SYNTHETIC STUDIES IN THE TERPENE FIELD.

T H E S I S

presented to the University of Glasgow

for the degree of Ph.D.

by

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1962

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I wish to express my appreciation of the help and the interest shown by Dr. W. Parker and Professor R. A. Raphael over the last three years. Their advice and guidance have been a constant source of encouragement to me.

I also wish to thank the Department of Scientific and Industrial Research for a Maintenance Award and Mr. J. M. L. Cameron of Glasgow University for micro analyses.

C O N T E N T S

Page

PART ONE

The Synthesis of 4-norclov-4-ene-3-one and Attempts at conversion to Clovene.

INTRODUCTION TO THE CHEMISTRY OF CARYOPHYLLENE.

(Formulae flowsheets for this section on page 18.)

CLASSICAL PHASE.

The name caryophyllene was originally given to the main component of the hydrocarbon mixture obtained from oil of cloves (from Eugenia caryophyllata). The early workers produced a variety of crystalline derivatives from the hydrocarbon[1] and its presence was demonstrated in several other essential oils e.g. African copaiba oil (from Oxystigmia mannii Harms), French lavender oil[2] and pine oil (from Pinus maritima)[3].

The first rationalization in caryophyllene chemistry came from Deussen[4] who suggested that caryophyllene was a mixture of unsaturated, isomeric hydrocarbons α, b.p.132-134°/16m.m. (optically inactive); β, b.p. 129-130°/14m.m. (α_D -8.5 to -9.5); γ, b.p. 125-125.5°/14.5 m.m. (α_D -26.17). The β and γ isomers were shown to be very similar, each giving a common dihydrochloride. They had the composition $C_{15}H_{24}$, had two double bonds and were therefore bicyclic. Neither was closely similar to α, which Deussen identified as humulene[5], a known sesquiterpene, $C_{15}H_{24}$ originally obtained from oil of hops (from Humulus Lupulus L.); catalytic hydrogenation showed that this latter was a monocycle with three non-conjugated double bonds[6]. During attempts to elucidate the structure of caryophyllene, oxidative degradation, especially ozonolysis, was found to produce several keto-carboxylic acids and dicarboxylic acids.[7,8,9,10].

(I) $C_{14}H_{22}O_4$: a diketo-carboxylic acid.
(II) $C_{11}H_{18}O_3$: a keto-carboxylic acid.

(III) $C_{10}H_{16}O_4$: A dicarboxylic acid, homocaryophyllenic acid.

(IV) $C_{9}H_{14}O_4$: A dicarboxylic acid, caryophyllenic acid.
(ii)

(V) $C_8H_{12}O_4$: a dicarboxylic acid, norcaryophyllenic acid.

(VI) $C_6H_{10}O_4$: a dicarboxylic acid.

(i) Na OBr (ii) Baeyer degradation.

The smallest degradation product, the dicarboxylic acid $C_6H_{10}O_4$, was identified as as-dimethylsuccinic acid (I). Norcaryophyllenic acid was found to give a monobromo derivative, which on treatment with base, followed by ozonolysis, gave as a primary product, α' - keto - $\alpha:\alpha$ - dimethylglutaric acid (5)[10,11]. Therefore norcaryophyllenic acid was (2)[11,12], and the reactions can be formulated as (2 to 5). Structure (2) was proved by synthesis[13,14]. $\beta:\beta$-Dimethyladipic acid (6) yielded $\alpha:\alpha'$- dibromo - $\beta:\beta$-dimethyladipate (7) which was closed to (8) by refluxing with sodium cyanide in ethanol. Treatment with concentrated mineral acid converted the nitrile esters into dl-trans-3:3-dimethylcyclobutane-1:2-dicarboxylic acid (9). Heating crude (9) with acetic anhydride, and then digesting the product with water gave a low yield of the corresponding cis-acid (10), which was resolved as neutral cinchonidine salts. Resolution of the trans forms was accomplished using neutral brucine salts. Only the d-trans-3:3-dimethylcyclobutane-1:2-dicarboxylic acid was identical with norcaryophyllenic acid.

There were doubts about the validity of the degradation work since it had been carried out on a mixture of hydrocarbons. However, ozonolysis of crystalline β-caryophyllene nitrosite gave the diketo-carboxylic acid

$C_{14}H_{22}O_4$, and the keto-carboxylic acid $C_{11}H_{18}O_3$, identical with the acids obtained from the caryophyllene mixture, showing that these latter were derived from β - caryophyllene[15]. As to the nature of the double bonds, ozonolysis of caryophyllene and its crystalline nitrosite gave formaldehyde, showing the presence of a terminal methylene group[15]. Catalytic hydrogenation reduced the double bonds at differing rates to gave a dihydro and then a tetrahydro compound[16,17]. The dihydrocaryophyllene on ozonization gave a monoketo-acid $C_{15}H_{26}O_3$, which when treated with sodium hypobromite gave a dicarboxylic acid $C_{14}H_{24}O_4$. This strongly suggested the partial grouping (11). Ruzicka[18], repeated the ozonolysis of caryophyllene[8] to the diketo-carboxylic acid $C_{14}H_{22}O_4$, and carried out a number of novel reactions on it, which with the information already accumulated, led him to suggest that it was (12) and that caryophyllene was (13). Thus in dilute base, (12) was converted to a keto-carboxylic acid $C_{14}H_{20}O_3$ (14), which could be oxidised to an unsaturated acid $C_{13}H_{18}O_4$ (15). This was reducible and could be ozonized to a keto dicarboxylic acid $C_{12}H_{18}O_5$ (16). At this stage, caryophyllenic acid was thought to be (17) rather than the alternative (18). Later, ozonolysis of dihydrocaryophyllene caused Ruzicka to reconsider (13) as an entirely suitable structure[19]. Dihydrocaryophyllene initially gave the keto-acid $C_{15}H_{26}O_3$ which underwent a haloform reaction to give the diacid $C_{14}H_{24}O_4$. The salt of this when pyrolysed, afforded two ketones, one being converted to a hydroxymethylene derivative which was successively ozonized and oxidised. This treatment gave a dicarboxylic acid $C_{13}H_{22}O_4$, on which pyrolysis produced a bicyclic ketone $C_{12}H_{20}O$. Such a sequence of reactions made it necessary for caryophyllene to possess at least a seven membered ring and caused Ruzicka to think that it must be a mixture of (13) and (19)[20].

MODERN PHASE:

THE CARBON SKELETON.

The results of Tribs[21] comprise the transition from the classical phase of the investigation. Using a number of methods, he produced a caryophyllene monoepoxide which when ozonized gave formaldehyde and a crystalline epoxy-ketone $C_{14}H_{22}O_0$. Treatment of the caryophyllene monoepoxide with alkaline potassium permanganate gave a mixture of isomeric diols, one being cleaved with lead tetra-acetate to the epoxy-ketone obtained above. The fact that this was not a methyl ketone tended to discredit (13) and (19), in place of which (20) was proposed. The epoxy ketone proved invaluable in establishing the correct structure of caryophyllene. Firstly, the infra-red spectrum prompted Sorm[22] to suggest that the carbonyl function formed part of a nine membered ring. From this postulate and with the acceptance of structure (21) for homocaryophyllenic acid, all the degradation results at this time seemed to be explicable on the basis of structure (22) or (23) for caryophyllene. The epoxy-ketone thus became (24) or (25) and the diols (26) or (27).

The elegant work on the epoxy ketone by Barton, substantiated and extended these results[23,24]. The transformation of the epoxy ketone into a non-enolic diketone (28) proved that the epoxide ring and the keto group were separated by at least two carbon atoms. In a second series of experiments, the epoxy ketone (25) was converted by base into an isomeric tricyclic hydroxy-ketone $C_{14}H_{22}O_2$ (29). Oxidation by chronic acid to a saturated diketone $C_{14}H_{20}O_2$ (30), was followed by selenium dioxide treatment, thus giving the unsaturated dione $C_{14}H_{18}O_2$ (31), which showed the presence of the chromophore - CO. CH=CH.CO - in the cisoid configuration. Further oxidation gave a

dicarboxylic acid $C_{12}H_{18}O_4$ (32) readily convertible into the anhydride (33). A reappraisal of Ruzicka's work[24] showed that the partial structure (11) could be extended by a methylene to (34), this then accounting for all of the fifteen carbon atoms which appear in the two fragments (35) and (36). Precisely how they were to be linked was a problem requiring the unambigous establishment of the structures of caryophyllenic and homocaryophyllenic acid.

It was known that caryophyllenic acid, when treated with methyl Grignard reagent, gave a tetramethyl diol (37) or (38) which oxidised in an anomalous fashion with chromic acid to give $\alpha:\alpha:\alpha':\alpha'$-tetramethylglutaric acid. Making the assumption that the rearrangement involved the hydroxyl group α to the ring as shown in (39), Barton[25] showed that four final products were possible. Of the oxidation intermediates only that produced by pathway 1 could yield the necessary acid. Thus caryophyllenic acid was (40) and not (41). It followed that homocaryophyllenic acid was (42) or (43), but since only one eight-carbon dicarboxylic acid had ever been obtained from caryophyllene, it had to be (43) as attack at either methylene α to a carboxyl group in (42) was equally likely; thus giving two acids. Although this structure for homocaryophyllenic acid (43) rendered Sorm's proposals (22) and (23) untenible, Barton did not challenge either of these initially[23] and must have felt that the arguements used to derive (43) were too speculative to be used without substantiation. Of the four acids, (41) was synthesised first[26], in the scheme shown. The Diels-Alder adduct was cleaved to give a keto-dicarboxylic acid (44). That this did not decarboxylate on heating was taken as proof of its structure. Reduction followed by purification via the diester and hydrolysis gave the acid (41). Separation and resolution of the trans

isomer showed that (41) was not caryophyllenic acid, which by exclusion was (40). A successful synthesis of (40) was eventually devised by Campbell and Rydon[27,28]. Ramage[29] by mild hydrolysis of dimethyl caryophyllenate, produced the half-ester (45), which underwent an Arndt-Eistert chain extension to the dicarboxylic acid (43). This proved very similar to degradative homocaryophyllenic acid but some discrepancies in the melting points of their derivatives did not allow the definite assignment of a cis or trans configuration to the carboxylate groups of the latter. By analogy with the smaller dicarboxylic acids, they were taken as trans, an assumption verified by Sorm[30] after studying the anhydride forming behaviour of pure homocaryophyllenic acid. As a result of this work, the only possible carbon skeleton for caryophyllene was (46) in which there could be two arrangements of the double bonds (47) and (48).

There was some dispute as to which of these was correct, centering largely on the two structures represented by (50) and (52), which could be proposed for the dicarboxylic acid having the grouping (32). That the corresponding anhydride failed to brominate or to isomerze with acetic anhydride or hydrochloric acid was evidence in favour of (52)[31]. However, Ramage[32] found that the diacid with diazomethane gave a diester which was hydrohysed to the corresponding acid ester and interpreted this as showing that only one of the carboxyl groups was tertiary (50). Further, he supposed that the secondary anion (49) would be less unstable than the tertiary one (51), cited by Barton. Barton[33] was able to show that since there were examples of secondary carboxyl groups being more hindered than tertiary, the conclusion that the hydrolysable carbomethoxyl grouping was secondary was not necessarily valid. Secondly (48)

possessed the necessary - CH_2 - $C(CH_3)$ = CH - while the alternative did not. Thirdly, structure (48) alone could be used to derive structures for the rearrangement products of caryophyllene, clovene and β -caryophyllene alcohol. Further degradations on caryophyllene itself[34] and X-ray analyses of halides from β-caryophyllene alcohol[35] verified Barton's conclusions.

It was not known then what feature, if any, distinguished the β and the γ forms of caryophyllene. The following reactions provided the answer. Both compounds, when treated with perphthalic acid gave a monoepoxide, the β reacting faster than the γ[36,37]. These monoepoxides on hydration yielded differing diols (57), which oxidised to the same diketone (58). Because of the close similarity between β and γ the only difference between the diols could have been the configuration at C9, this being due to trans and cis oxides (55) and (56), epimeric at C5, these in turn arising from trans and cis endoxyclic double bonds. Since β reacted the faster with perphthalic acid, it was the trans isomer, this being called simply caryophyllene. It followed that the slower reacting γ was the cis isomer, which was called isocaryophyllene. It has been suggested[37] that caryophyllene was probably an artefact, as it was isolated from dilute nitrous acid solutions, in which the ring double bond of β - caryophyllene could have isomerized readily.

REARRANGEMENT PRODUCTS.

Transannular reactions in the nine membered ring, with its two opposed double bonds, occur readily giving rise to tricyclic rearrangement products. Thus when caryophyllene was treated with sulphuric acid in ether[38], a mixture of tricyclic compounds was obtained. One was an unsaturated hydrocarbon $C_{15}H_{24}$, called clovene. The bulk of the material was a saturated, crystalline alcohol $C_{15}H_{26}O$, β-caryophyllene alcohol which gave rise to very stable derivatives, notably halides and an acetate. A third component, sometimes isolated was another alcohol, α-caryophyllene alcohol $C_{15}H_{26}O$ which was readily dehydrated to clovene.

When caryophyllene was treated with hydrogen peroxide to produce the monoepoxide (59) a diol $C_{15}H_{26}O_2$ was obtained as a biproduct[31]. One of the hydroxyl groups was oxidisable, giving a keto alcohol which on Wolff-Kishner reduction afforded β-caryophyllene alcohol. With the structure of caryophyllene established and permitting no double bond migration prior to cyclization or four-membered ring formation, only (60; R=OH) and (61) could represent the diol. Since a ketone was the result of chromic oxidation, the diol was more likely to be (60; R=OH). In accordance with this, the ketol (62) was reacted with selenium dioxide to give a diosphenol (63) which was oxidised with permanganate to a non-enolic but racemizable liquid keto acid $C_{13}H_{20}O_3$ (64). The other proposition (61) could not give these results. An X-ray investigation of the chloride and bromide from β-caryophyllene alcohol also proved that (60; R=H) was the correct structure and that the halides had the configuration shown (65; X=Cl, Br) with the four membered ring trans fused to the seven-membered ring and the hydrogen on C5 situated on the same side of the molecule as the methylene bridge.

Since C5 takes no part in the ring closure transformation, it formed a stereochemical reference point. Its configuration was arbitrarily taken as β, this also leading to the β-configuration for the methylene bridge. These halides could be readily degraded to the ketoacid (64) and since they had configurations parallel to the parent alcohol, 65; X=OH, represents in structure and configuration, β-caryophyllene alcohol (caryolan-1-ol).

It has been reported[39,40] that caryolan-1-ol, when boiled with phosphoric oxide, gave the hydrocarbon clovene. Under less vigorous dehydration conditions, two products were obtained[41], a hydrocarbon $C_{15}H_{24}$ thought to be clovene and an isomeric hydrocarbon which was called isoclovene. Isoclovene gave crystalline hydrohalides which were much less stable than the halides from caryolan-1-ol. An X-ray examination of the hydrochloride and hydrobromide showed that isoclovene was (66), in which the C5 hydrogen and the methylene bridge were still β [42]. The complex rearrangements necessary in the formation of isoclovene were outlined by Barton[42] (60)$\rightarrow$(67)$\rightarrow$(66). Repetition of the hydration[43] showed that the first hydrocarbon was definitely not clovene, but a new hydrocarbon which was called pseudoclovene. N-Bromosuccinimide treatment suggested that the hydrocarbon was not ditertiary α to the double bond, this being substantiated by the observation that the diacid formed on permanganate oxidation gave a dibromo derivative. It is tentatively proposed that pseudoclovene possesses structure (68).

With the structure of caryophyllene known, it was suggested on mechanistic grounds that clovene was (69) and that α-caryophyllene alcohol, which could be readily dehydrated to clovene was (70)[31]. The only crystalline derivative furnished by clovene was a mixture of isomeric

dibromides, treatment with zinc dust regenerating the hydrocarbon in a very pure state. Oxidation of clovene with chromic acid, alkaline permanganate and ozonolysis followed by hydrogenation and oxidation gave a dicarboxylic acid, clovenic acid. That this refused to react with N-bromosuccinimide or nitric acid and gave the anhydride with oxalyl chloride, was consistent with its being (71). Although direct substantiation was lacking, it was concluded[43] that since the acid was produced in good yield (30-50%) by several oxidation techniques involving both strongly acidic and basic media, skeletal rearrangement in its formation was extremely unlikely. To provide evidence for structure (69) clovenic acid was reduced to the diol (73), which it was hoped would dehydrate with rearrangement as shown via the carbonium ion (74), to a mixture of olefin-alcohols (75). These could then have been oxidised to a ketone (72) with its carbonyl group in a six-membered ring. No trace of the expected product (75) and (76), was encountered however, as dehydration of the diol (73) gave an ether, possibly (77) oxidation of which yielded a completely inert lactone (78).

We have seen that the epoxidation of caryophyllene gave rise to a caryolane derivative, 1:9-dihydroxycaryolane, 60; R=OH, (9-hydroxy- β -caryophyllene alcohol). From the same reaction mixture, a second diol $C_{15}H_{26}O_2$ was obtained[37,44]. This was oxidised to a dione followed by Wolff-Kisher reduction to give the saturated hydrocarbon clovane (79), also obtained by catalytic hydrogenation of clovene. By a consideration of the mode of cyclization, it was thought very likely that one of the hydroxyl groups was obtained by nucleophillic attack at C9 (80), the other at C5 by opening of the epoxide ring and that the diol was (57). The chemical evidence in favour of (57) was strong[44]. Mild oxidation gave the ketol (81) with infra-red absorption at

1730cm^{-1} (cyclopentanone), the corresponding acetate reacting with two equivalents of bromine. Further oxidation led to (58) with absorption at 1732cm^{-1} (cyclopentanone) and 1702cm^{-1}. (hexanone), which reacted with four equivalents of bromine, showing that each keto group was flanked by two α hydrogen atoms. Permanganate treatment gave the acid (82) in which the two carboxylate residues were cis. Selenium dioxide, followed by permanganate again produced first an α -dione (83), and then a tetracarboxylic acid (84). Smooth cyclization of the tetramethyl ester of this acid gave rise to a cyclopentanone (85). This could be degraded to p-cymene (86) and did not form an anhydride on melting, the first confirming the structure, the second, the stereochemistry.

ABSOLUTE STEREOCHEMISTRY.

In caryophyllene (53), with the endocyclic double bond trans, there are two favoured conformations of the nine-membered ring.[44] Both have the plane of the double bond perpendicular to the plane of the four-membered ring; the first (87) having the methyl group β and the second (88), having it α. In a cyclization, with the methyl group β attack on the endocyclic double bond by the incipient methylene bridge must be α this in turn being induced by a backside attack by a nucleophile at C8. As a result of these two nucleophilic attacks, inversion in configuration at C8 and C4 occurs to give a β orientated bridge and a β substituent at C5. This is the mode of formation of caryolan-1-ol. Closure in the other conformation must take place by β attack. However it appears that the α side of the molecule is too hindered for nucleophilic attack and thus β attack at C9 ensues, followed by a rearrangement which gives α attack at C8. This is the route by which clovane diol (89:X=OH) is produced.

Up to this point, all the stereochemistry discussed was relative to the β-configuration arbitrarily assigned to C5 in caryolane and simultaneously to C1 in caryophyllane and C5 in clovane. To find the absolute stereochemistry, the method of molecular rotation differences was employed on members of the caryolane and clovane series.[48] This consisted of a number of rules formulated by Klyne and Stokes[45] through studies on molecular rotation changes observed when triterpenoid and steroid hydrocarbons of known absolute stereochemistry were converted to ring D alcohols and their derivatives,[46,47]. Thus for the steroids shown (90; R=H; CH_3, 91; R=H; CH_3), when the group X was changed from hydrogen to β-hydroxyl, the rotation increased in a positive direction. Similarly, there was a positive increment in going from β-alcohol (90, 91; R=H: CH_3, X=OH) to β-acetate or benzoate. The opposite was true for the epimeric α-alcohols and their acyl derivatives. Application of these rules showed that in this instance, the stereochemical convention adopted coincided with the actual absolute stereochemistry.

Despite the suggestions in earlier work,[39,40] the caryolane and clovane skeletal types, as exemplified by (65) and (89), do not appear to be interconvertable. Thus dehydration of caryolan-1-ol is now known to give only isoclovene and pseudoclovene. While there is no record of clovane derivatives undergoing structural change, uncertainty exists over the exact nature of α-caryophyllene alcohol. The α-caryophyllene alcohol, m.p. 118.5-119.5°, 3:5-dinitrobenzoate m.p. 176.5-177°, obtained by acid hydration of caryophyllene, dehydrates readily to clovene in agreement with structure (92) proposed on mechanistic grounds. Nickon[49] finds that oxidation of α-caryophyllene alcohol to a ketone, followed by reduction with sodium in propanol gives in addition to the solid, a liquid epi- α -

caryophyllene alcohol, 3:5-dinitrobenzoate m.p. 129.5-130.5°, which is thought to be the epimer at C2. This oxidises to the same ketone as the solid α -caryophyllene alcohol. Now the diol (80) can be readily transformed into clovan-2α -ol, m.p. 97-98.5°, and clovan-2β -ol, m.p.95-96°, 3:5-dinitrobenzoate m.p. 134-135°. Despite the internal consistency of these two pieces of work, the two sets of alcohols are obviously not the same. It might be instructive to oxidise the two latter to see if a ketone, common to all four were obtained. If it were not, then a structural alteration might be indicated.

NATURAL PRODUCTS RELATED TO CARYOPHYLLENE.

The caryophyllene skeleton might have been expected to be unique, but a second class of sesquiterpene, the betulenols, was found to have a very similar constitution. From Betula alba, Sorm[50] isolated a liquid alcohol, $C_{15}H_{24}O$ called α -betulenol and a solid isomeric alcohol named β -betulenol. The infra-red spectrum of each, with absorption at 1637, 891 cm^{-1} (exomethylene), 1265 and 1258cm^{-1} (caryophyllene ring system) suggested that they were hydroxy derivatives of caryophyllene. Forcing catalytic hydrogenation in acetic acid of the α -compound gave a saturated alcohol $C_{15}H_{28}O$ as expected together with caryophyllane, showing that the original hydroxyl group was probably allylic. The saturated alcohol afforded a ketone which was situated in a medium ring (carbonyl absorption at 1706cm^{-1}). When caryophyllene monoepoxide (55) was subjected to the treatment shown (55)$\longrightarrow$ (93)$\longrightarrow$ (94)$\longrightarrow$ (95), the same ketone (95) was obtained. Hence in α -betulenol, the single oxygen function was situated on C5. The additional facts that cis disubstituted double bond absorption was absent in the

infra-red and that oxidation of α -betulenol gave homocaryophyllenic acid, reduced the number of possibilities to one (96). Oxidation of β -betulenol gave a ketone which had not been encountered previously. As this absorbed three equivalents of bromine, the oxygen had to be situated on carbon 3,5 or 7. Placement at C3 would run counter to the formation of homocaryophyllenic acid from β -betulenol; situation at C5 would give the known ketone (95); thus by exclusion β -betulenol was assigned structure (97), a constitution quite in accordance with the spectral data.

Treibs[51] isolated two different liquid alcohols $C_{15}H_{24}O$ from Betula lenta which he also named 'α-betulenol' and 'β-betulenol'. Spectrally, they were very similar to Sorm's alcohols and underwent hydrogenation to saturated products and caryophyllane. Oxidation with aluminium isopropoxide or manganese dioxide however gave aldehydes which reduced Tollen's and Fehling's solution and which oxidised to fifteen carbon monocarboxylic acids. Like Sorm's, these betulenols could also be oxidised under severe conditions to homocarypphyllenic acid. The least hindered of the three possible primary alcohols (98) was considered to be 'α-betulenol'. 'β-betulenol' was postulated at being (99) or (100). If it turns out that there are in fact only two betulenols, Sorm's conclusions would appear to be the less secure in that they were based on the product of a forcing hydrogenation, whereas Treibs obtained the aldehydes directly from the betulenols by a mild oxidation procedure.

It appears probable that two interesting sesquiterpenes, the hydrocarbon humulene $C_{15}H_{24}$ and the crystalline ketone zerumbone $C_{15}H_{22}O$ were derived from the specific biogenetic precursor of caryophyllene.

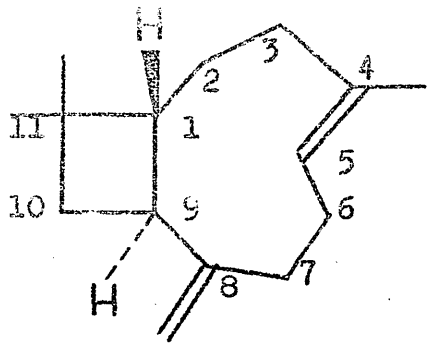
Humulene was a monocycle with three double bonds since it gave a hexahydro-compound, humulane[52,53] and a trisepoxide[54]. It was thought that the sesquiterpene was essentially an eleven-membered ring with methyl substituents placed as in caryophyllene, in which there were three double bonds. This was proved by two syntheses of 1:1:4:8-tetramethyl-cycloundecane (humulane)[55], the second of which (101 to 103) made elegant use of Kolbe electrolyses. Sorm found that humulene unfortunately was not homogeneous, since isomerization of the double bonds for which there appeared to be no one stable arrangement[56], occurred readily. Chiefly on biogenetic grounds, it was suggested that the humulene actually present in hydrocarbon extracts, α -humulene, was (104) as it possessed no exocyclic double bond. The less labile β -humulene, produced from it by isomerization, was considered to be (105).

Zerumbone[57,58] from Zingiber zerumbet, unlike humulene displayed an invariable infra-red spectrum with bands at 1662cm^{-1} (conjugated carbonyl); 1390,70cm^{-1} (gem-dimethyl); 970cm^{-1} (trans disubstituted double bond) and 830cm^{-1} (trisubstituted double bond), and ulta-violet absorption at λ_{max} 248 mμ, ϵ_{max} 8,480 due either to an $\alpha\beta$-unsaturated ketone or a cross-conjugated ketone. Forcing catalytic hydrogenation gave a hexahydrozerumbone which showed infra-red absorption at 1700cm^{-1} (medium ring ketone) and which on Clemmensen reduction afforded humulane. Since base treatment of zerumbone induced retroaldoization with the production of methyl ethyl ketone and since sodium in alcohol reduction furnished tetrahydrozerumbols, the principal ultra-violet absorption was probably due to the group (106). The nature of the remaining non-conjugated double bond became clear when

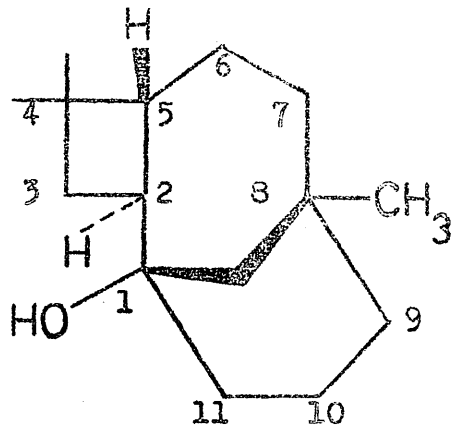
it was found that the tetrahydrozerumbols showed ultra-violet end absorption characteristic of a trisubstituted double bond. When attempts were made to fit these two chromophores into the humulane skeleton, the only uncertainty was the exact position of this isolated double bond. That it was placed 2(3) was finally shown by ozonolysis of zerumbol to as-dimethylsuccinic acid and laevulinic acid. A gratifying feature of (107) was that the disposition of the double bonds and the keto group were exactly those predicted by bio genetic theories.

The biogenesis of the above sesquiterpenes may be plausibly rationalised in the following manner. The first fifteen-carbon entity produced by enzymic modification and condensation of three mevalonate residues is farnesyl pyrophosphate (108), in which the allylic double bond may be cis (109) or trans (110). This basic structure can be elaborated to all the various sesquiterpene types by first, ionization of the allylic leaving group and then by interaction of one of the double bonds with the resulting cation. Thus farnesol can give rise to the cations (III) to (114)[59]. In (111) the simplest neutralization is by proton loss at C9 to give (115) which is α -humulene. It can be seen that C8 is doubly allylic and hence oxidises readily. The C8 ketone (107) is zerumbone. A more complex procedure involves interaction of one of the double bonds. The 6,7 bond is prevented from participating by the C1 hydrogen located internally between C6 and C10, however a concerted electron shift via the 2,3 bond gives rise as shown (116) to caryophyllene with its labourisously established stereochemistry. Treibs[51] has found that autoxidation of caryophyllene takes place readily to give three possible hydroperoxides (117) and that these react

with unoxygenated caryophyllene to give epoxides and leave secondary alcohols. If the epoxides rearrange as in (118) then in this we have reasonable modes of formation for both primary and secondary betulenols.

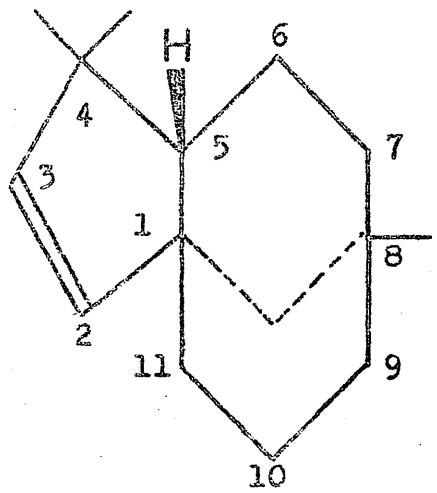


CARYOPHYLLENE
caryophyllane type

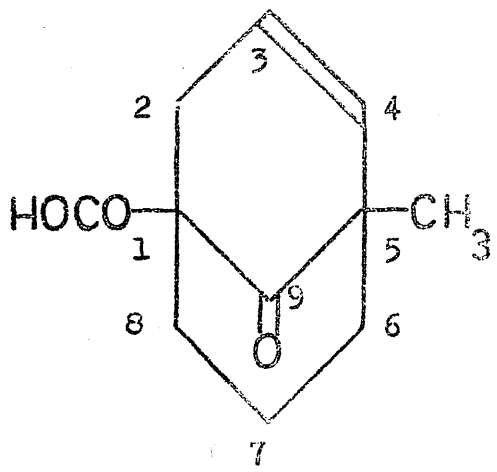


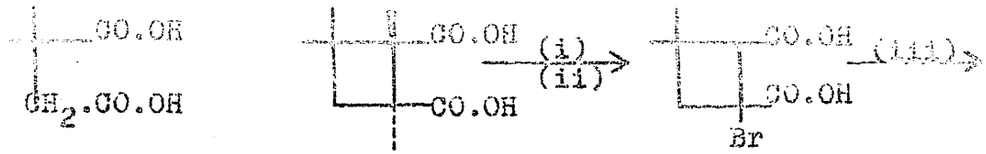
β-CARYOPHYLLENE ALCOHOL
caryolane type

CLOVENE
clovane type

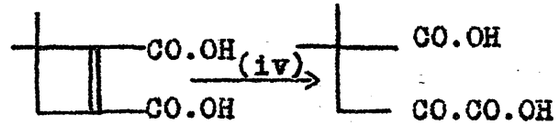


5-METHYLBICYCLO [3:3:1] NON-3-EN-9-ONE-1-CARBOXYLIC ACID
bicyclo [3:3:1] nonane type



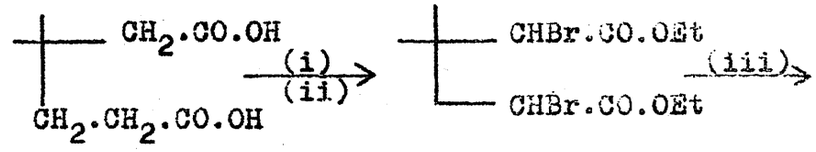


(1) (2) (3)

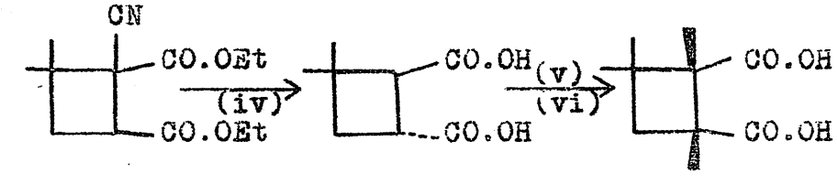


(4) (5)

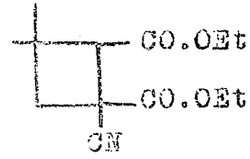
(i) PCl_5;
(ii) Br_2;
(iii) OH^-;
(iv) O_3.



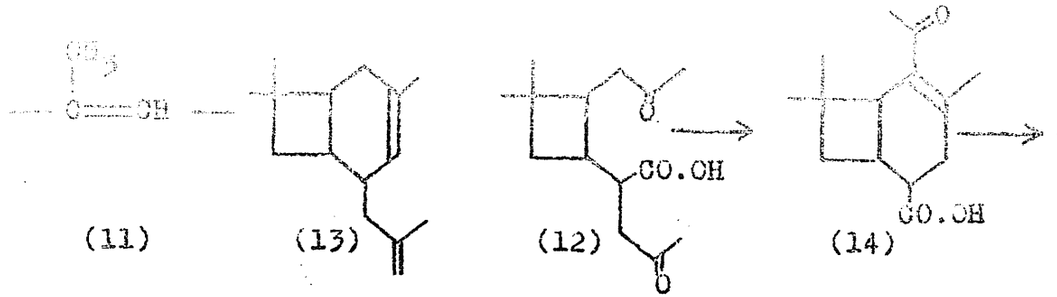
(6) (7)



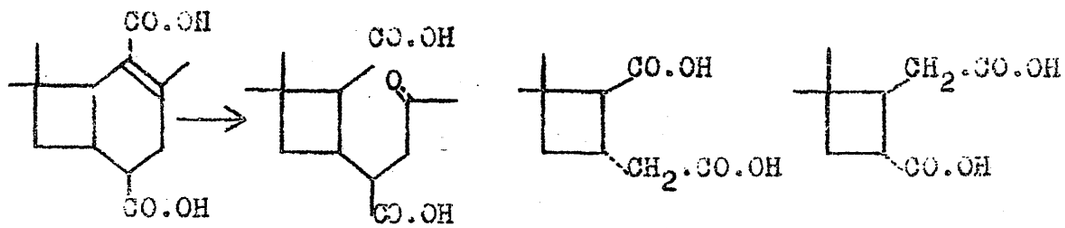
+ (8) (9) (10)



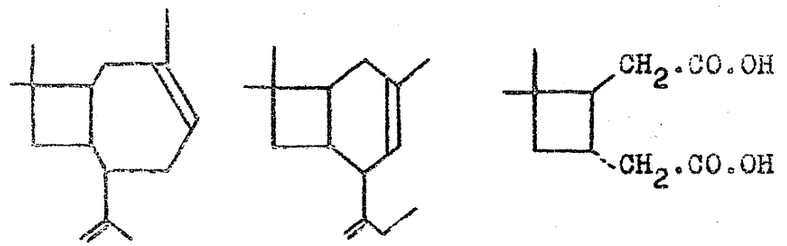
(i) $SOCl_2$; (ii) Br_2 ;
(iii) NaCN/EtOH ; (iv) c.HCl ;
(v) Acetic anhydride ;
(vi) H_2O/Heat.



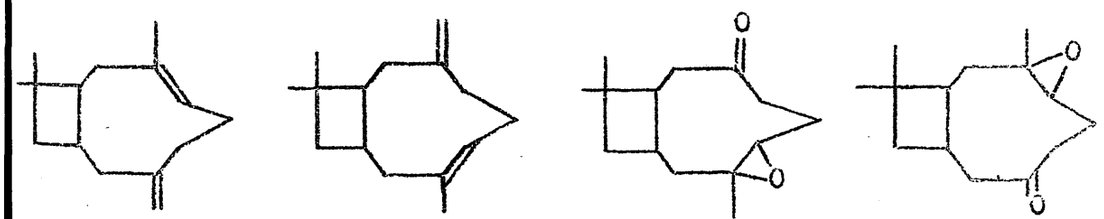
(11) (13) (12) (14)



(15) (16) (17) (18)

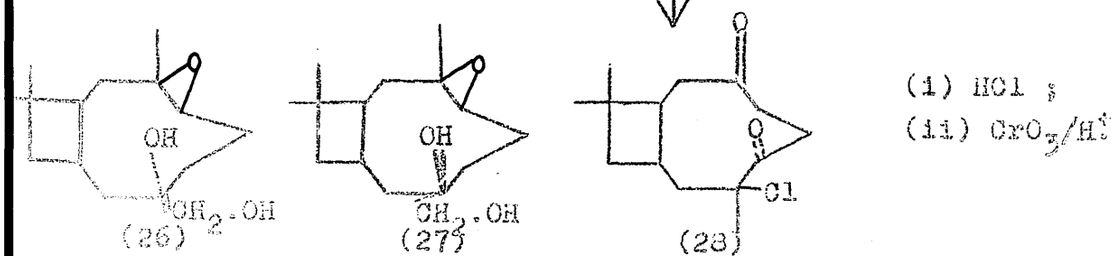


(19) (20) (21)



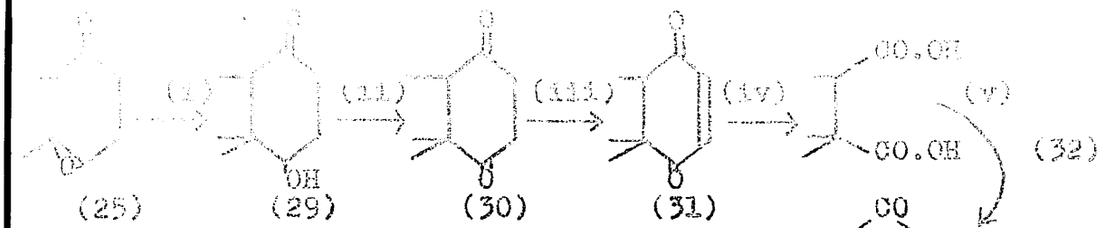
(22) (23) (25) (24)

(1), (ii)



(26) (27) (28)

(i) HCl ;
(ii) CrO_3/H^+

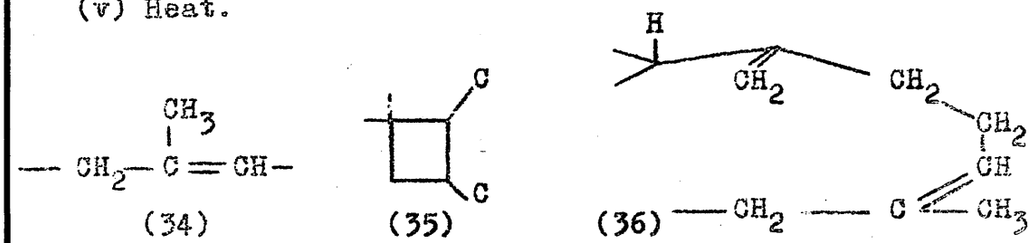


(25) (29) (30) (31) (32) (33)

(i) KOH/MeOH ; (ii) CrO_3/H^+ ;

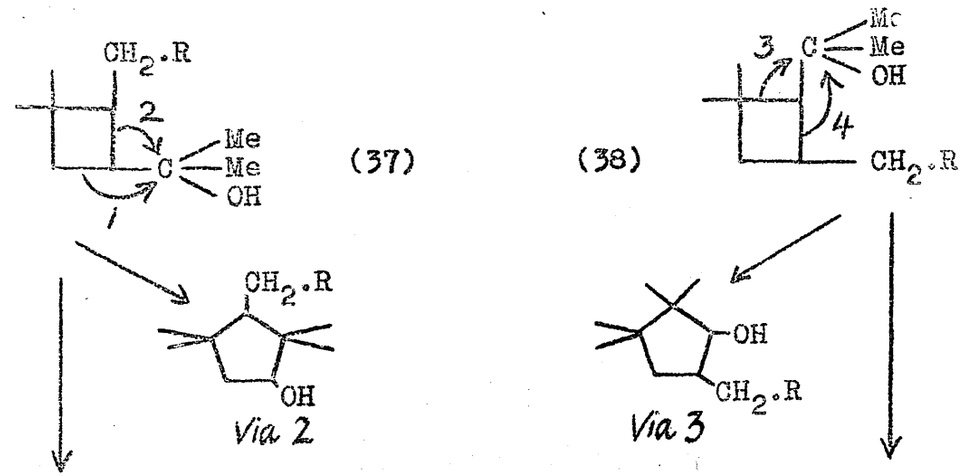
(iii) SeO_2 ; (iv) $KMnO_4/OH^-$;

(v) Heat.

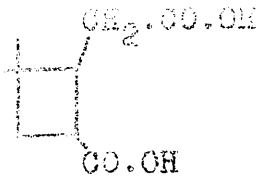


(34) (35) (36)

(39)



where R = $.C(CH_3)_2.OH$



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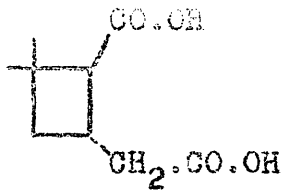
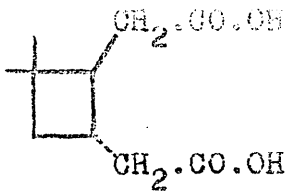
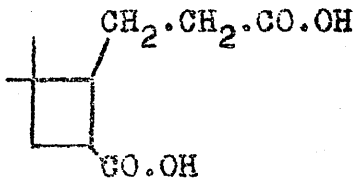


(41)



(42)



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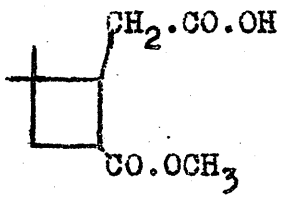

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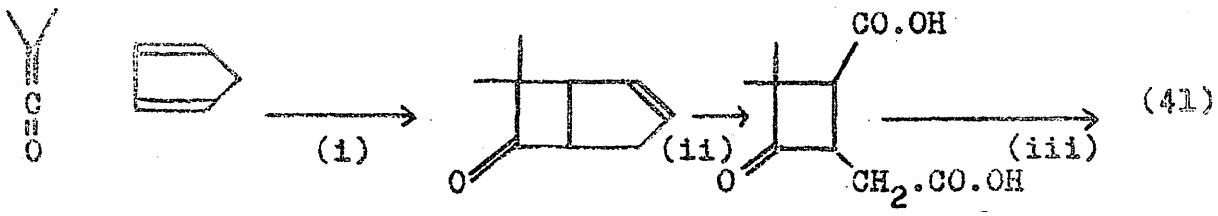
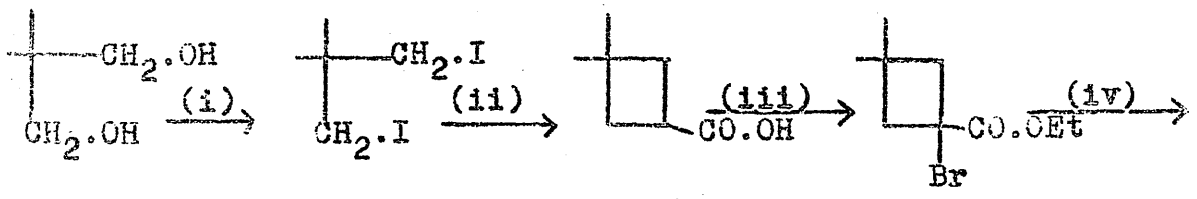
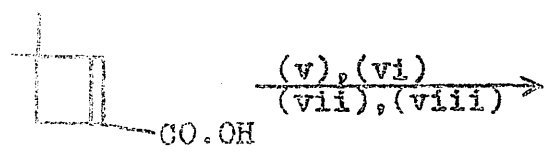


(i) Diels-Alder ; (ii) $KMnO_4/OH^-$; (iii) Huang-Minlon .

(44)





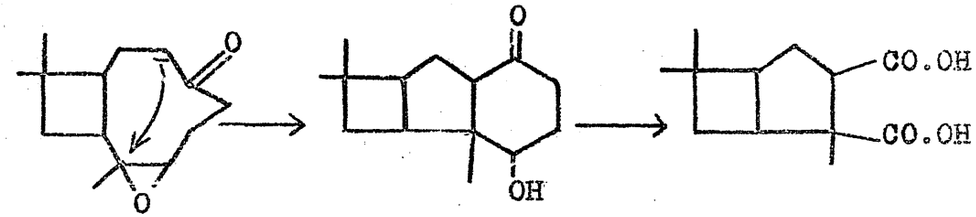
(40)

(i) MeI ; (ii) Diethyl malonate/base ; (iii) Hell, Volhard and Zellinski ; (iv) KOH/Toluene ; (v) CH_2N_2 (vi) Diethyl malonate ; (vii) Hydrolysis and Decarboxylation ; (viii) 180°, cHCl .

(46)

(47)

(48)



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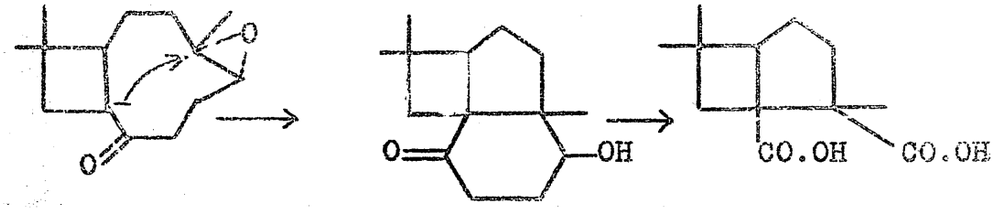

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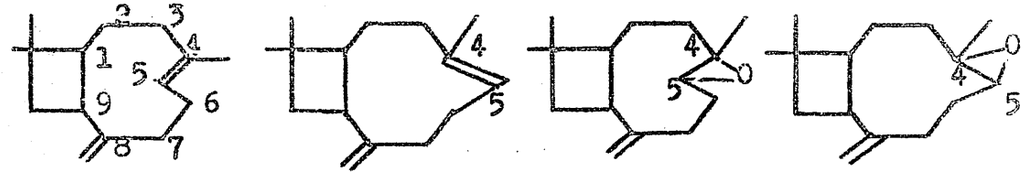
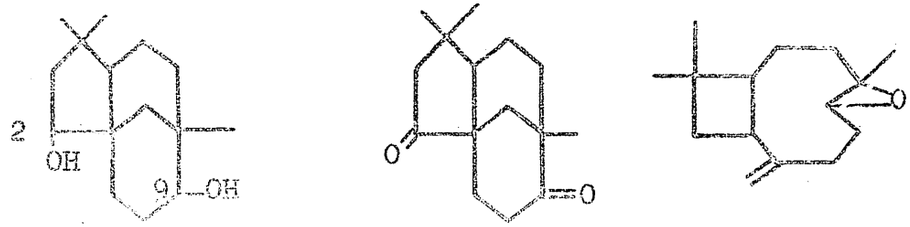
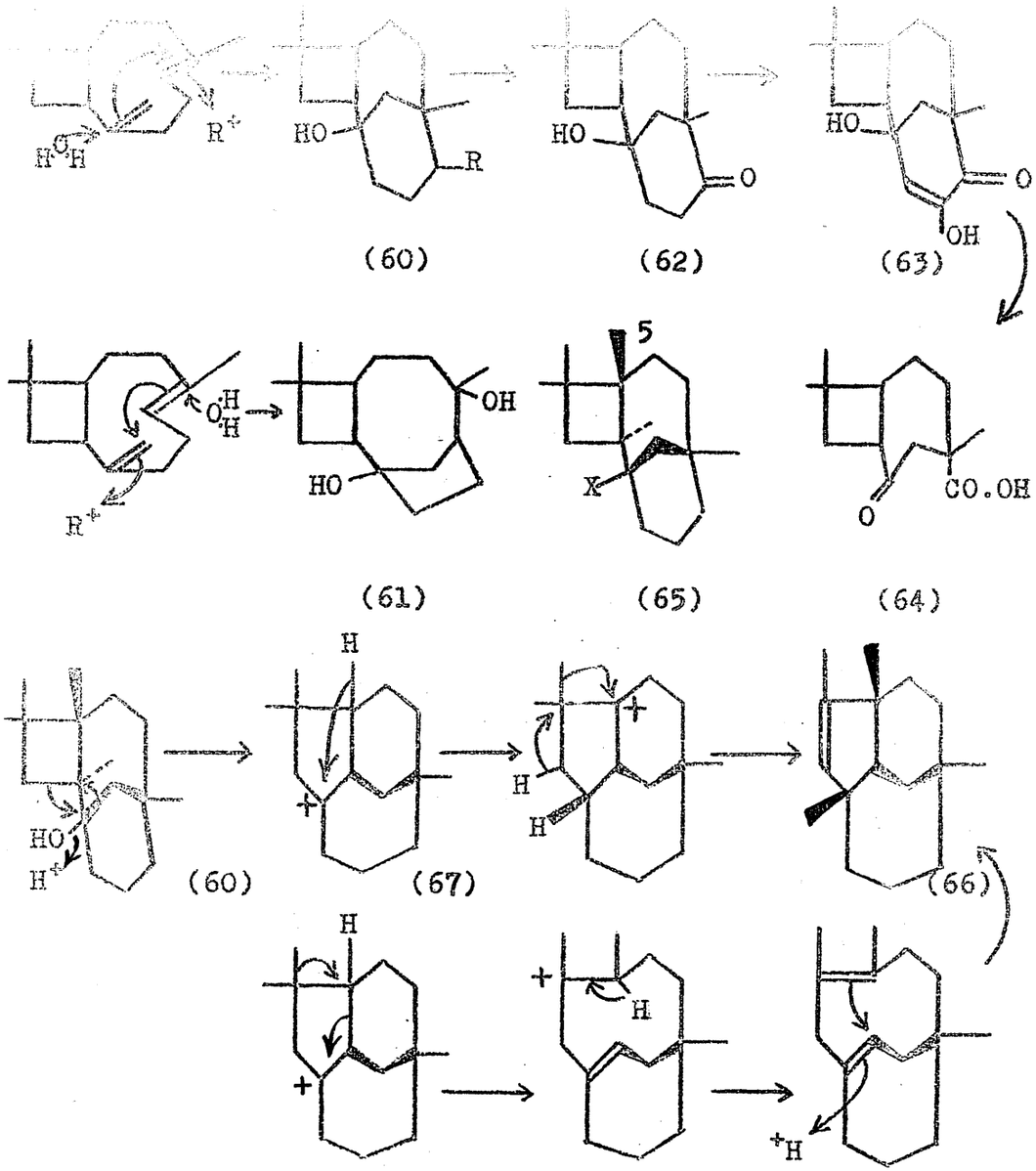


(53) (54) (55) (56)



(57) (58) (59)


HO
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(60)
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(66)
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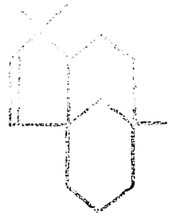
(68)



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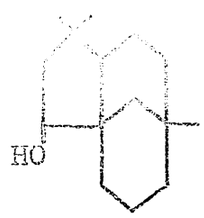

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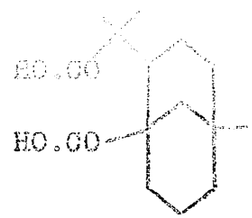

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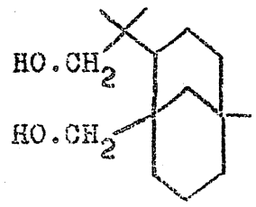

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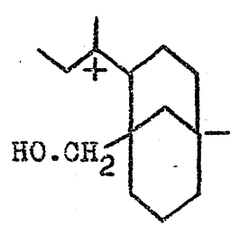

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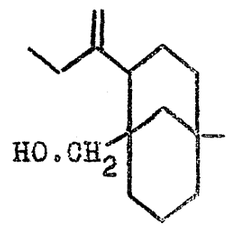

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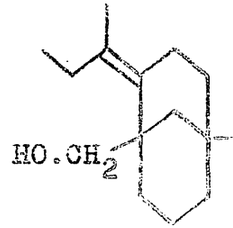

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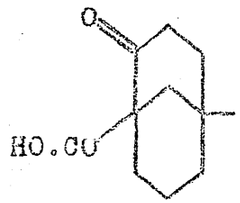

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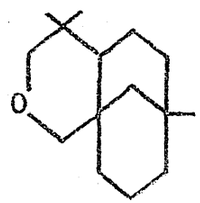

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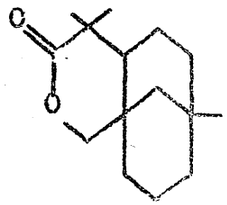

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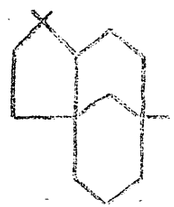

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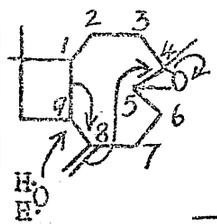

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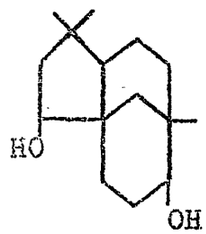

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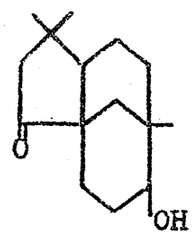

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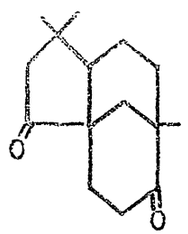

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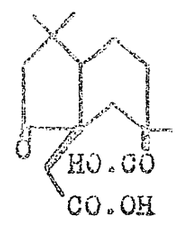

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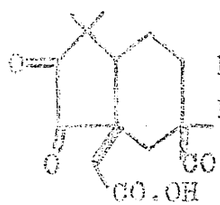

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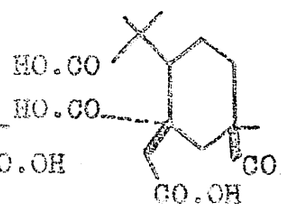

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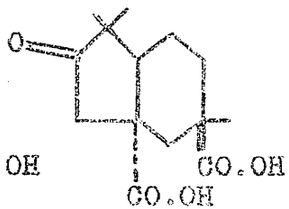

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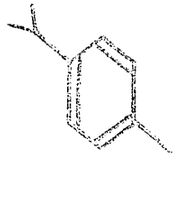

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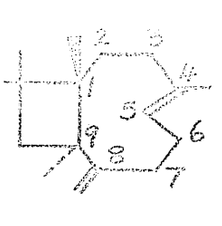

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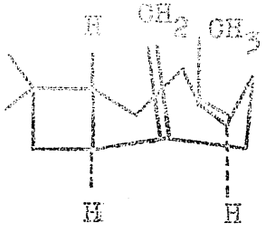

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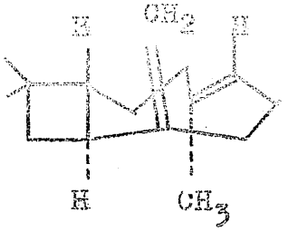

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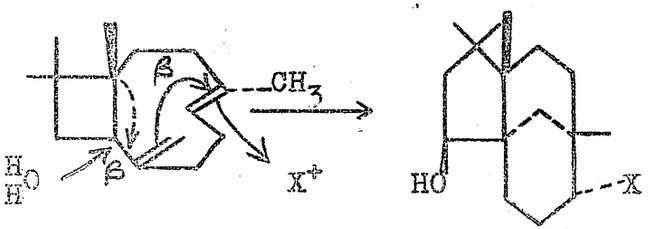

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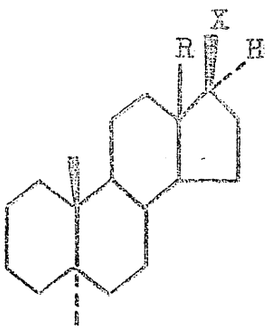

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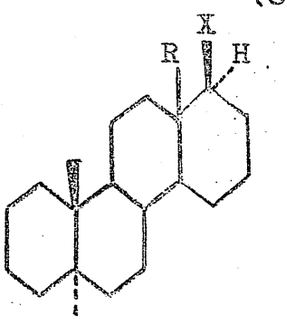

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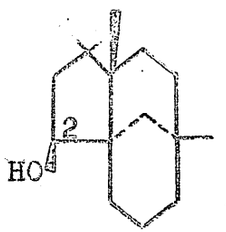

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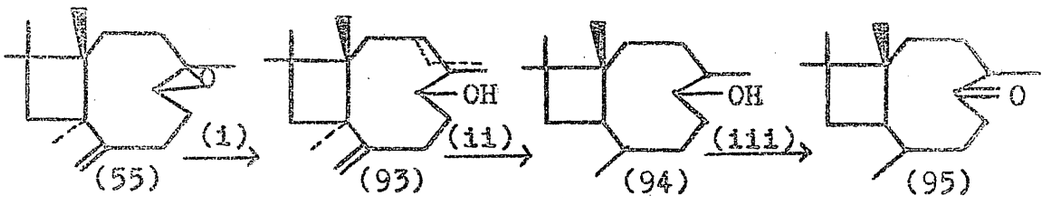
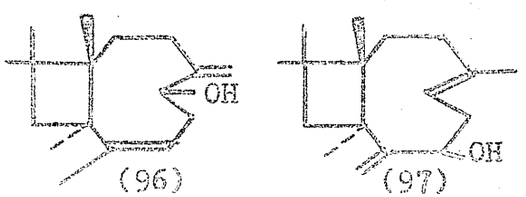
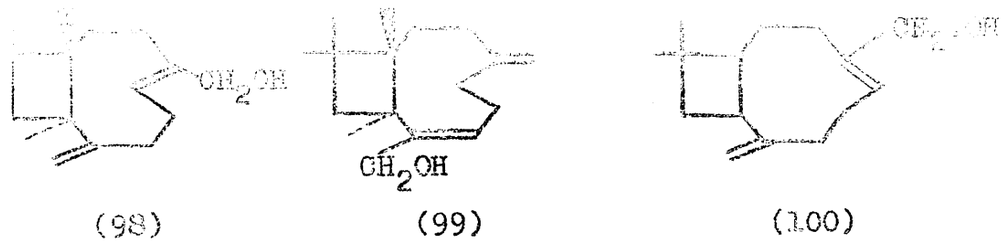


(55) (i) (93) (ii) (94) (iii) (95)

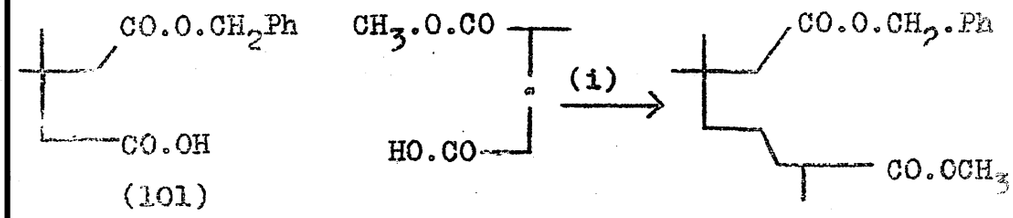
(i) Pyridinium bromide ; (ii) Catalytic hydrogenation ; (iii) CrO_3/H^+ .



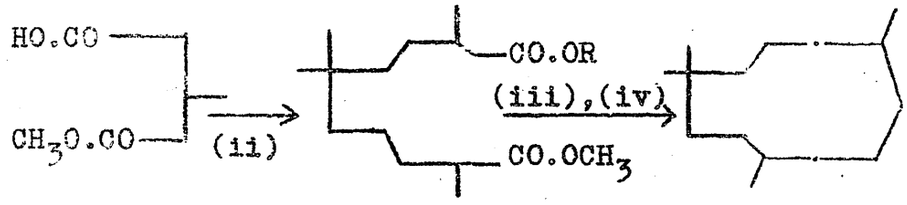
(96) (97)



(98) (99) (100)

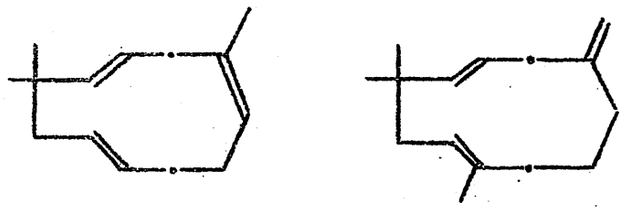


(101)

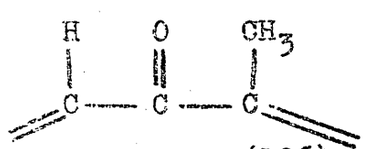


(102) (103)

(i),(ii) Kolbe electrolyses ; (iii) Acyloin condensation ; (iv) Zn/Hg ,acetic and hydrochloric acid .



(104) (105)



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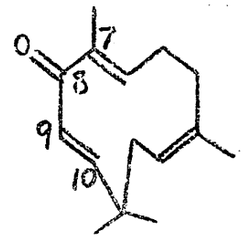
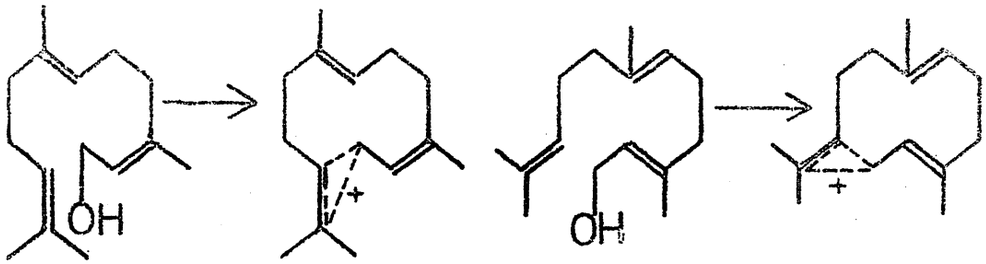


(107)

(I03)



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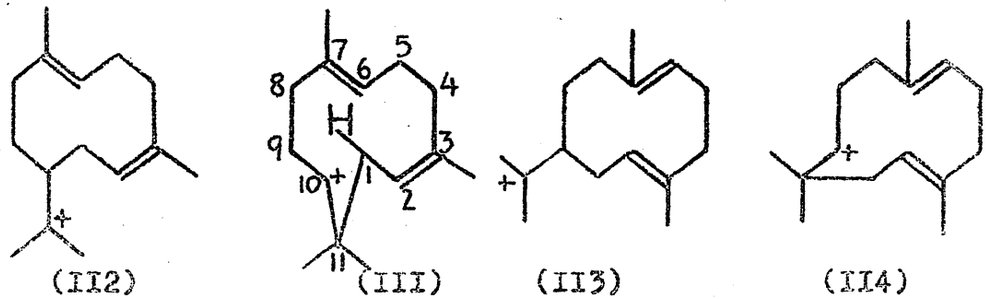

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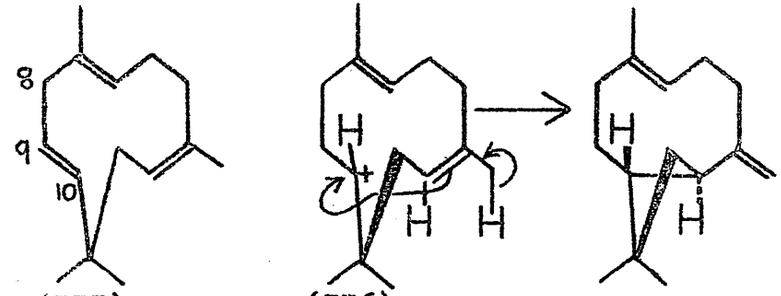

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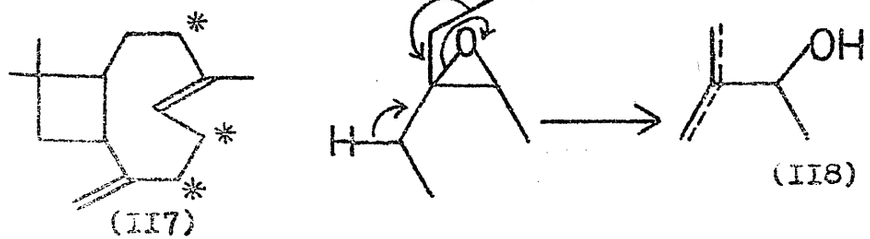


(II7) (II8)

THE SYNTHESIS OF 4-NORCLOV-4-ENE-3-ONE AND ATTEMPTS AT CONVERSION TO CLOVENE.

THEORETICAL

(Formulae flowsheets for this section on p.88)

PRODUCTION AND ELABORATION OF A BICYCLO [3:3:1] NONAN-3-ONE NUCLEUS

The monocyclic cation (1) is capable of undergoing two successive transannular reactions. The first of these is a natural process giving the bicyclic caryophyllene, while the second is induced by acid in vitro to yield the tricyclic artefact clovene. Hitherto, the only published synthetic work in this sphere has been the synthesis of caryophyllane by the elaboration of trans-homocaryophyllenic acid as shown (2 to 7)[60]. The current interest in this department in bridged-ring carbocycles has focussed attention on the unique tricyclic system of clovene. In the first attempt at the synthesis of this sesquiterpene[61], 3-methylcyclohex-2-enone (8) was treated with diethyl malonate to give the abnormal Michael adduct (9), from which the keto-acid (10; R=H) was obtained by acid hydrolysis. It was hoped that a triester of the form (11) could be produced, substituted at C1 in such a way that an intramolecular Dieckmann condensation could give only one bicyclo [3:3:1] nonone. However, no successful synthesis of (11) from either (8) or (10) could be devised. Instead methyl 3-methylcyclohexanone-3-acetate (10; R=CH_3) was condensed with malononitrile to give (12). Using sodium cyanide in dimethylformamide, it was found possible to add hydrogen cyanide across the double bond to give the trinitrile (13) as a crystalline mixture of inseparable isomers. Vigorous hydrolysis with fuming hydrochloric

acid and then esterification gave the triester (14), unsymmetrically substituted at C1. Treatment with potassium t-butoxide gave as expected, two bicyclic products 1-carbomethoxy-5-methylbicyclo [3:3:1] nonan-3-one (15) and 1-carbomethoxymethyl-5-methylbicyclo [3:2:1] octan-7-one corresponding to (15), crystallized.

To extend the side chain, the acid was converted to the acid chloride and condensed with isobutene in the presence of stannic chloride to give the β-chlorodiketone (17). When the crude product was passed down a short alumina column to remove polymerised isobutene, dehydrochlorination occurred to give the desired enedione (18). Despite treatment with various acids and bases under aqueous and anhydrous conditions, no tricyclic material was obtained. Steric interaction between the β-methyl on the enone side-chain and the methylene α to the 3-keto group was thought to be the main reason for this. As the 3-keto group had previously been shown to be unreactive, borohydride reduction of (18) yielded the allylic alcohol (19) exclusively. This was converted to the tosylate and brosylate but despite the less rigid system and the strong direction of the double bond polarization by the leaving groups, base failed to give any tricyclic material.

PRODUCTION AND ELABORATION OF A BICYCLO [3:3:1] NON-3-ENE NUCLEUS.

It was still felt that a bicyclononanone would be the ideal intermediate in a clovene synthesis. The form that this ketone would have to take was now dictated by the lesson learnt in the unsuccessful intramolecular Michael reactions attempted on the endione (18), namely that the activation

derived from the 3 keto group was not sufficient to bring about the desired condensation and by an observation made on a bicyclo [3:2:1] octanone (16). When the acid chloride corresponding to (16) was heated with aluminium chloride, quantitative conversion to the pseudoacid chloride (20) resulted, showing that additional ring formation of the type wanted was quite feasible even in the strained bicyclo-octane system provided that there was direct participation by the 7-keto group. Hence, by making the analogous 2-ketobicyclononane, we would expect that either a Dieckmann closure on a di-ester derived from a 2-ketononane (21) or a modification of the Robinson annelation technique[62] using an intermediate such as (22), would produce the clovane skeleton.

2-Methylcyclohexanone was condensed with diethyloxalate followed by pyrolytic elimination of carbon monoxide to give 2-carbethoxy-6-methylcyclohexanone (23). The 2-position was sufficiently activated to allow a low temperature Michael reaction with acrolein, the product being the expected aldehyde (24). This underwent an aldol condensation in cold concentrated sulphuric acid, affording a mixture of 1-carbethoxy-5-methylbicyclo[3:3:1] non-3-ene-9-one (25: R=CH_3) and two rearrangement products, an acid (26) and an unsaturated ketone (27)[63]. The acid, which tended to crystallise from the crude product was taken out completely by carbonate extraction and because of the inert nature of the 9-keto group in (25), the unsaturated ketone (27) was removed selectively as its semicarbazone. Thus despite the apparent complications introduced by these rearrangements, the sulphuric acid treatment could be made to yield large quantities of uncontaminated 9-keto-ester (25;R=CH_3) with infra-red

absorption at 1735cm^{-1} (ester), 1710cm^{-1} (ketone) and 710cm^{-1} (cis double bond). A less severe cyclization procedure involved refluxing the aldehyde with a mixture of acetic and hydrochloric acid, neutralization with sodium bicarbonate then giving the undehydrated aldol (28;R=H) with bands in the infra-red at 3500cm^{-1} (hydroxyl) 1735cm^{-1} (ester) and 1710cm^{-1} (saturated ketone). Dehydration of this aldol with concentrated sulphuric acid gives the same products as the aldehyde, showing that a bicyclic stage is involved in both rearrangements.

Although the sulphuric acid aldolisation was satisfactory, attempts were made to find a dehydration procedure for the aldol (28; R=H) which would not give rise to rearrangement products. Thus the alcohol was treated with acetic anhydride and pyridine to afford the acetate (28;R=CO.CH_3). However pyrolysis[64] in silicone oil at 180^{o} under reduced pressure failed to give any olefin, only acetate being recovered. The product of heating at 300^{o} was likewise only acetate. By reaction with ethyl chlorocarbonate, the alcohol was converted into the carbonate (28; R=CO.CH_3), but despite the fact that carbonates have been found to be more susceptible to pyrolytic elimination than acetates,[65] heating at 320-40^{o} for two hours still gave no olefin. It is difficult to understand why cis-elimination did not take place in this system. The C2,3,4 arc is quite mobile apparently allowing ring B to alternate between boat and chair conformations with$_{\wedge}^{out}$ steric objections. The pyrolysis should allow ring B to pass through the energetically unfavourable conformation (29), in which no matter the configuration of the acetate group, C-3, C-4, a C-3 to hydrogen bond and the C4 to acetate bond all lie in the same plane. Since the olefin when formed is quite stable,

it can only be that the lifetime of (29) is too short for elimination to occur. Rudloff[66] has described a novel dehydration technique in which several terpene alcohols, when heated in the presence of Woelm alumina gave unrearranged olefins in high yield. Heating (28; R=H) with alumina deactivated by pyridine gave a mobile liquid displaying no hydroxyl peak in the infra-red. However, the absence of cis-disubstituted double bond absorption at $710cm^{-1}$ showed that the dehydration had not given the required product.

In view of the possibility of cleaving the non-enolizable β-keto ester system, base hydrolysis of the keto-ester (25; $R=CH_3$) was approached with some trepidation. However, refluxing with methanolic potassium hydroxide for sixteen hours gave the corresponding acid (25; R=H) in high yield. Deliberate attempts in these laboratories to bring about fission of the carbonyl bridge with base have shown that this is only possible using potassium t-butoxide or sodamide in xylene[67]. In this context the interesting observation has been made that while prolonged heating at reflux with methoxide or ethoxide left the ring system intact, it brought about reduction of the 9-keto group to an alcohol.

The 9-carbonyl group had fulfilled its function in allowing the building of ring B and was removed at this stage by a Clemmensen reduction in which the acid (25;R=H) was heated at reflux in the three phase system of hydrochloric acid and xylene over amalgamated zinc. The product was fairly complex, most of it being a mixture of acids, the neutral residue consisting of two materials, possibly (30) and (31)[61]. It was shown that there were three acids present, unreacted 9-keto acid (25; R=H), the

product 5-methylbicyclo [3:3:1] non-3-en-1-carboxylic acid (33; R=H) and the 9-hydroxy acid (32; R=H). Esterification of this mixture[68] and treatment with sodium borohydride, converted the 9-keto ester (25; R=CH_3) into the 9-hydroxy ester (32;R=CH_3), thus reducing the number of components to two. These were then separated by absorption on alumina and chromatography, elution with petroleum ether giving pure 9-methylene ester (33; R=CH_3) with infra-red absorption at 1735cm^{-1} (carbomethoxyl) and 710cm^{-1} (double bond).

The next problem to be overcome in the projected synthesis, as outlined previously (p.21) was the introduction of a keto group in the 2-position to give, initially, 1-carbomethoxy-5-methylbicyclo [3:3:1] non-3-ene-2-one (34), catalytic reduction of the double bond then affording the desired saturated ketone (35). Straightforward allylic oxidation of the unsaturated ester (33; R=CH_3) with t-butyl chromate gave partial conversion to the enone (34) λ_{max} 230mμ, ϵ_{max} 4,600, but the reagent was difficult to control and brought about degradation of the bicyclononane nucleus. When the behaviour of chromium trioxide in acetic acid on (33; R=CH_3) was investigated, it was found that the product consisted of starting material, enone (34) and other oxidised material. Extreme difficulty was experienced in separating the enone from these impurities though repeated chromatography on silica eventually gave a sample λ_{max} 230mμ, E_{max} 6,900 with infra-red bands of almost equal intensity at 1735cm^{-1} (carbomethoxyl) and 1680cm^{-1} (conjuged ketone), which formed a pyrazolone in high yield. Hence this particular combination of oxidation and purification gave the 2-keto ester (34) almost exclusively, but due to the separation difficulties, the overall yield was low[69]. A new approach

to the allylic oxidation was of the utmost necessity at this stage. We required some technique which was stereospecific since only the 2-keto group could lead to a final ring closure and since a mixture of the 2- and 4- keto isomers would not be readily separable. The method selected also had to give reasonable yields (>50%) of ketone, as this was still a comparatively early stage in the synthesis. With these limitations in view, a promising method appeared to be allylic benzoyloxylation with cuprous bromide and t-butyl perbenzoate.

It has gradually come to be accepted that dissolved traces of metal salts, particularly copper halides, can influence the course of homolytic reactions by acting as homogeneous catalysts[70]. On its own, t-butyl perbenzoate breaks down to a t-butoxy radical and a benzoyloxy radical[71]. The t-butoxy radical fragments to give acetone and a methyl radical which reacts further while the benzoyloxy radical gives carbon dioxide and various aromatic materials. With cuprous bromide, the reaction sequence is as shown:-

$$Ph.CO.O.C(CH_3)_3 + Cu^+ \longrightarrow Ph.CO.O.Cu^+ + (CH_3)_3\ CO\bullet$$

$$(CH_3)_3\ CO\bullet \longrightarrow Acetone + CH_3\bullet$$

$$CH_3\bullet + Ph.CO.O.Cu^+ \longrightarrow Ph.\ CO.O.CH_3 + Cu^+$$

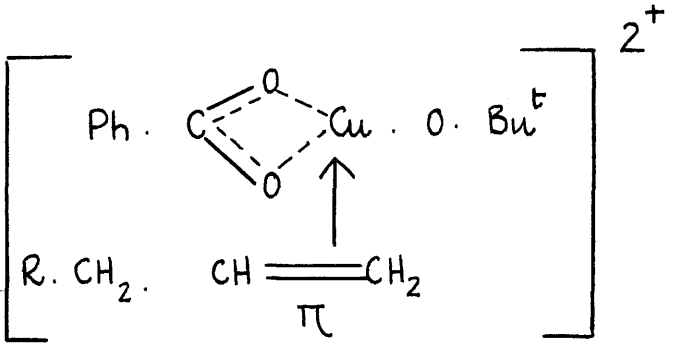
This extrusion of a methyl radical is not favoured[72] and becomes unnecessary if molecules with a labile hydrogen atom, often benzylic[73] or allylic[74] are introduced. The reaction then becomes:-

$$Ph.CO.O.C(CH_3)_3 + Cu^+ \longrightarrow Ph.CO.O.Cu^+ + (CH_3)_3\ CO\bullet$$

$$(CH_3)_3\ CO\bullet + H.R \longrightarrow (CH_3)_3C.OH + R\bullet \qquad (2)$$

$$R\bullet + Ph.CO.O.Cu^+ \longrightarrow Ph.CO.O.R + Cu^+ \qquad (3)$$

None of the radicals shown are free. They all participate in a free radical complex trapped by a cuprous ion. Thus allylbenzene, which undergoes a 'normal' free radical reaction with N-bromosuccinimide to cinnamyl bromide, reacts with t-butyl perbenzoate without rearrangement to give α-benzoyloxyallylbenzene[71]. One anomalous result, the formation of 3-benzoyloxybut-1-ene by cis and trans but-2-ene[75] might have been foreseen as the initial primary four-carbon radical is obviously very energetic and for this reason probably escapes trapping. Denny[76] has shown that the two oxygen atoms in the benzoyloxy radical become equivalent during the reaction and on the basis of this and the other observations suggests



as a representation of the state of the various reactents at the beginning of reaction (2), hydrogen abstraction then causing collapse of the complex and completion of the overall benzoyloxylation. With this literature background it seemed very probable that treatment of the unsaturated ester (33; R=CH_3) with t-butyl perbenzoate and cuprous bromide would furnish a 2-benzoyloxy compound without allylic rearrangement.

Accordingly, 1-carbomethoxy-5-methylbicyclo[3:3:1]non-3-ene (33; R=CH_3) was treated with t-butylperbenzoate in the presence of cuprous bromide. It had been hoped

to follow the course of the reaction by noting the disappearance of the peroxy band in the infra-red[71] but as this was difficult to identify even in the pure perester, the reaction was judged as being complete when two aliquots from the reaction mixture taken 40 minutes apart had the same infra-red spectrum. Chromatography on alumina gave almost 65% of starting material and 20% of the benzoyloxy compound (36). This was a thick oil with bands at 1740-1710cm^{-1} (carbomethoxy and benzoyloxy) and 1600, 1560cm^{-1} (aromatic). Methanolysis of the benzoate[77] followed by chromatography gave methyl benzoate and a liquid allylic alcohol (37) showing absorption at λ_{max} 3420cm^{-1} (hydroxyl) and 1730cm^{-1} (carbomethoxyl). Facile oxdiation with activated manganese dioxide in petrol then gave the enone (34) which had an ultra violet maximum at 230mμ, E_{230} 7,600 and an infra-red spectrum identical with that of the product of the t-butyl chromate oxidation of (33; R=CH_3). Catalytic reduction over palladium-charcoal afforded the saturated ketone (35), with infra-red absorption at 1735cm^{-1} (carbomethoxyl) and 1710cm^{-1} (saturated ketone), this completing the synthesis of 1-carbomethoxy-5-methylbicyclo [3:3:1] nonan-2-one. Although this synthetic procedure was longer than the one employing the direct allylic oxidation, purification of the intermediates was simpler and recycling unchanged unsaturated ester at the oxidation step provided an acceptable yield of enone (34) (~40%). Refluxing the saturated ketone (35) with Brady's reagent gave a pale yellow 2:4-dinitrophenylpyrazolone in good yield. Its production was obviously very satisfactory since it meant that the newly introduced ring keto group was beyond doubt in the 2-position and, in addition, that the introduction of the benzoyloxy group and the subsequent reactions had been affected without any sort of allylic rearrangement.

The significance of the pyrazolone ring formation itself was not overlooked as it gave a strong indication of the ease with which five-membered rings were formed in this system, a good augury for the construction of a carbocyclic five-membered ring in this position.

It seemed possible that a straightforward Reformatsky reaction between the saturated keto ester (35) and α -bromoisobutyric ester should yield a product with the complete carbon skeleton of clovenic acid, i.e. the first oxidation product of clovene and an intermediate which could function as a useful relay in the synthesis of the terpene itself. However, although (35) reacted vigorously with ethyl α -bromoisobutyrate, the product was so complex that it was impossible to say if any of the di-ester (38) or the corresponding dehydrated material had been formed. The failure of this condensation was ascribed to the steric effect of the gem-dimethyl group in the bromo-ester and so a fresh attempt was made using the simpler ethyl bromoacetate. The reaction was exothermic and decomposition of the zinc complex gave an oil, possibly (39) with infra-red bands at 3460cm^{-1}, (sharp, hindered hydroxyl) and 1730cm^{-1} (esters). This was dehydrated by pyrolysis with potassium hydrogen sulphate, non-hydroxylic material (40) being eluted in an alumina chromatogram of the residue. Hydrolysis of this product then gave a mixture of the corresponding acids as a thick oil with the anticipated infra-red spectrum. Due to the poor yields both in the condensation itself and the dehydration and because of the inevitable mixed nature of the dehydrated esters and acids, further reactions of this type were not attempted.

A fresh attempt to introduce a carbon side chain in the 2-position, involved the mesylate and tosylate of the allylic alcohol (37), by means of which it was hoped to alkylate the enamine of acetone (41), to give, via the intermediate (42), the desired keto ester (43). The apparent disadvantage of this scheme lay in the possibility of a S_N2' reaction, both in the formation of the tosylate and mesylate and in the alkylation step. However, when the alcohol (37) was refluxed with p-toluenesulphonyl chloride in pyridine, only unchanged starting material was recovered. Attempted mesylation with methanesulphonyl anhydride[78,79] gave a non-hydroxylic red oil with infra-red absorption at 1770cm^{-1} (lactone or anhydride) and 1725cm^{-1} (ester). Making the assumption, which is possibly unwarranted, that no rearrangement took place, a structure of the type (44) may be suggested for this product.

The failure of the alkylations and of the Reformatsky reactions, led to the adoption of the second method of elaboration the elusive five-membered ring of clovene outlined on page 21 . That is, we now considered synthesising a molecule with the carbon skeleton produced by fission of the 4-5 bond in clovane (45). From this (46), the tricyclic system could be derived by an aldol condensation requiring keto groups in the 2 and 2' positions. The ideal intermediate would be the substituted methyl isopropyl ketone(47) but as this might have been plagued by the same steric difficulties as the earlier intra-molecular Michael reactions on the eneone (18), a more realistic aim was the substituted methyl ethyl ketone (48). This could close to give a 4-norclovenone (49) methylation of which would be expected to give the geminal dimethyl ketone (50)[80] rather than the symmetrical

alternative (51). These proposals were all made possible by the t-butyl perbenzoate technique which would allow selective oxidation of the fairly elaborate molecules envisaged.

Accordingly, 5-methylbicyclo [3:3:1] non-3-ene-1-carboxylic acid (33; R=H) was treated with oxalyl chloride to give a quantitative conversion to the corresponding acid chloride which in turn reacted with diazomethane to furnish the desired diazoketone with infra-red absorption at 2100cm^{-1} (azo group) and 1620cm^{-1} (conjugated carbonyl). Wolff rearrangement in dioxan, in the presence of silver nitrate and ammonia, completed the Arndt-Eistert sequence to the amide homologue of the original acid, a crystalline solid with infra-red bands at 3400, 3200cm^{-1} (N-H) and 1670, 1620cm^{-1} (amide carbonyl). It was confidently expected that treatment of this amide with two equivalents of ethyl magnesium bromide would give the ketone (52), but despite prolonged heating in both ether and tetrahydrofuran, only pure amide was obtained from this reaction. The decrease in the positive character of the carbonyl carbon brought about by the adjacent nitrogen must have prevented attack of the carbonyl by both molecules of reagent. The amide was consistently inert, being largely unhydrolysed by refluxing with methanolic potassium hydroxide for twenty hours. The Arndt-Eistert procedure was therefore repeated as far as the diazoketone which was then decomposed by silver benzoate-triethylamine with methanol acting as solvent.[81] The ester produced, (53;R=CH_3), a liquid with infra-red absorption at 3000cm^{-1} (double bond) and 1720cm^{-1} (carbomethoxyl), was readily hydrolysed as before to the acid (53; R=H).

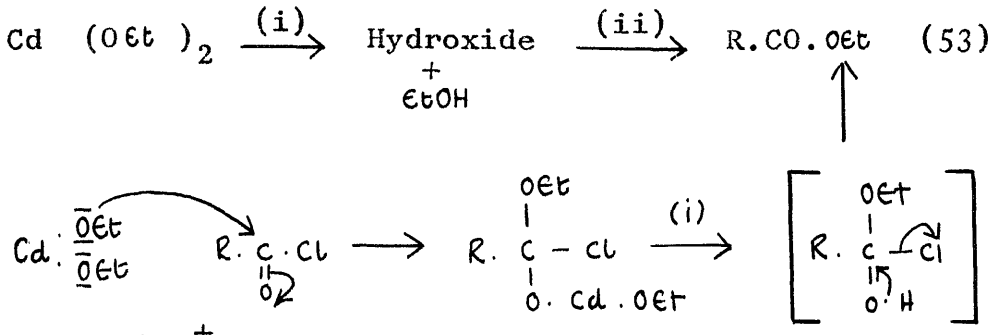
The use of lithium alkyls to produce ketones from acids[82] is well established and in an another attempt to

produce the ethyl ketone (52), preformed lithium ethyl was added to the acid (53; R=H). However the result was disappointing; hardly any neutral product was obtained, all of the material recovered being starting acid. Cadmium diethyl, formed from ethyl magnesium bromide and anhydrous cadmium chloride was the second organo-metallic compound to be tried in an attempt to produce the required ketone. The acid was firstly converted to the acid chloride, which had characteristic infra-red absorption at 1790cm^{-1}. In the recommended procedure[83], this was then to be added to excess cadmium diethyl in benzene, the resulting mixture being stirred and refluxed under nitrogen. On the scale used initially it was impossible to retain the solvent when both heating and nitrogen were employed, and so the nitrogen was omitted. The pasty complex produced was decomposed with acid to give an oil with a single sharp peak in the carbonyl region (1730cm^{-1}). Repeating the experiment on a larger scale gave an identical result: the product proving to be the ethyl ester (53; R=Et) since it was unreduced by borohydride and gave starting acid, identified by melting point and mixed melting point, on base hydrolysis. This is difficult to rationalize but it is known that Grignard reagents in the presence of oxygen give hydroperoxides, these then being reduced by further reagent to magnesium alkoxides.[84]

$$RMgX \xrightarrow{(i)} RO_2MgX \xrightarrow{(ii)} ROMgX$$

(i) O_2 ; (ii) RMgX.

When ethyl magnesium bromide is involved in this reaction, breakdown of the alkoxide to ethanol proceeds in high yield. It is possible that cadmium dialkyls form similar oxidation products and these might react in either of the way suggested below.



(i) H^+, H_2O; (ii) R.CO.Cl in a two phase system.

When the reaction between the acid chloride and cadmium diethyl was carried out under nitrogen, the product afforded a crystalline semicarbazone and showed the infra-red spectrum expected for the ketone (52) with absorption bands at 3100, 1650cm^{-1} (double bond) and 1710cm^{-1} (saturated ketone). A lactone or anhydride impurity, showing a small band at 1780cm^{-1}, was removed by chromatography. On the preparative scale ($\sim$15g.) this procedure gave a high yield ($>$ 80%) of analytically pure ethyl ketone (52) from the ester (53; R=CH_3).

The next step involved introduction of the 2-benzoyloxy group by the t-butyl perbenzoate method already worked out in the case of the simpler compound (33; R=CH_3). An attempt was made to form the ketal from (52) since we had no first-hand experience of the effect of the perester on a free ketone and could find no reference to this type of reaction in the literature. Although the first method employed, that of refluxing the ethyl ketone in benzene with ethylene glycol and acid, failed to give any of the desired product, heating (52) with ethylene glycol, ethyl orthoformate and naphthalenesulphonic acid did furnish the ketal (54), in good yield (60%), as a thick oil with infra-red absorption at 1080 - 1060cm^{-1} (-O.CH_2.CH_2.O-). This ketal reacted smoothly with t- butyl perbenzoate to give

an unexpectedly high yield of the benzoyloxy ketal (55) which showed infra-red absorption at 3000cm^{-1} (double bond); 1700, 1260cm^{-1} (ester), 1600, 1580, 760cm^{-1} (aromatic bands) and 1100-1040cm^{-1} (-O.CH_2.CH_2.O-). It was expected that the product of the benzoyloxylation would consist of two isomers, but disappointingly, the mixture was an oil, which due to its high viscosity, was extremely difficult to manipulate and could not be purified. This problem in laboratory technique was the only reason for abandoning what was otherwise a promising route to the diketone (48).

A second method of protecting the keto group in (52) involved reduction with borohydride to the corresponding alcohol (56); a thick oil, transparent in the carbonyl region but showing infra-red absorption at 3400cm^{-1} (hydroxyl). Treatment of this alcohol with t-butyl perbenzoate in the usual way, gave the 2-benzoyloxy compound (57) in only 17% yield. In view of this, the free ketone (52) was subjected to the same treatment,first with solvent and then without, this last method giving reasonable yields of (58) and an acceptable return of starting material which was recycled (table 1). One of the epimers of the keto benzoate (58) was a solid which could be isolated in low yield ($< 10\%$), but the bulk of the material, as detailed in the experimental section, was a viscous thermally unstable liquid which could not be induced to crystallize. This combination of properties made it necessary for most of the subsequent reactions to be carried out on keto benzoate purified by chromatography only. The four-hour treatment with sodium in methanol,which proved successful in cleaving the benzoate of the simple ester (36), when applied to (58) gave a complex product and no sample of

the expected keto alcohol (62) was isolated. It was thought that there might be two factors which could be preventing the straightforward removal of the benzoyloxy group in (58). The first involved allylic rearrangement of the 2-oxygen function under basic conditions, though the work on the simple benzoyloxy-ester tended to preclude this. An attempt to rule out the possibility of this rearrangement by prior catalytic reduction of the 3-double bond in (58) was unsuccessful. Both solid and liquid samples of the keto benzoate took up approximately one equivalent of hydrogen, but diminution in the intensity of the aromatic absorption bands indicated that hydrogenolysis of the 2-benzoyloxy group was a competing reaction.

Since the more probable cause of the side reactions in the base treatment of (58) was the free carbonyl function, the keto benzoate was reduced with borohydride to the benzoate alcohol (57). This was then hydrolysed as above for four hours to give a separable mixture of liquid and solid diol (60), but the yield was poor (39%) and improved only slightly when the reflux time was extended to eighteen hours (43%). In a fresh approach to the diol, the benzoate alcohol (57) was treated with lithium aluminium hydride. However refluxing (57) in ether with one equivalent of the reagent gave only starting material and while the product from treatment with more than two equivalents yielded approximately 40% of carbonyl free, hydroxylic material, it was impossible to say what proportions of (60) and (56) this contained.. Since the possibility of allylic rearrangement in hydrolyses of allylic esters is low provided a good ionizing solvent and a strong base are used[86], (57) was refluxed for four hours with sodium

hydroxide solution (4N) containing methanol to ensure a homogeneous solution. As before, a mixture of crystalline and liquid diol was obtained but the yield, compared to the methanolysis, was almost doubled.

To bring about allylic oxidation, a small quantity of the crystalline diol (60) was shaken with manganese dioxide in petroleum ether, initially for six hours but eventually for seventy-two. As with the methanolysis, the analogy with the simple ester series did not hold, for a considerable amount of diol was recovered unchanged. What product there was exhibited infra-red absorption at 1710cm^{-1} (saturated ketone) and 1680cm^{-1} (unsaturated ketone, half the intensity of the former). Effective oxidation of both hydroxyl groups was eventually accomplished by the addition of chromium trioxide in sulphuric acid to a solution of the diol (60) in acetone[87]. Although the diketone produced (61), a mobile liquid with infra-red bands of equal intensity at 1710cm^{-1} (saturated ketone) and 1680cm^{-1} (unsaturated ketone), was contaminated by a lactone absorbing at 1780cm^{-1}, the intensity of the ultra violet absorption at the expected wavelength, E_{228-32} 2,500, was inexplicably low. Separation of the lactone could not be achieved by chromatography or distillation, though the more volatile fractions did contain a smaller proportion of it. In the hope that the saturated ketone could be purified, the crude enone was catalytically reduced to (48), which on chromatography gave as the main fraction, a saturated ketone free from the lactone and with infra-red bands at 2900, 1470cm^{-1} (methylene groups) 1710cm^{-1} (saturated ketone) 1380-60cm^{-1} (methyl groups) and 1100cm^{-1} (carbon skeleton). However the simple nature of the infra-red spectrum was deceptive as gas-liquid chromatography of a

sample of (48) showed the presence of three components, the first eluted after eleven minutes, the second and main component eluted after twenty minutes and the last eluted after thirty-five minutes (Table 2,B).

The crude material was transparent in the ultra violet region but when allowed to stand with potassium t -butoxide in ethanol, gave absorption at λ_{max} 241-5mμ, E_{max} 2,500 which was raised to E_{max} 6,400 by refluxing with the same base in benzene. As the only permissible chromophore which could give rise to this band was the cyclopentenone in (49), we had, by means of a simple base treatment, produced the hitherto elusive tricyclic 4-norclovanone in approximately 50% yield from the three-component mixture. This comparatively high yield meant that the second band in plot B corresponded to the dione (48), as the first and third bands each formed less than 30% of the mixture. It seemed probable that the expected stereospecific benzoyloxylation of (52) had taken place and that the other two compounds had arisen during the hydrolysis or oxidation procedures. In the smooth production of (49) we realized our original aim of synthesising a cyclopentenone by an internal aldol reaction on the diketone (48), though the conversion of the benzoyloxy ketone (58) into (48) was not completely satisfactory. It was obvious that it would be difficult and wasteful to purify (48) or (49) and so an attempt was made to eliminate the byproducts at their source.

At this stage we were of the opinion that the main cause of the impurities was the chromic acid oxidation and that the problem they posed could be avoided and better yields obtained if manganese dioxide oxidation of the keto alcohol (62) could be employed. Hence the

keto benzoate (58) was hydrolysed directly with sodium hydroxide (4N) and methanol, to give a good yield of an oil, apparently (62), with infra-red bands at 3400cm^{-1} (hydroxyl); 3000, 1650cm^{-1} (double bond) and 1710cm^{-1} (ketone). A thirty-six hour treatment with manganese dioxide then gave a dione, with absorption at 1710,1680cm^{-1} (ketones, the latter slightly more intense), which on catalytic reduction furnished a saturated ketone with an infra-red spectrum identical with that of the sample from the chromic acid reaction sequence. However, when subjected to gas-liquid chromatography, this material produced a chromatogram (Table 2,A) which lacked the middle peak of the previous sample and in acoordance with this, failed to produce any absorption in the ultraviolet when treated with base at room temperature. It was found that the two components, eluted after nine and eleven minutes, could be separated from the third by a simple chromatogram on alumina. When the first two were refluxed with potassium t-butoxide in benzene, no ultraviolet absorption was obtained, but the mixture did give a semicarbazone which analysis showed was derived from a monoketone, either (52) or (63). The bulk of the material , component three, when refluxed with base as above, gave absorption of λ_{max} 267mμ, E_{max} 2,200 but failed to form any derivatives. Comparing plot B with A, it appears that the first eluted compound in B corresponds to one of the first two in A and is probably a monoketone, since separation on apiezon is largely a matter of molecular weight. While there is no counterpart in plot A for the peak in plot B at twenty minutes retention time, corresponding to the dione (48), the third components in A and B appear to correspond, the slow rate of elution coupled with their infra-red spectra, suggesting

that they are complex ketones of higher molecular weight than (48). Whatever the exact nature of the products of the reaction sequence affording plot A, it is certain that during the base treatment of (58), there were at least three readjustments in the nature and the number of the oxygen functions on the nonane nucleus. In view of these results, we felt we had no option but to repeat the reaction sequence which had given impure diketone (48) and <u>then</u> attempt to separate the mono and polyketones.

The ketone (52) was treated with t-butyl perbenzoate to give the benzoyloxy ketone, 58 (67%) as a pale yellow oil (84%) and a white solid (16%). Reduction of the solid isomer with sodium borohydride gave the hydroxy benzoate (57) as a colourless transparent glass which, probably because it was a mixture of two isomeric alcohols would not crystallize. Hydrolysis with aqueous methanolic base afforded the crystalline diol, 60 (75%), the melting point range after a single recrystallization (110-130^{o}) being considered satisfactory in that four isomeric alcohols could have been present. Even on this material, chromic acid treatment was a little severe, as oxidation produced the unsaturated ketone (61) contaminated by lactone (1770cm^{-1}) and a second impurity (1640cm^{-1}). Since it was known that neither fractional distillation nor chromatography could remove these, the crude enone (61) was catalytically reduced to the saturated ketone (48). However, although cautions elution of the saturated ketone from alumina gave what appeared by its infra-red spectrum to be impurity-free ketone, when samples taken from fractions 2 (petroleum ether), 11 (petroleum ether-benzene, 49:1) and 21 (petroleum ether-benzene, 4:1) were analysed for components on a silica chromatoplate, each showed a

similar complex composition. Accordingly, the various materials from the chromatogram were combined, distilled and the four resulting fractions subjected to gas-liquid chromatography as before. The first two were found to contain a large proportion of the first material to be eluted in plot B, while the last two were made up largely of the desired diketone (approximately 80%). The whole process was carried out unmodified on the liquid benzoyloxy ketone, to give a much larger amount of crude saturated ketone (48) which was chromatographed. A direct analysis by gas-liquid chromatography of the fractions obtained showed however that absorption chromatography was not as effective as distillation in isolating the required diketone. The materials were therefore combined and distilled to give diketone (48) of the same purity as above.

While we were unable to purify the dione (48) satisfactorily, the information already obtained as to the nature of the impurities present, made separation of the pure cyclopentenone (49) a definite possibility.

A sample of (48) containing monoketone material (15%) and high molecular weight ketone (10%) was heated under reflux with sodium ethoxide in benzene to bring the formation of the five-membered ring. The crude product had the expected ultra violet absorption at λ_{max} 241-5mμ, E_{max} 5,000 and an infra-red spectrum with bands at 1710cm^{-1} (cyclopentenone) and 1630cm^{-1} (conjugated double bond). Chromatography on a small active alumina column allowed most of the monoketone material to be separated, but the rest of the product was eluted as a mixture. When this was rechromatographed on a larger, less active column, a further quantity of monoketone was obtained

followed by the desired cyclopentenone (49), with an average ultra violet absorption of E_{max} 8,500. Distillation then split the crude cyclopentenone into two fractions. Application of gas-liquid chromatography to the first of these (E_{max} 7,500) gave a plot showing four peaks (table 2 C). Three of these, making up 40% of the mixture, were closely spaced at twenty minutes elution time, while the fourth was eluted after thirty minutes. The second distillation fraction (E_{max} 9,100) was similar, with the cyclopentenone (49), which was undoubtably responsible for the last peak, forming 80% of the mixture. In plot C, the separation between the two peak areas was considerable and the same result was obtained with a silica chromatoplate. However, absorption chromatography of the impure cyclopentenone on a silica column reversed this order of elution as the first fraction produced (benzene-chloroform, 7:3) had E_{max} 12,800-13,000. The degree of separation was also altered as most of the material eluted subsequently had an E_{max} between 8,000-10,000.

Since physical methods failed to give a completely pure sample of (49) in a last attempt to purify our material, the cyclopentenone with it attendant ketonic impurities was subjected to borohydride reduction. As only the cyclopentenone could furnish an allylic alcohol, it was hoped that this could be selectively oxidised and separated, but the product although transparent in the carbonyl region unexpectedly showed only weak hydroxyl absorption. Chromatography gave the expected alcohol, 66, (40%) and a similar amount of an olefin, λ_{max} 240-243mμ, E_{max} 10,000, presumed to be (67). Distillation afforded this as a colourless oil (bath $140^{o}/0.4$m.m) which on standing for forty-eight hours became very viscous and acquired an oxygen content (10%)

probably via one or more of the three possible allylic hydroperoxidations. The alcohol (66) which was obtained in the reduction was completely unaltered by shaking with manganese dioxide for sixty hours.

Due to this inability to purify our material, we had no means of obtaining direct analytical proof for the existence of the cyclopentenone and the loss in material which accompanied the various attempts at separation, made it impossible to effect the few changes necessary to convert (49) into clovene. However it was still feasible to extend the physical data which existed for the cyclopentenone and to prepare derivatives from it. Thus, prolonged catalytic reduction of (49) gave an impure sample of the corresponding cyclopentanone (68) with infra-red absorption at 1750cm^{-1} (cyclopentanone); 1700cm^{-1} (hexanone impurities) and a significant lack of absorption at 1640cm^{-1} (conjugated double bond). A sample of (49) was treated with Brady's reagent to furnish the required dark red 2:4-dinitrophenylhydrazone which analysed satisfactorily, though great difficulty was experienced in removing traces of an accompanying yellow 2:4-dinitrophenylhydrazone. The prospect of producing a gem-dimethyl group α to the carbonyl function in (49) was attractive in that the cyclopentanone product (50) would possess the total carbon skeleton of clovene and would exhibit a characteristic infra-red spectrum. Accordingly (49) was treated with potassium t-butoxide in benzene and methyl iodide, the resulting yellow oil being chromatographed to give the desired cyclopentanone (50) with a single band in the infra-red at 1750cm^{-1}. This ketone also furnished a yellow 2:4-dinitrophenylhydrazone which analysed satisfacorily. The goal of the work, namely the elaboration of a tricyclic system with the carbon skeleton of clovene had thus been achieved.

Appraisal

The information listed above shows that the annelation envisaged at the outset of the scheme is perfectly feasible, provided that the diketone (48) can be obtained in a pure form. Certainly the closure to the cyclopentenone (49) proceeded as expected to give a tricyclic product, the physical properties and derivatives of which are in good agreement with the proposed structure. Originally it was felt that the crux of the synthesis lay in the stereospecific introduction of an allylic oxygen function, with the modifications necessary to convert this function into a keto group assuming a less critical role and our early series of experiments on the olefin ester (33; $R=CH_3$), culminating in pyrazolone formation tended to bear this out. The difficulties encountered in the extension of this process to the ketone (52) stemmed from the unwanted rearrangement processes arising from the procedures which had to be adopted to hydrolyse the introduced benzoyloxy function when the simple methanolysis failed.

Concurrent work in these laboratories was produced an acceptable solution to the problem. Treatment of (33; $R=CH_3$) with selenium dioxide in acetic acid, unexpectedly gave a high yield of the allylic acetate, which on hydrolysis and oxidation with specially activated manganese dioxide, gave a sample of the keto ester (34). Catalytic reduction afforded (35) which significantly was smoothly converted to the pyrazolone. Although it might have been predicted that the oxidation under acid conditions would have given both 2- and 4- ketones, it is obvious that the initial acetoxylations and all the subsequent reactions proceed without allylic rearrangement. The entire procedure was applied to the homologated ester

(53; R=CH_3) to furnish the crystalline lactone (69). Reduction of this with lithium aluminium hydride gave the crystalline diol (70) manganese dioxide treatment then yielding (71). This was oxidised and catalytically reduc ed to (72) which readily formed an enol lactone (73), and like the lactone (69) was exclusively oxygenated in the 2-position. Conversion of the ketal of the ester corresponding to (72) via the acid chloride gave (48), mild base treatment then affording the pure 4-norclov-4-ene-3-one (49). This, like the cyclopentenone formed initially from the hydroxy-benzoate (57), gave a dark red 2:4-dinitrophenylhydrazone which did not depress the melting point of the sample obtained in this work. The pure cyclopentenone also underwent alkylation to give (50), the infra-red spectrum and 2:4-dinitrophenyl hydrazone of which were indistinguishable from those obtained in the work described inthis thesis.

If we were to use (50) as an intermediate in the synthesis of clovene, the only means of reducing the trisubstituted double bond would be catalytic hydrogenation, as it was taken out of conjugation with the carbonyl group by the methylation step. Although there is no guarantee that the less strained isomer (77), with cis ring fusion, would be produced preferentially, if it were, then reduction of the keto group to an alcohol followed by pyrolytic elimination of the resulting 3-oxygen function, would give the required olefin (74). A less drastic procedure[88] would involve the production of the toluene-p-sulphonylhydrazone from (77),which by analogy with the 2:4-dinitro phenylhydrazone should form readily. This would then be expected to decompose in the presence of sodium ethoxide in ethanol, to clovene (74). Should catalytic reduction of (50) prove

unsatisfactory, the precursor to clovene would then have to be (49), which could be reduced via the more favoured carbanion under Birch conditions, to (75). An attempt to effect this reduction on (49) because of the small scale employed gave only alcohol, presumed to be (76). If as expected, repeating the reduction on a larger scale did give a ketone of the correct stereochemistry, the only problem then to be faced in completing the synthesis of clovene would be the unequivocal production of the 4-gemdimethyl group in (77).

EXPERIMENTAL

All melting points were determined on a Kofler block. Infra-red absorption spectra of liquid films and nujol mulls were determined on a Perkin-Elmer Infracord spectrophotometer. Ultra-violet absorption spectra, measured on a Perkin-Elmer model 137 U.V.spectrophotometer and a Unicam S.P.500 spectrophotometer, refer to methanol solutions, unless stated otherwise.

The term 'petroleum ether' was applied to the light petrol fraction b.p. 40-60°.

The neutral alumina (Woelm), silicone oil (MS 550R, Hopkins and Williams) and activated manganese dioxide (Woolley) were used in the condition obtained from the supplier. Neutral alumina, prepared and classified after the method of Brockmann and Schodder was also obtained from Spence H alumina. Gas-liquid chromatography was carried out on a Pye 'Argon Chromatograph' with Celite 545 (120-150 mesh) acting as support for a 5% Apiezon L stationary phase.

3-(1-Carbethoxy-2-keto-3-methylcyclohexyl) propionaldehyde(24)

A mixture of acrolein (240ml) and 1-carbethoxy-5-methyl-cyclohexanone, 23, (550g.) was added dropwise with stirring over 4 hours to a cooled solution (~ -70°) of sodium (3.4g.) in dry ethanol (1100ml) containing hydroquinone (4.0g.). The thick mass was stirred under nitrogen for 16 hours and allowed to return to room temperature. Neutralization of the resulting oil with glacial acetic acid followed by removal of most of the ethanol at the pump, gave a viscous oil which was dissolved in ether (31.). After extracting with sodium bicarbonate solution, brine and drying over magnesium sulphate, the solvent was removed to give the crude aldehyde (739g.).

Distillation afforded a pale yellow oil, b.p.170-180°/ 0.1 mm., 440g. (61%) with infra-red absorption at 2700cm^{-1} (aldehyde) and 1720-1700cm^{-1} (broad band due to all three carbonyl functions).

1-Carbethoxy-4-hydroxy-5-methylbicyclo [3:3:1] nonan-9-one (28; R=H).

A mixture of the monocyclic aldehyde, 24 (409g.), glacial acetic acid (1636ml.) and hydrochloric acid (409ml. concentrated acid, 818 ml. water) was heated on a steam-bath for 90 minutes with occasional shaking and the dark brown solution left to stand at room-temperature for 36 hours. The solution was neutralized with sodium bicarbonate, saturated with salt, divided into batches (11.) and each of these extracted with ether (5x200 ml.). The combined extracts were washed with sodium bicarbonate solution, brine, dried and solvent removed to give a poor yield of alcohol (220g.). Distillation gave a very viscous colourless oil b.p. 140-160°/0.2 m.m., 160g., showing infra-red absorption at 3450cm^{-1} (hydroxyl), 1720-1700cm^{-1} (carbonyl functions) and 1260-40cm^{-1} (ester). On the small scale (5g.), when larger relative amounts of ether and aqueous diluents could be used, the yield of distilled product was higher (~ 70%).

Note: In the distillation, there was a considerable non-homogeneous fore-run (40g.) which on fractionation gave a sample b.p. 67°/0.2 m.m. n_D^{17} 1.4891, with infra-red bands at 3500cm^{-1}. (hydroxyl, half intensity of 28; R=H), 1720-1700cm^{-1} and 1240cm^{-1}. Analysis suggested a fairly saturated molecule (Found: C,68.55; H, 10.50 $C_{13}H_{24}O_3$ requires C, 68.40; H, 10.60%).

Formation and attempted pyrolysis of 1-carbethoxy-4-acetoxy-5-methyl bicyclo [3:3:1] nonan-9-one (28;R=CO.CH_3).

A solution of the alcohol, 28; R=H, (1.035g.) in dry pyridine (Analar, 10ml.) containing acetic anhydride (0.46g., 1.1 equivalents) was left at room-temperature for 16 hours and then poured into water (50ml.). The aqueous material was extracted with ether (3 x 50ml.) and these extracts washed with hydrochloric acid (2N, 3 x 30ml.), saturated bicarbonate solution and brine. Drying and solvent removal gave a viscous crude acetate (28; R=CO.CH_3) which distilled to give 1-carbethoxy-4-acetoxy-5-methylbicyclo [3:3:1] nonan-9-one as a colourless oil b.p. 120-125°/0.2m.m., 1.1g. (Found: C, 64.05; H, 8.05 $C_{15}H_{22}O_5$ requires C, 63.80; H, 7.85%), transparent in the hydroxyl region but with infra-red absorption at 1720cm^{-1} (carbonyl groups) and 1260cm^{-1} (acetoxyl and carbethoxyl).

A mixture of the acetate (1.0g.), zinc oxide (0.3g., 1.1 equivalents) and silicone fluid (5ml.) was heated on an oil bath under reduced pressure (0.08m.m.). The bath temperature was raised to 150° and held at that for 30 minutes, then the process repeated at 180°. When the temperature was raised to 230°, the contents of the flask distilled to give unchanged acetate. The acetate (0.8g.) was heated under introgen with silicone fluid (2ml.) at 300° for 40 minutes. As before, distillation of the residue gave only unchanged acetate.

Formation and attempted pyrolysis of ethyl 4-(1-carbethoxy-5-methylbicyclo [3:3:1] nonan-9-onyl)carbonate (28; R=CO.OEt).

Ethyl chlorocarbonate (4ml., excess) was added dropwise with shaking to the alcohol 28; R=H (0.72g.) in dry pyridine (10ml.) at 5°. After standing at room-temperature for 16 hours, the yellow solution was poured into ice-water (50ml.) and glacial acetic acid (20ml.).

The organic material was extracted with ether (3 x 50ml.) these extracts being combined, washed with hydrochloric acid (2N), saturated sodium carbonate solution and brine. Drying and removal of the ether gave the desired carbonate (0.73g.), the infra-red spectrum of which was transparent in the hydroxyl region, but otherwise very similar to that of the starting material.

A mixture of the unpurified carbonate (0.73g.) and silicone fluid (5ml.) was heated at 320-340° under reflux for 2 hours. The residue was taken up in ether, filtered free of carbonized material and distilled but no low-boiling fraction (< 120°) was obtained.

Attempted dehydration of 1-carbethoxy-4-hydroxy-5-methylbicyclo [3:3:1] nonan-9-one (28; R=H).

The alcohol, 28; R=H, (4.6g.) with Woelm alumina (neutral grade 1) containing pyridine (Analar, 0.16g.) was heated to 230-260° for 50 minutes. The mixture was extracted with ether (3 x 25ml.), the extracts washed with hydrochloric acid (3N), sodium bicarbonate solution, brine and dried over magnesium sulphate. Evaporation of the solvent gave a mobile liquid (3.7g.) with infra-red bands at 1720-1700cm^{-1} (ester and ketone) and 1240cm^{-1} (carbethoxyl), none at 3500cm^{-1} (hydroxyl) and inexplicably, none at 710cm^{-1} (cis double bond). Distillation gave no well defined fractions between 100-150°/20m.m. or with the higher boiling residue at 90-100°/0.15m.m. As none of these fractions had spectra similar to the olefin ester (25; R=CH_3), it appears that besides dehydration, extensive fragmentation of either the alcohol or the olefin took place.

1-Carbethoxy-5-methylbicyclo [3:3:1] non-3-ene-9-one (25; R=Et)

The aldehyde, 24, (440g.) was added dropwise over 5 hours to concentrated sulphuric acid (1500ml.) which was stirred

and cooled ($\sim 0^{\circ}C$). The mixture was then stirred for 16 hours, allowed to return to room-temperature and split into batches (100ml.). Each of these was poured into ice-cold brine (500ml.) and extracted with ether (2 x 150ml.). The combined extracts were reduced in volume to a third ($\sim$ 2l.), washed with sodium carbonate solution, brine and dried over magnesium sulphate. Removal of the solvent gave a dark oil (323g.) from which one of the rearrangement products, the aromatic acid (26), crystallized and was removed (5g.). Distillation gave a colourless product (273g.) b.p. $102\text{-}110^{\circ}/0.15$m.m., a mixture of the second rearrangement product, i.e. the unsaturated ketone (27), and the olefin ester (25;R=Et). A solution of this mixture in ethanol (800ml.) was left to stand at 0° with a solution of semicarbazide acetate (0.5 mole.) for 1 day. The solid semicarbazone ($\sim$ 20g.) was filtered off, the ethanol replaced by ether (1l.) and the solution washed with dilute brine to remove excess reagent. Drying and solvent removal gave crude olefin ester (25; R=Et) which distilled at $104\text{-}108^{\circ}/0.20$m.m., as a colourless oil, yield 190g. (47%), with infra-red absorption at 1730, 1260cm^{-1} (carbethoxyl), 1710cm^{-1} (ketone) and 1650, 710cm^{-1} (cis double bond).

5-Methylbicyclo [3:3:1] non-3-ene-9-one-1-carboxylic acid (25; R=H).

A solution of the olefin ester, 25; R= Et , (190g.) in methanol (3l.) was refluxed with potassium hydroxide (200g.) for 16 hours. The methanol was removed at the water-pump, the residue taken up in water (600ml.) and extracted with ether (2 x 100ml.). After cooling, the aqueous layer was acidified with sulphuric acid (6N) and extracted with ether (4 x 250ml.). The combined extracts were washed with brine, dried over magnesium sulphate and the solvent removed to give crude crystalline acid (200g.)

Recrystallization from benzene - petroleum ether (7:3) gave the desired acid (25; R=H), 127g., m.p.137-140°. When the mother liquors were adsorbed on silica and chromatographed, elution with benzene-chloroform (9:1) gave a further quantity of the acid, 8.7g.

Reduction of the 9-keto group to give 1-carbomethoxy-5-methylbicyclo [3:3:1] non-3-ene (33; R=CH_3)

A. Clemmensen reduction of the olefin acid (25; R=H)

Zinc powder (470g.) was shaken with a solution of mercuric chloride (47g.) in hydrochloric acid (24ml. concentrated acid, 240ml. water). After 5 minutes, the aqueous material was decanted, the amalgamated zinc washed with water (240ml.) and covered with hydrochloric acid (480ml. concentrated acid, 240ml. water). A mixture of this material, xylene (240ml.) and the olefin acid 25; R=H, (47g.) was heated under reflux for 20 hours, further concentrated acid (50ml.) being introduced after 3 and 7 hours.

The xylene layer was separated, the zinc filtered off and washed with hot ethyl acetate (3 x 100ml.). The aqueous residue was extracted with ether (500ml.) and ethyl acetate (2 x 500ml.) and then all the organic materials combined. After extraction with saturated sodium carbonate solution (5 x 100ml.) most of the ether and ethyl acetate were removed under reduced pressure, the residue being further extracted with sodium carbonate solution (4 x 70ml.). The carbonate extracts were combined, cooled, acidified with sulphuric acid (6N) and extracted with ethyl acetate (5 x 200ml.) these being washed with brine and dried over magnesium sulphate. The combined product, 110g. from three such experiments consisted mainly of (33; R=H) with smaller amounts of the hydroxy acid (32; R=H) and unreacted starting material (25; R=H).

B. Esterification of the acid mixture:

A solution of the acid mixture (110g.) in methylene chloride (165ml.) containing methanol (52g.) and concentrated sulphuric acid (0.08ml.) was heated at reflux for 16 hours. On cooling, ether (500ml.) was added and the organic layer extracted with sodium bicarbonate solution, brine and dried over magnesium sulphate. Removal of the solvent gave a mixture of methyl esters (85g.), chiefly (33; R=CH_3). The bicarbonate extract was acidified and the aqueous material extracted with ether (3 x 100ml.). The combined ether extracts were washed with brine, dried and the solvent removed to give unreacted acid (20.9g.).

C. Sodium borohydride treatment of the ester mixture to reduce any 9-keto ester (25; R=CH_3).

An ice-cold solution of the ester mixture (85g.) in methanol (400ml.) was treated with a solution of sodium borohydride (10g.) in water (100ml.) and after standing at room-temperature for 2 hours, the solution was acidified and the methanol removed at the pump. Ether (500ml.) was added, the organic layer extracted with sodium bicarbonate solution, brine and dried over magnesium sulphate to give a mixture of 9-methylene and 9-hydroxy esters (84g.).

D. Separation of pure 9-methylene ester (33; R=CH_3)

A mixture of 9-methylene and 9-hydroxy esters, (99g.) dissolved in petroleum ether was absorbed on alumina (2Kg.) and chromatographed. Elution with petroleum ether (60-80°, 12l.) gave the desired olefin ester, which distilled as a colourless mobile liquid, 37.09g. (33%) b.p.58-66°/0.15m.m. This had an infra-red spectrum with bands at 3000cm^{-1} (double bond), 1730, 1260cm^{-1} (carbomethoxyl) and 710cm^{-1} (double bond).

1-Carbomethoxy-5-methylbicyclo [3:3:1] non-3-ene-2-one (34)

A. Formation of 1-carbomethoxy-2-benzoyloxy-5-methylbicyclo [3:3:1] non-3-ene (36)

The olefin ester, 33; R=CH_3, (1.94g.) was stirred under nitrogen with anhydrous cuprous bromide (0.1g.) and heated to between 105-115° on an oil bath. t-Butyl perbenzoate (0.77g., 0.4 equivalents) was then added dropwise over 1 hour, heating being continued for a second hour. The reaction product, taken up in ether (50ml.) was filtered free of unreacted cuprous bromide, the organic solution washed with sodium carbonate solution, to remove dissolved copper salts, brine and dried over magnesium sulphate. Evaporation of the solvent gave an oil (2g.) which was absorbed on alumina (50g.) and chromatographed. Elution with benzene-petroleum ether (1:4) afforded unreated olefin ester (1.24g.) while further elution with chloroform gave the benzoyloxy ester (36), 0.57g. (19%), as a viscous oil, with infra-red absorption at 3000cm^{-1} (double bond), 1730-1700, 1270cm^{-1} (ester) and 1600,1580cm^{-1} (aromatic bands).

B. Methanolysis of (36) to 1-carbomethoxy-2-hydroxy-5-methylbicyclo [3:3:1] non-3-ene (37).

A solution of the benzoyloxy compound (0.57g.) in dry methanol (3ml.) was mixed with a solution of sodium (0.01g.) in dry methanol (5ml.) and the whole heated under reflux for 4 hours. On cooling, the solution was saturated with carbon dioxide, ether (25ml.) added, the organic material washed with dilute brine and dried.

The crude product was absorbed on alumina and chromatographed, elution with chloroform giving the alcohol ester (37), 0.2g. Distillation afforded the alcohol ester as a colourless liquid b.p. 74°/0.25m.m. n_D^{20} 1.5028, with infra-red bands at 3420cm^{-1} (hydroxyl) and 1730cm^{-1} (carbomethoxyl).

C. Allylic oxidation of (37)

The alcohol, 37, (0.2g.) dissolved in petroleum ether (10ml.) was shaken with activated manganese dioxide (3g.) for 6 hours. Filtration, followed by solvent removal gave the crude enone (0.18g.) λ_{max} 228-34mμ, E_{max} 7,600 with infra-red absorption at 1730cm^{-1} (carbomethoxyl) and 1680cm^{-1} (enone). This sample was almost identical with enone (34), produced by direct allylic oxidation of the olefin ester (33; R=CH_3). A solution of the enone (0.1g.) in methanol (5ml.) was treated with Brady's reagent (2ml.). After 10 minutes at room-temperature, water (20ml.) was added and the material extracted with benzene (2 x 20ml.). The extract was water-washed, dried and the residue chromatographed on bentonite-kieselguhr. Elution with benzene gave a 2:4-dinitrophenylhydrazone which crystallized from benzene as yellow needles m.p. 136-145°. Recrystallization from methanol gave red needles m.p. 168-170°. This behaviour corresponded with that of the 2:4-dinitrophenylhydrazones obtained from the enone produced by direct oxidation.

1-Carbomethoxy-5-methylbicyclo [3:3:1] nonan-2-one (35)

A solution of the enone, 34, (1.26g.) in ethyl acetate (50ml.) was shaken with palladium-charcoal (10%, 1.27g.). Hydrogen was taken up and removal of the catalyst and solvent gave crude saturated ketone (1.1.g). Distillation afforded this as a colourless liquid b.p. 96°/0.1m.m. n_D^{20} 1.4870, with infra-red absorption at 1730cm^{-1} (carbomethoxyl) and 1710cm^{-1} (saturated ketone). The saturated keto ester (0.142g.) dissolved in dry methanol (10ml.) was heated under reflux with Brady's reagent for 3 hours. Water (50ml.) was added, the organic material extracted with chloroform (2 x 30ml.), this then water-washed and dried over anhydrous magnesium sulphate. The red residue was chromatographed on bentonite-kieselguhr, elution with

benzene giving a yellow solid. Recrystallization from petroleum ether (60-80°, x 2) afforded yellow needles of 1-carbomethoxy-5-methylbicyclo [3:3:1] nonan-2-one-2:4-dinitrophenylpyrazolone m.p. 179-181° (Found: C,57.05; H14.75; N,15.55 $C_{17}H_{18}O_5N_4$ requires C, 57.00; H, 15.05; N, 15.65%). The pyrazolone of the keto ester (35) has also been prepared and alalysed.

Attempted formation of 1-carbomethoxy-2-tosyloxy-5-methylbicyclo [3:3:1] non-3-ene.

A solution of the hydroxy ester, 37, (0.113g.) in dry pyridine (2ml.) was mixed with p-toluenesulphonyl chloride (0.176g.) in pyridine and the resulting solution heated under reflux for 2 hours. The product was poured into sodium bicarbonate solution (20ml.) and the organic material extracted with ether (2 x 30ml.). The extracts were washed with water, hydrochloric acid (2N) brine and dried. Removal of the solvent gave unchanged hydroxy ester (0.05g.) as the sole product.

Attempted formation of 1-carbomethoxy-2-mesyloxy-5-methyl-bicyclo [3:3:1] non-3-ene.

Solid methanesulphonyl anhydride (0.62g., excess) was added with stirring to the hydroxy ester (0.36g.). The mixture was warmed to melt the anhydride and when the whole mass was fluid, a drop of concentrated sulphuric acid was added. After 30 minutes of gentle heating, the reaction was quenched by the addition of water (30ml.). An ether extract of the product was washed with bicarbonate, brine, dried and solvent removed to give a thick red oil. This was hydroxyl-free and had infra-red absorption at 1770cm^{-1} (shoulder, lactone or anhydride), 1730cm^{-1} and 1250cm^{-1} (probably carbomethoxyl). Chromatography on alumina and elution with benzene-chloroform (3:2) gave an oil with virtually the same spectrum as the crude product.

Attempted condensation of the keto-ester (35) with ethyl bromacetate.

A solution of the keto-ester (0.90g.) in benzene-ether (1:1,40ml.) was refluxed with ethyl bromacetate (1ml., 2 equivalents), zinc (1g.) and iodine (one crystal). After 90 minutes, ethyl bromacetate (1ml.) was added, and the reaction commenced. Every 30 minutes after this, small quantities of zinc and iodine were added till the total weight of zinc was 2g. and the reflux time was 6 hours. The metallic complex was decomposed with sulphuric acid (6N, 20ml.) and extracted with benzene (3 x 30ml.). The organic layer was washed with sulphuric acid (3N), sodium carbonate solution, brine and dried over magnesium sulphate to give a crude oil 39, (0.417g.) with infra-red absorption at 3500cm^{-1} (sharp, hydroxyl) and 1735-20cm^{-1} (esters).

The total product was heated with fused potassium hydrogen sulphate (1g.) till a liquid distilled out of the pyrolysate. The black residue was extracted with ether (50ml.) and water (50ml.) and the ether solution washed with this sulphate solution (iodine removal), sodium carbonate solution, brine and dried. Evaporation of the solvent gave an oil, 40, (0.35g.) which was hydroxyl-free but had bands at 1735cm^{-1} and 1250cm^{-1} (ester). Elution from alumina with petroleum ether-benzene (1:1) to benzene gave an oil (0.15g.), with a spectrum identical to the above, as the only major component.

The crude ester was hydrolysed by refluxing in dry methanol (20ml.) with potassium hydroxide (0.19g.) for 3 hours. The solvent was removed at the pump, the residue taken up in water (20ml.), ether extraction (2 x 20ml.) giving the neutral material (7mg.).

Acidification of the aqueous layer with hydrochloric acid (6N), followed by saturation with ammonium sulphate and re-extraction with ether (2 x 30ml.) gave, after washing with brine and drying, an acidic oil (0.11g.) with infra-red absorption at 2600cm^{-1} (bonded hydroxyl) and 1700cm^{-1} (carboxyl). This material could not be induced to crystallize.

5-Methylbicyclo [3:3:1] non-3-ene-1-carboxylic acid (33;R=H)
A solution of the olefin ester, 33; R=CH_3 (10.01g.) in methanol (250ml.) was refluxed with potassium hydroxide (Analar, 10g.) for 16 hours. The methanol was removed under reduced pressure and the resulting potassium salt dissolved in water (100ml.) Saturated brine (20ml.) was added and the solution extracted with ether (2 x 50ml.). The aqueous material was acidified with hydrochloric acid (6N), saturated with ammonium sulphate and extracted with ether (4 x 50ml.). The ethereal extracts were washed with brine (2 x 50ml.) and dried. The solvent was removed to give a solid, 8.71g. which when recrystallized from petroleum ether (60-80°) gave white needles of 5-methylbicyclo [3:3:1] non-3-ene-1-carboxylic acid, 33;R=H, m.p. 111-114° (Found: C,73.70; H, 8.85 $C_{11}H_{16}O_2$ requires C, 73.30; H, 8.95%).

5-Methylbicyclo [3:3:1] non-3-ene-1-carboxylic acid chloride.
The olefin acid, 33; R=H, (0.65g.) in dry benzene (Analar, 25ml.) was treated with oxalyl chloride (1.2g.) and allowed to stand at room temperature for 3 hours. When the benzene had been removed under reduced pressure, a further quantity of benzene (25ml.) was added and then removed to free the residual oil of all traces of reagent. The product, formed in quantitative yield, was a yellow liquid with a single band in the carbonyl at 1790cm^{-1}, and since it would not solidify, it was used directly in the preparation of the corresponding diazoketone.

5-Methylbicyclo [3:3:1] non-3-ene-1-acetic acid amide.
The crude acid chloride (0.69g.) dissolved in dry ether (25ml.) was added to a cold solution of diazomethane in ether and the solution allowed to stand at room temperature for 12-16 hours.

Note: On several occasions, when less than two equivalents of diazomethane were added, the product was a mixture of the desired diazoketone and unreacted acid chloride, with no trace of α-chloroketone. The reaction could be taken to completion simply by the addition of a further quantity of diazomethane solution and standing for 2 hours.

Removal of the ether under vacuum gave a thick yellow gum (0.6g.) displaying infra-red absorption at 3000cm^{-1} (double bond) and 2100, 1620cm^{-1} (diazoketone).

A solution of diazoketone (0.6g.) in dioxan (10ml.) was treated with 0.88 ammonia (15ml.) and 10% silver nitrate solution (10ml.). Refluxing the resulting mixture for 1 hour, filtering to remove silver solids and then concentrating at the pump gave a crude solid (0.45g.). Recrystallization from petroleum ether (60.80° x 3) gave rosettes of 5-methylbicyclo [3:3:1] non-3-ene-1-acetic acid amide m.p. 87-8°, (Found: C, 74.85; H, 9.65; N,7.30 $C_{12}H_{19}ON$ requires C, 74.55; H, 9.90; N, 7.25%) with infra-red absorption at 3400, 3200cm^{-1} (N-H) and 1700cm^{-1} (amide carbonyl.)

Attempted formation of 5-methylbicyclo [3:3:1]non-3-ene-1 acetic acid (53; R=H).
The amide (0.10g.) dissolved in methanol (10ml.) was heated under reflux with potassium hydroxide (0.11g.) for 24 hours. The methanol was removed on the pump, water (10ml.) and brine (10ml.) added and the aqueous solution extracted with ether (3 x 20ml.). These extracts

were washed and dried to give the neutral fraction (0.07g.) which was unhydrolysed amide. The aqueous material was acidified, saturated with ammonium sulphate and extracted with ether to give the acidic fraction (0.011g.) as an oil which would not crystallize.

Attempted formation of 1-(2′-Keto-n-butyl)-5-methylbicyclo [3:3:1] non-3-ene (52).

A solution of Grignard reagent ($\sim 6 \times 10^{-3}$ mole) in ether (5ml.) was prepared from magnesium (0.106g.) and ethyl bromide (0.60g.). The amide (0.3g.) dissolved in ether (5ml.) and mercuric chloride (0.05g.) were added to this solution, and the resulting mixture heated under nitrogen till the solvent refluxed. A white gelatinous complex was formed but aliquots taken after 1, 4 and 24 hours showed only starting material. The ether was replaced by tetrahydrofuran (5ml.) a further 2 equivalents of Grignard reagent were introduced and the mixture heated under reflux for 24 hours when the complex was decomposed with 6N sulphuric acid (5ml.). Saturated brine (10ml.) was added and the aqueous material extracted with ether (3 x 3ml.). Washing and drying of the extracts, followed by solvent removal gave only unchanged amide (0.21g.).

Methyl 5-methylbicyclo [3:3:1] non-3-ene-1-acetate (53;R=CH_3)

The acid chloride from 33; R=H, (9.0g.) was converted into the corresponding diazoketone (9.1g.) as before. This was immediately dissolved in dry methanol (50ml.) and the solution stirred gently at room temperature. When a few drops of a saturated solution of silver benzoate in triethylamine ($\sim$20% by weight silver benzoate) were added, black finely divided silver was precipitated and nitrogen was given off. When gas evolution slackened more amine solution was added ($\sim$2ml. used), but it ceased after 75 minutes (980ml., 90%) despite further

additions of catalyst. The crude product, diluted with ether (100ml.) was filtered and washed with brine to precipitate silver salts held in solution. The aqueous layer was extracted with ether (2 x 30ml.) and the combined organic material concentrated at the pump, thus removing most of the methanol. The residue was taken up in ether (200ml.), extracted with hydrochloric acid (6N), brine, saturated sodium carbonate solution, brine and dried. Removal of the solvent gave crude homologated ester (8.29g.) which was absorbed on alumina (150g.) and chromatographed, elution with petroleum ether giving the desired ester, (5.9g.) in a purer state. Fractionation afforded methyl 5-methylbicyclo [3:3:1] non-3-ene-1-acetate as a colourless liquid b.p. 61-63°/0.01m.m. n_D^{24} 1.4838 (Found: C, 75.05; H, 9.45 $C_{13}H_{20}O_2$ requires C, 74.95; H, 9.70%) with infra-red absorption at 3000cm^{-1} (double bond), 1730cm^{-1} and 1260cm^{-1} (ester).

Further elution with benzene-petroleum ether (4:1) gave the same ester (1.0g.) contaminated by an impurity showing infra-red absorption at 1775cm^{-1}.

5-Methylbicyclo [3:3:1] non-3-ene-1-acetic acid (53;R=H)

A solution of the ester, 53; R=CH_3 (31.74g.) in methanol (800ml.) was heated under reflux with potassium hydroxide (32g.) for 16 hours. The solvent was removed at the pump, water (200ml.) and brine (100ml.) added and the solution extracted with ether (2 x 100ml.). The aqueous layer was acidified with hydrochloric acid (6N), saturated with ammonium sulphate and extracted with ether (3 x 200ml.). The extracts were washed with brine, dried and the solvent removed to give a thick oil, 27.8g., which furnished a solid m.p. 35-45° on trituration with petroleum ether at -70°.

Recrystallization from petroleum ether (60-80°), afforded colourless needles of 5-methylbicyclo [3:3:1] non-3-ene-1-acetic acid m.p. 52-54° (Found: C, 74.15; H, 9.50 $C_{12}H_{18}O_2$ requires C, 74.20; H, 9.35%).

Attempted formation of 1-(2´-Keto-n-butyl)-5-methylbicyclo [3:3:1] non-3-ene (52) from the acid (53; R=H).

Ethyl iodide (0.69g., 4.4×10^{-3} mole) was added with stirring to lithium foil (strips, 0.12g.) in ether (5ml.) under nitrogen. The mixture was heated on a water-bath for 4 hours when most of the lithium had reacted to give a suspension of white solid in ether. This was poured in a stream of nitrogen through a glass wool plug into a solution of the acid, 53; R=H, (0.28g. 1.4×10^{-3} mole) in ether (10ml.). After refluxing for 1 hour, water (2oml.) was added and the solution extracted with ether (2 x 20ml.) This gave only a few milligrammes of neutral material. The aqueous layer was acidified and extracted with ether (3 x 20ml.). Washing the extracts with brine, drying over magnesium sulphate and evaporation of the ether furnished unchanged acid (0.21g.).

5-Methylbicyclo [3:3:1] non-3-ene-1-acetyl chloride.

The acid, 53, R=H (0.096g., 0.49×10^{-3} mole) dissolved in benzene (Analar, 20ml.) was treated with oxalyl chloride (0.5ml.) and the solution left at room temperature for 3 hours. The solvent benzene and an additional quantity (20ml.) were successively removed under reduced pressure to give a mobile yellow oil (0.09g.) with the expected infra-red spectrum of double bond at $3000cm^{-1}$ and acid chloride at $1790cm^{-1}$. The product was used immediately for the next step.

Attempted formation of 1-(2´-Keto-n-butyl)-5-methylbicyclo [3:3:1] non-3-ene (52) from the acid chloride corresponding to 53; R=H.

In this particular experiment nitrogen could not be used

because of the smallness of the scale. The Grignard reagent in ether (5ml.) prepared from magnesium (turnings, 0.049g.) and ethyl bromide (0.224g. 2×10^{-3} mole) was cooled in an ice bath and to it was added powdered anhydrous cadmium chloride (0.23g. 1.2×10^{-3} mole) with stirring over 5 minutes. The mixture was refluxed for 30 minutes, most of the ether was distilled off and replaced by benzene (10ml.).

The crude acid chloride (0.05g.) in benzene (5ml.) was then added dropwise with stirring to the cadmium diethyl in benzene (5ml.) and the whole refluxed for 1 hour. The complex was decomposed with dilute sulphuric acid (6N, 5ml.) brine (10ml.) added, followed by extraction of the organic material with benzene (10ml.) and ether (2 x 20ml.). The extracts were washed with sodium bicarbonate solution, brine and dried over magnesium sulphate. Removal of solvent gave a liquid which showed a single peak in the carbonyl at $1730 cm^{-1}$.

The experiment was repeated, the acid (0.8g.) giving a product (0.77g.) with an almost identical spectrum to the first product.

A solution of this product (0.77g.) in methanol (10ml.) was mixed with a solution of sodium borohydride (0.28g.) in water (10ml.). After standing at room temperature for 4 hours, most of the methanol was removed under reduced pressure, the residue acidified with dilute hydrochloric acid (6N) and brine (10ml.) added. Extraction with ether (2 x 30ml.) followed by washing of the extracts with brine, drying over magnesium sulphate and removal of the solvent gave no hydroxylic material.

The product of the borohydride treatment was then taken up in methanol (20ml.) and refluxed with potassium

hydroxide (1.0g.) for 20 hours. The methanol was removed at the pump, water (20ml.) and brine (10ml.) were added and the solution extracted with ether (2 x 20ml.) to give neutral material (0.03g.). The aqueous layer was acidified, saturated with ammonium sulphate and ether extracted (3 x 20ml.). The extracts were washed with brine and dried to give an oily product which was absorbed onto silica and chromatographed, elution with benzene giving the acid, 53; R=H, 0.28g., m.p.48-54°.

1-(2'-Keto-n-butyl)-5-methylbicyclo [3:3:1] non-3-ene (52)

A solution of ethyl magnesium bromide in ether (50ml.) from magnesium turnings (2.45g.) and ethyl bromide (11g.) under nitrogen was cooled in an ice-bath and powdered anhydrous cadmium chloride (9.5g.) was added to it with stirring over 15 minutes. After refluxing the mixture for 30 minutes, most of the ether was distilled off, this being replaced by benzene (30ml.) which in turn was replaced by more benzene (50ml.). The crude acid chloride in benzene (50ml.), produced quantitatively from the acid, 53; R=H, (6.94g.) and oxalyl chloride, was then added to the cadmium reagent cooled to 0°. When the addition was complete, the mixture was stirred and heated under reflux for 1 hour. The complex was then decomposed with cold sulphuric acid (6N, 50ml.) brine (50ml.) added, and the organic material extracted with ether (3 x 50ml.). The extracts were shaken with sodium bicarbonate solution, brine and dried, removal of the solvent giving a mobile liquid (7.0g.) which showed infra-red absorption in the carbonyl region at 1710cm^{-1}. Fractionation gave 1-(2'-Keto-n-butyl)-5-methylbicyclo [3:3:1] non-3-ene as a colourless liquid b.p. 68-72°/0.15m.m., N_D^{19} 1.4899, yield 6.2g. (83%) (Found: C, 81.25; H, 10.80 $C_{14}H_{22}O$ required C, 81.50; H, 10.75%). The corresponding semicarbazone crystallized

from ethanol (x5) as plates m.p.170-177° (Found: C, 68.15; H, 9.40; N, 16.15 $C_{15}H_{25}ON_3$ requires C, 68.40; H, 9.55; N, 15.95%).

Attempted formation of 1-(2'-Keto-n-butyl)-5-methylbicyclo [3:3:1]non-3-ene-1:4-dioxalane (54).

A solution of the ketone, 52 (0.49g.) in dry benzene (Analar, 40ml.) was heated under reflux with ethylene glycol (0.15g., 1:1 equivalent) and p-toluenesulphonic acid monohydrate (5mg.) in a Dean and Stark apparatus. Aliquots taken after 3 and 16 hours showed no change in the intensity of absorption of the carbonyl peak (1710cm^{-1}). Additional amounts of ethylene glycol (0.30g.) and the sulphonic acid (20mg.) were added and the solution heated under reflux for 48 hours. The benzene was then removed at the pump, the residue taken up in ether (50ml.) washed with brine and dried. This final product still had strong carbonyl absorption and very little ether absorption between 1100-1000cm^{-1}.

1-(2'-Keto-n-butyl)-5-methylbicyclo [3:3:1] non-3-ene-1:4-dioxalane (54).

The ketone, 52 (1.64g.) was shaken with ethylene glycol (3ml.) and ethyl orthoformate (6ml.) in the presence of naphthalene-β- sulphonic acid (0.047g.). The homogeneous solution was gradually heated on an oil bath and the volatile reaction products (ethanol, ethyl formate) collected as they formed. The bath temperature was held at 100° for 30 minutes, raised to 140° and held there for a further 30 minutes, the total reaction time being about 75 minutes. The non-volatile products were taken up in ether (50ml.) and the organic material extracted with sodium bicarbonate solution, brine and dried over magnesium sulphate. Removal of solvent gave a thick oil (2.4g.) with a small intensity hydroxyl at 3400cm^{-1},

no carbonyl and a strong band between 1060-1040cm^{-1}. This oil was absorbed on alumina (80g.) and chromatographed, elution with petroleum ether giving the expected ketal (1.74g.) free from hydroxylic material. Normal distillation gave 1-(2'-keto-n-butyl)-5-methylbicyclo [3:3:1] non-3-ene-1:4-dioxalane as a viscous colourless oil b.p. 84°/0.008m.m., n_D^{19} 1.4960 (Found: C, 76.50; H, 10.45 $C_{16}H_{26}O_2$ requires C, 76.75; H, 10.45%).

1-(2'-Keto-n-butyl)-2-benzoyloxy-5-methylbicyclo [3:3:1] non-3-ene 1:4-dioxalane (55)

The ketal, 54 (1.26g.) was stirred under nitrogen with powdered anhydrous cuprous bromide (0.1g.) and heated on an oil bath till the temperature reached 115°. t-Butyl perbenzoate (1.25g.) was then added dropwise over 40 minutes. During the 80 minutes total reaction time, the bath temperature was held between 110-120°. On cooling, the reaction products were taken up in ether (50ml.) and filtered free of unreacted copper solids. The organic material was washed with sodium carbonate solution, brine and dried over magnesium sulphate. Removal of the solvent gave a thick oil (1.78g.) which was adsorbed on alumina (60g.) and chromatographed. Elution with petroleum ether yielded unchanged ketal while elution with benzene petroleum ether (1:1) to benzene-chloroform (1:1) gave benzoyloxy ketal as an extremely viscous oil, which refused to crystallize, yield 1.51g. (54%). Molecular distillation gave 1-(2'keto-n-butyl)-2-benzoyloxy-5-methylbicyclo [3:3:1] non-3-ene-1:4-dioxalane as a colourless glass b.p.140-180°/0.1m.m. (Found: C, 74.20; H, 7.85, $C_{23}H_{30}O_4$ requires C, 74.55; H, 8.15%) with infra-red absorption at 1700cm^{-1} (unsaturated ester), 1600, 1580cm^{-1} (aromatic bands), 1280cm^{-1} (ester), 1100, 1070, 1020cm^{-1} (dioxalane) and 710cm^{-1} (monosubstituted aromatic ring).

1-(2'Keto-n-butyl)-2-benzoyloxy-5-methylbicyclo [3:3: 1] non-3-ene (58)

The ethyl ketone, 52, (9.351g., 4.55×10^{-2} mole) was heated to 110° under nitrogen with cuprous bromide (0.1g.). t-butyl perbenzoate (6.6g., 3.4×10^{-2} mole), was then added dropwise over 40 minutes, producing a dark green solution. After a total of 90 minutes at 110-120°, the product was cooled, diluted with ether (200ml.) filtered, washed with sodium bicarbonate solution, brine, dried and the solvent removed to give a thick oil (13.4g.). This was adsorbed on alumina (grade 3, 300g.) and chromatographed, elution with petroleum ether (1650ml.) giving unreacted ketone (4.97g., 46%). Elution with benzene (3l.) gave liquid benzoyloxy ketone (3.95g., 27%) and solid benzoyloxy ketone (1.08g., crude 7%). The liquid could not be distilled but the solid recrystallized (x3) from petroleum ether as colourless needles of 1-(2'-keto-n-butyl)-2-benzoyloxy-5-methylbicyclo [3:3:1] non-3-ene m.p.73-76° (Found: C,77.25; H, 7.95 $C_{21}H_{26}O_3$ requires C, 77.25; H, 8.05%) showing infra-red absorption at 1700, 1260cm^{-1} (ester), 1700cm^{-1} (ketone), 1600, 1580 and 710cm^{-1} (aromatic bands). The fine structure region between 1450-1000cm^{-1} was complex, but apart from a general improvement in resolution on purification, all samples of (58) had identical spectra.

Note:- Distillation of the oil gave a mobile liquid b.p.90-100°/0.3m.m., which solidified readily, trituration with petroleum ether affording colourless needles m.p. 120-122°. Our suspicions were confirmed when the infra-red spectrum of this solid proved to be that of an aromatic acid. Further distillation gave a non-crystalline, high boiling fraction b.p. > 140°/0.3m.m., which was combined with the

trituration residues and dissolved in ether. This solution was extracted with aqueous sodium carbonate solution dried and the solvent removed to give a neutral residue, which was chromatographed in an attempt to identify the non-acidic pyrolysis products. Elution from alumina with petroleum ether gave material showing infra-red absorption at 1710cm^{-1} (saturated ketone) and 3000, 1640cm^{-1} (double bond) but additional bands at 1080, 1040, 980cm^{-1} made the spectrum too complex for it to be that of (52). Further elution with the same solvent gave a mixture of the first component and what appeared to be a saturated ketone with infra-red absorption at 1735cm^{-1} but no strong band below 1300cm^{-1} and no ultra violet absorption. Comparison with the infra-red spectrum of authentic cyclo pentanone suggested that the ketone might be (59). Finally, elution with benzene furnished unchanged liquid benzoate (58), this making up the bulk of the neutral material.

1-(2′-Hydroxy-n-butyl)-2-benzoyloxy-5-methylbicyclo [3:3:1] non-3-ene (57)

The crystalline benzoyloxy ketone, 58, (4.26g., 1.3 x 10^{-2} mole) dissolved in methanol (100ml.) was cooled to 0^{o} and sodium borohydride (0.625g., approximately 3 equivalents) in water (20ml.)added over 15 minutes. After standing at room temperature for 3 hours, the solution was acidified, dilute brine (50ml.) added and most of the methanol removed at the pump. The residue was extracted with ether (3 x 50ml.) the combined extracts washed with brine, dried and the solvent removed to give a thick oil (4.29g.). This was adsorbed on silica (90g.) and chromatographed, elution

with chloroform giving the benzoyloxy alcohol (57) as a transparent glass, 3.84g., with infra-red absorption at 3500cm^{-1} (hydroxyl), 1700cm^{-1} (ester), 1600 and 1580cm^{-1} (aromatic bands).

Repeating the process with the liquid keto benzoate, 58, (15.3g.) gave a glass, 14.8g., of identical spectrum.

1-(2′-Hydroxy-n-butyl)-2-hydroxy-5-methylbicyclo [3:3:1] non-3-ene (60).

The borohydride reduction product, 57 (3.84g.) in methanol (200ml.) was heated under reflux with sodium hydroxide solution (20g. in 100g. water, 5N) for 3 hours. On cooling most of the methanol was removed at the pump, the residue diluted with brine (50ml.) and the aqueous material extracted with ethyl acetate-ether (1:1. 3 x 100ml.). This was washed with brine and dried, removal of solvent giving an oil (2.6g.) which solidified on trituration with ethyl acetate. One recrystallization from methanol gave a solid, 1.99g., m.p. 110-130°. Recrystallization from aqueous methanol (x4) gave colourless needles of 1-(2′-hydroxy-n-butyl)-2-hydroxy-5-methylbicyclo [3:3:1] non-3-ene., m.p. 145° (Found: C, 74.80; H, 10.75, $C_{14}H_{24}O_2$ requires C, 74.95; H, 10.80%) with an infra-red spectrum showing absorption at 3400cm^{-1}, but transparent in the carbonyl and aromatic regions.

The hydrolysis, repeated on the liquid benzoate alcohol, 57, (14.5g.) gave liquid diol, 60, (7.4g., 73%) and crystalline diol, 60, (2.0g., 19%), the later arising from unseparated, potentially solid keto benzoate, dissolved in the liquid isomer (58).

1-(2′-Keto-n-butyl)-5-methylbicyclo [3:3:1] non-3-ene-2-one (61).

The diol, 60, (4.0g., m.p. 110-130°) was dissolved in

ice-cold acetone (Analar, 500ml.) and a solution of chromium trioxide in sulphuric acid (8N, approximately 8ml.) added with swirling till a permanent orange colour was produced. Warm water (200ml., 50°) was added, the acetone removed under reduced pressure without external heating, the residue diluted with brine (100ml.) and extracted with petroleum ether (3 x 75ml., 60-80°). After the petrol extracts had been washed with brine and dried over magnesium sulphate, the solvent was removed to give a mobile yellow liquid (3.69g.) with infra-red absorption at 1710, 1680cm^{-1} (saturated and unsaturated ketones, equal intensity), and 1770cm^{-1} (possibly lactone, with an intensity two-thirds that of the main carbonyl bands). The ultraviolet spectrum of the liquid showed a low intensity absorption at the expected wavelength λ_{max} 228-232mμ, E_{max} 3,100 (ethanol).

Repeating this oxidation on the liquid diol (7.6g.) gave a product (7.06g.) of similar spectrum. Distillation of a sample of this material afforded two fractions, the more volatile of which contained only slightly less lactone than the undistilled product.

1-(2′-Keto-n-butyl)-5-methylbicyclo [3:3:1] nonan-2-one (48)
The crude ketone, 61, (3.69g.) was reduced by shaking with palladium charcoal (10%, 1.30g.) in ethyl acetate (150ml.) under hydrogen. After an uptake of 306ml. (80%) the catalyst and solvent were removed to give the saturated ketone, 48, (3.73g.) with infra-red bands at 1710cm^{-1}, (saturated ketone), 1770cm^{-1} (impurity, possibly lactone) and 1640cm^{-1}. This was adsorbed on alumina (65g., grade two neutral, Woelm) and chromatographed, elution with petroleum ether (7 x 70ml.) and various petroleum ether-benzene mixtures (24 x 70ml.) gave fractions each of which had a single sharp carbonyl peak (1710cm^{-1}). As the

eluting solvent became benzene rich, two peaks at 1040, 1020cm^{-1} became less intense and a peak at 1100cm^{-1} became more intense, otherwise the spectra were identical. These liquids were combined and a sample subjected to gas-liquid chromatography (5% Apiezon-Celite, flow rate 50ml. min.$^{-1}$ at 160^{o}), when a result, identical with plot B, table 2 was obtained. The remaining ketone (2.43g.) was distilled to give four fractions

1	50-80^{o}/0.15m.m.	
2	84-92^{o}	n_{21}^{D} 1.4868
3	92-94^{o}	n_{21}^{D} 1.4890
4	94-98^{o}	n_{21}^{D} 1.4903

All were transparent in the ultra violet region and possessed identical infra-red spectra. The results obtained when the fractions were analysed by gas-liquid chromatography were readily interpreted on the basis of plot B. The volatile fractions (one and two) consisted largely of the first material to be eluted in B, fraction three contained this material (20%) along with that forming the second band (75%), this second material (80%) and the third to be eluted (15%) making up the final fraction.

Footnote: The sample of 1-(2$^{\prime}$-keto-n-butyl)-5-methylbicyclo [3:3:1] non-2-one which gave rise to plot B, table 2 was obtained from the unseparated mixture of liquid and solid benzoyloxy ketones, with subsequent steps as described above for the solid benzoyloxy ketone.

The unsaturated ketone, 61, (7.06g.) obtained from the liquid diol, was reduced in a similar fashion to give a saturated ketone (6.8g.) with an infra-red spectrum identical to that of the ketonic materials obtained above. This material was adsorbed on alumina, chromatographed and

the fractions subjected to gas-liquid chromatography as before. Elution with petroleum ether (1l.) gave material (2.6g.) made up of the first component in B (60%) and the second component (25%). Elution with petroleum ether-benzene, 1:1, (2l.) gave further material made up of the compound in the second band (70%) and that in the last band (25%).

Alternate synthesis of 1-(2′-Keto-n-butyl)-5-methylbicyclo [3:3:1] nonan-2-one (48)

A. Hydrolysis.

The keto benzoate, 58, (1.059g.) in methanol (125ml.) was heated under reflux with aqueous sodium hydroxide (4N, 36ml.) for 4 hours. Most of the methanol was removed at the pump, brine (50ml.) was added and the alkaline solution extracted with ether (4 x 50ml.). These extracts were washed with brine (2 x 30ml.) and dried over magnesium sulphate, removal of the solvent affording a yellow oil (0.72g.) with bands in the infra-red at 3400cm^{-1} (hydroxyl) 3000, 1650cm^{-1} (double bond) and 1710cm^{-1} (saturated ketone) apparently the desired hydroxy ketone (62).

B. Oxidation.

The crude ketone (0.72g.) dissolved in petroleum ether (120ml.) was shaken with activated manganese dioxide (10g.) for 16 hours. Removal of the solvent and oxidising agent gave the dione, 61, (0.619g.) with ultraviolet absorption at λ_{max} 228-234mμ , E_{max} 2,100 (ethanol) and with an infra-red spectrum showing bands at 1710, 1680cm^{-1} (the latter being of higher intensity). Except for the absence of the peak at 1780cm^{-1} (lactone), the overall spectrum was very similar to that from the chromic acid oxidation product (see page 68).

C. Reduction.

A solution of the dione, 61, (0.61g.) in ethyl acetate (100ml.) was shaken with palladium-charcoal

(10%, 0.58g.) under hydrogen. When hydrogen uptake was complete (73ml.), the catalyst was filtered off and the solvent removed to give a mobile liquid, ostensibly 48, (0.46g.) with infra-red bands at 1710cm^{-1} (saturated ketones) and 1100cm^{-1} (carbon skeleton). A sample was subjected to gas-liquid chromatography when plot A, table 2, with its three peaks, was produced. The product was distilled, this giving a colourless liquid b.p. 112-120°/ 0.3m.m. (Found: C, 78.60; H, 10.80 $C_{14}H_{22}O_2$, 48, requires C, 75.7; H, 9.9, $C_{14}H_{24}O$, 63, requires C,80.7; H, 8.7%).

The ketonic material was combined, adsorbed on alumina and chromatographed, two fractions being obtained. The first, which was eluted in petroleum ether, consisted entirely of the first two components of plot A. It afforded a crystalline semicarbazone m.p.170-175°. (Found: C,67.70; H, 9.60; N, 15.50, $C_{15}H_{27}ON_3$, the monosemicarbazone corresponding to (63) requires C, 67.90; H, 10.25; N, 15.85%, while $C_{15}H_{25}ON_3$, the monosemicarbazone corresponding to (52) requires C,68.40; H, 9.60; N, 15.95%). The second fraction eluted in petroleum ether and benzene, consisted only of the third component in plot A. It gave no crystalline derivatives.

Base treatment of the first two components produced in the attempted synthesis of 1-(2′-Keto-n-butyl)-5-methyl-bicyclo [3:3:1] nonan-2-one (48).

A solution of the first two components of the product from the previous experiment (0.090g.) in benzene (Analar, 15ml.) was heated at reflux with potassium t-butoxide (0.142g.) under nitrogen for 3 hours. The organic material was diluted with ether (20ml.), acidified with glacial acetic acid, washed with sodium carbonate solution, brine and dried. Removal of the solvent gave an oil, transparent in the ultraviolet region and showing an infra-red spectrum identical to that of the starting material.

Base treatment of the third component produced in the attempted synthesis of 1-(2′-Keto-n-butyl)-5-methyl-bicyclo [3:3:1] nonan-2-one (48).

A solution of the third component from the mixture described above (0.075g.) in methanol (3ml.) was heated on a steam-bath with potassium hydroxide solution (2%, 12ml.) for 5 hours. The product was acidified with dilute sulphuric acid and the organic material extracted with ether (2 x 30ml.) These extracts were washed with sodium carbonate solution, brine, and dried, removal of the solvent giving a yellow oil. This produced absorption in the ultraviolet region at λ_{max} 267 mμ, E_{max} 2,200, while the infra-red spectrum was closely similar to that of the starting material.

Alternate synthesis of 1-(2′-Hydroxy-n-butyl)-2-benzoyloxy-5-methylbicyclo [3:3:1] non-3-ene (57)

1. Reduction of the free keto group

The ketone, 52, (0.361g., 1.74×10^{-3} mole) dissolved in methanol cooled to 0° (10ml.) was treated with a solution of sodium borohydride (0.14g., excess) in methanol (10ml.). The resulting solution was left at room temperature for 3 hours, when it was acidified with dilute hydrochloric acid and the methanol removed. The residue was taken up in ether (50ml.), washed with sodium carbonate solution, brine and dried over magnesium sulphate to give a thick oil (0.36g.), the infra-red spectrum of which was transparent in the carbonyl region but showed absorption at 3400cm^{-1} (hydroxyl) and 3000cm^{-1} (double bond).

2. Introduction of the allylic oxygen function.

A solution of t-butyl perbenzoate (0.33g.) in methanol (5ml.) was added with stirring to the crude alcohol, 56, (0.36g.) containing cuprous bromide (0.01g.) and heated to 106-118° under nitrogen. This temperature

range was maintained during the addition (60 minutes) and for a further 90 minutes when the reaction mixture was cooled and diluted with ether (50ml.). The organic layer was filtered, washed with sodium carbonate solution, brine and dried to give a crude yellow oil (0.36g.) which was adsorbed on silica and chromatographed. Elution with solvent mixtures less polar than benzene-chloroform (6:4) gave unrecognizable material while benzene-chloroform and chloroform elution gave a product (0.099g., 17%) with an infra-red spectrum showing bands at 3400cm^{-1} (hydroxyl); 1600, 1580, 720cm^{-1} (aromatic bands) and 1700, 1280cm^{-1} (ester) consistent with it being the desired hydroxy ester and identical with the spectrum obtained on borohydride reduction of the keto benzoate, 58, (page 67).

Alternate synthesis of 1-(2′-Hydroxy-n-butyl)-2-hydroxy-5-methylbicyclo [3:3:1] non-3-ene (60).

A solution of the above hydroxy ester, 57, (0.345g.) in dry methanol (5ml.) containing sodium (0.005g.) was refluxed for 3 hours. On cooling, water (5ml.) was added and the solution saturated with carbon dioxide. The organic material was extracted with ether (2 x 50ml.) and ethyl acetate (2 x 10ml.), the extracts combined, washed with brine, dried and the solvent removed to give a thick oil. This was adsorbed on silica and chromatographed, elution with benzene-chloroform (9:1) giving methyl benzoate, elution with chloroform giving a mixture of partially hydrolysed, partially esterified material, while methanol afforded a crystalline diol, (60) m.p. $\sim$ 100°, (0.057g., 25%) with no infra-red absorption in the carbonyl region, but a strong band at 3400cm^{-1} (hydroxyl), this comparing well with the diol produced by aqueous base hydrolysis of (57).

Repeating the experiment over 18 hours gave, 60, (0.095g., 43%).

Attempted preparation of 1-(2′-Hydroxy-n-butyl)-2-hydroxy-5-methylbicyclo [3:3:1] non-3-ene from the hydroxy ester (57) using lithium aluminium hydride.

Lithium aluminium hydride (0.059g., 1.5×10^{-3} mole) was heated at reflux in dry ether (15ml.) under nitrogen for 15 minutes. Hydroxy benzoate, 57, (0.341g., 1.04×10^{-3} mole.) was added to the resulting suspension and the mixture stirred under reflux for 75 minutes. On cooling, the excess reagent was decomposed by ethyl acetate which was also used to dilute the organic material. The organic solution was washed with hydrochloric acid (3N), brine, dried and the solvent removed to give virtually unchanged starting material. Repeating the experiment on hydroxy benzoate, 57, (0.27g.) with excess reagent (0.10g.) over 90 minutes reflux gave an oil which showed much diminished carbonyl absorption. The product was adsorbed on silica, elution with chloroform and methanol giving what appeared to be the desired diol, 60, (0.102g., 54%) as a liquid which would not solidify, showing infra-red bands at $3400cm^{-1}$ (hydroxyl) and approximately $1700cm^{-1}$ (low intensity, ester).

Attempted preparation of 1-(2′-Hydroxy-n-butyl)-5-methyl-bicyclo [3:3:1] non-3-ene-2-one (64)

The endiol (0.052g., crude) was shaken in petroleum ether (5ml.) with activated manganese dioxide (0.50g.) for 48 hours. The product exhibited a strong band at $3400cm^{-1}$ (hydroxyl) and a broad carbonyl with maxima at $1800cm^{-1}$ (low intensity), 1720 and $1680cm^{-1}$ (enone). A further quantity of endiol (0.064g., crystalline) in chloroform was subjected to a similar oxidation with manganese dioxide (0.5g.) over 72 hours. The material obtained showed infra-red absorption at $3400cm^{-1}$ (strong), $1700cm^{-1}$ (saturated ketone, strong), and $1680cm^{-1}$ (enone, shoulder). On standing, a quantity of solid separated out, this proving to be unreacted diol.

Attempted preparation of 1-(2′-Keto-n-butyl)-2-benzoyloxy-5-methylbicyclo[3:3:1] nonane (65).

A sample of crystalline benzoyloxy ketone, 58, (0.011g., analytically pure) in ethyl acetate (5ml) was shaken with palladium-charcoal (5%, 0.0105g.). After 24 hours, the hydrogen uptake was 0.91ml. (expected 0.98ml.). An oil was obtained on removing solvent and atalyst, in which compared to the starting material, the aromatic bands at 1600, 1580, 720cm^{-1} were reduced in intensity, as were several of the fine structure peaks between 1470-960cm^{-1}.

The procedure was repeated on the liquid benzoate (0.042g.) using palladium-charcoal (5%, 0.033g.) in ethyl acetate as before. The actual uptake (3.36ml.) was again short of the theoretical (3.5ml.) and the infra-red spectrum of the product was closely similar to that obtained from the solid.

Attempted preparation of 1-(2′-Keto-n-butyl)-2-hydroxy-5-methylbicyclo [3:3:1] non-3-ene (62) from the keto benzoate (58).

A sample of the liquid keto benzoate, 58, (0.26g.) was heated under reflux for 4 hours in a methanolic solution containing sodium (0.01g. in 10ml.). On cooling, water (10ml.) was added, the solution saturated with carbon dioxide and extracted with ether (2 x 20ml.). The extracts were shaken with brine, dried and the solvent removed to give a viscous oil which was adsorbed on silica and chromatographed. Elution with benzene gave the only sizeable portion of material, with an infra-red spectrum showing no hydroxyl peak at 3400cm^{-1} or ester peak at 1280-60cm^{-1} but a complex carbonyl with maxima at 1700 and 1680cm^{-1}.

The pilot experiments detailed below, which led to a successful synthesis of the tricyclic pentenone (49) were all carried out on samples of the saturated diketone (48) prepared from 1-(2′-Hydroxy-n-butyl)-2-benzoyloxy-5-methylbicyclo [3:3:1] non-3-ene (57) by aqueous base hydrolysis followed by chromic acid oxidation and catalytic reduction.

4-Norclov-4-en^{e}-3-one (49)

1. The diketone, 48, (0.149g., 90% pure by gas-liquid chromatography) dissolved in dry methanol (10ml.) containing potassium hydroxide (Analar, 0.23g.) was heated at reflux under nitrogen for 3 hours. Brine (20ml.) was added, most of the methanol removed under reduced pressure and the organic material, after acidification with glacial acetic acid, extracted with ether (2 x 50ml.). The combined extracts were washed with sodium bicarbonate solution, brine and dried to give a product (0.13g.) with infra-red bands at 1700cm^{-1} (cyclo pentenone and hexanones) and 1640cm^{-1} (cyclo pentenone double bond) and ultraviolet absorption of E_{241-5} 3,000.

Retreatment of the product with a similar basic solution for two hours raised this to E_{241-5} 4,500.

2. A solution of the diketone (0.168g., 90% pure, 0.7 x 10^{-3} mole) in sodium dried benzene (20ml.) was heated to reflux under nitrogen for 3 hours with sublimed potassium t-butoxide (0.10g., 0.95 x 10^{-3} mole). When the reaction was stopped, the solution was a deep purple colour. The organic material was diluted with ether (50ml.) acidified with glacial acetic acid, the solution washed with sodium bicarbonate solution, brine and dried. The resulting oil (0.163g.) had a single peak in the carbonyl region at 1700cm^{-1} and an ultraviolet absorption of λ_{max} 241-5mμ, E_{max} 2,500.

The ketonic material was resubjected to the same basic conditions for a further 4 hours. After work-up, the product had a broad carbonyl absorption, with no band at 1640cm^{-1} and was transparent in the ultraviolet.

Note: This was intended to be an improvement on a treatment of diketone, 48, (0.11g, purity uncertain, not analysed by gas-liquid chromatography) with potassium t-butoxide (0.069g., approximately 1.2 equivalents, unsublimed) in benzene. After 3 hours under nitrogen, the resulting solution was red-grey. On work-up, the yellow oil obtained (0.09g.) had an ultraviolet absorption of E_{241-5} 6,400 (ethanol) and infra-red peaks at 1700, 1640cm^{-1} (strong).

3. The diketone, 48, (3.315g., 80% pure, containing possibly mono and polyketones) was heated at reflux under nitrogen for 2 hours in benzene (Analar, 200ml.) with sodium ethoxide (2.0g., $\sim$2 equivalents). Acidification with dilute hydrochloric acid was followed by dilution of the benzene solution with ether (200ml.). The organic material was washed with sodium bicarbonate solution, brine, dried and the solvent removed to give a crude product (3.15g.) which exhibited an ultraviolet absorption of E_{241-5} 5,000 and had the expected infra-red spectrum.

This material was absorbed on alumina (neutral Woelm, grade 1,70g.) and chromatographed. Elution with petroleum ether (6 x 100ml.) gave material, possibly monoketonic (0.49g.) with infra-red absorption at 1730cm^{-1} (low intensity), 1700cm^{-1} and 1640cm^{-1} (trace). Elution from benzene-petroleum ether (1:9) to chloroform gave fractions with E_{241-5} lying between 4,600 and 6,200. These fractions were combined (2.73g.), adsorbed on less

active alumina (neutral Woelm, grade 3, 100g.) and rechromatographed. Elution with petroleum ether (4x200ml.) gave material (0.55g.) with E_{241-5} 2,500 and with infra-red absorption at 1705cm^{-1} and 1640cm^{-1} (trace). Elution with benzene-petroleum ether mixtures (7:3 to 4:1,5 x 200ml.) afforded impure cyclopentenone, 49, 1.05g., with E_{241-5} 8,200-9,000 and the intensity of the infra-red band at 1640cm^{-1} exceeding that at 1470cm^{-1} (methyl). Elution with benzene gave the polyketones remaining on the column (0.73g.), E_{241-5} 2,000, these fractions like the first showing only slight absorption at 1640cm^{-1}.

The impure cyclopentenone (1.05g.), E_{241-5} 8,200-9,000 was then fractionally distilled:

1. 79°/0.15m.m. E_{241-5} 7,500
2. 78°/0.15m.m. E_{241-5} 9,100

These were both subjected to gas-liquid chromatography (5% Apiezon-Celite, 160° flow rate ~30ml. per minute). The first distillation fraction showed three peaks at 20 minutes elution time, making up 40% of the fraction, and a single peak at 30 minutes, due to the pentenone, forming the remainder. In the second distillation fraction, the peaks at 20 minutes made up 20% of the fraction while the peak at 30 minutes formed the remaining 80%. A sample from this distillation fraction was absorbed on a silica chromatoplate and eluted with benzene-chloroform (3:7). Drying, spraying with ceric sulphate solution and heating (> 200°), gave a main spot thought to be due to (49) and a smaller one with a lower Rf, corresponding to the first compounds in the gas-liquid chromatogram.

<u>The 2:4-dinitrophenylhydrazone of 4-norclov-4-ene-3-one</u>. A sample of the cyclopentenone, 49, (0.078g.) from fraction one was dissolved in ethanol (3ml.) and treated with Brady's

reagent. After warming for 10 minutes, water (10ml.) was added and the organic material extracted with chloroform (2 x 20ml.), this being washed with brine and dried over magnesium sulphate. Removal of the solvent under reduced pressure gave a thick red oil which was absorbed on bentonite-kieselguhr and chromatographed. Elution with benzene gave a dark red oil which was dissolved in a minimum of benzene (2ml.), diluted with petroleum ether (2ml., 100-120°) and the benzene allowed to distil off. A red 2:4-dinitrophenylhydrazone then crystallized from the petroleum ether even on slight cooling. This procedure was repeated (x5) to give 4-norclov-4-ene-3-one-2:4-dinitrophenylhydrazone as large plates m.p.223-5°, λ_{max} 393-7mμ, E_{max} 30,800 (chloroform). (Found: C, 62.60; H, 6.35; N, 14.45. $C_{20}H_{24}O_4N_2$ requires C, 62.50; H, 6.30; N, 14.60%).

The remaining cyclopentenone, 49, (0.685g.) was adsorbed on silica (40g.) and chromatographed. Elution with benzene to benzene-chloroform, 4:1, (29 x 50ml.) gave no product, but the first fraction (fraction 30) eluted with benzene-chloroform (7:3), gave cyclopentenone (0.016g.) E_{max} 13,000. Further quantities of the same solvent (10 x 50ml.) gave samples with an E_{max} falling from 10,200 (fraction 34), to 8,300 (fraction 36) and finally to 6,600 (fraction 39.).

All of the material was combined, absorbed on a long thin silica column (40g.) and rechromatographed, but the separation achieved was only slightly better. Fairly pure cyclopentenone (0.22g.) E_{max} 10,000-11,000 was eluted with benzene-chloroform, 7:3, (5 x 25ml.) continued elution (5 x 25ml.) giving less pure ketone (0.27g.) E_{max} 6,000-7,000.

Note:- Using an alternative procedure, a sample of pure cyclopentenone (49) has been obtained. This exhibits λ_{max} 242-5mμ, E_{max} 14,500.

Attempted preparation of 4-norclov-4-ene-3-ol (66)

A sample of the cyclopentenone, 49, (0.27g., E_{max} 6,000-7,000 dissolved in ethanol (10ml.) cooled to 0^{o}, was treated with sodium borodydride (0.057g., approximately 3 equivalents) in water (5ml.) and the resulting solution left at room temperature for 2 hours. Acidification with dilute hydrochloric acid, followed by ether extraction (2 x 50ml.), washing of the extracts with brine solvent removed and drying gave virtually unchanged starting material. This was then treated with excess sodium borohydride for 16 hours, the infra-red spectrum of the product (0.25g.) showing no carbonyl absorption and only weak hydroxyl absorption at $3500cm^{-1}$. Absorption on silica (30g.) and chromatography, separated this material into a mobile liquid hydrocarbon (0.071g.) eluted with petroleum ether and a thick oily alcohol (0.104g.) eluted with chloroform. The hydrocarbon showed infra-red absorption at 820, $790cm^{-1}$ (strong, trisubstituted double bonds) and an ultraviolet spectrum at λ_{max} 240-43 mμ, E_{max} 10,000. Molecular distillation gave a sample for analysis which on standing for 48 hours became viscous and acquired an oxygen content (9-10%). (Found: C, 81.75; H, 9.55%). The infra-red spectrum now showed a broad low intensity carbonyl ($\sim 1700cm^{-1}$), the remainder of the spectrum showing similar characteristics to that of the original, but much less well resolved.

The alcohol (0.104g.) obtained above was dissolved in petroleum ether (b.p. 60-80^{o}, 10ml.) and shaken with activated manganese dioxide (1.0g.) for 60 hours. The product, after removal of oxidising agent and solvent still exhibited a strong hydroxyl band ($3400cm^{-1}$), but there was no carbonyl absorption.

Preparation of 4-norclovan-3-one (68)

A sample of the cyclopentenone, 49, (0.035g., E_{max} 7,800 ethanol) in ethyl acetate (10ml.) was shaken with palladium-charcoal (10%, 0.026g.). Hydrogen (1.46ml.) was taken up slowly over 40 hours, the product having peaks in the infra-red at 1750cm^{-1} (cyclopentanone), 1700cm^{-1} (cyclopentenone and saturated ketones) and 1640cm^{-1} (pentenone double bond). A further uptake of hydrogen occurred (0.094ml.) when this same material was shaken in ethyl acetate for 20 hours with Adam's catalyst (0.014g., platinum oxide). Removal of solvent and calalyst this time gave a liquid with peaks at 1750cm^{-1}, 1700cm^{-1}, (less intense than the first) and 1640cm^{-1} (trace). Chromatography of the product on alumina proved ineffective in separating the pure cyclopentanone.

Alkali metal-proton reduction of 4-norclov-4-ene-3-one(49)

A solution of the cyclopentenone, 49, (0.11g., E_{max} 9,100, 0.49 x 10^{-3} mole) in ether (5ml.) was added dropwise to a stirred blue solution of lithium metal (0.033g.) in liquid ammonia ($\sim$15ml.). Fifteen minutes after the last of the ketone had been introduced, stirring was stopped, solid ammonium chloride added and the ammonia allowed to evaporate off. The organic material was extracted with ether (2 x 20ml), the combined extracts washed with brine and dried to give an oil (0.096g.) with infra-red bands at 3500cm^{-1} (hydroxyl), 1745cm^{-1} (pentanone) 1700cm^{-1} (cyclopentenone and impurity ketones) and 1640cm^{-1} (double bond trace). As separation on this scale was difficult, the product was treated again with lithium-liquid ammonia to give the alcohols exclusively. However chromic acid oxidation of these alcohols in acetone, followed by chromatography, gave a poor yield (0.030g.) of material showing infra-red absorption at 1700cm^{-1}.

Clov-5(6)-ene-3-one (50)

The cyclopentenone, 49, (0.22g., E_{max} 11,000, 1.08×10^{-3} mole) in dry benzene (20ml.) was heated at reflux under nitrogen with potassium t-butoxide (0.204g., 1.7×10^{-3} mole, not sublimed) for 2 hours. This gave a dark green solution in which some of base remained undissolved. On cooling, methyl iodide (excess, calcium chloride dried) was added in small amounts over 20 minutes. The colour of the solution was discharged and a white precipitate of potassium iodide resulted. The mixture was then refluxed gently for 40 minutes with occasional shaking. After neutralization with glacial acetic acid, the solution was diluted with ether (50ml.), washed with sodium bicarbonate solution, brine and dried over magnesium sulphate to give a yellow oil (0.20g.) with infra-red absorption at $1750cm^{-1}$ (strong) and $1700cm^{-1}$ (weak). The product was adsorbed on alumina (neutral Woelm, grade 1, 10g.) and chromatographed, elution with benzene-petroleum ether (1:8, 8 x 100ml) giving clov-5(6)-ene-3-one, 0.045g., with infra-red absorption bands at 2900, 1750, 1700 (trace), 1470,1380 (singlet) and $1360cm^{-1}$ (trace). This sample of the cyclopentanone (50) must have been almost pure as the contaminants present in the cyclopentenone (49) were stable to base and produced absorption in the infra-red at approximately $1700cm^{-1}$.

The cyclopentanone, 50, (0.045g.) was warmed for 15 minutes with an excess of Brady's reagent. On standing, an orange-yellow 2:4-dinitrophenylhydrazone was obtained which recrystallized from methanol (x5) as plates m.p. 155-158° (less than 0.004g.). (Found: C, 62.90; H, 6.25; N - $C_{21}H_{26}O_4N_4$ requires C, 63.30; H, 6.60; N, 14.05%).

The sample of pure cyclopentenone, E_{max} 14,500 (ethanol) afforded by an alternative synthesis devised in these laboratories, gave a red 2:4-dinitrophenylhydrazone m.p. 219-222°, which did not depress the melting point of our sample. The pure cyclopentenone also gave the cyclopentanone (50) with an infra-red spectrum and orange-yellow 2:4-dinitrophenylhydrazone identical with those furnished by our material.

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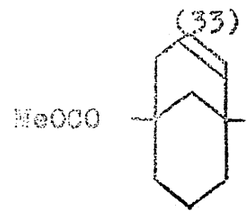
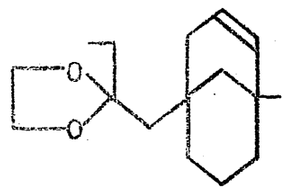
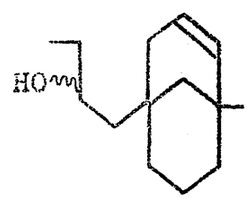
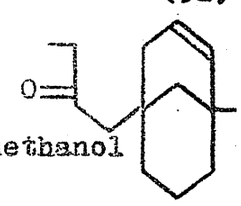
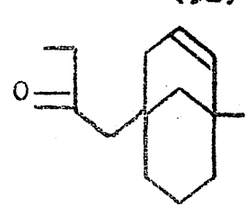
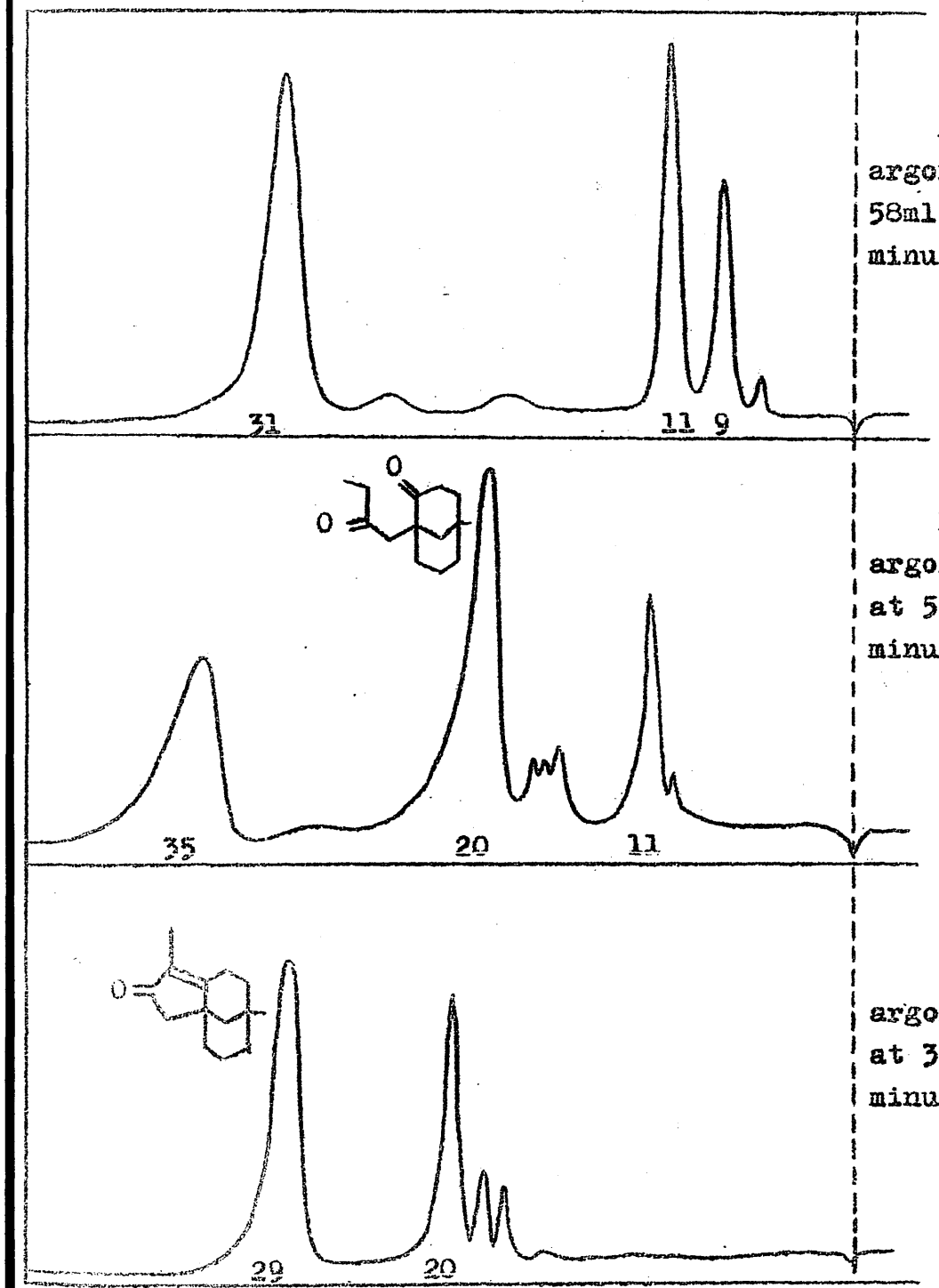
Starting Material	Percentage of benzoate produced in one reaction .	Percentage of starting material recovered from one reaction.
(33) 	19 21	64 63
(54) 	54 56	30 18
(57) 	17	none.
(52)  plus methanol	11	80
(52) 	29 31	46 38

TABLE ONE



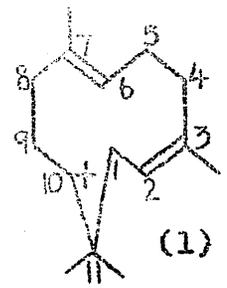
A
argon eluted at 58ml. per minute

B
argon eluted at 50ml. per minute

C
argon eluted at 30ml. per minute

Analyses carried out on 5% Apiezon-Celite.

TABLE TWO



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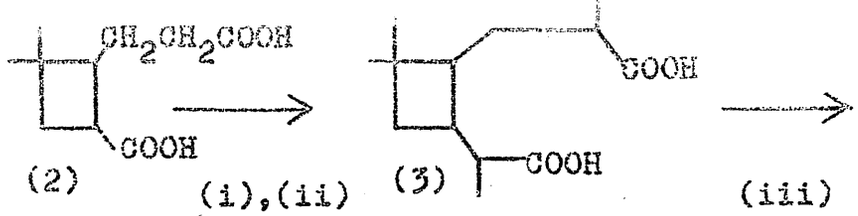
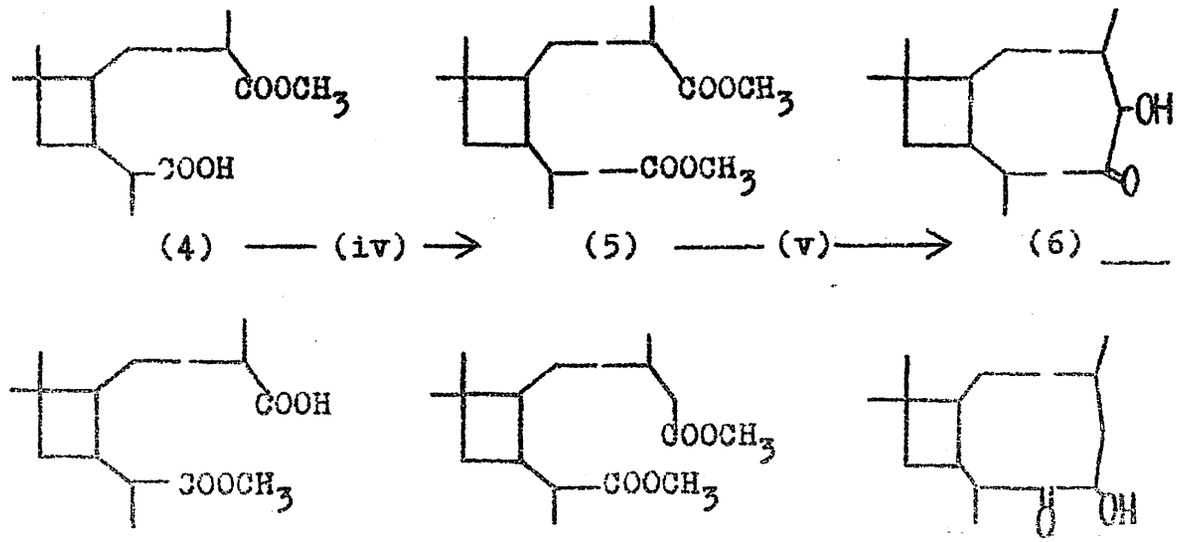
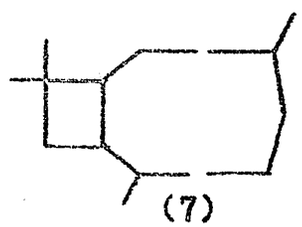


(2) (i),(ii) (3) (iii)

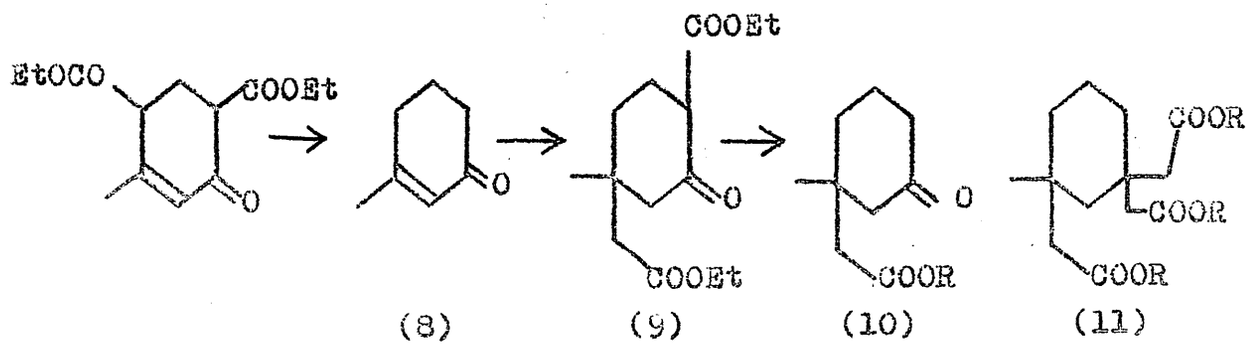


(4) (iv) (5) (v) (6) (vi)



(7)

(i) $SOCl_2$; (ii) CH_3CHN_2 ,Arndt-Eistert ; (iii) Esterification/ Partial hydrolysis ; (iv) CH_2N_2 , Arndt-Eistert ; (v) Acyloin condensation ; (vi) Zn/HCl.



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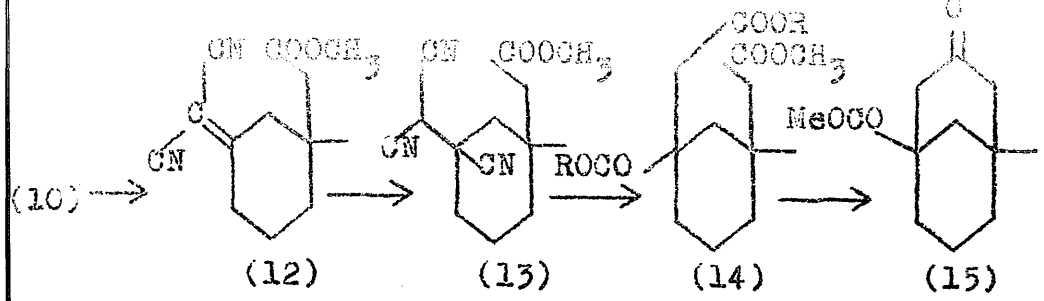

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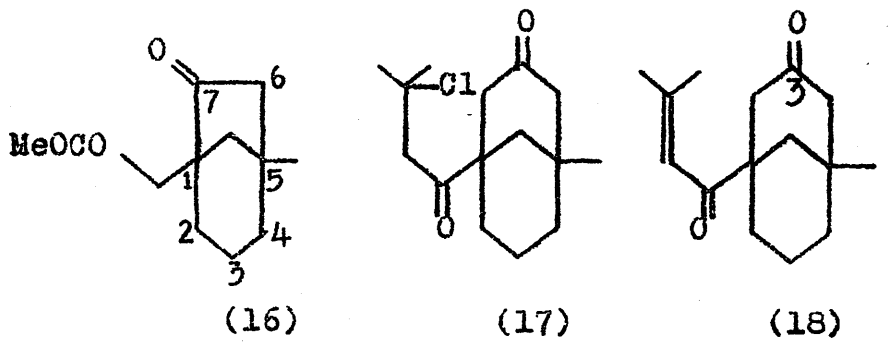

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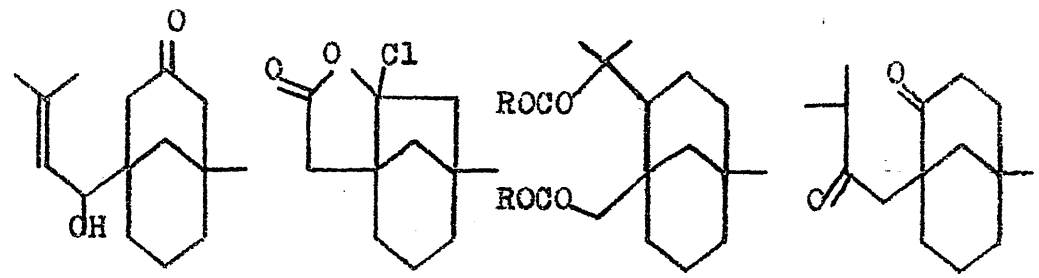

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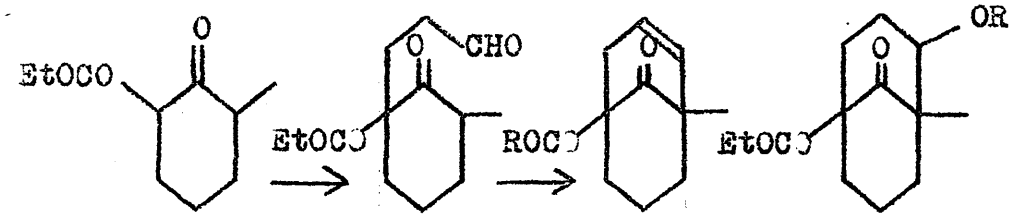

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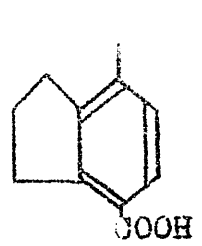

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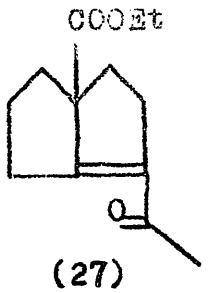

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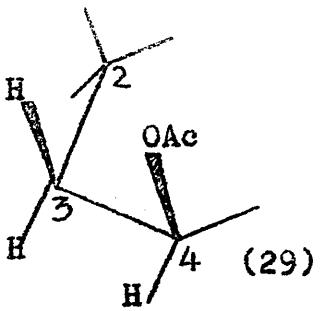

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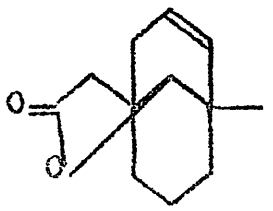

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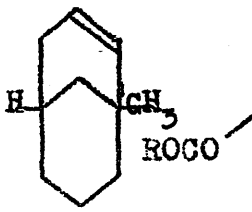

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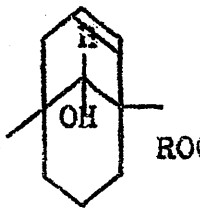

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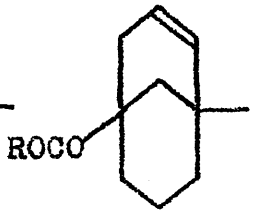

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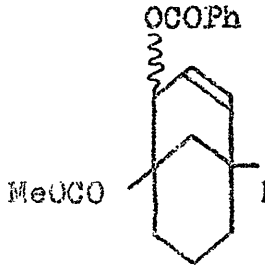

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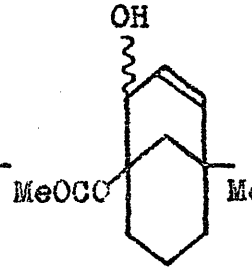

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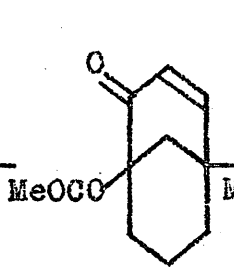

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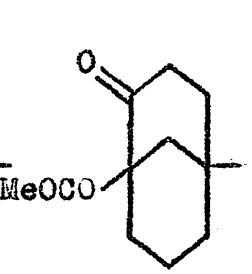

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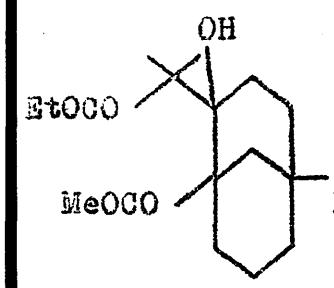

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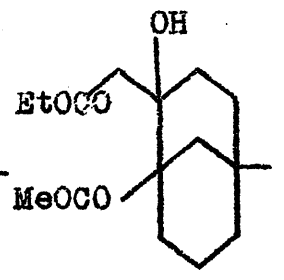

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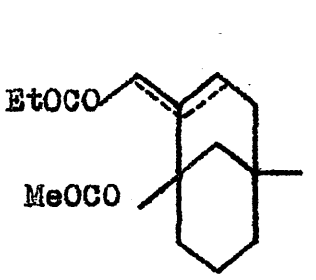

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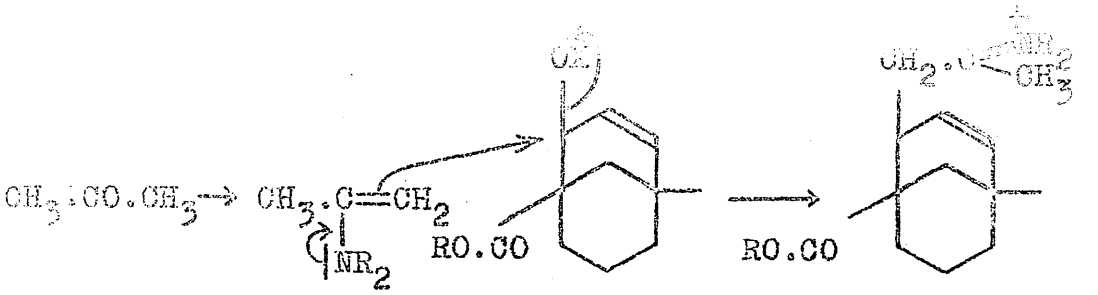

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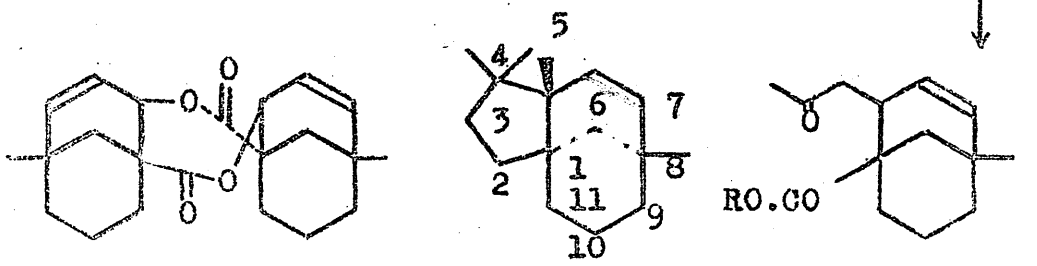

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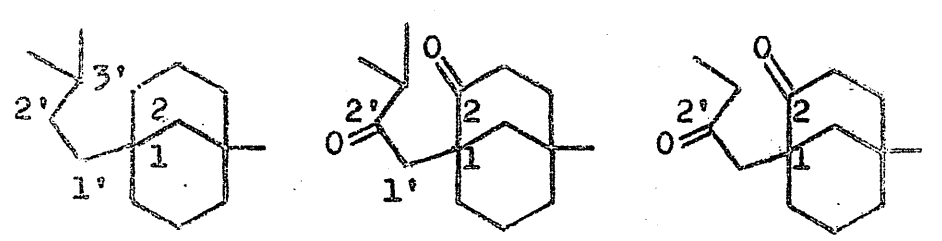

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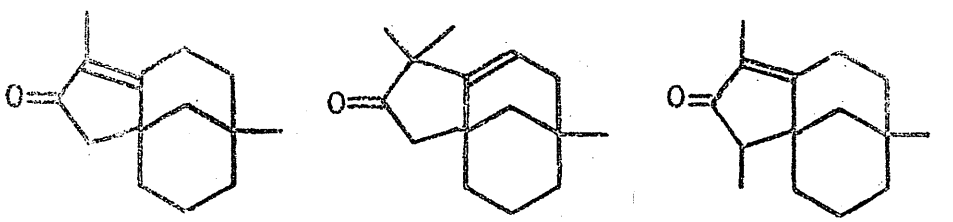

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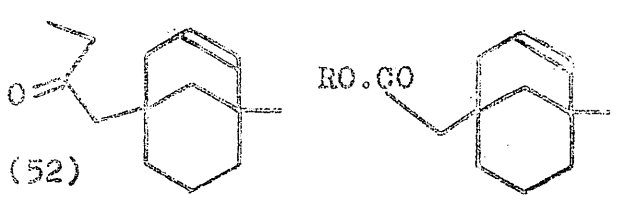

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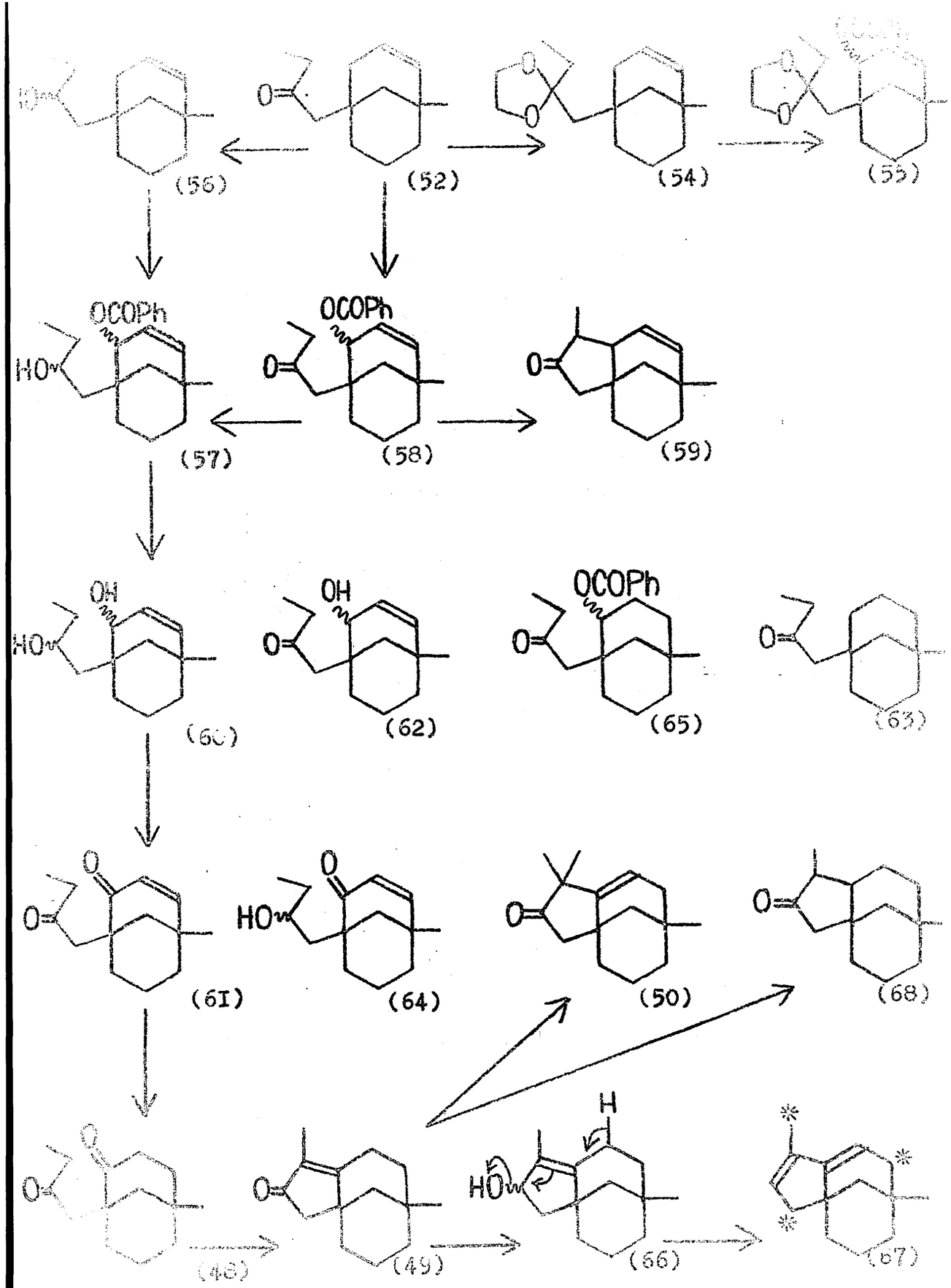
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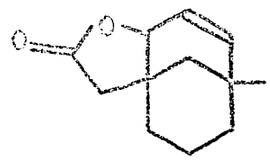

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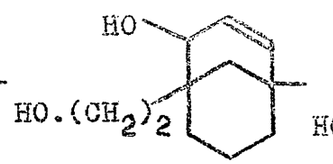

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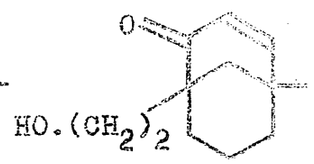

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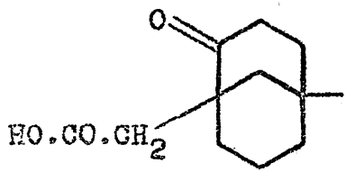

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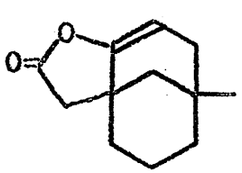

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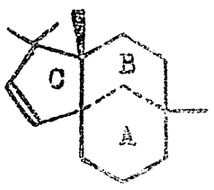

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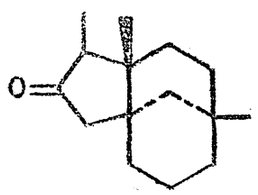

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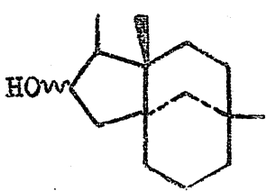

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PART TWO

Synthetic Approaches to Totarol.

SYNTHETIC APPROACHES TO TOTAROL

THEORETICAL

(Formulae flowsheets for this section on p. 124)

STRUCTURE

Totarol, a crystalline diterpene of composition $C_{20}H_{30}O$ was isolated from the wood of the totara tree (Podocarpus totara) by Easterfield and McDowell[1]. A chemical study undertaken by Short and his co-workers[2,3], showed that totarol possessed three double bonds which formed an aromatic ring and that the molecule was therefore tricyclic. Some of the reactions of the diterpene, namely the formation of a methyl ether, an acetate, a bromo derivative and coupling with diazotized amines indicated that totarol was a phenol, but its failure to give a positive ferric chloride test and its very slight solubility in strong aqueous base suggested that there was some bulky group masking the phenolic hydroxyl function.

In an attempt to find the overall structure of this compound, totarol and totarane (2), the hydrocarbon obtained from it by forcing catalytic hydrogenation, were subjected to vigorous selenium dehydrogenation. Totarol gave rise to I-methylphenanthrene and I-methyl-7-hydroxyphenanthrene[4] while totarane afforded a third aromatic product, which a later synthesis showed to be 1-methyl-8-isopropylphenanthrene.[5] Most of the original substituents were retained by the three products (3), (4) and (5) of a similar reaction carried out on totarol methyl ether under much less severe conditions. The most important of these (5) could also be obtained by further selenium treatment of (3). As 7-hydroxyphenanthrene

coupled with diazotized amines solely in the 8-position, the complete failure of (5) to couple could be rationalized only be placing the isopropyl group which flanked the phenolic hydroxyl function, in the 8-position.

Confirmation for this substitution pattern was provided by the infra-red spectrum of totarol, which exhibited absorption at 800cm^{-1} typical of a 1:2:3:4-tetrasubstituted aromatic ring. The spectrum also showed a hydroxyl band at 3500cm^{-1} due to the non-hydrogen bonded hydroxyl group of a cryptophenol rather than the more usual hydroxyl absorption at 3300cm^{-1}. Short and Wang therefore proposed that totarol was 1:1:12-trimethyl-7-hydroxy-8-isopropyl-1:2:3:4:9:10:11:12-octahydrophenanthrene (1) in which the stereochemistry of the A/B ring junction, by analogy with that established for other tricyclic diterpenes, was trans.

As selenium dehydrogenation, in which migration of alkyl groups is commonplace, had been used so extensively in this work, the non-complaince of the proposed structure (1) with the isoprene rule was an unsatisfactory feature. However, that (1) was in fact the correct structure was established by the success of two different synthetic approaches to the totarol nucleus by Barltrop[6] and Taylor[7].

It fell to Erdtmann[8] to establish the stereochemistry of the totarol molecule. From the heartwood of Tetraclinis articulata, he isolated a mixture of saturated and unsaturated ketones which, on catalytic hydrogenation and Clemmensen reduction, gave totarol. The saturated ketone was called totarolone $C_{20}H_{28}O_2$, and the single diol produced from it by borohydride reduction, totaradiol $C_{20}H_{30}O_2$. The difference in molecular rotation between totaradiol and its diacetate paralleled

that between hinokiol (6) and its diacetate, indicating that the environments of the asymetric centres in the two diols were similar. When a ring A contraction process, developed in the triterpene field[9] and specific for 3β hydroxyl functions, was applied to totaradiol, dehydration with rearrangement took place to give the isopropenyl-cyclopentane (9), which was cleaved to give the cyclopentanone (10) and acetone. As a result of these reactions, it was clear that the keto group of totarolone was situated in the 3-position.

In addition to the molecular rotation evidence, the similarities in the optical rotatory dispersion curves of totarolone, hinokione and lanost-8-ene-3-one(7), made it almost certain that the alicyclic rings of totarol were fused in a trans configuration. This in turn was verified by the isolation of the known trans-dicarboxylic acid (11) from a series of oxidative degredations carried out on the original phenol (1).

BIOGENESIS.

Although the biogenetic route to totarol is largely unknown, in the two most recent propositions it was considered to be a complex many-stage process involving either ferruginol (12; R=CH_3) or a simple derivative of it, probably the pyrophosphate (12; R=CH_2OPP.) as an intermediate. The first step was believed to be the cyclization of an acyclic diterpene with a regular sequence of four isoprene units such as geranylgeraniol (13), to manool (14) which in turn gave a pimarane skeleton (15) by loss of the allylic hydroxyl function and ring closure.[10] Rearrangement to form the isopropyl group, followed by the introduction of a hydroxyl function in the 6-position and dehydration furnished ferruginol (12; R=CH_3).

In the scheme devised by Wenkert[11], protonation of the aromatic ring in 12 (probably R=CH_2OPP.) occurred at C9, to give the cation (16) which rearranged as shown to the intermediate (17) this affording totarol on proton-loss and reduction of the 4-methyleneoxy function.

Johnson, King and Martin[12] studied the dimeric diterpene maytenone (18) and found that it gave pure propylene, the catechol (20) and 6-hydroxytotarol on pyrolysis. They postulated that maytenone might arise by the Wessley-type oxidation of ferruginol to the blocked dienone (19) which underwent self-condensation to the Diels-Alder adduct (18). In the light of this work, the biological production of the totarane skeleton could be explained if a natural process were found which brought about the same changes in the maytenone molecule as the pyrolysis. Maytenone apart, the structures found for the other oxygenated totarols appear to give little information as to the mode of formation of the parent

phenol. Thus the 4-hydroxymethylene function of totarol precursor (12;R=CH_2OPP.) employed by Wenkert, could be transformed in a simple manner to 4-hydroxymethylenetotarol (hydroxytotarol)[13,14] or oxidised to the 4-aldehyde (21) isolated from Podocarpus hallii by Cambie and Mander[14]. The formation of totarol-3-one and totarol-1-ene-3-one[8] would be readily explained if the cation present in the initital cyclization were the aerobic OH^+, while a labile benzylic hydrogen atom was probably responsible for 7-hydroxytotarol (22) occurring with totarol in Thujopsis dolbrata.[15]

SYNTHESES.

Attempts were made in this department to synthesise totarol by a route which employed acetylenic intermediates. The first synthesis to be undertaken was that of a simplified analogue of totarol, 7-hydroxy-1:2:3:4:9:10;11:12-octahydrophenanthrene.[16] In this, cyclohexanone was converted to the corresponding ethynyl carbinol which, as the Grignard derivative, was condensed with the methyl enol ether of cyclohexane-1:3-dione. The initial product of this reaction (23) rearranged in the presence of acid as shown to give the conjugated ketone (24). It had been expected that the medial triple bond in (24) would hydrate to give a 2′-ketone. As trans- α -decalones are more stable than cis, it was hoped by means of this keto group to control the stereochemistry of the A/B ring junction in the acid catalysed intra-molecular cyclization of (25) to (26). However, as it proved extremely difficult to effect hydration of the acetylenic bond in (24), it was thought unlikely that any hydration at all would be achieved in the more complex intermediate required in the synthesis of totarol itself. This step was therefore deleted and no provision made for controlling the mode of the final ring closure. Later enquiries have shown that with a bicyclic intermediate such as (25), a 6- or a 4-keto group does not lead to stereospecific ring closure e.g. Stork and Burghstahler[17] produced a mixture of cis- and trans-isomers in the closure of (27).

Substituting 2:2:6-trimethylcyclohexanone for the simple cyclohexanone, the synthetic method developed in the production of (24) was extended to afford (28). Catalytic reduction then gave the enone (29) and heating this with palladium-charcoal in mesitylene furnished the

desired phenol (30;R=H) along with a trace of the corresponding dehydrated material (31). Polyphosphoric acid cyclization at 160° of (30;R=CH_3), produced by methylation of (30; R=H) with dimethyl sulphate, then gave the octahydrophenanthrene (32). This liquid was though originally to consist exclusively of the trans-isomer but on general grounds it now seems more likely that it was a mixture of isomers. Certainly Barltrop obtained (32) as a mixture of isomers which significantly, could be separated into two crystalline components.

Before we could apply the techniques of the pilot syntheses to totarol, a procedure for the production of 2-isopropylcyclohexa-1:3-dione had to be found as the usual ketone alkylation method of treating the dione in base with an isopropyl halide[18] only served to give a high yield of the corresponding isopropyl enol ether. Eventually it was found that 2:4-dimethoxycyclohex-1:4-diene, produced by Birch reduction of resorcinol, could be smoothly alkylated by isopropyl iodide and sodamide in liquid ammonia solution. Brief acid hydrolysis then furnished the required dione in good yield, this in turn being converted quantitatively to the isobutyl enol ether actually used in the condensation step.[19]

Condensation between the Grignard derivative of 1-ethynyl-2:2:6-trimethylcycloxhexan-1-ol and the enol ether gave, as previously, the desired bicyclic conjugated ketone (33) as a partially solid mixture of isomeric ketones. An almost complete separation of these isomers was achieved using absorption chromatography and a good yield of the more abundent isomer (m.p.82-84°) was obtained on recrystallization from hexane. By contrast, the solubility of the higher melting isomer (92-94°) was such that it could hardly be induced to crystallize from

a saturated hexane solution. When 2:2:6-trimethyl-1-β (2-isopropyl-3-ketocyclohex-1-enyl) ethynylcyclohexan-1-ol, 33, (m.p. 82-84°) was catalytically reduced, it afforded equal amounts of a liquid saturated ketone (34) and a highly crystalline unsaturated ketone (35) but although the latter was readily purified, it proved impossible to free the saturated ketone from traces of the unsaturated compound.

The next step in the projected synthesis was the production of the phenol (36). No attempt was made to utilize the saturated ketone (34) for this transformation however, principally because of the great difficulty experienced in bringing about the apparently more favoured aromatization of the unsaturated ketone. The problem resolved itself into finding a technique which would be specific enough to aromatize (35) without eliminating or altering the nature of the teritary hydroxyl function. Thus, although a five-fold increase in the duration of the catalytic dehydrogenation required in the formation of (30), gave a good yield of an aromatic product from (35), this was largely crude non-crystalline olefin-phenol (37; R=H). Selenium dioxide oxidation of (35)[20] was even less selective, giving a crude inseparable mixture of fragmented ketones and phenols, while at the other extreme, high potential quinone treatment[21,22] not only left the hydroxyl group intact, but failed to alter the unsaturated ketone in any respect.

A chloroform solution of the enone (35) rapidly absorbed a single equivalent of free bromine to give a product transparent in the ultraviolet but with infra-red absorption at 1705, 1650, 1080 and 1040cm^{-1}, the last two peaks suggesting the presence of an ethereal oxygen

linkage. An elements test gave no response for halogen and in accordance with this, no alteration in the infra-red spectrum of the bromination product was observed on heating with collidine. The spectrally identical, halogen-free material, obtained after reaction with two equivalents of bromine, solidified, but despite repeated recrystallization no sharp-melting sample could be obtained, probably due to the presence of several similar keto-ethers. It was difficult to rationalize these results, but an indication of the processes involved was given when the enone (35) was heated with Claisen's solution. The product from this base treatment was an oil, transparent in the ultraviolet and the hydroxyl region of the infra-red but with bands at 1705, 1060, 1040 and 1025cm^{-1}, consistent with the spiro-ether formulation (38). This type of molecule might also arise in the bromination procedure by the halogenation of some site on the conjugated ketone chromophore of (35) followed by dehydrobromination with spiro-ether formation in such a way that conjugation was disrupted.

In view of this unexpected involvement of the tertiary hydroxyl group, the enone (35) was heated for thirty minutes in a carbon tetrachloride-chloroform suspension of N-bromosuccinimide[23,24] containing triethylamine as initiator. At this stage, no attempt was made to isolate the resulting bromo-compound which was treated directly with γ-collidine to bring about dehydrobromination in situ. This particular reaction gave a high yield of crystalline phenol (36), although most of it was isolated as 'neutral material' with only a small percentage coming from Claisen-alkali extracts of the crude product. Duplication of these reaction conditions gave non-crystallizable gums with infra-red

absorption at 3450, 1580 and 1560cm^{-1} typical of (36) but also with a strong band at 1700cm^{-1} due to a spiro-ketone. The relative amount of N-bromosuccinimide, the nature and the relative amount of the suspension medium[24,25] the nature of the initiator, the bromination reaction time, the total reaction time and the dehydrobrominating agent were all varied in an attempt to obtain a reproducible yield of (36), but the only predictable feature of these modifications was the production of the spiro-ketone. During these reactions, small quantities of the hydroxyphenol (36) were isolated, when it was found that owing to its extreme insolubility, the more obvious methods of synthesising phenol methyl ethers were quite unsuccessful.

Eventually an aromatization procedure was developed in which a thick gum with infra-red bands at 3400, 1700, 1600 and 1580cm^{-1} was produced when the enone (35) was heated under reflux with N-bromosuccinimide for an hour. Then, although it is doubtful if it served any useful purpose, the gum was heated with collidine to give a product of almost unchanged infra-red spectrum which was chromatographed on silica to furnish, surprisingly, a good yield (50-70%) of crude, though spectrally satisfactory, dehydrated phenol (37; R=H). This material solidified, but in marked contrast with the hydroxyphenol (36) was so soluble that it could not be purified by recrystallization. Since chromatography and distillation also failed to bring about any noticeable purification, the crude phenolic oil was used directly in the production of the phenol methyl ether (37; R=CH_3). Unexpectedly, the product recrystallized readily from hexane to give a good yield of pure 2:2:6-trimethyl-1-β-(2-isopropyl-3-methoxyphenyl) cyclohex-1-ene(37;R=CH_3) with infra-red absorption at 1600,1580,790,770,745cm^{-1} (1:2:3-trisubstituted aromatic ring) and 1040cm^{-1} (phenol ether).

After this latter method had been worked out, it was found that a brief, gentle treatment of (35) with N-bromosuccinimide followed by solvent evaporation at temperatures below 25°, gave a true bromo-enone. As isolated this was a white crystalline solid m.p.80-84° with infra-red absorption at 3400cm^{-1} (hydroxyl) and 1680cm^{-1} (bromoketone) and an ultraviolet band at λ_{max} 252-3mμ, E_{max} 10,600. The change observed in the position and intensity of the ultraviolet absorption of the enone and the bromoketone of $\Delta\lambda_{max}$ 4-5mμ, $\Delta\epsilon_{max}$ 2,600 was in agreement with any of the three possible bromo-compounds (39)[26] though facile conversion to a partially phenolic product probably excluded the 1'bromoketone, while the alternative γ-bromination to the 4-bromoketone was the one expected by analogy with the bromination of cholest-4-ene-3-one (40)[27] and acetylgiegerin (41)[28]. Unfortunately, this bromoketone was extremely unstable to heat, gentle warming in neutral or basic solvents invariably giving rise to a crude oil which infra-red spectroscopy showed to be a mixture of hydroxyphenol and spiro-ketone ($<$ 50%). The bromoketone was unaltered by standing in basic solutions at room temperature and this factor, coupled with its thermal instability, ruled out its use in the manner originally intended as an isolateable intermediate in the aromatization of the enone (35).

The manner of the cyclization of the aromatic system (42) has been studied by Barnes[29] who found that there were three possible carbonium-ion intermediates in such Friedel-Crafts reactions. The first, (43) was produced only at low temperatures and gave rise to spiro-compounds. The second was (44) an ion of intermediate energy which gave products with cis-fused alicyclic rings, while (45) the high energy form, could

give both cis- and trans-fused rings or a mixture of both. As only the third ion could lead to the production of the desired stereochemistry, (37; R=CH_3) was heated with polyphosphoric acid at 180°, but at this temperature, considerable degradation occurred. Similar treatment of (37; R=CH_3) at 90-95° gave an oil which solidified and recrystallized as needles of 1:1:4-trimethyl-7-methoxy-8-isopropyl-1:2:3:4:9:10:11:12-octahydrophenanthrene (46) m.p. 58-65° with infra-red absorption at 1600, 1250, 1110, 1050 and 805cm^{-1}.

There were considerable discrepancies however between this spectrum and that of natural totarol methyl ether in the 1400-1000cm^{-1} region and this was taken as an indication that the synthetic material was a mixture of cis- and trans-isomers. This conclusion was confirmed by gas-liquid chromatography. A solution of totarol methyl ether in α -methylnaphthalene gave a single peak at approximately twenty minutes elution time while the cyclization product afforded two peaks, one at twenty minutes and the second after almost forty minutes. As mixing the synthetic and the natural methyl ether still gave only two peaks, one of the synthetic components had to be identical with trans-fused totarol methyl ether, the other peak eluted after forty minutes being due to the cis-fused isomer.

The interest in totarol which originally stimulated this synthetic work lay in its belonging to a limited class of diterpene, its cryptophenolic behaviour and the apparent non-obeyance of the isoprene rule by its carbon skeleton. As virtually all the objects of our work, except perhaps the production of synthetic, optically active totarol, had been achieved by the

concurrent syntheses of totarol and 3-oxototarol methyl ether, it was decided to terminate our experiments at this stage with 1:1:12-trimethyl-7-methoxy-8-isopropyl-1:2:3:4:9:10;11:12-octahydrophenanthrene forming a very satisfactory justification for the initial synthetic scheme.

CONCURRENT SYNTHESES

The synthesis of totarol devised by Barltrop,[6] like the methods which we had developed, employed acetylenic intermediates. The phenol ether (47) obtained by condensation of 2:2:6-trimethylcyclohexanone and potassium-m-methoxyphenylacetylide, after catalytic reduction to (48), underwent intramolecular cyclization in the presence of polyphosphoric acid at 85° to give the octahydrophenanthrene (32) as a mixture of isomers from which the crystalline trans form was isolated. When treated with lithium in liquid ammonia, (32) gave two unsaturated ketones which formed the corresponding isopropyl ketones (49) with isopropyl iodide and potassium-t-amyloxide. Aromatization was then achieved by successive treatment of (49) with N-bromosuccinimide and collidine, to give a phenolic product which afforded a benzoate. Both of these materials were glasses but they gave infra-red spectra identical with those of crystalline natural totarol and the solid derived benzoate. A feature of this synthetic work was that the stereochemistry of the product was not established with certainty.

An entirely different approach was adopted by Taylor[7] in his synthesis of 3-oxototarol methyl ether. 1-Bromo-2-methoxynaphthalene (50) was modified successively to an isopropenylnaphthalene and then to an isopropyltetralin. Oxidation to the crystalline tetralone (51) and conversion to the α-methylketone (52) was followed by application of a Robinson annelation procedure to give the tricyclic enone (53). This was readily methylated to (54) which on reduction of the double bond, removal of the keto group and chromatography afforded totarol and 3-oxototarol methyl ether identical with the natural products.

EXPERIMENTAL

Unless stated otherwise, ethanol was the solvent employed in the determination of all ultraviolet spectra.

2-Isopropylcyclohexan-1:3-dione.

2:4-Dimethoxycyclohexa-1:4-diene (139g.) was added with stirring to a suspension of potassium amide, prepared from potassium (47g.) in liquid ammonia (1l.) at -70°. When sufficient isopropyl bromide (122g.) had been added to discharge the red colour of the solution, the mixture was acidified with ammonium chloride and the ammonia allowed to evaporate. The residue was extracted with ether (2 x 250ml.) and the solvent removed to give a mobile oil. This was then dissolved in aqueous methanol (1:1, 250ml.) and the solution heated on a steam-bath for 10 minutes with hydrochloric acid (2N, 75ml.). Most of the methanol was removed under water-pump pressure and on cooling the product was precipitated from the aqueous solution. The solid recrystallized from benzene-chloroform (1:1) as prisms of 2-isopropylcyclohexan-1:3-dione, 109g., λ_{max} 262mμ, E_{max} 14,200 (Found: C, 70.10; H, 9.05, $C_9H_{14}O_2$ requires C, 70.10; H, 9.15%).

This compound was then quantitatively converted to the corresponding isobutyl enol ether by the method of Frank and Hall.[19]

2:2:6-Trimethyl-1-β-(2-isopropyl-3-ketocyclohex-1-enyl) ethynylcyclohexan-1-ol (33)

A Grignard reagent was prepared in ether (2l., sodium dried) from magnesium (70g.) and ethyl bromide (360g.) 1-Ethynyl-2:2:6-trimethylcyclohexan-1-ol (235g.) was added dropwise with stirring to the ethyl magnesium bromide and the resulting material heated at reflux for 90 minutes. The solution was cooled, 3-isobutoxy-2-isopropylcyclohex-2-

ene-1-one (290g.) in dry benzene (200ml.) added and the mixture heated under reflux for 4 hours. When cool, the reaction mixture was poured on to crushed ice and dilute sulphuric acid, the organic layer separated, washed with brine, sodium carbonate solution, brine and dried over anhydrous magnesium sulphate. Removal of the solvent afforded a mobile brown oil, which when heated on a steam bath under oil pump pressure, gave a dark, very viscous residue (210g.). A sample of the crude non-volatile condensation product (1.09g.) in petroleum ether was adsorbed on alumina (70g.) and chromatographed. Elution with benzene-petroleum ether (4:1, 300ml.) afforded a crystalline solid, 0.13g., m.p. 87-93°, which recrystallized (x3) from a small volume of hexane as colourless cubes to give one isomer of 2:2:6-trimethyl-1-β-(2-isopropyl-3-ketocyclohex-1-enyl) ethynylcyclohexan-1-ol m.p.92-94°, λ_{max} 277-9 mμ, E_{max} 25,200 (Found: C, 79.25; H, 10.20, $C_{20}H_{30}O_2$ requires C, 79.45; H, 9.90%) showing infra-red absorption at 3400cm^{-1} (hydroxyl), 2200cm^{-1} (low intensity, medial acetylene), 1650cm^{-1} (conjugated carbonyl) and 1580cm^{-1} (strong, conjugated double bond). Elution of the column with benzene (1l.) and benzene-chloroform (4:1, 600ml.) gave a second solid, 0.42g., m.p.81-85°, which crystallized from hexane as colourless cubes of the second isomer of 2:2:6-trimethyl-1-β-(2-isopropyl-3-ketocyclohex-1-enyl) ethynylcyclohexan-1-ol m.p.82-84°, λ_{max} 276-8 mμ, E_{max} 23,200 (Found: C, 79.65; H, 9.70 $C_{20}H_{30}O_2$ requires C, 79.45; H, 9.90%). This, like the first isomer, had infra-red absorption at 3400, 1650 and 1580cm^{-1}, but a comparison of the fine structure produced by both isomers between 1400 and 800cm^{-1} showed considerable differences in the placement and intensity of the bands.

2:2:6-Trimethyl-1-β-(2-isopropyl-3-ketocyclohex-1-enyl) ethylcyclohexan-1-ol (35)

A solution of the doubly unsaturated ketone 33, (0.503g., m.p. 82-84°) in ethyl acetate (50ml.) was shaken under hydrogen with palladium charcoal (10%, 0.054g.) and in 1 hour approximately two equivalents of hydrogen were taken up. The catalyst and solvent were then removed to give a mixture of an oil and a solid, which due to the low solubility of the solid in petroleum ether were readily separated. The solid, 0.24g., recrystallized (x3) from ethyl acetate to give colourless cubes of 2:2:6-trimethyl-1-β-(2-isopropyl-3-ketocyclohex-1-enyl) ethylcyclohexan-1-ol, m.p. 168-171°, λ_{max} 248mμ, E_{max} 13,200 (Found: C, 78.50; H, 11.15, $C_{20}H_{34}O_2$ requires C, 78.45; H, 11.10%), showing infra-red absorption at 3400cm^{-1} (hydroxyl), 1650cm^{-1} (conjugated ketone) and 1600cm^{-1} (conjugated double bond). The oil, 0.25g., was chiefly 2:2:6-trimethyl-1-β-(2-isopropyl-3-ketocyclohexyl) ethylcyclohexan-1-ol, 34, and exhibited infra-red absorption at 3450cm^{-1} (hydroxyl), 1700cm^{-1} (cyclohexanone) and 1650, 1600cm^{-1} due to contamination with the hexenone. On standing, the oil yielded successive small crops of the highly crystalline hexenone, but as the saturated ketone would not distil and could not itself be induced to crystallize, it was never obtained in a pure state.

The second isomer of the ketone, 33, (0.146g., m.p. 92-94°) in ethyl acetate (30ml.) took up approximately two and a half equivalents of hydrogen when it was catalytically reduced over palladium charcoal (10%,0.018g.) Removal of catalyst and solvent afforded, as with the other isomer, a mixture of a liquid saturated ketone and a solid unsaturated ketone. The solid recrystallized from hexane as the second isomer of 2:2:6-trimethyl-1-β (2-isopropyl-3-ketocyclohex-1-enyl) ethylcyclohexan-1-ol

m.p. 112-114°, λ_{max} 248mμ, E_{max} 18,600, showing an infra-red spectrum very similar to the first isomer with absorption at 3400cm^{-1} (hydroxyl), 1650cm^{-1} (unsaturated ketone) and 1600cm^{-1} (conjugated double bond). The residual yellow oil consisted largely of the corresponding saturated ketone with absorption at 1700cm^{-1}.

Note: Due to the high solubility of the doubly unsaturated ketone, 33, m.p.92-94° and the relatively small amounts of it obtained from the crude condensation product, all subsequent work was performed on the enone, 35, m.p. 168-171°.

Attempted preparation of 2:2:6-trimethyl-1-β-(2-isopropyl-3-hydroxyphenyl) ethylcyclohexan-1-ol (36)

A. Direct Dehydrogenation.

(i) Using high potential quinones.

A solution of the enone, 35, (0.15g.) in xylene (25ml.) was heated at reflux with chloranil (0.123g., 1 equivalent) for 40 hours, and then extracted with sodium hydroxide solution (4N) until the aqueous material was free from the red colour produced by the quinol anion. The xylene layer was washed with brine, dried and the solvent removed to give crystalline starting material. The experiment was repeated in mesitylene with exactely the same result.

The enone, 35, (0.15g.) in benzene (25ml.) was heated under reflux with 2:3-dichloro-5:6-dicyanobenzoquinone (0.12g., 1.1 equivalents) for 20 hours. After the same work-up procedure as above, only unchanged starting material was obtained.

(ii) Using selenium dioxide.

A solution of the enone, 35, (0.478g.) in t-butanol (50ml.) was treated under nitrogen with acetic

acid (0.5ml.) and selenium dioxide (0.09g.) and the whole heated under reflux for 40 hours with additional quantities of selenium dioxide (0.09g.) being introduced after 14 and 34 hours. The material was cooled, filtered and the solvent removed to give a residue which was dissolved in ethyl acetate (50ml.). This solution was washed with saturated sodium carbonate solution, ammonium sulphide solution, aqueous ammonia, brine, dried and the solvent removed to give a brown oil with infra-red absorption at $3400cm^{-1}$ (broad hydroxyl band), $1730-1550cm^{-1}$ (several carbonyl and aromatic bands) and $750cm^{-1}$ (trisubstituted aromatic peak). The oil was dissolved in benzene, adsorbed on alumina and chromatographed; elution with benzene giving material showing infra-red bands at $3300cm^{-1}$ (low intensity, hydroxyl), $1700cm^{-1}$ (saturated ketone, presumably produced by disproportionation) and 1600, $1580cm^{-1}$ (aromatic bands). Continued elution with benzene gave similar material in which the amount of hydroxylic material had increased and which contained some unreacted enone. The very crude and complex nature of these and additional chromatography fractions bore witness to the severity and lack of specificity of selenium dioxide in this attempted reaction.

(iii) Using catalytic dehydrogenation in aromatic solvents.

a. A solution of the enone (0.058g.) in p-cymene (2ml.) was heated under reflux with palladium-charcoal (5%, 0.019g.) for 2 hours. On cooling, the enone crystallized from the solvent. After an additional 6 hours heating, the organic material was diluted with ether (20ml.) and extracted with Claisen's solution (3 x 10 ml.). The alkaline extracts were combined, neutralized with hydrochloric acid (6N) and extracted with ether (2 x 25ml.), which was washed with sodium carbonate solution, brine and dried to give a small amount of a non-phenolic oil.

b. A solution of the enone (0.054g.) in mesitylene (2ml.) was heated under reflux with palladium-charcoal (10%, 0.55g.) for 9 hours. Removal of solvent and catalyst afforded only starting ketone.

c. The previous experiment was repeated using the same ratio of catalyst to enone but with 24 hours heating. The crude non-crystalline product was adsorbed on alumina and chromatographed, elution with benzene-chloroform (1:1) yielding a small quantity of an oil with infra-red absorption at 1600cm^{-1} (possibly an aromatic band).

d. The duration of the experiment on the enone (0.41g.) was extended still further to 48 hours. The catalyst was then filtered off, the organic material diluted with ether (50ml.) and extracted with Claisen's solution (6 x 20ml.), this being neutralized and extracted with ether (3 x 50ml.) as before to give a phenolic oil (0.24g.) which was chromatographed on alumina (5g.). Elution with benzene-petroleum ether, 1:1, (2 x 50ml.) gave a colourless oil, 0.16g., thought to be 2:2:6-trimethyl-1-β-(2-isopropyl-3-hydroxyphenyl) ethylcyclohex-1-ene, 37; R=H, b.p. 160°/0.03m.m.(molecular distillation), λ_{max} 274-8mμ, E_{max} 2,350 with infra-red absorption at 3500cm^{-1} (phenolic hydroxyl), 1600cm^{-1} (low intensity, aromatic), 1580cm^{-1} (high intensity, aromatic), 1260cm^{-1} (phenolic hydroxyl) and 745cm^{-1} (trisubstituted aromatic ring). As a crystalline sample of the phenol could not be obtained, attempts were made to convert it into a crystalline derivative.

The phenol, 37; R=H, (0.126g.) was heated under reflux for 4 hours with acetic anhydride (2ml.) and anhydrous sodium acetate (0.5g.). The reaction mixture was poured into water, the organic material extracted with ether (3 x 20ml.), the extracts combined, washed with

bicarbonate solution, brine and dried. Removal of solvent gave a good recovery of starting material (0.093g.).

The phenol, 37; R=H, (0.093g.) in dry pyridine (5ml.) was then heated at reflux with benzoyl chloride (0.10g.) for 2 hours. On cooling, water (20ml.) was added, the organic material extracted with ether (3 x 20ml.) and the combined extracts washed with dilute hydrochloric acid, sodium carbonate solution, brine and dried. The thick oil, obtained when the solvent was removed, was dissolved in petroleum ether, adsorbed on alumina and chromatographed. Elution with benzene-petroleum ether, 1:1, (2 x 50ml.) afforded a small sample of the expected benzoate as a yellow solid which recrystallized from petroleum ether as plates, m.p. 128-135° with infra-red absorption at 1730cm^{-1} (ester); 1600, 1580cm^{-1} (aromatic bands); 1260cm^{-1} (ester), 740cm^{-1} (trisubstituted aromatic ring) and 710cm^{-1} (monosubstituted aromatic ring). This spectrum later proved to be identical to an authentic sample of 2:2:6-trimethyl-1-β-(2-isopropyl-3-benzoyloxyphenyl) ethylcyclohex-1-ene.

B. Indirect Dehydrogenation.

(i) Using free bromine.

a) When the enone, 35, (0.094g.) in chloroform (10ml.) was treated with one equivalent of bromine in carbon tetrachloride and shaken, the resulting solution immediately became colourless. The solvent was removed under reduced pressure with external heating to give a yellow oil with absorption in the infra-red at 1705, 1650, 1080, 1040cm^{-1} and transparent in the ultra-violet. An elements test gave a negative response for halogen. The oil was dissolved in chloroform (10ml.) and heated at reflux with γ-collidine (1ml.) for 1 hour. The organic

layer was diluted with ether (30ml.) washed with hydrochloric acid (6N), sodium carbonate solution, brine and dried, removal of the solvent giving an oil with an infra-red spectrum identical to that of the initial product.

b) The experiment was repeated with two equivalents of bromine to give a halogen-free oil, spectrally identical to the above product. No change in the infra-red spectrum was produced by refluxing the oil in γ-collidine/chloroform but the material obtained when the base and the solvent had been removed, solidified on standing and crystallized from petroleum ether as a white solid. However, repeated recrystallization (x4) from petroleum ether did not decrease the melting point range of 119-129°, indicating that the solid was a mixture.

c) Bromine in carbon tetrachloride was added dropwise with swirling to a solution of the enone, 35, (0.136g.) in chloroform (10ml.). When approximately two equivalents had been absorbed, evolution of hydrogen bromide commenced and after the introduction of between four and five equivalents, the uptake of bromine by the solution ceased. The solvent was then removed under water-pump pressure with external heating to give a dark brown oil showing infra-red absorption at 1720, 1700, 1650, 1560 and 1540cm^{-1}.

Base treatment of 2:2:6-trimethyl-1-β-(2-isopropyl-3-ketocyclohex-1-enyl) ethylcyclohexan-1-ol (35)

The enone, 35 (0.1g.) was heated to reflux with Claisen's solution (20ml.) for 6 hours, when the solution was diluted with ice-water (100ml.) and extracted with ether (3 x 20ml.). The combined extracts were washed with hydrochloric acid (3N), sodium carbonate solution and

dried, removal of the solvent giving a colourless oil which was absorbed on alumina and chromatographed. Elution with benzene afforded an oil (0.53g.) with infra-red absorption at 1710cm^{-1} (saturated ketone), 1480cm^{-1} (methyl), 1060, 1040 and 1030cm^{-1} (etherial oxygen linkage).

(ii) Using N-bromosuccinimide.

2:2:6-Trimethyl-1-β-(2-isopropyl-3-hydroxyphenyl) ethylcyclohexan-1-ol (36)

N-Bromosuccinimide (0.494g.) and triethylamine (2 drops) were added to a hot solution of enone, 35, (0.349g.) in carbon tetrachloride-chloroform (5:1, 30ml.) and the resulting suspension heated under reflux for 30 minutes γ-Collidine (2ml.) was added, the heating continued for 1 hour and the solids then filtered off. The organic solution was extracted with Claisen's solution (20x5ml.) washed with dilute acid, brine, dried and the solvent removed to give a brown oil (0.210g.). The alkaline extracts were neutralized, extracted with ether (4x20ml.) and these extracts repeatedly washed with water and dried. Removal of the solvent afforded a white powder (0.06g.) which crystallized from benzene-chloroform (1:1) as small white cubes of 2:2:6-trimethyl-1-β-(2-isopropyl-3-hydroxyphenyl) ethylcyclohexan-1-ol m.p.194-196° (Found: C, 78.85; H, 10.40, $C_{20}H_{32}O_2$ requires C, 78.95; H, 10.55%) with infra-red absorption at 3550cm^{-1} (tertiary hydroxyl, very sharp), 3300cm^{-1} (phenolic hydroxyl), 1600cm^{-1} (trace, aromatic), 1580, 790,755cm^{-1} (aromatic) and 1280cm^{-1} (phenolic hydroxyl). Trituration of the brown oil with petroleum ether gave a further amount of the hydroxy phenol, 36, (0.112g.).

AttAttempted preparation of 2:2:6-trimethyl-1-β-(2-isopropyl-3 3-methoxyphenyl) ethylcyclohexan-1-ol.

A suspension of the hydroxyphenol (0.042g.) in tetrahydrofuran (5ml.) was added to a stirred suspension of sodium hydride (approximately 0.007g.) in tetrahydrofuran (5ml.) and the resulting mixture heated under reflux for 15 minutes, during which hydrogen appeared to be evolved. On cooling, methyl iodide (0.020g.) was added and the resulting matieral stirred with gentle warming for 20 minutes. The solvent was then removed in a stream of air, the residue taken up in ethyl acetate (10ml.) and washed with water. Drying of the organic solution and removal of the solvent furnished unchanged starting material.

Excess etherial diazomethane solution was added to a suspension of the hydroxyphenol (0.052g.) in ether (4ml.) containing boron trifluoride etherate (1 drop). The resulting suspension was allowed to remain at room-temperature for 6 hours, during which it was shaken occasionally. The solvent was then removed in an air stream to give unchanged starting material.

Treatment of 2:2:6-trimethyl-1-β-(2-isopropyl-3-ketocyclohex-1-enyl) ethylcyclohexan-1-ol (35) with N-bromosuccinimide under various reaction conditions.

i) N-Bromosuccinimide (1.47g.) was added to a hot solution of the enone, 35, (1.85g.) in carbon tetrachloride (100ml.) and the resulting suspension heated at reflux for 110 minutes. γ-Collidine (20ml.) was then added and the mixture heated for a further 30 minutes when it was chilled, the solids filtered off and the filtrate diluted with ether (30ml.). The organic material was washed with hydrochloric acid (3N), sodium carbonate solution, brine, dried and the solvent removed under water-pump pressure with external heating. This treatment afforded an oil (1.31g.) with infra-red absorption at 3300cm^{-1} (weak, hydroxyl), 1700cm^{-1} (saturated ketone), 1600, 1580cm^{-1}, (aromatic bands) and 1060, 1040cm^{-1} (strong, spiro-ether).

ii) The enone, 35, (0.46g.) was heated in chloroform-carbon tetrachloride (3:10, 100ml.) containing triethylamine (2 drops) with N-bromosuccinimide (0.67g.). At reflux, the material was stirred vigorously. After 35 minutes of such treatment, γ-collidine (2ml.) was added dropwise to the bright orange solution and the heating continued for 30 minutes. On cooling, ether (40ml.) was added and the organic layer washed with water, hydrochloric acid (3N), sodium carbonate solution, brine, dried and the solvent removed to furnish an oil. This displayed infra-red bands at 3500cm^{-1} (shoulder), 3400cm^{-1} (hydroxyl), 1700cm^{-1} (spiro-ketone) and 1600, 1580cm^{-1} (strong, aromatic bands). Although this product contained a relatively low percentage of saturated ketonic material, it refused to crystallize and must therefore have been made up largely of the dehydrated phenol (37;R=H).

iii) A solution of the enone, 35, (0.25g.) in chloroform-carbon tetrachloride (1:4, 25ml.) containing N-bromo-succinimide (0.15g.) was irradiated with a 60 watt bulb for 16 hours. The solvent was removed from a sample under water-pump pressure and external heating to give an oil with strong absorption in the infra-red at 1700, 1060cm^{-1} (spiro-ketone) and weak bands due to starting material and an aromatic product. The bulk of irradiated suspension was heated under reflux for 120 minutes when the product gave an infra-red spectrum almost identical to the first. The solvent was removed, the non-volatile residue dissolved in γ-collidine (5ml.) and the solution refluxed for 1 hour. Ether (30ml.) was added and the solution washed with dilute hydrochloric acid, sodium carbonate solution, brine and dried. Evaporation of the solvent afforded a dark oil spectrally very similar to the original materials.

iv) A solution of the enone, 35, (0.27g.) in allyl bromide (5ml.) containing N-bromosuccinimide (0.19g.) was heated at reflux (70°) for 40 minutes. The solvent was then removed and the residual material heated under reflux with γ-collidine (5ml.) for 1 hour. Chloroform (25ml.) was added, the organic material extracted with water, dilute hydrochloric acid, sodium carbonate solution, brine and dried. Solvent removal afforded a brown oil with infra-red bands at 3400, 1650cm^{-1} (starting enone), 1700cm^{-1} (strong spiro-ketone) and 1600, 1580cm^{-1} (aromatic product).

v) N-Bromosuccinimide was heated in carbon tetrachloride with lithium carbonate but the two reagents did not interact. A mixture of enone, 35, (0.306g.), lithium carbonate (3 equivalents), N-bromosuccinimide (0.180g.) and dibenzoyl peroxide (0.005g.) was heated under nitrogen at reflux in carbon tetrachloride (15ml.)

for 40 minutes. The material was cooled, the solids filtered off and the solution diluted with ether. The organic layer was washed with brine, dried and the solvent removed to give an oil with absorption in the infra-red at 3400, 1650, 1600cm^{-1} (starting enone) and 1700cm^{-1} (strong, spiro-ketone).

vi) A solution of the enone, 35, (0.11g.) in carbon tetrachloride (2ml.) was heated at reflux with dibenzoyl peroxide (5mg.) and N-bromosuccinimide (0.088g.) until succinimide was produced (40 minutes). On cooling, the solids were filtered off and the solvent removed under water-pump pressure to give a brown oil with infra-red bands at 3400cm^{-1} (broad, hydroxyl), 1690cm^{-1} (originally thought to be spiro-ketone) and 1600, 1580cm^{-1} (weak, aromatic bands). There appeared to be no strong absorption 1060cm^{-1}. The oil was dissolved in dimethylformamide (2ml.) and the solution heated at reflux for 20 minutes under nitrogen with lithium bromide (0.1g.) and lithium carbonate (0.1g.). A work-up as in (v) gave an oil with absorption in the infra-red at 3400cm^{-1} 1700cm^{-1} (weak), 1650cm^{-1} (weak, starting enone) and 1600, 1580cm^{-1} (strong, aromatic bands).

Preparation of 2:2:6-Trimethyl-1-β-(2-isopropyl-3-hydroxyphenyl) ethylcyclohex-1-ene (37; R=H)

N-Bromosuccinimide (1.22g.) and dibenzoyl peroxide (0.005g.) were added to a hot solution of enone, 35, (1.95g.) in carbon tetrachloride (Analar, 25ml.) and the suspension heated at reflux. After 20 minutes, the N-bromosuccinimide had not reacted and dibenzoyl peroxide (0.005g.) was added. After 70 minutes heating, the solids were filtered off and the solvent removed under water-pump pressure on the steam bath. The residue was dissolved in carbon tetrachloride (20ml.) containing γ-collidine

(10ml.) and the solution heated under reflux for 30 minutes, On cooling, the organic material was washed with dilute hydrochloric acid (3N), brine and dried. Removal of the solvent gave a thick brown oil (1.61g.) which was adsorbed on silica (50g.) and chromatographed. Elution with petroleum ether-benzene (6:4) afforded an oil (1.27g.) with infra-red absorption at 3500cm^{-1} (phenolic hydroxyl) 1600, 1580, 810, 790, 755cm^{-1} (aromatic bands) and 1280cm^{-1} (phenolic hydroxyl). This material could not be distilled and although it solidified on standing, was so soluble even in n-pentane that it could not be purified by crystallization.

A sample of the crude dehydrated phenol (0.88g.) was heated under reflux in pyridine (20ml.) containing benzoyl chloride (0.8g.) for 2 hours. Water (50ml.) was added, the organic material extracted with ether (2 x 30ml.) these extracts being washed with dilute hydrochloric acid (3N) sodium carbonate solution, brine and dried. Removal of the solvent gave an oil which was adsorbed on alumina and chromatographed, elution with petroleum ether-benzene (6:4) furnishing a solid benzoate free from benzoic anhydride. This recrystallized from petroleum ether-benzene (1:1) as colourless needles of 2:2:6-trimethyl-1-β (2-isopropyl-3-benzoyloxyphenyl) ethylcyclohex-1-ene m.p. 147-148° (Found: C, 82.70; H, 8.55, $C_{27}H_{34}O_2$ requires C, 83.10; H, 8.70%) with infra-red absorption at 1735, 1260cm^{-1} (ester) and 1600, 1580, 805, 750,710cm^{-1} (aromatic bands).

Hydrolysis of 2:2:6-trimethyl-1-β-(2-isopropyl-3-benzoyloxyphenyl) ethylcyclohex-1-ene.

The benzoate (0.116g.) dissolved in dry methanol (20ml.) containing sodium (0.01g.) was heated under reflux for 4 hours. On cooling, the solution was saturated with carbon

dioxide, ether (20ml.) added, the organic material washed with brine and dried. The solvent was removed to give crystalline dehydrated phenol m.p. 65-67.5° which could not be crystallized from any solvent, even n-pentane.

A bromo compound derived from 2:2:6-trimethyl-1-β-(2-isopropyl-3-ketocyclohex-1-enyl) ethylcyclohexan-1-ol(35)

The enone, 35, (0.121g.) was dissolved in carbon tetrachloride (Analar, 5ml.) by gentle heating under reflux. N-bromo succinimide (0.07g.) and dibenzoyl peroxide (0.005g.) were added and the resulting suspension heated under reflux for fifteen minutes. The product was chilled, the succinamide filtered off and the solvent removed without external heating to give a yellow oil. Trituration with petroleum ether afforded a white crystalline solid m.p. 80-84° with infra-red absorption at 3450cm^{-1} (hydroxyl) and 1660cm^{-1} (α-bromoketone). The ultraviolet absorption of λ_{max} 252-3 mμ, E_{max} 10,600 compared with that of the parent enone showed a bathochromic shift of 4-5 mμ, and a reduction in the E_{max} of 2,600. This bromo compound was extremely unstable. It decomposed rapidly with the evolution of hydrogen bromide when left to stand at room-temperature with a trace of carbon tetrachloride or petroleum ether. Warming for 10 minutes in carbon tetrachloride, allyl bromide or pyridine gave a product with infra-red absorption at 1700cm^{-1} (saturated ketone), 1660cm^{-1} (bromo compound) and 1600, 1580cm^{-1} (aromatic bands). When a mixture of the bromo compound and hydroxy phenol, was allowed to stand in methanolic potassium hydroxide solution (2%), there was some selective conversion of the bromo compound to phenol, but the reaction was extremely slow and any attempts to accelerate it by means of heating gave the mixture obtained above.

Attempted preparation of 2:2:6-trimethyl-1-β-(2-isopropyl-3-methoxyphenyl) cyclohex-1-ene (37; R=CH_3)

Potassium t-butoxide (0.058g.1.5 equivalents) was added to the dehydrated phenol, 37; R=H, (0.093g.) dissolved in dry t-butanol (10ml.) and the resulting solution heated at reflux for 2 hours. On cooling, methyl iodide (0.1ml.) was added to the red solution, which was allowed to stand at room-temperature for 15 minutes, warmed gently for 30 minutes and then heated under reflux for 90 minutes. Most of the solvent was then removed at the pump, the organic residue taken up in ether (20ml.) and this washed with dilute acid, sodium carbonate solution, brine and dried. When the solvent was removed, only starting material was recovered.

Preparation of 2:2:6-trimethyl-1-β-(2-isopropyl-3-methoxyphenyl) cyclohex-1-ene (37; R=CH_3)

The dehydrated phenol, 37; R=H, (0.217g.) was dissolved in xylene (sodium dried, 10ml.) solid potassium t-butoxide (0.5g.) added and the whole heated at reflux under nitrogen for 16 hours. The red solution was cooled, methyl iodide (Iml. excess) added, and the resulting material warmed gently. After 15 minutes the colour of the solution discharged and a white precipitate was produced. The heating was stopped after 1 hour, when ether (30ml.) was added and the organic material repeatedly washed with brine and dried. Removal of the solvent gave a yellow oil (0.21g.) which was adsorbed on alumina and chromatographed. Elution with petroleum ether and petroleum ether-benzene (4:1) afforded a solid (0.14g.) which recrystallized from hexane as colourless plates of the desired phenol methyl ether, 37; R=CH_3, (0.1g.) m.p. 90-91° with infra-red absorption

at 1600, 1580cm^{-1} (aromatic bands), 1040cm^{-1} (phenol ether) and 790, 770, 745cm^{-1} (1:2:3-trisubstituted aromatic ring).

Attempted preparation of 1:1:12-trimethyl-7-methoxy-8-isopropyl-1:2:3:4:9:10:11:12-octahydrophenanthrene (46)

A mixture of the methyl ether, 37; R=CH_3 (0.090g.) was stirred under nitrogen with syrupy phosphoric acid (3g.) and phosphorus pentoxide (1.7g.). The thick mass was heated from 20° to 180° in 10 minutes and the temperature maintained at 180° for 45 minutes. On cooling, the acid material was cautously dissolved in water, neutralized with sodium hydroxide solution (3N) and the organic material extracted with ether (3 x 20ml.). The extracts were washed with saturated brine, dried and the solvent removed to give an oil which was adsorbed on alumina and chromatographed. Elution with petroleum ether gave a small sample ($<$ 0.01g.) of an oil with infra-red absorption at 1600cm^{-1} (aromatic band) 1050cm^{-1} (phenol ether) and 805cm^{-1} (probably 1:2:3:4-tetra substituted aromatic ring).

Preparation of 1:1:12-trimethyl-7-methoxy-8-isppropyl-1:2:3:4:9:10:11:12-octahydrophenanthrene. (46)

A mixture of syrupy phosphoric acid (2.9g.) and phosphorus pentoxide (0.90g.) was stirred under nitrogen with the phenol methyl ether, 37; R=CH_3, (0.096g.) at 90-100° for 40 minutes. The thick mass was dissolved in water, neutralized with saturated sodium carbonate solution and the organic material extracted with ether (3 x 15ml.). Washing the extracts with brine, drying and removal of the solvent gave an oil which as before was adsorbed on alumina (grade 1, neutral Woelm) and chromatographed. Elution with petroleum ether (60ml.) afforded a solid (0.077g.) which recrystallized from methanol-methylene

chloride as white cubes of 1:1:12-trimethyl-7-methoxy-8-isopropyl-1:2:3:4:9:10:11:12-octahydrophenanthrene m.p.58-65° with infra-red absorption at 1600cm^{-1}(aromatic), 1250, 1110cm^{-1} (carbon skeleton), 1050cm^{-1} (phenol ether) and 805cm^{-1} (single band, 1:2:3:4-tetra substituted aromatic ring). By comparison, totarol methyl ether also showed these absorption bands, but the two spectra differed in fine structure details. A solution of totarol methyl ether in α-methylnaphthalene was subjected to gas-liquid chromatography on 5% Apeizon-Celite and afforded a single band with an elution time of 26 minutes. Similar treatment of a mixture of totarol methyl ether and the synthetic octahydrophenanthrene (1:1) in α-methylnaphthalene, showed the presence of two components, the first eluted after 21 minutes and the second after 42 minutes. In a second run of this material, these peaks had elution times of 19 and 43 minutes. The octahydrophenanthrene was then analysed on its own, to afford bands at 17 and 44 minutes. Although it was obvious form these data that the synthetic octahydrophenanthrene was a mixture of isomers, one of which was identical with totarol methyl ether, a disturbing feature was the change in elution time of the two compounds. It is believed that this was due to changes in the properties of the column brought about by prolonged use (6 hours) at high temperature (200°C).

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28. *BARTON and PINHEY, Proc. Chem. Soc., 1960, 279; Hamilton, McPhail and Sim, J., 1962, 708.*

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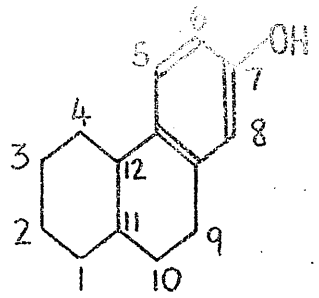
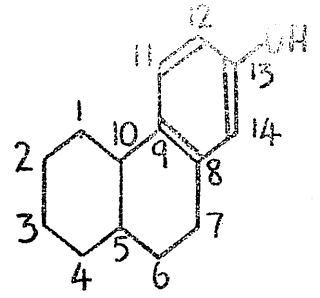
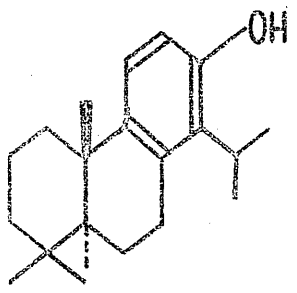


Phenanthrene numbering



Steroid numbering



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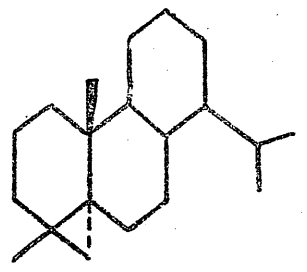

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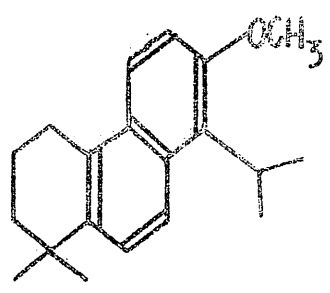

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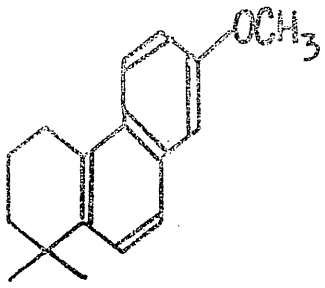

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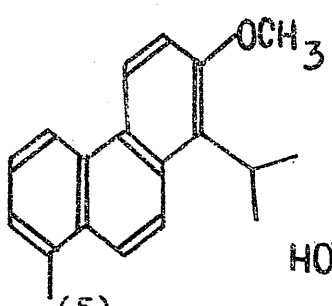

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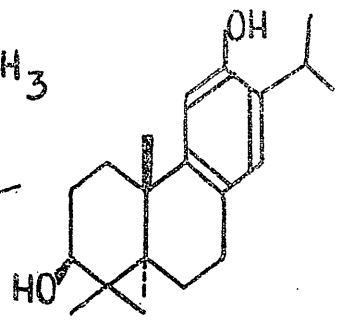

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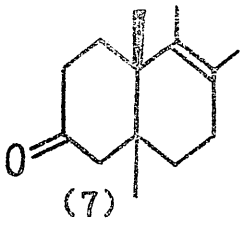

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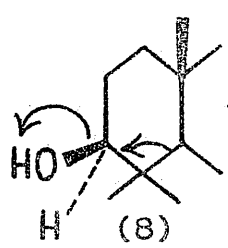
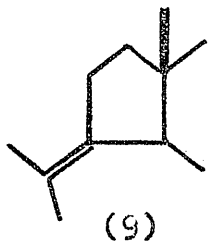


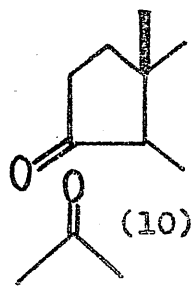
(8)

(i)



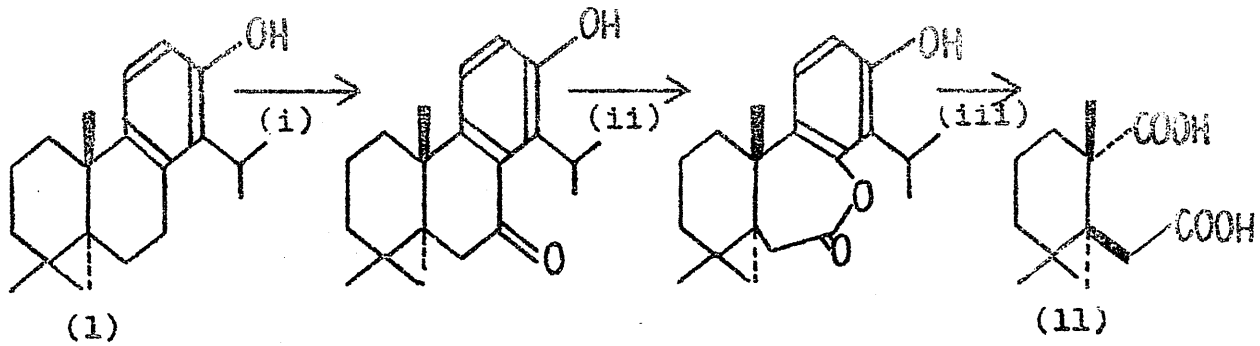
(9)

(ii)
(iii)



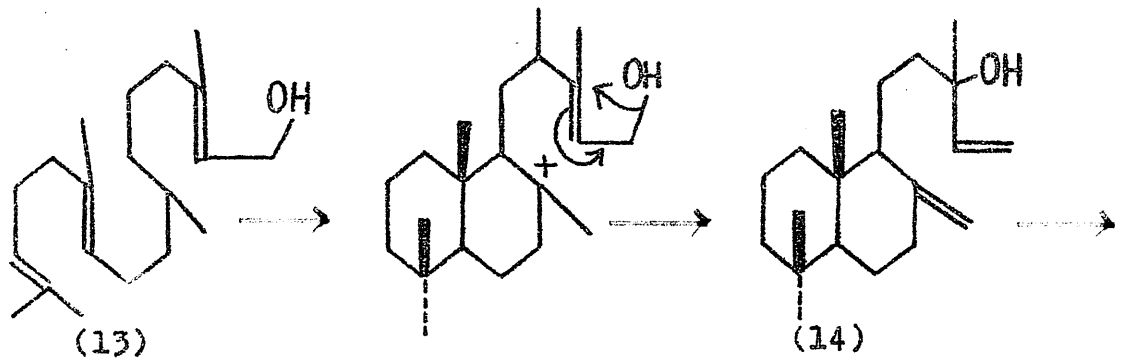
(10)

(i) PCl_5 ; (ii) OsO_4 ; (iii) $Pb(OAc)_4$.

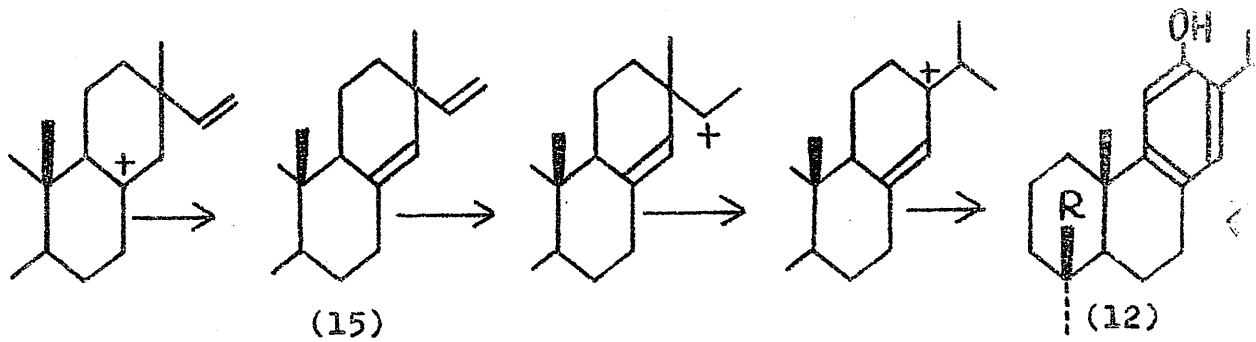


(1) (11)

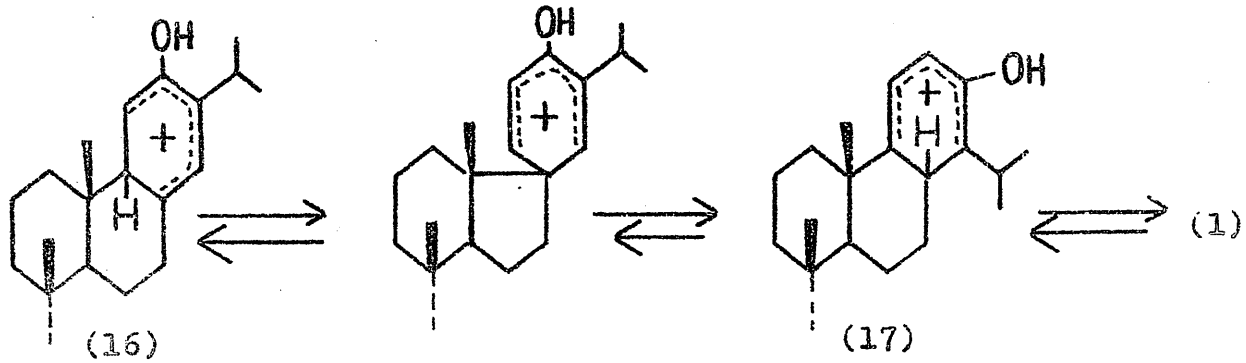
(i) CrO_3/H_2SO_4 ; (ii) Trifluoroperacetic acid ; (iii) O_3.



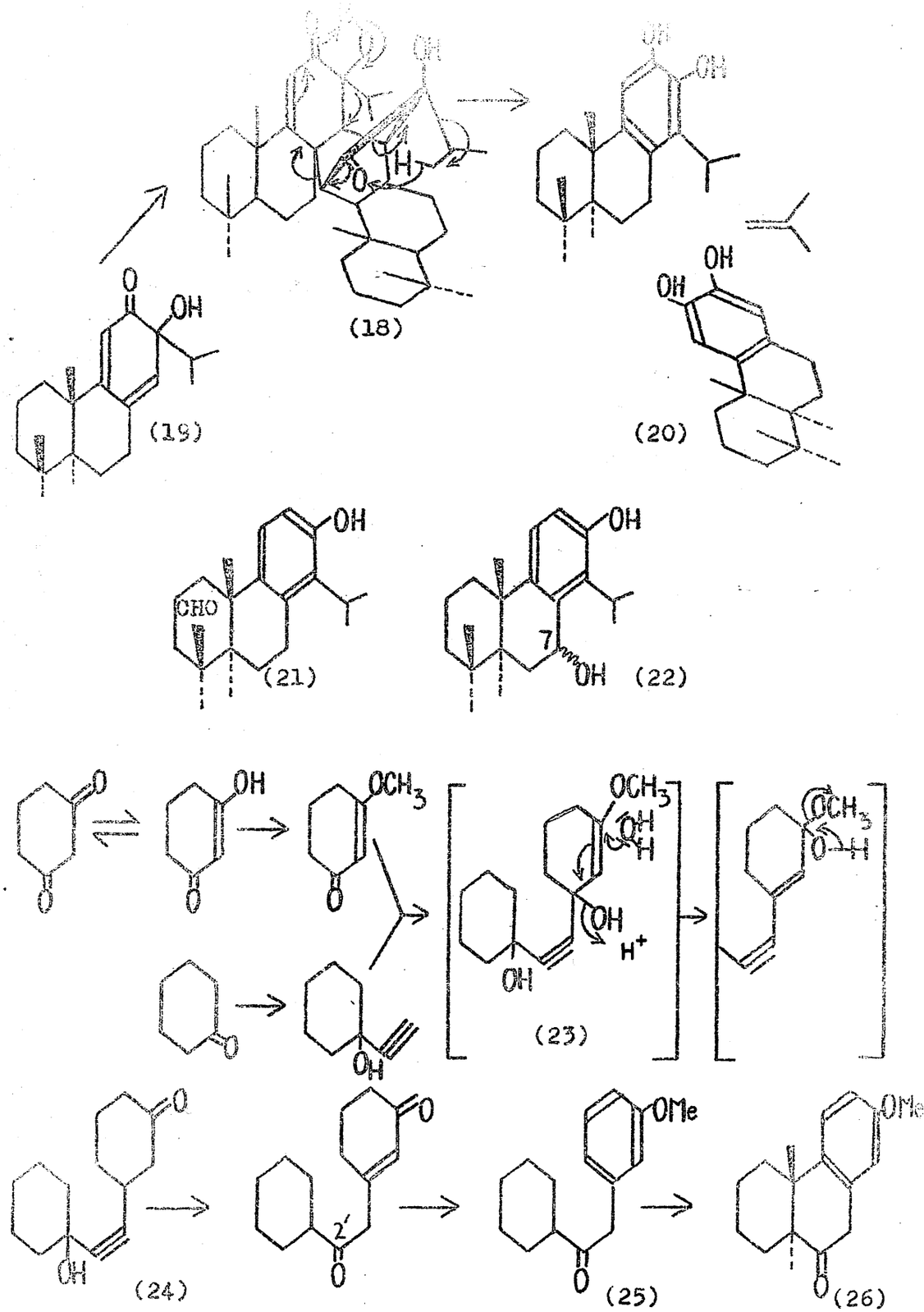
(13) (14)

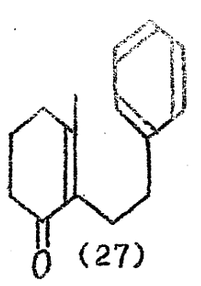


(15) (12)



(16) (17) (1).


OH
O
H
(18)
(19)
(20)
CHO
(21)
7
OH
(22)
OCH_3
H^+
(23)
OMe
(24)
2'
(25)
(26)



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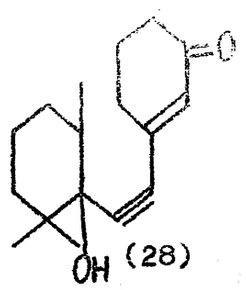

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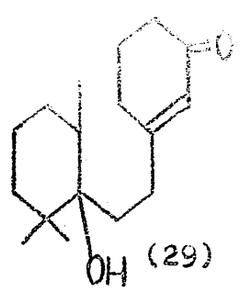

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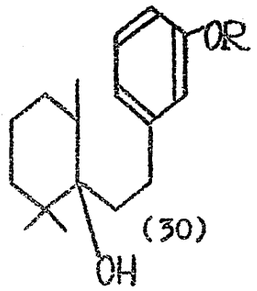

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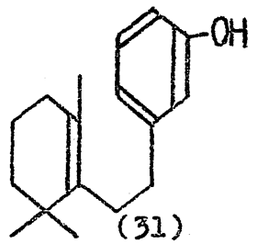

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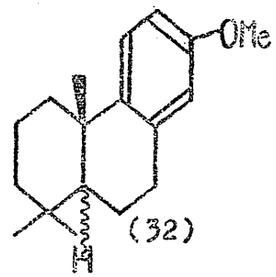

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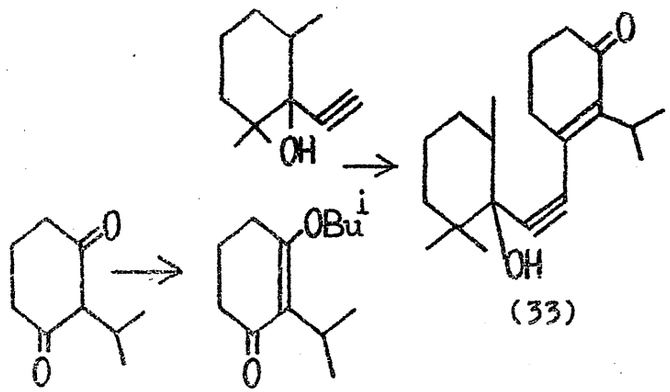

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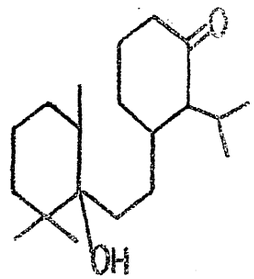

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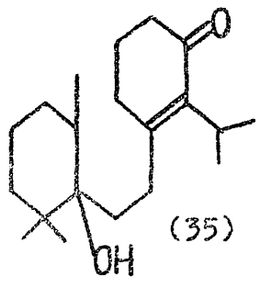

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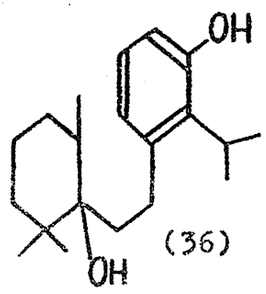

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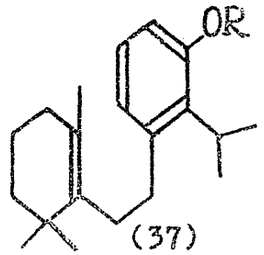

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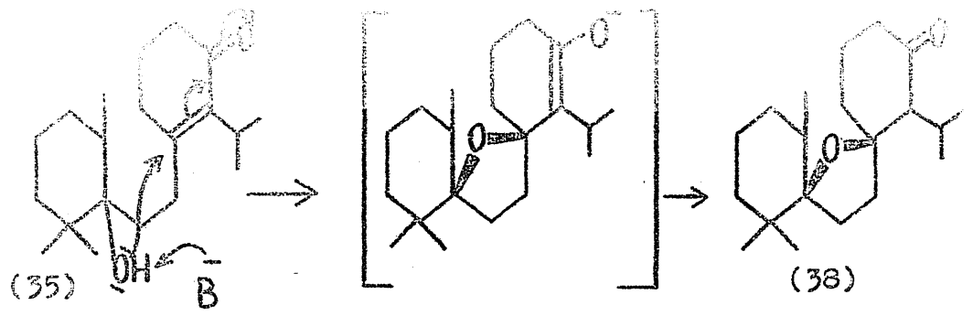
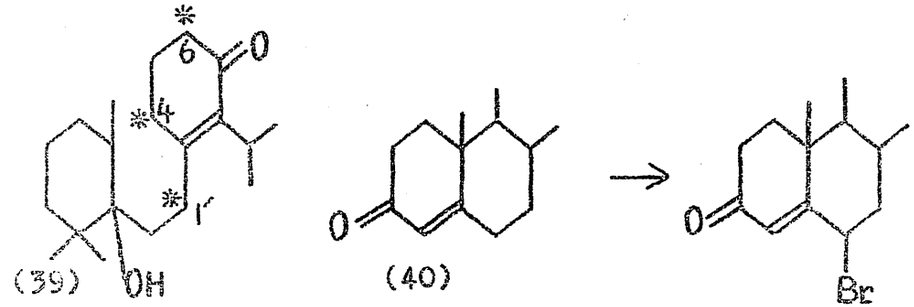
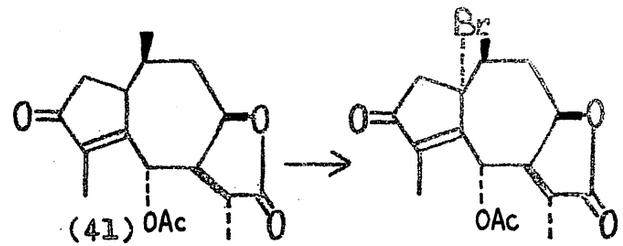
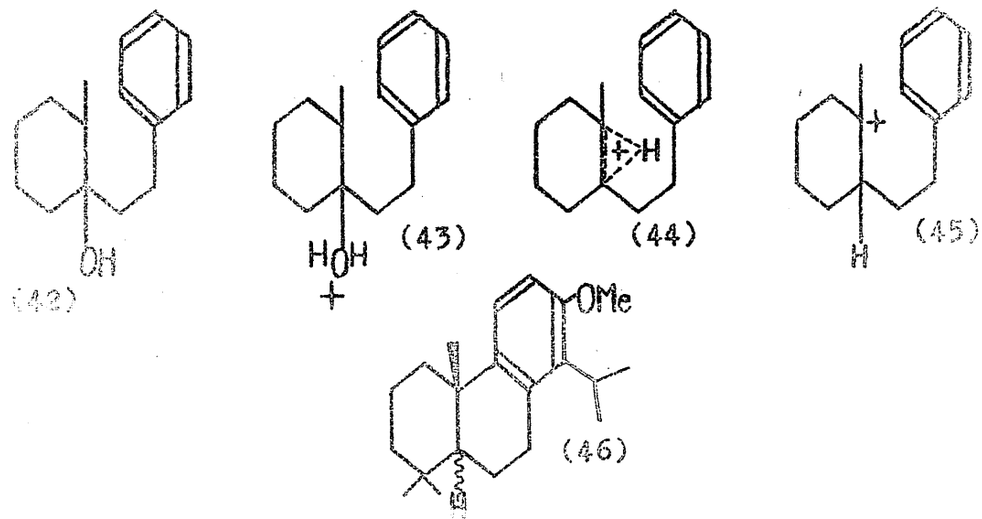
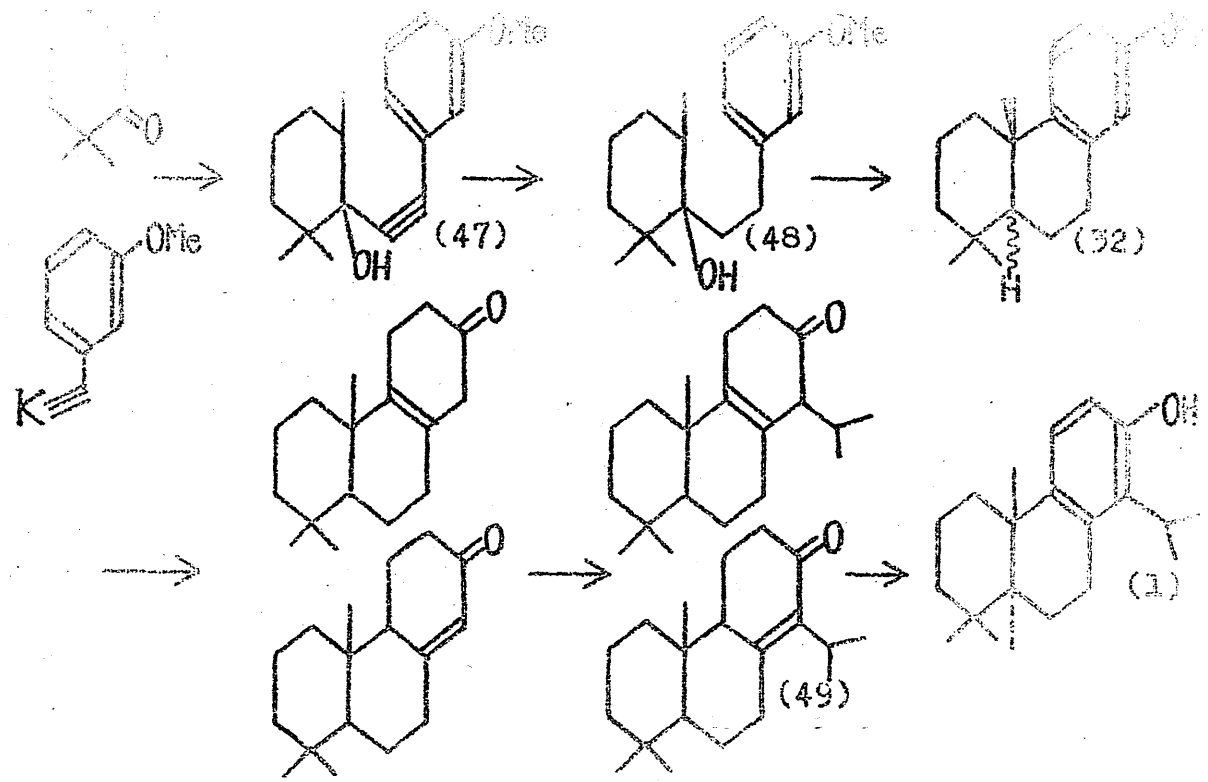
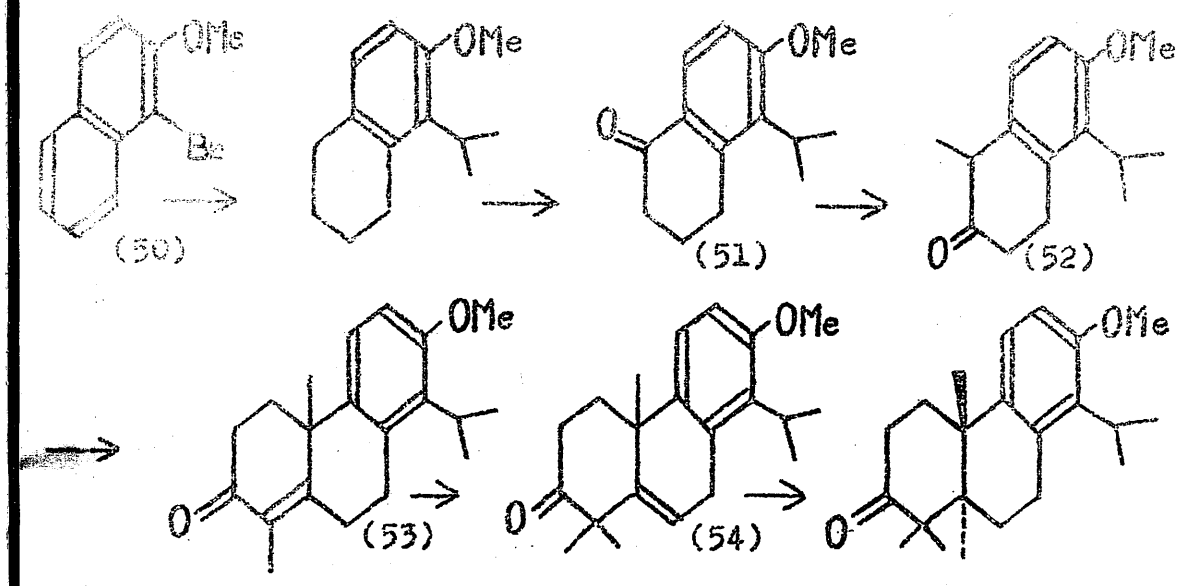

(35)
OH
B
O
O
(38)


(39)
OH
6
4
1'
O
(40)
O
Br


(41)
OAc
O
O
Br
OAc
O


(42)
OH
(43)
H
OH
+
(44)
H
(45)
H
OMe
(46)


OMe
OH
(47)
(48)
(32)
K
(1)
(49)


OMe
Br
(50)
(51)
(52)
(53)
(54)