SYNTHETIC STUDIES
IN THE
HIGHER TERPENES.

A thesis submitted for the

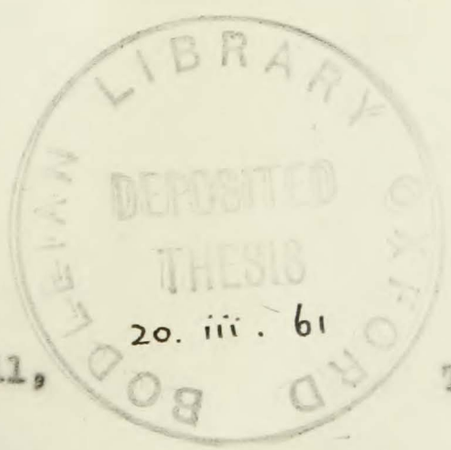
DEGREE OF DOCTOR OF PHILOSOPHY

in the

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by

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C O N T E N T S.

ABSTRACT		i
INTRODUCTION		1
Biogenesis		8
Synthetic approaches		11
References		19
Diagrams	following	27
SECTION I		28
Discussion		28
Notes on Experimental		40
Experimental		42
References		59
Diagrams	following	59
SECTION II		60
Discussion		60
Experimental		92
References		120
Diagrams	following	122
SECTION III		123
Discussion		123
Experimental		136
References		159
Diagrams		160

ABSTRACT.

The various groups into which the triterpenes are divided are defined and emphasis is placed on the structural relationships which exist between these groups. A brief description is given of the methods used in the determination of the structures of triterpenes with particular reference to β-amyrin (I), a member of the oleanane (II) group. Recent progress in the problems of biogenesis and the total synthesis of triterpenes is reviewed.

All approaches, so far investigated, to the synthesis of pentacyclic triterpenes involve the fusion of two bicyclic moieties representing rings A and B and rings D and E of the proposed structure. This thesis describes attempts to synthesise pentacyclic triterpenes of the oleanane (II) group, *via* the tetracyclic-*cis*-ketone (IIIa), the tetracyclic-*trans*-ketone (IIIc) or the tetracyclic-αβ-unsaturated-ketone (IVa).

The important bicyclic intermediates in these syntheses are 5-(2'-bromoethyl)-6-exomethylene-1,1,10-trimethyl-*trans*-decalin (Va), 7,7,10-trimethyl-*cis*-decal-2-one (VI) and 7,7,10-trimethyl-$\Delta^{1(9)}$-octal-2-one (VII); the preparation of the last two compounds has been reported previously by Halsall and Thomas.[2]

It was proposed originally to obtain the racemic modification of 5-(2'-bromoethyl)-6-exomethylene-1,1,10-trimethyl-trans-decalin from $\Delta^{8(14)}$-podocarpen-7-one (VIII), the synthesis of which requires large amounts of 2,2,6-trimethylcyclohexanone. A rapid technique was developed for the preparation of this compound in high yield from 2-methylcyclohexanone.

The availability of sclareol (IX), which is a suitable relay in the synthesis of (+)-5-(2'-bromoethyl)-6-exomethylene-1,1,10-trimethyl-trans-decalin (Va) led to the abandonment of the route via $\Delta^{8(14)}$-podocarpen-7-one. Oxidation of sclareol with potassium permanganate gave the enol-ether (X). Ozonolysis of the enol-ether (X), followed by decomposition of the ozonide (XI) with Raney nickel and reduction of the product with lithium aluminium hydride gave a mixture of 5-(2'-hydroxyethyl)-6-hydroxy-1,1,6,10-tetramethyl-trans-decalin (XII) and 5-(2'-hydroxyethyl)-6-exomethylene-1,1,10-trimethyl-trans-decalin (Vb). Treatment of either of these compounds with phosphorus oxybromide in pyridine gave (+)-5-(2'-bromoethyl)-6-exomethylene-1,1,10-trimethyl-trans-decalin (Va), from which ambreinolide (XXIII) was prepared.

The crude product, obtained after decomposing the ozonide (XI) with Raney nickel, was reduced with sodium borohydride but only small yields of compounds, which could be

characterised, were obtained. These were 5-(2'-hydroxyethyl)-6-acetoxy-1,1,6,10-tetramethyl-*trans*-decalin, 5-carboxymethyl-6-acetoxy-1,1,6,10-tetramethyl-*trans*-decalin and the lactone derived from 5-carboxymethyl-6-hydroxy-1,1,6,10-tetramethyl-*trans*-decalin. The first two of these compounds were obtained also by catalytic hydrogenation of the ozonide (XI); the lactone was the only compound isolated from the product obtained by oxidising the enol-ether (X) with sodium metaperiodate/osmium tetroxide.

It has been predicted[2,4] on theoretical grounds that 7,7,10-trimethyl-*cis*-decal-2-one (VI) should enolise towards C - 3. Alkylation of this compound with ethyl iodide gave 3-ethyl-7,7,10-trimethyl-*cis*-decal-2-one, from which a mixture of 3-ethyl-7,7,10-trimethyl-Δ^{3}-*cis*-octal-2-one and 3-ethyl-7,7,10-trimethyl-$\Delta^{1(9)}$-octal-2-one was obtained by brominating and dehydrobrominating. 7,7,10-Trimethyl-*cis*-decal-2-one (VI) was brominated in several ways and the crude product was dehydrobrominated to give, in all cases, a mixture of 7,7,10-trimethyl-Δ^{3}-*cis*-octal-2-one and 7,7,10-trimethyl-$\Delta^{1(9)}$-octal-2-one. The implications from the results of the alkylation and bromination/dehydrobromination experiments are discussed.

Alkylation of (±)-7,7,10-trimethyl-$\Delta^{1(9)}$-octal-2-one (VII) with (+)-5-(2-bromoethyl)-6-exomethylene-1,1,10-trimethyl-*trans*-decalin (Va) gave a mixture of the tetracyclic $\alpha\beta$-unsatur

ketones (IVa and b). A second product was obtained from this alkylation and may be a mixture of the isomeric tetracyclic-βγ-unsaturated-ketones (XIIIa and b). The tetracyclic-αβ-unsaturated-ketones (IVa and b) were reduced with lithium in liquid ammonia to give the tetracyclic-trans-ketones (IIIc and d) this mixture was resolved.

The C,30-alcohols (XIVa and/or b) were prepared from the tetracyclic-trans-ketones (IIIc and/or d) and lithium methyl, and they were treated with boron trifluoride etherate. A hydrocarbon (or mixture of hydrocarbons) was obtained and was stable to further treatment with acid. Possible products of this series of reactions are olean-18-ene (XV) and 18αH-olean-12-ene (XVI); neither of these compounds was isolated.

The tetracyclic-hydrocarbons (XVIIa and b) were obtained by treating the tetracyclic-αβ-unsaturated-ketones (IVa and b) with methyl magnesium iodide. Spectroscopic analysis of the product obtained by treating the tetracyclic-hydrocarbons (XVIIa and b) with boron trifluoride etherate, fluoroboric acid or aluminium trichloride in nitromethane indicated that the yields of olean-11(12),13(18)-diene (XVIII) (one of the expected products of this series of reactions) was greater than that obtained from the tetracyclic-allylic-alcohols (XIXa and b) by Corey and co-workers[1], who used acetic acid saturated with hydrogen chloride as the cyclising reagent.

An investigation was made into the stability of the conjugated diene system in 3β-benzoyl-olean-11(12),13(18)-diene to treatment with acid.

An attempt was made to prepare (+)-7,7,10-trimethyl-$\Delta^{1(9)}$-octal-2-one (XX) for use in the alkylation with (+)-5-(2'-bromoethyl)-6-exomethylene-1,1,10-trimethyl-*trans*-decalin (Va). Only partial resolution of (±)-7,7,10-trimethyl-$\Delta^{1(9)}$-octal-2-one (VII) was achieved using standard procedures. 10-Carbethoxy-7,7-dimethyl-$\Delta^{1(9)}$-octal-2-one (XXIa) has been resolved[5] and in the present work the racemic modification of this compound was converted into 7,7,10-trimethyl-$\Delta^{1(9)}$-octal-2-one by two routes. It is possible, therefore, to obtain the optical isomers of 7,7,10-trimethyl-$\Delta^{1(9)}$-octal-2-one (VII) by an indirect method.

The carbonyl group was protected by preparing the dioxolane-derivative (XXIIa), which was reduced with lithium aluminium hydride to give 10-hydroxymethyl-7,7-dimethyl-Δ^{8}-octal-2-one-2-dioxolane (XXIIb). In naming dioxolane derivatives in this abstract it is assumed that the double bond is in the Δ^{8} position; no evidence was obtained to confirm this. 10-Methanesulphonyloxymethyl-7,7-dimethyl-Δ^{8}-octal-2-one-2-dioxolane (XXIIc) was prepared by treating 10-hydroxymethyl-7,7-dimethyl-Δ^{8}-octal-2-one-2-dioxolane (XXIIb) with methane sulphonyl chloride. The two routes to 7,7,10-trimethyl-$\Delta^{1(9)}$-octal-2-one diverge at this stage. In the first method

10-methanesulphonyloxymethyl-7,7-dimethyl-Δ^{8}-octal-2-one-2-dioxolane (XXIIc) was converted to the dioxolane-methanethiol (XXIId), which without purification, was desulphurised with hydrazine. The dioxolane protecting group was removed from the product and 7,7,10-trimethyl-$\Delta^{1(9)}$-octal-2-one was isolated as its 2,4-dinitrophenylhydrazone.

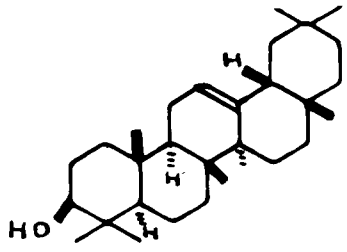
In the second method 10-methanesulphonyloxymethyl-7,7-dimethyl-Δ^{8}-octal-2-one-2-dioxolane (XXIIc) was converted to 10-iodomethyl-7,7-dimethyl-Δ^{8}-octal-2-one-2-dioxolane (XXIIe), which was reduced with lithium aluminium hydride. The product was hydrolysed and 7,7,10-trimethyl-$\Delta^{1(9)}$-octal-2-one was obtained.

10-(+)-Camphor-10-sulphonyloxymethyl-7,7,-dimethyl-Δ^{8}-octal-2-one-2-dioxolane (XXIIf) was prepared by treating 10-hydroxymethyl-7,7-dimethyl-Δ^{8}-octal-2-one-2-dioxolane (XXIIb) with (+)-camphor-10-sulphonyl chloride; the diastereoisomeric forms of the 2,4-dinitrophenylhydrazone were resolved by recrystallisation. Hydrolysis of the 2,4-dinitrophenylhydrazone with pyruvic acid and acetic acid gave 10-(+)-camphor-10-sulphonyloxymethyl-7,7-dimethyl-$\Delta^{1(9)}$-octal-2-one (XXIc) which was converted into 10-iodomethyl-7,7-dimethyl-$\Delta^{1(9)}$-octal-2-one (XXIb). This compound was obtained from 10-methanesulphonyloxymethyl-7,7-dimethyl-Δ^{8}-octal-2-one-2-dioxolane (XXIIc) by treating it with sodium iodide in acetic acid.

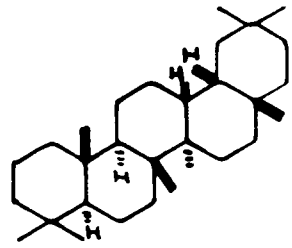
Reduction of either 10-(+)-camphor-10-sulphonyloxymethyl-7,7-dimethyl-Δ^{8}-octal-2-one-2-dioxolane (XXIIf) or 10-methanesulphonyloxymethyl-7,7-dimethyl-Δ^{8}-octal-2-one-2-dioxolane (XXIIe) with lithium aluminium hydride gave 10-hydroxymethyl-7,7-dimethyl-Δ^{8}-octal-2-one-2-dioxolane (XXIIb).

REFERENCES.

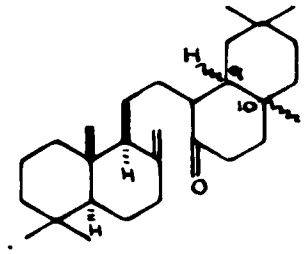
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2. Halsall and Thomas, J., 1956, 2431.
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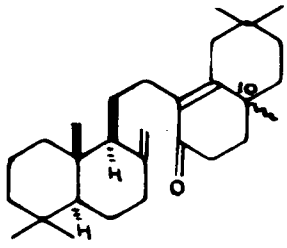
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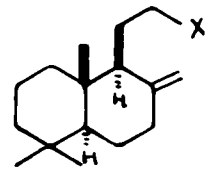
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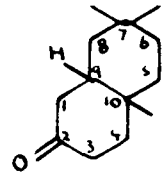
III a 10β Me; 9β H
b 10α Me; 9α H
c 10β Me; 9α H
d 10α Me; 9β H



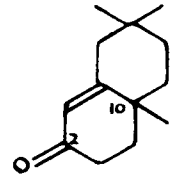
IV a 10β Me
b 10α Me



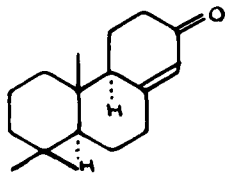
V a X = Br
b X = OH



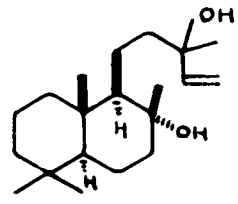
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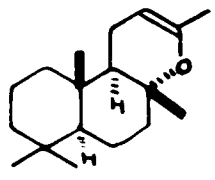
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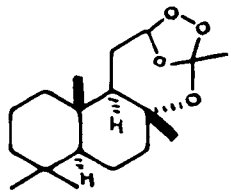
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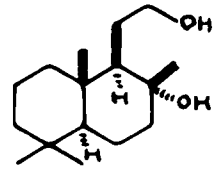
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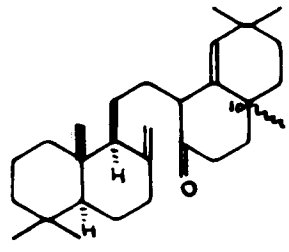
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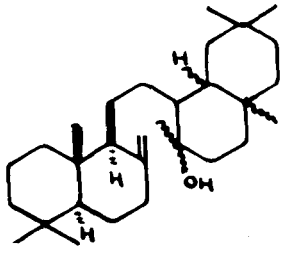
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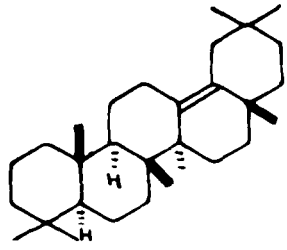
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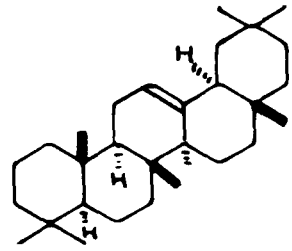
XIII a 10β Me
b 10α Me



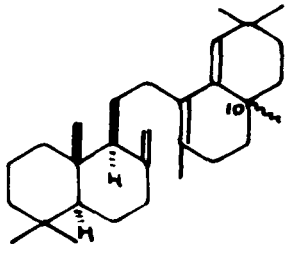
XIV a 10β Me; 9α H
b 10α Me; 9β H



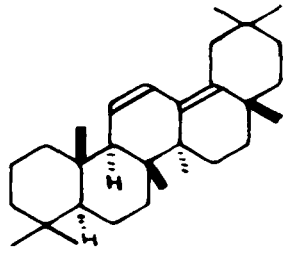
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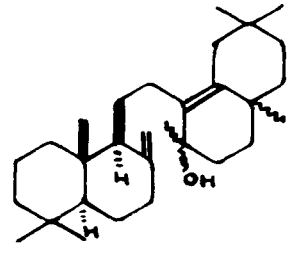
XVI



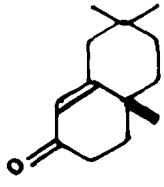
XVII a 10β Me
b 10α Me



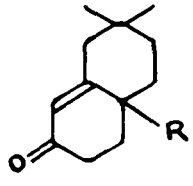
XVIII



XIX a 10β Me
b 10α Me

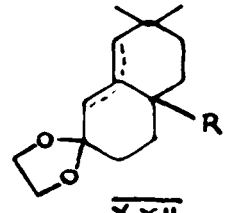


XX



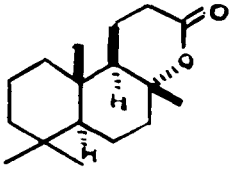
XXI

a R = COOEt
b R = CH_2I
c R = $CH_2 \cdot O \cdot SO_2$ · camphor.



XXII

a R = COOEt
b R = CH_2OH
c R = $CH_2 \cdot O \cdot SO_2Me$
d R = CH_2SH
e R = CH_2I
f R = $CH_2 \cdot O \cdot SO_2$ · camphor.



XXIII

The terpenes are a group of natural products which may be related structurally in terms of the 'biogenetic isoprene rule.'[1] This states that isoprene units (C_5) may combine to give aliphatic substances such as geraniol (A1), farnesol (A2), geranyl-geraniol (A3) and squalene (A4) and that these, after cyclisation and, in certain cases, rearrangement, are probable precursors of mono-(C_{10}), sesqui-(C_{15}), di-(C_{20}) and tri-(C_{30})-terpenes respectively. Comprehensive reviews of the chemistry of these compounds have been given by Simonsen *et al.*[2] and by de Mayo[3] and only triterpenes will be considered in this survey.

Triterpenes occur either as esters, glycosides or in the free state. They are subdivided into two classes, squalenoid and non-squalenoid. Only a few triterpenes have the same carbon skeleton as squalene[4] and they include ambrein (A5)[5], isolated from ambergris, α-onocerin (A6)[6], from restharrow, the dammarane diols (A7)[7] and hydroxyhopanone (A8)[8,9], from dammar resin.

The non-squalenoid triterpenes are members of either a tetracyclic or a pentacyclic group. The tetracyclic compounds have the same ring system as the steroids and three types are defined by the varying stereochemistry at C-13, C-14, C-17, and C-20 (see A9). Lanosterol (A9)[10], cucurbitol (A10)[11] and tirucallol (A11)[12] are representatives of each

type. It should be noted that classified among the tetracyclic triterpenes are a number of compounds containing thirty-one carbon atoms; these have the same relationship to lanosterol as ergostane has to the cholestane series in steroid chemistry. Examples are eburicoic acid (A12),[13] polyporenic acid A (A13),[14] dehydroeburicoic acid (A14),[15] tumulosic acid (A15) and polyporenic acid C (A16).

The pentacyclic triterpenes are distributed widely throughout the vegetable kingdom and are the largest group within the whole class of triterpenes.[25] Six hydrocarbons provide the skeletons from which all pentacyclic, non-squalenoid triterpenes can be derived. They are oleanane (A17), ursane (A18), lupane (A19), taraxastane (A20), taraxerane (A21) and friedelane (A22).

The elucidation of the structures and in particular the stereochemistry of the terpenes has depended to a large extent on modern physical techniques, such as X-ray analysis,[16] ultra-violet[17] and infra-red[18] spectroscopy, nuclear magnetic resonance[19] and mass spectrometry.[20] The methods of molecular rotation differences[21] and optical rotatory dispersion[22] have resolved many problems of absolute and relative stereochemistry. Chemical and physical behaviour may be interpreted in terms of molecular geometry.[23] The use of specific reagents in the steroid field has been

reviewed by Loewenthal[24] and the value of these reagents may be extended to terpene chemistry. The relationships between the various classes of triterpenes have been indicated by many elegant transformations, which are of considerable importance because degradative work is often limited by the lack of reactive centres. The application of these techniques can be demonstrated by a brief description of the determination of the structures of three triterpenes, β-amyrin (A23), α-amyrin (A24) and lanosterol (A9).

The gross carbon structure of β-amyrin was assigned by Haworth[26] from a consideration of the products of oxidation and dehydrogenation.[27,28,29,30] The mechanism for the contraction of ring A to give compounds of the type (A25),[31] when β-amyrin and related triterpenes are treated with phosphorus pentachloride, requires a C-3 equatorial hydroxyl group. The presence of a C-3 hydroxyl group, a C-10 methyl group and a C-5 hydrogen atom are indicated by the properties of a series of acids obtained by oxidative fission[32] of ring A of the ketone (A26), derived from hederagenin (A27).[33,34]

A number of important conclusions have resulted from a consideration of the products obtained by attack on the double bond in β-amyrin derivatives. Its position,

and the β-orientation[35,36,37] of the C-17 carboxyl group in oleanolic acid (A28),[38] are suggested by the facile formation of a δ-lactone (A29).[39] Pyrolysis of the ester (A30) yielded bicyclic products corresponding to rings A-B and rings D-E. In particular the keto-ester (A31) was isolated and correlated[40] with the acid (A32), obtained from ambrein (A5) and the diterpene manöol (A33). Both manöol and abietic acid (A34) can be converted[41] to the hydrocarbon (A35). This sequence of correlations establishes that the fusion of rings A-B in β-amyrin is the same as that of the diterpenes, which has been proved trans by a consideration of the dissociation constants of the acid (A36), obtained by oxidation[42,43] of abietic acid. A similar correlation with the 5α-steroids[44] has been provided. The absolute configuration of the steroids, and the di- and tri-terpenes, has been established by the methods of asymmetric synthesis[45] and molecular rotation differences.[46] There is a large positive molecular rotation difference (Δ value) between the A-nor-triterpene (A37) and the parent alcohol (A38) which is analogous to the Δ value for the corresponding steroid compounds (A39) and (A40), and opposite to that of the enantiomeric types (A41) and (A42).

Molecular rotation data have also confirmed the stereochemical relationship of β-amyrin to the tetracyclic

triterpenes, and the authenticity of these assignments has been demonstrated by the conversion[47] of cholesterol (A43) into lanosterol.

The stereochemistry of the B-C, C-D and D-E ring junctions has been elucidated as follows. 3-Acetoxy-11-keto-olean-12-ene (A44) is unstable to both acid and alkali, and the isomerisation product can be converted to the same diene (A45), obtainable directly from β-amyrin by a method which could not cause isomerisation at C-9. Hence the D-E ring junction must be fused in the unstable conformation and the B-C ring junction in the stable conformation.

The partial synthesis[48] of morolic acid (A46)[49] from siaresinolic acid (A47)[50] has been achieved *via* an intermediate ketone (A48), reduction of which under alkaline conditions must have resulted in the C-D ring fusion being in the most stable conformation. The C-17-nor-diene (A49) was obtained from morolic acid by a scheme which could not cause isomerisation of the C-13 hydrogen atom. The same diene is formed from siaresinolic acid, the C-13 hydrogen atom resulting from an intramolecular transition state which necessitates its β-configuration.

From this evidence two structures, (A50) and (A51), are possible for the methyl ester of siaresinolic acid, and it can be shown, from a consideration of the

stabilities of fused six-membered ring systems in terms of non-bonded interactions, as discussed by Johnson,[51] that the C-D ring fusion in (A50) must be more stable than that in (A51).

The only centres still to be discussed are at C-8 and C-9. The C-9 hydrogen atom must be axial and α, because of the facile dehydration of the C-11 axial alcohol[52] obtained from the hindered ketone (A52). Two possible structures (A53) and (A54) exist for β-amyrin; a decision in favour of the former (A53) has been made using the method of molecular rotation differences, and considering rings D,C and B of the triterpene to be enantiomeric in type to rings A,B and C of the A-B trans steroids.

X-ray studies of methyl oleanolate iodoacetate[53] have since confirmed the relative stereochemistry of the oleanane group of triterpenes.

The gross structure of α-amyrin (A24) has been determined largely by the efforts of Ruzicka, Jeger and co-workers,[54] and the complete stereochemistry elucidated[55] by a consideration of physical and chemical data. The assignment of configurations at all centres except C-13, C-19 and C-20 (see A24) has been confirmed by the conversion[56] of urs-11,13(18)- dienyl acetate (A56) into

olean-11,13(18)-dienyl acetate (A57).[57] The stability of the cis ring D-E junction and the inertness of the double bond are explained[58] in terms of 19β- and 20α-equatorial[59] methyl groups.[60,61] Alternative formulations are ruled out by this interpretation,[62] the complete proof of which has been attained by the partial synthesis of α-amyrin from glycyrrhetic acid (A58), a β-amyrin derivative.

A number of conversions of the lupane type of structure into oleanane derivatives has established the stereochemistry of rings C, D and E in lupenone (A59). Thus lupenone has been converted[63] into δ-amyrenone (A60), betulin (A61) into moradiol (A62)[64] and lupeol into a hydrochloride (A63).[65] Three products were obtained from this hydrochloride under suitable conditions, namely: germanicol (A64), 18-iso-β-amyranonol (A65) and lupeol.

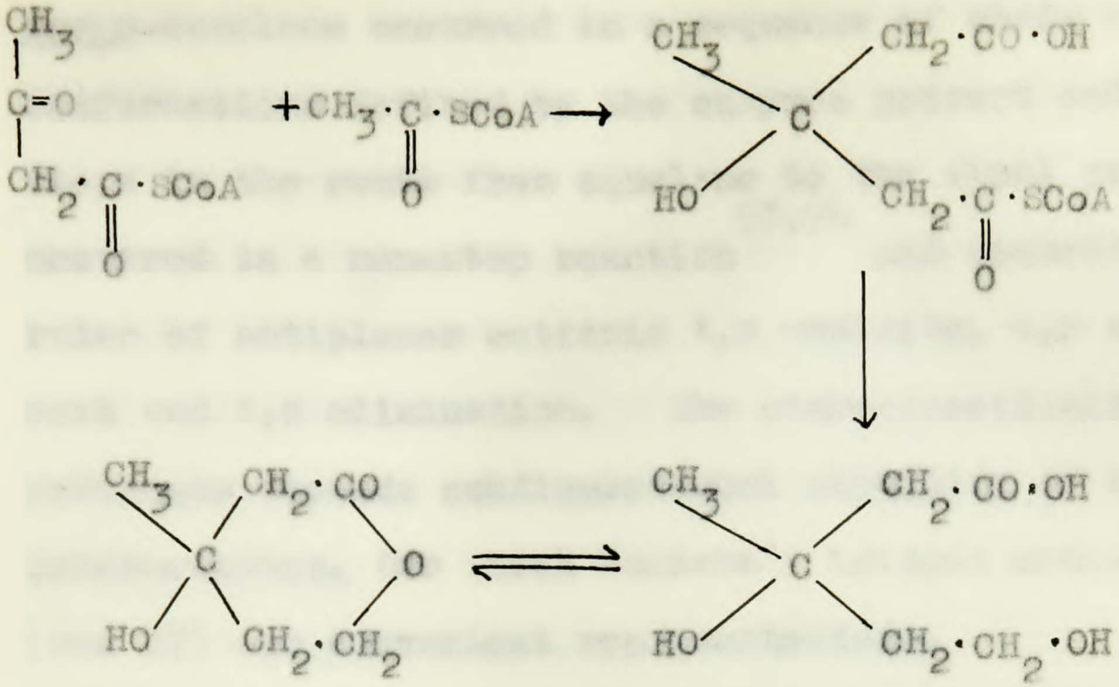
The determination of the structure of lanosterol (A9) has been carried out by McGhie,[66] Barton[67,68,69,70] and Ruzicka[71,72] and has been confirmed by X-ray analysis[73] of lanostenyl iodoacetate. The location of the side-chain at C-17 conflicts with the classical rule that terpenes are formed by the combination of isoprene units in a regular pattern. The biogenetic rule (page 1) embraces all known triterpenes and has been used to predict structural types,[74] later isolated from natural sources.

Three other pentacyclic triterpenes have structures which are closely related to the oleanane type and are of considerable biogenetic interest. They are taraxerol (A66), the partial synthesis[75] of which from the β-amyrin derivative (A67) has been recorded, glutinone (A68)[76,77] and friedelin (A69),[78] derivatives of both of which give olean-13(18)-ene on treatment with strong acid.[79,80] In the α-amyrin series bauerenol (A70)[81] is analogous to taraxerol. These structures represent the limiting types possible in the biogenetic scheme of Ruzicka.[82]

The Biogenesis of Triterpenes.

A growth promoting factor[83] for Lactobacillus acidophilus is the lactone (B1) derived from mevalonic acid; isotopic labelling at C-2 shows that it is incorporated[84] into cholesterol. Loss of carbon dioxide[85,86] generates a five-carbon 'isoprenoid' unit, which by self-condensation forms squalene.[142] Probable intermediates in the conversion of mevalonic acid to squalene are isopentenyl pyrophosphate (B2), geranyl pyrophosphate and farnesyl pyrophosphate, and Cornforth[87] has recently proposed a detailed mechanism for this conversion.

The biosynthesis of mevalonic acid from acetic acid follows the path:



Bloch has provided evidence[88] that squalene is a precursor of cholesterol in biological systems. Two schemes (B3)[89] and (B4)[90] are possible by which all-trans-squalene may cyclise to give cholesterol. Biosynthesis using labelled acetate has distinguished in favour of the latter (B4), which is based on the structure of lanosterol.

The demonstration by Arigoni[91] that mevalonic acid is a biogenetic precursor of soyasapogenol-A(B5) has provided the first direct experimental evidence on the biogenesis of pentacyclic triterpenes.

The importance[92] of lanosterol in steroid biogenesis led Ruzicka[1] to formulate analogous schemes for all triterpenes. It was assumed that cyclisation of all-

trans-squalene occurred in a sequence of chair and boat conformations defined by the enzymes present and that all steps in the route from squalene to the final product occurred in a non-stop reaction[93,94] and according to the rules of antiplanar cationic 1,2 addition, 1,2 rearrangement and 1,2 elimination. The stereospecificity of these processes demands configurational stability of the cationic intermediates, for which Ruzicka's bridged cation structures (see B7) are convenient representations.

The biogenesis of lanosterol requires the chair-boat-chair-boat conformation (B6) of all-trans-squalene. Cyclisation occurs under aerobic conditions[95,96] and is initiated by attack of a species such as (OH^+) on one of the terminal double bonds to give the cation (B7) from which lanosterol may be derived.

Cyclisation in the chair-chair-chair-boat conformation (B8) gives rise to the cations (B9) and (B10) from which euphol and tirucallol may be formed by rearrangement, or from which the dammaren-diols are derived by combination with (OH^-). (see Scheme1).

The order of the carbon atoms in the original squalene skeleton has been reversed during the rearrangement (B9→B10). Cyclisation of the side-chain of the cation (B10) in the boat form gives the pre-lupeol cation (B11)

from which the lupane, oleanane, ursane, taraxerane and friedelane skeletons may be derived. (see Scheme 1).

Cyclisation of squalene in the chair-chair-chair-chair-boat conformation gives rise to hydroxy-hopanone (A71)[97]; and two other triterpenes, α-onocerin (A72) and ambrein (A5) are formed by attack with (OH^+) and (H^+) respectively from both ends of the molecule simultaneously.

This biogenetic scheme has provided a rationalisation for the many structural types found among the triterpenes and for the mechanisms implicit in the transformations between these types. It is of note that there is evidence[98] that the friedelane skeleton, representing a structure in which the migration of methyl groups and hydrogen atoms has reached the limit possible in the pentacyclic system, is not the most thermodynamically stable structure.

Approaches to the Total Synthesis of Triterpenes.

The partial synthesis[99] of squalene hydrochlorides from farnesol, by Karrer and Helfenstein, has confirmed the gross structure of squalene (C1). Regeneration of a hydrocarbon from this synthetic product gave a complex mixture[100] of prototropic and geometrical isomers

of squalene. X-ray examination of the thio-urea clathrate has shown that natural squalene is the all-*trans* isomer,[101] and the clathrate has been used to isolate this isomer in a recent synthesis, by Dicker and Whiting,[102] from geranyl acetone and the diphosphorane of 1:4-dibromobutane. In an independent attempt by Trippett[103] it was not realised that cis-trans isomerism[102] about the newly formed double bonds could arise in a reaction of this type. Recently stereoselective syntheses have been reported by Isler and co-workers,[104] using a modification of Karrer's method, and by Cornforth, Cornforth and Mathew[105] by a route in which 3:5-dichloropentan-2-one (C2), *via* two molecules of homogeranyl chloride, supplied twenty five of the thirty carbon atoms.

The conversion of cholesterol into lanosterol and the other wool-fat triterpenes has already been referred to, and since the total synthesis of cholesterol has been reported,[106,107] this conversion constitutes the first total synthesis of a tetracyclic triterpene.

Attempts have been made to synthesise both the symmetrical pentacyclosqualene-(onocerane) and the oleanane-type skeletons.[108] Acid catalysed isomerisation of squalene is reported to give tetracyclosqualene (C3). Barton and Overton[110] have shown, however, that an analogous

compound, α-onoceradienedione (C4) gives, under mild acid conditions, β-onoceradienedione (C5), and under strong acid conditions, γ-onocerenedione (C6), from which pentacyclosqualene may be obtained by Wolff-Kishner reduction.

The routes to the pentacyclic system, so far investigated, all depend on the fusion of two bicyclic units representing rings A-B and rings D-E of the final triterpene. These routes have originated from a proposal, in 1956, by Halsall and Thomas,[134] who envisaged the attack of a bicyclic moiety (C7), with concomitant nucleophilic displacement of X, on a system (C8), activated at C*. The route should not involve any major stereochemical difficulties, for the presence of the carbonyl group α to C* would ensure that the entering group takes up the most stable configuration. The tetracyclic-ketone (C9) obtained should be a mixture of two racemates. The conversion of this ketone to the alcohol (C10) would introduce a new asymmetric centre, which, however, would be eliminated during the cyclisation which closes ring C. This cyclisation to give the required trans-anti-trans-anti-arrangement of rings A,B,C and D is the most difficult step in the whole route. Its feasibility has been demonstrated in the synthesis of olean-11,13(18)-diene (C11).[111]

A modification of this method is described in this thesis and involves the fusion of two bicyclic systems (C12) and (C13) to give a tetracyclic-ketone (C14), which has been prepared independently by Corey, Hess and Proskow.[112] An unsuccessful attempt was also made to prepare the tetracyclic-cis-ketone (C14a) from the cis-decalone (C15).

Three other methods have been used to join the two bicyclic moieties. They are:- (1.) Kolbé electrolytic decarboxylation (Corey and Sauers), (2.) Diels-Alder type condensation (Eschenmoser and co-workers), (3.) Fusion of two carbonyl units with acetylene (Sondheimer and Elad). The first two methods are particularly applicable to the synthesis of the symmetrical onocerane skeleton, whilst the third is equally well suitable for the preparation of either the onocerane or oleanane skeletons. Two other possible routes have been proposed by the Nottingham school. King Ritchie and Timmons[113] envisage an aldol condensation between the cis-decalone (C15) and an aldehyde (C16). Ritchie[114] has also suggested that the decalone (C17) may be coupled with the Grignard reagent derived from the rings D-E intermediate (C7) of the Halsall approach.

Kolbé electrolytic coupling[115] of two molecules of the (-)-lactone (C18) yielded the tetracyclic-diol (C19),

from which the α- and β- onocerenes were derived. The (-)-lactone (C18) was prepared by acid-catalysed isomerisation of the (+)-lactone (C20),[116] obtained by oxidation[117] of sclareol (C21). The C-8 and C-8' epimeric tetracyclic-diol (C22) has also been prepared from the (+)-lactone (C20) or the acetoxy-acid (C23). The racemic modification of the lactone has been obtained by acid-catalysed cyclisation[118] of α- or β- monocyclohomofarnesic acid (C24).

A stereospecific synthesis of the tetracyclic-diketone (C25) has been achieved,[119] by Eschenmoser and co-workers, by reduction of the Diels-Alder adduct (C26) from two molecules of the α-methylene-ketone (C27). This α-methylene-ketone was prepared from the product of cyclisation of farnesic acid. An attempt has also been made to prepare a tetracyclic precursor of the oleanane series by cross-dimerisation[120] of dissimilar α-methylene-ketones (C27) and (C28). The structure of the product has not been confirmed but can probably be represented as (C29).

Fusion[121] of two molecules of the trans-decalone (C30) with acetylene has given a mixture of meso-(C31) and racemic-(C32) tetracyclic-diols. The racemic modification was converted into racemic dinoronocerane (C33). Preparation of the acetylenic-hydroxy-benzoate (C34),[122] from the decalone (C35), has shown that the method is applicable to

decalones containing a C-7 methyl group. Sondheimer and Elad propose to couple this acetylenic derivative with a decalone (C36), suitable as a potential rings D-E of the final triterpene.[123] Investigation of methods of preparation of this decalone has involved an application of the Brown hydration reaction[109] to give the cis-and trans-decalones (C37), from the octalin (C38).

Considerable progress has been made towards the preparation of bicyclic intermediates. The synthesis of 4,4,9-trimethyl-trans-decal-8-one (C30) has been reported by Sondheimer[124] and by Halsall.[125] The main difference between the routes lies in the method of differentiating between the carbonyl groups in the intermediate (C39).[126] Sondheimer preferentially oxidised the allylic alcoholic grouping in the derived diol (C40), whilst the English workers preferred the more direct method of selectively reducing the saturated ketonic grouping in (C39) with sodium borohydride. 4,4,9-trimethyl-trans-decal-8-one is of importance as a precursor of diterpenes of the manool group.

Sondheimer,[122,124] using a modification of this route, has prepared (±)-1,1,6α,10β-tetramethyl-trans-decal-2β-ol-5-one (C35) from the tetrahydropyranyl ether of 8-hydroxy-4,4,9-trimethyl-decal-3-one (C41). This product

is the racemate of a degradation product of α-amyrin[127] and ursolic acid.[128] Kalvoda and Loeffel,[129] the Halsall group[130] and the Nottingham school[131,132] have also prepared this intermediate.

An elegant synthesis of the rings A-B intermediate (C42) has been described by Halsall, Rodewald and Willis.[133] Photo-oxidation of the diene (C43) formed an epi-dioxide (C44) from which the required product could readily be obtained *via* the αβ-unsaturated-ketone (C45).

The syntheses of the octalone (C13) and *cis*- and *trans*-decalones (C15) have been achieved by Halsall and Thomas[134] and are of major importance in the work described in this thesis (see p.61). Recently the *trans*-decalin (C48)[135] has been prepared.

The most significant advances in the field of synthetic triterpene chemistry have occurred in the past twelve months. Stork, Davies and Meisels[136] have reported the total synthesis of α-onocerin from two molecules of the (+)-acetoxy-keto-acid (C49) by Kolbé electrolytic coupling to give the dinoronocerin-ketone (C25). The additional methyl groups at C-8 and C-8' were introduced *via* the Grignard adduct with ethoxyacetylene magnesium bromide. The product, α-onocerin (C51), has been converted[137] to ∫-onocerin (C52), and this in turn to

hopenone-I (C53).[138] This represents, therefore, the first total synthesis of a naturally occurring pentacyclic triterpene.

The acetoxy-keto-acid (C49) is an intermediate of importance for the synthesis of triterpenes of the oleanane class.[139,140,141] It was obtained from the tricyclic-ketone (C54).

The synthesis[112] of olean-11,13(18)-diene (C11) from the (±)-enol-lactone (C56) and the Grignard derivative of the (+)-bromide (C57), obtained from either (+)-ambreinolide (C58) or sclareol (C21), has been reported by Corey and co-workers. Treatment of the intermediate $\alpha\beta$-unsaturated-ketone (C14 - see p. 14) with lithium methyl, followed by cyclisation, gave olean-11,13(18)-diene in 2% yield. An alternative method of preparing this diene is described in this thesis. Leggate[141] has synthesised a tetracyclic-ketone (C59), containing a carbethoxyl group at the rings D-E bridgehead, and certain aspects of the synthesis, which are related to the work described in this thesis, will be discussed.

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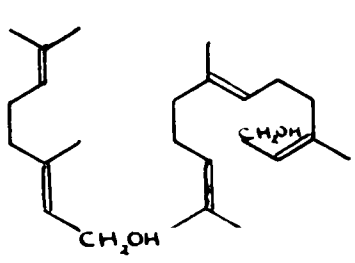
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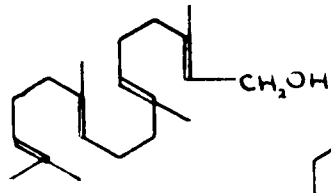
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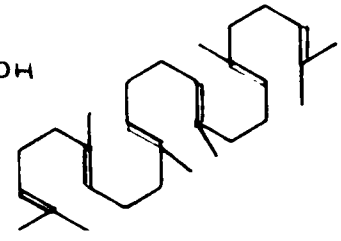
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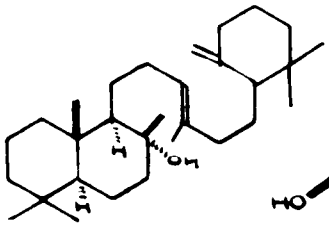
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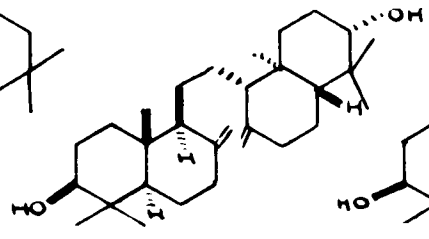
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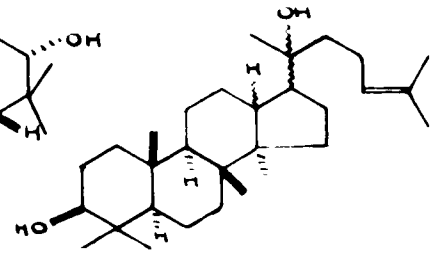
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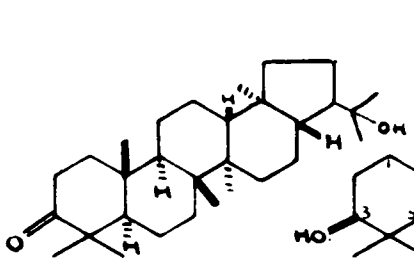
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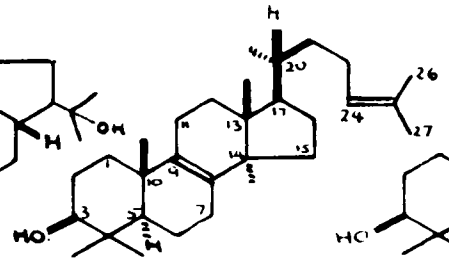
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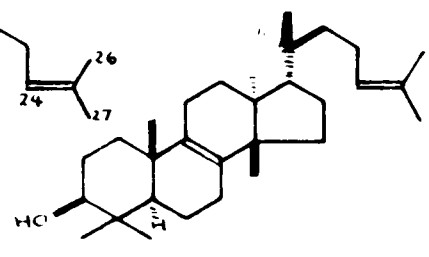
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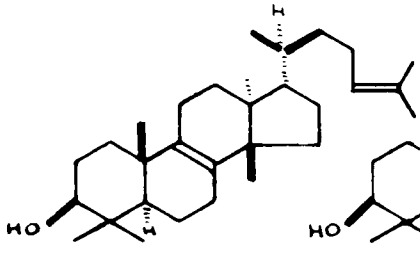
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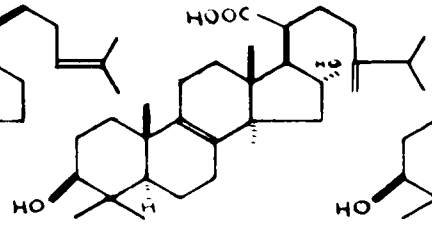
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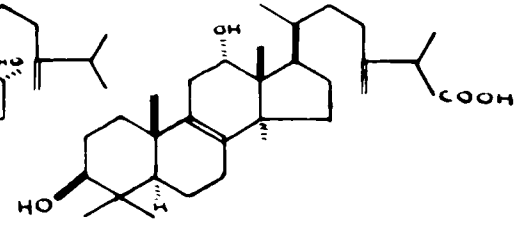
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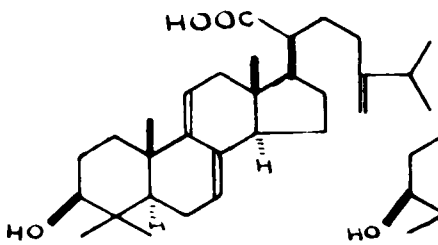
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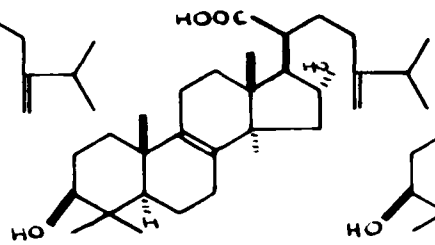
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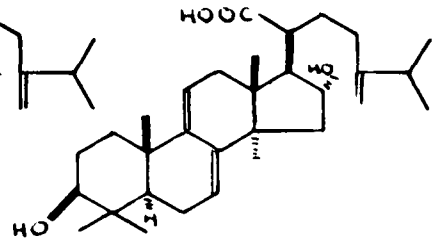
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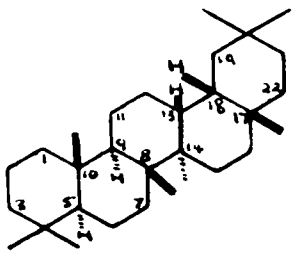
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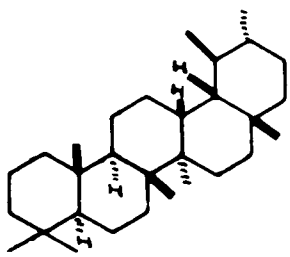
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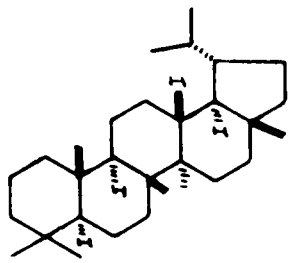
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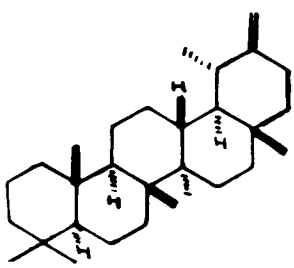
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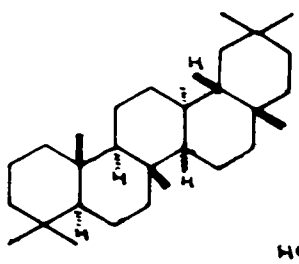
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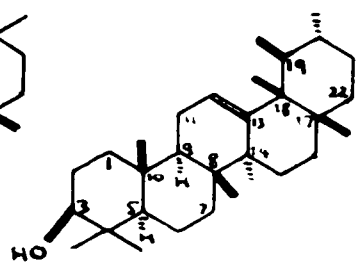
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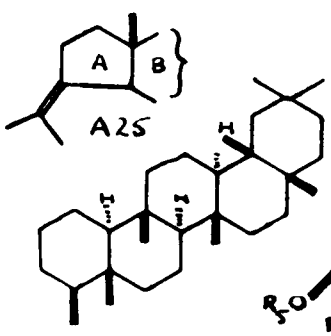
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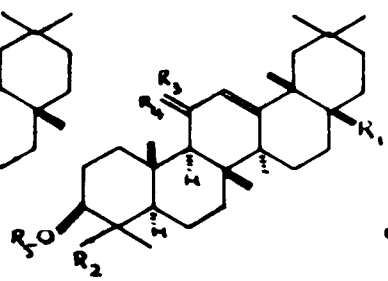


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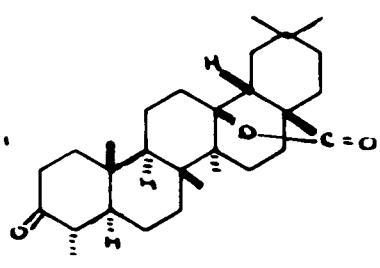


A25

A22



A23 $R_1=R_2=Me$; $R_3=R_4=R_5=H$.

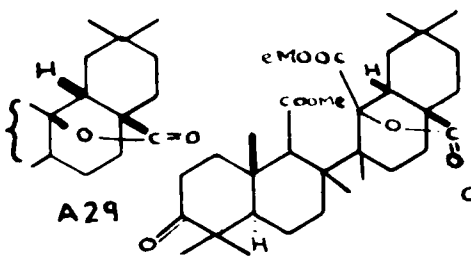


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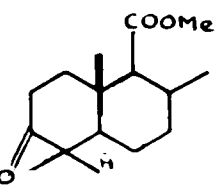
A27 R_1=COOH; $R_2=CH_2OH$;
$R_3=R_4=R_5=H$.

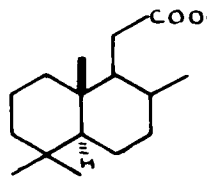
A28 R_1=COOH; R_2=Me;
$R_3=R_4=R_5=H$.

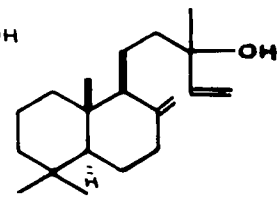
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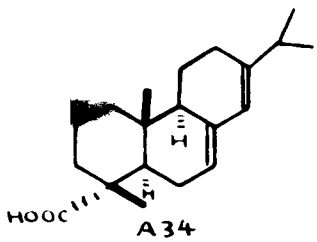

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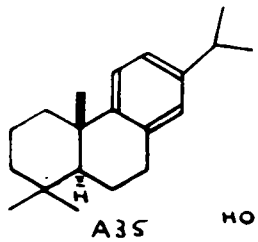
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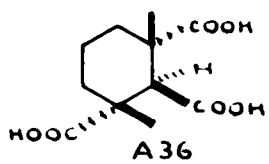

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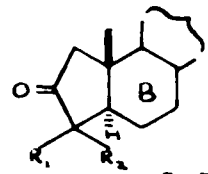

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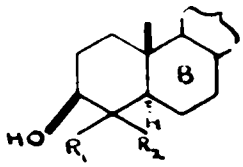

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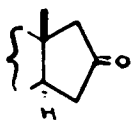

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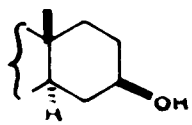

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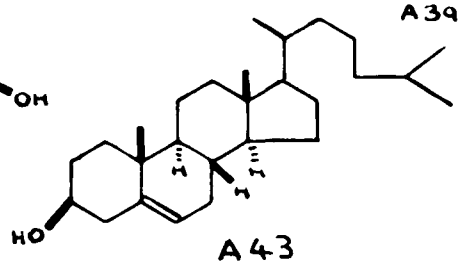

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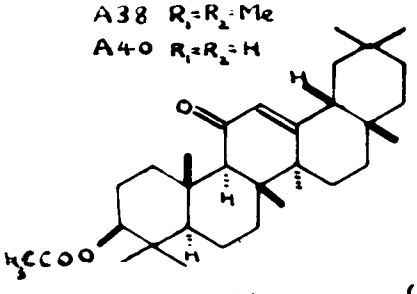

A37 $R_1=R_2=Me$
A39 $R_1=R_2=H$

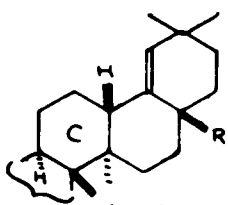

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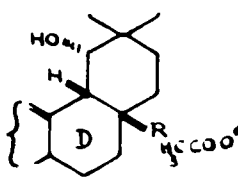

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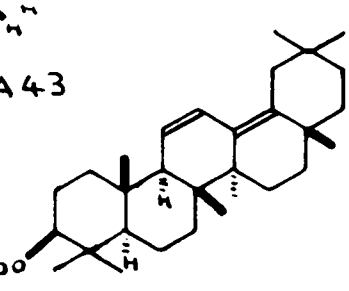

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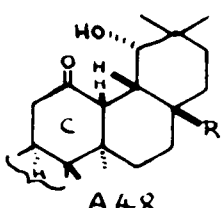

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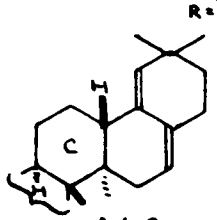

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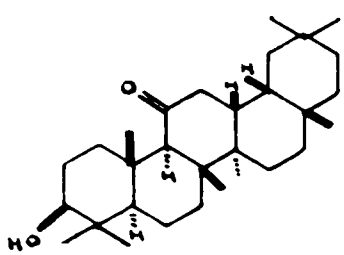

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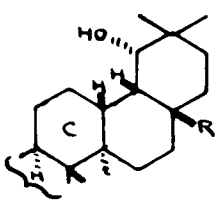

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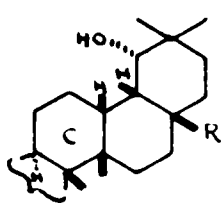

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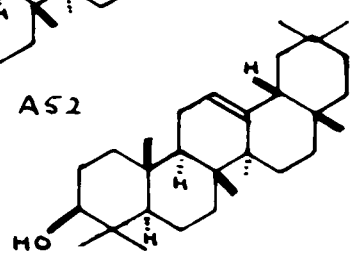

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A49

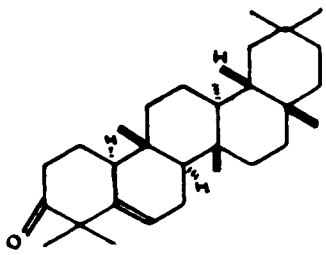

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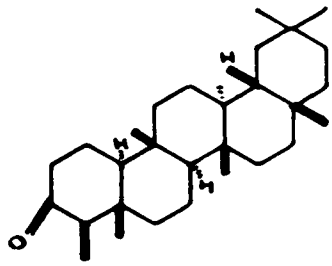

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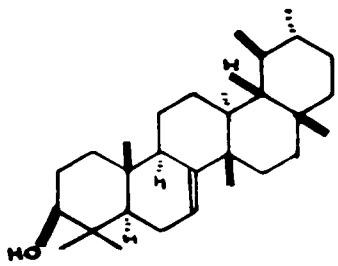
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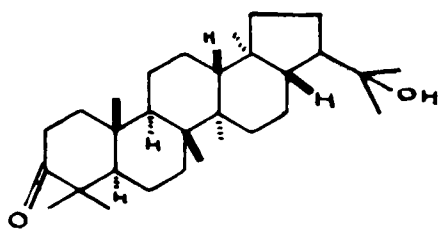
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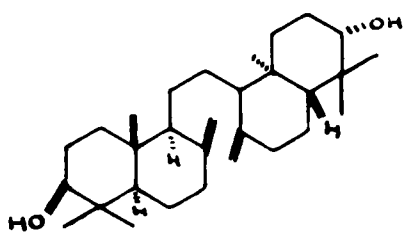
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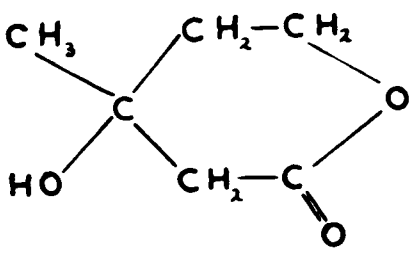
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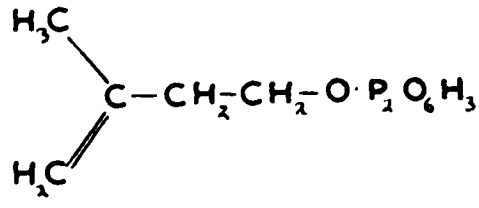
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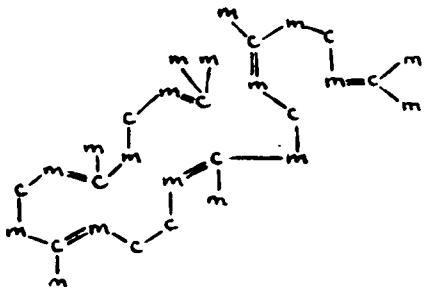
A72



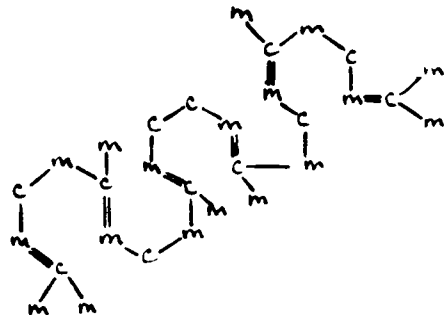
B1



B2

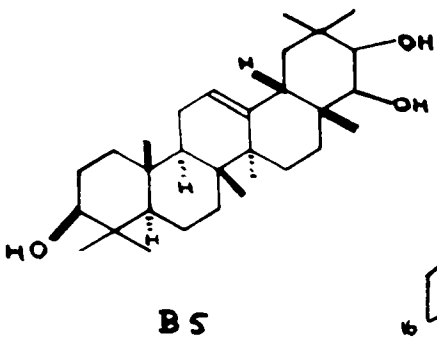


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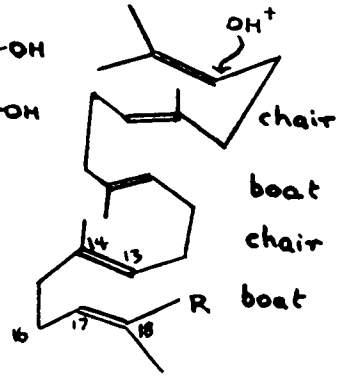


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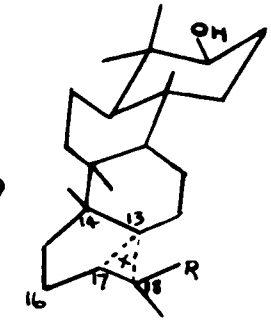
('m' from CH_3 ; 'c' from COOH of acetic acid)



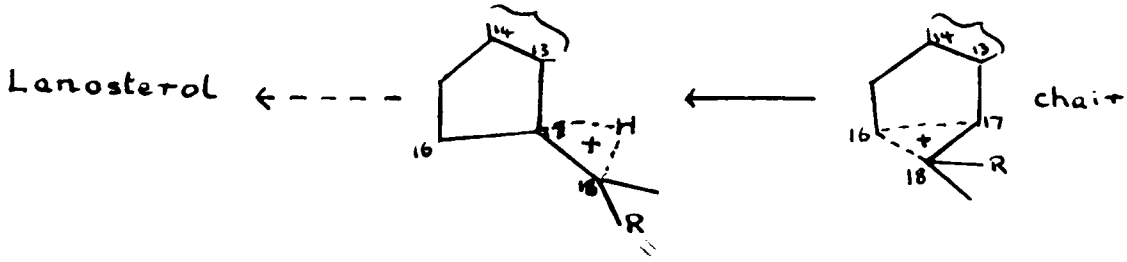
B5



B6

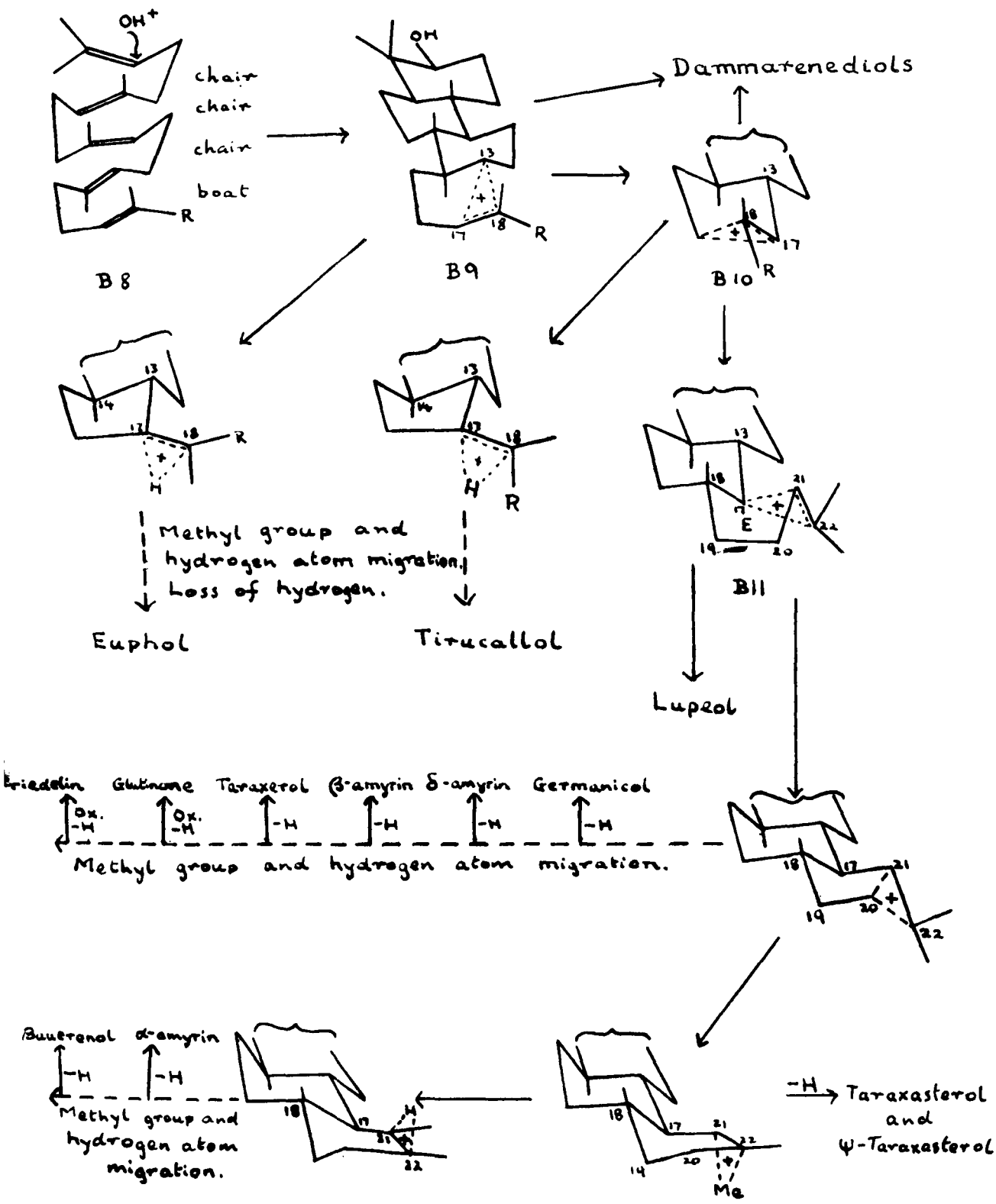


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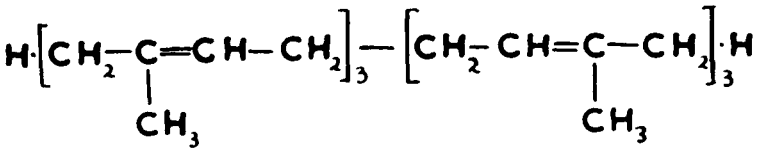


B8-B11

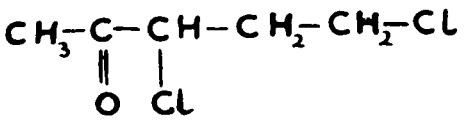
SCHEME I.


chair
chair
chair
boat
B 8
B 9
B 10
Dammarenediols
Methyl group and hydrogen atom migration. Loss of hydrogen.
Euphol
Tirucallol
B 11
Lupeol
Friedelin
Glutinone
Taraxerol
β-amyrin
δ-amyrin
Germanicol
Ox. -H
-H
Methyl group and hydrogen atom migration.
Bauerenol
α-amyrin
Methyl group and hydrogen atom migration.
-H
Taraxasterol and Ψ-Taraxasterol
Me

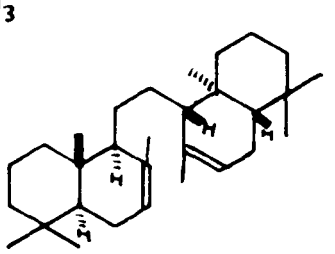
C1 – C14



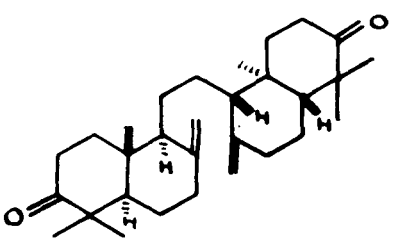
C1



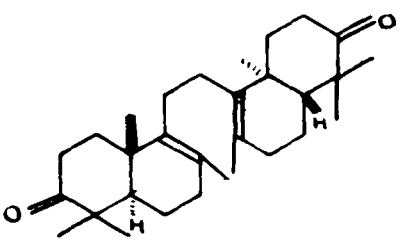
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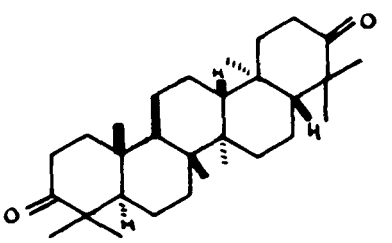
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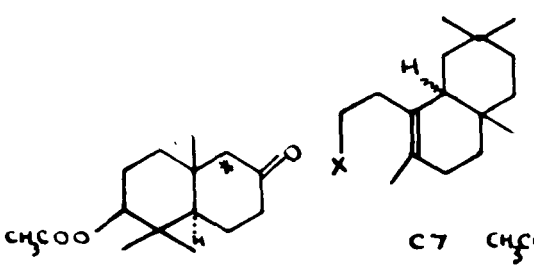
C4



C5

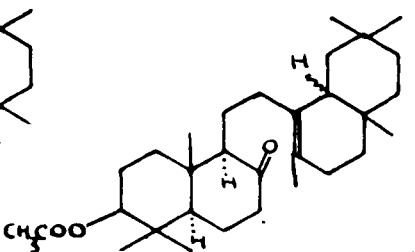


C6

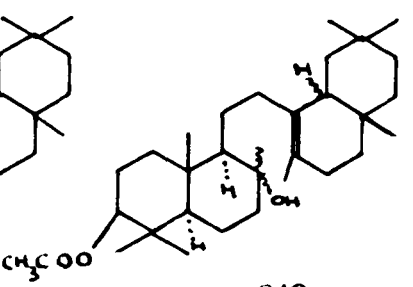


C8

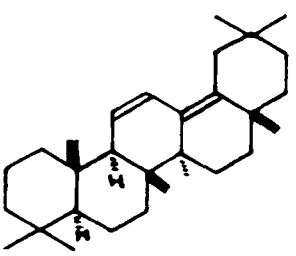
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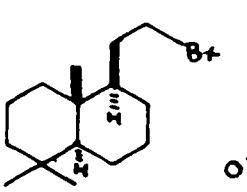
C9



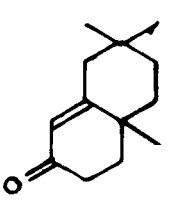
C10



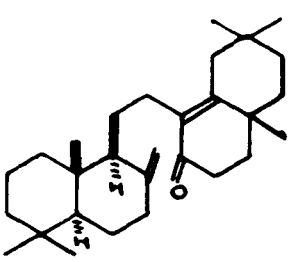
C11



C12

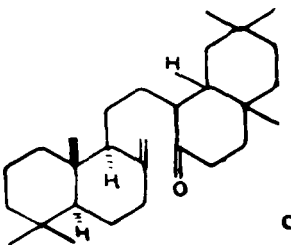


C13

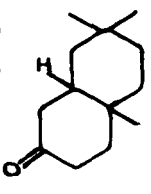


C14

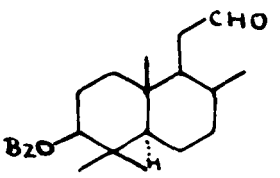
C14a-C34



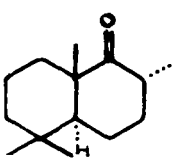
C14a



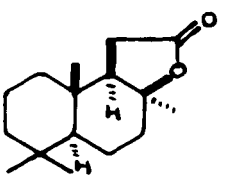
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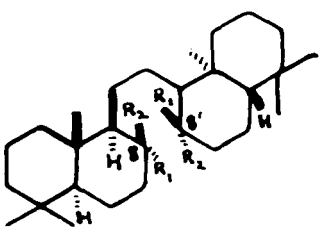
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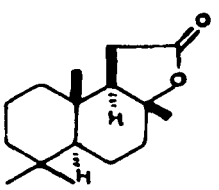
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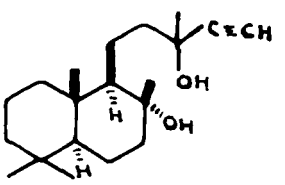
C18



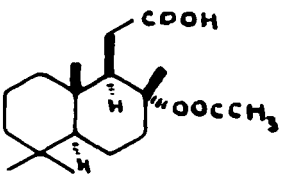
C19 R_2=OH; R_1=Me
C22 R_2=Me; R_1=OH



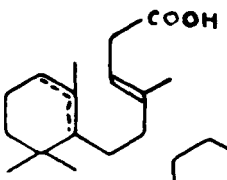
C20



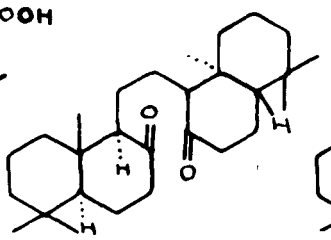
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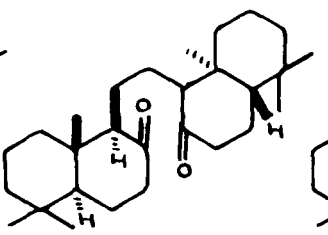
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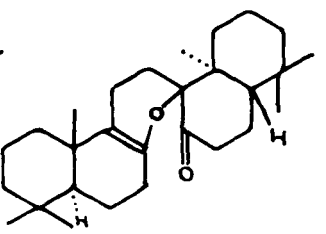
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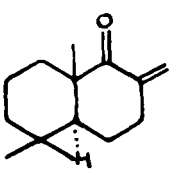
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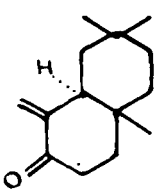
C25a



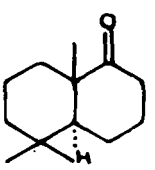
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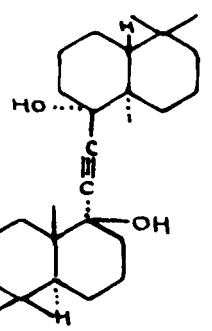
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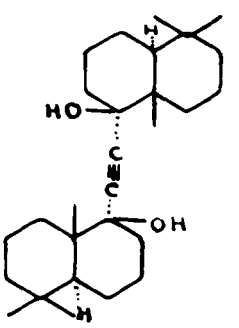
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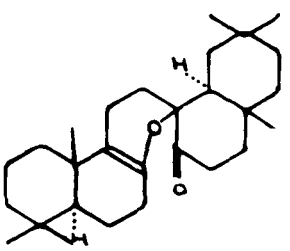
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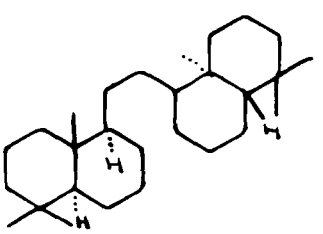
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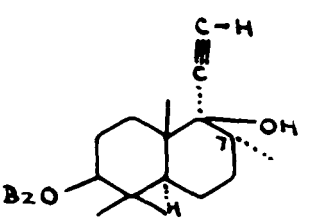
C32



C29

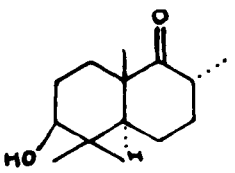


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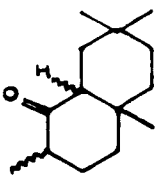


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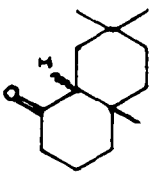
C35-C58



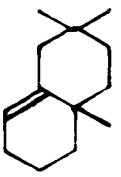
C35



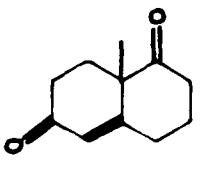
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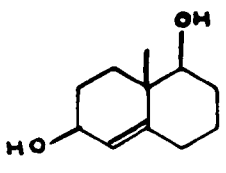
C37



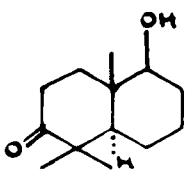
C38



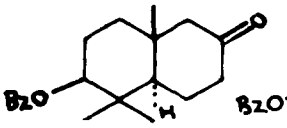
C39



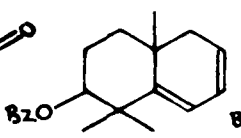
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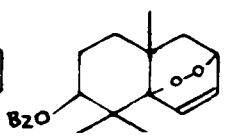
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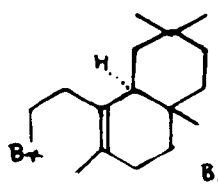
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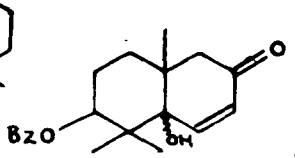
C43



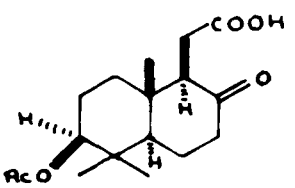
C44



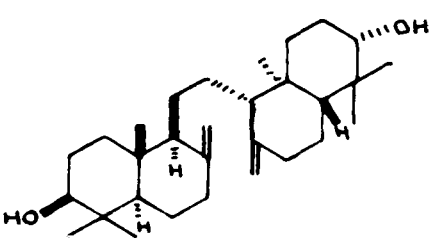
C48



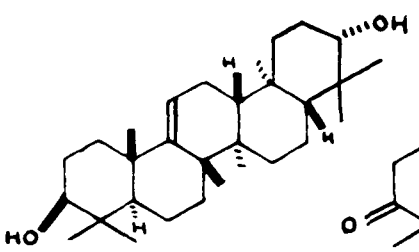
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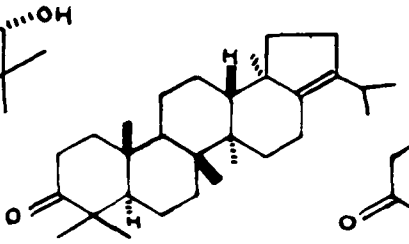
C49



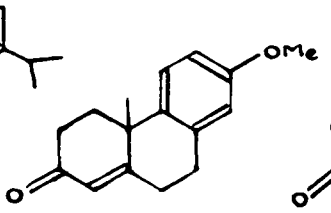
C51



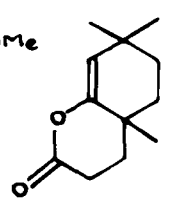
C52



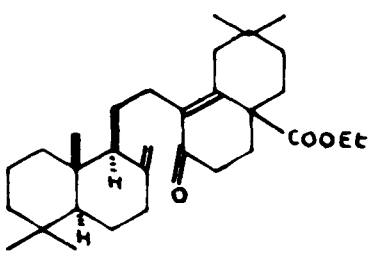
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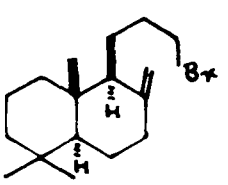
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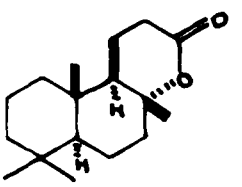
C56



C59



C57



C58

DISCUSSION. SECTION I.

The stimulus for the synthetic route already outlined (pp. 13 and 14) originated from a consideration of the preparative uses of $\Delta^{8(14)}$-podocarpen-7-one (D1), which has been described[1,2] by Barltrop and Rogers. Diterpenes have been synthesised[3,4,5] from this intermediate *via* the keto-acid (D2),[2,5] which is a product of ozonolysis. It was envisaged that this keto-acid could be the precursor of the methylene-bromide (D3), which would provide rings A and B of a triterpene structure. The isomeric bromide (D4) containing a tetra-substituted double bond would also be a useful intermediate, but the presence of the exocyclic methylene group in substances derived from (D3) was considered essential for their rapid infra-red spectroscopic identification. The synthesis of $\Delta^{8(14)}$-podocarpen-7-one is outlined in the steps (D5) $\longrightarrow$ (D7); (D5) was obtained by condensing sodio-*p*-methoxyphenylacetylene (D8) with 2,2,6-trimethylcyclohexanone (D9).

For a route of this nature to be practical, considerable quantities of 2,2,6-trimethylcyclohexanone were required. A commercial source was not available and published methods of preparation[6,7,8] involve tedious experimental procedures to give, in the main, unsatisfactory yields. A survey of existing methods revealed that the most suitable

was based on the direct methylation procedures of Cornubert and Haller,[9] and of Sabotka and Chanley,[6] but it would only be applicable if a technique was available to separate the required product efficiently from 2,2- and 2,6-dimethyl- and 2,2,6,6-tetramethylcyclohexanones. Sabotka et al. methylated 2-methylcyclohexanone to give a mixture of dimethylcyclohexanones, which was then further methylated. The experimental procedure was the same in both methylations, and involved the use of sodamide, and either methyl iodide or dimethyl sulphate, in benzene or ether. Pure 2,2,6-trimethylcyclohexanone was obtained in 25% overall yield by recrystallisation of semicarbazones. In the present work 2,2,6- trimethylcyclohexanone was isolated in 40% yield by fractional distillation through a column of 150 theoretical plates.[22] Attenburrow et al.[7] have fractionally distilled the crude product through a column of 80 theoretical plates but do not give experimental details.

A more rapid method of preparation, giving enhanced yields, has been developed. Both methylations were carried out in liquid ammonia using 1.2 moles of sodamide and 2.4 moles of methyl iodide. 2,2,6-Trimethylcyclohexanone was obtained in 66% overall yield by fractional distillation of the product. If 1.2 or 3.6 moles of methyl iodide were used in the methylations the yield diminished to 30%.

The low yield obtained in the presence of excess methyl iodide may be explained in terms of the equations:

$$\text{ketone} + NaNH_2 \rightleftharpoons \text{Na-enolate} + NH_3 \quad \ldots\ldots (1)$$

$$NaNH_2 + MeI \longrightarrow NaI + MeNH_2 \quad \ldots\ldots\ldots (2)$$

Sodamide is consumed more rapidly in the presence of excess methyl iodide, (as in (2)), and the equilibrium in (1) is forced to the left-hand side, thus reducing the proportion of enolate anion, which is the species necessary for methylation.

Loss of methyl iodide by evaporation is the probable cause of the poor yield resulting from the use of only 1.2 moles methyl iodide.

At this stage in the work sclareol (D10) became available in quantity. Since it is a much more suitable relay for the preparation of the (+)-methylene-bromide (D11), the work on podocarpenone was abandoned. Sclareol has been synthesised[4] from (+)-ambreinolide (D12), the racemic modification of which has been obtained[5] from $\Delta^{8(14)}$-podocarpen-7-one (D1). Alkylation of the (±)-octalone (D13) with this (+)-methylene-bromide will give rise to two epimers (D14a) and (D14b). It was hoped, also, to alkylate the <u>cis</u>-decalone (D13a) at C-1 but this was not achieved (see Section II).

The oxidation of sclareol with potassium permanganate affords either the enol-ether (D15) or the

hydroxy-ketone (D16). This oxidation was first studied by Ruzicka et al.[10] and has been investigated recently by Barltrop, Bigley and Rogers.[4] In the present work the main product was the enol-ether accompanied by a small amount of the hydroxy-ketone, which was dehydrated readily to the enol-ether by treatment with acid. It was expected that the acetoxy-aldehyde (D17), prepared from the enol-ether by fission of the double bond either with ozone or with osmium tetroxide and sodium metaperiodate, would give a high yield of the acetoxy-alcohol (D18) by reduction with sodium borohydride. This acetoxy-alcohol could be converted to the methylene-bromide (D11) via the glycol (D19) and a subsequent procedure described on p. 37. In addition it was hoped to prepare a hydroxy-bromide (D20), by the standard procedures for ascending homologous series, and to condense this with dihydro-β-ionone (D21) to give ambrein (A5), using the method described by Wittig and Schölkopf.[11]

Ozonolysis of the enol-ether at -36°, followed by decomposition of the ozonide with Raney nickel gave the acetoxy-aldehyde (D17) and the acetoxy-acid (D22). It has been reported[10,12] that the product contains 70% acetoxy-aldehyde after ozonolysis under these conditions. The earlier workers were unable to isolate the acetoxy-aldehyde without considerable losses in yield and in view of this no

attempt at isolation was made in the present work. The infra-red spectrum[13] of the acetoxy-aldehyde is characterised by the occurrence of only one carbonyl absorption band at 1721 $cm.^{-1}$ and also by a band at 2700 $cm.^{-1}$, due to the C - H stretching vibration of the aldehydic group. The presence of these bands in the infra-red spectrum of the product of ozonolysis was assumed to indicate the formation of the acetoxy-aldehyde.

The acetoxy-aldehyde was oxidised rapidly in the presence of air, and it was imperative to conduct all operations, after the ozonolysis, in an atmosphere of nitrogen. Despite this precaution some acid was always present in the product.

The mixture of acetoxy-aldehyde and acetoxy-acid was reduced with sodium borohydride, a reagent which selectively reduces aldehydes in the presence of esters and acids. The product, after removal of the acetoxy-acid, was separated by chromatography into four fractions. The required acetoxy-alcohol was isolated in only 5% yield. In addition a small amount of the lactone (D23) was obtained, presumably derived from the hydroxy-acid (D24), formed by hydrolysis of the acetoxy-acid (D22) under the mildly alkaline conditions of the experiment.

The reminder of the material was not crystalline. The infra-red spectrum of the major fraction (5% of total)

was similar to that of the acetoxy-alcohol but additional weak bands appeared in the 1200 - 1000 $cm.^{-1}$ region. A crystalline sample of the acetoxy-tosylate (D25) could not be prepared from this product so that no evidence was available to confirm the assumption that it consisted mainly of the acetoxy-alcohol.

The fourth fraction (3% of total) had a strong band at 1721 $cm.^{-1}$ in the infra-red but no hydroxyl absorption. This substance was not identified.

Authentic acetoxy-alcohol was recovered unchanged after chromatography on alumina, so that no losses could have occurred by decomposition of this compound during chromatography.

Reduction of the ozonide (D26) with Raney nickel[12] or Adam's catalyst, in an atmosphere of hydrogen, gave a neutral product identical with that obtained by the previous method, except that lactone was not present in the mixture. The proportion of acidic material was reduced to 20%. The proportion of acid present in the product obtained by the previous method was 30%, and the difference between these amounts may be caused by a 'Cannizzaro type' condensation of two molecules of acetoxy-aldehyde to give one molecule each of acetoxy-acid (D22) and acetoxy-alcohol (D18).

Stoll and Hinder[12] have reported that decomposition of the ozonide with Raney nickel gives nickel oxide, and that

hydrogen is absorbed only if Raney nickel is added in excess of the quantity required to react chemically with the ozonide. In the present work an excess of Raney nickel was used. However, only catalytic amounts of platinum oxide were necessary and in this case the uptake of hydrogen was approximately twice that in comparable reactions in which Raney nickel was used.

The uptake of hydrogen during catalytic reduction of the ozonide varied between 25% and 75% of the theoretical expected for complete conversion to the acetoxy-alcohol. The only apparent explanation for this inconsistency was that the proportion of ozonide varied in different experiments. It was observed qualitatively that the percentage uptake of hydrogen was greater in experiments in which the duration of ozonolysis was reduced.

It was not possible to prevent the formation of acid during the ozonolysis. The fact that oxygen was evolved spontaneously,[13] when the ozonide (D26) was treated with water, suggested an explanation not only for the formation of acid, but, also, for the formation of the uncharacterised material obtained by catalytic reduction of the ozonide, under conditions which were not expected to favour decomposition of the aldehyde. Thus it is possible that spontaneous decomposition of the ozonide may occur during ozonolysis to

give the acetoxy-aldehyde which may be unstable in the presence of excess ozone. Alternatively decomposition of the ozonide may give acid directly. In subsequent experiments the proportion of acid in the product obtained by Raney nickel decomposition of the ozonide was assumed to depend directly on the degree of decomposition occurring during ozonolysis.

Complete ozonolysis at -70° and 0° gave the same ratio of acidic to neutral material as in the ozonolysis carried out at -36°. In one experiment at -70° partial ozonolysis gave a product containing 90% unchanged enol-ether and there was no acid in the remaining 10%. Experiments in which ozonolysis was allowed to proceed for twice the time necessary to produce the blue colour, indicating an excess of ozone, yielded 60% acidic material. These facts may be interpreted by assuming that decomposition of the ozonide does occur spontaneously.

In no experiment could more than 7% of the authentic acetoxy-alcohol be isolated and an alternative route was investigated. Olefins are oxidised to aldehydes with osmium tetroxide and sodium metaperiodate, reagents first used by Lemieux and Rudloff.[14,15] The reaction proceeds *via* an intermediate glycol or acyloin, both of which are attacked by periodate. Oxidation of the enol-ether (D15) was expected to give the acetoxy-aldehyde as the major

product, but under the slightly alkaline conditions necessary, the lactone (D23) was the only compound isolated from the reaction. This result emphasised the ease both of oxidation of the aldehyde and also of hydrolysis of the tertiary acetate. The remainder of the material gave, after reduction with sodium borohydride, a neutral product identical with that obtained from the ozonolysis experiments.

Since this work was completed an alternative method of preparing the acetoxy-aldehyde has been published.[16] It involves the oxidation of sclareol with osmium tetroxide and sodium metaperiodate. Corey, Hess and Proskow[17] have reduced the acetoxy-aldehyde, prepared in this way, with sodium borohydride but have not yet published experimental details.

The glycol (D19) may be obtained from all the products of ozonolysis, discussed previously, by reduction[12] with lithium aluminium hydride. By using this glycol as the precursor of the methylene-bromide (D11), the sclareol available was utilised to the best advantage. Direct reduction[12] of the ozonide (D26) with lithium aluminium hydride gave the glycol (D19) in yields of 57-75%. It was accompanied always by its dehydration product, the ether (D27), in yields of up to 15%. In the present work it was found more satisfactory to decompose the ozonide with Raney nickel

before reducing with lithium aluminium hydride. With this technique the glycol was obtained in 55% yield. In addition, the methylene-alcohol (D28) was obtained in 10% yield. No previous mention of the formation of this substance has been made and it may be the precursor of the ether (D27), isolated by Stoll and Hinder.

Alkyl halides have been prepared from alcohols by reaction[18] with the adduct of triphenyl phosphite and either benzyl bromide or bromine. The original work showed that it should be possible to prepare primary halides selectively in the presence of tertiary alcohols. In the case of the glycol (D19) it was not possible to define conditions under which the tertiary hydroxylic group remained unattacked; infra-red analysis of the product suggested that the ether (D27) was one of the products of this reaction. Mild conditions gave unchanged glycol. Because of the failure to prepare, on the one hand the acetoxy-alcohol (D18) in reasonable yield, and on the other the hydroxy-bromide (D29), attempts to prepare an intermediate suitable for the synthesis of ambrein were postponed.

The (+)-methylene-bromide (D11) was prepared from the glycol (D19) by a one stage reaction with phosphorus oxybromide in pyridine. The course of the dehydration of the tertiary alcohol to give an exocyclic double bond was

predicted[19] from the known equatorial configuration of the C-7 hydroxyl group. The geometrical requirement of four trans coplanar centres is only achieved if the dehydration involves a hydrogen atom of the methyl group.

Considerable evolution of heat occurred when phosphorus oxybromide was added to the solution of the glycol and reproducible yields were only obtained if the temperature was kept below 20° during this addition. In early experiments this precaution was not taken and the recovery of organic material from the reaction mixture was always poor. The loss was caused probably by the formation of a water soluble salt by quaternisation of the primary bromide (D11) with pyridine.

This methylene-bromide was prepared also from the methylene-alcohol (D28) by a similar reaction. Treatment of the methylene-bromide with acid gave the isomeric bromide (D4) containing a tetra-substituted double bond.

The methylene-bromide was surprisingly unreactive and prolonged treatment was necessary to prepare the cyanide (D30), the acetate (D31), the alkyl-3-naphthyl ether and the S-alkyl-isothiouronium derivative. The methylene-acetate (D31) was identical with that obtained by dehydrating the primary acetate (D32) with phosphorus oxychloride in pyridine. The methylene-carboxylic acid (D33),

which is a degradation product of manoöl (D34), was prepared by alkaline hydrolysis of the methylene-cyanide (D30), and was cyclised[20] readily to give (+)-ambreinolide (D12). The Grignard derivative (D35) could not be prepared.

The resistance of the methylene-bromide to SN1 or SN2 displacement reactions may be due to steric interference by the remainder of the molecule. A possible alternative explanation is that in one conformation the carbon-bromine bond is close enough to the carbon-carbon double bond to induce a vinyl type unreactivity, as represented in the canonical structure (D36).

It is of interest to compare the melting points of the two acetates (D18) and (D32). The former melts at 129° and the latter at 40-41°. An explanation of this difference may be that in the case of the primary alcohol-tertiary acetate (D18), intermolecular hydrogen bonding occurs within the crystal lattice and that this is not possible in the case of the primary acetate-tertiary alcohol (D32).

Details of the use of the (+)-methylene-bromide (D11) as an intermediate in the synthesis of pentacyclic triterpenes are discussed in Section II of this thesis.

NOTES ON EXPERIMENTAL.

Unless otherwise stated:

1. Melting points were determined on a Kofler block and are corrected.
2. Specific rotations were measured in chloroform in a 1 dm. polarimeter tube at c = 1.0.
3. Ultra-violet absorption spectra were recorded in ethyl alcohol on a Cary recording Spectrophotometer, Model 14M.
4. Infra-red absorption spectra were recorded on a Perkin-Elmer Model 21 double beam instrument equipped with a sodium chloride prism.
5. Alumina used for chromatography was P. Spence Grade 'H'; deactivated alumina refers to Grade 'H' to which 5% of 10% aqueous acetic acid had been added.
6. Silica gel used for chromatography was Crosfield Borbsil Grade 60-120.
7. d-Quartz used was a gift from Messrs. Hilger and Watts, Scientific Instrument Makers, London, S.E.5.
8. Bench reagents used were 2N.
9. Petrol used for chromatography refers to petroleum ether, b.p. 40-60°.
10. Petrol used for recrystallisation refers to petroleum ether, b.p. 60-80°.

11. The following processes were carried out during the working up procedure of all experiments and are described in detail in the first experiment only.
a.) Water and the organic solvent specified were added to the crude reaction mixture. The two phases were separated and the aqueous phase was extracted twice with the organic solvent.
b.) The combined organic solutions were washed with saturated brine, dried with magnesium or sodium sulphate and then the solvent removed under reduced pressure.
Additional procedures will be indicated.

12. Dr. Strauss, Dr. Weiler and Mr. F. Hall were responsible for the analyses.

13. Infra-red and ultra-violet spectra, other than those recorded for analytical samples, were determined on an Infracord and a Manual spectrometer respectively.

EXPERIMENTAL. SECTION I.

2,2- and 2,6-Dimethylcyclohexanones.

2-Methylcyclohexanone (280g., 2.5 mol.) was added dropwise during 15 min. to a vigorously stirred solution of sodamide (prepared from sodium (58g., 2.52 mol.)) in liquid ammonia (2.5L.), contained in a ten litre flask. The solution was stirred for a further 15 min. and then methyl iodide (852g., 6 mol.) was added dropwise during 1 hr.. Stirring was continued for 3 hr., during which time ammonia was allowed to evaporate. Water (1500 c.c.) was added, the product was extracted with ether (3 x 400 c.c.) and the ethereal extract was washed thoroughly with hydrochloric acid. Unchanged 2-methylcyclohexanone was removed by means of its water-soluble bisulphite compound, obtained by shaking the ethereal extract with a solution of sodium metabisulphite (80g.) in water (200 c.c.). The ethereal solution was washed with saturated brine and dried with magnesium sulphate. Ether was removed under reduced pressure and the residue was distilled to give 2,2- and 2,6-dimethylcyclohexanones (252g., 80%), b.p. 168-176°. No attempt was made to separate this mixture.

2,2,6-Trimethylcyclohexanone.

a.) The mixture of 2,2- and 2,6-dimethylcyclohexanones (236g., 1.87 mol.), obtained in the previous

experiment, was added dropwise during 20 min. to a vigorously stirred solution of sodamide (from sodium (47g., 1.87 mol.)). The solution was stirred for a further 15 min. and then methyl iodide (655g., 4.5 mol.) added during 1 hr.. Stirring was continued for a further 2 hr., during which time ammonia was allowed to evaporate. Water (2L.) was added and the product extracted with ether. The ethereal extract was washed with hydrochloric acid and gave, after treatment in the usual way, a mixture of methylcyclohexanones, which was fractionally distilled through a column of 150 theoretical plates with a gauze packing.[21] 2,2,6-Trimethylcyclohexanone (215g., 82%) was collected, b.p. 178-179°/764 mm., n_D^{20} 1.4496. (Found: C, 77.2; H, 11.5. Calc. for $C_9H_{16}O$: C,77.1; H, 11.4%).

The semicarbazone was recrystallised from ethyl alcohol to give needles, m.p. 210°. (Found: C,60.9; H,9.6; N,21.1. Calc. for $C_{10}H_{19}N_3O$: C,60.9; H,9.6; N,21.3%). King, King and Toplis[8] quote b.p. 179-180°/763 mm., n_D^{17} 1.4508 for 2,2,6-trimethylcyclohexanone and m.p. 207-209° for the semicarbazone.

Sabotka and Chanley[6] quote b.p. 178.7°-179°/767 mm., n_D^{20} 1.4493 for 2,2,6-trimethylcyclohexanone and m.p. 207-208° for the semicarbazone.

b.) A mixture of 2,2- and 2,6-dimethylcyclo-

hexanones was prepared from 2-methylcyclohexanone (112g., 1 mol.) by the method of King, King and Topliss.[8] This mixture was then further methylated using the procedure described by Sabotka and Chanley.[6] The product was fractionally distilled as in (a.) to give 2,2,6-trimethylcyclohexanone (56g., 40% yield from 2-methylcyclohexanone), b.p. 178-180°/763 mm., n_D^{20} 1.4495. (Found: C,77.2; H,11.4%). Semicarbazone m.p. 210°.

Oxidation of Sclareol.

This preparation is based on the work of Ruzicka et al.[10] and of Bigley.[4] Sclareol was obtained from Firmenich et Cie., Geneva.

Finely powdered potassium permanganate (70g.) was added in small portions during 4 hr. to a solution of sclareol (40g., 0.13 mol.) in acetone (2l.), which was purified by distillation from potassium permanganate. The temperature must be kept below 0° during this addition. The suspension was stirred vigorously at -5° for 3 days, after which time the colour of the permanganate had almost disappeared. The slight excess of permanganate was destroyed by the addition of an aqueous solution of sodium metabisulphite. The manganese dioxide formed during the oxidation was collected and washed thoroughly with hot acetone.

The combined acetone solutions were evaporated and the residue taken up in ether. Isolation in the usual way gave an oil containing the enol-ether (D15) and the hydroxy-ketone (D16), ν(film), 3400, 1705, 1680 $cm.^{-1}$. A solution of this product in petrol (500 c.c., b.p. 60-80°) was shaken with hydrochloric acid (100 c.c.). The organic phase was separated, petrol evaporated and the residue distilled to yield the enol-ether (D15) (18g., 53%), b.p. 130-135°/0.07 mm., $\nu(CS_2)$, 1680 $cm.^{-1}$ (enol-ether), m.p. 42°, $[\alpha]_D$ = + 7° (in ethyl alcohol).

Ruzicka et al.[10] quote m.p. 45-46°, b.p. 120-125°/0.03 mm., $[\alpha]_D$ = + 5°.

Ozonolysis of the enol-ether (D15).

Ozone was passed at the rate of 12 litres/hr. through a solution of the enol-ether (10g., 0.038 mol.) in ethyl acetate (200 c.c.) at -36°. After 4 hr. a faint blue colour persisted and nitrogen was flushed through the system. The solution was poured into a stirred suspension of Raney nickel (10g.) in ethyl acetate (50 c.c.) at 0°. The resulting suspension was heated under reflux for 15 min. and then filtered. The residue, obtained after evaporating the solvent from the filtrate, was an oil (10g.), ν(film), 2700, 1721, 1248 (aldehyde and ester), 1715 $cm.^{-1}$ (acid).

There was broad absorption in the hydroxyl region. This material is referred to subsequently as the product of ozonolysis. All operations after the completion of ozonolysis were carried out in an atmosphere of nitrogen.

Further ozonolyses were carried out at -70° and 0° to give products which had similar infra-red spectra, and from which 5-carboxymethyl-6(e)-acetoxy-1,1,6,10-tetramethyl-trans-decalin (D22) (15-20%) was isolated by the method described in the next experiment.

The acetoxy-acid (60%) was isolated from an experiment, at -36°, in which ozonolysis was allowed to proceed for a further 4 hr. after the formation of the blue colour. Partial ozonolysis at -70° resulted in a decrease in the proportion of acetoxy-acid.

Reduction of the product of ozonolysis with sodium borohydride.

A solution of the product of ozonolysis (2.9g., 0.01 mol.) and sodium borohydride (3.8g., 0.1 mol.) in methyl alcohol (30 c.c.) containing sodium hydroxide solution (5 drops) was stirred at 20° for 1 hr. in an atmosphere of nitrogen. Water (150 c.c.) was added and the resulting solution, after neutralisation with hydrochloric acid, was extracted with ether (3 x 30 c.c.). The ethereal extracts were washed with sodium carbonate solution

(3 x 20 c.c.). The combined aqueous washings were acidified with hydrochloric acid and the precipitate was collected and recrystallised from petrol. 5-Carboxymethyl-6(e)-acetoxy-1,1,6,10-tetramethyl-trans-decalin (943 mg., 28%) separated as needles, m.p. 158°, $[\alpha]_D^{18}$ = -27°. (Found: C,69.9; H,9.7. Calc. for $C_{18}H_{30}O_4$: C,69.7; H,9.7%).

Stoll and Hinder[12] quote m.p. 156-157°.

(A similar procedure was used, in the previous experiment, to isolate this acetoxy-acid from a solution of the product of ozonolysis in ethyl acetate).

The ethereal solution remaining after this acid had been removed was worked up in the usual way to yield an oil (1.6g.), which was adsorbed on deactivated alumina (160g.). The following fractions were collected:

i.) petrol-benzene (480 c.c., 9:1), containing the lactone (D23) (31 mg., 1%), derived from 5-carboxymethyl-6(e)-hydroxy-1,1,6,10-tetramethyl-trans-decalin, m.p. 123° (needles from petrol), ν(nujol), 1760 $cm.^{-1}$ (lactone).

Stoll and Hinder[12] quote m.p. 123°.

ii.) petrol-benzene (320 c.c., 1:1), containing a gum (101 mg., 3%), which was not identified. ν (film), 1721, 1248 $cm.^{-1}$ (Infracord spectrum).

iii.) petrol-benzene (480 c.c., 1:4), containing 5-(2'-hydroxyethyl)-6(e)-acetoxy-1,1,6,10-tetramethyl-trans-

decalin (D18) (165 mg., 5%), m.p. 129° (needles from petrol). (Found: C,73.0; H,10.9. Calc. for $C_{18}H_{32}O_3$: C,72.9; H,10.8%). ν (nujol), 3400 (hydroxyl), 1748 and 1234 cm.$^{-1}$ (ester).

Stoll and Hinder[12] quote m.p. 130-132°.

iv.) benzene (1L.), containing an oil (1.7g., 55%) with an infra-red spectrum closely similar to that of fraction (iii). There were additional weak bands in the 1200-1000 cm.$^{-1}$ region.

A crystalline sample of the tosyl derivative of the acetoxy-alcohol (D18) could not be prepared from fractions (iii) or (iv).

Reduction of the ozonide (D26).

a.) With platinum oxide.

Excess ozone was removed from a freshly prepared solution of the ozonide (from 400 mg. enol-ether) in ethyl acetate (50 c.c.) by flushing nitrogen through the system and the solution was then transferred to a hydrogenation flask containing pre-reduced platinum oxide (50 mg.), ethyl acetate (10 c.c.) and acetic acid (1 drop). Hydrogen (40 c.c.) was absorbed during 13 hr.. (Theoretical value for 1 mole hydrogen: 34.5 c.c.). The suspension was filtered and products were isolated using the method

described in the previous experiment. The acetoxy-acid (D22) (71 mg., 15%), the acetoxy-alcohol (D18) (32 mg., 7%) and two fractions with infra-red spectra identical with those of fractions (ii) and (iv), pp.47 and 48, were obtained.

b.) With Raney nickel.

The procedure described in (a.) was repeated using Raney nickel (0.5 g.) instead of platinum oxide. Hydrogen (22 c.c.) was absorbed. The product contained the acetoxy-acid (90mg., 19%), the acetoxy-alcohol (27mg., 6%) and two other fractions identical with fractions (ii) and (iv) above.

The proportion of acetoxy-alcohol isolated from further experiments was never greater than 7% and the volume of hydrogen absorbed varied considerably. (see Discussion p. 34).

Oxidation of the enol-ether (D15).

A solution of the enol-ether (0.52g., 0.002 mol.) and osmium tetroxide (10.4mg., 0.00004 mol.) in dioxan (15c.c.) and water (5 c.c.), containing sodium hydroxide solution (0.5c.c.) was stirred at 60° for 5 min.. Finely powdered sodium metaperiodate (0.95g., 0.0042 mol.) was added in small portions during 30 min., during which time the colour of the solution changed from dark brown to pink. The solution

was stirred for a further 75 min. at 60°, and then water was added and the resulting solution was saturated with salt. The product, which was isolated *via* ether, was a gum (477mg.) (ν(film) 2700(w, aldehyde), 1760(lactone), 1721, 1248cm.$^{-1}$ (m, ester and aldehyde) and it was reduced with sodium borohydride under conditions similar to those described previously. The product (435mg.) was adsorbed on deactivated alumina (40g.) and the following fractions collected:

i.) petrol (160 c.c.), containing unchanged enol-ether (50mg.).

ii.) petrol-benzene (200 c.c., 9:1), containing the lactone derived from 5-carboxymethyl-6(e)-hydroxy-1,1,6,10-tetramethyl-*trans*-decalin (87mg., 18%), m.p. 123° (needles from petrol), ν(nujol), 1760cm.$^{-1}$ (lactone). (Found: C,77.1; H,10.2. Calc. for $C_{16}H_{26}O_3$: C,76.8; H,10.4%). Melting-point undepressed on admixture with an authentic sample prepared from the acetoxy-acid (D22) by the method of Stoll and Hinder,[12] who quote m.p. 123°.

iii.) petrol-benzene (120 c.c., 1:1), containing an oil (30mg., 3%), ν(film), 1721 and 1248cm.$^{-1}$ (Infracord) (cf. fraction (ii) p. 47).

iv.) benzene (200 c.c.), containing a gum (332mg.). The infra-red spectrum was identical to that of fraction (iv) p. 48.

5-(2'-Hydroxyethyl)-6(e)-hydroxy-1,1,6,10-tetramethyl-trans-decalin (D19).

The product of ozonolysis (from enol-ether (10g., 0.038 mol.)) was dissolved in ether (400 c.c.). Lithium aluminium hydride (4.8g., 0.136 mol.) was added and the suspension was heated under reflux for 3 hr.. The reaction mixture was cooled to 0° and excess lithium aluminium hydride was decomposed by cautious addition of a saturated solution of sodium sulphate, sufficient of which was added to coagulate the precipitate of aluminium hydroxide in the aqueous phase. The aqueous layer was separated and extracted with ether (2 x 50 c.c.). The crude product (10g.), isolated in the usual way, was a solid and was recrystallised from petrol. 5-(2'-Hydroxyethyl)-6(e)-hydroxy-1,1,6,10-tetramethyl-trans-decalin (5.6g., 58%) separated as needles, m.p. 131-132°; $[\alpha]_D^{18} = -17°$ (Found: C,76.0; H,11.6. Calc. for $C_{16}H_{30}O_2$: C,75.6; H,11.8%).

Stoll and Hinder[12] quote m.p. 132-133°.
This compound is referred to subsequently as the glycol (D19).

The solvent was evaporated from the mother liquors to give a residue (4g.) which was adsorbed on deactivated alumina (400g.). Elution with benzene-ether (1200 c.c., 4:1) gave, after removal of the solvent, 5-(2'-hydroxyethyl)-6-exomethylene-1,1,10-trimethyl-trans-

decalin (D28) (0.75g., 15%). ν (CS_2), 3500, 1052 (primary alcohol), 893cm.$^{-1}$ (exocyclic methylene). (Found: C,81.8; H,11.8. $C_{16}H_{28}O$ requires: C,81.4; H,11.9%).

Attempted preparation of 5-(2')-bromoethyl-6(e)-hydroxy-1,1,6,10-tetramethyl-trans-decalin (D29).

a.) Triphenyl phosphite (6g., 0.02 mol.) and benzyl bromide (3.2g., 0.02 mol.) were heated in a sealed tube at 170-180° for 6 hr. to yield triphenylphosphite-benzylobromide as a syrup. This syrup (380mg., 0.00084 mol.) was dissolved in ether (25 c.c.) and added to a stirred solution of the glycol (D19) (100mg., 0.00042 mol.) in ether/dioxan (50 c.c., 1:1) during 30 min. The mixture was heated under reflux for 4 hr., care being taken to exclude moisture throughout the series of operations. The mixture was cooled, petrol (200 c.c.) was added and the solution was filtered. Petrol was evaporated to leave a residue (110mg.) which was adsorbed on alumina (10g.). Elution with petrol gave, after evaporation, an oil (90mg.), ν (film), 1105cm.$^{-1}$ (s, cyclic ether); there was no absorption in the hydroxyl region. This product was not investigated but may contain the ether (D27).

b.) The glycol (D19) (508mg., 0.002 mol.) was added to molten triphenyl phosphite (620mg., 0.0022 mol.)

contained in a pyrex tube connected to a drying train. Bromine (1.1 c.c.) was added dropwise to the mixture, the temperature of which was kept below 5° during this addition. The reaction mixture was left at 20° for 24 hr., during which time the colour of the solution changed from dark to pale brown. Ether (200 c.c.) was added and the product, which was isolated in the usual way, was recrystallised from petrol. Unchanged glycol (D19) (490mg.) separated as needles, m.p. 129-130°, undepressed on admixture with an authentic sample.

Phosphorus oxybromide.

Acetic acid (11 c.c.) was added dropwise during 1 hr. to phosphorus pentabromide (65g.). The mixture was distilled to give phosphorus oxybromide as an oil, which solidified after cooling and which was used immediately in the following experiments.

5-(2′-Bromoethyl)-6-exomethylene-1,1,10-trimethyl-trans-decalin (D11).

a.) A solution of the glycol (D19) (8.6g., 0.038 mol.) in pyridine (600 c.c.), freshly distilled from potassium hydroxide, was cooled to 0° and phosphorus oxybromide (19.5g., 0.152 mol.) was added slowly so that the temperature remained below 20°. There was considerable evolution of heat.

The reaction mixture was left at 20° for 15 hr. and then poured into water (600 c.c.) and hydrochloric acid (400c.c., 4N). The product was extracted with ether (5 x 200 c.c.); the ethereal extract was washed repeatedly with hydrochloric acid (1N) and then worked up in the usual way. An oil (7.6g.) was obtained and was adsorbed on deactivated alumina (300g.). Elution with petrol (600 c.c.) gave, after distillation, 5-(2'-bromoethyl)-6-exomethylene-1,1,10-trimethyl-trans decalin (7g., 69%), b.p. (oil-bath) 140-150°/0.05mm., n_D^{16} 1.5268, $[\alpha]_D^{18}$ + 31°; $\nu(CS_2)$, 893cm.$^{-1}$ (exocyclic methylene). (Found: C,64.5; H,9.04; Br,26.4. $C_{16}H_{27}Br$ requires C,64.2; H,9.03; Br,26.8%).

The S-alkyl-isothiouronium and the alkyl-β-naphthyl-ether derivatives were only formed after prolonged treatment with the necessary reagents and would not crystallise.

b.) 5-(2'-Hydroxyethyl)-6-exomethylene-1,1,10-trimethyl-trans-decalin (D28) (0.7g., 0.003 mol.) was dissolved in pyridine (50 c.c.) and treated with phosphorus oxybromide (1.72g., 0.006 mol.) as in (a.). 5-(2'-Bromo-ethyl)-6-exomethylene-1,1,10-trimethyl-trans-decalin (0.47g., 53%) was obtained as an oil, b.p. (oil-bath) 145-150°/0.05mm., n_D^{16} 1.5267, $[\alpha]_D^{18}$ + 31°. (Found: C,64.8; H,9.3; Br,26.0%).

5-(2'-Bromoethyl)-1,1,6,10-tetramethyl-Δ^5-trans-octalin (D4).

Boron trifluoride-etherate (1 c.c., 48% BF_3) was added to a solution of the methylene-bromide (D11) (300mg., 0.001 mol.) in ether (2 c.c.). The mixture was left at 20° for 15 hr. in an atmosphere of nitrogen and then it was poured slowly into sodium bicarbonate solution (20 c.c., 0.5N). The product was isolated *via* ether in the usual way and was distilled to yield 5-(2'-bromoethyl)-1,1,6,10-tetramethyl-Δ^5-trans-octalin (D4) (215mg., 70%) as an oil, b.p. (oil-bath) 150-155°/0.05mm., ϵ_{2100} 4980, ϵ_{2400} 108. The infra-red spectrum showed no absorption which could be attributed to either tri- or di-substituted double bonds. (Found: C,64.3; H,9.2; Br,25.9. $C_{16}H_{27}Br$ requires: C,64.2; H,9.03; Br,26.8%).

The S-alkyl-isothiouronium derivative would not crystallise.

Ambreinolide.

The methylene-bromide (D11) dissolved in methyl alcohol (5 c.c.) was added to a solution of sodium cyanide (4g.) in water (5 c.c.) and the mixture heated under reflux for 48 hr.. 5-(2'-Cyanoethyl)-6-exomethylene-1,1,10-trimethyl-trans-decalin (D30) (70mg.) was isolated in the usual way *via* ether and was not characterised. ν (film), 2200cm.$^{-1}$ (w, cyanide). This crude material was heated

under reflux for 24 hr. in a solution containing water (10c.c.), methyl alcohol (3 c.c.) and sodium hydroxide (4g.). The solution was then acidified with hydrochloric acid and the precipitate was collected and recrystallised from aqueous ethyl alcohol. 5-(2'-Carboxyethyl)-6-exomethylene-1,1,10-trimethyl-*trans*-decalin (55mg.) separated as needles m.p.108°, ν(nujol) 3700-2500 (broad absorption), 1710 (acid), 1634, 885cm.$^{-1}$ (exocyclic methylene).

Ruzicka *et al.*[20] quote m.p. 108.5-109°.

This methylene-carboxylic acid (D33) was dissolved in glacial acetic acid (1 c.c.) and added dropwise, during 5 min., to a mixture of glacial acetic acid (5 c.c.) and concentrated sulphuric acid (2 c.c.) at 0°. The mixture was stirred at 0° for 2 hr. and then poured on to ice. The product (50mg.) was isolated *via* ether and was adsorbed on alumina (5g.). Elution with petrol-benzene (50 c.c., 1:2) gave, after evaporation, a solid which was recrystallised from chloroform-petrol. (+)-Ambreinolide (18mg., 17%) separated as needles, m.p.137°, undepressed on admixture with an authentic sample, $[\alpha]_D^{22}$ + 29° (Found: C,77.7; H,10.7. Calc. for $C_{17}H_{28}O_2$: C,77.3; H,10.6%)

Ruzicka *et al.*[20] quote m.p.139-140°, $[\alpha]_D$ + 31°.

5-(2'-Acetoxyethyl)-6-exomethylene-1,1,10-trimethyl-trans-decalin (D31).

(a.) From the glycol (D19)

Acetic anhydride (5.2 c.c., 0.05 mol.) was added to a solution of the glycol (D19) (1.25g., 0.005 mol.) in pyridine (50 c.c.). The mixture was left at 20° for 21 hr. and then poured into water (200 c.c.). Isolation of the product *via* ether gave an oil (1.64g.) which was adsorbed on alumina (150g.). Elution with benzene (750 c.c.) yielded, after evaporation, a solid which was recrystallised from petrol. 5-(2'-Acetoxyethyl)-6(e)-hydroxy-1,1,6,10-tetramethyl-trans-decalin (D31) (1.5g., 99%), separated as needles, m.p. 40-41°, $\nu(CS_2)$, 3550 (hydroxyl), 1736, 1235cm.$^{-1}$ (acetate). (Found: C,73.2; H,11.1. $C_{18}H_{32}O_3$ requires: C,73.0; H,10.8%).

This product (870mg., 0.003 mol.) was dissolved in pyridine (50 c.c.), containing phosphorus oxychloride (8c.c.). The mixture was left at 20° for 18 hr. and then poured into water (200 c.c.). The product (740mg.) was isolated *via* ether and was adsorbed on alumina (75g.). Elution with petrol gave, after distillation, 5-(2'-acetoxyethyl)-6-exomethylene-1,1,10-trimethyl-trans-decalin (D31) (690mg., 85%), b.p. (oil-bath) 120-125°/0.05mm., n_D^{16} 1.5003, $[\alpha]_D^{23}$ + 29°, $\nu(CS_2)$, 1735, 1232 (acetate), 879cm.$^{-1}$ (exocyclic methylene).

(Found: C,77.6; H,10.9. $C_{18}H_{30}O_2$ requires C,77.7; H,10.8%).

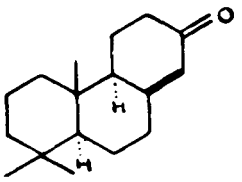
(b.) From the methylene-bromide (D11).

A solution of the methylene-bromide (D11) (300mg., 0.001 mol.) in acetic acid (4 c.c.), containing silver acetate (1.5g.) was heated under reflux for 45 hr.. The mixture was cooled and ether (100 c.c.) was added. Ammonium hydroxide solution was then added until the silver salts had dissolved. The product was isolated in the usual way and gave, after distillation, 5-(2'-acetoxyethyl)-6-exomethylene-1,1,10-trimethyl-*trans*-decalin (250mg., 87%) as an oil, b.p. (oil-bath) 115°/0.03mm., n_D^{19} 1.4999, $[\alpha]_D^{21}$ + 29°. The infra-red spectrum was identical with that of the product obtained in (a.). (Found: C,77.7; H,10.7%).

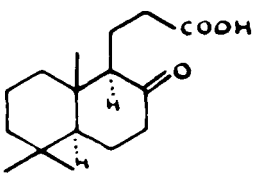
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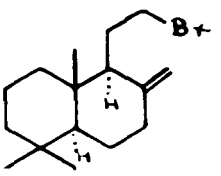
D1 - D24



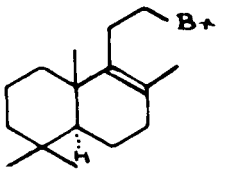
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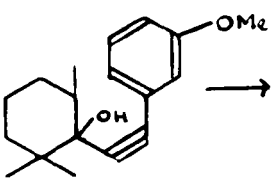
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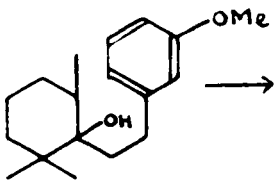
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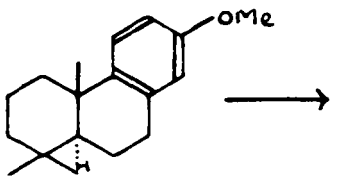
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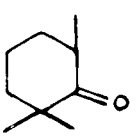


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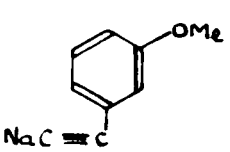


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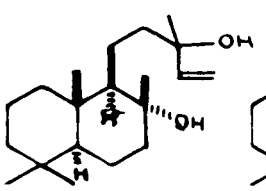
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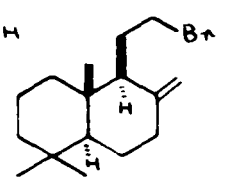
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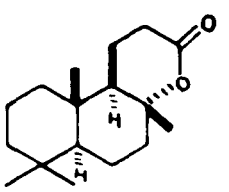
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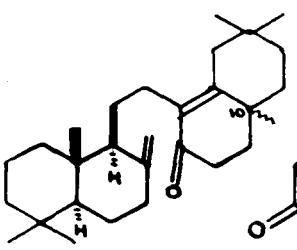
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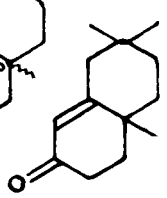
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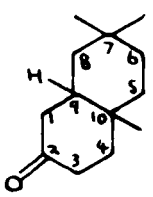
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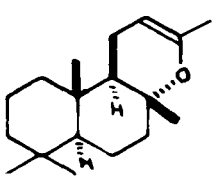
D14 a - C-10 αMe
b = C-10 βMe



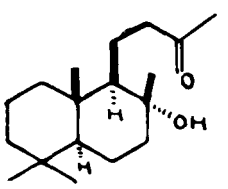
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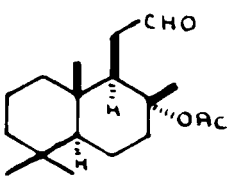
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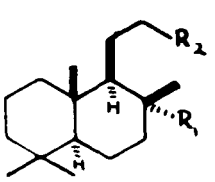
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D16



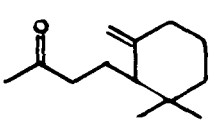
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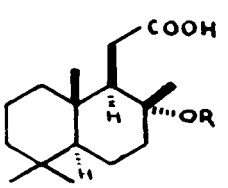
D18 R_1 = OOCCH$_3$
R_2 = OH

D19 R_1 = OH, R_2 = OH

D20 R_1 = OH; R_2 = CH_2Br



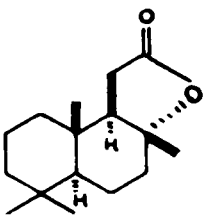
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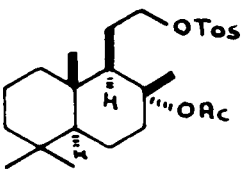
D22 R = $-\overset{O}{\overset{\|}{C}}-CH_3$

D24 R = H

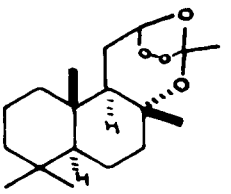
D23-D37



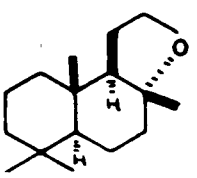
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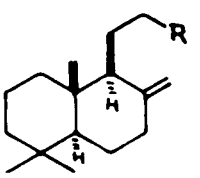
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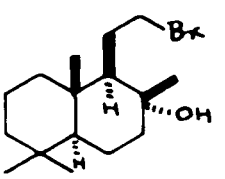
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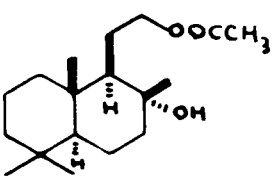
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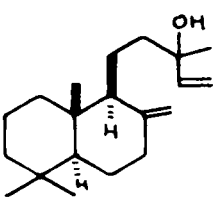
D28 R = OH
D30 R = CN
D31 R = $OOCCH_3$
D33 R = COOH



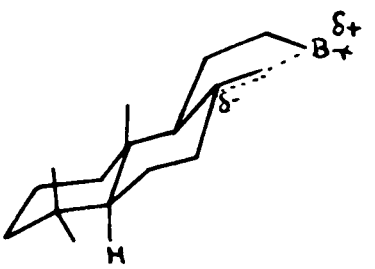
D29



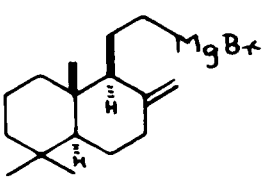
D32



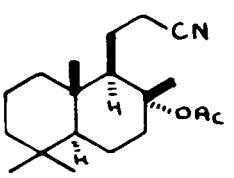
D34



D36



D35



D37

DISCUSSION. SECTION II.

Section I of this thesis described the preparation of a bicyclic intermediate (E1), which was suitable for use as the potential rings A and B in the synthesis of a pentacyclic triterpene of the oleanane group. The later stages of this synthesis are now considered in detail.

It was proposed to attach the (+)-methylene-bromide (E1) to C - 1 of the cis-decalone (E2), and/or the $\Delta^{1(9)}$-octalone (E3), by means of an alkylation, which would involve nucleophilic displacement of the bromine atom by the enolate anion of either the cis-decalone and/or the octalone. Alkylation of the (±)-cis-decalone would lead to a mixture of two diastereoisomers (E4, E5); the diastereoisomer (E4), corresponding to the natural series of triterpenes, could be elaborated by a method analogous to that proposed by Halsall and Thomas[1] and realised experimentally by Corey, Hess and Froskow[2] in the synthesis of olean-11(12), 13(18)-diene, described on p. 18. Treatment of the tetracyclic-cis-ketone (E4) with lithium methyl or methyl magnesium iodide should give a mixture of tertiary alcohols (E6a, E6b) which, after acid-catalysed cyclisation, would yield, among other products, any one or a mixture of the pentacyclic triterpenes (E7 - E12). It has been demonstrated[3,4] that treatment of olean-13(18)-ene (E7), olean-12-ene (E8), 18αH-olean-12-ene (E9) or olean-18-ene

(E10), with mineral acid, gives an equilibrium mixture of hydrocarbons from which a mixed crystal containing olean-13(18)-ene (E7) and 18α H-olean-12-ene (E9) is obtained by recrystallisation. There is no possibility, therefore, of obtaining a single compound from a cyclisation involving conditions which would allow thermodynamic equilibration of the initial product.

The synthesis of the cis-decalone (E2) has been described previously by Halsall and Thomas[1] and a similar route was followed in the present work. 2,5,5-Trimethylcyclohexan-1,3-dione (E13), prepared by methylating dimedone (E14), was treated with phosphorus trichloride to give the enol-chloride (E15), from which 2,5,5-trimethylcyclohexanone (E16) was obtained by reduction with lithium in ammonia.[5,6] Recently catalytic reduction of the enol-chloride (E15) has been reported to give enhanced yields of 2,5,5-trimethylcyclohexanone. 7,7,10-Trimethyl-$\Delta^{1(9)}$-octal-2-one (E3) was obtained in 10% yield by reaction of 2,5,5-trimethylcyclohexanone with the methiodide of 4-diethylaminobutan-2-one in the presence of sodamide. Catalytic reduction of this octalone (E3) gave 7,7,10-trimethyl-cis-decal-2-one (E2) in high yield.

The preparation of the $\Delta^{1(9)}$-octal-2-one (E3) from 2,5,5-trimethylcyclohexanone is an example of the Robinson ring extension, originally described by Robinson, du Feu and McQuillin.[7] Vinyl ketones, usually formed in situ

from a Mannich base, undergo a Michael addition to the enolate anion of a cyclic ketone to give a δ-diketone, which under the basic conditions of the reaction, cyclises to a $\Delta^{1(9)}$-octal-2-one by intramolecular aldol condensation and dehydration. The infra-red spectrum of the product obtained by the Robinson ring extensions described in this section of the thesis always had bands at 3400cm.$^{-1}$ (hydroxyl), 1708cm.$^{-1}$ (saturated ketone) and 1666cm.$^{-1}$ (unsaturated ketone). The bands at 3400cm.$^{-1}$ and 1708cm.$^{-1}$ may be attributed to the presence of either the β-hydroxydecalone (E17) or the intermediate (E18), which corresponds to the compound (E19) isolated[8] from the ring extension of the tricyclic ketone (E20a). This precursor was converted readily to 7,7,10-trimethyl-$\Delta^{1(9)}$-octal-2-one (E3) by treatment with ethanolic hydrochloric acid.

The yields of octalones, prepared by Robinson ring extensions are increased[9] by treating the cyclic ketones with the free Mannich base in the presence of catalytic amounts of sodium. In the present work 7,7,10-trimethyl-$\Delta^{1(9)}$-octal-2-one (E3) was obtained in22% yield from 4-diethylaminobutan-2-one.

The most satisfactory procedure for the Robinson ring extension under consideration is that of Eschenmoser.[10] 2,5,5-Trimethylcyclohexanone was condensed with methyl vinyl ketone in the presence of sodium ethoxide to give 7,7,10-tri-

methyl-$\Delta^{1(9)}$-octal-2-one (E3) in 54% yield, which is comparable to that quoted by Eschenmoser.

The discussions given by Halsall and Thomas[1] and by Dreiding[11] make it clear that enolisation of 7,7,10-trimethyl-cis-decal-2-one (E2) should be towards C-3 (see E2), in contrast to that direction of enolisation predicted from a consideration of the 3-keto steroids with a cis - A/B ring fusion. Dreiding has pointed out that, in general, there are two conformations possible for cis-decalones, namely (E20) and (E21); enolisation towards C-1 will occur only in the conformation (E20), in which the energy content is lowered on enolisation by the formation, at C-1, of a trigonal carbon atom, which is axial to ring B. This factor does not operate in conformation (E21), in which C-1 is in an equatorial relationship to ring B, and in this conformation the hyperconjugation effect directs enolisation towards C-3.

For unsubstituted cis-decal-2-ones the skew interaction between the axial hydrogen atoms at C-1 and C-7 in the conformation (E20) is removed in the conformation (E21), in which the carbon atoms C-2 and C-8 have a similar relationship. In addition the non-bonded interactions between the axial substituents at C-1, C-3 and C-10 are less for the conformation (E21), in which these substituents are hydrogen atoms, than for the conformation (E20), in which two of these

substituents are hydrogen atoms and the third is a methylene group. The conformation (E21) will be more stable, therefore, than the conformation (E20).

In the case of a 10-methyl-*cis*-decal-2-one, with the conformations (E22) and (E23), the non-bonded interactions are between two hydrogen atoms and, on the one hand, a methylene group (E22), and, on the other hand, a methyl group (E23). The stabilities of the conformations will probably be similar. A more significant non-bonded interaction occurs in the conformation (E24) of 7,7,10-trimethyl-*cis*-decal-2-one (E2). In this conformation there is a large interaction between C-1 and the axial methyl group at C-7 which is absent in the conformation (E25). It is likely that 7,7,10-trimethyl-*cis*-decal-2-one (E2), referred to subsequently as the *cis*-decalone, will exist almost completely in the conformation (E25) and that enolisation will occur towards C-3.

On the basis of these arguments, together with a consideration of the product obtained by bromination, followed by dehydrobromination, of the *cis*-decalone (E2), Halsall and Thomas[1] assigned the structure (E26) to the compound obtained by treating the *cis*-decalone with allyl bromide in the presence of a base. In the present work the authenticity of this assignment was confirmed from a consideration of the products obtained by bromination-dehydrobromination of an ethyl-*cis*-

decalone (E27) or (E28). Further bromination-dehydrobromination experiments were carried out on the cis-decalone and the results, discussed on p. 74, showed that there was ambiguity in the original work of Halsall and Thomas.[1]

An ethyl group could not be introduced into the cis-decalone under mild conditions at room temperature, similar to those described by Halsall and Thomas[1] for the preparation of 3-allyl-cis-decalone (E26). Cis-decalone was recovered also from attempts at alkylation via the pyrrolidine enamine (E29), using the conditions[12,13] originally developed by Stork et al.. A 20% yield of 1- or 3-ethyl-cis-decalone (E27) or (E28) was obtained in an alkylation with ethyl iodide and a ten mole excess of sodium tert-amyloxide. Unchanged cis-decalone was separated from the alkylated material by careful chromatography.

An 85% yield of 1- or 3-ethyl-cis-decalone was obtained by alkylating the cis-decalone with 3.2 moles ethyl iodide in the presence of 3.2 moles of potassium tert-butoxide in refluxing tert-butanol. The product was assumed to be homogeneous because it formed a sharp melting 2,4-dinitrophenylhydrazone in almost quantitative yield. There was a significant difference in the infra-red spectrum of the ethyl-cis-decalone compared with that of the cis-decalone. The intensities of the bands at 1372cm.$^{-1}$ and 1355cm.$^{-1}$ in the

cis-decalone (former considerably weaker) were reversed in the ethyl-cis-decalone (former slightly stronger). These bands were assigned to the -C-H deformation vibrations of methyl groups.

The 1- or 3-ethyl-cis-decalone was brominated in acetic acid and the crude product dehydrobrominated[15] with lithium carbonate in dimethylformamide to give a mixture of two octalones, which was resolved by chromatography. The major fraction (98% of total octalone) had an absorption maximum in the ultra-violet at 2370Å, and the second product, which was not characterised, had a maximum at 2410Å.

1-Ethyl- and 3-ethyl-cis-decalones can give rise to four octalones by bromination-dehydrobromination, namely: 1-ethyl-$\Delta^{1(9)}$-octal-2-one (E30) (2590Å), 1-ethyl-Δ^{3}-octal-2-one (E31) (2270Å), 3-ethyl-$\Delta^{1(9)}$-octal-2-one (E32) (2440Å) and 3-ethyl-Δ^{3}-octal-2-one (E33) (2370Å). The values in brackets represent the positions of the ultra-violet absorption maxima predicted by Woodward's rules.[18] A consideration of these figures indicated that the product obtained by alkylation of the cis-decalone with ethyl iodide was 3-ethyl-7,7,10-trimethyl-cis-decal-2-one (E27) and that this yielded a mixture of 3-ethyl-7,7,10-trimethyl-Δ^{3}-cis-octal-2-one (E33) and 3-ethyl-7,7,10-trimethyl-$\Delta^{1(9)}$-octal-2-one (E32) after bromination-dehydrobromination. The implications arising from the

formation of two octalones during this series of experiments are considered on p. 74.

In order to prepare a cis-decalone with a C-1 alkyl substituent, it was necessary to protect the C-3 position. This was achieved by preparing 3-anilinomethylene-7,7,10-trimethyl-cis-decal-2-one (E34) via the 3-formyl derivative (E35), using the method originally described by Birch and Robinson.[16] The overall yield of the 3-anilinomethylene derivative was 73%. The cis-decalone (E2) was recovered in high yield from this derivative by a two-stage hydrolysis procedure.[16] Hydrolysis with dilute acid gave a product consisting principally of the 3-formyl derivative, which was identified by its ultra-violet spectrum, λ max 2840Å (in ethyl alcohol), λ max 3150Å (in ethanolic sodium hydroxide). Hydrolysis of the 3-formyl derivative with dilute alkali gave the cis-decalone.

All attempts to introduce an ethyl group at C-1 of the 3-anilinomethylene-cis-decalone (E34) were unsuccessful. The product obtained in each attempt was a gum from which no identifiable material could be isolated by chromatography on alumina or silica gel. The infra-red spectrum of most of the products indicated that the C-3-anilinomethylene group was still largely intact and in each case it was removed by hydrolysis and the resulting decalone compared with

7,7,10-trimethyl-cis-decal-2-one (E2). This cis-decalone was the only ketonic material recovered from attempted alkylations using ethyl iodide and the following bases:

i.) potassium tert-butoxide (4-100 moles).

ii.) sodamide (10 moles) in benzene.

iii.) sodamide (large excess) in liquid ammonia.

iv.) sodium tert-amyloxide (4 moles) in benzene.

In each reaction a deep red colour was formed when the 3-anilinomethylene derivative (E35) was added to the base. This colour was dispelled by the addition of water and was attributed, therefore, to the presence of the enolate anion.

In one reaction sodium triphenylmethyl was used as the base under the conditions described by Renfrew and Hauser.[17] The product was a red tar and could not be identified.

In one case the infra-red spectrum of the product of attempted alkylation had bands at 1706cm.$^{-1}$ (saturated ketone) and 1650 - 1550cm.$^{-1}$ (β-hydroxy-$\alpha\beta$-unsaturated ketone) and these indicated that hydrolysis of the protecting group had occurred during the reaction. The ultra-violet spectrum showed a maximum at 2840Å, which was attributed to the presence of the 3-formyl derivative (E35). The product was chromatographed on alumina and 3-ethyl-7,7,10-trimethyl-cis-decal-2-one (E27)

was isolated in 10% yield. The formation of this material indicated that although enolisation could occur towards C-1 (red colour), the rate of alkylation at this position was negligibly slow compared to that at C-3.

3-Anilinomethylene derivatives are vinylogues of amides and would be expected to hydrolyse under the alkaline conditions of the reaction if moisture were present.

The product of a reaction in which a 100 mole excess of sodium tert-amyloxide was used as the base had no carbonyl absorption in the infra-red. It was thought that O-alkylation may have occurred but no further investigation was pursued.

An alternative method of protection was investigated. 7,7,10-Trimethyl-Δ^{3}-cis-octal-2-one (E36) can enolise only toward C-1. It was not possible to introduce either an ethyl or allyl group at this postion under conditions in which large excesses of ethyl iodide or allyl iodide and potassium tert-butoxide or sodium tert-amyloxide were used.

No further attempts were made to prepare a cis-decalone containing a C-1 alkyl substituent. An examination of models of 7,7,10-trimethyl-cis-decal-2-one in the conformation (E25) and of 7,7,10-trimethyl-Δ^{3}-cis-octal-2-one (E36) indicated that there was steric interference towards alkylation

at C-1, but that this should not have been great enough to prevent reaction at this position.

A discussion of the methods used for the preparation of 7,7,10-trimethyl-Δ^{3}-cis-octal-2-one is given now, before further alkylations are considered. It is reported[1] that bromination of 7,7,10-trimethyl-cis-decal-2-one (E2) with bromine in acetic acid containing hydrogen bromide, followed by dehydrobromination of the crude product with 2,4-dinitrophenylhydrazine,[19] gives the 2,4-dinitrophenylhydrazone of 7,7,10-trimethyl-Δ^{3}-cis-octal-2-one (E36) as the sole product. In the present work bromination-dehydrobromination experiments were carried out under a variety of conditions and in all cases a mixture of 7,7,10-trimethyl-Δ^{3}-cis-octal-2-one (E36) and 7,7,10-trimethyl-$\Delta^{1(9)}$-octal-2-one (E3) was obtained.

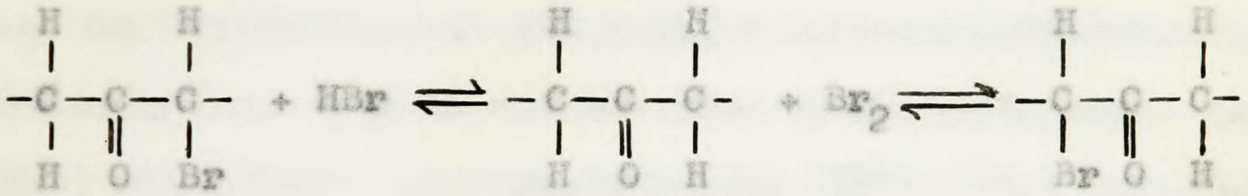
The crude product obtained after bromination was always a mixture, which contained some $\alpha\beta$-unsaturated ketone (ca. 1-5%) and which could not be resolved by chromatography on silica gel or alinina. In the latter case only the $\alpha\beta$-unsaturated ketone was recovered from the column. A possible explanation, accounting for the loss of the bromo-ketones(s), is that a Favorski rearrangement[20] had occurred under the alkaline conditions existing on the alumina column. The product of such a rearrangement would be an acid, for example (E37), and would be irreversibly adsorbed on alumina.

In the present work the crude product, obtained by brominating the cis-decalone (E2) under the conditions described by Halsall and Thomas,[1] was dehydrobrominated in three ways, namely: (i.) with lithium carbonate in dimethylformamide[15] (ii.) with γ-collidine, (iii.) with 2,4-dinitrophenylhydrazine.[19] The product obtained by the first two methods had a broad absorption maximum in the ultra-violet (λmax 2300-2370Å) and was resolved into three fractions by chromatography. The first fraction contained a small amount of unchanged cis-decalone (E2). The other two fractions were identified as 7,7,10-trimethyl-Δ^{3}-cis-octal-2-one (E36) (λmax 2280Å) and 7,7,10-trimethyl-$\Delta^{1(9)}$-octal-2-one (E3) (λmax 2390Å).

The third method of dehydrobromination involved heating the bromo-ketone(s) with 2,4-dinitrophenylhydrazine in acetic acid. The reaction mixture was then cooled and the 2,4-dinitrophenylhydrazone of 7,7,10-trimethyl-Δ^{3}-cis-octal-2-one (E36) separated. A second crop of crystals was obtained from the mother liquors and was identified as the 2,4-dinitrophenylhydrazone of 7,7,10-trimethyl-$\Delta^{1(9)}$-octal-2-one (E3). It was assumed that rearrangement had not occurred during dehydrobromination because the ratio of the yields of the two octalones was similar in each method.

Rearrangement does occur sometimes during dehydrobromination with γ-collidine.[21] For example 3-bromo-10-methyl-cis- or trans-decal-2-one (E38) gave a high yield of 10-methyl-$\Delta^{1(9)}$-octal-2-one (E39). In this case dehydrobromination with 2,4-dinitrophenylhydrazine yielded the 2,4-dinitrophenylhydrazone of 10-methyl-cis- or trans-Δ^{3}-octal-2-one (E40).

If rearrangement had not occurred during dehydrobromination then a mixture of bromoketones must have been formed during bromination. The method of bromination allowed thermodynamic equilibration of the initially formed bromo-ketone(s) by a mechanism[22] such as:



In a second experiment the cis-decalone (E2) was brominated with N-bromo-succinimide in the presence of calcium carbonate and the product was dehydrobrominated with lithium carbonate-dimethylformamide. A mixture was obtained in which the two octalones were present in the same ratio as that of the previous method. It is thought that bromination with N-bromosuccinimide proceeds by a free radical mechanism,[23] and it has been shown that bromination of the 3-keto steroids, under these conditions, gives the same products as those which

are obtained by brominating with bromine in acetic acid.

Bromination in the absence of hydrogen bromide prevents rearrangement of initially formed bromoketones by the mechanism postulated earlier. Halsall and Thomas[1] have reported that a crystalline 3-bromo-cis-decalone is formed in approximately 25% yield by brominating the cis-decalone in a solution of acetic acid containing sodium acetate. The reaction was much slower in the absence of hydrogen bromide and in our hands after three hours (the reaction time quoted[1]) only unchanged cis-decalone was isolated from the reaction mixture. In the present work the reaction was allowed to proceed for one day, at the end of which time the crude product was dehydrobrominated with lithium carbonate-dimethylformamide. The resulting mixture was resolved by chromatography into three fractions: (a.) cis-decalone (68%), (b.) 7,7,10-trimethyl-Δ^{3}-cis-octal-2-one (10%) and (c.) 7,7,10-trimethyl-$\Delta^{1(9)}$-octal-2-one (10%). It was not possible to formulate a plausible mechanism by which a bromoketone could isomerise under these conditons.

A further attempt to prepare the Δ^{3}-cis-octalone (E36) by brominating[24] the enol-acetate (E41) with bromine in pyridine/acetic acid solution also gave a mixture of the Δ^{3}-octalone (38%) and the $\Delta^{1(9)}$-octalone (16%). It was thought unlikely that rearrangement had occurred during the bromination

stage of this series of experiments. The enol-acetate, which was prepared from the cis-decalone by reaction with acetic anhydride in the presence of perchloric acid, showed only a single peak in the gas chromatogram. The peak, however, was broad and it was not possible to decide whether the enol-acetate used in this experiment was a single compound or a mixture of 2-acetoxy-Δ^{1}-and Δ^{2}-cis-decalones (E42) and (E41). In view of the other evidence, the latter might have been the case but no conclusions were drawn from this experiment.

There is only one apparent explanation that accounts satisfactorily for the results obtained in the series of alkylation and bromination experiments described. It is necessary to assume that the cis-decalone, whilst existing primarily in the conformation (E25), can also take up the conformation (E24). The rate of alkylation at C-1 is negligibly slow, even when reaction cannot occur at C-3, but the rate of bromination is of a similar order of magnitude to that of bromination at C-3. These deductions are based on the assumption that the proportions of bromo-ketones, in the products of bromination experiments, are directly related to the proportions of unsaturated ketones derived from them by dehydrobromination.

Bromination of the cis-decalone, under conditions in which thermodynamic equilibration of the initially formed

bromoketones could not occur, gave, therefore, an equimolecular mixture of bromoketones. This did not represent the most thermodynamically stable system and under equilibrating conditions the product consisted of a mixture of 3-bromo-cis-decal-2-one (E43) and 1-bromo-cis-decal-2-one (E44) in a ratio of approximately 2.4:1. Prolonged treatment of this product with hydrogen bromide in acetic acid did not alter the composition of the mixture obtained after dehydrobromination.

An explanation along similar lines accounts for the formation of two $\alpha\beta$-unsaturated ketones by bromination-dehydrobromination of 3-ethyl-7,7,10-trimethyl-cis-decal-2-one (E27). In this case the proportions of the 3-bromo- and 1-bromo-ketones present in the equilibrium mixture were influenced by the presence of the 3-ethyl group.

The synthesis of the tetracyclic $\alpha\beta$-unsaturated-ketones (E45a and b) will now be considered in detail. Alkylation of the (±)-octalone (E3) with the (+)-methylene-bromide (E1) proceeded smoothly in refluxing toluene and in good yield using sodium tert-amyloxide as the base. No tetracyclic ketone was obtained if benzene was used as the solvent. There is a fine balance between the reactivity of the halide and the nature and yields of the products obtained. For example Moyle[6] achieved only a low yield of 1-ethoxycarbonyl-methyl-7,7,10-trimethyl-$\Delta^{1(9)}$-octal-2-one (E46) under conditions analogous to those described above. Alkylation[26] of the

octalone with an excess of the tetrahydropyranyl ether of 2-bromoethanol in the presence of potassium tert-butoxide gave 1-(2-tetrahydropyranyloxyethyl)-7,7,10-trimethyl-$\Delta^{1(9)}$-octal-2-one (E47) in fair yield together with some of the Δ^{8}-isomer and some dialkylated product. Under these conditions Moyle[6] obtained only the diallyl compound (E48) from allyl iodide and the octalone (E3).

The product obtained from the alkylation of the (±)-octalone (E3) with the (+)-methylene-bromide (E1) was resolved into three components by chromatography on alumina. The first fraction contained unchanged (+)-methylene-bromide. The major product (68%) was a viscous oil, and was identified as a mixture of the diastereoisomeric forms of 1-alkyl-7,7,10-trimethyl-$\Delta^{1(9)}$-octal-2-one (E45a and b). (Alkyl in this context and throughout the remainder of this section refers to the alkyl radical obtained by loss of a bromine atom from the (+)-methylene-bromide (E1)). The infra-red spectrum had bands at 1666cm.$^{-1}$ (unsaturated ketone), 904 and 881cm.$^{-1}$ (exocyclic methylene), and the position of maximum absorption in the ultra-violet showed the expected shift to longer wavelengths (λmax 2500Å) compared to the absorption of the octalone (E3) (λmax 2390Å). It was not possible to resolve this mixture of diastereoisomers by low-temperature recrystallisation or by chromatography on alumina; in the

latter case considerable decomposition occurred. Crystalline specimens of oximes, semicarbazones or 2,4-dinitrophenyl-hydrazones could not be obtained despite repeated "recrystallisation" and chromatography. Leggate[25] prepared an analogous compound (E53a and b) from the 10-carbethoxy-octalone (E54) and found that the yields were improved by using diethylene glycol as the solvent.

The third fraction was not identified conclusively but there was evidence to suggest that it was a mixture of the diastereoisomeric forms of 1-alkyl-7,7,10-trimethyl-Δ^{8}-octal-2-one (E49a and b). It was a low-melting crystalline solid with no strong absorption in the ultra-violet. The infra-red spectrum indicated that the compound contained an exocyclic methylene group (ν, 885cm.$^{-1}$) and a saturated ketone in a six-membered carbocyclic ring (ν, 1709cm.$^{-1}$). Two structures were possible, therefore, for this compound, namely: 1-alkyl-7,7,10-trimethyl-Δ^{8}-octal-2-one (E49a and b) or the dialkyl compound (E50). Analytical data were consistent with the mono-alkyl formula (E49a and b), which was also suggested from a consideration of the amount of (+)-methylene-bromide (E1) used up in the experiment. Molecular-weight determinations were in fairly close agreement with the monoalkyl structure. This compound was stable to prolonged treatment with acid and did not react with lithium methyl under conditions

which converted the tetracyclic $\alpha\beta$- unsaturated-ketones (E45a and b) to a mixture of the tetracyclic-diols (E51a and b) and the tetracyclic-dienes (E64a and b).

The mixture of isomeric 1-alkyl-7,7,10-trimethyl-$\Delta^{1(9)}$-octal-2-ones (E45a and b) was reduced with lithium in liquid ammonia. In general, the product obtained by reduction of octalones under these conditions will be the more stable decalone, which may be either <u>cis</u> or <u>trans</u>, the important condition being that the newly introduced hydrogen atom must be axial to the ketone ring.[27] In this case the expected product was a mixture of the diastereoisomeric forms of 1-alkyl-7,7,10-trimethyl-<u>trans</u>-decal-2-one (E52a and b). The mixture was resolved by chromatography on alumina followed by several recrystallisations into two diastereoisomers, A and B, each of which was obtained in 10% yield.

Isomer B was more soluble in petrol and less strongly adsorbed on alumina than was isomer A. Isomer A had the lower melting-point (148-149°) and a positive rotation ($[\alpha]_D$ + 13.5°), whilst isomer B had a higher melting-point (156-157°) and a negative rotation ($[\alpha]_D$ - 7°). In the light of subsequent experiments (see page 85), which were not conclusive, isomer A was assigned the structure (E52a), which has a stereochemistry corresponding to that of the naturally occurring triterpenes. Isomer B would have,

therefore, the structure (E52b), which corresponds to an "unnatural" series with the stereochemistry of the D-E ring junction enantiomeric to that of the natural series. The infra-red spectra of these isomers, in nujol mull (see Table 1), had significant differences in the carbonyl and 900cm.$^{-1}$ regions. These variations were attributed to the different crystalline forms of the two isomers.

Table 1.

Isomer A	Nujol	1704cm.$^{-1}$	899cm.$^{-1}$
	CS_2	1712cm.$^{-1}$	907,883cm.$^{-1}$
Isomer B	Nujol	1715cm.$^{-1}$	906cm.$^{-1}$
	CS_2	1715cm.$^{-1}$	903,880cm.$^{-1}$

Table 2.

Compound	Infra-red absorption cm.$^{-1}$.
methylene-bromide (E1)	893
methylene-acetate (D31)	879
methylene-alcohol (D28)	893
methylene-acid (D33)	885
1-alkyl-Δ^{8}-octalones (E49a and b) or 1,1-dialkyl-Δ^{8}-octalones (E50)	888
1-alkyl-$\Delta^{1(9)}$-octalones(E45a and b)	904,881
1-alkyl-trans-decalone (E52b?)	903,880 906
1-alkyl-trans-decalone (E52a?)	903,883 899
1-alkyl-10-carbethoxy-$\Delta^{1(9)}$-octalone (E53a or b), prepared by Leggate.	900,880

The positions of the -C-H out-of-plane deformation bands of the exocyclic methylene group, in the infra-red spectra of the series of compounds prepared during the present work are given in Table 2.

The influences of environment are demonstrated from a consideration of the variation in the frequencies of this series. The split band occurring in the spectra of the 1-alkyl-trans-decalones and 1-alkyl-$\Delta^{1(9)}$-octalones may be attributed to a non-bonded interaction between the carbonyl group and the exocyclic methylene group.

The C,30-tetracyclic-alcohols (E51a and/or b) were prepared by treating the tetracyclic-saturated ketones (E52a and/or b) with an excess of lithium methyl. It was not expected that the addition of lithium methyl to the ketone would be stereospecific and the product of this reaction, which was an intractable gum, would be, therefore, a mixture of isomeric alcohols. This product had absorption bands at 3400cm.$^{-1}$ (hydroxyl) and 892cm.$^{-1}$ (exocyclic methylene) in the infra-red and it was used without purification in a series of attempted cyclisations.

It was expected (see p. 60) that the product of the acid-catalysed cyclisation of these alcohols would be a mixture of hydrocarbons, which might contain, among other compounds, pentacyclic systems such as olean-13(18)-ene (E7),

olean-12-ene (E8), 18α-olean-12-ene (E9), olean-18-ene (E10), olean-9(11)-ene (E12) and 18α-olean-9(11)-ene (E11). It was hoped that olean-13(18)-ene and 18α-olean-12-ene would be the principal constituents of the mixture[3] obtained by cyclisation under conditions in which thermodynamic equilibration of the product was possible.

It is thought that acid-catalysed cyclisation of a tetracyclic alcohol (E51a or b) will be initiated by the formation of a carbonium ion (E55), which would attack C-8 (triterpene numbering) to give an intermediate (E56). Loss of a proton from this intermediate, or from one of its isomers, would result in the formation of hydrocarbons with the oleanane carbon skeleton. It is possible that considerable rearrangement[36] of the initially formed pentacyclic system will occur under strongly acidic reaction conditions. Other products may arise by rearrangement of the intermediate cation (E55), before cyclisation, to give cations (e.g. E57) from which spiran structures (e.g. E58) may be derived. Stork[29] has suggested that very little cyclisation will occur and that the principal product, obtained by treating the tetracyclic-alcohols (E51a and b) with acid, will be a tetracyclic hydrocarbon (e.g. E59). The yields of pentacyclic material isolated from the cyclisations reported in the literature were low. Thus β-onocerenedione (E60)[30] and pentacyclosqualene

(E61)[31] were obtained in 10% yield and olean-11(12),13(18)-diene (E62)[32] in 2% yield; the yields in the first two examples were enhanced by the unique symmetry of the molecule.

In the present work the cyclisation was initiated with boron trifluoride-etherate. Spectroscopic analysis of the products indicated that they were hydrocarbons containing one or more double bonds. Attempts to isolate a pentacyclic compound were unsuccessful and were hindered by its weak adsorption on alumina and by the absence of functional groups with which the progress of purification processes could be followed spectroscopically.

The attempted cyclisation of the isomeric tetracyclic-alcohols (E51a and b) gave a product which was isolated, after chromatography and recrystallisation, as a low melting solid. The infra-red spectrum had bonds at 3030cm.$^{-1}$ and 821cm.$^{-1}$, which were attributed to the presence of a trisubstituted double bond. The peak intensity[14] (z) of the band at 821cm.$^{-1}$ (z,6) was compared with the intensities of the bands at 815cm.$^{-1}$ (z,30) and 828cm.$^{-1}$ (z,22) assigned by Cole and Thornton[33] to the trisubstituted double bond in β-amyrin. The intensity of the end-absorption in the ultra-violet (see Table 3) was compared with that of β-amyrin,[34] δ-amyrin,[34] β-amyrene,[34] δ-amyrene,[34] the (+)-bromide (E63) and with those values obtained by Ellington and Henkins[38] from a

consideration of a number of compounds containing tetra-substituted double bonds. In view of later work by Spring et al.[3] it is probable that the figures quoted for δ-amyrin and δ-amyrene are incorrect and apply to a mixture of 3-hydroxy-olean-13(18)-ene and 3-hydroxy-18α-H-olean-13(18)-ene and to a mixture of the corresponding desoxy compounds respectively.

Table 3.

Substance	ϵ_{2400}	ϵ_{2100}
Synthetic mixture	650	6000
δ-amyrin		7800
δ-amyrene	1000	
β-amyrin		3000
β-amyrene	110	
(+)-bromide (M63)	108	4980
>C=C< (not exocyclic)		3400-4700
>C=C< (doubly exocyclic)		10000-10700

Halsall[34] has shown that the intensity of the end absorption, due to isolated double bonds, is related closely to the degree of substitution and to the environment of those bonds. This relationship applies also to the peak intensities of infra-red bands and in view of this there is little justification for drawing conclusions from these data unless all the compounds, under consideration, are of known structure.

However an optimistic suggestion was made that the

product of cyclisation was completely pentacyclic and that it consisted of only two compounds, one (ca. 25% - - infra-red data) containing a trisubstituted double bond and the other (ca. 75%) containing a tetrasubstituted double bond. It was assumed that the values of ϵ_{2100} and ϵ_{2400} for the compound containing the trisubstituted double bond were similar to those for β-amyrin and β-amyrene. The contribution which this compound would make to the end-absorption of the product of cyclisation was subtracted from the observed value and from the resulting figures two values, namely ϵ_{2100} = 7,000 ϵ_{2400} = 830, were calculated for the end absorption of the compound containing the tetrasubstituted double bond.

A similar calculation was made assuming that the product of cyclisation was completely tetracyclic and that it contained two compounds, both of which had two double bonds. One compound (ca. 25%) was assumed to have 1 tetra- and 1 tri-substituted double bond and the other (ca. 75%) two tetrasubstituted double bonds. Values of ϵ_{2100} = 3,000 and ϵ_{2400} = 356 were calculated for the contribution of each tetrasubstituted double bond. These calculations must be regarded with reserve but seem to indicate that the product under consideration was a complex mixture.

The tetracyclic-alcohol (E51a or b) derived from the ketone (E45a or b), $[\alpha]_D$ - 7°, was treated with boron

trifluoride-etherate. The product, isolated as in the previous experiment, was a low melting solid with a positive rotation and its ultra-violet spectrum was identical with that of the material obtained from the tetracyclic-alcohols (E51a and b). The infra-red spectrum had bands at 828cm.$^{-1}$ and 815cm.$^{-1}$. The physical properties of this product were unchanged after it had been treated with either phosphoric acid or a mixture of sulphuric and acetic acids.

The product obtained from the tetracyclic-alcohol (E51a or b), derived from the ketone (E45a or b), $[\alpha]_D$ + 13.5°, was similar to the previous reaction product except that it had a negative rotation, $[\alpha]_D$ = -16°. This value was compared with that of the equilibrium mixture of olean-13(18)-ene and 18αH-olean-12-ene ($[\alpha]_D$ = -20°),[3] which has a melting point of 187°. On the basis of the rotation of this product the tetracyclic-ketone, from which it was derived, was assigned the absolute configuration (E45a).

Oxidation of the products of these cyclisations with selenium dioxide and chromic acid gave materials which could not be identified and these reactions were not pursued.

At this stage of the work the synthesis of olean-11(12),13(18)-diene (E62) was achieved by Corey *et al.*[32] It is probable that side-reactions, similar in nature to those described on page 81, occur during the cyclisation and may

account for the low yield (ca. 2%). Corey has pointed out that the characteristic ultra-violet spectrum of olean-11(12), 13(18)-diene (E62) is of immense value as a tool by which the progress of purification procedures can be followed.

In view of the failure to identify a pentacyclic compound in the reaction products obtained by treating the tetracyclic-alcohols (E51a and b) with acids, it was decided to investigate the cyclisation of the tetracyclic-hydrocarbons (E64a and b), which were obtained readily from the tetracyclic-$\alpha\beta$-unsaturated-ketones (E45a and b) by reacting them with a large excess of methyl magnesium iodide. It is reported[32] that the tetracyclic-$\alpha\beta$-unsaturated-ketones (E45a and b) react with lithium methyl to give the tetracyclic allylic-alcohols (E68a and b). In the present work this procedure resulted always in partial dehydration of the tertiary alcohols and the product was a mixture, containing the alcohols and the hydrocarbons, the proportions of which could be estimated spectroscopically. The mixture of tetracyclic-hydrocarbons (E64a and b) had an ultra-violet absorption spectrum characteristic of a heteroannular conjugated diene, λmax 2370(16,070), 2450(16,690), λ sh. 2525Å.

Another factor, which might account for the poor yields of pentacyclic materials, is the possible instability of the product under the conditions of cyclisation. A series

of experiments was carried out, therefore, to determine the stability of 3β-benzoyl-olean-11(12),13(18)-diene (E65) towards a number of acidic reagents any of which might be used to initiate cyclisation.

3β-Benzoyl-olean-11(12),13(18)-diene was prepared by oxidising 3β-benzoyl-olean-12-ene (E66) with selenium dioxide. The results of this series of experiments on the stability of the diene are given in Table 4; in each case the percentage recovery of the diene was calculated by comparing the extinction coefficient of the product at 2500Å with that of authentic 3β-benzoyl-olean-11(12),13(18)-diene, (λ max 2350(35,290), 2420(37,730), 2500(41,470) and 2590Å(26,530))

Table 4.

Reagent.	Time of reaction (hr.).	% recovery of diene benzoate.
BF_3Et_2O (20°)	15	75
HBF_4 in sulpholane (20°)	24	69
H_3PO_4/HAc (85°)	16	100
Polyphosphoric acid (85°)	15	100
BF_3 in chloroform (20°)	15	0
H_2SO_4/HAc (90°)	15	0
H_2SO_4/HAc (20°)	72	40
HAc/$HClO_4$ (20°)	48	75
HCl/HAc (20°)	24	80
$AlCl_3$ in nitromethane (20°)	24	80

It was evident, from a consideration of the results in Table 4, that a wide choice of reagents was available for the cyclisation.

A number of small scale (ca. 10mg.) experiments were carried out to determine the optimum conditions necessary for the cyclisation of the tetracyclic-hydrocarbons (E64a and b). The expected product was olean-11(12),13(18)-diene (E62) (λmax 2420(26,670), 2500(29,860), 2590Å(19,710)) together with its ring D/E enantiomer (E67), which should have a similar ultra-violet spectrum. Other products, containing a heteroannular conjugated diene system, would be expected to have similar spectra and their presence might be the cause of the slight variations in the relative intensities and the wavelengths (see Table 5) in the spectra of the products of the cyclisations, compared with the spectrum of authentic olean-11(12),13(18)-diene.

Products with ultra-violet spectra similar to the spectrum of olean-11(12),13(18)-diene were obtained by cyclisation with the reagents listed in Table 5. The 2590Å peak, which occurs in the authentic spectrum, appeared as a broad shoulder in each case. Cyclisation using the conditions described by Corey et al.[31] (hydrogen chloride in acetic acid) gave a product which had only a single

Table 5.

Reagent.	λ max Å(ϵ).
BF_3Et_2O	2420(4,948) 2510(4,596) 2590(sh.)
HBF_4 in sulpholane[36]	2420(5,546) 2500(5,325) 2580(sh.)
$AlCl_3$ in nitromethane/ether[35] (2:1)	2420(7,134) 2510(5,500) 2590(sh.)

absorption maximum at 2420Å. There were, in addition, slight shoulders at 2500Å and 2600Å.

The ultra-violet spectra of the products obtained in all other cyclisations did not show any maximum absorption. In each case there was intense end-absorption extending to 2800 - 3000Å. Slight shoulders were observed at approximately 2400, 2500 and 2600Å and it was assumed from these that some olean-11(12),13(18)-diene was present. Table 6 lists the reagents used in these cyclisations and summarises the intensities of the end-absorptions for the wavelengths at which shoulders appeared. The tetracyclic-hydrocarbons (E64a and b) were recovered from attempted cyclisations with phosphoric and polyphosphoric acids.

Table 6.

Reagent.	ϵ
HCOOH	(2100) 17,960 (2500) 4,110
HAc/$HClO_4$	(2031) 15,290 (2400) v. weak sh. (2480) 3,186 (2570) 1,913
H_2SO_4/HAc	(2032) 17,470 (2420) v. weak sh. (2500) 4,224 (2600) v. weak sh.
$AlCl_3$ in nitro-methane/HAc (1:2)	(2100) 16,800 (2420) 6,112 (2510) 5,290 (2590) 4,537

It was observed that a violet colour was formed when the cyclising agent (except phosphoric acid) was added to the tetracyclic-hydrocarbons and that the reagents listed in Table 5 produced a more intense colour than those listed in Table 6. During the course of the reaction the colour changed from violet to red and this change occurred much more slowly with the reagents listed in Table 5 than with those in Table 6. The colour change must be associated with a derivative of the conjugated diene system in (E64a and b) because no similar colours have been observed in the previous work.[37] It is of interest to note that Heilbron *et al.* observed a violet colour whilst investigating the cyclisation of squalene.

The results of the preliminary cyclisations indicate that the most suitable reagents are strong acids (e.g. HBF_4[36]) or electron acceptors (e.g. $AlCl_3$[35]). The importance of the choice of the solvent system is demonstrated by comparing the ultra-violet spectra of the products obtained from the cyclisations initiated with aluminium trichloride.

A large scale cyclisation has been carried out using aluminium trichloride in nitromethane and ether. Olean-11(12),13(18)-diene has not been isolated yet and a preliminary attempt to resolve the mixture obtained from this reaction has indicated that extensive chromatography will be necessary.

It is proposed to repeat the alkylation described in this section using the (+)-octalone (E70). Section III of this thesis describes the approaches investigated in the attempted preparation of this (+)-octalone.

EXPERIMENTAL. SECTION II.

2,5,5-Trimethylcyclohexan-1,3-dione.

Commercial dimedone was recrystallised from acetone and had m.p. 149°.

Dimedone (250g., 1.78 mol.) was methylated using the procedure described by Halsall and Thomas.[1] 2,5,5-Trimethylcyclohexan-1,3-dione (150g., 55%) was obtained m.p. 155-159° (decomp.).

Halsall and Thomas[1] quote m.p. 158-159° (decomp.).

3-Chloro-2,5,5-trimethylcyclohex-2-en-1-one.

A solution of 2,5,5-trimethylcyclohex-2-en-1-one (77g., 0.5 mol.) in anhydrous chloroform (500 c.c.) was treated with phosphorus trichloride (26 c.c.) using the conditions described by Halsall and Thomas.[1] 3-Chloro-2,5,5-trimethylcyclohex-2-en-1-one (43g., 49%) was obtained as an oil, b.p. 88°/20 m.m., n_D^{20} 1.4961.

Halsall and Thomas[1] quote b.p. 76-78°/4.8mm., n_D^{20} 1.4962.

2,5,5-Trimethylcyclohexanone.

A solution of the enol-chloride (E15) (100g., 0.58 mol.) in ether (300 c.c.) was added during 1 hr. to a solution of lithium (20g.) in liquid ammonia (2L). The procedure described by Halsall and Thomas[1] was followed and

2,5,5-trimethylcyclohexanone (31g., 38%) was obtained as an oil, b.p. 68°/14mm., n_D^{20} 1.4463; the 2,4-dinitrophenylhydrazone had m.p. 114-115°.

Halsall and Thomas[1] quote b.p. 71-73°/12mm., n_D^{20} 1.4460 for 2,5,5-trimethylcyclohexanone and m.p. 115-118° for the 2,4-dinitrophenylhydrazone.

7,7,10-Trimethyl-$\Delta^{1(9)}$-octal-2-one.

i.) 4-Diethylaminobutan-2-one and its methiodide were prepared using the procedures described by Halsall and Thomas[1].

ii.) Methyl vinyl ketone (200 c.c.) was purified by heating it under reflux for 2 hr. with acetic anhydride (60 c.c.). The mixture was fractionally distilled through a 12in. Dixon column and the fraction, b.p. 80-81°, was collected.

a.) Using the methiodide of 4-diethylaminobutan-2-one.

The experimental procedure is that used by Halsall and Thomas[1].

A solution of the methiodide of 4-diethylaminobutan-2-one (9.9g., 0.045 mol.) in absolute ethyl alcohol (12 c.c.) was added to a solution of freshly prepared sodamide (9.0g., 0.23 mol.) and 2,5,5-trimethylcyclohexanone (9.4g., 0.09 mol.) in absolute ethyl alcohol (25 c.c.). The mixture was stirred for 15 hr. at room temperature in an atmosphere of nitrogen and

then heated under reflux for 1 hr. and finally left at room temperature for a further 1 hr.. The reaction mixture was acidified with hydrochloric acid and the product, which was isolated *via* ether, was distilled to give:

i.) 2,5,5-trimethylcyclohexanone (5.1g., 54%), b.p.72°/15mm..

ii.) an oil (2.1g.), b.p. (oil-bath) 110-130°/0.1mm., ν(film), 3400,1708,1666cm.$^{-1}$.

A solution of this oil in ethyl alcohol (50 c.c.) and hydrochloric acid (4 c.c.) was left at 20° for 15 hr.. Water (250 c.c.) was added and the product, which was isolated *via* ether, was distilled to give 7,7,10-trimethyl-$\Delta^{1(9)}$-octal-2-one (1.8g., 14.2%), b.p. (oil-bath) 125-130°/0.1mm., λmax 2390Å(17,280), ν(film), 1666cm.$^{-1}$, n_D^{18} 1.5068. (Found: C, 81.2; H,10.7. Calc. for $C_{13}H_{20}O$: C,81.3; H,10.4%).

Halsall and Thomas[1] quote b.p. (bath) 110-115°/0.5mm. n_D^{20} 1.5070, λmax 2430Å(17,000).

The 2,4-dinitrophenylhydrazone separated as red needles from chloroform/ethyl alcohol, m.p. 151°, λmax 3910Å (21,120). (Found: C,61.1; H,6.5; N,15.0. Calc. for $C_{19}H_{24}N_4O_4$: C,61.3; H,6.5; N,15.1%).

Halsall and Thomas[1] quote m.p. 148.5-150° (plates from ethyl acetate/ethyl alcohol), λmax 3910-3930Å(22,250) (in chloroform/ethyl alcohol).

b.) Using 4-diethylaminobutan-2-one.

Sodium (0.6g.) was added in small pieces to a

mixture of 2,5,5-trimethylcyclohexanone (31.8g., 0.225 mol.) and 4-diethylaminobutan-2-one (7.5g., 0.051 mol.). The mixture was kept at room temperature in an atmosphere of nitrogen until all the sodium had dissolved and it was then heated at 135° for 3hr.. The mixture was cooled and acidified with hydrochloric acid. The product was isolated via ether and was treated, before distillation, with ethanolic hydrochloric acid as in (a.). The product obtained was distilled to give:

i.) 2,5,5-trimethylcyclohexanone (21g., 66%), b.p.72°/15mm..

ii.) 7,7,10-trimethyl-$\Delta^{1(9)}$-octal-2-one (9.6g., 22%), b.p. 79-80°/0.05mm., n_D^{20} 1.5061, λ max 2390Å(17,210). The 2,4-dinitrophenylhydrazone had m.p. 151°.

c.) Using methyl vinyl ketone.

2,5,5-Trimethylcyclohexanone (17.5g., 0.125 mol.) was added during 15 min., to a solution of sodium ethoxide (from sodium (1.5g., 0.065 mol.)) in absolute ethyl alcohol (100 c.c.). The mixture was stirred at -10° in an atmosphere of nitrogen and a solution of methyl vinyl ketone (24 c.c.) in dioxan (36 c.c.) was added dropwise during 1 hr.. The reaction mixture was kept at -5° for 20 hr. and at 20° for 1 hr.. Glacial acetic acid (5 c.c.) was added and ethyl alcohol was removed by distillation. Ether (300 c.c.) and water (300 c.c.) were added to the residue and the mixture was

shaken vigorously. The ethereal solution was separated and washed with sodium carbonate solution (3 x 50 c.c.) and the product, which was isolated in the usual way, was treated, before distillation, with ethanolic hydrochloric acid as in (a.). The product obtained was distilled to give:

i.) 2,5,5-trimethylcyclohexanone (3.5g., 20%), b.p.72°/15mm..

ii.) 7,7,10-trimethyl-$\Delta^{1(9)}$-octal-2-one (13g., 54%), b.p. 78-81°/0.05mm., n_D^{20} 1.5061. The 2,4-dinitrophenylhydrazone had m.p. 151°.

7,7,10-Trimethyl-cis-decal-2-one.

The procedure is that described by Halsall and Thomas.[1]

A solution of 7,7,10-trimethyl-$\Delta^{1(9)}$-octal-2-one (7.7g., 0.04 mol.) in ethyl acetate (100 c.c.) was hydrogenated in the presence of Adam's catalyst (0.2g.). Hydrogen (910 c.c., 0.041 mol.) was absorbed. The suspension was filtered, the filtrate was evaporated and the residue was recrystallised from petrol. 7,7,10-Trimethyl-cis-decal-2-one (7.5g., 96%) separated as needles, m.p. 68°, $\nu(CS_2)$, 1704cm.$^{-1}$. Halsall and Thomas[1] quote m.p. 67.5-68° (from aqueous methyl alcohol).

3-Ethyl-7,7,10-trimethyl-cis-decal-2-one.

a.) Alkylation using sodium tert-amyloxide as the base.

Freshly prepared sodium tert-amyloxide (1.7g.,

0.02 mol.) was added to a solution of the cis-decalone (E2) (390mg., 0.002 mol.) and ethyl iodide (3.1g., 0.02 mol.) in benzene (5 c.c.). The mixture was heated under reflux in an atmosphere of nitrogen for 6 hr.. Benzene (100 c.c.) was added and the resulting solution was washed with hydrochloric acid (3 x 25 c.c.). The product, which was isolated in the usual way, was an oil (400mg.) and was adsorbed on deactivated alumina (40g.). Two fractions were collected.

i.) petrol (160 c.c.), containing 3-ethyl-7,7,10-trimethyl-cis-decal-2-one (88mg., 20%), n_D^{17} 1.4828. The 2,4-dinitrophenylhydrazone separated as plates from ethyl acetate/ethyl alcohol, m.p. 185°.

ii.) petrol (300 c.c.), containing 7,7,10-trimethyl-cis-decal-2-one (300mg., 77%), m.p. 68°.

b.) Alkylation using potassium tert-butoxide as the base.

The cis-decalone (E2) (2.25g., 0.012 mol.) was added to a solution of potassium (1.7g., 0.04 mol.) in tert-butyl alcohol (10 c.c.). The mixture was kept at 50° for 5 min. and then ethyl iodide (11g., 0.07 mol.) was added and the resulting solution was heated under reflux for 3 hr. in an atmosphere of nitrogen. Water (200 c.c.) was added and the product was isolated via ether. An oil (2.6g.) was obtained and was adsorbed on deactivated alumina (250g.). Elution with petrol (1L) gave, after distillation, 3-ethyl-7,7,10-trimethyl-cis-decal-2-one (2.2g., 85%) as an oil,

b.p. (oil-bath) 150-155°/0.05mm., n_D^{17} 1.4829. (Found: C,81.5; H,12.0. $C_{15}H_{26}O$ requires: C,81.1; H,11.7%).

The 2,4-dinitrophenylhydrazone crystallised from ethyl acetate/ethyl alcohol as orange plates, m.p. 185-186°. (Found: C,62.5; H,7.8; N,14.2. $C_{19}H_{30}N_4O_4$ requires: C,62.7; H,7.5; N,13.9%).

3-Ethyl-7,7,10-trimethyl-Δ^3-cis-octal-2-one.

A solution of the 3-ethyl-cis-decalone (E27) (1.5g., 0.0068 mol.) in ether (50 c.c.) was stirred at room temperature and a solution of bromine (0.84g., 0.007 mol.) in acetic acid (9 c.c.) was added dropwise so that each drop was added only when the colour due to the previous drop had disappeared. Ether (100 c.c.) was added and the ethereal solution was washed with sodium sulphite solution (3 x 20 c.c.), sodium bicarbonate solution (3 x 20 c.c.), water (3 x 20 c.c.) and saturated brine. Evaporation of the ether gave an oil which was dissolved in dimethylformamide (20 c.c.), containing lithium carbonate (2g.). This mixture was heated at 100° for 2 hr. and then hydrochloric acid (50 c.c.) was added and the product (1.4g.), which was isolated *via* ether, was adsorbed on deactivated alumina (140g.). Elution with petrol (300 c.c.) gave, after evaporation, an oil (20mg.) which was not characterised but which was assumed to be 3-ethyl-7,7,10-trimethyl-$\Delta^{1(9)}$-octal-2-one, λmax 2410Å(9,500). Elution with

petrol-benzene (450 c.c., 9:1) gave, after distillation, 3-ethyl-7,7,10-trimethyl-Δ^{3}-cis-octal-2-one (0.64g., 43%), b.p. (oil-bath) 140-150°/0.05mm., λmax 2370Å(9,200). (Found: C,81.7; H,10.9. $C_{15}H_{24}O$ requires: C,81.8; H,10.9%). The 2,4-dinitrophenylhydrazone crystallised from ethyl alcohol as red needles, m.p. 156-157°. (Found: C,62.4; H,7.3; N,14.0. $C_{21}H_{28}N_4O_4$ requires: C,62.5; H,7.0; N,14.0%).

3-Formyl-7,7,10-trimethyl-cis-decal-2-one.

Freshly prepared sodium methoxide (4.6g., 0.084 mol.) was added to a solution of 7,7,10-trimethyl-cis-decal-2-one (5.4g., 0.028 mol.) and ethyl formate (5.3g., 0.14 mol.) in benzene (200 c.c.). The mixture was stirred at 25° for 15 hr. in an atmosphere of nitrogen and then poured into ice-cold water (100 c.c.). The aqueous phase was separated and the benzene solution was extracted with sodium hydroxide solution (4 x 50 c.c.).

Evaporation of the benzene solution gave unchanged cis-decalone (180mg.).

The combined alkaline extracts were acidified with hydrochloric acid and the crude 3-formyl-cis-decalone (E35) (5.6g., 91%) was isolated with ether in the usual way. A sample (100mg.) of this oil was adsorbed on silica gel (10g.). Elution with petrol-benzene (100 c.c., 1:1) yielded, after

evaporation, 3-formyl-7,7,10-trimethyl-cis-decal-2-one (95mg.) as a viscous oil, n_D^{22} 1.5605, λ max 2840Å(6,210), λ max(in 0.02N ethanolic sodium hydroxide solution) 3150Å(7,000), ν(film), 1690,1653,1600cm.$^{-1}$ (β-hydroxy-$\alpha\beta$-unsaturated ketone). (Found: C,75.3; H,9.8. $C_{14}H_{22}O_2$ requires: C,75.7; H,9.9%).

Sondheimer and Wolfe quote λ max (crude product) 2820Å(5,500).

3-Anilinomethylene-7,7,10-trimethyl-cis-decal-2-one.

The 3-formyl-cis-decalone (E35) (4.4g., 0.02 mol.) and N-methyl-aniline (2.6g., 0.024 mol.) were dissolved in benzene (200 c.c.), which was distilled slowly from the solution during 3 hr.. The residue was dissolved in ether (200 c.c.) and unchanged 3-formyl-cis-decalone was removed by washing the ethereal solution with sodium hydroxide solution (3 x 50 c.c.). The ethereal solution was evaporated and the residue was recrystallised from petrol. 3-Anilinomethylene-7,7,10-trimethyl-cis-decal-2-one (4.9g., 80%) separated as yellow plates, m.p. 132-133°, ν(nujol), 1666cm.$^{-1}$ ($\alpha\beta$-unsaturated ketone). (Found: C,81.4; H,9.1; N,4.4. $C_{21}H_{29}NO$ requires: C,81.0; H,9.3; N,4.5%).

Hydrolysis of 3-anilinomethylene-7,7,10-trimethyl-cis-decal-2-one.

A suspension of the 3-anilinomethylene-cis-decalone (E34) (311mg., 0.001 mol.) and hydrochloric acid

(100 c.c. 10%) was heated at 100° for 30 min.. The product was isolated with ether and was dissolved in sodium hydroxide solution (100 c.c., 20%). The solution was heated under reflux for 2 hr.. Extraction with ether gave, after treatment in the usual way, an oil (214mg.) which was adsorbed on deactivated alumina (20g.). Elution with petrol (200 c.c.) gave, after evaporation of the solvent, a solid which was recrystallised from petrol. 7,7,10-Trimethyl-cis-decal-2-one (151mg., 78%) separated as colourless needles, m.p.68°, undepressed on admixture with an authentic sample.

Attempted alkylation of 3-anilinomethylene-7,7,10-trimethyl-cis-decal-2-one.

a.) With potassium tert-butoxide.

The 3-anilinomethylene-cis-decalone (E34) (933mg., 0.003 mol.) was added to a solution of potassium (0.51g., 0.0135 mol.) in tert-butyl alcohol (10 c.c.)*. The mixture was heated under reflux in an atmosphere of nitrogen for 1 hr.; ethyl iodide (2.1g., 0.0135 mol.) was then added and refluxing was continued for a further 24 hr.. (More ethyl iodide (2.1g., 0.0135 mol.) was added after 6 hr. and after 12 hr.). Hydrochloric acid (200 c.c.) was added to the reaction mixture and the product† (1g.) was isolated with ether. The infra-red spectrum of the product was closely similar to that of the 3-anilinomethylene-cis-decalone. The product was hydrolysed

using the procedure described in the previous experiment and the cis-decalone (E2) (300mg., 51%) was recovered. (m.p.68°). No other ketonic material was obtained.

In a second experiment using 100 mole excess of base only 10% of cis-decalone was recovered.

b.) With sodamide in benzene.

Freshly prepared sodamide (1.17g., 0.03 mol.) was added to a solution of the 3-anilinomethylene-cis-decalone (933mg., 0.003 mol.) in benzene (20 c.c.). The subsequent experimental procedure was identical with that described after the asterisk in (a.). The cis-decalone (135mg. 23%) was the only ketonic material recovered.

c.) With sodamide in liquid ammonia.

Sodium (700mg.) was dissolved in liquid ammonia (50 c.c.) containing one crystal of ferric nitrate. When the blue colour had disappeared a solution of the 3-anilino-methylene-cis-decalone (103mg., 0.0003mol.) in ether (3 c.c.) was added and the mixture was stirred for 2 hr.. Ethyl iodide (12g.) was added and stirring was continued for 1 hr., during which time ammonia evaporated. Hydrochloric acid (100 c.c.) was added and a procedure similar to that described after the symbol † in (a.) was followed. The cis-decalone (20mg., 3%) was the only ketonic material recovered.

d.) With sodium tert-amyloxide.

Freshly prepared sodium tert-amyloxide (1.2g.,

0.0108 mol.) was added to a solution of the 3-anilino-methylene-cis-decalone (311mg., 0.001 mol.) and ethyl iodide (1.87g., 0.012 mol.) in benzene (6 c.c.). The solution was heated under reflux in an atmosphere of nitrogen for 24 hr.. A white precipitate separated during this time. Hydrochloric acid (50 c.c.) was added to the reaction mixture and the product was extracted with ether. Isolation in the usual way gave an oil (390mg.), λ_{max} 2840Å(810), ν(film), 1706 (saturated ketone), 1650-1590cm.$^{-1}$ (broad absorption, β-hydroxy-αβ-unsaturated ketone). This oil was adsorbed on deactivated alumina (25g.). Elution with petrol (150 c.c.) gave, after distillation, 3-ethyl-7,7,10-trimethyl-cis-decal-2-one (83mg., 13%), b.p. (oil-bath) 145-150°/0.04mm., n_D^{17} 1.4825. 2,4-Dinitrophenylhydrazone, m.p. 185°, undepressed on admixture with an authentic sample.

Bromination of 7,7,10-trimethyl-cis-decal-2-one.

The cis-decalone (E2) (1g., 0.0052 mol.) was dissolved in ether (25 c.c.) containing 1 drop of hydrobromic acid solution (50% w/v in acetic acid) and the mixture was stirred at 0°. A solution (51.2 c.c.) of bromine in acetic acid (prepared by dissolving bromine (0.525 c.c.) in acetic acid (100 c.c.)) was added dropwise, so that each drop was added only when the colour due to the previous one had disappeared. Ether (50 c.c.) was added and the ethereal

solution was washed with water (3 x 15 c.c.), sodium bicarbonate solution (6 x 15 c.c.), water (15 c.c.) and saturated brine. Evaporation of ether gave an oil (1246mg.), λmax 2300-2390Å(1,000). A pure bromoketone could not be isolated from this oil.

Dehydrobromination of the bromoketone(s).

The crude product obtained in the previous reaction was dehydrobrominated in three ways.

a.) With lithium carbonate/dimethylformamide.

A solution of this product (623mg.) and lithium carbonate (1g.) in dimethylformamide (5 c.c.) was heated under reflux for 2 hr.. Water (50 c.c.) was added and the product was isolated with ether. An oil (476mg.) was obtained and was chromatographed on alumina (50g.). Three fractions were collected:

i.) petrol-benzene (500 c.c., 4:1), containing the cis-decalone (E2) (50mg.), m.p. 68°

ii.) petrol-benzene (500 c.c., 1:1), containing 7,7,10-trimethyl-Δ^{3}-cis-octal-2-one (263mg., 59%), b.p. (oil-bath) 110-115°/0.05mm., λ max 2285Å(17,284). (Found: C,81.2; H,10.5. Calc. for $C_{13}H_{20}O$: C,81.3; H,10.4%). The 2,4-dinitrophenylhydrazone was recrystallised from chloroform-ethyl alcohol and separated as red needles, m.p. 208-209°, λ max 3820Å(21,350). (Found: C,61.1; H,6.6; N,15.2. Calc. for $C_{19}H_{24}N_4O_4$: C,61.3;

H,6.5; N,15.1%).

Halsall and Thomas[1] quote m.p. 207-209.5°, λ_{max} 3790Å(26,500) in chloroform-ethyl alcohol (1:1).

iii.) benzene-ether (200 c.c., 3:1), containing 7,7,10-trimethyl-$\Delta^{1(9)}$-octal-2-one (111mg., 25%), λ_{max} 2390Å(17,410). The 2,4-dinitrophenylhydrazone was recrystallised from chloroform-ethyl alcohol and had m.p. 151°, λ_{max} 3910Å(20,590).

In a second experiment the crude product (100mg.), obtained by brominating the cis-decalone using the conditions described previously, was dissolved in chloroform (4 c.c.) containing hydrobromic acid solution (0.5 c.c., 50% w/v in acetic acid). The mixture was left at 20° for 20 hr. and the product was then dehydrobrominated. Unchanged cis-decalone (E2), the Δ^{3}-octalone (E36) and the $\Delta^{1(9)}$-octalone (E3) were obtained in the same ratios as those of the first experiment.

b.) With γ-collidine.

The product (310mg.), obtained by brominating the cis-decalone (E2) using the procedure described previously, was dissolved in γ-collidine (5 c.c.) and the solution was heated at 150° for 2 hr.. Water was added and the product was isolated with ether and chromatographed on alumina. The Δ^{3}-octalone (E36) (71mg., 32%) and the $\Delta^{1(9)}$-octalone (E3) (29mg., 13%) were obtained.

c.) With 2,4-dinitrophenylhydrazine.

The crude product (310mg.), obtained by brominating

the cis-decalone using the procedure described previously, was dissolved in acetic acid (5 c.c.). 2,4-Dinitrophenylhydrazine (350mg.) was added and the mixture was heated at 90° for 5 min. in an atmosphere of nitrogen. The solution was cooled and the precipitate was recrystallised from chloroform-ethyl alcohol. The 2,4-dinitrophenylhydrazone of 7,7,10-trimethyl-Δ^{3}-cis-octal-2-one (214mg., 49%) separated, m.p.208-209°, λmax 3820Å(20,980).

Water was added to the mother liquors and the precipitate was recrystallised from chloroform-ethyl alcohol. The 2,4-dinitrophenylhydrazone of 7,7,10-trimethyl-$\Delta^{1(9)}$-octal-2-one (79mg., 18%) separated, m.p. 151°, λmax 3910Å(21,000).

Bromination of 7,7,10-trimethyl-cis-decal-2-one with N-bromosuccinimide.

N-Bromosuccinimide (136mg., 1.05 mol.) and Analar calcium carbonate (200mg.) were added to a solution of the cis-decalone (E2) (140mg., 0.0072 mol.) in carbon tetrachloride (25 c.c.). The suspension was irradiated with a 200 watt lamp for 25 min., the heat from the lamp being sufficient to keep the solution at the temperature of reflux. The solution was filtered and the filtrate was evaporated to yield an oil (203mg.) which was dehydrobrominated with lithium carbonate/dimethylformamide as described previously. The Δ^{3}-octalone

(E36) (75mg., 5%) and the $\Delta^{1(9)}$-octalone (E3) (29mg., 21%) were obtained.

Bromination of 7,7,10-trimethyl-cis-decal-2-one in the presence of sodium acetate.

A solution (4.3 c.c., 1.05N) of bromine in acetic acid was added to a solution of the cis-decalone (E2) (725mg., 0.0037 mol.) and sodium acetate (0.725g.) in acetic acid (10.9 c.c.) and water (2.2 c.c.). The mixture was left at 20° for 24 hr.. The solvent was removed under reduced pressure and the residue was dissolved in ether (50 c.c.) and water (25 c.c.). The product was isolated in the usual way and was dehydrobrominated with lithium carbonate/dimethyl-formamide as described previously. An oil (713mg.) was obtained and was chromatographed on alumina (70g.). Three fractions were collected:

i.) petrol-benzene (1L., 3:1), containing the cis-decalone (E2) (493mg., 68%), m.p. 68°

ii.) petrol-benzene (350 c.c., 1:1), containing the Δ^{3}-octalone (E36) (72mg., 10%), λmax 2285Å(17,520).

iii.) benzene-ether (210 c.c., 3:1), containing the $\Delta^{1(9)}$-octalone (E3) (70mg., 9.8%), λmax 2390Å(17,000).

Enol-acetylation of 7,7,10-trimethyl-cis-decal-2-one.

Acetic anhydride (0.625 c.c.) and perchloric acid

(0.02 c.c., 60%) were added to a solution of the cis-decalone (500mg., 0.0026 mol.) in carbon tetrachloride (9.5 c.c.). The mixture was left at 22° for 15 hr. in an atmosphere of nitrogen. Sodium bicarbonate (1g.) was added and the suspension was shaken for 2 min. and then poured into water (10 c.c.). Isolation *via* ether in the usual way gave an oil (564mg.) which was adsorbed on alumina (70g.). Elution with petrol (175 c.c.) gave, after distillation, 2-acetoxy-7,7,10-trimethyl-Δ^{1}-cis-octalin (535mg., 88%) (or the corresponding Δ^{2}-cis-octalin or a mixture of these two compounds), b.p. (oil-bath) 97-105°/0.07mm., n_D^{27} 1.3532, ν(film), 1754,1220cm.$^{-1}$ (ester). (Found: C,76.0; H,10.4. $C_{15}H_{24}O_2$ requires: C,76.3; H,10.2%).

Bromination of the enol-acetate(s) (E41 and/or E42).

A solution (3 c.c., 1.05N) of bromine in acetic acid was added to a solution of the enol-acetate(s) (E41 and/or E42) (472mg., 0.002 mol.) in pyridine/acetic acid (60 c.c., 10% v/v) and the mixture was left at 23° for 15 hr. in an atmosphere of nitrogen. Ether (200 c.c.) was added; the product was isolated in the usual way and was dehydrobrominated with lithium carbonate-dimethylformamide as previously. 7,7,10-Trimethyl-Δ^{3}-cis-octal-2-one (146mg., 38%) and 7,7,10-trimethyl-$\Delta^{1(9)}$-octal-2-one (62mg., 16%) were obtained.

Attempted alkylation of 7,7,10-trimethyl-Δ^{3}-cis-octal-2-one.

Conditions similar to those described on pp. 101-103 were used in attempts to introduce an ethyl or alkyl group at C-1 of 7,7,10-trimethyl-Δ^{3}-cis-octal-2-one. All were unsuccessful.

Alkylation of 7,7,10-trimethyl-$\Delta^{1(9)}$-octal-2-one with 5-(2-bromoethyl)-6-exomethylene-1,1,10-trimethyl-trans-decalin.

A solution containing 7,7,10-trimethyl-$\Delta^{1(9)}$-octal-2-one (3.84g., 0.02 mol.), 5-(2'-bromoethyl)-6-exomethylene-1,1,10-trimethyl-trans-decalin (6.5g., 0.022 mol.) and freshly prepared sodium tert-amyloxide (4.4g., 0.04 mol.) in toluene (6 c.c.) was heated under reflux in an atmosphere of nitrogen for 24 hr.. Ether (200 c.c.) and water (50 c.c.) were added; the ethereal solution was separated and washed with hydrochloric acid (3 x 30 c.c.) and the product was then isolated in the usual way. An oil (9.1g.) was obtained and was chromatographed on deactivated alumina (1000g.). The following fractions were obtained:

i.) petrol (3L.), containing the (+)-methylene-bromide (R1) (1.63g.).

ii.) petrol (4L.), containing a solid, probably 1-alkyl-7,7,10-trimethyl-Δ^{8}-octal-2-one (R49a and b) (1.68g., 25%), m.p. 73-81° (needles from petrol), λmax 2880Å(34), $\nu(CS_2)$, 3049, 1637

(double bond), 888 (exocyclic methylene), 1700cm.$^{-1}$ (ketone); ν(nujol), 3077, 1634, 888, 1709cm.$^{-1}$, $[\alpha]_D^{22}$ + 30° (M.W: 450; Calc. for $C_{29}H_{46}O$ (monoalkyl): 410; Calc. for $C_{45}H_{72}O$ (dialkyl): 628). (Found: C,85.0; H,11.1. $C_{29}H_{46}O$ requires: C,84.9; H,11.2. $C_{45}H_{72}O$ requires: C,85.0; H,11.5%).

iii.) petrol (8L.), containing 1-alkyl-7,7,10-trimethyl-$\Delta^{1(9)}$-octal-2-one (E45a and b) (4.52g., 68%), n_D^{24} 1.5238, $[\alpha]_D^{20}$ + 10°, $\nu(CS_2)$, 1666 (ketone), 3059 (double bond), 904,881cm.$^{-1}$ (exocyclic methylene), λ max 2500Å°(12,810). (Found: C,85.3; H,10.9. $C_{29}H_{46}O$ requires: C,84.9; H,11.2%).

Fraction (ii.) (60mg.) was dissolved in a solution containing ethyl alcohol (7 c.c.) and hydrochloric acid (3 c.c., 5N). The mixture was heated under reflux for 2 hr. and the product was then isolated in the usual way. The physical properties of the substance obtained were identical to those of the starting material.

1-Alkyl-7,7,10-trimethyl-trans-decal-2-one.

Lithium (1.5g.) was dissolved in liquid ammonia (200 c.c.) and a solution of 1-alkyl-7,7,10-trimethyl-$\Delta^{1(9)}$-octal-2-one (1.2g., 0.003 mol.) in ether (25 c.c.) was added dropwise during 5 min.. The mixture was stirred vigorously for 30 min. and then the lithium complex was decomposed with ammonium chloride. Ammonia was evaporated and the residue

was dissolved in ether (100 c.c.) and water (25 c.c.). The ethereal solution was washed with hydrochloric acid (3 x 15c.c.); the product was isolated in the usual way and was recrystallised from petrol. 1-Alkyl-7,7,10-trimethyl-trans-decal-2-one (E52a and b) (1.17g., 97%) separated as needles, m.p. 105-133°; $[\alpha]_D^{21}$ + 4°, ν(nujol), 1694cm.$^{-1}$ (ketone).

This compound (1g.) was chromatographed on alumina (150g.). Four fractions were collected:

i.) petrol (300 c.c.), 358mg., $[\alpha]_D^{21}$ - 2°

iii.) petrol (150 c.c.), 273mg., $[\alpha]_D^{21}$ 0.

iii.) petrol (150 c.c.), 179mg., $[\alpha]_D^{21}$ 0.

iv.) petrol (750 c.c.), 183mg., $[\alpha]_D^{21}$ + 7°

Each fraction was recrystallised from petrol. An isomer, B (120mg.), was obtained from fraction (i.) and was recrystallised twice from petrol. Isomer B (102mg.) separated as needles, m.p. 156-157°, $[\alpha]_D^{22}$ - 7°, ν(nujol), 3031, 1640 (double bond), 1715 (ketone), 906cm.$^{-1}$ (exocyclic methylene); ν(CS_2), 3031, 1637, 1715, 903, 880cm.$^{-1}$. (Found: C,84.2; H,11.5. $C_{29}H_{48}O$ requires: C,84.5; H,11.7%).

An isomer, A(110mg.), was obtained from the mother liquors of the recrystallisation of fraction (i.) and from the first crops of crystals obtained from the recrystallisation of fractions (ii.), (iii.) and iv.). This isomer was

recrystallised from petrol and separated as needles, m.p. 148-149°; $[\alpha]_D^{22}$ + 13.5°; ν(nujol), 3031, 1640 (double bond), 1704 (ketone), 899cm.$^{-1}$ (exocyclic methylene); $\nu(CS_2)$, 3031, 1637, 1712, 903, 883cm.$^{-1}$. (Found: C,84.3; H,11.9%).

1-Alkyl-2,7,7,10-tetramethyl-trans-decal-2-ol.

The tetracyclic-ketone(a) (E52a and/or b) (0.1g., 0.00024 mol.) were added to a solution (15 c.c.) of lithium methyl (from lithium (0.22g., 0.02 mol.)) in ether. The mixture was heated under reflux in an atmosphere of nitrogen for 4 hr., and was then diluted carefully with wet ether (100 c.c.). The product was isolated in the usual way and was an intractable gum (93mg.), ν(film), 3448 (hydroxyl), 889cm.$^{-1}$ (exocyclic methylene).

Attempted cyclisation of the above product.

i.) The tetracyclic-alcohols (E51a and b) (100mg.) were dissolved in ether (5 c.c.) and the solution was added dropwise to boron trifluoride etherate (0.4 c.c.). The mixture was left at 20° for 3 days in an atmosphere of nitrogen and was then diluted cautiously with wet ether (100 c.c.). The product (90mg.) was isolated in the usual way and was chromatographed on alumina (10g.). The following fractions were obtained (all eluted with petrol):

i.) 100 c.c., 6mg. (gum).

ii.) 25 c.c., 46mg. (solid).

iii.) 25 c.c., 7mg. (gum).

iv.) 25 c.c., 15mg. (gum).

v.) 25 c.c., 4mg. (gum).

Fraction (ii.) was recrystallised from chloroform-methyl alcohol. A substance (31mg.) separated as plates, m.p. 71-82°, $\nu(CS_2)$, 3030, 821cm.$^{-1}$ (7, 6), ϵ 2400 650, ϵ_{2100} 6,000. (Found: C,87.5; H,12.4. Calc. for $C_{30}H_{50}$: C,87.8; H,12.2).

ii.) The tetracyclic-alcohols (E51a or b), derived from the tetracyclic-ketone (E52a or b) $[\alpha]_D$ - 7°, were treated in a similar way. The product (25mg.) was obtained as plates, m.p. 65-73°, $[\alpha]_D^{21}$ + 43°, $\nu(CS_2)$, 3030, 828 (7, 6), 815(7, 7), ϵ_{2400} 659, ϵ_{2100} 5972.

This product (20mg.) was treated with either phosphoric acid (10 c.c., 85%) or sulphuric acid/acetic acid (10 c.c., 1:4v/v) under conditions similar to those described on pp. 115-116. The physical properties of the substance remained unchanged.

iii.) The tetracyclic-alcohols (E51a or b), derived from the tetracyclic-ketone (E52a or b) $[\alpha]_D$ + 13.5°, were treated with boron trifluoride etherate as described in (i.)

The product was obtained as plates, m.p. 72-78°; $[\alpha]_D^{21}$ - 16°; $\nu(CS_2)$, 3030, 828 (s, 6), 815cm.$^{-1}$ (s, 7), ϵ_{2400} 647, ϵ_{2100} 6,098.

The physical properties of this substance were unchanged after treatment with either phosphoric acid or a mixture of sulphuric and acetic acids.

3β-Benzoyl-olean-11(12),13(18)-diene.

β-Amyrin benzoate was isolated from Manila elemi resin using the procedure described by Vesterberg and Vesterlind.[39]

β-Amyrin benzoate was oxidised with selenium dioxide using conditions analogous to those described by Spring and co-workers.[40] 3β-Benzoyl-olean-11(12),13(18)-diene was obtained as plates, m.p. 253-257°; $[\alpha]_D^{23}$ - 31°; λ_{max} 2350 (35,290), 2420(37,730), 2510(41,470), 2600Å(26,530). (Found: C,84.1; H,9.7. Calc. for $C_{37}H_{52}O_2$: C,84.1, H,9.8%).

Experiments on the stability of 3β-benzoyl-olean-11(12),13(18)-diene towards treatment with acids.

a.) Boron trifluoride etherate.

Boron trifluoride etherate (1 c.c.) was added to a solution of the diene-benzoate (40mg.) in ether (3 c.c.) and the mixture was left at 20° for 15 hr. in an atmosphere of nitrogen. The solution was poured slowly into ice-cold

water (50 c.c.) and the product was extracted with ether (3 x 30 c.c.). The ethereal solution was washed with sodium carbonate solution (3 x 30 c.c., 10%), water and brine. Evaporation of ether left a solid (41mg.), λmax 2350(26,400), 2420(28,400), 2510(31,120), 2595Å(20,080). This solid was recrystallised from chloroform/methyl alcohol. The diene-benzoate separated as plates, m.p. 254-257°, $[\alpha]_D^{23}$ - 31°

In subsequent experiments in this series the ultra-violet data quoted refer to the crude product and melting points and rotations refer to the material obtained after recrystallisation. The working up procedure is omitted as it is identical with that described in (a.).

b.) Fluoroboric acid.

A solution (30 drops, 2%) of fluoroboric acid in sulpholane was added to a solution of the diene-benzoate (50mg.) in benzene (5 c.c.). The mixture was left at 23° for 24 hr.. A solid (44mg.) was obtained. λ max 2350(28,110), 2420(30,330), 2510(28,650), 2610Å(19,660). m.p. 253-257°, $[\alpha]_D^{23}$ - 31°

c.) Phosphoric acid/acetic acid.

A solution of the diene-benzoate (50mg.) in phosphoric acid (15 c.c., 85%) and acetic acid (15 c.c.) was stirred at 85° for 16 hr.. A solid (51mg.) was obtained. λmax 2350(35,080), 2420(37,600), 2510(41,220) 2590Å(26,750). m.p. 253-257°, $[\alpha]_D^{22}$ - 30°

d.) Polyphosphoric acid.

The diene-benzoate (50mg.) was added to a homogeneous mixture of phosphorus pentoxide (12.5g.) and phosphoric acid (10g., 85%). The suspension was stirred at 85° for 15 hr.. The product (47mg.) was a solid. λ max 2350 (34,800), 2420(37,000), 2510(41,240), 2590Å(26,400). m.p.253-257 $[\alpha]_D^{22}$ - 31°

e.) Boron trifluoride.

Boron trifluoride gas was passed into chloroform (25 c.c.) for 2 min.. The diene-benzoate (50mg.) was added and the mixture, which rapidly became bright orange in colour, was left at 20° for 15 hr. in an atmosphere of nitrogen. The product (28mg.) was a gum and was not identified. λ max 2460Å (19,870). There were no aromatic absorption bands in the infra-red spectrum.

f.) Sulphuric acid/acetic acid.

A solution of the diene-benzoate (50mg.) in benzene (15 c.c.) was added to concentrated sulphuric acid (10 c.c.) and acetic acid (40 c.c.). The mixture was heated at 90° for 15 hr.. The product (40mg.) was a tar. λ max 2285(15,430), 2600Å(7,039). The diene-benzoate was not recovered.

g.) Sulphuric acid/acetic acid.

A solution of the diene-benzoate (43mg.) in concentrated sulphuric acid (10 c.c.) and acetic acid (40 c.c.)

was left at 20° for 3 days. The product (38mg.) was a solid. λmax 2350(14,350), 2420(15,170), 2510(16,390), 2590Å(10,560). m.p. 254-257°, $[\alpha]_D^{22}$ - 31°.

h.) Acetic acid/perchloric acid.

A solution of the diene-benzoate (50 mg.) in acetic acid (15 c.c.), perchloric acid (1.5 c.c., 60%) and acetic anhydride (9 drops) was left at 20° for 48 hr.. The product (44mg.) was a solid. λ max 2350(26,670), 2420(28,000), 2510(30,990), 2590Å(20,500). m.p. 253-257°, $[\alpha]_D^{21}$ - 31°.

i.) Acetic acid saturated with hydrogen chloride.

A solution of the diene-benzoate (50mg.) in acetic acid (25 c.c.) saturated with hydrogen chloride was left at 20° for 24 hr.. The product was a solid. λ max 2350 (26,210), 2420(28,620), 2510(33,180), 2590Å(22,990). m.p. 254-257°, $[\alpha]_D^{22}$ - 30°.

j.) Aluminium trichloride in nitromethane.

A solution of the diene-benzoate (50mg.) in nitromethane (10 c.c.) and ether (5 c.c.) containing aluminium trichloride (2g.) was left at 20° for 24 hr.. A solid (51mg.) was obtained. λ max 2350(25,500), 2420(29,000), 2510(33,150), 2590Å(23,100). m.p. 253-257°, $[\alpha]_D^{20}$ - 31°.

The tetracyclic-hydrocarbons (E64a and b).

A solution of the tetracyclic-$\alpha\beta$-unsaturated-ketones (E45a and b) (410mg., 0.001 mol.) in ether (5 c.c.)

was added to a solution of methyl magnesium iodide (ca. 200 mole excess) in ether (150 c.c.). The mixture was heated under reflux for 3 hr.. Excess methyl magnesium iodide was destroyed by cautious addition of wet ether. Hydrochloric acid was then added to the suspension until all the solid had dissolved. The product was isolated in the usual way. The mixture of tetracyclic-hydrocarbons (E64a and b) obtained could not be resolved. A satisfactory analysis was not obtained. λmax 2370(16,070), 2450(16,690), 2525Å(sh.), ν(film), 3030, 1637 (double bonds), 887cm.$^{-1}$ (exocyclic methylene).

Attempted cyclisation of the tetracyclic-hydrocarbons (E64a and b).

Samples (10mg.) of the tetracyclic-hydrocarbons (E64a and b) were treated with various acidic reagents. The ultra-violet absorption spectra of the products are recorded on pp. 89 - 90 of the discussion. The experimental procedure was similar to that described previously in experiments on the stability of the diene-benzoate. The reagents and reaction temperatures and times were as listed below:-

i.) Boron trifluoride etherate (2 c.c.), 25°, 24 hr..

ii.) Fluoroboric acid in sulpholane (30 drops, 2%), 25°, 72hr..

iii.) Aluminium trichloride (2g.) in nitromethane (2 c.c.) and ether (1 c.c.), 25°, 96 hr..

iv.) Formic acid (25 c.c.), 100° for 4 hr. and 25° for 12 hr..

v.) Acetic acid (15 c.c.), perchloric acid (1.5 c.c., 60%),

acetic anhydride (9 drops), 25°, 96 hr..

vi.) Concentrated sulphuric acid (5 c.c.), acetic acid (20 c.c.), 20°, 24 hr..

vii.) Aluminium trichloride (2g.) in nitromethane (2 c.c.) and acetic acid (4 c.c.).

viii.) Acetic acid (20 c.c.) saturated with hydrogen chloride, 20° for 24 hr., 55° for 3 hr..

ix.) Phosphoric acid (5 c.c., 85%), acetic acid (2 c.c.), 85°, 16 hr., unchanged tetracyclic-hydrocarbon recovered.

x.) Phosphorus pentoxide (12.5g.), phosphoric acid (10g., 85%), 85°, 15 hr., unchanged tetracyclic-hydrocarbon recovered.

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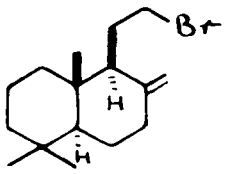
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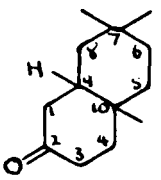
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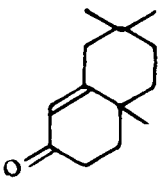
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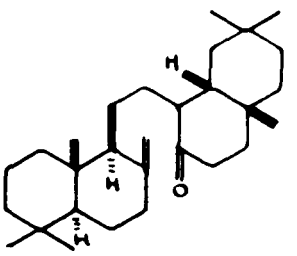
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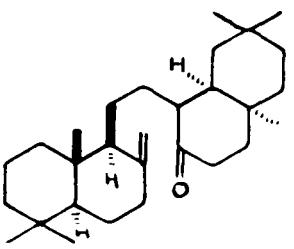
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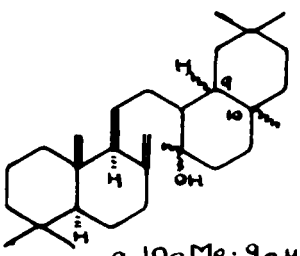
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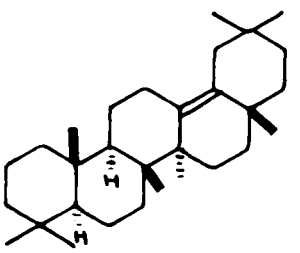
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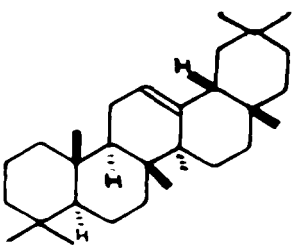
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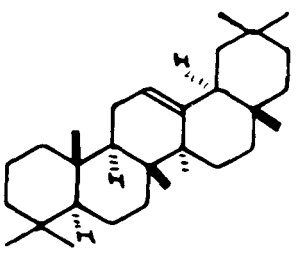
E6 a 10βMe; 9αH
b 10αMe; 9αH



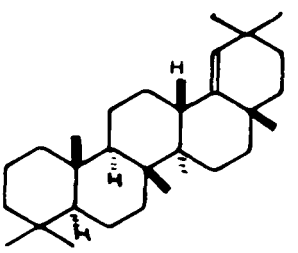
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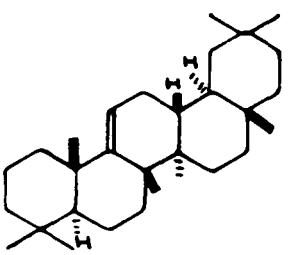
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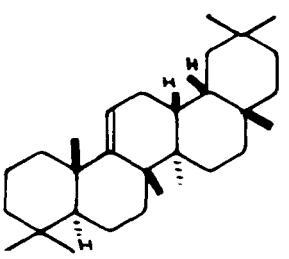
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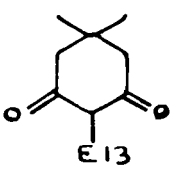
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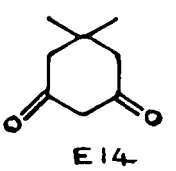
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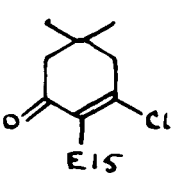
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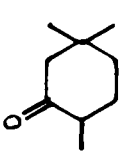
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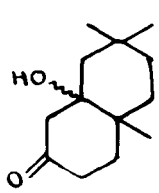
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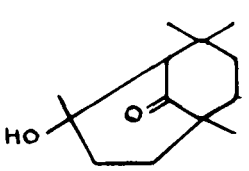
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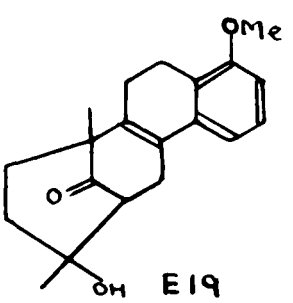
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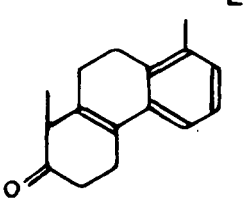
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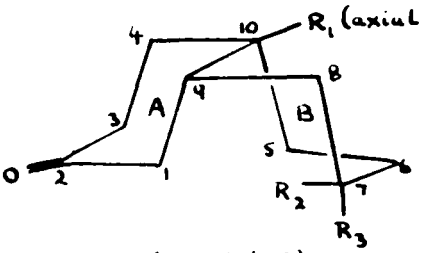


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E20a

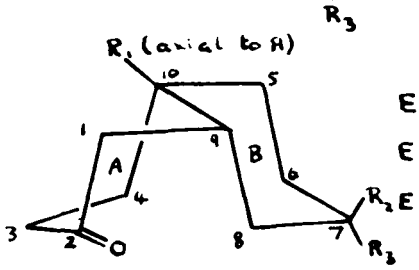
E20-E47



E20 $R_1 = R_2 = R_3 = H$

E22 $R_1 = Me$; $R_2 = R_3 = H$

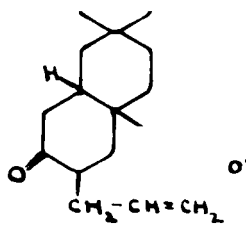
E24 $R_1 = R_2 = R_3 = Me$



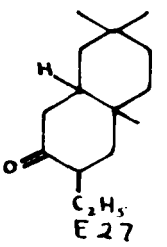
E21 $R_1 = R_2 = R_3 = H$

E23 $R_1 = Me$; $R_2 = R_3 = H$

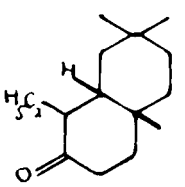
E25 $R_1 = R_2 = R_3 = Me$



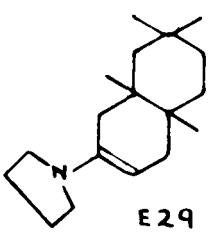
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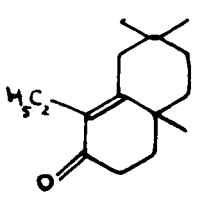
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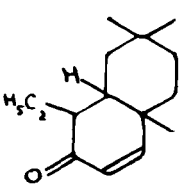
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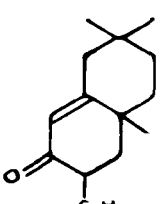
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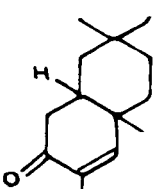
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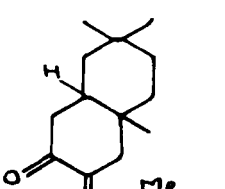
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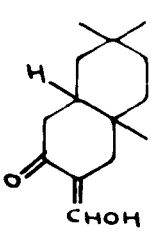
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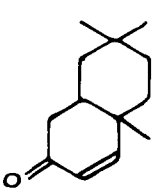
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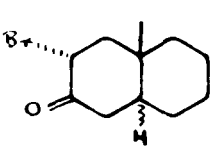
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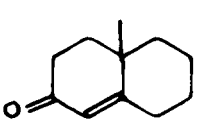
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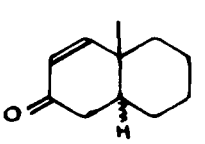
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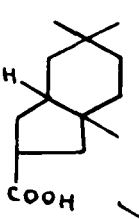
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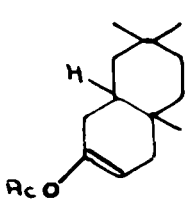
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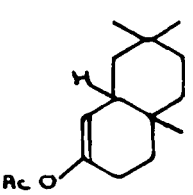
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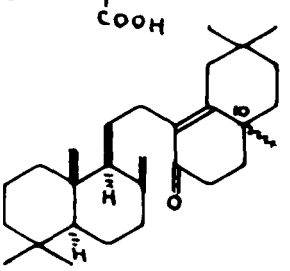
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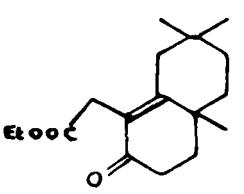


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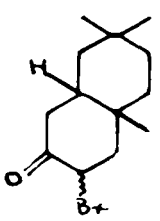


E45 a 10β Me

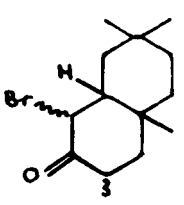
b 10α Me



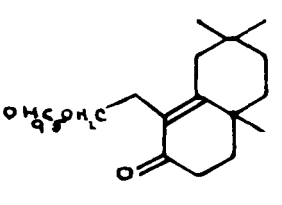
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E43

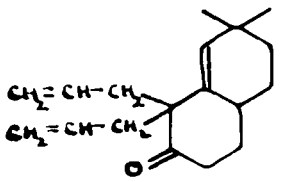


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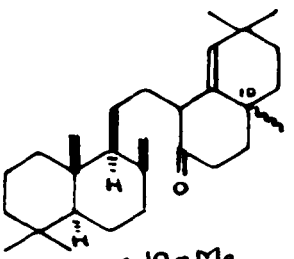


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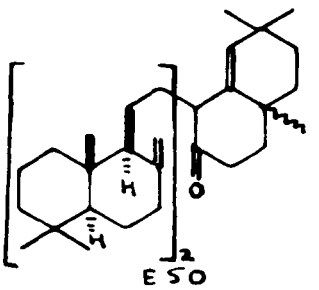
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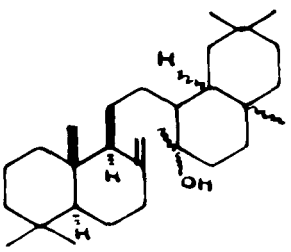
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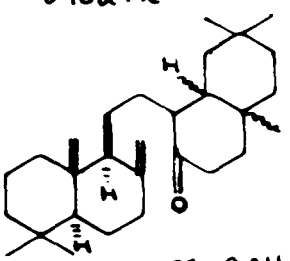
E49 a 10β Me
b 10α Me



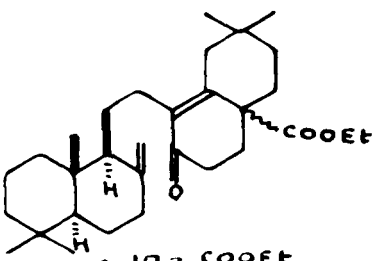
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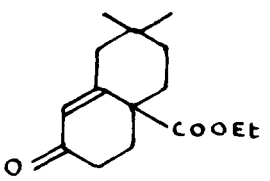
E51 a 10β Me; 9α H
b 10α Me; 9β H



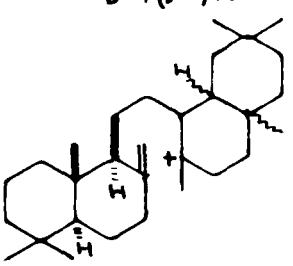
E52 a 10β Me; 9α H
b 9β H; 10α Me



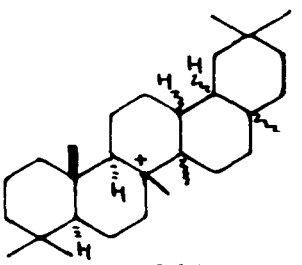
E53 a 10β COOEt
b 10α COOEt



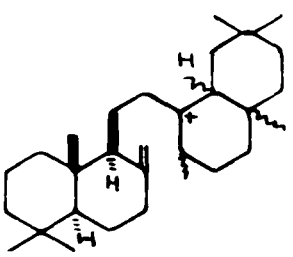
E54



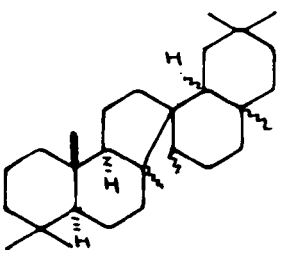
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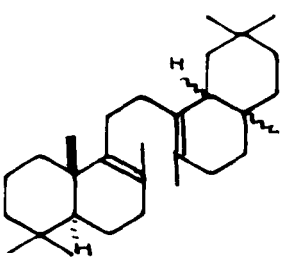
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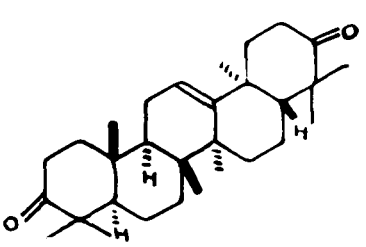
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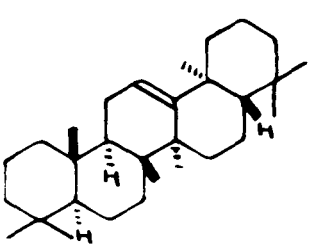
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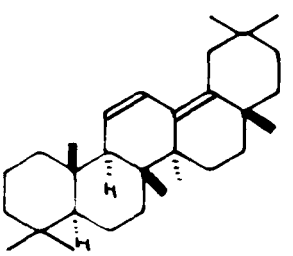
E59



E60

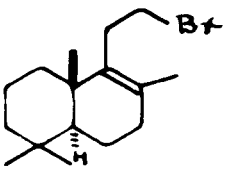


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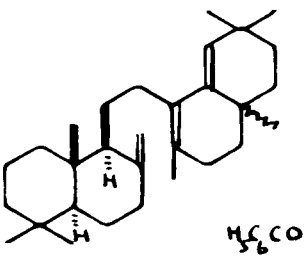


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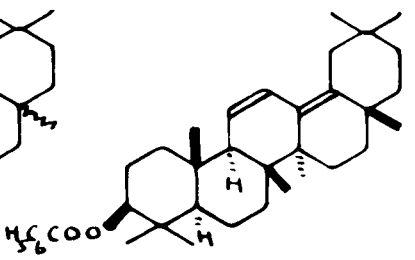
E63 – E70



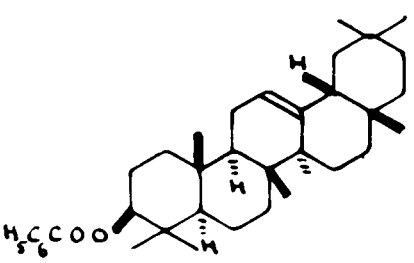
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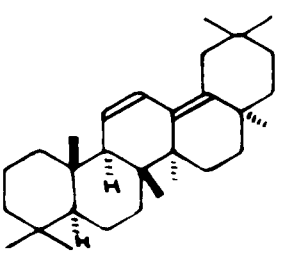
E 64 a - 10β Me
b = 10α Me



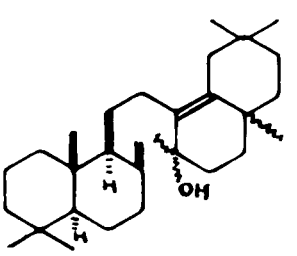
E 65



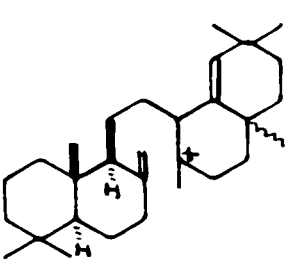
E 66



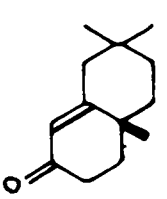
E 67



E 68 a = 10β Me
b = 10α Me



E 69



E 70

DISCUSSION. SECTION III.

Isolation of the β-amyrin derivatives (F1a and F2a) will be facilitated if compounds of the 17α-methyl series (e.g. F1b and F2b) are not present in the mixture of products obtained by the sequence of steps outlined in Section II. This state of affairs could be realised if the (+)-octalone (F3a) was used instead of the racemate in the alkylation with the (+)-methylene-bromide. Attempts to resolve the (±)-octalone (F3) are described now. Only poor yields of incompletely resolved materials were obtained despite considerable experimentation and none of the methods is suitable in practice.

The rotations of the resolved forms of the octalone were expected to be of the order ± 200°, by comparison with the rotation of (-)-9-methyl-Δ^{4}-octal-3-one (F4).[1] It should be possible to assign absolute configurations to the resolved forms of the octalone from a consideration of their optical rotatory dispersion curves.[2]

Octalone with a rotation of + 82° was obtained in the present work. There was no reason to believe that this represented a complete resolution but, even if it did, it gave ample justification for the rejection of all the methods discussed for resolving the octalone, because none of them gave an adequate yield of material with a rotation

of the order ± 82°. (see Table 7, p.127).

Ketones have been resolved[3] by means of their derivatives((-)-menthydrazones) prepared from (-)-menthyl-N-amino-carbamate (F5). The (-)-menthydrazone of the octalone (F3) was prepared in high yield and although it was stable to hydrochloric and sulphuric acids, the free ketone could be regenerated almost quantitatively by hydrolysing with a mixture[20] of pyruvic acid and aqueous acetic acid. No resolution could be effected by recrystallising the menthydrazones but a partial seperation of the diastereoisomers was obtained by chromatography on alumina. A summary of the highest rotations and yields achieved in the various attempted resolutions is given in Table 7, p. 127.

An alternative method of resolution involved the preparation of ketonic derivatives containing acidic (or basic) groups which would form diastereoisomeric salts with optically active bases (or acids).

The p-carboxyphenylhydrazone (F6) was prepared by the method of Anchel and Schoenheimer.[4] Salts of this acid with (-)-strychnine and (-)-brucine were obtained but considerable difficulty was experienced in their purification because they decomposed rapidly on exposure to air and, to a lesser degree, in solution. The free

acid, by contrast, was completely stable. The extent of the decomposition was so great that solutions of the salts deposited tar, rather than crystals, if they were kept for longer than forty-eight hours. No resolution was obtained by recrystallisation of the (-)-strychnine salts but a partial resolution was achieved by recrystallising the (-)-brucine salt from acetone or ethyl alcohol.

An attempt was made to decrease the solubility of the salts in polar solvents, such as ethyl alcohol, by adding petroleum ether to the solutions. Mixed crystals of the free acid and the salt were obtained, the presence of the free acid being detected spectroscopically. The carboxyl group of the acid absorbs at 1669cm.$^{-1}$ in the infra-red, whilst the carboxylate anion of the salts absorbs at 1610.cm.$^{-1}$.

p-Carboxyphenylhydrazone was regenerated from the salts by shaking them with potassium carbonate solution and ether. Tarry material was extracted in the ethereal layer and the free acid was precipitated by neutralising the aqueous solution. A sample of p-carboxyphenyl-hydrazone ($[\alpha]_D = -17^\circ$) was hydrolysed with pyruvic acid and gave octalone ($[\alpha]_D = -14^\circ$), thus indicating that the rotations of the acid derivatives were similar to those of the octalone.

Derivatives of ketones have been prepared with aminoxyacetic acid (F7)[4] and are more stable than the corresponding p-carboxyphenylhydrazones. The oxime (F8) was treated with monochloracetic acid to give a homogeneous product, which was either the N-ether (F9) or the O-ether (F10). The O-ether was expected to be the major product obtained by this method of preparation but no attempt was made to verify this because either ether was suitable for use in the resolution. No resolution was obtained by recrystallising the (-)-strychnine or (-)-brucine salts, from which the free acid was regenerated by the method described previously.

A partial resolution has been achieved by recrystallising the Girard's reagent 'P' derivative (F11) prepared from the octalone and Girard's reagent 'P'-(+)-camphor-10-sulphonate by the method of Girard and Sandulesco.[5] The required Girard's reagent 'P' was obtained from the commercially available Girard's reagent 'P' chloride (F12) and sodium (+)-camphor-10-sulphonic acid. Decomposition to free octalone occurred during recrystallisation of the Girard reagent 'P' derivatives if the solvents used were not scrupulously dry. Octalone was recovered from the salts by hydrolysis with dilute acid.

Inorganic complex salts[6,7] have been partly resolved by chromatography on an optically active adsorbent

TABLE. 7.

Reagent.	Solvent for chromatography or recrystallisation.	Yield of recovered acid.	Rotation of recovered acid.	Yield of recovered octalone.	Rotation of recovered octalone.
Chromatography of (-)-menthydrazone on alumina.	petrol:benzene (1:1).	----	----	<1% 1% * 98% *	-31° +18° 0
Recrystallisation of p-Carboxyphenylhydrazone salts. a.) strychnine.	All available.	100%	0	----	----
b.) brucine.	i.) acetone.	4.5% * 3.5% *	-8° -17°	---- 3.5% *	---- -14°
	ii.) ethyl alcohol.	2% 72% *	+10° + 1°	---- ----	---- ----
Recrystallisation of salts of aminoxyacetic acid derivatives.	All available.	100%	0	----	----
Recrystallisation of Girard's reagent 'P' derivative.	Ethyl alcohol/ di-isopropyl ether.	----	----	7% 91% *	-41° + 2°
Chromatography on d-quartz.	Petrol (30-40°).	----	----	4% * 5% * 13% * 55% * 17% 4.5% *	+82° +13° + 8° ± 1° -20° -51°

*Characterised by spectroscopic analysis only.

such as d-quartz.[8] Similar resolutions of organic compounds have been reported using d-lactose as the adsorbent. A partial resolution of the octalone was achieved by chromatography on d-quartz, activated by heating at 300°. The method was rapid and gave samples of octalone with a higher rotation than those obtained by the more conventional approaches. Unfortunately the ratio of octalone to adsorbent (1:1750) was too great for the method to be of practical value.

No further attempts were made to resolve the octalone but it has been shown that 7,7,10-trimethyl-$\Delta^{1(9)}$-octal-2-one (F21) can be prepared from 10-carbethoxy-7,7-dimethyl-$\Delta^{1(9)}$-octal-2-one (F14), which has been resolved[9] by recrystallising the (-)-brucine salt of the p-carboxyphenylhydrazine derivative. It was expected that the yield of resolved material, which was poor because of the instability of the brucine salt, could be improved by recrystallising optically active salts of the aminoxyacetic acid derivative (F13) (see p. 126).

The success of this resolution was attributed to the presence, at C-10, of a group larger than methyl, and it was thought that it should be possible to resolve 10-(+)-camphor-10-sulphonyloxymethyl-7,7-dimethyl-$\Delta^{1(9)}$-octal-2-one (F15) fairly readily. This proved to be so and

the details of this resolution together with a discussion of the method of preparation of the 10-methyl-octalone (F21) via the 10-carbethoxy-octalone (F14) are now given. This work provides a method by which the optical isomers of the 10-methyl-(F21), 10-hydroxymethyl-(F16) and 10-iodomethyl-(F22)-octalones may be prepared.

The steps in the conversion of the 10-carbethoxy-octalone (F14) to the 10-methyl-octalone (F21) are outlined in the sequence (F14)⟶(F17)⟶(F18)⟶(F19)⟶(F21). Two major problems had to be overcome in this conversion; the $\alpha\beta$- unsaturated ketone had to be preserved during reductive steps and rearrangement of the neopentyl type cation (F23) had to be prevented during displacement reactions such as (F19)⟶(F21). Recently [10,11,12,13] such displacements have been achieved.

The 10-carbethoxy-octalone (F14) was synthesised from dimedone by a route already used by Leggate.[9] The enol chloride (F24), prepared by treating dimedone with phosphorus trichloride, was reduced chemically to give 3,3-dimethylcyclohexanone (F25). This method is analogous to the one described previously for the preparation of 2,5,5-trimethylcyclohexanone (p. 61). Adams et al.[14] have prepared the β-keto-ester (F26) by condensing 3,3-dimethylcyclohexanone with diethyl oxalate and pyrolysing

the resulting α-keto-ester. A modification of the method of ring extension described by Dreiding and Tomasewski[10] has yielded the 10-carbethoxy-octalone (F14) in almost quantitative yield, by treating the β-keto-ester(F26) with methyl vinyl ketone and Triton B.

The ketonic group in the 10-carbethoxy-octalone (F14) was protected by preparation of the dioxolane (F17).[15] The position of the double bond in this compound, and in all subsequent dioxolane derivatives, has not been determined, but by analogy with the steroids[19] it would be expected to take up the Δ^{8} position. The free octalone was obtained readily from all dioxolane derivatives by mild acid hydrolysis.

Reduction of the dioxolane-ester (F17) with lithium aluminium hydride gave the dioxolane-alcohol (F18), from which the dioxolane-mesylate (F19) was obtained. It was not possible to purify the dioxolane-mesylate by distillation because considerable decomposition occurred at temperatures above 90°. The overall yield in the sequence of reactions from the 10-carbethoxy-octalone was 70%, and the methods used were similar to those described by Dreiding and Tomasewski[10] for the conversion of 10-carbethoxy-trans-decal-2-one (F27) to 10-methyl-trans-decal-2-one (F28).

The dioxolane-alcohol (F18) was the sole product obtained by reducing the dioxolane-mesylate with lithium

aluminium hydride. It had been hoped to prepare the 10-methyl-dioxolane (F29) by the reduction, in which the nature of the product is determined by the relative ease of attack at the carbon and sulphur atoms marked with an asterisk in (F30).

The 10-methyl-octalone (F21) was prepared from the dioxolane-mesylate by two routes both of which should be applicable to its preparation from the dioxolane-(+)-camphor-10-sulphonyloxymethyl derivative (F20).

The first approach was based on a method developed by Dreiding and Tomasewski.[10] The dioxolane-mesylate was heated with sodium hydrogen sulphide, a very powerful anionoid reagent, and the resulting dioxolane-methanethiol (F31), which was not isolated, was desulphurised with hydrazine.[17] The product, obtained after hydrolysis of the dioxolane, had a broad ultra-violet absorption peak of low intensity at 2300-2450Å. This should be compared with the sharp peak at ca. 2370Å characteristic of all the pure octal-2-one compounds of this series. 7,7,10-Trimethyl-$\Delta^{1(9)}$-octal-2-one was isolated in only 12% yield from this mixture as its 2,4-dinitrophenylhydrazone. The by-products were not investigated.

The second approach involved the preparation of the dioxolane-iodomethyl derivative (F32). In some cases[18]

tosylates of primary alcohols ($-CH_2-OTos$) are reduced to the hydrocarbon ($-CH_3$) with sodium iodide and acetic acid. Reduction of the dioxolane-mesylate with this reagent gave the 10-iodomethyl-octal-2-one (F22), hydrolysis of the dioxolane being caused probably by the presence of traces of moisture. This compound was also prepared by hydrolysing the product obtained from prolonged treatment of the dioxolane-mesylate with sodium iodide in acetone. The dioxolane-iodomethyl derivative (F32) was reduced with lithium aluminium hydride to give, after hydrolysis, 7,7,10-trimethyl-$\Delta^{1(9)}$-octal-2-one (F21) in 50% yield.

The products of these reactions undergo considerable rearrangement if the experimental conditions defined are not adhered to strictly. In one case the rearranged material has been investigated. Distillation of the hydroxymethyl-octalone (F16) was only practical if it was carried out rapidly. In one experiment slow distillation gave a 70% yield of a saturated ketone with infra-red absorption at 1706$cm.^{-1}$. There were no infra-red bands attributable to either a double bond or to a hydroxyl group, but analytical data indicated that the compound contained two oxygen atoms. A possible structure for this compound is represented by the cyclic ether (F33) but the complexity of the infra-red spectrum, in the region in which absorption

of the C-O-C linkage of ethers occurs, made it impossible to confirm this structure.

The dioxolane-alcohol (F18) does not react with (+)-camphor-10-sulphonyl chloride under the mild conditions at 20° sufficient to cause reaction with methane-sulphonyl chloride. 10-(+)-Camphor-10-sulphonyloxymethyl-7,7-dimethyl-$\Delta^{1(9)}$-octal-2-one-2-dioxolane (F20) was prepared in refluxing benzene. The product was hydrolysed to the 10-(+)-camphor-10-sulphonyloxymethyl-octalone (F15) with dilute acid. Both the dioxolane (F20) and the octalone (F15) were glasses, which could not be resolved by low-temperature recrystallisation or by chromatography on alumina. The 2,4-dinitrophenylhydrazone, however, was resolved by a short systematic fractional recrystallisation. Two isomers were obtained of constant rotation and melting-point and they had identical ultra-violet and infra-red spectra. One isomer, isolated in 7% yield, had $[\alpha]_D$ + 394° and the other, isolated in 0.6% yield, had $[\alpha]_D$ - 110°. 30% of the 2,4-dinitrophenylhydrazone obtained had a rotation greater than +330°, whilst 20% had a rotation less than -30°.

Hydrolysis of the 2,4-dinitrophenylhydrazone with a mixture of pyruvic acid and aqueous acetic acid gave the 10-(+)-camphor-10-sulphonyloxymethyl-octalone (F15)

in 85% yield. The 10-iodomethyl-octalone (F22) has been prepared in 53% yield from this compound by treatment with sodium iodide in refluxing dimethylformamide; this iodide was not formed even after prolonged treatment with sodium iodide in acetone.

The enhanced stability of the (+)- camphor-10-sulphonyloxymethyl derivative, compared with that of the mesylate, is indicative of the degree of steric hindrance introduced by replacing a methyl group by a camphor group. Because of this hindrance it was hoped that reduction of the dioxolane-(+)-camphor-10-sulphonyloxymethyl derivative (F20) with lithium aluminium hydride would occur by attack at C* (F30) rather than at S* as in the case of the mesylate. This was not so, however, and the dioxolane-alcohol (F18) was the sole product of the reduction.

If the 10-methyl-octalone (F21) is to be prepared in high yield from either the 10-(+)camphor-sulphonyloxymethyl-octalone (F15) or the 10-iodomethyl-octalone (F22), then conditions must be defined by which the dioxolane derivatives (F20) and (F32) can be prepared. Preliminary experiments have indicated that rearrangement of the angular substituent occurs during the ketalisation.

The possibility of utilising 10-hydroxy-methyl-7,7-dimethyl-$\Delta^{1(9)}$-octal-2-one in an alkylation

similar to that described in Section II is at present under consideration. The product of such an alkylation (P34) would be of value as an intermediate in the synthesis of oleanane derivatives containing a methyl, hydroxymethyl or carboxyl group at C-17.

EXPERIMENTAL. SECTION III.

N.B. i.) 7,7,10-Trimethyl-$\Delta^{1(9)}$-octal-2-one is referred to throughout the first part of this section as the octalone (F21).

ii.) Infra-red and ultra-violet data marked with an asterisk were determined on an Infracord and a Manual Spectrometer respectively.

(-)-Menthydrazone of the octalone (F21).

(-)-Menthyl-N-aminocarbamate was prepared by Mr. W. Smith in this laboratory and, after recrystallisation from petrol, had m.p. 101-102°; $M_D^{20} = -177°$ (in ethyl alcohol). Woodward et al.[3] quote m.p. 101.5-102°; $M_D = -171°$.

The octalone (F21) (1.92g., 0.01 mol.) and (-)-menthyl-N-aminocarbamate (2.14g., 0.01 mol.) were dissolved in ethyl alcohol (50 c.c.) and acetic acid (0.5 c.c.), containing sodium acetate (1g.). The solution was heated under reflux for 12 hr. and then water was added. The precipitate was collected and recrystallised from methyl alcohol. The (-)-menthydrazone (3.6g., 93%) separated as colourless needles, m.p. 181-185°; $[\alpha]_D^{20} = -45°$; λ max 2680Å(30,140). (Found: C,74.2; H,10.1; N,7.3. $C_{24}H_{40}N_2O$ requires: C,74.2; H,10.3; N,7.2%).

No significant change in the rotation or melting point of this material was obtained after it had been recrystallised from the following solvents:

i.) ethyl, butyl or tert-amyl alcohols.

ii.) aqueous methyl or ethyl alcohols.

iii.) aqueous acetone.

iv.) mixtures of methyl iso-butyl ketone or methyl ethyl ketone and petrol.

The (-)-menthydrazone (2g.) was adsorbed on alumina (200g.). The following fractions were obtained:

i.) petrol-benzene (200 c.c., 1:1).
50mg., m.p. 175-177°, $[\alpha]_D^{20} = -90°$.

ii.) petrol-benzene (1L., 1:1).
1.86g., m.p. 181-185°, $[\alpha]_D^{20} = -45°$.

iii.) petrol-benzene (200 c.c., 1:1).
70mg., m.p. 171-174°, $[\alpha]_D^{20} = -23°$.

Hydrolysis of (-)-menthydrazone.

The (-)-menthydrazone (50mg.), $[\alpha]_D^{20} = -90°$, was dissolved in a mixture of acetic acid (5 c.c.), pyruvic acid (1 c.c., 50%) and water (1 c.c.); the solution was heated under reflux for 1 hr. and then poured slowly into sodium carbonate solution (50 c.c.). The product was extracted with ether (3 x 20 c.c.) and the ethereal extract was washed with hydrochloric acid (5 x 10c.c.) and sodium carbonate solution (5 x 10 c.c.). The product was isolated in the usual way and was distilled to give

octalone (15mg.), b.p. (oil-bath) 140-155°/0.05mm., $[\alpha]_D^{20} = -31°$; λ^*_{max} 2390Å (17,130). (Found: C,81.2; H,10.6. $C_{13}H_{20}O$ requires: C,81.3; H,10.4%).

A similar procedure was used to regenerate the octalone from all hydrazone derivatives.

The (-)-menthydrazone, $[\alpha]_D^{20} = -45°$, gave an octalone, $[\alpha]_D^{22} = 0$, after hydrolysis. λ_{max} 2390Å(17,040).

The (-)-menthydrazone, $[\alpha]_D^{20} = -23°$, was hydrolysed and gave an octalone, $[\alpha]_D^{23} = +18°$; λ_{max} 2390Å(17,290). The infra-red spectra of both the partly resolved octalones were identical with the spectrum of the racemic octalone.

p-Carboxyphenylhydrazone of the octalone (F21).

The octalone (F21) (14.2g., 0.075 mol.) and p-carboxyphenylhydrazine (22.8g., 0.15 mol.) were dissolved in ethyl alcohol (300 c.c., 95%) containing acetic acid (10 drops). The solution was heated under reflux for 2.5 hr. and then ethyl alcohol (250 c.c.) was removed by distillation. The residue was distributed between potassium carbonate solution (300 c.c., 4%) and ether (300 c.c.). The aqueous phase was acidified with hydrochloric acid and the precipitate was collected and recrystallised from ethyl alcohol. The p-carboxyphenylhydrazone (20g., 80%) separated as pale yellow needles, m.p. 246-247°; λ_{max} 3450(65,210), 2330Å(17,430), ν^*(nujol), 1669cm^{-1} (carboxyl).

(Found: C,73.3; H,7.7; N,8.7. $C_{20}H_{26}N_2O_2$ requires: C,73.6; H,8.0; N,8.6%).

Attempted resolution of the p-carboxyphenylhydrazone.

a.) Via the (-)-strychnine salt.

The p-carboxyphenylhydrazone (6.5g., 0.02 mol.) and (-)-strychnine (6.5g., 0.02 mol.) were dissolved in boiling acetone (150 c.c.) and ethyl alcohol (10 c.c.). The solution was cooled and the (-)-strychnine salt (10.7g., 82%) separated as plates, m.p. 144-149° (decomp.), $[\alpha]_D^{20}$ = -24°, ν_{max} (nujol), 1610cm.$^{-1}$ (carboxylate anion). (Found: C,74.5; H,6.5; N,8.3. $C_{41}H_{48}N_4O_4$ requires: C,74.6; H,7.2; N,8.5%).

A large amount of tarry material was formed during the recrystallisation of this salt from all available alcohols and ketones. A mixture of this salt and p-carboxyphenylhydrazone crystallised from solutionsto which petrol was added.

The salt (0.5g.) was shaken with potassium carbonate solution (50 c.c.) and ether (50 c.c.). The aqueous phase was acidified and the precipitate collected and recrystallised from ethyl alcohol. p-carboxyphenylhydrazone (0.23g.) was obtained, m.p. 246°, $[\alpha]_D^{20}$ = 0.

b.) Via the (-)-brucine salt.

The p-carboxyphenylhydrazone (6.5g., 0.02 mol.) and (-)-brucine (7.8g., 0.02 mol.) were dissolved in

boiling ethyl alcohol (200 c.c.). The solution was cooled and the (-)-brucine salt (12.5g., 87%) separated as plates, m.p. 125-147° (decomp.), $[\alpha]_D^{22} = -34°$; ν^*(nujol), 1610cm.$^{-1}$. (Found: C,71.0; H,6.9; N,7.6. $C_{43}H_{52}N_4O_6$ requires: C,71.7; H,7.2; N,7.8%).

This salt was recrystallised from ethyl alcohol and gave the following fractions:

i.) 23mg., $[\alpha]_D^{22} = -40°$

ii.) 1.5g., $[\alpha]_D^{22} = -38°$

iii.) 4.5g.,(72%), $[\alpha]_D^{22} = -30°$

iv.) 0.13g.,(2%), $[\alpha]_D^{22} = -15°$

p-Carboxyphenylhydrazone, $[\alpha]_D^{22} = +10°$, m.p. 246°, was regenerated from the salt, $[\alpha]_D^{22} = -15°$, using the method described in (a.). (Found: N,8.4. $C_{20}H_{26}N_2O_2$ requires: N,8.6%).

The salt, $[\alpha]_D^{22} = -30°$ gave p-carboxyphenylhydrazone, $[\alpha]_D^{20} = +1°$, m.p. 246°, ν^*, 1669cm.$^{-1}$.

The salt, $[\alpha]_D^{22} = -34°$, was recrystallised from acetone and gave the following fractions, from two of which the free acid was regenerated:

i.) salt (0.22g., 3%), $[\alpha]_D^{24} = -52°$, gave p-carboxyphenylhydrazone, $[\alpha]_D^{24} = -17°$, ν^*(nujol), 1669cm.$^{-1}$, m.p. 246°.

ii.) salt (0.31g., 4%), $[\alpha]_D^{24} = -40°$, gave p-carboxyphenylhydrazone, $[\alpha]_D^{24} = -8°$ (Found: N,8.6%), m.p. 246°.

iii.) salt (4.1g.), $[\alpha]_D^{24} = -32°$

No further crystalline material could be obtained from the solution.

p-Carboxyphenylhydrazone, $[\alpha]_D^{24} = -17°$, was hydrolysed with pyruvic acid in aqueous acetic acid and gave an octalone, $[\alpha]_D^{24} = -14°$, λmax 2390Å(17,240).

The (-)-brucine salt was recrystallised from higher boiling ketones and alcohols but improved resolution was not achieved.

Aminoxyacetic acid derivative of the octalone (F21).

A solution of the octalone (2g., 0.011 mol.) in ethyl alcohol (10 c.c.) was added to a solution of sodium acetate (2g.) and hydroxylamine hydrochloride (2g.) in water (10 c.c.). The mixture was heated under reflux for 30 min.; water was added and the precipitate was collected and recrystallised from aqueous methyl alcohol. The oxime (F8) (2.1g., 97%) separated as needles, m.p. 120-121°. (Found: C,75.1; H,10.2; N,6.4. $C_{13}H_{21}NO$ requires: C,75.4; H,10.1; N,6.8%).

A solution of the oxime (2.1g., 0.01 mol.) in acetone (20 c.c.) was added to a solution of monochloracetic acid (4.7g., 0.05 mol.) and sodium hydroxide (2.8g., 0.07 mol.) in water (10 c.c.). The mixture was heated under reflux for 3 hr. and then acidified with hydrochloric acid. The

precipitate was collected and recrystallised from aqueous ethyl alcohol. A crystalline solid (1.5g., 76%) was obtained, m.p. 142-143°, ν(nujol), 3500-2500 (broad), 1738cm.$^{-1}$ (carboxyl). (Found: C,67.6; H,8.4; N,5.4. Calc. for $C_{15}H_{23}NO_3$: C,67.9; H,8.7; N,5.3%). This product was assumed to be the aminoxyacetic acid derivative (P10) of the octalone.

The <u>(-)-strychnine salt</u> was prepared from this derivative. m.p. above 200° with decomposition, $[\alpha]_D^{20} = -20°$, ν(nujol),1605cm.$^{-1}$ (carboxylate anion). (Found: N,7.3. $C_{36}H_{45}N_3O_5$ requires: N,7.0%).

The <u>(-)-brucine salt</u> was prepared from this derivative. m.p. above 200° with decomposition, $[\alpha]_D^{20} = -25°$, ν(nujol),1605cm.$^{-1}$. (Found: N,6.2. $C_{38}H_{49}N_3O_7$ requires: N,6.4%).

Neither of these salts could be resolved by crystallisation.

<u>Girard's reagent 'P'-(+)-camphor-10-sulphonate derivate (P11) of the octalone (P21)</u>.

A solution of sodium-(+)-camphor-10-sulphonic acid (1.3g., 0.005 mol.) in acetone/ethyl alcohol (10 c.c.,1:1) was added to a solution of Girard's reagent 'P' chloride (0.94g., 0.005 mol.) in ethyl alcohol (10 c.c.). The

mixture was left at 20° for 3 hr. and then the precipitate of sodium chloride was collected. The filtrate was added to a solution of the octalone (F21) (0.95g., 0.005 mol.) in ethyl alcohol (5 c.c.) and acetic acid (5 c.c.), and the mixture was heated under reflux for 1 hr.. Ether (50 c.c.) was added to the cooled solution and the precipitate was collected and recrystallised from ethyl alcohol/petrol. The Girard's reagent 'P'-(+)-camphor-10-sulphonate derivative (F11) (2.3g., 99%) separated as a microcrystalline solid, m.p. 80-140°, $[\alpha]_D^{20}$ = +15° (Found: C,64.0; H,7.7; N,7.4; S,5.4. $C_{30}H_{45}N_3O_5S$ requires: C,64.6; H,8.0; N,7.5; S,5.7%).

This salt (2.1g.) was recrystallised from ethyl alcohol/di-isopropyl ether and the following fractions were obtained.

i.) 150mg.(7%), $[\alpha]_D^{20}$ = -21°, m.p. 85-140°

ii.) 1.9g.(91%), $[\alpha]_D^{20}$ = +20°, m.p. 85-140°.

Fraction (i.) was shaken with hydrochloric acid (20 c.c.) and ether (50 c.c.). The ethereal solution was worked up in the usual way and the product was distilled to give octalone (20mg.), b.p. (oil-bath) 110-120°/0.05mm., $[\alpha]_D^{21}$ = -41°, λmax 2390Å(17,090). (Found: C,81.4; H,10.4. $C_{13}H_{20}O$ requires: C,81.3; H,10.4%).

Fraction (ii.) was treated in a similar way and gave an octalone $[\alpha]_D^{19}$ = +2°, λmax 2390Å(17,410).

Improved resolution was not obtained by recrystallising the salt from the following solvent sytems:

i.) Methyl ethyl ketone/petrol.

ii.) Acetone/di-isopropyl ether.

iii.) Methyl iso-butyl ketone/petrol.

It was necessary to use dry solvents for these recrystallisations.

Attempted resolution of the octalone (F21) by chromatography on d-quartz.

d-Quartz (350g., 60-120 mesh) was heated *in vacuo* at 150° for 12 hr. and at 300° for 1 hr.. Petrol was added and the slurry obtained was poured into a chromatographic column (100 x 1.2cm.). A solution of the octalone (200mg.) in petrol (1c.c.) was adsorbed on the quartz and the column was developed slowly with petrol. The following fractions were collected:

	Vol. of petrol (c.c.)	Wt. of octalone.	$[\alpha]_D^{21}$	$\epsilon^*(2390)$
i.)	185	8mg. (4%)	+82°	17,210
ii.)	5	10mg. (5%)	+13°	16,990
iii.)	5	26mg.(13%)	+ 8°	17,000
iv.)	5	110mg.(55%)	± 1°	17,150
v.)	5	34mg.(17%)	-20°	17,270
vi.)	5	9mg.(4.5%)	-51°	17,140

Fraction (v.) was distilled to give octalone, $[\alpha]_D^{22} = -22°$; (Found: C,81.2; H,10.9. Calc. for $C_{13}H_{20}O$: C,81.3; H,10.4%).

3-Chloro-5,5-dimethylcyclohex-2-en-1-one.

Commercial dimedone was recrystallised from acetone and had m.p. 148°.

Dimedone (125g.) was treated with phosphorus trichloride (45 c.c.) and the procedure described by Halsall and Thomas[21] was followed. 3-Chloro-5,5-dimethylcyclohex-2-en-1-one (98g., 70%) was obtained. b.p. 87-90° 20mm., n_D^{20} 1.4943, (Found: C,60.7; H,7.1; Cl,22.2. Calc. for $C_8H_{11}OCl$: C,60.6; H,7.0; Cl,22.4%).

3,3-Dimethylcyclohexanone.

The experimental procedure is similar to that of Halsall and Thomas.[21]

A solution of 3-chloro-5,5-dimethyl-cyclohex-2-en-1-one (95g., 0.6 mol.) in ether (250 c.c.) was added during 75 min. to a vigorously stirred solution of lithium (21g.) in liquid ammonia (2L.). The mixture was stirred for a further 45 min. and then ethyl alcohol (200 c.c.) was added. Ammonia was allowed to evaporate and then water (1 L.) was added. The product was isolated *via* ether, in the usual way, and was distilled to yield a mixture of 3,3-dimethylcyclohexanone and 3,3-dimethylcyclohexanol (26g.), b.p. 94-100°/20mm.. This mixture was dissolved in 'Analar' acetone (60 c.c.) and the solution was cooled to 0°

and stirred. Chromic acid (8N) was added dropwise until the orange colour persisted. The product was isolated via ether and was distilled to give 3,3-dimethylcyclohexanone (22g., 35%) as an oil, b.p. 88-90°/20mm., n_D^{22} 1.4462.

Leggate[9] quotes b.p. 66-68°/14mm., n_D^{22}, 1.4462. 2,4-Dinitrophenylhydrazone, m.p. 125-126° (from aqueous ethyl alcohol).

Leggate[9] quotes m.p. 123-126°.

2-Carbethoxy-5,5-dimethylcyclohexanone.

3,3-Dimethylcyclohexanone (32.8g., 0.26 mol.) was carbethoxylated by the method of Adams et al.[14] to give 2-carbethoxy-5,5-dimethylcyclohexanone (28g., 54%), b.p. 125-130°/20mm., n_D^{20} 1.4720, λ max 2560Å(10,230). Adams et al.[14] quote b.p. 125-128°/14mm., n_D^{20} 1.4716.

10-Carbethoxy-7,7-dimethyl-$\Delta^{1(9)}$-octal-2-one.

The experimental procedure is similar to that of Leggate.[9]

Methyl vinyl ketone was purified by the method described in Section II (p. 93).

An aqueous solution of benzyl trimethyl ammonium hydroxide (Triton B) (2 c.c., 40% w/v) was added to benzene/ethyl alcohol (100 c.c., 1:1) and the mixture was distilled slowly until its volume was 28 c.c.. This solution (12 c.c.) was added to 2-carbethoxy-5,5-dimethylcyclohexanone (30g., 0.15mol.)

and the mixture was cooled to 0°. A solution of methyl vinyl ketone (13g., 0.186 mol.) in benzene (15 c.c.) was added during 2.5 hr. with vigorous stirring. The mixture was stirred for a further 12 hr. at 20° and then more of the Triton B solution (15 c.c.) was added. The mixture was stirred for a further 12 hr. and then was dissolved in ether (200 c.c.). The ethereal solution was washed with water (3 x 30 c.c.), hydrochloric acid (3 x 30 c.c.) and sodium carbonate solution (3 x 30 c.c.). The product was isolated in the usual way and was distilled to yield 10-carbethoxy-7,7-dimethyl-$\Delta^{1(9)}$-octal-2-one (36g., 93%) as an oil, b.p. 105°/0.05mm., λmax 2370Å(17,350), m.p. 30° (from ether). 2,4-Dinitrophenylhydrazone, m.p. 165°, undepressed on admixture with an authentic sample.

Leggate[9] quotes m.p. 31-32° for the octalone and m.p. 165° for the 2,4-dinitrophenylhydrazone.

10-Carbethoxy-7,7-dimethyl-$\Delta^{8?}$-octal-2-one-2-dioxolane.

A solution of 10-carbethoxy-7,7-dimethyl-$\Delta^{1(9)}$-octal-2-one (10g., 0.04 mol.), p-toluene sulphonic acid (250mg.) and ethylene glycol (5.00g., 0.08 mol.) in benzene (750 c.c.) was heated under reflux for 24 hr.. The water formed during the reaction was removed continuously in a Dean and Stark apparatus. The solution was cooled and then

washed with sodium bicarbonate solution (3 x 100 c.c.). The product was isolated in the usual way and was distilled to yield 10-carbethoxy-7,7-dimethyl-$\Delta^{8?}$-octal-2-one-2-dioxolane (11.3g., 96%) as an oil, b.p. 105-108°/0.08mm., n_D^{25} 1.4799, $\nu(CS_2)$, 1730(ester), 1086cm.$^{-1}$ (dioxolane). (Found: C,69.2; H,9.0. $C_{17}H_{26}O$ requires: C,69.4; H,8.9%).

10-Hydroxymethyl-7,7-dimethyl-$\Delta^{8?}$-octal-2-one-2-dioxolane.

Lithium aluminium hydride (2.5g.) was added during 15 min. to a solution of the dioxolane-ester (P17) (9.6g., 0.025 mol.) in ether (150 c.c.). The suspension was heated under reflux for 16 hr. and then cooled to 0°. Excess lithium aluminium hydride was decomposed with saturated sodium sulphate solution (see p. 51) and the product was isolated via ether. 10-Hydroxymethyl-7,7-dimethyl-$\Delta^{8?}$-octal-2-one-2-dioxolane (7.0g., 85%) was obtained as an oil, b.p. (oil-bath) 135-140°/0.05mm., n_D^{25} 1.4975, $\nu(CS_2)$, 3623,1033(primary alcohol), 1089,(dioxolane), 819cm.$^{-1}$ (double bond). (Found: C,71.6; H,9.8. $C_{15}H_{24}O_3$ required: C,71.4; H,9.5%).

The 2,4-dinitrophenylhydrazone was prepared by adding an excess of Brady's reagent to a solution of the dioxolane-alcohol (P18) (50mg.) in concentrated hydrochloric acid/ethyl alcohol (2 c.c., 1:1). The precipitate obtained

after the solution had been diluted with water was collected and recrystallised from aqueous ethyl alcohol. The 2,4-dinitrophenylhydrazone separated as dark-red needles, m.p. 126-128°, ($\lambda\lambda_{max}$ 3830 (33,300), 2550Å(20,420). (Found: C,59.1; H,5.9; N,14.3. $C_{19}H_{24}N_4O_5$ requires: C,58.8; H,6.2; N,14.4%).

This procedure is suitable for the preparation of 2,4-dinitrophenylhydrazones from all dioxolane derivatives. It will not be described in subsequent experiments.

10-Hydroxymethyl-7,7-dimethyl-$\Delta^{1(9)}$-octal-2-one.

A solution of the dioxolane-alcohol (P18) (2.52g., 0.001 mol.) in concentrated hydrochloric acid and ethyl alcohol (20 c.c., 1:1) was warmed at 50° for 15 min.. Water (200 c.c.) was added and the product was isolated *via* ether in the usual way. An oil was obtained and was distilled rapidly to yield 10-hydroxymethyl-7,7-dimethyl-$\Delta^{1(9)}$-octal-2-one (1.8g., 87%), b.p. (oil-bath) 120-130°/0.08mm., n_D^{25} 1.5210, ν(CS_2), 3600-3400, 1036(primary alcohol), 1678 ($\alpha\beta$- unsaturated ketone), 830cm.$^{-1}$ (double bond), λ_{max} 2370Å (13,410). (Found: C,75.1; H,9.8. $C_{13}H_{20}O_2$ requires: C,75.0; H,9.6%).

In one experiment the distillation was carried out slowly and the product was an oil, b.p. (oil-bath)

90-135°/0.06mm., n_D^{21} 1.5092, $\nu(CS_2)$, 1706cm.$^{-1}$ (saturated ketone). (Found: C,75.3; H,9.8. Calc. for $C_{13}H_{20}O_2$: C,75.0; H,9.6. Calc. for $C_{13}H_{20}O$: C,81.1; H,10.4%). This substance was not identified.

10-Methanesulphonyloxymethyl-7,7-dimethyl-$\Delta^{8?}$-octal-2-one-2-dioxolane.

Methanesulphonyl chloride (1.14g., 0.01 mol.) was added dropwise during 10 min. to a solution of the dioxolane-alcohol (1.26g., 0.005 mol.) in pyridine (10 c.c.) at 0°. The solution was left at 0° for a further 20 min. and then at 20° for 1 hr.. It was then poured slowly into sodium carbonate solution (20 c.c.) and the product was isolated *via* ether. An oil (2g.) was obtained and was adsorbed on deactivated alumina (100g.). Elution with ether (400 c.c.) gave, after evaporation of the solvent at 20°, 10-methanesulphonyloxymethyl-7,7-dimethyl-$\Delta^{8?}$-octal-2-one-2-dioxolane (1.5g., 93%), $\nu(CS_2)$, 1342,1174,942(·C·O·SO_2·C·), 1091(dioxolane) 831,809cm.$^{-1}$ (double bond). (Found: S, 9.9. $C_{16}H_{26}O_5S$ requires: S,9.7%).

The 2,4-dinitrophenylhydrazone was recrystallised from chloroform/ethyl alcohol to give red needles, m.p.172-173°, λ max 3800(20,750), 2550Å(12,140). (Found: C,50.9; H,5.4; N,12.2; S,6.9. $C_{20}H_{26}O_7N_4S$ requires: C,51.5; H,5.6; N,12.0; S,6.9%).

Reduction of the dioxolane-mesylate (P19) with lithium aluminium hydride.

Lithium aluminium hydride (200mg.) was added to a solution of the dioxolane-mesylate (100mg., 0.0003 mol.) in ether (7 c.c.) and the suspension was heated under reflux for 20 hr.. The product was isolated in the usual way with saturated sodium sulphate solution and ether and was distilled to yield the dioxolane-alcohol (P18) (66mg., 95%), n_D^{25} 1.4975. The 2,4-dinitrophenylhydrazone was prepared in almost quantitative yield from this product and had m.p. 126°, undepressed on admixture with an authentic sample.

10-Iodomethyl-7,7-dimethyl-$\Delta^{1(9)}$-octal-2-one.

A solution of the dioxolane-mesylate (P18) (33mg., 0.0001 mol.) in acetic acid (2.5 c.c.) and acetic anhydride (0.5 c.c.), containing sodium iodide (1g.) was heated under reflux for 1 hr. and then was poured into sodium carbonate solution (50 c.c.). The product (38 mg.) was isolated in the usual way with ether and was adsorbed on deactivated alumina (10g.). Elution with petrol-benzene (100 c.c., 1:1) gave, after evaporation, a solid which was recrystallised from petrol. 10-Iodomethyl-7,7-dimethyl-$\Delta^{1(9)}$-octal-2-one (18mg., 57%) separated as needles, m.p. 96-97°, ν^{nujol}_{max} 1669cm.$^{-1}$ ($\alpha\beta$-unsaturated ketone), λ_{max} 2375Å (14,400). (Found: C,49.7; H,6.0; I,39.2.

$C_{13}H_{19}IO$ requires: C,49.1; H,6.0; I,40.0%). The 2,4-dinitrophenylhydrazone crystallised as red needles from chloroform/ethyl alcohol, m.p. 183-185°, $\lambda\lambda$ max 3825(34,420), 2575Å(20,500). (Found: C,46.0; H,4.4; N,11.4; I,25.1. $C_{19}H_{23}N_4O_4I$ requires: C,45.8; H,4.6; N,11.3; I,25.5%).

10-Iodomethyl-7,7-dimethyl-$\Delta^{8?}$-octal-2-one-2-dioxolane.

A solution of the dioxolane-mesylate (100mg., 0.0003 mol.) and sodium iodide (1g.) in acetone (5 c.c.) was heated under reflux for 12 hr.. 10-Iodomethyl-7,7-dimethyl-$\Delta^{8?}$-octal-2-one-2-dioxolane (100mg., 91%) was isolated, via ether in the usual way, as an oil (ν^{*}(film), 1088cm.$^{-1}$ (dioxolane)), which was characterised by preparing its 2,4-dinitrophenylhydrazone, m.p. 183-185°, undepressed on admixture with an authentic sample.

7,7,10-Trimethyl-$\Delta^{1(9)}$-octal-2-one.

a.) From the dioxolane-mesylate (E19).

Molten sodium hydrogen sulphide (5 c.c.), prepared[10] by bubbling hydrogen sulphide through molten sodium sulphide nonahydrate, was added to a solution of the dioxolane-mesylate (450mg., 0.0014 mol.) in dimethylformamide (5 c.c.) and the mixture was heated under reflux for 16 hr., during which time the colour changed from blue to green. The solution was poured into saturated brine (100 c.c.) and the

dioxolane-methanethiol (F31) (320mg.) was isolated *via* ether. This substance was not characterised. A solution of the dioxolane-methanethiol (320mg.), hydrazine hydrate (1 c.c.) and potassium hydroxide (120mg.) in ethylene glycol (2.5 c.c.) was heated under reflux for 2 hr.. The solution was diluted with water (80 c.c.) and the product (120mg.) was isolated *via* ether. ν^{t} (film), 1088cm.$^{-1}$ (dioxolane). A solution of this product in ethyl alcohol/concentrated hydrochloric acid (5 c.c., 1:1) was warmed at 50° for 5 min. and then poured into sodium carbonate solution (20 c.c.). Isolation *via* ether gave an oil (152mg.), λ max 2300-2450Å (5,000), ν^{t} (film), 1666cm.$^{-1}$ ($\alpha\beta$-unsaturated ketone). This crude material was treated with Brady's reagent and the precipitate obtained was recrystallised three times from chloroform/ethyl alcohol. The 2,4-dinitrophenylhydrazone of 7,7,10-trimethyl-$\Delta^{1(9)}$-octal-2-one (62mg., 12%) separated as red needles, m.p. 150-151°, undepressed on admixture with an authentic sample.

b.) From the dioxolane-iodomethyl derivative (F32).

Lithium aluminium hydride (700mg.) was added to a solution of the dioxolane-iodomethyl derivative (313g., 0.0009 mol.) in ether (5 c.c.) and the suspension was heated under reflux for 24 hr.. The product (303mg.) was isolated in the usual way and, after hydrolysis, was adsorbed on

deactivated alumina (25g.). Elution with benzene-ether (100 c.c., 5:1) gave, after distillation, 7,7,10-trimethyl-$\Delta^{1(9)}$-octal-2-one (82mg., 50°), n_D^{20}, 1.5059, λ_{max} 2390Å(17,340). 2,4-Dinitrophenylhydrazone m.p. 151° (from chloroform/ethyl alcohol) undepressed on admixture with an authentic sample.

10-(+)-Camphor-10-sulphonyloxymethyl-7,7-dimethyl-Δ^{8}-octal-2-one-2-dioxolane.

(+)-Camphor-10-sulphonyl chloride (5g., 0.02mol.) prepared[19] by the method of Hilditch, was added to a solution of the dioxolane-alcohol (P18) (2.52g., 0.01 mol.) in benzene (50 c.c.) and pyridine (5 c.c.). The solution was heated under reflux for 1 hr. during which time pyridine hydrochloride was precipitated. The solution was cooled and benzene (100 c.c.) and water (50 c.c.) were added. The organic layer was separated and washed with sodium bicarbonate solution (3 x 25 c.c.) and water (3 x 25 c.c.). The product (6.5g.), isolated in the usual way, was adsorbed on deactivated alumina (1kg.). Elution with benzene (3L.) gave, after evaporation, 10-(+)-camphorsulphonyloxymethyl-7,7-dimethyl-Δ^{8}-octal-2-one-2-dioxolane (3.75g., 80°) as a glass, $[\alpha]_D^{20}$ = +35°, $\nu(CH_2)$ 1753(saturated ketone), 1342,1171,950 (·C·O·SO_2·C·), 1093(dioxolane), 818-810cm.$^{-1}$ (double bond). (Found: C,64.4; H,8.2; S,7.4. $C_{25}H_{38}O_6S$ requires: C,64.4; H,8.2; S,6.9).

This compound could not be resolved by low-temperature crystallisation or by chromatography on alumina or silica gel.

10-Hydroxymethyl-7,7-dimethyl-$\Delta^{8?}$-octal-2-one-2-dioxolane was the sole product obtained by reducing the dioxolane-10-(+)-camphor-10-sulphonyloxymethyl derivative (F20) with lithium aluminium hydride under conditions similar to those described on p.151 for the reduction of the dioxolan-mesylate (F19).

2,4-Dinitrophenylhydrazone of the 10-(+)-camphorsulphonyl-oxymethyl-octalone (F15).

A solution of the dioxolane-10-(+)-camphorsulphonyl-oxymethyl derivative (F20) (11.65g., 0.025 mol.) in concentrated hydrochloric acid/ethyl alcohol (100 c.c., 1:1) was warmed at 50° for 5 min.. The product (10.5g.) was isolated in the usual way and dissolved in ethyl alcohol (40 c.c.). The solution was heated under reflux and a solution of 2,4-dinitrophenylhydrazine (5.36g., 0.0275 mol.) in methyl alcohol (115c.c.) and sulphuric acid (11.5 c.c., 98%) was added dropwise during 1 hr.. The solution was cooled and the precipitate was collected and recrystallised from aqueous acetone.

The 2,4-dinitrophenylhydrazone (15g., 100%) separated as orange needles, m.p. 70-125°, ν(nujol), 1752

(saturated ketone), 1333,1169,960 (·C·O·SO_2·C·), 832cm.$^{-1}$ (double bond), λλ max 3780-3830(27,570), 2550(15,190), λ sh. 2870Å. (Found: C,57.4; H,5.9; S,5.0. $C_{29}H_{38}N_4O_8S$ requires: C,57.8; H,6.3; S,5.3%).

Resolution of 10-(+)-camphor-10-sulphonyloxymethyl-7,7-dimethyl-$\Delta^{1(9)}$-octal-2-one-2,4-dinitrophenylhydrazone.

The 2,4-dinitrophenylhydrazone (14g.) was recrystallised from aqueous acetic acid. Three fractions were obtained:

i.) 7g., $[\alpha]_D^{24}$ = +206°

ii.) 2g., $[\alpha]_D^{24}$ = + 92°

iii.) 5g., $[\alpha]_D^{24}$ = + 49°

Fraction (i.) was recrystallised from chloroform/methyl alcohol. After three such crystallisations a fraction (0.98g., 7%) of constant melting point and rotation was obtained. m.p. 166-170°, $[\alpha]_D^{20}$ = +394° (Found: C,57.8; H,6.1; N,9.5; S,5.4. $C_{29}H_{38}N_4O_8S$ requires: C,57.8; H,6.3; N,9.3; S,5.3%).

Further crops (3.22g., 23%), $[\alpha]_D^{20}$ = (+)330-(+)350° were obtained from these recrystallisations.

Fraction (iii.) was recrystallised from methyl alcohol. After six such crystallisations a fraction (84mg., 0.6%) was obtained. m.p. 85-90°, $[\alpha]_D^{20}$ = -110° (Found: C,57.4;

H,6.0; N,8.9; S,5.1%).

Further crops (2.8g., 19%), $[\alpha]_D^{20}$ = (-)30-(-)50° were obtained from these recrystallisations.

The infra-red spectra, in nujol mull, and the ultra-violet spectra of these fractions were identical to those of the racemic compounds.

10-Iodomethyl-7,7-dimethyl-$\Delta^{1(9)}$-octal-2-one.

A solution of 10-(+)-camphor-10-sulphonyloxymethyl-7,7-dimethyl-$\Delta^{1(9)}$-octal-2-one-2,4-dinitrophenylhydrazone (400mg., 0.00066 mol.) acetic acid (16 c.c.), pyruvic acid (8 c.c., 50%) and water (2 c.c.) was heated under reflux for 1 hr.. Sodium bicarbonate solution (100c.c.) was slowly added and the product was extracted with ether (3 x 30 c.c.). The ethereal extract was washed with sodium bicarbonate solution (5 x 15 c.c.) and hydrochloric acid (5 x 15 c.c.) and then worked up in the usual way. An oil (450mg.) was obtained. A portion of this oil (150mg.) was adsorbed on deactivated alumina (10g.). Elution with benzene-ether (60 c.c., 9:1) gave, after evaporation, 10-(+)-camphor-10-sulphonyloxymethyl-7,7-dimethyl-octal-2-one (81mg., 85%) as a glass, $\nu(CS_2)$, 1754(saturated ketone), 1681(unsaturated ketone), 1342,1158,952(·C·O·SO$_2$·C·), 827, 808cm.$^{-1}$ (double bond), λmax 2370Å(18,180). (Found: C,65.2; H,7.9; S,7.9. $C_{23}H_{34}O_5S$ requires: C,65.4; H,8.1; S,7.8%).

This compound could not be resolved by low-temperature crystallisation or by chromatography on alumina or silica gel.

The remainder of the product (300mg.) obtained in this reaction was dissolved in dimethylformamide (5 c.c.) containing sodium iodide (3g.) and the mixture was heated under reflux for 20 min.. ater (50 c.c.) was added and the product was isolated with ether. An oil (283mg.) was obtained and was adsorbed on alumina (25g.). Elution with petrol/benzene (150 c.c., 1:1) gave, after evaporation, a solid which was recrystallised from petrol. 10-Iodomethyl-7,7-dimethyl-$\Delta^{1(9)}$-octal-2-one (106mg., 51%) separated as needles, m.p. 96-97° undepressed on admixture with an authentic sample, λmax 2375Å(14,970). The 2,4-dinitrophenylhydrazone had m.p. 183-184° undepressed on admixture with an authentic sample.

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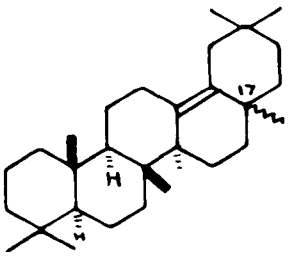
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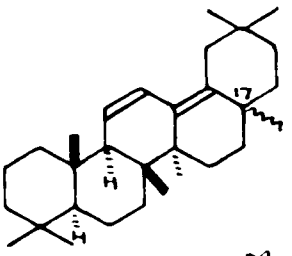
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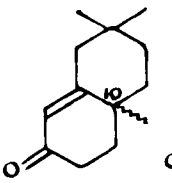
F1 – F34



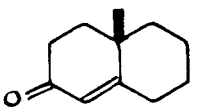
F1 a 17β Me
b 17α Me



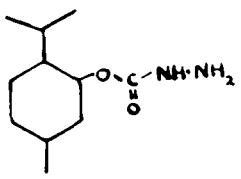
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b 17α Me



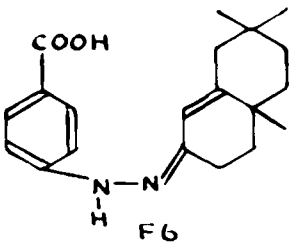
F3 a 10β Me
b 10α Me



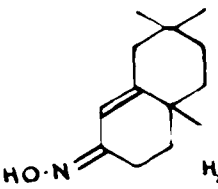
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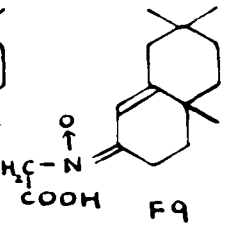
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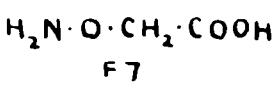
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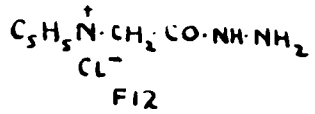
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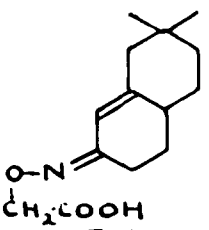
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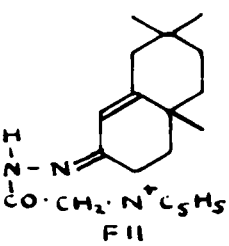
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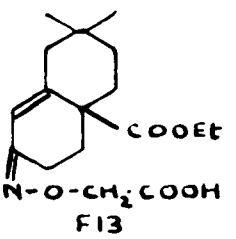
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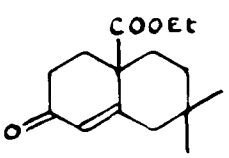
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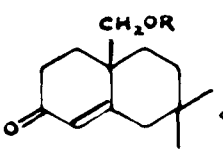
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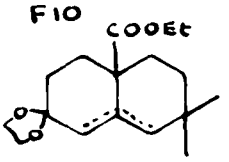
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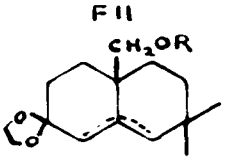
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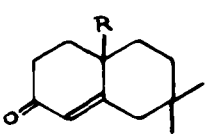
F15 R = -SO₂·C₁₀H₁₅O
F16 R = H



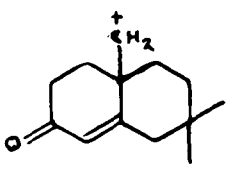
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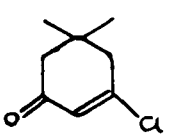
F18 R = H
F19 R = SO₂·CH₃
F20 R = -SO₂·C₁₀H₁₅O



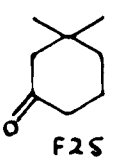
F21 R = CH₃
F22 R = CH₂I



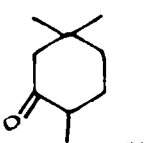
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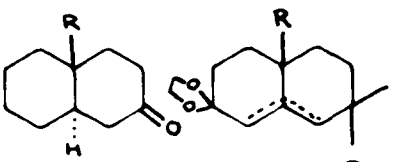
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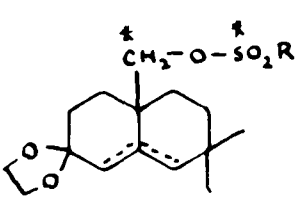
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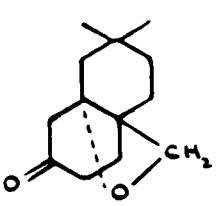
F26



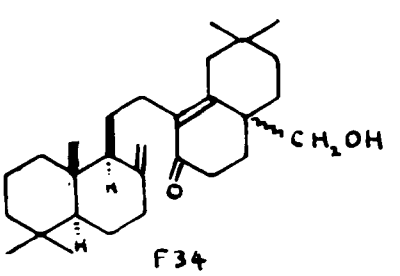
F27 R = COOEt
F28 R = Me
F29 R = Me
F31 R = CH₂SH
F32 R = CH₂I



F30



F33



F34