SYNTHETIC APPROACHES TO MEDIUM RINGS.

THESIS

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by

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SUMMARY.

Synthetic routes to 10-membered carbocycles via doubly-bridged tricyclic precursors have been investigated. Starting from dimedone, diethylsuccinylsuccinate and 2-phenylbicyclo-(3;3;1)-nonane-3,9-dione, several novel compounds and complex rearrangements were encountered but no tricyclic compounds were formed. In the course of these studies it was noted that non-enolisable β-diketones give rise to a characteristic $\nu(C{=}O)$ doublet in the infra-red of $\Delta\nu(C{=}O)$ ca. 30 cm.$^{-1}$.

The synthesis of a cyclodecane derivative by cleavage of the one carbon bridge of a bicyclo-(5;3;1)-undecenone, by a process already applied to a bicyclo-(3;3;1)-nonenone, has been studied. It was found, that for reasons of stereochemistry, this procedure is limited to smaller rings.

I wish to express my sincere appreciation and gratitude to my supervisor, Dr. G. L. Buchanan for the encouragement and assistance he has given me during the last three years and to Professor R. A. Raphael, F.R.S., for the opportunity to carry out this research.

I also wish to thank Mrs. F. Lawrie and Miss A. M. Robertson for recording the high resolution infrared absorption spectra; Mr. J. M. L. Cameron, B.Sc., and his staff for micro-analyses; Mr. J. Gall and Mr. J. Lennon for recording proton magnetic spectra; Mrs. J. McLean for recording mass spectra; Mr. G. Milmine and his staff for various large scale preparations and syntheses and Dr. G. Ferguson and Mr. R. Pollard for X-ray crystallographic studies.

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CONTENTS.

INTRODUCTION.

Interest in medium ring compounds containing eight to eleven carbon atoms has increased steadily over the past half century. The introduction of the "acyloin" condensation[1,2,3,] in 1947 by Prelog and independently by Stoll, effectively provided a synthetic route to simple medium carbocycles and served to stimulate research in this area. However in recent years, the greatest single factor contributing to the increasing interest in medium rings has been the discovery in nature of compounds containing carbon rings of nine, ten and eleven members in common plant constituents. Prior to this the existence of larger rings in nature had been established only in the macrocyclic fragrant ketones and these, moreover, were the products of animal metabolism.

Sorm[4] produced the first proof in 1949 of the occurrence of a medium sized alicylic ring in nature in the course of studies in caryophyllene, (1). Since then other sesquiterpenes isolated have been shown to contain similar ring systems, notably humulene (2), zerumbone (3), germacrone (4), and betulenols (5a) and (5b) and the series of sesquiterpene lactones of the pyrethrosin type (6).

The great ease with which unsaturated derivatives of germacrone (7) undergo stereospecific transannular cyclisation, most generally to compounds of the selinane (8) skeleton - that is in the case of the lactones into relatives of santonin (9) - suggests a biogenetic significance of such reactions. It appears likely that the cyclodecane type lactones are the primary products of nature and that lactones of the santonin and guaianolide (10) series are formed from the secondary processes analogous to the stereospecific transannular reactions. A further pointer in the same direction is the frequent occurrence of lactones of the germacrone series in the Compositae in which santonin derivatives commonly occur. Actual proof of the occurrence of such cyclisation reactions in nature is still lacking but several people are involved in radiotracer studies in an effort to throw more light on the situation.

The biogentic role of medium rings has been fully discussed by Hendrickson[5] in a paper considering the biogenesis of sesquiterpenes. He has postulated several ten and eleven membered ring intermediates, the conformation of which would direct both the structure and stereochemistry of the sesquiterpenes formed from them by further reactions. Scheme 1 outlines the two main pathways from which most of the bicyclic and large ring monocyclic sesquiterpenes can be envisaged to arise. This scheme is not complete and omits intermediates involved in the 6- ring monocyclic and carotane series of sequiterpenes. The cations (15), (16), (17) and (18) are formed via the non-classical intermediates (13) and (14) by ionisation of the allylic pyrophosphate grouping and participation of the terminal double bond of cis- and trans-farnesol, (11) and (12) respectively, leading to cyclisation.

Examples of the sesquiterpenes, which can be satisfactorily classified as arising from one of these cationic medium rings, are listed below. This is in no way a complete list.

a) Caryophyllene (1), α- and β- betulenol (5a) and (5b) and himachelene (19a) and (19b), longifolene (20),... etc., could all arise through (15).

b) Muurolenes (21), copaene (22), muskatone (23) and helminthosporal (24) all from (16).

c) Probably the largest group are formed via the cation (17) and include germacrone (4), linderane (25), Costunolide (26), parthenolide (27), pyrethrosin (28), arctiopicrin (29), scabiolide (30) and guaiane (31) sesquiterpenes.

d) Humulene (2) has been postulated to arise from the trans-farnesyl cation (18)[6].

Although the foregoing ideas regarding the biogenesis of sesquiterpenes are useful in applying some order to this class of compounds, it must be remembered that in nature the enzymic system bringing about the conversion of the pyrophosphate precursor to the sesquiterpene, would do so in a fully concerted manner and no structures with full formal charges could be tolerated. The interesting point which emerges from this treatment is the **fact** that medium sized rings would appear to play a major role in the biogenesis of smaller rings in the sesquiterpene field.

Apart from their occurrence in nature, medium sized rings have excited much interest in their own right. As a class, they behave abnormally in chemical reactions and are difficult to prepare. The existence of steric interference between non-adjacent atoms in medium rings is a direct result of the geometry of these systems. Brown[7] termed this I-strain and from it one can explain many of the less expected chemical characteristics of these systems. I-strain can be relieved in a medium ring by increasing the C-C-C angles of the ring. A driving force is thus produced for tetrahedral centres to convert readily to trigonal ones if given the opportunity. The enhanced rates of solvolysis of cyclodecyl bromides and tosylates and the dissociation of cycloalkanone cyanohydrins bear out this point. The reverse case of an Sp^2 centre changing to an Sp^3 one is consequently an unfavourable process, an effect which is exemplified in the lack of reactivity of cyclodecanone to ketonic reagents.

The lack of a uniform interdependence of physical and chemical properties with ring size has provided a formidable challenge to both physical and organic chemists. X-ray analysis techniques have been applied by Dunitz[8] and his co-workers, in an attempt to elucidate the conformations of the 9-, 10- and 12- membered cycloalkanones. Although the position of the hydrogen atoms have not been determined accurately, calculations, based on reasonable assumptions, show that transannular strain is a very real effect in the 9- and 10- membered analogues. The conformations obtained by Dunitz for these rings indicate a balance between I- and Baeyer strain with effectively no Pitzer strain in the 10- ring but some in the 9- ring, due to the partial eclipsing of the hydrogen atoms. The C-C-C angles average out at 117° in both 9- and 10- rings whereas a structural analysis of cyclododecanone showed the average C-C-C angles to be 112°. This is accompanied, in the latter system, by the reduction of both Pitzer and transannular strains.

A direct result of the increased strain in medium sized rings is illustrated by the graph, Figure 1 [9] which shows the ring size plotted against the excess energy of the cycloalkane over an infinite polymethylene chain.

Much of the chemistry of medium rings is governed by their conformation which, as has been indicated, often holds opposite sides of the ring in close proximity to each other. This proximity effect and the accompanying transannular reactions have been adequately reviewed recently by Cope, Martin and McKervey [10]. The reactions proceed through a variety of intermediates such as carbonium ions, carbenes, free radicals or a combination of these. However carbanion formation is a favourable process in a medium ring, as has already been discussed with respect to Sp^2 and Sp^3 hybridised centres, and probably the majority of transannular reactions result through an intermediate of this type. For this reason solvolytic and nucleophilic substitution reactions provide many of the examples.

The reaction of 1- methylcyclodecane - 1,6 - diol (32), deuterated at C_6, with phosphoric acid [11], demonstrates a 1,6 - hydride shift. The resulting product was 6- methylcyclodecanone containing only one deuterium atom per molecule. Although evidence has been forwarded for 1,5 - hydride shifts in cyclodecane rings, in this case an exclusively 1,6 - shift was observed. The reaction pathway is shown in Scheme 2.

The solvolysis of the longifolene derivative (33) provides an example of a 1,5 - hydride shift across a 9- membered ring[12], (Scheme 3). Transannular hydrogen transfer can occur by a free radical process as is seen in the case of the formation of the bicyclic alcohol by irradiation of (34)[13]. From just these few examples given it is clearly apparent that the chemistry of medium rings is an area of considerable potential for both physical and organic chemist.

Ruzicka and co-workers[14] prepared the many membered ring ketones, which they used as starting materials for other compounds of this group, by the pyrolysis in vacuo of the thorium, yttrium or cerium salts of aliphatic α,ω- dicarboxylic acids. However this method suffers from several disadvantages not least of these being the very low yields for carbocycles of greater than 9- members, in most cases being only a fraction of a percent. A graph of yield plotted against ring size is shown in Figure 2 [15].

The introduction of the dilution principle by Ziegler and co-workers[16] in 1933 improved the yields of macrocycles of 14- membered size and greater but did little to increase the yields of medium sized rings containing 8 to 12 carbon atoms. The basic steps involved in Ziegler's method are outlined in Scheme 4.

Other methods for synthesising rings of greater than medium size and using high dilution techniques include the improved Dieckmann reaction (Leonard 1959) employing potassium tertiary butoxide on the α,ω- long chain diester (36) and the route devised by Blomquist (1948) for ketene cyclisation (see Scheme 5).

No satisfactory route to medium rings was available until the introduction of the very advantageous acyloin synthesis [1, 2, 3], which allows the preparation, in very good yields of ring compounds having more than eight members. This synthesis leads from the easily accessible dicarboxylic acid esters in a simple way without using great dilutions, to macrocyclic acyloins, which can be easily converted into various other compounds. The reaction is recorded in Scheme 6 and the yields in Figure 2. The disadvantage of the acyloin condensation is that when unsaturated and substituted medium rings are required, the synthesis of the initial long chain diester to incorporate these features or substituents which will allow modification after ring closure, is most often both tedious and difficult. Thus it is necessary that other synthetic pathways be developed to cope with more complicated medium rings.

A very elegant demonstration of the synthesis of a nine membered ring is found in Corey's recent total synthesis of a caryophyllene [17]. The establishment of the desired bicyclo-(7:2:0)-undecane skeleton of caryophyllene posed the alternatives : (1) direct closure of a nine membered ring from an appropriately substituted cyclobutanone and (2) conversion of a cyclobutane derivative to a tricyclic structure of such a nature as to allow generation of the 9- membered ring from two smaller rings by bridge scisson. The difficulty of selectively introducing the necessary unsaturation after or before formation of the 9- ring in (1) led Corey to reject this method and concentrate on method (2). The essence of the synthesis is shown in a flow sheet (Scheme 7) and, as can be seen, the 9- ring is formed by the internal elimination of a toluenesulphonate grouping in a (4:3:0)-bicyclic system.

The basis of this elimination was reported previously by Wharton [19] in which he describes the smooth elimination in the monomesylate (37) with concomitant formation of the cyclodecane (38). A similar type of elimination reaction leading to 8- and 9- membered alicycles was published recently[18] and involves the scisson of the bridge in a (3:3:1)- and (4:3:1)- bicyclic system to give 8- and 9- rings respectively. The para-toluenesulphonates (39) and (40) on **treatment** with sodium ethoxide yielding (41) and (42).

Following on this was Marshall's[20] synthesis of a cyclodecene from cyclooctanone via a (5:3:1)-bicyclic compound by bridge fisson using the same reaction (see Scheme 8).

In the present investigation it was envisaged that bridge bicyclic molecules of type (43) or tricyclic structures of type (44) would prove to be suitable intermediates in synthetic routes to 10-membered rings.

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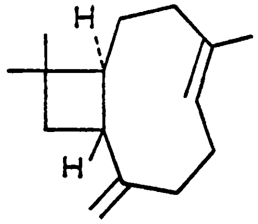

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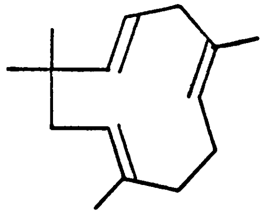

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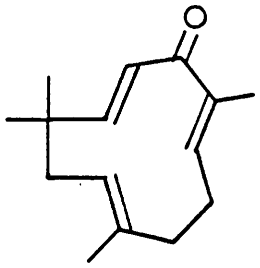

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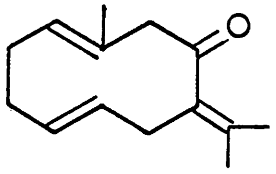

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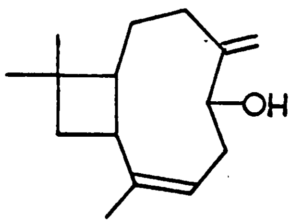

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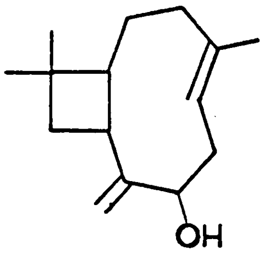

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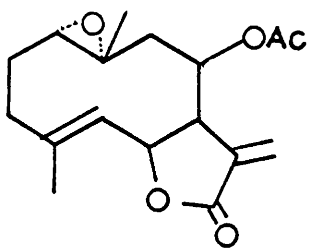

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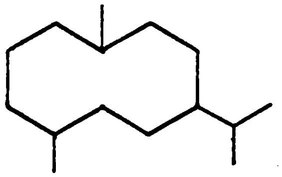

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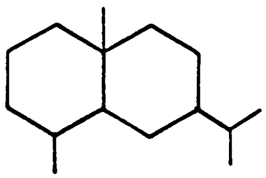

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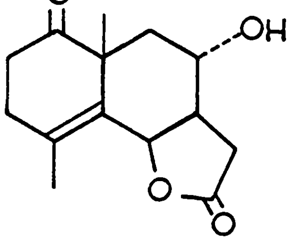

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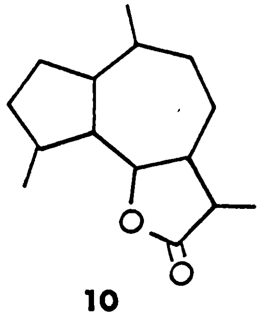

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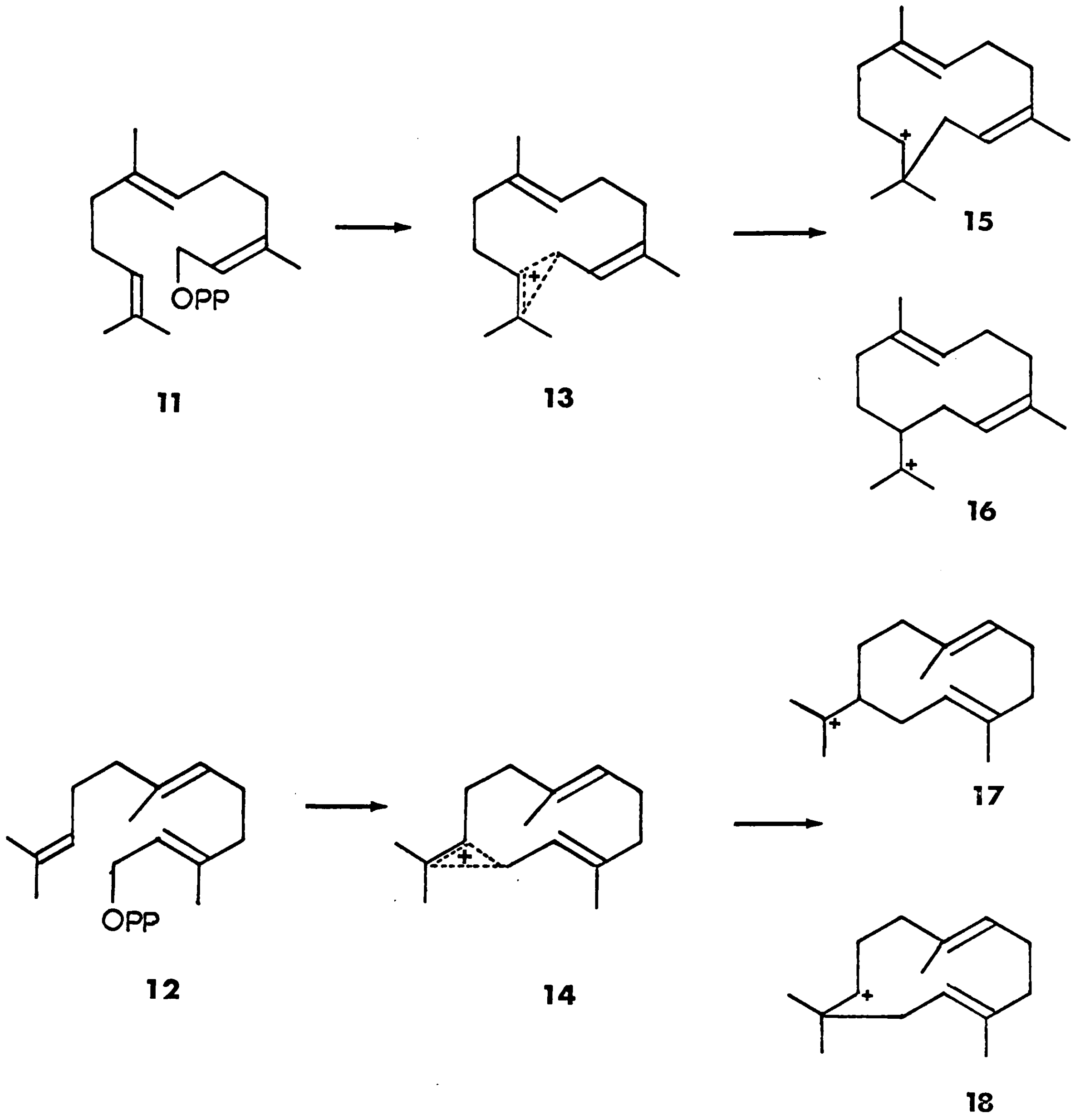
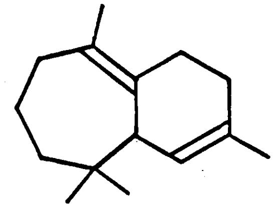


Scheme 1.



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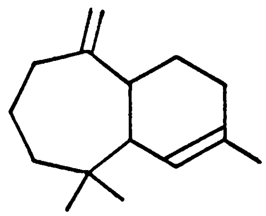

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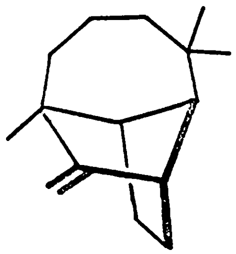

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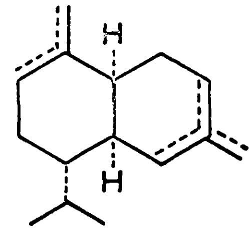

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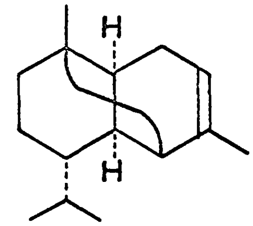

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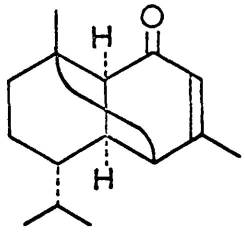

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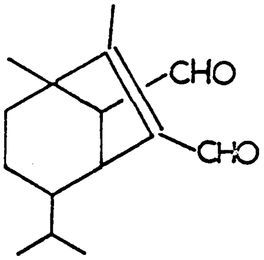

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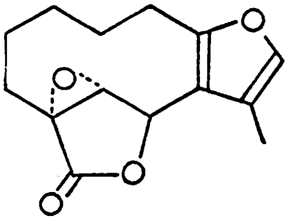

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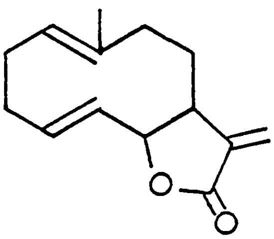

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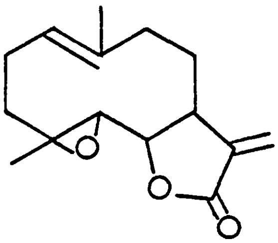

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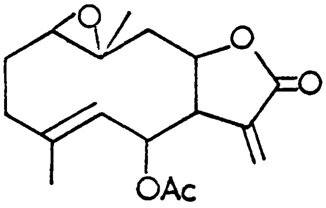

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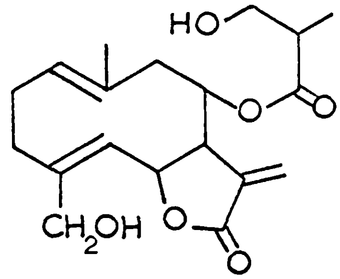

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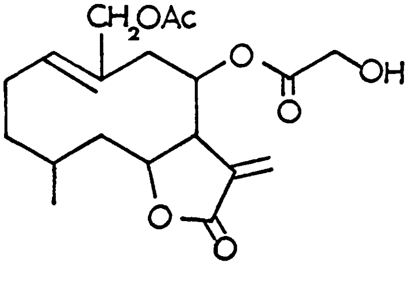

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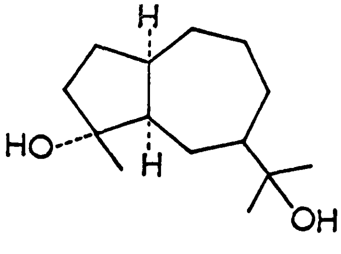

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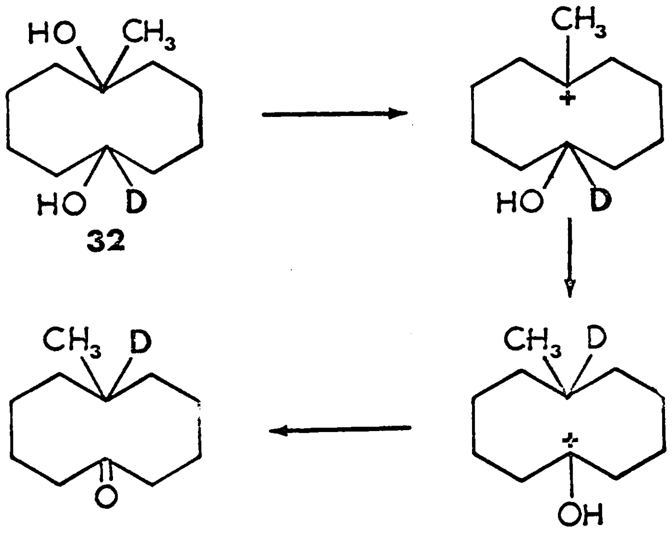

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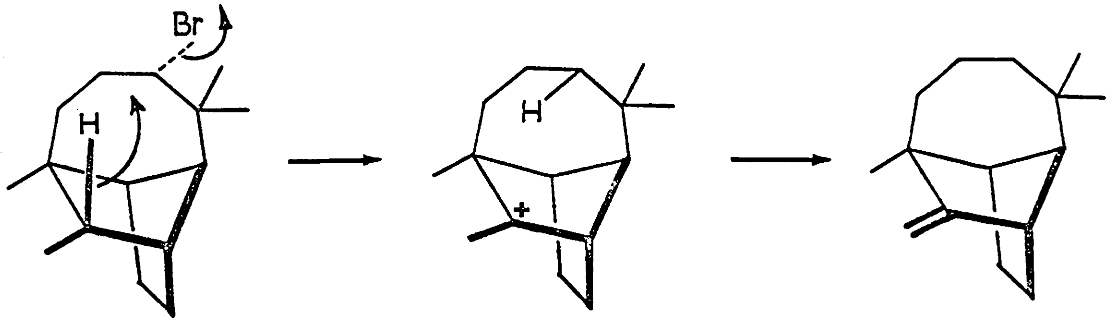

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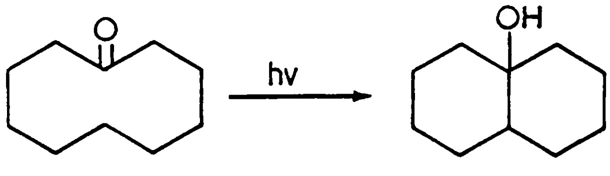

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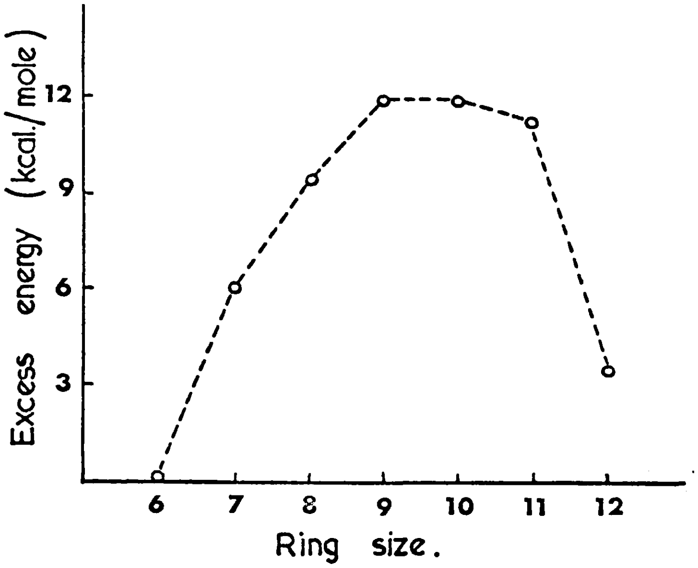
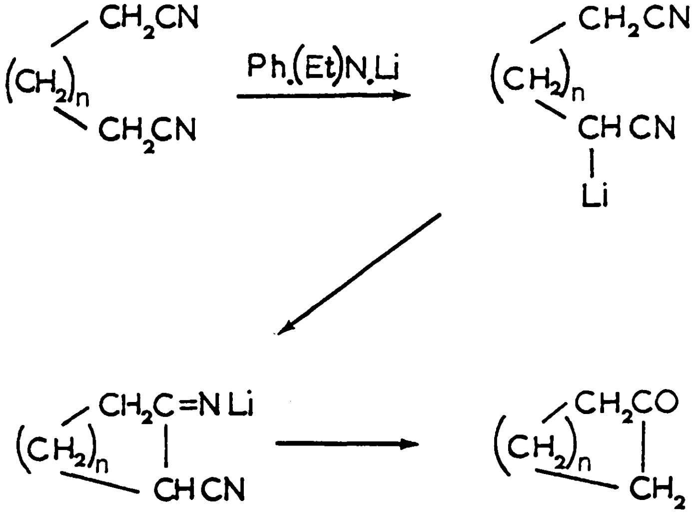


Figure 1.



Scheme 4.

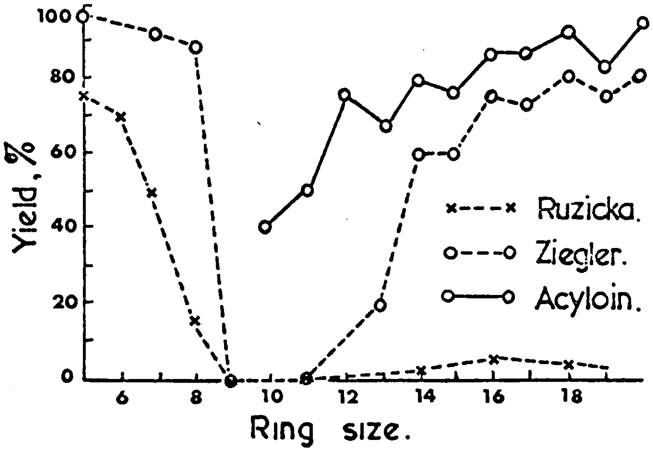
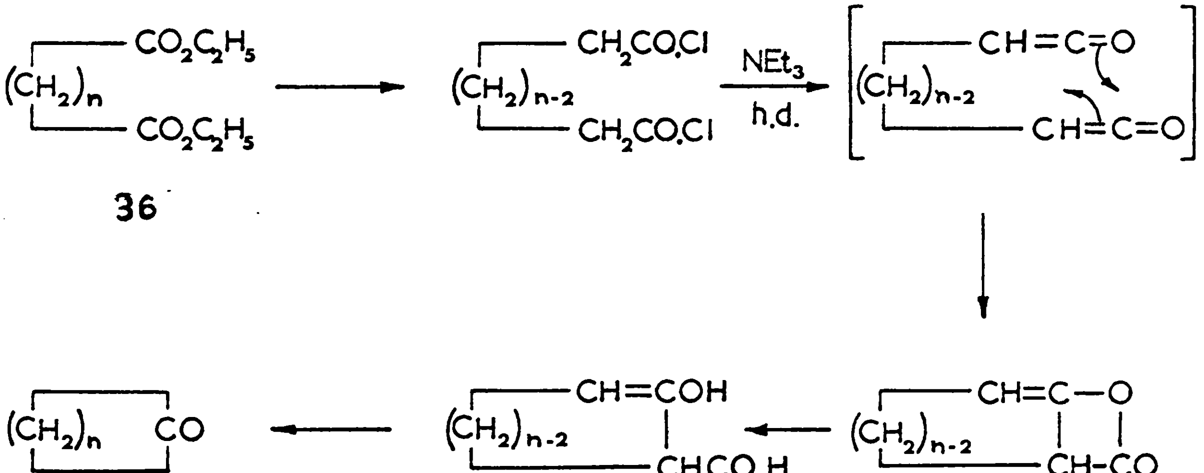
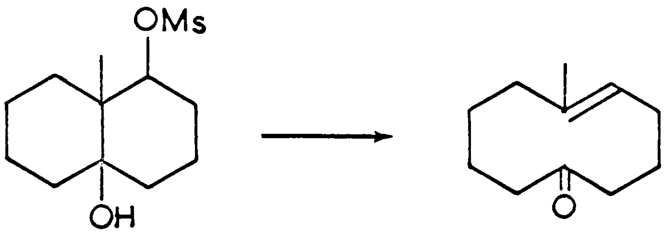


Figure 2.



Scheme 5.



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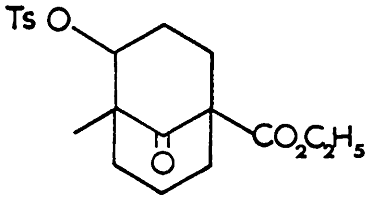

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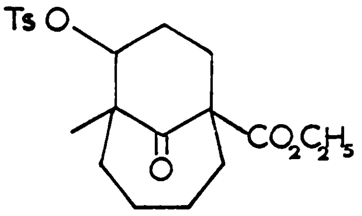

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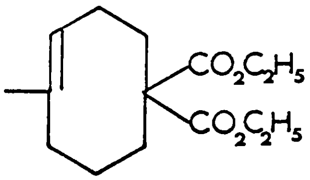

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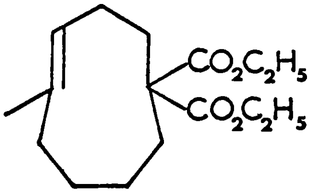

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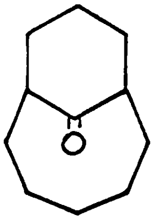

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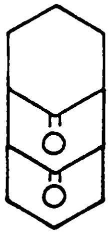

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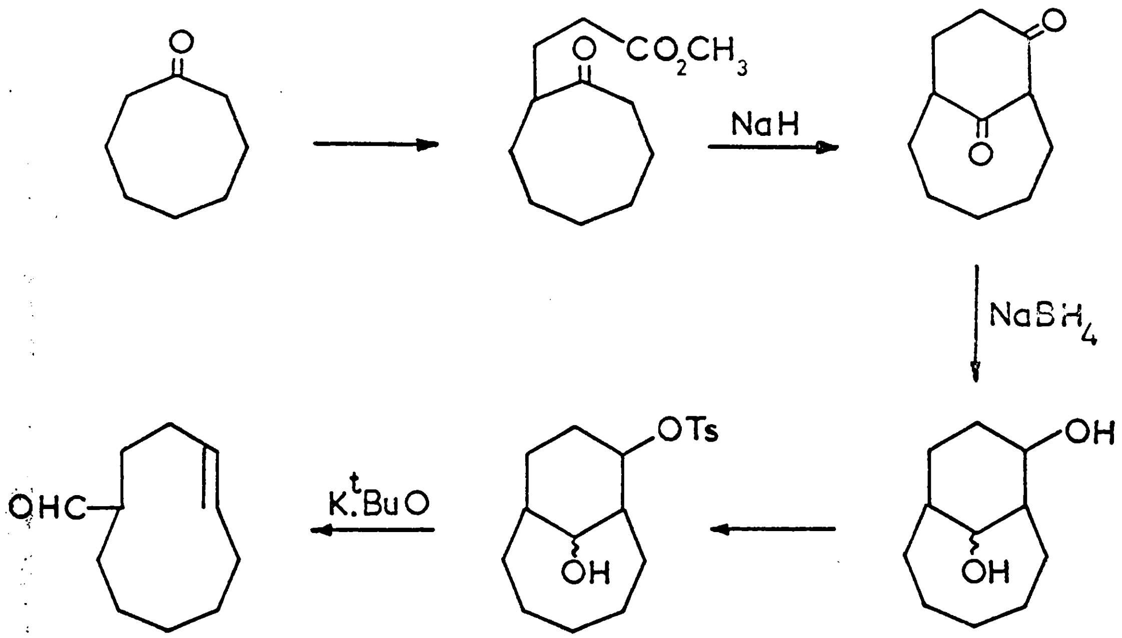


Scheme 8.

DISCUSSION.

PART I.

In recent years, in this department [1,2,] and elsewhere [3,4,], synthetic routes to medium rings via bicyclic precursors have been investigated. Application of these methods to the synthesis of ten membered and larger carbocycles are severly limited by the accessibility of suitable bicyclic compounds. However the use of a doubly bridged carbon skeleton of general type (1), which could be cleaved in such a way (2) to give a large ring, was considered a potentially useful approach to these rings. Readily available starting materials from which such a bridged system could be synthesised were sought and two different methods seemed feasible: either to build two separate three carbon bridges on to a doubly functional monocycle (3), or a single three carbon bridge on to a mono-functional bicycle (4). Both these approaches were investigated.

The two compounds chosen as starting materials for the first method were 5,5-dimethylcyclohexane-1,3-dione (5), dimedone, and diethylsuccinylsuccinate (6).

Although the envisaged tricyclic system (7), constructed from dimedone, appears comparatively rigid and fairly strained, a study of stereomodels (8) nevertheless indicated that it should be capable of an independent existence.

The condensation of the Mannich base (9) of acetophenone and dimedone yielded a mixture of products (10) and (11) of which only the former was alkali soluble. These compounds were readily identified by means of their infra-red spectra, which showed respectively, a bonded hydroxyl at 3200 cm.$^{-1}$ with $\nu_{CO}^{CCl_4}$ 1670 and 1622 cm.$^{-1}$ and in the non-enolisable product no hydroxyl absorption but $\nu_{CO}^{CCl_4}$ 1728 and 1694 cm.$^{-1}$. It was hoped to cyclise (10) and (11) to the bi- and tricyclic compounds (12) and (13).

In the preparation of (12) it would seem that the ready enolisation of the β-diketone (10) would lead to a reaction intermediate (14) which contravenes Bredt's Rule[5]. Despite this an apparently valid analogy existed in the literature[6], for it claimed, albeit without 'real' proof, that the aldehyde (15) is cyclised to (16) by mild acid treatment. It is also known [7], and corroborated in these laboratories, that (17) is cyclised to (18) under vigorous acid treatment.

Refluxing (10) in a mixture of concentrated hydrochloric acid and acetic acid, however, was almost totally ineffective. 70% of (10) was returned unchanged together with 14% of the retro-Michael product, dimedone. The neutral material from the reaction, comprising only a few percent, after distillation showed a broad poorly resolved νCO band and no νOH absorption in the infra-red. Although this data is consistent with (12) it is not definitive. This result substantiated the view that the predominantly enolic nature of a mono-substituted dimedone inhibits the formation of a bicyclic structure.

In order to prove this point further 2,5,5-trimethylcyclohexane-1,3-dione was condensed with the Mannich base (9) to yield (19) the cyclisation of which was attempted under acid conditions. In addition to starting material, the diketone afforded a mixture which was chemically separable into an acid (47%) and a neutral component (7%).

The acid, $C_{18}H_{24}O_4$ showed $\nu_{CO}^{CCl_4}$ 1753, 1709 and 1691 cm.$^{-1}$ in the infra-red and its n.m.r. spectrum exhibited 6 methyl protons at 8.93 τ (singlet, gem-dimethyls) and 3 at 8.87 τ (doublet). Methylene protons appeared at 7.2 τ (quartet $-\underline{CH_2}-COC_6H_5$) and at 7.48 and 7.41 τ (singlets, $-\underline{CH_2}-CO-$ and $-CH_2-CO_2H$ respectively). These facts are most plausibly explained by structure (20), which would arise by cleavage of the β-diketone system as in (21), i.e. before cyclisation to a bicyclic model (22) had occurred. Destruction of the dione system after closure to (22) would have led to (23) or, less likely, to (24), neither of which agree with all the physical data.

The neutral component, $C_{18}H_{20}O_2$ gave n.m.r. data compatible with structure (22), i.e. one vinyl proton as a triplet (3.93 τ, $J = 3.6$ cps.) and three unsplit methyl signals (the gem-dimethyl protons being in non-equivalent chemical environments in this structure). The infra-red spectrum was unusual in showing a split carbonyl absorption, the two peaks being separated by some 30 $cm.^{-1}$. This split carbonyl band is, however, a characteristic of non-enolisable β-diketones and is discussed in more detail in the Appendix. The low yield of (22) from the reaction indicates that the β-diketone system is too fragile under the conditions used.

Accordingly, there was little hope of carrying out the ring closure (11) to (13) originally planned. An attempted cyclisation of (11) gave a mixture from which no neutral product could be isolated.

A different method of cyclising a 3-carbon side chain had to be considered if dimedone was to prove a suitable starting material for the tricyclic model. The essence of this is shown in the Scheme (1), (25)→ (26)→ (27). (28) or (29); the bis-enol lactone (27) to be converted to either (29), by the 'Fujimoto' reaction using methyl magnesium bromide[8], or to (28) by a complex hydride reduction[9].

The diester (25) was synthesised by a modified method due to Nazarov[10] in 67% yield. Disubstitution was established on C_2 from the ultra-violet spectrum, λ_{max}^{EtOH} 221mμ and the expected splitting of the carbonyl stretching frequency in the infra-red (see Table 7.). The equivalent methyls of the gem-dimethyl group appeared in the n.m.r. at 8.9 τ as a singlet, the ester methyls at 6.39 τ (6H, singlet) and the methylenes of the six carbon ring are unsplit at 7.41 τ (4H).

Although several methods of hydrolysing (25) to (26) were attempted none was successful.

Ethanolic potassium hydroxide furnished a 60% yield of a colourless crystalline solid, $C_{12}H_{18}O_4$ which showed only a single methyl of a methyl ester at 6.26 τ (3H, singlet) in the n.m.r. The carbonyl absorption band in the infra-red was $\nu_{CO}^{CCl_4}$ 1751,1710 and 1623 cm.$^{-1}$ as expected for structure (30a). The 1623 cm.$^{-1}$ absorption being assigned to the carbonyl and carbon-carbon double bond stretching modes of the dimeric enol (31).

Both the mass spectrum, with a parent ion m/e 226 and fragmentation evidence compatible with a mono-methyl ester, and the ultra violet, λ_{max}^{MeOH} 264 mμ , substantiated a structure assignment of (30a).

Lithium iodide in refluxing pyridine treatment of (25) yielded no recognisable product. Acid hydrolysis of (25), with either concentrated or dilute hydrochloric acid, afforded cleavage and partially hydrolysed products. A sodium bicarbonate extract of the reaction mixture yielded two acids. The most abundant acid, after distillation, gave an infra-red spectrum with $\nu_{CO}^{CCl_4}$ 1741 (ε = 1470) and 1715 (ε = 367) cm.$^{-1}$. The loss of the typical 2,2-di-substituted-1,3-diketone system indicated that the latter had been destroyed to give (33a). The other acid, $C_{15}H_{22}O_6$, crystallised from petrol as a colourless solid. The n.m.r. spectrum showed that only one methyl ester was present 6.31 τ (3H - singlet), also the acidic proton of an acid at 2 τ (1H) and the gem-dimethyl grouping split to a doublet, 9.0 τ (6H). The splitting of this last signal was indicative of the non-equivalence of the methyl groups due to conformational asymmetry. The structure of the acid was finally confirmed to be (32) by the infra-red spectrum, which had $\nu_{CO}^{CCl_4}$ 1753 and 1713 cm.$^{-1}$, attributable to acid monomer and dimer respectively; 1724 cm.$^{-1}$ (ε =770), ester, and 1730 cm.$^{-1}$ (ε = 500) and 1697 cm.$^{-1}$ (ε = 990), the doublet from a fully substituted β-diketone system.

Methylation of both (33a) and (32) with diazomethane yielded the two components found in the neutral fraction of the hydrolysis. One of these corresponded to starting material (25) and the other to (33b). The formation of the latter in the hydrolysis was somewhat unexpected and constituted the methylation of an acid by methanol in acid solution. Proof of the structure of (33b) was obtained from the n.m.r. (6.38 τ, 9H singlet: methyl protons of the three esters; 8.95 τ, 6H, singlet: gem dimethyl protons), from the infra-red spectrum ($\nu_{CO}^{CCl_4}$ 1741 cm.$^{-1}$ (ε = 1470), 1715 cm.$^{-1}$ (ε = 367)) and from the micro-analysis ($C_{17}H_{28}O_7$).

The percentage yields from acid hydrolysis of (25) were determined by g.l.c. and found to be as follows: 15%-(25) returned, 20%-(32), 48%-(33a) and 17%-(33b).

Since the hydrolysis of (25) could not be achieved by any of the methods attempted, an alternative approach to the tricycle (28) by direct conversion of the diester (25) to (27) was investigated. The lactonisation of (35) to (36) using boron trifluoride in acetic acid has been studied in these laboratories [11] and found to proceed in over 70% yield. Similar treatment of (25), however, did not give the required bis-enol lactone (27) or even the mono-lactone (37). An acidic product, $C_{14}H_{18}O_5$, was isolated in 65% yield and finally formulated as (38). The most plausible mechanism for its formation is shown in Scheme A, and involves initial fisson of the β -diketone system followed by lactonisation and ring closure. Ultra-violet and infra-red spectra supported this structure. A value of $\lambda_{max.}^{EtOH}$ 252 mu.,($\varepsilon = 1.1 \times 10^4$) compared favourably with that for the model system (39), λ_{max}^{EtOH} 255mμ($\varepsilon = 1.11 \times 10^4$) [12]. Similarly in the i.r. the spectrum of (39) shows $\nu_{max}^{CCl_4}$ 1795, 1660 $cm.^{-1}$ while (38) has $\nu_{max}^{CCl_4}$ 1799 $cm.^{-1}$ (lactone), 1673 $cm.^{-1}$ (α , β -unsaturated carbonyl) and 1759, 1712 $cm.^{-1}$, (acid monomer and dimer).

An alternative structure isomeric with (38), formulated as (40) and formed as in Scheme B, was also in agreement with the physical data. Mass spectroscopy was used to confirm that the product was indeed (38). At first sight the spectrum appeared to agree with both structures with losses of m/e 59 and m/e 60, which could be due to rearrangements involving the acid grouping ((41), R=H; (42), R=H). However the breakdown M-266 to M-194 (i.e. loss of the fragment m/e 72) is more reasonably explained as a McLafferty [13] rearrangement

(Scheme C) of (38) rather than the somewhat unlikely cleavage shown in (40a), R=H. In an attempt to settle this point the methyl ester of the acid was prepared and subjected to mass spectroscopy. The resulting spectrum showed a loss of m/e 86 from the parent M-280. This corresponds to the same rearrangement as postulated in Scheme C and could not occur in (40) due to the lack of a suitable hydrogen in a position necessary for this 'type H' breakdown. No reasonable peak for m/e 72 loss corresponding to the cleavage (40a), R=CH_3, was found but loss of m/e 74 considered to be the rearrangement (41), R=CH_3 was observed.

Two further attempts to make (27) from (25) using different reagents were tried. The first of these, polyphosphoric acid, yielded a mixture of the lactone (38) and its methyl ester. Acetic anhydride, on the other hand, gave a quantitative return of the bis-vinyl ester (43) and no detectable lactone (27). The structure of (43), $C_{20}H_{28}O_3$ was established from the following physical data. In the n.m.r. the peaks observed were 4.45 τ, 2Ha, singlet; 6.36 τ, 6Hb, singlet; 7.85 τ, 6Hc singlet; 8.80 τ, 6Hd, singlet; 7.6 τ, 2H, multiplet and 8.15 τ, 2H, multiplet, and assigned as in (43a). The infra-red showed $\nu_{CO}^{CCl_4}$ 1770 cm.$^{-1}$ (vinyl ester), 1740 cm.$^{-1}$ (esters) and the ultra-violet, λ_{max}^{EtOH} 212 mμ.

The failure of acetic anhydride to lactonise (25) was disappointing as it is known [12] that conversion of 2-carbethoxyethyl-5,5-dimethylcyclohexane-1,3-dione to (39) proceeds in good yield under the same conditions. A study of a stereomodel of the bis-enol lactone (27) indicated that the structure, , although rigid, was fairly unstrained and should be capable of existence.

Further use of dimedone as starting material for the construction of a tricyclic model was discontinued at this point, as direct cyclisation of the diester (25) had been unattainable under any conditions used or considered and the β-diketone system had proved too sensitive to a wide variety of reagents.

Attention was turned to diethylsuccinylsuccinate (6) as a source for a similar tricycle (44). The envisaged route to (44) involved the condensation of two moles of acrolein with (6) to give (45), subsequent closure to (46) and dehydration to give (44). It was realised at the outset that ring closure of (45) could well take place in an alternative sense, but the possibility of the reaction proceeding in the desired way justified the experiment.

Diethylsuccinylsuccinate was prepared by a modification of the literature preparation[14], and fully characterised by infra-red, ultra-violet and n.m.r. spectroscopy (see experimental).

The preparation of the (3:3:1)-bicyclic structure (47) has been accomplished by Cope [3] from carbomethoxycyclohexanone and acrolein using sodium methoxide as condensing agent; the intermediate ketoaldehyde being ring closed with hydrochloric acid. In a recent paper [15] it is reported that in the presence of triethylamine, acrolein and 2-ethoxycarbonylcyclopentanone condense smoothly to yield (48) which can be cyclised by acid to a mixture of bicyclic alcohols (49). However this ring closure could also be effected by prolonged treatment with triethylamine and indeed the overall preparation of (49) could be carried out in one operation.

Diethylsuccinylsuccinate and acrolein were submitted to similar conditions (stirring for several days at room temperature). The resultant reaction oil was of a fairly complex nature. The first recognisable product to be isolated from this oil was the diethyl-ester of 2,5-dihydroxyterphthalic acid (50), as a highly crystalline yellow solid. The most effective method of minimising, and on some occasions completely inhibiting, its formation was to carry out the reaction in an atmosphere of nitrogen. (See experimental for physical characteristics).

Two colourless crystalline products A and B were isolated from the reaction mixture in varying yields, the relative amounts of each altering from one run to another in an inexplicable way.

Product **A** had a molecular weight of 332 and analysed for $C_{18}H_{20}O_6$. A molecular structure of this type indicated that is was formed by loss of two moles of water from a compound produced by the di-addition of acrolein to diethylsuccinylsuccinate. Of the two possible structures (44) and (51), the infra-red, ultra-violet and n.m.r. spectra eliminated (44) and favoured (51); viz. $\nu_{CO}^{CHCl_3}$ 1751 cm.$^{-1}$ (ester), 1720 cm.$^{-1}$ (Sh.), 1705 cm.$^{-1}$ (conjugated carbonyl) and 1623 cm.$^{-1}$ (ν C=C); λ_{max}^{EtOH} 264 mμ (817), 235 mμ (4960) and 205 mμ (5040). Although this disagrees with (44) it is also anomalous for (51). The expected value for (51), as calculated by Woodward's Rules, is about 241 mμ and the closest model system which could be found (52) shows λ_{max}^{EtOH} 240 mμ (6400). Non-conformity to Woodward's Rules for enone systems in strained environments is not unknown and an explanation for the anomaly in the present case may lie in that direction.

The n.m.r. of A indicated the presence of two equivalent vinyl protons (3.4τ , triplet, $J = 2.5$ cps.), and, apart from the ethyl protons of the esters, the remaining 8 methylene protons appeared between 6.8 and 8.0 τ as a complex series of peaks. As (44) requires a ratio of 2 : 3, vinyl : methylene protons, (disregarding esters), there was no doubt left that this was not the structure of A. Apart from the u.v., the physical data was in harmony with the bis-enone (51). Further proof of this was obtained from the mass spectrum in which the base peak, m/e 166, corresponded to a fragment of exactly half the molecular weight of the parent ion (M-332). This is most often indicative of the halving of a symmetrical molecule to give identical fragments, a feature which would explain the simple nature of the spectrum below m/e 166, (see Table 2 and (53)).

Evidence for the enone functions in the molecule was obtained by reduction with sodium borohydride in methanol to (54). This showed no absorption in the u.v. above 220 mμ and $\nu_{\mathrm{OH}}^{\mathrm{CCl}_4}$ 3620 (small), 3548 (Sh.) and 3480 cm.$^{-1}$ in the infra-red. An increase in molecular weight from 332 to 336 was observed, (mass spectroscopy). Attempts to convert compound A to the quinone (55), by hydrolysis and decarboxylation of the resulting di-acid, were unsuccessful.

In addition to the other crystalline product, B, which will be discussed at a later stage, the main reaction component, isolated by column chromatography, was a pale yellow viscous oil which was sensitive to both air and heat. Nevertheless a pure sample, (assayed by both g.l.c. and t.l.c.), was obtained for appraisal by physical methods. Micro-analysis and mass spectrometry showed it to have a molecular weight of 368. Its infra-red spectrum was interpreted in the following way: $\nu_{max}^{CCl_4}$ 3630 cm.$^{-1}$ (free hydroxyl); 3537,3493,3444 cm.$^{-1}$ (all strong, intra-hydrogen bonding of hydroxyls - dilution studies); 2737 cm.$^{-1}$ (aldehyde νCH); 1745 cm.$^{-1}$ (ester νCO); 1723 cm.$^{-1}$ (νCO) and 1706 cm.$^{-1}$.(bonded νCO). Confirmation of the aldehyde was found in the n.m.r. which exhibited a signal at 0.22 τ for the aldehyde proton/s. From the foregoing evidence it was decided that this was not a single compound but an equilibrium mixture of at least two compounds, (56) and (57). The tricyclic structure (46) was not considered since the equilibrium mixture was converted by distillation, simply and in high yield, to the previously isolated bis-enone (51). Any efforts to cyclise free aldehyde, in the mixture, by a variety of reagents only resulted in highly complex mixtures which discouraged further investigation.

Although the main component from the reaction of acrolein and diethylsuccinylsuccinate was synthetically unfruitful, as a means of furnishing the tricyclic compound

(44), the isolation of compound B promised to be of interest. In one particular run of the condensation 1.07g. of this alcohol B was isolated from 3.0g. of diethylsuccinylsuccinate. This is not an inconsiderable yield and warranted a more thorough examination.

The infra-red spectrum of B showed $\nu_{CO}^{CCl_4}$ 1741 and 1724 cm.$^{-1}$; $\nu_{OH}^{CCl_4}$ 3632 and 3585 cm.$^{-1}$. The carbonyl absorptions were assigned respectively as ester and normal cyclohexanone type. Together with the intensity of the 1741 cm.$^{-1}$ peak, the presence of two ester groupings was proved by careful integration of the n.m.r. spectrum, the number of protons in the molecule having been determined by a combination of micro-analysis ($C_{18}H_{24}O_8$) and mass spectroscopy ($P = 368$). Although the hydroxylic peaks in a nujol mull appeared strongly they were weak in carbon tetrachloride solution.

By re-running the initial n.m.r. sample, after addition of a little deuterium oxide, two main changes in the spectrum were observed which could only be accounted for by the presence of two separate hydroxyl groups in the molecule. One peak at 6.88 τ and the other at 8.45 τ were seen to disappear. The sharpening up of a poorly defined multiplet at 4.99 τ to a sharp doublet was also noticed and considered to be due to a proton α to one of the hydroxyls.

No aldehyde grouping could be detected in the n.m.r. spectrum.

From the information described it appeared that diethylsuccinylsuccinate had condensed with two molecules of acrolein. Furthermore it was apparent that the bis-adduct had undergone subsequent reaction involving the aldehyde functions to a compound containing two hydroxyls and a carbonyl grouping. As the alcohol B did not give a positive ferric chloride test and showed no absorption in the ultra-violet, it was assumed that the β -keto-ester systems in the starting material were no longer in a position to enolise in the alcohol B. In other words, initial and/or subsequent condensations of the acrolein moiety had occurred at these centres.

One of the most puzzling pieces of evidence, about the alcohol, was the appearance of a peak in the n.m.r. at 4.48 τ which integrated for one proton and was split to a fine triplet or quartet. That this was a vinyl proton was confirmed by catalytic hydrogenation (Pd/C.) to give one compound, an oil, which showed no absorption in the vinyl proton region of the n.m.r.

Although a considerable number of possible structures were drawn and adjudged they agreed with little of the evidence and only two, (59) and (60), were initially considered. Both are assumed to form via the dialdehyde (45) by different aldol condensations. They account for the presence, if not the splitting pattern of the vinyl proton, and they account for the absence of u.v. absorption.

Oxidation of B using standard Jones reagent afforded a highly crystalline product ($C_{18}H_{22}O_9$) which showed decrease in molecular weight from 368 to 366. This indicated that only one of the hydroxyls had oxidised. If it is assumed that no rearrangement of the molecule had taken place under the acidic conditions of the reaction, then one of the hydroxyls must have been tertiary or so hindered as to resist oxidation. The oxidation product showed $\nu_{CO}^{CCl_4}$ 1771, 1745, 1740 and 1724 cm.$^{-1}$ together with a very feeble hydroxyl around 3600 cm.$^{-1}$. The 1724 cm.$^{-1}$ absorption was unchanged from the alcohol B, the 1740 and 1745 cm.$^{-1}$ peaks appeared to be the two esters in non-equivalent environments leaving 1771 cm.$^{-1}$ as having arisen by oxidation of one of the hydroxyl groupings. The latter absorption was interpreted as an enol lactone system and such an oxidation product is compatible with (59) and (60). The value quoted by Nakanishi [16] for (61) is 1760 cm.$^{-1}$. Δ-lactones can however be shifted to even higher frequencies due to the introduction of ring strain by the fusion of the lactone to other cyclic systems[17,18].

Treatment of the alcohol B with either dilute sulphuric acid or para-toluenesulphonic acid in refluxing benzene, resulted in a compound which showed a loss of only one mole of water and had one additional vinyl proton (as seen from the n.m.r.). As the alcohol had two hydroxyl functions this dehydration experiment indicates that one of these is in a position which obstructs its dehydration. As the attempted dehydration of the oxidation product of B resulted in a quantitative return of starting material, it was deduced that the hydroxyl, which would not dehydrate, was the one that would not oxidise.

The proposed structures for the alcohol B, (59) and (60) were, for several reasons, very unsatisfactory.

Although their oxidation to (62) and (63) would explain the 1771 $c,m.^{-1}$ absorption, the stability of the second hydroxyl to oxidation is inexplicable. Similarly either (62) or (63) should dehydrate and (59) and (60) should lose two moles of water on dehydration. Furthermore, unless very long range coupling was invoked, neither of the alcohols agreed with the splitting of the vinyl proton in the n.m.r. or its increased splitting ($J = 3.5$ cps.) in their respective oxidation products. Structures (59) and (60) are therefore unsatisfactory.

Additional information about the nature of the alcoholic groups was furnished by running the n.m.r. spectrum in dimethyl sulphoxide as solvent. A doublet at 3.38 τ (J = 7 cps.) appeared in the spectrum, indicating that the hydroxyl is secondary; but available information [19] also showed that only very few hydroxyl protons resonate at such low field. Hemiacetals and hemiketal hydroxyl protons appear as doublets and singlets respectively at lower fields (ca. 3.4 τ) than normal, (e.g. tazettine (64) at 3.46 τ , singlet).

On this basis part of the structure of the alcohol B̲ was considered to be (65). The possibility that a second resonance, (dimethylsulphoxide) at 5.07 τ (triplet), was due to a primary alcohol was dismissed on the chemical evidence and instead assigned to the α - hydrogen of the hemiacetal coupling with a β -hydrogen. In a solution with deuterium oxide added this appears as a doublet (J = 9 cps.) at much the same field position. The 5.07 τ reasonance in dimethylsulphoxide solution was finally rationalised as two almost overlapping doublets, the overall J value of 16 cps. embracing the 7 cps. and 9 cps. couplings involved (see figure 1). This led to the postulation of the partial structure (66). The position of the second hydroxyl in the dimethylsulphoxide spectrum was possibly obscured by the methylenes of the esters centred at 5.86 τ, a peak being just visible at 5.95 τ.

Coupling the n.m.r. data with the chemical and physical evidence already discussed, the part structure (66) was extended to (67). This accounts for the enol lactone function in the oxidation product and the coupling of the vinyl proton with the allylic β - protons.

A third structure, which satisfies all the above data for the alcohol B, is (68) and the oxidation product would then be formulated as (69).

It is interesting to note that in the oxidation of the alcohol, that, if the reaction time with Jones reagent was prolonged, (say 12 hours), then the product isolated was a mixture of two carboxylic acids. The structures of these were not investigated but may well have been (70) and (71).

Other than the product of hydrogenation (72), two further compounds prepared from the alcohol B deserve mention. The first of these was formed by treatment of B with acetic anhydride and pyridine and from analysis ($C_{20}H_{26}O_9$) and mass spectroscopy (m/e .452) was considered to be a diacetate. The same product could also be prepared by refluxing B with isopentenyl acetate and para-toluenesulphonic acid, although this method also produced the so-called dehydration product.

The acetate showed no evidence of hydroxyl in the infra-red but the following carbonyl frequencies in carbon tetrachloride solution were noted : 1770 cm.$^{-1}$ (ε = 970), 1744 cm.$^{-1}$ (ε = 1070) and 1725 cm.$^{-1}$. It was thought that the 1770 cm.$^{-1}$ absorption represented possibly two vinylic acetate groupings. This was corroborated to some extent by the n.m.r. spectrum which showed a singlet methyl peak at 7.91 τ that integrated for six protons. As well as the vinyl resonance at 4.35 τ (finely split triplet), which was also present in B, a second absorption centred at 4.05 τ, (doublet, J = 9 c./sec.), appeared. Although several structures could be drawn (e.g. (73)) none of them would satisfy even the majority of the physical data.

The other compound which defied solution was the dehydration product. The fact that only one mole of water was lost on dehydration has already been discussed but a point, which has been omitted so far, is that no evidence of the remaining hydroxyl could be found in either infra-red or by deuterium oxide exchange experiments in the n.m.r. Furthermore, a second vinyl proton was produced during the reaction which appears at very low field, 3.41 τ

(very fine triplet). As with the acetate, the dehydration product must be the result of some extensive rearrangement within the molecule.

As both approaches to the tricyclic model, utilising a monocyclic bifunctional molecule as starting material, proved ineffectual, it was decided to attempt a 'tricyclic' synthesis from a bicyclic system by adding a suitable side chain to this and cyclising the resulting adduct to form the required product.

The bicyclic compound, 2-phenylbicyclo-(3:3:1)-non-2-ene-9-one, (18) was chosen as starting material for several reasons. This compound was readily accessible by a method, due to Cope [20], from the Mannich base (9) of acetophenone and cyclohexanone via the diketone (17) and subsequent cyclisation with acid. A 'bicycle' had to be selected that had suitable functionality on the C_9 position (74) and would allow directly, or after modification, cleavage of this carbon bridge in the final tricyclic structure. This was a necessary prerequisite when the ultimate goal was the formation of a ten membered carbocycle. The remaining requirement of the system was that it should be capable of conversion to a compound which would not only allow the condensation of a further three-carbon bridge from C_2 to C_4, but also have a similar functional group at C_3 as at C_9 to permit fisson at a later stage, On these grounds, (18) appeared to be a suitable bicyclic starting material. The phenyl grouping was perhaps the least desirable feature of the molecule as it would interfere chemically in certain reactions. Nevertheless it could be used to advantage in a stereochemical sense to direct conformation.

An appraisal of the most feasible centres on to which the three-carbon bridge could be constructed, shows that only the C_2 and C_4 sites, (or the corresponding C_6 and C_8), are suitable. A bridge from C_3 to C_5, for example, would be impossible as any condensation at C_5 which necessarily involves an ionic or partially ionic species is disallowed. This is an extension of Bredt's Rule[5] which postulates that a double bond cannot be sustained in the system (75) at a bridgehead site when $n \leq 4$. However such a bridge from C_3 to C_5 should be possible if the necessary addendum at C_5 is condensed prior to the formation of the initial bicyclic system. This latter course was not investigated but a method for attaching a carbon bridge across C_2 to C_4 is discussed in the following pages.

Procedures for the cleavage of one carbon bridges in a tricyclic system, (76), are considered more fully at a later stage, but the presence of the carbonyl groups at carbon atoms 3 and 9, would provide centres at which reaction, leading to fisson of the bridge, would be possible. The initial problem was conversion of (18) to the bicyclic dione (77). Two methods seemed feasible. The first, (Scheme 1), utilised the phenyl group to direct hydroxylation of the double bond by a hydroboration procedure and oxidation of the resulting diol to give the dione (77). The olefin, (18), was treated with diborane produced in situ from boron trifluoride etherate and lithium aluminium hydride. A considerable amount of investigation has been carried out on the reaction and mechanism of hydroboration [21], and the results of the hydroboration of a series of alkyl and aryl olefins clearly shows that the addition is controlled by electronic rather than steric factors. In general, the boron atom attaches itself to the less substituted carbon atom of the double bond. With styrene, terminal addition occurs to the extent of 80% with 20% on the secondary carbon. In cyclic systems the steric relationships become more important, and as cis-addition, (see Scheme 2), of the hydrogen-boron bond to the double bond occurs, the addition generally takes place on the most accessible side of the ring. This being the case, the expected boron complex from hydroboration of (18) should be (78), which on oxidation with alkaline hydrogen peroxide should proceed with retention of configuration to give the corresponding alcohol (79).

The major product, isolated in 58% yield from the hydroboration and oxidation of (18), was the diol (79). The configuration of the hydroxyl groups was deduced from a knowledge of the cis-addition mechanism, (Scheme 2), already described, and the infra-red spectrum which showed $\nu^{CHCl_3}_{CO}$ 3610 and 3617 cm.$^{-1}$, If the hydroxyl on the bridging carbon atom (C9) was syn to the ring carrying the phenyl group, then intramolecular hydrogen bonding, between the hydroxylic functions, would almost certainly occur, (81). As this was not observed the C_9 hydroxyl function was assumed to be anti.

The remaining components of the mother liquor from the hydroboration reaction were separated by column chromatography. First to be eluted from the column was a mixture of the syn- and anti-2-phenylbicyclo-(3:3:1)-non-2-ene-9-ols, (82) and (83). These structures were confirmed by comparative t.l.c. and g.l.c. with samples synthesised in a different way. The other two compounds present in the mixture were the epimeric diols (84) and

(85). Both analysed for $C_{15}H_{20}O_2$ and the styrene chromophore, observed in the u.v. of the starting material (18), had disappeared to allow the low intensity peaks of the aromatic nucleus to be seen (242,246,251,257 and 264 mμ). The syn-epimer, (84), showed strong intra-hydrogen bonding, (86), $\nu_{OH}^{CHCl_3}$ 3575 cm.$^{-1}$ (dilution study), together with free non-bonded hydroxyl, 3618 (sh.) and 3600 cm.$^{-1}$. The other isomer (85) however had only one hydroxylic stretching absorption in the infra-red (3600 cm.$^{-1}$). On oxidation with standard Jones reagent both diols gave the same ketol, (as proved by g.l.c.). This factor corroborated the postulated structures (84) and (85).

Yields of up to 65% of the diol (79) could be realised by the lithium aluminium hydride - boron trifluoride etherate procedure. Attempts to increase the yield included the use of sodium borohydride, as reducing agent, in diglyme as solvent but this method gave poorer returns of (79). Numerous procedures have been developed over the years for the preparation of diborane but investigation of these with respect to the present case were not pursued.

The reason why the yield could not be increased past about 65% is probably to be found in the difference in the ease of formation of the boron complex between the syn- and anti- isomeric alcohols (82) and (83). An analysis of the quantities of each of these, obtained in the hydroboration reaction, shows that only a trace of the anti-epimer is returned compared with 10-15% of the syn alcohol. Now, consideration of the relative amounts of each of these isomers formed in a lithium aluminium hydride or sodium borohydride reduction of the ketone (18), (see Table 3), shows that about three times as much of the anti-alcohol (83) to the syn-alcohol (82) is produced. Thus it would seem likely that, in the hydroboration reaction, the ketone function is first reduced to a mixture of (82) and (83) and that the boron complex is almost solely being formed with the anti-isomer (83) leaving (82) unreacted.

One method of increasing the overall yield of the diol (79) is to first reduce (18), separate the isomers (82) and (83) and hydroborate only (83) while oxidising the syn fraction to (18) which could then be recycled.

2-Phenylbicyclo-(3:3:1)-nonane-3,9-diol (79) was oxidised with standard Jones reagent to the dione (77) in 62% yield. This yield was increased to 73% by using sodium dichromate dihydrate in 96% sulphuric acid [22] as the oxidising agent. It analysed for $C_{15}H_{16}O_2$ and the mass spectrum had a parent ion at m/e 228. The infra-red showed two carbonyl absorptions, $\nu_{CO}^{CCl_4}$ 1723 and 1728 cm.$^{-1}$ due to the variance in environment of these functions. The assignable peaks in the n.m.r. were : doublet at 6.03 τ - Ha, finely split singlet at 2.72 τ - Hd and two multiplets, one centred at 7.17 τ, 4 protons - Hb and the other at 8.15 τ, 6 protons - Hc, (see 77a).

Scheme 3 represents the proposed alternative method for conversion of (18) to (77). This involved the epoxidation of the double bond, opening of the epoxide in the desired sense to the alcohol and oxidation to (77). As the acid catalysed opening of the epoxide ring would proceed through a carbonium ion, the ring would be expected to break preferentially at the most highly substituted carbon atom, the phenyl group stabilising the positively charged intermediate.

However, attempts to make the epoxide were unsuccessful. In a paper by Meinwald [23] the failure to epoxidise dehydronorcamphor (87) is discussed, and the suggestion made that the reduced activity of the olefinic double bond is due to the carbonyl function being held in such a position that it is particularly suitable for electron withdrawal, (see (88)), thus making the double bond unusually resistant to electro-philic attack. A similar phenomenon has been encountered and rationalised in this way by Woodward [24], who found that the non-conjugated double bond in the lactone (89) could not be selectively epoxidised with perbenzoic acid, undoubtly because of the electron release from the double bond to the lactonic carbonyl group. A situation which is fairly similar to this exists in (18). This effect should be removed in the reduced compound (83). Peracid treatment of the alcohol (83) followed by oxidation produced the dione (77) but the yield was sufficiently low to discourage further work on the epoxide route.

Several methods of constructing the three carbon bridge over the 3-keto group in the dione (77) were considered. As 1-ethoxycarbonyl-5-methylbicyclo-(3:3:1)-non-3-ene-9-one, (90), is readily prepared, as outlined in Scheme 4, it was proposed to apply the same series of reactions to (77) with the resultant formation of a tricyclic system (see Scheme 5). The stereochemical aspects of this scheme are of major importance. Any fairly large side chain condensed with the diketo-ester (91), on thermodynamic grounds might be expected to take up an equatorial position. However, the steric interaction of the C_7 methylene of ring A would tend to prevent condensation of the addendum, (e.g. acrolein), from the underside of the bicyclic system. (Approach from this side is necessary if an equatorial substituent is to result.) Thus on consideration of approach control one would expect an axial condensation (92a). Although the conformation of bicyclo-(3:3:1)-nonane has been shown to exist in the twin chair conformation, [26, 27] it is possible that the condensation product could take up a conformation which would place the side chain in a less strained environment, namely the chair-boat form (92b).

Cyclisation of (92a) to (93) should give one of the isomers : (93a), (93b), (93c) or (93d), the final conformations of rings A and C depending on the balance of steric interactions present. On the other hand, if the acrolein molecule had condensed equatorially to give (92c), then the possible isomers formed in subsequent cyclisation would be (93e), (93f), (93g) and (93h).

The synthetic scheme, (Scheme 5), was embarked on but considerable difficulty was encountered in preparing the diketo-ester (91). Carbethoxylation of (77) with sodium hydride and diethyl carbonate, a method due to Soloway and LaForge [28] and later improved by Ghandi [29], was attempted. Although base soluble material, which gave a positive ferric chloride test, was isolated from the reaction, both low yields and the presence of several by-products discouraged further work on this reaction series.

Failure to make the diketo-ester (91) in acceptable yield, suggested that the intermediate anion had difficulty in forming, but this was shown to be false by bromination of the dione (77) in high yield by shaking for a few minutes with a solution of bromine in chloroform. The bromine adduct was shown to be (94), $C_{15}H_{14}O_2Br_2$ by n.m.r. The doublet at 6.03 τ due to the proton on C_2 in the dione (77) had disappeared in the spectrum of (94). A doublet at 3.86 τ due to Ha, multiplets at 6.7 τ and 7.3 τ due to bridgehead protons and a multiplet centred at 8.45 τ for the remaining methylenes were observed.

The two reasons for introducing a carbethoxy group at the C_4 position were: a) to allow condensation of a side chain at that site and b) to provide a means by which the one carbon bridge, which would come from C_3, could be cleaved. 1-Ethoxycarbonylbicyclo-(3:3:1)-non-3-ene-9-one (47) undergoes a reverse acetoacetic ester condensation, (47) → (96), to give 1,5-diethoxycarbonyl-cyclo-oct-1-ene (96), However, the corresponding methyl analogue (90), does not undergo fisson in this way[30]. The reason suggested is that the bis-ester (98) formed, recyclises to (90) as the bridgehead substituent prevents the double bond moving into conjugation. Fisson of the C_3 bridge in (93) would, in the same way, produce a cyclo-octene (99) which could recyclise to starting material. This provided a second fairly strong reason for discontinuing this line of synthesis, (Scheme 5).

Formylation of the C_4 position was also considered and attempted in order to follow Scheme 6, but rejected owing to low yields.

The difficulty met in attempted carbethoxylation and formylation prompted the decision to condense a side chain directly on to the bicyclic system (77) and devise an alternative method of ring fisson.

1,3-dichlorobutene was condensed with (77), using potassium tertiary butoxide, to give an isomeric mixture of 2-phenyl-2-(3'-chlorobut-2'-enyl)-bicyclo-(3:3:1)-nonan-3,9-dione (100). From the physical data there did not appear to be any way of differentiating between the axial and equatorial epimer but for convenience one was referred to as A and the other B without knowing which was which. Both analysed for $C_{19}H_{21}O_2Cl$, had mass spectra, (P= 316 m/e), with breakdown patterns compatible with mono-chlorinated compounds and gave positive Beilstein tests. The n.m.r. spectra of both A and B showed loss of the 6.03 τ doublet, observed for the dione (77), and a sharpening of the aromatics to a clean singlet. Both of these facts indicate that condensation has occurred at C_2 position. Further proof of structure in the n.m.r. was the appearance of a triplet for the vinyl proton (4.82 τ, J=7 cps. in the case of A and 4.97 τ, J=8.5 cps. for B) and a singlet at 8.07 for the methyl grouping. The infrared spectrum of A had $\nu_{CO}^{CCl_4}$ 1717,1710; $\nu_{CC}^{CCl_4}$ 1663 cm.$^{-1}$ and of B had $\nu_{CO}^{CCl_4}$ 1721,1709 cm.$^{-1}$; $\nu_{CC}^{CCl_4}$ 1655 cm.$^{-1}$.

If the conformation of one of the epimers is as shown in (100a) then if ring closure proceeds in the desired way, ring B should take up the boat conformation and the other isomer, (100b), give the tricyclic compound with ring B in the chair form.

It is worth considering, at this point, the reaction by which the proposed cyclisation might take place. There are two general synthetic methods which have been employed to fuse an additional carbocyclic ring to a cyclic ketone. The first procedure, that of Robinson[31], is the cyclisation of a 1,5-diketone, such as (101a), with dilute acid or base. The second procedure, discovered by Wiohterle [32] and widely employed by Prelog [33,34], is the cyclisation of a 2-(3'-chlorocrotyl)-cyclohexanone, such as (102a), with concentrated sulphuric acid to a mixture of

(103a) and (104a), the ratio depending on the nature of the substituents R and R'. The product from the Robinson annelation reaction is the octalone (104a).

The mechanism of the Wichterle reaction is considered in Scheme 7 [35], where the chlorovinyl group is acting as a disguised carbonyl group which is liberated during the reaction [36]. The main factor determining whether the octalone (104) or the bicyclic -(3:3:1)-system (103) will result from this involves conformational energy differences. The energy difference, between the conformer with an axial butanone side chain and the equatorial side chain conformer should be smaller in the 2-methyl-2-(3'-oxobutyl)-cyclohexanone (101b) intermediate, than in the corresponding desmethyl analogue (101a) where the equatorial side chain would be greatly favoured. The bridged product might therefore be more easily formed from the former intermediate (101b). Thus it is not surprising that (102b) should give (103b) in high yield whereas (102a) gives both (103a) and (104a) in about equal amounts.

Stabilisation of the enol form (106), where R' is methyl, directs cyclisation completely to the (3:3:1)-bicyclic product (107). The diketones, (101a) and (101b), can be isolated when (102a) and (102b), respectively, are treated with concentrated acid for about 30 minutes at

$0^{o}C$. This would appear to invalidate any mechanism which involves protonation of the double bond, cyclisation and subsequent dehydrochlorination (see Scheme 8). No diketone (101c) can be isolated in the case of the dimethyl compound (102c), the reaction proceeding directly to the bicyclic product (103c). In the proposed cyclisation of (100) to the tricyclic structure (108) the phenyl substituent should direct ring closure to (108) rather than (109). In considering the conditions most suitable for the cyclisation 80% sulphuric acid was used to avoid the strong possibility of sulphonation of the benzene ring with 95% sulphuric acid.

As compound A was more readily obtained pure than B, it was subjected to acid treatment first. A white crystalline solid separated from the reaction mixture which analysed for $C_{19}H_{22}O_3$, and had the expected molecular weight of 298, (mass spectroscopy), for the tricyclic compound (108). The parent ion in the mass spectrum showed two separate losses, one of m/e 18 corresponding to loss of water, to give a m/e 280 peak and the other, which was the major pathway, a loss of m/e 44 to give a m/e 254 peak. Loss of m/e 44, from a compound which contains no nitrogen, is most often due to either CO_2 or CH_3CHO breaking off from the molecule. A source of CO_2 from the alcohol (108) is difficult to envisage and a loss of CH_3CHO would involve several improbable bond fissons. As loss of m/e 44 from the alcohol appears to be such a favourable process, (in fact it gives rise to the base peak of the spectrum), then, the latter (i.e. CH_3CHO) seems unlikely to be the m/e 44 fragment.

The carbonyl region in the infra-red spectrum of the alcohol showed a broad peak between 1720 and 1730 cm.$^{-1}$ in chloroform solution. Re-running the spectrum in a saturated carbon tetrachloride solution brought this absorption up to 1744 cm.$^{-1}$ which appeared too high for the expected structure (108), (c.f. (77) $\nu^{CCl_4}_{CO}$ 1723, 1728cm.$^{-1}$). It was considered that this might have been due to some type of geometrical strain.

An alternative structure for the alcohol was examined (110). This was disproved by the appearance of a mono-substituted benzene pattern in both the infra-red and ultra-violet spectra, and also by the n.m.r. which showed a sharp singlet for the aromatic protons. Excepting the latter, there were no peaks in the n.m.r. below 7.0τ and the only well defined one being at 8.49τ and integrating for three protons. This shift downfield of a methyl group indicates the possible attachment of an oxygen function to the same carbon. Structure (108) would be consistent with this. The rate of proton exchange of the hydroxyl was reduced by running an n.m.r. spectrum in dimethylsulphoxide [19] so as to observe the hydroxyl proton. As the hydroxyl resonance absorption appeared as a sharp singlet the tertiary nature of this group was confirmed.

The Wichterle reaction is normally accompanied by dehydration as already described in Scheme 7. Thus, it seemed peculiar that in the present case a similar pathway had not been followed. Despite considerable effort to dehydrate this alcohol under normal dehydrating conditions and also with reagents such as formic acid and perchloric acid in glacial acetic acid, known to dehydrate bicyclic systems of type (111) to (112), no evidence of dehydration was found. Although the inability of the alcohol to dehydrate could have been a conformational effect, the suspicion that the alcohol had undergone rearrangement, was heightened. A hydroxyl group at a bridgehead, for instance, would not dehydrate. No structures could be drawn, however, which would agree with the physical data in hand and the conclusion reached that any rearrangement that had taken place must have been of considerable complexity.

If the alcohol had in fact the structure (108) then it was of such a novel nature to require a conclusive determination of the conformation. On the other hand, if a rearrangement had taken place it was also of importance to determine its definite structure. In either case there was sufficient interest to warrant a structural proof by X-ray crystallography.

The alcohol was found to formylate readily on refluxing with 98% formic acid. The infra-red of this ester showed three carbonyl stretching absorptions 1743, 1732 and 1726 $cm.^{-1}$. If the first of these is assumed to be the initial carbonyl observed in the alcohol, then the other two must be due to the ester. The 1743 $cm.^{-1}$ absorption only appeared to be intense enough for one carbonyl grouping, which is at variance with the structure (113). The $\nu_{C-O}^{CCl_4}$ at 1170 $cm.^{-1}$ confirmed the C-O stretch of the ester. As was already found for the alcohol, the mass spectrum showed a very favourable loss of m/e 44, in this case from an ion M-280; the latter arising from loss of formic acid from the parent ion m/e 326. Again no rationalisation could be found for this fragmentation.

As the formate ester was easily prepared, it was decided to prepare the acetate of the alcohol in preparation for the formation of a bromoacetate derivative, which could be used in an X-ray study.

Under refluxing conditions, with isopropenyl acetate and paratoluenesulphonic acid the alcohol was converted quantitatively to its acetate. The intensity of the carbonyl stretching absorption at 1745 $cm.^{-1}$ in carbon tetrachloride indicated the presence of only two carbonyls. The n.m.r. data was consistent with (114), but as in the alcohol (108) and the formate ester (113), the mass spectrum showed loss of m/e 44. Together with initial loss of acetic acid, this resulted in a strong base peak at M-236. This indicates that the m/e 44 fragment is not lost from the centre carrying the hydroxyl and must take place at some other site in the molecule. A δ-lactone is known to give loss of CO_2 (m/e 44) under electron bombardment in some cases and, although the infra-red supported such a grouping, it could not be mechanistically rationalised. Base treatment of the alcohol, (sodium ethoxide or mild potassium hydroxide), did however render an unidentified acid, but no further investigation of this was made.

Addition of bromoacetyl bromide to the alcohol in a solution of benzene and pyridine and stirring overnight yielded a bromoacetate. Micro-analysis and mass spectrometry (P-419) confirmed a molecular formula of $C_{21}H_{23}O_4Br$, the latter having a fragmentation pattern consistent with the formate and acetate derivatives, (i.e. base peak, M-236). Again an anomalous infra-red for a structure of type (115) was recorded, $\nu_{CO}^{CCl_4}$ 1745 cm.$^{-1}$ ($\varepsilon = 840$).

A sample of the bromo-acetate containing crystals of the correct size for X-ray crystallography were prepared by dissolving the bromoacetate in ether and allowing the latter to evaporate off over several days.

The X-ray analysis was undertaken by Dr. G. Ferguson and Mr. R. Pollard [37] who reported as follows:-

> Rotation, oscillation, Weissenberg and precession photographs were taken with copper K-α ($\lambda = 1.542$ Å) and molybdenum K-α ($\lambda = 0.710$ Å) radiations. The cell dimensions were obtained from rotation and precession photographs, and the space group, $P2_1/c$, was determined uniquely from the systematic absences.
>
> Intensity data were obtained from equatorial and equi-inclinational upper layer photographs, taken from crystals rotated about the needle axis (a-crystal axis); the multiple film technique was employed [38]. Some 2,000 data were estimated visually by comparison with a calibrated strip, and were corrected for Lorentz, polarisation and rotation factors

appropriate to the upper layers [39]. Since small crystals were used no corrections for absorption were applied. The various layers were placed on the same scale by comparison of the observed and calculated structure amplitudes obtained from the three dimensional Patterson function.

The position of the bromine atom was found from the Patterson distribution and the remainder of the structure elucidated by the heavy atom method [40,41] and refined by Fourier and least-squares procedures on the Glasgow KDF9 computer. The value of R is now 14% and refinement of atomic parameters is continuing.

The structure and conformation of the molecule are shown in (119) and Figure 2 and a list of crystal data given below:-

<u>CRYSTAL DATA.</u>

Molecular Formula. - $C_{21}H_{23}O_4Br$.
Molecular Weight. - 419.331
System - monoclinic
a - 7.16 Å
b - 16.15 Å
c - 17.71 Å
β - 108° 40'
Unit Cell Volume - 1942 $Å^3$
No. of molecules/unit cell. - 4
Absent spectra - hol if l is odd
- oko if k is odd

CRYSTAL DATA, Continued:

Space Group - $P2_1/c$
No. of electrons/unit cell - 864
No. of intensities estimated - 2000

After determination of the structure several of the anomalous aspects of the physical data could be rationalised. In particular, the loss of m/e 44 in the mass spectrum must be due to a rearrangement in the lactone ring which can be depicted as shown in Scheme 9. Although water can be lost from the parent ion of the alcohol, (P-298), it is more favourably lost after the CO_2 splits off, (i.e. m/e 298 → m/e 254 → m/e 236). In the cases of the formate (117), acetate (118) and bromoacetate (119), losses of formic, acetic and bromoacetic acids respectively occur before loss of m/e 44. This is probably due to the fact that they can undergo a McLafferty [13] rearrangement (Scheme 10) whereas dehydration of the alcohol is a less favourable process.

The infra-red spectra were also readily explained and the n.m.r. data clarified. The methyl protons resonating at lower field due to the attachment of the oxygen of the lactone to the same carbon and not to a hydroxyl as in (108).

A mechanism for the conversion of the chloro-compound (100) to the alcohol is outlined in Scheme 11. It is now clear that compound A must have been the axial epimer (100b) and that the modified tricycle (123) has in fact been formed. The acid catalysed ring opening is reminiscent of a previously described reaction [1] in a strained bicyclo - (3:2:1) - octanone. Its operation in a complex bicyclo - (3:3:1)-nonanone presumably reflects the strain in this particular molecule.

It was decided not to subject compound B to acid treatment as a similar rearrangement to the one just described would almost certainly take place. Work on the synthesis of a tricyclic compound was discontinued at this stage.

PART II.

Cope, in two papers [20, 42] in 1950, established a synthesis of an eight membered ring compound by cleavage of the bridge of a (3:3:1)-bicyclic compound. The basis of this cleavage was the conversion of a ketone bridge in a (3:3:1)-bicyclic system to an oxime, rearrangement to the lactam and hydrolysis of this to an amino acid. Schemes 12 and 13 briefly outline the series of reactions undertaken in his reported cases.

The present work was undertaken to investigate the scope of this reaction sequence for the synthesis of a ten membered carbocycle.

Two bicyclic systems were considered as possible starting materials for modification to the ten carbon ring. The first was the (4:4:1)-bridged system (125), removal of the carbonyl bridge from which would lead to the required ring size. However, the condensation of a four carbon side chain to a cycloheptanone and subsequent cyclisation to a bicyclic compound is a particularly difficult problem[43], and at present only one such compound [44], allohimachalol (126), has appeared in the literature. On the other hand the (5:3:1)-bicyclic skeleton (127) has been synthesised by Prelog and his co-workers [33,45,46] and others, and, although little further work had been done on such a system, it appeared to be a more suitable starting material than the (4:4:1)-bicycle.

2-(3'-phenyl-3'-oxopropyl)-cyclo-octanone (128) was produced in 56% yield from cyclo-octanone and cyclised to a mixture of the unsaturated bicyclic ketones (129) and (130). G.l.c. indicated that the mixture was composed of 63 % and 37 % of (129) and (130), respectively. The infra-red of the major component showed $\nu_{CO}^{CCl_4}$ 1701 cm.$^{-1}$ and the ultra-violet, λ_{max}^{EtOH} 243 mμ ($\varepsilon = 12{,}400$), the latter being consistent with a normal styrene type chromophore (c.f. Table 4). N. m. r. indicated the presence of one vinyl proton (4.09 τ), which appeared as a triplet, agreeing favourably with the structure assignment (129). This was corroborated by an acceptable analysis, $C_{23}H_{24}O_4N_4$, for the 2,4-dinitrophenylhydrazine derivative.

Separation of (129) and (130) proved impractical as both ran closely on a t.l.c. plate and also on a column. On a small scale, however, separation was achieved by thick layer chromatography to provide sufficient material for i.r., u.v., and n.m.r. data to be collected. The carbonyl stretching frequency of the minor component (130) in the infra-red appeared at 1693 cm.$^{-1}$ with a shoulder at 1683 cm.$^{-1}$. The order of this absorption is close to the expected value for a α β -unsaturated compound, lack of planarity possibly contributing to the slightly higher value. The appearance of a doublet however may well be due to Fermi resonance, a feature which is observed in several other bicyclic ketones, (c.f. Table 5). The n.m.r. spectrum shows no vinyl protons and, except for the very finely split aromatic peak, no other absorption below 7.4 τ. The most conclusive evidence, apart from n.m.r., is the ultraviolet spectrum with λ_{max}^{EtOH} 263 mμ (ε = 12,200). No model system could be found with which a true comparison could be made owing to the unique conformation of such a system. Table 6 lists several of the most closely related systems.

Light absorption in the near ultra-violet can be regarded as resulting in transitions from a hybrid ground state, to which resonance forms, (particularly ionic forms), of higher energy content than classical structures make a relatively small contribution, to excited states to which resonance forms of higher energy content make a larger contribution.

A structural change which tends to decrease the planarity of the conjugated system might be expected to influence ultra-violet absorption properties in one of the following ways.

a) If the steric interference resulting in non-planarity is relatively small, then the characteristic transition of the chromophore might be restricted to vibrational states in which appropriate bonds are sufficiently extended to allow a large degree of non-planarity. Solution spectra representing band envelopes, rather than discrete bands, will then show little change in the wave length location, but the intensity of the absorption will be decreased since the transition will be restricted to a smaller number of vibrational states.

At the same time, bands, characteristic of the partial chromophore present in the non-planar configuration, will appear increasing in intensity as the intensity of the main band decreases.

b) If steric interference is large and resonance interaction takes place despite non-planarity, the energy level of the excited state will therefore be raised relatively to that of the ground state, i.e. the characteristic band itself will be displaced towards shorter wave lengths.

From the ultra-violet spectrum of (130) the hypsochromic shift of the main absorption band, from the expected value of about 280-290 m.μ. to 263 m.μ. , would indicate a fairly large degree of non-planarity in the enone system.

Although a pure sample of (130) was never analysed, a mixture of the isomers (129) and (130) analysed for $C_{17}H_{20}O$ and gave a mass spectral molecular weight of 240.

Theoretically the hydrogenation of a mixture of (129) and (130) should result in the one compound. When (129) was hydrogenated in ethanol using a 10 % palladilised charcoal catalyst a mixture of isomers was obtained which were thought to differ only in the stereochemistry at C_2, i.e. one with the phenyl grouping axial and the other equatorial. The mixture analysed for $C_{17}H_{22}O$, and had a molecular weight of 242. No absorption in the n.m.r. for a vinyl proton was observed. Loss of the double bond was further substantiated by the ultra-violet spectrum from which the 243 m.μ absorption had disappeared to be replaced by the low intensity peaks already mentioned in the spectra of the aryl bicyclic compounds (77), (79), (84), (85), etc., . The expected carbonyl absorption in the infra-red for (131) was found $\nu_{CO}^{CCl_4}$ 1701 cm.$^{-1}$. Hydrogenation of a mixture of (129) and (130) yielded the same mixture as hydrogenation of (129) alone. This was shown by both t.l.c. and g.l.c. analysis.

From the physical, and also the hydrogenation evidence, there seemed little doubt that the isomeric mixture obtained, by treating the diketone (128) with a mixture of hydrochloric and glacial acetic acids, was composed of the unconjugated (5:3:1)-bicyclic ketone (129) and the conjugated ketone (130). The latter is an example of the limiting case for a double bond to be situated at a bridgehead [5].

The difficulty in separating these isomers was sufficient to eliminate this method as a feasible means of preparing (129). Fortunately this problem was obviated by using para-toluene-sulphonic acid as the condensing agent and carrying out the reaction in benzene in a water separator. Although the reaction mixture turned black during the refluxing period, after distillation a good yield of 2-phenylbicyclo-(5:3:1)-undec-2-ene-11-one (129) was isolated free from the conjugated isomer (130). Very little of the latter was produced at all in the reaction and it could be eliminated completely by using shorter refluxing times.

Equilibration of the two isomers was possible by refluxing some pure (129) in a mixture of hydrochloric and acetic acids for three hours. 30 % of (129) isomerised to (130). Increased reaction times did not alter the isomeric ratio although times of greater than twelve hours were not employed. A similar isomerisation was observed by leaving (129) standing in an alcoholic solution of sodium ethoxide overnight.

Once a suitable method of preparing (129) had been obtained the latter was converted to its oxime (132) whose structure was established by physical means, (see experimental). Conversion of the oxime to the corresponding lactam (133) gave some trouble initially. The method used by Cope [20], was to stir the oxime with benzenesulphonyl chloride in pyridine for thirty minutes, but several attempts to apply this procedure to (132) yielded only starting material. Refluxing the mixture led to severe charring. However, when the oxime was heated at 100° with para-toluenesulphonyl chloride in pyridine for three hours, it was completely expended and the reaction mixture consisted of some five or six components, the major one of which, after separation, crystallised on standing.

The obvious charring and the by-products produced were virtually eliminated by carrying out the reaction at room temperature overnight. Yields of up to 70 % of the lactam (133) could be obtained in this way. A mol. wt. of 255 was established by mass spectroscopy and an empirical formula of $C_{17}H_{21}ON$ by micro-analysis. The ultra-violet spectrum showed λ_{max} 234 m.μ ($\varepsilon = 10{,}450$) and the infra-red $\nu_{CO}^{CCl_4}$ 1657 cm.$^{-1}$. These facts were not sufficient to unequivocally prove the structure of the lactam.

There were two possible directions in which the Beckmann rearrangement could have taken place depending on which bond in the bridge migrates, one giving rise to (133) and the other to (134). The difference between the resonance frequency, of a proton α to nitrogen and allylic to a double bond and that of a proton α to a carbonyl and allylic, was too indefinite to allow structure assignment from the n.m.r. spectrum. Cope, in the (3:3:1)-bicylic system, was only able to say that the oxime (135) had the structure shown, when, on hydrolysis, decarboxylation was able to take place. Suffice to comment at this stage that it seemed likely that the rearrangement of (132) would take place in the same sense as in Cope's reaction.

In the hydrolysis step, (135) → (136), Cope employed 6N hydrochloric acid and a 24 hour reflux time. Similar treatment of (133), however, did not yield the required amino acid (137), its hydrochloride or the decarboxylated analogue (130). Instead, a colourless crystalline solid was isolated in good yield which analysed for $C_{17}H_{21}ON$ and had a molecular weight of 255. The infra-red absorption spectrum had bands at 1663 and 1632 cm.$^{-1}$ and the ν C-H and νN-H region bore a marked resemblance to the corresponding region in the spectrum of (133). The greatest single clue to the structure of this compound was the u.v. spectrum which showed λ max at 250 m.μ ($\varepsilon = 8700$). Although the intensity seemed high the absorption wavelength was the right order for an α,β - unsaturated lactam [47], (c.f. (139) - λ max 251 mμ ($\varepsilon = 1,120$)). In the light of this the infra-red was studied more closely. The carbonyl frequency of (133) was 1657 cm.$^{-1}$ and it seemed unlikely that this should increase to 1663 cm.$^{-1}$ if α,β-unsaturation had been introduced. However, Edwards and Singh [48] have made the interesting observation, that α,β-unsaturation does not lower the carbonyl frequency of six and seven membered unsaturated systems (e.g. (139)) but appears to raise it a little. A similar observation has been made with certain bakankosine derivatives [49], which contain a cyclic 7-membered α,β-unsaturated lactam, average figures quoted being ν CO 1658 and ν C=C 1605 cm.$^{-1}$.

The evidence collected up to this point indicated that the hydrolysis product of (133) was the isomeric lactam (140).

Further proof of this was obtained from the n.m.r. spectrum which showed no vinyl proton and the resonance peak for the proton on the nitrogen appearing at 1.20 τ as a poorly defined doublet (J = 8 cps.). The characterisation of this compound as (140) necessarily proves that the initial lactam had structure (133) and not (134). The fact that the Beckmann rearrangement only produces one product is not rationalised by Cope but the explanation may well lie in the conformation of the intermediate oxime.

Concentrated hydrochloric acid was used in an attempt to hydrolyse the lactam (133) but only isomerised lactam (140) was isolated after 24 hours refluxing. Similarly, 2 hours refluxing with 5 % potassium hydroxide in ethanol yielded (140) together with trace amounts of other compounds; 6N hydrochloric acid in ethanol produced not only (140) but further neutral products, (not fully investigated), one of which at least was isomeric with starting material, (mass spectral, micro-analytical and infra-red evidence).

Despite his being able to hydrolyse the mon-phenyl lactam (135) in 24 hours, Cope found it necessary to reflux the diphenyl analogue (141) for 9 days before hydrolysis could be accomplished. Under similar treatment the lactam (133) was not hydrolysed but merely isomerised to (140).

In conclusion, it appears that the lactam (133) was isomerised to (140) and, although the latter probably hydrolysed to the amino acid (142), the geometry of its ten-membered ring was such that closure back to (140) took place. There seemed no reason to doubt that the α,β - unsaturated lactam was capable of hydrolysing. The scope of Cope's route to large rings via bicyclic systems would thus appear to be dependent on the ability of the intermediate amino acid to decarboxylate. Decarboxylation is facilitated by an β, γ-double bond, and the movement of the double bond into conjugation (i.e. (133) → (140)) has two effects : it prevents the decarboxylation and for reasons of geometry it encourages ring closure of any hydrolysed product (142) back to amide (140).

APPENDIX.

The infra-red stretching vibrations in symmetrical dicarbonyl compounds have been found to couple, resulting in two absorptions, one above and the other below the common frequency [51]. This effect has, however, been demonstrated only in a few types of compounds, mainly in acyl and aroyl peroxides [52], acid anhydrides [53, 54], cyclic malonates [55] and more recently in cyclic β-diketone systems [56, 57]. Nevertheless the origin of the splitting can only be guessed at without detailed solvent studies.

In the course of the present investigation, a series of 2,2-disubstituted 1,3-cyclic diketones was studied and verification of the νCO splitting phenomenon obtained.

In the absence of rotational isomerism, the splitting of the carbonyl into a doublet could be due to either Fermi resonance or dipole interaction, (vibrational coupling). Differentiation between these two effects can be made by checking the peak separation ($\Delta\nu$) and the relative intensities of the peaks in a series of solvents.

The solvents selected in the present study were hexane, carbon tetrachloride, chloroform and acetonitrile and the infra-red carbonyl absorption frequencies recorded in Table 7. These results disproved Fermi resonance and confirmed vibrational coupling. The following significant points are apparent from this table.

1) The peak separation, ($\Delta\nu$), is constant at <u>ca.</u> 30 cm.$^{-1}$, or a little greater, in all cases.

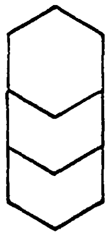
2) The value of $\Delta\nu$ is unaffected by solvent polarity.

3) The relative intensities (ε) of the peaks are unaffected by solvent polarity.

4) The effect is observable in cases where enolisation is forbidden by substitution.

Bellamy and Beecher [58] attributed the 1733 and 1706 cm.$^{-1}$ peaks in a solution spectrum of dimedone to the non-enolised keto group of the enol form and the free keto form respectively. Abramovitch [55], however, suggests that this doublet may well have its origin in vibrational coupling of the two free carbonyl groups. This problem has not been resolved to date; solvent studies, in this case, have only confused the issue further by the observation that the 1706 cm.$^{-1}$ peak disappears at high dilution. Further to this, in the present work, no evidence of dipolar interaction was found in any 2-monosubstituted 1,3-cyclic diketones.

It is concluded that the occurrence of a doublet of $\Delta\nu$ ca, 30 cm.$^{-1}$ is diagnostic of a non-enolisable cyclic β - diketone system.



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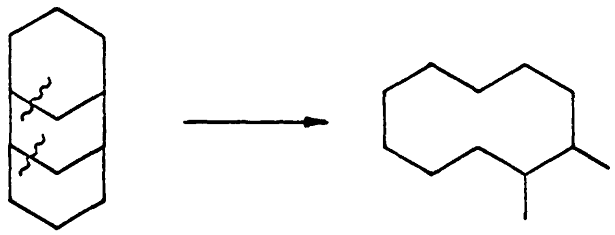

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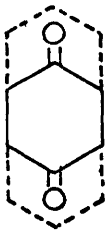

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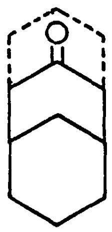

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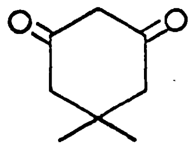

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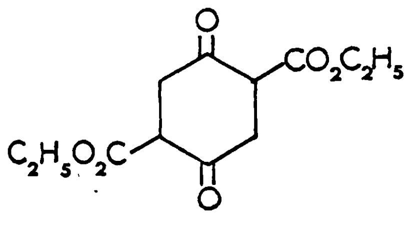

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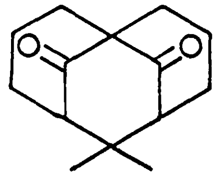

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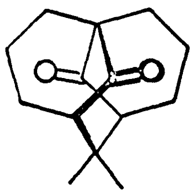

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$Ph.CO.CH_2CH_2N(CH_3)_2$

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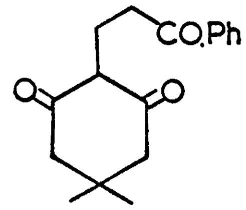

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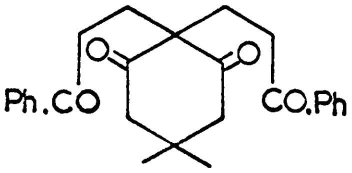

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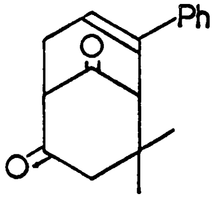

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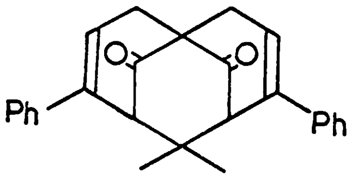

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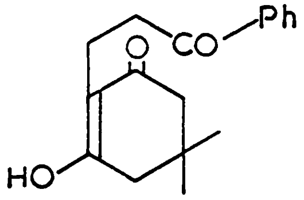

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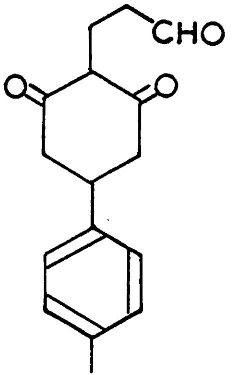

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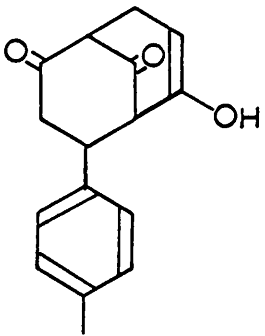

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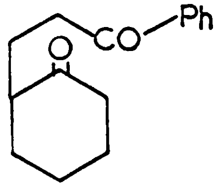

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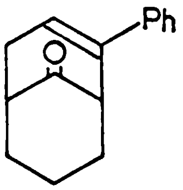

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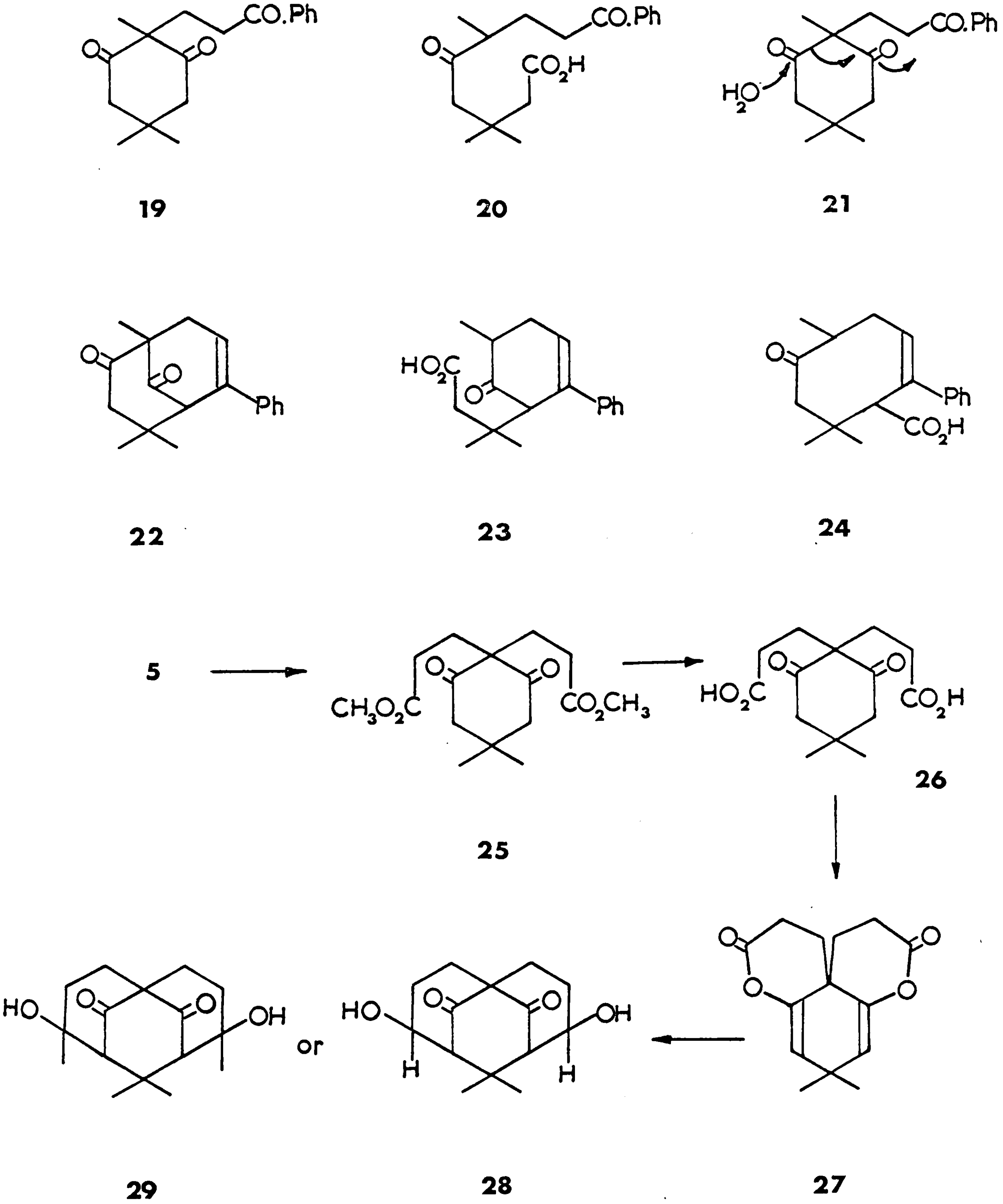

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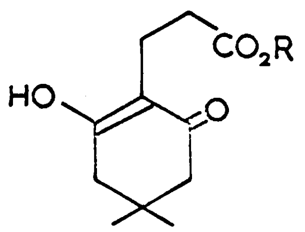
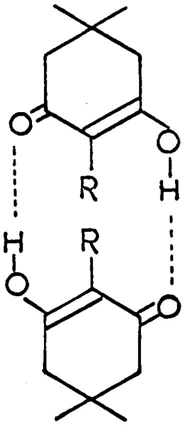
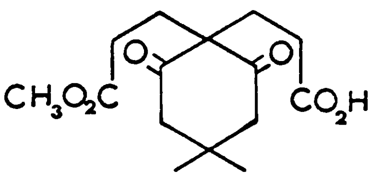


30 a, R=CH_3
b, R=H



31 R=$CH_2CH_2CO_2CH_3$



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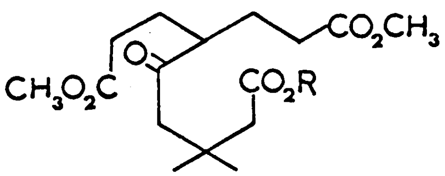
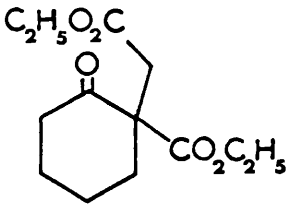


33 a, R=H
b, R=CH_3



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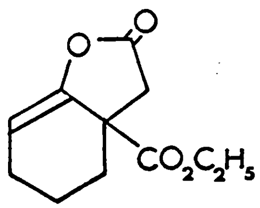

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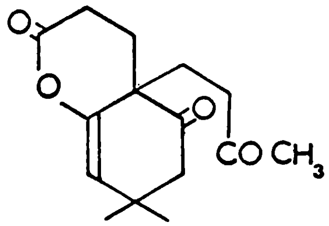

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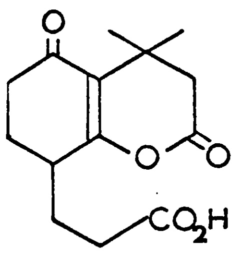

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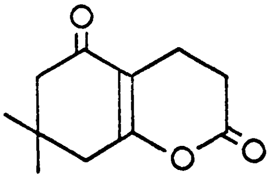

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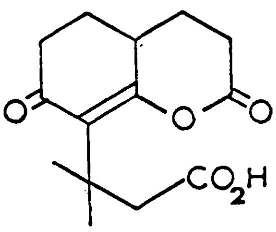

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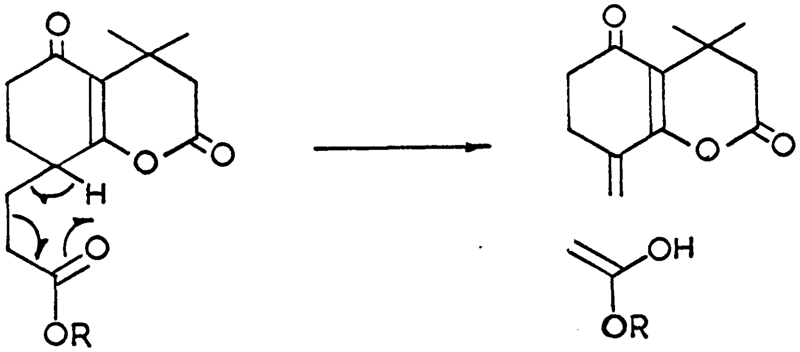
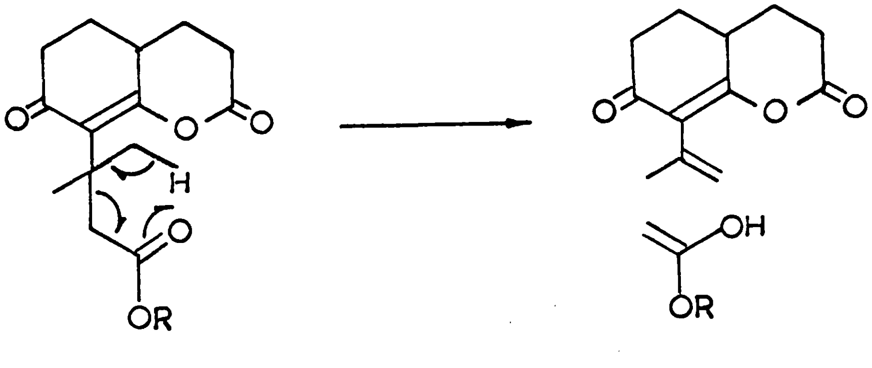


41 R = H or CH_3



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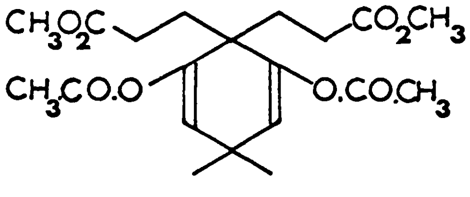

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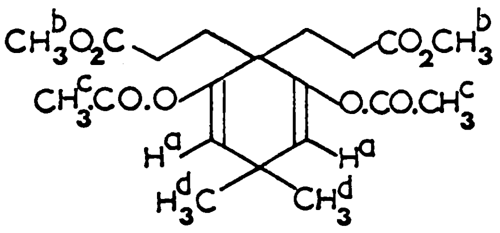

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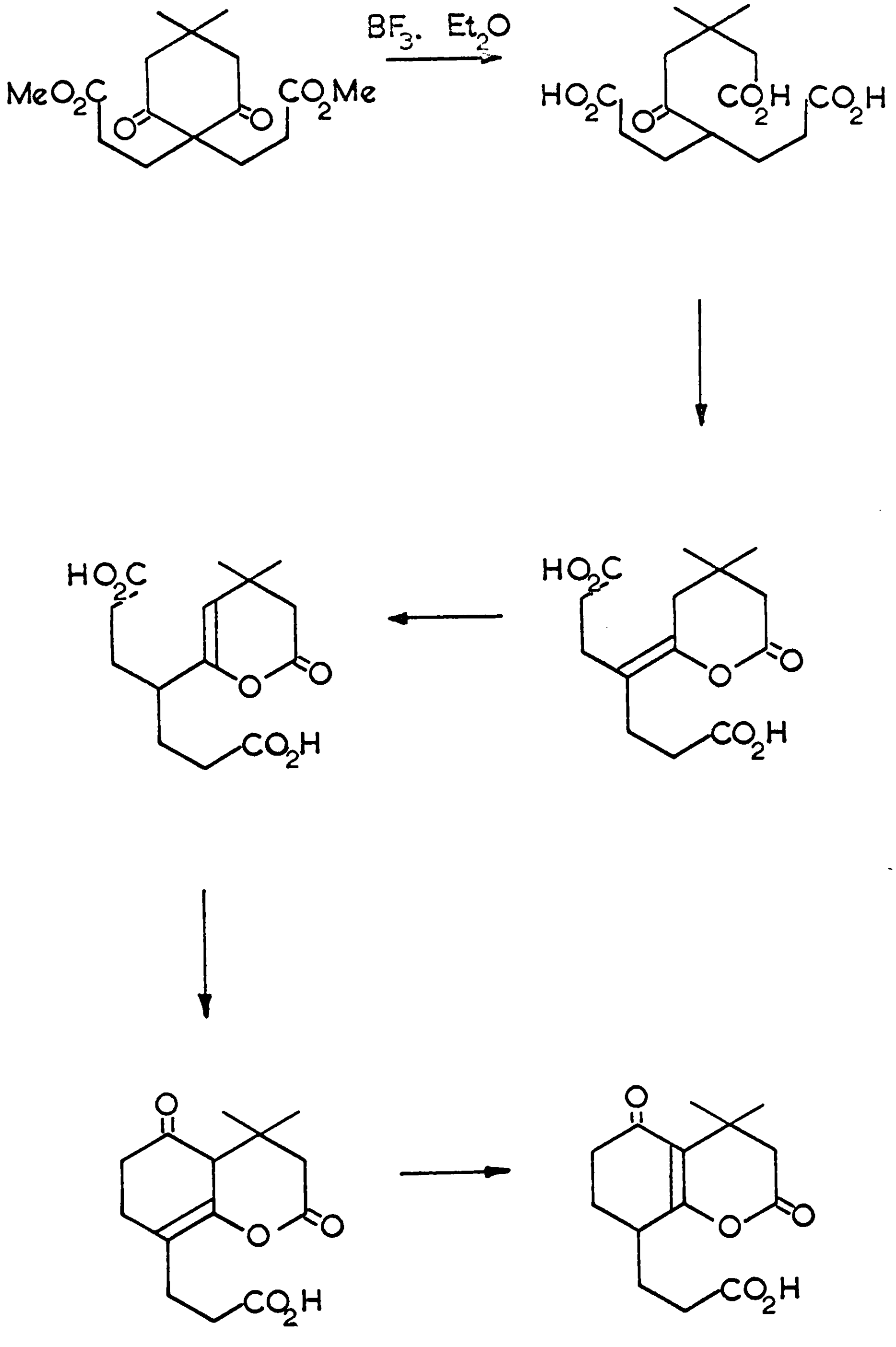
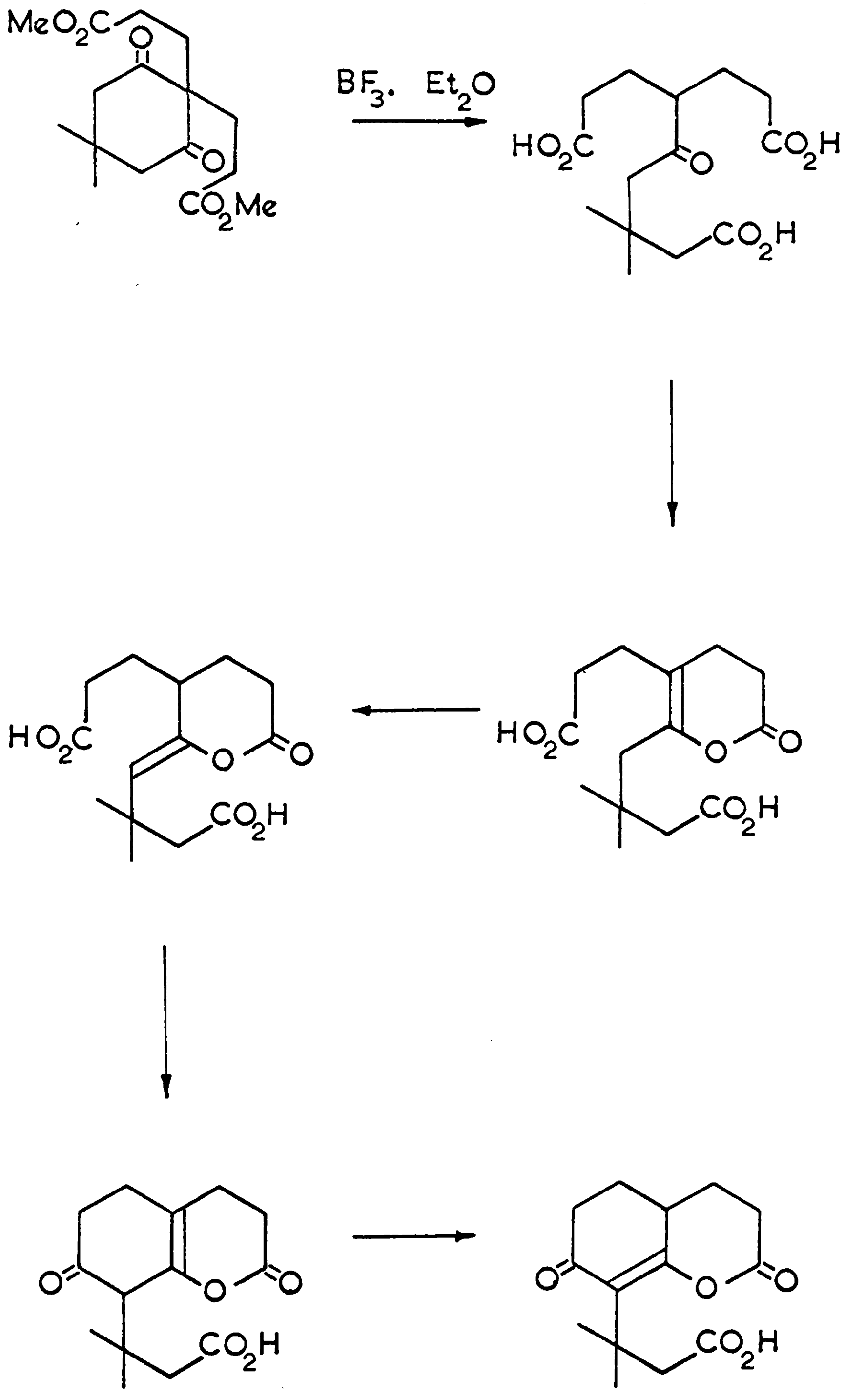


BF$_3$. Et$_2$O
MeO$_2$C
CO$_2$Me
HO$_2$C
CO$_2$H
CO$_2$H
HO$_2$C
CO$_2$H
HO$_2$C
CO$_2$H
CO$_2$H
CO$_2$H

Scheme A.



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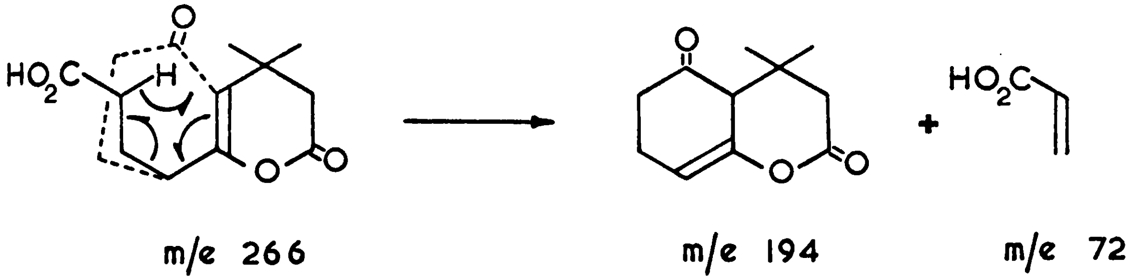

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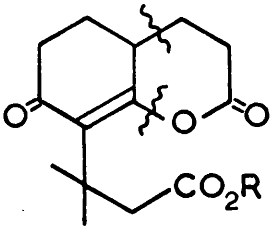
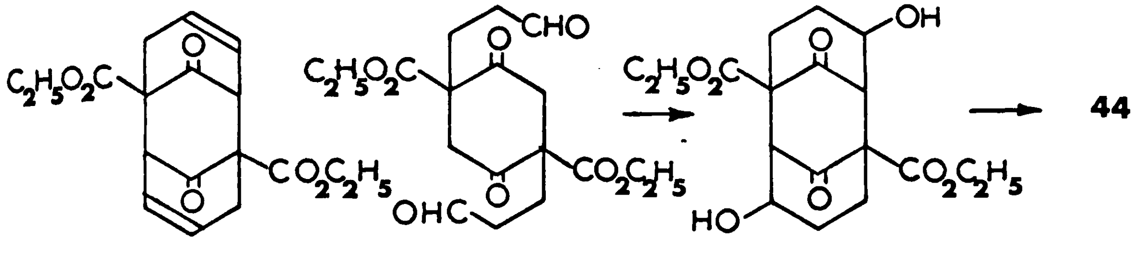


40a (R = H or CH_3)



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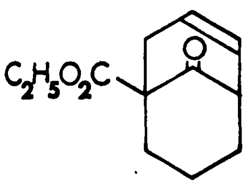

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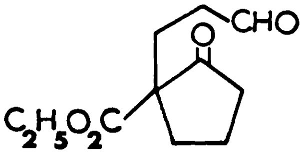

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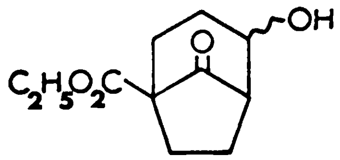

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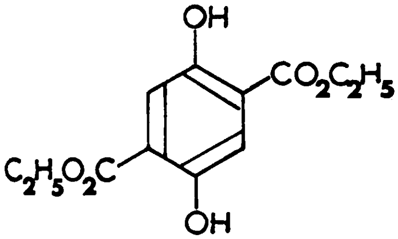

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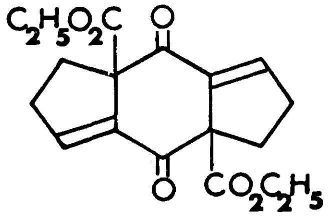

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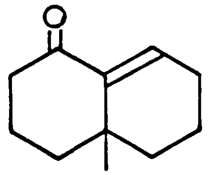

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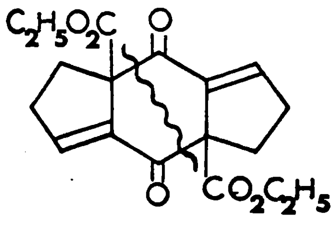

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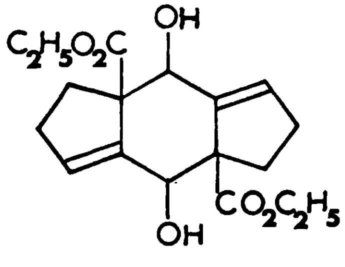

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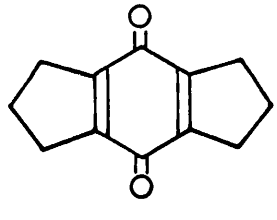
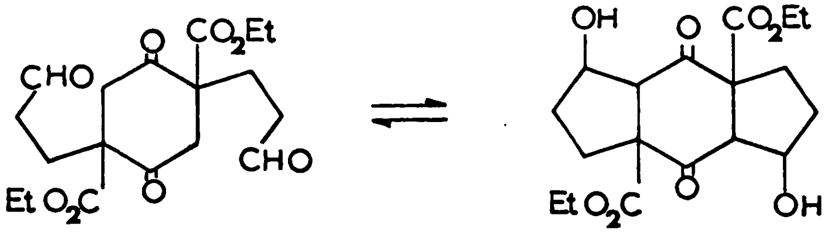


55

BASE PEAKS m/e		FRAGMENTATIONS
332	–	Parent ion
166	–	Symmetrical halving
138	–	166 – (CO)
93	–	166 – (CO_2Et)
63	–	93 – (CO) or 138 – (CO_2Et)

Table 2.



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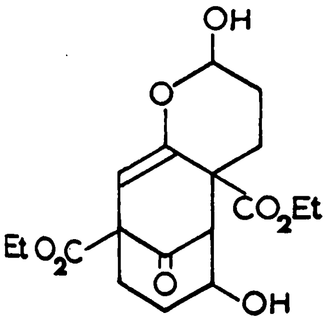

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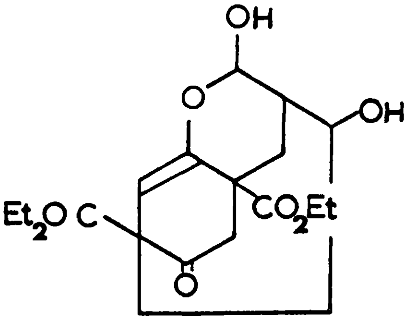

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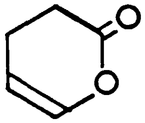

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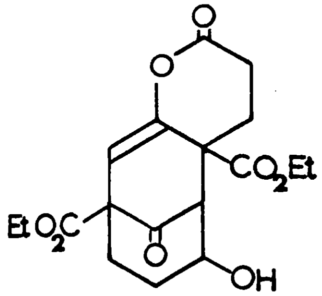

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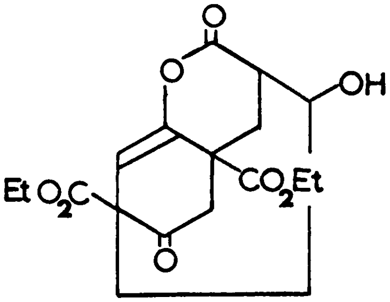

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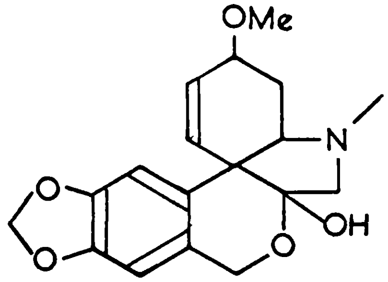

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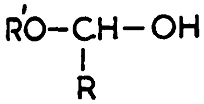
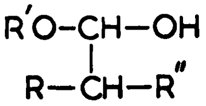


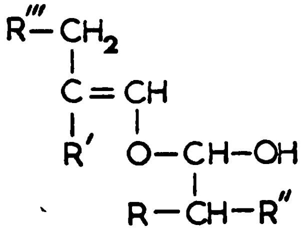
$$R'O-\underset{\displaystyle R}{\underset{|}{CH}}-OH$$

65



$$R'O-\underset{\displaystyle R-CH-R''}{\underset{|}{CH}}-OH$$

66



$$\begin{array}{rcccccl} R'''- & CH_2 & & & & & \\ & | & & & & & \\ & C & = & CH & & & \\ & | & & | & & & \\ & R' & & O & - & CH & -OH \\ & & & & & | & \\ & & & & R- & CH & -R'' \end{array}$$

67

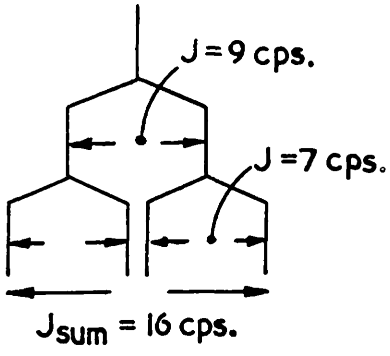
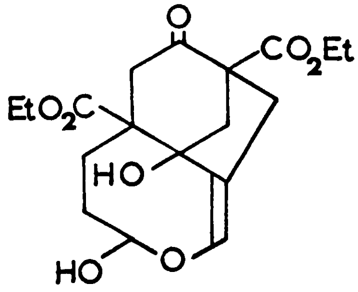


Figure 1.



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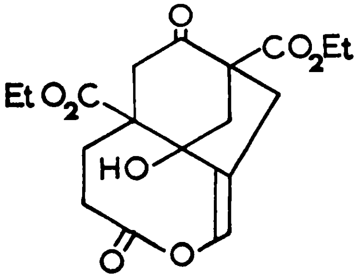

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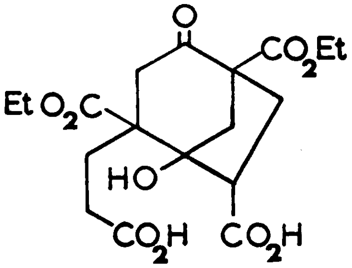

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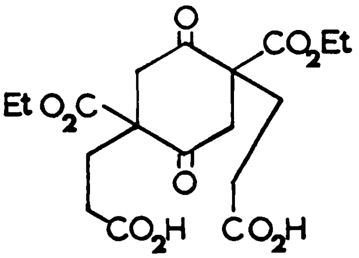

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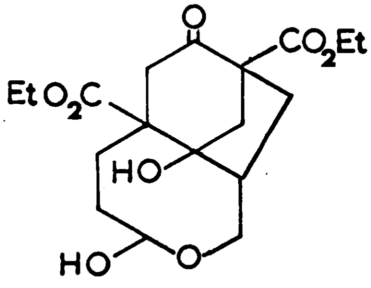

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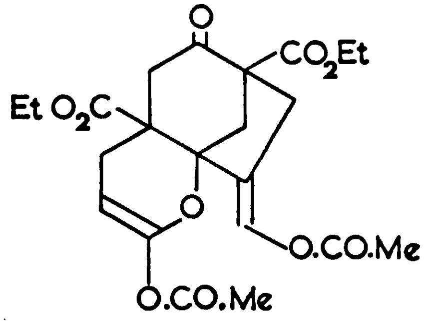

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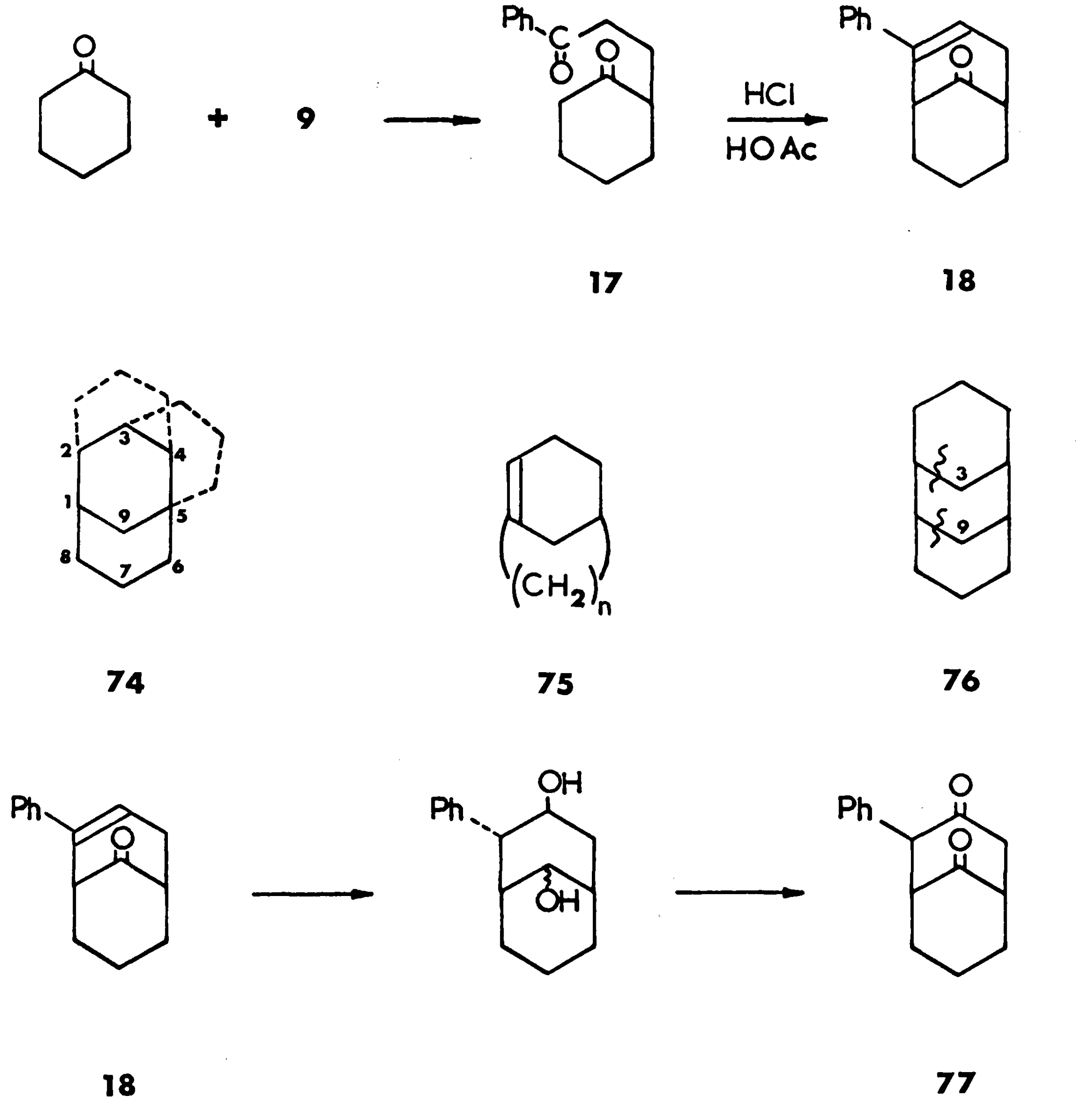
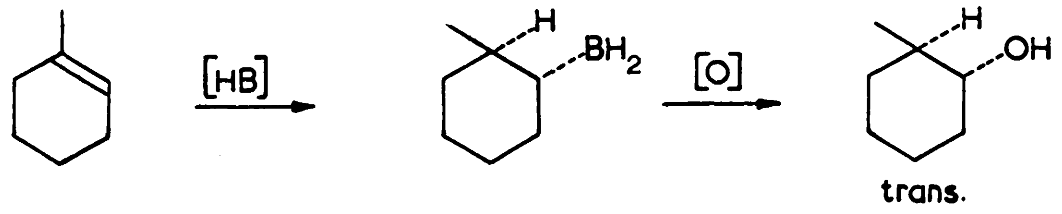
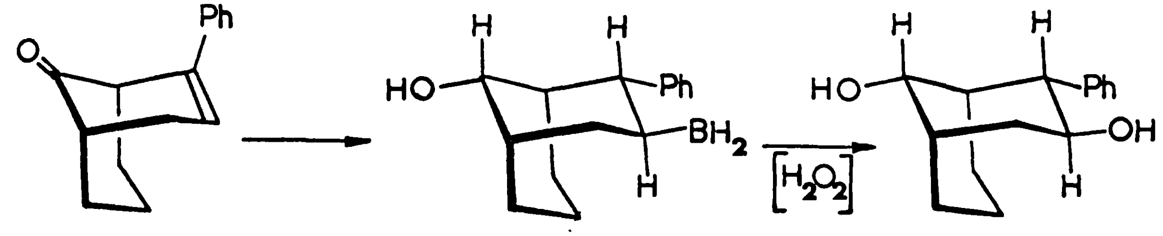


Scheme 1.



Scheme 2.



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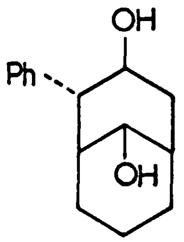

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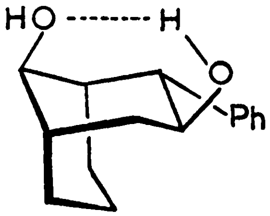

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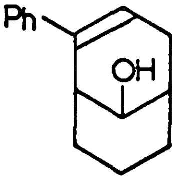

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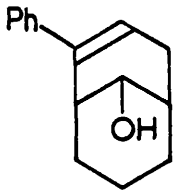

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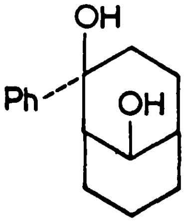

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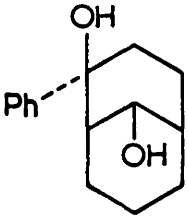

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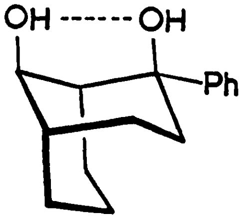

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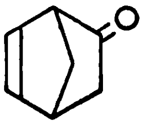

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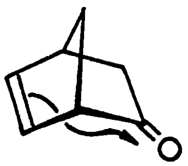
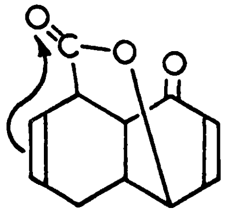


88

Reagent	-	$LiAlH_4$/Ether	$NaBH_4$/Methanol
Syn alcohol	-	22%	27%
Anti alcohol	-	78%	73%

Table 3.



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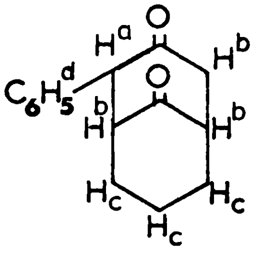

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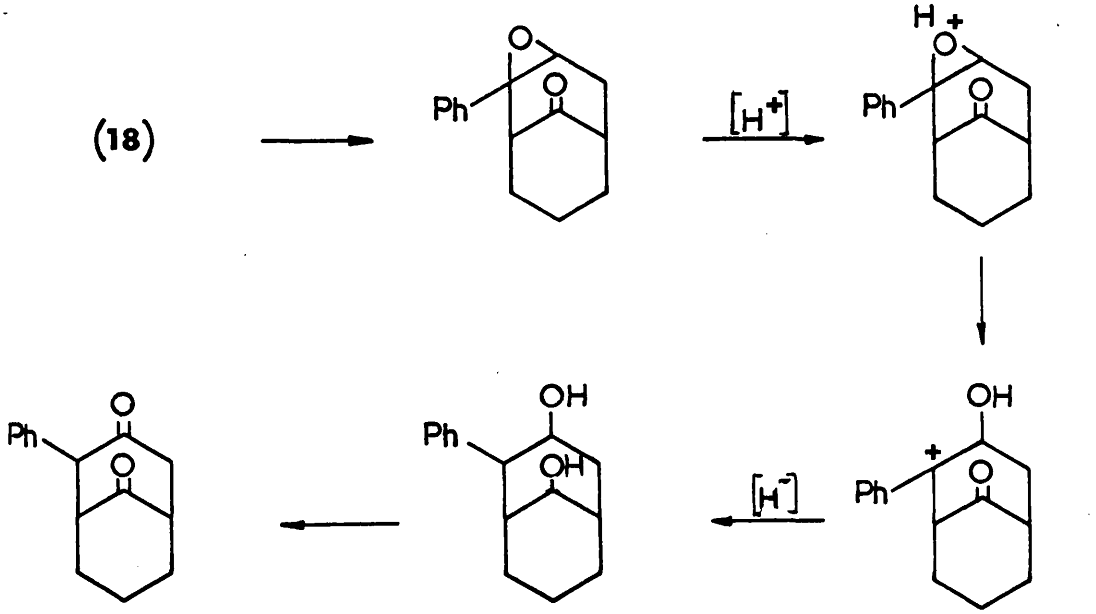
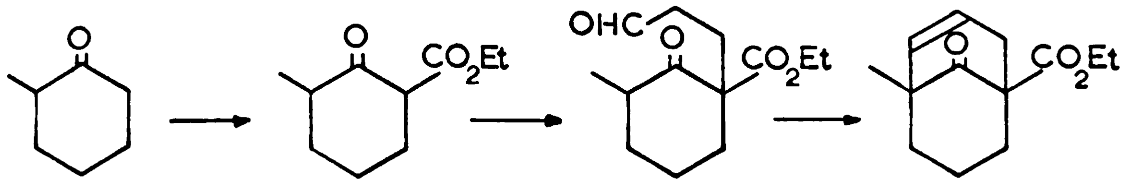


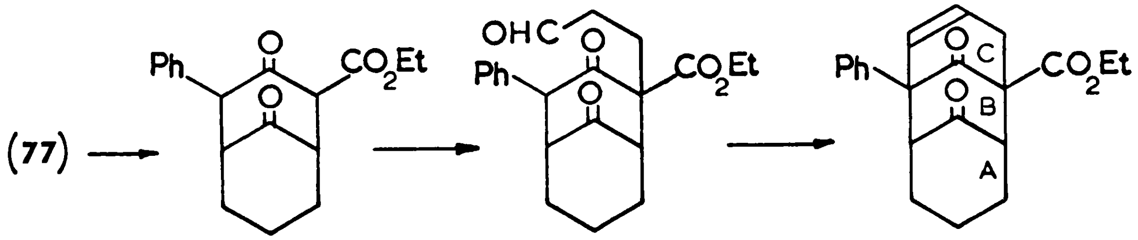
77

Scheme 3.



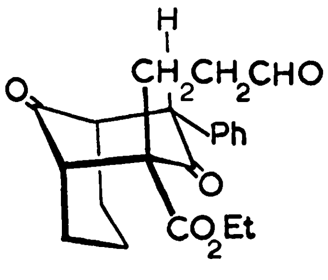
90

Scheme 4.



91 **92** **93**

Scheme 5.



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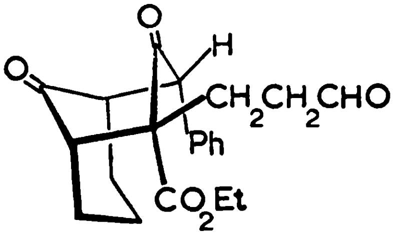

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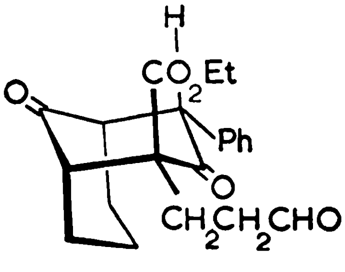

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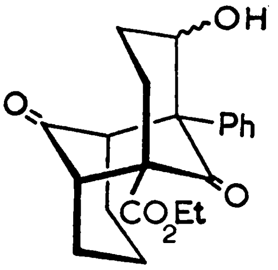

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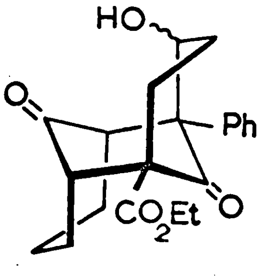

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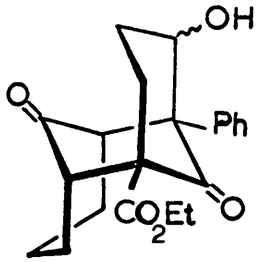

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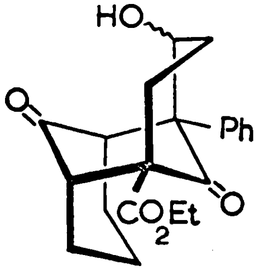

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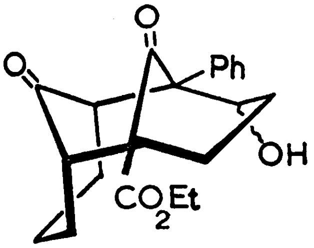

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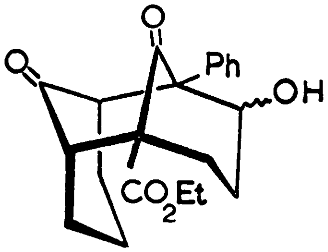

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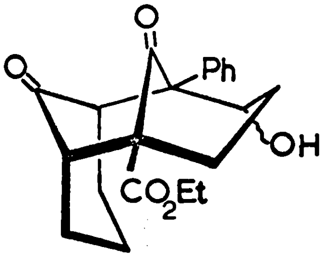

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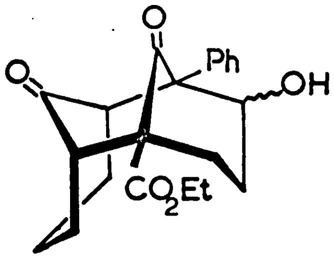
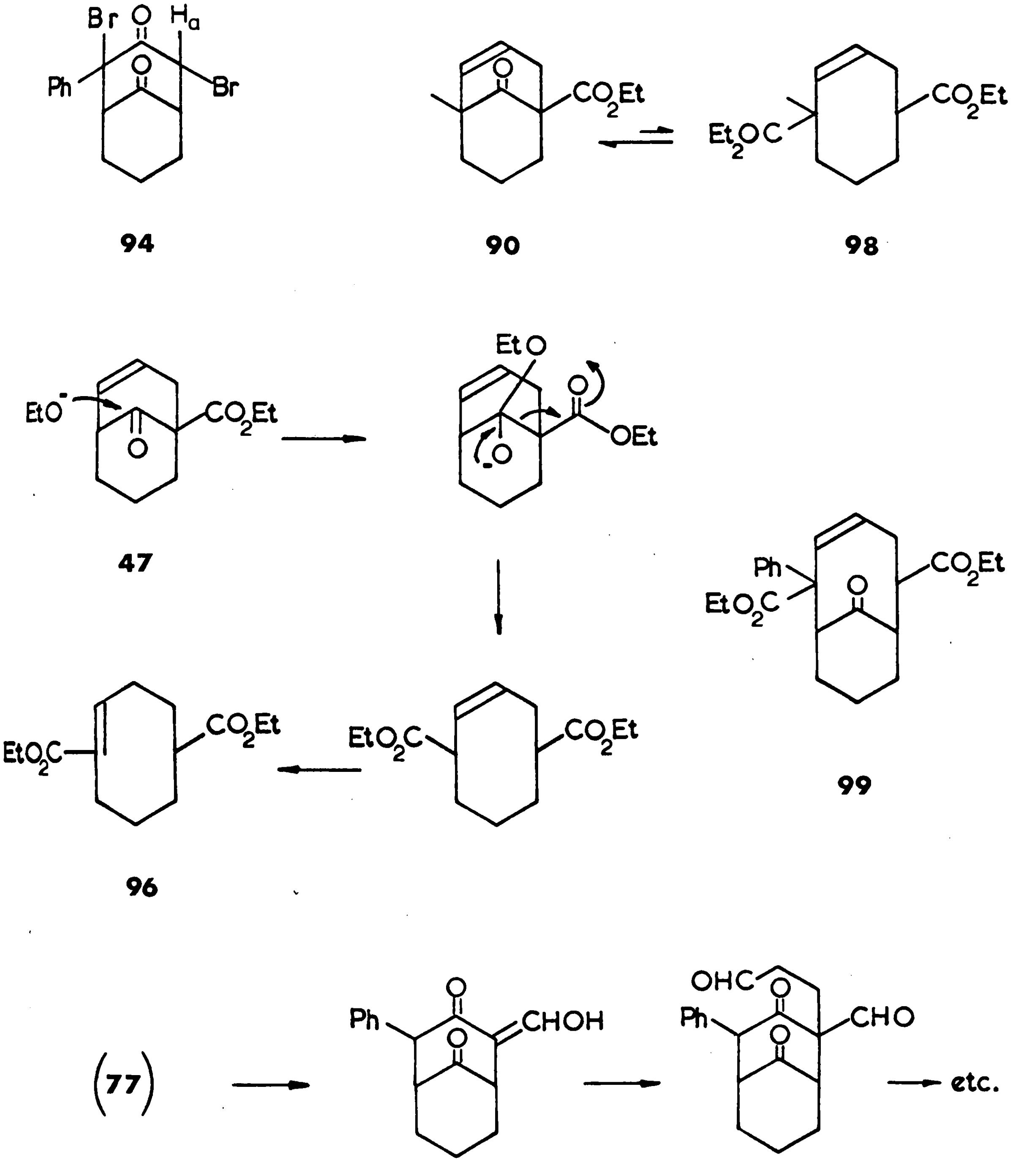
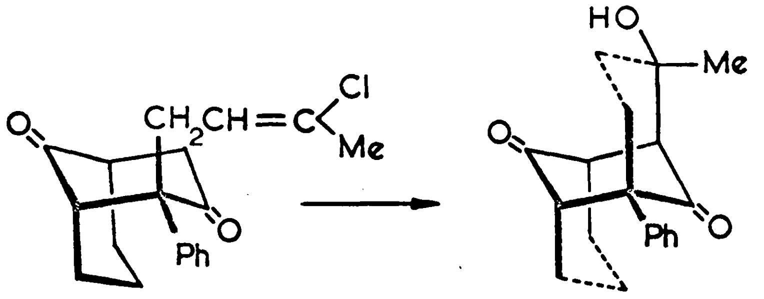


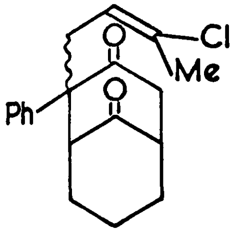
93h


Br
O
H_a
Ph
Br
94
CO2Et
90
Et2OC
CO2Et
98
EtO-
CO2Et
47
EtO
O
OEt
O-
EtO2C
CO2Et
EtO2C
CO2Et
96
Ph
EtO2C
CO2Et
99
(77)
Ph
CHOH
OHC
Ph
CHO
etc.

Scheme 6.



100 b



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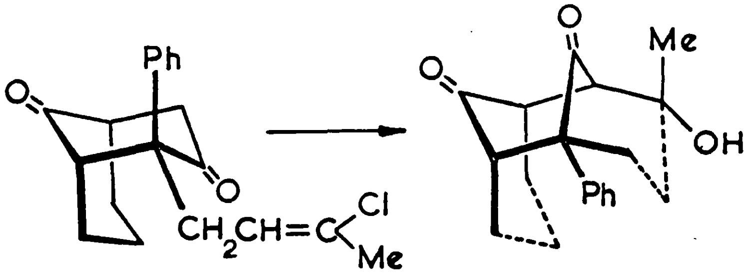
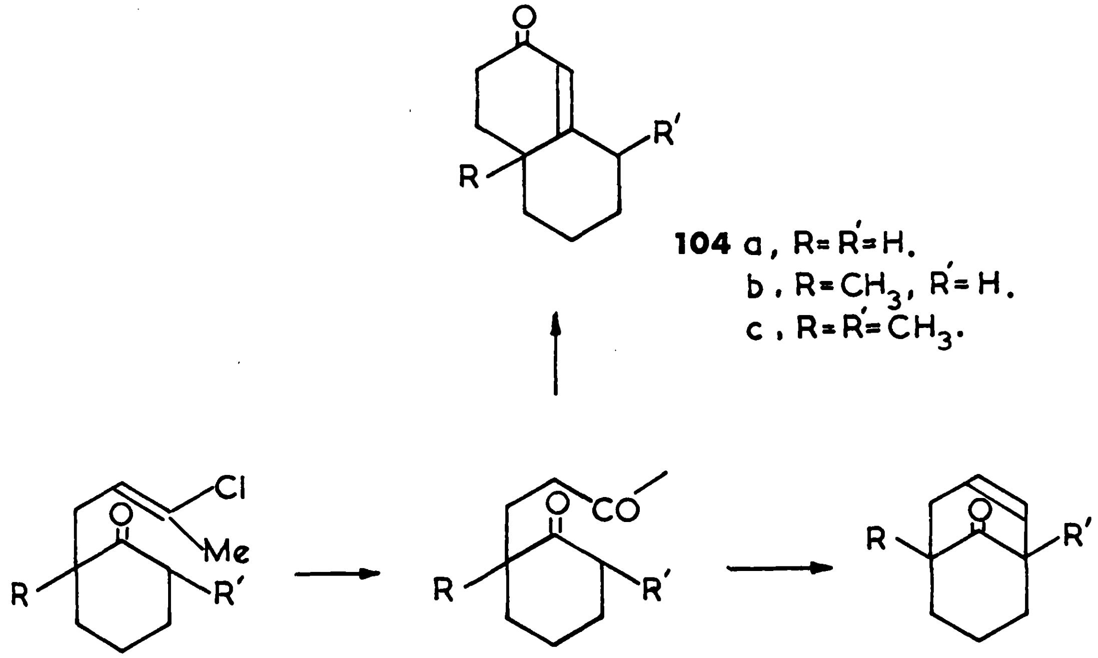


100 a

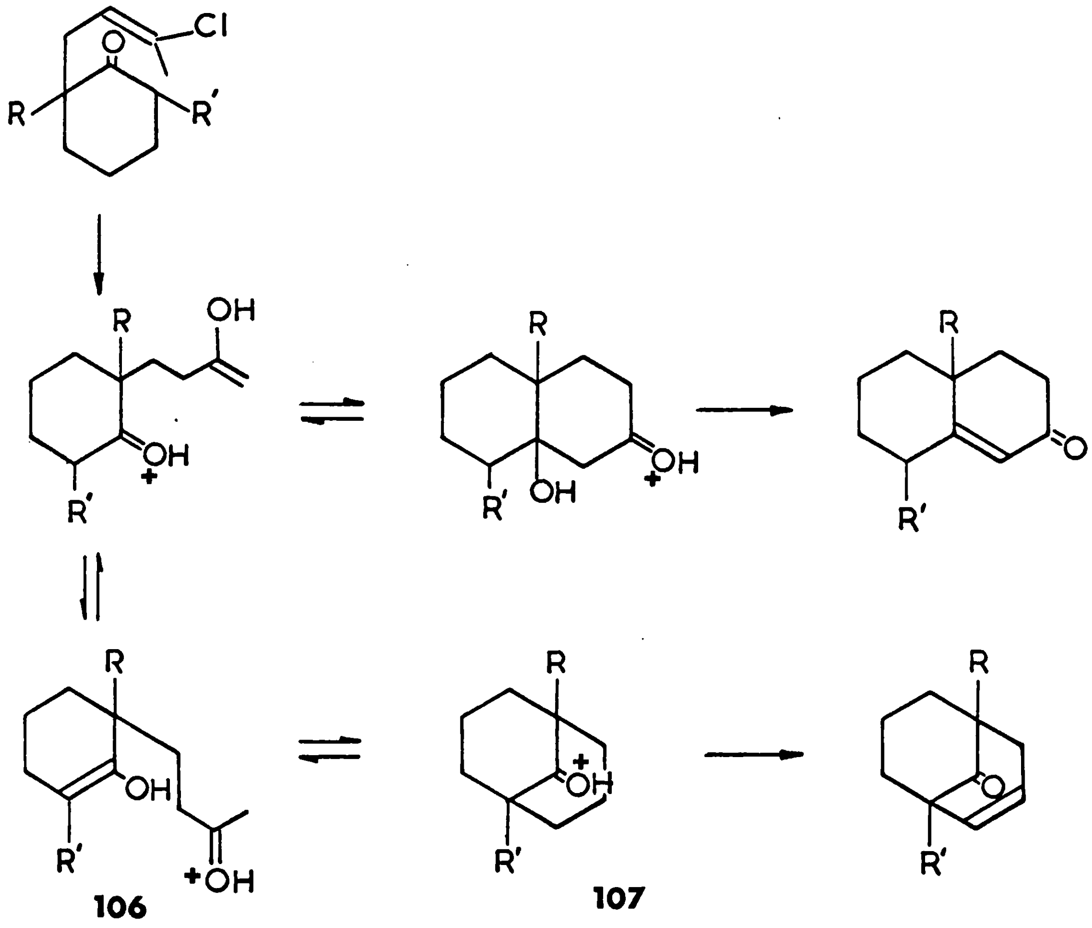


104 a, $R=R'=H$.
b, $R=CH_3$, $R'=H$.
c, $R=R'=CH_3$.

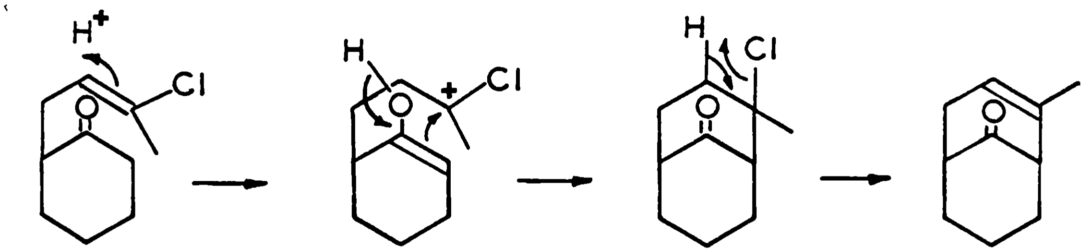
102 a, $R=R'=H$.
b, $R=CH_3$, $R'=H$.
c, $R=R'=CH_3$.

101 a, $R=R'=H$.
b, $R=CH_3$, $R=H$.
c, $R=R'=CH_3$.

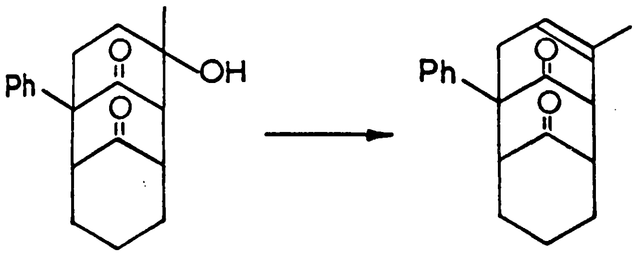
103 a, $R=R'=H$.
b, $R=CH_3$, $R'=H$.
c, $R=R'=CH_3$.



Scheme 7.



Scheme 8.



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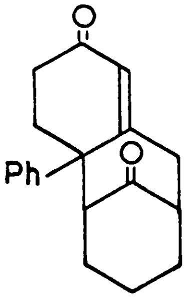

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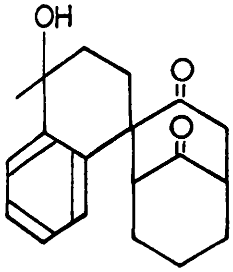
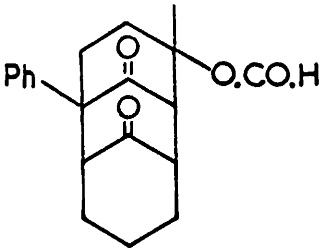


110

111

112



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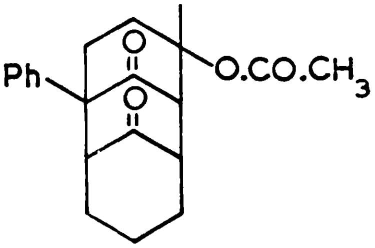

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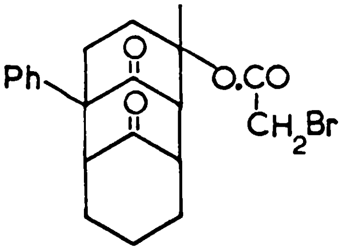

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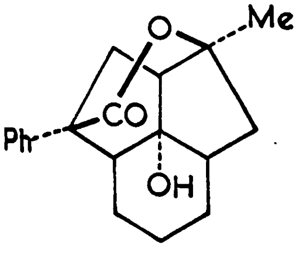

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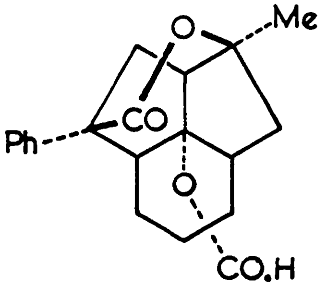

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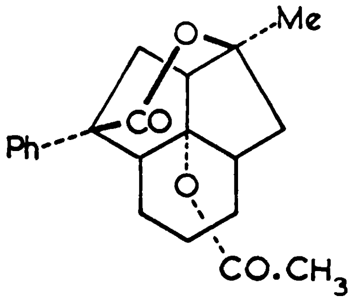
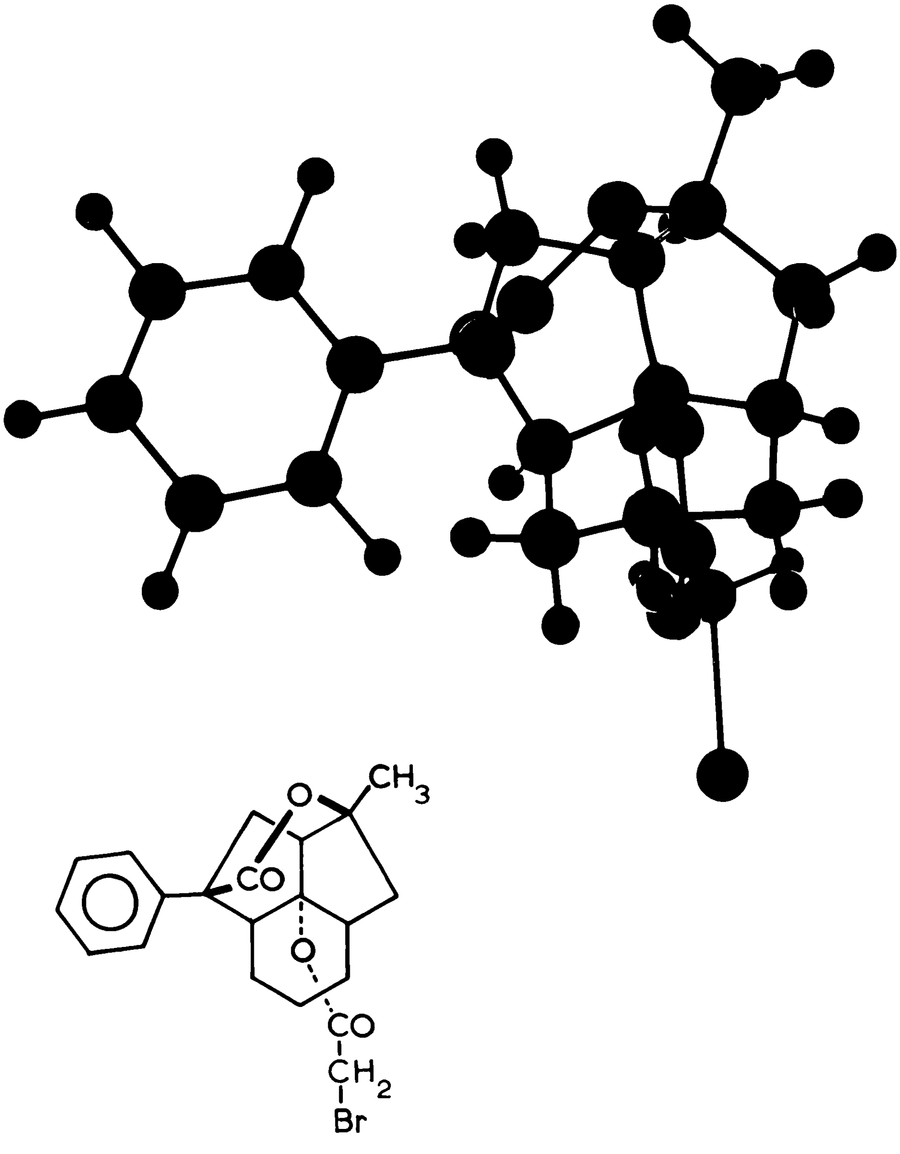
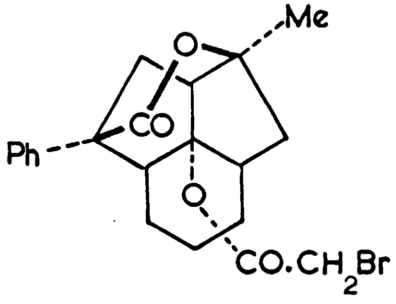


118

Figure 2.





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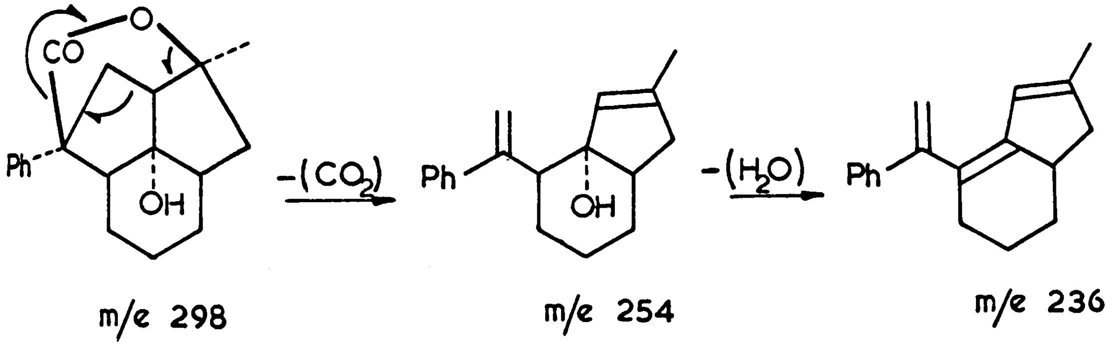
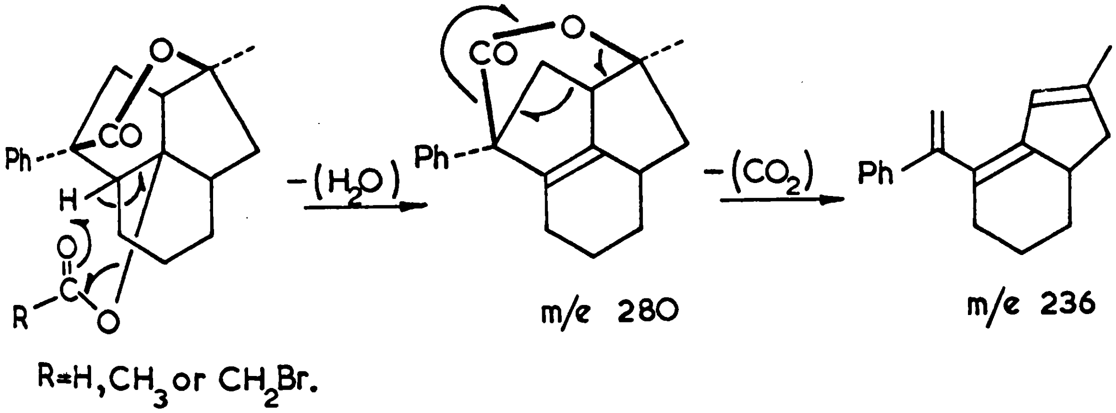
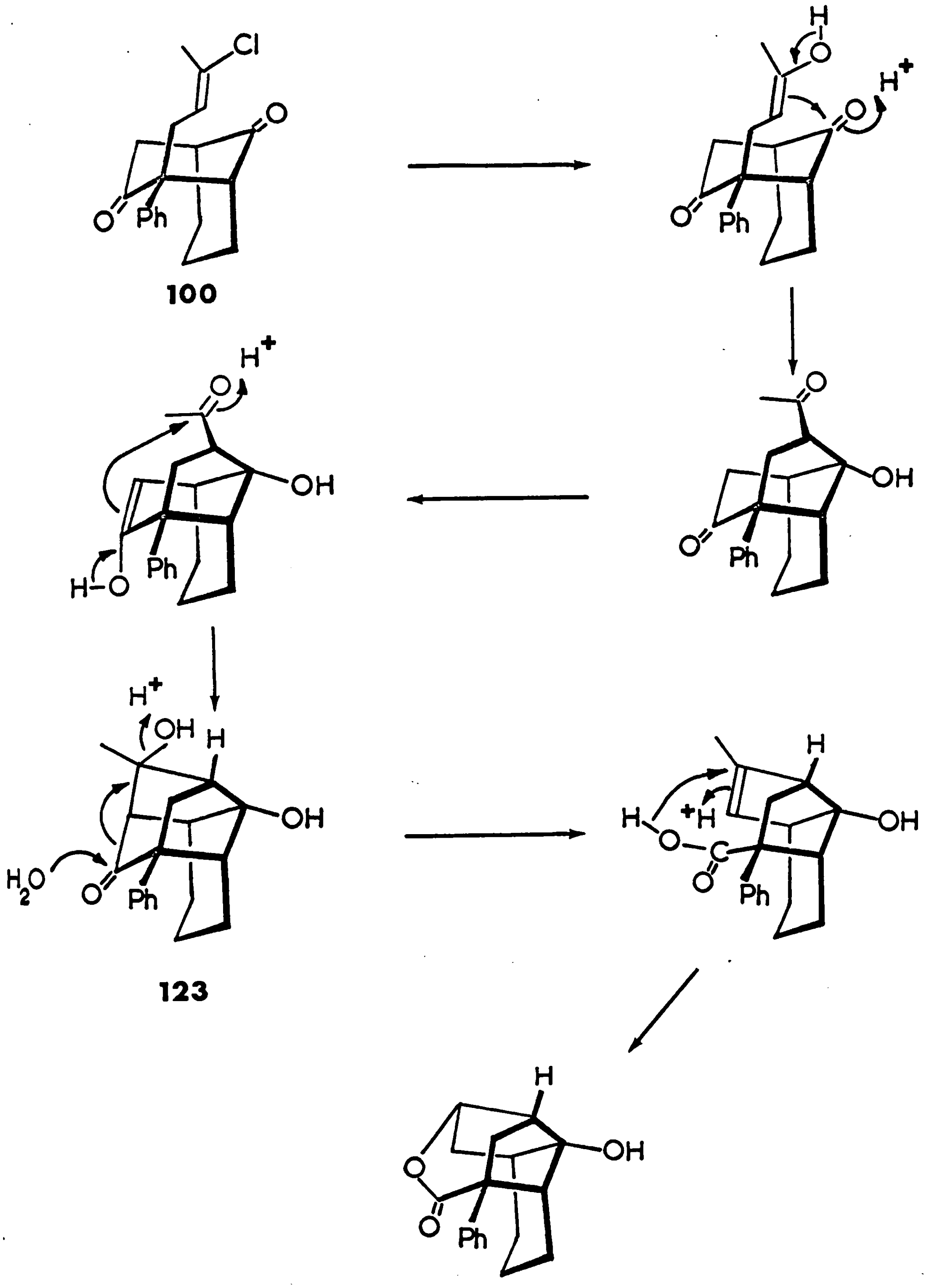


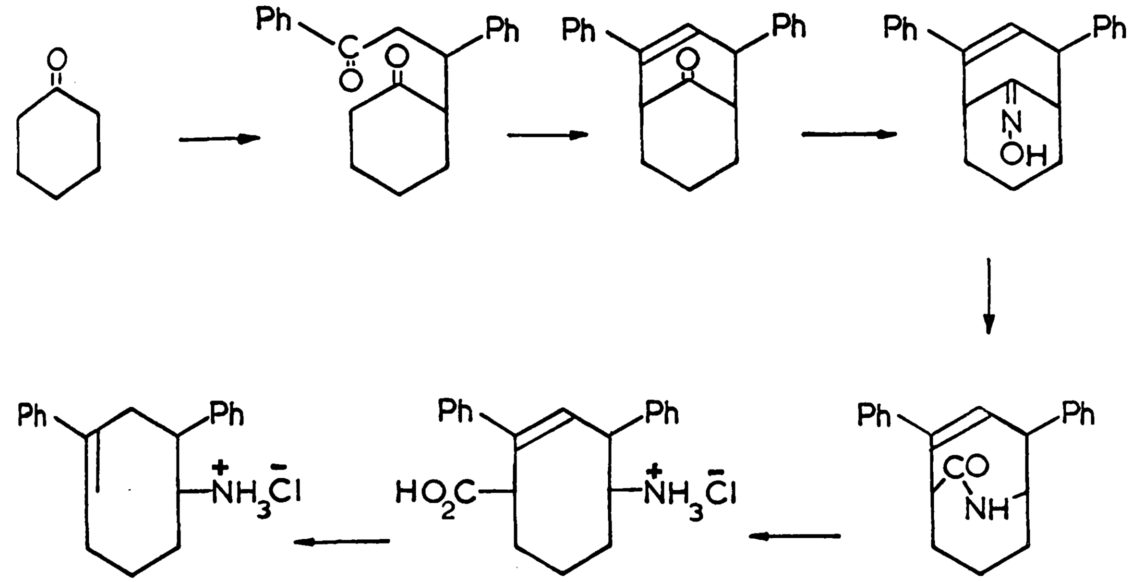
Scheme 9.



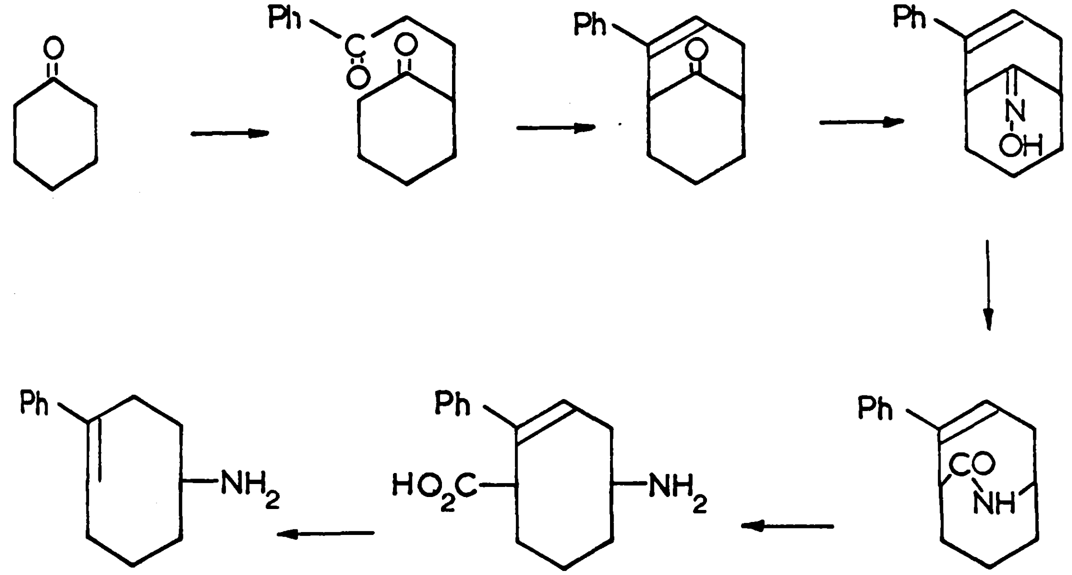
Scheme 10.


Cl
O
O
Ph
100
H
O
H+
O
O
Ph
O
OH
O
Ph
H+
O
OH
H-O
Ph
H+
OH
H
OH
H2O
O
Ph
123
H
OH
H
+H
O
C
O
Ph
H
OH
O
O
Ph

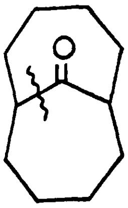
Scheme 11.



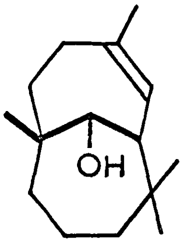
Scheme 12.



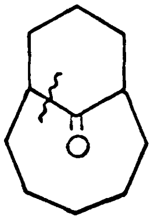
Scheme 13.



125



126



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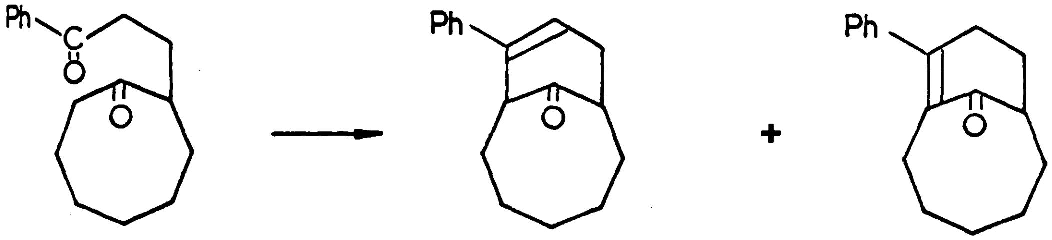


128 **129** **130**

Table 4.

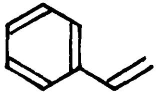
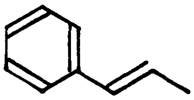
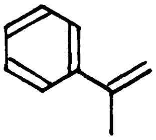
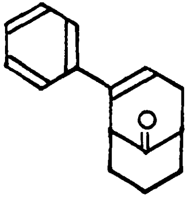
	λ_{max}(mμ)	ϵ
	248	14,000
	251	17,000
	243	11,000
	247	8,130

Table 5.

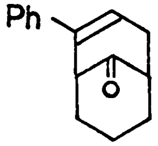
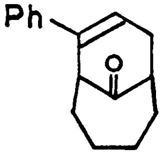
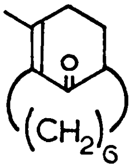
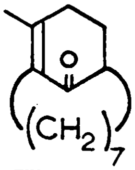
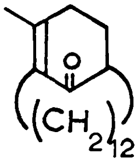
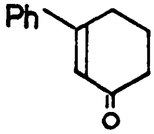
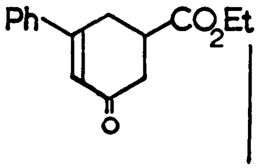
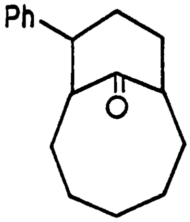
Compound	$\nu_{CO}^{Cl_4}$ cm^{-1}
	1732 1722
	1718 1710

Table 6.

	λ_{max} (mμ)	Log ε
	251	4.0
	251	4.1
	250	–
	283	4.29
	284	3.89



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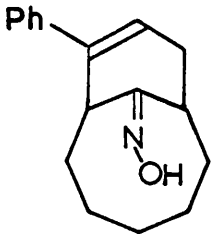

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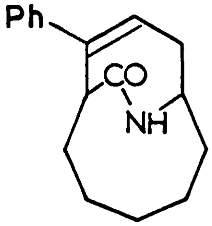

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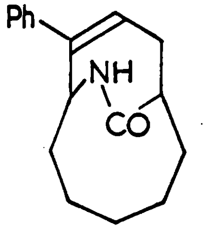

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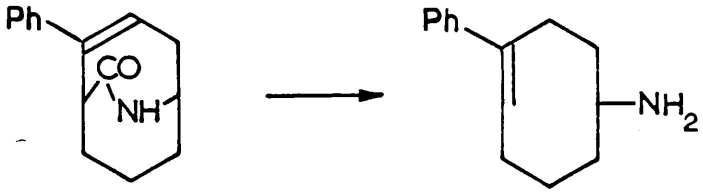
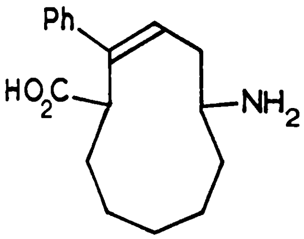


135 **136**



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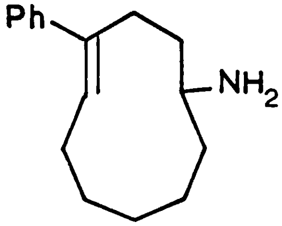

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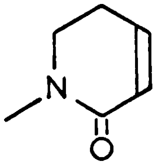

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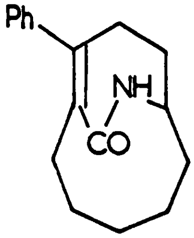

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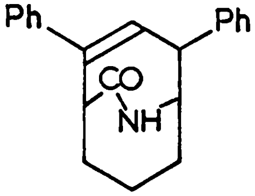

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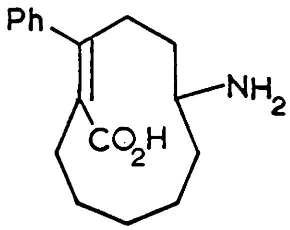

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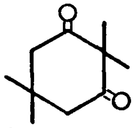
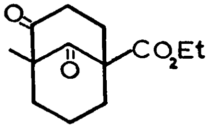
Table 7.

Compound	Hexane		CCl_4		$CHCl_3$		$CH_3.CN$	
	(cm^{-1}.)		(cm^{-1}.)		(cm^{-1}.)		(cm^{-1}.)	
	1736 1705 Δ 31	368 817	1734 1700 Δ 34	394 980	1730 1694 Δ 36	364 930	1730 1695 Δ 35	357 945
(25).	* 1747 1730 (sh) 1698 Δ 32	480 710	*1742 1731 (sh) 1698 Δ 33	540 700	*1735 1727 (sh) 1694 Δ 33	510 700	*1738 1727 (sh) 1693 Δ 34	540 750
(19).	1733 • 1702 Δ 31	348 895	1730 •1698 Δ 32	310 1045	1727 •1694 Δ 33	347 1090	1728 •1694 Δ 34	545 1700
(22).			1740 1707 Δ 32	617 930				
	1748 * 1739 1717 Δ 31	553 732 1060	1743 *1734 1711 Δ 32	497 753 1008	1739 *1729 1707 Δ 32	475 725 895	1741 *1732 1709 Δ 32	436 704 734

• Accompanied by shoulder, assigned to phenyl conjugated carbonyl.

* Ester band.

EXPERIMENTAL.

All melting points were determined on a Kofler block. Routine infra-red spectra of liquid films and nujol mulls were recorded on a Unicam SP. 200 and SP. 200 G spectrophotometers and quantitative infra-red absorption spectra on a Unicam SP. 100 double beam spectrometer, equipped with an SP.130 sodium chloride prism grating double monochromator operated under vacuum conditions.

Ultra-violet absorption spectra, measured on a Unicam SP.800 spectrophotometer, refer to solutions in ethanol unless otherwise stated.

Nuclear magnetic resonance spectra were obtained on the Varian HA 100 and Perkin-Elmer R 10 spectrometers, using approximately 0.3 molar solutions of deuterochloroform, unless otherwise indicated, with tetramethylsilane as internal standard.

Gas-liquid chromatography was carried out on a Pye Argon and Perkin-Elmer F11 Gas Chromatographs. Chromatoplates, both for analytical and preparative use, were made by the method of Stahl using Kieselgel G (Merck).

High resolution mass spectra were recorded on the A.E.I. MS 9 mass spectrometer.

2,2-Bis-(2'-Benzoylethyl)-dimedone, (11), and 2-(2'-benzoylethyl)-dimedone, (10).

β-Dimethylaminopropiophenone (21.5 g.) and dimedone (55.5 g.) were mixed with continuous stirring and slowly heated to 140°. The temperature was maintained at 140° for 45 min., and, after cooling, the resulting gum was taken up in ether and extracted with aqueous sodium carbonate. The residual ether solution was then evaporated, yielding 2,2-bis-(2'-benzoylethyl)-dimedone (3 g.) which crystallised from benzene in colourless needles, m.p. 160°, ($\nu_{CO}^{CCl_4}$ 1728, 1694 $cm.^{-1}$.). Found, C, 76.79; H, 7.27; $C_{26}H_{28}O_4$ requires C, 77.2; H, 6.9 %.

The alkaline extract was acidified and extracted with ether. This ethereal solution was then washed with water, dried over magnesium sulphate and evaporated, affording a crude solid which was shown by thin plate chromatography to be contaminated with dimedone. The crude product (21.4 g.) was chromatographed in benzene on alumina and eluted with benzene. 2-(2'-Benzoylethyl)-dimedone was recrystallised from ether in colourless needles, m.p. 148°. The infra-red spectrum (CCl_4) showed a broad OH band 3350-3050 $cm.^{-1}$, carbonyl bands at 1670 and 1622 $cm.^{-1}$ and a band at 1647 $cm.^{-1}$ ascribed to the C=C of the enol. Found C, 75.23; H, 7.40; $C_{17}H_{20}O_3$ requires C, 75.0; H, 7.35%.

Attempted cyclisation of 2-(2'-Benzoylethyl)-dimedone (10).

2-(2'-Benzoylethyl)-dimedone (5 g.) in glacial acetic acid (40 ml.) was treated with concentrated hydrochloric acid (10 ml.) and boiled under reflux for 30 hrs. The solvent was then removed under vacuum and _ca_. 100 ml. of water was added. A benzene extract of this mixture was extracted with alkali and the residual benzene solution was washed with water, dried over magnesium sulphate and evaporated. The gummy product (_ca_. 400 mgm.) was distilled under high vacuum and thereafter showed a broad poorly resolved band at 1740-1600 cm.$^{-1}$; there was no OH absorption. Although this data is consistent with structure (12), it is not definitive. The low yield discouraged further pursuit of this product.

The alkaline extract was acidified, and on working up, it yielded starting material (_ca_. 3.5 g.) together with dimedone (5) formed by breakdown of the triketone (10).

Attempted Cyclisation of 2,2-bis-(2'-benzoylethyl)-dimedone (11).

0.9 g. of 2,2-bis-(2'-benzoylethyl)-dimedone were refluxed with 8 ml glacial acetic acid and 2 ml of concentrated hydrochloric acid for 24 hours and then left standing for a further 48 hours. The acetic acid was removed under reduced pressure and 30 ml of water added.

The benzene extract of this solution was water washed and extracted with alkali, washed with water and dried ($MgSO_4$). Removal of solvent left 60 mgs. of starting material. The alkaline washings on acidification and extraction were seen to contain 4 compounds, 2 of which were only present in trace amounts. Separation of the two main fractions was obtained on a silica gel column made up in benzene.

The major component was a colourless crystalline solid (needles), the structures of which, although not fully established was almost certainly the acid formed by cleavage of the β-diketone system.

2-Methyl-dimedone. (Modification of the method employed by Halsall: J. Chem.Soc., 2431 (1956).)

Methyl iodide (15 ml) was added slowly to a cooled solution of dimedone (28g.) in alcoholic sodium ethoxide, (4.6g. of sodium in 60 ml absolute ethanol), and the mixture warmed on a steam bath for 3 hours. The alcohol was removed under reduced pressure and the residue dissolved in benzene. A sodium carbonate extract of this on acidification, yielded 2-methyl-dimedone which recrystallised from dilute alcohol as prismatic needles, m.p. 158°-9°, (literature value, 158-9°).

2-Methyl-2-(2'-Benzoylethyl)-dimedone (19).

β-Dimethyl-aminopropiophenone (12 g.) was added to 2-methyldimedone (11.3 g.) and slowly heated to 140°. The temperature was maintained at 140° for 45 minutes and, after cooling, the reaction mixture was dissolved in ether, washed with aqueous sodium bicarbonate, then with water, dried over magnesium sulphate and evaporated. The residue crystallised from light petroleum (60-80°) in colourless needles, m.p. 99°, ($\nu_{CO}^{CCl_4}$ 1731, 1698 cm.$^{-1}$). Yield *ca*. 5 g. Found: C,75.21; H, 7.22; $C_{18}H_{22}O_3$ requires C, 75.53; H, 7.69%.

Attempted Cyclisation of 2-methyl-2-(2'-benzoyl-ethyl)-dimedone (19).

5 g. of 2-methyl-2-(2'-benzoylethyl)-dimedone (19) were refluxed with 40 ml glacial acetic acid and 10 ml concentrated hydrochloric acid for 14½ hours and left standing for a further 4 hours. The acetic acid was removed as completely as possible under reduced pressure and the mixture then treated with 100 ml of water and extracted with benzene. The benzene solution in turn was extracted with alkali, washed with water and dried. This yielded 0.33 g. of 2-phenyl-5,8,8-trimethylbicyclo-(3,3,1)-non-2-en-6,9-dione (22), (7%), as colourless crystals which were recrystallised from petroleum ether (40-60°) m.p. 123-4°,

I.R.(CCl_4)1741, 1708 cm.$^{-1}$. Found: C = 80.65; H = 7.08; $C_{18}H_{20}O_2$ requires C = 80.65; H = 7.51 %

The alkaline washings on acidification and extraction yielded 2.5 g i.e. 47% of the acid (8) as a white crystalline solid mp 51-2°. Found: C = 70.91; H = 7.59; $C_{18}H_{24}O_4$ requires C * 71.06; H = 7.89%. I.R.(CCl_4) 1753, 1709 cm.$^{-1}$.

A considerable quantity of starting material was also returned and increased yields of the two products can be obtained by increased reaction time.

2,2-Bis-(2'-Carbomethoxyethyl)-dimedone (25) and 2-(2'-Carboxy-ethyl)-dimedone (30b).

Sodium metal (1.0g; 0.0435 m) was dissolved in dry ethanol (60 ml) before addition of dimedone (28g; 0.070 m) and methyl acrylate (17.2g; 0.215 m). The mixture was refluxed for 4 hours and the ethanol removed under reduced pressure. The residue was poured into a dilute solution of sodium hydroxide and the solid di-addition product, as the diester (25), filtered off. This was recrystallised from petroleum ether (60-80°) or ethanol as colourless crystalline plates, m.p. 80-81°, (30g, 67% yield).

The ultra-violet showed λmax. 221 mμ and the n.m.r., 6.39 τ (6H, singlet), 7.41 τ (4H, singlet), 7.94 τ (8H, triplet) and 8.9 τ (6H, singlet). A solution study in the infra-red showed the following ν_{CO} : hexane, 1747,1730 (sh) and 1698 cm.$^{-1}$; carbontetrachloride, 1742, 1731 (sh) and 1697 cm.$^{-1}$; chloroform 1742 and 1694 cm.$^{-1}$ and acetonitrile 1738, 1727 (sh) and 1693 cm.$^{-1}$.

The basic solution was washed with ether and the dissolved ether removed from the solution by bubbling nitrogen through it. The pH was adjusted to 4 with 4 normal hydrochloric acid and the yellowish brown oil formed extracted out with ether. After removal of solvent, unreacted dimedone was washed out with benzene. The residue was washed with cold ether and then recrystallised from hot water to give the required acid (30b).

The structure was established by methylation with diazomethane and comparison by g.l.c. with a sample of 2-(2'-carbomethoxyethyl)-dimedone obtained from a later experiment.

Three separate columns were used for this comparison:-

Column.	Temperature. (°C)	Flow Rate. (ml/min)	Retention. Times(mins).
1% PEG A	160	50	4.12, 6.72
1% NGS	150	50	8.28, 14.96
1% APL	150	50	5.05, 9.75

The second peak in each injection was considered to be a by-product of the methylation, the methyl ether of the enolic form of 2-(2'-carbomethoxyethyl)-dimedone (i.e. of 30a).

Hydrolysis of 2,2-Bis-(2'-Carbomethoxyethyl)-dimedone (25).

(a) Potassium Hydroxide/Methanol.

932 mgs., (0.0036 moles) of the ester (25) and 200 mgs., (0.0036 moles), potassium hydroxide in 50 ml. of methanol were stirred overnight at room temperature. Most of the methanol was removed under reduced pressure and the residue flooded with water. This was washed with ether before separation into neutral and acidic fractions with sodium bicarbonate. The neutral fraction consisted of a negligible quantity of a yellow oil whereas the acidic material solidified to a white crystalline solid which on recrystallisation from a mixture of petroleum ether (60-80) and ethyl acetate gave approximately 400 mgs., (ca.60%) of a white crystalline solid m.p. 137-8°. Found: C, 63.24; H, 7.95; $C_{12}H_{18}O_4$ requires C, 63.70; H, 8.02%. Mass spectrum: **P** = 226 m/e - cracking pattern indicates presence of a methyl ester. $\nu_{CO}^{CCl_4}$ 1710, 1751 and 1623 cm.$^{-1}$, as expected of (30a). U.V. 264 mμ (methanol). N.M.R. 0.7 τ (1H bump), 6.26 τ (3H singlet), 7.44 τ, 7.72 τ (8H multiplets), 8.96 τ (6H singlet).

(b) Lithium Iodide/Pyridine.

The lithium iodide for this reaction was rendered free of water by heating it at 180° on an oil bath for 3 hours under water pump pressure.

19 g. of anhydrous lithium iodide and 2 g. of the diester (25) in 200 ml. of anhydrous pyridine were refluxed for 1.5 hours and then left standing for 2.5 days at room temperature. The pyridine was distilled off and the remaining residue flooded with water. An ether extract of this was separated into acidic and neutral components. The former consisted of approximately 140 mgs. of a yellow oil which was neglected and the latter furnished unchanged starting material. The recovery, however, was very poor and indicated the formation of a water soluble material at some stage.

(c) Dilute Hydrochloric Acid/Methanol.

The diester (25) (25 g.,) was treated with 100 ml. of 6N hydrochloric acid in 50 ml. methanol under reflux for 22 hours. The methanol was removed and the residue, after flooding with water, was divided into acid and neutral fractions with sodium bicarbonate. The acidic material (17.2 g.,) was shown by t.l.c. to be two compounds **A** and **B** and substantiated, after esterification with diazomethane, by g.l.c. The acid **A** on esterification gave starting material (25) - by g.l.c. analysis. **A** was a crystalline solid, recrystallised from a petroleum ether (60-80°) - diethyl ether system - m.p. 94-5°. Found: C, 60.64; H, 6.74. $C_{15}H_{22}O_6$ requires C, 60.39; H, 7.43%. $\nu_{CO}^{CCl_4}$ 1753 and 1713 (CO_2H); 1742 (ε 770) (ester); 1730 and 1697 (C = O) cm.$^{-1}$. N.M.R. ($CDCl_3$) 2 τ(1H bump), 6.31 τ (3H singlet), 7.34 τ (4H singlet), 7.82 τ (8H narrow multiplet), 8.4 τ (1H narrow multiplet), 9.0 τ (6H doublet). From the above information the infra-red spectrum indicates the presence of the substituted β -diketone system, $-CO-C.R_2-CO-$,& the existence of an acid and an ester. The split methyl signal in the nuclear magnetic resonance spectrum points to asymmetry resulting in non equivalent methyl signals - also the presence of a single ester function.

The only structure compatible with all these data is 2,2-(2'-carbomethoxyethyl-2'-carboxyethyl)-dimedone (32).

Compound **B**, after purification by thick layer chromatography, distilled at 70-73°/0.1 min. Found: C, 59.40; H, 7.93. $C_{17}H_{28}O_7$ requires C, 59.29; H, 8.19%. $\nu_{CO}^{CCl_4}$ 1741 (ε 1470) and 1715 (ε 367) cm.$^{-1}$. It appears to be the cleavage product (33a). Proportions of **A** and **B** formed in the reaction were 27% **A** and 73% **B**. The neutral fraction consisted of 41% starting material and 59% of the esterified analogue of B (33b). These percentages were obtained by g.l.c. on a 1% QF 1 Column (175° and 45 ml/min.) : retention times of A and B respectively, (after esterification with diazomethane), 16.24 and 10.88 minutes.

Boron Trifluoride Etherate/Acetic Acid treatment of (25).

The diester (25), (2 g.,) was refluxed with 10 ml. of BF_3 in 20 ml. acetic acid for 2.5 hours. Most of the acetic acid was removed by distillation under reduced pressure before flooding with water. The aqueous solution was extracted with sodium bicarbonate solution. This extract by acidification and ether extraction yielded 1.231 g. of a light yellow oil which furnished a white crystalline solid m.p. 125°C. The crude reaction oil was approximately 90% composed of this compound (65% yield). Found: C, 63.51; H, 6.74; $C_{14}H_{18}O_5$ requires C, 63.15; H, 6.81%. $\nu_{CO}^{CCl_4}$ 1799, 1759 and 1712 (CO_2H), 1673 and 1633 $cm.^{-1}$. N.M.R., 0.15 τ (1H), 7.49 τ (6H), 8.0 τ (5H) and 8.71 τ (6H, singlet). Mass Spectrum: P = 266. U.V. $\lambda_{max.}$ 252 $m\mu$, $\varepsilon = 6850$. The only structures which agree with all the physical data and can be reasonably accounted for by a chemical mechanism are (38) and (40).

Mass Spectroscopy could agree with the second structure on the basis of a 72 mass units loss at the first breakdown. To test this, the acidic lactone was esterified with diazomethane to give a viscous liquid b.p. 140°/0.01 m.m. Found: C, 63.77; H, 7.34. $C_{15}H_{20}O_5$ requires C, 64.27; H, 7.19%. $\lambda_{max.}$ 252 mμ (ε = 7,000); $\nu_{CO}^{CCl_4}$ 1800, 1742, 1672 and 1633 $cm.^{-1}$. N.M.R. indicates a methyl ester. Mass spectrum: P = 280. The spectrum has a cracking pattern with a breakdown involving a loss of 86 mass units, which discounts the second structure (40) for the acidic lactone and favours the first (38).

Polyphosphoric Acid treatment of (25).

One g. of the diester was heated on a steam bath for one hour with 20 g. of polyphosphoric acid. The mixture was then poured on to 50 g. of ice and extracted with ether, washed and dried over $MgSO_4$. Solvent removal furnished a pale yellow oil. A bicarbonate extract of this yielded the acidic lactone, (38), already isolated. The neutral fraction consisted of its methyl ester and starting material. The three components occurred in 30, 50 and 20% yields.

Preparation of Diethylsuccinyl succinate (6).

This method is a modification of the literature proparation in Organic Reactions 1, 283.

54 g. of sodium wire were covered with a minimum amount of toluene to which was added 406 g. of

diethyl succinate and 30 ml. of dry ethanol.

This was refluxed for 24 hours and then excess sodium destroyed with ethanol, and acidified when cold with ice cold dilute sulphuric acid. The mixture was left overnight, filtered and the crystalline diethylsuccinyl succinate washed with water. The toluene layer was separated off from the filtrate and removed under reduced pressure to leave a further crop of the crystalline product, which was re-crystallised with the first from a 95% ethanol solution treated with animal charcoal. This gave 200 g. (68%) of diethylsuccinyl succinate as pale yellow crystalline needles: m.p. 126-7^{o}, (Lit. value 126-7^{o}). I.R.(CCl_4), 1668, 1624 cm.$^{-1}$ (no ν_{O-H}); N.M.R. -2.25 τ (s); 5.72 τ(q) 6.82 τ(s); 8.67 τ(t) U.V., $\lambda_{max.}$ 243 mμ .

Treatment of Diethylsuccinyl succinate with Acrolein.

Several variations of this method were tried, i.e. changes in solvent, reaction time, reaction atmosphere etc., but the products obtained from each, although the same, were in different quantities. A fairly general procedure is as follows:

4.15 g. of acrolein were added carefully to an ice cold, stirred solution of 9.5 g. of diethylsuccinyl succinate, and 1 ml. of triethylamine in 400 ml. of tetrahydro furan. The mixture was stirred in an atmosphere of nitrogen for twenty hours.

The solution was then neutralised with glacial acetic acid and the tetrahydro-furan removed under reduced pressure. The residue was taken up in ether and washed successively with sodium chloride solution, water, saturated sodium bicarbonate and water. This was dried over magnesium sulphate and the ether removed to leave a pale yellow oil.

This yellow oil consisted of a mixture of several components, three of which could be separated out by crystallisation.

1) First to crystallise out was a yellow solid which was recrystallised from ethanol as yellow needles, m.p. 134-135.5°. This was shown to be the diethyl ester of 2,5-dihydroxyterphthalic acid (literature value of m.p. 135.5°). Found: C, 57.14; H, 5.37; $C_{12}H_{14}O_6$ requires C, 56.69; H, 6.07% and its molecular weight shown to be 254 (mass spectroscopy). I.R., $\nu_{max.}^{nujol}$ 3480 cm.$^{-1}$ (bonded hydroxyl), 1690 cm.$^{-1}$ (conjugated carbonyl of ester)and in the n.m.r. the following peaks were observed: 0.12 τ (2H, singlet, hydroxyls); 2.66 τ (2H, singlet, aromatics); 5.59 τ (4H, quartet, methylenes of esters) and 8.56 τ (6H, triplet, methyls of esters).

The remaining oil was taken up in a small quantity of ether and cooled. A white crystalline material separated out which, depending on conditions, was either A or B.

2) A had a m.p. of 184°. Found: C, 64.86; H, 5.96; $C_{18}H_{20}O_6$ requires C, 65.05; H, 6.07%. I.R. $\nu_{max.}^{CCl_4}$ 1751, 1720 (sh), 1705 and 1623 cm.$^{-1}$; U.V., $\lambda_{max.}$ 264 mμ (ε = 8170), 235 mμ (ε = 4960) and 205 mμ (ε = 5040). Mass Spectrum had parent ion at m/e 332 and base peak at m/e 166. N.M.R. showed 3.4 τ (fine triplet, 2H), 5.91 τ (quartet, 4H) 8.87 τ (triplet, 6H) and 7.0-8.0 τ (unresolved multiplet, 8H). It was concluded that this was the bis-enone (51).

3) B: colourless crystalline solid, m.p. 140°. Found: C, 58.37; H, 6.14; $C_{18}H_{24}O_8$ requires C, 58.69; H, 6.57%. Mass Spectroscopy showed parent ion of m/e 368 which exhibited a facile loss of 2 moles of water to give m/e 332. U.V. $\lambda_{max.}$ 210 mμ ; I.R. $\nu_{max}^{CCl_4}$ 1741, 1724, 3632 and 3585 cm.$^{-1}$; N.M.R. $CDCl_3$:- 2.83 τ (5H singlet), 4.48 τ (1H, finely split triplet), 4.99 τ (1H, poorly defined multiplet), 5.86 τ (4H, quartet), 6.88 τ (1H), 8.45 τ (1H, singlet), 8.75 τ (6H, triplet); D_2O:- 5.07 τ (1H, doublet, J = 9 cps.); dimethylsulphoxide:- 3.38 τ (1H, doublet, J = 7 cps.) and 5.07 τ (1H, two overlapping doublets, J sum = 16 cps.). This compound was assigned the tricyclic

structure (68).

4) The remaining viscous yellow oil contained at least five components, the main one of which was the major product of the reaction. This was separated from the remainder on a grade 4 alumina column made up in light petroleum (60-80^{o}) and gradient elution, (100% petroleum ether to 100% ethyl acetate), carried out. This was considered to be an equilibrium mixture of (56) and (57). Its ready decomposition, when exposed to air, made it difficult to obtain pure and its distillation impossible. Found: C, 58.42; H, 7.02; $C_{18}H_{24}O_8$ requires C, 58.69; H, 6.57%; molecular weight of 368 (by mass spectroscopy); I.R. $\nu_{max.}$ 1745, 1723, 1706, 3630, 3537, 3493, 3444 and 2737 cm.$^{-1}$; U.V., no absorption above 220 mμ; N.M.R. showed aldehydic proton, 0.22 τ.

Oxidation of (68).

0.488 g. of the alcohol (68) were cooled in an ice bath in 20 ml. of acetone. This solution was treated with Jones' reagent until the solution was a permanent orange colour. Extraction with ether, water washing and $MgSO_4$ drying of the extracts yielded an ether solution affording, on evaporation, 0.3694 g. of a white crystalline product. This was recrystallised from ethanol m.p. 158-159^{o} (78.5% yield), $FeCl_3$ test - negative, no U.V., I.R.(CCl_4), 1771, 1745, 1740, 1724 and 1614 cm.$^{-1}$ (no OH band). $C_{18}H_{22}O_8$ requires C = 59.01; H = 6.05 found C = 59.06; H = 6.13%, Mass spectrum showed parent ion m/e 366. This compound was considered to be the enol lactone (69).

Dehydration of (68).

a) The alcohol (68), (50 mgs.,), was refluxed overnight in a water separator with para-toluene sulphonic acid, (5 mgs.,), and benzene (20 ml.,). Solid potassium carbonate was added and the mixture left standing at room temperature for 4 hours before filtration. The filtrate was washed with brine until neutral, dried over anhydrous magnesium sulphate and the benzene solvent removed to yield an oily crystalline mixture. This was recrystallised from an ethyl acetate - petroleum ether (60-80°) system, or ethanol, as a colourless crystalline solid, (41 mgs.,- 85% yield), m.p. 131-2°, the structure of which was never completely determined. Found: C, 62.09; H, 6.02; $C_{18}H_{22}O_7$ requires C, 61.71; H, 6.33%. I.R. ($CHCl_3$) 1745, 1737, 1724, 1683 and 3435 cm.$^{-1}$. U.V. showed only end absorption at 216 mμ. Mass spectrum showed parent ion of m/e 350. N.M.R., 341 τ (very finely split singlet, 1H) and 4.52 τ (doublet, J = 4 cps., 1H); in deuterium oxide very little change was observed in the spectrum, except for a slight alteration at <u>ca</u>. 7.7 τ and in dimethylsulphoxide solution no change could be seen.

b) The alcohol (68), (30 mgs.,) was left standing in a mixture of dilute sulphuric acid (10 ml.,) and ethanol (30 ml.,) for 3½ days. This was then heated on a steam bath for 1 hour and the ethanol removed under reduced pressure. The residue was flooded with water and ether extracted. This extract was brine washed, dried (magnesium sulphate) and solvent removed to give an oily crystalline mixture (25 mgs.,). Recrystallisation from ethanol gave, in high yield, the product already obtained in the dehydration of the alcohol (68) by para-toluene sulphonic acid treatment, (i.e. a)), (mixed melting point, t.l.c., g.l.c., and infra-red comparison).

<u>Hydrogenation of (68).</u>

The alcohol (68), (500 mgs.,), was stirred with 10% palladilised charcoal (500 mgs.,) in ethanol (100 ml.,) in an atmosphere of hydrogen at room temperature. Removal of the catalyst, by filtration, and solvent, under reduced pressure, yielded a quantitative amount of the reduced product (72) as a colourless oil. The parent ion in the mass spectrum was m/e 370. I.R., ν (CCl_4) 1745, 1723, 1700, 3635, 3545 and 3460 $cm.^{-1}$. U.V. - only end absorption observed and in the n.m.r. no absorption in the

3.0–5.0 τ region.

Acetylation of (68).

1) The alcohol (68), (74 mgs.,), was refluxed overnight with para-toluene sulphonic acid (5 mgs.,) and isopropenyl acetate (8 ml.,). The reaction mixture was treated with solid potassium carbonate and the isopropenyl acetate removed under reduced pressure. The residue was taken up in ether, washed with brine, dried with magnesium sulphate and solvent removed to yield a colourless oil. This crystallised on standing and by t.l.c. analysis was shown to consist of two components. Separation of these was accomplished by thick layer chromatography. One had a melting point of 131-2° and was shown to be the dehydration product already isolated, and the other to be the product of acetylation, the structure of which, further than its being a diacetate, was not elucidated. M.p. 123-5°; found: C, 58.64; H, 6.70; $C_{22}H_{28}O_{10}$ requires C, 58.40; H, 6.24%; I.R. $\nu_{max.}$ (CCl_4) 1770 cm.$^{-1}$ (970), 1744 cm.$^{-1}$ (1070, and 1725 cm.$^{-1}$; U.V.,-only end absorption. N.M.R. showed 4.05 τ (1H, doublet, J = 9 cps.), 4.35 τ (1H, singlet), 5.75 and 5.83 τ (4H, superimposed quartets), 7.93 τ (6H, singlet) and 8.68 and 8.71 τ (6H superimposed triplets). The mass spectrum, (P = 452 m/e), showed two different losses, one of m/e 60 and the other of m/e 42. These

could be assigned as acetic acid and ketene respectively which indicated that one of the acetates was attached to a saturated centre and that the other was vinylic.

2) The alcohol (68), (143 mgs.,), was refluxed for 90 minutes with a mixture of acetic anhydride (1.5 ml.,) and anhydrous pyridine (3 ml.,). After cooling, the reaction mixture was poured on to ice and the white crystalline solid precipitated was filtered off. This was shown by mixed melting point, t.l.c. and infra-red to be the same diacetate as already isolated and reported above, (i.e.1)).

Reduction of (51) to (54).

The bis-enone (51), (113 mgs.,), was stirred with a mixture of sodium borohydride (50 mgs.,), methanol (40 ml.,) and water (4 ml.,) for several hours at room temperature before leaving overnight. Although (53) was not initially very soluble in the methanol, the solution became homogeneous as the reaction proceeded. The mixture was then flooded with water (100 ml.,) and ether extracted. This extract was washed with water, dried over magnesium sulphate and solvent removed to yield 73 mgs. of a white crystalline solid (60-70% yield), m.p. 150^{o}, (ethyl acetate) I.R., $\nu_{max.}$ (CCl_4) 3620, 3548, 3480, 1737 cm.$^{-1}$; U.V. Spectrum showed complete disappearance of the 264 mμ absorption of (51); N.M.R., 4.05 τ (2H, finely split), 5.84 τ (4H, quartet), 7.57 τ (8H multiplet) and 8.79 τ (6H, triplet). The mass spectrum had a parent ion of m/e 336.

2,2'-Dimethylaminopropiophenone Hydrochloride.

This Mannich base was prepared as its hydrochloride by the method given in Org.Rns., Coll.Vol. III, 305.

2-(2'-Benzoylethyl)-Cyclohexanone (17).

This diketone was prepared by a modification of the method used by Gill et al. J.Amer.Chem.Soc., 74, 4923 (1952).

2,2'-Dimethylaminopropiophenone was liberated from its hydrochloride by treatment with aqueous sodium hydroxide and ether extraction of the precipitated free base. Freshly prepared Mannich base and re-distilled cyclohexanone, in a molar ratio of 1:3, were heated together at 160° for 20 minutes; evolution of dimethylamine was observed. The cooled reaction mixture was exactly neutralised with glacial acetic acid and extracted with ether. The latter was subsequently washed with brine, dried and concentrated. Excess cyclohexanone was removed on a water pump and the residue distilled under reduced pressure to give a pale yellow oil which solidified on cooling. The diketone, (17), crystallised from light petroleum as white needles, m.p. 48-50°. (17) was obtained in 80% yield.

2-Phenylbicyclo-(3:3:1)-non-2-ene-9-one (18).

The method of Cope and Hermann was used, J.Amer. Chem.Soc., 72, 3405 (1950).

A solution of the diketone (17) in glacial acetic acid (250 ml.,) and concentrated hydrochloric acid (50 ml.,) on heating under reflux for 16 hours afforded the required ketone, (18), as a yellow oil, b.p. 130-133°/0.15 m.m., (22g., 74% yield), which solidified on trituration with light petroleum. The solid was recrystallised from a 2:3 mixture of cyclohexane and pentane, m.p., 52-53°, (62.5% yield). $\lambda_{max.}$ 247 mμ (ε = 8,100); ν_{CO} (hexane) 1732 (444), 1722 (313) cm.$^{-1}$, (carbon tetrachloride) 1729 (291), 1715 (437) cm.$^{-1}$ and (chloroform) 1736 (504), 1724 (160) - splitting of the carbonyl absorption was thus considered to be due to Fermi resonance. The n.m.r. showed 3.8 τ, J = 4 cps.

Hydroboration of 2-Phenylbicyclo-(3;3:1)-non-2-ene-9-one (18).

6.271 g. of lithium aluminium hydride were suspended in 50 ml of sodium dry ether and the suspension cooled to 0°C in an ice bath. A solution of 7 g. of 2-phenylbicyclo-(3:3:1)-non-2-ene-9-one in 30 ml. of dry ether was slowly added to this suspension. Maintaining the ice cooling, 27.72 g. of BF_3 etherate were added and the mixture stirred. After addition of all the boron trifluoride etherate the ice bath was removed and stirring continued for a further 2½ hours at room temperature.

Excess lithium aluminium hydride was destroyed by the careful addition of 50 ml. acetone. The mixture was then treated with 20 ml. of $3\overline{N}$ sodium hydroxide and 20 ml., 30% hydrogen peroxide and stirred overnight.

150 ml. of water was added and the ether layer separated. The remainder was extracted with ether (2x100 ml.,) and the combined ether extracts and solution was washed with ferrous sulphate until no change in colour was observed. The solution was further washed with water and the ether removed under reduced pressure to give 5.247 g. of a light yellow oil. This was placed in a little benzene and left overnight and yielded 2.019 g. of 2-phenylbicyclo-(3:3:1)-nonane -3,9-diol (79). The remaining oil, (3.228 g.,) consisted mainly of this diol together with four other secondary products.

A further 2.42 g. of 2-phenylbicyclo-(3:3:1)-nonane,-3,9-diol (79) were separated out by column chromatography to give an overall yield of 4.439 g., (58%) m.p. 178-9° $C_{15}H_{20}O_2$ requires C = 77.55; H = 8.65. **Found:** C = 77.27; H, 8.52%. I.R. ($CHCl_3$) 3610, 3617 $cm.^{-1}$.

Separation of the remaining compounds in the mother liquors was achieved by column chromatography using a silica gel column. First to be eluted from the column was a mixture of syn- and anti- 2-phenylbicyclo-(3;3;1)-non-2-ene-9-ols, (82) and (83) respectively. Comparative t.l.c. and g.l.c. with authentically synthesised samples proved the identity of these two alcohols. Also I.R. solution spectra, anti-alcohol 3635 cm.$^{-1}$, no C=O; Syn alcohol, 3634, 3596 and 3505 cm.$^{-1}$.

The epimeric diols (84; 85) syn-, and anti-2-phenylbicyclo—(3,3,1)-non-2,9-diol were eluted from the column separately, the syn before the anti alcohol. They were both crystalline solids and had the following physical characteristics:-

Syn-2-phenylbicyclo-(3;3;1)-non-2,9-diol (84). I.R. ($CHCl_3$) 3618 (shoulder), 3600 and 3575 cm.$^{-1}$: U.V. 242, 246, 251, 257, 264 mμ ; m.p. 140-3°; Found: C,= 76.95; H, = 8.27; $C_{15}H_{20}O_2$ requires C = 77.55; H= 8.68%.

Anti-2-phenylbicyclo-(3,3,1)-non-2,9-diol (85). I.R. ($CHCl_3$), 3610 cm.$^{-1}$ (only); U.V. 241, 247, 252, 258, 264 mμ ; m.p. 167-170°; Found: C = 77.67; H = 8.55; $C_{15}H_{20}O_2$ requires C = 77.55; H = 8.68%.

Both these diols on oxidation with standard Jones' reagent gave the same keto-alcohol.

Hydroboration of (18) with sodium borohydride and boron trifluoride etherate in diglyme as solvent was also carried out. However this method gave poorer yields of the diol (80) than the lithium aluminium hydride procedure and was consequently disregarded in favour of the latter.

Oxidation of 2-Phenylbicyclo-(3;3;1)-nonane-3,9-diol, (79) to (77).

(a) 1.468 g. of 2-phenylbicyclo-(3;3;1)-nonane-3,9-diol were dissolved in 20 ml. of acetone and the solution cooled to 0°C in an ice bath. A standard solution of Jones' oxidising reagent was slowly added with stirring until the solution took on a permanent orange colouration. 20ml. of water were then added and the solution extracted thoroughly with ether (3x50 ml.,). The combined ether extracts were washed with water and dried with $MgSO_4$. Solvent removal left 1.2785 g. of 2-phenylbicyclo-(3;3;1)-nonane-3,9-dione (77). This was recrystallised from an ethyl acetate - petroleum ether (60-80°) solvent system m.p. 147-8°; ca. 60% yield; Found: C, 78.89; H, 6.98; $C_{15}H_{16}O_2$ requires C = 78.92; H = 7.06%; I.R. (CCl_4) 1723, 1728 cm.$^{-1}$; Mass Spec., P = 228 m/e; $\lambda_{max.}$ 227, 247, 252, 258 and 264 mμ. In the n.m.r. peaks at 2.72 τ (5H, very finely split), 6.03 τ (1H, doublet, J= 6 cps.), 7.17 τ (4H, multiplet) and 8.1 τ (6H, multiplet).

(b) The alternative procedure for the oxidation of (79) uses oxidising conditions described by Brown, J.Amer.Chem. Soc., 83, 2952 (1961).

Sodium dichromate dihydrate (10 g., 16.6 m.moles) was dissolved in 96% sulphuric acid (7.5 ml., 67 m.moles, diluted to 50 ml.,) and the solution added to a suspension of the diol (79), (10 g.,), in ether (50 ml.,) over 25 mins. The reaction was stirred for 2 hours while maintaining the temperature between 25 and 30°. The aqueous layer was washed with ethyl acetate and these washings added to the ether solution. The combined organic solution was washed with sodium bicarbonate and brine and dried over anhydrous magnesium sulphate. Solvent removal yielded 8.5 g. of a crystalline solid which on recrystallisation from ethyl acetate - petroleum ether (60-80°) gave 7.1 g., (72.5% yield), of the dione (77).

Attempted epoxidation of 2-Phenylbicyclo-(3;3;1)-non-2-ene-9-one, (18).

1 g., of 2-Phenylbicyclo-(3;3;1)-non-2-ene-3-one was heated with 3 ml. of 15% H_2O_2 and 3 ml. of 10% aq. NaOH in 15 ml. ethanol, for 10 minutes on a steam bath. The solution slowly changed from colourless to pale straw yellow. When left overnight a white inorganic solid

separated out.

The solution was refluxed for a further 2 hours on the steam bath, the colour changing to light brown. Most of the ethanol was removed under reduced pressure and the residue poured into 100 ml. of water. This was left overnight. A white crystalline solid was precipitated, 0.25 g.,; m.p. 51-53^{o} which was shown to be starting material by mixed m.p.

The mother liquor was extracted with ether but no evidence of epoxidation was found.

(An attempted epoxidation by means of performic acid gave a similar result).

<u>Reduction of 2-Phenylbicyclo-(3;3;1)-non-2-ene-9-one (18) with (a) $LiAlH_4$ in ether and (b) $NaBH_4$ in aq. methanol.</u>

(a) 0.9 g. of lithium aluminium hydride were suspended in 20 ml. of ether and 1 g. of 2-phenylbicyclo-(3;3;1)-non-2-ene-9-one in 10 ml. of ether added slowly, with stirring, to the suspension. The mixture was stirred overnight under gentle reflux. Excess $LiAlH_4$ was destroyed with moist ethyl acetate and 30 ml. of water added. The solution was extracted with ether (3x30 ml.,) and the extracts washed with water and dried ($MgSO_4$). Solvent removal left a clear oil which on trituration with petroleum ether (40-60^{o}) gave white crystals. Yield of clear oil - 0.97 g., (96%).

A g.l.c. study on this oil indicated it to consist of 78% anti- and 22% syn- alcohol.

I.R. spec. of the white crystals showed them to be purely the anti form.

(b) 0.25 g. of sodium borohydride was added to a solution of 1 g. of 2-phenylbicyclo-(3;3;1)-non-2-ene-9-one in 20 ml. methanol and 6 ml. of water. This was allowed to stand overnight at room temperature. 100 ml. of water were added and the precipitated oil was extracted with ether (3x20 ml.,). After drying, $MgSO_4$, and solvent removal 0.92 g. of a colourless oil were obtained (91%). G.L.C. indicated 73% - anti, 27% - syn.

<u>Anti-alcohol</u> (83): m.p. 79-80°; I.R. (CCl_4) 3635, 1495 and 1060 cm.$^{-1}$, no C=O band. Found: C, 83.77; H, 8.01; $C_{15}H_{18}O$ requires C, 84.07; H, 8.47%. U.V. λmax. = 248 mμ ; G.L.C. Retention time 16.4 ins. 10% PEG,A 15 ins./hr.

<u>Syn-alcohol</u> (82): As yet, never isolated as pure sample. I.R. (CCl_4) - (some anti present). 3634, 3596 and 3505 cm.$^{-1}$. G.L.C. Retention time 12.4 ins. 10% PEG,A 15 ins./hr.

Peracetic Acid treatment of 2-phenyl-9-hydroxybicyclo-(3;3;1)-non-2-ene, (83).

Peracetic acid (J.Amer.Chem.Soc., 68, 907 (1946)): Glacial acetic acid (10 g.,) was added dropwise to concentrated sulphuric acid (0.11 ml.,), the temperature being maintained at 22-23° by a water bath. 90% hydrogen peroxide (9.1 g.,) was added dropwise, with stirring, to the mixture and the resulting solution stirred overnight (ca. 16 hours). The mole ratio of H_2O_2 to AcOH being 1.5 : 1.0.

The unsaturated alcohol (83), (0.187 g.,), was dissolved in glacial acetic acid (12 ml.,) and the peracetic acid mixture (1 ml.,) added dropwise. The solution was kept at 40° for 5 hours and then poured into hot water (95-100°) and well stirred. After cooling to room temperature this was extracted with ether and the extract washed with brine before drying (magnesium sulphate).

The yellow oil, (0.163 g.,), obtained by solvent removal was refluxed at 100° with excess 2 normal sodium hydroxide before pouring into dilute hydrochloric acid and ether extracting. Brine washing and magnesium sulphate drying of this extract and subsequent solvent removal yielded an oil, (0.16 g.,), which contained some three components, (t.l.c. analysis). Oxidation of this mixture with standard Jones reagent at 0^{o} gave a corresponding mixture, one component of which, by both t.l.c. and g.l.c. analysis, was shown to be (77). Separation of this component by column chromatography and its infrared analysis confirmed this.

Both low yield and separation difficulties made this method impractical for the efficient synthesis of (77).

Attempted Formylation of (77).

2-Phenylbicyclo-(3;3;1)-nonane-1,9-dione, (77), (4.0 g.,; 1 equivalent) in benzene (100 ml.,) was added, at ice temperature, to a suspension of dry powdered sodium methoxide (1.2 g., sodium) in benzene (50 ml.,). Ethyl orthoformate (3.9 g.,; 3 equivalents) in benzene (50 ml.,) was added to this and the flask left overnight at room temperature. The solution was poured on ice and the benzene layer washed well with aqueous sodium hydroxide. These washings were added to the aqueous fraction, acidified and ether extracted. Brine washing and magnesium sulphate drying of this extract followed by removal of solvent yielded 1.21 g. of a yellow oil. Although this gave a positive reaction with ferric chloride, it consisted of some six or seven components and an identification of a formylated product as one of these was not conclusive.

Starting material (2.43 g.,) was recovered from the benzene layer. Longer reaction times were found to increase the proportion of base soluble material produced but did not decrease its complexity.

Attempted Carbethoxylation of (77).

(a) Ethyl Oxalate and Sodium Ethoxide.

A solution of ethyl oxylate (0.458 g.,) and 2-phenyl-bicyclo-(3;3;1)-nonane-3,9-dione in ethanol (18 ml.,) was added slowly to an ice cold, stirred, ethanolic solution of sodium ethoxide (0.4 g. sodium in 2 ml. ethanol). This was stirred at 0° for 1 hour and then at room temperature for 6 hours. The reaction mixture was decomposed by pouring it on to concentrated sulphuric acid (1 ml.,) in a flask immersed in an ice bath. Flooding with water and benzene extraction, subsequent washing of this extract with brine, drying ($MgSO_4$) and removal of benzene yielded a quantitative return of starting material (77).

(b) Diethyl Carbonate and Sodium Hydride.

A dispersion of sodium hydride in oil (4.2 g., 50% dispersion, 0.0088 m.) was placed in a flask under nitrogen and diethylcarbonate in tetrahydrofuran (15 ml.,) added dropwise. This mixture was refluxed and the dione, (77), (1.0 g.,) in tetrahydrofuran (10 ml.,) added over a period of 3½ hours and refluxing continued for a further hour. Excess sodium hydride was destroyed by careful addition of water before removal of the solvent. The residue was flooded with water and extracted with ether. This extract after brine washing yielded crystalline starting material (77), (ca. 0.8 g.,).

The aqueous fraction on acidification with 6 normal hydrochloric acid and ether extraction yielded an insignificant quantity of a light yellow oil.

2,4-Dibromo-2-phenylbicyclo-(3;3;1)-nonane-3,9-dione, (94).

The dione (100 mg.), (77), in chloroform was treated with excess of bromine in chloroform until the colour persisted, then heated at 100° for a few minutes and finally evaporated. The colourless solid product, m.p. 205-6° gave a positive Beilstein test. Found: C, 46.52; H, 3.64. $C_{15}H_{14}O_2Br_2$ requires C, 46.33; H, 3.63%. $\nu_{CO}^{CCl_4}$ 1741 and 1735 cm.$^{-1}$. N.M.R., 3.86 τ (1H, doublet), 6.7 and 7.3 τ (2H, multiplets); 8.45 τ (6H, multiplet).

2-Phenyl-2-(3'-chlorobut-2'-enyl)-bicyclo-(3;3;1)-nonane-3,9-dione, (100).

A suspension of KOBu^t, prepared from 0.094 g., (0.0024 moles) of potassium, in 30 ml. of dry benzene, was treated with a solution of 0.5 g., (0.0024 moles) of dione (77) in 20 ml. dry benzene and cooled to 0°. To this was added 0.398 g., (0.024 moles) of 1,3-dichlorobut-2-ene and the mixture was refluxed for 4 hours, poured on to ice, acidified with dilute HCl and extracted with ether. The extract was washed with saturated sodium bicarbonate then brine, dried and evaporated. There resulted 0.645 g. of an oily crystalline mixture which by t.l.c. indicated the presence of two compounds, *A* and *B* together with some starting material; g.l.c. corroborated this (0.5% APL/175°) giving the following proportions of compounds present, 57% of *A*, 33% of *B* and 10% of starting material. A mixture of *A* and *B* crystallised out from the reaction mixture. *A* and *B* could be separated from each other and from starting material by column chromatography on Grade II alumina and eluting with a 5% mixture of ethyl acetate in petroleum ether (60-80°). (The material being introduced on to the column in chloroform solution).

A separated out as white crystalline needles, m.p. 175-6^{o} (recrystallised from petroleum ether (60-80^{o})) and gave a positive Beilsteintest. Found: C, 71.45; H, 6.49. $C_{19}H_{21}O_2Cl$ requires C, 71.86; H, 6.68%. I.R. (CCl_4) 1717, 1710 and 1663 cm.$^{-1}$. N.M.R., 4.97 τ (1H, triplet, J = 7 cps.), 8.09τ(3H, singlet). The mass spectrum - (P = 316 m/e) - gave conformation of the presence of chlorine from the large peak due to P+2 ion and from loss of 35 mass units from parent.

Compound B recrystallised in needle crystals - m.p. 164-5^{o}, gave a positive Beilstein test and gave physical data of a very similar nature to Compound A. It was considered to be isomeric. Found: C, 71.64; H, 6.26. $C_{19}H_{21}O_2Cl$ requires C, 71.86; H, 6.68%. I.R. (CCl_4) 1721, 1709 and 1655 cm.$^{-1}$. N.M.R. 4.82 τ (1H, triplet: J = 7-8 cps.), 8.06 τ (3H, singlet). Mass spectrum P= 316.

Treatment of 2-Phenyl-2-(3'-chlorobut-2'-enyl)-bicyclo-(3;3;1)-nonane-3,9-dione, (100), with acid.

(a) Polyphosphoric acid:

2-Phenyl-2-(3'-chlorobut-2'-enyl)-bicyclo-(3;3;1)-nonane-3,9-dione (100), (50 mgs.), was stirred and heated on a steam bath with polyphosphoric acid (1.0 g.,) for one hour. The resulting dark solution was poured into ice water and the amorphous solid precipitated filtered off. Ether extraction of the remaining solution yielded a negligible quantity of a light yellow oil. The solid consisted of some four to five compounds, the two major of which were isomers, with similar infra-red and ultra-violet spectra, the latter showing $\lambda_{max.}$ 275 mμ. No further investigation of this mixture was made.

(b) Concentrated Sulphuric Acid.

The addition of concentrated sulphuric acid to an ice cooled flask containing the chloro-compound (100), (50 mgs.,), resulted in a mixture of several compounds which were water soluble. This indicated sulphonation of the aromatic ring and thus unsatisfactory conditions of reaction for isolation of a ring closed product.

(c) 80% Sulphuric Acid.

80% Sulphuric Acid (3 ml.,) was added dropwise to (100), (50 mgs.,), in a flask cooled in an ice bath. Hydrogen chloride gas was evolved and the flask then left overnight at room temperature. The mixture was poured into ice cold water and a white amorphous solid was precipitated. The suspension was extracted with ether and, after brine washing, this was dried over anhydrous magnesium sulphate. Removal of solvent yielded a white crystalline solid (38 mgs.,) which on recrystallisation from ethanol had a melting point of 221-2°. This was the rearranged product, the tricyclic lactone (116).

Found: C, 76.02; H, 7.35. $C_{19}H_{22}O_3$ requires C, 76.48; H, 7.43%. I.R. ($CHCl_3$) 1720-30 cm.$^{-1}$ (broad peak), 3595 cm.$^{-1}$; ν(CCl_4) 1744 cm.$^{-1}$, 3597 cm.$^{-1}$. N.M.R., ($CDCl_3$) 2.61 τ (5H, singlet), 8.49 τ (3H, singlet, methyl); (dimethyl sulphoxide) 4.97 τ (1H, singlet, hydroxyl). The mass spectrum - (P = 298 m/e) - showed loss of m/e 44 fragment to give m/e 254 iom. U.V. no absorption above 220 mμ.

<u>Attempted dehydration of (116)</u> - prior to determination of structure.

(a) The alcohol (116), (10 mgs.,), was refluxed with para-toluensulphonic acid, (1 mg.,), in dry benzene (25 ml.,) in a water separator for 20 hours. Only unchanged starting material was recovered.

(b) The alcohol (116), (10 mgs.,), was stirred overnight in an 0.1N solution of perchloric acid [50] in glacial acetic acid (10 ml.,). Only unchanged starting material was recovered.

(c) The alcohol (116), (3.5 mgs.,), was refluxed for 1 hour with 80% sulphuric acid (7.5 ml.,). The badly charred reaction mixture yielded a poor recovery of organic material which contained no starting material and showed no evidence of dehydration, (infra-red and n.m.r.).

(d) The alcohol (116), (3.5 mgs.,), was refluxed on a steam bath for one hour with polyphosphoric acid (5.0g.,). The oil isolated from the reaction mixture contained two compounds, neither of which showed loss of water, (mass spectral data).

(e) The alcohol (116), (5 mgs.,), was refluxed with phosphorous oxychloride (4 drops) and pyridine (2 ml.,) for 2.5 hours. The two major products still showed hydroxyl absorption in the infra-red and no vinyl proton absorption in the n.m.r. spectrum.

(f) The alcohol (116), (2 mgs.,), was refluxed in 98% formic acid (2 ml.,) for 100 minutes. The formic acid was then removed under reduced pressure; final traces being azeotroped off with benzene. The remaining yellow oil crystallised on standing and recrystallisation from ethanol yielded a colourless crystalline solid, m.p. 172-3^{o}; yield-quantitative. The following physical data showed this to be (117), the formate ester of (116). The mass spectrum - (P = 326 m/e) - showed loss of m/e 46, followed by m/e 44 to give a base peak of 236 m/e. I.R., CCl_4, 1743, 1732, 1726 (sh), 1176 cm.$^{-1}$. U.V. showed only end absorption.

Acetylation of the alcohol (116).

A mixture of the alcohol (116), (13.4 mgs.,), isopropenyl acetate (4 ml.,) and para-toluenesulphonic acid (1 mg.,) was refluxed for 12 hours. Removal of excess isopropenyl acetate under reduced pressure yielded a crystalline residue. This was dissolved in ethyl acetate (30 ml.,) and washed with water (3x50 ml.,). Drying over anhydrous magnesium sulphate, filtration and solvent removal gave a colourless solid, (18 mgs.,), which was recrystallised from an ethyl acetate-petroleum ether (60-80°) solvent system to yield plate crystals, m.p. 198-9°, 14 mgs., (91.5% yield). This was the acetate (118) of the alcohol. I.R. (CCl_4) 1745 $cm.^{-1}$ ($\varepsilon = 968$) and 1176 $cm.^{-1}$; U.V., only end absorption observed; n.m.r., 2.63 τ (5H, singlet, aromatics), 7.98 τ (3H, singlet, acetate methyl) and 8.47 τ (3H, singlet, methyl). The parent peak in the mass spectrum was m/e 340 and consecutive losses of m/e 60 and m/e 44 gave rise to a base peak at m/e 236.

Bromoacetylation of the alcohol (116).

The alcohol (116), (40 mgs.,), was dissolved in a mixture of benzene (10 ml.,) and dry pyridine (4 drops) before addition of bromoacetyl bromide (1 ml.,). A white flocculant precipitate of the acetyl pyridinium salt was produced and the reaction stirred at room temperature overnight. Ice was added and the aqueous solution extracted with ethyl acetate. This was washed with saturated sodium bicarbonate and brine solutions before drying over magnesium sulphate. Removal of solvent yielded the colourless crystalline bromoacetate (119). It was purified by thick layer chromatography followed by crystallisation from a minimal amount of diethyl ether, m.p. 153°. A sample of (119) was run on a silver nitrate thin layer chromatographic plate and developed with a ferrocein solution. The characteristic yellow colouration of the spot indicated the presence of bromine. A Beilstein test was also positive. Found: C, 60.49; H, 5.91. $C_{21}H_{23}O_4Br$ requires C, 60.29; H, 5.50%. Mass spectrum - (P = 419) - showed consecutive losses of m/e 139 and m/e 44 gave rise to the base peak m/e 236; the P+2 peak was large, confirming the presence of bromine. I.R. (CCl_4), 1745 $cm.^{-1}$ ($\varepsilon = 840$); U.V., no absorption above 220 mμ .

1-Ethoxycarbonyl-4-hydroxy-5-methylbicyclo-(3;3;1)-non-9-one.

β-(1-Ethoxycarbonyl-2-keto-3-methylcyclohexyl)-propionaldehyde was cyclised by the method of Murray et al, Tet., 18, 55 (1962), to give the required bicyclic alcohol.

Oxidation of Ethyl-5-methylbicyclo-(3;3;1)-non-4-ol-9-one-carboxylate.

A standard solution of chromium trioxide in sulphuric acid (Jones' reagent) was added dropwise to a stirred solution of ethyl-5-methylbicyclo-(3;3;1)-non-4-ol-9-one-carboxylate (5.8 g.,) in acetone (200 ml.,) at 0°C, until a permanent orange colour was obtained. This took 4.4 ml. of oxidising solution. The mixture was diluted with water (500 ml.,) and extracted with ether (3x100 ml.,). The ethereal extracts were washed with water and dried ($MgSO_4$). Removal of solvent and distillation gave 4.77 g. of a colourless oil (b.p. 127°/0.18 m.m.). Slight rubbing with a spatula induced crystallisation, and re-crystallisation from petroleum ether (60-80°) gave a white crystalline solid, m.p. 79-80°. This was ethyl-5-methyl-bicyclo-(3;3;1)-non-4,9-dione-1-carboxylate. Yield 5.1 g., - 89%. Analysis Found: C, = 65.95; H, = 7.32. $C_{13}H_{18}O_4$ requires C = 65.53; H = 7.61%. I.R. (CCl_4) 1745, 1736 and 1713 cm.$^{-1}$.

A dinitrophenylhydrazine derivative was prepared and purified on a Bentonite Kieselguhr column - m.p. 194-5°.

2-(3'-Phenyl-3'-oxopropyl)-cyclooctanone (128).

β-dimethylaminopropiophenone hydrochloride (10.7 g., 0.05 m), (as prepared in Org. Rns., Coll. Vol. 3, 305), was dissolved in water (500 ml.,) and $4\bar{N}$ Sodium hydroxide (50 ml.,) added. The liberated phenyl vinyl ketone was extracted with ether (3x100 ml.,) and washed with brine (2x100 ml.,). The ether was removed under reduced pressure on a 50° water bath and the residue added slowly to a flask containing refluxing cyclooctanone (19.0 g., 0.15 m.,) and the refluxing continued for 2 hours. The temperature during this time was maintained at about 210° and steps taken for removal of the dimethylamine evolved during the reaction. The reaction mixture was acidified to pH 7 with concentrated hydrochloric acid, taken up in ether (200 ml.,) and washed with sodium bicarbonate (100 ml.,), brine (3x200 ml.,) and dried over magnesium sulphate. Distillation of the residue left by solvent removal yielded unchanged cyclooctanone together with 2-(3'-phenyl-3'-oxopropyl)-cyclooctanone (128), (7.2 g., 56% yield), b.p. $160-2^{\circ}/2.0$m,m. Found: C, 79.03; H, 8.58; $C_{17}H_{22}O_2$ requires C = 78.38; H = 8.54%. I.R., $\nu_{max.}$ (CCl_4) 1692 and 1700 cm.$^{-1}$, (combined peak had $\varepsilon = 530, \Delta\nu_{\frac{1}{2}} = 25$ cm.$^{-1}$ and A = 4.68), (nujol) 690 and 750 cm.$^{-1}$. N.M.R. showed the 5 aromatic protons split to two multiplets (2H and 3H) and a complex series of peaks between 7.0 and 8.0 τ equivalent to 5H. U.V. had benzenoid bands at 208 and 280 mμ and an electron transfer band at 242 mμ .

Cyclisation of 2-(3'-phenyl-3'-oxopropyl)-cyclooctanone (128).

(a) 2-(3'-phenyl-3'-oxopropyl)-cyclooctanone (128), (2.0 g.,), glacial acetic acid (10 ml.,) and concentrated hydrochloric acid (2 ml.,) were refluxed together for 16 hours. Most of the acetic acid was removed under reduced pressure and the residue diluted with water before extraction with benzene. This extract was washed with saturated sodium bicarbonate, brine and dried over anhydrous magnesium sulphate. Removal of solvent yielded 1.72 g. of a brown oil which on distillation gave a pale yellow oil (1.55 g.,), b.p. <u>ca</u>. 140°/2 m.m. which by g.l.c. was shown to contain two compounds together with a trace of starting material. These two products were separated by preparative thick layer chromatography.

The major component (63%) was the desired 2-phenylbicyclo-(5;3;1)-undec-2-ene-11-one (129). The 2,4-dinitrophenyl-hydrazine derivative of this, a yellow crystalline solid m.p. 174-5°, gave the following analysis figures: Found, C, 65.85; H, 5.58; N, 13.6. $C_{23}H_{24}O_4N_4$ requires C, 65.72; H, 5.72; N, 13.34%.

I.R., $\nu_{CO}^{CCl_4}$ 1701 cm.$^{-1}$; in the n.m.r. the aromatic proton absorption was only very finely split also 4.09 τ (1H, triplet, vinyl); U.V., $\lambda_{max.}$ 243 mμ (ε = 12,400) and 213 mμ . Mass spectrum confirmed molecular weight of 240.

The minor component (37%) was shown to be 2-phenylbicyclo-(5;3;1)-undec-1-ene-11-one (130). I.R. ν(CCl_4) 1693 and 1683 (sh) cm.$^{-1}$; U.V., $\lambda_{max.}$ 263 mμ (ε = 12,200) and 212 mμ . In the n.m.r. spectrum the aromatic proton resonance peak was only finely split, no vinyl proton absorption was observed and other than the aromatics no absorption below 7.4 τ.

(b) Para-toluenesulphonic acid (2.0 g.) in benzene (50 ml.) was refluxed in a Dean and Stark water separator for 30 minutes before addition of 2-(3'-phenyl-3'-oxopropyl)-cyclooctanone (2.5 g.). This was refluxed for 2½ hours and the para-toluenesulphonic acid neutralised by addition of anhydrous sodium carbonate and left overnight. The solution was filtered and the benzene filtrate washed with brine (4x100 ml.). Removal of solvent under reduced pressure gave a deep red oil which changed to pale yellow on distillation. Analysis of this oil by g.l.c. indicated it to consist almost entirely of 2-phenylbicyclo-(5;3;1)-undec-2-ene-11-one (129) with only about 1 or 2%

of the other isomer (130), 2-phenylbicyclo-(5;3;1)-undec-1-ene-11-one present.

Isomerisation of (129).

(1) Hydrochloric acid - acetic acid.

2-Phenylbicyclo-(5;3;1)-undec-2-ene-11-one, (150 mgs.) was refluxed in a mixture of 6$\bar{N}$ hydrochloric acid (5 ml.) and glacial acetic acid (5 ml.) for three hours. The solution turned a light purple colour and then yellow. After removal of acetic acid under reduced pressure, the residue was flooded with water and ether extracted. This was washed with saturated sodium bicarbonate solution, brine and then dried, (magnesium sulphate), before removal of solvent to yield a light yellow oil. This was shown by t.l.c. and g.l.c. to be composed of the conjugated isomer (130) and the initial unconjugated isomer (129) in the ratio of 30% to 70%. The following retention times were observed for these isomers.

COLUMN.	TEMP. (^{o}C)	FLOW RATE. (ml/min)	RETENTION TIME. (mins)	ISOMER.
1% QF1	150^{o}	42	15.25	(130)
			16.65	(129)
5% QF1	175^{o}	34	25.5	(130)
			27.7	(129)

(2) Sodium ethoxide in ethanol.

When the unconjugated bicyclic ketone (129) was left standing in a solution of sodium ethoxide in ethanol, a similar mixture of the isomers (129) and (130) resulted as in the hydrochloric-acetic acid equilibration.

2-Phenylbicyclo-(5;3;1)-undecane-11-one, (131).

The unsaturated bicyclic ketone (129), (500 mgs.), was dissolved in absolute ethanol (30 ml.) and hydrogenated in an atmosphere of hydrogen using a 10% palladium on carbon powder catalyst at room temperature. The resulting colourless viscous oil, isolated by filtration and solvent removal, was shown to consist of two compounds, by both g.l.c. and t.l.c. analysis. These were considered to be the axial and equatorial isomers of 2-phenylbicyclo-(5;3;1)-undecane-11-one (131). Found: C, 84.03; H, 8.85. $C_{17}H_{22}O$ requires C, 84.25; H, 9.15%. U.V. λ max. 222, 242.5, 248, 259, 264 and 268 mμ ; I.R., $\nu_{CO}^{CCl_4}$ 1701 cm.$^{-1}$. No vinyl proton appeared in the n.m.r. spectrum and the aromatic protons exhibit only very fine splitting. A parent ion of m/e 242 was recorded in the mass spectrum.

2-Phenylbicyclo-(5;3;1)-undec-2-ene-11-one oxime, (132).

2-Phenylbicyclo-(5;3;1)-undec-2-ene-11-one (2.0 g. 0.0083 m.) and hydroxylamine hydrochloride (0.72 g. 0,013m) were refluxed together in a solution of dry pyridine (4 ml.) and absolute ethanol (4 ml.) for 10 hours. On removal of solvent under reduced pressure, water (20 ml.) and concentrated hydrochloric acid (4 ml.) were added to the residue and the mixture extracted with benzene. This extract was washed with 6 normal hydrochloric acid (2x20 ml.), sodium bicarbonate (3x20 ml.), brine (3x20 ml.) and dried over anhydrous magnesium sulphate. Solvent removal yielded an almost colourless viscous oil from which the oxime (132) crystallised with nitromethane, as a colourless crystalline solid (1.8 g., 85% yield) m.p. 120°. Found: C, 80.09; H, 8.13; N, 5.709. $C_{17}H_{21}ON$ requires C, 79.96; H, 8.29; N, 5.49%. The parent ion in the mass spectrum is m/e 255 with large losses of m/e 17 and m/e 18 to give m/e 238 and m/e 237 respectively. I.R., $\nu_{CN}^{CCl_4}$ 1652 cm.$^{-1}$ ($\varepsilon = 30.8$); $\nu_{OH}^{CCl_4}$ 3599, 3256 cm.$^{-1}$, (the 3256 cm.$^{-1}$ absorption is due to inter-hydrogen bonding as shown by its disappearance on dilution). U.V. $\lambda_{max.}$ 242 mu ($\varepsilon = 12,500$) and 206 mμ . The n.m.r. spectrum shows the following 0.82 τ (1H, broad peak, disappears on addition of deuterium oxide to sample), 4.2 τ (1H), 5.5 τ

(1H, broad peak) and 6.34τ (1H broad peak).

5-Amino-2-phenylcyclodec-2-ene carboxylic acid-ε-lactam (134).

A mixture of 2-phenylbicyclo-(5;3;1)-undec-2-ene-11-one oxime (132), (200 mgs.), and para-toluenesulphonyl chloride (300 mgs.) dissolved in dry pyridine (5 ml.) was left at room temperature for 14 hours. The colour of the solution changed from a light yellow colour to a wine red one during this time. Water (20 ml.) was added to the solution and the mixture poured into 6 normal hydrochloric acid (2x30 ml.), brine solution (3x40 ml.) and dried over anhydrous magnesium sulphate. Filtration and removal of solvent yielded a light yellow oil (180 mgs.) which quickly solidified on standing. This was recrystallised from an ethyl acetate-petroleum ether (60-80^{o}) solvent system as colourless crystals, (140 mgs., 70% yield), m.p. 128-130^{o}. This was the desired ε-lactam (134). Found: C, 80.19; H, 8.03; N, 5.53. $C_{17}H_{21}ON$ requires C, 79.96; H, 8.29; N, 5.49%. The mass spectrum had a parent ion m/e 255. I.R., $\nu_{CO}^{CCl_4}$ 1657 cm.$^{-1}$ also $\nu_{NH}^{CCl_4}$ 3412, 3281 and 3190 cm.$^{-1}$, (the last two absorptions could be suppressed on dilution). U.V., $\lambda_{max.}$ 206 mμ ($\varepsilon = 25,500$) and 234 mμ ($\varepsilon = 10,450$). In the n.m.r. spectrum, the proton carried by the nitrogen resonates at 1.02 τ (broad doublet, J = 8 cps.) and the vinyl proton at 4.32 τ (doublet, $J = 6$ cps.). There is further fine splitting of the latter absorption.

Hydrolysis of (134).

(a) 6$\overline{N}$ Hydrochloric acid.

5-Amino-2-phenylcyclodec-2-ene carboxylic acid-ε-lactam (134), (62 mgs.) was refluxed for 24 hours in 6$\overline{N}$ hydrochloric acid (12 ml.). The reaction mixture was flooded with water and extracted with ethyl acetate. This extract was brine washed (3x20 ml.) dried over anhydrous magnesium sulphate and the solvent removed under reduced pressure to yield a light yellow oil (58 mgs.) which solidified, on trituration with ether, as colourless crystals (55 mgs.), m.p. 149-150°. This was shown to be the isomeric lactam (140), 5-amino-2-phenylcyclodec-1-ene carboxylic acid-ε—lactam. Found: C, 80.05; H, 8.13; N, 5.748. $C_{17}H_{21}ON$ requires C, 79.96; H, 8.29; N, 5.49%. I.R. $\nu_{max.}$ (CCl_4) 1663, 1632 cm.$^{-1}$ and $\nu_{CN}^{CCl_4}$ 3421, 3268 and 3192 cm.$^{-1}$; (the 3268 and 3192 cm.$^{-1}$ absorptions could be suppressed on dilution). U.V., $\lambda_{max.}$ 250 mμ ($\varepsilon = 8{,}700$) and 207 mμ ($\varepsilon = 10{,}300$). The molecular weight was 255 (mass spectroscopy). N.M.R., 1.20 τ (1H, doublet, $J = 8$ cps.) and the absence of any vinylic proton absorption.

(b) 6$\bar{N}$ Hydrochloric acid - 9 days.

Treatment of the lactam (134) with 6$\bar{N}$ hydrochloric acid under reflux conditions for 9 days yield only (140).

(c) Concentrated hydrochloric acid.

A 24 hour reflux of the lactam (134) with concentrated hydrochloric acid again yielded the same isomerised lactam (140).

(d) 6$\bar{N}$ Hydrochloric acid in ethanol.

When the lactam (134) was refluxed with dilute hydrochloric acid in ethanol, as solvent, the isomerised lactam (140), together with several other neutral products, were formed. Of the latter the main one appeared to be a further isomer of the initial lactam (134). The infrared spectrum was very similar to (134) and the mass spectrum indicated a molecular weight of 255. The other products were only present in trace amounts.

(e) Potassium hydroxide in ethanol.

The lactam (134) when refluxed with 5% potassium hydroxide in ethanol for 2 hours, yielded an almost quantitative amount of isomerised lactam (140) together with trace amounts of by products.

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