SYNTHETIC APPROACHES TO CARYOPHYLLENE.

THESIS

presented to the University of Glasgow
for the degree of Ph.D.

by

Alexander McKillop

1963

I should like to express my sincere gratitude to Professor R. A. Raphael, F.R.S., and to Dr. G. L. Buchanan for the encouragement and assistance they have given me during the last three years.

I also wish to thank Mrs. F. Lawrie for the recording of infra-red absorption spectra, Miss M. Mackay for recording proton magnetic resonance spectra, Mr. J. M. L. Cameron, B.Sc., and his staff for micro analyses, and Mr. G. Milmine for his assistance in many large scale preparations and syntheses.

The work described in this thesis was performed during the tenure of a Maintenance Award from the Department of Scientific and Industrial Research, (1960-62), and of a Scholarship from the Salters' Institute of Industrial Chemists, (1962-63), and to these bodies I should like to express my gratitude.

SUMMARY

Starting respectively from 2-methylcyclohexanone and 2-methylcycloheptanone, a synthetic route to 8- and 9-membered carbocycles has been developed via the bicyclo-[3:3:1]-nonane and bicyclo-[4:3:1]-decane systems. In particular, 1-methyl-5-methylenecyclooct-1-ene and 1-methyl-5-methylenecyclonon-1-ene have been synthesised as models for a projected synthesis of caryophyllene. Alternative routes to certain intermediates have been investigated to establish the most direct and conservative approach to olefins of this type, and the purity of the products has been established by spectroscopic methods. An attempt has been made to extend these methods to a synthesis of isocaryophyllene.

CONTENTS

Page

THE CHEMISTRY OF CARYOPHYLLENE

APPENDIX

THE SYNTHESIS OF 1-METHYL-5-METHYLENECYCLOOCT-1-ENE AND 1-METHYL-5-METHYLENECYCLONON-1-ENE

THE CHEMISTRY OF CARYOPHYLLENE.

INTRODUCTION.

It is possible that caryophyllene, the main hydrocarbon constituent in oil of cloves (from Eugenia caryophyllata) and occurring in a number of other essential oils, has been the object of more intense and prolonged investigation than any other single sesquiterpene. Yet its structure, and an explanation of its many rearrangements under different conditions, have only recently become known, and as yet no successful synthesis has been achieved. *

The long period which has elapsed since its discovery in clove oil by Ettling in 1834[1] and the elucidation of its structure can be ascribed to three main factors. Firstly, pure samples of caryophyllene were almost certainly not available until the fairly recent use of modern physical techniques, with the result that much of the early work is ambiguous and to some extent inexplicable. In the second place, apart from the macrocyclic fragrant ketones (which are products of animal metabolism) plant products which embodied a medium sized ring of nine, ten or eleven carbon atoms were unknown. Indeed, the synthesis of medium sized ring compounds was extremely

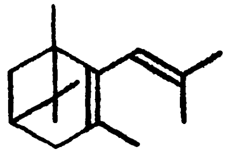
* See appendix p.23 .

difficult and expensive until the innovation of the acyloin condensation, and the properties of those compounds which had been prepared and examined seemed to confirm the view that comparable ring systems would be absent in nature. Caryophyllene was the first terpene containing a medium sized ring to have its structure elucidated, though many more have since been reported. [2] Finally, caryophyllene and some of its derivatives undergo a variety of skeletal rearrangements which could only be fully explained when the structure of the hydrocarbon itself was known.

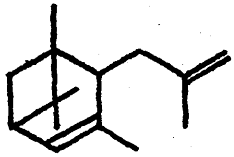
This review is intended as a summary of the work involved in determining the absolute structure of caryophyllene and an outline of some of the reactions of caryophyllene and some of its derivatives. There have been few attempts to synthesise caryophyllene-type structures reported, and those for which information is available are discussed briefly. The now accepted terminology, viz. caryophyllene and iso-caryophyllene, is used throughout. [3]

THE DETERMINATION OF THE STRUCTURE OF CARYOPHYLLENE.

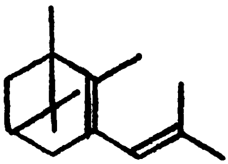
In the earlier literature there is some confusion of terms, and the names α-, β- and γ-caryophyllene recur. α-Caryophyllene is now recognised as the sesquiterpene humulene, while β- and γ-caryophyllene are now referred to as caryophyllene and iso-caryophyllene respectively. In reviewing the chemistry of caryophyllene, the accumulation



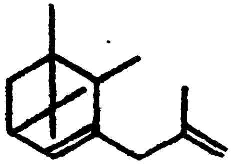
(1)



(2)



(3)

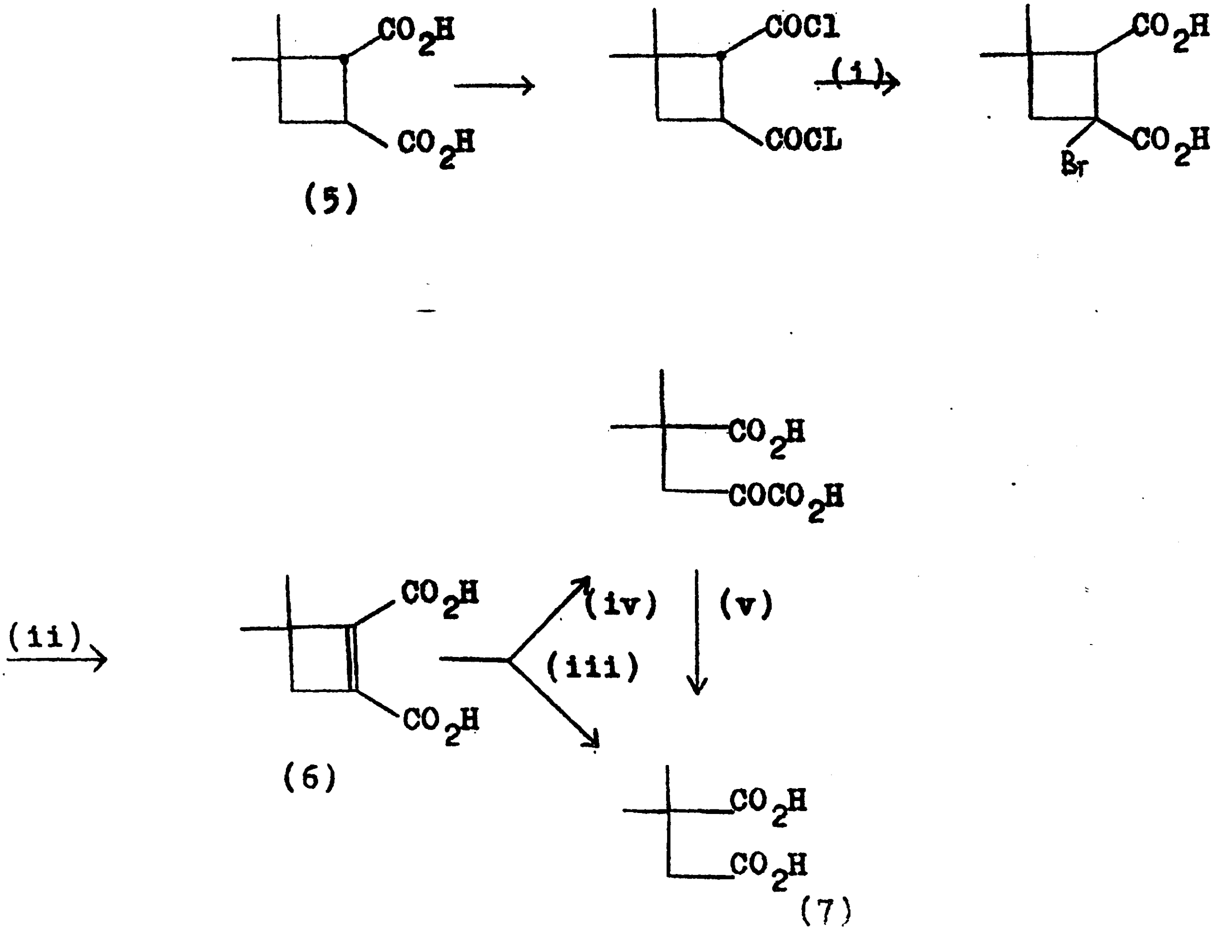


(4)

of knowledge which led to a final understanding of the structure and reactions of this remarkable compound falls quite naturally into two distinct phases. These are (1) the period 1875 - 1939, when the classical approach to structural elucidation was adopted, many derivatives being prepared and characterised, and the standard degradative techniques of the time being applied; and (2) the period 1939 - 1956, during which a more refined approach, both practically and theoretically, led to complete knowledge of the caryophyllene molecule and a fuller understanding of much of the earlier work.

(1) THE PERIOD 1875 - 1939.

The composition $C_{15}H_{24}$ [4] and the presence of two ethylenic double bonds in caryophyllene [5] having been quickly established, it followed that the compound was bicyclic. The prolonged investigations of Deussen [6] led to the proposal of a substituted *cyclo*butane ring and, following on the permanganate oxidations performed by Haarmann,[7] Semmler and Meyer proposed the first structures (1) and (2) for caryophyllene, basing their conclusions on ozonolysis experiments.[8] Similar types of structures, (3) and (4), but based on the isoprene rule, were proposed by Busse.[9] These proposed structures, however, and other variations on them [10] carried no great influence, because (a) there was no evidence, physical or chemical, in



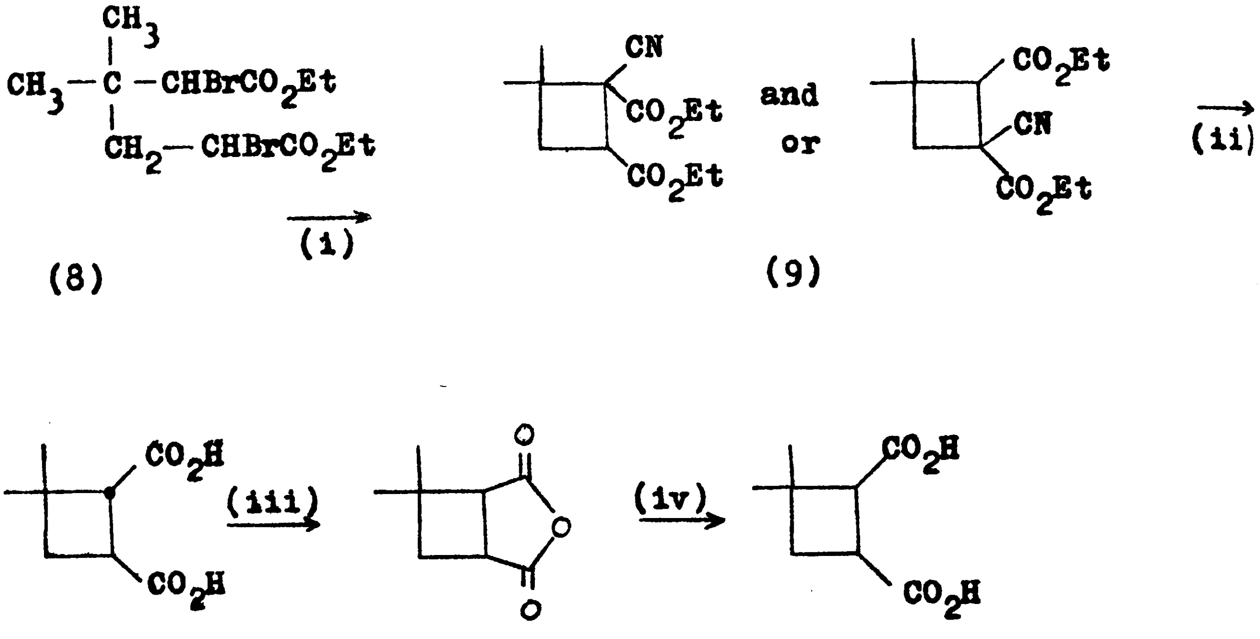
(i) Br_2 , (ii) KOH/EtOH , (iii) CrO_3 , (iv) O_3 , (v) H_2O_2.

favour of a system of conjugated double bonds, and (b) the expected products of oxidation, i.e. the cyclobutane acids were unknown.

As a result of this lack of experimental confirmation, attention was focussed on the cyclobutane carboxylic acids derived from the oxidation of caryophyllene. 7,8,11,12,13. The monocyclic oxidation products of caryophyllene were as follows :

(i) $C_{14}H_{22}O_4$: a diketocarboxylic acid,
(ii) $C_{11}H_{18}O_3$: a ketocarboxylic acid,
(iii) $C_{10}H_{16}O_4$: a dicarboxylic acid, which was called homocaryophyllenic acid,
(iv) $C_9H_{14}O_4$: a dicarboxylic acid, which was called caryophyllenic acid,
(v) $C_8H_{12}O_4$: a dicarboxylic acid which was called norcaryophyllenic acid.

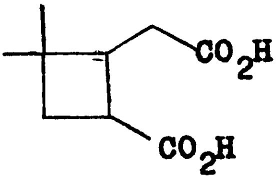
One further important degradation product was an acyclic dicarboxylic $C_6H_{10}O_4$, which was shown to be 1:1-dimethylsuccinic acid, and with this degradation product known, Ramage and Simonsen [14] established that d-transnorcaryophyllenic acid was in fact 1:1-dimethylcyclobutane-2:3-dicarboxylic acid by the following reaction sequence. The acid (5) was converted to its di-acid chloride which, on treatment with bromine, gave the mono- and dibromo derivatives. The monobromo-acid, after dehydrobromination, yielded the substituted cyclobutane (6) which was degraded



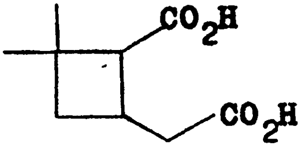
(8) (9)

(5) (10)

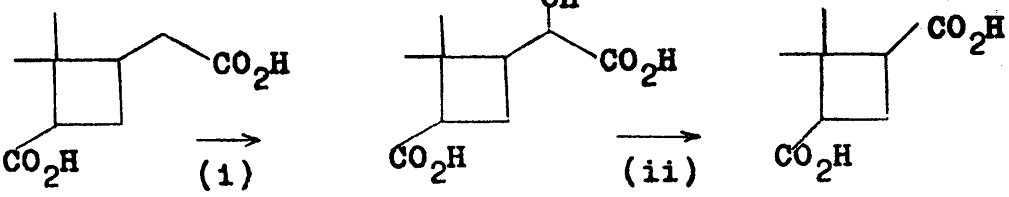
(i) NaCN/EtOH, (ii) HCl, (iii) $(CH_3CO)_2O$, (iv) H_2O.



(11)



(12)



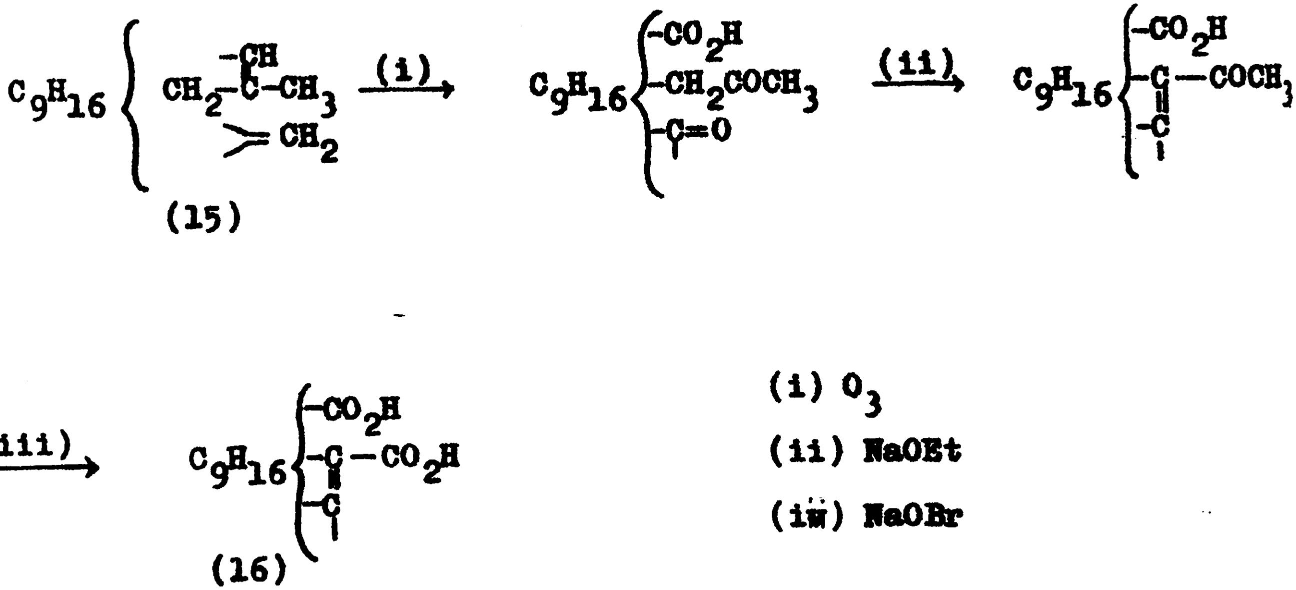
(13) (14)

(i) Br_2 then $Ba(OH)_2$, (ii) PbO_2.

by standard methods to 1:1-dimethylsuccinic acid (7).

The structure and stereochemistry of norcaryophyllenic acid was finally proved by Rydon [15] by synthesis as follows. Ethyl α:α-dibromo-β:β-dimethyl adipate (8) was cyclised to the cyano ester (9) by refluxing with sodium cyanide in ethanol. Hydrolysis and decarboxylation with concentrated hydrochloric acid gave racemic trans-3:3-dimethyl*cyclo*butane-1:2-dicarboxylic acid (5) which was identical with that derived from caryophyllene. When the crude acid was heated with acetic anhydride and the resulting anhydride carefully hydrolysed with water, the corresponding racemic cis-3:3-dimethyl*cyclo*butane-1:2-dicarboxylic acid (10) was obtained. Both the d,l-cis and trans-norcaryophyllenic acids were resolved, and only *d*-transnorcaryophyllenic acid proved identical with that derived from natural sources.

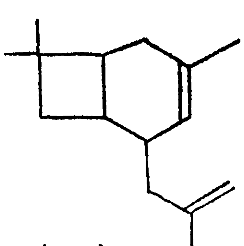
It now followed that another degradation product, caryophyllenic acid, could be assigned the structure (11) or (12), since it could be degraded to transnorcaryophyllenic acid in a manner analogous to the degradation of pinic to norpinic acid - c.f. (13) ---> (14). Attempts were made to decide which of these structures, (11) or (12), was in fact that of caryophyllenic acid,[12] but confusing results were obtained which were not satisfactorily explained until much later. [16] The configuration in caryophyllenic acid was assigned by



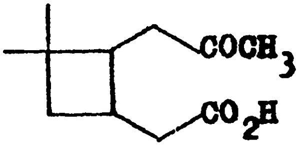
(i) O_3

(ii) NaOEt

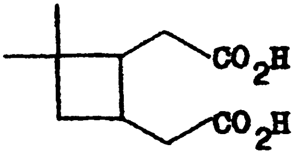
(iii) NaOBr



(17)



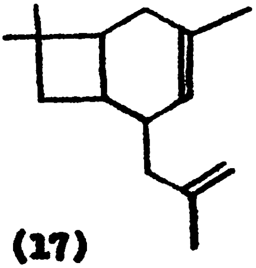
(18)



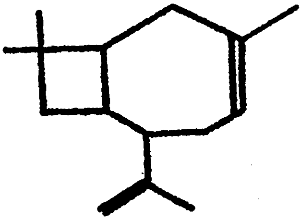
(19)

analogy with the nor acid, but this was rigorously proved by Ramage and Simonsen,[17] using the anhydride technique as outlined above for norcaryophyllenic acid. There being two possible structures for caryophyllenic acid, it followed that there were four possible structures for homocaryophyllenic acid; this situation could not be resolved and a position of stalemate existed with respect to the degradation products.

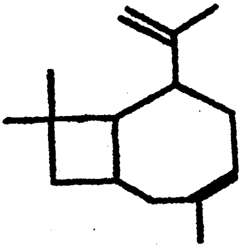
Interest reverted to oxidative techniques and Ruzicka and Wind,[12] using standard techniques, confirmed the nature of the two ethylenic linkages as (a) a terminal double bond $>C=CH_2$ and (b) a trisubstituted double bond carrying a methyl group. More important, however, they showed that the trisubstituted double bond could be expanded to include a methylene group, i.e. $-CH_2-\overset{CH_3}{\overset{|}{C}}=CH-$, in the following manner. Ozonolysis of caryophyllene gave a diketo acid, the methyl ester of which, on treatment with sodium ethoxide, gave an unsaturated keto acid. This compound, on treatment with hypobromite, gave an unsaturated di-acid, and this sequence can be represented schematically as in (15)--->(16). As a result of this work, Ruzicka[18] proposed structure (17) for caryophyllene and the structure (18) for the monoketo acid from which homocaryophyllenic acid was obtainable by hypobromite oxidation, and so Ramage and Simonsen formulated homocaryophyllenic acid as (19).[19]



(17)



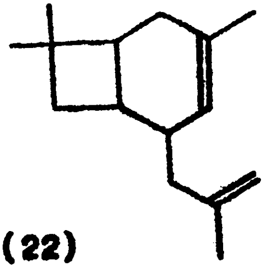
(20)



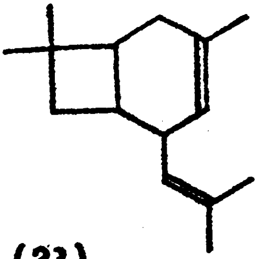
(21)

Unsuccessful attempts were made to synthesise the acid (19) while work by Ruzicka [20] and by Ramage and Simonsen [21] on the neutral products of ozonolysis added confusion to the overall picture, since the results were interpreted as supporting evidence for the rather unusual isobutenyl side-chain in (17). Rydon [22] challenged Ruzicka's formula (17) for caryophyllene on purely theoretical grounds and was the first to propose a ring of greater than six carbon atoms in caryophyllene, with the structures (20) and (21). Ruzicka [23] reinvestigated the ozonolysis of dihydrocaryophyllene in an attempt to verify these structures, and, although providing no direct proof of these structures, he demonstrated for the first time that caryophyllene must have one ring of at least seven carbon atoms. Ozonolysis of dihydrocaryophyllene gave a keto acid which, on hypobromite oxidation, gave a di-acid; pyrolysis of the salt of this acid gave a ketone whose hydroxymethylene derivative, on ozonolysis, gave another di-acid. The salt of this acid gave, on pyrolysis, another ketone and not, as would happen if caryophyllene were (17), a substituted glutaric anhydride. This result led Ruzicka to consider that caryophyllene was a mixture of (17) and (20), although neither structure could fully accommodate the known facts.

The close similarity between caryophyllene and isocaryophyllene had long been recognised, and it was



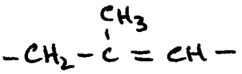
(22)



(23)

suggested that, using Ruzicka's structure for caryophyllene, they were structural isomerides of the type (22) and (23). Ramage and Simonsen, however, showed this to be untenable,[24] and it was thereafter assumed that the two compounds were stereoisomerides.

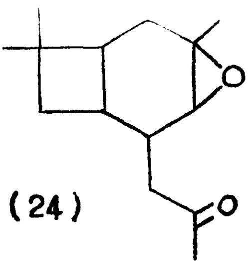
By 1939, therefore, the structure of caryophyllene was still seriously in doubt, with no proposed formula accommodating more than a fraction of the experimental observations. The results of the investigations to this point may be summarised as follows : (i) carophyllene is a bicyclic, doubly unsaturated sesquiterpene hydrocarbon; (ii) six of the carbon atoms are located in the form of a *cyclo*butane ring with an appended gem-dimethyl group; (iii) the second ring must contain at least seven carbon atoms; and (iv) the two ethylenic linkages are present in the form of a terminal double bond $>C=CH_2$ and the grouping



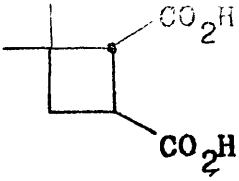
$-CH_2-\overset{CH_3}{\overset{|}{C}}=CH-$.

(2) THE PERIOD 1939 - 1956.

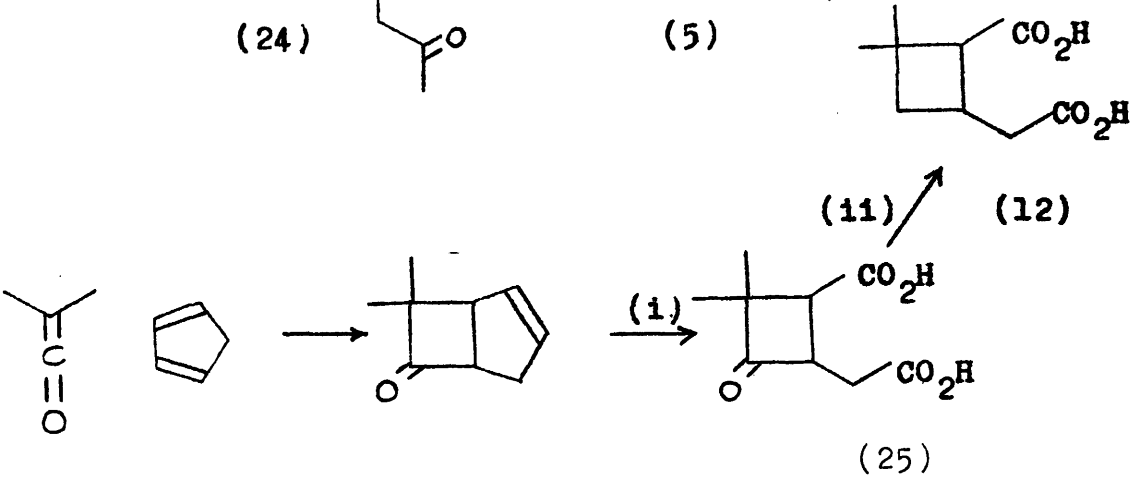
In 1947, Treibs began a series of experiments the results of which were of the greatest importance.[25] Using hydrogen peroxide, and later perbenzoic acid, he obtained a crystalline monoepoxide which, on ozonolysis, gave a keto-epoxide and formaldehyde, showing that the more heavily substituted double bond had been involved in oxide formation. On the basis of Ruzicka's formula (17) for



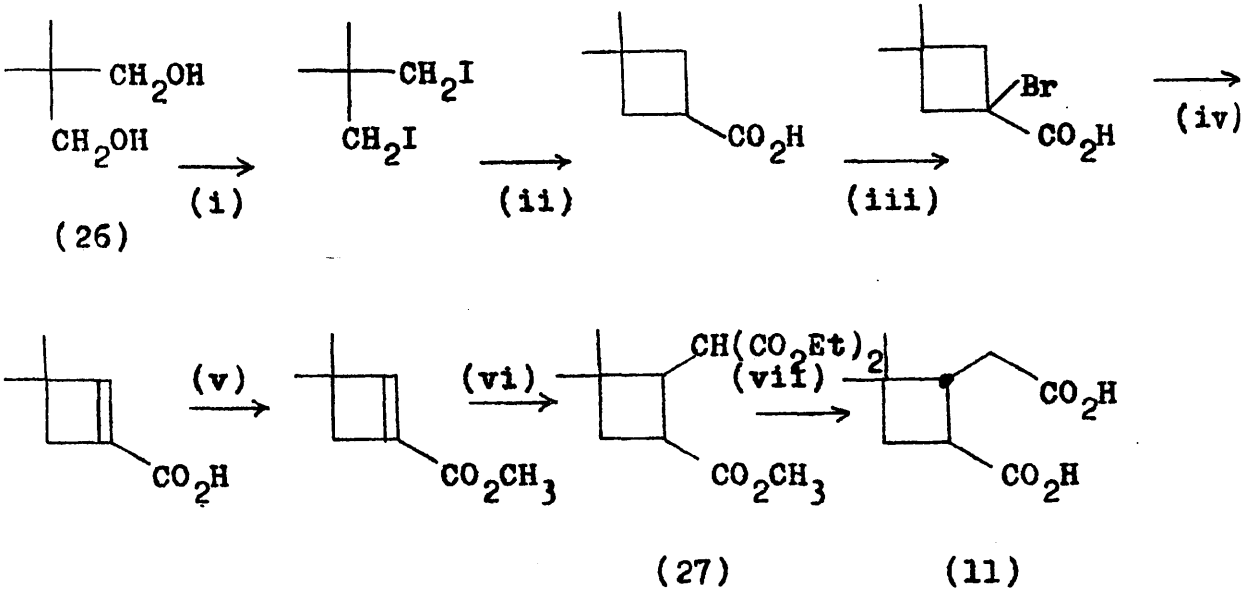
(24)



(5)

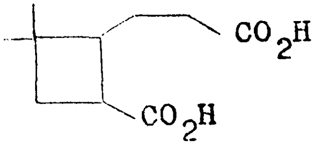


(i) $KMnO_4/OH^-$, (ii) $H_2N.NH_2/KOH$.

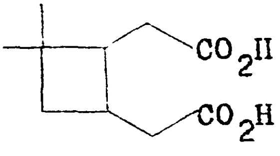


(i) Ph_3PO_3/MeI, (ii) $CH_2(CO_2Et)_2$, OH^-, $-CO_2$, (iii) $SOCl_2$, P/Br_2,
(iv) KOH, (v) CH_2N_2, (vi) $CH_2(CO_2Et)_2$, (vii) OH^-, $-CO_2$.

(28)

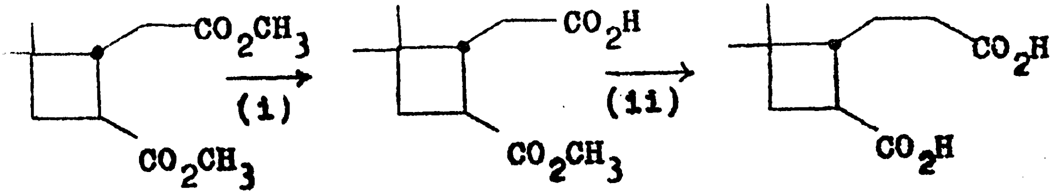


(29)



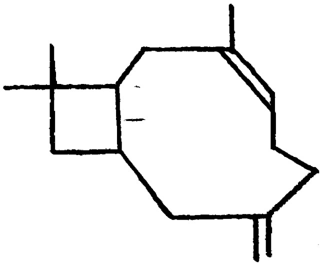
caryophyllene, this oxidoketone should have had the structure (24), but did not give a bromoform test. Treibs made the monoepoxides of both caryophyllene and isocaryophyllene and carried out a number of reactions with them, none of which he could satisfactorily explain, but which were brilliantly accounted for later by Barton (q.v.). The isolation of these pure crystalline derivatives was a great step forward in the structural investigations and superseded earlier work on the oxidation of dihydrocaryophyllene with selenium dioxide [26] and with perbenzoic acid.[27]

The structures of the cyclobutane acids had meanwhile been taken up again, and the correct structures of these compounds were determined. d-Transnorcaryophyllenic acid was known to have the structure (5) while the acid (12) was synthesised in both cis and trans forms and shown to be different from caryophyllenic acid [28] (24') ---→ (25). By exclusion, caryophyllenic acid was ascribed the structure (11), and this was proved by synthesis of this compound as shown in the scheme (26) ---→ (27). Both cis and trans racemic acids were prepared and resolved, the trans form proving identical with genuine caryophyllenic acid.[29] There now remained only two possibilities for the structure of homocaryophyllenic acid, viz. (28) or (29), and of these, structure (28) was shown to be correct by Dawson and Ramage,[30] who

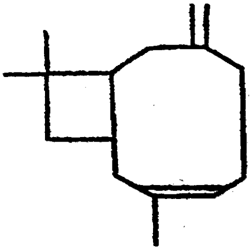


(30) (28)

(i) Half hydrolysis, (ii) Arndt-Eistert.



(31)

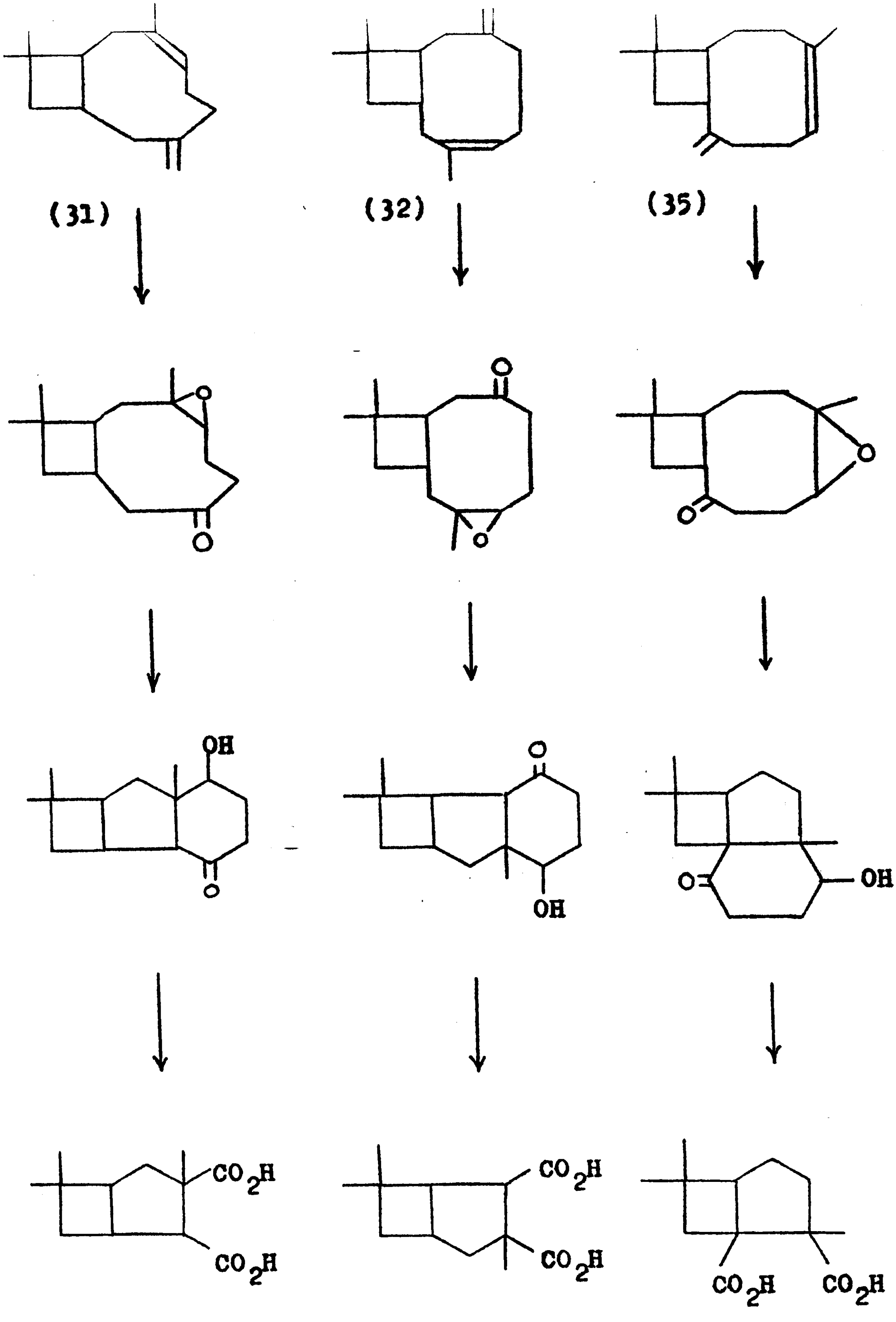


(32)

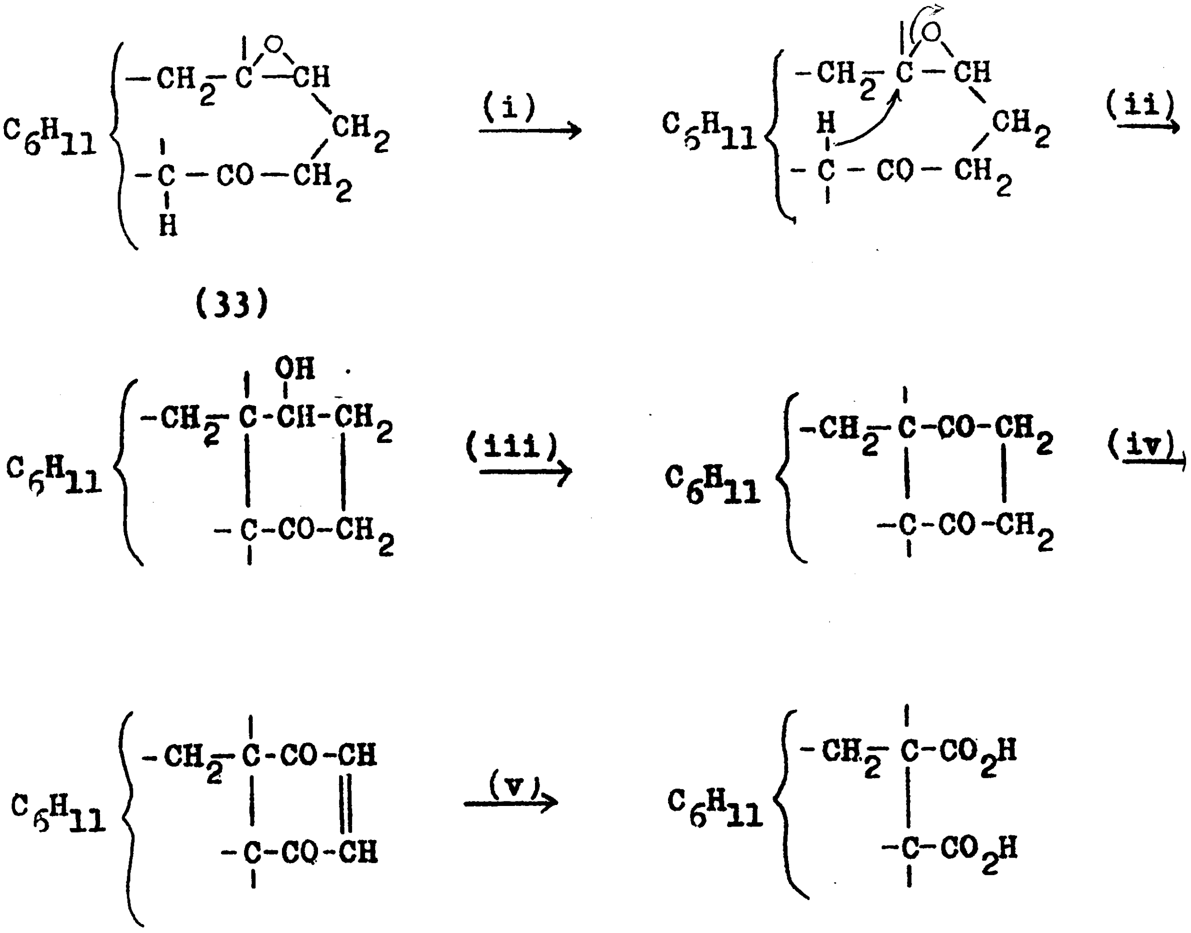
synthesised both acids, the synthesis of homocaryophyllenic acid being shown in (30) ---→ (28).

Meanwhile, Sorm and his co-workers made the novel proposal that caryophyllene contained a nine-membered ring,[31] their conclusions being based on an infra-red study of the carbonyl absorption of the oxidoketone first prepared by Treibs, although chemical evidence in favour of a nine-membered ring was later advanced.[2] Consequent upon this work, Sorm proposed the structures (31) and (32) for caryophyllene.

Simultaneously, and also working with Treib's oxidoketone, Barton and Lindsey provided excellent proof of the presence of a nine membered ring in the following manner.[32] Treatment of the oxidoketone with chloroformic acid gave a chlorohydrin which, on oxidation with chromic acid, gave a chlorodiketone. This chlorodiketone was not enolisable and so the epoxide ring could not have been in a position β:γ- to the carbonyl group. Having obtained this preliminary evidence, they refluxed the oxidoketone with methanolic potassium hydroxide and obtained an isomeric tricyclic substance which contained one hydroxyl and one carbonyl group. Chromic acid oxidation afforded the corresponding diketone which on treatment with selenium dioxide gave a fully conjugated ene-1:4-dione system, whose ultra-violet absorption spectrum indicated a cisoid arrangement. This was



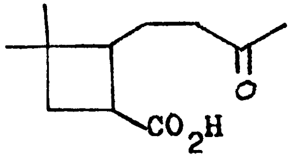
(36) (37) (38)



(33)

(34)

(i) OH^-, $-H^+$, (ii) $+H^+$, (iii) CrO_3, (iv) SeO_2, (v) $KMnO_4$

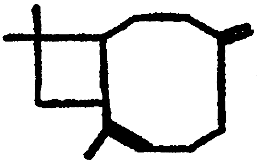


(39)

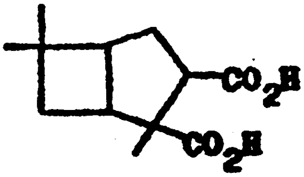
supported by the fact that permanganate or nitric acid oxidation gave a saturated bicyclic dicarboxylic acid which very readily formed an anhydride. The ease of formation of the anhydride, together with the other evidence, suggested a substituted succinic acid, and the above reactions could be summarised as (33) ---> (34).

Since the C_6H_{11} fragment contained the dimethy<u>cyclo</u>butane entity known to be present in caryophyllene, all the carbon atoms are accountable at each stage, and Barton and Lindsey, while allowing that Sorm's structures for caryophyllene might be correct, suggested a third possible structure, namely (35). With the three possible structures (31), (32) and (35) for caryophyllene, and following out the scheme outlined in (33) ---> (34), the overall reactions may be summarised as shown in (31) ---> (36), (32) ---> (37) and (35) ---> (38).

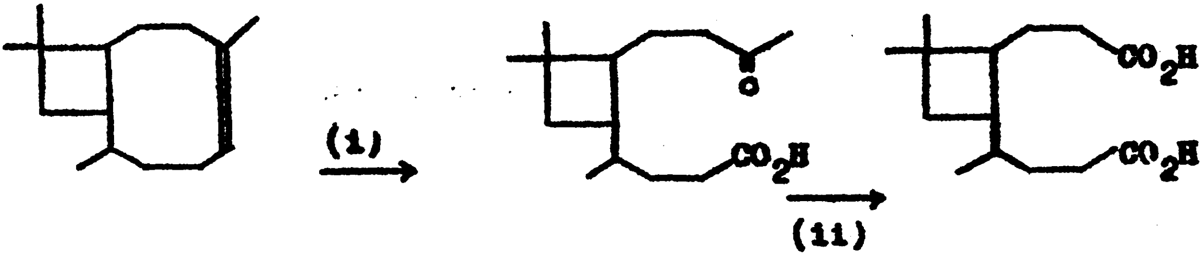
Independently of this work, but following on it, Dawson and Ramage proved that the structures (31) and (32) for caryophyllene could not be correct and suggested yet another possible structure.[33] They found that permanganate oxidation of pure caryophyllene nitrosite gave three main products, one of which was the keto-acid (39), and which could be smoothly oxidised with hypobromite to homocaryophyllenic acid. This acid (39) cannot possibly be formed from structures (31) or (32) and this observation, together with valid objections by Barton (q.v.) showed these



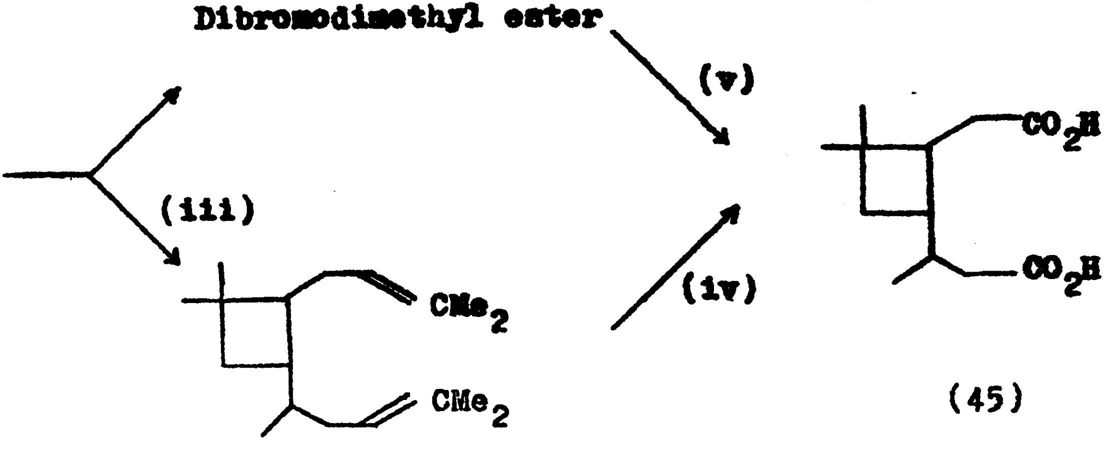
(40)



(41)



(42) (43) (44)



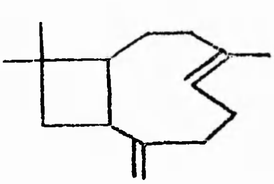
(45)

(i) O_3, (ii) NaOBr, (iii) Dimethyl ester, MeMgI, $(CO_2H)_2$, (iv) CrO_3, (v) Aqueous Na_2CO_3 then $KMnO_4$.

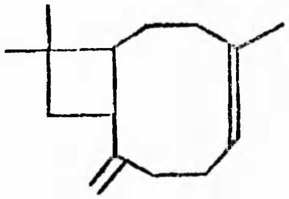
structures to be inadequate. Ramage and Whitehead, however, suggested the structure (40) for caryophyllene, and this could reasonably accommodate most of the known facts then understood. The main objection to this structure was that if the procedure developed by Barton and Lindsey were followed out, the di-acid (41) would be formed, in which there is a relatively unhindered secondary carboxyl group (c.f. the di-acids (36) and (37)). This acid (41) should therefore (like acids (36) and (37)) react with bromine, whereas the acid derived from caryophyllene, (38), gave no bromo derivative and reacted entirely in the manner of a di-tertiary carboxylic acid.

Final evidence in favour of Barton's structure came from experiments by Atwater and Reid,[35] who ozonised dihydrocaryophyllene (42) to give the keto-acid (43). This was oxidised to the dicarboxylic acid (44) with hypobromite, and this acid degraded in unambiguous fashion to the di-acid (45). The final product (45) could not possibly have resulted if caryophyllene had had the structure (40) as proposed by Ramage and Whitehead.

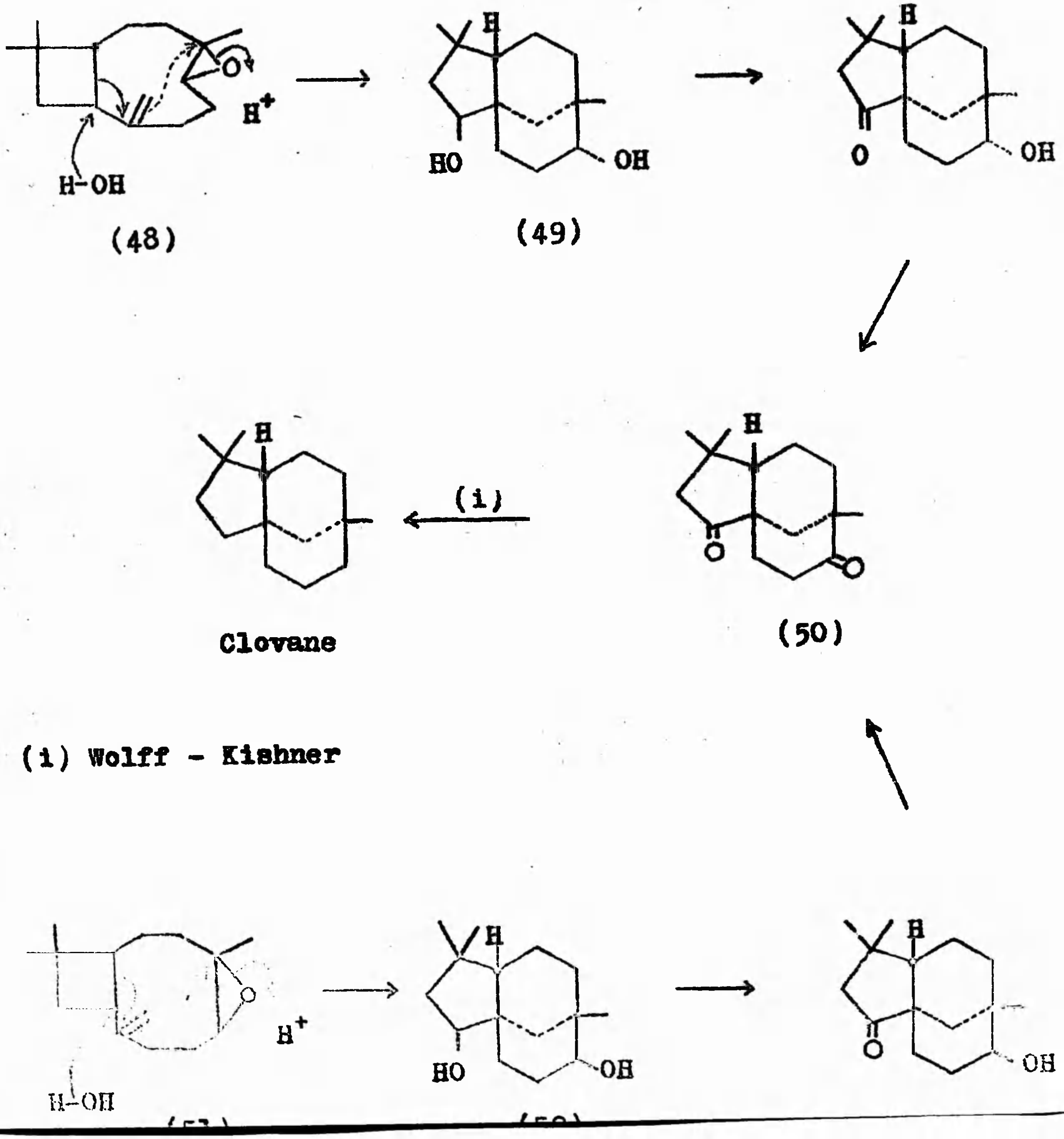
The carbon skeleton of caryophyllene having been determined, it remained to determine the structure of isocaryophyllene. The two compounds were known to give the same dihydrochloride, different nitrosochlorides and the same dihydrocaryophyllene (in fact dihydroisocaryophyllene). It was shown that the two hydrocarbons



(46)



(47)

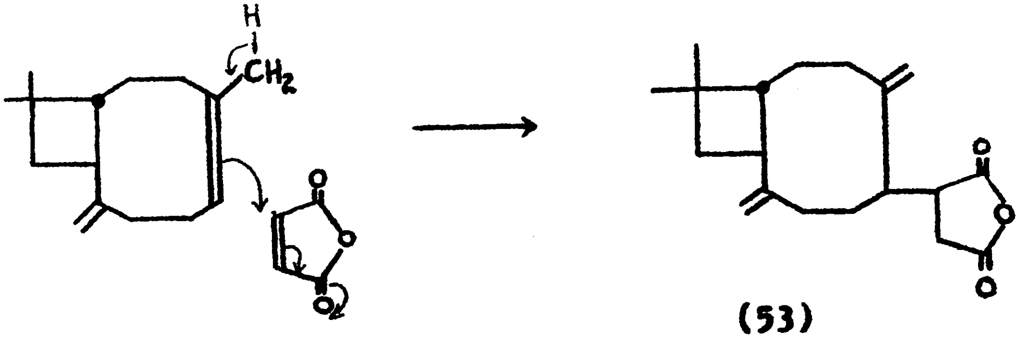


(i) Wolff - Kishner

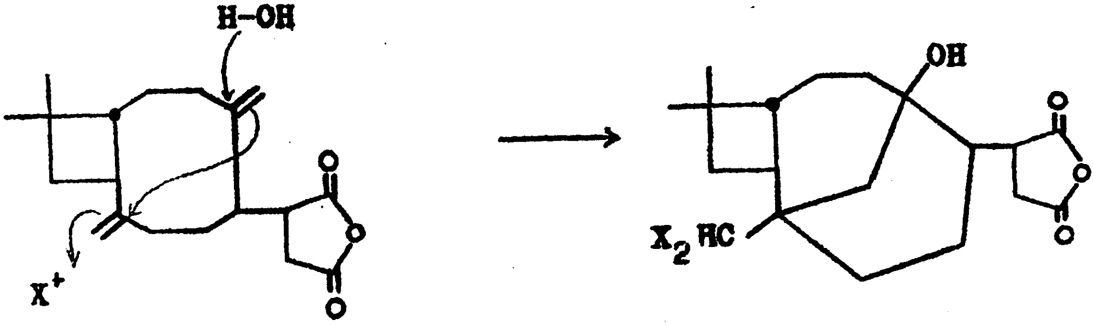
are in fact geometrical isomers about the endocyclic double bond, caryophyllene and isocaryophyllene having respectively the structures (46) and (47). Caryophyllene was assigned the more strained trans configuration because it reacted quicker with perphthalic acid than the cis form, [3] a finding in keeping with Prelog's observations in the cis and trans cyclononene and cyclodecene series. [36] The two isomers differ, however, in the oxides they give with per acids, facts which were adequately explained by Barton (q.v.) and which served as further confirmation of the geometrical nature of the isomerism. It is not yet clear whether isocaryophyllene occurs as such in nature, and it is possible that it is an artefact of caryophyllene produced during the chemical treatment of this compound.

THE TRICYCLIC DERIVATIVES OF CARYOPHYLLENE.

A series of base-catalysed rearrangements occur with the monoepoxides of caryophyllene and isocaryophyllene which have been fully elucidated as follows.[2,37] Treatment of caryophyllene oxide (48) with mild base gave the crystalline diol (49) which could be oxidised in stages to the diketone (50). Similar cyclisation of the stereoisomeric isocaryophyllene oxide (51) gave the isomeric diol (52) which could again be oxidised in stages to the same diketone (50). The constitution of the diketone (50) was rigorously established by Barton and his co-workers, [38]



(53)



(54)

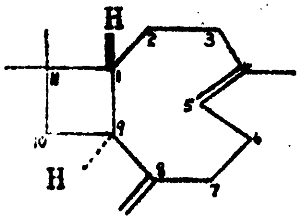
so that this work constituted additional evidence as to the geometrical nature of the isomerism in the caryophyllenes.

Although the double bonds in caryophyllene are not conjugated, Ruzicka and Zimmermann in 1933 reported the formation of a 1:1-adduct with maleic anhydride,[39] and catalytic hydrogenation experiments showed that the adduct still retained two double bonds.[40] It has since been shown that many mono-unsaturated olefins can give maleic anhydride adducts in which the anhydride residue is attached to the saturated carbon of an allylic system,[41] and this explanation was formally accepted for caryophyllene.[42] Following on original degradations of the adduct by Ruzicka,[43] Nickon has shown that its structure is (53),[44] and it has been shown that with electrophilic reagents (X = Br, H) the caryophyllene-maleic anhydride adduct can undergo cyclisation to a further type of tricyclic system, as in (54).

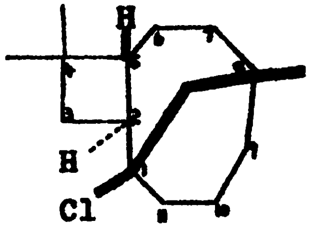
The acid-catalysed rearrangements of caryophyllene have so far proved the most interesting, and among the products which have been isolated are the tricyclic compounds caryolan-1-ol (β-caryophyllene alcohol), α-caryophyllene alcohol, and the hydrocarbons clovene, isoclovene and psuedoclovene.[45,46] Caryolan-1-ol has been shown to have the structure (55) by Barton, Bruun and Lindsey,[47] and this was confirmed and the absolute stereochemistry established by the X-ray determination of the structure of the corresponding chloride(56) by Robertson and Todd[48] and by molecular rotation studies by Barton and Nickon (q.v.). This X-ray investigation, moreover, provided for the first time direct proof of the trans fusion of the bicyclic system in the caryophyllene series.

The crystalline chloride (56) was first reported by Wallach and Walker,[49] and the replacement of hydroxyl by chlorine proceeds with retention of configuration, such are the steric requirements of the bridgehead carbonium ion. The mechanistic implications here are of importance and in this case, and in other fields, have become the subject of investigation.[50]

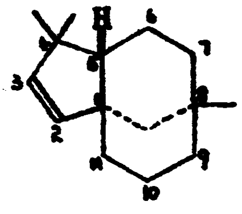
α-Caryophyllene alcohol, for which the structure (57) has been tentatively proposed, can be dehydrated[51] to give the hydrocarbon clovene (58) (or an isomer of clovene), the structure for which, and mode of formation, was suggested by Eschenmoser and Gunthard[52] and by Barton, Bruun and Lindsey.[47] A rigorous proof of the structure of clovene has been forwarded by Barton and his co-workers, and by Lutz and Reid.[53,54] Of the two remaining tricyclic hydrocarbons which have been reported, namely isoclovene and psuedoclovene, the latter has been tentatively assigned the structure (59), while X-ray studies have shown that isoclovene has the structure



(61)



(62)

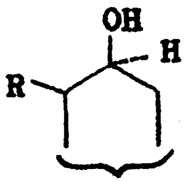


(63)

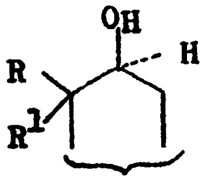
(60).[55,46.] Despite the suggestions in the earlier literature, the caryolane and clovene skeletal types do not seem to be interconvertible (q.v.). Thus dehydration of caryolan-1-ol is now known to give isoclovene and psuedoclovene; conversely, there is no record of clovane derivatives undergoing structural change, although the inconsistences in the α-caryophyllene alcohol field may in fact be due to such a structural change.

ABSOLUTE STEREOCHEMISTRY.

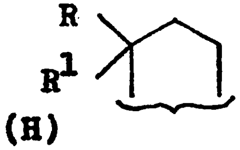
When discussing the stereochemistry and reactions of caryophyllene the hydrogen atom at C_1 is taken as the reference centre, since its configuration is unchanged in all the reactions and transformations, and it was arbitrarily assigned the β-configuration (61). The configuration of this hydrogen atom was taken by analogy with the C_5 hydrogen atom in β-caryophyllene chloride (62), whose β configuration was proved by X-ray methods. Similarly the hydrogen at C_5 in clovene was taken as β, (63). Confirmation of the absolute stereochemistry of caryophyllene and its derivatives was provided by Barton and Nickon, [56] using molecular rotation studies. Among others, Klyne and Stokes [57] had proposed a useful molecular rotation rule for correlation of appropriately substituted *cyclo*hexanols or *cyclo*pentanols with D-glyceraldehyde. Thus the cyclic secondary alcohols of the



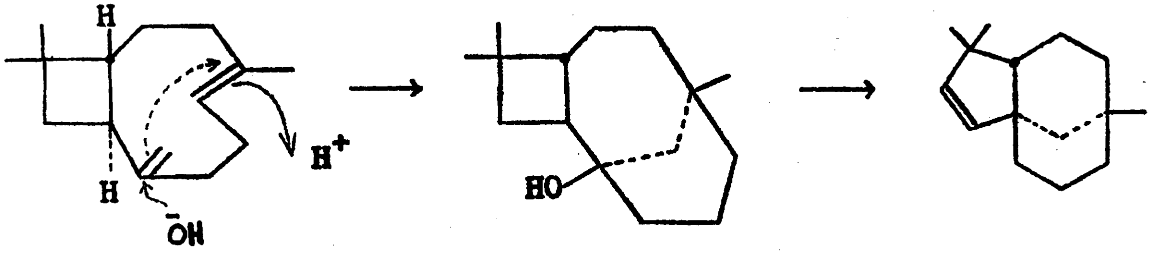
(64)



(65)



(66)



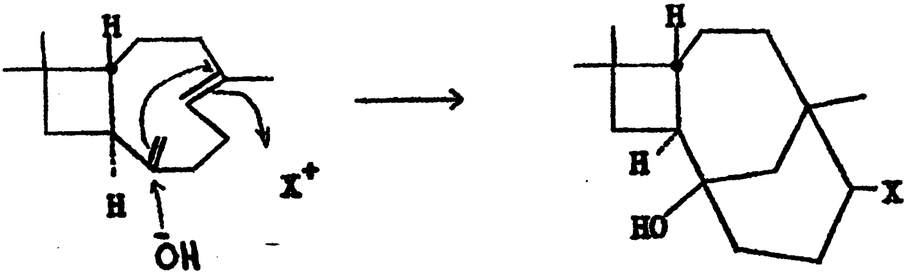
(67)

(58)

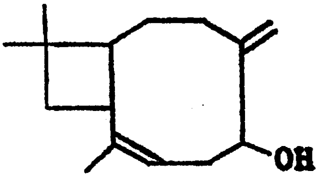
absolute stereochemistry (64) or (65) (where R and R^1 are alkyl or part of a further ring) usually afford positive molecular rotation increments on acylation. The molecular rotation contribution of the secondary hydroxyl group with respect to the parent saturated structure (66) is also, in general, positive. Conversely, parallel negative molecular rotation changes are observed for the epimeric alcohol.

These rules were applied to a number of tricyclic derivatives of caryophyllene, using benzoate and acetyl derivatives, and gave excellent agreement with the calculated changes, assuming the absolute stereochemistries as in (61), (62) and (63). Since the constitution and relative stereochemistry of the compounds used had been rigorously established in earlier work, these results confirmed that the correct absolute stereochemistry had been assigned to caryophyllene.

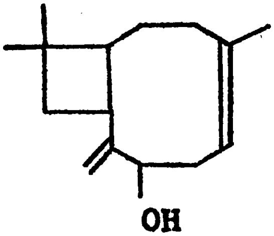
A conformational study of the caryophyllene molecule shows that, because it is trans within a C_9 ring, the endocyclic ethylenic linkage must lie with its plane perpendicular to that of the cyclobutane ring. If the 4-methyl group projects downwards (relative to the upward β-hydrogen at C_1), then only β-attack is possible, which will lead to clovane-type cyclisation as in (67) ---→ (58). If, however, the 4-methyl group projects upwards, only α-attack is possible, leading to caryolane



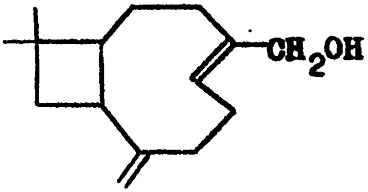
(68) (69)



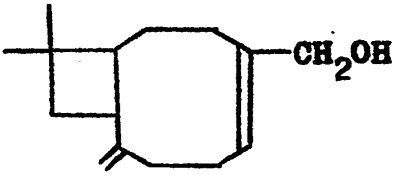
(70)



(71)



(72)



(73)

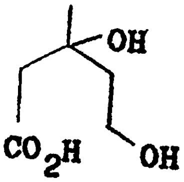
type cyclisation as in (68) ---→ (69). From the above discussion, it is obvious that caryolan-1-ol and clovene belong to different stereochemical classes, and it is not therefore surprising that dehydration of caryolan-1-ol does not give clovene, as might be expected if the configuration of the methylene bridge in both compounds were the same.[58]

SESQUITERPENES WITH MEDIUM SIZED RINGS.

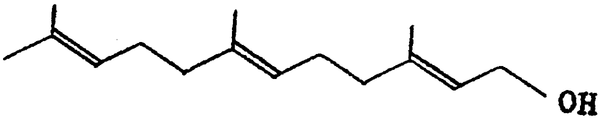
Although caryophyllene was the first sesquiterpene known to have a medium sized ring, it is no longer unique in that respect, and a considerable number are now known.[2] Until recently, however, caryophyllene was the only sesquiterpene known to have a nine-membered ring. A group of related compounds, the betulenols, have since been discovered and investigated, but as yet there is no agreement on the structures of these compounds, Sorm and his co-workers [2,59] proposing the structures (70) and (71) while Treibs and Lossner [60] prefer the structures (72) and (73). The relationship of the betulenols to caryophyllene, however, and the presence of a nine-membered ring has been rigorously established.

BIOGENESIS.

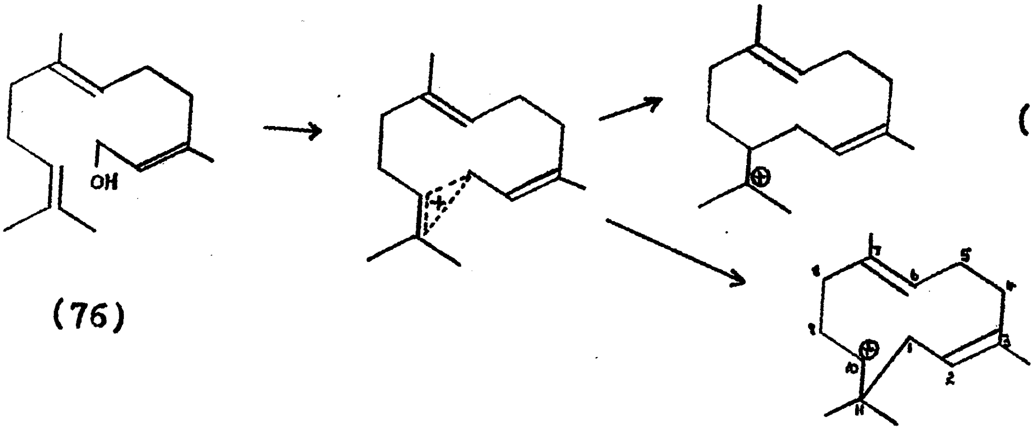
The now accepted isoprenoid unit in terpene biosynthesis is mevalonic acid, (74) three molecules of



(74)



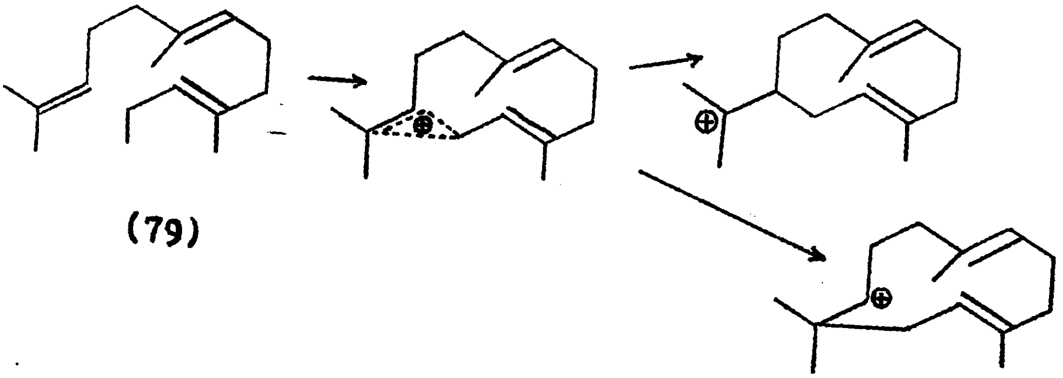
(75)



(76)

(77)

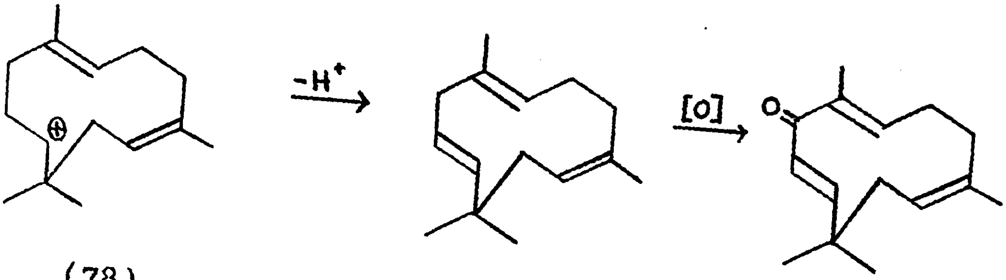
(78)



(79)

(80)

(81)



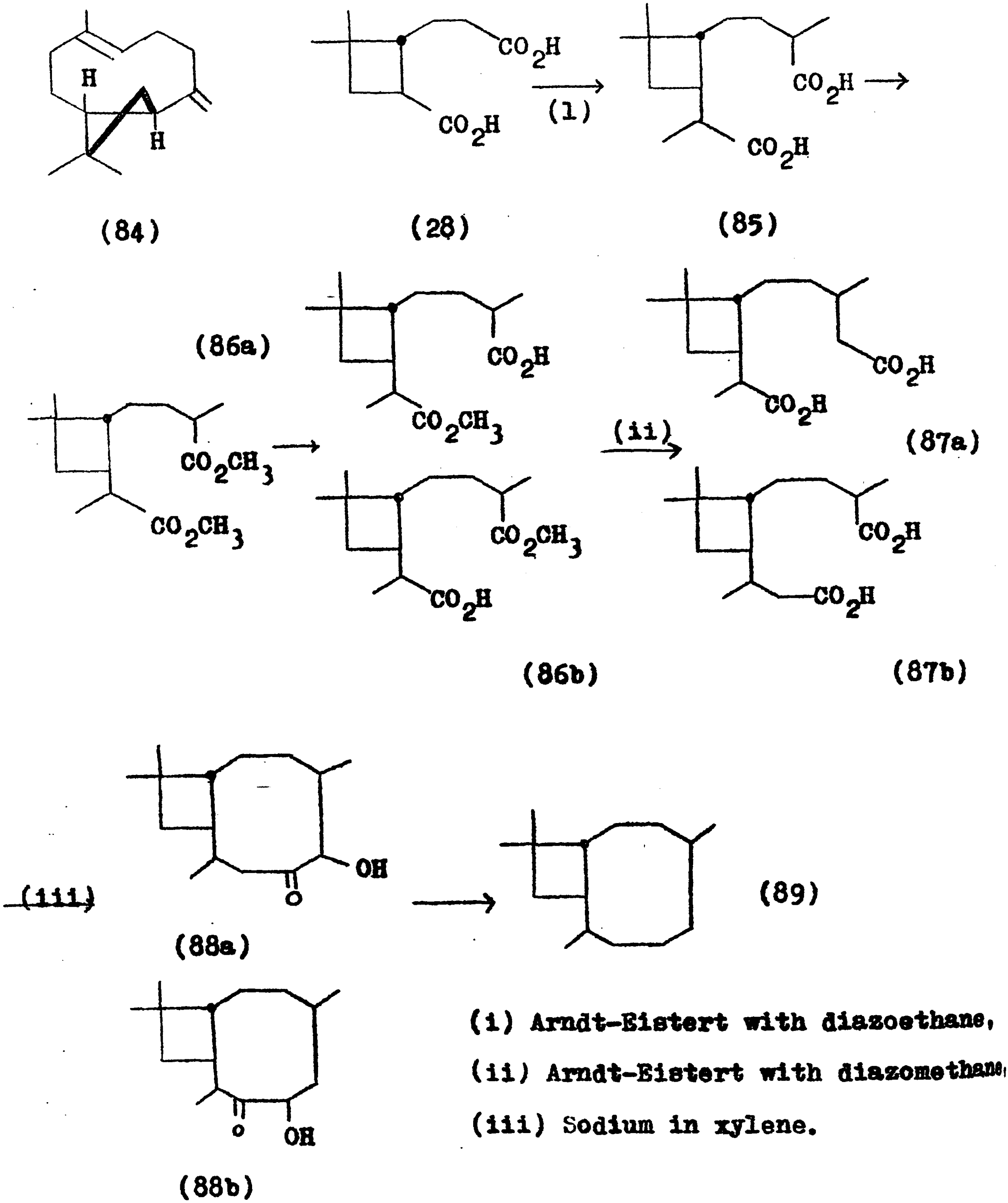
(78)

(82)

(83)

which can self condense with decarboxylation to give the simple acyclic sesquiterpene farnesol (75), which can exist in cis or trans forms. Biogenesis of the sesquiterpenes from farnesol is considered [62] to involve ionisation of the allylic hydroxyl and cyclisation of one of the other double bonds on to the cation thus formed. Thus, starting with cis-farnesol (76), and utilising the terminal double bond in cyclisation, cations (77) and (78) are formed. Similarly, starting with trans farnesol (79), and again utilising the terminal double bond, cations (80) and (81) are formed. [62] The large number of sesquiterpenes which arise through cyclisation involving the terminal double bond can be shown to arise either from cis-farnesol via cation (78), or from trans-farnesol via cation (80), these two cations being the most stable electronically and sterically. Simple deprotonation of cation (78), for example, gives humulene (82), which, with a doubly allylic methylene group, is easily elaborated to zerumbone (83).

From examination of models of cation (78) two facts emerge : (a) the double bonds are not very close together for cyclisation, and (b) one of the hydrogen atoms at C_1 is turned inside the ring, lying somewhere between C_6 and the cationic C_{10}. Neutralisation of the cis cation can occur by attack of one of the double bonds on the C_{10} cation. The Δ^{6-7} bond, however, is blocked by the C_1



(i) Arndt-Eistert with diazoethane,

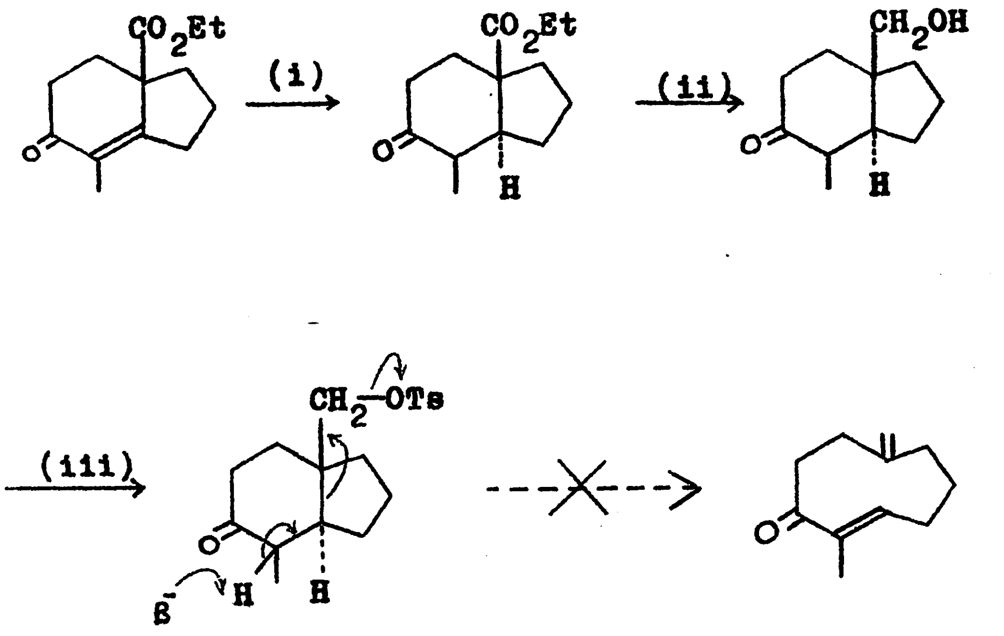
(ii) Arndt-Eistert with diazomethane,

(iii) Sodium in xylene.

hydrogen atom, and attack is only possible with the Δ^{2-3} double bond which, with a concerted loss of hydrogen from the C_3 methyl group, yields caryophyllene (84) directly. The known stereochemistry of caryophyllene, i.e. a trans-fused four membered ring and a trans double bond at C_{6-7}, is a direct consequence of the conformation of cation (78).

SYNTHESIS IN THE CARYOPHYLLENE FIELD.

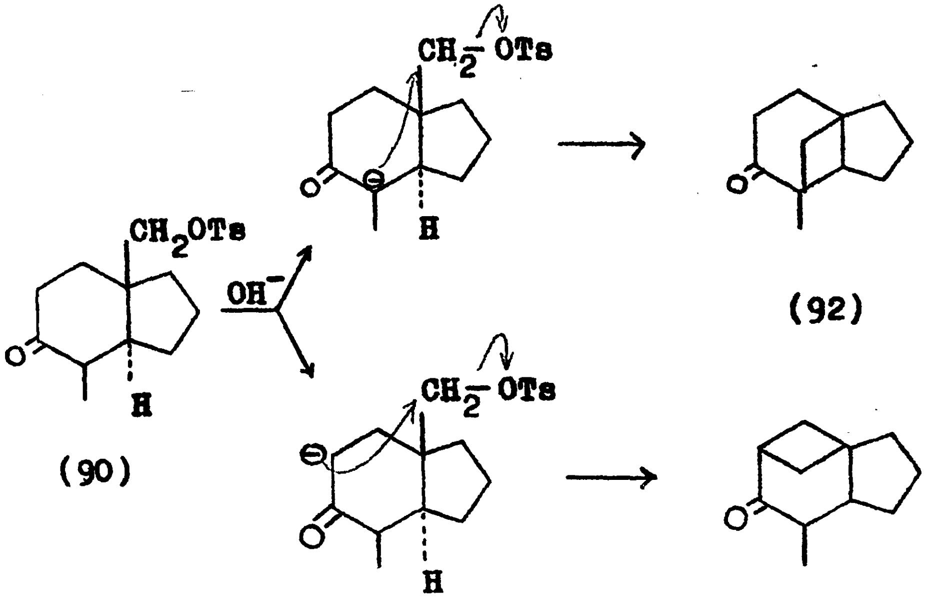
The synthesis of caryophyllane by Sorm and his co-workers [63] is the only synthesis of a caryophyllene type molecule which has been reported so far. Using as starting material pure transhomocaryophyllenic acid obtained from the degradation of caryophyllene, they treated the di-acid chloride under Arndt-Eistert conditions to give the di-acid (85). Conversion to the dimethyl ester and half hydrolysis gave a mixture of acids (86a) and (86b) which was again treated under Arndt-Eistert conditions to give the mixture of acids (87a) and (87b). Treatment of the dimethyl esters with sodium in xylene gave a mixture of acyloins (88a) and (88b) which, on modified Clemmensen reduction,[64] gave as final product perhydrocaryophyllene (89). According to these workers, the identity of the synthetic sample was established by infra-red studies and by comparison of the infra-red spectrum with that of a sample prepared by the catalytic reduction of caryophyllene. They do not, however, mention any separation of isomers,



(90)

(91)

(i) H_2/Pd, (ii) $LiAlH_4$, (iii) TsCl in pyridine.



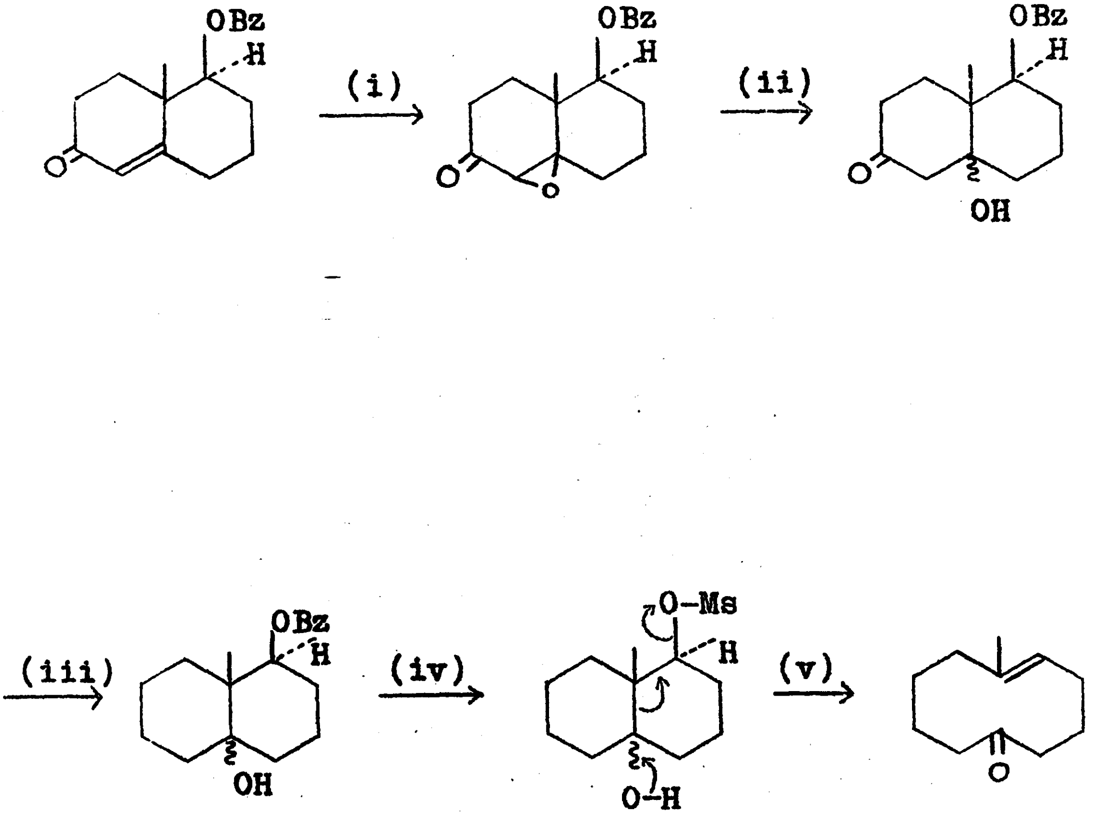
(92)

(90)

(93)

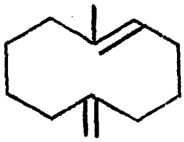
which would be expected from such a hydrogenation of caryophyllene, so that the absolute identity of these infra-red spectra is questionable. The same possibility of error may be present in their work on the betulenols, where once again they rely heavily on infra-red studies, and at the moment much of the infra-red work of Sorm and his school is subject to serious criticism.[65]

Apart from the synthesis of caryophyllane, no other attempted syntheses of caryophyllene-type molecules have been reported. The little information that has been published indicates that efforts are being made to synthesise model compounds of eight, nine or ten membered rings with the same distribution of endo-exo double bonds as in caryophyllene, since this is one of the main problems in a synthesis of the terpene itself. The nature and position of the double bonds (1:5) are such that the standard synthetic methods for medium sized rings are prohibited. As a result, a more promising approach would seem to lie in the application of so-called " fragmentation reactions "[66] in which some suitable bicyclic system is elaborated to give the medium sized carbocycle. In one of the first recorded approaches to the nine-membered of caryophyllene,[67] the tosylate (90) was synthesised as shown and treated with base in an attempt to obtain the compound (91). This compound was not obtained, however, and the products were established as the tricycloketones



(94)

(95)



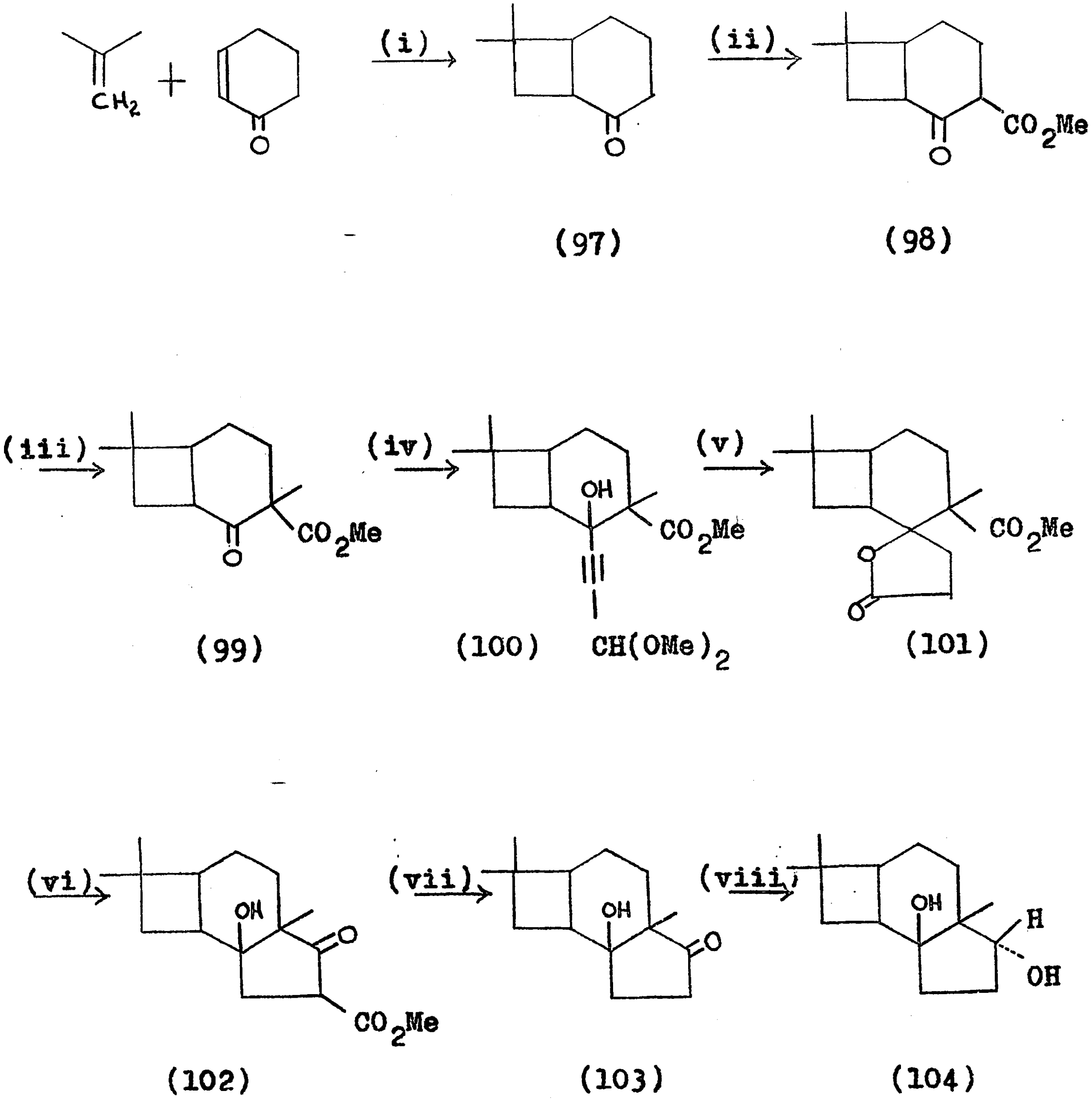
(96)

(i) H_2O_2/alk., (ii) $H_2N.NH_2$/MeOH/H^+, (iii) Zn/Hg/HCl, (iv) OH^- then CH_3SO_2Cl, (v) KO<u>t</u>-Bu in HO<u>t</u>-Bu.

(92) and (93).

A successful synthesis of 1-methylcyclodec-1-ene-6-one (95) has been reported by Wharton,[68] who synthesised the mesylate (94) as shown. When treated with base, this mesylate underwent a 1:3-elimination reaction to give the decanone (95) which could, if required, be converted to the hydrocarbon (96). Although the author does not indicate the stereochemistry of the tertiary hydroxyl group, an examination of models reveals that the cis configuration is more sterically favourable for elimination than the trans (although the extent to which the steric conditions control these reactions seems to vary according to the compound).

The main object of the work described in this thesis was to investigate the possibility of elaborating suitable bicyclic systems into medium sized rings for the following reasons : (a) besides being a challenging exercise in synthesis itself, the properties of the bicyclic systems themselves are of interest, (b) any new or amended methods for the synthesis of medium sized rings are of importance, (c) medium sized rings are known to undergo many types of rearrangements and these could be investigated, and (d) successful syntheses of analogues of the nine-membered ring of caryophyllene would be an important basis for a projected synthesis of the terpene itself.



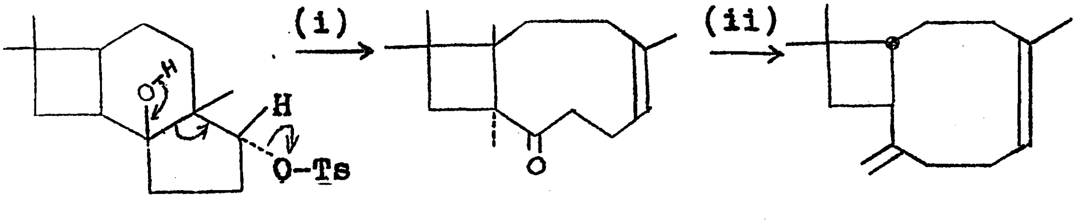
(i) hv/-40°, (ii) $CO(OMe)_2$/NaH/dioxan, (iii) MeI/base, (iv) LiC C.$CH(OMe)_2$, (v) H_2/Pd then CrO_3/HAc, (vi) $CH_3SOCH_2^-$, (vii) OH^-, (viii) $NaBH_4$.

APPENDIX

THE TOTAL SYNTHESIS OF d,l-CARYOPHYLLENE AND d,l-ISOCARYOPHYLLENE.

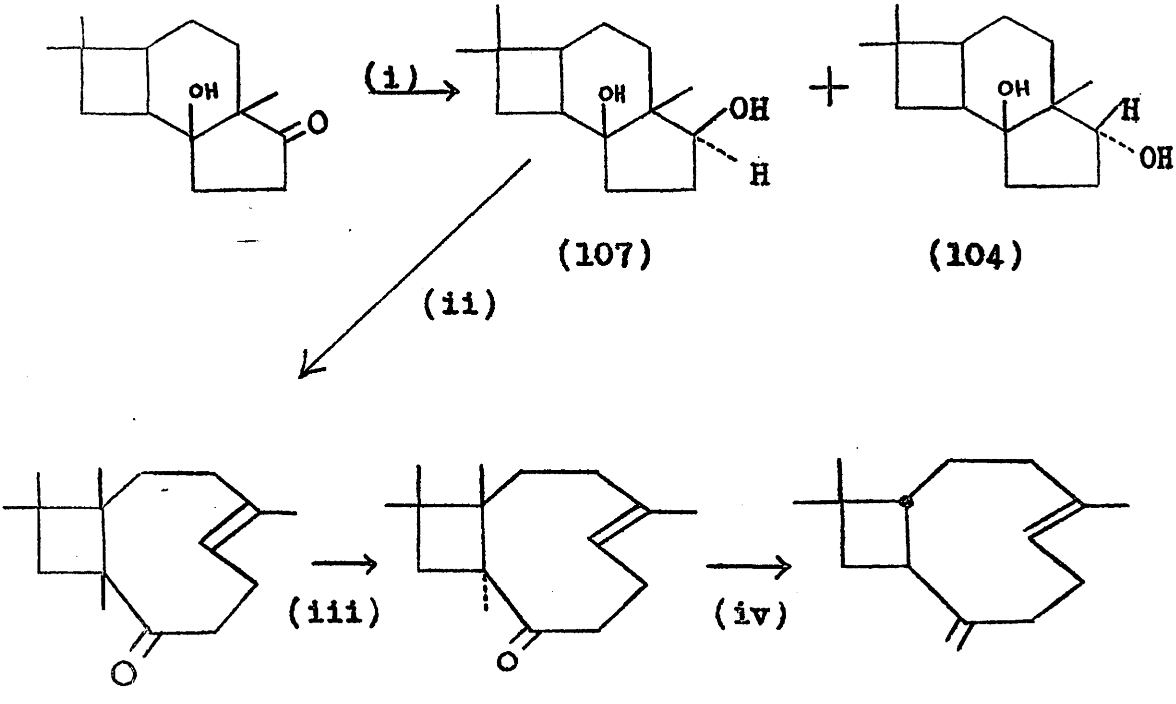
Details of the first total synthesis of d,l-caryophyllene and d,l-isocaryophyllene have been published recently by Corey, Mitra and Uda.[69] Photochemical addition of isobutylene to 2-cyclohexenone gave 7:7-dimethylbicyclo-[4:2:0]-octanone-2 (97) as a mixture of cis and trans forms. The predominant trans form was isomerised to the cis form, and this in turn converted to the β-keto ester (98) by treatment with dimethyl carbonate and sodium hydride in dioxan. Methylation of (98) with methyl iodide in base to the ketone (99) followed by condensation with the lithio derivative of the dimethyl acetal of propargyl aldehyde gave the acetylene (100). Catalytic reduction of the acetylene group and oxidation of the aldehyde with chromic acid was followed lactonisation to the spiro-lactone (101).

Treatment of this lactone with methylsulphinyl carbanion in dimethyl sulphoxide resulted in rearrangement to the tricyclic ketone (102) which was converted to the hydroxy ketone (103) by hydrolysis and decarboxylation. Reduction of this ketone with sodium borohydride, sodium in moist ether or lithium aluminium hydride furnished the trans diol (104) (i.e. methyl and hydroxyl trans).



(105) (106) (47)

(i) CH$_3$SOCH$_2^-$ then BuO$^-$, (ii) Ph$_3$PCH$_2$.



(107) (104)

(108) (109) (46)

(i) H$_2$/Raney nickel, (ii) TsCl/pyridine then CH$_3$SOCH$_2^-$, (iii) NaO*t*-Bu, (iv) Ph$_3$PCH$_2$

Treatment of the monotosylate ester (105) of this diol with methylsulphinyl carbanion resulted in fragmentation of the bicyclic system and the production of the required C_9 ring. The product from this process, as expected, had a cis ring junction, and so it was not isolated, epimerisation to the trans form being effected during the reaction by refluxing with sodium t-butoxide. The final product was the ketone (106), and treatment of this compound with methylene triphenylphosphorane under Wittig conditions gave d,l-isocaryophyllene (47), identical with a genuine sample.

When the tricyclic ketone (103) was reduced with Raney nickel, a mixture of diols was obtained, one of which proved to be the diol (104). The other isomer was assumed to be the cis form (107), and when the monotosylate of this diol was treated with methylsulphinyl carbanion, the trans cycloolefin (108) was obtained, in which the ring junction is cis. Prolonged treatment of this ketone with sodium t-butoxide effected isomerisation to the required trans form (109), which under Wittig conditions, gave d,l-caryophyllene (46), identical with that derived from natural sources.

REFERENCES

1. Ettling, Annalen, 1834, 9, 68.
2. Sorm, Pure and Applied Chemistry, 1961, 2, 533.
3. Aebi, Barton and Lindsey, Chem. and Ind., 1953, 487.
   J., 1953, 3124.
4. Church, J., 1875, 113.
5. Bruhl, Ber., 1888, 21, 163.
6. Deussen, Annalen, 1912, 388, 136. (and references therein). J. prakt. Chem., 1929, (ii), 122, 261. (and references therein).
7. Haarmann, Ber., 1909, 42, 1062, 1910, 43, 1505.
8. Semmler and Meyer, Ber., 1911, 44, 3657.
9. Busse, Abt.d. Wissensch. Chem. Pharm. Ins. Moscow, 1924, 10, 77.
10. Ramage and Simonsen, J., 1935, 1581.
11. Deussen and Hacker, J. prakt. Chem., 1927, (ii), 117, 273; 1929, (ii), 122, 261.
12. Ruzicka, Bardhan and Wind, Helv. Chim. Acta, 1931, 14, 423.
13. Evans, Ramage and Simonsen, J., 1935, 532.
14. Ramage and Simonsen, J., 1934, 1806.
15. Rydon, J., 1936, 593; 1937, 1340.
16. Barton, J. Org. Chem., 1950, 15, 457.
17. Ramage and Simonsen, J., 1936, 741.
18. Ruzicka, Chem and Ind., 1935, 54, 509.

19. Ramage and Simonsen, J., 1937, 73.

20. Ruzicka, Zimmermann and Haber, Helv. Chim. Acta,
1936, 19, 346.

21. Ramage and Simonsen, Chem. and Ind., 1939, 58, 447.

22. Rydon, Chem. and Ind., 1938, 57, 123.

23. Ruzicka, Haber, Plattner, Deshapande and Studer,
Helv. Chim. Acta, 1939, 22, 716.

24. Ramage and Simonsen, J., 1938, 1208.

25. Treibs, Chem. Ber., 1947, 80, 56.

26. Rydon, J., 1939, 537.
Naves and Perrottet, Helv. Chim. Acta, 1941, 24, 789.
Treibs, Chem. Ber., 1938, 71, 1794.
Ruzicka et. al., Helv. Chim. Acta, 1939, 22, 716.

27. Rydon, J., 1939, 537.
Naves and Perrottet, Helv. Chim. Acta, 1941, 24, 789.
Treibs, Chem. Ber., 1947, 80, 56.

28. Dawson and Ramage, J., 1950, 3523.

29. Campbell and Rydon, Chem. and Ind., 1950, 312.
J., 1953, 3002.

30. Dawson and Ramage, J., 1951, 3382.

31. Sorm, Dolejs and Pliva, Coll. Czech. Chem. Comm.,
1950, 15, 186.

32. Barton and Lindsey, Chem. and Ind., 1951, 313.
J., 1951, 2988.

33. Dawson and Ramage, Chem and Ind., 1951, 461.

34. Ramage and Whitehead, J., 1954, 4436.

35. Atwater and Reid, Chem. and Ind., 1953, 688.

36. Prelog, Schenker and Gunthard, Helv. Chim. Acta, 1952, 35, 1602.

Prelog, Schenker and King, Helv. Chim. Acta, 1953, 36, 471.

37. Ramage and Whitehead, J., 1954, 4336.

Barton and de Mayo, Quart. Rev., 1957, 189.

38. Aebi, Barton, Burgstahler and Lindsey, J., 1954, 4659.

39. Ruzicka and Zimmermann, Helv. Chim. Acta, 1935, 18, 219.

40. Ruzicka, Plattner and Balla, Helv. Chim. Acta, 1941, 24, 1219.

41. Adler, Pascher and Smitz, Ber., 76B, 1943, 27.

42. Plattner and Werner, Helv. Chim. Acta, 1944, 27, 1010.

43. Ruzicka, Plattner and Werner, Helv. Chim. Acta, 1943, 26, 966.

44. Nickon, J. Amer. Chem. Soc., 1955, 77, 1190.

45. Robertson, Kerr and Henderson, J., 1925, 1944; 1926, 62.

46. Halsall and Theobald, Quart. Rev., 1962, 101.

47. Barton, Bruun and Lindsey, Chem. and Ind., 1951, 910.

J., 1952, 2210.

48. Robertson and Todd, Chem and Ind., 1953, 431.

J., 1955, 1254.

49. Wallach and Walker, Annalen, 1892, 271, 285.

50. Applequist and Roberts, Chem. Rev., 1954, 54, 1065.

51. Bell and Henderson, J., 1930, 1971.

52. Eschenmoser and Gunthard, Helv. Chim. Acta, 1931, 14, 570.

53. Lutz and Reid, Chem. and Ind., 1953, 749.
J., 1954, 2261.

54. Nickon, Perfumery Essent. Oil Record, 1954, 154.

55. Clunie and Robertson, Proc. Chem. Soc., 1960, 82.

56. Barton and Nickon, J., 1954, 4665.

57. Klyne and Stokes, J., 1954, 1979.
Stokes and Bergmann, J. Org. Chem., 1952, 17, 1194.
Mills, Chem. and Ind., 1953, 212.

58. Lutz and Reid, Chem. and Ind., 1953, 437.
J., 1954, 2265.

59. Sorm, Holub, Herout, and Horak, Coll. Czech. Chem. Comm., 1959, 24, 3730.

60. Treibs and Lossner, Chem. Ber., 1960, 634, 124.

61. Ruzicka, Experientia, 1953, 9, 357.

62. Hendrickson, Tetrahedron, 1959, 7, 82.

63. Sorm, Jarolim, Streibl and Dolejs, Coll. Czech. Chem. Comm., 1957, 22, 1277.
Chem. and Ind., 1957, 154, 1956.

64. Prelog, Schenker and Gunthard, Helv. Chim. Acta, 1952, 35, 1598.

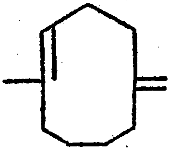
65. Private communication from Dr. G. Eglinton, University of Glasgow.

66. Grob, " I.U.P.A.C. Kekule Symposium ", Butterworths, London, 1959, p.114.

67. Brown, Ph.D. Thesis, University of Columbia.

68. Wharton, J. Org. Chem., 1961, 26, 4781.

69. Corey, Mitra and Uda, J. Amer. Chem. Soc., 1963, 85, 362.

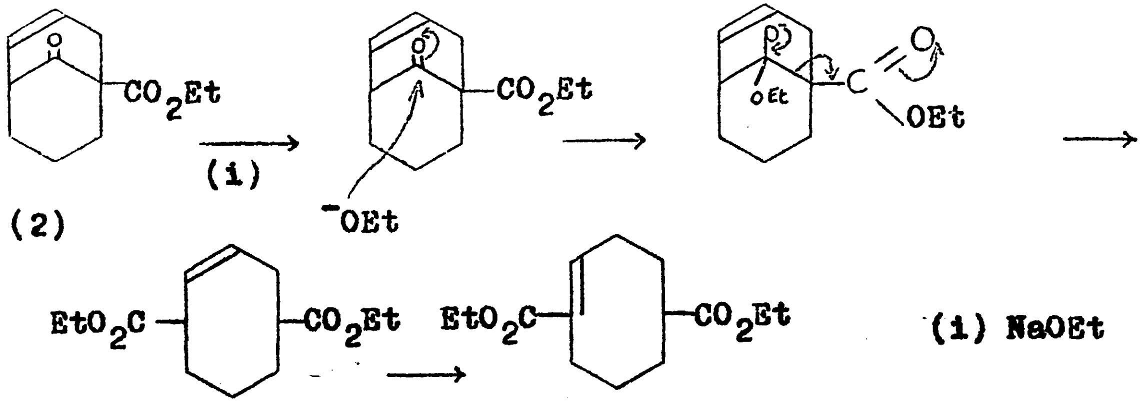


(1)

THE SYNTHESIS OF 1-METHYL-5-METHYLENECYCLOOCT-1-ENE AND 1-METHYL-5-METHYLENECYCLONON-1-ENE.

When studied from the point of view of synthesis, caryophyllene at first sight presents a deceptively simple problem. A more detailed examination, however, quickly reveals that this hydrocarbon incorporates three structural features which, taken together, exclude completely any synthesis along classical lines. These are: (1) the largely stereochemical problem of the trans-fused bicyclo- (7:2:0)-system, (2) the nine-membered carbocyclic ring with its 1:5-distribution of endo-exo double bonds, and (3) the stereochemical complication of the endocyclic trisubstituted double bond lying trans within a C_9 ring. Of these three factors, it was felt that the synthesis of the medium sized ring might prove the greatest obstacle in any planned synthesis of the terpene itself, and accordingly a synthesis of the monocyclic model compound for caryophyllene, viz. 1-methyl-5-methylenecyclonon-1-ene (1) was undertaken.

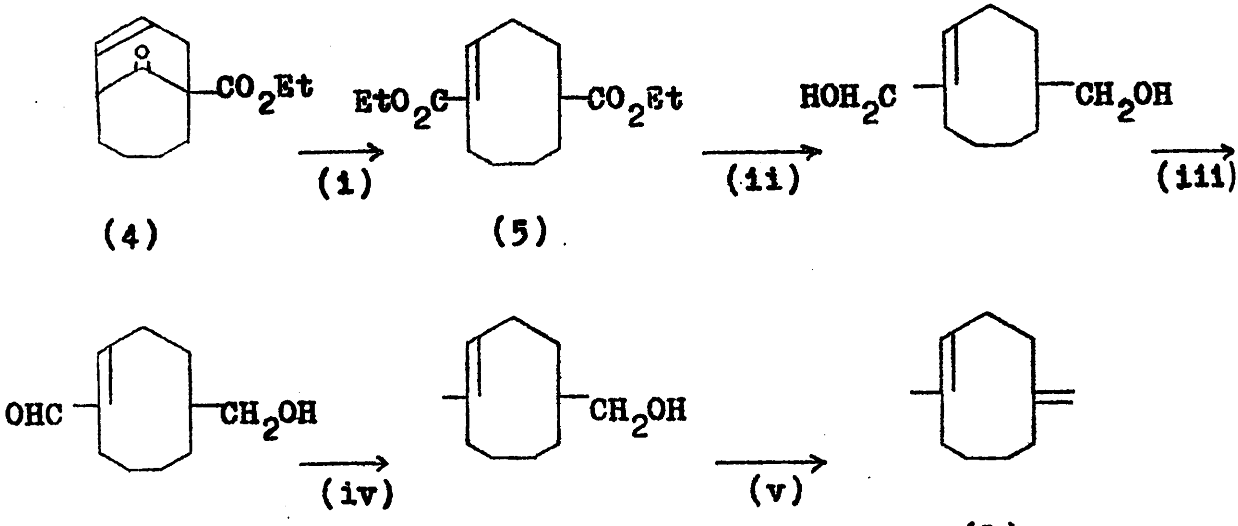
As mentioned previously, the use of some "fragmentation reaction" seems to offer a convenient method for the synthesis of medium sized carbocycles, some of which, if suitably substituted, might be elaborated to the required model compound (1). One interesting reaction of this type has been reported by Cope[1], in which the readily available α:α-



(2)

(3)

(i) NaOEt

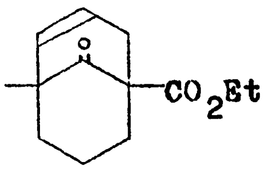


(4)

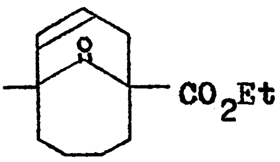
(5)

(1)

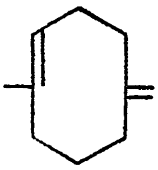
(i) NaOEt, (ii) LiAlH$_4$, (iii) MnO$_2$, (iv) H$_2$N.NH$_2$/NaOEt, (v) acetic anhydride then pyrolysis.



(6)



(7)

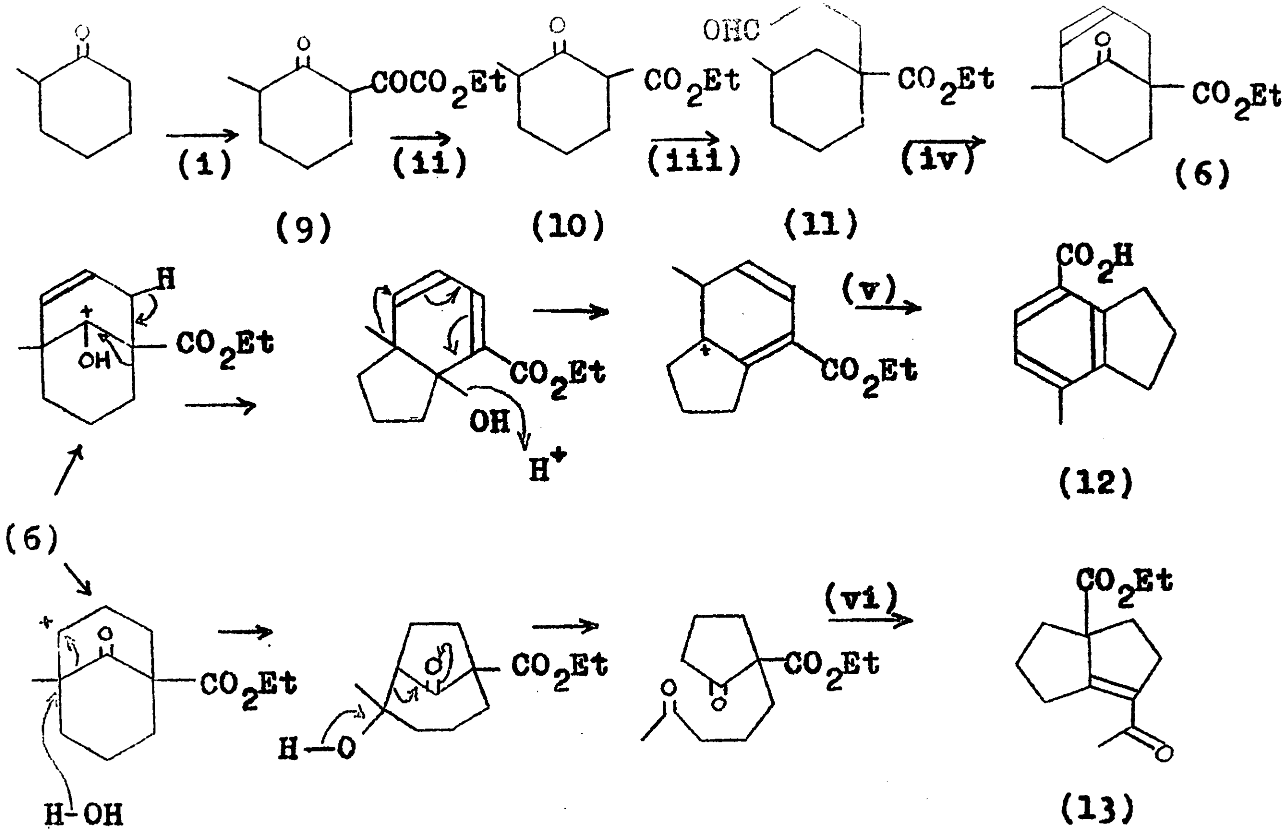


(8)

disubstituted β-keto ester 1-ethoxycarbonylbicyclo-[3:3:1]-non-3-ene-9-one[2] (2) undergoes a reverse acetoacetic ester condensation, (2) ---> (3), to give 1:5-diethoxycarbonylcyclooct-1-ene (3). Were this process to be carried out with the corresponding bicyclo-[4:3:1]-ester (4), then the product would be the cyclononene diester (5), which might be elaborated into the required di-olefin (1) by a route such as (5) ---> (1).

For some time now, however, 1-ethoxycarbonyl-5-methylbicyclo-[3:3:1]-non-3-ene-9-one (6) has been a key synthetic intermediate in this department[3], and its synthesis has been thoroughly investigated. The obvious advantage in having the methyl group already present weighed heavily in favour of using the corresponding bicyclo-[4:3:1]-ester (7) in attempted fragmentation reactions rather than the nor-methyl series. Synthesis of the bicyclo-[4:3:1]-system, however, requires 2-methylcycloheptanone as starting material, and this ketone is difficult and tedious to prepare. Consequently, a further series of model experiments was undertaken using the more readily accessible bicyclo-[3:3:1]-ester (6). In this way it was possible to investigate a number of possible syntheses of the analogous olefin 1-methyl-5-methylenecyclooct-1-ene (8), and, by comparison of the salient features of each, allow a more direct approach to be made to the synthesis of the C_9 model.

Base catalysed condensation of 2-methylcyclohexanone



(9) (10) (11) (6)

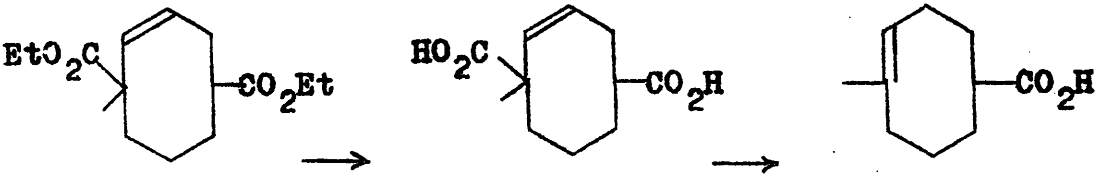
(12)

(6)

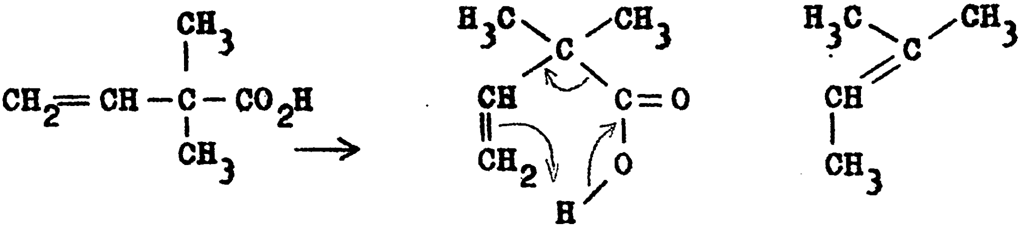
(13)

(i) $(CO_2Et)_2$/NaOEt, (ii) 180°, (iii) CH_2 CHCHO/NaOEt, (iv) H_2SO_4

(v) $-H^+$, hydrolysis, (vi) aldolisation.



(14) (15) (18)

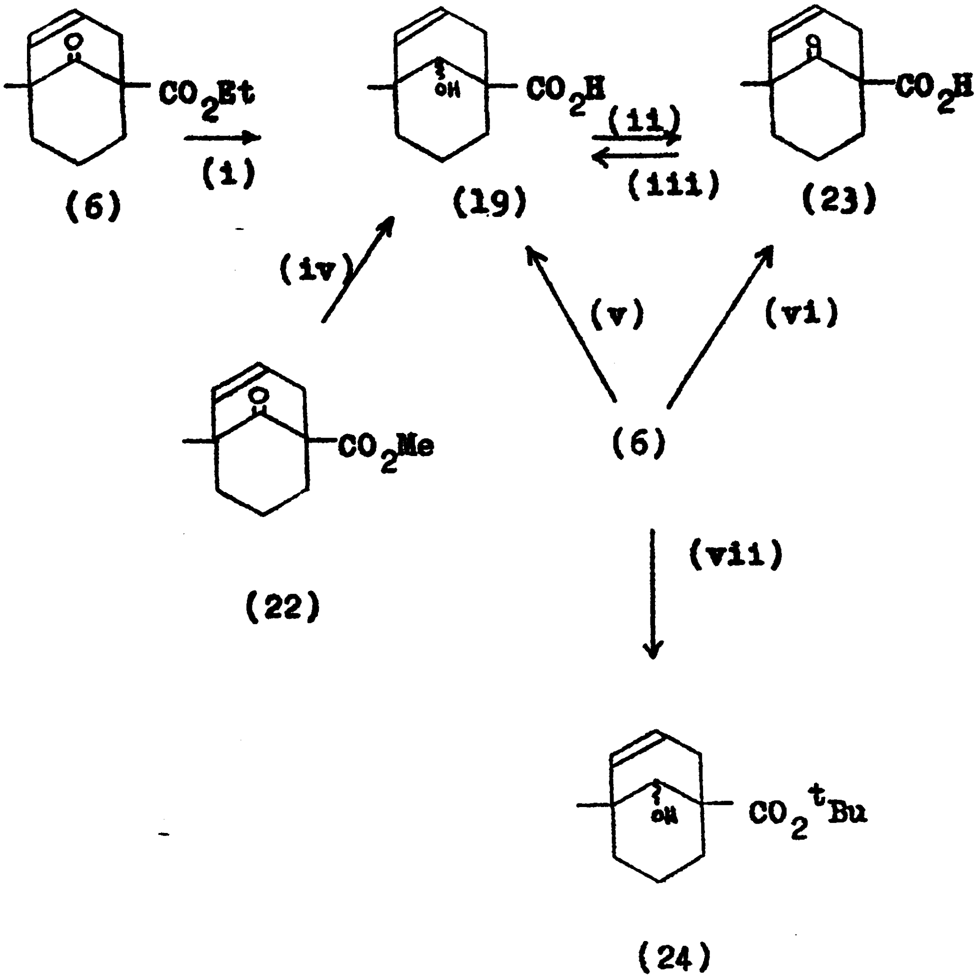


(16) (17)

with diethyl oxalate gave, via the glyoxalate ester (9), 2-methyl-6-ethoxycarbonylcyclohexanone (10). Addition of acrolein under modified Michael conditions[2] furnished the substituted propionaldehyde (11) which, with concentrated sulphuric acid, underwent internal aldolisation followed by dehydration to give a mixture of 1-ethoxycarbonyl-5-methylbicyclo-[3:3:1]-non-3-ene-9-one (6) (45-50%), 7-methylindan-4-carboxylic acid (12) (3-5%), and the ester (13) (5-10%). The components of the reaction mixture are easily separated and the structures and possible modes of formation of the two by-products have been fully elucidated, i.e. (11) ---→ (12) and (11) ---→ (13)[3].

A reverse acetoacetic ester condensation with (6) should furnish 1-methyl-1:5-diethoxycarbonylcyclooct-2-ene (14), concomitant shift of the double bond into conjugation with the ester carbonyl group being in this case prohibited. The corresponding dicarboxylic acid (15), however, has a double bond located $\beta:\gamma$ to a tertiary carboxyl group, and $\beta:\gamma$-unsaturated carboxylic acids are well known to undergo facile decarboxylation with resultant shift of the double bond[4] as in (16) ---→ (17). On this basis, the expected product of decarboxylation of the di-acid (15) is 1-methylcyclooct-1-ene-5-carboxylic acid (18) in which the remaining carboxylic group is properly situated for elaboration to an exomethylene group.

In actual fact, treatment of the ester (6) under the



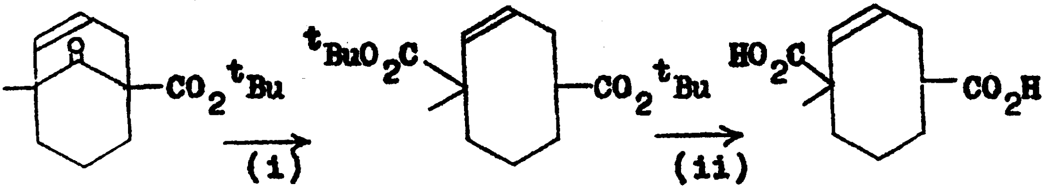
(i) NaOEt/EtOH, (ii) CrO_3, (iii) $NaBH_4$, (iv) NaOMe/MeOH, (v) KOH/EtOH for 3-5 days, (vi) KOH/EtOH for 4-12 hours, (vii) KO^tBu/HO^tBu

Treatment of (6) or (22) with sodamide in xylene gave (19).

conditions described by Cope[1] yielded a crystalline hydroxy acid which was shown to be 5-methyl-9-hydroxybicyclo-[3:3:1]-non-3-ene-2-carboxylic acid (19) by re-oxidation to the keto-acid (23). Formula (19) carries no stereochemical implications, but the same epimer is obtained by borohydride reduction of the keto-acid (23).

Treatment of the corresponding methyl ester (22) with sodium methoxide under the same conditions as were used for the ethyl ester gave the same hydroxy acid (19). A more surprising case of reduction was found with the bicyclic ester (6), for, when treated with potassium hydroxide in ethanol under normal hydrolysis conditions (4-12 hours reflux) the corresponding keto-acid (23) was obtained in good yield. Much longer refluxes, however, (3-5 days), resulted once more in high yields of the hydroxy acid (19). An even more surprising example has been found by another worker in this department[5], who found that treatment of the bicyclic ester (6) with potassium <u>t</u>-butoxide in <u>t</u>-butanol resulted in both reduction of the carbonyl group and alcoholysis of the side chain to give the hydroxy <u>t</u>-butyl ester (24).

In order to avoid reduction of the 9-keto group it was decided to carry out the reaction in a non-reducing medium, and so we employed the Haller-Bauer modification[9], which involves cleavage of non-enolisable β-keto ester or β-diketone systems with sodamide in an inert solvent. Prolonged refluxes were again necessary, and when either the bicyclic ethyl



(25) (26) (15)

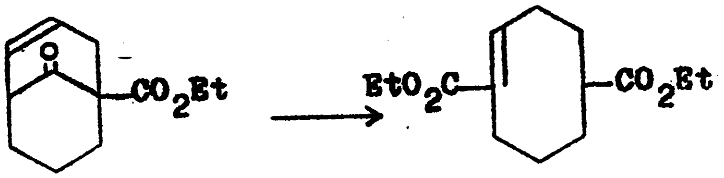
(i) KO^{t}Bu/HO^{t}Bu or NaNH$_2$ in xylene, (ii) OH$^-$.

ester (6) or methyl ester (22) was treated with sodamide in xylene the product was again the hydroxy acid (19), the alkoxide ion liberated in the ammonolysis acting as a reducing agent.

It is obvious from the above results that not only must the reaction be carried out in a non-reducing medium, but that the C_1 carbalkoxy residue must not contain any potential reducing agent. These conditions immediately limited the number of usable compounds to two, namely the keto-acid (23) and the t-butyl ester (25). Accordingly the t-butyl ester (25) was treated with potassium t-butoxide in tbutanol and did in fact undergo a reverse acetoacetic ester condensation to give a poor yield of the cyclooctene di-t-butyl ester (26) which, on hydrolysis, gave the dicarboxylic acid (15).

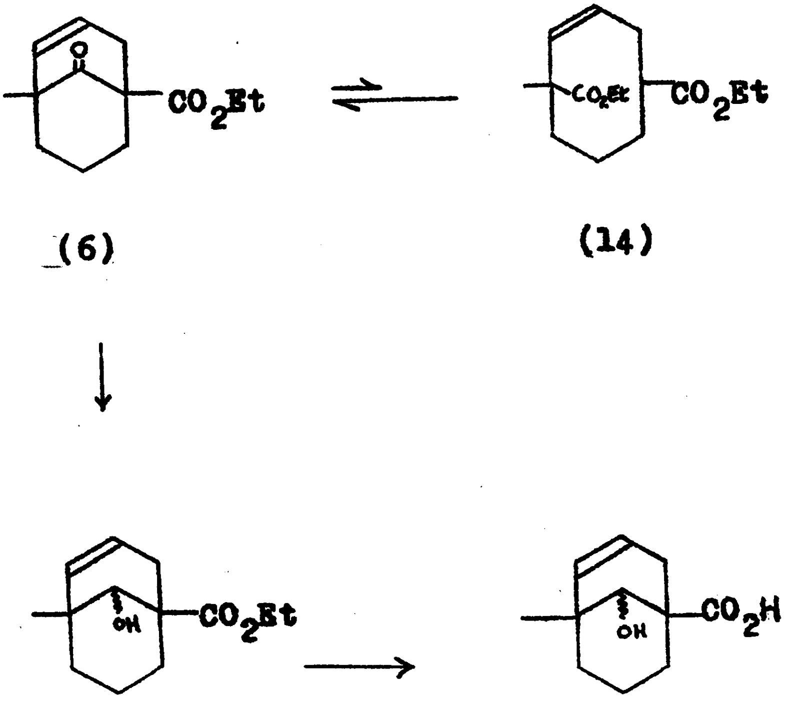
Of the two issues which arise here, namely the reduction of the 9-keto function and the hydrolysis of the ester side-chain, the former is the more unexpected. Hydrolysis of esters under Meerwein - Ponndorf - Verley reduction conditions has been widely observed [6], and in this case is also probably due to the difficulty of maintaining completely anhydrous conditions during the long periods of reflux necessary to achieve completeness of reaction (3 - 6 days).

The Meerwein - Ponndorf - Verley type of reduction of the carbonyl group in the weak reducing media described above is surprising, and at first sight it appears that a bicyclic



(2)

(3)



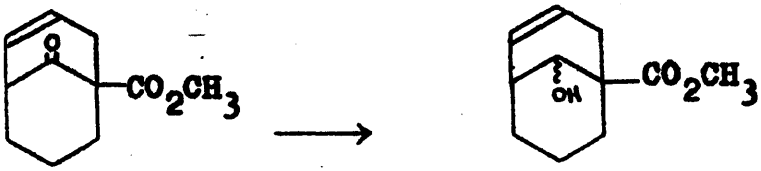
(6)

(14)

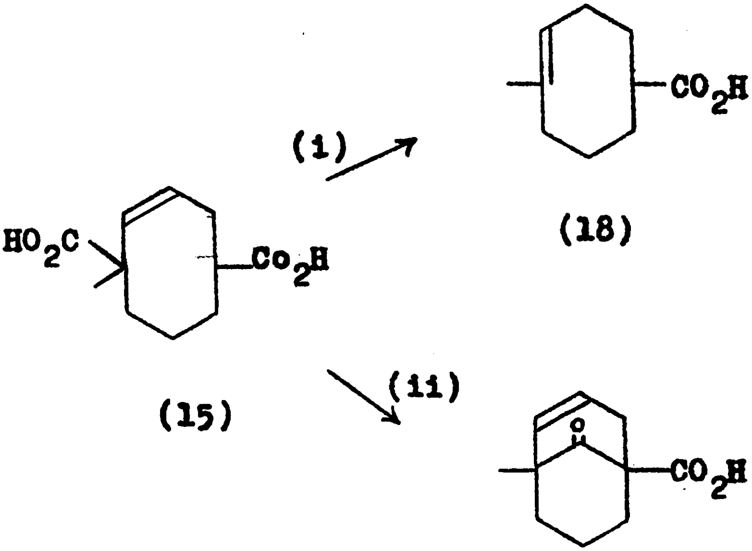
(19)

system carrying a methyl group at the bridgehead (e.g. (6)) is sterically unfavourable to attack by alkoxide ion. An examination of models shows that approach of reagents to the 9-keto function is effectively hindered from all directions, which corresponds with the experimental observations that the keto-ester (6) does not form a semicarbazone or 2:4-dinitrophenylhydrazone, and reacts sluggishly with sodium borohydride or under Clemmensen conditions, several treatments being necessary to achieve complete reduction. The nor-methyl ester (2) used by Cope, on the other hand, allows fairly free access of reagents to the carbonyl group and reacts normally under the above conditions. However the successful ring-opening by t-butoxide invalidates this argument.

It seems more likely that base treatment produces a monocyclic diester (14) which, because of the peculiar geometry of this cyclooctene, can readily recyclise to the bicyclic keto-ester (6). Consequently there will exist an equilibrium (6) $\rightleftharpoons$ (14) which will be disturbed only when some reduction such as (6) $\longrightarrow$ (19) takes place, and this will lead in time to total reduction of the 9-keto function. By comparison, Cope's nor-methyl ester (2) gives the cyclooctene diester (3), whose geometry does not encourage recyclisation. In short, the presence of the bridgehead methyl group prevents the movement of the double bond, which is vital from the point of view of the stability of the product.



(20) (21)



(18)

(15)

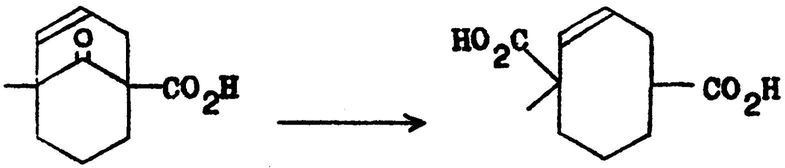
(23)

(i) Cu/quinoline, (ii) 270°.

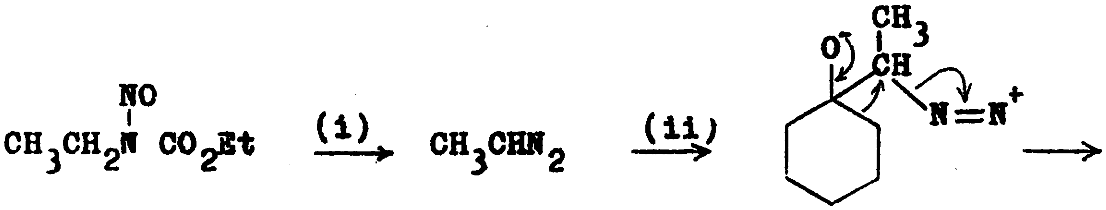
The reduction of non-enolisable β-keto ester and β-diketone systems under similar conditions to those described above has been reported [7], and benzil is known to be reduced to benzoin on treatment with ethoxide or isopropoxide [8]. A further example which closely parallels that discussed above is the reduction of the bicyclo ester (20) to the hydroxy ester (21) on treatment with magnesium methoxide, although in this case the reaction is fairly rapid (16 hours).

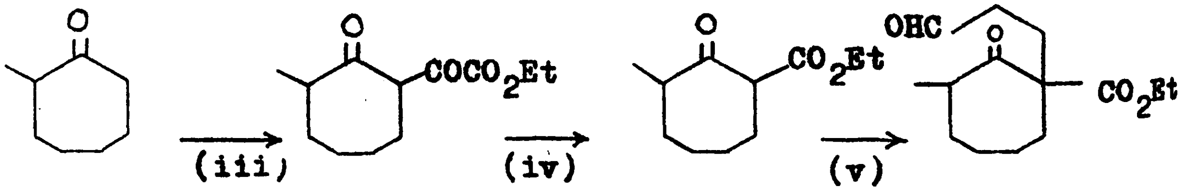
The acid (15) , as expected, underwent decarboxylation smoothly in quinoline to give the required cyclooctene carboxylic acid (18), which was characterised as its amide (q.v.). It is interesting to note that when purely thermal decarboxylation of the di-acid (15) was attempted (heating in a sealed tube) the main product was the bicyclic acid (23). Treatment of the <u>t</u>-butyl ester with sodamide in xylene followed by hydrolysis also gave a poor yield of the required di-acid (15), but neither of these processes were of synthetic use, since the overall yield from bicyclic <u>t</u>-butyl ester to cyclooctene monocarboxylic acid was only of the order of 3 - 8%.

The structure (18) of the monocarboxylic acid is consistent with titration and hydrogenation data, and with its infra-red spectrum (832 cm.$^{-1}$, cis trisubstituted double bond), but a more precise proof will be described later (see page 47).



(23) (15)



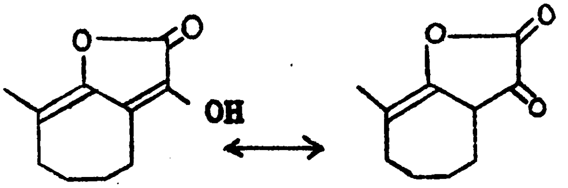


(27) (28) (29) (30)

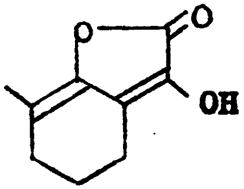
(i) KOH, (ii) cyclohexanone, (iii) $(CO_2Et)_2$/NaOEt, (iv) 200°, (v) CH_2 CHCHO/NaOEt.

The only remaining compound which could be used in this type of reaction, i.e. the keto-acid (23), was in fact treated with sodamide in xylene. The experimental difficulties here proved very great, the sodium salt of the acid precipitating out of solution, thus causing incompleteness of reaction and complicating the isolation of the desired product. Small amounts of the monocyclic di-acid (15) were obtained in this way, but , as in the case of the t-butyl ester, the method had no synthetic value. These shortcomings proved serious objections to the projected synthetic route, and the following observations in the synthesis of the bicyclo-[4:3:1]-system ruled out completely the possibility of using the above scheme to obtain the required C_8 and C_9 carbocycles.

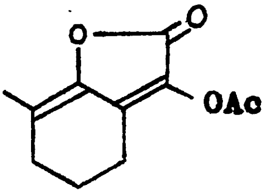
The bicyclo-[4:3:1]-system was synthesised in the same manner as the bicyclo-[3:3:1]-system, 2-methylcycloheptanone (27) being prepared by ring expansion of cyclohexanone with diazoethane [10,11,12,13], and elaborated to the substituted propionaldehyde (30) as before. During the course of one preparation of 2-methyl-7-ethoxycarbonylcycloheptanone (29), however, a mixture of products was obtained, namely the liquid glyoxalate ester (28), and a neutral crystalline solid. The solid product (which was unstable, and rapidly decomposed to a pasty solid and then to an oil) was soluble in base but could be reprecipitated with acid, showing it to be lactonic. The infra-red spectrum showed bands at 3300 $cm.^{-1}$



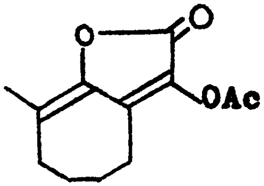
(31A)



(31B)



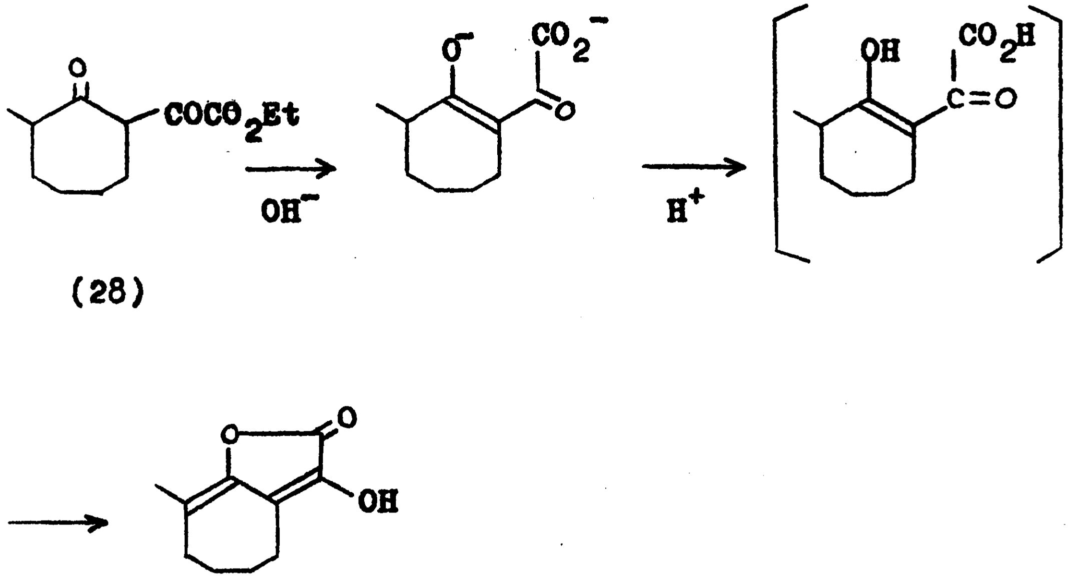
(31C)



(31D)

TABLE I

	(31A)	(31B)	(31C)	(31D)
$\lambda_{max.}$	295	290	285	289
log.ε	4.25	4.28	4.30	4.25

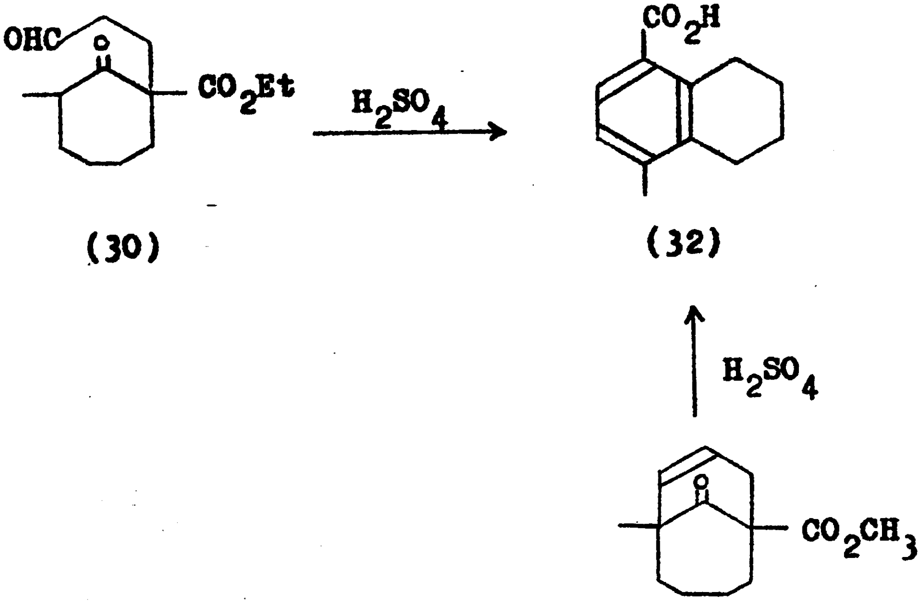


(28)

(31A)

appears quite possible. In the presence of aqueous base, hydrolysis occurs, and the hydroxy acid formed on acidification rapidly lactonises. As a check on the possibility of this mechanism, 2-methylcyclohexanone was condensed with diethyl oxalate using ordinary commercial "absolute" alcohol as solvent. this gave a high yield (60%) of the cyclohexane lactone (31 B) and a low yield of the glyoxalate ester (9), the properties of the lactone (31 B) and its enol- acetate (31 C) being in full agreement with the published data. Many unsuccessful attempts were made to reconvert the lactone (31 A) to the glyoxalate ester (28), but the only useful product which could be obtained from it (in low yield) was 2-methylcycloheptanone.

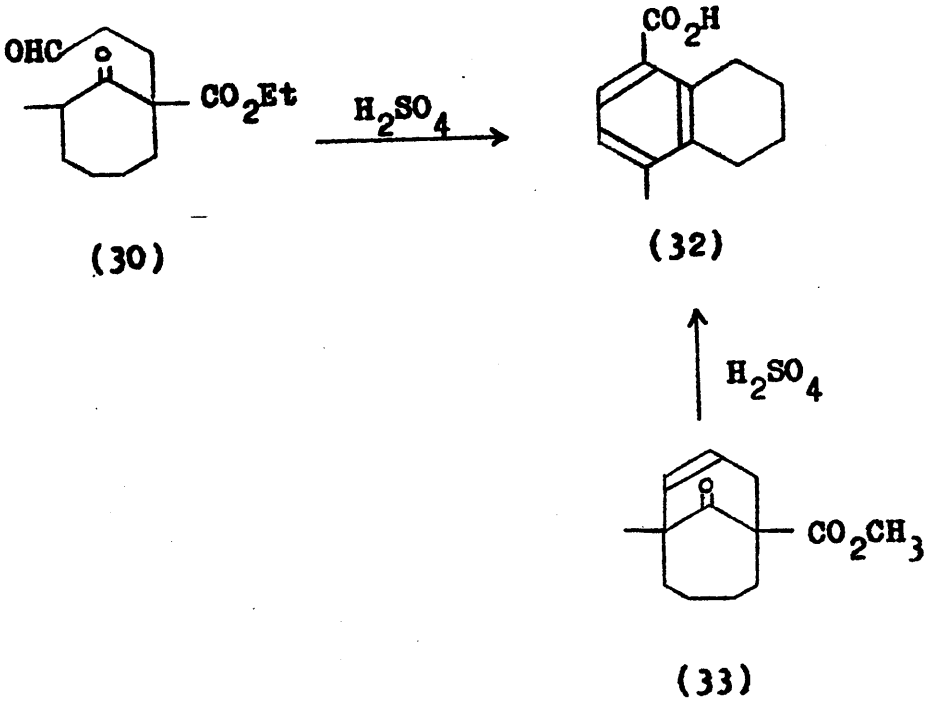
When the substituted propionaldehyde (30) was treated with concentrated sulphuric acid the neutral fraction of the product consisted of a complex mixture of oils which could not be separated, and which showed no evidence of containing any bicyclo-[4:3:1]-material. Many attempts were made to prepare the bicyclo-[4:3:1]-compounds by this method, but all proved unsuccessful. It was at first assumed that the bicyclo-[4:3:1]-olefins were unstable compounds, but the preparation of a number of these compounds by another route showed this assumption to be invalid, the bicyclo-[4:3:1]-series proving to be as stable as the bicyclo-[3:3:1]-series. Investigation of the acidic product from the above reaction, however, yielded a crystalline



(30)

(32)

(33)

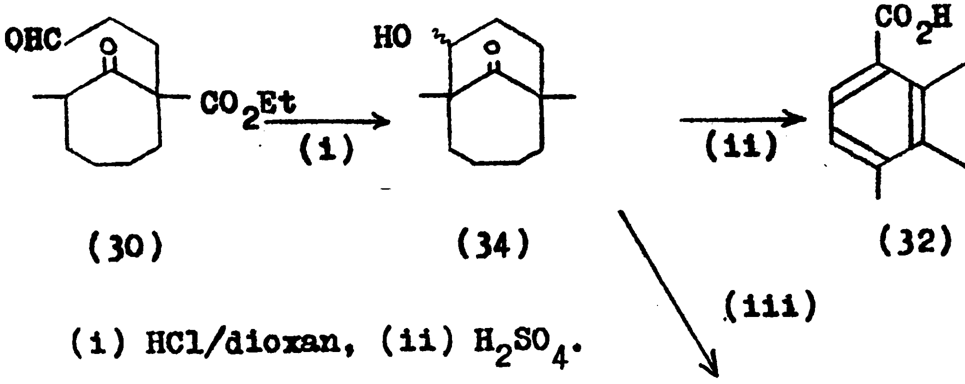


(30) (32) (33)

aromatic acid which, by analogy with the bicyclo-[3:3:1]-series, was assumed to be 5-methyltetralin-8-carboxylic acid (32). The proof of the structure of this compound is discussed later (see p. 42).

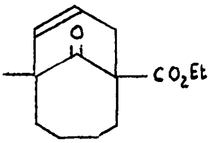
One interesting fact concerning the acidic by-product in the above reaction was the yield - 15-20%, as compared to the bicyclo-[3:3:1]-series, where the yield of 4-methyl-indan-7-carboxylic acid (12) was only 3-5%. The high yield of tetralin carboxylic acid (32) indicated that, although the bicyclo-[4:3:1]-series was stable in itself, the compounds in it were not stable to concentrated sulphuric acid. As a check on this possibility, a genuine sample of the bicyclo-[4:3:1]-ester (33), whose adventitious preparation will be described later (see p.58), was treated with concentrated sulphuric acid. The usual work-up in this reaction gave 25-30% of a crystalline aromatic acid which proved to be 5-methyltetralin-8-carboxylic acid (32), while the neutral product was a highly coloured complex mixture of oils from which neither starting material (33) nor any other bicyclo-[4:3:1]-material could be separated. This result appears to confirm the postulation that the bicyclo-[4:3:1]-compounds are unstable to concentrated sulphuric acid, although a reasonable explanation for this instability is difficult to advance.

The only bicyclo-[4:3:1]-compound which could in fact be prepared from the substituted propionaldehyde (30) was

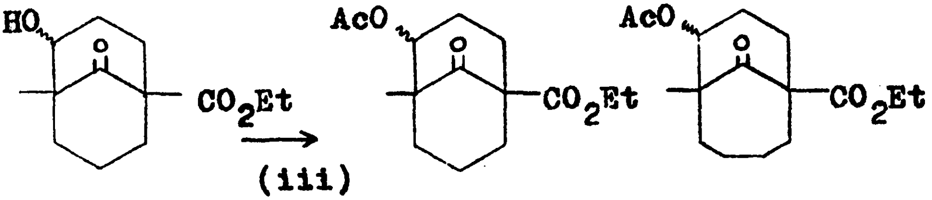


(30) (34) (32)

(i) HCl/dioxan, (ii) H_2SO_4.

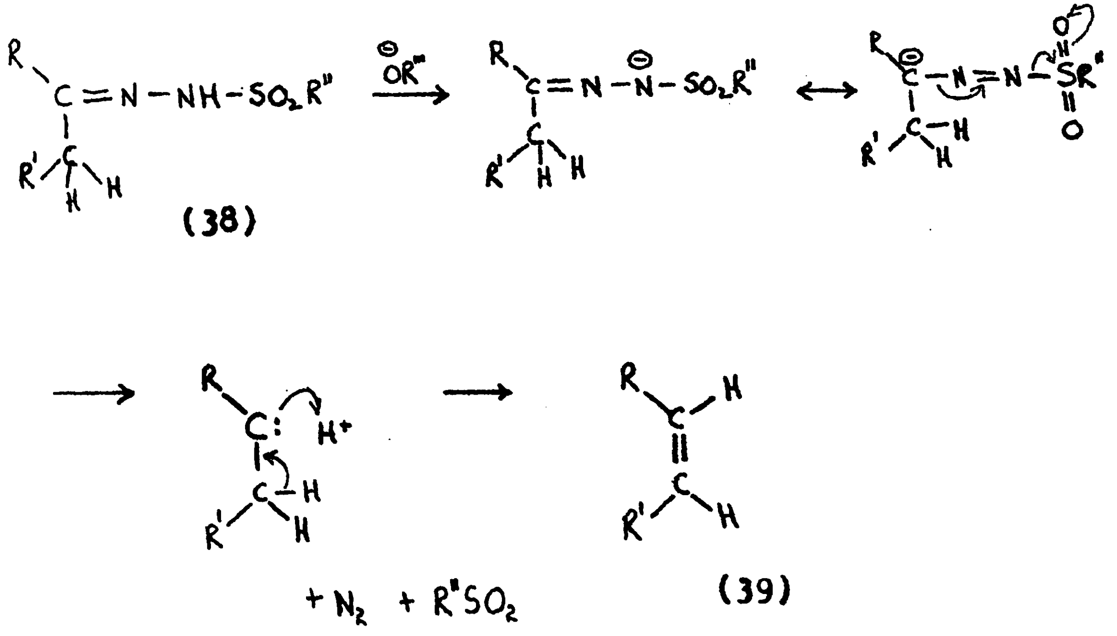


(33A)



(35) (36) (37)

(iii) acetic anhydride in pyridine.

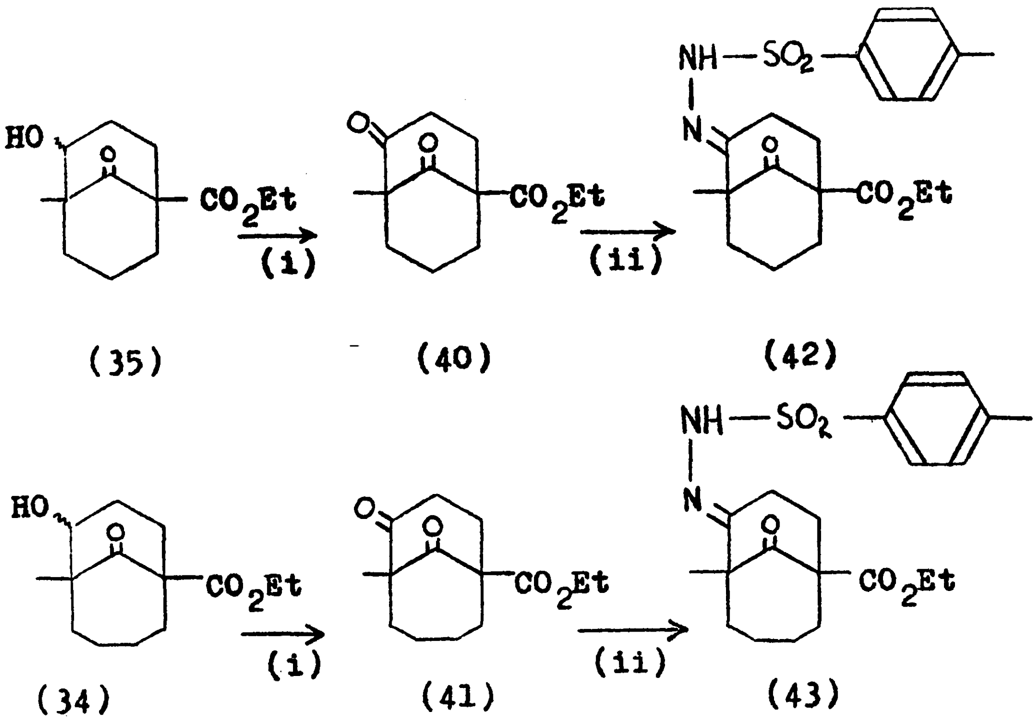


(38) (39)

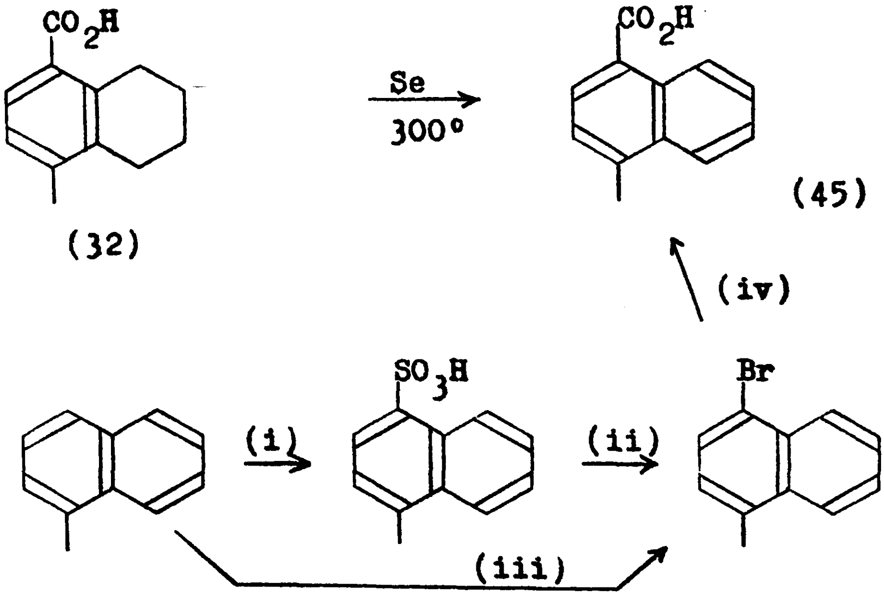
the alcohol (34), obtained as a mixture of epimers by cyclising the aldehyde with hydrochloric acid in dioxan, and some attempts were made to convert this alcohol into the desired olefin (33 A). Dehydration by means of cold concentrated sulphuric acid gave the same product (32) as was obtained direct from the aldehyde (30). Since it had been shown by other workers [17] that the corresponding alcohol (35) in the bicyclo-[3:3:1]-series could not be transformed into the ester (6) by phosphorus oxychloride or by pyrolysis of the carbonate ester, these routes were not investigated.

However an examination of models shows that these bicyclo systems are reasonably mobile, and cis elimination of, e.g. an acetate residue, should be quite feasible, especially since the olefinic product is quite stable. Accordingly, the acetates of both the bicyclo-[3:3:1]- and bicyclo-[4:3:1]-alcohols, i.e. (36) and (37), were prepared and pyrolysed under a variety of standard conditions, but in no instance was any olefinic product obtained, the acetates being recovered unchanged.

The decomposition of toluene-p-sulphonylhydrazones with alkali has been shown to proceed smoothly in many cases with the production of the corresponding olefin in high yield, e.g. (38) ---> (39) [18]. Accordingly, the toluene-p-sulphonylhydrazones (42) and (43) were prepared in both the bicyclo-[3:3:1]- and bicyclo-[4:3:1]-series



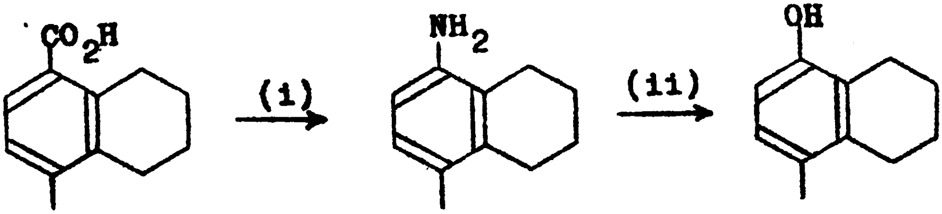
(i) CrO_3, (ii) p-toluenesulphonylhydrazone in ethanol.



(i) H_2SO_4, (ii) Br_2, (iii) Br_2/CCl_4, (iv) Mg/Et_2O, CO_2, H^+.

from the corresponding diketones (40) and (41) respectively, the latter being obtained by chromium trioxide oxidation of the alcohols (34) and (35). Treatment with base, however, gave no olefinic product, the tosyl hydrazones being recovered largely unchanged. It is difficult to explain the uniform lack of success of the above operations, since in no case is there any major obstacle to the known mechanisms of the various reactions.

As mentioned earlier, 5-methyltetralin-8-carboxylic acid (32) was obtained as a by-product in treatment of the aldehyde (30) with sulphuric acid. Analysis and spectral measurements confirmed the postulated structure, the infra-red spectrum showing absorption at 3300-2300 cm.$^{-1}$ (acidic hydroxyl group), 1600 cm.$^{-1}$ (aromatic C $=$ C stretch), and 1700 cm.$^{-1}$ (aromatic carboxyl group), while the ultra-violet spectrum showed absorption of λ_{max} = 242 m.μ. (log ξ = 3.92) and λ_{max} = 284 m.μ. (log ξ = 3.12). This aromatic acid has not been reported, and direct proof was obtained in the following manner. Dehydrogenation with selenium gave a good yield of 1-methyl-4-naphthoic acid (45), which was identical with a sample synthesised by two independent routes as shown in (46) ---→ (47) [19,20] and (48) ---→ (47) [21]. However, aromatisations under such conditions have been known to induce methyl migration, and much more compelling proof was obtained by treatment of 5-methyltetralin-8-carboxylic acid (32) with hydrazoic acid



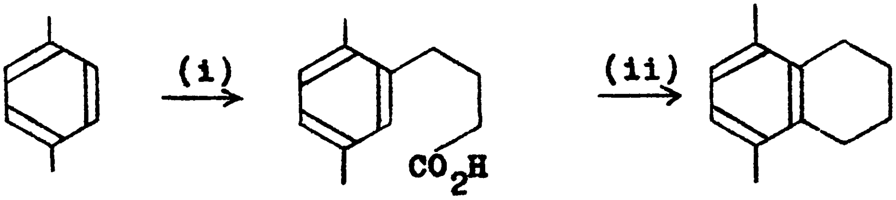
(32) (49) (50)

(i) HN_3, (ii) HNO_2 then hot water.

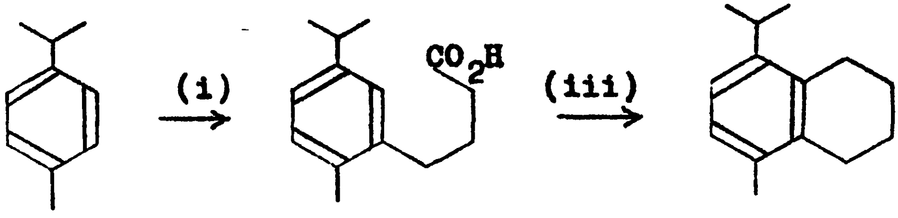
under Schmidt reaction conditions [22], which gave 5-methyl-8-aminotetralin (49) in high yield. The amine was converted via the diazonium salt to 4-methyl-5,6,7,8,-tetrahydronaphthol (50), which was identical with a genuine sample supplied by Professor M.S. Newman [23].

Final proof of the structure of the rearrangement product was obtained by synthesis, although this proved to be more difficult than expected. In the first attempt at synthesis, p-bromotoluene was treated with succinic anhydride under Friedel and Crafts conditions, but the product, a crystalline carboxylic acid, contained no halogen and analysed for $C_{11}H_{12}O_4$. Both the migration of halogen atoms in halobenzenes [24] and the replacement of a halogen by a hydroxyl group [25] are known to be catalysed by aluminium chloride, the former process occurring during the reaction and the latter taking place during the work-up of the reaction mixture. The product from the attempted succinoylation of p-bromotoluene is isomeric with the cresotoyl propionic acids, but its properties are coincident with none of them, and, to date, this compound has not been identified. A number of variations in the reaction conditions and isolation procedure were attempted with both p-bromotoluene and p-chlorotoluene, but the only product which was obtained (70%) was the above unidentified acid.

As an alternative approach, both 5:8-dimethyltetralin

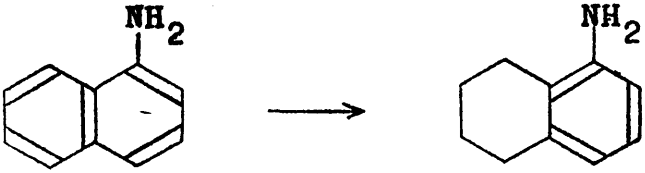


(51) (51B) (52)

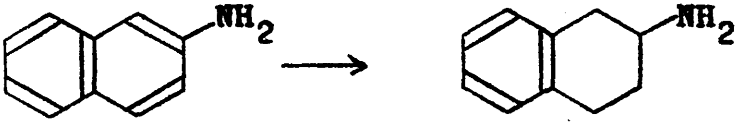


(53) (53B) (54)

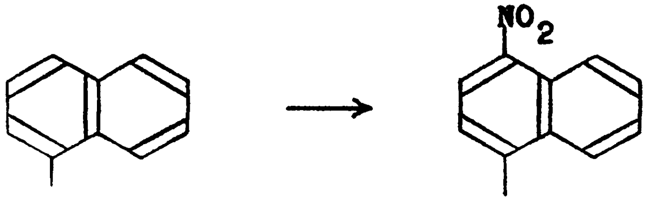
(i) succinic anhydride/$AlCl_3$ then HCl and Zn/Hg, (ii) H_2SO_4 then HCl and Zn/Hg, (iii) $PCl_5/AlCl_3$ then HCl and Zn/Hg.



(55) (56)



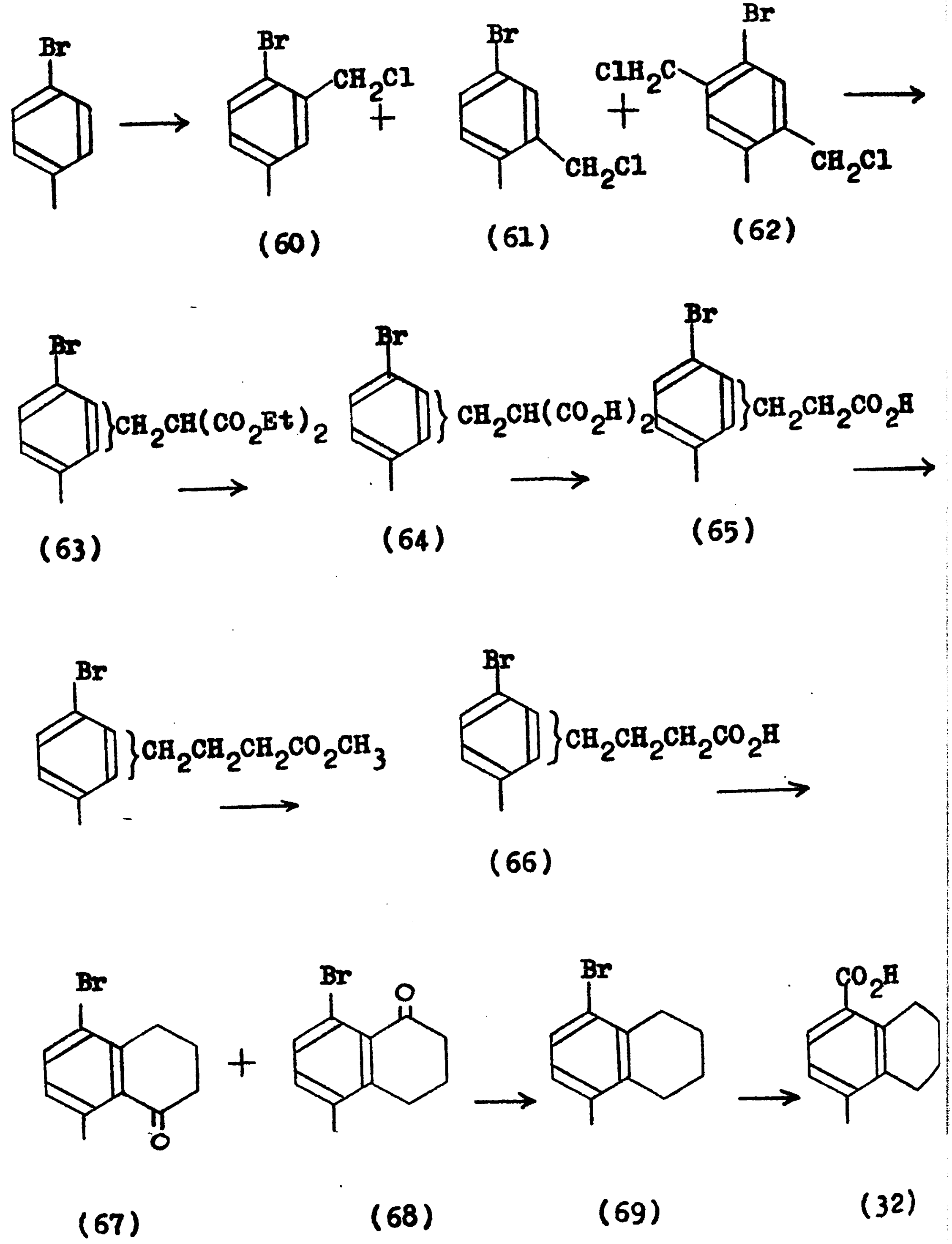
(57) (58)



(59) (59A)

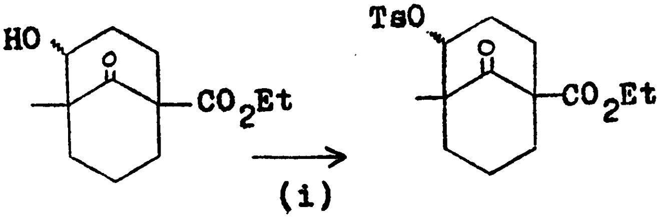
(52) and 5-methyl-8-isopropyltetralin (54) were synthesised in a straightforward manner as shown in (51) ---→ (52) [26] and (53) ---→ (54) [27]. Both p-xylene and p-cymene have been oxidised in high yield, by a variety of methods, to p-toluic acid and it was hoped that the tetralins might also be oxidised to the required tetralin carboxylic acid (32). Many attempts at oxidation were made, using chromyl chloride [28], nitric acid, potassium permanganate, chromium trioxide in acetic anhydride [29], and potassium ferricyanide [30], but all proved unsuccessful, no recognisable acidic product being obtained. It is quite possible that oxidation did not in fact take place at the methyl or isopropyl side chain, but occurred at the reactive benzylic carbon atoms of the saturated ring.

A further synthetic approach was based on the fact that α-naphthylamine (55) can be reduced with sodium in amyl alcohol to give 1-aminotetralin (56), whereas β-naphthylamine (57) under the same conditions gives 6-aminotetralin (58) [31]. The nitration of 1-methylnaphthalene (59), however, is a very vigorous reaction [32], and with technical 1-methylnaphthalene was impossible to control. The yield of crude solid material was very low (15 - 20 %) and the mixture was impossible to separate. With very pure 1-methylnaphthalene (purified via the sulphonic acid) the reaction was controllable, but once again the yield of solid material was low (30%) and the mixture of mono-, di-, and trinitro-

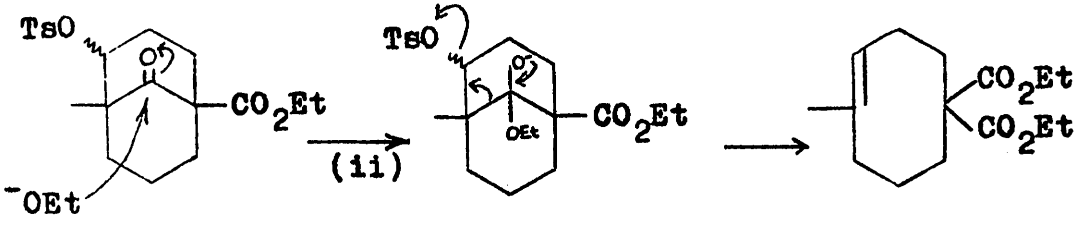

Br
CH2Cl
ClH2C
(60)
(61)
(62)
CH2CH(CO2Et)2
CH2CH(CO2H)2
CH2CH2CO2H
(63)
(64)
(65)
CH2CH2CH2CO2CH3
CH2CH2CH2CO2H
(66)
O
CO2H
(67)
(68)
(69)
(32)

isomers proved very difficult to separate . No further progress was made with this synthesis.

5-Methyltetralin-8-carboxylic acid (32) was finally synthesised as follows. Treatment of pure p-bromotoluene with formaldehyde and hydrogen chloride under Blanc reaction conditions [33] gave a mixture of monochloromethyl derivatives (60) and (61) in the ratio 8:1 = (60):(61), together with 5 - 10% of the dichloromethyl derivative (62). Condensation of the mixture of monochloromethyl derivatives with diethyl malonate gave the corresponding mixture of substituted malonic esters (63), hydrolysis of which with barium hydroxide gave the mixture of acids (64). These could be separated by fractional crystallisation, but it was convenient to decarboxylate the mixture to give the mixed propionic acids (65). Treatment of the mixture of acid chlorides with diazomethane under Arndt - Eistert conditions followed by hydrolysis of the esters so formed gave the substituted butyric acids (66). Cyclisation with aluminium chloride under Friedel - Crafts conditions yielded a mixture of the tetralones (67) and (68) which could also be separated by fractional crystallisation, but the bulk of which was reduced under modified Clemmensen conditions [33] to give the required 5-methyl-8-bromotetralin (69). Carbonation of the Grignard complex of (69), followed by hydrolysis, gave 5-methyltetralin-8-carboxylic acid (32), which was identical with that obtained as a by-product in the bicyclo-[4:3:1]-series.



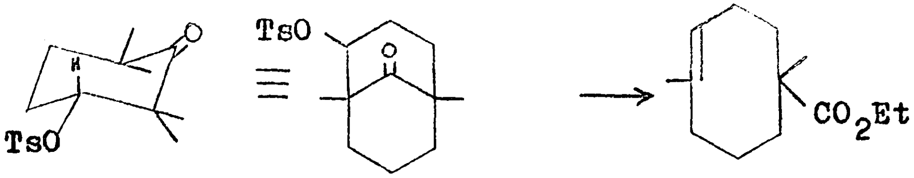
(35) (70)



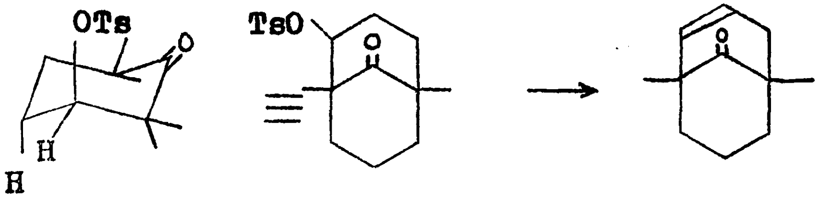
(70) (71)

(i) TsCI/pyridine, (ii) NaOEt in EtOH.

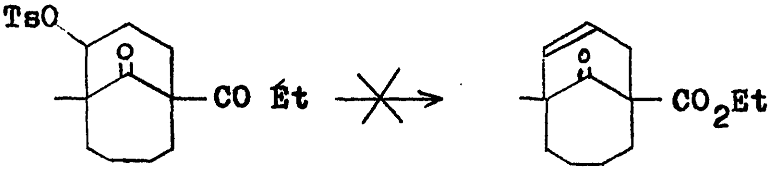
The structure of the aromatic acid having been confirmed, it still remained to find some method by which eight and nine membered rings could be synthesised via bicyclo-[3:3:1]-nonane and bicyclo-[4:3:1]-decane systems. Reverse acetoacetic ester reactions being impossible in the bicyclo-[4:3:1]-system, the only remaining possibility lay in utilising the bicyclo-[4:3:1]-alcohol (34). Working once again with the more readily available bicyclo-[3:3:1]-alcohol (35), treatment with p-toluenesulphonyl chloride in pyridine gave the corresponding tosylate ester (70) as a mixture of epimers. When this mixture was treated with ethoxide a very rapid reaction (2-4 mins.) ensued, sodium p-toluenesulphonate was precipitated, and the product consisted of two neutral products. These were easily separable and one of them was identified as unchanged tosylate (70), presumably the axial epimer. The other proved to be 1:1-diethoxycarbonyl-5-methylcyclooct-4-ene (71), and the mechanism of this fragmentation reaction would seem to involve a simple β-elimination of the tosyloxy group, with formation of a trisubstituted double bond. The alcohol (35) is almost certainly a mixture of axial and equatorial epimers. An examination of models reveals that the equatorial tosylate is suitably aligned to undergo the elimination reaction shown, while the axial tosylate can only undergo an ionic dehydrotosylation to give the olefin. In fact, both of these processes have been demonstrated by



(72) equatorial (73)

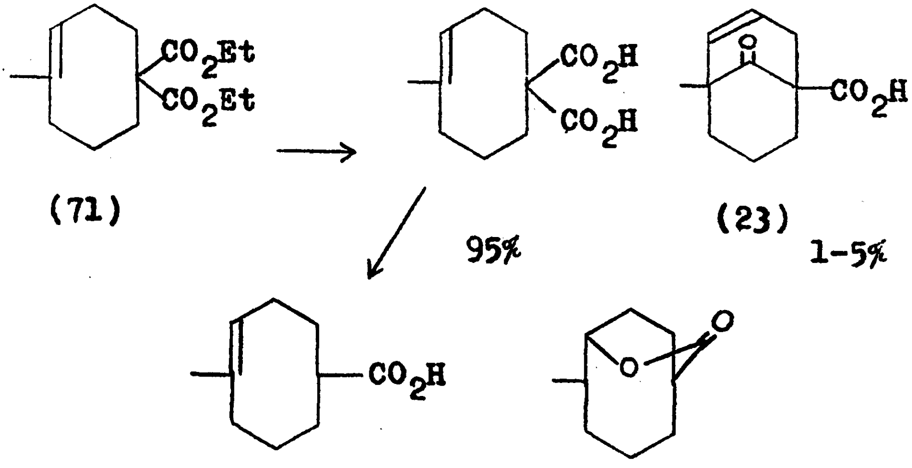


(74) axial (75)



(44) (33A)

axial



(71) (23)

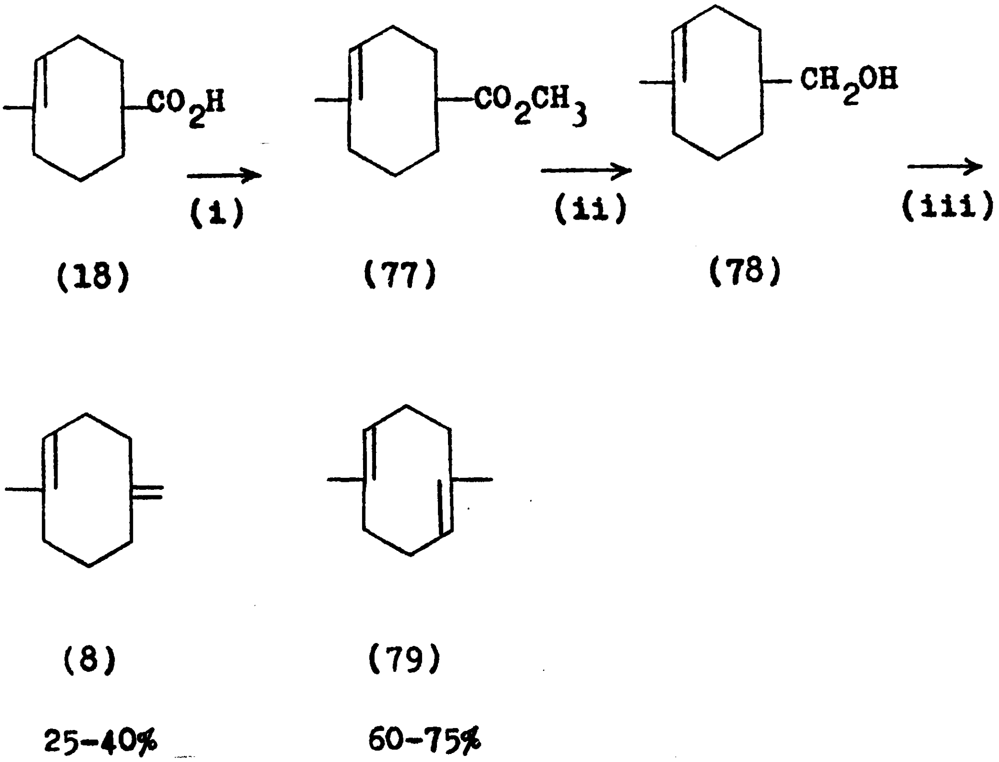
95% 1-5%

(18) (76)

J. Martin [34] in the 1:5-dimethylbicyclo-[3:3:1]-nonane series, where the epimeric alcohols can be easily separated and treated independently, i.e. (72) ---→ (73) and (74) ---→ (75).

Martin also noted that the equatorial tosylate reacted much more rapidly than its axial epimer, and it may be assumed that this holds equally for the tosylate mixture (70). Consequently, it is easy to adjust the experimental conditions to give only one olefinic product, i.e. (71). The by-product must be the unreacted axial tosylate. An unsuccessful attempt was made to convert the crude axial tosylate (44) to the olefin (33A) by the prolonged action of ethoxide, but the compound was returned unchanged.

Hydrolysis and decarboxylation of the cyclooctene diester (71) proceeded fairly smoothly to give the cyclooctene carboxylic acid (18), identical with the product previously described (see page 36). The lactone (76) ($\nu_{C=O}$ = 1735 cm.$^{-1}$) and the bicyclo acid (23) ($\nu_{C=O}$ = 1740 cm.$^{-1}$ and 1705 cm.$^{-1}$) occurred as by-products at this stage. The formation of the lactone (76) is almost certainly a thermal effect, the amount of lactone increasing if a slow fractional distillation of the product is attempted. Base catalysed rearrangement of the cyclooctene diester (71) during hydrolysis is responsible for the production of the bicyclo acid (23), but this and other related rearrangements will be discussed later. The lactone (76) proved almost impossible to separate at this stage,



(18) (77) (78)

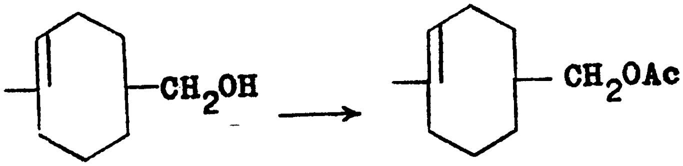
(8) (79)

25–40% 60–75%

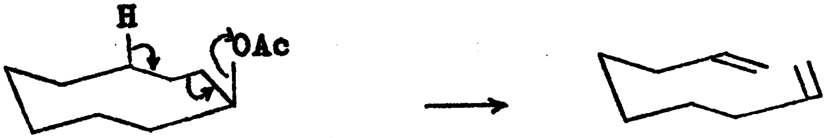
(i) CH_2N_2, (ii) $LiAlH_4$, (iii) H_3BO_3

but its removal was easily effected later in the reaction sequence. The above series of transformations is easily carried out experimentally and the overall yield from the alcohol (35) to the acid (18) is reasonable (30-50%), so that it was possible to investigate fully a number of processes by which the carboxyl group in the acid (18) might be elaborated to an exomethylene group.

Treatment of the acid (18) with diazomethane gave the corresponding methyl ester (77), which, on reduction with lithium aluminium hydride furnished the alcohol (78). The dehydration of alcohols with boric acid is a well known preparative method for olefins,[35] and when the alcohol (78) was distilled from boric acid, dehydration took place in high yield (70-80%) to give the expected mixture of bis-olefins, viz. (8) and (79). Infra-red and nuclear magnetic resonance investigation of the mixture indicated that this method resulted in formation of an exocyclic double bond ($\nu_{c=c}$= 1643 cm.$^{-1}$ and 884 cm.$^{-1}$, N.M.R. showed a doublet at 5.3τ), but it was clear from quantitative infra-red measurements that the exomethylene product was the minor constituent (ε_{884} = 43) whilst the endocyclic isomer was the major constituent (ε_{814} = 38). Analysis of the mixture by gas-liquid chromatography indicated that the exocyclic form (8) was being formed in yields of 25-40%, while the endocyclic form accounted for 60-75% of the mixture. The gas phase chromatogram of this



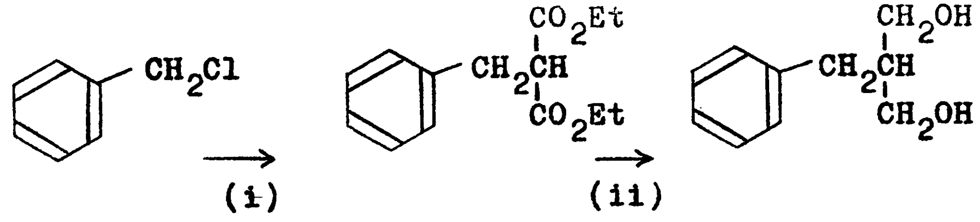
(78) (80)



(81) (82)

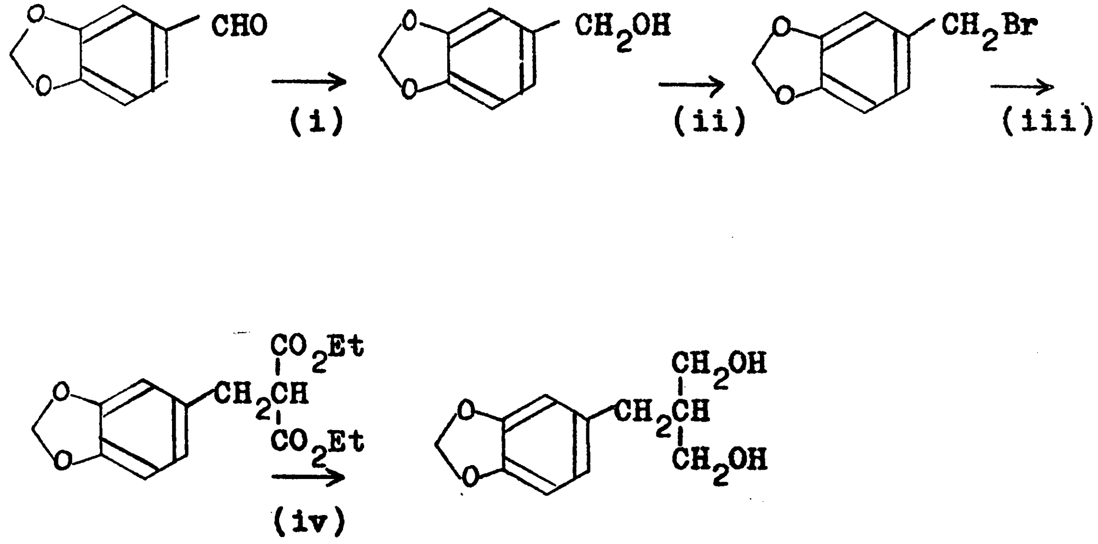
product indicated that it would be feasible, if necessary, to separate the components by this technique, but this was not undertaken, pure samples of the desired olefin (8) being available in other ways.

The pyrolysis of acetate, carbonate, benzoate, hydrogen phthalate and xanthate esters of alcohols is another widely used technique for the preparation of olefins [36], and although cyclic secondary alcohols invariably lead to mixtures of isomers, many instances are known in which pyrolysis of the ester of a side chain primary alcohol gives the exocyclic double bond exclusively [37]. Accordingly the acetate (80) of the alcohol (78) was pyrolysed to give a high yield of pyrolysate (80%), the infra-red and nuclear magnetic resonance spectra of which showed clearly the presence of a terminal double bond grouping $>C=CH_2$. The respective absorptions corresponding to the trisubstituted double bond, however, were absent in both spectra, and the spectra of the product from acetate pyrolysis differed substantially from those of the product from boric acid pyrolysis. The product from pyrolysis of the acetate (80) has not been identified, but is possibly acyclic, the pyrolysis having proceeded with ring cleavage. Such behaviour is now recognised to be general in medium sized rings [36], the pyrolysis of cyclononyl acetate (81), for example, giving ring cleavage via 1:4-transannular elimination, the product being 1:8-nonadiene (82) [38].



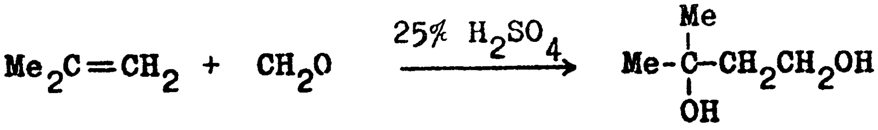
(91)

(i) $CH_2(CO_2Et)_2$/NaOEt, (ii) $LiAlH_4$.



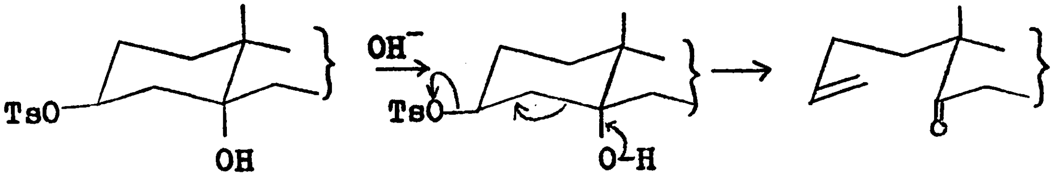
(92)

(i) CH_2O/NaOH, (ii) HBr, (iii) $CH_2(CO_2Et)_2$/NaOEt, (iv) LiAlH

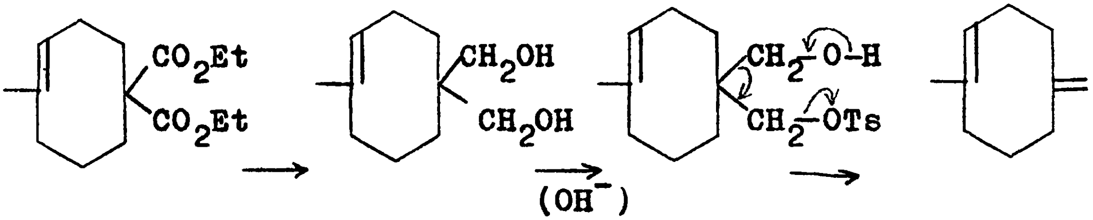


$$Me_2C{=}CH_2 + CH_2O \xrightarrow{25\%\ H_2SO_4} Me-\overset{Me}{\underset{OH}{C}}-CH_2CH_2OH$$

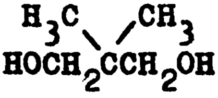
(83) (84)



(85) (86)

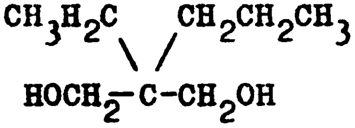


(71) (87) (8)



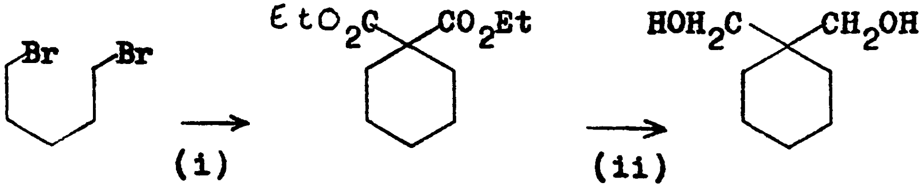
$$\overset{H_3C\ \ CH_3}{HOCH_2CCH_2OH}$$

(88)



$$\overset{CH_3H_2C\ \ \ CH_2CH_2CH_3}{HOCH_2-C-CH_2OH}$$

(89)

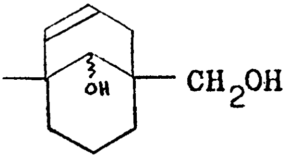


(90)

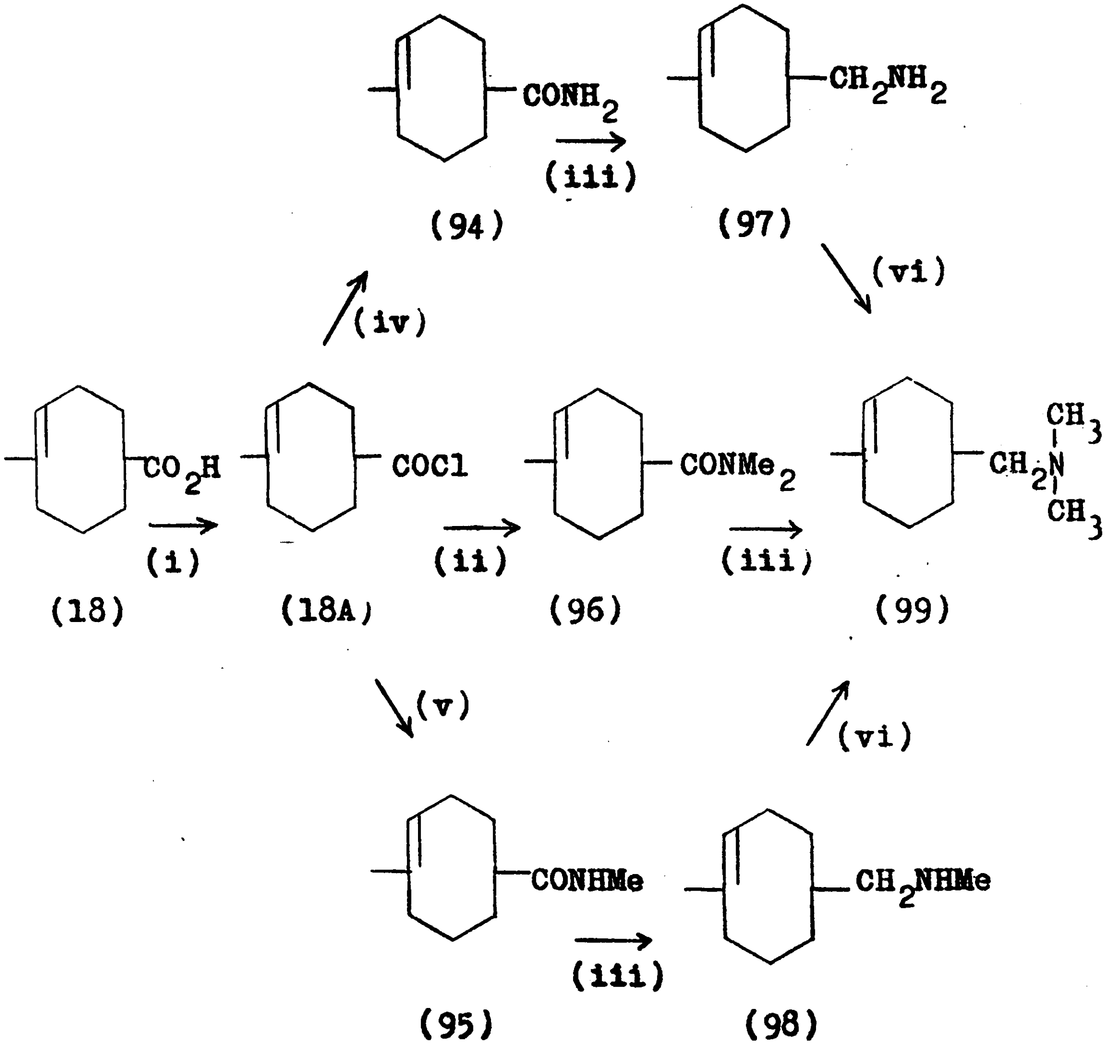
(i) $CH_2(CO_2Et)_2$/NaOEt, (ii) $LiAlH_4$

Another route to the bis-olefin (8) envisaged making use of the retro-Prins reaction. The Prins reaction is the acid catalysed condensation of aldehydes with olefins to give 1:3-diols,[39] e.g. (83) ---→ (84), and many cases of a retro-Prins reaction are known,[40] e.g. the alkaline cleavage of cyclohexane-1:3-diol monosulphonates, (85) ---→ (86), in the steroid field.[41] It was considered a possibility that if the cyclooctene diester (71) could be reduced to the diol (87), then the monotosylate ester of this diol might undergo a retro-Prins reaction on treatment with base to furnish the required olefin (8). With this object in mind a series of simple 1:3-diols was assembled, namely 2:2-dimethylpropane-1:3-diol, (88), 2-ethyl-2-butylpropane-1:3-diol, (89), 1:1-dihydroxymethylcyclohexane, (90), 2-benzylpropane-1:3-diol, (91), and 2-piperonylpropane-1:3-diol, (92). The first two of these diols were commercially available, and the others were synthesised as shown. The monotosylate esters of these diols were prepared with difficulty and treated under a variety of conditions, but no successful retro-Prins reaction was achieved, the products from most of the reactions consisting almost entirely of unreacted ester, and in some cases some polymeric, tarry material.

Concurrently with the above model investigations, attempts were made to reduce the diester (71) to the 1:3-diol (87) with lithium aluminium hydride. This proved



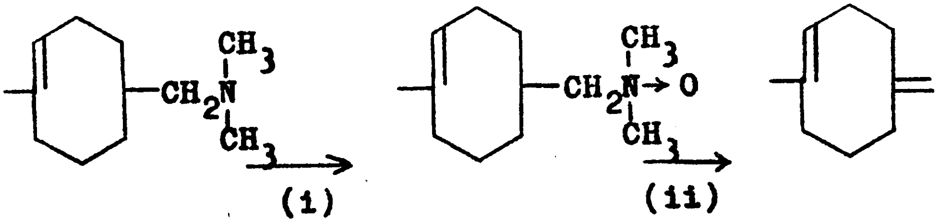
(93)



(i) $(COCl)_2$, (ii) $NHMe_2$, (iii) $LiAlH_4$, (iv) NH_3, (v) NH_2Me, (vi) CH_2O/HCO_2H.

difficult in that it took 30-40 hours reflux with excess lithium aluminium hydride to achieve complete reduction, and the product was in fact a crystalline diol. It was not, however, the expected monocyclic diol, and was easily shown to be the bicyclo-[3:3:1]-diol (93) , being identical with a genuine sample of this compound. This rearrangement will be discussed later (see page 58). The above model experiments on the retro-Prins reaction were discontinued at this stage as a direct result of the lack of success in preparing the required monocyclic diol (87).

By far the most successful method of preparation of the exocyclic double bond was by pyrolysis of the amine oxide, known as the Cope reaction. Treatment of the cyclooctene carboxylic acid (18) with oxalyl chloride followed by ammonia, methylamine, or dimethylamine gave the corresponding amide (94), N-methylamide (95), or N:N-dimethylamide (96) in acceptable yields (60 - 80%). The lactonic impurity (76) which was present with the acid (18) was easily separated from the solid primary and secondary amides, but could not be removed from the tertiary amide at this stage. Reduction of the amides with lithium aluminium hydride proceeded in high yield to give corresponding amines (97), (98) and (99), all of which could be obtained in a pure state. The primary and secondary amines were methylated by the Eschweiler-Clarke technique [47] to give the tertiary amine (99), and a comparison of overall yields from acid to



(99) (100) (8)

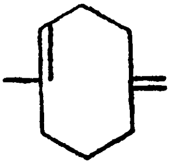
(i) H_2O_2/MeOH, (ii) 160°.

tertiary amine by the three routes showed that, contrary to recent findings [48], there was no appreciable advantage in synthesis of the tertiary amine via the primary or secondary amide.

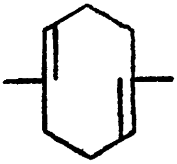
The tertiary amine was smoothly oxidised to the oxide (100) with the hydrogen peroxide-methanol system [49] and pyrolysed at 160° to give the required bis-olefin (8) in 60% yield [50]. The infra-red spectrum of the bis-olefin (8) showed the expected absorptions for the exocyclic double bond, viz. 3064 $cm.^{-1}$ (C-H stretching vibration), 1639 $cm.^{-1}$ (C=C stretching vibration) and 890 $cm.^{-1}$ (out of plane deformation. $\varepsilon = 186$ and $\Delta\nu_{\frac{1}{2}} = 7$ $cm.^{-1}$). The trisubstituted double bond showed the expected absorptions at 3032 $cm.^{-1}$ (C-H stretching vibration), 1668 $cm.^{-1}$ (C=C stretching vibration) and 822 $cm.^{-1}$ (C-H out of plane deformation. $\varepsilon = 70$ and $\Delta\nu_{\frac{1}{2}} = 11$ $cm.^{-1}$).

The proton magnetic resonance spectrum showed the single vinyl proton as a multiplet centred at 4.65 τ and the two protons of the exocyclic double bond as a doublet at 5.28 and 5.31 τ. The eight allylic protons (excluding the methyl group) showed clearly as a multiplet at 7.84 - 8.1 τ, while the methyl group was a doublet at 8.31 and 8.34 τ . Only two protons are of the cyclohexane type (at C_7) and these appeared as a broad, unresolved multiplet at 8.25 - 8.60 τ .

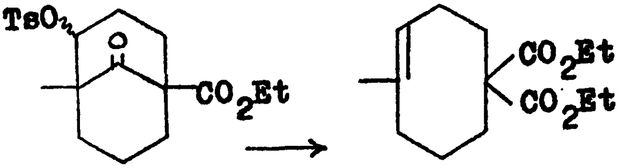
Quantitative estimation of the infra-red and proton magnetic resonance spectra of the bis olefin and comparison



(8)

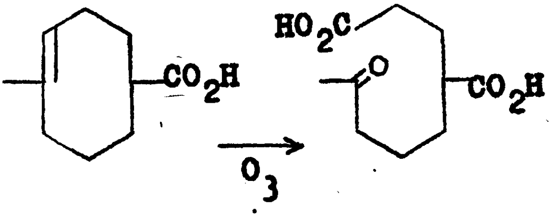


(79)



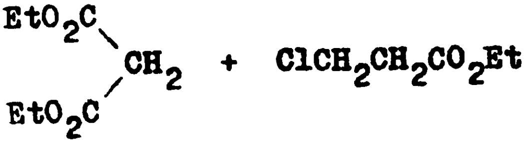
(70)

(71)



(18)

(101)



$$\begin{matrix} EtO_2C & \\ & CH_2 \\ EtO_2C & \end{matrix} \quad + \quad ClCH_2CH_2CO_2Et$$

$$\begin{matrix} EtO_2C & \\ & CHCH_2CH_2CO_2Et \\ EtO_2C & \end{matrix}$$

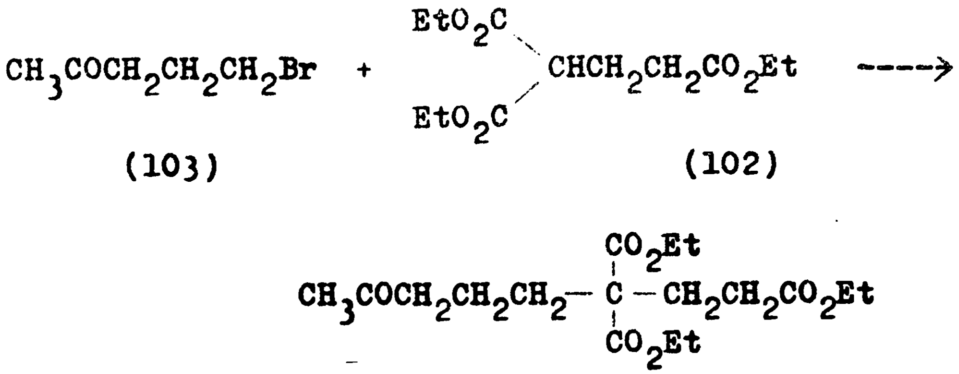
(102)

with the data available for known compounds indicated that the olefin (8) comprised 90-95% of the pyrolysate, isomerisation to the olefin (79) almost certainly accounting for the slight discrepancy.

Having successfully synthesised 1-methyl-5-methylenecyclooctene-1 and determined the most conservative and direct approach to the analogous C_9 compound, it was thought prudent to obtain more concrete evidence that the bridge-fission reaction (70) ---→ (71) had indeed given rise to an eight-membered carbocycle.

The obvious approach to this problem seemed to involve oxidation of the trisubstituted double bond of 1-methylcyclooct-1-ene-5-carboxylic acid (18) to give the acyclic keto-diacid (101), which could be compared with a genuine sample. Attempts were therefore made to oxidise the trisubstituted double bond of (18) under the conditions described by Rudloff [51], but without success. Ozonolysis of (18) with an oxidative work-up (H_2O_2) [52], however, gave a high yield of the desired di-acid (101) as a low melting solid. This compound was identical with a genuine sample of 7-ketooctane-1:3-dicarboxylic acid (101), synthesised as follows.

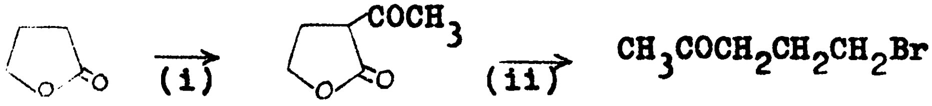
Base-catalysed condensation of diethyl malonate with ethyl β-chloropropionate yielded 1:1:3-triethoxycarbonylpropane (102) [53]. It was hoped that condensation of this substituted malonic ester with 5-bromopentan-2-one (103)



$$CH_3COCH_2CH_2CH_2Br + \begin{array}{l} EtO_2C \\ \quad\;\; \rangle CHCH_2CH_2CO_2Et \\ EtO_2C \end{array} \dashrightarrow CH_3COCH_2CH_2CH_2-\underset{CO_2Et}{\overset{CO_2Et}{C}}-CH_2CH_2CO_2Et$$

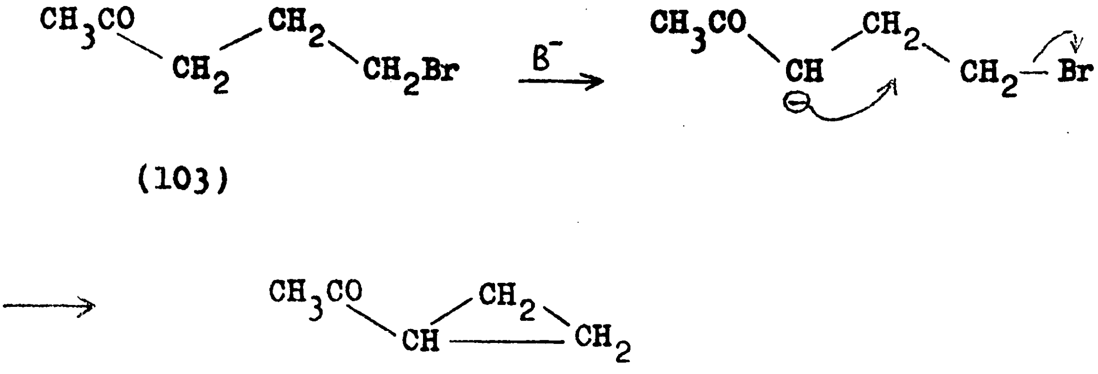
(103) (102)

(104)



(106) (105) (103)

(i) Na/CH_3CO_2Et , (ii) HBr.



(103)

(107)

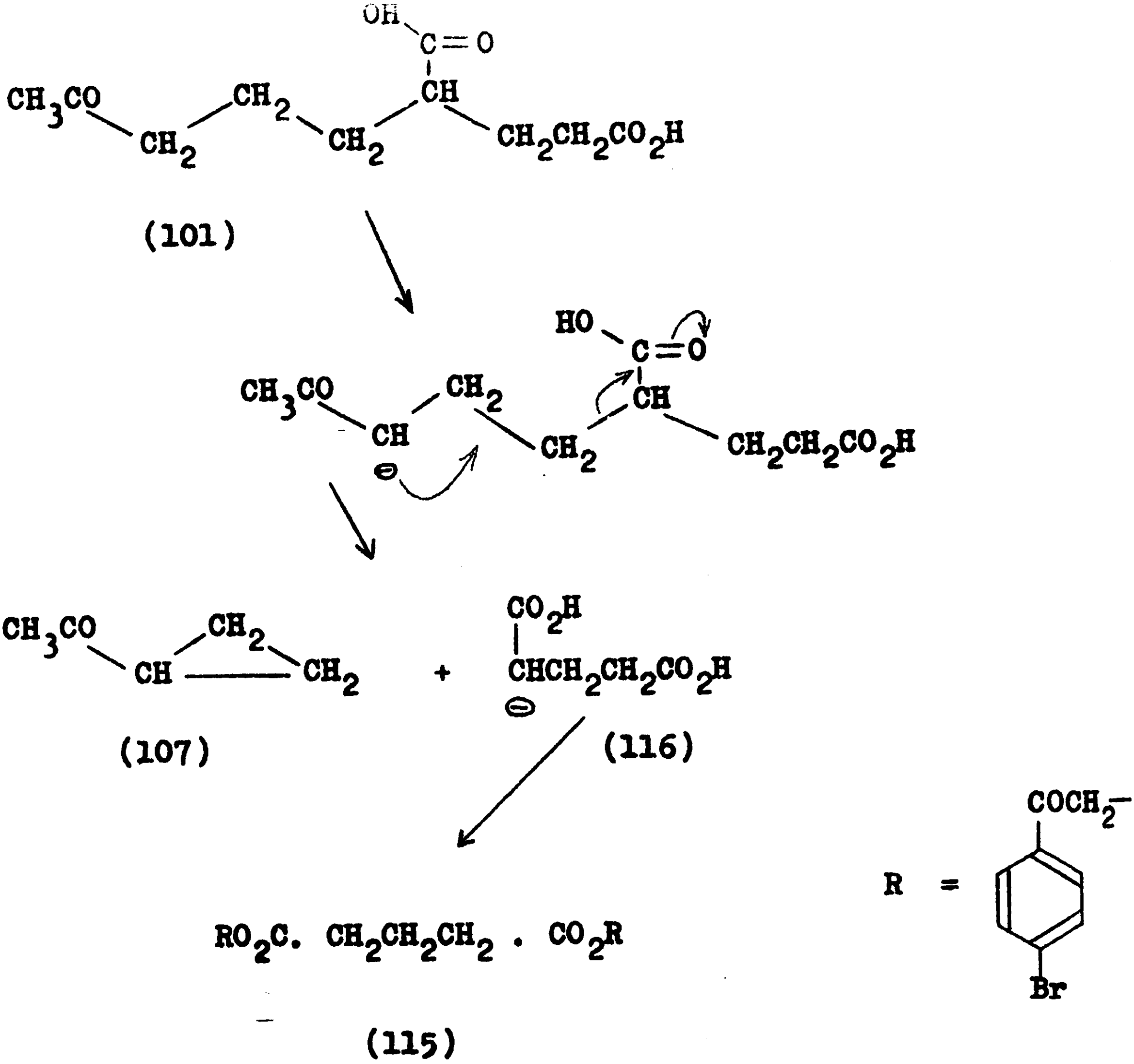
would give the keto-triester (104), from which the desired acid (101) could be obtained by hydrolysis and decarboxylation. α-Acetobutyrolactone (105), synthesised from the readily available γ-butyrolactone (106) by treatment with sodium and ethyl acetate [54], was converted to 5-bromopentan-2-one (103) on treatment with hydrobromic acid [55].

When 5-bromopentan-2-one was added to a solution of the sodium salt of the tri-ester (102), sodium bromide was precipitated immediately and two neutral products were isolated from the reaction mixture. These consisted of a volatile ketone and unchanged tri-ester (102). The ketonic product was identified as cyclopropylmethyl ketone (107), and was identical (infra-red spectra, 2:4-dinitrophenylhydrazone, m.pt. and mixed m.pt.) with a genuine sample of cyclopropylmethyl ketone (Aldrich Chemicals). The cyclopropylmethyl ketone is formed by base-catalysed cyclisation of the 5-bromopentan-2-one ((103) ---→ (107)), and this indeed is a well known method for the preparation of cyclopropyl compounds from halogenoketones [56]. So unstable is 5-bromopentan-2-one that pure samples, on standing at room temperature for 48 hours in soda-glass test-tubes, go black, hydrogen bromide is evolved, and cyclopropylmethyl ketone is formed.

5-Chloropentan-2-one (109), which is somewhat more stable than the bromo compound (but which, on standing, deteriorates in a similar manner) was synthesised as shown

(108) ---→ (109) [57,58]. Condensations of this compound with the tri-ester (102) were also attempted under a variety of conditions, but in no instance was any of the desired tri-ester (104) obtained, cyclisation of the halogenoketone to cyclopropylmethyl ketone being the preferred reaction. To circumvent this awkward cyclisation it was obvious that the activating carbonyl group had to be removed as such, and the simple alternative lay in working with a terminal acetylenic group which could, when required, be easily hydrated to give a methyl ketone grouping.

Tetrahydrofurfuryl chloride (110) [59] was added to sodamide in liquid ammonia to give pent-4-yn-1-ol (111) in high yield [60]. Distillation of the tosylate ester (112) of this alcohol from a solution of calcium bromide in 2-(2-ethoxyethoxy)-ethanol [61] furnished 5-bromopent-1-yne (113), which, on condensation with the tri-ester (102), gave the acetylenic tri-ester (114). Hydration of the acetylene was easily accomplished by a variety of methods [62,63] to give the required keto-triester (104), which, on hydrolysis and decarboxylation, gave the keto-diacid (101) identical with the product obtained from ozonolysis of the cyclooctene carboxylic acid (18). One further interesting reaction was encountered during attempts to prepare a derivative of the keto-diacid (101). When this compound was treated with p-bromophenacyl bromide under very slightly basic conditions, a crystalline di-ester was obtained, the

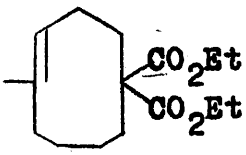

(101)
(107)
(116)
(115)
R =
COCH₂–
Br
NaOEt


TsO
CO₂Et
NaOEt
EtOH
CO₂Et
CO₂Et

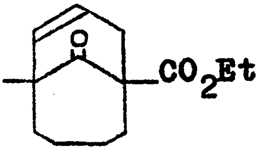
(116) (117)

analysis for which, however, did not correspond with that required for the bis-p-bromophenacyl ester of the acid (101). This experiment was repeated with the same result, the same compound being obtained. This by-product, bearing in mind the cyclisations of the 5-haloketones to cyclopropylmethyl ketone, fitted the data for the bis-p-bromophenacyl ester of glutaric acid (115) and, in fact, was this derivative, being identical with a sample prepared in the normal manner from glutaric acid. The relative stability of the α-carbanion of glutaric acid (116) makes the glutaric acid residue a fair leaving group, and according to the most plausible mechanism, cyclopropylmethyl ketone is formed by cyclisation of the side chain. The process was repeated exactly as above, but omitting the p-bromophenacyl bromide, i.e. (101) ---→ (107), and the neutral product of reaction gave a 2:4-dinitrophenylhydrazone identical with that of cyclopropylmethyl ketone. This reaction in fact might be regarded as a novel type of retro-Michael reaction.

Having firmly established the nature of the critical fragmentation reaction discussed above, the synthesis of the C_9 analogue of isocaryophyllene was now undertaken. Treatment of the bicyclo-[4:3:1]-tosylate (116) with sodium ethoxide in ethanol proceeded exactly as in the previous series, the crude reaction mixture being composed of unchanged axial tosylate and 1:1-diethoxycarbonyl-5-methylcyclonon-4-ene (117). Difficulty was immediately encountered, however, in the



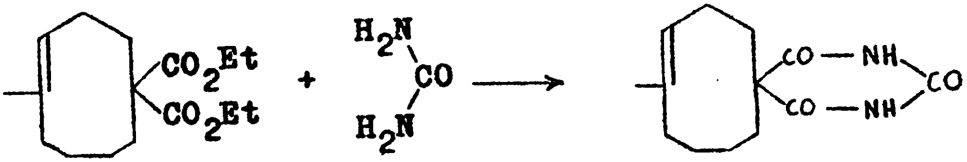
(117)



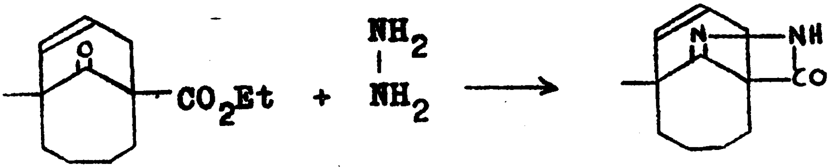
(118)

isolation of the required di-ester (117). Attempted distillation of the reaction mixture gave ~20% of the required di-ester in a fairly pure state, but thereafter the tosylate in the distilling flask became black in colour, decomposition set in, and the mixture set to a black, tarry mass. The low yield available by distillation techniques was undesirable, and in later experiments the unchanged tosylate was separated by chromatography on Woelm grade 1 "neutral" alumina. This too had its disadvantages, since the infra-red spectra of the product showed cis-double bond absorption at 720 cm.$^{-1}$ and took on some of the characteristics of a bicyclo-[4:3:1]-spectrum *. Thin plate chromatography revealed that the product from column chromatography consisted in fact of two compounds, but no method of separation was established. From the infra-red spectrum, this mixture appeared to consist of the required di-ester (117) and the bicyclo-[4:3:1]-ester (118). That these were in fact the components of the mixture was demonstrated as follows :

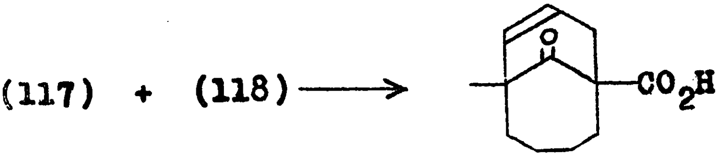
* The bicyclo-[3:3:1]-nonane and bicyclo-[4:3:1]-decane compounds have very characteristic infra-red spectra, the whole region from 4000-650 cm.$^{-1}$ being highly resolved and the individual peaks sharply delineated. The cyclooctene and cyclononene compounds, however, have diffuse, poorly resolved infra-red spectra with few, if any, of the absorptions sharply outlined.



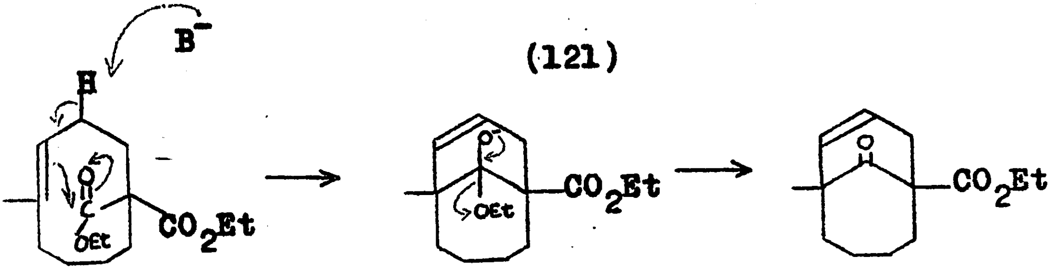
(117) (120)



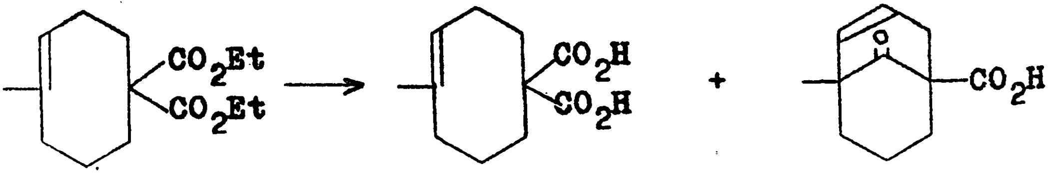
(118) (119)



(121)



(117A) (118)

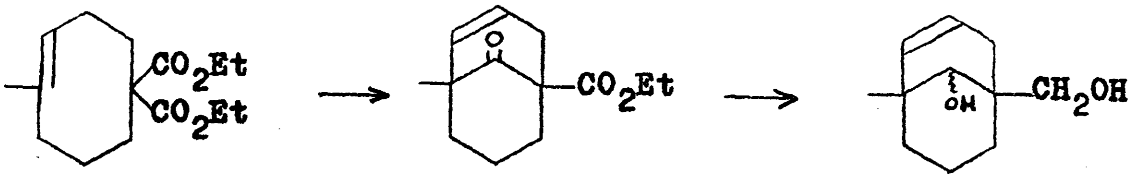


(71) (122) (23)

(i) treatment of a sample of chromatographed material with hydrazine hydrate gave the crystalline pyrazolone (119), and (ii) treatment of some of the same sample with urea and sodium ethoxide gave the crystalline barbituric acid derivative (120).

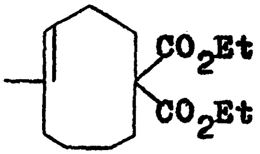
The bicyclo-[4:3:1]-ester (118) must be formed by rearrangement of the cyclononene di-ester (117) during chromatography, the alumina being sufficiently basic to catalyse the reaction. This postulation is confirmed by the fact that when hydrolysis of the above mixture was effected by refluxing with methanolic potassium hydroxide, only one product was obtained, namely the bicyclo-[4:3:1]-acid (121). This procedure was in fact used in a preparative sense to synthesise a number of bicyclo-[4:3:1]-compounds for comparison with those obtained by other more ambiguous methods. The above rearrangement, while occurring to a much greater extent and taking place much more readily than any in the bicyclo-[3:3:1]-field, provided the answer to a number of hitherto unexplained experimental observations.

One probable mechanism is outlined in the scheme shown in (117 A) ---→ (118). In the case of the cyclooctene di-ester (71), hydrolysis can be effected in the normal manner to give the required di-acid (122), but in every case the bicyclo-[3:3:1]-acid (23) is formed as a by-product (3-5%). When the cyclooctene di-ester (71) was treated with lithium aluminium hydride the product was the bicyclo-

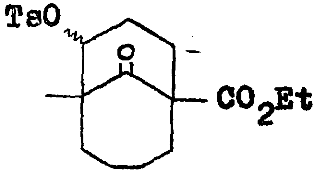


(71)

(93)



(117)

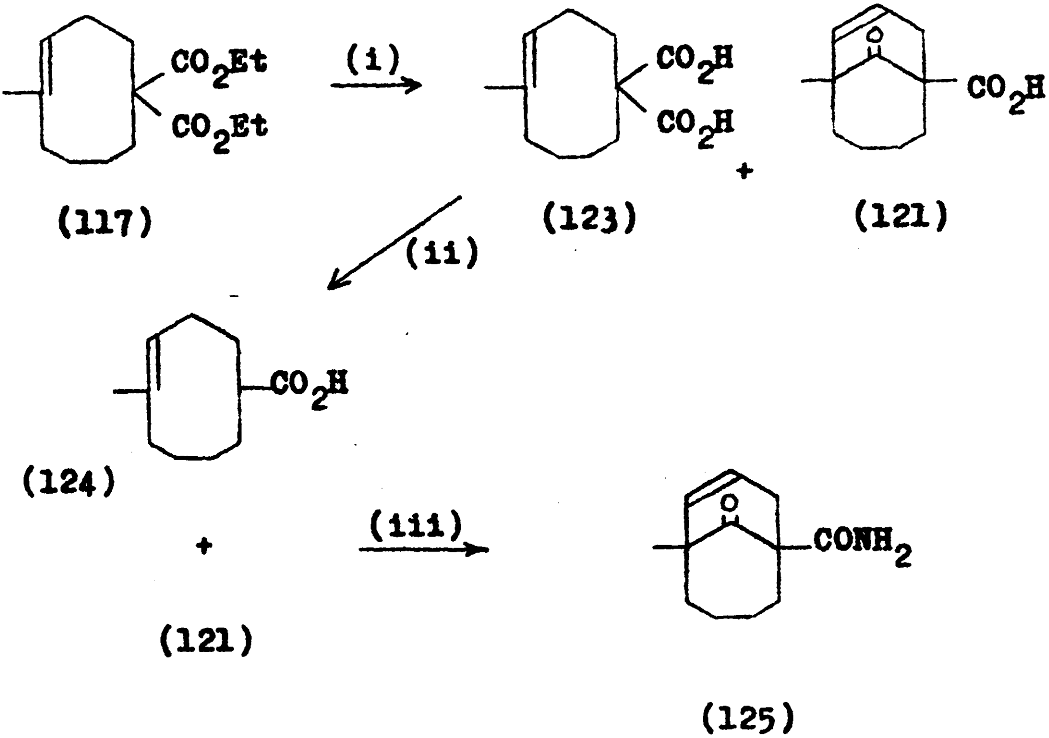


(116)

[3:3:1]-diol (93), and once again the above mechanism probably accounts for the rearrangement.

Transannular rearrangements are of course well known in the case of eight, nine and ten-membered carbocycles[64], the ease with which they occur being a direct result of the unique stereochemistry of these compounds[64,65]. One direct geometric consequence of the highly strained, compact, medium sized ring systems is that groups placed on opposite sides of the ring are forced into close proximity. Consequently, many medium sized carbocycles undergo cyclisation to an energetically more favourable bicyclic system with remarkable ease and under very mild conditions. In the case of the cyclononene di-ester (117), one of the ester groups must lie at least partially "inside" the ring. In this situation the field effect of the π-electrons of the double bond is a stabilising factor which assists the polarisation of the carbonyl group, the overall consequence being the very facile removal of the allylic proton at C_3.

Many attempts were made to avoid this cyclisation, but with no success. Rapid chromatography of the mixture of tosylate and di-ester ((116) + (117)) obtained from the fragmentation process gave a mixture of monocyclic and bicyclic esters. Hydrolysis of this mixture was attempted using barium hydroxide [66], methanolic potassium bicarbonate[67], boiling water in a sealed tube [68], lithium iodide in pyridine (halolytic fission) [69], and under acid conditions,

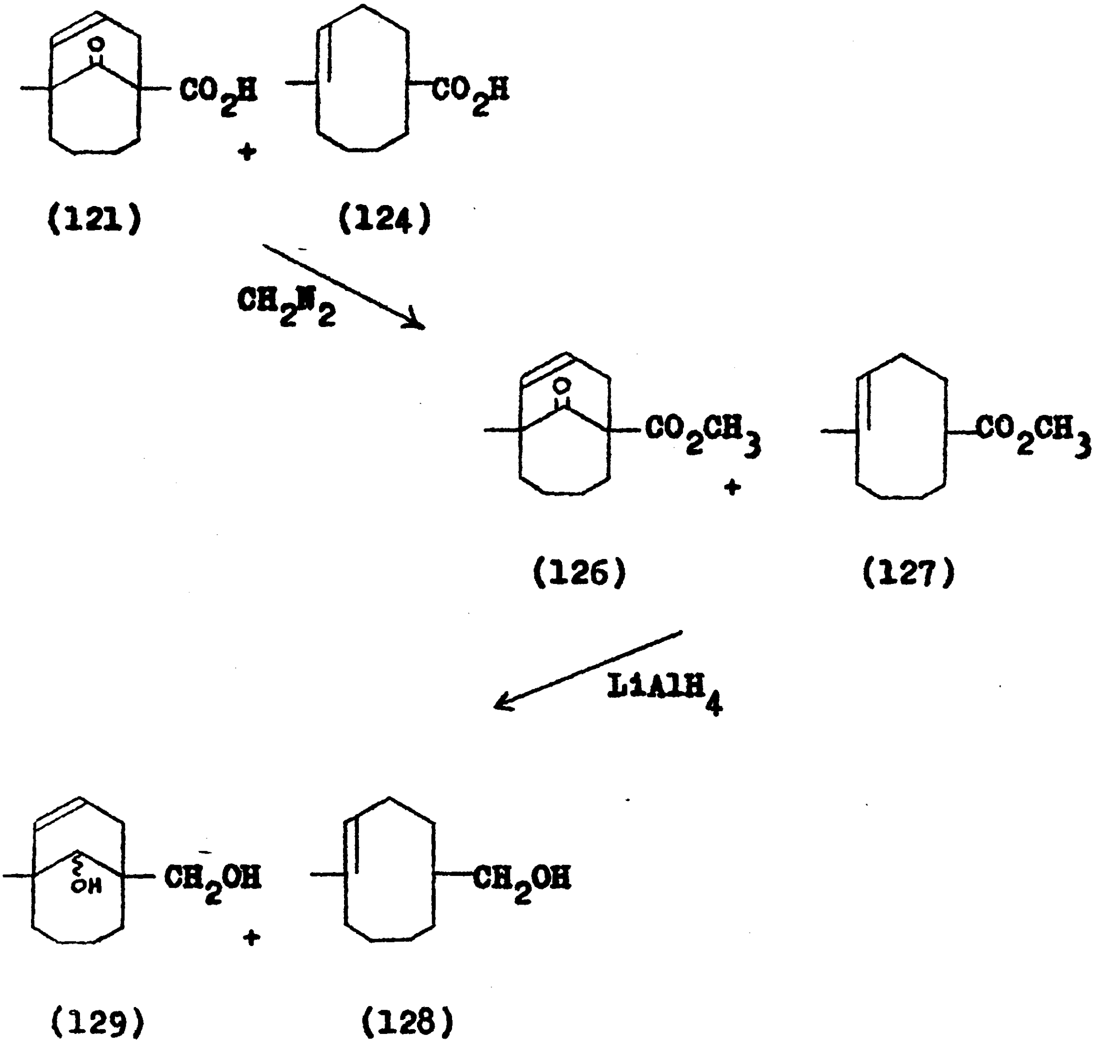


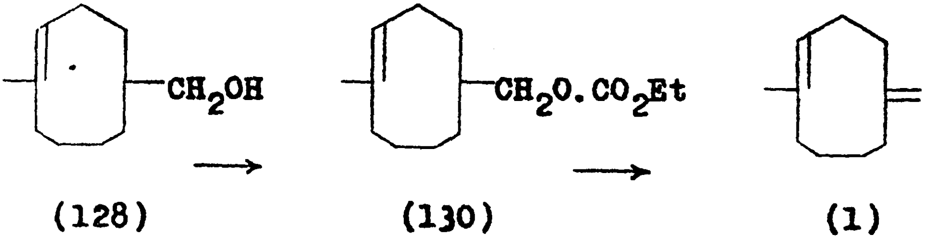
(i) KOH/MeOH at 20°, (ii) reflux in pyridine with glass powder, (iii) $(COCl)_2$ then 0.880 ammonia.

but in no case was the yield of bicyclo acid below 60-70% except in the attempted halolytic fission, which proved unsuccessful. It became apparent that an increase in the amount of bicyclo material was inevitable at this stage, and the best conditions found for the hydrolysis were simply to treat the ester mixture with methanolic potassium hydroxide at room temperature. This produced a mixture of acids which (on the basis of later work) was rich in cyclononene di-acid (123).

Decarboxylation of the di-acid (123) to the cyclononene monocarboxylic acid (124) also proved somewhat more troublesome than in the previous series. Simply heating the mixture resulted in even more of the bicyclo-[4:3:1]-acid (121) being formed, and the most conservative method was found to be refluxing the mixture of acids in pyridine with some glass powder to assist the evolution of carbon dioxide. Treatment of this mixture of mono- and bicyclic acids with oxalyl chloride and then ammonia gave only one product, namely the bicyclo-[4:3:1]-amide (125). The cyclononene acid appears to undergo some other side reaction (which has not yet been elucidated) under these conditions, and, despite many attempts and careful examination of the products of reaction, no monocyclic amide could be isolated.

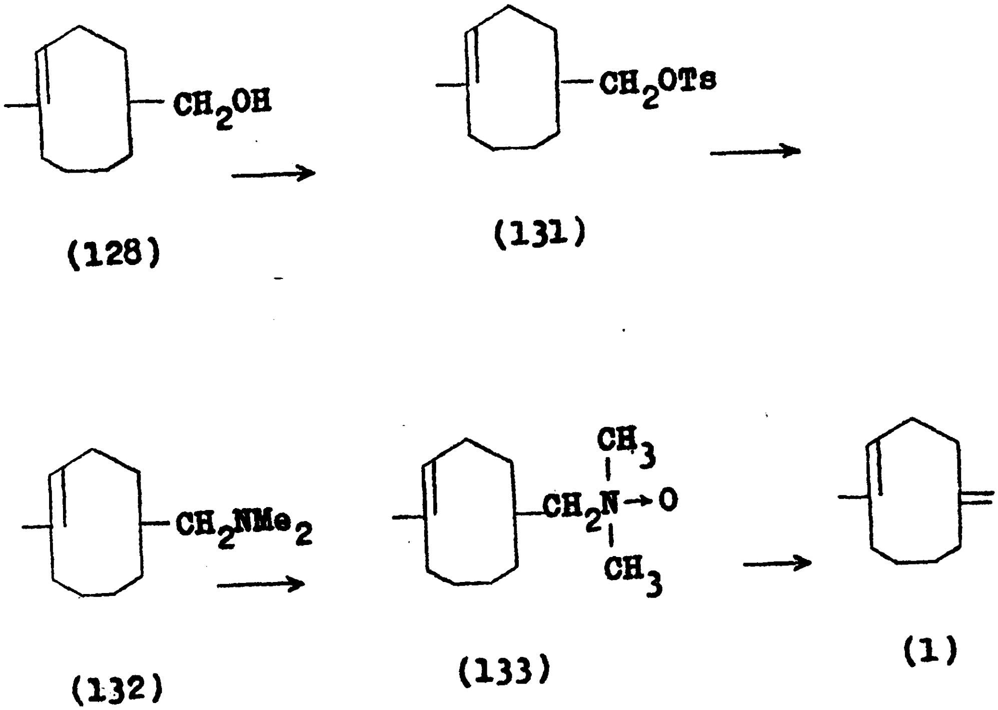
Failure to prepare any of the amides in this series proved a serious liability at this stage, since the alternative routes investigated in the previous series were


CO2H
CO2H
(121)
(124)
CH2N2
CO2CH3
CO2CH3
(126)
(127)
LiAlH4
OH
CH2OH
CH2OH
(129)
(128)


CH2OH
CH2O.CO2Et
(128)
(130)
(1)

by no means as efficient as that via the amides. Having, however, no alternative, the mixture of acids (121) and (124) was treated with diazomethane to give a mixture of corresponding esters (126) and (127) which could not be separated. Reduction of the mixture of methyl esters gave an easily separated mixture of monocyclic alcohol (128) and bicyclic diol (129) in approximately equal amounts. It appears likely that the bridge-fission reaction (116) ---> (117) goes in high yield, but that in each subsequent step some cyclisation to bicyclo material takes place.

Although the pyrolysis of acetates of cyclononane alcohols is known to involve ring cleavage, this is true only when the temperature of pyrolysis is above 400°. Other esters, including carbonates and carbamates, are known to pyrolyse at lower temperatures without degradation or rearrangement [36,70]. Attempts were made to obtain the carbamate ester of the alcohol (128) with phenyl isocyanate, but the two compounds did not react, even under forcing conditions, and the alcohol was recovered unchanged. The carbonate ester (130) formed readily, however, and was pyrolysed by refluxing it in diethyl phthalate. The product from this reaction showed absorption at 1640 $cm.^{-1}$ and 890 $cm.^{-1}$ in the infra-red spectrum characteristic of an exocyclic double bond, but it was obviously contaminated by some by-product. Attempts were made to obtain this olefin in a pure state, but without success, and the purest sample


CH$_2$OH
(128)
CH$_2$OTs
(131)
CH$_2$NMe$_2$
(132)
CH$_3$
CH$_2$N→O
CH$_3$
(133)
(1)

obtained contained approximately 25-30% of the required bis-olefin (based on infra-red spectral data).

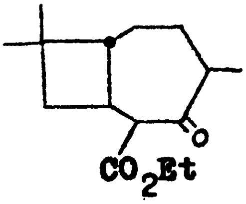
The solvolysis of arylsulphonate esters of alcohols in dimethylsulphoxide is known to give high yields of the corresponding olefins [71]. Accordingly, the p-toluenesulphonate ester (131) of the alcohol (128) was prepared in the normal manner and refluxed in dimethylsulphoxide containing a little potassium bicarbonate. The mixture went black, and the only product which could be isolated was a black gum, whose infra-red spectrum showed no evidence of any exocyclic double bond.

Solvolytic replacement of a tosyloxy group by an amine is a well established preparative method [72], and treatment of the tosylate (131) with ethanolic dimethylamine gave an acceptable yield (60%) of the corresponding tertiary amine (132). The N-oxide of this compound, prepared in the usual way, was pyrolysed in high yield (70%) to give the required bis-olefin (1).

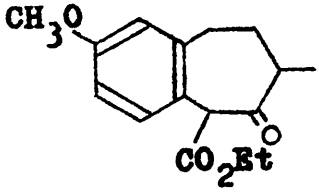
The infra-red spectrum showed absorption due to the exocyclic double bond at 3068 cm.$^{-1}$ (C-H stretching vibration), 1637 cm.$^{-1}$ (C=C stretching vibration) and at 886 cm.$^{-1}$ (out of plane deformation. ξ = 160 and $\Delta\nu\frac{1}{2}$ = 7 cm.$^{-1}$). The trisubstituted double bond showed absorption at 3040 cm.$^{-1}$ (C-H stretching vibration), 1664 cm.$^{-1}$ (C=C stretching vibration) and 832 cm.$^{-1}$ (C-H out of plane deformation. ξ = 45 and $\Delta\nu\frac{1}{2}$ = 9 cm.$^{-1}$). The proton magnetic resonance spectrum was similar to that of the C_8 compound, the single vinyl proton showing as a triplet at 4.55 τ (J = 7.7 c.p.s.) and the other two olefinic protons as a doublet at 5.1 and 5.27 τ (J = 1 c.p.s.), with further unresolved splitting. The methyl group showed as a singlet at 8.36 τ , the eight allylic protons as a multiplet centered at 7,88 τ and the four cyclohexane like protons as an unresolved multiplet at ~ 8.45 τ .

Both the proton magnetic resonance spectrum and the infra-red absorption spectrum were similar to those of a pure sample of caryophyllene with regard to the absorptions of the double bonds, and from these spectra the product was estimated to be 90-95% pure. Gas-phase chromatography of the product revealed the presence of minor traces of impurities, but confirmed the other quantitative estimations, indicating 90-95% purity.

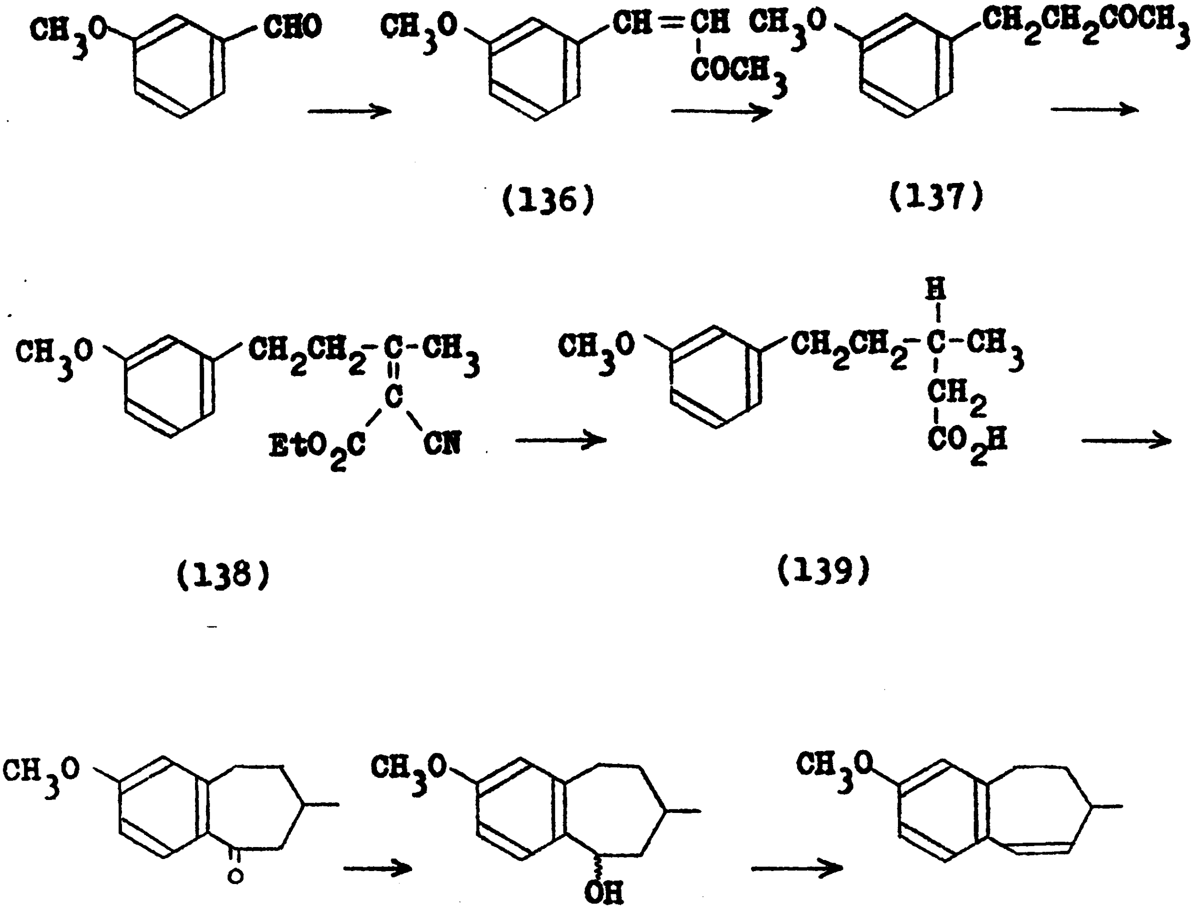
After the various difficulties in the above synthesis had been overcome, the process was relatively simple to carry out and, despite working with mixtures for a number of stages, at no time was the yield so low that it proved a practical objection to the scheme. Consequently, and concurrently with the above investigations, a synthesis of isocaryophyllene was undertaken. Apart from the stereochemistry of the endocyclic double bond, the major difficulty in the synthesis is the trans-fused bicyclo-[7:2:0]-system of the caryophyllenes. With this in mind it was obvious that, in order to utilise the experience gained in the



(134)



(135)



(136)

(137)

(138)

(139)

(140)

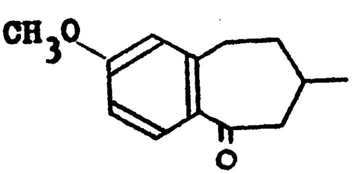
(141)

(142)

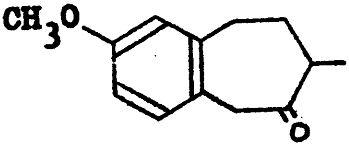
synthesis of the above bis-olefins, the starting material for a synthesis of isocaryophyllene was the bicyclo-[5:2:0]-nonane derivative (134). The scheme which was devised for the synthesis of this compound entailed the synthesis of the benzsuberone (135), from which, by reduction of the aromatic ring, methylation and stepwise ring contraction, it was hoped to synthesise the required starting material (134).

Condensation of m-methoxybenzaldehyde with acetone[73] gave a moderate yield (40-50%) of m-methoxybenzylidene acetone (136), catalytic reduction of which gave the saturated ketone (137). Condensation of this ketone with ethyl cyanoacetate [74] to the ester (138) followed by reduction and hydrolysis and decarboxylation [75] gave 3-methyl-5-m-anisylpentanoic acid (139). Cyclisation of this acid with polyphosphoric acid [76] gave 5-methyl-1:2-5′-methoxybenzocyclohept-1-ene-3-one (140), and it was intended to"shift" the carbonyl group from the 3- to the 4-position by the standard procedure - i.e. reduction of the ketone to the alcohol, dehydration to the olefin, epoxidation and rearrangement of the epoxide [77].

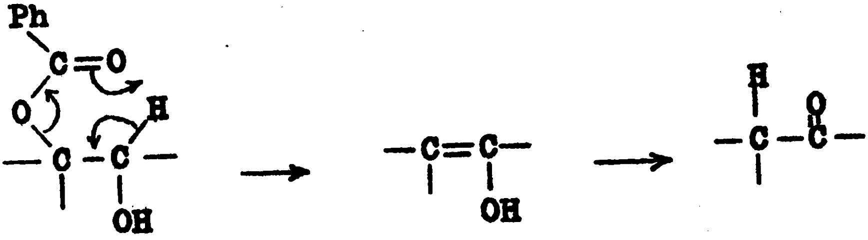
Accordingly, the benzsuberone (140) was reduced to the alcohol (141) with sodium borohydride and dehydrated to the benzsuberene (142). Treatment of this compound with perbenzoic acid in the normal manner gave a neutral compound the infra-red spectrum of which showed bands at 3300 cm.$^{-1}$ (hydroxyl), 1705 cm.$^{-1}$ (conjugated ester) and at 710 and



(140)

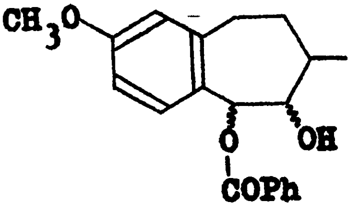


(143)



(144)

(145)

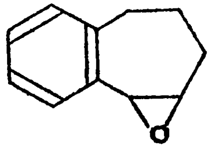


(146)

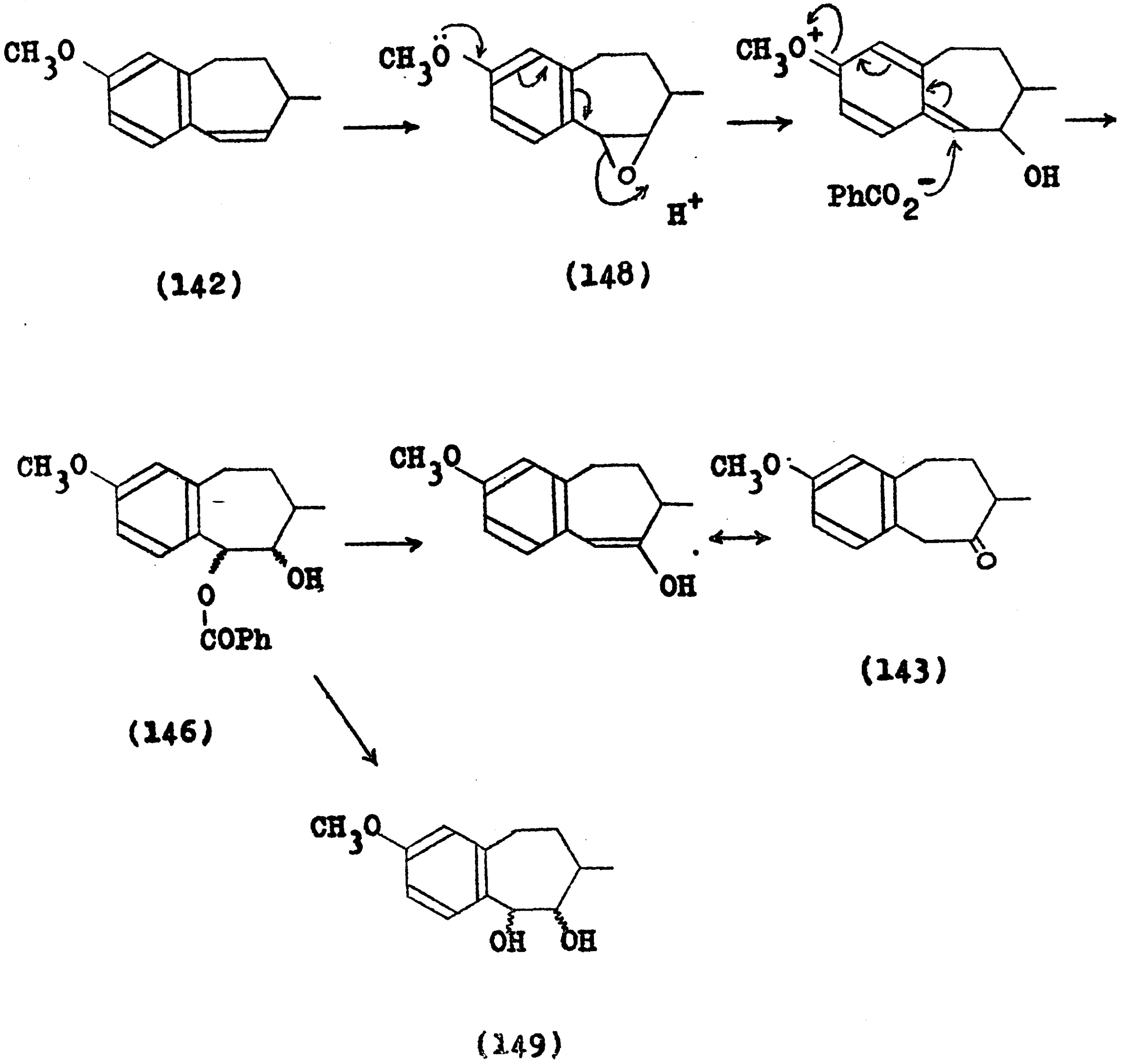
760 cm.$^{-1}$ (phenyl group). This compound was obviously not the required epoxide and would not distil. When heated to 180-200°, however, the compound rapidly decomposed to give a liquid which distilled and a solid which sublimed. The solid was easily identified as benzoic acid and the liquid, isomeric with the benzsuberone (140), showed carbonyl absorption in the infra-red spectrum at 1700 cm.$^{-1}$, but was otherwise similar to the infra-red spectrum of the benzsuberone (140). The ultra-violet, infra-red and proton magnetic resonance spectra of this liquid indicated that it was in fact the required isomeric benzsuberone (143).

This being the case, the final pyrolysis step must involve a cis elimination of benzoic acid, viz. (144) ---> (145), and consequently, the neutral intermediate product must be the glycol monobenzoate (146). The isomeric glycol monobenzoate must be excluded here, for, quite apart from mechanistic considerations, pyrolysis of this ester would lead to the conjugated benzsuberone (140) which would have been easily identifiable (light absorption characteristics and 2:4-dinitrophenylhydrazone).

The issue of greatest interest arising from the above observations is the facile ring opening of the intermediate epoxide under the relatively mild acidic conditions. (There seems little reason to go against modern opinion that the action of perbenzoic acid on olefins leads, as a first step anyway, to formation of the corresponding epoxide).[78]



(147)

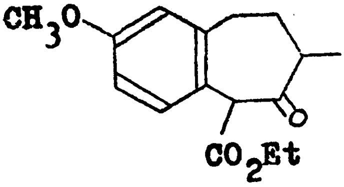


CH3O
(142)
CH3Ö
H+
(148)
CH3O+
PhCO2-
OH
CH3O
OH
O
COPh
(146)
CH3O
OH
CH3O
O
(143)
CH3O
OH
OH
(149)

Ring opening of epoxides under the more acidic conditions of aqueous formic acid (and to a lesser extent acetic acid) is of course a well known phenomenon, [78] but with perbenzoic acid only a few special instances of such behaviour have been reported, [79] and it is of importance to note that benzsuberene oxide (147) is inert to the action of benzoic acid. [77]

Two possible mechanisms suggest themselves in explanation of the above ring opening. (i) The conjugative effect of the benzene ring is greatly enhanced by that of the alkoxy group (these two effects have been recognised as influencing greatly the stereochemistry and mechanism of epoxide ring opening) [80] and, in the formal mechanistic sense, the ring opening may be imagined as following the course outlined in (142) ---→ (143). Were this mechanism operative in this case, then being of the S_N1 type, it should lead to a mixture of cis- and trans-glycol monobenzoates. (ii) Formation of the epoxide being assumed, the next step might simply involve the normal mode of acid-catalysed ring opening of the epoxide to give the trans-glycol monobenzoate. The main objection to this mechanism lies in the fact that benzsuberene oxide itself is completely stable under these conditions, and shows no tendency to undergo ring opening.

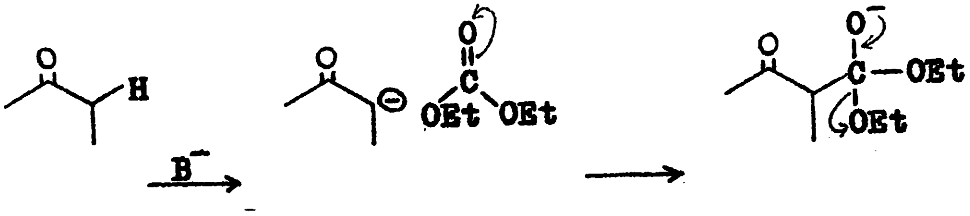
Each of these mechanisms appears to be inadequate in



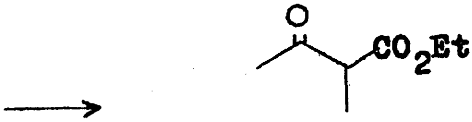
(135)

one respect; the first because it does not lead exclusively to the trans-glycol monobenzoate which is considered to be necessary for the cis elimination mechanism (144) ---> (145), and the second because it does not explain the difference in behaviour between the simple epoxide (147) and its methoxy derivative (148). However an examination of models reveals that both the cis- and trans-glycol monobenzoates can be suitably aligned to undergo a cis elimination of benzoic acid and in this sense the stereochemistry of the intermediate ester is not of prime importance. The stereochemistry of the cycloheptane ring is known to be substantially different from that of the cyclohexane ring,[81] especially with respect to the 1:2-disubstituted compounds. Thus both the cis and trans forms of cycloheptane-1:2-diol will form boric acid complexes and cyclic isopropylidene ethers with acetone.[82] In short, the stereochemistry of the glycol monobenzoate in the above reaction is virtually unimportant, cis elimination of benzoic acid being equally feasible with either form. For this reason it appears that mechanism (i) adequately explains the abnormal reaction of the benzsuberene (142) with perbenzoic acid.

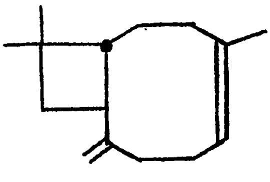
Having thus achieved the rearrangement of the 3-keto function to the 4-position, it remained to carbethoxylate the 3-position to give the required ester (135). Unfortunately, the presence of the methoxyl group which



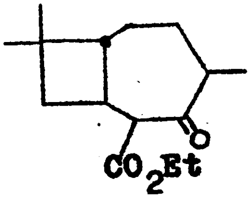
(150)



(151)



(152)



(134)

had proved so valuable in effecting opening of the epoxide was now a distinct disadvantage. Two main methods are available for the direct carbethoxylation of activated methylene groups, namely condensation with diethyl oxalate and condensation with diethyl carbonate,[83] and both of these processes require the formation or participation of a carbanion α to the keto group, e.g. (150) ---> (151). In this case, however, the substituted benzene ring can enter into conjugation with the C_3 carbanion and so delocalise the charge, effectively prohibiting attack by the electrophile. Several attempts were made to carbethoxylate the benzsuberone (143) using the powerful medium of diethyl carbonate and sodium hydride, but with no success, and the synthesis was abandoned at this stage.

APPRAISAL.

Apart from any intrinsic merit, the work described above illustrates the potential value of bicyclic systems as a source of particularly substituted medium sized rings which are otherwise inaccessible. In particular, this work demonstrates the feasibility of a total synthesis of isocaryophyllene (152) from the bicyclic keto-ester (134).

EXPERIMENTAL

All melting points were determined on a Kofler block. Routine infra-red spectra of liquid films and nujol mulls were determined on a Perkin-Elmer Infracord spectrophotometer. Quantitative infra-red absorption spectra were determined on a Unicam S.P. 100 double beam spectrophotometer equipped with an S.P. 130 sodium-chloride prism grating double monochromator operated under vacuum conditions. Ultra-violet absorption spectra, measured on a Perkin-Elmer model 137 U.V. spectrophotometer and a Unicam S.P. 500 spectrophotometer refer to solutions in ethanol unless otherwise stated.

Nuclear magnetic resonance spectra were determined on an A.E.I. R.S. 2 high resolution magnetic spectrometer, and gas-liquid chromatography was carried out on a Perkin-Elmer Fractometer 451 using a Golay (capillary) column (50 metres, polypropylene glycol).

1-Ethoxycarbonyl-5-methylbicyclo-[3:3:1]-non-3-ene-9-one (6)

This compound was synthesised as described by Murray, Parker, Raphael and Jhaveri [3] as a colourless oil b.p. 110°/0.45mm., $n_D^{22} = 1.4907$. The infra-red spectrum showed absorption at 1735, 1260 cm.$^{-1}$ (carbethoxyl), 1705 cm.$^{-1}$ (ketone), and 710 cm.$^{-1}$ (cis disubstituted double bond).

5-Methylbicyclo-[3:3:1]-non-3-ene-9-one-1-carboxylic acid (23)

Hydrolysis [3] of (6) with methanolic potassium hydroxide gave a 73% yield of the required carboxylic acid as colourless needles m.p. 141-143° from benzene-light petroleum (b.p. 60-80°).

5-Methylbicyclo-[3:3:1]-non-3-ene-9-ol-1-carboxylic acid (19)

A solution of the acid (23) (5 g.) in aqueous methanol was treated at room temperature with excess of an aqueous solution of sodium borohydride. After standing for 3 hours, the mixture was acidified (6N H_2SO_4), saturated with ammonium sulphate and extracted with ether (3 x 30 ml.). The combined extracts were washed (satd. $(NH_4)_2SO_4$), dried ($MgSO_4$), and the solvent removed to leave a colourless solid which crystallised from benzene as needles, m.p. 171-173° (5.2 g., 95%). The infra-red spectrum showed absorption at 3500 cm.$^{-1}$ (hydroxyl), 3400-2700 cm.$^{-1}$ (acidic hydroxyl), and 1735, 1250 cm.$^{-1}$ (carboxyl). [84]

1-Methoxycarbonyl-5-methylbicyclo-[3:3:1]-non-3-ene-9-one (22)

A solution of the acid (23) (1.75 g.) in anhydrous ether (20 ml.) was treated with excess of a dry ethereal solution of diazomethane [85] and the mixture allowed to stand at room temperature for 12 hours. After addition of a little acetic acid, the mixture was treated with dilute sodium bicarbonate solution, water and dried ($MgSO_4$). Removal of the solvent left a colourless oil which rapidly solidified (1.83 g., 95%). Crystallisation from light petroleum (b.p. 60-80°) gave the methyl ester (22) as needles m.p. 81-83° [3] showing absorption in the infra-red spectrum at 1730, 1260 $cm.^{-1}$ (carbomethoxyl) and 1705 $cm.^{-1}$ (ketone).

1-t-Butoxycarbonyl-5-methylbicyclo-[3:3:1]-non-3-ene-9-one (25)

A 500 ml. Pyrex, heavy walled, narrow mouthed pressure bottle was charged with 10 ml. of ether, 0.5 ml. of concentrated sulphuric acid and 6 g. of the acid (23). The bottle was cooled to 0°, 8 ml. of isobutylene was added, and the bottle, stoppered and securely wired, was left in the dark for 3 days. [86] The bottle was then cooled (-10°) and opened, and the contents poured into a separating funnel containing 25 ml. of water, 7 g. of sodium hydroxide and 25 g. of ice. The ethereal layer was separated, the aqueous layer extracted with ether (2x10 ml.) and the combined extracts dried (K_2CO_3).

Removal of the solvent left a colourless oil showing absorption in the infra-red spectrum at 1730, 1265 $cm.^{-1}$ (<u>t</u>-butoxyl), 1705 $cm.^{-1}$ (ketone) and at 1385, 1365 $cm.^{-1}$ (<u>t</u>-butyl). Distillation gave 6.22 g. of the <u>t</u>-butyl ester (25) (81%), b.p. 86°/0.005 mm. and

n_D^{20}= 1.4779. (Found, C, 71.60% , H, 8.74%. $C_{15}H_{22}O_3$ requires C, 71.97%, H, 8.86%). The distilled material solidified on standing and crystallised (methanol) as needles m.p. 47-49°.

Attempted reverse acetoacetic ester condensations.

A. The ethyl ester (6) with sodium ethoxide. Treatment of the ethyl ester (6) under the conditions described by Jhaveri [8] gave a mixture of 1-ethoxycarbonyl-5-methylbicyclo-[3:3:1]-non-3-ene-9-ol , b.p. 80°/0.05 mm. (Found C, 69.4% , H, 8.8%. $C_{13}H_{20}O_3$ requires C, 69.6% , H, 8.9%) and 5-methylbicyclo-[3:3:1]-non-3-ene-9-ol-1-carboxylic acid (19), m.p. 172° (Found C, 67.3% , H, 7.9%. $C_{11}H_{16}O_3$ requires C, 67.3% , H, 8.2%).

B. The methyl ester (22) with sodium methoxide.

A solution of the ester (22) (1 g.) in sodium ethoxide (from 0.5 g. of sodium in 30 ml. of methanol) was refluxed for 20 hours. The solvent was distilled off under reduced pressure, the residual yellow oil diluted with water, acidified (6N HCl), and extracted with ether (2 x 30 ml.). The extracts were dried ($MgSO_4$) and the solvent removed to leave a yellow oil which partly solidified. Trituration with ethyl acetate gave a small amount of crystalline material whose infra-red spectrum indicated that it was the hydroxy acid (19) (3500 cm.$^{-1}$ (hydroxyl) and 3400-2700 cm.$^{-1}$ (acidic hydroxyl)). The oil showed absorption at 3500 cm.$^{-1}$ (hydroxyl) and 1730, 1260 cm.$^{-1}$ (carbomethoxyl) and was unhydrolysed hydroxy-methyl ester. Hydrolysis was completed by refluxing in methanolic potassium hydroxide, when, after the normal work-up, a crystalline acid was obtained showing absorption in the infra-red spectrum at 3500 cm.$^{-1}$ (hydroxyl), 3400-2700 cm.$^{-1}$ (acidic hydroxyl) and 1730, 1270 cm.$^{-1}$ (carboxyl). The product from hydrolysis of the oil was identical with the crystalline product obtained above and melted in the range 145-168°. Crystallisation from benzene gave 0.60 g. of hydroxy acid (19), m.p. 168-171°, mixed m.p. 167-170°.

C. <u>The ethyl ester with ethanolic potassium hydroxide.</u>

A mixture of the ethyl ester (6) (1 g.) and potassium hydroxide (2 g.) in ethanol (50 ml.) was refluxed for 30 hours and then evaporated to dryness. The residue was dissolved in water, extracted with ether, and the extracts discarded. The alkaline solution was acidified (6N H_2SO_4), saturated with ammonium sulphate, and extracted with ether (3 x 20 ml.). The extracts were washed with saturated ammonium sulphate solution, dried ($MgSO_4$), and the solvent removed to leave a brown semi-solid. Crystallisation from ethyl acetate gave needles, m.p. 166-169°, which had an infra-red spectrum identical with that of the hydroxy acid (19) (mixed m.p. 166-170°).

D. <u>The ethyl ester with sodamide in xylene.</u>

A mixture of the ester (6) (5 g.) and freshly prepared sodamide [87] (3.9 g.) in xylene (150 ml.) was refluxed for

5 days, after which the solvent was removed by distillation under reduced pressure. Water was added, the mixture acidified (6N HCl) and the solution extracted with ether (3 x 50 ml.). The combined extracts were washed with water and dried ($MgSO_4$). Removal of the solvent left a viscous yellow oil showing absorption in the infra-red spectrum at 3500 $cm.^{-1}$ (hydroxyl), 3400-2700 $cm.^{-1}$ (acidic hydroxyl), 1735, 1270 $cm.^{-1}$ (carboxyl) and 1705 $cm.^{-1}$ (ketone). When the gum was dissolved in benzene and left to crystallise slowly an acid was obtained, m.p. 160-167°, (3.1 g.) whose infra-red spectrum was identical with that of the hydroxy acid (19).

E. The methyl ester (22) with sodamide in xylene.

Following the same procedure as was used for the ethyl ester in D above, a mixture of the hydroxy acid (19) and unchanged methyl ester was obtained.

F. The acid (23) with sodamide in xylene.

The keto-acid (23) (2 g,) and freshly prepared sodamide (1.56 g.) were refluxed in xylene (50 ml.) for 3 days. The solvent was then distilled off under reduced pressure to leave a brown solid which was dissolved in water. After washing with ether, the alkaline solution was acidified (6N HCl) and extracted with ether (3 x 30 ml.), the extracts dried ($MgSO_4$), and the solvent removed. The residual yellow paste would not crystallise, but careful washing with ether removed coloured material and unchanged bicyclic acid (23). Crystallisation from benzene-light petroleum (b.p. 60-80°) then gave a colourless powder, m.p. 143-144° whose infra-red spectrum showed absorption at 3500-2500 cm.$^{-1}$ (acidic hydroxyl) and 1740-1710 cm.$^{-1}$ (carboxyl), but was otherwise diffuse and showed none of the fine structure associated with the bicyclo-[3:3:1]-nonane compounds. This compound was in fact 1-methyl-cyclooct-2-ene-1:5-dicarboxylic acid (15) (Found C, 62.81% , H, 8.28%. $C_{11}H_{16}O_4$ requires C, 62.25% , H, 7.60%). A mixed m.p. with the acid (23) showed softening from 116° and melted in the range 124-142°.

Titration against standard base gave an equivalent weight of 98 (calculated for (15) : 106). The double bond was not located in the infra-red spectrum but was confirmed by microhydrogenation in ethyl acetate with 10% palladium on charcoal as catalyst (11.1 mgms. of acid (15) absorbed 1.01 ml. of hydrogen; calculated uptake is 1.17 ml.).

G. The t-butyl ester (25) with sodamide in xylene.

A mixture of the ester (25) (2.5 g.) and freshly prepared sodamide (2 g.) was refluxed in xylene (100 ml.) for 3 days. The same work-up as used in F above gave a viscous yellow oil which would not crystallise. An attempt was made to purify this product by conversion to the methyl ester. Treatment of the acid with diazomethane in the usual manner gave the ester as a colourless oil, b.p.

93-96°/0.09 mm., n_D^{25}= 1.4798. The ester was then hydrolysed with methanolic potassium hydroxide to give the acid (15) as a colourless oil which would not crystallise, but whose infra-red spectrum was identical with that of the product described in F above.

H. <u>The t-butyl ester (25) with potassium t-butoxide in t-butanol</u>.

Freshly cut potassium (1.5 g.) was dissolved in dry *t*-butanol (100 ml.), the ester (25) (3 g.) added, and the mixture refluxed for 30 hours. The dark red reaction mixture was poured into water, acidified (6N HCl) and extracted with ether (4 x 50 ml.). The combined ethereal extracts were then extracted with dilute sodium bicarbonate solution, this alkaline solution acidified (6N HCl), extracted with ether, and the extracts dried ($MgSO_4$). Removal of the solvent left a viscous oil whose infra-red spectrum showed absorption at 3400-2700 cm.$^{-1}$ (acidic hydroxyl), 1735, 1260 cm.$^{-1}$ (*t*-butoxy), 1705 cm.$^{-1}$ (ketone) and 1385,1365 cm.$^{-1}$ (*t*-butyl). The oil was a mixture of the acid (23) and the half *t*-butyl ester of the di-acid (15).

The above mixture was then hydrolysed with methanolic potassium hydroxide to give a mixture of the acids (15) and (23). Treatment of this mixture with diazomethane gave a mixture of methyl esters, crystallisation of which gave the solid bicyclo-ester (22), m.p. 80° (light petroleum, b.p. 60-80°). The residual oil was hydrolysed with methanolic potassium hydroxide to give a viscous oil which would not crystallise, but whose infra-red spectrum was identical with that of the acid (15).

1-Methylcyclooct-1-ene-5-carboxylic acid (18).

This compound was obtained by decarboxylation of the di-acid (15), the procedures used being as follows.

A. Heating with copper powder. The di-acid (15) (1.3 g.) was mixed with copper powder (1 g.) and heated at 270° for 22 hours in a sealed Carius tube. The tube was cooled (-70°), opened, and the black oil dissolved in ether. The ethereal solution was extracted with 1N sodium hydroxide (3 x10 ml.), the alkaline extracts acidified (6N HCl), this solution extracted with ether (3 x 10 ml.) and the extracts dried ($MgSO_4$). Removal of the solvent left a yellow oil which, on distillation, gave 0.84 g. of a colourless oil, b.p. 90-92°/0.08 mm. (Found C,71.04%, H, 8.52%. $C_{10}H_{16}O_2$ requires C, 71.39% , H, 9.59%. The discrepancy is due to traces of the acid (23)). Molecular weight determination by mass spectrometry gave the value 170 ± 3 (calculated value 168). The amide (94) was prepared in the usual way (oxalyl chloride followed by ammonia) m.p. 174°, and was identical with a sample prepared by another route (see p. 105). This acid showed absorption in the infra-red spectrum at 3300-2800 cm.$^{-1}$ (acidic hydroxyl), 1720, 1260 cm.$^{-1}$ (carboxyl) and 820 cm.$^{-1}$

(cis trisubstituted double bond).

B. Thermal decarboxylation. The above procedure and work-up was repeated exactly, except that no copper powder was added. The product which was isolated was a crystalline acid, m.p. 138-140°, whose infra-red spectrum was identical with that of the bicyclo acid (23). A mixed m.p. showed no depression , 136-140°.

C. Heating with copper powder in quinoline. A mixture of the di-acid (15) (0.5 g.), copper powder (0.043 g.), and quinoline (0.85 ml.) was heated to 250° in a metal bath and the gas evolved was measured (46 ml. Theoretical evolution : 53 ml.). The mixture was cooled, extracted with ether and the ethereal extracts washed with 2N sodium hydroxide. The alkaline extracts were acidified (6N HCl), extracted with ether (4 x 10 ml.), and dried ($MgSO_4$). Removal of the solvent and distillation gave 0.33g. of a colourless oil whose infra-red spectrum was identical with that of the product from A above.

2-Methylcycloheptanone (27)

N-Nitroso-N-ethylurethane (180 g.) was added dropwise over an hour to a stirred solution of cyclohexanone (120 g.) in alcoholic potassium hydroxide (480 ml., 1.25%), the temperature being held at 10-15°. Addition completed, the mixture was stirred at room temperature for a further hour, after which the solvent was distilled off under reduced pressure. The residue was diluted with water, extracted with ether (3 x 300 ml.) and the extracts dried ($MgSO_4$). Fractional distillation then gave 99 g. of a colourless oil, b.p. 172-186°, which, on refractionation, gave 77 g. (50%) of 2-methylcycloheptanone, b.p. 178-184° and n_D^{21} = 1.4469. ($\nu_{C=O}$ = 1700 cm.$^{-1}$). 2:4-Dinitrophenylhydrazone, yellow needles (ethanol) m.p. 111° [88], and semicarbazone, colourless needles (aqueous methanol) m.p. 124-127° [89]. Gas-liquid chromatography with celite 545 acting as a support for a 10% polyethylene glycol stationary phase indicated a purity of greater than 95%.

2-Ethoxycarbonyl-7-methylcycloheptanone (29).

A mixture of 2-methylcycloheptanone (75 g.) and diethyl oxalate (103 g.) was cooled to -10° and added dropwise to a stirred solution of sodium (13.8 g.) in anhydrous ethanol (220 ml.) cooled to -10°. The resultant orange solution was stirred overnight at 0° and then at room temperature for 72 hours. The reaction mixture was then poured on to crushed ice, acidified (conc. HCl) and the precipitated yellow oil separated. The aqueous layer was extracted with ether (3 x 250 ml.), the combined extracts added to the oil and the whole washed with water, saturated sodium bicarbonate solution,water and dried ($MgSO_4$). Removal of the solvent left a clear red oil which was heated on the steam bath under vacuum for 2 hours. Decarbonylation was effected by adding powdered glass to the oil and heating at 200-220° for six hours.

Fractional distillation of the resultant black oil furnished 2-ethoxycarbonyl-7-methylcycloheptanone (42 g., 36%) as a colourless mobile oil, b.p. 80-84°/0.05 mm. and n_D^{21}= 1.4609. The corresponding pyrazolone was prepared by refluxing the ester (2 g.) and 100% hydrazine hydrate (1 g.) in methanol (10 ml.) for 1.5 hours. Removal of the solvent left a colourless solid which crystallised as needles from aqueous ethanol, m.p. 222-224° (Found C, 65.24% , H, 8.49% , N, 16.96%. $C_9H_{14}ON_2$ requires C, 65.03% , H, 8.49% , N, 16.85%.)

The lactone (31 A)

The condensation of 2-methylcycloheptanone and diethyl oxalate was carried out as described above, but using anhydrous ethanol which had been lying about for some time. When the glyoxalate ester was isolated, a solid precipitated from the oil. This solid was filtered off and washed with a little ethanol. The residual oil was in fact the required glyoxalate ester (28).

The solid by-product (50% yield) crystallised as long needles from aqueous ethanol, m.p. 175-177°. (Found C, 66.19% , H, 6.67%. $C_{10}H_{12}O_3$ requires C, 66.65% , H, 6.71%.). The infra-red absorption spectrum showed absorption at 3300 cm.$^{-1}$ (bonded hydroxyl), 1720 cm.$^{-1}$ (conjugated lactone) and 1660, 1640 cm^{-1} (double bonds), while the ultra-violet spectrum showed absorption of $\lambda_{max.}$ = 295 m.μ. (ξ = 18,400).

The corresponding enol-acetate (31 D) was prepared by refluxing the lactone (2.5 g.) in acetic anhydride (5 ml.) for 1.25 hours. The solvent was removed by distillation under reduced pressure and the solid residue crystallised from ethyl acetate as colourless needles, m.p. 118° (1.25 g.). (Found C, 64.73% , H, 6.09%. $C_{12}H_{14}O_4$ requires C, 64.85% , H, 6.35%.). The infra-red spectrum showed unresolved carbonyl absorption at 1750-1720 cm.^{-1} (acetate and lactone) and at 1680, 1630 cm.^{-1} (double bonds), while the ultra-violet spectrum showed absorption of $\lambda_{\text{max.}}$ = 289 m.μ. (ξ = 18,000).

Both the lactone and the enol-acetate described above were unstable compounds and decomposed to an oily paste in a few days.

<u>The lactone (31 B)</u>

Condensation of 2-methylcyclohexanone with diethyl oxalate in the usual way, but using commercial alcohol instead of anhydrous ethanol, gave a 40% yield of the lactone (31 B). The isolation of this product followed the same pattern as for the lactone (31 A). The lactone crystallised from aqueous ethanol as large prisms, m.p. 137-140°. (Found C, 59.39% , H, 6.57%. $C_9H_{10}O_3$ requires C, 65.05% , H, 6.07%). The infra-red spectrum was practically identical with that of the lactone (31 A) and the ultra-violet spectrum showed absorption of $\lambda_{\text{max.}}$ = 290 m.μ. (ξ = 19,300).

The enol acetate (31 C) was prepared in the same manner as the enol-acetate (31 D), and crystallised from aqueous ethanol as colourless needles, m.p. 79°. (Found C, 63.49% , H, 5.59%. $C_{11}H_{12}O_4$ requires C, 63.45% , H, 5.81%). The ultra-violet spectrum showed absorption of $\lambda_{max.}$ = 285 m.μ. (ξ = 20,200).

The properties of both the lactone (31 B) and its enol-acetate (31 C) were in agreement with the published data [14,15,16], but both of these compounds were very unstable and rapidly decomposed.

β-(1-Ethoxycarbonyl-2-keto-3- methylcycloheptyl)-propionaldehyde (30)

This aldehyde was synthesised in exactly the same manner as is described for the synthesis of β-(1-ethoxycarbonyl-2-keto-3-methylcyclohexyl)-propionaldehyde [3] and in65% yield, as a colourless viscous oil, b.p. 130-132°/0.1 mm., n_D^{21}= 1.4790. (Found C, 65.97% , H, 8.96%. $C_{14}H_{22}O_4$ requires C, 66.11% , H, 8.72%). The infra-red spectrum showed the carbonyl region as a broad, poorly resolved band at 1745-1700 cm.$^{-1}$, and characteristic absorption at 2720 cm.$^{-1}$ (aldehyde C-H stretch).

Oxidation of this aldehyde with silver oxide in the usual manner[90] furnished β-(1-ethoxycarbonyl-2-keto-3-methylcycloheptyl)-propionic acid as a viscou oil, b.p. 161°/0.7 mm., n_D^{20}= 1.4772 (m.p. 30-32°). (Found C, 62.09% , H, 8.07%. $C_{14}H_{22}O_5$ requires C, 62.20% , H, 8.20%).

1-Ethoxycarbonyl-6-methyl-7-hydroxybicyclo-[4:3:1]-decan-10-one (34)

A. Cyclisation with hydrochloric acid and dioxan.

A mixture of the aldehyde (30) (3 g.), dioxan (20 ml.) and conc. hydrochloric acid (20 ml.) was heated on the steam bath for 3 hours and then held at room temperature for 2 hours. The mixture was poured into saturated sodium chloride solution (100 ml.) and extracted with ether (2 x 50 ml.). The combined extracts were washed with saturated sodium chloride solution, dried ($MgSO_4$), and the solvent removed to leave a dark brown oil (2.6 g.). Fractional distillation gave 2.37 g. (79%) of the required alcohol as a colourless viscous oil, b.p. 131°/0.07 mm., $n_D^{20} = 1.4970$. (Found C, 65.89%, H, 8.74%. $C_{14}H_{22}O_4$ requires C, 66.11%, H, 8.72%). The infra-red spectrum showed hydroxyl absorption at 3400 $cm.^{-1}$.

B. Cyclisation with hydrochloric acid and acetic acid.

A mixture of the aldehyde (30) (3 g.), acetic acid (12 ml.), conc. hydrochloric acid (3 ml.) and water (6 ml.) was heated on the steam bath for 1 hour and held at room temperature for 5 hours. The reaction mixture was neutralised with saturated sodium bicarbonate solution and the precipitated oil extracted with ether (3 x 30 ml.). The combined extracts were washed with water, dried ($MgSO_4$) and the solvent removed. Distillation gave 2.1 g. (68%) of the required alcohol, b.p. 134°/1 mm., $n_D^{21} = 1.4969$.

1-Ethoxycarbonyl-4-hydroxy-5-methylbicyclo-[3:3:1]-nonan-9-one (35)

Cyclisation of the aldehyde (11) with hydrochloric acid and acetic acid as described by Murray et al. [3] gave an 80% yield of the alcohol (35) as a colourless oil, b.p. 130°/0.05 mm. and n_D^{21}= 1.4934.

Treatment of the aldehyde (30) with concentrated sulphuric acid. The aldehyde (30) (5 g.) was added dropwise with stirring to conc. sulphuric acid (15 ml.) held at 0°. The dark red mixture was stirred overnight, poured on to ice and thoroughly extracted with ether (5 x 50 ml.). The combined extracts were washed with dilute sodium bicarbonate (2 x 15 ml.), dried ($MgSO_4$), and the solvent removed Thin plate chromatography of the resulting red oil showed it to be a complex mixture, and both distillation and column chromatography proved unsuccessful in separating the components.

Acidification of the alkaline extracts, however, gave a precipitate of a colourless solid which was extracted with ether and purified by crystallisation from ethyl acetate as needles, m.p. 190-192°. The infra-red spectrum showed absorption at 3100-2800 cm.$^{-1}$ (acidic hydroxyl), 1695 cm.$^{-1}$ (conjugated carboxyl) and 1600,1500 cm.$^{-1}$ (aromatic skeletal vibration). The ultra-violet spectrum showed absorption of $\lambda_{max.}$ = 242 m.μ. (log.ξ = 3.95) and 284 m.μ. (log.ξ = 3.10). This evidence, and by analogy with the results of Murray et al.[3], suggests that this compound is 5-methyltetralin-8-carboxylic acid (32). (Found C, 75.56% , H, 7.44%. $C_{12}H_{14}O_2$ (32) requires C, 75.76% , H, 7.42%).

When the alcohol (34) was treated with conc. sulphuric acid, the same result was obtained, the aromatic acid (32) being produced in 5% yield, and the residue consisting of a complex mixture of oils which could not be separated.

Treatment of 1-ethoxycarbonyl-6-methylbicyclo-[4:3:1]-dec-7-ene-10-one (33) with concentrated sulphuric acid.

Addition of the ester (33) (100 mg.) to conc. sulpuric acid (5 ml.) gave a deep purple solution. After standing for 30 hours the mixture was worked up as described above and gave 20 mg of 5-methyltetralin-8-carboxylic acid (32), m.p. 186-190° (sublimed at 150°/0.5 mm.). The neutral fraction of the reaction mixture consisted of the same mixture of oils as is described above.

1-Ethoxycarbonyl-4-acetoxy-5-methylbicyclo-[3:3:1]-nonan-9-one (36)

A mixture of the alcohol (35) (10 g.) and acetic anhydride (25 ml.) in pyridine (30 ml.) was refluxed for 1 hour. The cooled reaction mixture was then poured into ice water (50 ml.) and extracted with ether (3 x 30 ml.). The combined extracts were washed with saturated sodium bicarbonate solution, water, 6N hydrochloric acid and dried ($MgSO_4$). Removal of the solvent and distillation gave the acetyl derivative (36) (9.05 g.) as a colourless oil, b.p. 132°/0.45 mm., $n_D^{21} = 1.4820$. (Found C, 64.05%, H, 7.91%. $C_{15}H_{22}O_5$ requires C, 63.81%, H, 7.85%). The infra-red spectrum showed a broad unresolved carbonyl band at 1750-1700 cm.$^{-1}$, but was transparent in the hydroxyl region.

1-Ethoxycarbonyl-6-methyl-7-acetoxybicyclo-[4:3:1]-decan-10-one (37)

Following exactly the procedure used for the acetoxy derivative (36) above, the compound (37) was synthesised in 80% yield as a colourless oil, b.p. 121°/0.08 mm., $n_D^{20} = 1.4890$. (Found C, 65.10%, H, 8.23%. $C_{16}H_{24}O_5$ requires C, 64.84%, H, 8.16%).

Attempted pyrolysis of the acetates (36) and (37).

The acetate (36) (0.5 g.) was passed through a 1 metre tube packed with glass helices and held at 520°, using nitrogen as a carrier and under vacuum conditions. The product was collected in a liquid air trap and was identified by its infra-red spectrum as unchanged acetate. The process was repeated three times with the same sample, but in each case the acetate was recovered unchanged.

Similarly the acetate (37) was pyrolysed at 550° and at 1 mm. and 20 mm. pressure. Once again the acetate was recovered unchanged.

1-Ethoxycarbonyl-5-methylbicyclo-[3:3:1]-nonan-4:9-dione (40)

A standard solution of chromium trioxide in sulphuric acid [91] was added dropwise to a stirred solution of the alcohol(35) (5.8 g.) in acetone (200 ml.) held at 0° until a permanent orange colour was obtained (4.4 ml. of oxidising solution). The mixture was diluted with water (500 ml.), extracted with ether (3 x 100 ml.), the ethereal extracts washed with water and dried ($MgSO_4$). Removal of the solvent and distillation gave 4.77 g. of the diketone (40) as a colourless oil, b.p. 127°/0.18 mm., n_D^{25}= 1.4860. (Found C, 65.25% , H, 8.05%. $C_{13}H_{18}O_4$ requires C, 65.53% , H, 7.61%). The corresponding mono-2:4-dinitrophenylhydrazone crystallised as yellow needles from acetic acid, m.p. 195-196° (Found C, 54.59% , H, 5.14% , N, 13.21%. $C_{19}H_{22}N_4O_7$ requires C, 54.54% , H, 5.30% , N, 13.39%).

1-Ethoxycarbonyl-6-methylbicyclo-[4:3:1]-decan-7:10-dione (41)

Using exactly the same procedure as for the diketone (40) above, 4.8 g. of the alcohol (34) gave 4.17 g. (88%) of the diketone (41) as a colourless oil, b.p. 122°/0.5 mm., n_D^{20}= 1.4940. (Found C, 66.68% , H, 8.20%. $C_{14}H_{20}O_4$ requires C, 66.64% , H, 7.99%). The corresponding mono-2:4-dinitrophenylhydrazone crystallised as yellow needle clusters from acetic acid, m.p. 130-131°. (Found C, 55.38% , H, 5.82% , N, 12.74%. $C_{20}H_{24}N_4O_7$ requires C, 55.55% , H, 5.59% , N, 12.96%).

The p-toluenesulphonylhydrazone (42)

A mixture of the dione (40) (2 g.) and p-toluenesulphonylhydrazine (1.56 g.) in ethanol (15 ml.) was refluxed for 15 min.. Water (10 ml.) was then added to the hot solution, which, on cooling, deposited the required derivative as a pale-yellow solid. Crystallisation from aqueous ethanol gave 2.15 g. (64%) of glistening plates, m.p. 138-140°. (Found C, 59.30%, H, 6.55%, N, 6.93%. $C_{20}H_{26}N_2O_5S$ requires C, 59.11%, H, 6.44%, N, 6.89%).

The p-toluenesulphonylhydrazone (43)

In exactly the same manner as for the derivative (42), 0.89 g. of the diketone (41) gave 1.18 g. (80%) of the required derivative (43) as glistening plates, m.p. 130-132°. (Found C, 60.12%, H, 6.65%, N, 6.81%. $C_{21}H_{28}N_2O_5S$ requires C, 60.01%, H, 6.67%, N, 6.67%).

Attempted decomposition of the p-toluenesulphonylhydrazone (42) with base.

A solution of (42) (1 g.) in a 1.3N solution of sodium in ethylene glycol (0.3 g. of sodium in 10 ml. of glycol) was refluxed for 1.5 hours. The reaction mixture was diluted with water (50 ml.) and extracted with ether (3 x 25 ml.), the combined extracts washed with dilute sodium carbonate and dried ($MgSO_4$). Removal of the solvent left a pale-yellow solid which rapidly solidified. Crystallisation from aqueous ethanol gave 0.7 g. of unchanged tosylhydrazone (42), m.p. 136-138°, undepressed on admixture with a genuine sample.

1-Methyl-4-naphthoic acid (45)

A mixture of selenium powder (250 mg.) and 5-methyltetralin-8-carboxylic acid (250 mg.) was heated for 20 hours in a metal bath held at 300°. The black residue was extracted with ether (5 x 5 ml.) and the extracts washed with 4N sodium hydroxide. Acidification of the alkaline extracts (6N HCl) gave a colourless solid which was extracted with ether. Removal of the solvent and crystallisation from dilute acetic acid gave needles (83 mg.) m.p. 173-175°, undepressed on admixture with a genuine sample of 1-methyl-4-naphthoic acid.

1-Methyl-4-bromonaphthalene (47)

A. Direct bromination. Pure 1-methylnaphthalene (12 g.) was treated with bromine (13.5 g.) in carbon tetrachloride (25 ml.) according to the literature procedure.[19] This gave 7.1 g. (38%) of pure 1-methyl-4-bromonaphthalene as a colourless oil, b.p. 169-172°/15 mm.

B. Via the sulphonic acid. Treatment of pure 1-methylnaphthalene with sulphuric acid gave 1-methylnaphthalene-4-sulphonic acid (48) as a colourless solid.[21] Treatment of the potassium salt of this acid with bromine gave 1-methyl-4-bromonaphthalene as a yellow oil (25%), b.p. 100-102°/0.15 mm., $n_D^{22} = 1.6501$.

1-Methyl-4-naphthoic acid (45)

Formation of the Grignard complex of 1-methyl-4-bromonaphthalene [20] and carbonation with dry-ice gave a 52%

yield of 1-methyl-4-naphthoic acid, m.p. 174-175°. The best method of purification was found to be sublimation, the acid subliming as needle clusters at 140°/0.2 mm..

5-Methyl-8-aminotetralin (49)

Treatment of 5-methyltetralin-8-carboxylic acid (1 g.) with hydrazoic acid (4.5 moles) in the normal manner[22] gave 0.55 g. of 5-methyl-8-aminotetralin as a colourless oil, b.p. 102°/0.8 mm., n_D^{20}= 1.5841. (Found C, 81.71%, H, 9.10%, N, 8.73%. $C_{11}H_{15}N$ requires C, 81.93%, H, 9.38%, N, 8.69%). The corresponding benzoate (Schotten-Baumann conditions) crystallised from methanol as colourless needles, m.p. 207°. (Found C, 81.38%, H, 7.23%, N, 5.10%. $C_{18}H_{19}NO$ requires C, 81.47%, H, 7.22%, N, 5.28%).

4-Methyl-5,6,7,8,-tetrahydronaphthol (50)

5-Methyl-8-aminotetralin (0.1 g.) was added to a hot, stirred solution of conc. sulphuric acid (0.1 ml.) in water (1 ml.). A further 1 ml. of water was added, the mixture cooled to 0° and a solution of sodium nitrite (0.1 g.) in water (1 ml.) added dropwise to the stirred suspension of amine sulphate. The mixture was stirred at 0° for 30 mins. to ensure complete diazotisation (positive starch iodide) and then stirred and heated in a water bath at 50° for 20 mins. The resulting black oil was steam distilled and the distillate was extracted with ether (3 x 10 ml.), and the combined extracts dried ($MgSO_4$). Removal of the solvent left a pale-yellow oil whose infra-red spectrum showed absorption at 3300 cm.$^{-1}$ (hydroxyl), and which rapidly solidified. Crystallisation from petroleum ether (b.p. 60-80°) gave 4-methyl-5,6,7,8,-tetrahydronaphthol (48 mg.) as a colourless solid (needles), m.p. 83-84°, undepressed on admixture with a genuine sample.[23]

Attempted succinoylation of p-bromotoluene.

Succinic anhydride (33 g.) and dry, powdered aluminium chloride (88 g.) were added in turn to a stirred solution of p-bromotoluene (60 g.) in carbon disulphide (200 ml.) and the final mixture stirred and refluxed for 24 hours. The colourless carbon disulphide layer was then decanted off and the residue decomposed with ice and hydrochloric acid (conc., 160 ml.). The resultant dark brown solid was filtered off, washed well with ice-cold water and dissolved in sodium carbonate solution. Treatment with charcoal and then acidification gave 46 g. of a fawn coloured solid which crystallised from aqueous ethanol as pale-yellow plates, m.p. 103-109°. Repeated crystallisation from carbon tetrachloride gave 34 g. of product as colourless plates, m.p. 118-121°. (Found C, 63.04% , H, 5.77%. $C_{11}H_{12}O_4$ requires C, 63.44% , H, 5.81%).

The same result was obtained when p-chlorotoluene was used.

5:8-Dimethyltetralin (52)

Condensation of *p*xylene with succinic anhydride under Friedel-Crafts conditions [26] gave β-2:5-dimethylbenzoylpropionic acid (51 A) in 52% yield as a colourless solid, m.p. 68°. Clemmensen reduction to γ-2:5-dimethylphenylbutyric acid proceeded in 87% yield and ring closure with sulphuric acid gave a 43% yield of 5:8-dimethyltetralone-1 (51 C) as a colourless oil, b.p. 99-102°/0.05 mm. Clemmensen reduction of the tetralone furnished a 60% yield of 5:8-dimethyltetralin (52) as a colourless oil, b.p. 76-78°/0.3 mm., n_D^{20} = 1.5461.

5-Methyl-8-isopropyltetralin (54)

Succinoylation of *p*-cymene under the conditions described by Dev and Guha [27] gave a 55% yield of β-2-methyl-5-isopropylbenzoylpropionic acid (53 A) as a colourless solid, m.p. 74-75°. Clemmensen reduction proceeded in high yield (88%) to give γ-2-methyl-5-isopropylphenylbutyric acid (53 B) as a colourless oil b.p. 158°/0.15 mm., n_D^{20} = 1.5174. Treatment of this acid with phosphorus pentachloride and aluminium chloride gave a 61% yield of 5-methyl-8-isopropyltetralone-1 (53 C) as a colourless oil, b.p. 110-112°/0.15 mm., n_D^{19} = 1.5537. Clemmensen reduction of this ketone then furnished 5-methyl-8-isopropyltetralin (54) as a colourless, mobile oil, b.p. 140-146°/14 mm. , n_D^{18} = 1.5385.

Attempted oxidations of 5:8-dimethyltetralin and of 5-methyl-8-isopropyltetralin.

All attempted oxidations were carried out under standard conditions, using chromyl chloride,[28] nitric acid, potassium permanganate, chromium trioxide in acetic anhydride,[29] and potassium ferricyanide,[30] but in no instance was any recognisable product obtained, the products of reaction consisting of intractable gums which defied purification.

1-Methyl-4-nitronaphthalene (59A)

Treatment of technical 1-methylnaphthalene with nitric acid resulted in an uncontrollable reaction and the production of a black gummy solid which was difficult to purify. Crystallisation from ethanol gave 15-20% of crude 1-methyl-4-nitronaphthalene, m.p. 60-70°. When pure 1-methylnaphthalene was used, a mixture of mono-, di- and tri-nitro isomers was obtained from which a 30% yield of 1-methyl-4-nitronaphthalene could be be obtained, m.p. 68-71°, by repeated fractional crystallisation from ethanol.

Synthesis of 5-methyltetralin-8-carboxylic acid (32)

(i) 2- and 3-Chloromethyl-4-bromotoluene (60) and (61)

Treatment of *p*-bromotoluene with hydrogen chloride and zinc chloride exactly as described by Fieser and Seligman[33] gave a 43% yield of a mixture of the chloromethyl derivatives (60) and (61) as a colourless lachrymatory oil b.p. 124-5°/15 mm., n_D^{19}= 1.5814 , and 5% of the dichloromethyl derivative (62) as colourless needles from benzene, m.p. 122-124°.

(ii) Diethyl 2 (5)-bromo-5 (2)-methylbenzylmalonate (63)
Following the literature procedure exactly, [33] this mixture of esters was obtained in 95% yield as a colourless, viscous oil b.p. 142-144°/0.2 mm., n_D^{14}= 1.5119.

(iii) 2(5)-Bromo-5(2)-methylbenzylmalonic acid (64)
Hydrolysis of the above mixture of esters (63) with hot ethanolic barium hydroxide [33] gave a quantitative yield of the mixture of malonic acids (64), m.p. 144-148°, as a colourless crystalline solid which was not purified.

(iv) β-2(5)-Bromo-5(2)-methylphenylpropionic acid (65)
The above mixture of malonic acids was decarboxylated in 95% yield [33] to the mixture of propionic acids (65). Distillation gave this mixture as a viscous, colourless oil b.p. 164-166°/1.8 mm., n_D^{20}= 1.5505, which slowly set solid, m.p. 38-42°.

(v) γ-2(5)-Bromo-5(2)-methylphenylbutyric acid (66)
Oxalyl chloride (30 ml.) and dimethylformamide (1 ml.) were added to a solution of the mixed acids (65) (35 g.) in anhydrous benzene (250 ml.), and the mixture allowed to stand overnight. Removal of the solvent left a colourless oil showing absorption in the infra-red spectrum at 1820 cm.$^{-1}$ (acid chloride). This oil was not purified further but was dissolved in anhydrous

ether and treated with excess of an ethereal solution of diazomethane. Removal of the solvent left a yellow oil showing absorption in the infra-red spectrum at 2200 cm.$^{-1}$ (diazoketone). This diazoketone was dissolved in anhydrous methanol, stirred and a solution of silver benzoate in triethylamine added dropwise. When evolution of nitrogen had ceased, the solution was filtered free of silver salts and the solvent removed. Ether was then added to the sludge and the last of the silver salts filtered off. The ethereal solution was washed with acid (6N HCl), and base (satd. $NaHCO_3$) and dried ($MgSO_4$). Removal of the solvent and distillation gave 33 g. (85%) of the required mixture of methyl esters as a colourless oil, b.p. 106°/0.04 mm, n_D^{17}= 1.5331. (Found C, 52.94 , H, 5.52%. $C_{12}H_{15}O_2Br$ requires C, 53.18% , H, 5.58%).

Hydrolysis of the mixture of methyl esters was effected in the usual manner with methanolic potassium hydroxide, and gave 27.5 g. (85%) of the mixture of butyric acids (66) as a viscous, colourless oil, b.p. 166-168°/0.05 mm., n_D^{20}= 1.5550. (Found C, 51.70% , H, 4.84%. $C_{11}H_{13}O_2Br$ requires C, 51.40% , H, 5.09%). Again this oil slowly set solid. (m.p. 48-60°).

(vi) <u>5(8)-Bromo-8(5)-methyltetralone-1 (67) and (68)</u>

Following exactly the procedure developed by Fieser and

Seligman,[33] cyclisation of the butyric acids (66) under Friedel-Crafts conditions gave an 87% yield of a mixture of the tetralones (67) and (68) as a fawn coloured solid. Fractional crystallisation from ether gave the tetralone (68) as long pale-pink needles (ether) m.p. 105°. (Found C, 55.11% , H, 4.70%. $C_{11}H_{11}BrO$ requires C, 55.25% , H, 4.64%). The other isomer (67) crystallised from ether-petroleum ether (b.p. 60-80°) as long colourless needles m.p. 98-100°. The infra-red spectrum showed absorption at 1690 $cm.^{-1}$ (conjugated carbonyl), and the ultra-violet spectrum showed absorption at $\lambda_{max.}$ = 219 m.μ. ($\log.\xi = 4.39$), 255 m.μ. ($\log.\xi = 3.83$) and 309 m.μ. ($\log.\xi = 3.37$).

5-Methyl-8-bromotetralin (69)

Modified Clemmensen reduction of the mixture of tetralones (67) and (68) gave 5-methyl-8-bromotetralin (69) as a colourless, mobile oil b.p. 84-86°/0.2 mm., $n_D^{19} = 1.5809$. (90% yield) (Found C, 59.07% , H, 6.13%. $C_{11}H_{13}Br$ requires C, 58.68% , H, 5.82%).[33]

(viii) 5-Methyltetralin-8-carboxylic acid (32)

Clean, dry magnesium turnings (0.21 g.) were placed in a flask and the flask baked in a free flame while sweeping continuously with dry nitrogen. Anhydrous ether (1 ml.), 5-methyl-8-bromotetralin (0.1 ml.) and ethyl bromide (0.05 ml.) were added and the reaction started by the application of a hot water bath. A solution of 5-methyl-

8-bromotetralin (1 g.) in anhydrous ether (10 ml.) was then added over 2 hours, the reaction being kept at a steady reflux. After refluxing for a further hour the mixture was cooled, a further 5 ml. of ether was added and solid carbon dioxide was added until reaction was completed.

The cold reaction mixture was hydrolysed with 6N sulphuric acid and the ethereal layer separated and dried ($MgSO_4$). Removal of the solvent and crystallisation from ethyl acetate gave 0.66 gm. of 5-methyltetralin-8-carboxylic acid as colourless needles m.p. 188-190°. (Found C, 75.86% , H, 7.15%. $C_{12}H_{14}O_2$ requires C, 75.76% , H, 7.42%). The infra-red spectrum of this product was identical with that of the product obtained as a rearrangement product in the bicyclo-[4:3:1]-series and the ultra-violet spectrum showed absorption at λ_{max} = 242 m.μ. (log.ξ = 3.92), 284 m.μ. (log.ξ = 3.12).

1-Ethoxycarbonyl-4-tosyloxy-5-methylbicyclo-[3:3:1]-nonan-9-one (70)

A solution of the alcohol (35) (2.1 g.) and recrystallised p-toluenesulphonyl chloride (2.10 g.) in dry pyridine (10 ml.) was allowed to stand at room temperature for 5 days. The reaction mixture was then poured on to ice (10 g.) and the mixture allowed to stand at room temperature for a further 2 days. The product was extracted with ether (3 x 10 ml.), the combined extracts washed with acid (6N HCl), base (satd. $NaHCO_3$), water, and dried ($MgSO_4$). Removal of the solvent left a yellow, viscous oil which would not crystallise, and which was not purified further (2.05 g., 60%). The infra-red spectrum was transparent in the hydroxyl region and showed absorption at 1605, 1500 $cm.^{-1}$ (aromatic skeletal vibration) and at 1360, 1180 $cm.^{-1}$ (sulphonate).

1:1-Diethoxycarbonyl-5-methylcyclooct-4-ene (71)

To a solution of sodium ethoxide in ethanol (from 0.64 g. of sodium and 11.2 ml. of anhydrous ethanol, 0.52 molar solution) was added 2 g. of the crude tosylate (70). the mixture was stirred at room temperature for 5 mins. and sodium p-toluenesulphonate was precipitated; to ensure completion of reaction the reaction mixture was stirred and refluxed for a further 2 hours. The cooled reaction mixture was poured into water (75 ml.) and acidified to congo red (6N HCl). The mixture was extracted with ether and the extracts washed with saturated sodium bicarbonate solution and dried ($MgSO_4$). Removal of the solvent left a yellow oil showing absorption in the infra-red spectrum at 1605, 1500 $cm.^{-1}$ (aromatic skeletal vibration), 1360, 1185 $cm.^{-1}$ (sulphonate) and 825 $cm.^{-1}$ (cis trisubstituted double bond). This mixture of unchanged (axial) tosylate and product could be separated in either of two ways. Distillation gave the required cyclooctene diester (71) (0.84 g., 62%) as a colourless oil b.p. 120-122°/ 0.2 mm., n_D^{25}= 1.4722. (Found C, 67.57% , H, 8.73%. $C_{15}H_{24}O_4$ requires C, 67.2% , H, 9.0%). If this method is used, the tosylate remains as an involatile residue which sets to a black gum. The other procedure is rapid chromatography on Woelm grade 1 neutral alumina, when the ester (71) is eluted with benzene, the tosylate (70) being eluted with 50% benzene in chloroform.

The ester (71) showed absorption in the infra-red spectrum at 1725, 1260 cm.$^{-1}$ (carbethoxyl) , 1485 cm.$^{-1}$ (skeletal vibration) and 830 cm.$^{-1}$ (double bond).

1-Methylcyclooct-1-ene-5-carboxylic acid (18)

A solution of potassium hydroxide (20 g.) in water (50 ml.) was added to a solution of the diester (71) (12.9 g.) in methanol (400 ml.) and the mixture refluxed for 16 hours. The methanol was then distilled off under reduced pressure, water added to the residue and the mixture extracted with ether (the extracts discarded). The alkaline solution was then acidified (6N HCl), extracted with ether (3 x 50 ml.), and the extracts dried ($MgSO_4$). Removal of the solvent and distillation gave 5.25 g. (65%) of a colourless oil from which a small amount of crystalline material separated. Recrystallisation of these crystals from benzene gave 0.35 g.

of colourless needles m.p. 137-140°, the infra-red spectrum of which was superimposable on that of the bicyclo acid (23) (m.p. 141-143°, mixed m.p. 136-140°). This impurity was always encountered at this hydrolysis but was seldom separated at this stage, the yield being only 2-5%.

The infra-red spectrum of the residual oil showed absorption at 3500-2700 cm.$^{-1}$ (acidic hydroxyl), 1745 cm.$^{-1}$ (lactone), 1725, 1270 cm.$^{-1}$ (carboxyl) and 830 cm.$^{-1}$ (double bond). The lactone (76) was not separated at this stage, and, in fact, slow distillation of the acid -lactone mixture gave a product rich in lactone, the 1745 cm.$^{-1}$ lactone absorption increasing in intensity and the 1725 cm.$^{-1}$ band decreasing in intensity. The acid (18) did not give an accurate analysis due to the small amounts of bicyclo acid (23) present.

1-Methyl-5-methoxycarbonylcyclooct-1-ene (77).

Excess of a dry ethereal solution of diazomethane was added dropwise to a solution of the acid (18) (plus lactone) in ether and the mixture allowed to stand at room temperature for 16 hours. Removal of the solvent left a yellow oil transparent in the hydroxyl region of the infra-red spectrum and showing absorption at 1745 cm.$^{-1}$ (lactone), 1725, 1260 cm.$^{-1}$ (carbomethoxyl) and 825 cm.$^{-1}$ (double bond). Distillation gave 3.6 g. (70%) of the ester (77) as a colourless, pleasant smelling oil b.p. 69°/0.1 mm., n_D^{25}= 1.4750. (Found C, 72,28% , H, 9.85%. $C_{11}H_{18}O_2$ requires C, 72.49% , H, 9.96%).

1-Methyl-5-hydroxymethylcyclooct-1-ene (78)

A solution of the ester (77) (3.25 g.) in anhydrous ether (20 ml.) was added dropwise to a stirred solution of lithium aluminium hydride (2.1 g.) in ether (50 ml.). The mixture was stirred and refluxed for 2 hours and then stirred at room temperature for a further 18 hours. Excess lithium aluminium hydride was decomposed with ethyl acetate and then saturated sodium sulphate solution. Sulphuric acid (6N) was added to dissolve the slurry of salts, the ethereal layer separated and the aqueous layer extracted with ether (2 x 30 ml.). The extracts were dried ($MgSO_4$) and the solvent removed and distillation gave 2.16 g. (79%) of the alcohol (78) as a colourless oil b.p. 104-106°/12 mm., n_D^{18}= 1.4938. (Found C, 77.67% , H, 11.39%. $C_{10}H_{18}O$ requires C, 77.86% , H, 11.76%). The infra-red spectrum showed absorption at 3500 cm.$^{-1}$ (hydroxyl) and 830 cm.$^{-1}$ (cis trisubstituted double bond).

Dehydration of the alcohol (78) with boric acid.

A mixture of the alcohol (78) (0.38 g.) and boric acid (0.14 g.) was heated slowly to 300° and held at that temperature for 40 mins. The cooled reaction mixture was extracted with ether to give 0.18 g. of a yellow oil which was distilled to give a mixture of the olefins (8) and (79) as a colourless mobile oil b.p. 175-185°. (Found C, 88.24% , H, 11.07%. $C_{10}H_{16}$ requires C, 88.16% , H, 11.84%). The infra-red spectrum showed absorption at 3063, 1665, 814 cm.$^{-1}$ (exocyclic double bond , ξ=43) and 3008, 1633 and 884 cm.$^{-1}$ (cis tri-substituted double bond , ξ=38). The isomer (8) of this mixture is obviously the minor component. The proton magnetic resonance spectrum showed the protons of the exocyclic double bond as a doublet at 5.2 and 5.3 τ. Gas-liquid chromatography showed that these two components accounted for some 95% of the product, and indicated 60-75% of (79) and 25-40% of (8).

<u>1-Methyl-5-acetoxymethylcyclooct-1-ene (80)</u>

A mixture of the alcohol (78) (0.5 g.) and acetic anhydride (2 ml.) in pyridine (5 ml.) was refluxed for 15 mins. The reaction mixture was poured on to ice, extracted with ether (3 x 10 ml.), the combined extracts washed with acid (6N HCl), base (satd. $NaHCO_3$) and dried ($MgSO_4$). Distillation then furnished 0.57 g. (90%) of the acetate (80) b.p. 135°/19 mm., n_D^{u}= 1.4730. (Found C, 73.35% , H, 10.30%. $C_{12}H_{20}O_2$ requires C, 73.43% , H, 10.27%). The infra-red spectrum showed absorption at 1740, 1270 cm.$^{-1}$ (acetoxy) and 832 cm.$^{-1}$ (double bond).

Pyrolysis of the acetate (80)

Pyrolysis at 480°/11 mm. proved totally unsuccessful, the acetate being returned unchanged. Accordingly, the acetate (80) (0.5 g.) was pyrolysed at 500-550° at atmospheric pressure and in a slow stream of nitrogen by passage through a 1 metre column packed with glass helices. The product was collected in a liquid air trap, dissolved in ether, washed with saturated sodium bicarbonate solution and dried ($MgSO_4$). Removal of the ether and distillation gave 0.2 g. of a colourless oil, b.p. 136-139°, n_D^{17}= 1.4700. The infra-red spectrum showed absorption at 3060, 1660 and 890 cm.$^{-1}$ (exocyclic double bond), but there was also multiple absorption in the region 1200-900 cm.$^{-1}$ which was not assigned. The proton magnetic resonance spectrum was extremely complex and was not assigned. Chromatography on grade 1 neutral alumina was unsuccessful in purifying the compounds of this mixture.

1:1-Dihydroxymethylcyclohexane (90)

Condensation of 1:5-dibromopentane with diethyl malonate after the method described by Dox and Yoder [42] gave a 56% yield of 1:1-diethoxycarbonylcyclohexane as a colourless, mobile oil, b.p. 124-128°/14 mm., n_D^{20}= 1.4461. Reduction of this ester in the same manner as was described for the alcohol (78) gave an 84% yield of the diol (90) as colourless needles (benzene) m.p. 95°. [92]

2-Benzylpropane-1:3-diol (91)

Base catalysed condensation of diethyl malonate with benzyl chloride [93] gave a 58% yield of diethyl benzylmalonate as a colourless oil b.p. 150- 153°/5 mm.. Reduction of this ester with lithium aluminium hydride (see preparation of the diol (90)) gave a 75% yield of 2-benzylpropane-1:3-diol (91) as colourless plates m.p. 64° from carbon tetrachloride. (Found C, 71.90% , H, 8.57%. $C_{10}H_{14}O_2$ requires C, 72.26% , H, 8.49%).

2-Piperonylpropane-1:3-diol (92)

Crossed Cannizzaro reaction of piperonal with formaldehyde [44] gave an 87% yield of piperonyl alcohol as colourless needles m.p. 58° (light petroleum b.p. 60-80°). Treatment of this alcohol with hydrobromic acid[45] gave a 95% yield of piperonyl bromide as long colourless needles m.p. 49° (light petroleum b.p. 60-80°). Condensation of this bromide with diethyl malonate [46] gave diethyl 2-(3:4-methylenedioxy)-benzylmalonate as a colourless oil b.p. 130°/0.15 mm. (Found C, 61.45% , H, 6.07%. $C_{15}H_{18}O_6$ requires C, 61.21% , H, 6.17%). Reduction with lithium aluminium hydride then gave 2-piperonylpropane-1:3-diol (92) as colourless plates m.p. 91-92° from carbon tetrachloride (67% yield). (Found C, 62.69% , H, 6.59%. $C_{11}H_{14}O_4$ requires C, 62.84% , H, 6.71%.).

Attempted retro-Prins reactions.

The monotosylate esters of the diols (88), (89), (90), (91) and (92) were prepared and treated under a variety of conditions, but with no success.[94]

Treatment of 1:1-diethoxycarbonyl-5-methylcyclooct-4-ene (71) with lithium aluminium hydride.

A solution of the ester (71) (5 g.) in anhydrous ether (25 ml.) was added dropwise over an hour to a stirred solution of lithium aluminium hydride in ether (250 ml.). The mixture was refluxed for 16 hours and then worked up in the usual manner to give an oil which showed absorption in the infra-red spectrum at 3400 c.m.$^{-1}$ (hydroxyl) and at 1725 cm.$^{-1}$ (ester). This oil was therefore retreated with fresh lithium aluminium hydride for a further 24 hours, and the product in this case was a solid which crystallised from benzene-light petroleum (b.p. 60-80°) as large colourless plates, m.p. 134-136°. The infra-red spectrum showed absorption at 3400, 1050 cm.$^{-1}$ (hydroxyl) and at 710 cm.$^{-1}$ (cis disubstituted double bond). The infra-red spectrum showed the characteristic fine structure associated with the bicyclo-[3:3:1]-nonane compounds, and was in fact superimposable on the spectrum of the bicyclo diol (93). (Found C, 72.83% , H, 9.45%. (93) $C_{11}H_{18}O_2$ requires C, 72.49% , H, 9.96%). The diol (93) was prepared by reduction of the ester (6) with lithium aluminium hydride in the usual way[34] and crystallised from ethyl acetate-petroleum ether (b.p. 60-80°) as colourless needles m.p. over the range 110-140°.

1-Methylcyclooct-1-ene-5-carboxylic acid chloride (18 A)

A mixture of the acid (18) (4.7 g.) and oxalyl chloride (4.8 ml.) in anhydrous benzene (50 ml.) was allowed to stand at room temperature overnight. Removal of the solvent left a pale-yellow oil whose infra-red spectrum showed absorption at 1815 $cm.^{-1}$ (acid chloride) and 1745 $cm.^{-1}$ (lactone). This mixture of acid chloride and lactone was not purified.

1-Methylcyclooct-1-ene-5-carboxamide (94)

The acid chloride (18 A) (4.5 g.) was added dropwise over 15 mins. to 0.880 ammonia (25 ml.) held at 0°. The mixture was stirred during the addition and for a further 15 mins. after addition was complete. The tacky solid was then filtered off, washed well with water and then with petroleum ether (b.p. 60-80°) to remove the lactone (76). The solid amide then crystallised as needle clusters from ethyl acetate, m.p. 174-175°. (Found C, 71.60% , H, 10.32% , N, 8.18%. $C_{10}H_{17}NO$ requires C, 71.81% , H, 10.25% , N, 8.38%). The infra-red spectrum showed absorption at 3300, 3150 $cm.^{-1}$ (N-H stretch), 1660 $cm.^{-1}$ (amide carbonyl) and 820 $cm.^{-1}$ (cis trisubstituted double bond).

The petroleum ether washings were dried ($MgSO_4$) and the solvent removed. Distillation then gave the lactone (76) as a colourless mobile oil, b.p. 66°/0.5 mm. and n_D^{22}= 1.4770. (Found C, 71.53% , H, 8.99%. $C_{10}H_{16}O_2$ requires C, 71.39% , H, 9.59%). The infra-red spectrum showed absorption at 1745 cm.$^{-1}$ (lactone).

The yield of amide in the above preparation was 3.73 g. (80%) and of lactone was 0.45 g. (10%, yields based on the acid (18)).

1-Methylcyclooct-1-ene-5-N-methylcarboxamide (95)

The acid chloride (18 A) (4.4 g.) was added to a stirred, ice-cold, aqueous solution of methylamine (25% methylamine, 15 ml.). After stirring the mixture for 15 mins. the product was extracted with ether (3 x 15 ml.) and the extracts dried ($MgSO_4$). Removal of the solvent left a brown oil which would not crystallise and whose infra-red spectrum showed absorption at 3300 cm.$^{-1}$ (N-H stretch) (1745 cm.$^{-1}$ (lactone) 1650 cm.$^{-1}$(amide carbonyl) and 825 cm.$^{-1}$ (double bond). Distillation gave 0.41 g. of the lactone (76) b.p. 76-78°/1 mm. and 3.03 g. of the N-methylamide (95) as a colourless oil b.p. 138-140°/1 mm. which rapidly solidified. Crystallisation from petroleum ether (b.p. 100-120°) gave the amide as colourless needle clusters, m.p. 85-86°. (Found C, 72.81% , H, 10.65%, N, 7.45%. $C_{11}H_{19}NO$ requires C, 72.88% , H, 10. 57% , N, 7.73%).

1-Methylcyclooct-1-ene-5-N:N-dimethylcarboxamide (96)

The same procedure was used here as was used for the amide

(95), the acid chloride (18 A) (7 g.) being added to a 33% aqueous solution of dimethylamine (25 ml.). The same work up gave a yellow oil whose infra-red spectrum showed lactone absorption at 1745 $cm.^{-1}$ and amide absorption at 1650 $cm.^{-1}$. Fractional distillation proved unsuccessful as a method of separation, the two compounds co-distilling over the range 70-90°/0.15 mm. Attempts to separate the components by chromatography on grade 1 Woelm neutral alumina also proved unsuccessful, a mixture of lactone and amide being eluted even with petroleum ether (b.p. 40-60°). No further attempts were made to separate these two compounds, and the lactone was easily separated at a later stage.

<u>1-Methyl-5-aminomethylcyclooct-1-ene (97)</u>

The amide (94) (2 g.) was suspended in anhydrous ether (90 ml.) and lithium aluminium hydride (1 g.) was added in small amounts over 30 mins. at such a rate as to maintain a steady reflux. Addition completed, the mixture was stirred and refluxed gently for a further 30 mins.. The flask was then cooled in an ice-bath and excess reagent decomposed by the dropwise addition of 1 ml. of water, 1 ml. of 15% sodium hydroxide solution, and 3 ml. of water in turn [95]. After vigorous stirring for 20 mins., the granular precipitate was filtered off, washed with warm ether and the ethereal solution dried ($MgSO_4$). Distillation then gave 1.36 g. (75%) of the amine (97) as a colourless oil b.p. 114-116°/22 mm., n_D^{17} = 1.4978. (Found C, 78.11% , H, 12.67% , N, 8.89%. $C_{10}H_{19}N$ requires C, 78.35% , H, 12.50% , N, 9.14%). The corresponding picrate derivative crystallised from ethanol as yellow plates m.p. 189-190°. (Found C, 50.03% , H, 5.67% , N, 14.42%. $C_{16}H_{22}N_4O_7$ requires C, 50.26% , H, 5.80% , N, 14.65%).

The amine showed absorption in the infra-red spectrum at 3400,3300 cm.$^{-1}$ (N-H stretch) and 823 cm.$^{-1}$ (cis tri-substituted double bond).

1-Methyl-5-N-methylaminomethylcyclooct-1-ene (98)

Reduction of the secondary amide (95) in exactly the same way as described above for the amide (94) furnished the secondary amine (98) in 56% yield as a colourless oil, b.p. 96-99°/15 mm. (Found C, 79.27% , H, 12.44% , N, 8.12%. $C_{11}H_{21}N$ requires C, 78.97% , H, 12.65% , N, 8.37%). The infra-red spectrum showed absorption at 3250 cm.$^{-1}$ (N-H stretch) and 820 cm.$^{-1}$ (double bond).

1-Methyl-5-N:N-dimethylaminomethylcyclooct-1-ene (99)

(i) By reduction of the tertiary amide (96). A solution of 4.6 g. of the amide-lactone mixture (from preparation of (96)) in 35 ml. of ether was added dropwise over 1 hour to a stirred suspension of lithium aluminium hydride (1 g.) in ether (35 ml.). The mixture was then stirred at room temperature for 24 hours and excess reagent decomposed with ethyl acetate followed by saturated sodium sulphate solution. The inorganic salts were filtered off and the ethereal solution extracted with 6N sulphuric acid (2 x 10 ml.). The inorganic salts were dissolved in 6N sulphuric acid (15 ml.) and the combined acid extracts made strongly basic with conc. sodium hydroxide solution. The resulting gelatinous mixture was extracted with ether (3 x 15 ml.) and the extracts dried (K_2CO_3). Distillation then gave 3.5 g. of the tertiary amine (99) as a colourless oil b.p. 108-109°/14 mm., n_D^{20}= 1.4760. (Found C, 79.30% , H, 12.60% , N, 7.45%. $C_{12}H_{23}N$ requires C, 79.49% , H, 12.79% , N, 7.72%). The corresponding picrate crystallised from ethanol as yellow needles m.p. 123-124°. (Found C, 52.41% , H, 6.38% , N, 13.53%. $C_{18}H_{26}N_4O_7$ requires C, 52.67% , H, 6.39% , N, 13.65%).

The infra-red spectrum showed strong absorption at 2720 cm.$^{-1}$ (N-methyl groups) and 820 cm.$^{-1}$ (double bond).

(ii) By methylation of the primary amine (97) Technical 98% formic acid (2.714 g.) was added dropwise to the amine (97) (1.772 g.) held at 0°. Formaldehyde (2.774 g. of 37% aqueous solution) was added and the mixture heated on the steam bath for 16 hours. Conc. hydrochloric acid was added to the cooled reaction mixture and water and excess formic acid removed by distillation under reduced pressure. The viscous residue was made strongly alkaline with 10% sodium hydroxide solution and the product isolated by steam distillation and ether extraction of the distillate. Distillation then gave 1.56 g. (75%) of the tertiary amine as a colourless oil b.p. 102-105°/15 mm., n_D^{20}= 1.4762. (ν_{N-Me} = 2720 cm.$^{-1}$).

(iii) By methylation of the secondary amine (98). The procedure here was exactly as for the primary amine (97) in (ii) above, and gave an 80% yield of the tertiary amine (99) as a colourless oil b.p. 100-103°/14 mm., n_D^{19}= 1.4769. (n.b. only 1 mole of formaldehyde used).

The N-oxide (100)

A solution of the amine (99) (1 g.) in methanol (2 ml.) was cooled to 0° and 2 g. of 35% hydrogen peroxide added over 20 mins. The solution was then allowed to stand at room temperature for 48 hours. Adams' catalyst (PtO_2) was added and the mixture stirred at room temperature for 24 hours. The solution was filtered free of platinum oxides and the solvents removed by distillation under reduced pressure from a water bath held at 35°. The residual yellow oil was not purified further. The picrate derivative of the amine oxide crystallised from ethanol as brilliant yellow needles m.p. 115-116°. (Found C, 50.66% , H, 6.18% , N, 13.20%. $C_{18}H_{26}N_4O_8$ requires C, 50.70% , H, 6.15% , N, 13.14%).

The yield in the above preparation was 0.94 g. , and this procedure was found to be superior to the other general method (aqueous solution) 48 in which 1 g. of amine gave 0.77 g. of the amine oxide.

1-Methyl-5-methylenecyclooct-1-ene (8)

The amine oxide (100) (0.9 g.) was placed in a 10 ml. flask, 1 ml. of water added and the flask packed with glass wool. This was connected to two traps in series, each cooled to -5,-10° and the system evacuated (15 mm.). The flask was immersed in an oil bath which was heated slowly to 100° and then to 160° over a further 30 mins. Pyrolysis proceeded rapidly at 120-160° and, when complete, the traps were washed out with ether. The ethereal solution was washed with 2N sulphuric acid (10 ml.) and dried ($MgSO_4$). Distillation then gave 0.435 g. (58%) of the bis-olefin (8) as a colourless, volatile oil, b,p. 138-140°, n_D^{26} = 1.4822.

The infra-red spectrum showed absorption at 3064, 1639 and 890 cm.$^{-1}$ (exocyclic double bond, $\varepsilon_{890} = 186$, $\Delta\nu_{\frac{1}{2}} = 7$ cm.$^{-1}$) and at 3032, 1668 and 822 cm.$^{-1}$ (cis tri-substituted double bond, $\varepsilon_{822} = 70$, $\Delta\nu_{\frac{1}{2}} = 11$ cm.$^{-1}$). The proton magnetic resonance spectrum showed the single vinyl proton as a multiplet centered at 4.65 τ and the two protons of the exocyclic double bond as a doublet at 5.28 and 5.31 τ. The eight allylic protons (excluding the methyl group) showed as a multiplet at 7.84-8.1 τ, while the methyl group group was a doublet at 8.31 and 8.34 τ. Only two protons are of the cyclohexanone type and these appeared as a broad unresolved band at 8.25-8.6 τ.

7-Ketooctane-1:3-dicarboxylic acid (101)

Attempted oxidation of the acid (18) under the conditions described by Rudloff [51] proved unsuccessful, and the acid was recovered unchanged. The acid (18) (0.552 g.) was therefore dissolved in chloroform, the solution cooled to -70° and ozone passed through until a starch-iodide test for excess ozone proved positive. The mixture was allowed to come to room temperature, 3 ml. of 30% hydrogen peroxide in 4 ml. of acetic acid was added, and the mixture stirred on the steam bath for 1 hour. The mixture was diluted with water, excess peroxide destroyed with ferrous sulphate, and the product extracted with ether (4 x 40 ml.). Removal of the solvent and distillation gave 7-ketooctane-1:3-dicarboxylic acid (101) (0.437 g.) as a viscous colourless oil b.p. 138-140°/0.3 mm., n_D^{20} = 1.4432. (Found C, 55.42%, H, 7.22%. $C_{10}H_{16}O_5$ requires C, 55.54%, H, 7.46%). The infra-red spectrum was very diffuse and showed the acidic hydroxyl as a broad band at 3400-2700 cm.$^{-1}$ On standing this acid went partly solid, but melted above 15°.

1:1:3-Triethoxycarbonylpropane (102)

Condensation of diethyl malonate with ethyl β-chloropropionate as described by Ruzicka et al. [53] gave a 70% yield of the triester (102) as a colourless oil b.p. 163-164°/16 mm., n_D^{19} = 1.4350.

α-Acetobutyrolactone (105) Treatment of γ-butyrolactone after the method of Reppe [54] with ethyl acetate gave a 15% yield of α-acetobutyrolactone (105) as a colourless oil b.p. 131-132°/15 mm. , n = 1.4565.

5-Bromopentan-2-one (103)

Treatment of α-acetobutyrolactone with hydrobromic acid according to the literature procedure [55] gave a 36% yield of 5-bromopentan-2-one (103) as a colourless oil b.p. 80-82°/21 mm., n = 1.4560. This compound decomposed rapidly to a black oil which smelled strongly of hydrogen bromide.

Attempted preparation of 1:3:3-triethoxycarbonyl-7-ketooctane. (104)

5-bromopentan-2-one (1 g.) was added dropwise to a solution of sodio salt of (102) . (from 0.138 g. of sodium dissolved in 2.1 ml. of anhydrous ether, followed by 3.12 g. of (102)) held at 60°. The mixture was refluxed for 2 hours, then diluted with water and extracted with ether (3 x 10 ml.). Distillation gave 0.509 g. of a volatile liquid b.p. 101-107°, n = 1.4077 and 1.4 g. of a colourless oil b.p. 160-162°/15 mm., n = 1.4354. The higher boiling fraction was identified (infra-red spectra) as unchanged triester (102), and the lower boiling fraction as cyclopropylmethyl ketone (107), (infra-red absorption at 1700 cm.$^{-1}$ (ketone) and 1015 cm.$^{-1}$ (cyclopropyl group)). A sample of genuine cyclopropylmethylketone showed identical absorption in the infra-red spectrum and the two spectra were superimposable. The 2:4-dinitrophenylhydrazone of the by-product was prepared in the usual way and crystallised from methanol-ethyl acetate as dark red needles mp. 148-151°. A sample of genuine 2:4-dinitrophenylhydrazone was prepared and had m.p. 148-150°, mixed m.p. with the above derivative 148-150°.

5-Chloropentan-2-one (109)

Treatment of acetoacetic ester with ethylene oxide[57] gave a 64% yield of α-acetobutyrolactone (105), b.p. 129-130°/15 mm., $n_D^{20} = 1.4560$. Distillation of this compound from hydrochloric acid gave a 65% yield of 5-chloropentan-2-one as a colourless oil b.p. 63-64°/15 mm., $n_D^{20} = 1.4383$.[58] On standing for a few weeks, this compound decomposes to a brown oil and smells of hydrogen chloride.

A number of attempts were made to condense this chloroketone with the triester (102), but in each case the products of reaction were cyclopropylmethylketone and the unchanged ester (102).

Pent-4-yn-1-ol (111)

Treatment of tetrahydrofurfuryl chloride with sodamide according to the literature procedure gave an 83% yield of pent-4-yn-1-ol as a colourless mobile oil b.p. 60°/15 mm., $n_D^{21} = 1.4447$.[60] ($\nu_{C\equiv C} = 2090$ cm.$^{-1}$).

5-Bromopent-1-yne (113)

Treatment of pent-4-yn-1-ol with p-toluenesulphonyl chloride in pyridine gave a 67% yield of the corresponding tosylate (112) ester[61]. Distillation of this ester from 2-(2-ethoxyethoxy)-ethanol containing calcium bromide gave a 52% yield of 5-bromopent-1-yne (113) as a colourless oil b.p. 130-131°, $n_D^{21} = 1.4641$.[61] ($\nu_{C\equiv C-H} = 3250$ cm.$^{-1}$).

1:3:3-Triethoxycarbonyloct-7-yne (114)

The triester (102) (6.92 g.) was added to a solution of sodium (0.62 g.) in ethanol (25 ml.) and the mixture heated to 40°. 5-Bromopent-1-yne (3.9 g.) was added dropwise over 20 mins. to the stirred mixture and the whole refluxed for 2 hours. The mixture was diluted with water, extracted with ether (3 x 30 ml.) and the extracts dried ($MgSO_4$). Distillation gave 5.5 g. (65%) of the ester (114) as a colorless oil b.p. 154-155°/ 0.9 mm., $n_D^{21} = 1.4530$. (Found C, 62.24%, H, 7.92%. $C_{17}H_{26}O_6$ requires C, 62.56%, H, 8.03%). The infra-red spectrum showed absorption at 3250 cm.$^{-1}$ (acetylenic hydrogen) and 1730 cm.$^{-1}$ (ester).

1:3:3-Triethoxycarbonyl-7-ketooctane (104)

A solution of the ester (114) (3.6 g.) in methanol (10 ml.) was added slowly to a catalyst mixture prepared by warming together red mercuric oxide (0.5 g.), boron trifluoride etherate complex (0.2 ml.), trichloroacetic acid (10 mg.) and methanol (1 ml.). The mixture was shaken at room temperature for 2.5 hours, poured into 6N sulphuric acid and the product extracted with ether (3 x 10 ml.). Distillation gave 2.8 g. of a colourless oil b.p. 140°/0.06 mm., n_D^{23} = 1.4489 whose infra-red spectrum showed broad carbonyl absorption at 1735-1700 cm.$^{-1}$ and showed no acetylenic proton absorption at 3250 cm.$^{-1}$ (Found C, 59.08%, H, 8.18%. $C_{17}H_{28}O_7$ requires C, 59.28%, H, 8.19%).

7-Ketooctan-1:3-dicarboxylic acid (101)

Attempted hydrolysis with strong acid (conc HCl/AcOH) and strong base(conc. NaOH) proved totally unsuccessful, the products being intractable gums.

The triester (114) (3.8 g.) was refluxed for 8 hours with a solution of barium hydroxide (16 g.) in water (200 ml.). The mixture was cooled, the barium salt filtered off and washed with ether. Acid (6N HCl) was added, the mixture heated under vacuum to remove the solvent and the organic material extracted with boiling ethanol. The ethanol was distilled off and the residual yellow gum distilled up a Carius tube to give a colourless oil b.p. 170°/0.14 mm., n_D^{21} = 1.4440. (Found C, 55.35%, H, 7.63%. $C_{10}H_{16}O_5$ requires C, 55.54%, H, 7.46%). The infra-red spectrum of this product was identical with that of the diacid obtained from the ozonolysis of the acid (18).

The yield of acid (101) from the above hydrolysis was very low (10%), and the isolation of the product was tedious. A better method of hydrolysis was by using hydrochloric acid - acetic acid after the method of Sorm and Dolejs [75], when a 77% yield of the acid was obtained.

Attempts were made to prepare a bis p-bromophenacyl ester derivative by treatment of the acid with p-bromophenacyl bromide in the usual way.[96] The product in every case was a colourless solid which crystallised as needles from ethanol m.p. 135-136°. (Found C, 48.05%, H, 3.45%. The bis-p-bromophenacyl ester of the acid (101), $C_{26}H_{26}Br_2O_7$ requires C, 51.19%, H, 4.29%). This derivative was found to be the bis p-bromophenacyl ester of glutaric acid (115), m.p. 136° ($C_{21}H_{18}Br_2O_6$ (115) requires C, 47.94%, H, 3.45%). A genuine sample of this derivative (115) was prepared from glutaric acid in the usual way and had m.p. 135-136°, mixed m.p. with the above derivative 134-136°.

The acid (101) was refluxed in 5% sodium hydroxide for 2 hours, the cooled mixture saturated with potassium carbonate and extracted with ether. This gave a small amount of yellow oil whose infra-red spectrum was identical with that of cyclopropylmethylketone and which gave a 2:4-dinitrophenylhydrazone m.p. 146-151°, undepressed on admixture with a genuine sample of cyclopropylmethylketone 2:4-dinitrophenylhydrazone.

1-Ethoxycarbonyl-6-methyl-7-tosyloxybicyclo-[4:3:1]-decan-10-one (116)

This compound was prepared in exactly the same way as the bicyclo-[3:3:1]-tosylate (70), the yields being of the order 70-85%. The crude yellow oil was not purified, and showed absorption in the infra-red spectrum at 1605, 1500 cm.$^{-1}$ (aromatic skeletal vibration) and 1355, 1180 cm.$^{-1}$ (sulphonate).

1:1-Diethoxycarbonyl-5-methylcyclonon-4-ene (117)

The same procedure was used here as was used for the preparation of the diester (71), and the reaction proceeded as rapidly, sodium p-toluenesulphonate being precipitated in a few minutes. The same work up as for (71) gave a yellow oil whose infra-red spectrum, besides showing the absorptions of the unchanged tosylate, showed a weak absorption at 710 cm.$^{-1}$ characteristic of the bicyclo double bond.

When distillation of this mixture was attempted, about 20% of the expected quantity of diester (117) distilled as a colourless oil b.p. 114°/0.7 mm., n_D^{20}=1.4812. (Found C, 68.41%, H, 9.54%. $C_{16}H_{26}O_4$ requires C, 68.05%, H, 9.54%). The residue in the distilling flask was a black oil which began to decompose, giving off white fumes. The mixture rapidly set to a black glass from which no further products could be obtained. Distillation, though it gave fairly pure samples of the diester, was a wasteful process and was not used in future runs.

The method used to isolate the diester was chromatography on grade 1 neutral alumina (Woelm). The diester was eluted with benzene and unchanged tosylate with chloroform. The infra-red spectra of the fractions of diester obtained in this way, however, showed absorption at 710 cm.$^{-1}$ (cis disubstituted double bond) characteristic of the bicyclo systems. Thin plate chromatography confirmed that the product from column chromatography consisted of two main components, and infra-red spectra indicated these as being the monocyclic ester (117) and the bicyclic ester (118). A sample of chromatographed material was used to confirm the nature of the two components as follows.

A mixture of the ester mixture (0.5 g.) and 100% hydrazine hydrate (0.5 g.) in methanol (5 ml.) was refluxed for 2 hours. Removal of the solvent left a yellow gum which would not crystallise, but which sublimed as colourless needles at 140°/0.7 mm. This compound is the bicyclo pyrazolone (119),and had m.p. 163-164°. (Found C, 70.76% , H, 7.93% , N, 13.63%. $C_{12}H_{16}N_2O$ requires C, 70.56% , H, 7.90% , N, 13.72%).

The barbiturate derivative (120) was prepared by a standard procedure [97] from the ester mixture and urea. The derivative crystallised from aqueous methanol as colourless chunky crystals, m.p. 257-259°. (Found C, 62.59% , H, 6.99% ,N, 11.06%. $C_{13}H_{18}N_2O_3$ requires C, 62.38% , H, 7.25% , N, 11.19%).

Chromatography thus results in a mixture of the esters (117) and (118) the latter being least abundant. The yield of ester mixture is quite reasonable, 54 g. of bicyclo-[4:3:1]-tosylate (116) giving, after chromatography and distillation, 16.2 g. of the ester mixture. Many attempts were made to separate these esters but without success.

Attempted hydrolysis of the diester (117)

Hydrolysis of pure diester (117) (obtained by distillation of the tosylate - ester mixture) with methanolic potassium hydroxide in the usual way (16 hour reflux) gave a yellow gum which distilled as a viscous oil at 136-140°/0.8 mm. This oil rapidly solidified and crystallised as chunky prisms from benzene-light petroleum (b.p. 60-80°) m.p. 145-146°. The infra-red spectrum was sharply resolved in all regions, characteristic of the bicyclo systems, and showed absorption at 3300-2800 $cm.^{-1}$

(acidic hydroxyl), 1740, 1270 (carboxyl) and 1700 cm.$^{-1}$ (ketone) and 710 cm.$^{-1}$ (cis disubstituted double bond). This evidence suggested that this compound was the bicyclo acid (121), and this was confirmed by analysis. (Found C, 69.20% , H, 7.51%. $C_{12}H_{16}O_3$ (121) requires C, 69.21% , H, 7.74%). The analysis figures do not correspond with those of either the monocyclic diacid (122) or mono-acid (124).

The corresponding methyl ester was prepared in the usual way by treating the acid with diazomethane and crystallised from hexane as large prisms, m.p. 63-64°. (Found C, 70.42% , H, 8.19%. $C_{13}H_{18}O_3$ requires C, 70.24% , H, 8.16%).

The corresponding hydroxy acid was prepared in the usual way by reduction of the 10-keto function with sodium borohydride and crystallised from petroleum ether (b.p. 80-100°) as large chunky prisms m.p.103-105°. (Found C, 68.76% , H, 8.63%. $C_{12}H_{18}O_3$ requires C, 68.54% , H, 8.63%).

Vigorous hydrolysis of the ester (117) always resulted in an 80-95% yield of the bicyclo acid (121), and this procedure was therefore used to prepare the bicyclo-[4:3:1]-compounds which had otherwise proved inaccessible.

Other processes which were tried as a means of hydrolysis were barium hydroxide,[66] methanolic potassium bicarbonate,[67] boiling water in a sealed tube,[68] lithium iodide in pyridine,[69] and a variety of acid conditions but in all these instances (except lithium iodide, where the ester was recovered unchanged) the amount of bicyclo acid was of the order 60-70%.

Hydrolysis of the mixture of esters (117) and (118).

The best method of hydrolysis was found to be as follows. A solution of the ester mixture (4.77 g.) and potassium hydroxide (2.8 g.) in methanol (50 ml.) was allowed to stand at room temperature for 5 days. The mixture was then diluted with water, extracted with ether, and the extracts discarded. The alkaline solution was acidified (6N HCl) , extracted with ether (3 x 30 ml.), and the extracts dried. Removal of the solvent left a pale yellow viscous oil whose infra-red spectrum showed absorption at 820 cm.$^{-1}$ (trisubstituted double bond) and at 710 cm.$^{-1}$ (disubstituted double bond). This oil was comprised of a mixture of the bicyclo acid (121) and the monocyclic acid (123), and was not purified.

Decarboxylation of the di-acid (123).

The product from the above hydrolysis was dissolved in pyridine (25 ml.), powdered glass (0.5 g.) was added, and the mixture refluxed for 2 hours. The reaction mixture was poured into 6N hydrochloric acid and the product extracted with ether (3 x 30 ml.). Removal of the solvent left a yellow oil which partly solidified (bicyclo acid (121)), (yield 3.5 g.). The bicyclo acid (121) could be largely removed if required, but this was seldom done at this stage.

When thermal decarboxylation of the di-acid (123) was attempted by ordinary distillation of the mixture of acids, the product set almost completely solid and the yield of bicyclo acid (121) rose to 70-80%.

Treatment of the mixture of acids (121) and (124) with oxalyl chloride.

A solution of 2.6 g. of the mixture of acids (121) and (124) in benzene (25 ml.) was treated in the usual way with excess oxalyl chloride. Removal of the solvent left a yellow oil which was treated with 0.880 ammonia as in the preparation of the amide (94). This gave a colourless solid (1.3 g.) which crystallised from ethyl acetate - petroleum ether (b.p. 60-80°) as long colourless needles m.p. 122-123°. The infra-red spectrum clearly showed that this amide was bicyclic (double bond at 710 cm.$^{-1}$), in fact the amide (125). (Found C, 69.45% , H, 9.81% , N, 6.40%. $C_{12}H_{17}NO_2$ (125) requires C, 69.54 , H, 8.27% , N, N, 6.76%). Many attempts were made to prepare the amide of the acid (124) but all were unsuccessful, the only other products of reaction being intractable gums.

Preparation of the mixture of esters (126) and (127).

The mixture of acids (121) and (124) (4 g.) was dissolved in anhydrous ether (15 ml.), excess of a dry ethereal solution of diazomethane added, and the mixture allowed to stand at room temperature for 16 hours. Removal of the solvent left a pale yellow oil whose infra-red spectrum showed absorption at 820 cm.$^{-1}$ (trisubstituted double bond) and at 710 cm.$^{-1}$ (disubstituted double bond). Attempts were made to separate these two esters (126) and (127) both by fractional distillation and by chromatography on grade 1 neutral alumina, but were unsuccessful.

1-Methyl-5-hydroxymethylcyclonon-1-ene (128) and 1-hydroxymethyl-6-methylbicyclo-[4:3:1]-dec-7-ene-10-ol (129)

The above mixture of methyl esters (126) and (127) was reduced in the usual way with lithium aluminium hydride in ether. The normal work up gave 3.2 g. of a colourless oil whose infra-red spectrum showed strong absorption in the hydroxyl region at 3400-3200 cm.$^{-1}$, the expected double bonds at 820cm.$^{-1}$ and 710 cm.$^{-1}$, and was transparent in the carbonyl region. This mixture was chromatographed on 60 g. of Woelm grade 1 neutral alumina, when a complete separation was effected. The monocyclic alcohol (128) was eluted as a colourless oil with chloroform, and the bicyclic diol (129) as a colourless crystalline solid with 50% chloroform in methanol.

Distillation gave 0.608 g. of the alcohol (128) as a colourless oil b.p. 88-89°/0.8 mm., n_D^{18}= 1.4998. (Found C, 78.78% , H, 11.90%. $C_{11}H_{20}O$ requires C, 78.51% , H, 11.98%). The infra-red spectrum showed absorption at 3400 cm.$^{-1}$ (hydroxyl) and 820 cm.$^{-1}$ (cis trisubstituted double bond).

Crystallisation from ethyl acetate - petroleum ether (b.p. 60-80°) gave 0.84 g. of the bicyclic diol (129) as colourless prisms m.p. 97-99°. (Found C, 73.52% , H, 10.27%. $C_{12}H_{20}O_2$ requires C, 73.43% , H, 10.27%). The infra-red spectrum showed absorption at 3300-3250 cm.$^{-1}$ (hydroxyls) and at 710 cm.$^{-1}$ (cis disubstituted double bond).

Attempted preparation of the carbamate ester of the alcohol (128).

A mixture of the alcohol (128) (0.25 g.) and phenyl isocyanate (0.19 g.) was heated on the steam bath for 5 mins. No solid product was obtained and distillation gave 0.2 g. of unchanged alcohol. This was dissolved in carbon tetrachloride (10 ml.), phenyl isocyanate (0.15 g.) was added and the mixture refluxed for 3 hours. Removal of the solvent left a mixture of phenyl isocyanate and unchanged alcohol distillation of which gave 0.18 g. of alcohol.

Formation and pyrolysis of the carbonate ester (130).

Ethyl chlorocarbonate (2.5 ml.) was added dropwise with shaking to a solution of the alcohol (128) (0.235 g.) in pyridine (3 ml.) held at 0°. After standing at room temperature for 16 hours the mixture was poured into water (50 ml.) and glacial acetic acid (20 ml.). Extraction with ether (3 x 30 ml.) followed by washing with 2N hydrochloric acid, saturated sodium carbonate solution and drying ($MgSO_4$) gave, on removal of the solvent, a colourless oil whose infra-red spectrum showed absorption at 1745 $cm.^{-1}$ (carbonate) and was transparent in the hydroxyl region.

Pyrolysis of this ester was effected by refluxing it in diethyl phthalate for 4 hours. The cooled mixture was chromatographed on 60 g. of grade 1 neutral alumina when a small amount of a volatile oil was eluted with petroleum ether (b.p. 40-60°) and then the diethyl phthalate with the same eluant. The first fraction showed absorption in the infra-red spectrum at 1660, 890 $cm.^{-1}$ (exocyclic double bond) but also showed absorption in the region 1200-950 $cm.^{-1}$ due to some by-product. Attempts were made to separate these components by distillation and chromatography, but without success.

Pyrolysis of the ester in silicone fluid (MS 200/ 1000 CS) also gave some of the required olefin (infra-red spectrum) but resulted in fragmentation of the silicone fluid. The silicone by-products could not be separated, however, and this method was discarded.

The p-toluenesulphonate ester (131)

p-Toluenesulphonyl chloride (0.35 g.) was added to a solution of the alcohol (128) (0.25 g.) in pyridine (10 ml.) and the mixture allowed to stand at room temperature for 4 days. The product was isolated in exactly the same manner as was used for the tosylate (70) as a colourless oil (0.38 g.) whose infra-red spectrum was transparent in the hydroxyl region and showed absorption at 1600, 1500 cm.$^{-1}$ (aromatic skeletal vibration) and at 1355, 1190 cm.$^{-1}$ (sulphonate). This tosylate was not purified further.

Attempted solvolysis of the tosylate (131).

A solution of the tosylate (131) (0.5 g.) and sodium bicarbonate (0.5 g.) in dimethylsulphoxide (10 ml.) was refluxed for 16 hours. The black reaction mixture was poured into water and extracted with petroleum ether (b.p. 40-60°) (3 x 10 ml.). Removal of the solvent left a black gum whose infra-red spectrum showed no evidence of either an exocyclic double bond or of the tosylate residue, and which could not be purified.

1-Methyl-5-N:N-dimethylaminomethylcyclonon-1-ene (132)

A solution of the tosylate (131) (2 g.) in 30% aqueous dimethylamine was vigorously refluxed for 16 hours. The cooled reaction mixture was diluted with water and extracted with ether (3 x 50 ml.). The ethereal extracts were extracted with 6N hydrochloric acid (5 x 20 ml.), the acidic extracts made strongly basic (4N NaOH) and then extracted with ether (3 x 30 ml.) and the extracts dried ($MgSO_4$). Removal of the solvent and distillation gave 0.46 g. (38%) of a colourless oil b.p. 116°/17 mm., n_D^{24} = 1.4800. (Found C, 79.70% , H, 13.02% , N, 7.04%. $C_{13}H_{25}N$ (132) requires C, 79.93% , H, 12.90% , N, 7.17%). The infra-red spectrum showed absorption at 2725 cm.$^{-1}$ (N-methyl groups) and 825 cm.$^{-1}$ (double bond). Although the yield is low, work up of the neutral fraction of the reaction gave 0.76 g. of unchanged tosylate (131), identified by its infra-red spectrum, and on this basis the yield of tertiary amine (132) is 61%.

The corresponding picrate crystallised from aqueous ethanol as an amorphous powder melting in the 110-130°, and could noy be purified for analysis.

The N-oxide (133).

Oxidation of the amine (132) with methanolic hydrogen peroxide in exactly the same way as described for the oxide (100) gave an 88% yield of the oxide (133) as a pale yellow viscous oil which was not purified further.

The corresponding picrate crystallised from aqueous ethanol as yellow needle clusters m.p. 107-110° C, 51.81% , H, 6.24% , N, 12.85%. $C_{19}H_{28}N_4O_8$ requires C, 51.81% , H, 6.41% , N, 12.72%).

1-Methyl-5-methylenecyclonon-1-ene (1)

The pyrolysis of the N-oxide (133) was carried out in exactly the same manner as that of the N-oxide (100). This gave a 50% yield of the bis-olefin (1) as a colourless oil b.p. 166-168°. (Found C, 87.68% , H, 12.07%. $C_{11}H_{18}$ requires C, 87.92% , H, 12.08%).

The olefin showed absorption in the infra-red spectrum at 3068, 1637, 886 cm.$^{-1}$ (exocyclic double bond, $\epsilon_{886} = 160$ and $\Delta\nu\frac{1}{2} = 7$ cm.$^{-1}$) and at 3040, 1664, and 832 cm.$^{-1}$ (cis trisubstituted double bond, $\epsilon_{832} = 45$, $\Delta\nu\frac{1}{2} = 9$ cm.$^{-1}$). The proton magnetic resonance spectrum was similar to that of the olefin (8), the single vinyl proton showing as a triplet at 4.55 τ (J = 7.7 c.p.s.) and the other two olefinic protons as a doublet at 5.1 and 5.27 τ (J = 1 c.p.s.), with further unresolved splitting. The methyl group showed as a singlet at 8.36 τ and the 8 allylic protons as a multiplet at 7.88 τ, the 4 cyclohexane like protons showing as an unresolved multiplet at 8.45 τ.

Gas phase chromatography on polypropylene glycol showed only minor traces of impurities and confirmed the purity as being greater than 90%.

m-Methoxybenzylidene acetone (136)

Condensation of *m*-methoxybenzaldehyde with acetone in the presence of sodium hydroxide [73] gave a 43% yield of *m*-methoxybenzylidene acetone (136) as a colourless oil b.p. 132-134°/0.07 mm., n_D^{25} = 1.5925. The corresponding 2:4-dinitrophenylhydrazone crystallised from acetic acid as red needle clusters m.p. 217-218°. (Found C, 57.11%, H, 4.45%, N, 15.68%. $C_{17}H_{16}N_4O_5$ requires C, 57.30%, H, 4.53%, N, 15.72%). The infra-red spectrum of the ketone showed 1660 cm.$^{-1}$ (conjugated carbonyl) and at 1615, 685 cm.$^{-1}$ (double bond).

m-Methoxybenzyl acetone (137)

A solution of the keto-olefin (136) (10 g.) in ethyl acetate was hydrogenated in the usual way, using 10% palladium on charcoal (1 g.) as catalyst. When uptake of hydrogen had ceased the solution was filtered through celite 535 to remove the catalyst and the solvent removed. Distillation gave 9.1 g. (90%) of the required ketone (137) as a colourless oil b.p. 106-108°/0.1 mm., n_D^{22} = 1.5192. (Found C, 73.86%, H, 7.93%. $C_{11}H_{14}O_2$ requires C, 74.13%, H, 7.92%). The absorption of the carbonyl group in the infra-red spectrum was at 1700 cm.$^{-1}$ The corresponding 2:4-dinitrophenylhydrazone crystallised from 5% acetic acid in ethanol as orange needles m.p. 108-110°. (Found C, 57.16%, H, 4.84%, N, 15.43%. $C_{17}H_{18}N_4O_5$ requires C, 56.98%, H, 5.06%, N, 15.64%).

Ethyl 2-cyano-3-methyl-5-m-anisylpent-2-eneoate (138)

A mixture of the ketone (137) (10 g.), ammonium acetate (0.91 g.), ethyl cyanoacetate (7.1 ml.), acetic acid

(2.6 ml.) and dry benzene (15 ml.) were refluxed for 6 hours, using a Dean and Stark apparatus to separate the water as it was formed. The cooled reaction mixture was diluted with ether (50 ml.), washed with water (2 x 25 ml.), brine (2 x 25 ml.) and dried ($MgSO_4$). Removal of the solvent and distillation gave 9.2 g. of the ester (138) as a colourless oil b.p. 144-145°/0.07 mm., n_D^{22} = 1.5304. (Found C, 70.44%, H, 7.18%, N, 5.25%. $C_{16}H_{19}NO_3$ requires C, 70.31%, H, 7.01%, N, 5.13%). The infra-red spectrum showed absorption at 2200 $cm.^{-1}$ (C≡N group), 1710 $cm.^{-1}$ (ester), and 1605 $cm.^{-1}$ (double bond), while the ultra-violet spectrum showed absorption of $\lambda_{max.}$ = 202 m.μ. (log. ε = 4.48) and $\lambda_{max.}$ = 225 m.μ. (log. ε = 4.19).

3-Methyl-5-m-anisylpentanoic acid (139)

A solution of the ester (138) (10 g.) in ethanol was hydrogenated in the usual way using 10% palladium on charcoal as catalyst. The same work up as was used in the preparation of (137) gave 7.5 g. of the saturated ester as a colourless oil b.p. 148-150°/0.05 mm., n_D^{17} = 1.5060. (Found C, 69.49%, H, 7.58%, N, 5.12%. $C_{16}H_{21}NO_3$ requires C, 69.79%, H, 7.69%, N, 5.09%). The above ester was added to a mixture of hydrochloric acid (40 ml.) and acetic acid (20 ml.) and the whole refluxed for 16 hours. Water was then added and the product extracted with ether (3 x 40 ml.) and the extracts dried ($MgSO_4$). Removal of the solvent and distillation gave 4.2 g. (70%) of the acid (139) as a colourless, viscous oil b.p. 150°/0.05 mm., n_D^{18} = 1.5200. (Found C, 70.00% , H, 7.97%. $C_{13}H_{18}O_3$ requires C, 70.24% , H, 8.16%). The infra-red spectrum showed absorption at 3500-2500 cm.$^{-1}$ (acidic hydroxyl) and 1710 cm.$^{-1}$ (acidic carbonyl).

5-Methyl-1:2-5'-methoxybenzocyclohept-1-ene-3-one (140)

The acid (139) (5 g.) was added dropwise to a vigorously stirred solution of polyphosphoric acid (125 ml.) held at 80° and the mixture then heated on the steam bath for 2 hours. The reaction mixture was poured on to ice (500 g.), extracted with ether (3 x 100 ml.) and the extracts dried ($MgSO_4$). Removal of the solvent and distillation gave 2.5 g. (55%) of the benzsuberone (140) as a colourless oil b.p. 132-133°/0.8 mm., n_D^{23} = 1.5620. (Found C, 76.42% , H, 7.72%. $C_{13}H_{16}O_2$ requires C, 76.44% , H, 7.90%). The conjugated carbonyl group absorbed in the infra-red spectrum at 1655 cm.$^{-1}$; and the ultra-violet spectrum showed absorption of $\lambda_{max.}$ = 204 m.μ. (log.ϵ=4.15), 225 m.μ. (log.ϵ = 4.09) and 274 m.μ. (log.ϵ = 4.13%).

The corresponding 2:4-dinitrophenylhydrazone crystallised from ethanol-ethyl acetate as large, deep red needles m.p. 167-168°. (Found C, 59.48% , H, 5.47% , N, 14.54%. $C_{19}H_{20}N_4O_5$ requires C, 59.37% , H, 5.24% , N, 14.58%).

5-Methyl-1:2-5′-methoxybenzocyclohept-1-ene-3-ol (141)

A solution of the ketone (140) (1.73 g.) in 10% aqueous methanol (5 ml.) was added to a solution of sodium borohydride (1.5 g.) in 50% aqueous methanol (10 ml.) and the mixture allowed to stand at room temperature overnight. It was then acidified with 6N sulphuric acid, saturated with ammonium chloride and extracted with ether (3 x 20 ml.). The combined extracts were washed with ammonium chloride solution and dried ($MgSO_4$). Removal of the solvent left a colourless oil which rapidly solidified and crystallisation of which from benzene gave 1.53 g. (88%) of the benzsuberol (141) as needles m.p. 113-114°. (Found C, 75.51%, H, 8.85%. $C_{13}H_{18}O_2$ requires C, 75.69%, H, 8.80%). The infra-red spectrum was transparent in the carbonyl region and showed absorption at 3200 cm.$^{-1}$ (hydroxyl).

5-Methyl-1:2-5′-methoxybenzocyclohepta-1:3-diene (142)

A mixture of the alcohol (141) (2 g.) and conc. sulphuric acid (3 g.) in AnalaR methanol (15 ml.) was heated on the steam bath for 1.25 hours. Water was added, the precipitated oil extracted with ether (3 x 20 ml.) and the ethereal extracts washed with water and dried ($MgSO_4$). Distillation gave 1.7 g. (92%) of the benzsuberene (142) as a colourless oil b.p. 152-153°/15 mm., n_D^{21}= 1.5755. (Found C, 83.14%, H, 8.23%. $C_{13}H_{16}O$ requires C, 82.93%, H, 8.57%). The infra-red spectrum showed absorption at

1605 cm.$^{-1}$ (double bond) and was transparent in the hydroxyl region, while the ultra-violet spectrum showed absorption of $\lambda_{max.}$ = 208 m.μ. (log.ξ = 4.46) and $\lambda_{max.}$ = 264 m.μ. (log.ξ = 4.33).

5-Methyl-1:2-5′-methoxybenzocyclohept-1-ene-4-one (143)

A solution of perbenzoic acid in chloroform (3.34 g. of acid in 70 ml. of $CHCl_3$) was added to a stirred solution of the olefin (142) (3.76 g.) in chloroform (12 ml.). The mixture was stirred at 0° for 6 hours and at room temperature for a further 16 hours. The solution was then washed with base (4N NaOH), dried ($MgSO_4$) and the solvent removed to leave a colourless, viscous oil whose infra-red spectrum showed absorption at 3300 cm.$^{-1}$ (hydroxyl), 1705 cm.$^{-1}$ conjugated ester) and 710,760 cm.$^{-1}$ (phenyl group). This data fitted for the glycol monobenzoate (146) and this was proved as follows.

Hydrolysis of a sample of this oil in the usual way with methanolic potassium hydroxide (16 hour reflux) gave a 75% yield of the diol (149) as colourless needles m.p. 172-174° (ether-petroleum ether (b.p. 40-60°)). (Found C, 70.39% , H, 8.17%. $C_{13}H_{18}O_3$ requires C, 70.24% , H, 8.16%). This diol showed no absortion in the carbonyl region and no absorption due to a phenyl group at 760 and 710 cm.$^{-1}$

When the oil (146) was heated at 180-200°/0.5 mm. it rapidly decomposed, a solid subliming into the condenser and a liquid distilling over. This mixture was extracted with ether and washed with base (4N NaOH). The alkaline extracts were acidified (6N HCl) when a colourless solid precipitated. This solid was filtered off and crystallised from water m.p. 118-120°. The infra-red spectrum was identical with that of benzoic acid (m.p. 121°). The ethereal solution containing the neutral product of reaction was dried ($MgSO_4$) and the solvent removed to leave a colourless oil whose infra-red spectrum showed absorption at 1700 $cm.^{-1}$ (ketone) but was otherwise similar to that of the conjugated ketone (140). The ultra-violet spectrum showed that there was no conjugation in the molecule other than the substituted benzene ring. This compound was the non-conjugated benzsuberone (143). Distillation gave 2.4 g. (60%) of the ketone (143) as a colourless oil b.p. 119°/ 0.4 mm. , n_D^{21}= 1.5435, which slowly solidified on standing, m.p. 40-46°. (Found C, 76.26% , H, 7.91%. $C_{13}H_{16}O_2$ requires C, 75.44% , H, 7.90%).

The corresponding 2:4-dinitrophenylhydrazone crystallised from 10% chloroform in ethanol as yellow needle clusters m.p. 168-170°. (Found C, 59.16% , H, 5.07% , N, 14.59%. $C_{19}H_{20}O_5N_4$ requires C, 59.37% , H, 5.24% , N, 14.58%).

Reduction of the ketone (143) with sodium borohydride in the usual manner gave a 90% yield of the corresponding alcohol as a colourless, viscous oil which could not be obtained crystalline but which distilled at 160°/0.5 mm. (n_D^{19} = 1.5400). (Found C, 76.00% , H, 8.77%. $C_{13}H_{18}O_2$ requires C, 75.69% , H, 8.80%).

Attempted carbethoxylation of (143)

Many attempts were made to carbethoxylate the ketone (143) using the standard procedure of sodium hydride and diethyl carbonate [80], but without any success, the ketone being recovered unchanged. The amount of sodium hydride was increased enormously, but with no more success.

REFERENCES.

1. Cope, Graham and Marshall, J. Amer. Chem. Soc., 1954, 76, 6159.
2. Cope and Synerholm, J. Amer. Chem. Soc., 1950, 72, 5228.
3. Murray, Parker, Raphael and Jhaveri, Tetrahedron, 1962, 18, 55.
4. See inter alia Arnold, Elmer and Dodson, J. Amer. Chem. Soc., 1950, 72, 4359.
5. Wilds, " Organic Reactions ", Vol. 11, Wiley, 1947, p.192.
6. Lund, Chem. Ber., 1937, 70, 1520.
7. Lachmann, J. Amer. Chem. Soc., 1923, 45, 1509.
8. Jhaveri, Ph.D. Thesis, 1960, University of Glasgow.
9. Hamlin and Weston, "Organic Reactions", Vol. 1X, Wiley, 1957, p.1.
10. Hartman and Phillips, Org. Synth., Coll. Vol. 11, 464, (1943).
11. Von Pechmann, Ber., 1895, 28, 856; 1898, 31, 2643.
12. Adamson and Kenner, J., 1939, 181.
13. Wilds and Meader, J. Org. Chem., 1948, 13, 763.
14. Plattner and Jampolsky, Helv. Chim. Acta, 1943, 26, 687.
15. Kotz and Mayer, J. prakt. Chem., 1913, 88, 266.
16. Kotz and Michels, Annalen, 1906, 211, 350.

17. I.R. Maclean, Ph.D. Thesis, 1962, University of Glasgow.

18. Bamford and Stevens, J., 1952, 4735.

19. Robinson and Thomson, J., 1932, 2016.

20. Mayer and Sieglitz, Ber., 1922, 55, 1839.

21. Fieser and Seligman, J. Amer. Chem. Soc., 1939, 61, 136.

22. Wolff, " Organic Reactions ", Vol. 111, Wiley, 1947, p.307.

Briggs, de Ath and Ellis, J., 1942, 61.

23. Newman and Mekler, J. Org. Chem., 1961, 26, 336.

24. Thomas, " Anhydrous Aluminium Chloride in Organic Chemistry ", Reinhold, 1941, p.692.

25. Heller, Ber., 1913, 46, 1497.

26. Barnett and Sanders, J., 1933, 434.

27. Dev and Guha, J. Ind. Chem. Soc., 1948, 25, 13.

28. Fergusson, Chem. Rev., 1946, 237.

29. Lieberman and Connor, Org. Synth., Coll. Vol. 11, 441, (1943).

30. Weissgerber and Kruber, Ber., 1919, 52, 352.

Haworth, Letsky and Mavin, J., 1932, 1782.

31. Bamberger and Althausse, Ber., 1888, 21, 1786.

Bachmann and Morin, J. Amer. Chem. Soc., 1944, 66, 553.

Green and Rowe, J., 1918, 955.

Waser and Mollering, Org. Synth., Coll. Vol. 1, 499, (1946).

32. Vesely et al., Coll. Czech.Chem. Comm., 1929, 1, 498.
Thompson, J., 1932, 2310.

33. Fieser and Seligman, J. Amer. Chem. Soc., 1935, 57, 942.

34. Private communication from J. Martin, University of Glasgow.

35. O'Connor and Nace, J. Amer. Chem. Soc., 1955, 77, 1578.
Brandenburg and Galat, J. Amer. Chem. Soc., 1950, 72, 3275.

36. See inter alia Cope and Yongquist, J. Amer. Chem. Soc., 1962, 84, 2411.

37. See inter alia De Puy, J. Amer. Chem. Soc., 1958, 81, 643.

38. Blomquist and Taussig, J. Amer. Chem. Soc., 1955, 77, 6399.

39. Arundale and Mikeska, Chem. Rev., 1952, 51, 505.

40. Smith, J., 1957, 2690.
Archer, Lewis and Zenitz, J. Amer. Chem. Soc., 1958, 80, 959; 1957, 79, 3839.

41. Henbest, Clayton and Smith, J., 1957, 1982.

42. Dox and Yoder, J. Amer. Chem. Soc., 1921, 43, 1367.

43. Conrad, Annalen, 1880, 204, 175.

44. Davidson and Bogert, J. Amer. Chem. Soc., 1935, 57, 905.

45. Robinson and Robinson, J., 1914, 1463.

46. Karrer and Mitarb, Helv. Chim. Acta, 1923, 6, 915.

47. Clarke, Gillespie and Weisshaus, J. Amer. Chem. Soc., 1933, 55, 4571.

Skita and Rolfes, Ber., 1920, 53, 1242.

Moore, " Organic Reactions ", Vol. V, Wiley, 1947, p. 301.

48. Baumgarten, Bowen and Okamoto, J. Amer. Chem. Soc., 1957, 79, 3145.

49. Blomquist and Schlaefer, J. Amer. Chem. Soc., 1961, 83, 4547.

Cope, Pike and Spencer, J. Amer. Chem. Soc., 1953, 75, 3212.

50. Cope, " Organic Reactions ", Vol. XI, Wiley, 1960, p. 317.

51. Lemieux and Rudloff, Canad. J. Chem., 1955, 33, 1701, 1710.

52. Wilms, Annalen, 1950, 567, 96.

53. Ruzicka, de Almeida and Brack, Helv. Chem. Acta, 1934, 17, 183.

Emery, Ber., 1891, 24, 282.

54. Reppe et al., Annalen, 1955, 596, 164.

55. Bachetti and Fiecchi, Gazz. Chim. Ital., 1953, 83, 1037.

56. Zelinsky and Dengin, Ber., 1922, 55, 3360.

Cannon, Ellis and Leal, Org. Synth., Vol. 31, 74, (1951).

57. Kunjanz, Celincev and Osetrova, Comptes Rendus (Doklady) Acad. Sci. U.R.S.S. 1934, 1, 315.

58. Cannon, Ellis and Leal, Org. Synth., Vol. 31, 74, (1951).

59. Brooks and Snyder, Org. Synth., Coll. Vol. 111., 698, (1955).

60. Jones, Eglinton and Whiting, Org. Synth., Vol. 33, 68, (1953).

61. Eglinton and Whiting, J., 1956, 3650.

62. Islam and Raphael, J., 1952, 4086.
Hamlet, Henbest and Jones, J., 1951, 2652.

63. Newman, J. Amer. Chem. Soc., 1953, 75, 4160.
Billiamora and Macglachlan, J., 1954, 3257.

64. Sorm, Pure and Applied Chemistry, 1961, 2, 533.

65. Sicher, Progr. Stereochem., Vol. 3, p. 202.
Sicher et al., Bull. Soc. chim. France, 1960, 1438.
Prelog, Bull. Soc. chim. France, 1960, 1433.
Prelog, J., 1950, 420.
Huisgen, Angew. Chem., 1957, 69, 341.

66. Michael and Ross, J. Amer. Chem. Soc., 1931, 53, 2408.
Fieser and Seligman, J. Amer. Chem. Soc., 1935, 57, 942.

67. Sengupta, Sengupta and Khastgir, Tetrahedron, 1960, 11, 67.

68. Vincent, Thompson and Smith, J. Org. Chem., 1939, 3, 603.

68. Meerwein and Schurmann, Annalen, 1913, 398, 196.

69. Elsinger, Schreiber and Eschenmoser, Helv. Chim. Acta, 1960, 43, 113.

Eschenmoser et al., Helv. Chim. Acta, 1961, 44, 540.

70. O'Connor and Nace, J. Amer. Chem. Soc., 1952, 74, 5454; 1953, 75, 2118.

71. Nace, J. Amer. Chem. Soc., 1959, 81, 5428.

72. Baker and Querry, J. Org. Chem., 1950, 15, 413.

Montgomery and Wiggins, J., 1946, 393.

King and Bigelow, J. Amer. Chem. Soc., 1952, 74, 3338.

Pierce et al., J., 1955, 694.

73. Bauer and Vogel, J. prakt. Chem., 1913, (11), 88, 332.

74. Baker, J. Amer. Chem. Soc., 1943, 65, 1576.

Cope et al., J. Amer. Chem. Soc., 1941, 63, 3452.

75. Sorm and Dolejs, Coll. Czech. Chem. Comm., 1954, 19, 559.

76. Gilmore and Horton, J. Amer. Chem. Soc., 1951, 73, 1411.

77. Crabb and Schofield, J., 1958, 4276.

78. Swern, " Organic Reactions ", Vol. V11, Wiley, 1953, p.378.

79. Swern, Chem. Rev., 1949, 45,

Parker and Isaacs, Chem. Rev., 1959, 59, 737.

80. Curtin, Bradley and Hendrickson, J. Amer. Chem. Soc., 1956, 78, 4064.

Brewster, J. Amer. Chem. Soc., 1956, 78, 4063.

81. Boeseken, Rec. Trav. chim., 1939, 58, 856.

82. Hermans and Maan, Rec. Trav. chim., 1938, 57, 643.

83. Yuh-Lin, Chen and Barthel, J. Amer. Chem. Soc., 1953, 75, 4287.

Gandhi, Vig and Mukherjii, Tetrahedron, 1959, 7, 236.

84. R.D.H. Murray, Ph.D. Thesis, University of Glasgow, 1960.

85. Arndt, Org. Synth., Coll. Vol. 11, 165, (1943).

86. McCloskey, Fonken, Kluiber and Johnson, Org. Synth., Vol. 34, 26 (1954).

87. Org. Synth., 25, 25 (1945); 30, 72, (1950).

88. Stork and Borowitz, J. Amer. Chem. Soc., 1960, 82, 4307.

89. Adamson and Kenner, J., 1939, 181.

90. Cope et al., J. Amer. Chem. Soc., 1950, 72, 5228.

Campaigne and Lesner, Org. Synth., Vol. 33, 94, (1953).

91. Bowden, Heilbron, Jones and Weedon, J., 1946, 39.

92. Franke and Sigmund, Monatsh., 1915, 46, 70.

93. Fischer, Ber., 1904, 37, 3064.

94. S. Robertson, B.Sc. Thesis, University of Glasgow, 1962.

95. Micovic and Mihailovic, J. Org. Chem., 1953, 18, 1190.

96. Vogel, " A Textbook of Practical Organic Chemistry ", Longmans, Green and Co., 1956, p.362.

97. Vogel, " A Textbook of Practical Organic Chemistry ", Longmans, Green and Co., 1956, p.1001.