APPROACHES TO THE SYNTHESES OF ACORONE AND LYCOPODINE

THESIS

presented to the University of Glasgow

for the Degree of Ph.D.

by

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1966

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I wish to express my sincere appreciation of the advice and encouragement readily given by my supervisors, Drs. W. Parker and J. Martin during the past three years. I should also like to thank Professor R.A. Raphael, F.R.S., for his continued interest and enthusiasm.

My thanks are also due to Mr. J.M.L. Cameron, B.Sc., and his staff, for micro-analyses, to Mrs. F. Lawrie and Miss A.M. Robertson for infrared spectra, to Dr. J. Martin and the staff of the Mass Spectrometry Department for mass spectra, to Messrs. J. Gall and J. Lennon for nuclear magnetic resonance spectra, and finally to Mr. G. Milmine for technical assistance.

I am grateful to the Carnegie Trust for the Universities of Scotland for the award of a Research Scholarship, to provide for my maintenance over the last three years.

CONTENTS

SUMMARY

PART I

Various attempts to synthesise acorone, or a mixture of two or more of the three possible isomeric acorones, acorone, isoacorone and cryptoacorone, are described. The course of the synthesis was successful up to a late stage, but attempts either to introduce an isopropyl group into 4-ethoxycarbonyl-1,7-dimethylspiro(5,4)decan-3,6-dione, or to effect internal cyclisation of ethyl 2-isopropyl-5-(4-methyl-5-oxocyclohex-1(6)-enyl)-3-oxohexanoate, proved fruitless; if either of these reactions had been accomplished, a compound with the gross structure of acorone would have been readily obtainable. The feasibility of the synthetic route was proven by the facile synthesis of desisopropylacorone.

PART II

The successful synthesis of the novel ring system, 5,8a-propanoperhydroquinoline, is reported as a model series of reactions for the projected total synthesis of lycopodine. The former compound was prepared by a sequence of elaborations of the ubiquitous bicyclo(3,3,1)nonane system, all conversions being accomplished in high yield. En route, the scope of the acid-catalysed isomerisation of 1-ethoxycarbonylbicyclo(3,3,1)-

non-3-en-9-ones was examined, and now appears to be a general process. A study was made of the possible mechanism of this isomerisation.

With the successful completion of the synthesis of a model system, attention was focussed on the application of the derived results to the construction of a compound with the gross structure of lycopodine.

PART I

Approaches to the Synthesis of Acorone.

INTRODUCTION

The extreme sparseness of naturally occurring spiranoid compounds, excepting the non-carbocyclic sapogenins typified by diosgenin (1) and tomatidine (2), underlines the interest in such compounds as acorone (3), agarospirol (4), and illudin S (5) and M (6), which are the only spiranoid sesquiterpenes known to date.

Acorone (3) and its two stereoisomers isoacorone and cryptoacorone were isolated from the oil of the Sweet Flag (Acorus calamus L.) in 1948 by Herout and Sorm[1,2], and an exhaustive structural and stereochemical study was completed in 1964[3]. Agarospirol (4), a sesquiterpenoid alcohol, was isolated by Jain and Battacharrya[4] in 1959 from the essential oil of fungus-infected agarwood (Aquilaria agallocha Roxb.). A series of papers[5,6,7] culminated in 1965, when the structure was proved and the stereochemistry was postulated[8]. Illudin S (5) and M (6) were isolated by Anchel et al.[9,10] from the Jack-o'-lantern mushroom (Clytocybe illudens) in 1950. After investigation of these two anti-tumour factors, Anchel[11] proposed the correct

structures. Concurrent with these investigations, Nakanishi et al.[12] isolated an anti-tumour factor, lampterol, from the poisonous mushroom (Lampteromyces japonicus (Kawam) Sing.), and showed it to be identical with illudin S (5). An X-ray analysis, coupled with optical data, defined the absolute stereochemistry as shown.

In the following paragraphs, the work on acorone and its isomers will be discussed in detail. In 1948, the Czechoslovakian workers Herout and Sorm reported the isolation of two isomeric sesquiterpenoid diketones, $C_{15}H_{24}O_2$, from the oil of the Sweet Flag (Acorus calamus L.); in addition, they obtained a third diketone, thought to be isomeric with the previous two[1,2]. These three compounds they named acorone (m.p. 101°), isoacorone (m.p. 97°), and neoacorone (m.p. 86°) respectively.

Catalytic hydrogenation of both acorone and isoacorone afforded dihydro derivatives, this observation being taken to indicate the presence of a double bond. This assumption was substantiated by the results of perphthalic acid oxidation of the parent compounds, which led to isomeric crystalline compounds, $C_{15}H_{24}O_3$. However, in the course of further work on the constitution of these compounds, it was found that the compounds obtained on catalytic hydrogenation were the keto-alcohols (7), and the isomeric

substances obtained on perphthalic acid oxidation were lactones formed by oxidation of one cyclic keto group, the lactones (8) being acoronolide and isoacoronolide. Therefore, the parent structure had to be that of a saturated bicyclic diketone. The infrared spectrum of acorone showed two carbonyl absorption maxima at 1728 and 1709 $cm.^{-1}$ in chloroform solution, assigned respectively to a cyclopentanone and a cyclohexanone carbonyl[13]. The ultraviolet spectra of acorone and isoacorone, with low-intensity absorption maxima around 300 mμ, excluded the possibility of the two compounds being α- or β-diketones. It was observed that acorone and isoacorone differed in the stereochemistry of an alkyl group adjacent to one keto group, as they are interconvertible by base-catalysed enolisation, giving in each case an acorone-isoacorone ratio of 65 : 35. Neoacorone gave the same equilibrium ratio, but neoacorone itself was never detected in the equilibrium mixture.

Continuing their investigations, the Czechoslovakian workers studied the oxidation and dehydrogenation of various derivatives of acorone and isoacorone, the results obtained prompting them to postulate a spirane skeleton for acorone[14,15]. Sulphur dehydrogenation of acorenone (9) yielded a product with one aromatic ring and a cyclohexanone moiety. The expansion of the cyclopentane ring

indicated that the carbon atom common to the five- and six-membered rings was quaternary, since aromatisation could not take place without concurrent rearrangement.

The conversion of acoranone (10) to the hydroxymethylene derivative (11) proved that the cyclopentanone carbonyl was flanked by a methylene group. Catalytic dehydrogenation of the dicarboxylic acid (12), obtained by oxidation of (11), afforded a mixture of 4-ethyltoluene (13) and 4-isobutyltoluene (14), accompanied by propionic (15) and isovaleric (16) acids. These two acids were also obtained from acorone by a different route. Ozonolysis of the monobenzylidene derivative (17) yielded the keto-anhydride (18), which on pyrolysis as the barium salt (19) furnished propionic (15) and isovaleric (16) acids, and two $\alpha:\beta$ unsaturated ketones. The carbon framework of the two ketones was established by conversion to the corresponding benzene derivatives (13) and (14).

The formation of cadalene (20) from acordiene (21) again suggested rearrangement and enlargement of the five-membered ring; the formation of 1,7-dimethyl-4-isopropylnaphthalene (22) by an analogous rearrangement was predicted, and indeed was observed in the dehydrogenation of isoacordiene (21). Herout and Sorm concluded that all the above observations could only be interpreted on the

basis of structure (3) for acorone.

In 1959, the authors published a paper on the stereochemistry of acorone, isoacorone and neoacorone[16]. Utilising optical rotation differences, rotatory dispersion curves, dipole moments and thermodynamic stabilities, they postulated the probable configurations of acorone and its isomers. The first information was provided by the calculation of the molecular rotation differences between the parent diketones (3) and the keto-alcohols (7). These were observed to be of the same order in all three cases, ca. 300^{o}, being of the same sign for acorone and neoacorone, but of opposite sign for isoacorone. These facts were interpreted as indicating that the methyl group adjacent to the carbonyl group in the six-membered ring has the same configuration in acorone and neoacorone, whereas in isoacorone it has the opposite configuration. It was observed that the rotatory dispersion curves of acorone and isoacorone were mirror images, and the shapes of both curves corroborated the fact that the six-membered rings of acorone and isoacorone are related as mirror images. The dispersion curve of neoacorone had practically the same shape as that of acorone.

The dipole moments of acorone (5.11 D), isoacorone (2.39 D) and neoacorone (4.39 D) were so different that

it was possible to utilise them in a more detailed stereochemical study. By comparing theoretical calculations of the dipole moments for various chair conformations of the six-membered ring in acorone and the observed value, the partial conformation (23) was assigned to acorone. The conformations of isoacorone and neoacorone could not be ascertained with the same degree of accuracy, but it was considered probable that the cyclohexane ring of neoacorone was in the same conformation (23) as that of acorone, whereas that of isoacorone adopted the other possible conformation (24). The cyclohexane methyl groups were assigned equatorial conformations, due to free-energy considerations. It is seen from formula (23) and (24) that the six-membered rings of acorone and neoacorone are mirror images of that of isoacorone, which is in accordance with their optical properties. The occurrence of the two different chair conformations for the six-membered ring in acorone and isoacorone was ascribed to the preference of the cyclohexane methyl group to retain an equatorial conformation even when it assumes the opposite configuration.

The relative configuration of the isopropyl group in acorone and its isomers was deduced from treatment of the three hydroxyketones (7) with alkali under mild conditions.

The hydroxyketone derived from neoacorone underwent isomerisation under these conditions, the change being detected in the rotatory dispersion curve, whereas those from acorone and isoacorona did not isomerise. This configurational change indicated that the carbon atoms attached to the isopropyl group in acorone and neoacorone were of opposite configuration; this carbon atom probably has the same configuration in acorone and isoacorone.

Further information was gleaned from the observed steric hindrance to which the methylene group α to the cyclohexane carbonyl is subjected: for example, the preparation of the monobenzylidene derivative (17) of acorone, the methylene group attacked being α to the cyclopentane carbonyl. This hindrance was ascribed to either the methyl or the isopropyl group on the five-membered ring lying on the same side of the cyclohexane ring as the cyclohexane carbonyl function.

However, in 1962, Herout and Sorm made the surprising discovery that neoacorone was not homogeneous, but was in fact a molecular compound of acorone and a new isomer, which they aptly called cryptoacorone (3)[17]. Cryptoacoronol (7) was obtained in a pure state by preparative thin-layer chromatography of 'neoacoronol', achieving a separation of acoronol and the less polar cryptoacoronol. The pure keto-

alcohol was then oxidised to the parent diketone, cryptoacorone (3, m.p. 107-108°). Cryptoacoronol is easily isomerised quantitatively to isoacoronol, hence the reason for thin-layer as opposed to column chromatography, where the contact with the adsorbent is by necessity of much longer duration.

The Czechoslovakian workers, continuing their studies, presented an unambiguous proof[18] of the position of the cyclopentanone carbonyl, which had never been rigorously determined, by a sequence of reductions and oxidations of acoronol (7), which was prepared this time by reduction with the stereoselective reducing reagent, lithium hydridotri-t-butoxyaluminate; due to different steric environments, only the cyclohexanone carbonyl is reduced. Baeyer-Villiger oxidation of acoronol (7) afforded the hydroxylactone (25), which on reduction with lithium aluminium hydride gave the triol (26). The triol was oxidised to the corresponding diketo-acid (27), which on pyrolysis as the barium salt afforded n-butyric acid (28). The alternative formulation for acoronol (29) would give, after identical treatment, isocaproic acid (30), which was not detected. Hence the position of the cyclopentanone carbonyl must be as shown in (3). These observations are also true for the stereoisomers isoacorone and crypto-

acorone.

The final publication[3] in this series appeared in 1964, when Herout and Sorm determined the absolute configurations of the isopropyl group, the two methyl groups, and the spirane carbon atom in all three isomers. They also postulated the conformations of the three compounds. The absolute configuration of the methyl group on the cyclohexane ring was determined by a study of the three ketolactones (8). The molecular rotations of these compounds and of the potassium salts of the corresponding hydroxyacids were determined, and the molecular rotatory differences calculated. The lactone rotatory contribution was positive for acoronolide, and negative for isoacoronolide and cryptoacoronolide. Therefore, according to the Hudson-Klyne rule[19], the methyl group in acoronolide has the absolute configuration shown in (31), whereas that in isoacoronolide and cryptoacoronolide has that shown in (32). Since Baeyer-Villiger oxidation proceeds without inversion[20], the same configurations can be ascribed to the parent diketones.

The absolute configuration of the isopropyl group on the cyclopentane ring of acorone and isoacorone was determined in a similar manner. The cyclohexane carbonyl was protected as its alcohol, and the corresponding hydroxy-

lactones (25) prepared in a manner analogous to the previous case. The molecular rotatory differences were positive in each case, accordingly the isopropyl group has the same configuration in acorone and isoacorone, shown in the alternative formulae (33) and (34) for the hydroxylactone derived from acorone, and (35) and (36) for that derived from isoacorone; these alternatives differ only in the configuration of the spirane carbon atom.

Difficulties were encountered in the case of cryptoacoronol, since under the conditions of the Baeyer-Villiger oxidation, which required to be catalysed by p-toluenesulphonic acid due to the sluggishness of the reaction with ketoalcohols, an acid-catalysed isomerisation occurred, and the sole product was the hydroxylactone derived from isoacorone. The conclusion drawn was that the isopropyl group of cryptoacorone was of opposite configuration to that of acorone and isoacorone, and accordingly may be represented by the alternative formulae (37) and (38).

The large difference in specific rotation between acorone, α_D^{20} $+144^o$, and isoacorone, α_D^{20} -90^o, provided the researchers with a further stereochemical clue. The difference is too large to be accommodated merely by the different configuration of the methyl group in the cyclohexane ring. The postulated explanation is that the

cyclohexane ring changes conformation in that epimer where the methyl group is in the axial configuration to allow the methyl group to be equatorial in both cases, thus giving rise to two different chair conformations. This assumption was substantiated from studies of the rotatory dispersion curves, where acorone shows a strong positive Cotton effect, and isoacorone a strong negative effect.

Once again, cryptoacorone presented a more anomalous situation. According to the Hudson-Klyne rule, the methyl group on the cyclohexane ring of cryptoacorone has the same configuration as in isoacorone, but the rotatory dispersion curve of cryptoacorone shows a strong positive Cotton effect. In addition, the measured dipole moment of cryptoacorone did not agree with either of the two chair conformations possible for the six-membered ring, as are present in acorone and isoacorone respectively. The authors explained these anomalies by proposing a twist form for the cyclohexane ring in cryptoacorone, which can now be represented by the alternative formulae (39) and (40).

To sum up so far, acorone can be represented by the alternatives (41) and (42), isoacorone by (43) and (44), and cryptoacorone by (39) and (40) respectively. By a comparison of the calculated dipole moments for these six structures and the observed values, it was possible to

assign unambiguously the formulae (41) and (43) to acorone and isoacorone respectively. Although the observed dipole moment of cryptoacorone lay between the two calculated values, formula (39) was assigned to cryptoacorone, since it can be epimerised to isoacorone, a change of configuration of the spirane carbon atom being impossible during the epimerisation.

To complete this study, only one asymmetric centre remains undefined, that of the carbon bearing the methyl group on the cyclopentane ring. The authors inferred this configuration indirectly from the different stabilities of cryptoacorone and isoacorone, which have an identical configuration of the cyclohexane ring. In view of the fact that cryptoacorone readily changes configuration of the isopropyl group to a more stable configuration, it is reasonable to assume that the cyclopentane methyl group is entering into 1,3 interaction with the isopropyl group. Herout and Sorm interpreted this as meaning that in cryptoacorone the cyclopentane methyl and isopropyl groups were of a cis configuration, whereas those of acorone and isoacorone were in the more stable trans configuration. However, it has been shown[21] that for 1,3-alkyl groups on substituted cyclopentanones, the cis isomer is the more stable. Accordingly, they concluded finally that acorone,

isoacorone, and cryptoacorone were best represented by the formulae (45), (46), and (47) respectively.

The stereochemical formulation (45) proposed[3] for acorone has recently been contradicted by Sim[22] in an X-ray study of the p-bromobenzenesulphonyl hydrazone of acorone. The absolute stereochemistry of this derivative is represented as (48), where the cyclopentanone methyl and isopropyl groups are trans. The cyclohexanone methyl group would be expected to be equatorial, as was found by Herout and Sorm in their optical rotatory dispersion measurements in solution, whereas in this crystal it is seen to be axial. However, for conformers which differ only slightly in energy, packing forces, for example van der Waals forces, can favour in the crystal a conformation which is present only to a small extent in solution. Therefore, one must be cautious in the extrapolation of solid-state conformational results to solution chemistry. If this latter stereochemical formulation (49) for acorone is accepted as being correct, then, applying the results of Herout and Sorm, isoacorone and cryptoacorone can be represented stereochemically as (50) and (51) respectively.

An interesting side-line arose when Herout and Sorm[2] attempted the reduction of acorone under Wolff-Kishner conditions. The expected product, acorane (52), was isol-

ated in very low yield, the bulk of the reactant undergoing some decomposition process. To investigate this further, the authors heated acorone with powdered sodium hydroxide at 230°, subsequent isolation yielding a dicarboxylic acid in 70% yield. This oily acid was found on analysis to be isomeric with acorone, and to be di-unsaturated, as two moles of hydrogen were absorbed on catalytic reduction; thus the acid was monocyclic. The ultraviolet spectrum of the acid, with an absorption maximum at 260 mμ, log ε 3.67, inferred that the di-unsaturation was present as a conjugated diene. The authors did not postulate a structure for this compound, but two feasible alternatives are (53) and (54), which could arise by the routes shown. With the advent of 100 Mc/s. nuclear magnetic resonance instruments and mass spectrometry, the structural elucidation of this isomeric acid would make an interesting problem for future study.

The complete dominance by the Czechoslovakian workers in this field of study of acorone and its stereoisomers was partially broken in 1964 by Birch[23], who isolated and identified acoric acid (55), which was obtained from the acidic fraction of the oil of the Sweet Flag. Whether acoric acid is a genuine biosynthetic product or an autoxidation product is debatable, but in either case it is

clearly derivable by oxidative fission of the five-membered ring of acorone, from which the stereochemistry of the acid is derived. Indeed, oxidation of acorone monoxime (56) with oxygen in the presence of potassium t-butoxide gave, after regeneration of the carbonyl function, acoric acid (55).

A plausible scheme for the biogenesis of acorone (3) has been postulated by Ramage[24] and Roberts[25]. Cis-farnesol pyrophosphate (57) is considered[26,27] to cyclise via the carbonium ions (58) and (59) to give bisabolene (60). Protonation of bisabolene (60) could then give either the related tertiary (61) or secondary (62) carbonium ions, which on further cyclisation afford the tertiary carbonium ions (63) and (64) respectively. Deprotonation of either of these to the neutral analogues (65) or (66) afford skeletons, each of which having the inherent potentiality for oxygenation to furnish acorone (3).

Battacharrya et al.[8] have proposed a biogenetic scheme for the formation of agarospirol (4). Opening of the tetrahydrofuran ring of the naturally occurring dihydroagarofuran (67), followed by bond migration, could give the spiranoid cation (68), which on deprotonation affords agarospirol (4). It is of interest to note that agarospirol is isolated only from fungus-infected agarwood, whereas

dihydroagarofuran (67) is derived from fungus-free wood. This infers that there is an additional enzyme present in the fungus to effect the above transformation.

The suggested biogenetic scheme[11,12] for the formation of the illudins raises the interesting possibility of the intermediacy of humulene (69), which is considered[25] to be derived from trans-farnesol pyrophosphate (70). Humulene (69), after cyclisation and suitable oxygenation to afford the tricyclic intermediate (71), gives, by further bond migration and a hydride shift, a compound (72) with the required carbon framework and virtually correct oxygenation pattern. This compound (72) is readily elaborated to illudin S (5) and M (6).

DISCUSSION

The range of practical synthetic approaches to carbocyclic spiro compounds is vast[28]. One of the simplest procedures is the cyclisation of a 1,1-disubstituted monocyclic compound, e.g., by an intramolecular Wurtz reaction (a), or a modified Favorski reaction (b). Other relatively unsophisticated methods include internal Claisen or Dieckmann condensations (c), condensations with oxalic, malonic, succinic, and etc., diesters (d), and the gem-dialkylation[29] of a cyclic ketone with an α,ω-dibromide (e).

More sophisticated procedures are seen in those methods involving generation and subsequent rearrangement of carbonium ions, e.g., in the acid-catalysed pinacol rearrangement of cyclic vic-tertiary diols (f), deamination of cyclic vic-tertiary amines with nitrous acid (g), and the acid-catalysed cyclisation of suitable dienes[28] (h). A novel procedure is found in the use of an Ar_1-5 reaction[30] (i), involving in the simplest case a p-(ω-brosyl)-alkyl phenol. This cyclises under the influence of base to afford a spirodienone, as shown. However, this reaction is extremely structure-sensitive; the leaving group, though not necessarily brosyl, must be primary, due to the high rate of E1 and/or E2 elimination of secondary and tertiary derivatives:

the length of the alkyl chain is also critical, that of four carbon atoms being optimum[31]. A relatively new route utilises the thermal cyclisation of a suitable α-β, ε-ζ diethylenic ketone, where high yields of the desired substituted spirane, or mixtures of spiranes, are obtained (j)[32].

With regard to the specific problem of the synthesis of compounds with the gross structure of acorone (3), it was observed that acorone itself was a 1,5-diketone, the normal product from a Michael condensation between the active methyl or methylene group of a saturated ketone and an α,β-unsaturated ketone. There are two suitably substituted enediones, (73) and (74), which, on intramolecular Michael condensation, could feasibly create the acorone structure directly. Accordingly, the more readily accessible cyclohexenone (73) was chosen as the key precursor in this synthesis.

R. Ramage[24], in this department, developed a synthesis of the enedione (73) along the following lines. The starting material, 4-methyl-3-nitroacetophenone[33] (75), was converted to β-(3-methoxy-4-methylphenyl)butyric acid[34] (76) by standard methods. This elaboration involved reduction of the nitro group to the amino function (77) by means of iron and hydrochloric acid, followed by diazotisation to afford the phenol (78), which on treatment with dimethyl sulphate gave the corresponding methyl ether (79); a Reform-

atsky reaction between this compound and zinc and ethyl bromoacetate, followed by dehydration and catalytic hydrogenation, furnished, on saponification, the desired butyric acid (76). Condensation of the corresponding acid chloride with dibenzyl isopropylmalonate and hydrogenolysis of the resulting dibenzyl ester (80) gave a β-ketomalonic acid (81), which smoothly decarboxylated to the desired ketone (82).

The carbonyl function in (82) was protected by ketal formation to give (83), which, on Birch reduction[35] and subsequent treatment with mineral acid, yielded the required enedione (73). This compound could not be induced to undergo an internal Michael reaction. The sole product of such attempts was an α,β-unsaturated cyclohexenone, $C_{15}H_{22}O$, considered to be the compound (84), which could only have arisen by an intramolecular aldol reaction, as shown, the desired acyclic carbanion not being formed.

It should be noted at this point that no stereospecific approach was adopted in the initial synthetic incursions. If separation of the ultimate complex mixture of stereoisomeric spiranes should prove impossible, then an optical resolution at some stage in the sequence, possibly resolving the aromatic acid (76), could be performed. This would enable one to fix the stereochemistry of the side-chain methyl group. Thus, in the final product, one asymmetric centre would be fixed,

two would be epimerisable, with the last asymmetric centre, that of the carbon bearing the spiro fusion, unknown. This would greatly facilitate the separation of the products. In preparation for this ultimate separation, gas-liquid chromatography (g.l.c.) conditions were determined, after much effort, such that good separation was achieved between acorone, isoacorone and cryptoacorone. With regard to the spiro fusion, it is of interest to note that, from a synthetic point of view, cyclisation as planned must come from the lower face of the cyclohexenone moiety in order to give any of the natural acorone isomers, as shown in (85).

Since the enedione (73) resolutely refused to undergo an internal Michael reaction, Ramage decided to synthesise the enone β-ketoester (86), since carbanion formation at the methylene group flanked by a carbonyl and an ester grouping would be greatly enhanced. This enone β-ketoester (86) did indeed undergo a facile internal Michael reaction, affording the spiro β-ketoester (87), but concrete proof of subsequent elaborations to the acorone structure was lacking. Accordingly, it was decided to repeat Ramage's synthesis, with some experimental modifications, and to attempt to complete this synthetic attack on acorone.

Lithium-liquid ammonia reduction[35] of the previously obtained β-(3-methoxy-4-methylphenyl)butyric acid (76) gave

a product, which after esterification with diazomethane and chromatography on silica gel was observed to be a mixture of conjugated (88) and non-conjugated (89) ketoesters. Partial separation was achieved, with the non-conjugated ketoester (89) showing absorption maxima in the infrared at 1740, 1720 and 1670 $cm.^{-1}$, whereas the conjugated isomer (88) showed maxima at 1740, 1675 and 1630 $cm.^{-1}$. No large scale separation of the isomers from each other was deemed necessary. The ketal ester (90) derived from the mixture of ketoesters by treatment with ethyl orthoformate and ethylene glycol[36] was shown to be homogeneous by thin-layer chromatography (t.l.c.). The ketal acid (91), obtained from the ketal ester by base hydrolysis and careful acidification, was treated with a solution of methyl lithium[37] in ether to afford the corresponding methyl ketone (92) in 90% yield.

Elaboration of the ketone to the desired β-ketoester (93) was achieved by treatment with sodium hydride and diethyl carbonate in refluxing tetrahydrofuran[38]. Repetition of Ramage's standard conditions failed to yield the β-ketoester, but employment of a high-dilution technique afforded the desired compound (93) in a yield of 65%. Attack at the methyl group is expected both from theory and by analogy[39]. Base-induced enolisation normally occurs from the side of the less-substituted α-carbon atom, due to the inductive effect

of the alkyl substituents on the α'-carbon atom. Formation of the primary carbanion in an aprotic solvent excludes the possibility of equilibration involving the potential secondary carbanion.

The enone β-ketoester (86) was produced from the ketal (93) by exchange ketalisation[40] with excess acetone in the presence of p-toluenesulphonic acid. Intramolecular base-catalysed cyclisation of the enone β-ketoester (86) yielded the desired 4-ethoxycarbonyl-1,7-dimethylspiro(5,4)decane-3,6-dione in 90% yield. The course of this reaction was particularly amenable to ultraviolet spectroscopic examination, since the cyclohexenone chromophore at 239 mμ diminishes as the cyclisation proceeds. There is a concomitant bathochromic shift from 276 to 282 mμ in the absorption maximum of the β-ketoester enol tautomer, due to formation of the spiro β-ketoester (87).

At this stage, Ramage treated the spiro β-ketoester (87) with isopropyl iodide and sodium ethoxide in ethanol, and obtained a very low yield, about 15%, of neutral material, which showed no apparent β-ketoester enol chromophore in the ultraviolet, and gave no coloration with ethanolic ferric chloride. Hydrolysis and decarboxylation of this material in refluxing acetic acid and concentrated hydrochloric acid gave as product a diketone, which exhibited absorption max-

ima in the infrared at 1743 and 1710 cm.$^{-1}$. The carbonyl region was compatible with the desired structure, and it was reported that "the fingerprint region was similar, though not identical to the naturally occurring acorone isomers".

Repetition of this procedure afforded initially a neutral material in similar yield. This product exhibited absorption maxima in the infrared at 1740 and 1710 cm.$^{-1}$, showed no β-ketoester enol chromophore in base in the ultraviolet, and gave no coloration with ethanolic ferric chloride. However, its t.l.c. behaviour indicated a number of compounds. Notwithstanding, this total product was hydrolysed and decarboxylated as before, but the product obtained was shown to be desisopropylacorone (94), which was prepared separately by hydrolysis and decarboxylation of the spiro β-ketoester (87). Desisopropylacorone (94) shows infrared absorption maxima at 1743 and 1710 cm.$^{-1}$, measured as a film, whereas all the naturally occurring acorones have an abnormally low absorption for the cyclopentanone carbonyl function[2] at around 1720 cm.$^{-1}$.

A number of different bases and alkylating agents were used in an attempt to form the isopropyl β-ketoester (95); isopropyl iodide and sodium ethoxide in ethanol, with inverse addition; isopropyl bromide and potassium t-butoxide in t-butanol; isopropyl iodide and potassium t-butoxide in

t-butanol. A method of alkylating hindered β-ketoesters has been reported in the literature[41], where use was made of the alkyl bromide, sodium iodide and sodium hydride in benzene and dimethylformamide; this was also attempted. A radically different method was performed, using boron trifluoride gas and di-isopropyl ether[42], which could proceed via the mechanism shown (96). The sole product in every case, apart from material arising from considerable decomposition, proved to be, after hydrolysis and decarboxylation, desisopropylacorone (94). From models, it is readily seen that the site of alkylation is extremely sterically hindered, this hindrance precluding any facile orthodox alkylation with the bulky isopropyl moiety. One feasible explanation of these results, which seem to indicate initial alkylation to a small extent, is that after hydrolysis and decarboxylation, a retro-Michael reaction of the alkylated material occurs, with consequent fragmentation. A less drastic method of effecting hydrolysis and decarboxylation [43] was therefore performed, that of heating the alkylation product with water in a sealed tube at 200°. This procedure gave comparable results to those obtained by the previous method.

An alternative lay in the possibility of deactivating the two carbonyl functions in the spiro β-ketoester (87), then treating the ethyl ester with methyl magnesium iodide,

the product from which, on dehydration and hydrogenation, followed by regeneration of the carbonyl groups, should furnish the desired acorone structure. However, attempts at bis-ketalisation and sodium borohydride reduction, to afford the bis-ketal (97) and diol (98) respectively, proved to be abortive, complex mixtures of products being obtained in each case. Indeed, an attempt to bis-ketalise acorone itself led to a complexity of products, as seen from t.l.c.

Attention was refocussed on the ketal β-ketoester (93), which theoretically could be isopropylated, the enone liberated, and the system subsequently cyclised. An initial attempt to perform this alkylation made use of isopropyl iodide and sodium ethoxide in ethanol; this led to predominant O-alkylation, as seen from the infrared spectrum of the product, which exhibited absorption maxima at 1670 and 1620 $cm.^{-1}$, and the ultraviolet spectrum, with an absorption maximum at 233 mμ, these data being compatible with the suspected structure of the product (99). Since a less polar medium would not favour O-alkylation, isopropyl iodide and sodium hydride in cyclohexane were used. Other attempts involved boron trifluoride gas and di-isopropyl ether[42]; isopropyl bromide and potassium t-butoxide in t-butanol; isopropyl bromide, sodium iodide and sodium hydride in benzene and dimethylformamide[43]; isopropyl bromide and potassium

t-amylate in t-amyl alcohol: all of these conditions returned the starting material unchanged, with some inevitable decomposition.

Alkylation was eventually achieved in 60% yield, by the use of isopropyl iodide and potassium t-butoxide in t-butanol, to afford the desired ketal isopropyl β-ketoester (100), which, on mass spectral analysis, showed the required parent ion and, among others, an ion corresponding to (101). The enone isopropyl β-ketoester (102) was produced from the ketal by exchange ketalisation[40] with excess acetone in the presence of p-toluenesulphonic acid.

Numerous attempts were made to effect internal cyclisation of the enone isopropyl β-ketoester (102), namely: potassium hydroxide in ethanol; potassium t-butoxide in t-butanol; sodium ethoxide in ethanol; sodamide in ether; sodium hydride in ether; and the methylsulphinyl carbanion[44] in dimethyl sulphoxide. In his elegant synthesis[45] of longifolene (103), Corey performed an internal Michael reaction quite analogous to the one desired here. His conditions, involving triethylamine and ethylene glycol, were therefore used. None of these methods induced the desired reaction to occur, the products being either starting material or unidentifiable degradation products.

The anomaly apparent in this cyclisation failure as

compared with the extremely facile cyclisation of the unsubstituted enone β-ketoester (86) deserves some explanation. It is unlikely that steric reasons alone account for the observed failure. One possible further explanation is that in the unsubstituted case, the generated O-enolate anion (104) can effect stabilisation by abstraction of the active β-ketoester methine proton to afford the resonance-stabilised β-ketoester carbanion (105); in the case of the enone isopropyl β-ketoester (102), there is no active β-ketoester methine proton available for abstraction in the cyclised O-enolate anion (106), hence the position of equilibrium probably lies preponderantly on the side of the initially-formed, comparatively more stable β-ketoester carbanion (107), thus precluding the desired cyclisation. This explanation obviously holds only for aprotic media; with hydroxylic solvents, mainly degradation is observed.

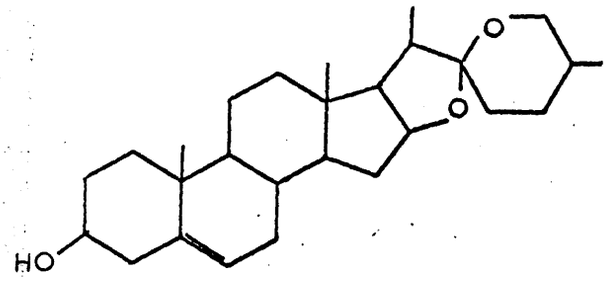
An attempt to reduce selectively the enone carbonyl of the enone isopropyl β-ketoester (102) with sodium borohydride, in a strongly basic medium to effect protective enolisation of the β-ketoester ketone carbonyl group, gave a product which showed infrared absorption maxima at 3500-3300, 1730 and 1715 $cm.^{-1}$; the ultraviolet spectrum, with neutral or basic solution, showed no significant absorption above 220 mμ. Accordingly, the product was probably the diol ester (108),

the split ester carbonyl observed in the infrared spectrum being due to partial intramolecular hydrogen bonding with the adjacent hydroxyl group. Treatment of this product with manganese dioxide, to effect oxidation of the allylic hydroxyl group, afforded a compound which showed absorption in the infrared at 3500-3300, 1730, 1715, 1675 and 1630 $cm.^{-1}$; the ultraviolet spectrum in neutral solution exhibited a characteristic enone chromophore absorption at 238 mμ, but on addition of base, the intensity of this absorption dropped rapidly to zero. These observations are compatible with the hydroxy-enone ester structure (109), which on treatment with base could undergo internal cyclisation to the furan derivative (110). Chromium trioxide-sulphuric acid oxidation of the hydroxy-enone ester gave a product which was identical in its infrared and ultraviolet spectra, and t.l.c. behaviour with the starting enone isopropyl β-ketoester (102). If the allylic alcohol (111) had been obtained, it was planned to attempt an S_N2' reaction on the corresponding allylic tosylate (112), which would have yielded the spiro compound (113), elaboration of which would have given the acorone structure.

This proposed reaction sequence would also have been extremely useful in achieving a degree of stereospecificity in the total scheme. It has been shown[46] that in an S_N2'

reaction, the attacking group enters cis to the leaving group; hence, if both allylic alcohols had been obtained and their individual configurations established, then one would, by analogy, know the stereochemistry of the spiro centre created in the cyclisation.

Since all the attempts described above constitute a reasonably exhaustive range of procedures, it is plausible to assume that the ultimate synthesis of compounds with the acorone structure could be attacked more profitably by a completely different route, e.g., one of the synthetic methods mentioned at the beginning of this section, such as an Ar_1-5 reaction (i)[30], or thermal cyclisation of a suitably substituted α-β,ε-ζ diethylenic ketone (j)[32]. As an added reason for abandoning the synthesis at what is apparently a late stage, it might be as well to remind the reader at this point that the lack of success enjoyed applies to the non-stereospecific route, and that a great deal more work and subtle modification would be necessary for a stereospecific synthesis. It is interesting to note the similarity, both in structure and stereochemistry, of acorone (3) and cedrene (114)[47], which, if it could be degraded, would provide an ideal precursor for the synthesis of acorone.



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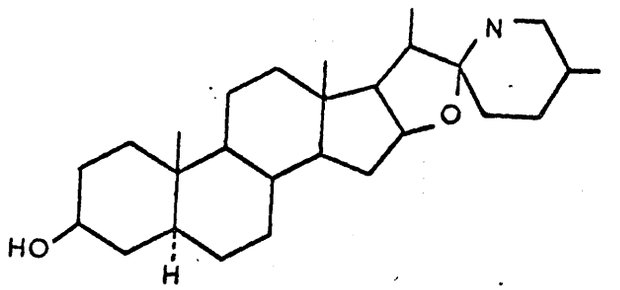

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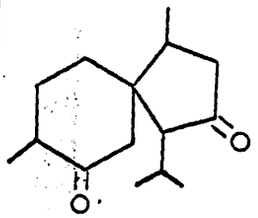

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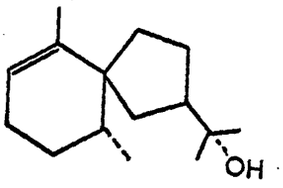

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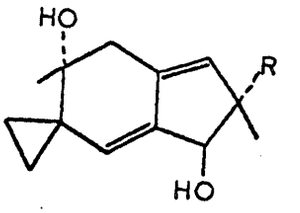

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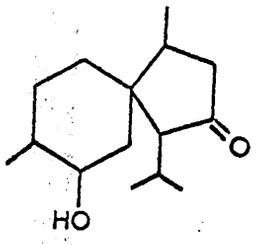
6, R=CH_3



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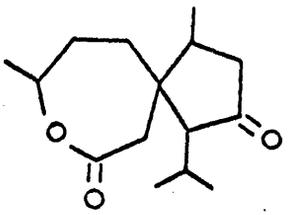

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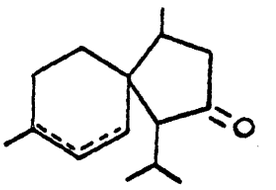

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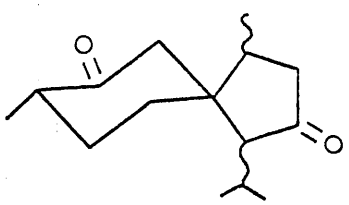

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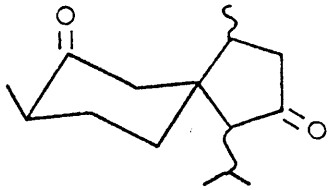

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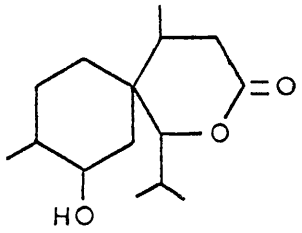

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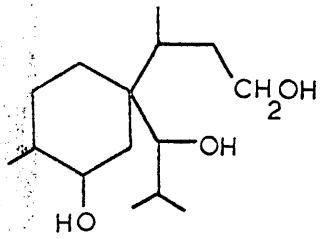

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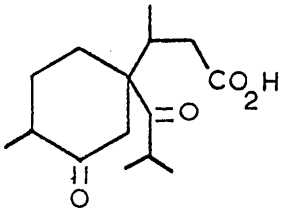

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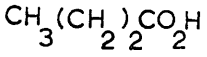

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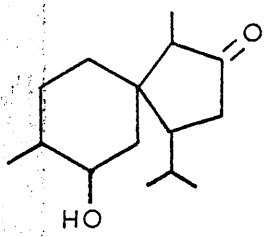

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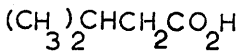

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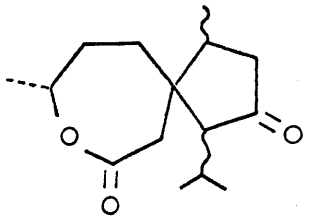

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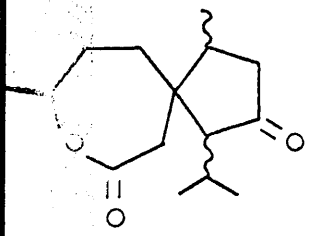

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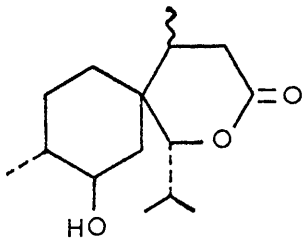

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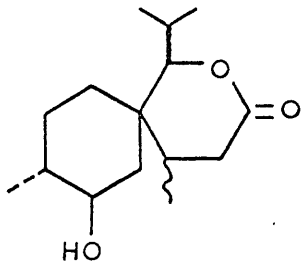

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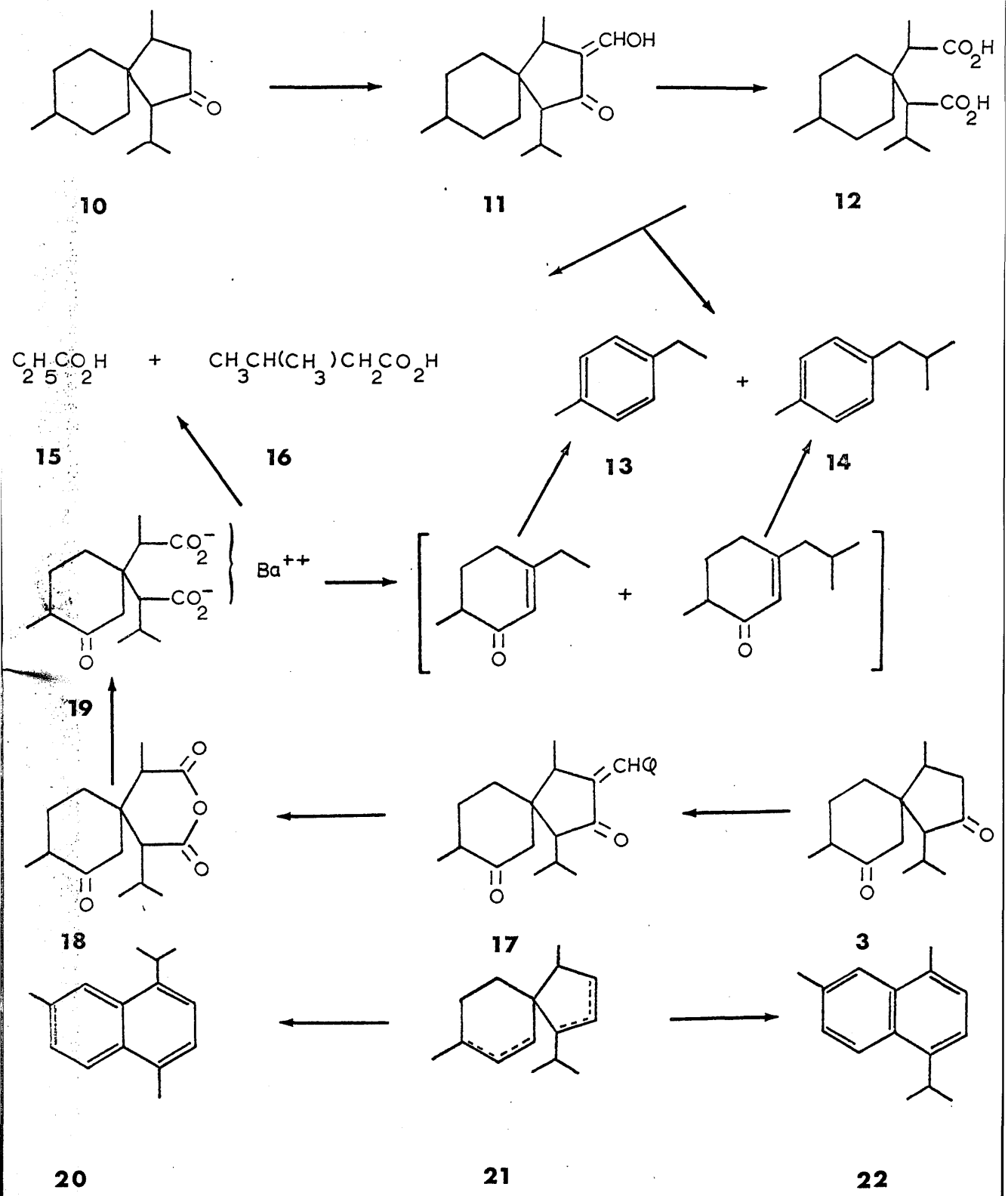
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CO2H
CO2H
10
11
12
C2H5CO2H
+
CH3CH(CH3)CH2CO2H
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+
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CO2-
Ba++
+
19
CHO
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17
3
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21
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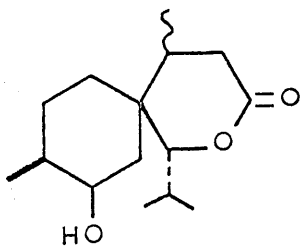

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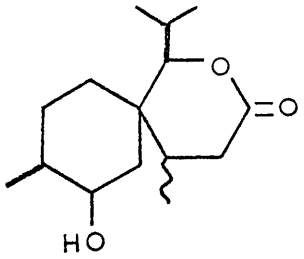

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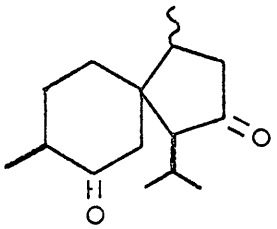

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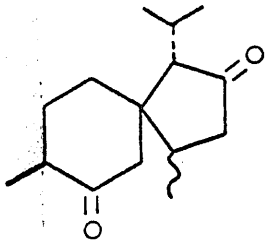

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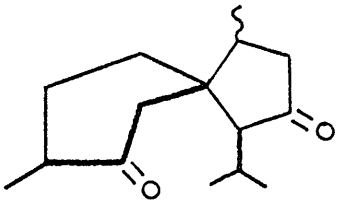

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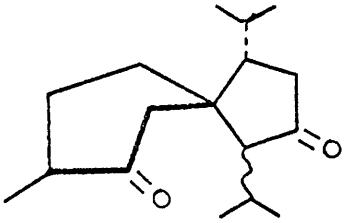

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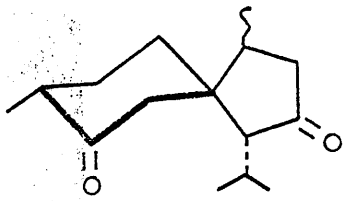

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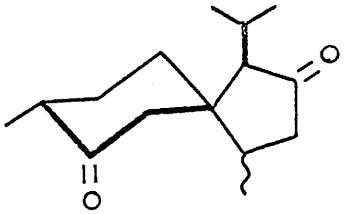

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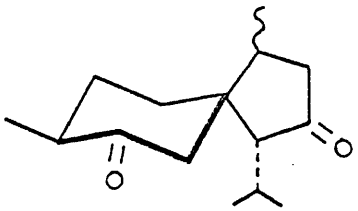

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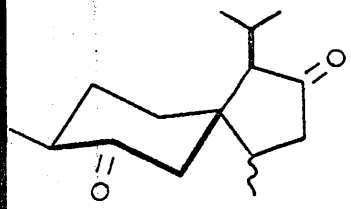

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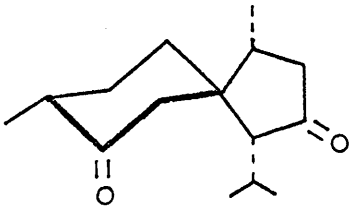

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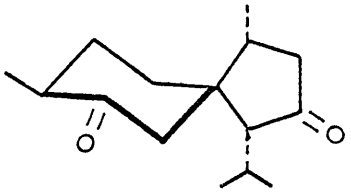

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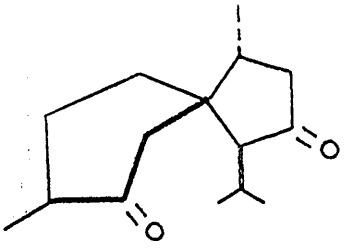

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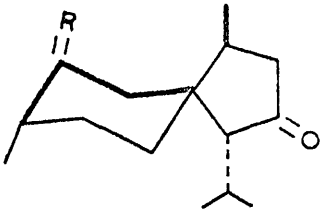

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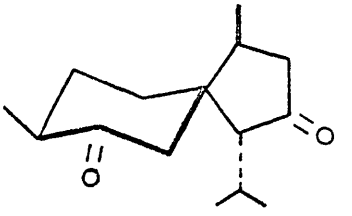
49, R = O



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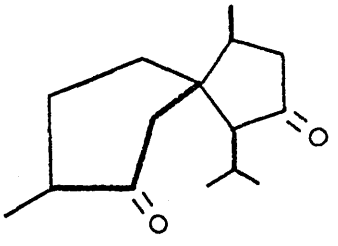

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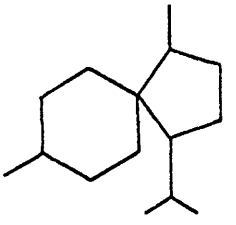

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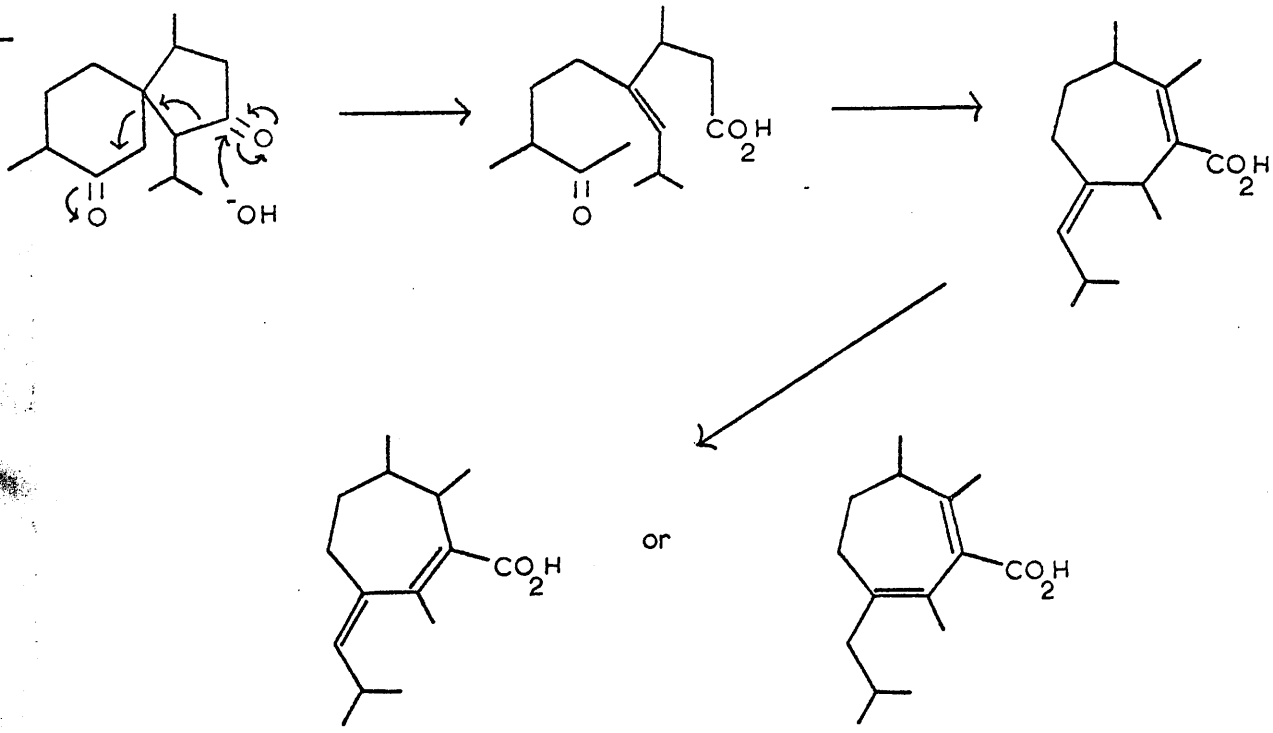

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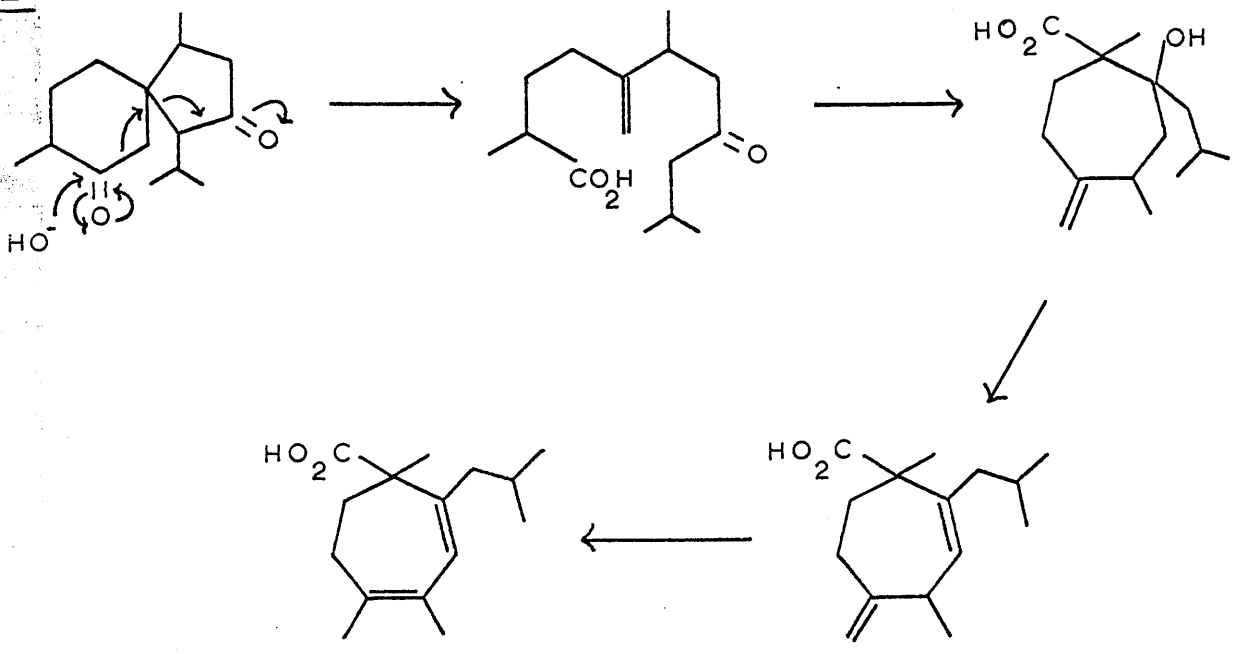

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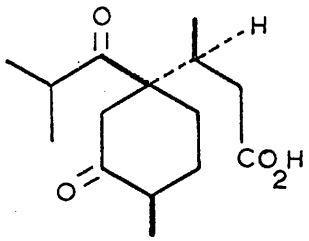

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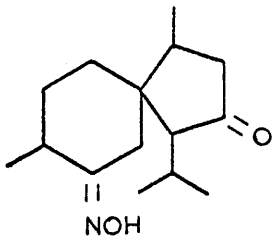

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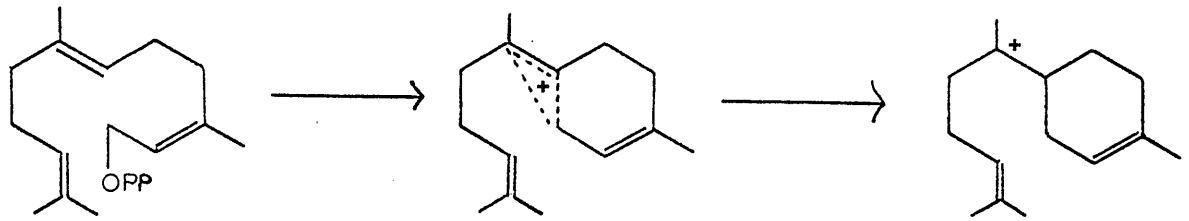

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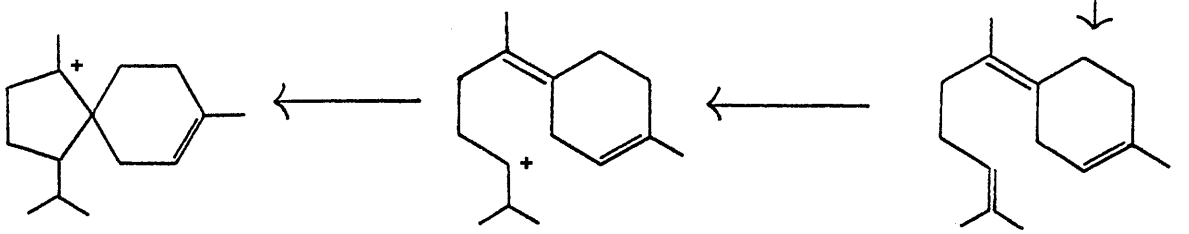

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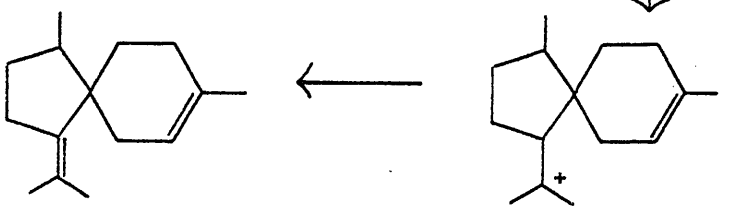
66 61



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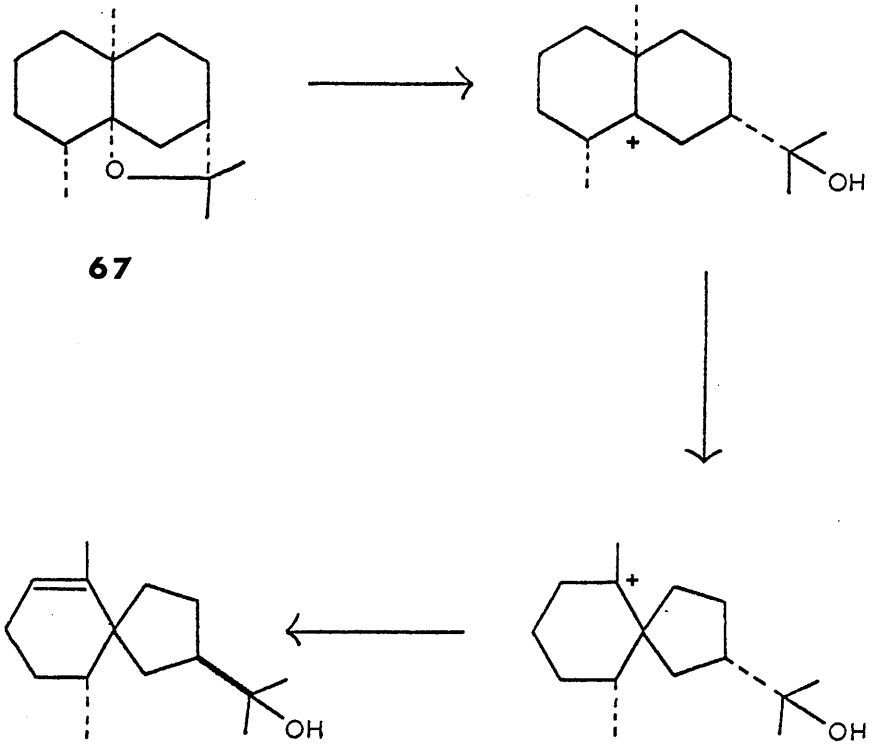

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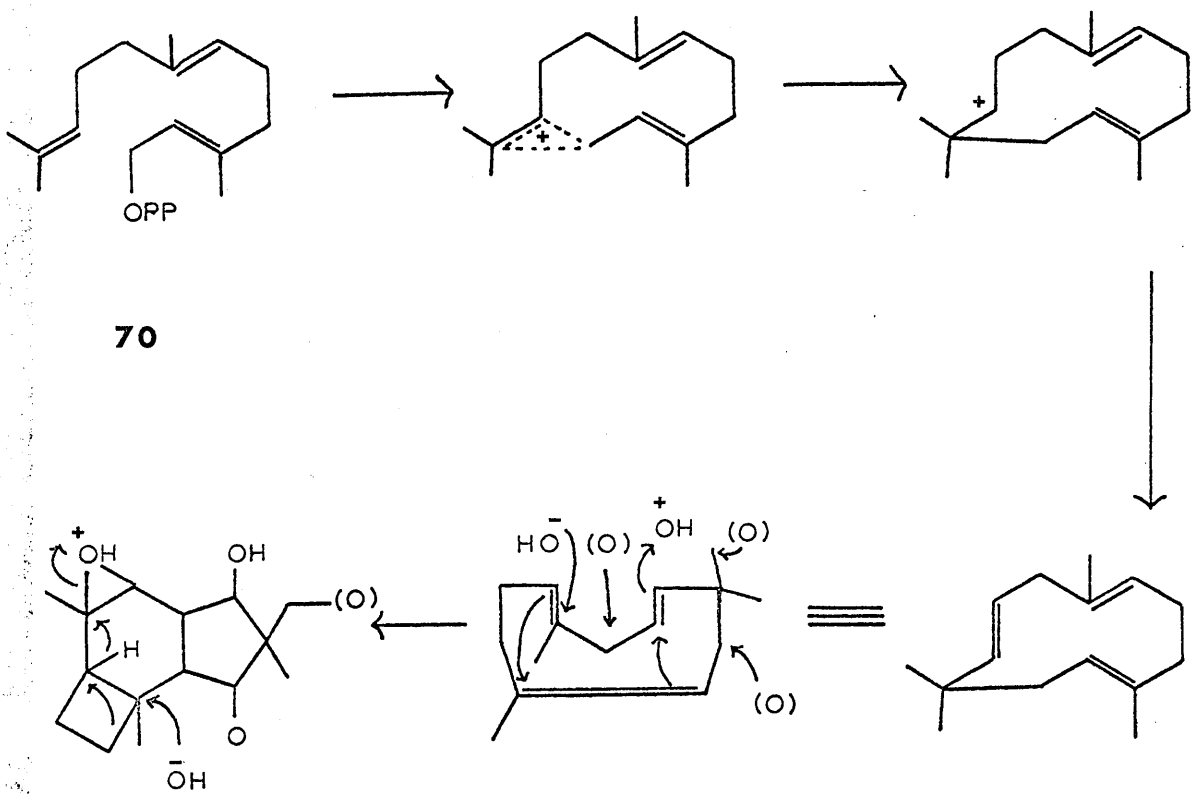
4

68



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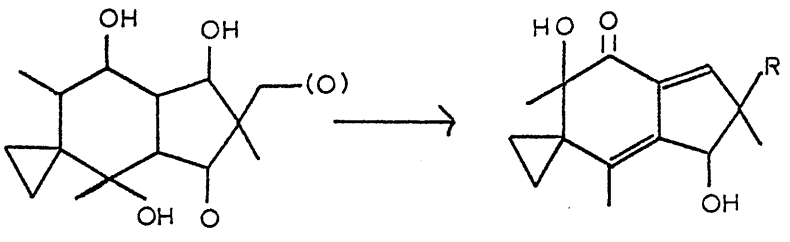
71

69

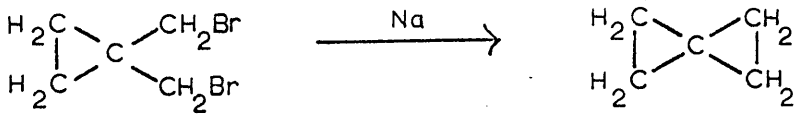


72

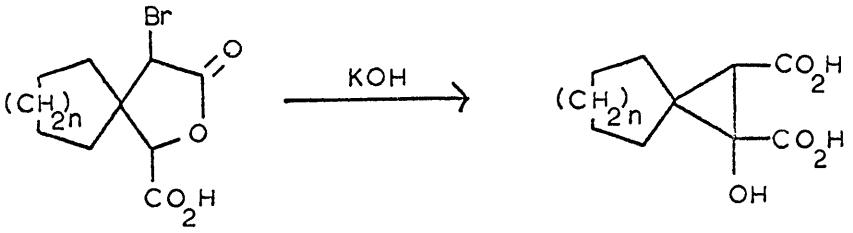
5, R = CH_2OH

6, R = CH_3

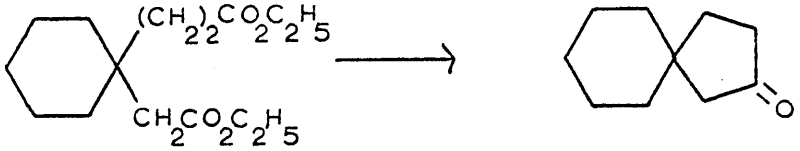
a


H2C
CH2Br
C
H2C
CH2Br
Na
H2C
CH2
C
H2C
CH2

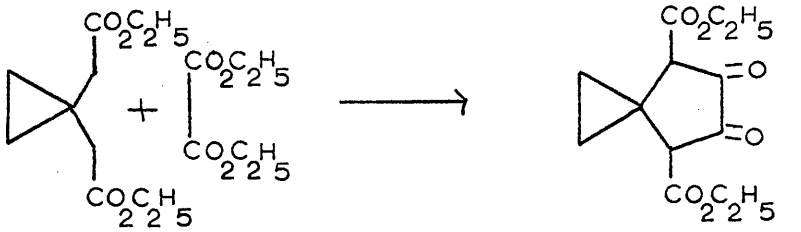
b


Br
O
(CH2)n
O
CO2H
KOH
CO2H
(CH2)n
CO2H
OH

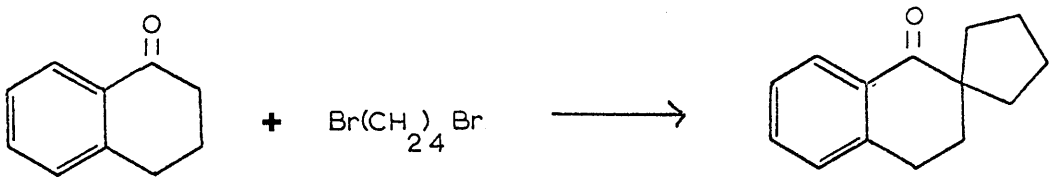
c

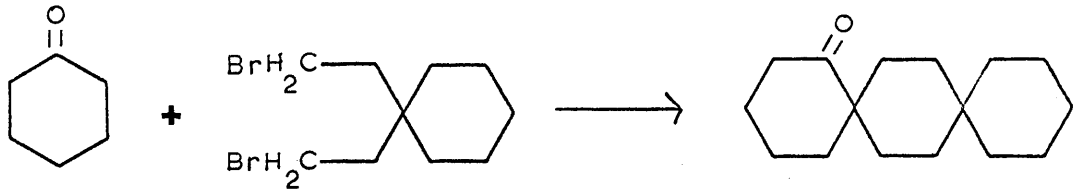

(CH2)2CO2C2H5
CH2CO2C2H5
O

d


CO2C2H5
CO2C2H5
CO2C2H5
CO2C2H5
O
O
CO2C2H5

e





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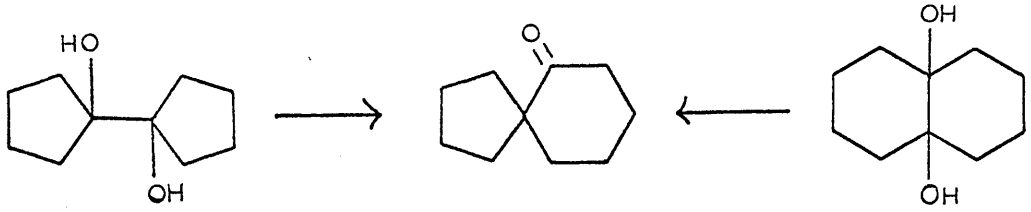

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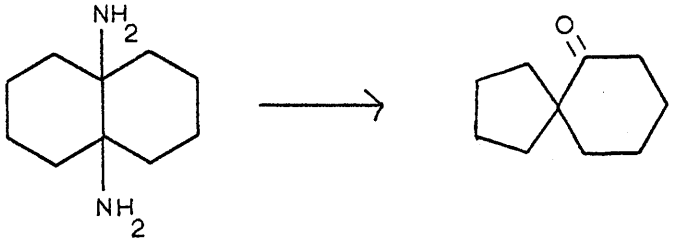
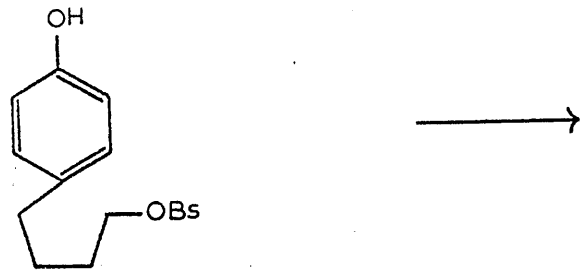
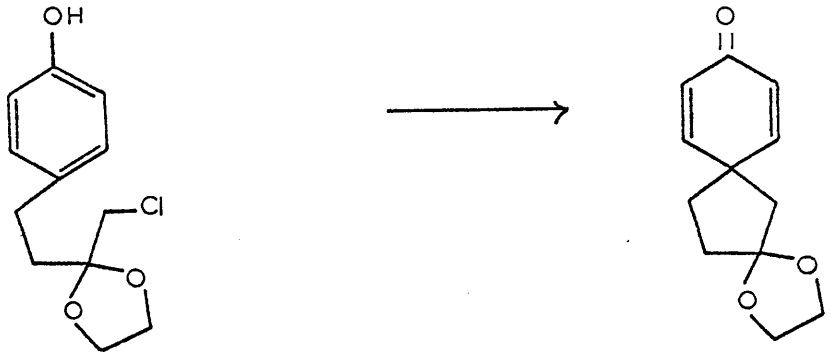


h

i





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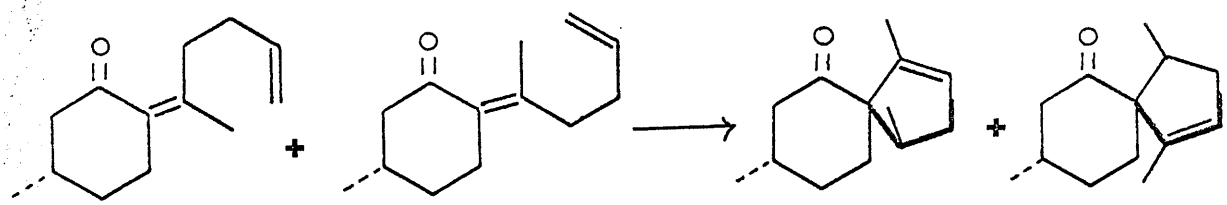

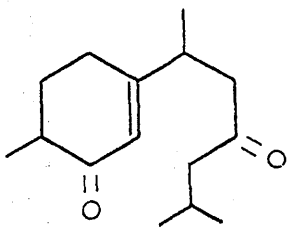

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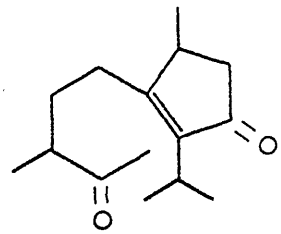

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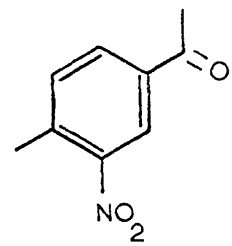

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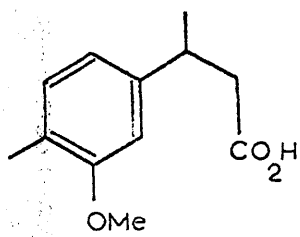

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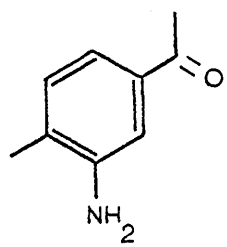

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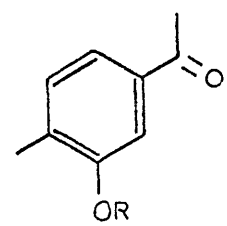
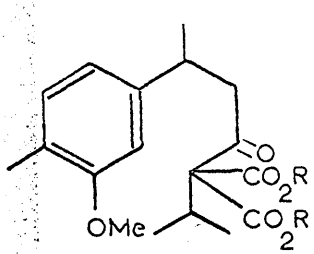


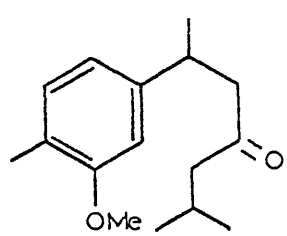
78, R=H

79, R=Me



80, R=CH_2O

81, R=H



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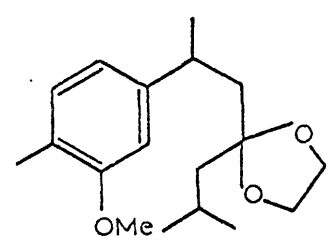

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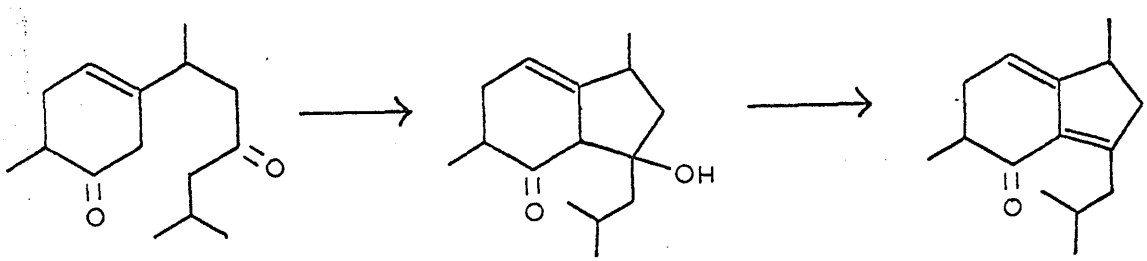

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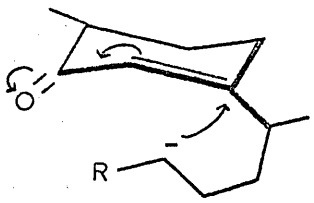

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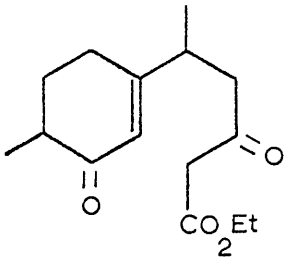

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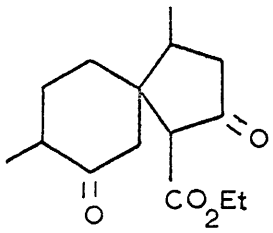

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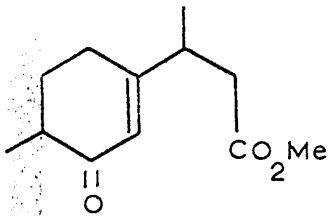

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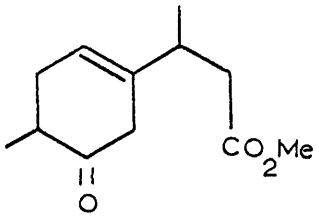

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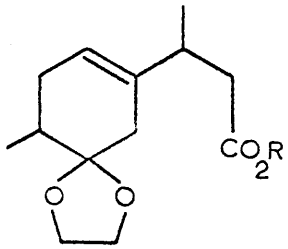
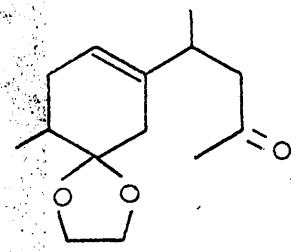


90 R=Me

91 R=H



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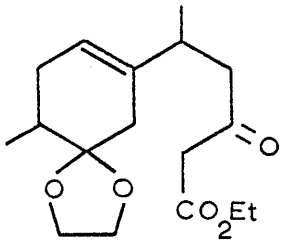

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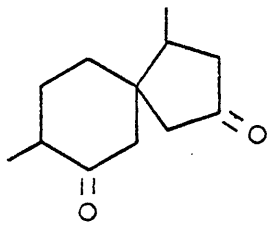

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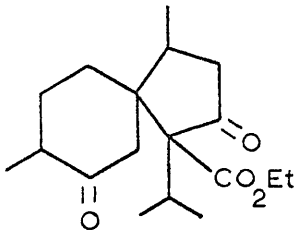

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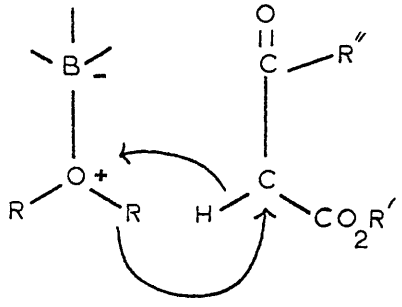

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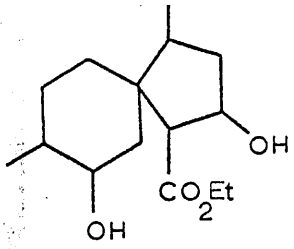

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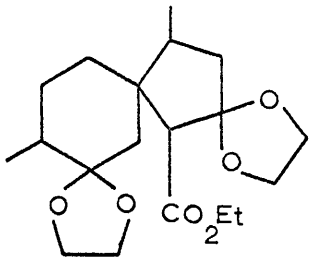

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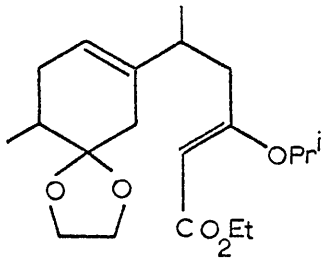

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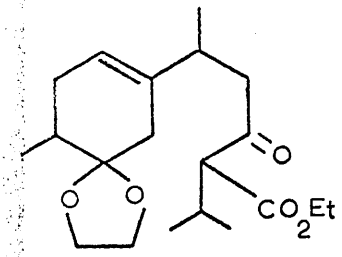

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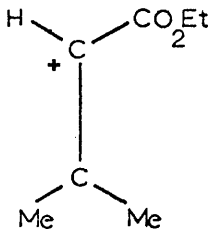

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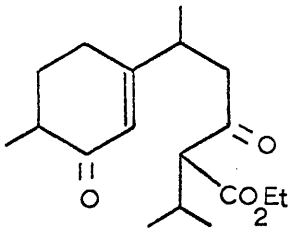

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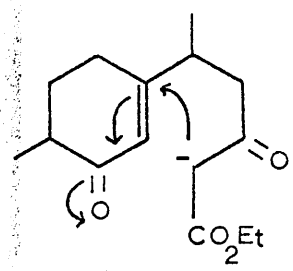

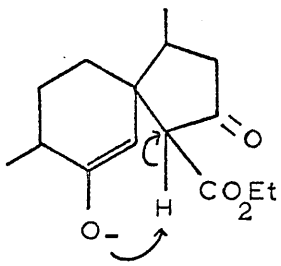

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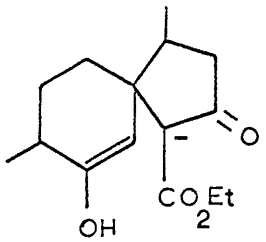

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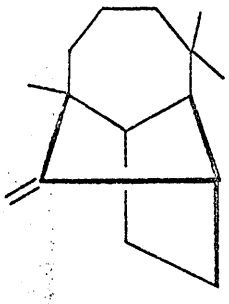

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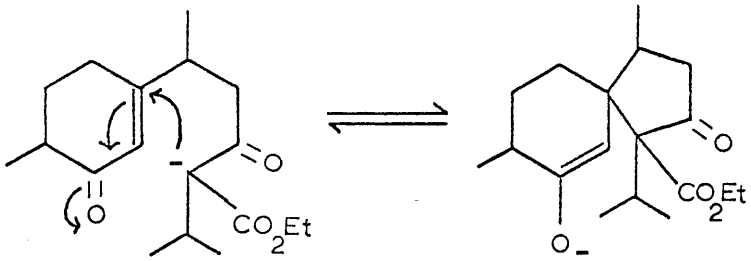
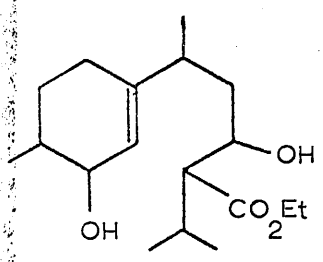


107 **106**



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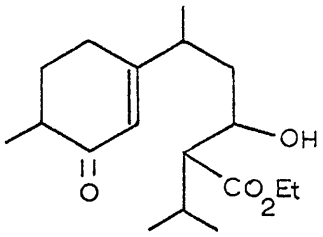

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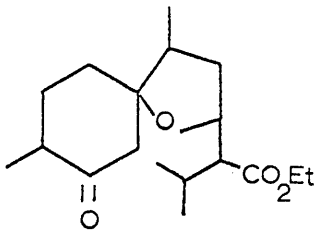

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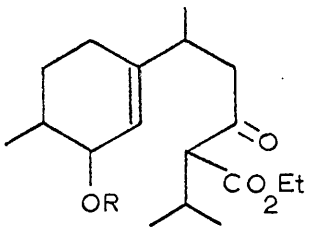
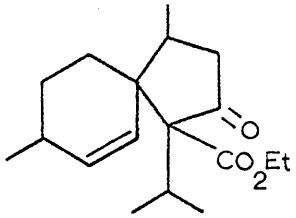


111, R = H
112, R = Ts



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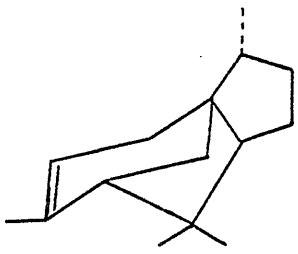


114

PART I

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. Analytical gas-liquid chromatography was performed on a Pye Argon Chromatograph: column, 10% Peg A (for the separation of the acorone isomers, a 5% QF1 column was used); 175°; pressure, 18 p.s.i.; flow rate, 50 ml./min. All organic extracts were dried over anhydrous magnesium sulphate.

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 SP. 800 instrument; base refers to the addition of three drops of sodium hydroxide (4N) to both the sample and reference cells. Routine infrared spectra were measured on a Unicam SP. 200 instrument, and for high resolution spectra, on a Unicam SP. 100 double-beam infrared spectrophotometer equipped with

* The comments on experimental procedure in the preamble to the section below also apply to that of Part II.

an SP. 130 sodium chloride prism-grating double-monochromator, operated under vacuum. All routine spectra in this present experimental series were determined as liquid films: in the second experimental section, the physical state is quoted. Nuclear magnetic resonance spectra were measured on a Perkin-Elmer 60 Mc./s. instrument, equipped with an integrator. The samples were run in carbon tetrachloride or deuterochloroform solution, with tetramethylsilane as internal reference.

Where appropriate, all solvents and liquid reagents were thoroughly purified in the requisite manner; all solid reagents were recrystallised.

β-(3-Methoxy-4-methylphenyl)butyric acid (76)

This compound was obtained by the procedure of Lindahl[34].

Methyl β-(3-oxo-4-methylcyclohexenyl)butyrates (88 and 89)

A solution of the acid (76; 15g.) in tetrahydrofuran (75 ml.) was added slowly to liquid ammonia (1.5 l.), followed by small cubes of lithium (22 g.), added over twenty minutes, with stirring in an atmosphere of nitrogen. The blue solution was stirred a further two hours, then isopropanol (300 ml.) was added over ninety minutes. The solution became white after about fifteen minutes. The ammonia was allowed to evaporate, leaving a residue which was dissolved in ice and hydrochloric acid (6N), then extracted with ethyl acetate (4X300 ml.). The organic extracts were combined, washed with brine, and dried. Removal of solvent afforded the crude product as a gum (15 g.), which on esterification with diazomethane gave a material seen to be inhomogeneous by t.l.c. This mixture was adsorbed on silica gel from 1% ether/light petroleum (b.p. 60-80°), and elution with 50% ether/light petroleum (b.p. 60-80°) effected a partial separation of the conjugated (88) and unconjugated (89) enone esters (10.5 g. total). The unconjugated enone

ester (89) was an oil, $\nu_{max.}$ 1740, 1720 and 1670 cm.$^{-1}$.

A pure sample of the conjugated enone ester (88), also an oil, b.p. 105°/0.07 mm., n_D^{25} 1.4865, $\nu_{max.}$ 1740, 1675 and 1630 cm.$^{-1}$, $\lambda_{max.}$ 237 mμ (ε = 15,500), furnished a semicarbazone, m.p. 153°. (Found: C, 58.60; H, 7.65; N, 15.65. $C_{13}H_{21}N_3O_3$ requires C, 58.40; H, 7.90; N, 15.90%).

Methyl β-(5-ethylenedioxy-4-methylcyclohex-1(2)-enyl) butyrate (90).

The mixture of enone esters (88 and 89, 7.1 g.) was heated with ethyl orthoformate (16 ml.), ethylene glycol (8 ml.) and p-toluenesulphonic acid (100 mg.) in an oil bath at 130-150° until distillation of ethanol ceased. The mixture was cooled, ether added, and the solution washed with saturated sodium bicarbonate solution, brine, and dried. Evaporation of solvent, followed by chromatography of the residue on alumina (Spence 'H'), afforded the pure ketal ester, shown to be homogeneous by t.l.c., as an oil (5.84 g.), b.p. 150°/0.05 mm., n_D^{23} 1.4812, $\nu_{max.}$ 1735, 1090, 1080, 1040, and 960 cm.$^{-1}$. (Found: C, 66.20; H, 8.55. $C_{14}H_{22}O_4$ requires C, 66.10; H, 8.70%).

β-(5-Ethylenedioxy-4-methylcyclohex-1(2)-enyl butyric acid (91)

The ketal ester (90, 36.8 g.) was stirred at 100° for forty-five minutes with a solution of sodium hydroxide (6 g.) in water (500 ml.). The cooled, homogeneous solution was carefully neutralised at 0° with hydrochloric acid (6N), then extracted with ether (3X200 ml.). The ethereal extracts were combined, washed with brine, dried and the solvent removed to afford the ketal acid (91) as a thick gum (32.2 g.), $\nu_{max.}$ 3200-2700, 1700, 1090, 1080, 1040 and 960 cm.$^{-1}$.

4-(5-Ethylenedioxy-4-methylcyclohex-1(2)-enyl)pentan-2-one (92)

A solution of methyl lithium (from lithium, 1.35 g., and methyl iodide, 14 g.) in ether (75 ml.) was added over five minutes to a stirred solution of the ketal acid (91, 5 g.) in ether (75 ml.), in an atmosphere of nitrogen. After initial precipitation of the lithium salt of the ketal acid, the solution clarified, then slowly turned opaquely white. The reaction mixture was heated under reflux under nitrogen, with stirring, for two hours, then cooled, water added carefully, and the ethereal solution washed with brine and dried. Removal of solvent afforded the methyl ketone (92) as a mobile oil (4.4 g.), b.p. 110°/0.05 mm., $n_D^{24.5}$ 1.4835, $\nu_{max.}$ 1710,

1090, 1080, 1040 and 960 cm.$^{-1}$. (Found: C, 70.35; H, 9.35. $C_{14}H_{22}O_3$ requires C, 70.55; H, 9.30%).

The combined aqueous layers were carefully acidified, and the starting acid (91, 270 mg.) isolated in the usual manner. This was combined with other batches of recovered acid and recycled.

Ethyl 5-(5-ethylenedioxy-4-methylcyclohex-1(2)-enyl)-3-oxo-hexanoate (93)

A solution of the methyl ketone (92, 4 g.) in tetrahydrofuran (50 ml.) was added over four hours to a refluxing solution of sodium hydride (50% dispersion in mineral oil, 3 g.), and diethyl carbonate (4 g.) in tetrahydrofuran (100 ml.) under an atmosphere of nitrogen. The solution was heated under reflux for a further six hours, then most of the solvent was removed *in vacuo*. Light petroleum and water were added, and the aqueous layer separated and carefully acidified with sulphuric acid (6N). Extraction of this with ether, followed by washing the ethereal solution with saturated sodium bicarbonate solution, brine and drying, afforded, on removal of solvent, the desired β-ketoester (93, 2.6 g.). Re-extraction of the petrol layer with sodium hydroxide solution (4N) gave, after acidification and ether

extraction, a further portion (0.74 g.) of the β-ketoester.

Chromatography of the total product on silica gel gave the pure β-ketoester (93) as an oil (3.3 g.), b.p. 130°/ 0.05 mm., $n_D^{24.5}$ 1.4849, $\nu_{max.}$ 1740, 1715, 1660-1640, 1090, 1080, 1040 and 960 $cm.^{-1}$, $\lambda_{max.}$ (base) 279 mμ (ε = 21,590). Found: C, 65,50; H, 8.15. $C_{17}H_{26}O_5$ requires C, 65.80; H, 8.45%).

Ethyl 5-(4-methyl-3-oxocyclohex-1(2)-enyl)-3-oxohexanoate (86)

A solution of the ketal β-ketoester (93, 500 mg.) in acetone (25 ml.) containing p-toluenesulphonic acid (50 mg.) was heated under reflux for three hours. The course of the reaction was monitored by the increasing absorption in the ultraviolet of the cyclohexenone chromophore being created at 235 mμ. After completion of the reaction, the acetone was removed in vacuo, ether and water added, the ethereal extract washed with saturated sodium bicarbonate solution, brine and dried. Evaporation of solvent afforded the desired enone β-ketoester (86) as an oil (436 mg.), b.p. 160°/ 0.08 mm., n_D^{24} 1.4932, $\nu_{max.}$ 1740, 1715, 1675 and 1630 $cm.^{-1}$, $\lambda_{max.}$ (base) 239 mμ (ε = 16,400), 276 mμ (ε = 20,200), $\lambda_{max.}$ (neutral) 235 mμ, (ε= 16,400). (Found: C, 67.50; H, 8.60. $C_{15}H_{22}O_4$ requires C, 67.65; H, 8.35%).

4-Ethoxycarbonyl-1,7-dimethylspiro(5,4)decan-3,6-dione (87)

The enone β-ketoester (86, 575 mg.) was added to a solution of potassium hydroxide in ethanol (0.2N, 39 ml.), and the cyclisation monitored by the fall in the ultraviolet absorption of the enone chromophore at 239 mμ, and the concomitant bathochromic shift of the β-ketoester enol tautomer chromophore from 276 to 282 mμ. After two hours, the solution was acidified with glacial acetic acid, and the solution evaporated *in vacuo* to dryness. The residue was taken up in ether, washed with saturated sodium bicarbonate solution, brine and dried. Removal of solvent yielded the spiro β-ketoester (87) as an oil (500 mg.), b.p. 110°/0.05 mm., n_D^{25} 1.4875, $\nu_{max.}$ 1750, 1730-1700, 1650-1610 cm.$^{-1}$, $\lambda_{max.}$(neutral) 250 mμ (ε = 3,000), $\lambda_{max.}$(base) 284 mμ (ε = 13,500). The mass spectral molecular weight was 266 (Calculated molecular weight, 266). (Found: C, 67.95; H, 8.60. $C_{15}H_{22}O_4$ requires C, 67.65; H, 8.35%).

1,7-Dimethylspiro(5,4)decan-3,6-dione (desisopropylacorone) (94)

A solution of the spiro β-ketoester (87, 250 mg.) in a mixture of glacial acetic acid (70 ml.), concentrated hydrochloric acid (35 ml.) and water (7 ml.) was refluxed

for two hours under an atmosphere of nitrogen. After removal of solvent *in vaduo*, the residue was dissolved in ether, the ethereal solution washed with sodium hydroxide solution (4N), brine and dried. Evaporation of solvent afforded the dione, *desisopropylacorone* (94) as a gum (156 mg.), b.p. $90^{o}/0.05$ mm., n_{D}^{24} 1.4980, $\nu_{max.}$ 1745 and 1710 $cm.^{-1}$. (Found: C, 73.90; H, 9.25. $C_{12}H_{18}O_{2}$ requires C, 74.20; H, 9.35%).

Attempted alkylations of 4-*ethoxycarbonyl*-1,7-*dimethyl*-*spiro*(5,4)*decan*-3,6-*dione* (87)

a. To a solution of the β-ketoester (87, 80 mg.) in ethanol (20 ml.) was added an ethanolic solution of sodium ethoxide (0.75N, 0.5 ml.), and the mixture stood at room temperature for one hour. Isopropyl iodide (0.3 ml.) was added, and the solution heated under reflux for twenty-four hours, at which time there was no discernible change in the ultraviolet spectrum from that of the starting material. The reaction mixture was cooled, acidified with glacial acetic acid, and most of the solvent removed *in vacuo*. The residue was taken up in ether, the ethereal solution washed with sodium hydroxide solution (4N, 4X10 ml.), brine and dried. Removal of solvent left an oil (20 mg.), $\nu_{max.}$ 1740

and 1710 cm.$^{-1}$, with no significant absorption in basic solution in the ultraviolet above 220 m , but it was a complex product, as seen from t.l.c. This product was heated under reflux in an atmosphere of nitrogen with a solution of glacial acetic acid (6 ml.), concentrated hydrochloric acid (4 ml.) and water (0.5 ml.) for two hours. Most of the solvent was removed in vacuo, and the residue dissolved in ether. The ethereal solution was washed with sodium hydroxide solution (4N), brine and dried. Removal of solvent afforded a dark brown semi-solid (10 mg.) whose infrared spectrum, with absorption bands at 1745 and 1710 cm.$^{-1}$, was comparible with that of desisopropylacorone (94), and whose t.l.c. behaviour indicated the presence of this latter compound, accompanied with some decomposition, but none of the acorone isomers.

b. To a solution of sodium (5 mg.) in ethanol (1 ml.) was added a solution of the β-ketoester (87, 50 mg.) in ethanol (3 ml.). After standing for one hour at room temperature, the above-described procedure was performed, with the same result.

c. A solution of the β-ketoester (87, 54 mg.) in t-butanol (3 ml.) was added to a solution of potassium (12.7 mg.) in

t-butanol (3 ml.). The mixture was heated under reflux for one hour, then stirred at room temperature for a further four hours. Isopropyl bromide (0.15 ml.) was added, and the solution heated under reflux for twelve hours. Isolation of the product in the normal manner afforded a brown oil (45 mg.), which, per se and on subsequent hydrolysis and decarboxylation, proved to be the same complex mixture as was obtained previously.

This procedure was repeated using isopropyl iodide, with identical results.

d. A solution of the β-ketoester (87, 50 mg.) in benzene (1 ml.) was added to a suspension of sodium hydride (50% dispersion in mineral oil, 10 mg.) in benzene (10 ml.) and dimethylformamide (7 ml.), and the mixture heated under reflux for thirty minutes. To the cooled solution was added sodium iodide (30 mg.), followed by a solution of isopropyl bromide (20 mg.) in benzene (1 ml.), and reflux continued. After twenty-four hours, the solution was poured on to cooled hydrochloric acid (6N), and the mixture extracted with ether. The organic layer was washed with saturated sodium bicarbonate solution, brine and dried. Evaporation of solvent afforded a brown oil (40 mg.), which was seen from its infrared spectrum and t.l.c. comparison to be starting material (87).

e. Boron trifluoride gas (from sodium fluoroborate, 20 g., boric oxide, 3 g. and concentrated sulphuric acid, 20 ml.) was passed into a solution of the β-ketoester (87, 50 mg.) in di-isopropyl ether (0.1 ml.) at 0^{0} for ten minutes, with stirring. Stirring was continued at room temperature for twenty-four hours, after which time a solution of sodium acetate (1 g.) in water (5 ml.) was added. The solution was extracted with ether, the ethereal extract washed with saturated sodium bicarbonate solution, brine and dried. Removal of solvent yielded a gum (40 mg.), which, from its infrared spectrum and t.l.c. comparison, was seen to be starting material (87).

Attempted alkylations of ethyl 5-(5-ethylenedioxy-4-methyl) 3-oxohexanoate (93)

a. A solution of the ketal β-ketoester (93, 420 mg.) in ethanol (20 ml.) was treated with an ethanolic solution of sodium ethoxide (0.75N, 5 ml.), then heated under reflux for thirty minutes. Isopropyl iodide (3 ml.) was added to the cooled solution, and reflux continued for a further three hours. The cooled solution was neutralised with glacial acetic acid, and evaporated in vacuo to dryness. The residue was taken up in ether, the ethereal solution washed with

saturated sodium bicarbonate solution, brine and dried. Removal of solvent left an oil (303 mg.), whose t.l.c. behaviour showed great complexity, and whose infrared spectrum, with absorption bands at 1670 and 1620 $cm.^{-1}$, and ultraviolet spectrum, $\lambda_{max.}$ 233 mμ, indicated predominantly O-alkylation, with formation of (99).

b. A solution of the ketal β-ketoester (93, 100 mg.), in cyclohexane (10 ml.) was added to a suspension of sodium hydride (50% dispersion in mineral oil, 25 mg.) in cyclohexane (10 ml.), then the solution was heated under reflux for thirty minutes. A solution of isopropyl iodide (1 ml.) in cyclohexane (5 ml.) was added to the cooled solution, and reflux continued. No reaction had occurred after twenty-four hours, as the ultraviolet spectrum, $\lambda_{max.}$(base) 279 mμ, of an aliquot indicated the presence of solely starting material (93). Subsequent isolation in the usual manner afforded unchanged ketal β-ketoester (93, 88 mg.)

c. Boron trifluoride gas (from sodium fluoroborate, 4 g., boric oxide, 0.6 g. and concentrated sulphuric acid, 4 ml.) was passed into a solution of the ketal β-ketoester (93, 300 mg.) in di-isopropyl ether (150 mg.) at 0^{o} for ten minutes, with stirring. The reaction mixture was allowed to

stand at room temperature for twenty-four hours, after which time sodium acetate (1 g.) in water (5 ml.) was added. The solution was extracted with ether, the ethereal extract washed with saturated sodium bicarbonate solution, brine and dried. Removal of solvent yielded a yellow mobile oil (247 mg.). The infrared spectrum, $\nu_{max.}$ 1740, 1715, 1675 and 1630 $cm.^{-1}$, and ultraviolet spectrum, $\lambda_{max.}$(neutral) 237 mμ, $\lambda_{max.}$(base) 237 and 277 mμ, showed the presence of liberated enone and also unalkylated β-ketoester. The total product was heated under reflux with acetone (25 ml.) and p-toluenesulphonic acid for three hours. Usual isolation procedures afforded the product as a dark mobile oil (203 mg.). Neither infrared nor ultraviolet spectra, nor t.l.c. evidence suggested the presence of a significant amount of the desired isopropylated compound (102).

d. A solution of the ketal β-ketoester (93, 300 mg.) in benzene (5 ml.) was added to a suspension of sodium hydride (50% dispersion in mineral oil, 50 mg.) in benzene (15 ml.) and dimethylformamide (10 ml.), and the solution heated under reflux for thirty minutes. To the cooled solution was added sodium iodide (160 mg.), followed by a solution of isopropyl bromide (130 mg.) in benzene (5 ml.), and reflux continued. After twenty-four hours, the solution was poured

on to cooled hydrochloric acid (6N), and the mixture extracted with ether. The organic layer was washed with saturated sodium bicarbonate solution, brine and dried. Evaporation of solvent yielded a brown oil (275 mg.), which was shown to be starting material (93) by t.l.c. comparison.

e. To a solution of potassium (11.8 mg.) in t-butanol (3 ml.) was added a solution of the β-ketoester (93, 57.7 mg.) in t-butanol (3 ml.). The mixture was heated under reflux for one hour, then stirred at room temperature for a further three hours, after which time isopropyl bromide (0.05 ml.) was added to the solution. Reflux was continued for twenty-four hours. Isolation in the usual manner afforded the product (42 mg.), which proved to be starting material (93) on t.l.c. comparison.

A similar sequence was performed using potassium t-amylate in t-amyl alcohol, with identical results.

Ethyl 2-isopropyl-5-(5-ethylenedioxy-4-methylcyclohex-1(2)-enyl)-3-oxohexanoate (100)

A solution of the ketal β-ketoester (85, 1.88 g.) in potassium t-butoxide in t-butanol (from potassium, 501 mg., and t-butanol, 25 ml.) was heated under reflux for one hour.

Isopropyl iodide (4 ml.) was added to the cooled solution, and reflux continued for a further forty hours. After removal of excess t-butanol *in vacuo*, water was added, and the solution carefully acidified with hydrochloric acid (6N). The mixture was extracted with ether, the ethereal extract was washed with saturated sodium bicarbonate solution, brine, and dried. Removal of solvent afforded the crude product (1.86 g.) which, on purification by chromatography on silica gel, yielded the pure *isopropyl ketal* β-*ketoester* (100) as a thermally-unstable oil (1.25 g.), n_D^{25} 1.4982, $\nu_{max.}$ 1735, 1710 and 1640-1610 $cm.^{-1}$, $\lambda_{max.}$ (base) 288 mμ (ε= 3,166). Mass spectral molecular weight was 352 (Calculated molecular weight, 352); the mass spectral fragmentation pattern also substantiated the proposed structure. The n.m.r. spectrum shows the required presence of five methyl groups in the region of 9τ.

Ethyl 2-*isopropyl*-5-(4-*methyl*-5-*oxocyclohex*-1(6)-*enyl*)-3-*oxohexanoate* (102)

A solution of the alkylated ketal β-ketoester (100, 450 mg.) in acetone (50 ml.) containing p-toluenesulphonic acid (50 mg.) was heated under reflux for three hours. After this time, the reaction was complete, as seen from

the absorption of the generated enone chromophore in the ultraviolet at 238 m having gained maximum intensity. The acetone was removed in vacuo, and the residue dissolved in ether. The ethereal solution was washed with saturated sodium bicarbonate solution, brine and dried. Evaporation of solvent furnished the enone isopropyl β-ketoester (102) as an oil (360 mg.), b.p. 130°/0.5 mm., $n_D^{24.5}$ 1.4876, $\nu_{max.}$ 1750, 1715, 1675 and 1640-1610 $cm.^{-1}$, $\lambda_{max.}$ (neutral) 236 mμ (ε= 16,400), $\lambda_{max.}$ (base) 238 mμ (ε= 16,400), 288 mμ (ε= 3,200). (Found: C, 69.81; H, 8.98. $C_{18}H_{28}O_4$ requires C, 70.10; H, 9.15%).

Attempted internal Michael reactions

a. The enone isopropyl β-ketoester (102, 50 mg.) was added to a solution of potassium hydroxide in ethanol (0.2N, 20 ml.), and subsequent changes monitored by the ultraviolet spectrum of the solution. After twenty-four hours at room temperature, the intensities of both the enone and β-ketoester enol chromophore absorption maxima had decreased considerably. However, on subsequent isolation, the product obtained was an extremely complex mixture (30 mg.), with much apparent degradation.

b. A solution of potassium (1 mg.) in t-butanol (10 ml.) was added to the enone isopropyl β-ketoester (102, 25 mg.), and the mixture was stirred at room temperature under nitrogen. Isolation in the usual manner after twenty-four hours gave the product (20 mg.). T.l.c. comparison showed this to be starting material (102).

c. A solution of potassium (4 mg.) in t-butanol (10 ml.) was added to the enone isopropyl β-ketoester (102, 27 mg.), and the solution heated under reflux in an atmosphere of nitrogen for twenty-four hours. Normal isolation procedures gave the product (20 mg.), which, on t.l.c., showed complete fragmentation.

d. A solution of sodium (0.8 mg.) in ethanol (10 ml.) was added to the enone isopropyl β-ketoester (102, 10.5 mg.). The resulting solution was stood at room temperature for twenty hours, after which time no further changes were observed in the ultraviolet, both the enone and β-ketoester enol chromophore intensities having decreased. Subsequent isolation yielded a product (8.5 mg.) which, on t.l.c. comparison, proved to be starting material (102) and degradation products.

e. Sodamide (1 mg.) was added to a solution of the enone isopropyl β-ketoester (102, 25 mg.) in ether (5 ml.), and the solution heated under reflux in an atmosphere of nitrogen for twenty-four hours. The solution was then cooled, acidified with hydrochloric acid (6N), the ethereal extract washed with saturated sodium bicarbonate solution, brine and dried. Removal of solvent afforded the product as a gum (20 mg.), which appeared as a streak on t.l.c., with no visible concentration at any one area.

Similar results were obtained by the use of sodium hydride (50% dispersion in mineral oil).

f. Sodium hydride (50% dispersion in mineral oil, 20 mg.) was washed with light petroleum (b.p. 40-60^{o}) to remove mineral oil, then stirred with dimethylsulphoxide (3 ml.) at 70^{o} for forty-five minutes under nitrogen. The solution was cooled to room temperature, the enone isopropyl β-ketoester (102, 200 mg.) in dimethylsulphoxide (2 ml.) added, and the resulting solution stirred at room temperature under nitrogen for twenty-four hours. The solution was acidified with hydrochloric acid (6N), extracted with ether, the ethereal extract washed with saturated sodium bicarbonate solution, brine and dried. Removal of solvent afforded the product as an oil (185 mg.), which was seen to be

starting material (102) by t.l.c. comparison.

g. A mixture of the enone isopropyl β-ketoester (102, 160 mg.), triethylamine (100 mg.) and ethylene glycol (2 ml.) was sealed in a nitrogen-filled Carius tube, which was then heated at 230° for twenty-four hours. The tube was cooled, opened carefully, and the contents poured on to water. Extraction of the aqueous solution with pentane/methylene chloride (2 : 1), followed by washing of the organic extract with brine, drying, and removal of solvent gave the product as an oil (66.8 mg.). Preparative t.l.c. of this product gave no component with the expected spectral characteristics. No starting material was recovered.

Attempted selective reduction of the enone isopropyl β-ketoester (102)

A solution of the enone isopropyl β-ketoester (102, 100 mg.) in ethanol (5 ml.) and sodium hydroxide solution (4N, 5 ml.) was treated with excess sodium borohydride for four hours at room temperature. The solution was diluted with brine, extracted with ether, the ethereal extract washed with brine and dried. Removal of solvent yielded the product (108) as an oil (96 mg.), $\nu_{max.}$ 3500-3300,

1730 and 1715 cm.$^{-1}$, with no significant absorption above 220 mμ in the ultraviolet in neutral or basic solution.

A portion of the product (108, 30 mg.) was shaken in chloroform (25 ml.) with manganese dioxide (100 mg.) for two days, after which time the suspension was filtered through Celite, and the filtrate evaporated to dryness, to give the product (109) as an oil (28 mg.), $\nu_{max.}$ 3500-3300, 1730, 1715, 1675 and 1630 cm.$^{-1}$, $\lambda_{max.}$ (neutral) 238 mμ ; the intensity of the enone chromophore in the ultraviolet dropped to zero within five minutes on the addition of base.

A portion of the latter product (109, 10 mg.) was dissolved in acetone and treated at 0^{o} with chromium trioxide/sulphuric acid solution. Normal isolation procedures afforded a compound (8 mg.) whose infrared and ultraviolet spectra were identical with the starting enone isopropyl β-ketoester (102), as was its t.l.c. behaviour.

PART II

Approaches to the Synthesis of Lycopodine.

INTRODUCTION

Over the years, the numerous Lycopodium species have proved to be a natural treasure chest of alkaloids[48]. The first alkaloid to be isolated[49] was lycopodine (115) in 1881, initially from Lycopodium complanatum L., although it was found later to be quite ubiquitous in its distribution in the species. In subsequent years, many more alkaloids were isplated from the dozen or so species studied. They are moderately toxic, but owing to the inedible nature of the plants, there are no records of poisoning of animals or man. They do have pharmacological properties[50,51], such as stimulation and contraction of the uterus, paralysis, etc., none of which have been found useful in medicine.

It was not until much more recent times, however, that any substantial progress was made in the structural elucidation of these interesting compounds. The initial breakthrough was accomplished with the determination[52] of the structure of annotinine (116) in 1956 at the University of New

Brunswick, and indeed Canadian workers, notably Wiesner, Ayer, McLean and Anet, dominate this field of natural product studies.

The correct structure for annotinine (116), the major alkaloid of Lycopodium annotinum L., was postulated in 1956 as one of three possibilities by Wiesner et al.[52]. In 1957, these workers[53] rigorously proved the validity of one of these structures, this conclusion being corroborated by an X-ray analysis[54] of the corresponding bromohydrin, which also revealed the relative configuration of annotinine as (116). The same stereochemistry for all the asymmetric centres was deduced from a detailed analysis[55] of the chemical evidence.

The structure of lycopodine was elucidated in 1960 by Harrison and McLean[56], who showed that all known reactions of the alkaloid could be accommodated by the formula (115). They first proposed[57] that lycopodine, like annotinine, contains a hexahydrojulolidine skeleton, and that many reactions of the compound may be explained by the partial structure (117).

The interaction of lycopodine with cyanogen bromide gave rise to two isomeric cyanobromolycopodines, α and β, portrayed by (118) and (119) respectively. In compound (118), the bromine was exchanged for an acetoxy group, the latter

saponified to a primary alcohol, and the alcohol oxidised to a carboxylic acid without loss of carbon. The reduction of the keto group in this ketoacid with sodium borohydride yielded a hydroxy-acid which failed to lactonise. Hydrolysis of the cyano group in the ketoacid and esterification of the resulting amino acid with diazomethane gave the compound (120) by spontaneous closure of a lactam ring. According to the infrared amide carbonyl frequency of (120) at 1635 $cm.^{-1}$, this lactam ring was at least six-membered. The compound (120) was reduced with lithium aluminium hydride to dihydrolycopodine, also obtainable by the action of the same reagent on lycopodine (115).

An attempt to displace the bromine in (119) with potassium acetate yielded the very unreactive enol ether (121). However, the use of silver acetate made possible the displacement of the bromine by an acetoxy group in (119). Hydrolysis of the resulting acetate yielded a primary alcohol, which was oxidised to a ketoacid without loss of carbon. Reduction of the keto group in the latter compound by sodium borohydride gave the lactone (122), which, according to its infrared carbonyl absorption band at 1743 $cm.^{-1}$, was probably six-membered.

Since the carbonyl frequency of lycopodine itself (1700 $cm.^{-1}$) corresponds to a cyclohexanone ketone, it is clear

that all the data discussed up to this point are compatible with the partial formula (117) for lycopodine. The bromine in α-cyanobromolycopodine (118) was removed by hydrogenolysis, and the resulting α-cyanolycopodine was used as the most suitable compound for the definition of the environment of the keto group. Bromination of α-cyanolycopodine gave an uncharacterised dibromide, which was hydrolysed by alkali to (123). The ultraviolet ($\lambda_{max.}$ 280 mμ, logε= 4) and infrared (strong bands at 1660 and 1640 cm.$^{-1}$) spectra of this compound supported its formulation as an enolised α-diketone. α-Cyanolycopodine also yielded a monobenzylidene derivative, which by treatment with selenium dioxide gave a mixture of two products, namely the hydroxy compound (124) and the unsaturated compound (125). Ozonolysis of benzylidene-α-cyanolycopodine afforded the enolic α-diketone (123). On the other hand, ozonolysis of the hydroxybenzylidene compound (124) gave the hydroxydiketone (126). This latter compound had ultraviolet ($\lambda_{max.}$ 420 mμ, logε= 2.5) and infrared (strong band at 1724 cm.$^{-1}$) spectra fundamentally different from those of compound (123), and it showed no enolic properties. Hydrogenolysis readily converted the non-enolic compound (126) into the fully enolised compound (123).

These studies indicate that the only hydrogen available

for enolisation in the diketone (123) is replaced by the hydroxyl in the diketone (126). Consequently, the carbon atom indicated by an arrow in (126) must be either quaternary of represent a bridgehead towards which enolisation is impossible. This conclusion, coupled with the fact that lycopodine analysed for one C-methyl group on a Kuhn-Roth determination, was the basis for the extension of the partial structure (117) into the complete structure (115).

Formula (115) explains very well the formation of 7-methyl- and 5,7-dimethylquinoline on the dehydrogenation of lycopodine. It is clear that these products must originate from rings A and D of lycopodine. The reason why no quinoline dehydrogenation product corresponding to rings A and B was isolated must be due to the fact that the ABC-hexahydrojulolidine system was destroyed by a reverse Mannich reaction with the formation of the intermediate (127). This compound may cleave according to (a) by a reverse Michael reaction and yield, after dehydrogenation, 7-methylquinoline; or it may cleave pyrolytically according to (b), with the ultimate formation of 5,7-dimethylquinoline.

A further, important corroboration of structure (115) was the finding that both α- and β-cyanodihydrolycopodine (128) and (129) respectively, possess the n-propyl chain.

Both compounds yielded 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 explain all the discussed chemical information and at the same time be reasonably related to annotinine (116), it seems that the formula (115) has been conclusively established by the work described above.

Lycopodine (115) and annotinine (116) are the major Lycopodium alkaloids, but a large number of minor, related alkaloids have been isolated. Initially, some of these were designated by number or letter, but the majority have been assigned names and structures. As a result of these structural elucidations, it was observed that they fall naturally into two distinct classes, namely those with a hexahydrojulolidine skeleton, and those containing a pyridine or pyridone ring or some modification thereof.

Those with the hexahydrojulolidine skeleton are lycopodine (115), annotinine (116), dihydrolycopodine[58] (130) and its acetate[59] (131), acrifoline[60] (132), lycofoline[61] (133) and its diacetate[62] (134), lycoclavine[63] (135) and its acetate[63] (136), clavolonine[64,65] (137), annofoline[66] (138), lycodoline[67] (139), flabelliformine[68] (140),

flabelline[69] (141), fawcettiine[64,65] (142) and its acetate[64,65] (143), lofoline[70,71] (the C-12 epimer of fawcettiine), annotine[72] (144), lycofawcine[73,74] (145) and its acetate[62] (146), lyconnotine[75] (147), and base L.20[76] (148). All of these compounds are obviously closely related biogenetically. A considerably modified member of this group is serratinine[77] (149), believed[78] to be connected biogenetically with lycodoline (139).

The stereochemistry of the alkaloids with the lycopodine skeleton was elucidated in an elegant study by Anet[71]. By interrelating the structures of typical compounds in this group by means of their oxidation and reduction products, he showed that the stereoformula (150) for lycopodine was representative of almost all of them. The two exceptions are annofoline (138) and acrifoline (132), which, as they both exist partly as internally hydrogen-bonded hydroxy-ketones and partly as hemi-ketals, must possess ring D in a boat conformation, as shown in stereoformula (151) for annofoline. The absolute stereochemistry of serratinine (149) has been postulated by the use of n.m.r. spectroscopy and optical data[78].

The second class of Lycopodium alkaloids, those with a pyridine or pyridone ring or some modification thereof, is comparatively small. The only member of this class poss-

essing a pyridine ring is lycodine[73, 79-81] (152), the structure of which was postulated by Anet[79]. The validity of this structure was proved[82] by the conversion of β-obscurine (153) to lycodine. Anet[81] also succeeded in correlating lycodine (152) with lycopodine (115). In view of the earlier correlation of β-obscurine with lycodine, and of the known stereochemistry of lycopodine, it is possible to represent the two obscurines, lycodine and lycopodine by the skeletal stereoformula (154).

A considerable biogenetic modification, involving loss of one carbon by decarboxylation instead of cyclisation to afford ring A, would give rise to selagine[83] (155). α-Obscurine[80] (156), β-obscurine[80] (153) and sauroxine[84,85] (the C-12 epimer of α-obscurine) are the only alkaloids of this group possessing an N-methyl function. The remaining members are des-N-methyl-α-obscurine[86] (157), hydroxydes-N-methyl-α-obscurine[87] (158) and flabellidine[87] (159).

The biogenetic scheme for the formation of the Lycopodium alkaloids was first postulated by Conroy in a private communication with Wiesner, at a time when the structure of only annotinine (116) was known. Conroy[88] proposed the formal biogenetic intermediate (160), which is envisaged as arising by an aldol condensation between two straight-chain eight-carbon poly-β-ketoacids. This truly inspired suggestion has

proved capable of encompassing all the other Lycopodium alkaloids whose structures have since been elucidated, although, as yet, there is little experimental verification for the proposed scheme.

The route to annotinine (116) is considered to involve oxidation at C-8 to carboxyl to afford structure (161), then condensation between C-12 and C-15 and further elaboration to yield (162), which possesses a cyclobutane ring. A Mannich reaction between C-4 and C-13 of this compound and ammonia, followed by lactamisation, yields the structure (163). Subsequent conversion to annotinine (116) is unexceptional. Annotine (144) is also derivable by a similar route.

The other Lycopodium alkaloids are considered to arise by a different pathway. Initial condensation between C-8 and C-15 in the intermediate (160) yields the compound (164). A Mannich reaction between C-4 and C-13 in this latter intermediate and ammonia, with subsequent lactamisation, yields the structure (165), which is a plausible precursor of lycopodine (115), and its related analogues, for example, annofoline (138). If the Mannich reaction on (164) is not followed by lactamisation, the intermediate (166) is obtained by reaction of the carbonyl group at C-5 with ammonia, followed by dehydration. Selagine (155) can then arise by pyridone ring formation and decarboxylation at C-9.

α-Obscurine (156), β-obscurine (153) and sauroxine are also biogenetically related to the intermediate (166), as is lycodine (152), the latter probably via β-obscurine. The remaining alkaloids are derivable in a similar manner, with slight modifications. Serratinine (149) is considered[78] to be derived from lycodoline (139) or some close relative, possibly via the intermediates (167), (168) and (169). This assumption appears reasonable, since lycodoline and serratinine occur together naturally, and the proposed absolute configuration of serratinine coincides with that of an alkaloid which might be expected to arise from the lycodoline-type alkaloids by the proposed transformation.

A vindication of part of this biogenetic scheme was provided[89] by the conversion of lycopodine (115) to annofoline (138). It has been suggested that lycopodine may be a central intermediate in the biogenesis of the Lycopodium alkaloids, in that it may be oxygenated at C-8 to yield alkaloids of the annofoline type. Lycopodine was converted into the corresponding lactam (170) by oxidation with potassium permanganate in acetone. This lactam gave, on reduction with sodium borohydride, the dihydrolactam (171), which was assigned an axial hydroxyl configuration due to its conversion to dihydrolycopodine (130) on reduction with lithium aluminium hydride. Oxidation of the dihydro-

lactam (171) with lead tetra-acetate yielded the cyclic ether (172), which on treatment with boron trifluoride and acetic acid gave the acetoxy-olefin (173). Reaction of the olefin with diborane, followed by treatment with alkaline hydrogen peroxide, afforded the alcohol (174), the stereochemistry of which was inferred on the assumption that addition of diborane would occur from the less hindered side of the olefinic bond. The lactam carbonyl was also removed during the hydration, an unexpected occurrence. Oxidation of the hydroxy-compound (174) with chromium trioxide in pyridine yielded O-acetylannofoline (175), which, on hydrolysis, afforded annofoline (138), identical with an authentic sample.

The number of published synthetic approaches to the Lycopodium alkaloids is rather small, the main contributors being Wiesner and Ayer. Wiesner's first publication[90] in this vein appeared in 1964, when he succeeded in synthesising a degradation product (176) of lyconnotine (147). m-Anisidine, on treatment with 1-bromo-3-chloropropane, furnished a 30% yield of the tricyclic phenol (177), which, on catalytic hydrogenation over Raney nickel, gave the vinylogous lactam (178). Reaction of this latter compound with methyl iodide gave the methiodide (179), which, on treatment with isobutyl lithium followed by acid hydrolysis of the

resulting enol-ether, afforded, in 7% yield, the racemic ketone (180); this latter compound possessed, among other properties, an infrared spectrum identical to that of the natural degradation product (176).

The second paper[91] in this series described the attempted synthesis of lycopodine (115). The salt (179) previously obtained[90] was treated with allyl magnesium bromide, followed by acid hydrolysis, to afford the ketone (181) in 15% yield. The presence of Bohlmann bands[92,93] in the infrared spectrum of this compound indicated the existence of the wrong stereochemistry (182) at the B/C ring fusion. (Bohlmann bands are observed when two or more C-H bonds are trans-diaxial to an adjacent nitrogen lone-pair of electrons). Prolonged contact of the compound with basic alumina effected epimerisation to the desired tricyclic ketone (183), which showed no Bohlmann bands. When this latter compound was heated under reflux with hydrobromic acid, a 1 : 1 mixture of the tetracyclic alcohol (184) and the corresponding bromide (185) was obtained in quantitative yield. Sodium amalgam reduction of the bromide (185) afforded the tetracyclic amine (186).

In the same publication[91], another approach was described. Dihydroorcinol (187) was converted, by treatment with 3-aminopropan-1-ol followed by pyridine hydriodide, to

the vinylogous lactam (188), which was then elaborated to the corresponding N-methyl compound (189). Treatment of this compound with isopropyl iodide afforded the salt (190), which, on reaction with allyl magnesium bromide, gave the enol ether (191). When this enol ether was stirred with sulphuric acid, the alcohol (192) and not the expected alcohol (193) was obtained, a hydride shift having taken place. The occurrence of this phenomenon has a number of analogies in the literature[94-96].

In the third and most recent publication in the series, Wiesner[97] reported on the use of photochemical additions as synthetic tools in this field. Although the work described was purely exploratory, the ultimate goal was annotinine (116). Light-induced addition of allene to the lactam (194) gave the isomeric exomethylene cyclobutane compounds (195) and (196). Conversion of the keto group of (195) to the ethylene ketal, followed by hydrogenation over platinum oxide in ethanol and deketalisation, effected the stereospecific transformation of (195) to (197), which possesses the correct stereochemistry for the methylcyclobutane ring of annotinine (116). The exploitation of this new photochemical reaction for the synthesis of annotinine, starting with the tricyclic system (198), is an obvious possibility.

Ayer[98], in 1965, described an interesting cycle of

reactions, starting and finishing with lycopodine (115). Reduction of the unsaturated lactam (173), previously[89] obtained from lycopodine, afforded with lithium aluminium hydride the unsaturated alcohol (199), which showed intramolecular hydrogen-bonding in the infrared. Oppenauer oxidation of this alcohol yielded the ketone (200), which, on reduction with sodium-liquid ammonia-methanol furnished the alcohol (201). This alcohol (201), when dissolved in 75% sulphuric acid, was transformed to lycopodine (115) in quantitative yield by the hydride shift shown. The reaction sequence delineated above is of great potential value in the synthesis of lycopodine and related alkaloids, since it provides a method of inserting a hydrogen atom from the more hindered side of C-15, a result not readily achieved by other means.

In a very recent publication, Ayer[99] reported on a method for the construction of substituted cis-trans-hexahydrojulolidines, the system present in lycopodine (115). Reduction of the tricyclic amine (202) with lithium-ammonia followed by dissolution of the product in ethylene glycol containing perchloric acid yielded the ketal immonium perchlorate (203). Treatment of the immonium salt with methallyl magnesium chloride gave the unsaturated ketal (204). The presence of Bohlmann bands[92,93] in the infrared spectrum

of (204) indicated that it possessed either the cis-cis or trans-trans stereochemistry at the ring junctions. The observation that it reacted sluggishly with methyl iodide indicated that it was the cis-cis system, which was expected on theoretical grounds, since it results from addition of the Grignard reagent to the less hindered side of the salt (203). Catalytic hydrogenation of (204), followed by deketalisation, provided the ketone (205), which probably exists in the conformation (206), in which ring closure to the required bicyclo(3,3,1)nonane system is impossible. It was therefore necessary to develop a method of transforming cis-cis-hexahydrojulolidines of type (206) into cis-trans compounds such as (210). It was felt that the isomerisation might be accomplished via the α,β-unsaturated ketone (208) derived from (206). Because of the conformational mobility at the nitrogen atom, it should be possible for the ketone (208) to adopt the other conformation (209). This change would involve an inversion of ring A at the nitrogen and a transformation of the resultant boat into a new chair form, with simultaneous transformation of the unsaturated ring from one half-chair form to the other half-chair. From models, it was seen that (209) might be in fact the favoured conformation of the unsaturated ketone.

The hydrobromide of the ketone (206) was converted to

the corresponding equatorial bromoketone (207) by treatment with one equivalent of bromine. Dehydrobromination of (207) was achieved by use of semicarbazine in acetic acid, followed by regeneration of the keto group from the resulting semicarbazone. The unsaturated ketone did not exhibit Bohlmann bands[92,93] in its infrared spectrum, indicating that it existed predominantly in the desired conformation (209).

Reduction of the unsaturated ketone (209) with lithium-ammonia yielded a ketone isomeric with (205), but which did not show Bohlmann bands, and hence must be the desired cis-trans ketone (210). The great potential of this sequence lies in the possibility of preparing functionalised derivatives of (210), for example (211), which could be cyclised to afford the tetracyclic ring system of lycopodine.

DISCUSSION

This study was initiated by the observation that the majority of the Lycopodium alkaloids possess a bicyclo-(3,3,1)nonane skeleton. As a vast amount of accumulated knowledge on the reactions and stereochemistry of this s stem has its origin in these laboratories[100-106], it was decided to approach the synthetic problem using a bicyclo-(3,3,1)nonane framework as the basic building block. The alkaloid of choice was lycopodine (115), represented for clarity as (212), since not only did it seem the simplest in terms of functionality, but also because the proposed reaction sequence had potential for modification at some later stage to afford a range of closely-related alkaloids, namely, annofoline (138), acrifoline (132), clavolonine (137), dihydrolycopodine (130), fawcettiine (142) and flabelline (141). Stereochemical planning promised to be more straight-forward, since it should require more standard methods than the acorone case, with its peculiar difficulties due to the spirane structure.

The bicyclo(3,3,1)nonane derivative selected was the aromatic compound (213), potentially derivable from 1-ethoxy-carbonyl-6-methoxy-2-tetralone (214) and methacrolein by the method of Cope[107]. It was then proposed to introduce a

nitrogen function at C-1, to which could be attached a three-carbon side-chain, to give the representative formula (215). Activation of the terminal carbon atom on the side-chain by, for example, a carbonyl function on the penultimate carbon atom, followed by cyclisation with the C-9 carbonyl grouping, could give the tetracyclic system represented by (216). Birch reduction[35] of the anisole ring, followed by ozonolysis of the resulting cyclohexenone, should furnish the ketoacid (217), which, by lactamisation and a suitable reduction and oxidation sequence, could afford a compound with the gross structure of lycopodine.

There would be, however, three centres of undefined stereochemistry involved in the final product. On the first of these (C-7), the methyl group can have an axial or the desired equatorial disposition on a chair cyclohexane ring. Ayer[98] has made it possible to obtain the correct stereochemistry by chemical means; an acid-catalysed hydride shift on the unsaturated alcohol (201) affords lycopodine (212) directly. It is also possible that the final product in the sequence will possess the desired equatorial disposition. The alternative configuration, i.e., with an axial methyl group, is observed in annofoline (138) and clavolonine (137), where the substituted cyclohexane ring undergoes a flip to the boat conformation, in which the methyl group once more

adopts a quasi-equatorial disposition.

The second asymmetric centre is at C-9. The two possibilities involve the C-9 proton being either syn or anti to the potential C-3 carbonyl function. These epimers should be distinguishable by their infrared spectra, where the former (218) should exhibit Bohlmann bands[92,93], observed when two or more C-H bonds are trans-diaxial to an adjacent nitrogen lone-pair of electrons. These bands should be absent in the latter, desired anti structure (219). A possible alternative to this method of differentiation lies in the comparison of the association constants[108] of the two amines in the presence of a phenol, the constants being determined by infrared spectrometry. The nitrogen lone-pair electrons in the anti case (220) are less sterically hindered than those of the corresponding syn epimer (221), thus favouring stronger association in the former case.
A third potential means of discrimination lies in the novel ultraviolet chromophore found in σ-coupled p-electron systems. Cookson et al.[109] have observed that the diaza-adamantanone (222), which is analogous in stereochemistry with the desired anti epimer (219), exhibits relatively strong ultraviolet absorption, $\lambda_{max.}$ 262 mμ, ε = 3,600; this absorption is due to σ-coupled p-electron interaction between the nitrogen lone-pair electrons and the π-electrons in the

carbonyl double bond, the interaction being possible since the p-electron clouds are near-parallel. The diazabicyclo-(3,3,1)nonan-9-one derivative (223), analogous to the syn epimer (218), shows no significant ultraviolet absorption, as here the p-electron clouds are not parallel.

If the anti epimer should prove to be absent, then the asymmetric centre (C-9) could be made epimerisable by the introduction of a carbonyl function at C-10. If separation of the two epimers should prove impracticable, then a feasible stereospecific sequence would be an S_N2' reaction of the hydroxy-tosylate (224) or hydroxy-trichlorobenzoate[46] as shown, to afford the correct stereochemistry in the product (225). This, however, would require the leaving group to be equatorial, a conformation attainable by a stereoselective method of reduction, e.g., sodium-liquid ammonia-methanol, which would give the thermodynamically more stable, equatorial configuration in the product; such a reduction process would seriously complicate the synthetic sequence, since it would also attack the anisole ring.

The third and last asymmetric centre is that at C-2. This presents no real problem, since it is adjacent to a latent carbonyl function at C-3, making it potentially epimerisable.

Since the synthetic sequence delineated above involves

complex systems and novel reactions, the initial use of a simpler model system was considered prudent. This model approach would be valuable in its own right, since , if successful, it would lead to the new basic tricyclic system, 5,8a-propanoperhydroquinoline (or 13-azatricyclo(3,3,1,$4^{1,9}$)-tridecane) (226).

Accordingly, the bicyclo(3,3,1)nonane selected as being most appropriate was ethyl 7-methylbicyclo(3,3,1)non-3-en-9-one-1-carboxylate (227), synthesised by the method described[110] in the literature for the preparation of ethyl bicyclo(3,3,1)non-3-en-9-one-1-carboxylate (228). Treatment of 4-methylcyclohexanone with diethyl oxalate and sodium ethoxide, followed by thermal decarbonylation of the intermediate glyoxalate ester, afforded ethyl 4-methylcyclohexanone-2-carboxylate (229). This β-ketoester underwent a Michael condensation with acrolein in the presence of a catalytic amount of sodium ethoxide to give the propionaldehyde (230), which was treated with concentrated sulphuric acid to effect cyclisation and dehydration to the desired bicyclic compound. Subsequent isolation yielded a small amount of neutral material; no acidic material was recovered. Chromatography of the neutral product separated pure crystalline ethyl 7-methylbicyclo(3,3,1)nonen-9-one-1-carboxylate (231), in a disappointing yield of 5% from the propionald-

ehyde (230).

As a preparation of starting material, this yield was obviously unacceptable. The reason for such a yield is not obvious; experience in our own[103] and other laboratories[111] has shown that the ease of cyclisation of the propionaldehyde is very dependent on the size of the cyclanone ring, though not on its substitution, evidenced by the fact that the simpler ethyl bicyclo(3,3,1)non-3-en-9-one-1-carboxylate (228) was synthesised by an identical sequence[110] in 70% yield, the product having a melting-point of 46-47.5° (lit., m.p. 48-49.4°). On analytical t.l.c. of this product, two compounds were observed[112] in the ratio of 4.7 to 1, this ratio being determined by g.l.c. analysis and confirmed by preparative t.l.c. separation. This latter separation technique afforded two crystalline compounds, m.p. 45-45.5° and 58.5-59.5° (4.7 to 1) respectively, both analysing correctly for $C_{12}H_{16}O_3$. Their relationship as the double-bond isomers (228) and (234) was readily established, as each gave the same dihydro compound (237) on catalytic hydrogenation. Prolonged treatment of either isomer with concentrated sulphuric acid gave the same equilibrium mixture of (228) and (234) (1.2 to 1) by a protonation-deprotonation mechanism. Production of these two isomeric species in cyclisations of this type seems general; re-examination of the cyclisation

of the methyl analogue[101] (238) resulted in the isolation of the two corresponding isomers (239) and (240) (2.8 to 1). The former compound (239) is important, as it was a key intermediate in the synthesis of (±) clovene, carried out in these laboratories[105], when the compound used was assumed to be pure (239).

The unambiguous positioning of the double bonds in these compounds was achieved by n.m.r. spectroscopy. Thus, the isomer m.p. 45-45.5° exhibited the following olefinic proton signals (Figure 1), consistent with structure (228): H_b, two triplets centred at 3.99 τ ($J_{H_b-H_a}$ = 9 c.p.s.; $J_{H_b-H_{c,d}}$ = 4 c.p.s.) and H_a, a quartet of triplets centred at 4.39 τ ($J_{H_a-H_b}$ = 9 c.p.s.; $J_{H_a-H_e}$ = 6 c.p.s.; $J_{H_a-H_{c,d}}$ = 2 c.p.s.). The isomer m.p. 58.5-59.5° showed the following olefinic signals (Figure 2), compatible with (234): H_b, two triplets centred at 3.98 τ ($J_{H_b-H_a}$ = 9 c.p.s.; $J_{H_b-H_{c,d}}$ = 4 c.p.s.), and H_a, two triplets centred at 4.38 τ ($J_{H_a-H_b}$ = 9 c.p.s.; $J_{H_a-H_{c,d}}$ = 2 c.p.s.). The homologous (239) showed (Figure 3): H_b, two triplets centred at 4.09 τ ($J_{H_b-H_a}$ = 9 c.p.s.; $J_{H_b-H_{c,d}}$ = 4 c.p.s.) and H_a, two quartets centred at 4.76 τ ($J_{H_a-H_b}$ = 9 c.p.s.; $J_{H_a-H_{c \text{ or } d}}$ = 2.5 c.p.s.; $J_{H_a-H_{c \text{ or } d}}$ = 2 c.p.s.), whereas its isomer (240) showed (Figure 4): H_b, two triplets centred at 4.08 τ ($J_{H_b-H_a}$ = 9 c.p.s.; $J_{H_b-H_{c,d}}$ = 4 c.p.s.), and H_a, two triplets centred at 4.45 τ ($J_{H_a-H_b}$ = 9 c.p.s.;

$J_{H_a-H_{c,d}}$ = 2 c.p.s.).

It is noteworthy that <u>one</u> of the allylic protons in (228) and (239) is selectively deshielded. Thus in (228), the allylic protons are seen as (Figure 1): H_c, two multiplets centred at 6.55 τ ($J_{H_c-H_d}$ = 20 c.p.s.), and H_d, two quartets centred at 7.55 τ ($J_{H_d-H_c}$ = 20 c.p.s.; $J_{H_d-H_b}$ = 4 c.p.s.; $J_{H_d-H_a}$ = 2 c.p.s.), while in (234) they are seen as (Figure 2): $H_{c,d}$, an unresolved multiplet centred at 7.38 τ. In (239) (Figure 3), H_c is seen as two multiplets centred at 6.6 τ ($J_{H_c-H_d}$ = 18 c.p.s.), and H_d as two quartets centred at 7.61 τ ($J_{H_d-H_c}$ = 18 c.p.s.; $J_{H_d-H_b}$ = 4 c.p.s.; $J_{H_d-H_a}$ = 2 c.p.s.), while in (240) the allylic protons are seen as (Figure 4): $H_{c,d}$, two doublets centred at 7.55 τ ($J_{H_{c,d}-H_b}$ = 4 c.p.s.; $J_{H_{c,d}-H_a}$ = 2 c.p.s.). That the 1-ethoxycarbonyl grouping is responsible for the observed deshielding is shown by the n.m.r. spectrum of the hydrocarbon[103] (241), which exhibits the expected two doublets (Figure 5) in the allylic region centred at 7.58 τ ($J_{H_{c,d}-H_b}$ = 4 c.p.s.; $J_{H_{c,d}-H_a}$ = 2 c.p.s.).

T.l.c. examination of ethyl 7-methylbicyclo(3,3,1) non-en-9-one-1-carboxylate (231) showed the 3-ene isomer (227) to be predominant, exhibiting the expected n.m.r. spectrum (Figure 6), but it proved impossible to isolate the 2-ene isomer (232) in a pure state, due to contamination by

another compound of almost identical polarity. Attempts to equilibrate the pure 3-ene (227) with sulphuric acid effected complete degradation, no neutral or acidic material being isolated.

Due to current interest[94-96, 98] in transannular reactions in the bicyclo(3,3,1)nonane system, where the occurrence of transannular hydride shifts has been demonstrated, an attempt was made to elucidate the mechanism of the above isomerisation, which could proceed either by simple protonation-deprotonation or protonation-hydride shift-deprotonation. Accordingly, the optical resolution of bicyclo-(3,3,1)non-3-en-9-one-1-carboxylic acid (235) was undertaken. Protonation of the resolved acid would lead initially to the carbonium ion (242). This ion could then deprotonate to give (235) and (236); isolation of the equilibrated acid, followed by esterification and chromatographic separation of the 3-ene isomer, would, after hydrolysis, return the 3-ene acid (235), which should show no loss of optical activity. However, racemisation would occur if there were a 3,7-hydride shift in the carbonium ion (242) to give the carbonium ion (243). Deprotonation of (243) would lead to (244) and (245), which are enantiomers of (235) and (236) respectively. If the above sequence were repeated, i.e., isolation, esterification, separation and hydrolysis,

the recovered 3-ene acid should be optically inactive, or at least show a decrease in optical activity; the degree of racemisation would depend on the extent of hydride shift. The pure 3-ene acid (235) failed to form crystalline salts with brucine, quinine, strychnine or cinchonine, but did with quinine methohydroxide[113]. The latter salt was subjected to fractional crystallisation, and a partial resolution of the diastereoisomeric mixture was achieved. On regeneration of the free acid (235), however, a specific rotation of only $+1^{o}$ was observed. This was not sufficiently significant to be utilised in any experiment involving measurement of change of optical rotation. It has been shown[114] recently that in the bicyclo(3,3,1)nonane system a 3,7-hydride shift does not occur if a C-9 carbonyl function is present, as in this case. This would seem to substantiate the simpler protonation-deprotonation mechanism.

Returning to the main synthetic topic, the next problem was the introduction of a nitrogen function at C-1 in the bicyclo(3,3,1)nonane skeleton; the bicyclic unit used was ethyl bicyclo(3,3,1)nonen-9-one-1-carboxylate (246), since it was more readily available than the 7-methyl homologue (231). Two elaborative procedures were performed; the first, involving a Beckmann rearrangement, necessitated the formation of ethyl 9-ethylenedioxybicyclo(3,3,1)nonen-1-carbox-

ylate (247), which was readily obtained by treatment of ethyl bicyclo(3,3,1)nonen-9-one-1-carboxylate (246) with ethyl orthoformate and ethylene glycol in the presence of p-toluenesulphonic acid[36]. The ketal ester, which exhibited a single carbonyl peak in the infrared, $\nu_{max.}$ 1735 cm.$^{-1}$, was hydrolysed with base and carefully acidified with dilute sulphuric acid to give the corresponding ketal acid (248). Treatment of this latter compound with a solution of methyl lithium[37] in ether afforded the methyl ketone (249), $\nu_{max.}$ 1700 cm.$^{-1}$, in 86% yield. The corresponding oxime (250) was obtained by treatment with hydroxylamine hydrochloride and potassium hydroxide in refluxing methanol; due to the disparity in size of the substituent groups, i.e., the bicyclic function and the methyl group, the oxime almost definitely exists in the desired <u>anti</u> configuration, as shown. Treatment of the oxime (250) with sodium hydride in ether, followed by p-toluenesulphonyl chloride at 0°, afforded the corresponding oximino-tosylate[115] (251). This compound was very unstable; accordingly it was dissolved immediately in 80% ethanol-water, and heated under reflux to effect rearrangement. The isolated product proved to be, after chromatography, the desired acetamido-ketone (252), $\nu_{max.}$ 1710, 1680 and 1540 cm.$^{-1}$, the ketal grouping being lost since p-toluenesulphonic acid was liberated in the rearrangement,

regenerating the ketone in the solvent system used. Unfortunately, the yield of acetamido-ketone (252) was only 20%. Had this reaction been accomplished in high yield, it was planned to hydrolyse the acetamide moiety to the parent amine, then attach the requisite side-chain.

The second procedure, involving a Curtius reaction, consisted of treating bicyclo(3,3,1)nonen-9-one-1-carboxylic acid (253) with ethyl chloroformate and triethylamine to form the mixed anhydride[116,117], which was converted to the acid azide (254). The azide was heated at 100^{o} in toluene to effect rearrangement to the isocyanate (255), $\nu_{max.}$ 2250 and 1730 $cm.^{-1}$, which was treated *in situ* with benzyl alcohol to yield the benzyl carbamate (256), $\nu_{max.}$ 3450, 1720 and 1510 $cm.^{-1}$, the first isolated intermediate. A by-product from this reaction sequence was the symmetrical urea (257), which arose from reaction of the intermediate isocyanate (255) with traces of moisture. Catalytic hydrogenation of the benzyl carbamate (256) should theoretically yield the keto-amine (258), and indeed the crystalline product obtained analysed correctly for this compound, but the infrared spectrum showed hydroxyl absorption, $\nu_{max.}$ 3200-3150 (broad), amine absorption, $\nu_{max.}$ 3330 and 3260 (sharp) $cm.^{-1}$, but no carbonyl absorption, all indicating the dimer (259), which is incapable of dehydration to a dihydropyrazine derivative.

Mass spectral hot-box or probe sampling techniques effected scission of the dimer (259), and only the monomer (258) was detected.

Since this keto-amine dimer was not readily amenable to further elaboration, an alternative method of removal of the benzyloxycarbonyl moiety was sought. Treatment of the benzyl carbamate (256) with hydrogen bromide in glacial acetic acid[118] at 0^{o} gave the amine hydrobromide (260), $\nu_{max.}$ 1720 $cm.^{-1}$, as a white solid in almost quantitative yield. Reaction of the amine hydrobromide with acetic anhydride in pyridine gave the same acetamido-ketone (252) as was previously obtained in the Beckmann reaction sequence.

The next elaboration involved attachment to the nitrogen atom of a pyruvoyl grouping; this moiety possesses the requisite chain length, the required activation of the terminal carbon atom, and, of course, is suitable for N-acylation. Initially, the acylation was accomplished by forming the mixed anhydride[119] of pyruvic acid and ethyl hydrogen carbonate (obtained by the reaction of pyruvic acid with triethylamine and ethyl chloroformate in chloroform solution), to which was added the amine hydrobromide (260) as a slurry in chloroform. This was followed by a final addition of triethylamine, to liberate the keto-amine (258) <u>in situ</u>, in order to preclude the possibility of dimerisation of the

keto-amine. The above procedure did indeed give the desired pyruvamide (261) in 40% yield, along with a similar amount of the ethyl carbamate (262). This latter product, though thermally unstable, was identified by its infrared spectrum, $\nu_{max.}$ 3410, 1750, 1735 and 1500 cm.$^{-1}$, its n.m.r. spectrum, which showed a characteristic ethyl proton absorption pattern, and its mass spectrum, which showed the required parent molecular ion. The formation of the above mixture is not without precedent[120]; in this case the two possible sites of attack appear to be equally favourable, to afford the two products as shown (263). Satisfactory separation of the two compounds by column chromatography, fractional crystallisation or distillation proved to be impracticable, it being impossible to obtain the pyruvamide in a pure state by any means other than preparative t.l.c.

A very marked improvement was observed when pyruvic acid was activated as its ester with phosphorus oxychloride[121]. Reaction of the amine hydrobromide (260) with this reactive intermediate in the presence of triethylamine afforded the pyruvamide (261) in 90% yield as a crystalline solid, $\nu_{max.}$ 1733 and 1686 cm.$^{-1}$; $\lambda_{max.}$ (neutral) 241 mμ (ε= 2,456), $\lambda_{max.}$ (base) 275 mμ (ε= 2,035).

The next stage, that of cyclisation to afford the tricyclic enone lactam (264), proved difficult to accomplish,

On determining the ultraviolet spectrum of the pyruvamide (261) in alcoholic base on a spectroscopic scale, a hypsochromic shift from 275 to 255 mμ, with an approximately three-fold increase in intensity of absorption, was observed to occur within thirty minutes; this was considered indicative of cyclisation. However, repetition of these conditions on a larger scale returned the starting pyruvamide (261) unchanged. These observations could be accommodated by the formation of an initial aldol product (265), which, during isolation, could undergo a retro-aldol reaction, re-forming (261). Other unsuccessful cyclisation procedures involved the use of p-toluenesulphonic acid in benzene; triethylamine benzoate[122]; sulphuric acid; and the methylsulphinyl carbanion in dimethylsulphoxide[44]; all of these methods returned starting material unchanged, with the exception of sulphuric acid, which caused complete degradation.

Variable success was achieved with the use of sodium hydride in benzene. Ultimately, ideal conditions were achieved using sodium hydride in tetrahydrofuran, which had been freshly distilled from lithium aluminium hydride. Under these conditions, a reproducible yield of 70% could be obtained. The enone lactam (264), a pale yellow solid, $\nu_{max.}$ 1694, 1685 and 1647 $cm.^{-1}$; $\lambda_{max.}$ 258 mμ (ε= 11,350), was highly polar on t.l.c., possibly due to a large contr-

ibution from the imidol tautomer (266). In this connection, it is interesting to note that the success of each cyclisation run was diagnosed by the separation of a granular solid from the tetrahydrofuran solution; this solid was presumed to be the sodium salt of the imidol tautomer.

The sole problem remaining was that of the simplification of the heterocyclic ring to give the basic tricyclic amine (267). Catalytic hydrogenation of the tricyclic enone lactam (264) afforded a mixture of the keto- (268) and hydroxy-lactams (269), which, on treatment with sodium borohydride, yielded the pure hydroxy-lactam (269), showing considerable intramolecular hydrogen bonding in the infrared, $\nu_{max.}$ 3508, 3366 and 1654 $cm.^{-1}$. The hydroxy-lactam (269) was converted to the corresponding acetate (270) by treatment with acetic anhydride in pyridine. Aware of analogies[123-125] with the reactions of normal α-acetoxy-ketones, and with the intention of removing the acetate group, the acetoxy-lactam (270) was treated with zinc and glacial acetic acid, but the starting acetate was recovered unchanged. It has been shown[126], however, that additional activation in the molecule, for example by a neighbouring hydroxyl group, is often required to help bind the molecule to the zinc surface. Sodium borohydride reduction of the enone lactam (264) afforded the doubly-unsaturated hydroxy-

lactam (271), $\nu_{max.}$ 3550, 3380, 1660 and 1647 cm.$^{-1}$.

Birch reduction of the enone system was attempted, in the hope of achieving a stereospecific insertion of a hydrogen atom at C-9. Lithium aluminium hydride reduction was also performed, but both this and the former method gave complex mixtures of intractible products.

A radically new method was devised via the lactim ether (272), obtained[127] in 85% yield by treatment of the enone lactam (264) with triethyloxonium fluoroborate[128], Et_3OBF_4. The lactim ether (272), $\nu_{max.}$ 1686 and 1632 cm.$^{-1}$, $\lambda_{max.}$ 255 mμ (ε= 14,050), was a volatile, non-polar solid; the non-polarity lends weight to the assumption that the extreme polarity of the enone lactam (264) was due to it being mainly in the imidol tautomer form (266). On reduction with lithium aluminium hydride in ether, a single product with a mass spectral molecular weight of 291 was obtained, the infrared spectrum indicating the presence of a carbinolamine and the absence of a carbonyl group, $\nu_{max.}$ 3500-3200 cm.$^{-1}$; the n.m.r. spectrum of the corresponding diacetate showed no ethyl proton absorption pattern. This evidence is compatible with the carbinolamine structure (273), which may arise by the mechanism shown (274). The carbinolamine was readily converted to the corresponding acetamido-acetate (275), $\nu_{max.}$ 1739 and 1662 cm.$^{-1}$.

Hydrogenation of the acetamido-acetate (275) in ethyl acetate over palladium-charcoal afforded a mixture of three compounds, which were shown to be the saturated acetamido-acetate (276), the unsaturated acetamide (278), and the desired saturated acetamide (279), in the ratio of 2 :1 :1; these ratios were determined by g.l.c. analysis and confirmed by a preparative t.l.c. separation. The identities of the two acetamides (278) and (279) were deduced from their mass spectra (Figures 7 and 8 respectively), which showed the correct molecular weights and fragmentation patterns for the proposed structures; other spectral features were also consistent with the structural assignments.

Hydrogenation of (275) in acetic acid over platinum black gave a mixture of the saturated acetamido-acetate (276) and the saturated acetamide (279) in approximately equal proportions. To our delight, when the hydrogenation was repeated using palladium-charcoal in ethanol containing a few drops of perchloric acid[129], a quantitative yield of the pure crystalline acetamide (279), $\nu_{max.}$ 1643 $cm.^{-1}$, was obtained. (At this point, it should be noted that although complete reduction of the heterocyclic ring would normally produce two geometrical isomers due to asymmetric saturation of C-9, the simultaneous reduction of the isolated carbon-carbon double bond in the bicyclo(3,3,1)nonane

moiety results in the two compounds (280) and (281) being epimeric, thus one isolates a racemic mixture).

This gratifying result was checked by following an alternative route to the acetamide (279). Specific hydrolysis of the doubly-unsaturated acetamido-acetate (275) afforded the acetamido-alcohol (282), which was oxidised with chromium trioxide in sulphuric acid to the corresponding enone (283), $\nu_{max.}$ 1683, 1668 and 1639 $cm.^{-1}$, $\lambda_{max.}$ 228.5 $m\mu$ (ε = 11,550). Treatment of this enone with ethanedithiol and boron trifluoride etherate yielded the thioketal (284), $\nu_{max.}$ 1655 $cm.^{-1}$, which, on treatment with Raney nickel in refluxing ethanol[130], gave a mixture of variously hydrogenated compounds. Exhaustive hydrogenation of this mixture in ethyl acetate over palladium-charcoal afforded one pure product, identical in all respects with the more easily obtained acetamide (279).

Thus, the general ground plan in the model system has been shown to be perfectly feasible, all stages being realised in high yields. Attention was now turned* to the more elaborate scheme leading to lycopodine (212). The serious problems inherent in the formation of the benzobicyclo(3,3,1)nonane derivative (214) have been overcome successfully.

The number of published syntheses[131, 132, 133] of simple 2-tetralones is small, and, until recently, the methods employed have been laborious. One of these methods[133], remarkable in its apparent simplicity, consisted of treating p-methoxyphenylacetyl chloride with ethylene in the presence of aluminium chloride; this was reported to furnish 6-methoxy-2-tetralone (285) in high yield. Numerous attempts to perform this reaction, however, met with a total lack of success, despite numerous precautions. Fortunately, a synthesis of 6-methoxy-2-tetralone (285) was published[134] recently, using the readily available[135] 6-bromo-2-naphthol (286) as starting material. The Grignard reagent of the corresponding methyl ether was added, as a solution in tetrahydrofuran, to a solution of trimethyl borate in ether, followed by 15% hydroger

* The following elaborations were performed in collaboration with B. Shroot.

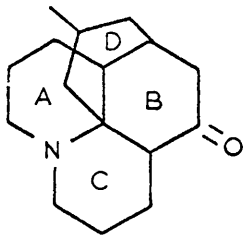
peroxide solution containing ammonium chloride. Subsequent isolation of the product, 6-methoxy-2-naphthol (287), followed by reduction with sodium-liquid ammonia-t-butanol[132], afforded 6-methoxy-2-tetralone (285) in good yield.

Elaboration of the tetralone (285) to the desired 1-carbalkoxy derivative (215) proved much more difficult than had been foreseen. The standard technique involving the use of dimethyl oxalate and sodium methoxide could not be applied, since this is reported[136] to give the aromatised tautomer (288) of the intermediate 3-glyoxalate (289). One alternative, that of reacting the corresponding pyrrolidine enamine (290) with ethyl chloroformate, was attempted; the enamine double bond is known[137] to be styrenoid, as shown. No reaction was observed to occur when the recommended[137] ratio of enamine to ethyl chloroformate was used; however, when a 2 : 1 mixture of benzene and ethyl chloroformate was used as solvent instead of benzene alone, reaction occurred to give the diester (291). Variation of conditions may have produced the desired compound, but at this point it was obtained by a more direct route. Initial attempts using sodium hydride and diethyl carbonate[38] had given unidentifiable products, but use of sodium hydride and dimethyl carbonate, as solvent and reactant[138], gave an 80% yield of the desired compound (292).

The feasibility of using methacrolein as acceptor in a Michael reaction with 2-ethoxycarbonylcyclohexanone has been demonstrated in these laboratories[139], where the ketols (293) were obtained on cyclisation of the intermediate propionaldehyde (294). Accordingly, the β-ketoester (292) was treated with methacrolein in the presence of a catalytic amount of sodium methoxide in methanol, to afford the substituted propionaldehyde (295). Cyclisation of this with dilute aqueous hydrochloric acid in dioxan[107] afforded the ketols (296), acetylation of which gave the four possible stereoisomeric acetates (297), as indicated by g.l.c. analysis. This work is at a rather preliminary stage, but the results obtained so far have been most encouraging.

The further elaboration of this system along the previously delineated path is under active investigation. A two-pronged approach is being adopted. The first scheme aims at removal of the oxygenation at C-6; it is planned to protect the C-9 carbonyl group, then to hydrolyse and oxidise the C-6 function to the ketal-ketone (298). Epimerisation of this with base should yield the thermodynamically more stable, desired equatorial C-7 methyl epimer. Removal of the C-6 carbonyl group by standard methods and regeneration of the C-9 carbonyl group should yield one pure epimer, with the C-7 methyl group in the correct configuration (299).

The second approach involves retention of the C-6 acetate function, which could be converted, say, in compound (300) to carbonyl, etc.; though this scheme involves several initial transformations being carried out on mixtures of stereoisomers, it offers the valuable bonus of great flexibility for conversion of the final product to other Lycopodium alkaloids, and in particular clavolonine (137), shown for clarity as (301).



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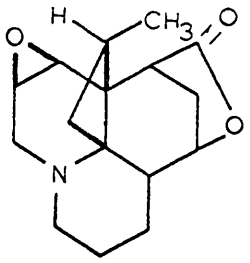

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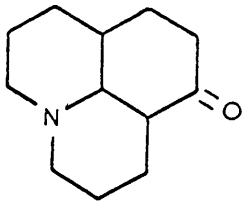

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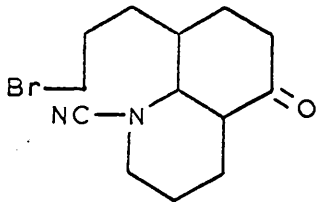

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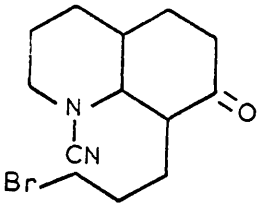

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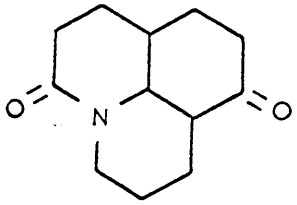

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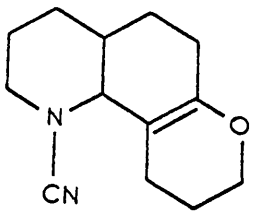

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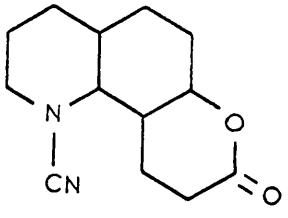

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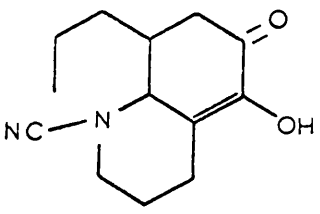

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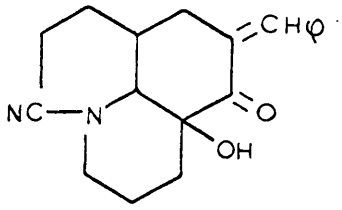

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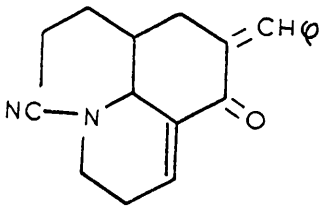

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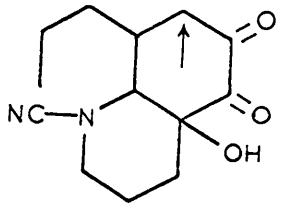

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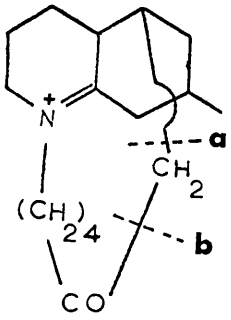

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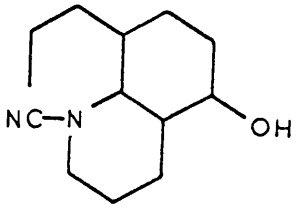

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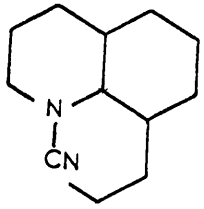

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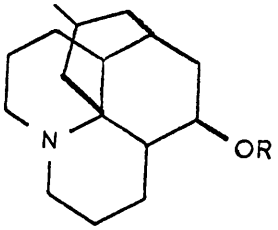

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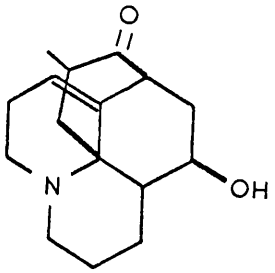

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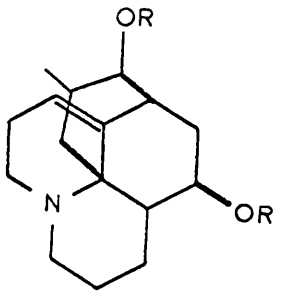

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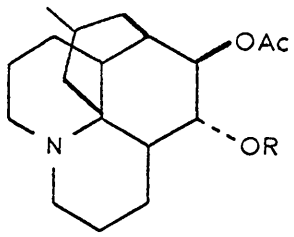

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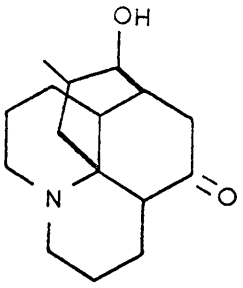

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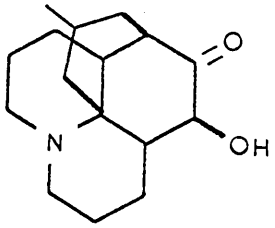

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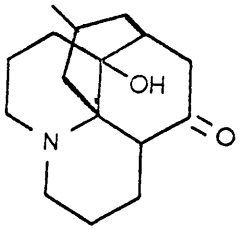

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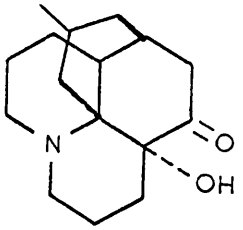

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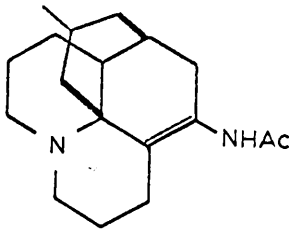

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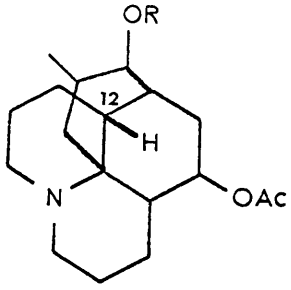

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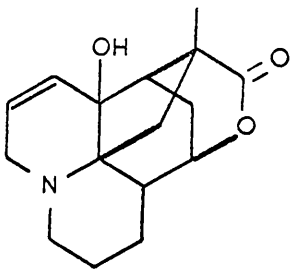

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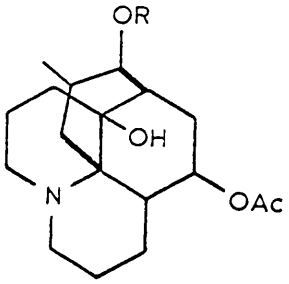

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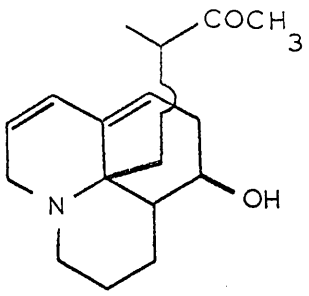

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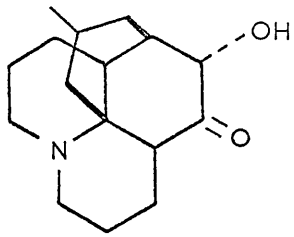

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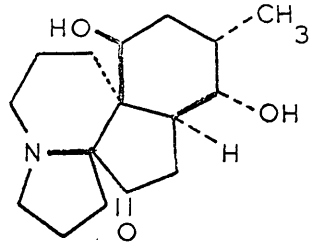

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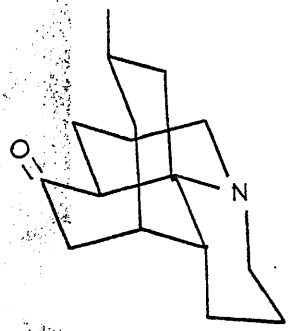

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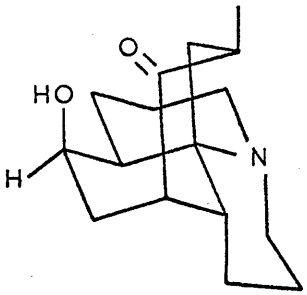

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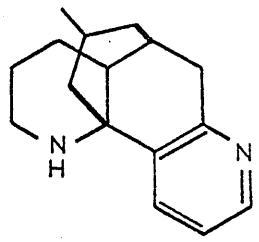

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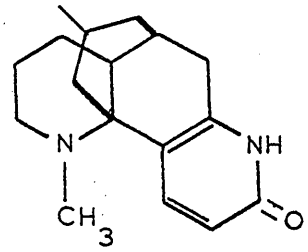

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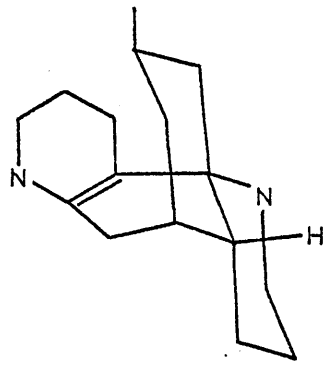

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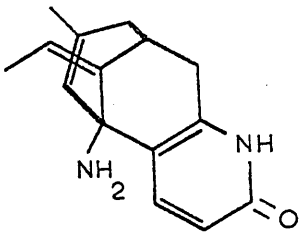

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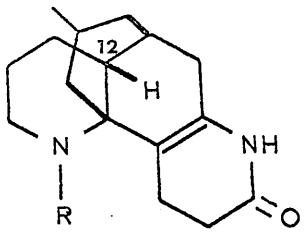
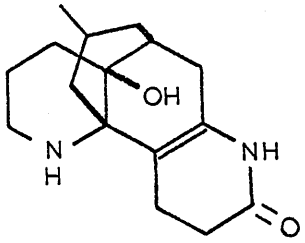


156 R = CH_3

157 R = H



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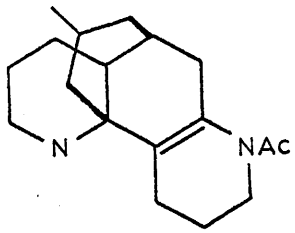

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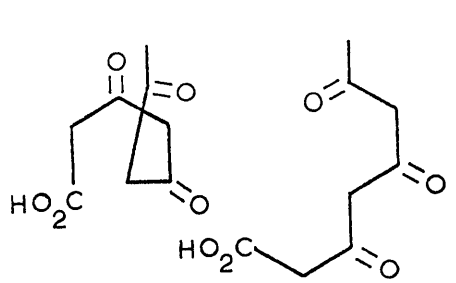

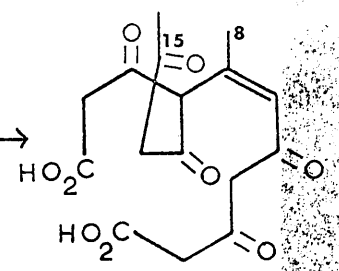

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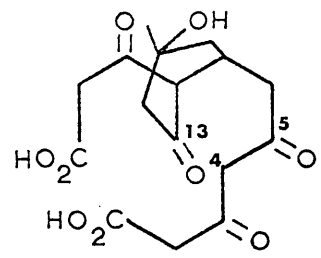

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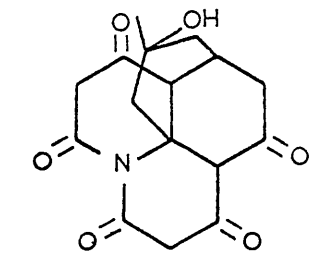

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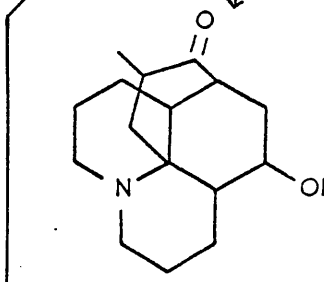

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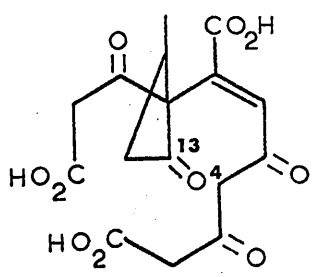

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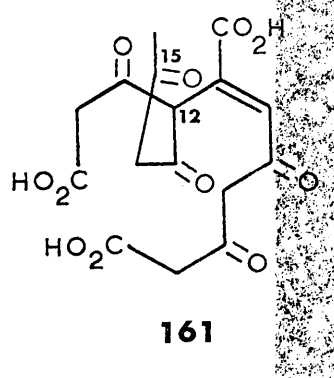

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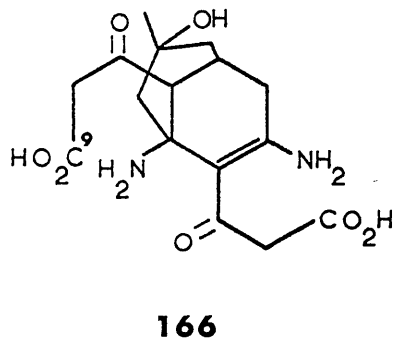

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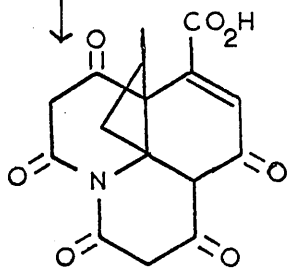

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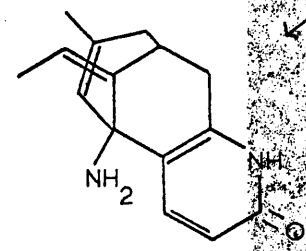

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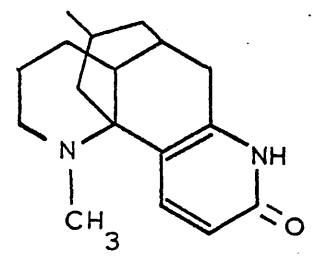

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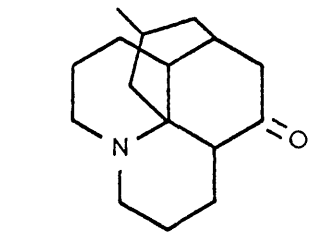

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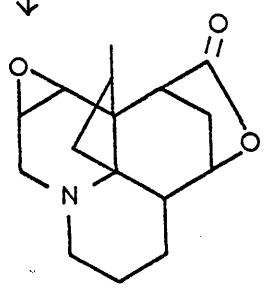

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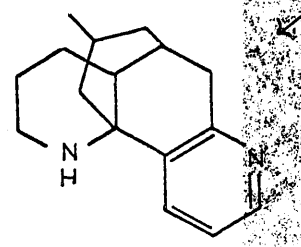

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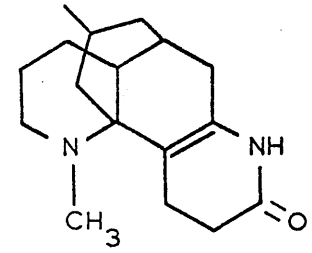

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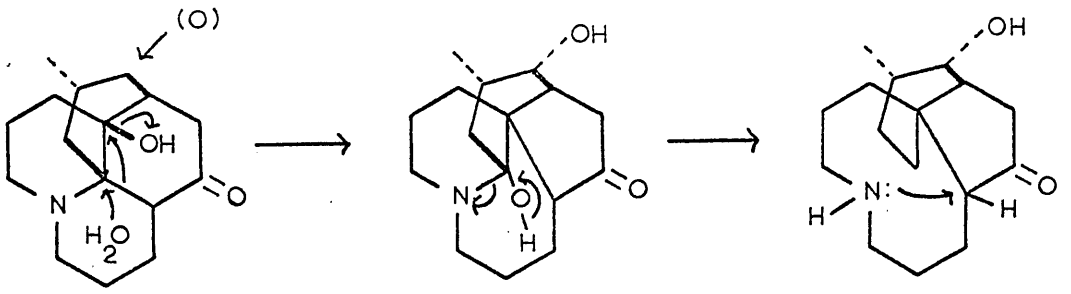
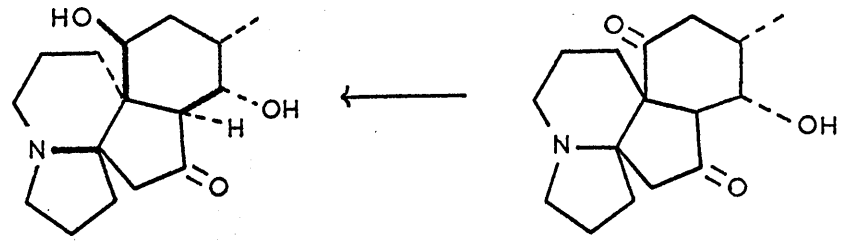
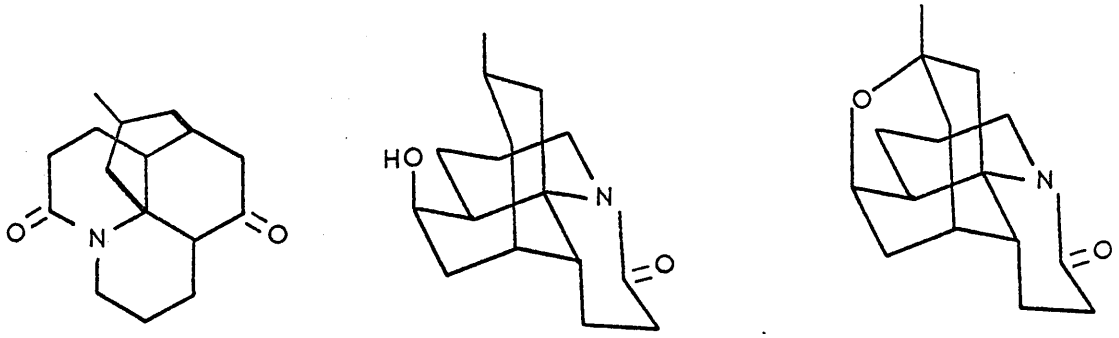


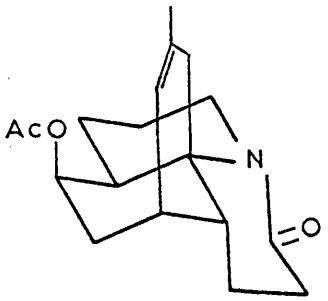
139 **167** **168**



149 **169**



170 **171** **172**



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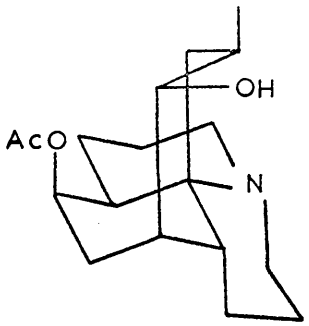

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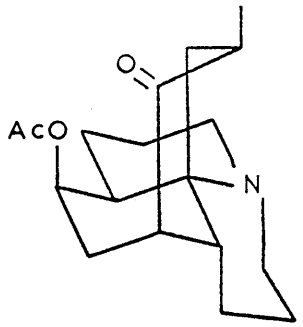

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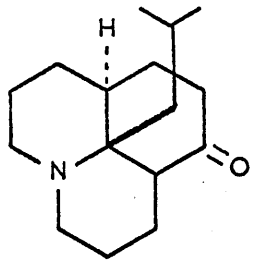

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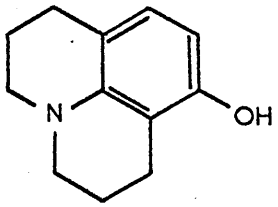

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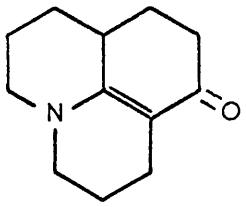

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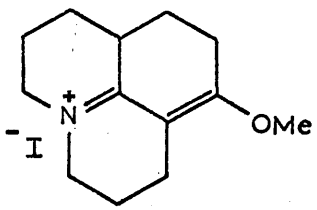

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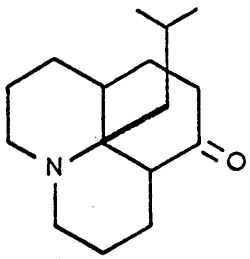

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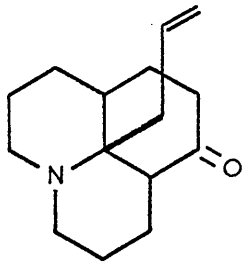

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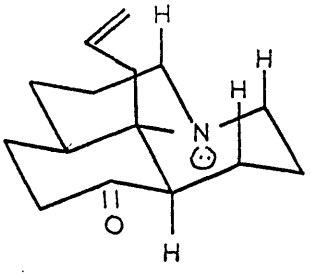

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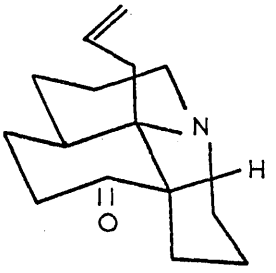

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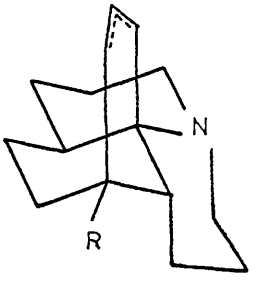
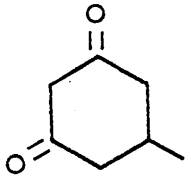


184, R = OH

185, R = Br

186, R = H



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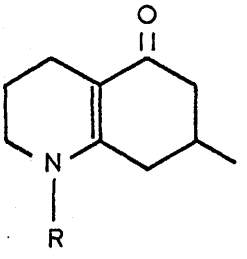
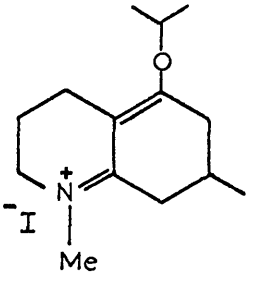


188, R = H

189, R = Me



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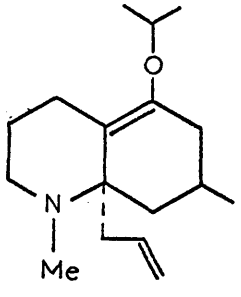

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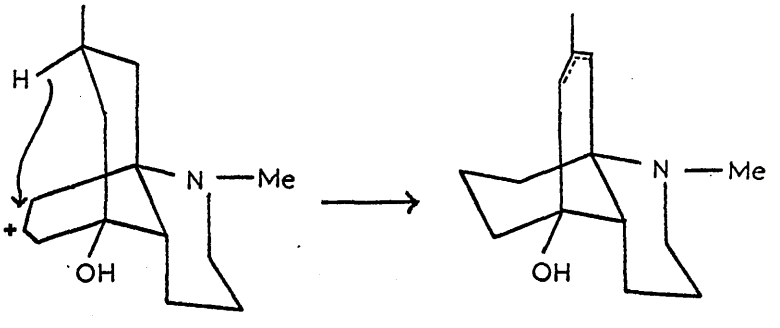

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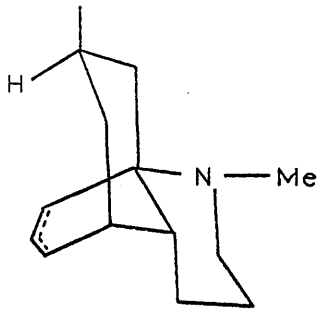

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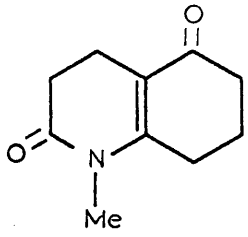

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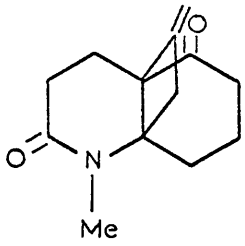

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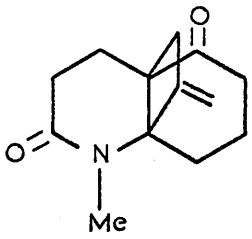

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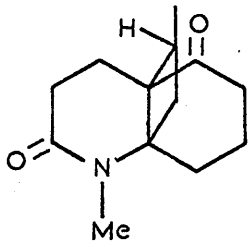

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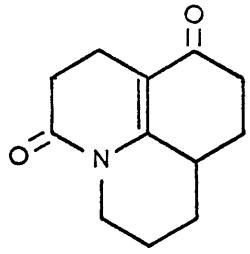

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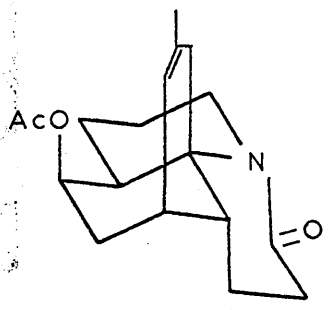

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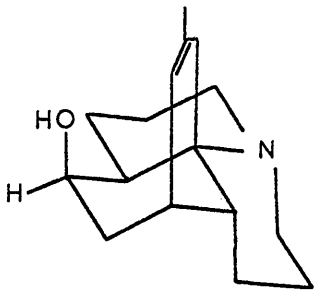

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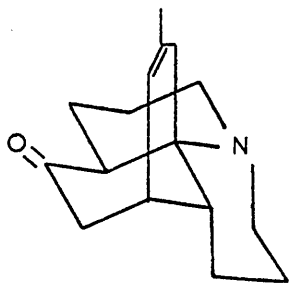

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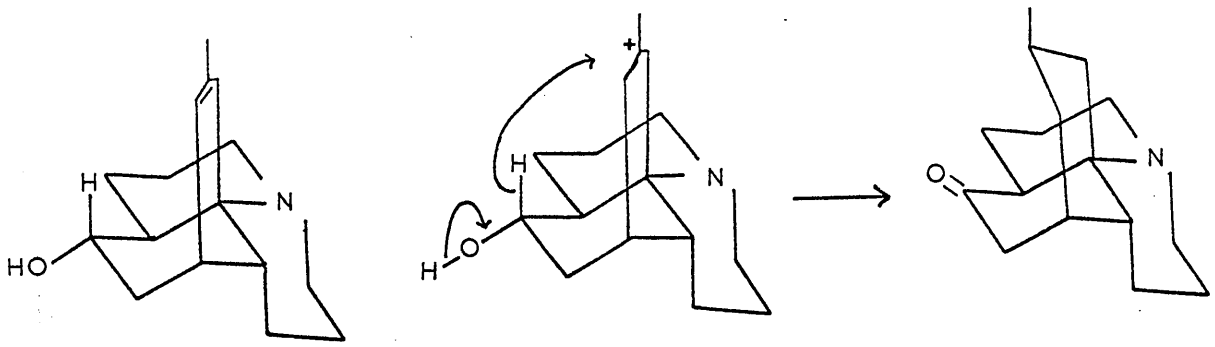
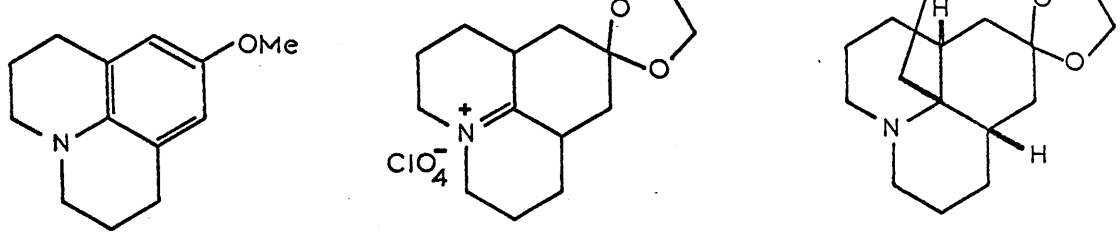
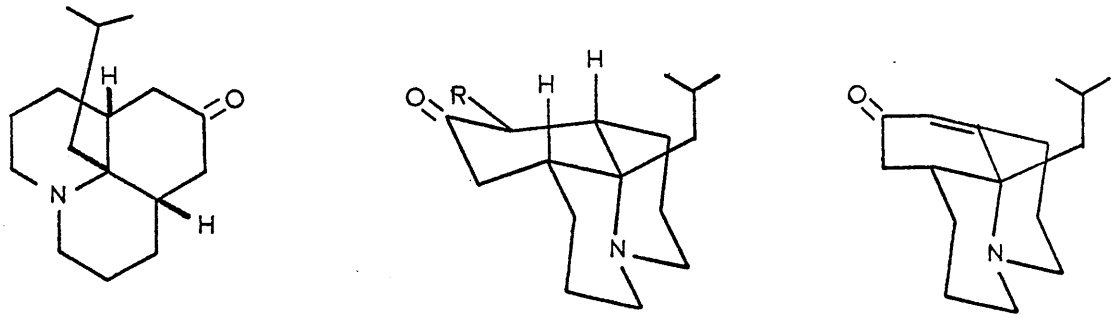


201 **115**

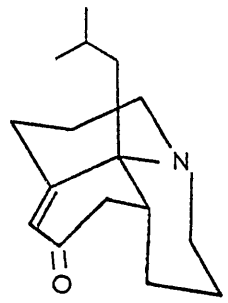


202 **203** **204**

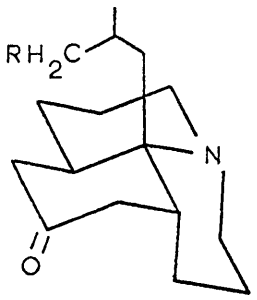


205 **206**, R = H **208**

207, R = Br

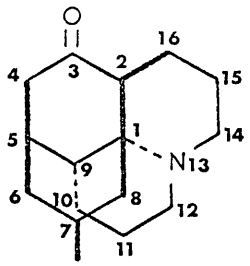


209

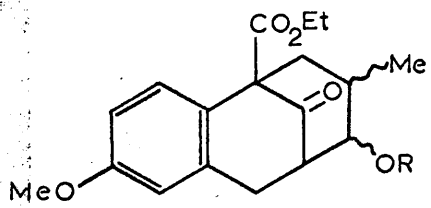


210, R = H

211, R = OTs



212



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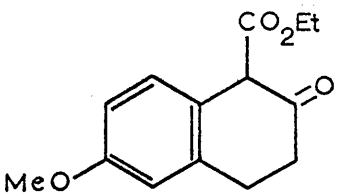
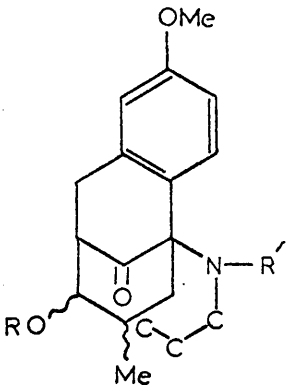


214



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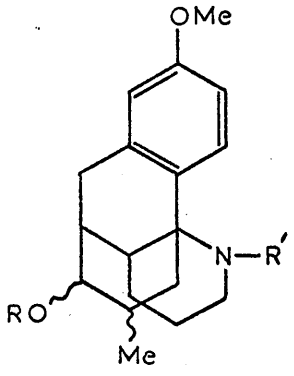

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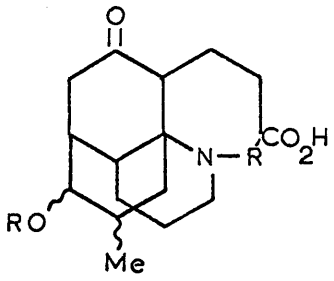

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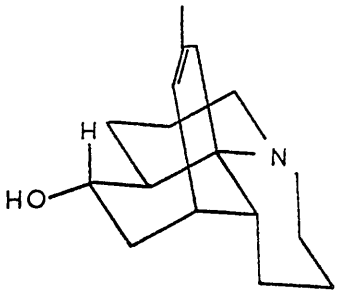
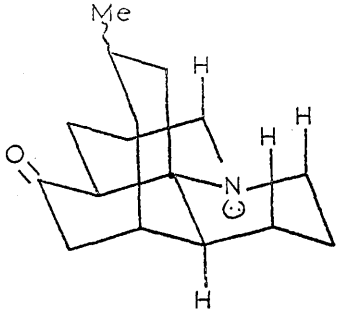
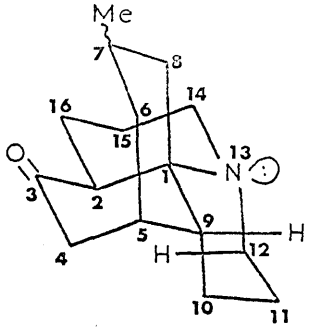


201



218



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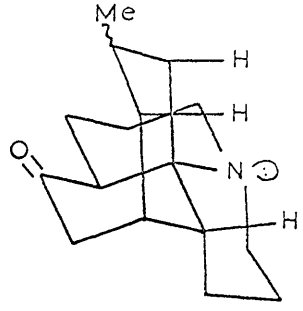

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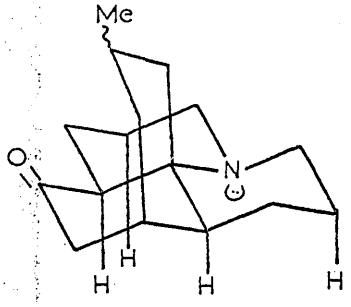
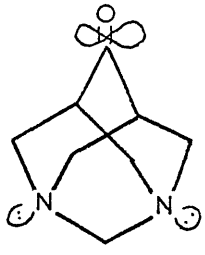


221



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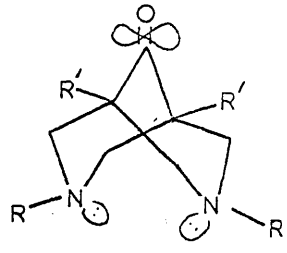

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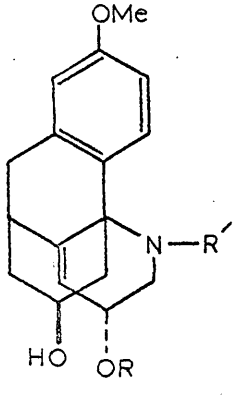
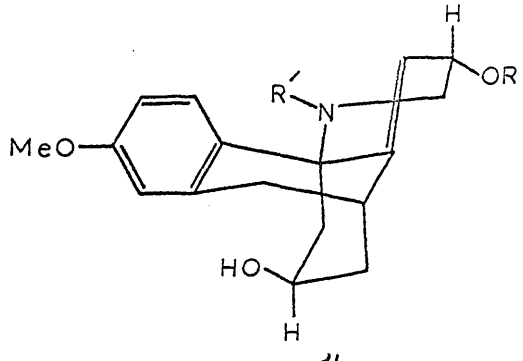
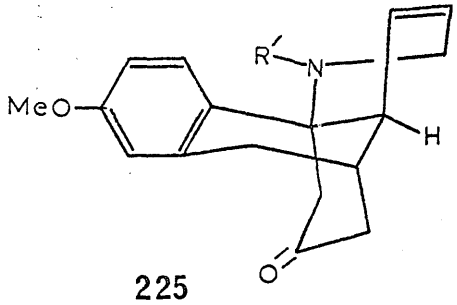
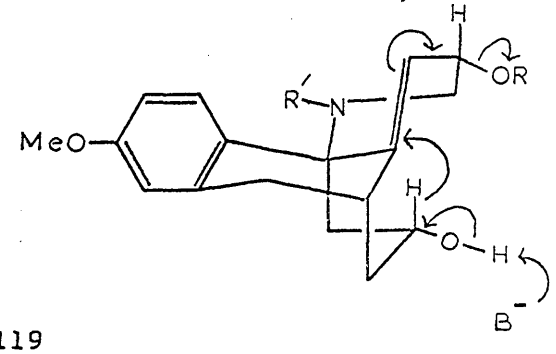


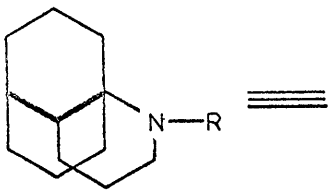
224 R = Ts or $OCC_6H_2Cl_3$

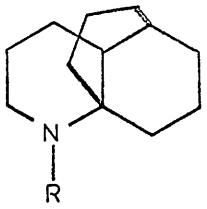




225







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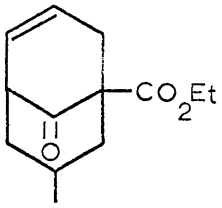

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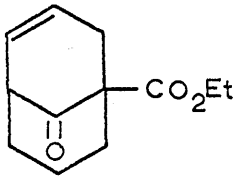

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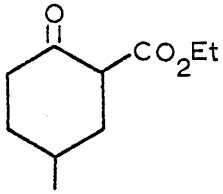

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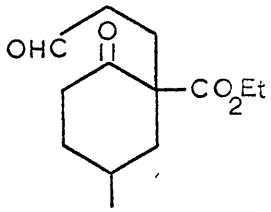
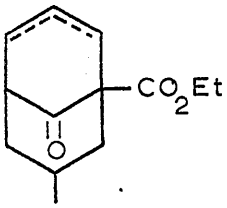


230



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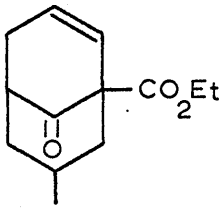

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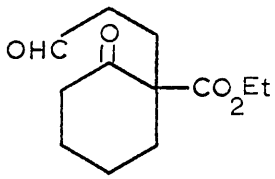

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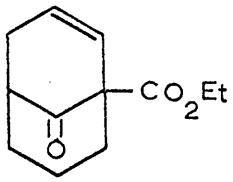

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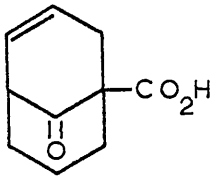

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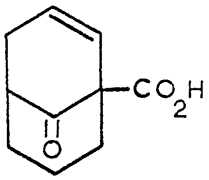

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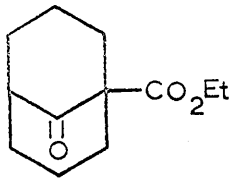

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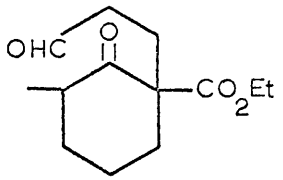

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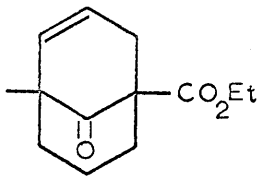

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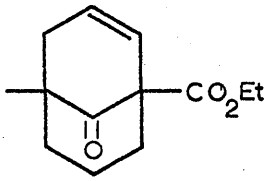

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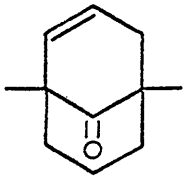

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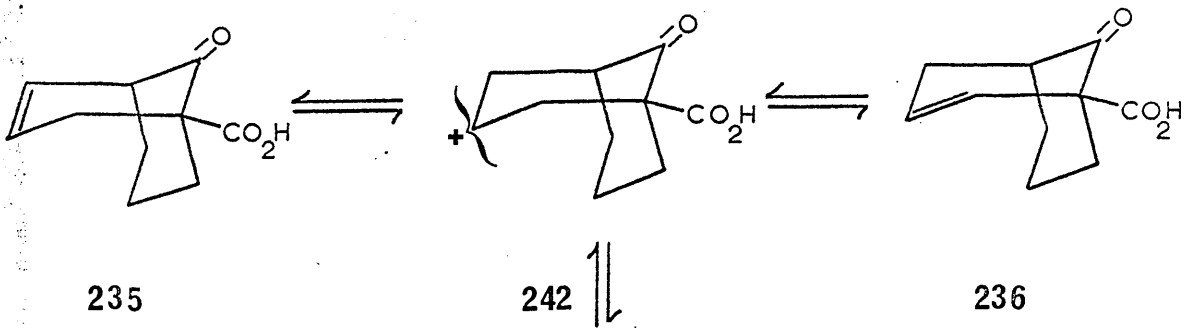
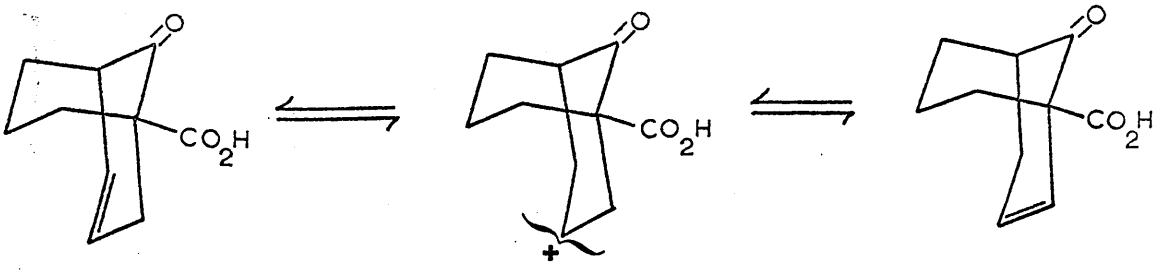
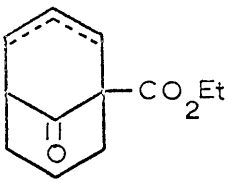


235 242 236



244 243 245



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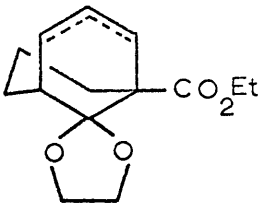

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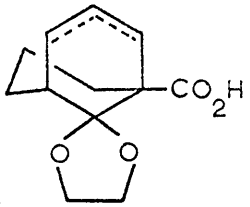

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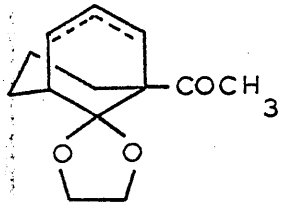

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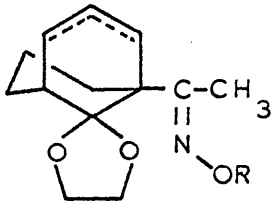
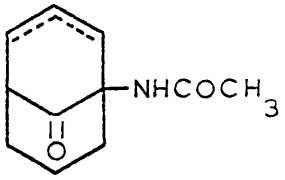


250, R = H
251, R = Ts



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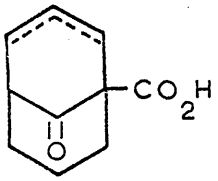

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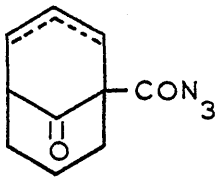
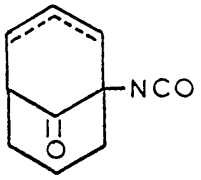
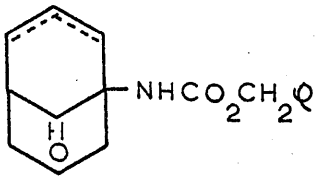


254



255



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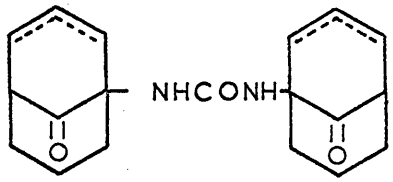

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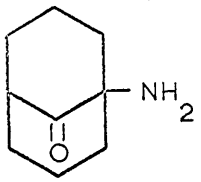
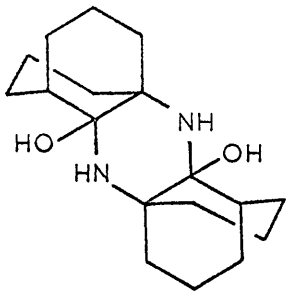
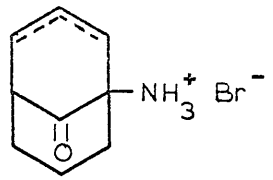


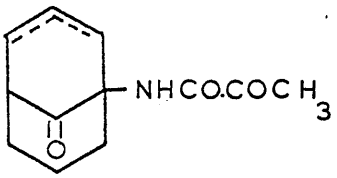
258



259



260



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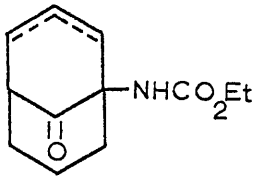
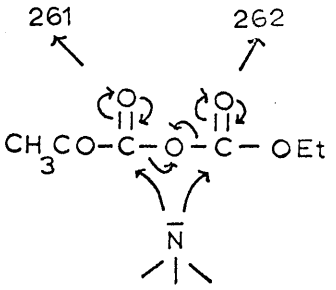
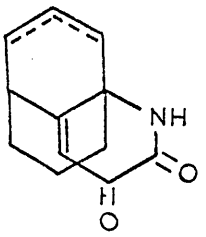


262



263



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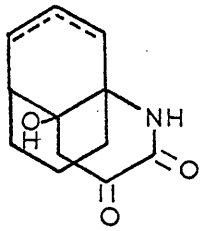

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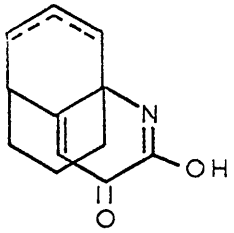
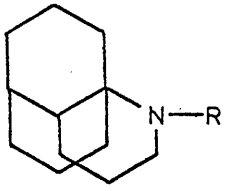
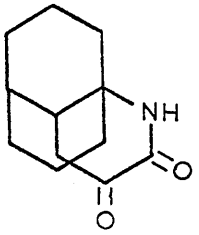


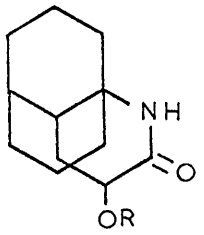
266



267

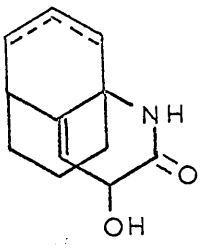


268



269, R = H

270, R = Ac



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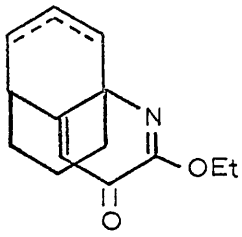

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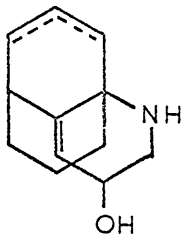

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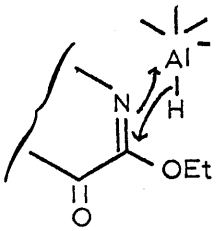

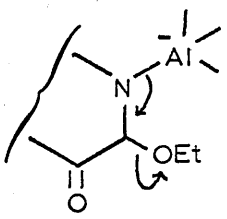

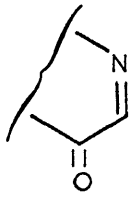

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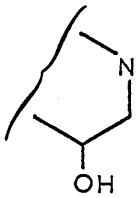

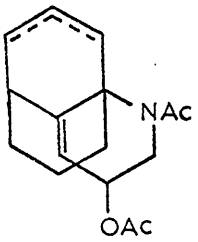

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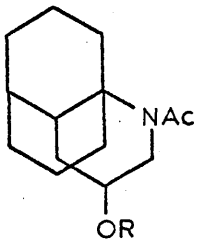

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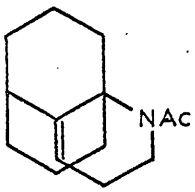
277 , R = H



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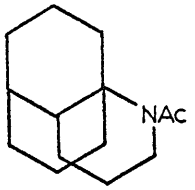

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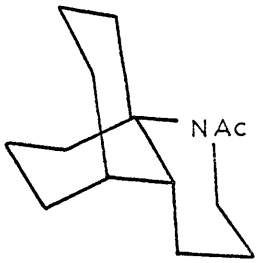

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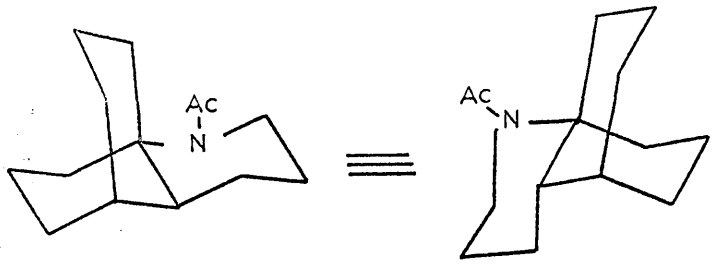

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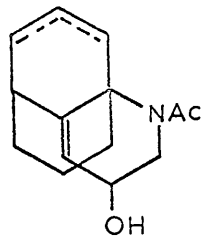

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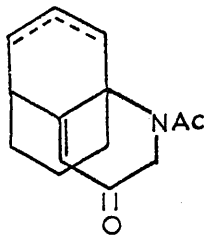

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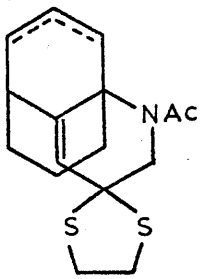

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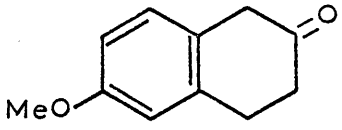

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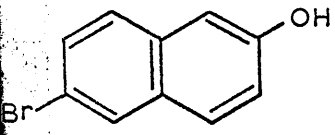

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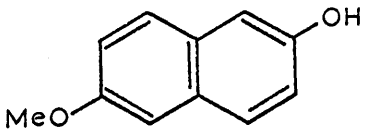

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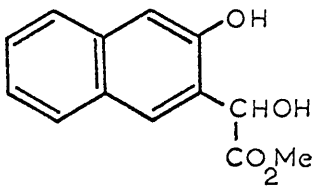

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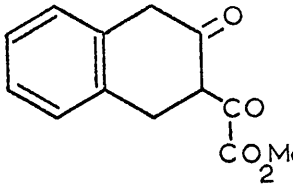

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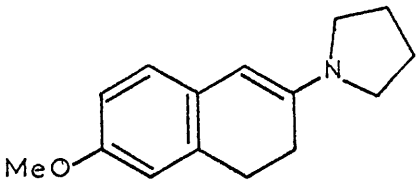

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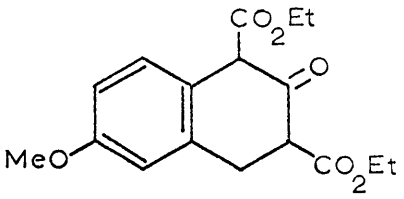

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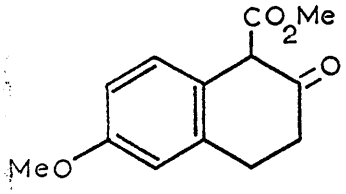

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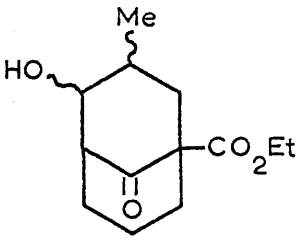

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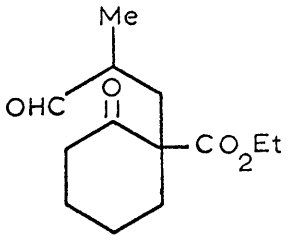

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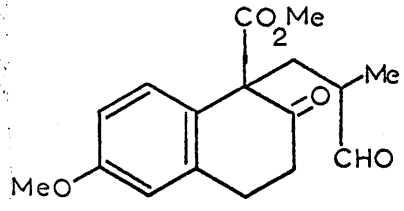

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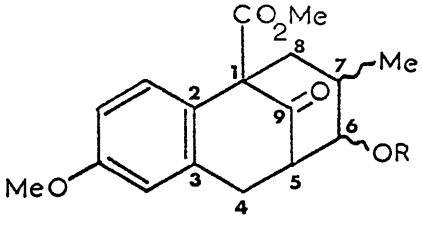

296, R = H

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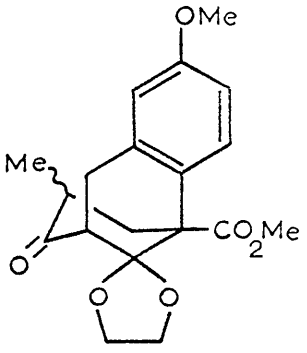

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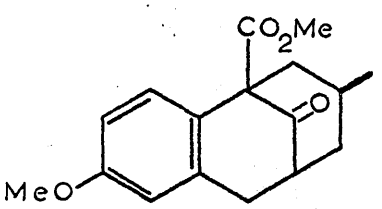

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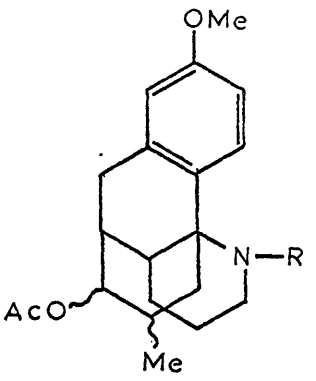

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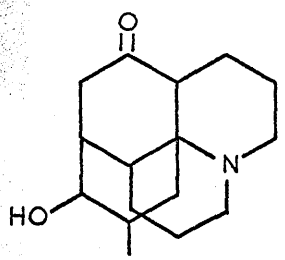
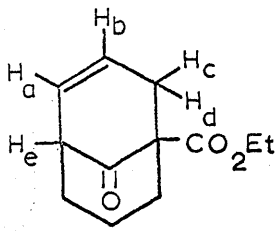


301

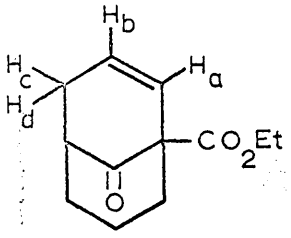
Figure 1



228

Proton	Chemical Shift τ	Multiplicity	Coupling Constants, c.p.s.
H_b	3.99	2 triplets	$J_{H_b-H_a} = 9$ $J_{H_b-H_{c,d}} = 4$
H_a	4.39	4 triplets	$J_{H_a-H_b} = 9$ $J_{H_a-H_e} = 6$ $J_{H_a-H_{c,d}} = 2$
H_c	6.55	2 multiplets	$J_{H_c-H_d} = 20$
H_d	7.55	2 quartets	$J_{H_d-H_c} = 20$ $J_{H_d-H_b} = 4$ $J_{H_d-H_a} = 2$

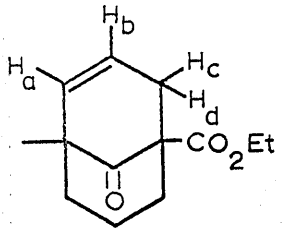
Figure 2



234

Proton	Chemical Shift τ	Multiplicity	Coupling Constants, c.p.s.
H_b	3.98	2 triplets	$J_{H_b-H_a} = 9$ $J_{H_b-H_{c,d}} = 4$
H_a	4.38	2 triplets	$J_{H_a-H_b} = 9$ $J_{H_a-H_{c,d}} = 2$
$H_{c,d}$	7.38	multiplet	

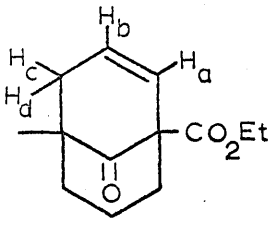
Figure 3



239

Proton	Chemical Shift τ	Multiplicity	Coupling Constants, c.p.s.
H_b	4.09	2 triplets	$J_{H_b-H_a} = 9$ $J_{H_b-H_{c,d}} = 4$
H_a	4.76	2 quartets	$J_{H_a-H_b} = 9$ $J_{H_a-H_c \text{ or } d} = 2.5$ $J_{H_a-H_c \text{ or } d} = 2.5$
H_c	6.6	2 multiplets	$J_{H_c-H_d} = 18$
H_d	7.61	2 quartets	$J_{H_d-H_c} = 18$ $J_{H_d-H_b} = 4$ $J_{H_d-H_a} = 2$

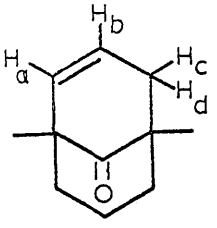
Figure 4



240

Proton	Chemical Shift τ	Multiplicity	Coupling Constants, c.p.s.
H_b	4.08	2 triplets	$J_{H_b-H_a} = 9$ $J_{H_b-H_{c,d}} = 4$
H_a	4.45	2 triplets	$J_{H_a-H_b} = 9$ $J_{H_a-H_{c,d}} = 2$
$H_{c,d}$	7.55	2 doublets	$J_{H_{c,d}-H_b} = 4$ $J_{H_{c,d}-H_a} = 2$

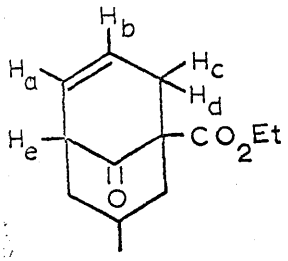
Figure 5



241

Proton	Chemical Shift τ	Multiplicity	Coupling Constants, c.p.s.
H_b	4.18	2 triplets	$J_{H_b-H_a} = 9$ $J_{H_b-H_{c,d}} = 4$
H_a	4.75	2 triplets	$J_{H_a-H_b} = 9$ $J_{H_a-H_{c,d}} = 2$
$H_{c,d}$	7.58	2 doublets	$J_{H_{c,d}-H_b} = 4$ $J_{H_{c,d}-H_a} = 2$

Figure 6



227

Proton	Chemical Shift τ	Multiplicity	Coupling Constants, c.p.s.
H_b	4.01	2 triplets	$J_{H_b-H_a} = 9$ $J_{H_b-H_{c,d}} = 4$
H_a	4.38	4 triplets	$J_{H_a-H_b} = 9$ $J_{H_a-H_e} = 6$ $J_{H_a-H_{c,d}} = 2$
H_c	6.58	2 multiplets	$J_{H_c-H_d} = 19$
H_d	7.58	2 quartets	$J_{H_d-H_c} = 19$ $J_{H_d-H_b} = 4$ $J_{H_d-H_a} = 2$

Figure 7

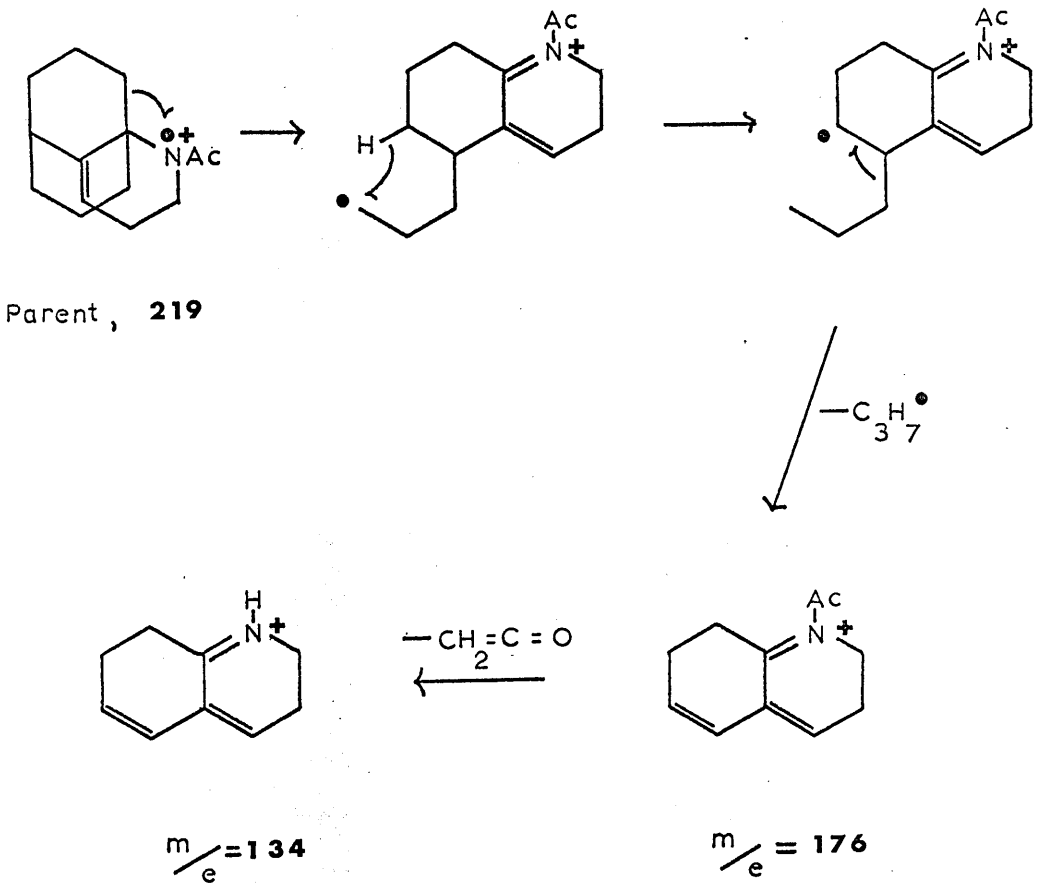
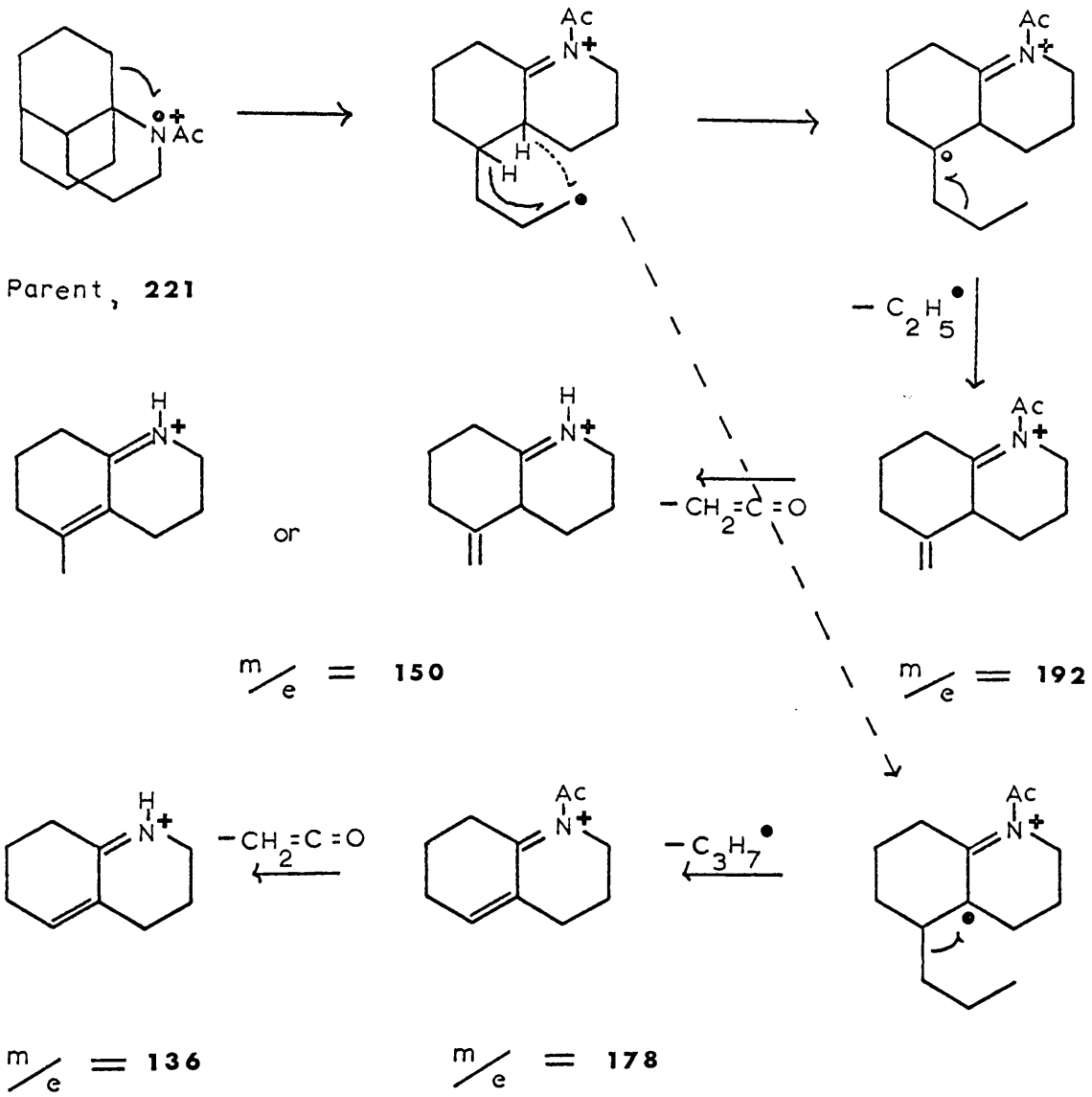


Figure 8


Parent, 221
or
$-C_2H_5^{\bullet}$
$-CH_2=C=O$
$m/e = 150$
$m/e = 192$
$-CH_2=C=O$
$-C_3H_7^{\bullet}$
$m/e = 136$
$m/e = 178$

EXPERIMENTAL

The experimental procedure involved here has been described in the preamble to the Experimental section of Part I (pp. 47 and 48).

2-Ethoxycarbonyl-4-methylcyclohexanone (229)

This compound was prepared in a manner analogous to that described in the literature for the preparation of 2-ethoxycarbonylcyclohexanone ('Organic Syntheses', Coll. Vol. II, p. 531). The β-ketoester (229) was obtained in 49% yield, b.p. 126°/20 mm., n_D^{24} 1.4830, $\nu_{max.}$(film) 1745, 1720, 1680 and 1620 $cm.^{-1}$, $\lambda_{max.}$(neutral) 257 mμ (ε = 7,444), $\lambda_{max.}$(base) 284 mμ (ε= 6,237). (Found: C, 66.09; H, 8.86. $C_{10}H_{16}O_3$ requires C, 66.19; H, 8.75%).

4-Methyl β-(1-ethoxycarbonyl-2-oxocyclohexyl)propionaldehyde (230)

This compound was prepared by the method of Cope and Synerholm[110].

Ethyl 4-methylbicyclo(3,3,1)nonen-9-one-1-carboxylate (231)

The keto-aldehyde (230, 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 hours, then poured on to ice, and extracted twice with ether. The ethereal

extracts were combined, washed with saturated sodium bicarbonate solution, brine and dried. (Acidification of the bicarbonate washings afforded no ether-soluble acidic material). Removal of solvent under reduced pressure furnished a brown oil (5.5 g.). Chromatography on alumina (Spence 'H', 150 g.) gave white crystals (880 mg.), which were purified by sublimation to give the pure ketoester (231), m.p. 50-52°, $\nu_{max.}$(Nujol) 3100, 1740, 1715, 1660, 720 and 695 $cm.^{-1}$.

A solution of the ketoester (231, 99 mg.) and hydrazine hydrate (100%, 0.1 ml.) in ethanol (5 ml.) was heated under reflux for twenty-four hours, and evaporated under reduced pressure to give the crude pyrazolone (74 mg.). This was recrystallised twice from benzene as white needles, m.p. 123-131°. (Found: C, 69.58; H, 7.69; N, 14.74. $C_{11}H_{14}N_2O$ requires C, 69.45; H, 7.42; N, 14.72%).

Thin-layer chromatography of the sublimed material (231, 150 mg.), with 10% ethyl acetate-light petroleum (b.p. 60-80°) for development, separated the pure 3-ene isomer (227, 77 mg.), m.p. 50-51°. It was impossible to isolate the 2-ene isomer (232) in a pure state, due to contamination by a compound of virtually identical polarity.

β-(1-Ethoxycarbonyl-2-oxocyclohexyl)propionaldehyde (233)

This compound was prepared by the method of Cope and Synerholm[110].

Ethyl bicyclo(3,3,1)non-3- and 2-en-9-one-1-carboxylate (228) and (234)

The keto-aldehyde (233, 48 g.) was added in fine droplets, with vigorous stirring, to concentrated sulphuric acid (96 ml.), cooled in an ice-salt bath. The mixture was left at room temperature for four hours, and poured on to ice, when the product separated as a non-filterable semi-solid. The total mixture was extracted twice with ether, the ethereal extracts were combined, washed with saturated sodium bicarbonate solution, brine and dried. (Acidification of the bicarbonate washings afforded solely cyclohexanone-2-carboxylic acid). Removal of solvent under reduced pressure afforded a brown solid (27 g.). Chromatography on alumina (Spence 'H', 150 g.) gave pale yellow crystals (26 g.), m.p. 46-47.5°. T.l.c. of these (150 mg.), with 10% ethyl acetate-light petroleum (b.p. 60-80°) for development, separated the two components, (228), sublimed as white needles (99.4 mg.), m.p. 45-45.5°, $\nu_{max.}$ (Nujol) 3100,

1740, 1715, 1660, 720 and 695 cm.$^{-1}$ (Found: C, 68.92; H, 7.73. $C_{12}H_{16}O_3$ requires C, 69.21; H, 7.74%), and (234), sublimed as white needles (21.7 mg.), m.p. 58.5-59.5°, $\nu_{max.}$(Nujol) 3100, 1735, 1715, 1660 and 720 cm.$^{-1}$ (Found: C, 69.34; H, 7.74%).

The accurate ratio of (228) to (234) was determined by evaluation of peak areas on g.l.c. analysis, and was found to be 4.7 to 1.

A solution of the pure ketoester (228, 100mg.) and hydrazine hydrate (100%, 0.1 ml.) in ethanol (5 ml.) was heated under reflux for twenty-four hours, and evaporated under reduced pressure to give the crude pyrazolone (75 mg.). This was recrystallised twice from benzene as white needles, m.p. 217-218° (sealed tube) (Found: C, 68.17; H, 6.67; N, 16.02. $C_{10}H_{12}N_2O$ requires C, 68.16; H, 6.86; N, 15.90%). The pyrazolone of (234) was obtained similarly as white needles, m.p. 195-196° (sealed tube) (Found: C, 67.94; H, 6.88; N, 16.04%).

Bicyclo(3,3,1)non-3- and 2-en-9-one-1-carboxylic acid (235) and (236)

A suspension of the pure ketoester (228, 100 mg.) in aqueous sodium hydroxide (2N, 10 ml.) was stirred till a clear solution was obtained. The solution was acidified with

dilute sulphuric acid (6N) and extracted twice with ether. The ethereal extracts were combined, washed with brine and dried. Removal of solvent under reduced pressure afforded the crude product (78 mg.) which, after two recrystallisations from methylcyclohexane, gave the pure acid (237) derived from (228) as white prisms, m.p. 139.5-140° (lit., m.p. 133.8-134.3°), $\nu_{max.}$(Nujol) 3500-2700, 1720, 1695, 1660, 720 and 695 cm.$^{-1}$. (Found: C, 66.65; H, 6.45. $C_{10}H_{12}O_3$ requires C, 66.65; H, 6.71%). The isomeric acid (236) derived from (234) was obtained similarly as white prisms, m.p. 143-144°, $\nu_{max.}$(Nujol) 3500-2700, 1720, 1700, 1660 and 720 cm.$^{-1}$. (Found: C, 66.76; H, 6.82%).

Ethyl bicyclo(3,3,1)nonan-9-one-1-carboxylate (237)

A solution of either pure ketoester (228 or 234, 45 mg.) in ethyl acetate (AnalaR, 20 ml.) was separately hydrogenated over 10% palladium-charcoal (5 mg.) until uptake of hydrogen ceased. The catalyst was filtered off through Celite, and the solvent removed under reduced pressure, to give the saturated ester (237), which was shown to be the same from (228) and (234) by thin-layer and gas-liquid chromatography. Sublimation afforded a white solid (38 mg.), m.p. 26-32°. (Found: C, 68.29; H, 8.68. $C_{12}H_{18}O_3$ requires

C, 68.55; H, 8.63%). The correspondimg pyrazolone crystallised from ethanol as white prisms, m.p. 221-222° (sealed tube) (Found: C, 67.23; H, 7.73; N, 15.59. $C_{10}H_{14}N_2O$ requires C, 67.39; H, 7.92; N, 15.72%). The corresponding acid crystallised from methylcyclohexane as white needles, m.p. 136-137° (lit., m.p. 138.6-139.4°) (Found: C, 65.91; H, 7.64. $C_{10}H_{14}O_3$ requires C, 65.92; H, 7.74%).

Isomerisation of (228) and (234) with sulphuric acid

Separate solutions of the pure ketoesters (228 and 234, 50 mg.) in concentrated sulphuric acid (5 ml.) were stirred at room temperature overnight, then poured on to ice. The solutions were extracted with ether, the ethereal solutions washed with saturated sodium bicarbonate solution, brine and dried. Removal of solvent under reduced pressure gave the products (47 mg.), which in each case was shown by g.l.c. analysis to contain only (228) and (234), in the ratio of 1.2 to 1.

Ethyl 5-methylbicyclo(3,3,1)non-3- and 2-en-9-one-1-carboxylate (239) and (240)

This liquid material was prepared according to the published method[101]. Some of the product (100 mg.), on t.l.c. with three portions of 5% ethyl acetate-light petroleum (b.p. 60-80°) for development, was separated into the 3-ene (239, 70 mg.), n_D^{19} 1.4898, $\nu_{max.}$(film) 3100, 1735, 1720, 1660, 710 and 690 $cm.^{-1}$. (Found: C, 70.03; H, 7.96. $C_{13}H_{18}O_3$ requires C, 70.24; H, 8.16%) and the 2-ene (240, 19.5 mg.), n_D^{19} 1.4867, $\nu_{max.}$(film) 3100, 1740, 1720, 1660, and 720 $cm.^{-1}$. (Found: C, 70.20; H, 7.98%). The ratio of (239) to (240) was determined from peak areas on g.l.c., and was found to be 2.8 to 1.

Attempted resolution of bicyclo(3,3,1)non-3-en-9-one-1-carboxylate (235)

Quinine methohydroxide was prepared as directed by Major and Finkelstein[113]. The ketoacid (235, 600 mg.) was added to an aqueous solution of quinine methohydroxide (0.0575N, 16 ml.) and left for thirty minutes. The water was removed under reduced pressure, the temperature being kept below 30°, to yield a white solid (1.5 g.), which was

found to crystallise readily from methanol-ether. The crop from the first fractional crystallisation was found to have a specific rotation of $(\alpha)_D^{22}$ -118.7°. Five further crystallisations produced the following specific rotations: $(\alpha)_D^{22}$ -121.2°, -138.2°, -141°, -147.6° and -147.9° respectively. The final crop (90 mg.) was dissolved in methanol and chromatographed on Amberlite IR-120 (H) resin, to liberate the ketoacid. The free ketoacid (235) was crystallised from methylcyclohexane to give the pure compound (30 mg.) as prisms, m.p. 139-140°, $(\alpha)_D^{22}$ +0.955°.

Ethyl 9-ethylenedioxybicyclo(3,3,1)nonen-1-carboxylate (247)

Ethyl bicyclo(3,3,1)nonen-9-one-1-carboxylate (246, 5 g.) was heated with ethyl orthoformate (20 ml.), ethylene glycol (9 ml.) and p-toluenesulphonic acid (50 mg.) in an oil-bath at 130-150° until distillation of ethanol ceased. The mixture was cooled, ether added, and the solution washed with saturated sodium bicarbonate solution, brine and dried. Removal of solvent under reduced pressure, followed by chromatography of the residue on silica gel, afforded the pure ketal ester (247) as a colourless oil (5.37 g.), b.p. 130°/0.4 mm., n_D^{20} 1.5009; $\nu_{max.}$ (film) 1735, 1090, 1080, 1040 and 960 $cm.^{-1}$. (Found: C, 66.37; H, 8.15. $C_{14}H_{20}O_4$ requires

C, 66.65; H, 7.99%).

9-Ethylenedioxybicyclo(3,3,1)nonene-1-carboxylic acid (248)

The ketal ester (247, 5 g.) was stirred at 100° for thirty minutes in an aqueous solution of sodium hydroxide (3N, 100 ml.). The cooled, homogeneous solution was carefully acidified at 0° with dilute sulphuric acid (6N), then extracted twice with ether. The ethereal extracts were combined, washed with brine and dried. Evaporation of solvent yielded the ketal acid (248, 4.01 g.), which, on crystallisation from methylcyclohexane, gave white prisms, m.p. 123-125°, $\nu_{max.}$(Nujol) 3200-2700, 1710, 1090, 1080, 1040 and 960 cm.$^{-1}$.

1-Acetyl-9-ethylenedioxybicyclo(3,3,1)nonene (249)

A solution of methyl lithium (from lithium, 0.7 g., and methyl iodide, 7 g.) in ether (50 ml.) was added to a stirred solution of the ketal acid (248, 2.8 g.) in ether (50 ml.) over five minutes, in an atmosphere of nitrogen. After initial precipitation of the lithium salt of the ketal acid, the solution clarified then slowly turned opaquely white. The reaction mixture was refluxed under nitrogen with

stirring for two hours, then cooled, water added carefully, and the ethereal solution washed with brine and dried. Evaporation of solvent under reduced pressure, followed by chromatography of the residue on silica gel, afforded the methyl ketone (249) as a low-melting colourless solid (2.4 g.), b.p. 135^{o}/0.2 mm., $\nu_{max.}$(film) 1710, 1090, 1080, 1040 and 960 $cm.^{-1}$. (Found: C, 69.90; H, 8.26. $C_{13}H_{18}O_3$ requires C, 70.24; H, 8.16%).

1-Acetyl-9-ethylenedioxybicyclo(3,3,1)nonene oxime (250)

A solution of the methyl ketone (249, 1 g.), hydroxylamine hydrochloride (500 mg.) and potassium hydroxide (500 mg.) in methanol (90 ml.) and water (10 ml.) was heated under reflux for forty-eight hours. The methanol was removed under reduced pressure, and the residue partitioned between methylene chloride and water. The aqueous layer was re-extracted with methylene chloride, and the organic layers combined, washed with brine and dried. Removal of solvent gave the crude oxime, which, on crystallisation from benzene-light petroleum (b.p. $40-60^{o}$), gave white needles (250, 952 mg.), m.p. $157-158^{o}$, $\nu_{max.}$(Nujol) 3300-3200, 1680, 1090, 1080, 1040 and 960 $cm.^{-1}$. (Found: C, 65.80; H, 7.87; N, 5.67. $C_{13}H_{19}NO_3$ requires C, 65.80; H, 8.07; N, 5.90%).

1-Acetyl-9-ethylenedioxybicyclo(3,3,1)nonene oximino-tosylate (251)

The oxime (250, 650 mg.) and sodium hydride (washed with light petroleum (b.p. 40-60°) to remove mineral oil, 275 mg.) were stirred in ether (25 ml.) for twenty-four hours. The suspension was cooled to 0°, and p-toluenesulphonyl chloride (600 mg.) added. Stirring was continued for three hours at room temperature, then the suspension was filtered through Celite. Removal of solvent under reduced pressure at 0° yielded the crystalline oximino-tosylate (251, 986 mg.), $\nu_{max.}$(Nujol) 1680, 1600, 1500, 1195, 1180, 1090, 1080, 1040 and 960 $cm.^{-1}$.

1-Acetamidobicyclo(3,3,1)nonen-9-one (252)

The oximino-tosylate (251, 980 mg.) in ethanol (40 ml.) and water (10 ml.) was heated under reflux for thirty minutes. The ethanol was removed under reduced pressure, and the residue taken up in dilute sodium hydroxide (4N). The solution was extracted twice with ether, the ethereal extracts were combined, washed with brine and dried. Removal of solvent under reduced pressure, followed by chromatography of the residue on silica gel, gave the pure acetamide

(252) as a low-melting, colourless solid (120 mg.), b.p. $140^{o}/0.1$ mm., $\nu_{max.}$(film) 3400-3300, 1710 and 1680 $cm.^{-1}$. (Found: C, 68.25; H, 7.85; N, 7.40. $C_{11}H_{15}NO_2$ requires C, 68.37; H, 7.82; N, 7.25%).

Benzyl bicyclo(3,3,1)nonen-9-one-1-carbamate (256)

A solution of bicyclo(3,3,1)nonen-9-one-1-carboxylic acid (253) was prepared by adding sufficient acetone to a suspension of the acid (253, 38 g.) in water (250 ml.). The solution was cooled to 0^{o}, and triethylamine (40 g.) in acetone (30 ml.) added with stirring. A solution of ethyl chloroformate (30 g.) in acetone (30 ml.) was added slowly at 0^{o}, the mixture stirred for thirty minutes at 0^{o}, and a solution of sodium azide (30 g.) in water (40 ml.) added dropwise. After being stirred at 0^{o} for one hour, the mixture was poured on to ice, and the separated oil extracted with ether, the ethereal extract washed with brine and dried. (Acidification of the aqueous layer gave, on ether extraction, the starting acid, 12.4 g.). The oily residue (29 g.) obtained by evaporation of solvent was heated in toluene (100 ml.) at 100^{o} for four hours, when evolution of nitrogen had ceased. Evaporation of a portion of this solution gave the isocyanate (255) as an oil, $\nu_{max.}$(film) 2250, 1730 $cm.^{-1}$.

Benzyl alcohol (25 g.) was added to the main toluene solution, and heating continued at 100° for four hours. Evaporation of solvent, followed by chromatography of the residue on silica gel, afforded the benzyl carbamate (256) as a thermally-unstable, pale yellow oil (49 g.), $\nu_{max.}$(film) 3450, 1720 and 1510 cm.$^{-1}$.

A by-product obtained by chromatography was the sym-urea (257, 1 g.), which, on crystallisation from acetone, gave white needles, m.p. 244-245°, $\nu_{max.}$(Nujol) 3350, 1720, 1625 and 1550 cm.$^{-1}$. (Found: C, 69.24; H, 7.19; N, 8.56. $C_{19}H_{24}N_2O_3$ requires C, 69.49; H, 7.37; N, 8.53%).

Catalytic hydrogenation of the benzyl carbamate (256)

A portion of the benzyl carbamate (1.24 g.) in ethyl acetate (AnalaR, 50 ml.) was hydrogenated over 10% palladium-charcoal (50 mg.) till uptake of hydrogen ceased. The catalyst was filtered off through Celite, and the solvent removed under reduced pressure, to give the keto-amine dimer (259), which, on crystallisation from light petroleum (b.p. 60-80°), gave white needles (500 mg.), m.p. 174-175°, $\nu_{max.}$ (Nujol) 3330, 3260, 3200-3150 cm.$^{-1}$. (Found: C, 70.78; H, 10.07; N, 8.83. $C_{18}H_{30}N_2O_2$ requires C, 70.55; H, 9.87; N, 9.14%). Mass spectral molecular weight, determined using

either a hot-box or probe sampling technique, was 153 ($C_9H_{15}NO$ requires 153).

1-Aminobicyclo(3,3,1)nonen-9-one hydrobromide (260)

The benzyl carbamate (256, 48 g.) was added slowly to a solution of hydrogen bromide in acetic acid (50% solution, 100 ml.) at 0° with stirring, evolution of carbon dioxide being vigorous. Stirring was continued at 0° for forty-five minutes, and the solution poured slowly into ether (1 l.). The resulting solid was separated by filtration and washed well with ether. Drying of the solid gave the amine hydrobromide (260) as a white solid (24.3 g.), $\nu_{max.}$(Nujol) 3200-2700 and 1720 $cm.^{-1}$.

Treatment of the amine hydrobromide (260) with acetic anhydride in pyridine afforded solely 1-acetamidobicyclo-(3,3,1)nonen-9-one (252), as shown by t.l.c. and infrared spectral comparison with an authentic sample.

1-Pyruvamidobicyclo(3,3,1)nonen-9-one (261)

a. Mixed anhydride procedure

Pyruvic acid (2.6 g.) was dissolved in chloroform (AnalaR, 30 ml.) and a solution of triethylamine (3 g.) in

chloroform (AnalaR, 5 ml.) added dropwise. Ethyl chloroformate (3.2 g) in chloroform (AnalaR, 5 ml.) was added slowly, with stirring, to the cooled solution; stirring was continued for one hour at 0^{o}, the system being protected from moisture with a silica gel drying tube. The amine hydrobromide (260, 3.8 g.) was added, with stirring, as a slurry in chloroform (AnalaR, 10 ml.), followed by a final addition of triethylamine (1.4 g.), this latter addition clarifying the solution. The solution was stirred at room temperature for four hours, then washed with saturated sodium bicarbonate, brine and dried. Evaporation of solvent, followed by chromatography of the residue on silica gel, afforded the pyruvamide (261) as moist crystals (1.8 g.). A portion of this product (150 mg.), on t.l.c. with 50% ethyl acetate-light petroleum (b.p. $60-80^{o}$) for development, afforded the pure pyruvamide (261), which crystallised from light petroleum (b.p. $40-60^{o}$) as white needles (60 mg.), m.p. $84-86^{o}$, $\nu_{max.}(CCl_4)$ 3352, 3018, 1733.5, 1686, 1652.5, 1507 and 1235 $cm.^{-1}$, $\lambda_{max.}$(neutral) 241 mμ (ε= 2,456), $\lambda_{max.}$(base) 275 mμ (ε= 2,035). (Found: C, 64.85; H, 6.70; N, 6.35. $C_{12}H_{15}NO_3$ requires C, 65.14; H, 6.83; N, 6.33%), and a thermally-unstable colourless oil (56 mg.), shown to be ethyl bicyclo(3,3,1)nonen-9-one-1-carbamate (262), $\nu_{max.}$ (film) 3410, 1750, 1735 and 1500 $cm.^{-1}$, it possessing a

characteristic ethyl proton absorption pattern in the n.m.r.: a triplet (3H) at 8.9 τ (J= 7 c.p.s.), and a quartet (2H) at 6.08 τ (J= 7 c.p.s.). Mass spectral molecular weight was 223 (Calculated molecular weight, 223).

Increasing the concentration of pyruvic acid, i.e., effectively reducing the concentration of ethyl chloroformate, produced no change in the ratio of the two products. This observation rules out the possibility of simple acylation of the liberated amine with ethyl chloroformate in the presence of triethylamine.

b. Phosphorus Oxychloride method

A solution of pyruvic acid (4.03 g.), triethylamine (7.2 ml.) and the amine hydrobromide (260, 10 g.) in tetrahydrofuran (200 ml.) was cooled to -15°. Phosphorus oxychloride (9.25 g.) and triethylamine (16.8 ml.) in tetrahydrofuran (50 ml.) were added dropwise to the stirred solution at -15°, and stirring was continued for one hour at room temperature. Water (40 ml.) was added, and the tetrahydrofuran removed under reduced pressure. The residue was taken up in ether, the ethereal solution washed with water, saturated sodium bicarbonate, brine and dried. Removal of solvent gave the crude pyruvamide (261), which crystallised from light petroleum (b.p. 40-60°) as white needles

(8.5 g.), m.p. 84-86°, t.l.c. and infrared comparison showing them to be identical with an authentic sample.

11, 12-Dioxo-13-azatricyclo(3,3,1,$4^{1,9}$)trideca-2,9- and 3,9-diene (264)

The pyruvamide (261, 6.4 g.) was dissolved in tetrahydrofuran (freshly distilled from lithium aluminium hydride, 1 l.), and sodium hydride (50% dispersion in mineral oil, 3.2 g.) added. The suspension was heated under reflux for twelve hours, a granular solid having separated out from the solution within the first thirty minutes. The suspension was cooled, excess tetrahydrofuran was removed under reduced pressure, and water added carefully to destroy unreacted sodium hydride. The residue was taken up in chloroform, and the chloroform solution washed with dilute hydrochloric acid (1N), brine and dried. Removal of solvent under reduced pressure gave the enone lactam, contaminated with mineral oil. Trituration with ether, followed by centrifugation and decantation, gave the enone lactam (264), which crystallised from chloroform-light petroleum (b.p. 60-80°) as white prisms (4 g.), m.p. 228-231°, $\nu_{max.}$(KCl disc) 3191, 1694, 1685, 1647, 1225 and 722 cm.$^{-1}$, $\nu_{max.}$($CHCl_3$) 3360, 3230-3130, 1690.5 and 1643.5 cm.$^{-1}$, $\lambda_{max.}$ 258 mμ

(ε= 11,350). Mass spectral molecular weight was 203. (Calculated molecular weight, 203). (Found: C, 70.58; H, 6.19; N, 6.49. $C_{12}H_{13}NO_2$ requires C, 70.92; H, 6.45; N, 6.89%).

11-Hydroxy-12-oxo-13-azatricyclo(3,3,1,$4^{1,9}$)tridecane (269) and its acetate (270)

A solution of the enone lactam (264, 200 mg.) in ethyl acetate (AnalaR, 100 ml.) was hydrogenated over 10% palladium-charcoal (25 mg.) for twenty-two hours, when uptake of hydrogen had ceased. The catalyst was filtered off through Celite, and the solvent removed to give the solid product (205 mg.), $\nu_{max.}$(Nujol) 1738, 1695 and 1650 cm.$^{-1}$, considered to be a mixture of the α-keto- and α-hydroxy-lactams, (268) and (269) respectively. The total product was reduced with sodium borohydride in methanol and water to afford the α-hydroxy-lactam (269), which crystallised from chloroform-ether as white needles (170 mg.), m.p. 245-246^{o}, $\nu_{max.}$($CHCl_3$) 3508, 3366 and 1654 cm.$^{-1}$. Mass spectral molecular weight was 209. (Calculated molecular weight, 209). (Found: C, 68.77; H, 9.20; N, 7.00. $C_{12}H_{19}NO_2$ requires C, 68.87; H, 9.15; N, 6.69%).

The α-hydroxy-lactam (269, 50 mg.) was treated with

acetic anhydride and pyridine to give the α-acetoxy-lactam (270), which, after sublimation, crystallised from light petroleum (b.p. 60-80°) as white needles (45 mg.), m.p. 137-139°, $\nu_{max.}$ (Nujol) 3200, 3100, 1740 and 1680 $cm.^{-1}$. Mass spectral molecular weight was 251. (Calculated molecular weight, 251). (Found: C, 66.73; H, 8.44; N, 5.72. $C_{14}H_{21}NO_3$ requires C, 66.91; H, 8.42; N, 5.57%).

Action of Zinc and Acetic Acid on the α-acetoxy-lactam (270)

A solution of the α-acetoxy-lactam (270, 56 mg.) in glacial acetic acid (AnalaR, 50 ml.) was heated under reflux for twenty-three hours with zinc powder (AnalaR, 10 g.). The suspension was cooled, the solid removed by filtration through Celite, and the solvent removed under reduced pressure. The residue was dissolved in chloroform, washed with water, saturated sodium bicarbonate, brine and dried. Evaporation of solvent under reduced pressure gave the product (50 mg.), which was shown, by infrared and t.l.c. comparison, to be the starting α-acetoxy-lactam (270).

11-Hydroxy-12-oxo-13-azatricyclo(3,3,1,$4^{1,9}$)trideca-2,9- and 3,9-diene (271)

The enone lactam (264, 100 mg.) was reduced with sodium borohydride in methanol and water. Normal isolation procedures yielded the unsaturated α-hydroxy-lactam (271), which crystallised from ethyl acetate as white prisms (74 mg.), m.p. 221-224°, $\nu_{max.}$(KCl disc) 3550, 3380, 1660, 1647 and 1614 $cm.^{-1}$. Mass spectral molecular weight was 205. (Calculated molecular weight, 205.) (Found: C, 69.84; H, 7.41; N, 6.82%. $C_{12}H_{15}NO_2$ requires C, 70.22; H, 7.37; N, 6.82%).

11-Oxo-12-ethoxy-13-azatricyclo(3,3,1,$4^{1,9}$)trideca-2,9,12- and 3,9,12-triene (272)

A solution of the enone lactam (264, 3 g.) and triethyloxonium fluoroborate (10 g.) in methylene chloride (50 ml.) was stirred for five hours in an atmosphere of nitrogen. Anhydrous sodium carbonate (AnalaR, 20 g.) was added, and stirring continued for a further four hours. The suspension was filtered, and the filtrate concentrated in vacuo. Chromatography of the residue on silica gel gave the lactim ether (272), which sublimed as white prisms (2.9 g.), m.p. 91-92°, $\nu_{max.}$(CCl_4) 3016, 1686 and 1632 $cm.^{-1}$, $\lambda_{max.}$ 255 mμ (ε = 14,050)

Mass spectral molecular weight was 231. (Calculated molecular weight, 231). (Found: C, 72.90; H, 7.07; N, 6.295. $C_{14}H_{17}NO_2$ requires C, 72.70; H, 7.41; N, 6.06%). The n.m.r. spectrum showed a characteristic ethyl proton absorption pattern: a triplet (3H) at 8.85 τ (J= 7 c.p.s.), and a quartet (2H) at 5.84 τ (J= 7 c.p.s.).

N-Acetyl 11-acetoxy-13-azatricyclo(3,3,1,$4^{1,9}$)trideca- 2,9- and 3,9-diene (275)

A suspension of the lactim ether (272, 3.5 g.) and lithium aluminium hydride (3 g.) in ether (200 ml.) was heated under reflux for twenty-four hours, with stirring. The suspension was cooled, excess lithium aluminium hydride was decomposed with moist ether, and the supernatant ethereal solution was decanted. The residue was washed twice with ether, the ethereal extracts were combined, washed with brine and dried. Evaporation of solvent afforded the crude carbinolamine (273) as a gum (2.5 g.), $\nu_{max.}$(film) 3500-3200 $cm.^{-1}$. Mass spectral molecular weight was 191. (Calculated molecular weight, 191.)

The crude carbinolamine (273, 2.4 g.) was treated with acetic anhydride in pyridine to afford, after chromatography on silica gel, the acetamido-acetate (275), which, after

sublimation, crystallised from light petroleum (b.p. 40-60°) as white needles (2.83 g.), m.p. 96.5-98°, $\nu_{max.}(CCl_4)$ 3012, 1739 and 1662 $cm.^{-1}$. Mass spectral molecular weight was 275. (Calculated molecular weight, 275). The n.m.r. spectrum showed a singlet (6H) at 7.98 τ for the two acetyl methyl groups; an ethyl proton absorption pattern was completely absent. (Found: C, 69.63; H, 7.84; N, 5.315. $C_{16}H_{21}NO_3$ requires C, 69.79; H, 7.69; N, 5.09%).

Catalytic hydrogenation of the acetamido-acetate (275)

a. A solution of the acetamido-acetate (275, 150 mg.) in ethyl acetate (AnalaR, 50 ml.) was hydrogenated over 10% palladium-charcoal (25 mg.) for seven hours, when uptake of hydrogen had ceased. The catalyst was filtered off through Celite, and the solvent removed under reduced pressure to give the product as an oil (140 mg.), shown by t.l.c. examination to contain three components. The total product was stirred for two hours with dilute sodium hydroxide (2N, 20 ml.) with slight warming, the solution was cooled, extracted with ether, the ethereal extract washed with brine and dried. Removal of solvent under reduced pressure afforded a semi-solid (99 mg.), which was shown by t.l.c. examination to consist of a polar compound and two of the

original, less polar components. Preparative t.l.c. separation of these gave the three compounds individually free of contamination. The least polar of these (12.8 mg.), $\nu_{max.}$(film) 1650 and 880 cm.$^{-1}$, was deduced to be the unsaturated acetamide (278); mass spectral molecular weight (see Figure 7) was 219 (Calculated molecular weight, 219). The intermediate compound (14.2 mg.), $\nu_{max.}$(film) 1650 cm.$^{-1}$, was deduced to be the saturated acetamide (279); mass spectral molecular weight (see Figure 8) was 221 (Calculated molecular weight, 221). The mass spectral fragmentation patterns of these two compounds were compatible with their proposed structures. The most polar compound (33.9 mg.) proved to be the saturated acetamido-alcohol (277), which crystallised from ethyl acetate-ether as white needles, m.p. 146-147°, $\nu_{max.}$(Nujol) 3500-3300, 1635 cm.$^{-1}$. (Found: C, 70.87; H, 9.73; N, 6.134. $C_{14}H_{23}NO_2$ requires C, 70.85; H, 9.77; N, 5.90%). This last compound must have been present in the original mixture as the saturated acetamido-acetate (276).

G.l.c. analysis of the original mixture showed that the saturated acetamido-acetate (276), the saturated acetamide (279) and the unsaturated acetamide (278) were present in the ratio of 2 : 1 : 1, respectively.

b. A solution of the acetamido-acetate (275, 250 mg.) in glacial acetic acid (AnalaR, 50 ml.) was hydrogenated over platinum black (from platinum oxide, 50 mg.) for six hours, when uptake of hydrogen had ceased. The catalyst was filtered off through Celite, and the solvent removed under reduced pressure. The residue was taken up in ether, the ethereal solution washed with water, saturated sodium bicarbonate, brine and dried. Removal of solvent gave an oil (233 mg.), shown by t.l.c. and g.l.c. analysis to consist of the saturated acetamido-acetate (276) and the saturated acetamide (279), in the ratio of 1 : 1. The unsaturated acetamide was absent.

N-Acetyl 13-azatricyclo(3,3,1,$4^{1,9}$)tridecane, or N-acetyl 5,8a-propanoperhydroquinoline (279)

A solution of the acetamido-acetate (275, 500 mg.) in ethanol (50 ml.) containing perchloric acid (0.5 ml.) was hydrogenated over 10% palladium-charcoal for twenty-four hours. The catalyst was filtered off through Celite, and saturated sodium bicarbonate (10 ml.) added to neutralise the perchloric acid. The ethanol was removed under reduced pressure, and the residue taken up in ether, washed with brine and dried. Evaporation of solvent under reduced

pressure gave the product (402 mg.), shown by t.l.c. and g.l.c. comparison to be solely the saturated acetamide (279), which, after sublimation, solidified as white prisms, m.p. 48-49°, $\nu_{max.}(CCl_4)$ 1743 $cm.^{-1}$. The n.m.r. spectrum showed the acetyl methyl protons as a singlet (3H) at 8.14τ. (Found: C, 75.63; H, 10.40; N, 6.10. $C_{14}H_{23}NO$ requires C, 75.97; H, 10.47; N, 6.33%).

N-Acetyl 11-hydroxy-13-azatricyclo(3,3,1,$4^{1,9}$)trideca-2,9- and 3,9-diene (282)

The acetamido-acetate (275, 500 mg.) was stirred at 70° for two hours with dilute sodium hydroxide (2N, 45 ml.). The solution was cooled, extracted with ethyl acetate, the organic solution washed with brine and dried. Removal of solvent under reduced pressure gave the acetamido-alcohol (282), which crystallised from ether as white plates (415 mg.), m.p. 134-135°, $\nu_{max.}(CCl_4)$ 3590, 3018 and 1660 $cm.^{-1}$. (Found: C, 72.31; H, 8.10; N, 6.15. $C_{14}H_{19}NO_2$ requires C, 72.07; H, 8.21; N, 6.00%).

N-Acetyl 11-oxo-13-azatricyclo(3,3,1,$4^{1,9}$)trideca-2,9- and 3,9-diene (283)

The acetamido-alcohol (282, 422 mg.) in acetone (10 ml.) was treated with excess Jones reagent at 0^{o} for thirty minutes. Water (100 ml.) was added, and the solution extracted with ethyl acetate. The extract was washed with saturated sodium bicarbonate, brine and dried. Removal of solvent under reduced pressure, followed by chromatography on silica gel, afforded the enone (283), which crystallised from light petroleum (b.p. 60-80^{o}) as white needles (353 mg.), m.p. 109-110.5^{o}, $\nu_{max.}(CCl_4)$ 1683, 1668 and 1639 $cm.^{-1}$, $\lambda_{max.}$ 228.5 mμ (ε = 11,550). Mass spectral molecular weight was 231. (Calculated molecular weight, 231). (Found: C, 72.40; H, 7.29; N, 6.261. $C_{14}H_{17}NO_2$ requires C, 72.70; H, 7.41; N, 6.06%).

N-Acetyl 11-ethylenedithio-13-azatricyclo(3,3,1,$4^{1,9}$)trideca-2,9- and 3,9-diene (284)

A solution of the enone (283, 130 mg.), ethanedithiol (0.5 ml.) and boron trifluoride etherate (0.1 ml.) in chloroform-ether (1 : 1, 5 ml.) was left at room temperature for twenty-four hours. Ether (100 ml.) was added, and the

organic solution washed twice with dilute sodium hydroxide solution (4N), brine and dried. Removal of solvent under reduced pressure gave the crude thioketal (284), which crystallised from light petroleum (b.p. 60-80°) as white prisms (98 mg.), m.p. 130-131°, $\nu_{max.}$ ($CHCl_3$) 1651 $cm.^{-1}$. Mass spectral molecular weight was 307. (Calculated molecular weight, 307). The n.m.r. spectrum showed a singlet (4H) at 6.60τ. (Found: C, 62.59; H, 6.99; N, 4.7. $C_{16}H_{21}NOS_2$ requires C, 62.53; H, 6.89; N, 4.56%).

Action of Raney nickel on the thioketal (284)

A portion of the thioketal (284, 11.2 mg.) in ethanol (25 ml.) was heated under reflux with Raney nickel (W2, 50 mg.) for twenty-four hours. The mixture was cooled, the solid removed by filtration through Celite, and the solvent evaporated under reduced pressure. The product (9.5 mg.) was seen by t.l.c. examination to consist of at least three components.

The total crude product in ethyl acetate (AnalaR, 25 ml.) was hydrogenated over 10% palladium-charcoal for twenty-four hours. The catalyst was filtered off through Celite, and the solvent removed under reduced pressure. The product (8 mg.) was seen to be solely the saturated acetamide (279),

as shown by t.l.c. and infrared comparison with an authentic sample.

6-Methoxy-2-tetralone (285)

This compound was prepared from 6-bromo-2-naphthol (286), according to the method of Darling and Kidwell[134], in 35% yield, m.p. 28-30° (lit., m.p. 33-34°), $\nu_{max.}$(film) 1710 cm.$^{-1}$.

1,3-Diethoxycarbonyl-6-methoxy-2-tetralone (291)

A solution of the tetralone (285, 3 g.) in benzene (20 ml.) was added slowly to a refluxing solution of pyrrolidine (2.8 ml.) in benzene (30 ml.). Reflux was continued for two hours under a Soxhlet extractor containing calcium hydride, the system being in an atmosphere of nitrogen. The solution was cooled, evaporated to dryness under reduced pressure, and the residue crystallised from light petroleum (b.p. 40-60°), to give the pyrrolidine enamine (290) as steel-grey needles (1.9 g.), m.p. 67-68.5°, $\nu_{max.}$(Nujol) 1610 cm.$^{-1}$.

A solution of the enamine (290, 1 g.) in benzene (100 ml.) and ethyl chloroformate (50 ml.) was heated under reflux for twenty hours in an atmosphere of nitrogen. The solution was cooled, then stirred for forty-five minutes with 10% aqueous hydrochloric acid. The organic layer was separated,

washed with brine and dried. Removal of solvent gave the crude product (800 mg.), which was adsorbed from light petroleum (b.p. 60-80°)-ether (1 : 1) on to silica gel; elution with 20% ethyl acetate-light petroleum (b.p. 60-80°) afforded the diester (291), which crystallised from ethanol as pale yellow needles (340 mg.), m.p. 68-70°, $\nu_{max.}$(Nujol) 1740, 1675, 1640, 1620 and 1510 $cm.^{-1}$, $\lambda_{max.}$(base) 285 mμ (ε= 30,040). Mass spectral molecular weight was 320. (Calculated molecular weight, 320). (Found: C, 63.71; H, 6.04. $C_{17}H_{20}O_6$ requires C, 63.74; H, 6.29%).

1-Methoxycarbonyl-6-methoxy-2-tetralone (292)

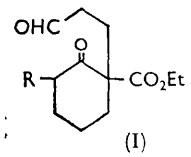
A solution of the tetralone (285, 20 g.) in dimethyl carbonate (150 ml.) was added to a suspension of sodium hydride (50% dispersion in mineral oil, 7.1 g.) in dimethyl carbonate (100 ml.). Methanol (0.5 ml.) was added, and the suspension heated under reflux for three hours. The suspension was cooled, poured on to ice-cold dilute sulphuric acid (6N), and extracted with ether. The organic extract was washed with water, saturated sodium bisulphite solution, brine and dried. Removal of solvent under reduced pressure gave an oil (24 g.), which was adsorbed from light petroleum (b.p. 60-80°) on to silica gel; elution with 10% ether-light

Preprinted from the Journal of the Chemical Society, October 1965, (1077), pages 5764—5766.

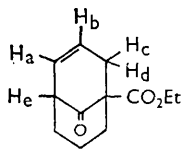
1077. *Bridged Ring Systems. Part VII.* The Acid-catalysed Cyclisation of β-(1-Ethoxycarbonyl-2-oxocyclohexyl)propionaldehyde*

By E. W. Colvin and W. Parker

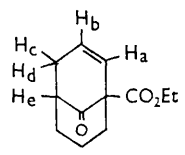
It has previously been shown in this Series that the acid-catalysed cyclisation of the oxo-aldehyde (I; R = Me) to the bicyclo[3,3,1]nonane (IV) is accompanied by the formation of two rearrangement products, ethyl 2-acetylbicyclo[3,3,0]oct-1(2)-ene-5-carboxylate and 7-methylindane-4-carboxylic acid.[1] To test the generality of these rearrangements, a re-examination of the similar cyclisation of the lower homologue (I; R = H), previously reported by Cope and Synerholm,[2] was undertaken. However, sulphuric acid treatment of (I; R = H) furnished no trace of rearrangement products of the above type, and the substance obtained, m. p. 46—47·5° (lit., m. p. 48—49·4°), seemed to be the ketone (II) reported previously. Thin-layer chromatography of this seemingly homogeneous product separated it into two crystalline isomers, m. p. 45—45·5° and 58·5—59·5° (4·7 : 1). Their relationship as the double-bond isomers (II) and (III) was readily established as each gave



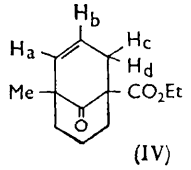
(I)



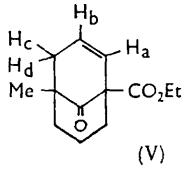
(II)



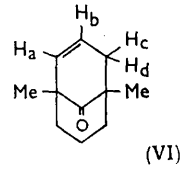
(III)



(IV)



(V)



(VI)

the same dihydro-compound on catalytic hydrogenation. Prolonged treatment of each isomer with sulphuric acid gave the same equilibrium mixture of (II) and (III) (1·2 : 1) by the obvious protonation–deprotonation mechanism. Production of these two isomeric species in cyclisations of this type seems general; re-examination of the cyclisation of (I; R = Me) resulted in the isolation of the corresponding two isomers (IV) and (V) (2·8 : 1).

The position of the double bond in each compound was shown by the n.m.r. spectrum. Thus, the isomer of m. p. 45—45·5° exhibited the following olefinic proton signals, showing it to possess structure (II): H_b, two triplets centred at 3·99 τ [$J(H_a\text{–}H_b) = 9$; $J(H_b\text{–}H_{c,d}) = 4$ c./sec.]; H_a, a quartet of triplets centred at 4·39 τ [$J(H_a\text{–}H_b) = 9$; $J(H_a\text{–}H_e) = 6$; $J(H_a\text{–}H_{c,d}) = 2$ c./sec.]. The isomer of m. p. 58·5—59·5° showed the following olefinic signals, compatible with (III): H_b, two triplets centred at 3·98 τ [$J(H_b\text{–}H_a) = 9$; $J(H_b\text{–}H_{c,d}) = 4$ c./sec.]; H_a, two triplets centred at 4·38 τ [$J(H_a\text{–}H_b) = 9$; $J(H_a\text{–}H_{c,d}) = 2$ c./sec.]. The homologue (IV) showed: H_b, two triplets centred at 4·098 τ [$J(H_b\text{–}H_a) = 9$; $J(H_b\text{–}H_{c,d}) = 4$ c./sec.]; H_a, two quartets centred at 4·76 τ [$J(H_a\text{–}H_b) = 9$; $J(H_a\text{–}H_{b\text{ or }d}) = 2{\cdot}5$; $J(H_a\text{–}H_{c\text{ or }d}) = 2$ c./sec.]. Its isomer (V) showed: H_b, two triplets centred at 4·08 τ [$J(H_b\text{–}H_a) = 9$; $J(H_b\text{–}H_{c,d}) = 4$ c./sec.]; H_a, two triplets centred at 4·45 τ [$J(H_a\text{–}H_a) = 9$; $J(H_a\text{–}H_{c,d}) = 2$ c./sec.].

It is noteworthy that one of the allylic protons in compounds (II) and (IV) is selectively

* Part VI, P. Doyle, I. R. Maclean, R. D. H. Murray, W. Parker, and R. A. Raphael, *J.*, 1965, 1344.

deshielded. Thus, in (II), the allylic protons are seen as: H_c, two multiplets centred at 6·55 τ [$J(H_c$–$H_d) = 20$ c./sec.]; H_d, two quartets centred at 7·55 τ [$J(H_d$–$H_c) = 20$; $J(H_d$–$H_b) = 4$; $J(H_d$–$H_a) = 2$ c./sec.]. In (III) they are seen as: $H_{c,d}$, an unresolved muliplet centre at 7·38 τ. In (IV), H_c is seen as two multiplets centred at 6·6 τ [$J(H_c$–$H_d) =$ 18 c./sec.], and H_d as two quartets centred at 7·61 τ [$J(H_d$–$H_c) = 18$; $J(H_d$–$H_b) = 4$; $J(H_d$–$H_a) = 2$ c./sec.], while in (V) the allylic protons are seen as: $H_{c,d}$, two doublets centred at 7·55 τ [$J(H_{c,d}$–$H_b) = 4$; $J(H_{c,d}$–$H_a) = 2$ c./sec.]. That the 1-ethoxycarbonyl grouping is responsible for this deshielding is shown by the n.m.r. spectrum of the hydrocarbon (VI),[3] which exhibits the expected two doublets in the allylic region centred at 7·58 τ [$J(H_{c,d}$–$H_b) = 4$; $J(H_{c,d}$–$H_a) = 2$ c./sec.].

Experimental.—Melting points were recorded on a Kofler hot-stage apparatus, and are corrected. Thin-layer chromatoplates (1 mm. thick) were prepared from Kieselgel G (Merck). Analytical gas chromatography was performed on a Pye Argon Chromatograph (column, 10% Peg A; 160°; pressure, 18 p.s.i.; flow rate, 50 c.c./min.). N.m.r. data were obtained, with a Perkin-Elmer 60 Mc. instrument, for carbon tetrachloride solutions, tetramethylsilane being used as internal reference. Infrared spectra were obtained with a Unicam S.P. 200 instrument, for Nujol mulls unless stated otherwise.

β-(1-*Ethoxycarbonyl*-2-*oxocyclohexyl*)*propionaldehyde* (I; R = H). This compound was prepared by the method of Cope and Synerholm.[2]

Ethyl 9-*oxobicyclo*[3,3,1]*non*-3- *and* -2-*ene*-1-*carboxylate* (II) *and* (III). The oxo-aldehyde (48 g.) was added in fine droplets to concentrated sulphuric acid (96 ml.), cooled in an ice–salt bath. The mixture was left at room temperature for 4 hr., poured on to ice, and the product separated as a non-filterable semi-solid. The total mixture was extracted twice with ether, the extracts were combined, washed with sodium hydrogen carbonate solution and brine, and dried ($MgSO_4$). (Acidification of the hydrogen carbonate washings afforded solely 2-oxocyclohexanecarboxylic acid.) Removal of solvent under reduced pressure furnished a brown solid (27 g.). Chromatography on alumina (Spence H; 150 g.) gave pale yellow crystals (26 g.), m. p. 46—47·5°. Thin-layer chromatography of these (150 mg.), with 10% ethyl acetate–light petroleum (b. p. 60—80°) for development, separated the two components; (II) sublimed as *needles* (99·4 gm.), m. p. 45—45·5°, $\nu_{max.}$ 3100, 1740, 1715, 1660, 720, 695 cm.$^{-1}$ (Found: C, 68·9; H, 7·75. $C_{12}H_{16}O_3$ requires C, 69·2; H, 7·75%), and (III) sublimed as *needles* (21·7 mg.), m. p. 58·5—59·5°, $\nu_{max.}$ 3100, 1735, 1715, 1660, 720 cm.$^{-1}$ (Found: C, 69·4; H, 7·75%). The ratio of (II) to (III) (4·7 : 1) was determined from peak areas on gas chromatography.

A solution of the pure oxo-ester (II) (100 mg.) and hydrazine hydrate (100%; 0·1 ml.) in ethanol (5 ml.) was refluxed for 24 hr., and evaporated to dryness under reduced pressure, to give the crude pyrazolone (75 mg.). This was recrystallised twice from benzene, to afford *needles*, m. p. 217—218° (sealed tube) (Found: C 68·15; H, 6·65; N, 16·0. $C_{10}H_{12}N_2O$ requires C, 68·15; H, 6·85; N 15·9%). The pyrazolone of (III) was obtained similarly as *needles*, m. p. 195—196° (sealed tube) (Found: C, 67·95; H, 6·9; N, 16·05%).

A suspension of the pure oxo-ester (II) (100 mg.) in aqueous sodium hydroxide (2N; 10 ml.) was stirred until a clear solution was obtained. This was acidified with sulphuric acid (6N) and extracted twice with ether. The extracts were combined, washed with brine, and dried ($MgSO_4$). Removal of solvent under reduced pressure afforded the crude product (78 mg.) which, after two recrystallisations from methylcyclohexane, gave the pure acid derived from (II) as prisms, m. p. 139·5—140° (lit., 133·8—134·3°), $\nu_{max.}$ 3500—2700, 1720, 1695, 1660, 720, 690 cm.$^{-1}$ (Found: C, 66·65; H, 6·45. Calc. for $C_{10}H_{12}O_3$: C, 66·65; H, 6·7%). The isomeric acid from (III) was obtained similarly as prisms, m. p. 143—144°, $\nu_{max.}$ 3500—2700, 1720, 1700, 1660, 720 cm.$^{-1}$ (Found: C, 66·75; H, 6·8%).

A solution of either pure oxo-ester (II) or (III) (45 mg.) in ethyl acetate (AnalaR; 20 ml.) was separately hydrogenated over 10% palladium–charcoal (5 mg.) until uptake ceased. The catalyst was filtered off through Celite, and the solvent removed under reduced pressure, to give the saturated ester, which was shown to be the same from (II) and (III) by thin-layer and gas chromatography. Sublimation afforded a *solid*, m. p. 26—32° (Found: C, 68·3; H, 8·7. $C_{12}H_{18}O_3$ requires C, 68·55; H, 8·65%). The *pyrazolone* crystallised from ethanol in prisms, m. p. 221—222° (sealed tube) (Found: C, 67·25; H, 7·75; N, 15·6. $C_{10}H_{14}N_2O$ requires C, 67·4; H, 7·9; N, 15·7%). The corresponding acid crystallised from methylcyclohexane in

needles, m. p. 136—137° (lit., 138·6—139·4°) (Found: C, 65·9; H, 7·65. Calc. for $C_{10}H_{14}O_3$: C, 65·9; H, 7·75%).

Isomerisation of (II) *and* (III) *with sulphuric acid.* Separate solutions of the pure oxo-esters (II) and (III) (50 mg.) in concentrated sulphuric acid (5 ml.) were stirred overnight at room temperature, and poured on to ice. The solutions were extracted with ether, and the extracts washed with sodium hydrogen carbonate solution and brine, and dried ($MgSO_4$). Removal of solvent under reduced pressure gave the product (47 mg.), which in each case was shown by gas chromatography to contain only (II) or (III), in the ratio 1·2 : 1.

Ethyl 5-methyl-9-oxobicyclo[3,3,1]*non-2- and -3-ene-1-carboxylate* (V) *and* (IV). This liquid compound was prepared according to the published method [1] Some of the product (100 mg.), on thin-layer chromatography with three portions of 5% ethyl acetate–light petroleum (b. p. 60—80°) for development, was separated into the 3-*ene* (V) (70 mg.), n_D^{19} 1·4898, $\nu_{max.}$ (liquid film) 3100, 1735, 1720, 1660, 710, 690 cm.$^{-1}$ (Found: C, 70·05; H, 8·0. $C_{13}H_{18}O_3$ requires C, 70·25; H, 8·15%), and the 2-*ene* (VI) (19·5 mg.), n_D^{19} 1·4867, $\nu_{max.}$ (liquid film) 3100, 1740, 1720, 1660, 720 cm.$^{-1}$ (Found: C, 70·2; H, 8·0%). The ratio of (V) to (VI) (2·8 : 1) was determined from peak areas on gas chromatography.

The authors are indebted to Professor R. A. Raphael for helpful discussions, and to Mr. J. M. L. Cameron, B.Sc., and his associates for microanalyses. One of us (E. W. C.) gratefully acknowledges a Carnegie Research Scholarship.

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Printed in Great Britain by Richard Clay (The Chaucer Press) Ltd., Bungay, Suffolk.

petroleum (b.p. 60-80°) gave the desired β-ketoester (292) as a colourless oil (22 g.), b.p. 130°/0.8 mm., $\nu_{max.}$(film) 1740, 1720, 1640, 1610, 1570 and 1510 $cm.^{-1}$, $\lambda_{max.}$(neutral) 250 mμ (ε = 13,300), 285 mμ (ε= 6,200), $\lambda_{max.}$(base) 281 mμ (ε= 18,200). Mass spectral molecular weight was 234. (Calculated molecular weight, 234). (Found: C, 66.40; H, 5.67. $C_{13}H_{14}O_4$ requires C, 66.66; H, 6.02%).

The β-ketoester (292) gave an intense green colour with ethanolic ferric chloride solution.

2-Methyl-3-(1-methoxycarbonyl-6-methoxy-2-tetralone)propionaldehyde (295)

An ice-cold mixture of the β-ketoester (292, 20.5 g.) and methacrolein (12.5 g.) was added over one hour to a stirred solution of sodium methoxide (from sodium, 200 mg., and methanol, 500 ml.) containing hydroquinone (100 mg.) at -70°. The solution was allowed to warm to room temperature, stirring being continued for one hour. The solution was neutralised with glacial acetic acid, and the solvent removed under reduced pressure. The residue was dissolved in ether, the ethereal solution washed with saturated sodium bicarbonate solution, brine and dried. Removal of solvent under reduced pressure gave the crude keto-aldehyde

(295) as a gum (31 g.), $\nu_{max.}$(film) 1740-1720 cm.$^{-1}$. Mass spectral molecular weight was 304. (Calculated molecular weight, 304).

Methyl 6-hydroxy-7-methyl-3'-methoxy-2:3-benzobicyclo-(3,3,1)non-2-en-9-one-1-carboxylate (296)

A solution of the crude keto-aldehyde (295, 31 g.) in dioxan (150 ml.) was added, with stirring, to an ice-cold mixture of dilute hydrochloric acid (6N, 100 ml.) and dioxan (150 ml.), in an atmosphere of nitrogen. The solution was stirred at room temperature for twenty-four hours, then poured on to water and extracted with ether. The organic layer was separated, washed with saturated sodium bicarbonate solution, brine and dried. Removal of solvent afforded the crude ketols (296) as a gum (27 g.), $\nu_{max.}$(film) 3600-3400, 1740-1720 cm.$^{-1}$.

Treatment of a portion of the crude ketols (296, 7 g.) with acetic anhydride in pyridine afforded the crude acetates (297) as a gum (8 g.). This was adsorbed from light petroleum (b.p. 60-80^{o})-ethyl acetate (2 : 1) on to silica gel; elution with 10% ethyl acetate-light petroleum (b.p. 60-80^{o}) yielded the pure acetates (297) as a colourless gum (5.2 g), $\nu_{max.}$(film) 1740 and 1720 cm.$^{-1}$.

G.l.c. analysis of the mixture (5% QF1, 200°, 35 ml/min.) indicated the presence of four acetates.

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