120°; $\nu_{max.}$ (KCl disc) 3,300-2,500, 1740 and 1704 $cm.^{-1}$. (Found: C, 63.95; H, 6.20. $C_{17}H_{20}O_6$ requires C, 63.75; H, 6.30%)

*The original ether extract was washed with brine and dried. Removal of the solvent gave the diones, 240, (0.2 g.) m.p. 163-167° undepressed on admixture with an authentic sample.

$\Delta^{1,10}$-2-Oxa-4-methyl-6-methoxycarbonyl-3'-methoxy-7,8-benzobicyclo(4,4,0)dec-1,7-diene-3-one (245).

(a) A solution of the crystalline keto-acid, 246, (0.3 g.) in acetic anhydride (AnalaR, 20 ml.) was heated under reflux for three hr., then fused sodium acetate (0.05 g.) was added and reflux continued for a further four hours. Normal isolation procedure afforded a yellow oil (0.25 g.) which solidified on trituration with ether. Analytical t.l.c., developed in ethyl acetate-light petroleum (2:5) showed this product to consist of two components in the ratio (1:1) which were separated by preparative t.l.c.. The upper spot proved to be the enol-lactone, 245, which crystallised from ethyl acetate-light petroleum (2:1) as needles, m.p. 144-146°; $\nu_{max.}$ (Nujol) 1740, 1720 and 1680 $cm.^{-1}$. The n.m.r. spectrum revealed the vinylic proton as a triplet (1H) centred at τ, 4.2 (J= 4 c.p.s.). (Found: C, 67.60; H, 6.15. $C_{19}H_{18}O_5$ requires C, 67.55; H, 6.00%)

The lower spot was the enol-acetate, 257, identical in all respects with an authentic sample.

(b) A solution of the keto-acid, 246, (0.5 g.) in 1M acetic anhydride-10^{-3}M perchloric acid-ethyl acetate solution (50 ml.) was set aside at room temperature for ten minutes. The reaction

mixture was then washed with saturated sodium hydrogen carbonate solution, brine, dried and the solvent removed in vacuo to furnish a white solid (0.5 g.) which was re-crystallised from ethyl acetate-light petroleum (2:1) to furnish a single enol-lactone, 245, (0.2 g.) identical with an authentic sample.

Reduction of the enol-lactone with complex hydride.

The crystalline enol-lactone, 245, (0.25 g.) was treated with a suspension of lithium hydridotri-t-butoxy-aluminate (0.33 g.) in dry tetrahydrofuran in the usual way. Normal isolation procedure yielded the axial ketols, 242a, as a yellow oil (0.23 g.); $\nu_{max.}$ (film) 3,500 and 1740-1720 $cm.^{-1}$. A portion of the crude product was acetylated in the usual manner and subjected to g.l.c. analysis (5% Q.F.1., 225°, 35 ml./min.) which indicated the presence of two components in the ratio 1:1, R_t = 17.5 and 22.5 min..

The corresponding p-toluenesulphonates, 242c, were obtained as a colorless viscous oil, $\nu_{max.}$ (film) 1740, 1720, 1200, 1190 and 700 $cm.^{-1}$. These derivatives were purified by preparative t.l.c. to remove small quantities of unreacted ketols.

Reduction of the diones, 240, with lithium hydridotri-t-butoxyaluminate.

A suspension of lithium hydridotri-t-butoxyaluminate (0.41 g.) in dry tetrahydrofuran (5 ml.) was added with stirring to a solution of the diones, 240, (0.37 g.) in dry tetrahydrofuran (5 ml.) and the solution heated under reflux for two hours. 6N hydrochloric acid was then added to the cooled solution and the reaction mixture was then extracted with ether. The combined organic extracts were washed with brine, saturated sodium hydrogen carbonate solution, brine and dried. Removal of the solvent in vacuo gave a yellow oil (0.35 g.) which partially crystallised from ethyl acetate-light petroleum (1:2) to yield the starting diones (0.1 g.). Evaporation of the mother liquors afforded the equatorial ketols, 243a, as an oil (0.2 g.); $\nu_{max.}$ (film) 3,500 and 1740-1710 $cm.^{-1}$. Acetylation of this fraction followed by g.l.c. analysis (conditions as above) revealed the presence of two compounds in the ratio 1:1, R_t = 20.5 and 26 min..

The corresponding p-toluenesulphonates, 243c, were obtained as a colorless oil after purification by t.l.c., $\nu_{max.}$ (film) 1740-1720, 1200, 1190 and 700 $cm.^{-1}$.

Methyl-7-methyl-3'-methoxy-2,3-benzobicyclo(3,3,1)non-2,6-diene-9-one-1-carboxylate (152).

(A) Pyrolysis procedures.

(a) Pyrolysis of the mixed acetates (239b)

The mixed acetates, 239b, were heated in a Woods alloy bath held at 350°, for thirty min.. The reaction mixture was then dissolved in ether and the carbonaceous material filtered off. The filtrate was then washed with saturated sodium hydrogen carbonate solution, brine, dried and the solvent removed in vacuo to give a yellow oil which on g.l.c. analysis (5% Q.F.1., 225°, 35 ml./min.) showed mainly starting material to be present.

(b) Pyrolysis of the mixed carbonates (239c)

The mixed carbonates, 239c, (5 g.) were heated in a Woods alloy bath held at 350° for twenty min.. The dark-brown product was dissolved in ether, washed with saturated sodium carbonate solution, brine and dried. Removal of the solvent under reduced pressure afforded a viscous brown oil (4 g.) which was adsorbed on alumina (grade III basic, 120 g.) from ether-light petroleum (1:2). Elution with light petroleum-ethyl acetate (50:1) afforded a pale yellow solid which was recrystalised from ethyl acetate-light petroleum

(1:2) to furnish the keto-olefin, 152, (0.2 g.) as clusters of needles, m.p. 104.5-105°; $\nu_{max.}$ (KCl disc) 1740, 1720, 824, 815, 812 and 808 $cm.^{-1}$; $\nu_{max.}$ (CCl_4) 1747 and 1733 $cm.^{-1}$. The n.m.r. spectrum (100 Mc./s.) revealed a singlet (3H) at τ, 8.44 assigned to C=C-Me; singlet (3H) at τ, 6.34 assigned to COOMe; singlet (3H) at τ, 6.30 assigned to ArOMe; and a multiplet (1H) at τ, 4.74 assigned to the vinylic proton. (Found: C, 71.35; H, 6.05. $C_{17}H_{18}O_4$ requires C, 71.30; H, 6.35% Mass spectral molecular weight was 286. Calculated molecular weight, 286.)

The variants of this procedure are summarised in Table 3.

The above keto-olefin, 152, was hydrolysed with 2N aqueous sodium hydroxide to furnish the corresponding keto-acid, 152 COOMe replaced by COOH, which crystallised from aqueous methanol as clusters of needles, m.p. 210-218°; $\nu_{max.}$ (KCl disc) 3,300-2,600, 1710, 1690, 840, 820 and 798 $cm.^{-1}$. (Found: C, 66.05; H, 6.30. $C_{16}H_{16}O_4.1H_2O$ requires C, 66.20; H, 6.25%)

(B) Solvolysis procedures.

(a) A solution of the axial tosylates, 242c, (0.07 g.) in 10% aqueous acetic acid (20 ml.) was heated under reflux for twelve hours. The solution was then taken to dryness, the residue dissolved in ether, washed with brine and dried. Removal of the solvent under reduced pressure afforded a carboxylic acid (0.035 g.) which was treated with diazomethane in the normal manner to furnish the crude olefin-ester, 152, and subsequent recrystallisation from ethyl acetate-light petroleum (1:2) yielded a pure sample, m.p. 104-105°, undepressed on admixture with an authentic sample. Spectral, chromatographic and analytical data were identical with those of an authentic sample.

(b) A solution of the equatorial tosylates, 243c, (0.1 g.) in 10% aqueous acetic acid (20 ml.) were solvolysed as above . Normal isolation procedure, followed by treatment of the product with diazomethane yielded a viscous oil (0.05g.) which was adsorbed on to silica gel (5 g.) from benzene-light petroleum (1:2). Elution with ethyl acetate-light petroleum (1:50) afforded the olefin ester, 152, (0.01 g.). Further elution with ethyl acetate-light petroleum (4:5)

afforded the ketols, 243a, (0.03 g.) which on g.l.c. analysis of the corresponding acetates, 243b, (conditions as above) revealed the presence of two components in the ratio (1:1) R_t= 20.5 and 26 min..

A portion of the above ketol fraction was oxidised with Jones reagent in the normal manner to give the diones, 240, identical in all respects with an authentic sample.

(c) A solution of the four epimeric tosylates, 239d, (2g.) in 10% aqueous acetic acid (50 ml.) were solvolysed as above. Normal isolation procedure followed by treatment of the crude product with diazomethane afforded a viscous oil (1.5 g.) a small portion of which was acetylated and shown by g.l.c. analysis (conditions as above) to contain three components. Co-injection experiments established that the least polar peak corresponded to the olefin, 152, and the remaining components were the equatorial acetates, 243b, R_t= 20.5 and 26 min.. Column chromatography of the above product on silica gel (30 g.) afforded the olefin, 152, (0.6 g.) and the ketols, 243a, (0.6 g.).

(d) A solution of the axial tosylates, 242c, (0.025 g.) in dry acetic acid[121] (12 ml.) containing fused sodium

acetate (0.005 g.) was heated under reflux for thirty-six hours. The solution was then taken to dryness, water (10 ml.) added and the mixture extracted with ether. The combined ethereal extracts were washed with brine, saturated sodium carbonate solution, brine and dried. Removal of the solvent in vacuo yielded the keto-olefin, 152, (0.008g.) as sole product.

(e) A solution of the equatorial tosylates, 243c, (0.04 g.) in dry acetic acid (12 ml.) containing fused sodium acetate (0.004 g.) was heated under reflux for thirty-six hours. Normal isolation procedure furnished a brown oil (0. 014 g.) which by g.l.c. analysis (conditions as above) was shown to consist of two components in the ratio (3:1), the former being the olefin, 152, and the latter an acetate, R_t= 22.5 min..

(f) A solution of the four epimeric tosylates, 239d, (1.8 g.) in dry acetic acid (50 ml.) containing fused sodium acetate (0.35 g.) was heated under reflux for thirty-six hours. Normal isolation procedure followed by column chromatography of the recovered oil (1.1 g.) on silica gel (30 g.) gave the olefin, 152, (0.5 g.) and a white solid (0.38 g.) which was recrystallised from ethyl acetate-light petroleum (1:2) to

furnish the axial acetate, 248, as prisms, m.p. 136-138° $\nu_{max.}$ (KCl disc) 1736, 1718, 1244, 1220 and 812 cm.$^{-1}$. The n.m.r. spectrum showed, a doublet (3H) at τ, 9.1 (J= 6 c/s) assigned to C(7) methyl protons; a singlet (3H) at τ, 7.9 assigned to OCOMe; a singlet (6H) at τ, 6.2 assigned to superimposed ArOMe and COOMe; multiplet (1H) at τ, 4.75, width at half-height, 3 c.p.s., assigned to the C(6) methine proton. G.l.c., R_t= 22.5 min. (conditions as above). (Found: C, 65.80; H, 6.70. $C_{19}H_{22}O_6$ requires C, 65.90; H, 6.40%)

The above acetate, 248, was reduced with sodium borohydride in the usual manner to furnish the alcohol, 250, which was recrystallised from ethyl acetate-light petroleum (1:2) to afford an analytical sample as clusters of needles, m.p. 161-163°, $\nu_{max.}$ (Nujol) 3,550, 1730-1720, 1240 and 840 cm.$^{-1}$, $\nu_{max.}$ (CCl_4) high dilution, 3592 cm.$^{-1}$. The n.m.r. spectrum revealed, a doublet (3H) at τ, 9.1 assigned to the C(7) methyl protons; singlet (3H) at τ, 7.6 assigned to OCOMe; a multiplet (1H) at τ, 4.9, width at half-height, 3 c.p.s., assigned to the C(6) methine proton. (Found: C, 65.65; H, 6.95. $C_{19}H_{24}O_6$ requires C, 65.50; H, 6.95%)

Catalytic hydrogenation of the olefin (152).

(a) Solutions of the olefin, 152, in ethyl acetate (AnalaR) were hydrogenated separately over, 10%, 5%, and 1% palladium on carbon catalysts at atmospheric pressure for twenty-four hours. The reaction mixtures were then filtered through Celite 535, the filtrates taken to dryness in vacuo, and the products subjected to g.l.c. analysis (1% Q.F.1., 175°, 45 ml./min.) which showed that in all three cases three peaks in the ratio 10:1:1, R_t= 9.5, 10.25 and 12 min. respectively, the first peak giving peak enhancement on co-injection with a sample of starting olefin.

(b) A solution of the olefin, 152, (0.09 g.) in ethanol (15 ml.) was hydrogenated over 10% palladium on carbon (0.05g.) for twelve hours. Normal isolation procedure afforded a colorless oil (0.09 g.) $\nu_{max.}$ (film) 3,500, 1740, 1720 and 820 $cm.^{-1}$, which on g.l.c. analysis (conditions as above) indicated the presence of three components in the ratio 2:1:1, R_t= 8.25, 10.25 and 12 min. respectively. Treatment of this product with Jones reagent furnished an oil (0.08 g.) $\nu_{max.}$ (film) 1740, 1720 and 810 $cm.^{-1}$, which on g.l.c. analysis (conditions as above) revealed two components in

the ratio (1:1.4) R_t= 10.25 and 12 min. respectively which were assigned to the axial ketone,169, and equatorial ketone, 168, respectively. In the n.m.r. spectrum (100 Mc./s.) of the above product the C(7) methyl protons appeared as a doublet (3H) centred at τ, 9.2 (J= 6 c.p.s.). Micro-distillation furnished an analytical sample, b.p. 200°/ 0.05 mm. (bath temp.). (Found: C, 71.00; H, 7.20. $C_{17}H_{20}O_4$ requires C, 70.80; H, 7.00% Mass spectral molecular weight was 286. Calculated molecular weight 286.)

A sample of the above product was reduced with sodium borohydride in the usual manner to furnish a mixture of the corresponding alcohols, 251, as an oil, $\nu_{max.}$ (film) 3,500, 1730 and 820 $cm.^{-1}$. The n.m.r. spectrum (100 Mc./s.) of which showed two doublets (each (3H)) at τ, 9.2 and 9.6, (J= 6 c.p.s. in each case), assigned to the C(7) methyl protons in, 252a and 253a, respectively.

(c) A solution of the olefin, 152, (0.07 g.) in ethanol (15 ml.) was hydrogenated over 1% palladium on carbon (0.05 g.). Normal isolation procedure and treatment of the crude product with Jones reagent furnished the starting olefin, 152, and the epimeric ketones, 168 and 169a, in the ratio 10:1:9 as estimated by g.l.c. analysis (conditions as above).

Methyl-equatorial,7-methyl-3'-methoxy-2,3-benzobicyclo-(3,3,1)non-2-ene-9-one-1-carboxylate (168).

A solution of the olefin, 152, (0.8 g.) in ethanol (50 ml.) was hydrogenated over 5% palladium on carbon (0.2 g.) for sixteen hours. Normal isolation procedure gave a colorless oil (0.8 g.) $\nu_{max.}$ (film) 3,500, 1740, 1720 and 820 $cm.^{-1}$, which on treatment with Jones reagent afforded a white solid (0.8 g.). G.l.c. examination (conditions as above) of this product indicated the presence of two components in the ratio 1:10, R_t= 10.25 and 12 min. respectively. This product was recrystallised from ethyl acetate-light petroleum (1:2) to yield the pure equatorial ketone,168, as prisms (0.6 g.) m.p. 125-127°; $\nu_{max.}$ (KCl disc) 1740, 1718, 870, 852, 818 and 806 $cm.^{-1}$. The n.m.r. spectrum (100 Mc./s.) revealed the C(7) methyl protons as a doublet (3H) centred at τ, 9.2 (J= 6 c.p.s.). The product was homogeneous by g.l.c. analysis (1% Q.F.1., 175°, 45 ml./min.) R_t= 12 min.. (Found: C, 70.60; H, 7.15. $C_{17}H_{20}O_4$ requires C, 70.80; H, 7.00%)

Alkaline hydrolysis of the ketone, 168, furnished the corresponding carboxylic acid,168 COOMe replaced by COOH, which was recrystallised from aqueous methanol to give an

analytical sample (plates) m.p. 257-260°; $\nu_{max.}$ (Nujol) 3,300-2,600, 1720-1690 and 820 cm.$^{-1}$. (Found: C, 66.00; H, 7.05. $C_{16}H_{18}O_4.1H_2O$ requires C, 65.75; H, 6.90%)

A portion of the above saturated ketone,168, was reduced with sodium borohydride in the usual manner to furnish the corresponding alcohols,252a, as an oil; $\nu_{max.}$ (film) 3,500 and 1730 cm.$^{-1}$. The n.m.r. spectrum (100 Mc./s.) revealed the C(7) methyl protons as a doublet (3H) centred at τ, 9.2 (J= 6 c.p.s.).

The above alcohols, 252a, were hydrolysed with aqueous base in the usual manner to give the corresponding hydroxy-acids, 252b, which crystallised from aqueous methanol as prisms, m.p. 160-167°; $\nu_{max.}$ (Nujol) 3,500-2,600 and 1700-1690 cm.$^{-1}$. (Found: C, 67.70; H, 7.54. $C_{16}H_{20}O_4.\frac{1}{2}H_2O$ requires C, 67.35; H, 7.40%)

Methyl-axial,7-methyl-3'-methoxy-2,3-benzobicyclo(3,3,1) non-2-ene-9-one-1-carboxylate (169= 169a).

A solution of the olefin, 152, (1 g.) in ethyl acetate (AnalaR, 20 ml.) was hydrogenated in the presence of 5% rhodium on carbon (0.3 g.) at atmospheric pressure. After eight hours one molar equivalent of hydrogen had been absorbed.

Normal isolation procedure yielded a colorless oil (1 g.) which solidified on standing. Recrystallisation of the product from ethyl acetate-light petroleum (1:2) furnished the axial ketone, 169a, as small needles (0.9 g.) m.p. 82-84°; $\nu_{max.}$ (KCl disc) 1742, 1724, 1232, 854, 846, 818 and 810 cm.$^{-1}$; $\nu_{max.}$ (CCl_4) 1746 and 1732 cm.$^{-1}$. In the n.m.r. spectrum (100 Mc./s.) the protons attached to C(7) were revealed as a doublet (3H) centred at τ, 9.18 (J= 6 c.p.s.). This product was homogeneous by g.l.c. analysis (same conditions as above) R_t= 10.25 min.. (Found: C, 70.50; H, 7.00. $C_{17}H_{20}O_4$ requires C, 70.80; H, 7.00%)

The above ketone, 169a, was hydrolysed, in the usual manner to the corresponding carboxylic acid, 169a COOMe replaced by COOH, which crystallised from aqueous methanol as needles, m.p. 240-248°; $\nu_{max.}$ (Nujol) 3,300-2,600, 1720-1690 and 820 cm.$^{-1}$. (Found: C, 65.95; H, 7.15. $C_{16}H_{18}O_4.1H_2O$ requires C, 65.75; H, 6.90%)

A portion of the ketone, 169a, was reduced with sodium borohydride in the usual manner to give the corresponding alcohols, 253a, as a colorless oil; $\nu_{max.}$ (film) 3,500 and 1730 cm.$^{-1}$. In the n.m.r. spectrum (100 Mc./s.) the C(7) methyl protons appeared as a doublet (3H) at τ, 9.6 (J= 6 c.p.s)

The corresponding hydroxy-acids, 253b, crystallised from

aqueous methanol as plates, m.p. 170-174°; $\nu_{max.}$ (Nujol) 3,500-2,600 and 1700 $cm.^{-1}$. (Found: C, 67.55; H, 7.60. $C_{16}H_{20}O_4 \cdot \frac{1}{2} H_2O$ requires C, 67.35; H, 7.40%)

Methyl-7-methyl-9-ethylenedioxy-3'-methoxy-2,3-benzobicyclo(3,3,1)non-2,6-diene-1-carboxylate(254).

A solution of the olefin,152, (0.3 g.) in benzene (AnalaR, 10 ml.) was added to a mixture of ethylene glycol (1 ml.) p-toluenesulphonic acid (0.05 g.) in dry benzene (AnalaR, 20 ml.) refluxing under a Soxhelet extractor containing calcium hydride. After a twelve hours reflux period the cooled solution was washed with brine, saturated sodium hydrogen carbonate solution brine and dried. Removal of the solvent under reduced pressure furnished a white solid which was recrystallised from ethyl acetate-light petroleum (1:2) to afford the olefin-ketal, 254, as needles (0.4 g.) m.p. 149-151°; $\nu_{max.}$ (KCl disc) 1720, 1250, 1130, 1090, 1030 and 820 $cm.^{-1}$. (Found: C, 68.70; H, 6.50. $C_{19}H_{22}O_5$ requires C, 69.05; H, 6.70%)

Attempted catalytic hydrogenation of the enol-acetate (257).

A solution of the enol-acetate, 257, (0.02 g.) in dioxan (AnalaR, 30 ml.) was shaken in an atmosphere of hydrogen with platinum oxide (0.01 g.) for twelve hours. Normal isolation procedure furnished an oil (0.02 g.) $\nu_{max.}$ (film) 3,500 and 1720-1740 $cm.^{-1}$, which was treated with Jones reagent in the normal manner to furnish only the starting enol-acetate.

Benzyl-7-methyl-3'-methoxy-2,3-benzobicyclo(3,3,1)non-2-ene-9-one-1-carbamate (258f).

(A) Mixed anhydride procedure.

A solution of the keto-acid, 258a, was prepared by adding sufficient acetone to a suspension of the acid, 258a, (0.35 g.) in water (2 ml.). This solution was then cooled in ice, triethylamine (0.2 ml.) in acetone (2 ml.) added with stirring followed by ethyl chloroformate (0.15 ml.) in acetone (2 ml.) and the resultant solution then stirred for thirty min. at room temperature. A solution of sodium azide (0.09 g.) in water (2 ml.) was added dropwise and stirring continued for one hour. The reaction mixture was

poured into ice and the separated oil extracted with ether, washed with brine and dried. (Acidification of the aqueous layer gave, on ether extraction, the starting acid (0.2 g.). The oily neutral product (0.1 g.) ($\nu_{max.}$ (film) 2,400, 1720, and 1710 $cm.^{-1}$) was heated under reflux in dry toluene for twenty hours. Evaporation of a portion of this solution furnished the isocyanate, 258e, as a viscous oil, $\nu_{max.}$ (film) 2,600 and 1720 $cm.^{-1}$.

Benzyl alcohol (0.2 ml.) was then added to the bulk of the toluene solution and the resultant solution was heated under reflux for twenty hours. Evaporation of the solvent gave a viscous oil (0.2 g.) which was adsorbed on to silica gel (12 g.) from ethyl acetate-light petroleum (1:3). Elution with ethyl acetate-light petroleum (1:5) yielded the benzyl-carbamate, 258f, (0.17 g.) as a viscous oil $\nu_{max.}$ (film) 3,400, 1720 and 1510 $cm.^{-1}$. (Mass spectral molecular weight, 379. Calculated molecular weight 379.)

(B) Phosphorus oxychloride procedure.

(a) A solution of triethylamine (0.35 ml.) phosphorus oxychloride (0.45 ml.) in dry tetrahydrofuran (5 ml.) was added dropwise with stirring to a solution of the keto-acid, 258a, (1 g.) in dry tetrahydrofuran (15 ml.) containing

activated sodium azide[125] (0.3 g.). The resultant mixture was stirred for three hours and normal isolation procedure then furnished the starting acid (0.035 g.), which was discarded, and a neutral fraction (0.8 g.) $\nu_{max.}$ (film) 2,400, 1720 and 1710 $cm.^{-1}$, which was dissolved in dry toluene, heated under reflux for twenty hr., benzyl alcohol (0.35 g.) added and heating continued for a further twenty hours. This solution was then taken to dryness to furnish the benzyl carbamate, 258f, (0.17 g.) identical to the product obtained above.

(b) The above procedure (a) was repeated using benzene as the solvent. Although no acidic component was recovered the isolated neutral fraction showed anomolous ester absorption in its infrared spectrum and consequently further elaborations were not carried out using this material.

(c) A solution of the keto-acid, 258a, (0.14 g.) in dry benzene (10 ml.) was added slowly to a stirred suspension of triethylamine (0.3 ml.) phosphorus oxychloride (0.06 ml.) and activated sodium azide (0.035 g.) in dry benzene (10 ml.). Normal isolation procedure furnished no acidic material and a neutral product which was heated with dry toluene in the usual manner to afford the isocyanate, 258e, which was treated with benzyl alcohol (0.03 g.) to afford the carbamate (258f).

Amine hydrobromide (258g).

(a) A solution of the benzyl-carbamate, 258f, (0.17 g.) in anhydrous ether was treated with reagent-grade hydrobromic acid in acetic acid (AnalaR, 0.3 ml.) to furnish an intractible tar.

(b) A solution of the benzyl carbamate, 258f, (0.19 g.) in anhydrous ether was treated with dry hydrobromic acid,[128] to give, on evaporation of the solvent, a viscous oil, which was then heated in vacuo to remove benzyl bromide. Trituration of the residue with dry ether afforded the amine hydrobromide, 258g, as a hygroscopic amorphous solid, $\nu_{max.}$ (Nujol) 3,500-2,500, and 1720 $cm.^{-1}$. When this product was treated with acetic anhydride and pyridine the corresponding acetamide, 258i, was obtained as a viscous oil, $\nu_{max.}$ (film) 3,400, 1720, 1670 and 1510 $cm.^{-1}$.

Amine hydrochloride (258h)

A solution of the isocyanate, 258e, (0.13 g.) in toluene (20 ml.) was slowly added to vigorously stirred concentrated hydrochloric acid and the resultant mixture heated for one hr.. The aqueous layer was then separated, taken to dryness in vacuo and the residue azeotropically dried with three

successive portion of toluene (20 ml.) to furnish the amine hydrochloride, 258h, as a colorless glass, which on treatment with acetic anhydride and pyridine yielded the acetamide, 258i, (0.1 g.) identical to the product obtained by procedure (b) (above).

1-Pyruvamido-7-methyl-3'-methoxy-2,3-benzobicyclo(3,3,1)non-2-ene-9-one (258j= 154).

(a) Via the amine hydrobromide (258g)

A cooled suspension of pyruvic acid (0.08 g.) triethylamine (0.13 ml.) and the amine hydrobromide, 258g, (0.2 g.) in dry tetrahydrofuran (5 ml.) was treated with a solution of triethylamine (0.13 ml.) phosphorus oxychloride (0.08 ml.) in dry tetrahydrofuran (5 ml.) with stirring. After one hr. water (10 ml.) was added and the solvent removed in vacuo. The product was then dissolved in ether, washed with brine, saturated sodium hydrogen carbonate solution, brine and dried. Removal of the solvent furnished a purple oil (0.15g.) which was purified by preparative t.l.c. using ethyl acetate-light petroleum (2:5) for development, to furnish the pyruvamide, 258j, (0.03 g.) as a viscous oil, $\nu_{max.}$ (film) 3,400, 1720, 1680 and 1510 $cm.^{-1}$, $\lambda_{max.}$ 209, 280 and 287 nm..

(Mass spectral molecular weight, 315; calculated 315)

(b) Via amine hydrochloride (258h)

The above procedure was repeated using the amine hydrochloride, 258h, (0.1 g.). Normal isolation and purification procedures furnished the pyruvamide, 258j, (0.01 g.) as an oil.

Methyl-equatorial,7-methyl-9-ethylenedioxy-3'-methoxy-2,3-benzobicyclo(3,3,1)non-2-ene-1-carboxylate (261a).

The equatorial ketone,168, (0.3 g.) was treated with ethylene glycol (1 ml.) p-toluenesulphonic acid (0.005 g.) in benzene solution in the normal manner. The saturated ketal ester, 261a, (0.2 g.) was obtained after normal isolation procedure, and crystallised from ethyl acetate-light petroleum (1:2) as clusters of needles, m.p. 163-165°; $\nu_{max.}$ (Nujol) 1720, 1250 and 1000 $cm.^{-1}$. (Found: C, 68.90; H, 7.05. $C_{19}H_{24}O_5$ requires C, 68.65; H, 7.30%)

A mixture of the above ester,261a, (0.5 g.) potassium hydroxide (0.2 g.) and ethylene glycol (10 ml.) was heated under reflux for twenty min.. Water (10 ml.) was then added and the resultant solution extracted with ether. Acidification of the aqueous extract furnished the corresponding carboxylic acid, 261b, as an oil (0.4 g.) $\nu_{max.}$ (film)

3,500-2,600 and 1700 $cm.^{-1}$.

A portion of the above acid, 261b, was treated with diazomethane in the usual manner to furnish the crystalline ketal ester, 261a, identical with an authentic sample.

Attempted preparation of the ketal-acid chloride (261d)

A solution of the ketal-acid, 261b, (0.1 g.) oxalyl chloride (AnalaR, 2 ml.) and dry benzene (20 ml.) was heated under reflux for twenty-four hr.. Removal of the solvent in vacuo furnished only starting material.

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Ethyl-β-(2-oxocyclohexyl)-propionate (270a) was prepared by the method of Stork.[131]

β-(2-Oxocyclohexyl)-propionic acid (270b) was prepared by by the literature procedure.[131]

$\Delta^{1,6}$-2-Oxabicyclo(4,4,0)decen-3-one (268) and $\Delta^{1,10}$-2-Oxabicyclo(4,4,0)decen-3-one (269).

A solution of the above keto-acid, 270b, (10 g.) and

freshly fused sodium acetate (0.5 g.) in acetic anhydride (AnalaR, 250 ml.) was heated under reflux for four hr.. After removal of acetic anhydride by azeotropic distillation with xylene under reduced pressure, the residual brown oil was dissolved in ether, washed with brine, saturated sodium hydrogen carbonate solution, brine and dried. Removal of the solvent *in vacuo* furnished an oil (7 g.) which was adsorbed on silica gel (220 g.) from light petroleum. Elution with ether-light petroleum (1:4) gave $\Delta^{1,6}$-2-*oxa*-*bicyclo*(4,4,0)*decen*-3-*one*, 268, (5.2 g.); b.p. 86°/0.5 mm.; n_D^{20} = 1.5403; $\nu_{max.}$ (CCl_4) 1772, 1709, 1152 and 1115 $cm.^{-1}$. (Found: C, 70.40; H, 7.9. $C_9H_{12}O_2$ requires C, 71.05; H, 7.95%)

Further elution with the same solvent mixture gave $\Delta^{1,10}$-2-*oxabicyclo*(4,4,0)*decen*-3-*one*, 269, (1.1 g.), which sublimed as a white solid, m.p. 42-43°; $\nu_{max.}$ (CCl_4) 1766, 1683 and 1150 $cm.^{-1}$. The n.m.r. spectrum revealed the vinylic proton as a multiplet (1H) at τ, 4.73. (Found: C, 70.55; H, 7.65. $C_9H_{12}O_2$ requires C, 71.05; H, 7.95%)

β-(2-*Oxocyclohexyl*)-*propionaldehyde* (271)

A suspension of lithium hydridotri-t-butoxyaluminate (22.1 g.) in dry tetrahydrofuran (150 ml.) was added dropwise over two hours to a stirred solution of the tetra-

substituted enol-lactone, 268, (12 g.) in tetrahydrofuran (75 ml.) held at -70° in a nitrogen atmosphere. The mixture was allowed to attain room temperature, stirred for a further fifteen hours, then acidified with 6N hydrochloric acid, and thoroughly extracted with ether. The combined organic extracts were washed with brine, saturated sodium hydrogen carbonate solution and dried. Removal of the solvent in vacuo afforded a pale yellow oil (10.7 g.) which on distillation under reduced pressure furnished pure β-(2-oxocyclohexyl)-propionaldehyde, 271, (8.0 g.) b.p. 86-89°/0.8 mm.; n_D^{23} 1.4743.

Reduction of $\Delta^{1,10}$-2-oxabicyclo(4,4,0)decen-3-one (269).

(a) A solution of the trisubstituted enol-lactone, 269, (8.1 g.) in dry tetrahydrofuran (100 ml.) was treated with lithium hydridotri-t-butoxyaluminate (16.3 g.) as described above. Normal isolation procedure afforded a neutral oil (3.1 g.) and the keto-acid, 270b, (3.8 g.), the latter representing 47% recovery of unreacted enol-lactone hydrolysed during isolation. The neutral material was adsorbed on silica gel (91 g.) from benzene-light petroleum (1:1). Elution with ether light petroleum (3:2) separated a yellow oil (1.7 g.) from which 1-hydroxy-2-oxabicyclo(4,4,0)decane, 274, crystallised

on standing. Recrystallisation from pentane afforded an analytical sample as prisms, m.p. 65-70° (dehydration on heating); $\nu_{max.}$ (CCl_4) 3590, 1077 and 943 $cm.^{-1}$. (Found: C, 68.5; H, 9.90. $C_9H_{16}O_2$ requires C, 69.20; H, 10.30%)

Further elution with ether afforded a semi-solid mixture of ketols, 272 and 273, (1.25 g.) which were separated by preparative t.l.c. using ethyl acetate-light petroleum (1:5) for development. Axial, 2-hydroxybicyclo(3,3,1)nonan-9-one, 272, crystallised from ethyl acetate-light petroleum (1:3) as prisms, m.p. 169-171° (sealed tube); $\nu_{max.}$ (CCl_4) 3622, 1731 and 955 $cm.^{-1}$; the n.m.r. spectrum showed a multiplet (1H) at τ, 5.75, with a width at half-height of 8 c.p.s., assigned to the carbinyl proton. (Found: C, 70.15; H, 8.70. $C_9H_{14}O_2$ requires C, 70.10; H, 9.10%)

The corresponding p-toluenesulphonate, 272 OH replaced by $OSO_2C_7H_7$, crystallised from methanol as plates, m.p. 122-123°. In the n.m.r. spectrum of this derivative the C(2) methine proton appeared as a multiplet (1H) at τ, 4,9, with a width at half-height of 8 c.p.s.. (Found: C, 62.65; H, 6.65. $C_{16}H_{20}O_4S$ requires C, 62.35; H, 6.55%)

Finally, a portion of the ketol mixture direct from chromatography was acetylated in the usual manner and shown by g.l.c. analysis (10% A.P.L., 150°, 55 ml./min.) to contain

two components in the ratio 95:5, R_t= 13.55 and 15.25 min. respectively, which were assigned to the axial and equatorial acetates, 272 and 273 (OH replaced by OAc), respectively.

(b) A stirred solution of the trisubstituted enol-lactone, 269, (1.19 g.) in dry tetrahydrofuran (20 ml.) was treated with a suspension of lithium hydridotri-t-butoxyaluminate (1.98 g.) in dry tetrahydrofuran (10 ml.) in the usual manner. The reaction mixture was allowed to reach room temperature and then heated under reflux for sixteen hours. Normal isolation procedure a neutral vicous oil (0.56 g.) and keto-acid, 270b, (0.2 g.).

A portion of the crude neutral material was acetylated in the usual manner and was shown by g.l.c. analysis (conditions as above) to contain the equatorial and axial epimers in the ratio 1.5:1.

(c) The trisubsituted enol-lactone, 269, (0.45 g.) was reduced with lithium hydridotri-t-butoxyaluminate (0.75 g.) in the usual manner. The reaction mixture was allowed to reach room temperature and was then stirred for four days in a nitrogen atmosphere. Normal isolation procedure gave a neutral component (0.14 g.) and the keto-acid, 270b, (0.15 g.)

Acetylation of the neutral component followed by g.l.c. analysis (conditions as above) indicated the presence of only one epimer, 272 (OH replaced by OAc).

The analytical and spectral data of the above compounds, and their derivatives have also been described by Dr. T. Stewart.[98]

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SUMMARY

The preparation of a series of substituted bicyclo-(3,3,1)nonane derivatives which possess the requisite functionality for rings B and D of lycopodine is described, culminating in the direct application of these results towards an attempt at a stereospecific synthesis of lycopodine.

The model compounds were prepared by treatment of a suitably substituted cyclohexyl-β-keto-ester with acrolein or methacrolein to furnish the corresponding substituted β-(1-ethoxycarbonyl-2-oxocyclohexyl)-propionaldehyde. These keto-aldehydes were then treated with either hydrochloric acid or triethylamine to furnish the corresponding ethyl-epimeric, hydroxybicyclo(3,3,1)nonan-9-one-1-carboxylates. Various unfruitful attempts to convert these ketols (and their derivatives) into the corresponding bicyclic-keto-olefin are described. In the event it was found that solvolysis of the axial p-toluenesulphonate esters in 10% aqueous acetic acid furnished the desired olefin in high yield.

The difficulties encountered in the preparation of 1-methoxycarbonyl-6-methoxy-2-tetralone are described,* together with a complete spectral and chemical proof of the proposed structure. A Michael reaction between this β-keto-ester and

methacrolein then furnished two diastereoisomeric keto-aldehydes which on treatment with hydrochloric acid afforded four epimeric ketols. Buffered acetolysis of the corresponding p-toluenesulphonates then gave methyl-7-methyl-3'-methoxy-2,3-benzobicyclo(3,3,1)non-2,6-diene-9-one-1-carboxylate, in good yield. Catalytic hydrogenation of this olefin over 5% palladium on carbon resulted in the equatorial methyl dihydro derivative, and reduction over 5% rhodium on carbon furnished the axial methyl dihyro derivative. These stereochemical assignments were made with the aid of nuclear magnetic resonance spectroscopy. Insertion of the nitrogen atom and the attempts to construct ring A are then reported.

The reductive rearrangement of δ-enol-lactones to furnish the thermodynamically less stable axial bicyclic ketol, is discussed in the addendum. Further evidence in favour of the proposed mechanism* is presented.

*included publication.