INVESTIGATIONS IN THE BICYCLO(3,3,1)NONANE SYSTEM

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During our work on the properties, reactions and uses of the bicyclo(3,3,1)nonane system, we have come to regard it as an inexhaustible source of interesting and frequently, surprising chemistry. In the following pages we draw on basic alicyclic chemistry related to bridged ring compounds, adamantanes, medium-sized rings and cyclohexanes, to interpret our results. The combination of rigidity and flexibility in the framework of this bridged system gives rise to a versatility which, on reflection, is almost unique for a molecule of nine carbon atoms.

PART I

The Synthesis of trans, meso-2,6-Dimethyl-2,6-dicarboxycyclohexylacetic Acid, a Key Diterpene Oxidation Product.

INTRODUCTION

Abietic acid (1), a tricyclic diterpene obtained from colophony (rosin) of pinewood, is the most important member of a class of compounds known collectively as the 'resin acids'. The history[1] of isolation and structure determination of this member of the series presents almost a century of unbroken effort. From the first description of the acid[2] in 1874, through the classic researches of Ruzicka and his co-workers between 1922 and 1942, to the partial synthesis[3] in 1961, a mass of data has been collected; this introduction records only the highlights. In particular, the role played by key degradation products, the tricarboxylic acids (2) and (3), will be discussed. Especially pertinent to the present study, are the lessons gleaned from no less than five unsuccessful attempts, reported between 1935 and 1960, to synthesise these compounds.

Abietic acid, $C_{20}H_{30}O_2$, contains two olefinic double bonds, and is therefore tricyclic. Dehydration[1] afforded a C_{18}-phenanthrene derivative, retene[4], identical with 1-methyl-7-isopropylphenanthrene (4, R=Me) synthesised by Haworth[5], whereas prior conversion to abietinol (5), followed by dehydration and dehydrogenation, produced homoretene[6] identical with (4, R=Et) synthesised again, by Haworth[7].

The presence of the ethyl side-chain in (4, R=Et) established that one methyl and the carboxyl group were geminal on C_1 in abietic acid; a Namethkin rearrangement during dehydration of 5 explained the ethyl group of (4, R=Et).

In a series of papers[8] published between 1938 and 1942, Ruzicka and his co-workers established the relative positions of the double bonds and the isopropyl side-chain in abietic acid, particularly by isolation of 1-methyl-7-hydroxyphenanthrene (6) from dehydration and dehydrogenation of previously hydroxylated abietic acid derivatives. With this information, the partial structure (7) could be derived, leaving undecided the position of the remaining methyl group, invariably removed in dehydrogenation, and the stereochemistry of the molecule. It was with respect to assignment of these details that the C_{12}- and C_{11}-acids, (2) and (3) respectively, proved invaluable.

Oxidation of abietic acid with nitric acid or potassium permanganate produced these products[9] and also 2,6-dimethylcyclohexanone[10] (8). The 1,3-relationship of the methyl groups in (2) and (3) were ascertained by dehydrogenations to hemimellitene (9, R=Me) and m-xylene (9, R=H) respectively. The remaining methyl group in abietic acid (1) was therefore attached to the angular position (C_{12}), common to rings A and C .

By means of a series of selective ester and anhydride formations and hydrolyses, Ruzicka[11] inter-related the steric surroundings of the central, secondary carboxyl group in (3) with those of the tertiary groups in both acids, and with that of the primary carboxyl of 2, thereby arriving at the gross structures of both. The cis-relationship

of the 1,3-carboxyl groups could be deduced from the ease of anhydride formation in both cases. Further proof of the structure of the C_{11}-acid came from its degradation to the unsaturated dicarboxylic acid (10), subsequently converted to the lactone (11). Both of these products were later synthesised by Rydon[12] from the cyanohydrin of 2,6-dimethyl-2-carbethoxycyclohexanone, which was dehydrated to the nitrile-ester (12), further converted in alkali and in acid to 10 and 11 respectively.

The cis-relationship of the tertiary carboxyl groups (and necessarily therefore, of the methyl groups) in the tricarboxylic acids, creating meso-structures, was directly inferred in the early work, from the lack of optical activity in both compounds. The ease of 1,3-anhydride formation, described above, confirmed this stereochemical assignment. It only remained to determine whether the C_2- carboxyl (or acetic acid residue) was related in a cis- or trans-manner to the two cis-carboxyl groups on C_1 and C_3. With this information, the relative stereochemistry of the three asymmetric centres on ring A of abietic acid could be defined, assuming that no inversion occurred during the oxidative degradations leading to the tricarboxylic acids.

Two attempts to synthesise the acids - in 1935 and again in 1947 (see below) - were unsuccessful, leading only to other epimers, or to mixtures. In any case, both of these routes suffered from a lack of steric control which would have precluded complete definition of the products, even if they had been sterically pure. The solution of the stereochemical problem came in 1948, from analysis of a series of

thermodynamic dissociation constants of all the mono- and di-methyl esters of the C_{11}-acid (3) by Barton and Schmeidler[13a]. These authors established the trans, meso-configuration represented in 3. The A/C-trans ring fusion and the relative configuration at C_1, both represented in the formula (1) for abietic acid, were therefore assigned by them, on the basis of their work on the C_{11}-degradation product.

Since no comparable study of the C_{12}-acid, nor any inter-conversion of the two acids has been reported, it has been assumed that the two acids are stereochemically analogous. It should be mentioned here that stereochemical extrapolations from the C_{12}-acid to abietic acid would be more reliable than from the C_{11}-acid, which, unlike its homologue, is theoretically epimerisable at C_2, and could conceivably have undergone inversion under the strenuous oxidative conditions employed in its formation. Our successful synthetic route to the C_{12}-acid, reported below, by virtue of rigorous control of the stereochemistry at all three asymmetric centres, therefore constitutes more than a confirmation of assignments made by Barton and Schmeidler as to the stereochemistry of several diterpene acids[13a].

One more stereochemical feature of abietic acid (1) - apart from the absolute configuration - remains to be discussed. The tricarboxylic degradation products did not lead to any information on the nature of the B/C-ring fusion, that is, whether the hydrogen atom on C_{13} is in a cis- or trans- relationship to the C_{12}-methyl group. The more stable

trans, C_{12}-C_{13} arrangement was preferred[1] since the acidic conditions used in the preparation of abietic acid would provide a means whereby the more stable configuration at C_{13} would be taken up. Further support for this assignment comes from more recent studies[13b].

Since many other diterpenes were related by interconversions[1] with abietic acid and its derivatives, the work described above had an important bearing on the whole field of diterpene chemistry. In particular, dextropimaric acid (13) and levopimaric acid (14), precursors of abietic acid, and probably the main sources of the latter, by conversion under acid conditions used in its isolation from natural sources, could then be described.

An interesting diterpene correlation arose from the isolation of optically active isomers of the C_{11}- and C_{12}- acids described above, from degradation of agathene-dicarboxylic acid (15). It could be immediately inferred from the activity that these acids (16, R=CO_2H or CH_2CO_2H) had tertiary carboxyl groups related in a 1,3-trans manner, unlike those in the meso-isomers 2 and 3. Although agathene-dicarboxylic acid (15) contains the same A/C-trans ring fusion as in abietic acid (1) the C_1-methyl and -carboxyl configurations are inverted[14].

The last phase of the history of abietic acid includes the synthesis of dehydroabietic acid[15] (17) and of abietic acid itself[3]. dl-Dehydroabietic acid[16] (17) was synthesised by Stork and Schulenberg[15] in the following manner. The starting material, 1-methyl-6-isopropyl-2-tetralone (18) was obtained from a Birch reduction of 6-isopropyl-2-naphthol, followed by specific α-mono-methylation. A Robinson-Mannich

condensation with ethyl vinyl ketone afforded the tricyclic enone (19). Alkylation of 19 with ethyl bromoacetate, which involved a transposition of the double bond, was followed by formation of the thioketal and alkaline hydrolysis, producing, as the only isomer which could be isolated, the compound 20. Desulphurisation of the methyl ester of 20 with Raney nickel, followed by hydrolysis and hydrogenation gave dl-homodehydroabietic acid (21) whose infrared spectrum was identical with that of an authentic sample. Barbier-Wieland degradation of 21 then gave dl-dehydroabietic acid (17) identical in the infrared with d-dehydroabietic acid, thus confirming its structure and relative stereochemistry.

More recently[3] Burgstahler and Worden completed the formal synthesis of abietic acid (1). Reduction of natural dehydroabietic acid (17) with lithium in ethylamine afforded the acid (22). Treatment of the latter with concentrated hydrochloric acid in ethanol produced the isomeric abietic acid (1) in high yield.

Despite the success of the syntheses described above, neither of the C_{11}- or C_{12}-tricarboxylic acids (3 or 2) was obtained from no less than five routes designed between 1935 and 1960. In 1935, Arbusow and Schapshinskaja[17] reported an attempted synthesis from the dimethyltetracarboxylic acid (23), prepared without control of product stereochemistry. Decarboxylation, removing one of the C_2-carboxyls of 23, afforded a viscous oil which was, not surprisingly a mixture, which could not be resolved, of some of the four possible stereoisomers of the C_{11}-acid (3).

In 1947 the first attempt to synthesise the C_{12}-acid (2) met with a similar lack of success. Mukherjee[18] prepared the chloro-triethyl ester (24) by Reformatsky addition of ethyl bromoacetate to 2,6-dimethyl-2,6-dicarbethoxycyclohexanone, followed by replacement of the hydroxyl group by halogen, with thionyl chloride in pyridine. Various attempts to convert this product to the known C_{12}-acid (2) were uniformly unsuccessful. The 1,2-anhydride (25) finally obtained was not that of the C_{12}-acid.

Rao and Bagchi[19] achieved the control, unfortunately in the wrong manner, of the relative stereochemistry of two centres in the C_{12}-acid target, by using the indanone (26, R=Et) as a synthetic precursor. Since cis ring fusion is generally preferred over trans fusion in such indanones, one would predict that at least two adjacent oxidised groups arising from 26 would be cis-related, unlike the situation in the C_{12}-degradation product of abietic acid. In the event, oxidation of the indanone with concentrated nitric acid, and base hydrolysis of the product afforded the crude tricarboxylic acids as a gum. This, in acetic acid solution, deposited a solid product which had the same melting point as the authentic C_{12}-acid (2). The melting point of the latter, however, was depressed by admixture with the synthetic material, and the infrared spectra of the authentic and synthetic acids were different.

The latest attempt to synthesise the C_{12}-acid (2) was reported[20] by Banorjee and Mahaptra, in 1960. They prepared the analogous indanone-methyl ester (26, R=Me) by a different route from that used by Rao and Bagchi, but found that degradation of this compound also gave

an isomer of the authentic C_{12}-acid. Prior to the report of Banorjee and Mahaptra, a fifth synthetic attempt had been made by Parker[21]. Although this was also unsuccessful, the basic device for steric control of the 1,3-cis substitution in the C_{12}-acid was reapplied in the successful synthesis reported in the present work. For this reason, Parker's work merits more detailed discussion at this stage.

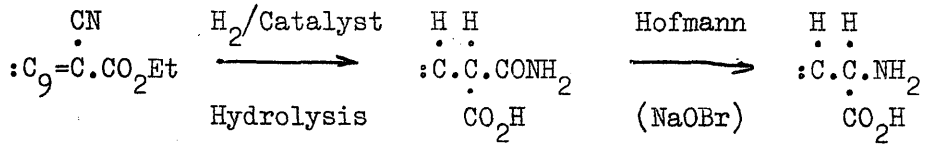
It had been noted[22] that bromination of 2,6-dimethylcyclohexanone gave only the cis-dimethyldibromoketone. If the same specificity applied in addition of formaldehyde, the resulting cis-2,6-di(hydroxymethyl)-2,6-dimethylcyclohexan-1-ol (27) would be a useful starting material. Oxidation to cis-2,6-dimethyl-2,6-dicarboxycyclohexanone, and elaboration of the central oxo-function to carboxyl (or acetic acid residue) would provide, at least, a mixture of the required C_{11}- (or C_{12}-) acid and the C_{11}- (or C_{12}-) acid isomeric at C_1. Unfortunately the initial step led only to a low yield of a mixture of epimeric triols.

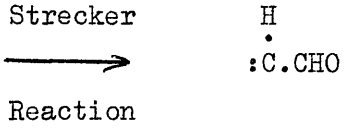
More rigorous steric control was planned in the major route. Exhaustive formaldehyde addition to cyclohexanone afforded the symmetrical pentol (28) which was dehydrated to the bicyclic ether (29, R=CH_2OH, R'=OH). With concentrated nitric acid the latter was oxidised to 1,5-dicarboxy-3-oxabicyclo(3,3,1)nonan-9-one (29, R=CO_2H, R'= =O). In this compound, the carboxyl groups are necessarily cis-related in the fused-ring framework. Elaboration of the 9-oxo-function and cleavage of the ether ring, followed by conversion of the two one-carbon residues so obtained to methyl groups, would be expected to produce the required steric arrangement at the two non-adjacent quaternary centres. An

additional advantage to be accrued from use of (29, R=CO_2H;R'= =O) as an intermediate was the resistance of the bridgehead carboxyls to decarboxylation in the double β-ketoacid system. As designed, Reformatski addition of ethyl bromoacetate to the oxo-diester (29, R=CO_2Me; R'= =O), followed by dehydration and hydrogenation of the resulting double bond, afforded a separable mixture of the epimeric triesters (30, 31; R=Me; R'=Et). Although the overall yield was poor, and the C_9-stereochemistry could not be specifically assigned, it was hoped that ether fission by hydrogen iodide, say, applied to one of the esters would yield the dihalide (32, R=Me; R'=Et), easily convertible to the required C_{12}-tricarboxylic acid (2a). The other triester would, of course, give the C_{12}-acid epimeric at C_1. Unfortunately, of all the known methods of ether fission applied, some had no effect and the remainder caused extensive degradation.

This impasse marked the end of the main route, but the results of auxiliary reactions applied to the hindered 9-oxo-function are of interest, in view of the present study. In fact, all alternatives to the Reformatsky reaction on (29, R=CO_2Me; R'= =O) gave even poorer yields of intermediates. No Wittig reaction could be induced between this ketone and methoxymethylenetriphenylphosphonium bromide, in an attempt to obtain the αβ-unsaturated ester (33, R=Me); the glycidic ester (34, R=Me) from reaction with ethyl chloroacetate[54] could not be purified. Finally, a scheme was devised[23] for conversion of the ketone to the aldehyde (35, R=Me), a potential precursor of the C_{11}-tricarboxylic acid (3). This involved Knoevenagel condensation with ethyl

cyanoacetate to give (36, R=Me) and further treatment as detailed below:





Once again, this scheme was thwarted by the lack of reactivity of the 9-oxo-function, in this case to Knoevenagel condensation.

As will be seen from the following discussion, the final and successful route to the C_{12}-tricarboxylic acid (2) features the development of alternative techniques, specifically to overcome such difficulties in elaborating the 9-oxo-function in a related bridged bicyclic system.

DISCUSSION

The importance of synthetic confirmation of the structures of the C_{11}- and C_{12}-tricarboxylic acids (3 and 2 respectively) lies in their relationship to the detailed structure of their common precursor, abietic acid (1). It is therefore necessary to establish that their formation under severe degradative conditions is accomplished without inversions of configuration. Although the trans, meso stereochemistry of the C_{11}-acid (3), and its resistance to inversion under prolonged acidic conditions were known[13a], the correlation between this product and the diterpenes remained dependent on the assumption that no prior inversion had occurred.

Because the secondary carboxyl of the C_{11}-acid shares an α-hydrogen with the adjacent asymmetric carbon, a propensity to inversion by reversible loss of that proton, undoubtedly exists. It also follows that any synthetic route would require careful control of reaction conditions to avoid ambiguity. For these reasons, the non-epimerisable C_{12}-acid (2), whose steric relationship to abietic acid (1) is more reliable, was the preferred synthetic goal.

The necessity for strict steric control in such a synthesis was demonstrated by the worthless attempts using substituted cyclohexane compounds[17,18] and indanes[19,20]. The attempt of Parker[21] to apply this control was obviously sound in principle, failing only because

of unforseen preparative difficulties. The projected sixth attempt was devised to overcome such troubles, while employing the same basic method of ensuring the correct stereochemistry of the product.

An alternative intermediate to the oxabicycloketone (29, R=CO_2Me; R'= =O) used by Parker, was required, containing a ring-cleavage centre - carbon, carbon double bond in place of ether oxygen - and the same C_9-oxo-function, for elaboration to an acetic acid residue, as in 1,5-dimethylbicyclo(3,3,1)non-2-en-9-one (37). The oxidation levels of C_2 and C_4 after ring cleavage would then be more suitable for conversion of these two centres to carboxyls. The other cis-related substituents - the methyl groups - could be most profitably introduced initially, at bridgehead positions C_1 and C_5.

The available methods of synthesis of bicyclo(3,3,1)nonanes, in this case from 2,6-dimethylcyclohexanone (8) were then examined. Reported syntheses[24a-h] almost invariably use α-carbethoxycyclohexanones, providing an active methine for condensation or alkylation. The noteable exception[25] - by use of enamine activation[26] of cyclohexanone itself - cannot be applied to α,α'-dialkylcyclohexanones.

Although condensation of 8 with acrolein[24c] to give 41 does not occur[27], alkylation with 3-chloro-1,1-diethoxypropane[24c] gave a low yield of 3-(1,3-dimethyl-2-oxocyclohexyl)propionaldehyde diethyl acetal (38). This was heated with hydrochloric acid in dioxan, affording the required bicyclic ketol as its two epimers (39a and 39b; both R=H), and a considerable quantity (40%) of the corresponding ethyl ethers (39a and 39b; both R= Et). Formation of the latter is rationalised in

terms of the accepted mechanism[28] for acetal hydrolysis if we assume that reaction of the positively charged intermediate (40) follows the mechanism shown, rather than reaction by the normal route to the ketoaldehyde (41) and thence by aldolisation to the bicyclic ketol mixture (39a,b; R=H).

Various attempts to dehydrate this mixture proved unpromising. It had been shown[29] that dehydration of the analogous ketol mixture (42) was unusually difficult, and even pyrolysis of acetate and carbonate esters produced complex mixtures. Dehydration of the same ketol mixture in sulphuric acid was known[24g] to give acceptable yields of the simple product (43) along with significant amounts of 7-methylindane-4-carboxylic acid (44) and ethyl 2-acetobicyclo(3,3,0)oct-1(2)-ene-5-carboxylate (45). Mechanisms depicted in schemes A and B respectively, are essentially those proposed by the authors for the formation of these rearranged products. (The writer prefers scheme C for formation of 44 , involving the ketene intermediate (47), this accounting for eventual isolation of the acid and not the ethyl ester. There is no obvious reason why the aromatic ester group, if it were first formed, should be hydrolysed in preference to those of 43 and 45.) No bicyclo(4,2,1)nonane derivative, such as (46, R=CO_2Et) was detected.

Dehydration of the dimethylketols (39a,b; R=H) in sulphuric acid produced a distinctly different result. No acidic material analogous to 44 was isolated, and the product was largely polymeric. When heated with boric acid[30], the ketol mixture gave four major products - an aromatic hydrocarbon fraction identified as 4-methylindane[31] (48, R=H),

(15% yield), the required synthetic intermediate (37); 5-methyl-2-acetobicyclo(3,3,0)oct-1(2)-ene (49), in 13% yield and finally, 10% of a non-conjugated unsaturated ketone, to which the structure (46, R=Me) has been tentatively assigned.

The structure (46, R=Me) is based on the following evidence: analysis for $C_{11}H_{16}O$; carbonyl (1740 $cm.^{-1}$) and trisubstituted double bond (1650, 820 $cm.^{-1}$) indicated by the infrared spectrum; formation of a 2,4-dinitrophenylhydrazone (sterically prevented in 37, but probably facile in 46); end-absorption only, in the ultraviolet. The αβ-unsaturated enone product (λ_{max} 252 mμ, ε 10,100) exhibited chemical and physical properties consistent with its formulation as 49. This was confirmed by catalytic hydrogenation to 50 , and synthesis of an identical ketone from 45[24g], by the route indicated. The experimental details of this conversion are recorded in Appendix A, following the main experimental section.

It seems that although skeletal rearrangements analogous to those reported [24g] for 42 can occur in the dimethyl series, the alternative substitution results in different behaviour (for example, in sulphuric acid); the alternative dehydrating conditions (heating in boric acid) cause extrusion of an angular methyl group to give (48, R=H) rather than rearrangement without carbon loss, leading as this would, to (48, R=Me)[32]. Finally, isolation of an additional bicyclic system in the form of (46, R=Me) supports the suggested mechanisms[24g] for the rearrangements. Current work on the acetolysis[27] of the separated tosylates (39a and 39b, $R=SO_2C_6H_4CH_3$), should lead to additional

results pertinent to these mechanisms. It seems likely that the bicyclo(4,2,1)nonane and subsequent bicyclo(3,3,0)octane systems arise by trans-antiparallel participation of the C_1-C_9 bond in elimination of the equatorial 2-substituent, as indicated in space formulae 51 et seq.

To return to the synthetic aspect - the low yield (23%) of the ketone (37), and the necessity for tedious separation from rearranged material made the above route an unattractive proposition. Various routes to the keto-aldehyde (41) were then considered. Since alkylation as an initial step was feasible, if not completely satisfactory, alternatives were applied. Alkylation of 8 with allyl bromide, to give (52, R=CH=CH_2) and with propargyl bromide, to give (52, R= C≡CH) both proceeded in moderate and poor yields respectively.[27] Conversion of the acetylenic ketone to the keto-aldehyde (41) by hydroboration[33] would have been a feasible continuation, but the alkylation yield eliminated the usefulness of that route. The allyl ketone (52, R= CH=CH_2) could be similarly converted to the primary alcohol (53, R=CH_2OH) but further development would then be difficult, since the main problem in these initial stages would be the dearth of efficient methods of obtaining aliphatic aldehydes. In addition, competitive reductions of the ketonic carbonyl group would surely complicate the processes.

In contrast to the use of acrolein, mono-Michael addition of acrylonitrile[34] to the dimethyl ketone (8) could not be satisfactorily controlled. When equi-molar proportions were used, the main product was

the bis-adduct (54, R= CN). An attempt to cyclise the corresponding keto-diacid (54, R= CO_2H) to the diketone (55) in acetic anhydride led to an interesting aside. Contrary to Blanc's rule, and experience in medium-ring chemistry, the monomeric anhydride (56) was formed. The structure was indicated by analysis for $C_{14}H_{22}O$, mass spectrum (molecular weight 252), infrared and proton magnetic resonance spectra, and by reconversion to the parent acid by cold, mild aqueous base treatment.

When cyanoethylation was carried out in the presence of a large excess[35] of the ketone (8), the mono-adduct (53, R= CN) was obtained in low yield. Conversion of this nitrile to the aldehyde (41) by Stephen reduction[36] was unsuccessful[27], as was an attempt to perform an intramolecular condensation in base, to the imino-ketone (57). The only product from the latter reaction was the enol-lactam (58), analogous to products obtained by other workers[37] from 5-oxonitriles. Hydrolysis of the nitrile (53, R= CN) and also of the enol-lactam (58) in aqueous base, afforded the crystalline keto-acid (53, R= CO_2H).

A more specific route to the latter keto-acid was developed. Cyanoethylation of ethyl 1,3-dimethyl-2-oxocyclohexanecarboxylate[38] (59), under strictly controlled conditions[39], led to ethyl 3-2'-cyano-ethyl-1,3-dimethyl-2-oxocyclohexanecarboxylate (60). Aqueous basic hydrolysis then brought about succesive hydrolysis and decarboxylation at the tertiary carbon, and hydrolysis of the nitrile grouping, producing the keto-acid (53, R= CO_2H), identical with the previous sample, in high overall yield.

Loewenthal[40] had introduced a convenient route to the bicyclo-(3,2,1)octane moiety (62) of gibberelic acid derivatives, by cyclisation of the keto-acid system of (61) with boron trifluoride-acetic acid complex, under mild conditions. Similar conversions of the keto-acid (53, R=CO_2H) and of its methyl ester (53, R=CO_2Me) to 1,5-dimethylbicyclo(3,3,1)nonan-2,9-dione (63) could not be induced, nor could the cyclisation of the ester to the diketone, under the influence of potassium t-butoxide be achieved. The inherent stability of the β-dicarbonyl system in 63 was not in question, as it was obtained from bicyclic precursors (see below).

Conversions of the now readily available keto-acid (53, R=CO_2H) or its derivatives, to the keto-aldehyde (41) next received attention. The reduction of esters to aldehydes by di-isobutyl aluminium hydride[41] could not be applied, because of the necessity for preservation of the more reactive, ketonic carbonyl group of (53, R=CO_2Me). In common with the standard Rosenmund technique[42], the more modern hydride methods of aldehyde formation, using lithium hydridotri-t-butoxyaluminate[43] and tri-n-butyl tin hydride[44] require the prior conversion of (53, R= CO_2H) to the corresponding acyl chloride (53, R= COCl). It was hoped that the more reactive halogen would be preferentially attacked by hydride in this case.

The plans at this stage were once again thwarted, by the observation that the acid chloride was spontaneously converted, even at room temperature, to the enol-lactone (64), with loss of hydrogen chloride by some process equivalent to the one indicated in 65. The same

enol-lactone was more conveniently prepared by treatment of the keto-acid (53, R= CO_2H) with sodium acetate in refluxing acetic anhydride[39]. The initial setback caused by the instability of the acid chloride (53, R= COCl) was turned to profit when it was realised that the enol-lactone (64) incorporated a means of protecting the ketonic carbonyl group in (53), while allowing reduction of the terminal function R, now the lactone carbonyl. Parham and Huestis[45] had reported the first complex hydride reduction of an unsaturated lactone to a hemi-acetal, in the conversion of dihydrocoumarin (66) to the hemiacetal (67) of 2-(2-hydroxyphenyl)propionaldehyde. It was hoped that lithium hydridotri-t-butoxyaluminate[43] would at least produce a similar reduction of 64 to the enol-hemiacetal (68) of the required keto-aldehyde (41).

In the event, the result was even more gratifying on several counts. An excellent yield of the hydroxyketones (39, a,b,; R= H) was obtained in this one step. Moreover, the bulky hydride had a stereospecific function; the product obtained by isolation in acidic conditions contained the crystalline, 'axial' epimer (39a, R= H) in large enough predominance (ca. 90%) over the equatorial epimer (39b, R= H) to allow separation of the former in a pure state. Since only the epimer (39a, R= H) led to the required unsaturated ketone (37), as will be described below, the result of the hydride reduction was especially favourable, and marked the successful conclusion of the search for an efficient route to our key synthetic intermediate.

The rearrangement which accompanies hydride reduction of the enol-lactone (64) is analogous to that encountered in construction of ring A (71) in steroid syntheses[39,46], after addition of Grignard reagents to enol-lactones (69). The bridged intermediate (70) was shown[46] to consist of a mixture of epimers, the one having an axial hydroxyl being predominant. Mechanistically, the stereospecificity of the product indicates that nucleophilic attack of hydride ion (or the anionic Grignard moiety) on the lactone carbonyl is not followed by a ring-opening (72-73, R= complex hydride residue) during work-up, since any similar process would be followed in turn by a thermodynamically controlled closure to a different mixture (39a + 39b) of hydroxy-ketones (R = H). Although this leaves an explanation based on intra-molecular change, current mechanistic suggestions[47,48] involving what is essentially a four-centre reaction, indicated in the present case by 74, seem doubtful to us. Consequently, current work in these laboratories is being directed towards a more satisfactory explanation.

Although the hydroxyketone (39a, R= H) was the major product when the reaction was worked up in acid, failure to add the latter - by destroying the hydride complex with water alone - gave a liquid mixture of epimers (39a = 39b; both R= H) which appeared to have the same composition as the mixture obtained by aldol closure of the acetal (38) in the earlier work. Equilibration of the two β-hydroxyketones, via the open keto-aldehyde (41) - in base, but not in acid - was suspected, and verified in the following manner. The mixture of hydroxyketones was oxidised with chromium trioxide[49] to a single diketone (63), and

and reduction of this, with one mole of lithium hydridotri-t-butoxy-aluminate[43] gave the liquid epimer (39b, R= H) distinguishable from the crystalline epimer in its spectroscopic and chromatographic behaviour. A series of experiments, making use of thin layer chromatographic analysis, was then devised to investigate their equilibration. (These experiments, and others relating to the configurational assignments to (39a, R=H) and (39b, R= H) are described in detail in Appendix B to the main experimental section.)

It was found that both pure epimers were recovered unchanged after prolonged treatment with strong aqueous acid at room temperature. Parallel runs in aqueous base, however, separately converted the epimers to a common equilibrium mixture, in which the liquid epimer (39b, R=H) predominated (ca. 3:1) as in the product from the acetal (38). The relationship between the various products was checked by formation and subsequent separation (when necessary) of toluene-p-sulphonates . A tosylate, m.p. 145°, was obtained from the crystalline hydroxyketone (39a, R= H) and also, in low yield, from the the equilibrium mixtures. A second tosylate, m.p. 114°, was obtained from the liquid epimer (39b, R= H), and also, in higher yield than the first, from the same equilibrium mixtures.

Further reduction of the crystalline hydroxyketone (39a, R= H) with lithium aluminium hydride afforded a diol mixture (75 + 76) from which the sulphite ester (75a) of the diaxial diol (75) was obtained in high yield, by treatment with thionyl chloride in pyridine.[46]

Solutions of this diol mixture, at high dilution, exhibited both free and intra-bonded hydroxyl bands in the infrared, at 3634 and 3526 $cm.^{-1}$ respectively. On the other hand, the diol mixture (77 + 78), obtained by similar reduction of the liquid epimer (39b, R= H) showed no such evidence of intra-hydrogen bonding.

It can be seen from models that no matter what conformation (see Part III) is adopted by any of the four possible 1,5-dimethylbicyclo-(3,3,1)nonan-2,9-diols (75-78), only one, the 'diaxial-in-twin-chair' member, 75, in which the two oxygen atoms are about 2.5 Å distant, is capable of internal hydrogen-bonding, and of conversion to a cyclic sulphite ester (75a). The assigned configurations (39a and 39b, R= H) for the crystalline and liquid epimers are also supported by the expected predominance of the more stable (equatorial) epimer in equilibrium mixtures. Gas-liquid chromatograms, for elevated temperatures, reveal a unique peak for either of the hydroxyketones or for mixtures. Co-chromatography can be excluded as a possible explanation since the same behaviour was observed under several sets of conditions and by the observation (see Part IV) that the simple 2-hydroxy analogues (9-desoxycompounds) were easily separated by the same technique. It seems most likely that both epimers are completely converted to the open aldehyde (41) under the high temperature conditions employed in this technique.

Perhaps the most striking evidence for the assigned configurations (39a and 39b; both R= H) comes from the reactions of the corresponding

tosylates mentioned above. The axial tosylate (39a, R= $SO_2C_6H_4CH_3$) was converted smoothly into the unsaturated ketone (37) in excellent yield, by treatment with sodium ethoxide in boiling ethanol, over twenty hours. The trans-antiparallel elimination of toluene-p-sulphonic acid is depicted in 79. On treatment of the same epimer with lithium aluminium hydride, the reduction of the carbonyl group occurred first, and only from the less hindered side distant from the bulky aromatic group, as depicted in 80. Sluggish hydrogenolysis[50] of the tosylate group, to give the saturated 9-hydroxycompound (80b) in low yield (18%) occurred simultaneously with β-elimination of tosylate (also depicted in 80), which led to a higher yield (54%) of the sterically pure syn-2-en-9-hydroxy-compound (80a) . Both products are described in Part IV (80a = (168, R= H); 80b = (172, R= H)).

The behaviour of the equatorial tosylate (39b, R= $SO_2C_6H_4CH_3$) was very different. In this case, trans-antiparallel participation of the C_1-C_9 bond, after nucleophilic attack at the central carbonyl group by ethoxide ion (as in 81) led to a quantitative yield of ethyl 1,5-dimethylcyclo-oct-4-ene-1-carboxylate (82, R= CO_2Et) in a few minutes at 50°C. Hydride reduction of the tosylate afforded as major product (75%) the corresponding primary alcohol (82, R= CH_2OH) , again by hydride attack on the central carbonyl, with concomitant (?) ring opening, presumably leading to the aldehyde (82, R= CHO), which would be further reduced by excess reagent to (82, R= CH_2OH) . Competing hydrogenolysis[50] of the tosylate group, and carbonyl reduction, accounts

for the simultaneous formation of 80b (16%). The relationship between (82, R= CO_2Et) and (82, R= CH_2OH) was checked by reduction of the former by lithium aluminium hydride, to an alcohol identical with that obtained by the reductive ring-opening reaction.

These results provide a clear explanation of the steric necessities for ring-opening, earlier observed in our laboratories[51]. In that case,(presumably) epimeric tosylates (83) with sodium ethoxide (0.5 moles) gave a moderate yield of cyclo-octene diester (84) and unchanged tosylate (the axial epimer) in a few minutes. When a molar quantity of base was used, and the reaction time prolonged, the mixture produced (obviously 84, along with the simple β-elimination product 43) could not be resolved. It should be mentioned that the structure of 85, derived from 84 by hydrolysis and decarboxylation, was proved by ozonolysis to the keto-dicarboxylic acid (86), which was then synthesised by an unambiguous route[51].

Returning once again to the synthesis of the tricarboxylic acid (2) - the base elimination from (39, R= $SO_2C_6H_4CH_3$) could now be used as an excellent source of the required unsaturated ketone (37). A second route to 37, from the keto-ester[24g] (43) was also developed. Exhaustive reduction of this ester with lithium aluminium hydride gave a crystalline mixture of diols (87, R= CH_2OH). Selective esterification to the primary mono-tosylates (87, R= $CH_2OSO_2C_6H_4CH_3$), which were hydrogenolysed[50] with the same hydride reagent to the mixture of epimers (87, R= CH_3) and finally, oxidation with chromium

trioxide[49], to the ketone (37) completed the conversion from 43 in an overall yield of about 80%.

The next phase of the synthesis involved elaboration of the central carbonyl function in 37. The results of Parker[21] (see p. 9) and also the lack of reactivity[27] of 37 towards methoxymethylenetriphenylphosphorane, eliminated Wittig and Knoevenagel reactions as likely means of reaching the immediate target, 88, where R was, or could be converted to, carboxyl. Difficulties arose from (a) steric hindrance to reagent approach, and (b) unfavourable crowding between R and either one of the bridgehead methyl groups in 88, once the exo-double bond on C_9 was formed. This was evidenced[52] in the steric inhibition to planarity of the αβ-enal system of 89, which has similar crowding around the two-carbon chain, and in the instability of compounds (88, R= CHO) and (88, R= CO_2H) prepared later in this work. The absence of one bridgehead methyl group relieves this situation very markedly - Corey[53] obtained the enol ether (90) in 90% yield, by reaction of the corresponding bridged ketone with methoxymethylenetriphenylphosphorane.

Reformatsky addition[54] of ethyl bromoacetate to the ketone (37), under forcing conditions, afforded the hydroxy-ester (91, R= Et), which was isolated as the corresponding crystalline hydroxy-acid (91, R= H) after alkaline hydrolysis of the crude product. Depending on the conditions and isolation procedure, yields of 15-30% were obtained. An alternative route[55], from 37, via the ethoxyethynyl carbinol (92), rearranged[55] in dilute sulphuric acid to (91, R= Et),

led to the same acid (91, R= H) in 20% yield. The analogous 3-oxa-bicyclo(3,3,1)nonane compound[21] (29, R= CO_2Me, R'= =O), and hindered ketones in general[56] are known to undergo Reformatsky and related reactions[56] in moderate-to-poor yields.

All recorded methods[54] for dehydration of β-hydroxy-esters and -acids were carried out on (91, R= Me or H) without success. In a final effort, treatment of the methyl esters (91, R=Me) with thionyl chloride, followed by dehydrochlorination in boiling quinoline (230^{o}) and final alkaline hydrolysis, afforded the unstable αβ-unsaturated acid (93, R= H) in abysmal yield (3%). This exceptional resistance to dehydration was taken to be another indication of the high degree of crowding in the system (88), as compared with the more stable situation in compounds (for example 91,92) where C_9 is tetrahedral, and the substituents lie in a plane normal to the C_1-C_9-C_5 plane through the bridgehead methyls.

Before proceeding with alternatives to Reformatsky addition to 37, a more direct route, to the nitriles (94, R= CN) as precursors of the C_{11}-tricarboxylic acid (3), was attempted. A mixture of the epimeric methanesulphonates (94, R= OSO_2Me), which are described in Part IV, was treated with sodium cyanide in dimethylformamide at room temperature, in the hope that a simple substitution[57] might occur. In fact, only unchanged material was recovered. At higher temperature, elimination of methanesulphonic acid, with rearrangement (see Part IV) produced a mixture of hydrocarbons.

It was expected that nucleophilic attack of a linear reagent on the hindered carbonyl of 37 would produce more favourable results than Reformatksy addition. Treatment of 37 with sodium acetylide in dimethylformamide, a technique[58] known to be especially suitable for hindered ketones, gave a crystalline mixture of the ethynyl carbinols (95, R= OH) in excellent yield. Normal acetylation techniques are unsuitable for such hindered hydroxyl groups; accordingly, the elegant method of Attenburrow et al.[59] was employed. Addition of one molar equivalent of ethyl magnesium bromide to the carbinols (95, R= OH), followed by treatment with acetic anhydride, afforded the epimeric crystalline acetates (95, R= $OCOCH_3$) in 60% yield.

The work of Landor and Landor[52] supplied the analogy and conditions for the next two stages in the synthesis. Pyrolysis of a suspension of the ethynyl acetates (95, R= $OCOCH_3$) and zinc oxide, in silicone oil at 200°, followed by distillation, afforded the liquid allene acetate (96, R= $OCOCH_3$) in 90% yield. The spectroscopic data on this compound which is formed by the cyclic reaction depicted in 97, was in agreement with that reported by Landor and Landor[52] for similar compounds. Being the enol-acetate of the αβ-unsaturated aldehyde (88, R= CHO), the allene acetate was readily hydrolysed[52] to the latter, in dilute methanolic hydrochloric acid at room temperature. This crystalline aldehyde decomposed to intractable polymer on standing at room temperature over a few days, or less. This instability probably arises from the interaction of the methyl and formyl groups, which is certainly

as severe in (88, R= CHO) as in the previously described aldehyde (89), as seen by examination of molecular models. The comparatively low intensity of absorption (ε 5418) at 248 mμ in the ultraviolet , recorded for 89, was attributed[52] to steric inhibition of conjugation by the methyl groups, which forbid planarity of the αβ-enal chromophore. The situation in (88, R= CHO) is, if anything, more serious, the bridged system preventing the adoption of pseudo-planar conformations to relieve crowding. Despite this, the ultraviolet maximum at 244 mμ for (88, R= CHO) has a normal intensity (ε 17900). It may be that further conjugation, arising from overlap of the π-orbitals of the isolated double bond and the enal system, across space[60], enhances what would otherwise be a low absorption intensity. There is no striking bathochromic shift, however, which might be expected if this were the case.

Catalytic hydrogenation of the dienal (88, R= CHO) was not specific, leading to the tetrahydro-product (98, R= CHO); Jones' oxidation[49] of this aldehyde led to a sharp-melting crystalline acid (98, R= CO_2H), confirming that saturation of the isolated bond leads to a symmetrical structure incapable of stereoisomerism at C_9.

Specific hydrogenation of the conjugated double bond in (88, R= CHO) was achieved by use of lithium in ammonia[61] but the reaction did not proceed to completion. Mixtures of the enol (88, R= CH_2OH), the dihydro-aldehyde (99, R= CHO) and the dihydroalcohol (99, R=CH_2OH) were obtained, but no efficient separation could be effected on a

large scale. However, when the crude product was treated with manganese dioxide in chloroform at room temperature, only the unwanted allylic alcohol (88, R= CH_2OH) was affected, being oxidised to the starting dienal (88, R= CHO). The reduction with lithium in ammonia was then repeated. By means of this recycling technique, the proportion of the desired mono-unsaturated alcohol (99, R= CH_2OH) in the mixture, was increased. Reduction of (88, R= CHO) with sodium in alcohol produced similar results. Reactions designed to confirm the relationships between the various products, the starting material and the required acid (99, R= CO_2H) , are summarised below:

(i) (99, R= CHO) and (99, R= CH_2OH) $\xrightarrow{CrO_3}$ (99, R= CO_2H)

(ii) (88, R= CH_2OH) $\underset{\leftarrow NaBH_4/MeOH}{\xrightarrow{MnO_2/CHCl_3}}$ (88, R= CHO)

(iii) (88, R= CHO) $\xrightarrow{'AgOH'/base}$ no reaction

(iv) (88, R= CHO) $\xrightarrow{CrO_3,\ 50^\circ}$ (88, R= CO_2H) , 10%
+ (88, R= CHO) unchanged
+ 37

(v) Crude Li/NH_3 product $\xrightarrow{CrO_3,\ 0^\circ}$ (99, R= CO_2H)
+ (88, R= CO_2H), trace
+ (88, R= CHO)
+ 37

Reaction (i) represents the route to the desired epimeric bicyclononylacetic acids; (ii) provides a chemical indication of the

structure of the allylic alcohol (88, R= CH_2OH) produced by carbonyl reduction alone, from the dienal (88, R= CHO); (iii) confirms the earlier comments on steric crowding involving the formyl group in (88, R= CHO), while (iv) indicates that oxidative attack of the conjugated double bond, leading to the ketone (37) competes favourably with attack at the aldehydic carbon (see also (v)); the αβ-unsaturated acid (88, R= CO_2H), although impure, was essentially identical in the infrared spectrum with the acid (93, R= H) obtained earlier by dehydration of the Reformatsky product (see p.25).

There was nothing to be gained from tedious purification on a large scale, immediately after the lithium in ammonia reduction step. The crude mixed product obtained by recycling (88, R= CHO) in the reducing step, was therefore oxidised (see reaction (v) above) and the neutral material discarded. The acidic fraction was esterified (diazomethane) and the mixture of epimeric esters (99, R= CO_2Me) purified by chromatography. A full literature search revealed no alternative methods of performing the specific reduction of the conjugated double bond, and since the above procedure led to an acceptable yield of the required esters (99, R= CO_2Me) - about 25% overall from (88, R= CHO) - in three steps, no more elegant route was sought.

At this stage, it was necessary to separate the epimeric mixture (99, R= CO_2Me) into its components, the syn-ester (100, R= CO_2Me) and the anti-ester (101, R= CO_2Me) and to characterise each of them.

Analytical gas-liquid chromatograms revealed two components, 'ester A', the less polar, and 'ester B', in the ratio 1:2. On a preparative scale, ester A was obtained as a colourless liquid, and ester B as a crystalline solid, m.p. 28-29°. The configurations which were finally established will be assumed at this stage to simplify the following discussion - viz., ester A is the syn-epimer (100, R= CO_2Me) and ester B, the anti-epimer (101, R= CO_2Me). Specimens of the corresponding acids A and B (100 and 101, R= CO_2H) and alcohols A and B (100 and 101, R= CH_2OH) were prepared by standard methods. The physical and chemical data for all six compounds were consistent with their respective formulations as to gross structure (99, R= CO_2Me, CO_2H and CH_2OH) . The sections (i) - (iii) below, with reference to Tables 1 and 2, and Figures 1 (a) - (d), deal with the assignment of stereochemistry to the series A and B, epimeric at C_9.

(i) Mode of formation

Electronic aspects of lithium-in-ammonia reduction and the nature of transition states[62] are difficult to assess in this case. From a qualitative point of view, access to the conjugated double bond of the enal (88, R= CHO) is easier from the 'cyclohexenyl' side (projection 102) than from the cyclohexanyl side (103). A predominance of the anti- (101) over the syn - (100) system would be expected from the reduction, and this prediction was in accord with the anti:syn ratio of 2:1 for the ester mixture obtained.

TABLE 1

Infrared Spectra of the Series 'A' and 'B'

Ester A	Ester B	Acid A	Acid B	Alcohol A	Alcohol B
Normal Concentrations in Carbon Tetrachloride: ($cm.^{-1}$)					
3014	3016	3563	3538	3637	3638
2950	2950	3015	3016	+	+
2933	2934	1757*	1760*		
2908	2907	1708	1708	inter-	inter-
2870	2870	1646*	1656*	hydroxyl	hydroxyl
2843	2848	1377	1375	hump.	hump.
2825	2832	1370	1373		
1742a	1743b	1308	1306		
1679*	1656*	1292	1288	3013	3018
1433	1433				
1370	1370	etc.	etc.		1656**
1307	1304				
1286	1288				
	1262				
1155	1158				
1029	1022				
997	1000				
High Dilution, in Carbon Tetrachloride:					
				3636	3638
				3538	***
Normal Concentrations, in Carbon Disulphide:					
970	991			708e	709f
854	965				
832	855				
707c	705d				
High Dilution, in Carbon Disulphide:					
		710	712		
		674	694		

$\Delta\nu_a^{\frac{1}{2}}$	$cm.^{-1}$
a,	19
b,	19
c,	17
d,	9
e,	8
f,	8

* Weak, obscured by strong $\nu_{C=O}$ band

** Distinct band, not resolved from background in alcohol A.

*** No distinct intra-bonded hydroxyl band.

TABLE 2

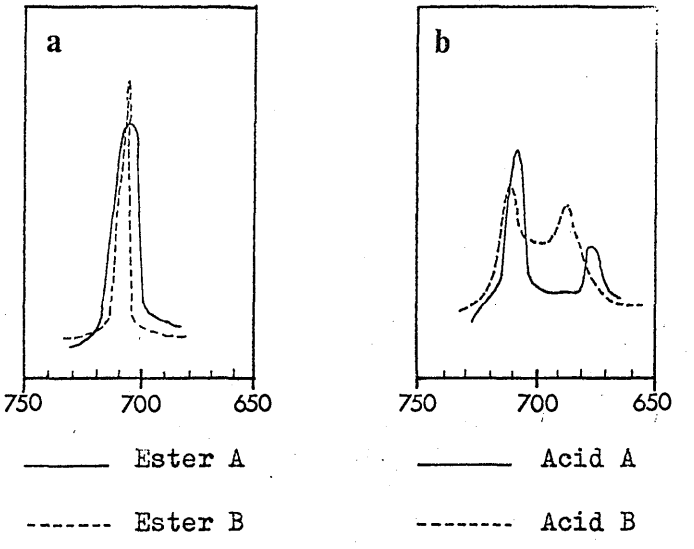
P.M.R. Spectra of Esters A and B*

Ester A (100, R= CO_2Me)			Ester B (101, R= CO_2Me)		
τ**	No. of protons	Assign-ments	τ	No. of protons	Assign-ments
9.15	3	a	9.20	3	a
9.07	3	b	9.10	3	a
8.60	6	c	8.90		
			8.79)	7	c + d
			8.60)		(d?)
8.20	3	d + e	8.02	2	e
7.86	2	f	7.77	2	f
7.77)			7.69)		
6.39	3	g	6.40	3	g
4.91	1	h	4.88	1	h
4.75)			4.72)		
4.30	1	i	4.40	1	i
4.10)			4.25)		

* Compare formulae 104 - 106

** Tetramethylsilane, as internal reference, τ = 10; carbon tetrachloride solutions; 60Mc/sec.

Fig. 1 (a-d) : Details from high resolution infrared spectra ($cm.^{-1}$) of C-9 epimeric series A and B.



(ii) Infrared spectra of series A and B

d in Table 1; the background

with detailed discussion and

references to similar cases can be found in Part II of this thesis.

(a) Electronic interaction caused by the proximity of the carbomethoxyl group and the double bond account for broadening of the olefinic C-H out-of-plane deformation band ($\gamma_{=C-H}$) in the spectrum of ester A (100, R= CO_2Me) where this band, at 707 $cm.^{-1}$, has a half-band width ($\Delta\nu^a_{\frac{1}{2}}$) of 17 $cm.^{-1}$ For comparison, ester B (101, R= CO_2Me), which cannot support such an interaction, exhibits $\gamma_{=C-H}$ at 705 $cm.^{-1}$, $\Delta\nu^a_{\frac{1}{2}}$ = 9 $cm.^{-1}$ (see Fig. 1a)

(b) The spectra of the corresponding acids A and B show split $\gamma_{=C-H}$ bands (Fig. 1b). The wider splitting ($\Delta\gamma_{=C-H}$) in the case of the acid A (100, R= CO_2H), of 36 $cm.^{-1}$ (710 and 674 $cm.^{-1}$) indicates closer approach of the polar carboxyl group to the double bond in that case. For comparison, acid B (101, R= CO_2H) shows $\gamma_{=C-H}$ at 712, 694 $cm.^{-1}$, and a $\Delta\gamma_{=C-H}$ value of 18 $cm.^{-1}$

(c) In the alcohols A and B the C=C stretching regions ($\nu_{C=C}$) are significantly different. Alcohol A (100, R=CH_2OH) shows no distinguishable band in the 1650 $cm.^{-1}$ region (Fig. 1c), a situation which may arise from multiplet formation due to the proximity of the hydroxyl group to the double bond. In the spectrum of alcohol B (Fig. 1c) there is a definite and unique $\nu_{C=C}$ absorption band at 1656 $cm.^{-1}$

(d) At high dilution, the hydroxyl stretching (ν_{OH}) region in the spectrum of alcohol A (100, R= CH_2OH) reveals a weak intra-bonded hydroxyl absorption at 3538 $cm.^{-1}$, consistent with partial O-H...π bonding, in addition to the free hydroxyl band at 3636 $cm.^{-1}$ (see Fig. 1d). Alcohol B (101, R=CH_2OH) shows only a free ν_{OH} band at 3638 $cm.^{-1}$, corresponding to the configuration in which intra bonding, O-H...π , cannot occur.

(e) General similarity between the spectra of esters A and B, recorded in Table 1 (total, 41 bands) leaves no doubt that these compounds are structurally identical, differing only in stereochemistry.

(iii) Proton magnetic resonance spectra of esters A and B

The p.m.r. spectra recorded in Table 2 are completely consistent with the assigned structures for ester A and ester B (see 104) . Because of the difficulties in predicting long range shielding or deshielding effects in general, the p.m.r. spectra were not decisive in making stereochemical assignments in these cases. The chemical shifts between corresponding signals in the two esters, however, are worthy of analysis. In each ester, equivalence of the protons (f) (see 104) is indicated by the clean doublet signal for these protons (centred at τ= 7.81, 7.73 respectively, for esters A and B), singly split by the C_9 - methine proton (d), (J_{df} = 5 c.p.s.). In turn, this equivalence

in each case suggests free rotation[63] of the ester group about the carbon bearing the protons (f). If we assume that both the double bond and the ester groups have small shielding effects on various protons in esters A and B, the results, discussed in terms of the extremes of conformation 105 for ester A and 106 for ester B, are consistent.

In ester A, the double bond shields the methylene protons (f), τ = 7.81, in 105(i) ; (cf. 7.73 in ester B). The carbomethoxyl group shields the allylic protons (e), τ = 8.20, in 105(ii); (cf. 8.02 in ester B). In ester B, the double bond apparently shields the methine proton (d), τ = 8.60 or higher, in 106(i); (cf. 8.20 in ester A; base of combined (d) + (e) signal is 8.0 - 8.4); in this case, the assignments cannot be very definite, since the double bond in other compounds (see Part IV) appears to deshield the methine proton. Finally, the ester group shields the ring protons in ester B: for protons (c), τ = 8.6-8.9, centre 8.8. The increased multiplicity of the signal may arise from the effect of the nearby ester group (see 106(ii)). Ester A shows a strong sharp band at 8.60 for the protons (c).

The p.m.r. spectra therefore provide, at least, a self-consistent set of comparisons which correspond with the stereochemistry assigned to the series A and B.

The situation was then very favourable in that the predominant ester B, which was crystalline, also had the necessary stereochemistry (101, R= CO_2Me) for its degradation to the trans, meso-C_{12}-acid (2c). The next phase of the synthesis involved the removal of C_3 and the conversion of C_2 and C_4 to carboxyl groups. This required prior oxidation of the allylic C_4, and to this end we drew on experience gained from allylic oxidations of the related unsaturated esters[29,64,160] (107, R=CO_2Me and 107 R= CH_2CO_2Me), and of 1,5-dimethylbicyclo(3,3,1)-non-2-ene (107, R=CH_3), (see Part IV).

The mixture of epimeric esters A and B was heated under reflux with selenium dioxide in acetic acid. Aftertreatment for longer periods than wereusually necessary, some unchanged ester was recovered. Various reaction times were used, and it became apparent from G.L.C. analysis of products, that ester A reacted much more slowly than ester B. Moreover, the rate difference was sufficient to allow virtually specific oxidation of Ester B, in mixtures of the two. Since this could be used to eliminate the series A more conveniently than tedious preparative gas chromatographic methods (manual temperature programming of 100μl. batches), the oxidative step was carried out on the originally isolated A/B mixture. The product obtained - a mixture of the epimeric allylic acetates (108, R= CO_2Me, R' = $OCOCH_3$) and unchanged syn- ester A (100, R=CO_2Me) - was heated with a catalytic amount of sodium methoxide in methanol. The specific ester exchange so effected, involving only the allylic group in (108, R= CO_2Me, R'= $OCOCH_3$) and chromatographic

separation, afforded 24% of pure, unchanged ester A (100, R=CO_2Me); the epimeric hydroxy-esters (108, R= CO_2Me, R'= OH) were obtained in 78% yield (based on the ester B content of the original A/B mixture). The corresponding crystalline hydroxy-acid (108, R=CO_2H, R'= OH), m.p. 84-98°C was obviously a mixture of C_4-epimers. Jones' oxidation[49] of the methyl esters afforded a crystalline enone-ester (m.p . 59.5-60°) whose analysis, infrared and ultraviolet spectra were consistent with the structure (109, R= Me). The p.m.r. spectrum was also in accord, showing identical doublets centred at τ= 3.90 , (C=C(H)-C=O) and 3.44 (C(H)=C-C=O) , $J_{ab} = J_{ba}$ = 9.6 c.p.s., for olefinic protons in the enone system of (109, R= Me).

Returning to the resistance of ester A (100, R= CO_2Me) to allylic oxidation, this must be due to the presence of the acetic ester side-chain. Since ester B (101, R= CO_2Me) and also the compounds (107, R= Me, CO_2Et or CH_2CO_2Et) undergo reaction with comparable rates, the side-chain in ester B can have no such effect. These comparisons provide very strong chemical evidence in favour of the proposed stereochemistry for esters A and B. It was at first thought that in ester A, the <u>syn</u>- side chain carboxyl group might have an electronic deactivating effect on the double bond, of the type proposed to account for the lack of reactivity of the double bond in certain Δ^3-cyclohexenic compounds. It has been claimed[65] that intramolecular π -interactions (111) in compounds of type (110) causes anomalous difficulty in hydrogenation of the double bond (not observed in the corresponding acetals), lack of general carboxyl reactivity and inertness of allylic bromine atoms. The authors do not quote

spectroscopic features, due to the C=C and C=O π-systems, which one would expect to be considerably modified by intramolecular bonding (111), if that indeed were the cause of such departures from normal chemical behaviour.

After prolonged treatment with selenium dioxide, both ester A (100, R= CO_2Me) and alcohol A (100, R= CH_2OH) do undergo oxidation. The syn-enone-ester (112), derived from the former, was prepared in the manner used to obtain the anti- epimer (109, R= Me). Since the ester and the alcohol of syn-series A were equally more difficult to oxidise at C_4 than the anti- ester B, the lack of reactivity cannot be assigned to carboxyl-olefin π-bonding across space. The absence of striking differences in infrared and p.m.r. spectra of esters A and B support this view. It is probable that the only operative effect of the syn-side-chain in ester A (100, R= CO_2Me) is steric, the rotating group sweeping the more available β-face of the unsaturated ring, and hindering attack at the allylic centre C_4. The C_9-chain in ester B (101, R= CO_2Me) is, of course, too distant from C_4 to exert any steric effect on reaction.

To complete the synthesis, further oxidative techniques were applied to cleave the enone system of 109. Chromic oxide in acetic acid, and ozone were found to be drastic, leading to complex degradation mixtures. A series of hydroxylation experiments, via osmate esters[66], were carried out on model compounds[64], on ester A (100, R= CO_2Me) and on the enone (109, R=Me) itself. The results are summarised below:

Substrate	Product	Yield %
(113, R= =O), model[64]	114, (R= =O)	62
(113, R= -OH), model[64]	114, (R= -OH)	50
(100, R= CO_2Me), model	115*	77
(109, R= Me)	116	37

The yields of hydroxylated material varied with each example, but at this stage, the lowest yield, for the diolone (116) was considered tolerable, provided further steps were less wasteful. Cleavage[67] of the diols(114, R= =O), (114, R= -OH) and (115) however, led to further hydroxy-compounds, although periodate was definitely consumed in all the reactions. This could only be explained by assuming that ring opening had occurred, but that the groups so formed had undergone subsequent change. The yield of product from the diolone (116) was prohibitive, and the hydroxylation method for opening the enone ring of (109, R= Me) was abandoned. Nevertheless, the unusual course of the periodate oxidation[67] in the models were examined further. The crude periodate oxidation product from the diolone-ester (114, R= =O) showed strong hydroxyl and carboxyl absorption in the infrared, but no evidence of the presence of aldehyde (at 2800 $cm.^{-1}$). Further oxidation with chromium trioxide in acetone afforded only a crystalline anhydride-ester (infrared bands at 1805, 1770; 1740 $cm.^{-1}$) in high yield.

* The diol-ester (115) will also be mentioned later (p. 41) in connection with attempts to lactonise the corresponding 2,3-dihydroxy-*syn*-acid.

The triol-ester (114, R= -OH)/periodate product also showed strong hydroxyl absorption, but the carbonyl band, at 1740 $cm.^{-1}$, was weaker than that of the primary product from the diolone-ester (above). Jones' oxidation[49] afforded the same crystalline anhydride, again in high yield.

To explain these results, the dialdehydes (117, R= CHO) and (117, R= H) presumably first formed from (114, R= =O) and (114, R= OH) respectively, must undergo some further change. Intra-molecular hemi-acetal formation, with unavoidable 1,3-diaxial crowding as the driving force, would give rise to the structures (118, R= CHO) and (118, R= H) respectively. Further oxidation would then lead to the anhydride (119) in both cases (with facile loss of carbon monoxide where R= CHO). These suggestions are supported by the infrared spectral characteristics of all the compounds. The significant absence of any of the free dicarboxylic acid from either of the final oxidations, particularly supports the involvement of the cyclic structures 118 (R= H) and 118 (R= CHO). A similar case of spontaneous bridge formation to relieve non-bonded interactions, was provided during the degradation of helminthosporal[68]. The ketodicarboxylic acid (120) and the anhydride (121) are readily converted to the unusual bridged dilactone (122).

The model enone-ester[64] (113, R= =O) was used in investigating oxidations with dilute acidified permanganate. The preliminary test proved very encouraging, since the reagent was rapidly decolourised when added to a solution of (113, R= =O) in acetone at room temperature.

When a permanent excess of reagent was visibly present, the reaction mixture afforded a clean, crystalline acidic product (47%), whose infrared spectrum was consistent with the structure (123). A second, neutral product (16%) was identical with the anhydride obtained earlier from (113, R= =O) by more devious oxidation involving osmate ester cleavage to diol, followed by periodate and chromium trioxide oxidations.

On the basis of this success, the permanganate oxidation was repeated on the enone-ester (109, R=Me). The neutral product (30%) and the acidic product (40%) were both sharp-melting, crystalline solids, whose analyses and infrared data corresponded with the assignments for the required products - (124, R= Me) and (125, R= Me, R'= H) respectively. The dicarboxylic acid was converted to the same anhydride above its melting point.

Both products were smoothly converted by alkaline hydrolysis to the same solid tricarboxylic acid, whose infrared spectrum (KCl disc) was virtually identical with that of an authentic sample of the C_{12}-tricarboxylic acid, kindly supplied by Dr. Jeger of Zürich. After recrystallisation from glacial acetic acid, the authentic and synthetic samples melted over the same ranges, depending on the rate of heating and the particle size. Using the heating rate prescribed by Ruzicka[11], the bulk of both samples melted over the range 208-212° (literature value[11], 212-213°). The sensitivity[11,19] of the melting point, presumably due to the tendency for anhydride formation, reduces the

TABLE 3

Analysis of the Mass Spectrum of Methyl trans, meso-2,6-Dimethyl-2,6-dicarbomethoxycyclohexylacetate, (125, R= R'= Me).

Process			Metastable Ion Mass	
Upper ---	Lower Ion	Loss	Calc.*	Observed
300	268	32	239.5	239.5
269	241	18	216.1	216
209	181	28	156.5	156.5
241	181	60	135.5	135.5
181	149	32	122.5	122.5
149	121	28	98.2	98.2
93	91	2	89	89

* $M = \frac{(\text{Lower Ion})^2}{\text{Upper Ion}}$, approximately, where both ions are abundant.

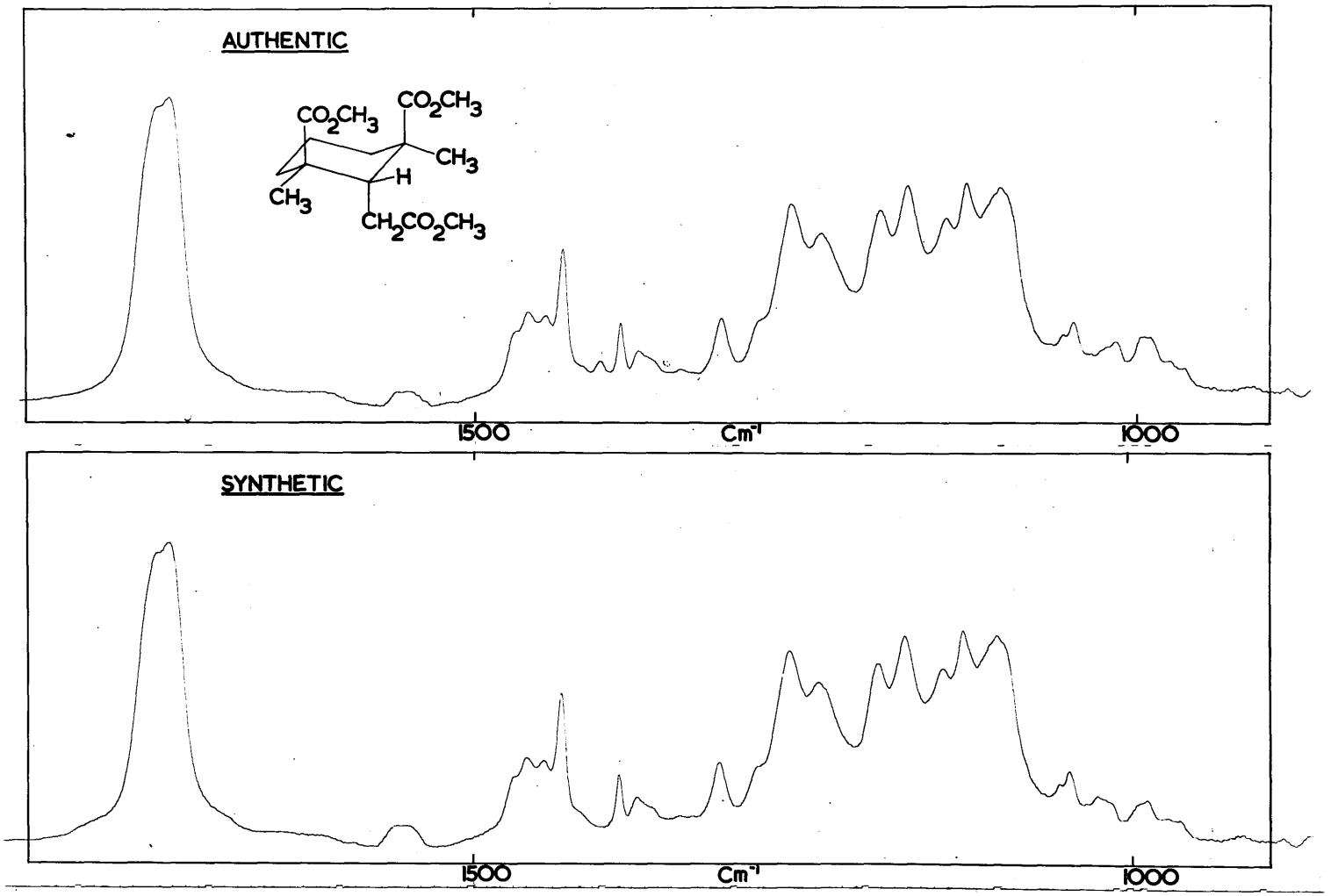

AUTHENTIC
CO_2CH_3
CO_2CH_3
CH_3
H
CH_3
$CH_2CO_2CH_3$
1500
Cm^{-1}
1000
SYNTHETIC
1500
Cm^{-1}
1000

Fig. 2

usefulness of this property as a criterion of identity. Accordingly, the corresponding authentic and synthetic trimethyl esters (125, R= R'= Me) were prepared with diazomethane. Gas-liquid chromatograms of the esters, on three columns at three temperatures, were identical, and the samples pure; thin layer chromatograms, infrared spectra at high resolution (Fig. 2) and mass spectra of the two samples were also identical.

The p.m.r. spectrum of the synthetic triester (125, R= R'= Me) was entirely consistent with the structure assigned to it: quaternary methyls, at 8.85 (τ-value, tetramethylsilane as internal reference); three unresolved ester methyls, at 6.41; triplet centred on 7.90 (J = 5.4 c.p.s.) for the two α-methylene protons, the signal split by the methine proton; a weak quartet at 6.73 (J= 5.4 c.p.s.) is assigned to the methine proton, coupled with the α-methylene protons, and apparently very strongly deshielded by some or all of the ester carbonyls.

A total of 43 significant, common ions were counted in the mass spectrum, (parent peak 300, calculated, 300 for $C_{15}H_{24}O_6$) and the cracking pattern (Table 3) revealed the essential features of the breakdown : loss of CH_3O. and CH_3OH (300 $\longrightarrow$ 269, 268 ion masses); loss of 59 and 60 ($OCOCH_3$ and $HOCOCH_3$) from the parent leads to ions of mass 241, 240; further similar loss, from the second tertiary ester group, leads to ions of mass 182, 181, the most abundant in the spectrum. Loss of the remaining ester group leads to an ion of mass 121; at this

stage, the residual 1,2,3,-trimethylcyclohexane-derived ion of that mass readily loses two one-carbon fragments to give an ion of mass 93. Finally, rearrangement of this C_7 ion would be expected to occur (with loss of two hydrogen atoms), leading to the stable tropylium ion, of mass 91. Some of these processes, and the corresponding observed and calculated metastable ion masses, are recorded in Table 3.

With the proof of the expected trans, meso stereochemistry of the tricarboxylic acid (2) came vindication of the stereochemical arguments employed en route. Even so, during and after the synthesis* many attempts were made to provide direct chemical evidence for the syn relationship of the carboxyl and double bond in acid A (100, R= CO_2H) by lactonisation[69]. Acid B (101, R=CO_2H) was used in several cases as a control .

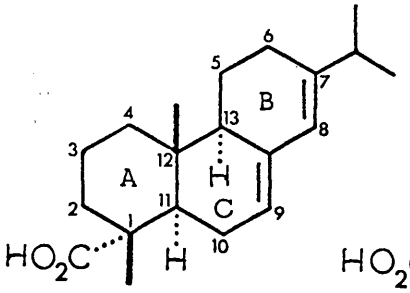
From acid A, with (a) toluene-p-sulphonic acid in refluxing benzene (b) concentrated sulphuric acid (c) boiling 50% aqueous sulphuric acid[69] (d) methanesulphonic acid[70] and (e) boron trifluoride in acetic acid, no lactonic material such as (126, R= H) was recovered. Iodo-lactonisation[71], which was planned to lead from (100, R= CO_2H) to (126, R= I), was also ineffective. Finally, none of the hydroxy-acids derived from 112 and 115, or 127 (from 112 by catalytic hydrogenation, ester hydrolysis and carbonyl reduction) could be persuaded to lactonise.

* See also J. Martin, W. Parker and R.A. Raphael, J., in press.

Treatment (e) above, of acid A led to four acidic (g.l.c. of esters) and six neutral (g.l.c.) products, one of the latter grossly predominating. The infrared spectrum of the neutral fraction was fairly clean, and noteable features were bands at 1740 and 720 $cm.^{-1}$; aqueous alcoholic base produced no change in the product; a solid, orange 2,4-dinitrophenylhydrazone was obtained in good yield. These features are consistent with the formation of the unsaturated ketone (128) by a process involving an acylium ion as indicated in 129, which does compete[69] with acid-induced lactonisation of unsaturated acids. The complexity of the product discouraged a more rigorous examination.

The general applicability of such lactonisation reactions leads us to suspect that some feature peculiar to this bicyclic system is responsible for the uniform lack of success. Assuming thermodynamic control of the acid-catalysed process[69], it would seem that equilibrium does not favour the closed tricyclic structure (130), which is destabilised by a strong C_3-C_7 endo-hydrogen interaction, absent in the unsaturated acid A (100, R= CO_2H); this repulsion (see Part III) is normally relieved by distortion of both three-carbon bridges in the saturated bicyclo(3,3,1)nonane system. The necessary conformational rigidity imposed by lactone formation may increase this destabilisation. Such complications do not apply in the formation of the ketone 129, which would normally be expected[69] to form only a minor part of the product of acid-catalysed lactonisation of (100, R= CO_2H).

PART I [1 – 130]



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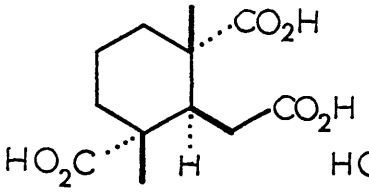

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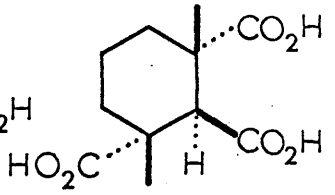

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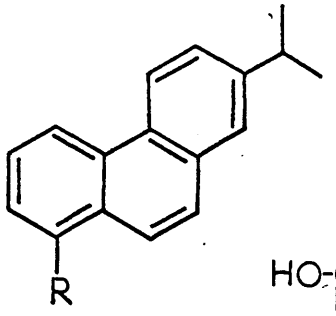

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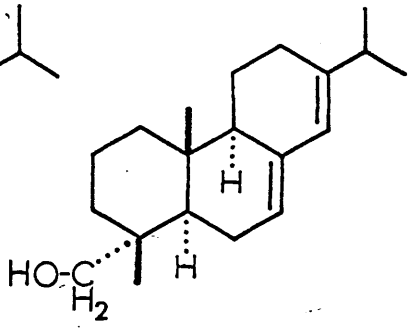

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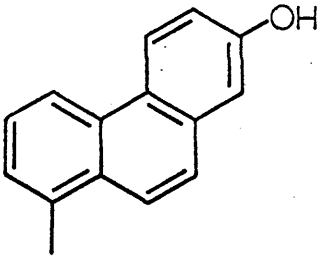

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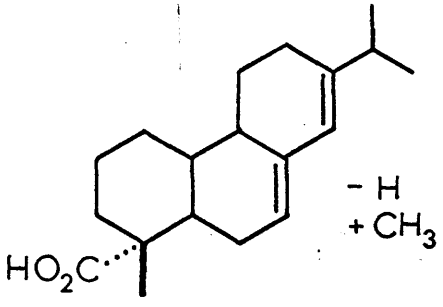

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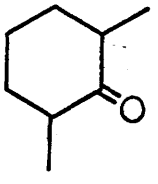

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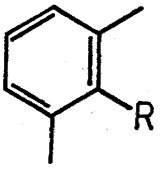

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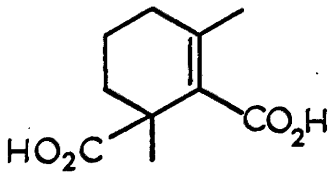

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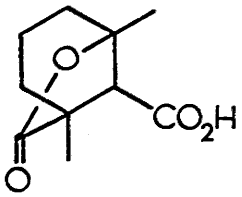

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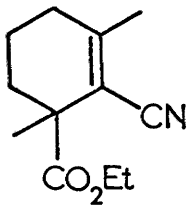

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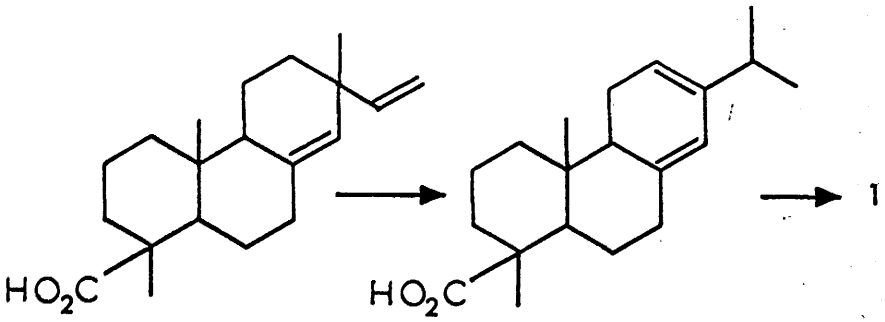

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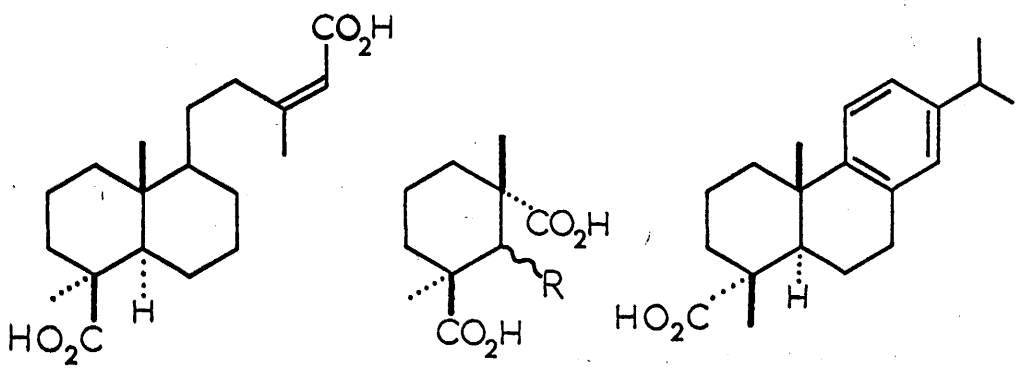

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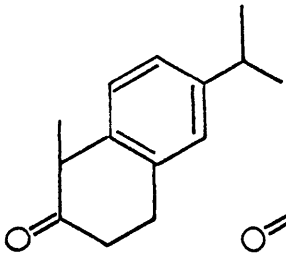

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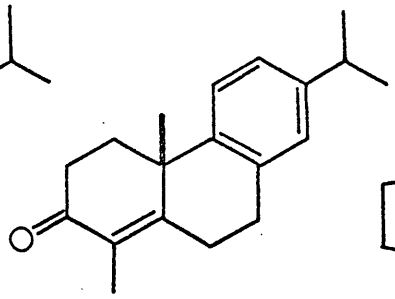

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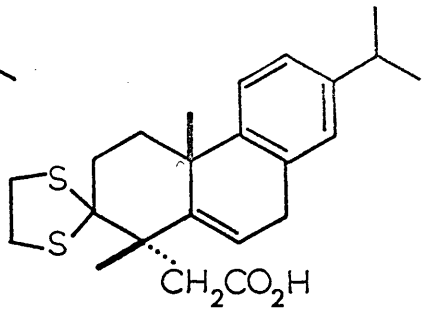

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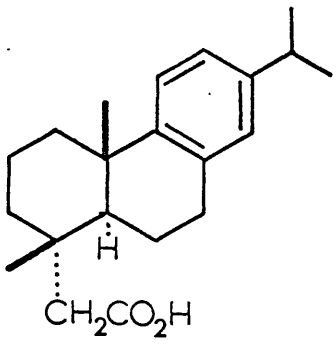

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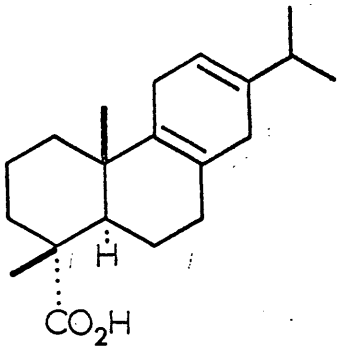

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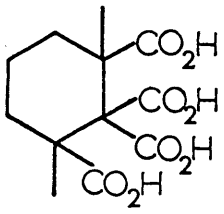

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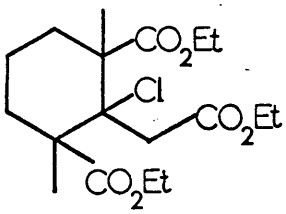

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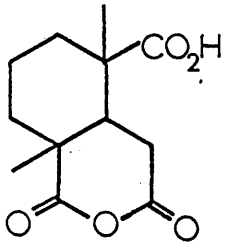

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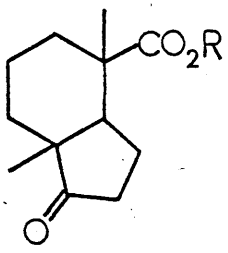

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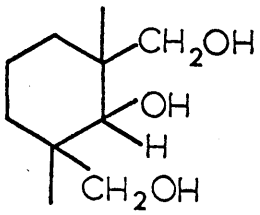

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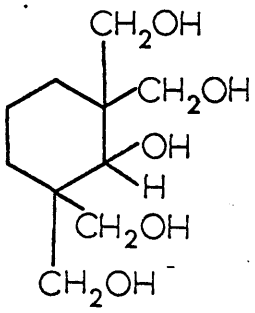

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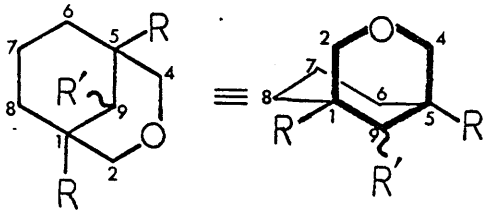

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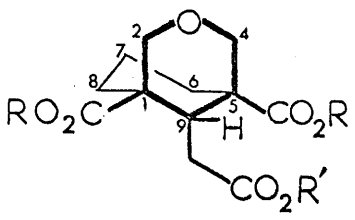

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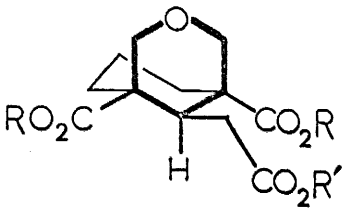

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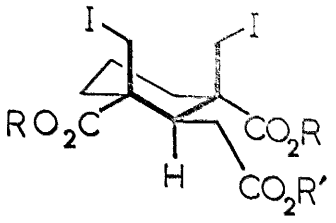

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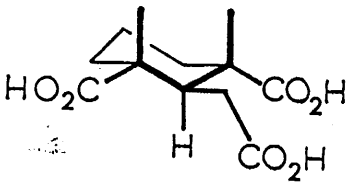

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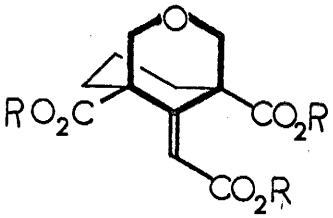

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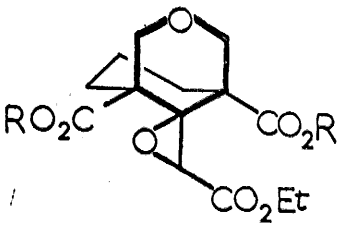

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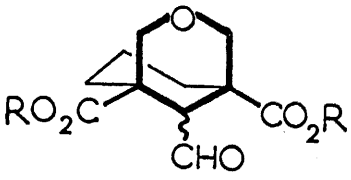

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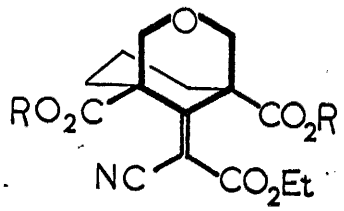

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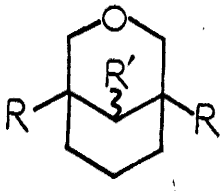

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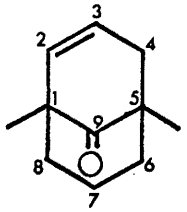

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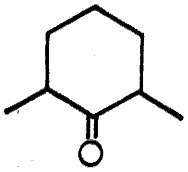

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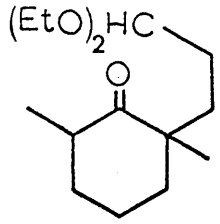

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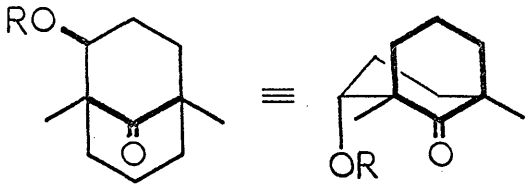

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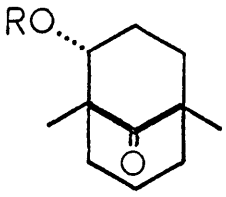

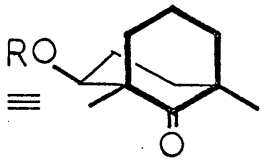

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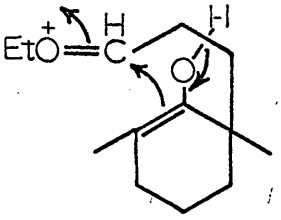

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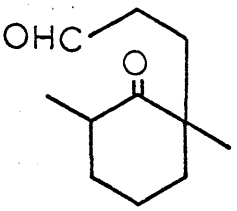

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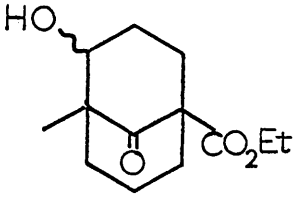

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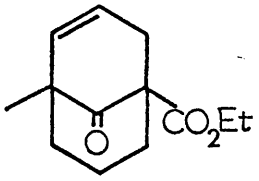

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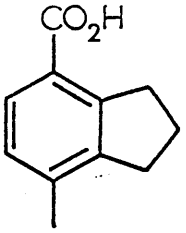

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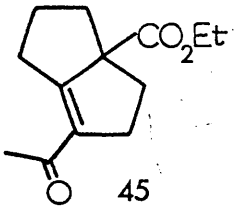

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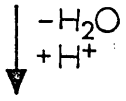
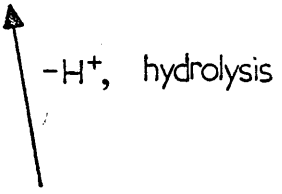
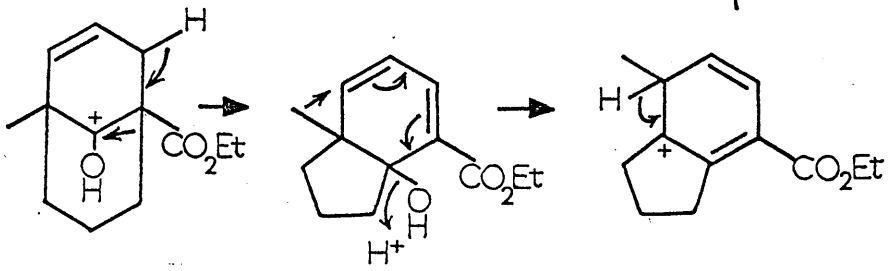


$-H_2O$
$+H^+$

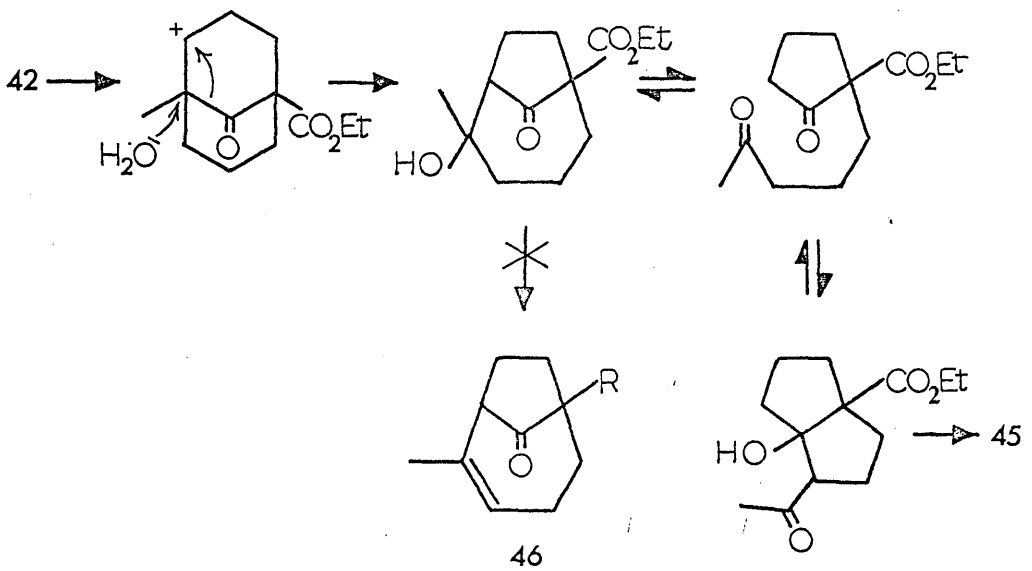


$-H^+$, hydrolysis

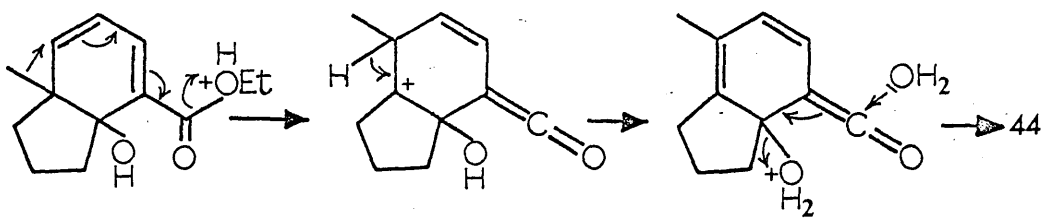
Scheme A

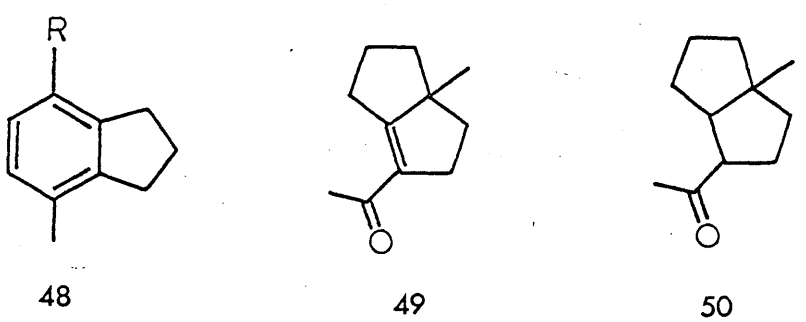


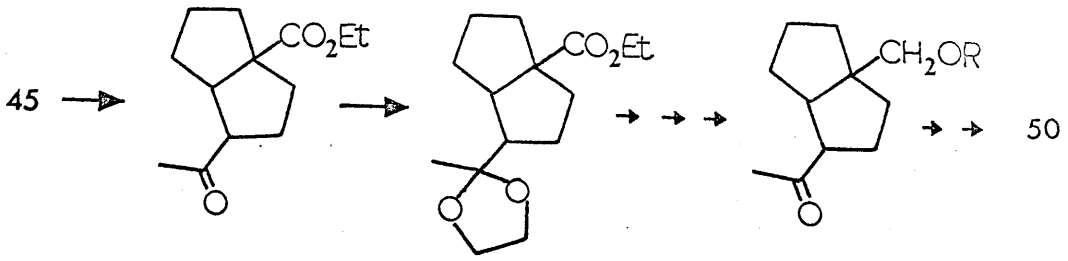
Scheme B

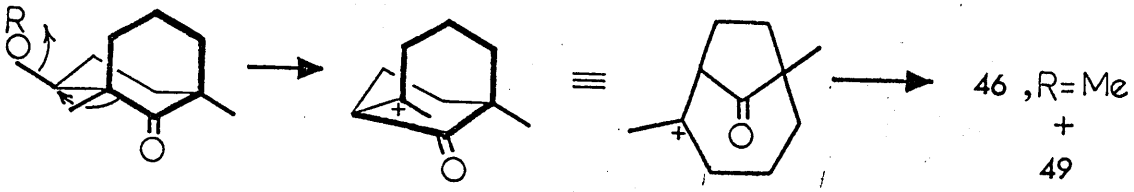


Scheme C









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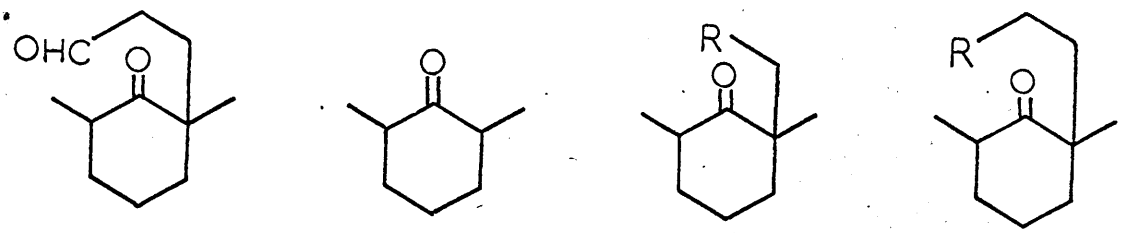

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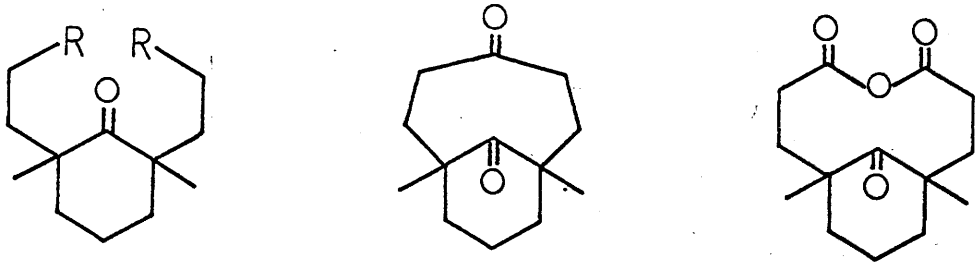

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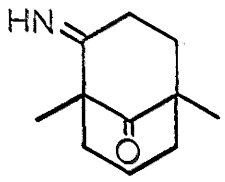

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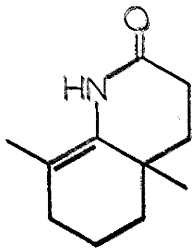

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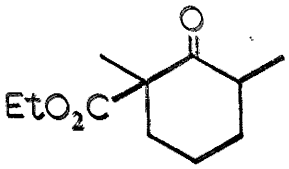

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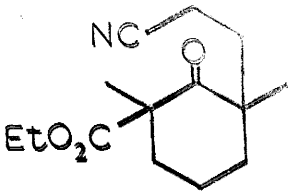

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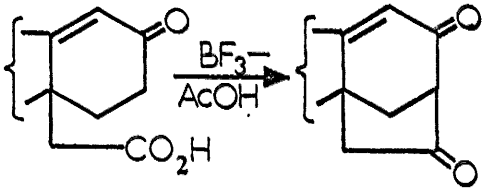

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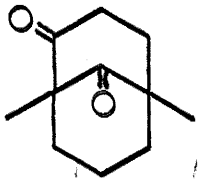

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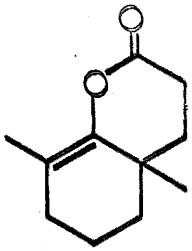

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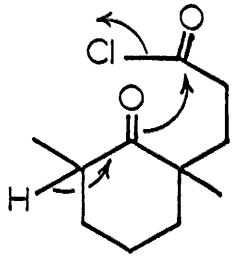

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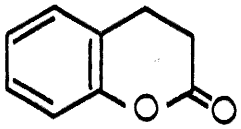

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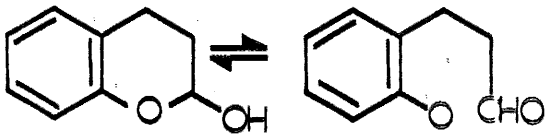

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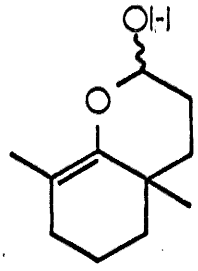

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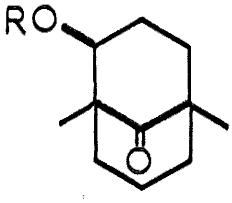

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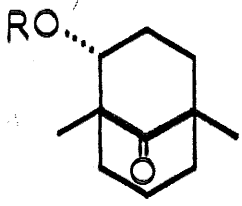

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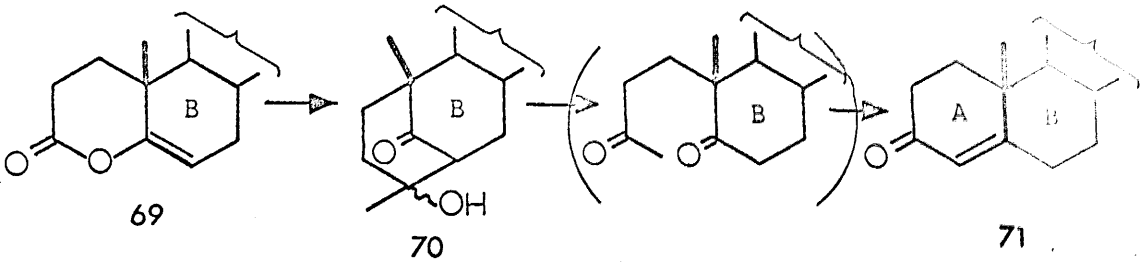

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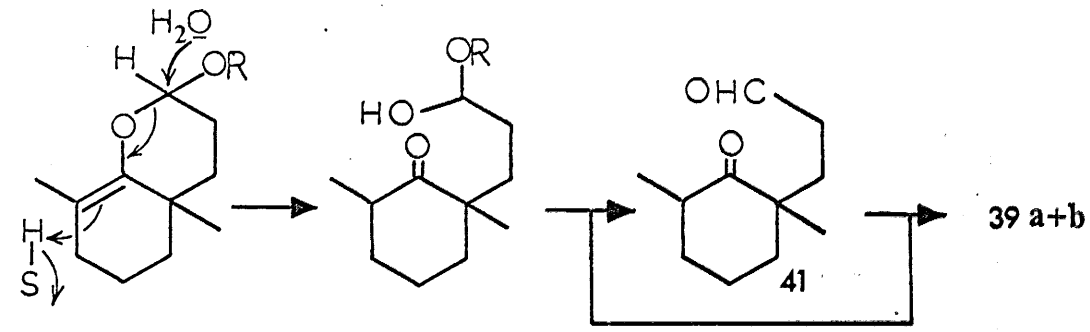

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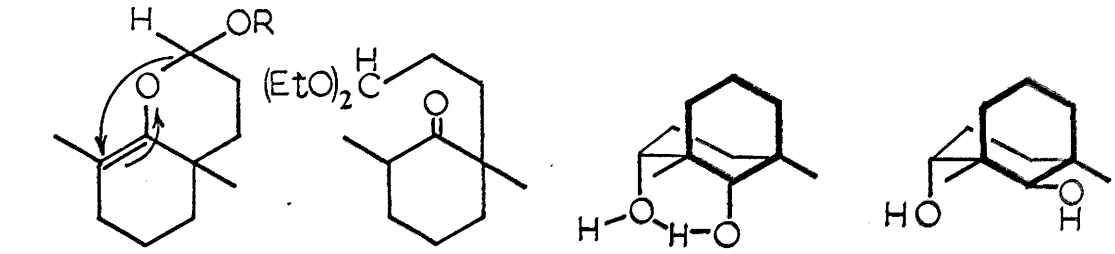

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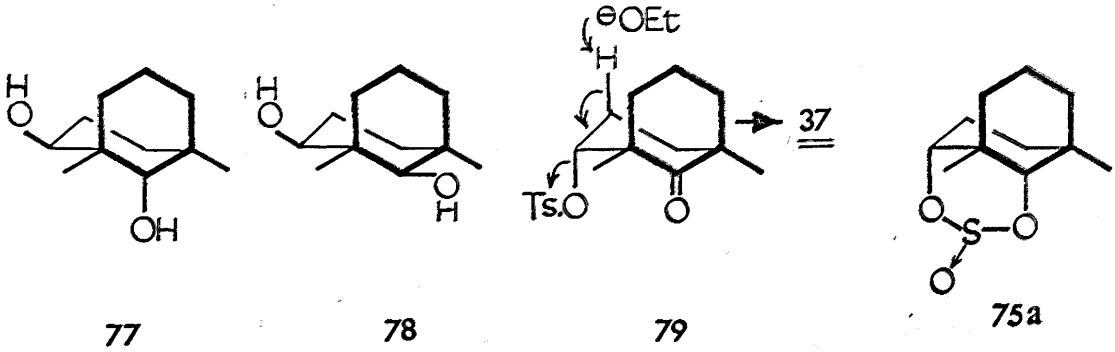

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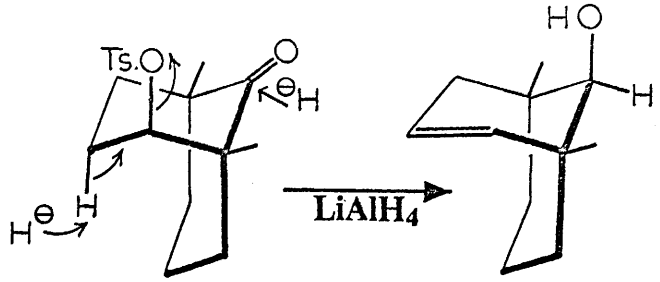
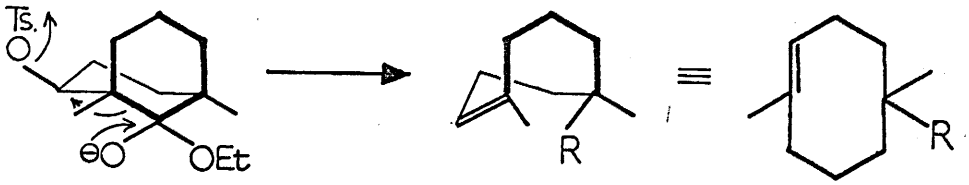


80 80a (168, R = H) 80b (172, R = H)



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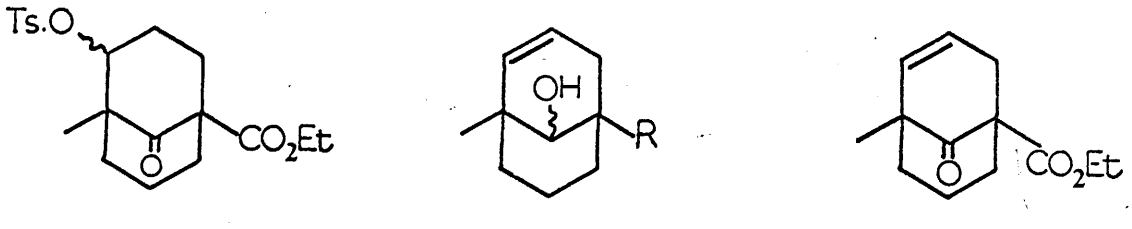

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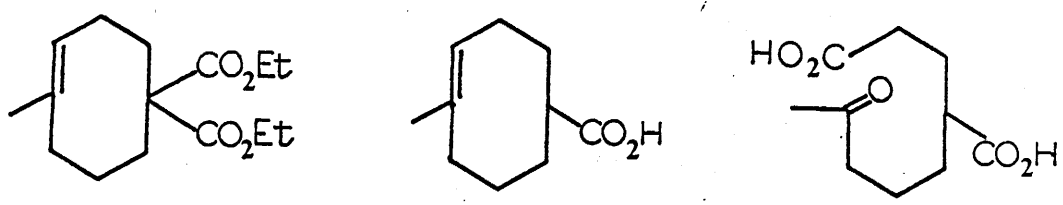

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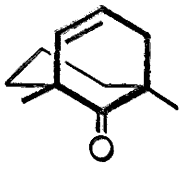

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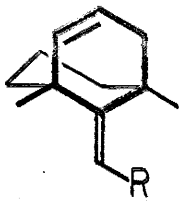

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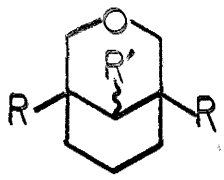

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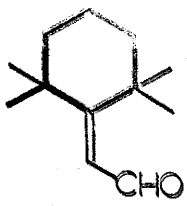

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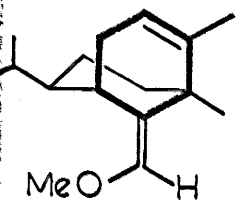

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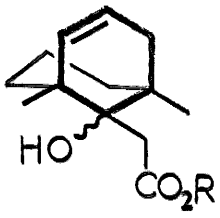

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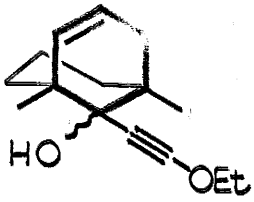

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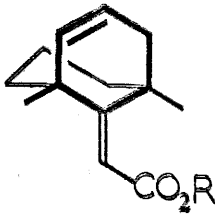

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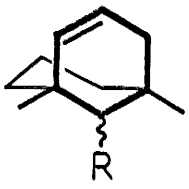

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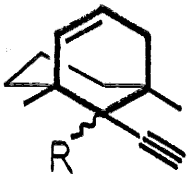

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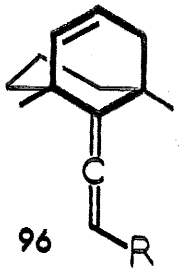

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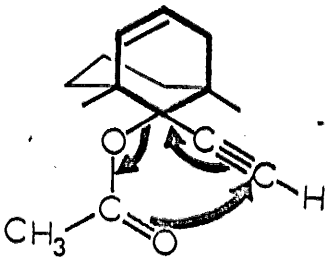

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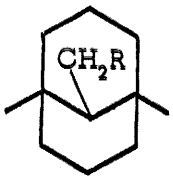

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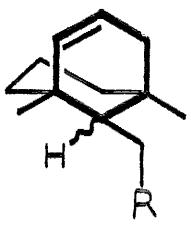

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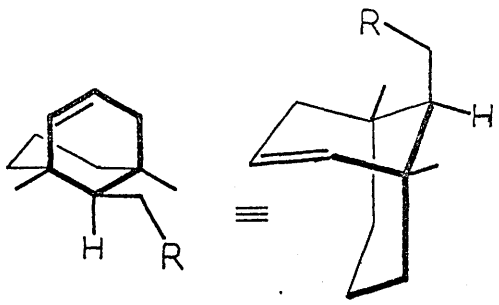

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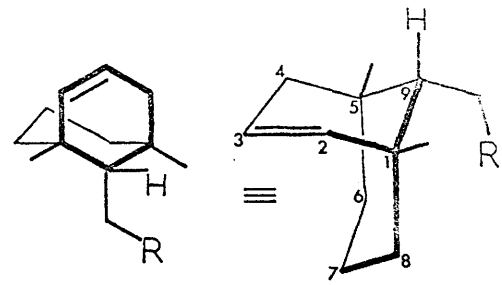

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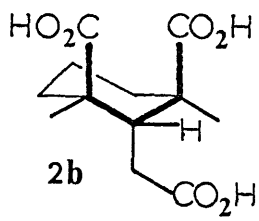

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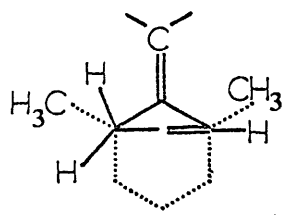

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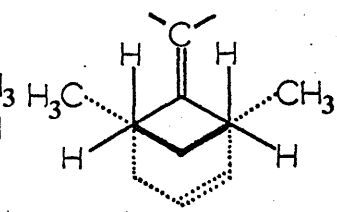

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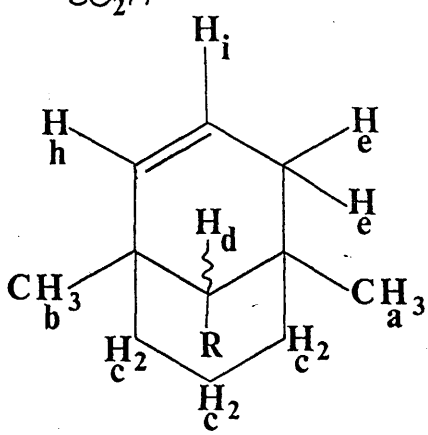

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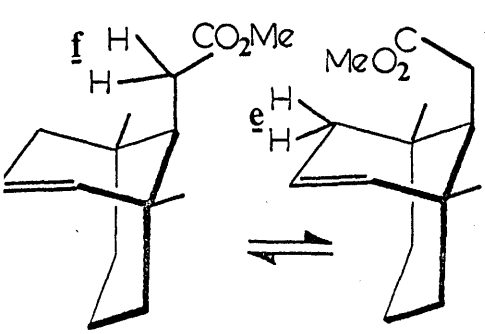
— 104 —



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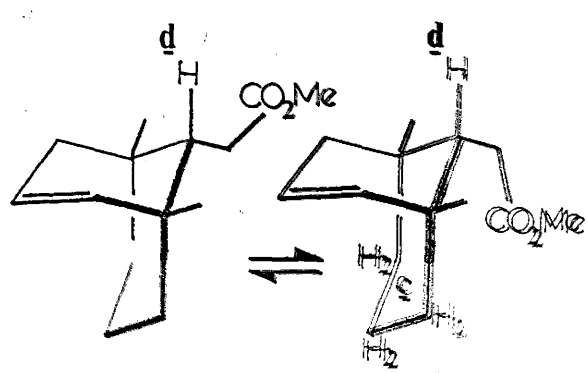

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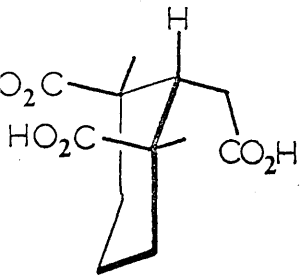

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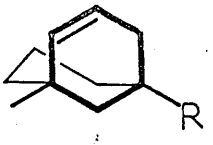

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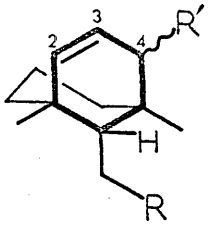

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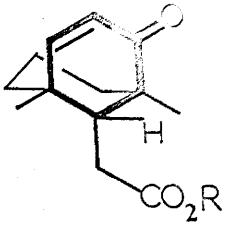

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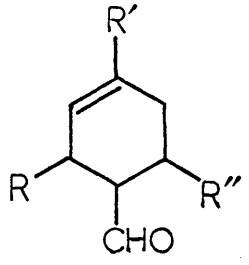

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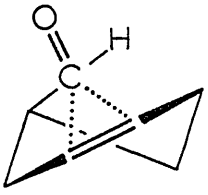

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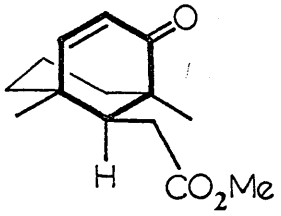

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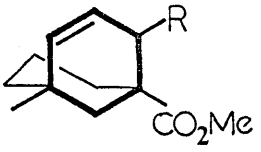

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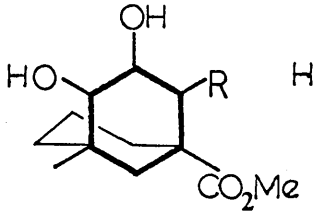

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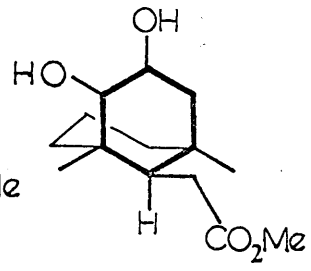

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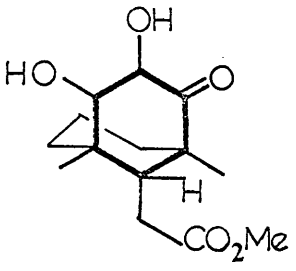

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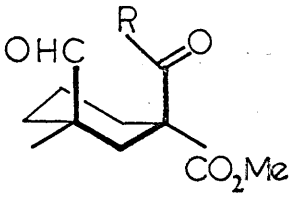

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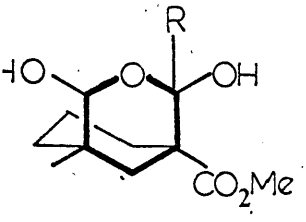

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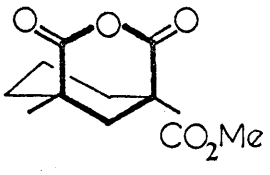

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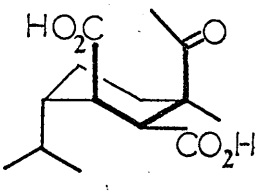

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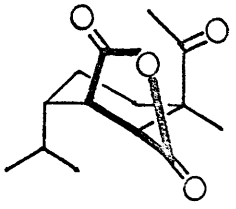

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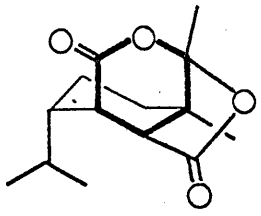

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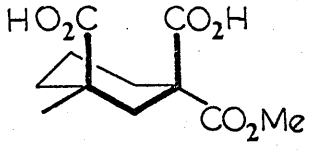

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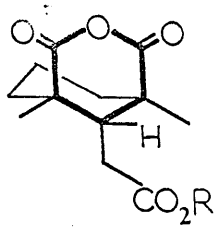

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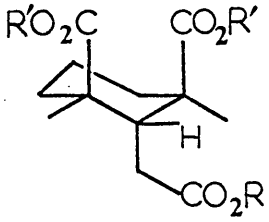

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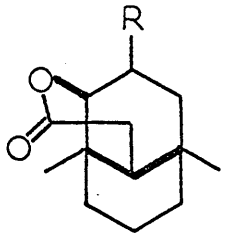

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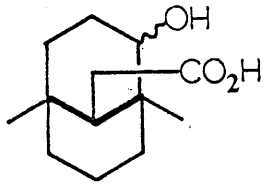

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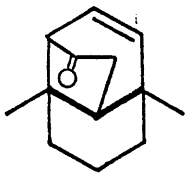

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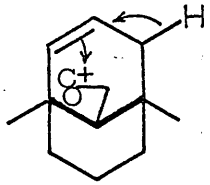

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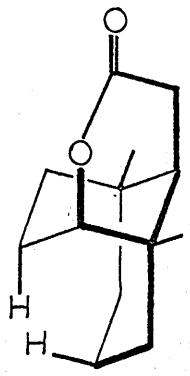

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PART I

EXPERIMENTAL*

Melting points were recorded on a Kofler block and are corrected; boiling points are uncorrected. The alumina used for routine chromatography (Spence's type H) was acid-washed and activated by Brockmann and Schodder's method[72]. Light petroleum refers to the fraction of b.p. 40-60° unless otherwise stated. Thin layer chromatoplates were prepared[73] from Merck's 'Kieselgel G'. Analytical gas-liquid chromatograms were run on the Pye-Argon Chromatograph and on the Perkin Elmer 'Fractometer'. The Aerograph 'Autoprep' A-700 model was used for preparative g.l.c. separations.

Mass spectra were determined on an A.E.I. M.S.9 spectrometer. Ultraviolet absorption spectra refer to ethanol solutions unless otherwise stated, and were measured with a Unicam S.P. 500 model, or subsequently with the automatic Unicam S.P. 800 instrument. Routine infrared spectra , from liquid films unless otherwise stated, were measured on a Perkin Elmer 'Infracord' or Unicam S.P. 200 model; where high resolution is specified, spectra were recorded linearly in $cm.^{-1}$ as percentage transmission with a Unicam S.P. 100 double-beam

* The comments on experimental procedure in the preamble to the section below also apply to the experimental sections of Parts II, III and IV.

infrared spectrophotometer equipped with an S.P. 130 sodium chloride prism-grating double monochromator operated under vacuum; more details of this instrument and of purification of solvents used, for solution spectra, are included in the preamble to the experimenta section of Part II, which deals with accurate infrared spectral measurements. Proton magnetic resonance spectra were measured with tetramethylsilane as internal reference in carbon tetrachloride solutions of samples; where automatic integration of the signals was required, a Perkin Elmer 60 Mc/s. instrument was used. Earlier spect were recorded on the A.E.I. R.S.2 spectrometer, operating at 60 Mc/s.

Ethyl 1,3-Dimethyl-2-oxocyclohexanecarboxylate (59)

This compound was prepared by the method of Haworth and Barker, J., 1939, 1301.

2,6-Dimethylcyclohexanone (8)[21]

A solution of 2,6-dimethyl-2-carbethoxycyclohexanone (i.e. ethyl 1,3-dimethyl-2-oxocyclohexanecarboxylate, 59), (108.6 g.) and potassium hydroxide (92.5 g.) in methanol (250 ml.) was held at 40°C for 24 hr., then diluted with water and steam-distilled. The ketone was extracted from the distillate with ether, the ethereal solution dried, and the solvent removed. The residual oil was distilled at atmospheric pressure, furnishing the ketone (46.5 g., 72%) as a colourless liquid, b.p. 169-170°, n_D^{25} 1.4450.

3-(1,3-Dimethyl-2-oxocyclohexyl)propionaldehyde Diethyl Acetal (38)

A solution of 2,6-dimethylcyclohexanone (37.8 g.) in dry xylene (50 ml.) was added to a stirred suspension of sodamide (11.7 g.) in xylene (600 ml.) at 30° under nitrogen, and the mixture refluxed until no more ammonia was evolved (ca. 12 hr.), and a yellow gelatinous suspension had been formed. A solution of 3-chloropropion-

aldehyde diethyl acetal[74] (55.0 g.) in dry xylene (100 ml.) was then added in 40 min. and the mixture refluxed for 22 hr. The brown mixture was cooled, washed with saturated brine solution and dried ($MgSO_4$), and solvent removed *in vacuo*. Fractional distillation of the residual oil gave the *acetal* (38), (9.6 g.), b.p. 90-98°/0.15 mm. A second distillation afforded an analytical sample, b.p. 92-95°/0.15 mm., n_D^{22} 1.4732, $\nu_{max.}$ 1695, 1120 and 1050 $cm.^{-1}$ (Found: C, 70.45; H, 10.1. $C_{15}H_{28}O_3$ requires C, 70.25; H, 11.0%).

The 2,4-dinitrophenylhydrazone of the free aldehyde crystallised from ethanol as yellow needles, m.p. 138-140° (Found: C, 56.45; H, 5.85; N, 15.6. $C_{17}H_{22}N_4O_5$ requires C, 56.35, H, 6.1; N, 15.45%).

2-Hydroxy-1,5-dimethylbicyclo(3,3,1)nonan-9-one (39 a + b, R= H) and 2-Ethoxy-1,5-dimethylbicyclo(3,3,1)nonan-9-one (39 a + b, R= Et).

A solution of the acetal (38, 55.7 g.) in dioxan (200 ml.) containing 6N-hydrochloric acid (50 ml.) was heated under reflux for 4 hr., cooled, diluted with saturated brine, and evaporated under reduced pressure. The residue was extracted with ether (2 x 100 ml.), the combined extracts were washed with aqueous sodium carbonate solution, water and dried, and the solvent removed to give a dark brown oil (51 g.) A sample of this oil (22 g.) was adsorbed on silica gel (200 g.) from benzene. Elution with this solvent gave the *ethoxy-ketones* (39 a + b, R= Et), (7.5 g.) b.p. 128-133°/15 mm., n_D^{21} 1.4758, $\nu_{max.}$ 1710, 1200 and

980 $cm.^{-1}$ (Found: C, 74.1 ; H, 10.3. $C_{13}H_{22}O_2$ requires C, 74.25; H, 10.55%).

Further elution with benzene-chloroform (1:3) gave the hydroxy-ketones (39 a + b, R= H), (14.5 g.) as a mixture of epimers, m.p. 35-50°, $\nu_{max.}$ (in Nujol) 3500-3350, 1700, 1060-1040, and 980 $cm.^{-1}$ (see also Part II), (Found: C, 72.25; H, 9.75. $C_{11}H_{18}O_2$ requires C, 72.50; H, 9.95%).

A solution of the mixed hydroxy-ketones (3.97 g.) and toluene-p-sulphonyl chloride (4.20 g.) in pyridine (10 ml.) was warmed on a steam-bath for 1 hr., and kept at room temperature for 15 hr., then diluted with ethyl acetate (50 ml.) and water (50 ml.). The separated organic layer was washed with dilute hydrochloric acid, saturated sodium carbonate solution, and dried. Removal of solvent gave a pale yellow solid, 6.5 g., m.p. 110-130°, which was fractionally crystallised from benzene-light petroleum. The early crops (1.5 g.) crystallised from ethanol as colourless plates to give one epimeric toluene-p-sulphonate m.p. 145-146° (decomp.), $\nu_{max.}$ (in Nujol) 1710, 1350, 1190, 1180, 923, 900 amd 875 $cm.^{-1}$ (Found: C, 64.0; H, 7.4. $C_{18}H_{24}O_4S$ requires C, 64.25; H, 7.2%). Later fractions (3.0 g.) crystallised from ethanol to give the second pure epimeric toluene-p-sulphonate as colourless plates, m.p. 114-115°, $\nu_{max.}$ (in Nujol) 1710, 1350, 1190, 1180, 943, 870 and 817 $cm.^{-1}$ (Found: C, 64.15; H, 7.2%).

Dehydration of Hydroxy-ketones (39 a + b, R= H).

(a) By sulphuric acid:

Ice-cold concentrated sulphuric acid (2 ml.) was added with shaking to the hydroxy-ketones (1.04 g.) and the mixture was kept for 20 hr. at room temperature, then poured on ice, neutralised with aqueous sodium hydrogen carbonate solution, and extracted with ether. The ethereal extracts were washed with water, dried and evaporated, to give a red glass (0.75 g.)

(b) By boric acid:

The hydroxy-ketones (5.0 g.) and crystalline boric acid (2.5 g.) were heated under reflux at 300-320° for 90 min. The cooled mixture was extracted with ether, and the extract washed with saturated sodium hydrogen carbonate solution, then dried and evaporated to a brown, mobile liquid (3.33 g.) This was adsorbed on alumina (300 g.) from light petroleum; elution with the same solvent gave a liquid mixture of hydrocarbons (0.61 g.), b.p. 85-96°/9 mm., n_D^{22} 1.5230, $\lambda_{max.}$ (in 'iso-octane') 251 (ε, 1300) and 273 mμ(ε, 580), whose infrared spectrum ($\nu_{max.}$ 1600, 850, 800-750, 717 $cm.^{-1}$) was very similar to that of 4-methylindane[32].

Further elution with light petroleum gave 1,5-dimethylbicyclo(3,3,1) non-2-en-9-one (37, 1.05 g.), b.p. 86-87°/9 mm., n_D^{20} 1.4900, a volatile colourless liquid with a strong camphor-like odour. It

solidified and crystallised from light petroleum at -70° as prisms, m.p. 25-26°, $\nu_{max.}$ 2930, 1700, 1640, 720 and 695 $cm.^{-1}$, τ = 8.96, 8.92, 7.52 (centre of multiplet) and 4.46 (centre of 4 triplets at 4.1, 4.2, 4.64 and 4.8), (Found: C, 80.5; H, 9.8. $C_{11}H_{16}O$ requires C, 80.45; H, 9.85%). The ultraviolet absorption spectrum, $\lambda_{max.}$ (in EtOH), 291 mμ(ε, 42), did not exhibit a high extinction coefficient of $n \rightarrow \pi^*$ absorption[75] characteristic of many ketones with neighbouring double bonds and, in addition showed no evidence of $\pi \rightarrow \pi^*$ absorption.

The 2,4-dinitrophenylhydrazone could not be prepared under the usual conditions, presumably owing to steric hindrance.

Elution of the column with benzene gave a yellow ketonic product (0.48 g.), b.p. 40-44°/0.06 mm., n_D^{23} 1.4875, $\nu_{max.}$ 1740, 1710 and 1650 $cm.^{-1}$, slightly contaminated with the hydroxy-ketones (39 a + b, R= H The 2,4-dinitrophenylhydrazone of the ketone crystallised from ethyl acetate-methanol as orange needles, m.p. 145-146° (Found: C, 59.45; H, 5.95; N, 16.35. $C_{17}H_{20}N_4O_4$ requires C, 59.3; H, 5.85; N, 16.25%).

Elution of the column with chloroform gave a pale yellow oil (0.06 g.), b.p. 54-55°/0.7 mm., n_D^{21} 1.5070 whose 2,4-dinitrophenylhydrazone crystallised from ethanol as dark red needles, m.p. 172-174°, (Found: C, 59.0; H, 5.75; N, 16.3. $C_{17}H_{20}N_4O_4$ requires C, 59.3; H, 5.85; N, 16.25%). The semicarbazone crystallised from ethanol as needles, m.p. 209-211° (decomp.), (Found: C, 65.15; H, 8.5; N, 18.9. $C_{12}H_{19}N_3O$ requires C, 65.1; H, 8.65; N, 19.0%). The manner of formation

of this ketone, and its physical and chemical properties, are in agreement with its formulation as 2-acetyl-5-methylbicyclo(3,3,0)oct-1(2)-ene[24g] (49). This assignment was checked by synthesis of the dihydroketone (50) from 2-acetyl-5-carbethoxybicyclo(3,3,0)oct-1(2)-ene[24g] (45) as described in Appendix A to this experimental section.

1,3-Dimethyl-2-oxocyclohexylpropionitrile (53, R= CN)

A mixture of 2,6-dimethylcyclohexanone (8, 25.2 g.) and 40% w/w aqueous Triton B (0.8 g.) was stirred at 0°C, and acrylonitrile (2.65 g.) added over 15 min. The mixture was set aside at room temperature for 15 hr., then acidified with 3N-hydrochloric acid, washed with brine, dried and distilled. The excess ketone (18 g.) was removed as a forerun on distillation, followed by the required product (2.17 g., 24%), b.p. 119-126°, leaving a large non-volatile residue. Redistillation afforded the pure keto-nitrile , b.p. 128°/0.8 mm., n_D^{20} 1.4745 , $\nu_{max.}$ 2220, 1700, 1120, 1005, 950, 860 $cm.^{-1}$; (Found: C, 73.5; H, 9.65; N, 7.6. $C_{11}H_{17}NO$ requires C, 73.70; H, 9.56; N, 7.81%).

1,3-Dimethyl-2-oxocyclohexylpropionic Acid (53, R= CO_2H).

The above nitrile (0.50 g.) was added to a 10% aqueous potassium hydroxide solution (5 ml.) and heated under reflux for 18 hr. The acidic material (0.51 g.) was recovered in the usual manner, and found to be identical in all respects with the acid produced by basic hydrolysis and decarboxylation of 1,3-dimethyl-3-carbethoxycyclohexylpropionitrile (see below).

1,3-Dimethyl-2-oxocyclohexyl-1,3-dipropionic Acid (54, R= CO_2H) and the Corresponding Anhydride (56).

Acrylonitrile (7.95 g.) in t-butanol (50 ml.) was added in 30 min. to a stirred mixture of 2,6-dimethylcyclohexanone (8, 12.6 g.) and 40% w/w aqueous Triton B (5.75 g.) in t-butanol (400 ml.) held at 50°, in a nitrogen atmosphere, and the solution stirred at the same temperature for 20 hr. After cooling, the reaction mixture was acidified with 3N-hydrochloric acid, and extracted with ether (500 ml.). The first ether extract was combined with two further extracts, each of 200 ml., and washed with brine and sodium hydrogen carbonate solution, and dried. Removal of solvent afforded a brown oil (9.95 g.) which did not distil below 180°/0.08 mm.

The crude product was suspended in 20% aqueous potassium hydroxide (100 ml.) and heated under reflux for 16 hr. After acidification,

the precipitated acid was washed on a filter, with water, dried, and recrystallised from petroleum ether (b.p. 60-80°) - ethyl acetate to give the keto-dicarboxylic acid (54, R= CO_2H, 3.5 g.) as colourless prisms, m.p. 135-137°, $\nu_{max.}$ (in Nujol) 1700; 1310-1280, 1210, 940, 860 $cm.^{-1}$; (Found, C, 62.35; H, 8.35. $C_{14}H_{22}O$ requires C, 62.20; H, 8.20%).

The keto-dicarboxylic acid (5.5 g.) was heated under reflux with acetic anhydride (50 ml.) for 3 hr., excess reagent removed in vacuo and the residue heated 200°/0.5 mm. A sublimate (1.8 g.) was collected, dissolved in ethyl acetate (20 ml.), washed with sodium carbonate solution, and saturated brine, and dried. The solid (1.8 g.) recovered from the dried ethyl acetate solution was recrystallised from ethyl acetate-light petroleum as white prisms, and then sublimed to give the anhydride, m.p. 139-140°, $\nu_{max.}$ (in CCl_4, high-resolution) 1763, (strong shoulder) 1754; very complex fingerprint region, with strong, sharp bands at 1267, 1244, 1215, 1174, 1149, 1087, 1013, 986, and 958 $cm.^{-1}$; abnormally high ν_{C-H} bands at 3012 and 3010-2980 $cm.^{-1}$, and a complex methylene scissoring region, which showed bands at 1485, 1469, 1453, 1440 and 1417 $cm.^{-1}$; methylenes α to the carbonyls of the anhydride, 1384 $cm.^{-1}$; τ = 8.78; 8.36; 7.46 (centre of multiplet). The mass spectrum showed a parent peak at 252 (calc. 252), consistent with the structure 56. (Found: C, 67.4; H, 8.15. $C_{14}H_{20}O_4$ requires C, 66.64; H, 7.99%). The anhydride dissolved in 4N-NaOH and was thus reconverted to the parent acid, m.p. and m.m.p. 133-136°.

Attempted Preparation of 2-imino-9-oxo-1,5-dimethylbicyclo-(3,3,1)nonane (57).

Potassium (0.195 g.) was dissolved in t-butanol (75 ml.) and the stirred solution heated under reflux in a nitrogen atmosphere; a solution of 1,5-dimethyl-2-oxocyclohexylpropionitrile (53, R= CN, 0.87 g.) in t-butanol (50 ml.) was added in 1 hr., and refluxing continued for 16 hr. The cooled solution was acidified with 2N-sulphuric acid, solvent removed in vacuo and the residue diluted with saturated brine (50 ml.) and extracted with ether (100, 50, 25 ml.). The combined ether extracts were washed with aqueous sodium hydrogen carbonate solution and dried. Removal of solvent afforded a pale yellow solid, which crystallised from light petroleum as colourless prisms, m.p. 85-87°, $\nu_{max.}$ (in Nujol) 3200, 1660, 1205 $cm.^{-1}$ (Found: C, 73.55; H, 9.35; N, 7.75. $C_{11}H_{17}ON$ requires C, 73.70; H, 9.56; N, 7.81%). The analysis excluded the possibility of the imino-ketone (57) having been formed. By analogy with other results[37] and in agreement with the data above, the product was probably the enamine-lactam (58).

Only the keto-acid (53, R= CO_2H) could be recovered from the hydrolysis with 6N-hydrochloric acid , under reflux for 18 hr., and with the same acid at room temperature over two days.

Ethyl 3(2'-cyanoethyl)-1,3-dimethyl-2-oxocyclohexanecarboxylate (60)

Acrylonitrile (8.0 g.) in t-butanol (20 ml.) was added in 30 min. to a stirred solution of ethyl 1,3-dimethyl-2-oxocyclohexane-carboxylate[38] (59, 9.38 g.) and 40 % aqueous Triton B (6 g.) in t-butanol (50 ml.) under nitrogen, and the mixture warmed at 50-60° for 6 hr.[39] The solution was acidifed with dilute hydrochloric acid, the solvent removed under reduced pressure, and the residue extracted with ether (3 x 50 ml.) . The combined extracts were washed with saturated sodium carbonate solution and water, then dried, and evaporated to give a brown oil ; fractional distillation gave the keto-nitrile , b.p. 116-130°/0.2 mm. (8.65g.) Redistillation afforded a sample, b.p. 129°/0.2 mm, n_D^{21} 1.4730 , $\nu_{max.}$ 2210, 1730, and 1700 $cm.^{-1}$ (Found: C, 66.85; H, 8.2; N, 5.55. $C_{14}H_{21}NO_3$ requires C, 66.9; H, 8.4; N, 5.55%).

β-(1,3-Dimethyl-2-oxocyclohexyl)propionic Acid (53, R= CO_2H)

The preceding nitrile (1.00 g.) was heated under reflux for 24 hr. in 30% methanolic potassium hydroxide (25 ml.), cooled, and diluted with saturated brine, and an ethereal extract (50 ml.) rejected. The aqueous alkaline layer was acidified with dilute hydrochloric acid and extracted with ether (2 x 50 ml.), and the combined ethereal extracts were washed with saturated brine solution and dried, and the

solvent was removed to give the keto-acid (53, R= CO_2H ; 0.72 g.) which crystallised from ethyl acetate-light petroleum as an epimeric mixture in colourless prisms, m.p. 84-88°, $\nu_{max.}$ (in Nujol) 1700-1695 (superimposed C=O) 1300, 1210, 1000, 950-930, 860, 770, 745 $cm.^{-1}$ (Found: C, 66.85; H, 9.05. $C_{11}H_{18}O_3$ requires C, 66.65; H, 9.15%) Repeated crystallisation from light petroleum (60-80°) gave what appeared to be a single epimer, m.p. 93-94°. Treatment of the keto-acid with diazomethane in ether gave the methyl ester (53, R= CO_2Me) , b.p. 100°/0.06 mm., n_D^{24} 1.4625, $\nu_{max.}$ 1735, 1700, 1200, 1170, 1005 and 860 $cm.^{-1}$ (Found: C, 67.65; H, 9.3. $C_{12}H_{20}O_3$ requires C, 67.9; H, 9.5%).

Attempted Preparation of Dione (63)*

(a) Boron trifluoride-ether complex (0.2 ml.) was heated with the acid (53, R= CO_2H) , (0.5 g.) in acetic acid (2 ml.) containing acetic anhydride (0.05 ml.) at 100°C for 3 hr., set aside at room temperature for 12 hr., and poured into an excess of sodium hydrogen carbonate solution. The neutral ether extract contained no product; acidification of the alkaline aqueous solution, and extraction, furnished only starting material.

* For later preparation of 63, see Appendix B to this experimental section.

(b) A solution of the methyl ester (53, R= CO_2Me), (0.87 g.) in anhydrous ethanol (20 ml.) was added in 30 min. to a stirred solution of sodium (0.09 g.) in ethanol (30 ml.) at room temperature under nitrogen. The mixture was heated under reflux for 18 hr., cooled, neutralised with dilute hydrochloric acid, and evaporated under reduced pressure. The residue was extracted with ether, the extract washed with brine, and the solvent removed, leaving unchanged starting material.

The Enol-lactone (64).

(a) The acid (53, R= CO_2H ; 0.28 g.) and acetic anhydride (2.0 ml.) were heated under reflux for 2 hr., anhydrous sodium acetate (10 mg.) was added, and heating continued for an additional 2 hr. Acetic anhydride was removed under reduced pressure, and the residue diluted with saturated brine solution, and extracted with ether (2 x 10 ml.). The combined ethereal extracts were washed with saturated sodium hydrogen carbonate solution, brine, and dried. Removal of solvent gave the enol-lactone (64, 0.26 g.) which crystallised from light petroleum as hexagonal prisms, m.p. 47-48°, $\nu_{max.}$ 1740, 1680, 1250, 1190, 1165, 1150, 1120-1100, and 1010 $cm.^{-1}$ for a Nujol mull. (Found: C, 73.55; H, 8.75. $C_{11}H_{16}O_2$ requires C, 73.3; H, 8.95%)

(b) Oxalyl chloride (25 g.) was added to a solution of the keto-acid (53, R= CO_2H; 18.0g.) in dry benzene, and the mixture held at 0° for

10 hr. The solvent and excess reagent were removed under reduced pressure at room temperature, and the residue distilled to give a colourless liquid, (10 g.), b.p. 98-100°/0.2 mm., which solidified and crystallised as in (a) to give prisms, m.p. 47-48°, undepressed by admixture with the product from (a).

Reduction of the Enol-lactone (64)

A suspension of lithium hydridotri-t-butoxyaluminate, prepared by adding dry t-butanol (16.6 g.) in dry tetrahydrofuran (50 ml.) to a suspension of lithium aluminium hydride (2.58 g.) in tetrahydrofuran (50 ml.), was added in 30 min. to a stirred solution of the enol-lactone (9.0 g.) in tetrahydrofuran (30 ml.) at -70°.[45] The mixture was allowed to reach room temperature (in one hr.), then poured into ice-cold saturated brine (100 ml.). The inorganic insoluble matter was removed by filtration through Celite 535, and the filtrate extracted with ether (5 x 30 ml.). The combined ethereal extracts were washed with saturated brine and dried and the solvent removed to give a colourless, viscous oil (8.3 g.) showing absorption in the infrared identical with that of the hydroxy-ketones (39 a + b, R= H) obtained as described above. Thin-layer chromatograms of this product and the hydroxy-ketones (39 a + b, R= H) were identical, both showing separation of two epimers. A specimen of the crude

product was heated with toluene-p-sulphonyl chloride in pyridine, as described for the hydroxy-ketones (39 a + b), (R= H). Two crystalline esters, m.p. 145-146° and 114-115°, respectively, were separated by fractional distillation, and these were identical with the epimeric toluene-p-sulphonates obtained from (39 a + b, R= H), (m.p., mixed m.p., infrared spectra).

When the reduction mixture was worked up with dilute hydrochloric acid, a solid product (8.3 g, 90%) was obtained, and seemed to consist substantially of one epimer, as it gave only the toluene-p-sulphonate of m.p. 145-146°in high yield. Crystallisation of this product from benzene-light petroleum gave a pure epimer (39a, R= H), as prisms, m.p. 73-75°, τ = 9.1,9.01, 8.15, 6.65, and 6.02; (Found: C, 72.25; H, 9.75. $C_{11}H_{18}O_2$ requires C, 72.5; H, 9.95%)

Supplementary work on the epimeric ketols and their tosylates, directed principally towards establishing their stereochemistry, are described in Appendix B.

1,5-Dimethylbicyclo(3,3,1)non-2-en-9-one (37)

A solution of sodium (1.06 g.) in dry ethanol (30 ml.) was added in 5 min. to a stirred suspension of the toluene-p-sulphonate of m.p. 145-146° (12.9 g.) in dry ethanol (100 ml.) and the mixture was refluxed for 20 hr., then cooled, neutralised with acetic acid, diluted with water (200 ml.) and extracted with light petroleum (3 x 100 ml.). The combined petroleum extracts were washed with saturated sodium hydrogen carbonate solution, and saturated brine, and dried. Removal of solvent gave a yellow oil (5.93 g.) which was adsorbed on neutral Woelm alumina (100 g.) from light petroleum. Elution with light petroleum-ether (20:1) gave the ketone (37, 5.6 g.), m.p. 25 -26°, identical with the compound obtained as described above.

1- Hydroxymethyl-5-methylbicyclo(3,3,1)non-3-en-9-ol (87, R= CH_2OH)

The ester[24g] (43, 138g.) was added in dry ether (500 ml.) in 1 hr. to a refluxing solution of lithium aluminium hydride (30 g.) in ether (1000 ml.) and heated under reflux for 16 hr. The excess of hydride was destroyed by ethyl acetate, followed by dilute sulphuric acid. The separated ether layer, was combined with two further extracts of the aqueous layer, washed with saturated brine solution, and dried. Crystallisation of the residue after removal

of solvent gave the diol (87, R= CH_2OH; 104 g.), m.p. 100-125°. Recrystallisation from benzene-light petroleum gave the epimeric mixture, m.p. 127-133°, as white plates, $\nu_{max.}$ 3400-3300, 1060-1030, 1650 and 710 $cm.^{-1}$ (Found: C, 72.7; H, 9.65. $C_{11}H_{18}O_2$ requires C, 72.5; H, 9.95%).

The diols (87, R= CH_2OH, 91 g.) and toluene-p-sulphonyl chloride (96 g.) in pyridine (250 ml.) were set aside for 20 hr. at 0°, and the solvent was then removed under reduced pressure. The residue was diluted with saturated brine and extracted with ether (2 x 300 ml.) and the combined ethereal extracts were washed with dilute hydrochloric acid and saturated sodium carbonate solution and dried. Removal of solvent gave an oil which solidified in trituration with ether. Recrystallisation from ethyl acetate-light petroleum gave prisms of the primary mono-toluene-p-sulphonate (152 g.), m.p. 65-67°, $\nu_{max.}$ 3475, 1070, 910, 860, 840, and 712, 705 $cm.^{-1}$, of (87, R= CH_2OH), (Found: C, 64.6; H, 7.1. $C_{18}H_{24}O_4S$ requires C, 64.25; H, 7.2%)

1,5-Dimethylbicyclo(3,3,1)non-2-ene-9-one (37)

A solution of the last mentioned ester (55.4 g,) in dry ether (200 ml.) was added in 1 hr. to a stirred solution of lithium aluminium hydride (10 g.) in ether (250 ml.) and the mixture was heated under reflux with stirring for 25 hr. The mixture was worked up as above, giving a solid epimeric mixture (27.0 g.) of the alcohols* (168 and 169; both R= H). This was dissolved in acetone (250 ml.) and cooled in ice. Jones' reagent (46 ml.) was added with cooling and shaking, and the mixture was diluted with water (1000 ml.) and extracted with light petroleum (2 x 250 ml). The extracts were washed with saturated sodium hydrogen carbonate and water, dried, and evaporated. The volatile oily residue (26.0 g.) was adsorbed on alumina (250 g.) from light petroleum. Elution with the same solvent, and with benzene-light petroleum (1:1) gave the ketone (37, 23 g.) (mixed m.p., infrared spectrum, thin layer chromatography).

* For a description of these epimeric alcohols, see Part IV.

9-Hydroxy-1,5-dimethylbicyclo(3,3,1)non-2-enyl-9-acetic Acid, (91, R= H).

(a) A solution of 1,5-dimethylbicyclo(3,3,1)non-2-en-9-one (37) (1.64 g.) and ethyl bromoacetate (1.85 g.) in benzene (25 ml.) was added dropwise, with stirring, to a mixture of activated granular zinc[54] (6.0 g.) , benzene (10 ml.) and iodine (0.01 g.) heated under reflux. Additional portions of zinc (2 g.) were added after 3, 6 and 16 hr, and heating continued for a further 2 hr. The cooled mixture was acidified with acetic acid, and the excess zinc removed by decantation. The decanted liquid was combined with ether washings of the zinc, and the combined solutions washed with saturated brine solution, aqueous sodium carbonate solution, and dried. Removal of solvent gave a brown oil, 2.32 g., which was adsorbed on silica gel (60 g.) from benzene. Elution with the same solvent separated a mixture (1.3 g.) of the starting ketone and the required hydroxy-ester (91, R= Et) from intractable products.

A portion of this mixture (0.68 g.) was dissolved in methanol (10 ml.), water (2 ml.), containing potassium hydroxide (1 g.), and the mixture heated under reflux for 30 min. From this solution, a white crystalline acidic product (0.29 g.), 25% from ketone 37, was recovered in the usual manner. A pure sample of the hydroxy-acid was obtained by repeated recrystallisation from benzene-light petroleum as highly refractive prisms, m.p. 145-150, 163-165°;

$\nu_{max.}$ (in Nujol) ca. 3300; 1700; 1210, 1195, 1045, 705 $cm.^{-1}$
(Found: C, 69.6; H, 8.75. $C_{13}H_{20}O_3$ requires C, 69.61; H, 8.99%).

The corresponding methyl ester (91, R= Me), prepared in the usual manner, by treatment of (91, R= H) with diazomethane in ether, was obtained as a colourless oil, $\nu_{max.}$ 3400, 1710, 705 $cm.^{-1}$

(b) Activated zinc wool[54] (15 g.), 1,5-dimethylbicyclo(3,3,1)-non-2-en-9-one (37, 5.08 g.), benzene (120 ml.) and ether (120 ml.) were mixed and heated under reflux with stirring, while a solution of ethyl bromoacetate (5.0 g.) in ether (20 ml.) was added, over 15 min. After 2 hr. with no apparent reaction, iodine (0.02 g.) was added with no effect. Finally, a violent reaction was initiated by adding a drop of mercury. After this had subsided, the mixture was refluxed over 6 hr., during which fresh portions of zinc (5 g.) were added at hourly intervals. The product was isolated and hydrolysed as in procedure (a); the same hydroxy-acid (91, R= H; 2.2g; 32%) and unchanged ketone (37, 2.4 g.) were recovered.

(c) Activated zinc shot[54] (16-30 mesh, 80 g.), ketone (37; 21 g.), benzene (50 ml.) and toluene (50 ml.) were mixed and heated under reflux with stirring. Ethyl bromoacetate (60 g.) in toluene (60 ml.) was added dropwise with stirring, and reaction initiated by addition of a small amount of mercury. After two hours the mixture was cooled, filtered through glass wool, and the filter washed with benzene (20 ml).

The filtrate and washings were added to a fresh portion of zinc shot (50 g.) and ethyl bromoacetate (20 ml.) and heating under reflux with stirring was repeated. Fresh zinc and bromo-ester were used once again, in the same way, and the reaction mixture finally acidified with acetic acid, filtered free from zinc, and added to water (200 ml.) and ether (500 ml.). The separated yellow organic layer was washed with dilute ammonia solution until no more colour was removed, and finally with saturated brine solution. A thick brown oil (25 g.) was recovered from the dried ethereal layer, and was fractionally distilled at 0.25 mm. The first and second fractions (108-132°, 7.0 g.) and (132-160°, 1.1 g.) consisted mainly of unchanged ketone (37), and obviously contained some of the required hydroxy-ester (91, R= Et), from infrared spectra. Hydrolysis of the last fraction in aqueous methanolic potassium hydroxide, and subsequent separation of neutral and acidic products gave (i) unchanged ketone (37, 0.75 g.) contaminated with the corresponding alcohols (168, 169; R= H, see Part IV), (thin layer chromatograms and infrared spectra); (ii) semi-solid lactonic material (1.6 g.) , $\nu_{max.}$ (in Nujol), 1780 $cm.^{-1}$ and (iii) <u>hydroxy-acid</u> (91, R= H; 4.6 g., 15%), identical with samples obtained as in (a) and (b) above, (m.p., mixed m.p., infrared spectra).

(d) Ethyl bromide (7.6 g.) in ether (25 ml.) was added with stirring to magnesium (1.7 g.) in ether (50 ml.) and reaction completed by heating under reflux for 30 min., under nitrogen. The Grignard solution was cooled to -10° and a solution of ethoxyacetylene[55] (6 g.) in ether (50 ml.) added dropwise over 15 min. The mixture was heated under reflux for 1 hr., cooled in ice, and 1,5-dimethylbicyclo(3,3,1)non-2-en-9-one (37, 9.7 g.) in ether (20 ml.) added over 15 min. The mixture was stirred for 1 hr. at 0°C, heated under reflux for 1 hr., then cooled, and saturated ammonium chloride solution added. The ether layer was separated, washed with saturated brine solution, and concentrated to 50 ml. (An aliquot from this solution, after evaporation of solvent, afforded a brown oil, whose infrared spectrum, $\nu_{max.}$ 3400, 2210, 1700, 1220-1190, 1050-980, 940, 835, 720, 695 $cm.^{-1}$, indicated the presence of a mixture of unchanged ketone (37) and the required ethoxyethynyl carbinol (92).)

The ethereal solution was stirred with aqueous sulphuric acid (10%, 100 ml.) for 5 hr. at room temperature. The ethereal layer was separated, washed with saturated brine solution, and dried. Alkaline hydrolysis of the total product, as in (a) above, allowed the subsequent separation of unchanged ketone (37, 2.3 g.) from the required hydroxy-acid (91, R=H, 2.75 g., 20%), identical with the product from procedures (a), (b) and (c) in all respects.

Attempted Dehydration[54] of 9-Hydroxy-1,5-dimethylbicyclo(3,3,1)-non-2-enyl-9-acetic Acid (91, R= H).

(a) A specimen of the hydroxy-acid (91, R= H) was recovered unchanged from heating at 170° over 30 min.

(b) A solution of the hydroxy-acid (91, R= H), 0.03 g., and phosphorus oxychloride (0.5 g.) in pyridine (5 ml.) was heated under reflux for 2 hr. The cooled mixture was diluted with water (20 ml.) and extracted with ether (3 x 20 ml.). The combined ethereal extracts were washed with dilute hydrochloric acid, saturated brine solution, and dried. The total product, (0.01 g.), a brown oil, had virtually no carbonyl absorption in the infrared, and unexplained bands at 895 and 850 $cm.^{-1}$.

(c) Procedure (b) was repeated, but heating under reflux replaced by warming on a steam-bath over 30 min. The product was isolated as in (b). An intractable mass was obtained, with a very complex carbonyl region in the infrared ($\nu_{max.}$ 1810, 1760, 1740 $cm.^{-1}$) and devoid of hydroxyl absorption. Hydrolysis of the product in methanol(2 ml.) containing potassium hydroxide (0.05 g.), by heating under reflux for 30 min., led to an equally uncompromising secondary product.

Attempted Dehydration of Methyl 9-Hydroxy-1,5-dimethylbicyclo-(3,3,1)non-2-enyl-9-acetate (91, R= Me).

(a) A solution of the hydroxy-ester (91, R= Me, 0.10 g.) and phosphorus oxychloride (0.4 g.) in pyridine (2 ml.) was held at room temperature for one hr. and then heated under reflux for 30 min. After isolating the product as in (b) above, it was found to consist of unchanged starting material.

(b) A solution of the hydroxy-ester (91, R= Me, 0.03 g.) in acetic anhydride (2 ml.) was warmed at 100° for 2 hr. The solution was poured into sodium carbonate solution, left for 30 min., and then extracted with ether. The extract was washed with sodium carbonate solution, and dried. Removal of solvent left a residue of unchanged hydroxy-ester.

(c) A solution of the hydroxy-ester (91, R= Me, 0.05 g.) in formic acid (98%, 1 ml.) was warmed on a steam bath for 30 min. and worked up in the usual manner. The product, a yellow oil, 0.03 g., had an infrared spectrum inexplicable by invoking any simple transformation : bands at 1770 and 1740 $cm.^{-1}$ could not be due to the ester carbonyl of the

original methyl ester (at 1700 $cm.^{-1}$). Disappearance of the hydroxyl band could be the result of formyl ester formation, but this would account for only one carbonyl band. More significantly, the band at 1700 $cm.^{-1}$, due to =C-H deformation, arising from the cis-double bond in the starting material, was completely absent.

(d) The hydroxy-ester (91, R= Me, 0.10 g.) was mixed with solid potassium hydrogen sulphate (0.5 g.), and the mixture heated to 210°. Water was driven off, and the dried sublimate (0.06 g.) was found to be identical in the infrared with the product from procedure (c). This excluded even formylation of the hydroxyl group, as part explanation of the absorption spectrum of the product from that treatment.

(e) A solution of the hydroxy-ester (91, R= Me, 1.40 g.) and thionyl chloride (0.5 ml.) in pyridine (10 ml.) was for 3 hr. heated under reflux, and after cooling, was poured into an excess of dilute hydrochloric acid, and extracted with ether (3 x 50 ml.). The combined ethereal extracts were washed with dilute hydrochloric acid, saturated brine solution, sodium hydrogen carbonate solution, and finally again with brine, and dried. Removal of solvent gave a dark red oil (1.0 g),

which showed no hydroxyl absorption in the infrared , and $\nu_{max.}$ 1720 $cm.^{-1}$, 710 $cm.^{-1}$

The crude product was dissolved in benzene (10 ml.) and collidine (2 ml.) and the solution refluxed over 15 hr. After isolation in the usual manner, the product was unchanged in the infrared. Refluxing collidine itself, (b.p. 170°) was then used, again, without effect on the primary product.

1,5-Dimethylbicyclo(3,3,1)non-2-enylidene-9-acetic Acid, (93, R= H).

A solution of the hydroxy-ester (91, R= Me, 0.70 g.) and thionyl chloride (0.25 g.) in pyridine (5 ml.) was heated and worked up as in (e) above. The crude product (0.50 g.) was dissolved in quinoline (5 ml.) and heated under reflux for 5 hr. The quinoline was distilled at reduced pressure, the residue dissolved in ether, and washed successively with dilute sulphuric acid, saturated brine, sodium hydrogen carbonate, and brine solutions. After drying, removal of solvent afforded a mobile oil (0.15 g.) which was adsorbed on alumina (Woelm, neutral) from benzene. Elution with the same solvent, and with ether, gave a mixture of several products (thin-layer chromatography). Hydrolysis of the combined fractions with aqueous

methanolic potassium hydroxide afforded a semi-solid mass (0.025 g.) of acidic material, isolated in the usual manner. After sublimation at 105°/0.01 mm., this appeared as a waxy solid, m.p. 90-94°, assumed to be the required αβ-unsaturated acid , $\nu_{max.}$ (in Nujol) 1700 $cm.^{-1}$, medium bands at 1400, 1380, 1290, 1215, 1210, 820 $cm.^{-1}$, and the C=C-H deformation band of the cis-disubstituted double bond at 705 $cm.^{-1}$; (Found: C, 75.7; H, 8.7. $C_{13}H_{18}O_2$ requires C, 75169; H, 8.80%).

The sample decomposed to an oil, after a few days at room temperature.

Attempted Preparation of Ethyl 1,5-Dimethylbicyclo(3,3,1)non-2-enylidene-9-acetate (91, R= Et).

A mixture of 1,5-dimethylbicyclo(3,3,1)non-2-en-9-one (37, 1.0 g.), ethoxyacetylene[55] (5 g.) and boron trifluoride etherate (0.3 ml.) in ether (10 ml.) was held at room temperature for 1 hr. The solution was washed with aqueous sodium hydrogen carbonate solution, saturated brine solution, and dried. Removal of solvent and excess ethoxyacetylene under reduced pressure gave only unchanged starting material. There was no evidence of the formation of the intermediate ethoxyethynyl carbinol (92).

Attempted Preparation of 9-Cyano-1,5-dimethylbicyclo(3,3,1)-non-2-ene (94, R= CN).

(a) An epimeric mixture of 9-methanesulphonyloxy-1,5-dimethyl-bicyclo(3,3,1)non-2-ene* (168 and 169; both R= $MeSO_2$), (0.43 g.) in dry dimethylformamide (1 ml.) was added to a stirred suspension of sodium cyanide (0.59 g.) in dimethylformamide (5 ml.) and the mixture warmed on a steam-bath for 2 hr. The cooled mixture was poured into water (25 ml.) and extracted with ether (3 x 25 ml). The combined extracts were washed successively with saturated brine, dilute hydrochloric acid, aquoous sodium hydrogen carbonate, and brine solutions, and dried. Removal of solvent under reduced pressure left a residue of unchanged methanesulphonyl esters.

(b) A stirred mixture of methanesuphonyl esters*(168, 169; R= $MeSO_2$), (0.40 g.), sodium cyanide (0.59 g.) potassium iodide (0.02 g.) and dimethylformamide (15 ml.) was heated under reflux for 17 hr. The cooled mixture was worked up as in (a) above, to give a colourless oil (0.32 g.) which exhibited neither nitrile nor sulphonyl ester bands in the infrared, and was not hydroxylic. Absorption at 1650, 1620 and 1600 $cm.^{-1}$, along with strong bands at 810,760, 740, 700, and 690 $cm.^{-1}$ all indicated that the product was a mixture of

* see Part IV for a description of these compounds.

unsaturated hydrocarbons, formed by elimination of methanesulphonic acid, with rearrangement.

9-Ethynyl-9-hydroxy-1,5-dimethylbicyclo(3,3,1)non-2-ene (95, R= OH).

A suspension of sodamide (15 g.) in dimethylformamide (300ml.) was cooled to -20°, and saturated with dry acetylene. A solution of 1,5-dimethylbicyclo(3,3,1)non-2-en-9-one (37, 20.1 g.) in dry dimethylformamide (100 ml.) was added over 30 min., and the reaction mixture stirred over three hours, while the temperature was allowed to rise to ca. 20° [58]. The mixture was poured into iced water (500 ml.), excess 6N-sulphuric acid added carefully, and the resulting mixture extracted with ether (2 x 500 ml.). The combined ethereal extracts were washed with saturated sodium hydrogen carbonate solution, saturated brine, and dried. Removal of solvent under reduced pressure afforded a low melting semi-crystalline material (23 g.), which was adsorbed on silica gel (250 g.) from light petroleum, and eluted with ether-light petroleum (1:9) to give the epimeric ethynyl carbinols (21.0 g. 90%), m.p. (60) 85-100°, which crystallised from light petroleum as colourless prisms, m.p. (95) 110-112° (with sublimation below the melting point); $\nu_{max.}$ (high resolution in CCl_4) 3622, 3309, 3020, 2110, 1656, 1041, 990, and (in CS_2) 833, 736 and 703 $cm.^{-1}$ (Found: C, 82.1; H, 9.8.

$C_{13}H_{18}O$ requires C, 82.06; H, 9.54%).

Attempts to separate the epimers of the ethynyl carbinol by column chromatography and by thin-layer techniques, were unsuccessful.

9-Acetoxy-9-ethynyl-1,5-dimethylbicyclo(3,3,1)non-2-ene (95, R= $OCOCH_3$)

A cold solution of ethyl magnesium bromide (from 7.92 g. magnesium) in ether (300 ml.) was added over 30 min. to a stirred solution of the ethynyl carbinol (95, R= OH, 57.0 g.) in ether (400 ml.) held at 0° . The mixture was heated under reflux for one hour, cooled, and a solution of acetic anhydride (67 g.) in ether (200 ml.) added with stirring over one hour[59]. After heating under reflux for one hour, the mixture was cooled and saturated aqueous ammonium chloride added. The ethereal solution was separated, washed with saturated brine, and dried. The crude product (68 g.) recovered from this solution, was recrystallised from light petroleum, from which 42 g. (60%) of crystalline product was obtained. The remainder (26 g.) was a semi-solid mass, a mixture of the acetoxy- and unchanged hydroxy-compounds, from the infrared spectrum. Sublimation at 100°/0.3 mm. afforded an analytical sample of the ethynyl acetate, m.p. 149-150° ,

(sublimes as a mosaic on cover plate of block); $\nu_{max.}$ (high-resolution, in CCl_4) 3312, 3022, 2115, 1662, 1225, 1217, 1042, 1017 $cm.^{-1}$; (in CS_2 solution) , 726, 711, 694 $cm.^{-1}$ (Found: C, 77.55; H, 8.65. $C_{15}H_{20}O_2$ requires C, 77.55; H, 8.68%).

No separation of epimers was observed during the purification stages. The hydroxy-compounds (95, R= OH) and the ethynyl acetates (95, R=$OCOCH_3$) had identical retention factors, on thin-layer chromatoplates.

1,5-Dimethylbicyclo(3,3,1)non-2-enylidene Vinyl Acetate, (96, R= $OCOCH_3$)

A stirred mixture of the ethynyl acetates (95, R= $OCOCH_3$; 42.0 g.), zinc oxide (7.2 g.) and silicone oil (Hopkins and Williams MS 550 R, 42 ml.) was heated in an oil bath. The bath temperature was raised from room temperature to 200° in 20 min., and maintained at 200-210° for 20 min.[52] After cooling, the mixture was diluted with light petroleum and ether (25 ml each), and filtered. The filtrate was washed with aqueous sodium hydrogen carbonate solution, saturated brine solution, and dried. Distillation afforded the allene acetate (37.1 g., 88%), b.p. 79-82°/0.07 mm. Redistillation gave an analytical sample, 81-82°/0.07 mm.; n_D^{18} 1.5232 ; ν_{max}: 1960, 1760, 1670, 1220; 1040, 930, 850, 790 and

710 $cm.^{-1}$. (Found: C, 77.45; H, 8.35. $C_{15}H_{20}O_2$ requires C, 77.55; H, 8.68%).

1,5-Dimethylbicyclo(3,3,1)non-2-enylidene-9-acetaldehyde (88, R=CHO)

A solution of the allene acetate (96, R= $OCOCH_3$; 37 g.) in methanol (150 ml.) containing concentrated hydrochloric acid (25 ml.) was stirred for one hour at room temperature. The solution was diluted with water (1000 ml.) and extracted with light petroleum (2 x 250 ml.) . The combined extracts were washed with sodium hydrogen carbonate solution, brine, and dried. The crude semi-solid product was crystallised from light petroleum to give 22.3 g. (74%) of colourless solid. Recrystallisation from light petroleum afforded an analytical sample of the dienal as prisms, m.p. 66-68°; $\lambda_{max.}$ (in EtOH) 224 mμ , (ε, 17900), $\nu_{max.}$ (in CCl_4) 1690, 1615, 1160, 1095, 1085, 1045 $cm.^{-1}$; (in Nujol) 710 $cm.^{-1}$ (Found: C, 82.15; H, 9.4. $C_{13}H_{18}O$ requires C, 82.06; H, 9.54 %).

The 2,4-dinitrophenylhydrazone of (88, R= CHO), prepared in the usual manner, and eluted in chloroform from Bentonite-Kieselguhr for preliminary purification, crystallised from chloroform-ethyl acetate as fine, dark red needles, m.p. 188-190°. (Found: C, 61.45; H, 5.85: N, 15.2. $C_{19}H_{22}N_2O_4$ requires C, 61.61;

H, 5.99; N, 15.13%)

Notes: (i) The aldehydic C-H absorption characteristic was absent from solution and mull spectra of this αβ-unsaturated aldehyde, (88, R= CHO).

(ii) Samples left at room temperature, even in solution in inert solvents, decompose rapidly to a thick, probably polymeric mass.

Reduction of 1,5-Dimethylbicyclo(3,3,1)non-2-enylidene-9-acetaldehyde (88, R= CHO).

(a) Lithium (2.70 g.) was dissolved in liquid ammonia (150 ml.) and the dienal (88, R= CHO ; 2.0 g.) in dry ether (30 ml.) added over 10 min., with stirring[64]. The ammonia was allowed to evaporate (ca. 1 hr.) after which an excess of 1:1 methanol-ether was added, carefully, to destroy the remaining lithium. The mixture was diluted with water (200 ml.) and extracted well with ether. The extracts were combined, washed with saturated brine, and dried. The crude oily product (2.0 g.) was adsorbed on silica gel (30 g.) from light petroleum. Elution with the same solvent, containing 5% ether, separated an oil (0.24 g.), which crystallised slowly on standing, and had an infrared absorption pattern consistent with the structure (99, R= CHO),

i.e. resulting from reduction of the conjugated double bond ($\nu_{max.}$ 1725, 2700; shoulders at 3020, 1670, and a very strong band at 710 $cm.^{-1}$). Elution with light petroleum - ether (9:1) removed an oily material (1.10 g.), which appeared to be a mixture of the mono-unsaturated alcohol (99, R= CH_2OH) and the aldehyde (99, R= CHO) obtained from the previous fractions, (bands at 1725 and 710 $cm.^{-1}$, as in the aldehyde, but with additional strong bands at 3300 and 1040 $cm.^{-1}$) . Further elution with ether - light petroleum (1:1), and finally with ether, gave a viscous oil (0.65 g.), $\nu_{max.}$ 3400, 1650, 1100-1000, 970, 850, 710 $cm.^{-1}$. This material was later shown to be the dienol (88, R= CH_2OH), arising from reduction only of the aldehydic carbonyl, by virtue of its easy oxidation with manganese dioxide, back to the dienal (88, R= CHO). The characteristic bands chosen for diagnosis of this allylic alcohol system were those at 1650 $cm.^{-1}$ (much stronger than for normal $\nu_{C=C}$ bands), and at 850 $cm.^{-1}$, the C-H deformation band of the trisubstituted double bond.

Thin-layer chromatography revealed that none of these fractions from chromatography was completely pure, but the dienol (88, CH_2OH) was absent from the first (aldehyde) fraction.

(b) Sodium (3.5 g.) was added in small pieces to a solution of the dienal (88, R= CHO, 1.50 g.) in dry ethanol (50 ml.) over two hours. The resulting dark brown solution was diluted with water (200 ml.) and extracted with light petroleum (3 x 100 ml.) The combined extracts were washed with saturated brine solution and dried. Removal of solvent at reduced pressure left a dark brown oil (1.5 g.) which was distilled at 0.05 mm. No boiling point separation was observed, and the material collected (b.p. 94-120°) was obviously a mixture (infrared spectra and refractive indices of successive fractions), similar in composition to the second and third fractions from chromatography of the product obtained as in (a) above.

Oxidation of Mixtures obtained by Reduction of the Dienal (88, R= CHO

(i) The first two fractions from (a) above (1.34 g.) containing mainly (99, R= CHO) and (99, R= CH_2OH), were combined, dissolved in acetone (10 ml.), cooled in ice and excess Jones' reagent[49] added dropwise. The mixture was allowed to stand at room temperature for 2 hr., diluted with water (30 ml.) and extracted with ether (2 x 50 ml.) The combined ether extracts were washed with saturated brine solution, and the acidic material taken up in aqueous sodium hydrogen carbonate solution. The neutral and acidic components were separately isolated in the usual manner. The acidic product (0.65 g.) solidified on cooling, but could not be crystallised satisfactorily without excessive losses. The neutral portion (0.70 g.) was shown to be a mixture of the dienal (88, R= CHO) and 1,5-dimethylbicyclo(3,3,1)non-2-en-9-one (37), by comparison of thin-layer chromatograms and infrared spectra, with those of the pure dienal and ketone. The latter arises from oxidation of the more susceptible double bond.

(ii) Oxidation of the product of reduction with sodium and ethanol (see (b) above), with Jones' reagent, as in (i) above, led to acidic (0.23 g.) and neutral (0.63 g.) material of similar composition to those obtained in (i), as seen from infrared

spectra, and thin-layer chromatograms.

(iii) The third fraction from chromatography in (a) above (mainly the dienol, (88, R= CH_2OH), 0.65 g.) was dissolved in chloroform (20 ml.) and shaken with manganese dioxide (4.0 g.) for 10 hr. The mixture was filtered and solvent removed from the filtrate , to give only the crystalline dienal (88, R= CHO), 0.64 g., (90%), homogeneous on thin-layer plates

Methyl 1,5-Dimethylbicyclo(3,3,1)non-2-enylidene-9-acetate (99, R= CO_2Me). :

Reduction of 1,5-Dimethylbicyclo(3,3,1)non-2-enylidene-9-acetaldehyde, with Recycling; Oxidation and Esterification of the Acidic Product.

A solution of the dienal (88, R= CHO, 15.7 g.) in ether (150 ml.) was added over 20 min. to a solution of lithium (7 g.) in liquid ammonia (1000 ml.), and stirred over 2 hr. The excess lithium was destroyed by careful addition of an excess of 1:1-methanol-ether and the ammonia allowed to evaporate. Excess 6N-sulphuric acid was added, and the solution extracted with ether (2 x 500 ml.) after dilution with saturated brine solution (500 ml.). The combined ethereal extracts were washed with brine, saturated sodium hydrogen carbonate solution, and dried, and solvent removed.

The crude oily product was dissolved in chloroform (100 ml.) and shaken with manganese dioxide (20 g.) for 12 hr. After filtration and removal of solvent, the product was returned to a solution of lithium in ammonia, and the reduction and isolation carried out as before.

The total product was dissolved in acetone (300 ml.) and

Jones' reagent (8N CrO_3 in dilute sulphuric acid) added to the ice-cold, stirred solution. After standing at room temperature for 1 hr., the mixture was diluted with water (1000 ml.) and extracted with ether (2 x 250 ml.). The combined ethereal extracts were washed with saturated brine solution, and the acidic material separated in aqueous sodium hydrogen carbonate solution. From the aqueous alkaline extract, after acidification, extraction in ether, etc., a pale yellow solid (8.4 g.) was isolated. The neutral product (6.0 g.) was similar to that obtained by oxidations (i) and (ii) above, and was discarded.

The total acid product was esterified by treatment with diazomethane in the usual manner. The crude methyl ester contained an impurity (probably the αβ-unsaturated ester (88, R= CO_2Me)), absorbing at 1690 $cm.^{-1}$ in the infrared. The mixture was adsorbed on neutral Woelm alumina (200 g.) from light petroleum, and eluted with the same solvent, and with ether - light petroleum (1:20), which separated the required epimeric ester mixture (4.51 g.), $\nu_{max.}$ 3020, 1744, 1160, 1040, 860, 705 $cm.^{-1}$.

Thin layer chromatography revealed that the material eluted in more polar solvent mixtures was a complex mixture of minor products; these were discarded.

Summary of Yields in Conversions of the Dienal (88, R= CHO) to the Methyl Esters (99, R= CO_2Me)

The acidic products from oxidations (i) and (ii) above, were also esterified, and the methyl esters chromatographed until pure. The yield from the recycled reduction, oxidation and esterification procedure, without intermediate purification, was 25%, calculated from the dienal .

With lithium/ammonia reduction, chromatography, and oxidation of selected fractions, followed by ester formation and purification, the yield was 18%.

Reduction with sodium/alcohol, distillation, oxidation and esterification afforded 8.5%, again calculated from the dienal.

1,5-Dimethylbicyclo(3,3,1)non-2-enylidene-9-ethanol (88, R= CH_2OH)

Sodium borohydride (2g.) was added in 10 min., in small portions, to a solution of the dienal (88, R= CHO, 2.0 g.) in methanol (10 ml.) and the solution held at room temperature for 3 hr. After dilution with water (50 ml.) and acidification with 6N-sulphuric acid, the solution was extracted with ether (2 x 50 ml.), the combined extracts washed with saturated sodium hydrogen carbonate solution, and saturated brine, and dried. Removal of solvent under reduced pressure afforded a viscous oil (1.9 g.) which was virtually pure (thin-layer chromatography) and identical with a sample of the dienol isolated from the product of reduction of the dienal (88, R= CHO) with lithium in liquid ammonia.

Oxidation of 1,5-Dimethylbicyclo(3,3,1)non-2-enylidene-9-acetaldehyde (88, R= CHO).

(a) A solution of the dienal (88, R= CHO, 0.7 g.) in methanol (20 ml.) was added to silver oxide in base (prepared by addition of excess 6N-sodium hydroxide to a solution of 2 g. of silver nitrate in 20 ml. water), and the mixture shaken for

2 hr. at room temperature. After acidification with dilute nitric acid, and removal of precipitated silver metal by filtration, the filter was washed with methanol, the washings and filtrate combined, extracted with ether, and the extract washed with water, sodium hydrogen carbonate solution, and dried. After removal of solvent, only unchanged dienal was recovered. No organic material was recovered from the bicarbonate extract.

(b) Jones' reagent (0.55 ml., 8N CrO_3 in dilute sulphuric acid) was added to an ice-cold solution of dienal (88, R= CHO, 0.40 g.) over 15 min. The reagent was very slowly consumed. After 2 hr. at room temperature, an additional quantity (0.3 ml.) of reagent was added. After 30 min., water (10 ml.) was added, and the resulting mixture extracted with ether (2 x 50 ml.). The neutral and acidic components were separated in the usual manner. The waxy acidic product (0.03 g.) could not be crystallised satisfactorily from ethyl acetate-light petroleum mixtures, but the infrared spectrum was identical with that of 1,5-dimethylbicyclo(3,3,1)non-2-enylidene-9-acetic acid, (88, R= CO_2H) previously obtained from the Reformatsky experiments, and subsequent dehydration. The neutral material (0.32 g.) was again, a mixture of the dienal (88, R= CHO) and the ketone (37), from infrared and thin-layer chromatographic properties.

1,5-Dimethylbicyclo(3,3,1)nonan-9-ylacetic Acid (98, R= CO_2H)

A solution of the dienal (88, R= CHO, 0.05g.) in ethyl acetate (5 ml.) was hydrogenated over palladium-charcoal (10%, 0.02 g.) for 1 hr., when the hydrogen uptake corresponded to 2 double bonds per molecule, with no observed break in the uptake rate. After removal of catalyst by filtration through Celite 535, the solvent was removed under reduced pressure, leaving a low-melting semi-solid product, which showed no olefinic absorption in the infrared, and was obviously the fully hydrogenated aldehyde (98, R= CHO), $\nu_{max.}$ 1730 $cm.^{-1}$.

The crude product (0.048 g.) was oxidised with Jones' reagent in the usual manner, and the resulting acid (98, R= CO_2H), crystallised as colourless prisms, m.p. 137-138.5°, from ethyl acetate - light petroleum.

A small sample of the methyl ester (98, R= CO_2Me) was prepared using diazomethane in ether, and its homogeneity was established by thin-layer chromatography.

Gas-liquid Chromatographic Separation of Methyl 1,5-Dimethyl-bicyclo(3,3,1)non-2-enyl-9-acetate Epimers , (100, 101, R= CO_2Me)

(a) The epimeric methyl esters (100, R= CO_2Me and 101, R= CO_2Me) were separated on a Pye-Argon gas chromatograph, using an analytical column of 10% Apiezon L on 80 - 100 mesh Embacel, at 150°, with a gas flow of 40 ml. per minute. Under these conditions, the faster moving epimer, 'ester A' had a retention time of 13.2 minutes ; the slower epimer 'ester B' was retained for 14.9 minutes. By integration of the traces, a ratio of 1 : 2 for quantities of ester A: ester B was calculated, assuming equal detector responses.

(b) On a 10% poly(ethylene glycol adipate)/80-100 Embacel column, at 150°, gas flow 38 ml. per min., retention times were 18.9 min. for ester A, and 22.9 min. for ester B, the ester A: ester B ratio being 1: 1.9 by trace integration.

(c) Separation on a preparative scale was achieved using the Aerograph (Autoprep) A-700 model, and a 20ft. Ucon (polar) column, (10%), with nitrogen (at 52 p.s.i.) as carrier, and a hot-wire detector. Small samples (ca. 20 microlitres) could be separated at a column temperature of 178-180°, but for larger samples ,

in ether (50 ml.) and the mixture heated under reflux for 4 hr.[50] The crude alcohol isolated from the reaction, had no characteristic sulphonate bands in the infrared, but the required hydroxyl band (3400 $cm.^{-1}$) and an enhanced C-CH_3 band, at 1370 $cm.^{-1}$, had appeared.

The total product (0.56 g.) in acetone (10 ml.) was treated, at 0°C with a slight excess of Jones' reagent[49]. The mixture was then diluted with water (100 ml.), extracted with light petroleum (2 x 30 ml.), the extracts combined, washed with water and sodium hydrogen carbonate solution, and dried. After solvent removal, distillation of the colourless oil (0.51 g.) afforded the ketone b.p. 121-122°/23 mm., n_D^{20} 1.4859, $\nu_{max.}$ 1700, 1370, 1170, 1060 $cm.^{-1}$ (Found; C, 79.2; H, 10.9. $C_{11}H_{18}O$ requires C, 79.46; H, 10.92%)

The 2,4-dinitrophenylhydrazone crystallised from ethyl acetate-methanol as orange prisms, m.p. 109-111° (Found: C, 59.15; H, 6.35. $C_{17}H_{22}N_4O_4$ requires C, 58.94; H, 6.40; N, 16.18%. N, found, 16.2%).

The infrared spectrum of this derivative was identical with that of an amorphous sample prepared after hydrogenation of the rearrangement product (49). The latter sample was difficult to crystallise satisfactorily, and good samples, for a mixed melting point test, could not be obtained. The ketone itself, and the hydrogenated rearrangement product, were identical in the infrared.

Alcohol A:

Ester A (0.03 g.) in ether (2 ml.) was added to a stirred suspension of lithium aluminium hydride (0.02 g.) in ether (2 ml.) and the mixture held at room temperature for 12 hr. Water was added carefully, and the mixture acidified (6N-hydrochloric acid) and the ether separated, washed with saturated brine, sodium hydrogen carbonate solution, and dried. The alcohol was obtained as a colourless viscous oil (0.028 g.) after removal of solvent, and was purified by chromatography on silica gel. The homogeneity of the product was established by thin-layer chromatography, and by gas-liquid chromatography. For the latter, a 10% poly(ethylene glycol adipate)/80-100 mesh Embacel column was used, at 150°, with a gas-flow rate of 40 ml. per min. Under these conditions, the retention time of the alcohol A was 32.2 minutes.

Ester B :

The more polar component from gas-liquid chromatographic separation of the epimeric mixture, ester B, solidified on cooling, to a mass of colourless prisms, m.p. 28-29°.

Acid B:

A specimen of ester B was hydrolysed under the same conditions as above and the acid B crystallised from ethyl acetate-light

petroleum as colourless plates, m.p. 153-154°. A small sample was sublimed for analysis ; (Found, C, 74.75; H, 9.4. $C_{13}H_{20}O_2$ requires C, 74.96; H, 9.68%).

The mixed melting point of acids A and B was found to be 115 - 135°.

Alcohol B:

A sample of ester B was reduced with lithium aluminium hydride under conditions identical with those used for conversion of ester A to alcohol A. The alcohol B was purified by chromatography on silica gel, from which a low-melting solid was obtained. Purity was checked by gas-liquid chromatography , on the same column, under the same conditions described for alcohol A. The retention time of alcohol B was found to be 37.8 min., under these conditions.

Specific Allylic Oxidation of Ester B:

Anti- Methyl 4-Hydroxy-1,5-dimethylbicyclo(3,3,1)non-2-enyl-9-acetate (108, R= CO_2Me, R' = OH).

The epimeric mixture of esters (100, 101; both R= CO_2Me, 2.18 g.), selenium dioxide (0.63 g.), acetic acid (50 ml.) and acetic anhydride (2 ml.) were mixed and heated under reflux for 1 hr. with stirring.[64] After cooling, the mixture was diluted with light petroleum (50 ml.) and filtered free of precipitated selenium. Water (200 ml.) was added to the filtrate, and the organic layer separated, washed twice with sodium hydrogen carbonate solution, followed by saturated brine solution, and dried.

The crude yellow oily residue obtained after solvent removal was added to a suspension of silver powder (0.1 g.) in benzene (20 ml.) and heated under reflux for 30 min. The metal was removed by filtration of the suspension through Celite 535, and the filtrate evaporated. An attempt, at this stage, to separate products by chromatography on Woelm (neutral) alumina was unsuccessful (diagnosed by thin-layer chromatography).

The combined fractions from the column (2.20 g.) were dissolved in dry methanol (25 ml.) in which sodium (0.02 g.) had been dissolved. The solution was heated under reflux for 2 hr.,

cooled, diluted with water (200 ml.) and extracted with ether (3 x 50 ml.). The combined ethereal extracts were washed thoroughly with saturated brine solution, and dried. The recovered pale yellow oil (1.96 g.) was adsorbed on silica gel (80 g.) from light petroleum. The material eluted in light petroleum (0.05g.) was discarded. Elution with ether - light petroleum (1 : 20) separated a colourless oil (0.53 g.) which appeared very similar in the infrared, to the starting material. Gas-liquid chromatography revealed, however, that this material was entirely unchanged ester A , (100, R= CO_2Me) containing no ester B, and identical in the infrared, and on g.l.c., with a sample of pure ester A obtained from preparative g.l.c. Elution with ether - light petroleum (1:1) yielded a colourless oil (1.3 g.) which was identified as the required allylic alcohol (108, R= CO_2Me, R' = OH) ; $\nu_{max.}$ 3550; 1735; 1310, 1280. 1200, 1160, 1010, 870, 770, 710 $cm.^{-1}$

The corresponding acid (108, R= CO_2H, R'= OH) , prepared by alkaline hydrolysis in the usual manner, crystallised from ethyl acetate - light petroleum as minute colourless needles, m.p. 84-98° (probably epimeric at C_4); $\nu_{max.}$ (in Nujol) 1705, 1310, 1280, 1040, 1010, 930, 770 $cm.^{-1}$ (Found: C, 69.35; H, 9.1. $C_{13}H_{20}O_3$ requires C, 69.61; H, 8.99%).

Anti- Methyl 4-Oxo-1,5-dimethylbicyclo(3,3,1)non-2-enyl-9-acetate (109, R= Me).

The 2-en-4-ol ester (108, R= CO_2Me, R'= OH; 1.20 g.) in chloroform (50 ml.) was shaken at room temperature for 17 hr. with manganese dioxide (15 g.). After filtration, the chloroform was evaporated, and the crude oily product (1.0 g.) adsorbed on neutral Woelm alumina (20 g.) from light petroleum. The required enone-ester (109, R= Me; 0.75 g.) was eluted slowly in a range of mixtures of ether and light petroleum (1:20 - 1:1), but was nevertheless homogeneous* , appearing as one peak, retention time 20.7 min., on gas-liquid chromatography on a Pye-Argon chromatograph, with a column of 10% poly (ethylene glycol adipate) at 150°, and a gas flow rate of 32 ml. per min. The oil solidified on standing, and crystallised from light petroleum as colourless prisms, m.p. 59.5 - 60° ; $\nu_{max.}$ (in Nujol), 1740, 1675; 1300, 1280, 1260, 1200, 1000, 840, 820, 700 $cm.^{-1}$;

* This behaviour - very slow elution of one compound, even by a series of solvents of increasing polarity - is characteristic of many ester compounds in the bicyclo(3,3,1)nonane series[29, 64].

$\lambda_{max.}$ (EtOH) 233 mμ(ε, 6850) ;τ= 9.05 (Me, 3H), 8.94 (Me, 3H), 7.64 ($-C\underline{H}_2-CO_2CH_3$), 6.37 ($-CH_2-CO_2C\underline{H}_3$) ; 3.99, 3.82 ($C=\underset{\underset{H}{|}}{C}-C=O$) ; 3.52, 3.36 ($\underline{H}-C=C-C=O$).

(Found: C, 71.0; H, 8.25. $C_{14}H_{20}O_3$ requires C, 71.16; H, 8.53%).

The corresponding acid (109, R= H), prepared by alkaline hydrolysis in the usual manner, crystallised from ethyl acetate - light petroleum as colourless prisms, m.p. 130 - 132°; $\lambda_{max.}$ (EtOH) 232 mμ (ε, 7400); (Found: C, 70.45; H, 8.1. $C_{13}H_{18}O_3$ requires C, 70.24; H, 8.16%).

Allylic Oxidation[64] of Ester A:

Syn- Methyl 4-Oxo-1,5-dimethylbicyclo(3,3,1)non-2-enyl-9-acetate (112, R= Me).

Ester A (100, R= CO_2Me; 0.1 g.) , selenium dioxide (0.10 g.), acetic acid (5 ml.) and acetic anhydride (0.25 ml.) were mixed and heated under reflux with stirring for 17 hr. There was no discoloration in the first hour of heating but thereafter, the suspended solid became slowly darker. The product was isolated in the same manner as the allylic oxidation product of ester B (above

and similarly heated under reflux in benzene with silver powder. No attempt was made to purify the crude acetoxy-ester, which appeared on thin layer chromatography, to be a mixutre of acetate (predominant) and the corresponding, more polar, alcohol (this was confirmed by comparison with the allylic hydroxy-ester obtained below). The expected strong (superimposed) carbonyl absorption at 1730 $cm.^{-1}$, and enhanced $C-CH_3$ band at 1370 $cm.^{-1}$, appeared in the infrared spectrum of a thin film.

The acetoxy-ester (0.10 g.) was hydrolysed by heating under reflux in aqueous methanolic potassium hydroxide (1:5, 6 ml., 0.10g.) and the hydroxy-acid (0.075g.) isolated in the usual manner. No neutral material was isolated, indicating the absence of any tendency for spontaneous lactonisation.

The crude hydroxy-acid was converted to the corresponging methyl ester (0.077 g.) by diazomethane and the product ($\nu_{max.}$ 3300, 1705 $cm.^{-1}$) oxidised with Jones' reagent in the usual manner to the syn-enone-ester (112, R= Me) , 0.068 g., which crystallised on standing. A sample sublimed at 100°/0.1 mm., had m.p. 46-47°, $\lambda_{max.}$ in ethanol, 238 mμ, (ε, 6440), inflexion, 214 mμ ; $\nu_{max.}$ (in Nujol) 1725, 1660; 1160, 940, 700 $cm.^{-1}$; (Found: C, 71.05; H, 8.35. $C_{14}H_{20}O_3$ requires C, 71.16; H, 8.53%).

Incomplete Allylic Oxidation of Alcohol A (100, R= CH_2OH)

Alcohol A (0.102 g.), selenium dioxide (0.05 g.), acetic acid (4 ml.) and acetic anhydride (1.0 ml.) were mixed and heated under reflux for 4 hr. No red coloration or blackening occurred in the first hour of heating. The product was isolated as in the allylic oxidation of ester A (above). Thin-layer chromatograms of the product, when compared with a sample of the acetate of alcohol A (prepared from a small sample of alcohol A with acetic anhydride in pyridine, and isolated in the usual way) indicated that this was the main component of the mixture obtained; the minor, more polar component was taken to be the diacetate.

The crude product was hydrolysed with aqueous methanolic potassium hydroxide under reflux, and subsequently oxidised with manganese dioxide in chloroform, in the manner described before; the crude product showed minimal absorption at 1670 $cm.^{-1}$ in the infrared, confirming the suspicion that allylic oxidation, in the first place, was grossly incomplete.

Low Yield Oxidations of Anti- 1,5-Dimethyl-4-oxobicyclo(3,3,1)-non-2-enyl-9-acetic Acid (109, R= H).

(a) The anti- enone-acid (0.042 g.) and chromium trioxide (0.2 g.) were dissolved in acetic acid (5 ml.) and the solution heated under reflux with stirring for 30 min. The solution was cooled, diluted with water (50 ml.) and extracted with ether (3 x 25 ml.) after saturating with sodium chloride . The combined extracts were washed with saturated brine solution, and dried. Removal of solvent gave a very small amount (0.002 g.) of a greasy film, which could not be induced to crystallise.

(b) The enone-acid (0.013 g.) in ethyl acetate (5 ml.) was saturated with ozone at -70°C. The solution was mixed with hydrogen peroxide (30% aqueous, 5 ml.) and acetic acid (0.1 ml.) and shaken with occasional warming for 1 hr. The aqueous layer was saturated with sodium chloride, and the ethyl acetate solution, washed with saturated brine, and dried. Removal of solvent afforded a viscous, greasy oil (0.005 g.) which showed acidic features in the infrared , with a broad carbonyl band, but no anhydride bands around 1800 $cm.^{-1}$ The product could not be crystallised, and its complete solubility in ether, suggested that none of the required tricarboxylic acid was present.

Osmylation Experiments:[66] Hydroxylations of:

(i) Methyl 1-Methyl-4-oxobicyclo(3,3,1)non-2-enyl-5-acetate[64], (Model Compound, 113, R= =O).

The enone-ester (0.25 g.) was dissolved in dry ether (10 ml.) and pyridine (0.237 g.) added. To this mixture, was added a solution of osmium tetroxide (0.305 g.) in ether (10 ml.) and the mixture held at room temperature for 15 hr. The dark brown complex of osmate and pyridine was collected on a filter, washed with ether, and suspended in ethyl acetate (10 ml.). Gaseous hydrogen sulphide was passed into the suspension for 30 min., the precipitated osmium sulphide removed by filtration, and the solvent removed from the filtrate in vacuo. The crude diolone-ester (114, R= =O; 0.180g., 62%) was homogeneous on thin-layer chromatograms; $\nu_{max.}$ 3550; 1740-1700 $cm.^{-1}$

(ii) Methyl 1-Methyl-4-hydroxybicyclo(3,3,1)non-2-enyl-5-acetate[64], (Model Compound, 113, R= OH).

The enol-ester (0.50 g.) obtained by reduction of the enone (113, R= =O) with sodium borohydride in methanol, was osmylated as in (i) with osmium tetroxide (0.635 g.), and pyridine (0.47 g.) in ether. The triol-ester (114, R= OH, 0.29 g., 50%), recovered from

the decomposed complex, was pure on thin-layer plates; $\nu_{max.}$ 3500 (very strong), 1740 $cm.^{-1}$.

(iii) Anti- Methyl 1,5-Dimethyl-4-oxobicyclo(3,3,1)non-2-enyl-9-acetate (109, R= Me).

The enone-ester (0.083 g.) was treated as above, with osmium tetroxide (0.100g.) and pyridine (0.079 g.) in ether. The purple crystalline complex was decomposed as before, and the crude product purified by chromatography on silica gel. Ether as eluant removed the required oily diolone-ester (116, 0.035 g., 37%); $\nu_{max.}$ (in CCl_4) 3560, 3460; 1740, 1700 $cm.^{-1}$.

(iv) Syn- Methyl 1,5-Dimethylbicyclo(3,3,1)non-2-enyl-9-acetate (100, R= CO_2Me, ester A).

Ester A (0.10 g.) was treated as above, in this case using pyridine (0.120 g.) and osmium tetroxide (0.130 g.) in ether. The brown amorphous complex was decomposed as above , and the viscous diol-ester (115, 0.085 g., 77%) so obtained was homogeneous on thin-layer chromatograms; $\nu_{max.}$ 3550; 1740; 1050-1000 $cm.^{-1}$

Periodate Oxidation[67] of Osmylation Products:

(a) The diolone-ester (114, R= =O, 0.15 g.), from (i) above, in methanol (5 ml.) was mixed with an aqueous solution of sodium periodate (5%, 10 ml.) and stirred for 1 hr. at room temperature, after which a precipitate of sodium iodate had been deposited. Water (50 ml.) was added, and the solution extracted with ethyl acetate (4 x 50 ml.). The combined extracts were washed with saturated brine solution, and dried. The oily product still showed strong hydroxyl absorption in the infrared ($\nu_{max.}$ 3550; 1740; 1200-1100 (very intense), 1000 $cm.^{-1}$). There was no indication from the spectrum, of the presence of aldehyde. It was returned to the same aqueous methanolic sodium periodate mixture as above and stirred over 12 hr. at room temperature. After re-isolation as above, the product was identical in the infrared, and on thin-layer chromatograms, with the product from treatment for 1 hr. The latter technique indicated that the product consisted of two main compounds, and two subsidiary components.

(b) The triol-ester (0.25 g.) from (ii) above, was treated overnight with 5% sodium periodate solution (20 ml.) as in (a) above. The product showed similar infrared absorption characteristics ($\nu_{max.}$ 3550, 1740, no aldehyde bands around 2700 $cm.^{-1}$), although the carbonyl intensity was weaker, and distinct bands appeared in the multiplet between 1200 and 1000 $cm.^{-1}$. On thin layer plates, the product was seen to consist of very similar constituents as in (a) above.

(c) The diolone (116, 0.035 g.) from (iii) above was oxidised with sodium periodate solution as usual, and gave a viscous oil (0.028 g.) which exhibited a complex infrared spectrum (broad OH band between 3500 and 3300 $cm.^{-1}$ (weak); 1740, 1700 (sh) $cm.^{-1}$). A complex series of stains was obtained from thin layer chromatographic examination.

Further Oxidation of Primary (Periodate) Oxidation Products:

(i) The crude product (0.10 g.) from (a) was dissolved in acetone (2 ml.) and titrated with Jones' reagent[49] at 0°C. The mixture was diluted with water (10 ml.) and extracted with ethylacetate (3 x 20 ml.). The combined extracts were washed with saturated brine solution, and then with saturated sodium hydrogen carbonate solution, and dried. The alkaline extract was acidifed and re-extracted with ethyl acetate, after saturating with sodium chloride, but no organic material was recovered from this. The neutral product, a colourless solid, obtained after removal of solvent from the first extract, crystallised from ethyl acetate - light petroleum as prisms, m.p. 150-153°; $\nu_{max.}$ (in CCl_4) 1805, 1770, 1760-1740 $cm.^{-1}$, identified as 119.

(ii) The product from (b) above, after Jones' oxidation, gave the same anhydride (m.p., mixed m.p. infrared spectrum) as that obtained from (i) above.

(iii) Jones' oxidation of the product from (c) above, gave a very poor yield (0.005 g.) of non-crystalline product. The yields in this series, precluded its use as a suitable oxidative route from the anti-enone-ester (109, R= Me) to the monocyclic system required.

Model Experiment :

Permanganate Oxidation of Methyl 1-Methyl-4-oxobicyclo(3,3,1)-non-2-enyl-5-acetate (113, R= =O).

A stirred solution of the enone-ester model compound[64] (113, R= =O, 0.10 g.) in acetone (5 ml.) at room temperature was titrated with acidified aqueous potassium permanganate (2.5% in N sulphuric acid), until a permanent pink coloration persisted in the supernatant liquid; manganese dioxide was removed by filtration through Celite 535, and the filter washed with acetone (10 ml.) . The filtrate and washings were diluted with saturated brine solution (20 ml.) and extracted with ether (3 x 50 ml.). From the ether solution of the product, acidic and neutral fractions were separated by extraction with sodium hydrogen carbonate solution, and isolation in the usual way. The solid acidic product (0.065 g.) crystallised from ethyl acetate as prisms, m.p. 185-195°, $\nu_{max.}$ (in Nujol) 1720, 1700 $cm.^{-1}$
The neutral product (0.020 g.), also solid, proved to be identical with the anhydride-ester (119,) previously obtained from model osmylation and oxidation experiments on the enone-ester (113, R= =O).

Methyl 2,6-Dimethyl-2,6-dicarboxycyclohexylacetate (125, R= Me, R'= H) and the Corresponding Anhydride, Anti- Methyl 1,5-Dimethyl-2,4-dioxo-3-oxabicyclo(3,3,1)nonanyl-9-acetate (124, R= Me).

The anti-enone-ester (109, R= Me, 0.167 g.) in acetone (2 ml.) was titrated with a cold acidic aqueous solution of potassium permanganate (2.5% in N sulphuric acid), with stirring, until the supernatant liquid had a persistent colour of excess reagent. The mixture was then diluted with saturated brine solution (50 ml.), filtered, and the filter washed with acetone (5 ml.) and ethyl acetate (50 ml). The filtrate and washings were shaken, separated, and the aqueous layer extracted with a further three portions of ethyl acetate (20 ml.). The extracts were combined and washed with saturated brine solution. The acidic material was removed by extraction with saturated sodium hydrogen carbonate solution. The neutral material (0.06 g.) recovered from the dried ethyl acetate extract crystallised on cooling, and a pure sample of the ester-anhydride crystallised from ether - light petroleum as colourless needles, m.p. 130-131°; $\nu_{max.}$ (in CCl_4), 1800, 1760, 1743; 1383, 1230, 1130, 1086, 1030 $cm.^{-1}$; (Found: C, 61.25; H, 7.05. $C_{13}H_{18}O_5$ requires C, 61.40; H, 7.14%)

Acidification of the alkaline extract, followed by saturation with sodium chloride , and extraction with ethyl acetate, finally

afforded the solid acidic product (0.08 g.). A pure sample of the triacid-monomethyl ester crystallised from ethyl acetate as prisms, m.p. 172-175°. The sample underwent what appeared to be a transition in the crystal state, between 140 and 150°, before melting; $\nu_{max.}$ (in CCl_4) 1740, 1710; 1370, 1280, 1260, 1155 $cm.^{-1}$ (Found: C, 57.45, H, 7.55. $C_{13}H_{20}O_5$ requires C, 57.34; H, 7.40%)

Above the melting point, the sample loses water, to form the anhydride. found to be present from the 'second' melting point 125-128°. A melted and re-solidified sample was identical with the anhydride in all respects.

Trans, meso-2,6-Dimethyl-2,6-dicarboxycyclohexylacetic Acid (125, R=R'=H; and 2).

A mixture of the anhydride-ester (124, R= Me) and the triacid monomethyl ester (0.087 g.) was heated under reflux in aqueous methanolic potassium hydroxide (1:2, 15 ml., 0.30 g.) for 2 hr. The solution was diluted with saturated brine solution (20 ml.), and extracted with a portion of ether (20 ml.) which was discarded. The aqueous alkaline layer was acidified with dilute sulphuric acid and extracted with ethyl acetate (3 x 50 ml.). The extracts were combined, washed with brine solution, and dried. Removal of

solvent afforded the tricarboxylic acid (0.053 g.) as a colourless solid, m.p. (195) 205-210°. After two recrystallisations from glacial acetic acid, the melting point was raised to 208-212° *; $\nu_{max.}$ (KCl disc, high resolution), 1714, 1550 (broad), 1460, 1390 $cm.^{-1}$ The infrared spectrum was virtually identical with that of an authentic sample of the C_{12}-tricarboxylic acid.[11] (Found: C, 55.90; H, 7.20. $C_{12}H_{18}O_6$ requires C, 55.81; H, 6.98%).

The corresponding trimethyl ester was prepared in the usual manner by treatment of the acid with diazomethane, and was identical in the infrared with a sample of authentic triester, prepared in the same way: $\nu_{max.}$ (in CCl_4), high resolution, 1732, shoulder at 1740; 1430, 1389, 1260, 1237, 1194, 1173, 1145, 1128, 1105 $cm.^{-1}$ (see Fig. 2 in the preceding Discussion.); τ = 8.85(6H); 7.90(2H),

* It was found that a mixed melting point was not the best criterion of identity. Presumably due to the tendency for anhydride formation, the authentic and synthetic samples showed considerable variation in melting points, between 200 and 215°, depending on particle size and rate of heating. Under the strictly controlled conditions prescribed by Ruzicka[11] the bulk of the authentic, synthetic and mixed samples melted over the range 208-212° (literature value, 212-213°).

6.41 (9H); 6.73 (1H, quartet).

The authentic and synthetic triesters were pure, and indistinguishable on thin-layer chromatograms, and on gas-liquid chromatograms (run on three columns: 1% Poly (ethylene glycol) on Embacel, at 150°; 10% Apiezon L/Embacel at 200°; 1% cyclohexanedimethanolsuccinate/Embacel, at 175°). The mass spectra of synthetic and authentic esters were also identical (Parent, 300; calc. 300); the cracking pattern is analysed in the Discussion of Part I.

Some Attempts to Confirm the syn-Relationship Between the Cyclohexene Ring, and the C_9-side-chain in the A Series, (100). Lactonisation Studies[69].

(i) The acid A (100, R= CO_2H; 0.05 g.) was warmed at 100° for 10 min., with concentrated sulphuric acid (0.5 ml.). The neutral material recovered appeared to be the dimeric anhydride (0.03 g.), $\nu_{max.}$ 1780, 1740 $cm.^{-1}$; 705 $cm.^{-1}$. Base hydrolysis of this material regenerated impure acid A.

(ii) The acid A (100, R= CO_2H; 0.10 g.) and p-toluene-sulphonic acid monohydrate (0.35 g.) in benzene (5 ml.) was heated under reflux for 1 hr. The benzene solution was washed with water, dried, and solvent removed. Only unchanged acid was recovered.

(iii) A sample of mixed acids A and B (100, 101, both R= CO_2H), 1.04 g.,in sodium hydrogen carbonate solution (0.5N, 30 ml.), was mixed with a solution of iodine (2.54 g.) and potassium iodide (5.0 g.) in water (15 ml) and the mixture left in the dark for 24 hr.[71] No precipitate was deposited; the solution was acidified (6N-sulphuric acid) and treated with excess sodium hydrogen sulphite solution. The cleared solution was then extracted

with ether (3 x 50 ml.), the extracts combined, washed with saturated brine solution, and dried. Only unchanged starting material was recovered.

(iv) A sample of the syn-acid A (100, R= CO_2H; 0.100 g.) was dissolved in acetic acid (1 ml.) containing boron trifluoride etherate (0.2 ml.). The solution was heated under reflux for 2 hr., diluted with water, extracted with ether, and the combined extracts washed with saturated brine solution, sodium hydrogen carbonate solution, and dried. The alkaline extract was acidified and the resulting precipitated acid collected by filtration, and air-dried. A specimen was treated with diazomethane, and the esters chromatographed (analytically) on a 0.5% Apiezon L column at 150°. Four major components were revealed.

The neutral product obtained from the first extraction (0.06 g.) was examined on the same column, and found to consist of at least six components, one largely predominating. The infrared spectrum ($\nu_{max.}$ (in CCl_4), 1740 $cm.^{-1}$, 1750 (shoulder), 720 $cm.^{-1}$) was unlike any previously encountered in the series. No change in the product was produced by warming with aqueous sodium hydroxide solution. The crude material, with acidified 2,4-dinitrophenylhydrazine solution, afforded a solid derivative. No attempt was made to separate pure components of the mixture.

(v) Acid A (0.10g.) and methanesulphonic acid (0.40g.) were mixed and warmed on a steam bath for 15 min.[70] Water, (10 ml.) was added, and the mixture extracted with ether. The extract was washed with sodium hydrogen carbonate solution, and dried, but no neutral material was obtained from solvent evaporation.

(vi) No lactonic material was obtained from any of the following operations:

(a) Hydrolysis of *syn* methyl 4-hydroxy-1,5-dimethylbicyclo-(3,3,1)non-2-enyl-9-acetate (precursor of 112), followed by acidification with dilute acid.

(b) Hydrolysis of crude *syn* methyl 2,3-dihydroxy-1,5-dimethyl-bicyclo(3,3,1)non-2-enyl-9-acetate (115) and subsequent acidification.

(c) Reduction of the *syn* enone-ester (112), by hydrogenation, followed by borohydride reduction in the usual manner, to 127.

Note: Control experiments with the acid B (101, R= CO_2H) were carried out, under the relevant conditions, in the cases (ii) and (v) above. Again, no lactonisation was detected.