

APPROACHES TO THE SYNTHESIS OF
THE HIGHER TERPENES

A thesis submitted for the
DEGREE OF DOCTOR OF PHILOSOPHY
in the

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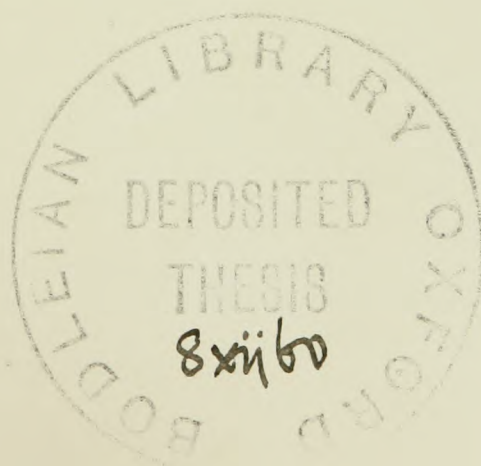
by

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The author wishes to thank Dr. J.A. Barltrop for his guidance and encouragement throughout this work; also Dr. N. A. J. Rogers and Mr. J.D. Rushton for a number of helpful discussions; the members of the spectroscopy department in this laboratory for their co-operation; and Miss M. Bowen for her patience in the typing of this thesis.

The authors suggest that the following
 method is suitable for the determination of
 the concentration of the solution to be measured.
 The method is based on the principle that the
 intensity of the scattered light is proportional to
 the concentration of the solution. The method is
 simple and accurate and can be used for the
 determination of the concentration of solutions
 of various substances. The method is described
 in detail in the following sections.

ABSTRACT

A method is described for the determination of the
 concentration of a solution of a substance in a
 solvent. The method is based on the principle that
 the intensity of the scattered light is proportional
 to the concentration of the solution. The method
 is simple and accurate and can be used for the
 determination of the concentration of solutions
 of various substances.

It is well known that the intensity of the
 scattered light is proportional to the concentration
 of the solution. This principle is the basis of the
 method described in this paper. The method is
 simple and accurate and can be used for the
 determination of the concentration of solutions
 of various substances. The method is described
 in detail in the following sections.

The various structural types into which the 'higher terpenes' are divided are defined; recent work on problems of their biogenesis and total synthesis is reviewed. A synthetic route to the pentacyclic structure (VII) is proposed. The tetracyclic precursor (VI) of this was to be obtained by alkylation of 10-carbethoxy-7,7-dimethyl- $\Delta^{1(9)}$ -octalin-2-one (V) with the methylene bromide (IV, R=H or OH).

A possible route for the preparation of this bromide (R=OH) is outlined (I-IV); this involves the degradation of the aromatic ring of the tricyclic ketone (II) to give the keto-acid (III). As the first stage of this synthesis, the tricyclic unsaturated ketone (I) has been prepared.

Attempts to prepare 2,6-dihydroxynaphthalene as a possible source of 6-methoxy-1-methyl-2-tetralone, by fusing sodium 2-hydroxynaphthalene-6-sulphonate with alkali, failed. Reduction of 6-methoxynaphthalene using Raney nickel in acidic solution gave, among other products, 6-methoxytetralin which was oxidised to 6-methoxy-1-tetralone. The latter reacted with methyl magnesium iodide to give a tertiary alcohol which, in the presence of acids, gave the expected 6-methoxy-1-methyl-3,4-dihydronaphthalene, together with 6-methoxy-1-methylnaphthalene and 6-methoxy-1-methyl-

tetralin, the products of its own dismutation, as reported by Jacques and Kagan¹. A possible mechanism for this dismutation is proposed, and the effects of the conditions of dehydration on this reaction were studied. The dihydronaphthalene, when treated with lead tetra-acetate, gave a diacetate which rearranged in low yield under strongly acid conditions to 6-methoxy-1-methyl-2-tetralone. Ring extension of this tetralone gave the tricyclic ketone (I).

Alternative methods for the preparation of 6-methoxy-1-methyl-2-tetralone were investigated. Reaction of 6-methoxy-1-methyl-3,4-dihydronaphthalene with perbenzoic acid gave, not the epoxide, but a hydroxy-benzoate which was also rearranged to the required tetralone, although the yield obtained by Howell and Taylor² could not be repeated. The crystalline material isolated in low yield from the product of the peracid treatment was formulated as 1-benzoyloxy-2-hydroxy-6-methoxy-1-methyltetralin; reasons for this formulation are discussed. Treatment of the dihydronaphthalene with formic acid gave an α -ketol from which 6-methoxy-1-methyl-2-tetralone could not be obtained. Attempts to prepare this tetralone from 2-benzal-6-methoxy-2-tetralone were unsuccessful because 1,4-addition products appeared to be formed in the Grignard reaction. Anti-Markownikoff hydration of 6-methoxy-1-methyl-3,4-dihydronaphthalene under the Brown conditions³ gave a product which the results of subsequent oxidation suggested to be a mixture of 6-methoxy-

1-methyl-2- and 4-tetralols.

The publication⁴ of a synthetic route very similar to that adopted in the present work resulted in the work being suspended.

5-(2'-Bromoethyl)-6-methylene-1,1,10-trimethyl-trans-decalin was prepared by a route developed by Rushton⁵. Oxidation of sclareol with potassium permanganate gave the enol ether (VIII) which, after ozonolysis and reduction with lithium aluminium hydride, afforded the glycol (IX). The required bromide was obtained by treating the last compound with phosphorus oxybromide.

10-Carbethoxy-7,7-dimethyl- $\Delta^{1(9)}$ -octalin-2-one, containing the potential D and E rings of the pentacyclic system, was synthesised from dimedone. The enol chloride derived from dimedone was reduced with lithium in liquid ammonia (30% yield) and by catalytic hydrogenation (50-70%) to 3,3-dimethylcyclohexanone, which was carbethoxylated to 2-carbethoxy-5,5-dimethylcyclohexanone⁶. The required octalone was produced in nearly quantitative yield from this compound by ring extension.

The products of catalytic and lithium-ammonia reduction of the octalone were compared.

Resolution of the octalone was not possible when its menthylhydrazone was used, but was at least partly achieved by the use of the (-)brucine salt of the p-carboxyphenyl-

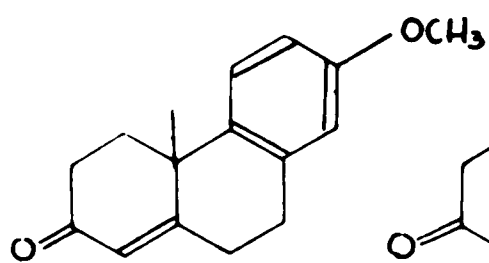
hydrazone, although the yield was poor and the method laborious.

Conditions for alkylating the octalone without decomposition were defined in model experiments using n-propyl iodide. To obtain even small quantities of tetracyclic material under such conditions it was necessary to employ the iodo-derivative (IV, R=H, X=I), which is more reactive than the corresponding bromo-compound. The latter reacted if diglyme was used as the solvent, as suggested by Zook⁷. In this reaction both the iodo- and the bromo-compounds gave two tetracyclic products; the possibility that they are the two enantiomorphs of the ketone (VI) is discussed.

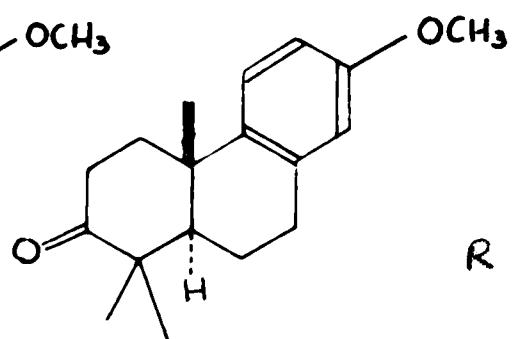
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3. Brown and Rao, J.Amer.Chem.Soc., 1956, 78, 2582, 5694; 1959, 81, 6423, 6428; J.Org.Chem., 1957, 1136.
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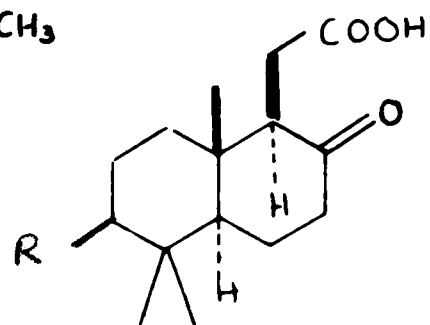
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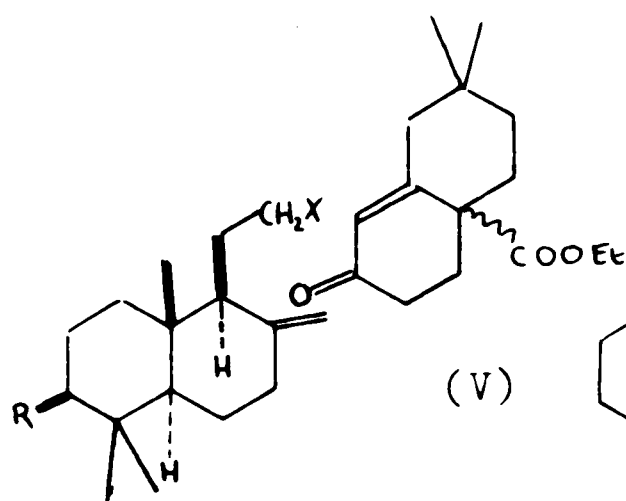
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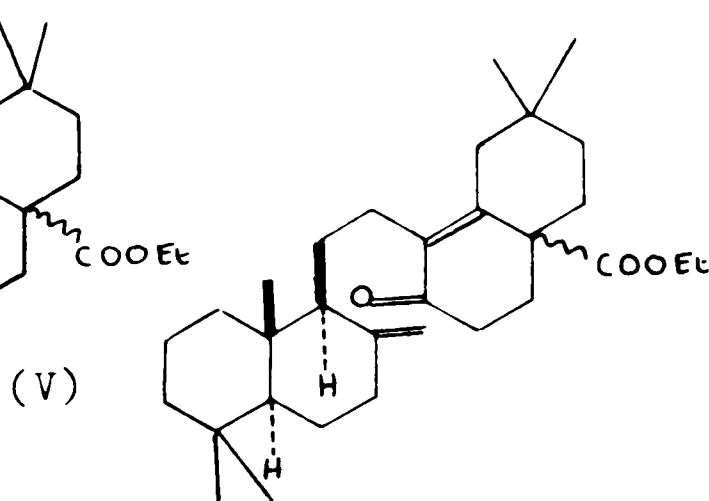
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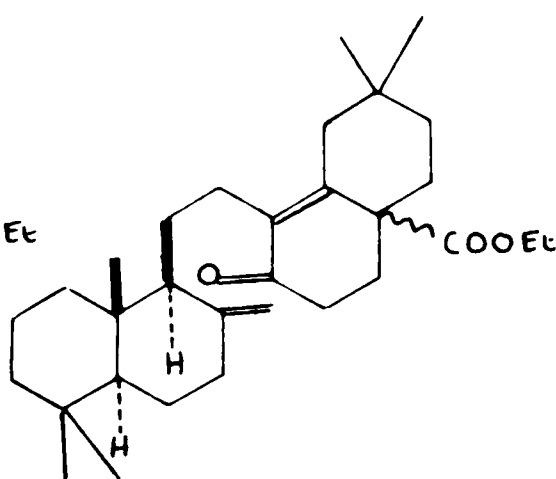
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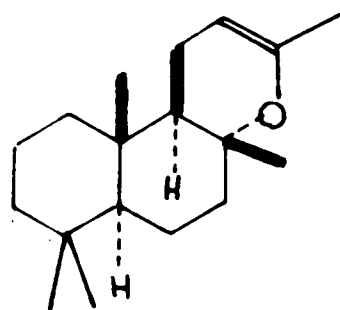
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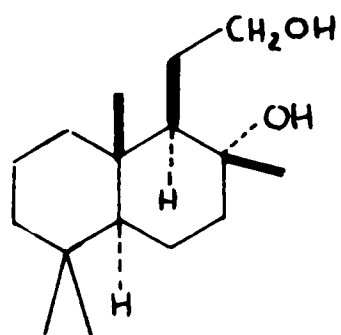
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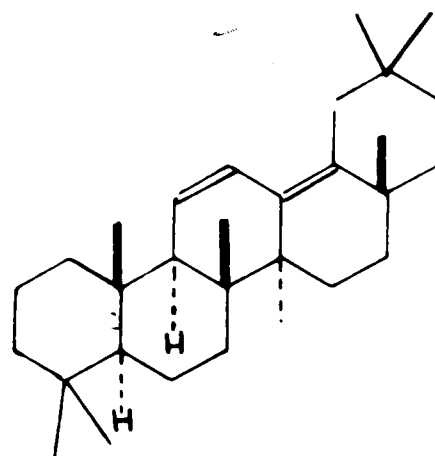
(VI)



(VIII)



(IX)



(VII)

Corrigendum to p.104

The following is to be inserted between the first paragraph (ending "as solvents.") and the second paragraph (beginning "The minor product"):

Alkylation of the octalone (F13) with the bromide (F1) in diglyme at 90-100° gave a ca. 35% yield of the three alkylated products A, B and C. No alkylation took place at the lower temperature (30°) at which the original experiments of Zook and Russo¹⁸ had been carried out.

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INTRODUCTION.

The total syntheses of cholesterol^{1,2} in the last decade marked the culmination of an intensive study of steroid chemistry, occasioned in a greater part by the discovery of the physiologically active adreno-cortical and sex hormones.

The investigation of the di- and tri- terpenes, a group of natural products both structurally and biogenetically related to the steroids, had until recently advanced less rapidly. This was due in part to the absence, in general, of any physiological significance to stimulate interest, and in part to the practical difficulties encountered in their investigation. Thus, isolation of homogeneous, solvent-free products was difficult; structural elucidation was complicated, especially in the triterpenes, by the paucity of reactive centres as starting points for degradation; and the solution of stereochemical problems, possibly even more complex than those encountered in the steroids, necessitated a theoretical basis and experimental methods only recently made available. The rapid progress of the last fifteen years is the result of the appearance of new techniques, often developed in the first place for use in the steroid field, for the solution of these problems.

Modern methods of isolation owe much to chromatographic techniques, especially of adsorption on silica or alumina,

The methods of partition³ and paper partition⁴ chromatography, and of counter current distribution have also been used. The application of vapour phase chromatography⁶ is a possible development of the near future.

Pioneering work in structural elucidation depended mainly on dehydrogenation methods⁷, still widely used but now⁸ supplemented by physical techniques such as X-ray analysis; ultraviolet⁹ and infrared¹⁰ spectroscopy; and nuclear magnetic resonance¹¹ which has been used, for example, for the detection of furan rings¹² in diterpenes such as cafestol (A14). Mass spectrometry has been applied to the accurate determination of molecular formulae¹³. The use of molecular rotation differences¹⁴ and optical rotatory dispersion measurements¹⁵ has resolved many problems of both relative and absolute stereochemistry. Of recent advances, however, that with the widest implications for both structural elucidation and synthetic approaches, is the development of conformational analysis¹⁶ as a means of interpreting chemical and physical behaviour in terms of molecular geometry. Complementary to this theoretical advance is the introduction of new, highly specific reagents, the value of which in steroid chemistry¹⁷ has recently been reviewed by Loewenthal.

Interest in terpene chemistry has been stimulated by

recent work on their biosynthesis (viz p.9). This has resulted in the replacement, by a biogenetic definition, of the empirical isoprene rule¹⁰⁰ which had defined the terpenes as having structures constructed of 5-carbon isoprene units arranged regularly or irregularly. The new 'biogenetic' isoprene rule⁹⁸ embraces the increasing number of terpenes, including the tetracyclic triterpenes, which do not obey the empirical rule, and also the 'terpenoids' as defined by Ruzicka¹⁰⁰ : natural products which, though related to the terpenes, have structures in which the number of carbon atoms is not divisible by five. 'Biogenetic feasibility' now becomes a valid criterion in the elucidation of unknown structures.

Work on the di- and tri- terpenes prior to 1952 has been comprehensively reviewed by Simonsen and his co-authors¹⁸, and de Mayo's more recent review¹⁹ describes the more important developments up to 1956.

The majority of the diterpenes are either bi-^{or} ~~and~~ tri-cyclic. There are three important basic types of carbon structure. These are the tricyclic abietane (A1) and pimarane (A3) skeletons exemplified by abietic acid²⁰ (A2) and dextropimaric acid (A4)^{21,14b} respectively; and the bicyclic seco-pimarane (A5) skeleton exemplified by

agathenedicarboxylic acid (A6)^{22,14b} and the alcohols
 manool (A7)^{23,25} and scareol (A8)^{24,25}. Structures which
 contain aromatic rings are found in the terpenoid podocarpic
 acid (A9)^{26,27} with an 18-carbon atom skeleton, and in the
 phenols ferruginol (A10)^{26,28} and totarol (A11)^{29,30} of
 which the latter is an example of a diterpene not obeying
 the isoprene rule.

Recent work in the diterpene field, which has been
 reviewed by Tsutsi³¹ and Tsutsi³¹, includes the elucidation
 of a number of very complex structures, such as roseno-
 lactone (A12)³², gibberellic acid (A13)^{33,34} and cafestol (A14)
³⁵, which may be considered as degenerate forms of the skeletal
 types defined above.

With three notable exceptions all the triterpenes of
 known structure are members either of a 'steroidal' tetra-
 cyclic, or of a pentacyclic, group. The exceptions are
 squalene (A15) and the squalenoid alcohols, ambrein (A16)^{36,37}
 and α -onoceradienediol (α -onocerin) (A17)^{38,39}, so called
 because they may be constructed from squalene by a cyclisation,
 starting simultaneously from both ends of the molecule,
 without rearrangement of the carbon skeleton. The
 tetracyclic dammarenediols (I) and (II) (A21) and their
 oxygenated derivatives⁴⁰, and the pentacyclic

hydroxyhopanone (A22)⁴¹ also have structures indicative of a cyclisation of the squalene molecule from one end without rearrangement, and are therefore of great biogenetic interest. Zeorin (A23)⁴² is also believed to possess the same gross carbon structure of hydroxyhopanone though lacking the ubiquitous 3-hydroxyl function.

Karrer and Halfen⁴³stein proved the symmetrical gross structure of squalene by a synthesis in which two molecules of farnesyl bromide (A24) were condensed to give a product yielding a hydrochloride identical with that of natural squalene. This synthetic product was, however, a complex mixture of prototropic and geometrical isomers⁴⁴, whereas X-ray examination⁴⁵ of the thiourea clathrate has shown natural squalene to have the all-trans geometry. The same clathrate has been used to isolate the all-trans form from mixtures of geometrical isomers in recent syntheses by Isler⁴⁶, using a modification of Karrer's method; by Dicker and Whiting⁴⁷; by Trippet⁴⁸; and by Cornforth⁴⁹ who used a stereoselective route.

Acid treatment of squalene produces a complex mixture of cyclisation products^{50,51}, including a tetracyclosqualene for which structure (A19)⁵² has been proposed though no experimental evidence for this assignment has been published.

Attempts to identify pentacyclosqualene (A20) among the cyclisation products have been unsuccessful, but Barton³⁸ and Overton³⁸ have shown that in strongly acidic conditions α -onocerin (A17) and its derivatives cyclise to compounds having the pentacyclosqualene (α -onocerane) structure. Under milder acidic conditions structures of the β -onocerane type (A18)³⁹ are obtained.

The structure of lanosterol (A25), first isolated from wool fat⁵³, was demonstrated by both degradative⁵⁴ and X-ray⁵⁵ methods and confirmed by a synthesis from cholesterol by Woodward and Barton⁵⁶. Lanosterol is founder member of a group of 30- and 31-carbon atom alcohols and acids which may be considered either as triterpenes or, as does Fieser⁵⁷ in a recent review, as 4:4:14-trimethylsteroids. The extra carbon atom of the 31-carbon structures has always been found at the C-24 position and such structures therefore bear the same relation to the 30-carbon structures as does ergosterol to cholesterol. With the exception of the dammerenediols, all members of this tetracyclic group are related to one of three parent structures - lanosterol (A25), euphol (A26)^{58,60} and tirucallol (A27)^{59,60} - which differ in points of stereochemistry but have a common carbon skeleton.⁶¹

In a comprehensive review of the pentacyclic

triterpenes which had been isolated up to 1956, White lists 80 of known and 73 of unknown constitution, illustrating that this is by far the largest class of terpenes. Though their biological function is obscure, pentacyclic triterpenes may occur in almost any part of a plant, both in the free state and as glycosides or esters. Until recently all known triterpene structures could be derived from one of three hypothetical hydrocarbons, oleanane (A28), ursane (A29) and lupane (A30). Between 1951 and 1954 complete stereochemical assignments were made for β -amyrin (A31a), $\mathcal{L}$ -amyrin (A35)⁶² and lupeol (A36)^{63,64}, the representative members of the three sub-groups, though the structure assigned to $\mathcal{L}$ -amyrin was challenged by Spring^{65,66}. The controversy was resolved in favour of the original formulation by the partial synthesis of $\mathcal{L}$ -amyrin from glycerhettic acid⁶⁷ (A37). Lupeol and $\mathcal{L}$ -amyrin have been related to β -amyrin by rearrangement reactions.

Compounds of the β -amyrin type are the most numerous in nature and include a number in which oxidation at C-24 has occurred, in particular oleanolic acid (A32)⁶⁸. Corresponding C-24 alcohols such as erythrôdiol (A33)^{68,69} and one aldehyde (A34)⁷⁰, are also known. The gross carbon structure of β -amyrin was deduced⁷¹ from dehydrogenation

data and confirmed by a variety of degradative work^{72,73}, which also proved the position of the hydroxylic and olefinic functions. Ambrein (A16) and oleanolic acid have been shown to have the same configuration at the trans A/B ring junction by their degradation to a common product (A38)⁷³. Ambrein has been similarly correlated with the diterpenes and the 5 α -steroids⁷⁴. The absolute configuration of the steroids and the di- and tri- terpenes has been established both from a consideration of molecular rotation differences^{14c} and by the method of asymmetric synthesis⁷⁶.

The use of conformational arguments, mainly by Barton⁷⁷, enabled the assignment of the configurations at C-27, C-18, C-14 and C-9 in the β -amyrin series. Still unknown were the configuration at C-8 and the relationship of the known configurations in the C,D and E rings to those at the A/B ring junction. Consideration of the stability of the molecule in terms of non-bonded interactions allowed only two possible structures, (A31a) and (A31b)^{77,78}. Molecular rotation difference measurements^{14a} suggested the former to be the correct structure and this was later confirmed by X-ray studies⁷⁹.

Recently pentacyclic structures, other than the three basic types defined above, have been found though these

new structures can be related to the latter by acid catalysed rearrangements. Taraxasterol (A39) and ψ -taraxasterol (A40) are closely related to lupenone-1 (A41), a rearrangement product of lupeol. Derivatives of friedelin (A42), glutinone (A43) and taraxerol (A44) undergo remarkable acid catalysed rearrangements to β -amyrin structures. They are also biogenetically related to β -amyrin in being formed from the same cationic precursor by a series of methyl shifts. The search for structures similarly related to α -amyrin has been rewarded by the elucidation of the structure of baurenol (A45).

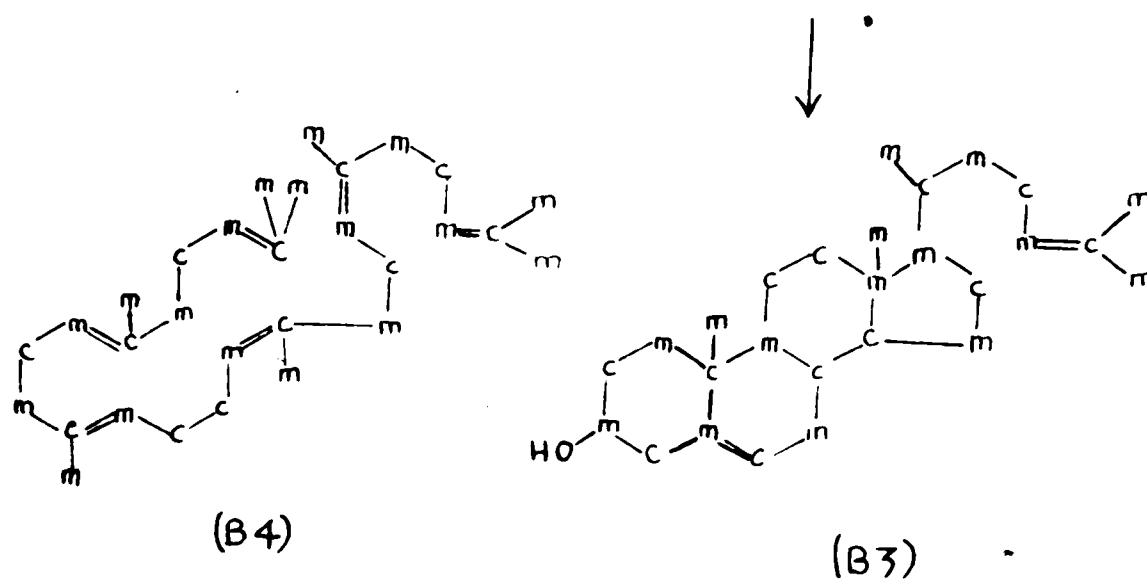
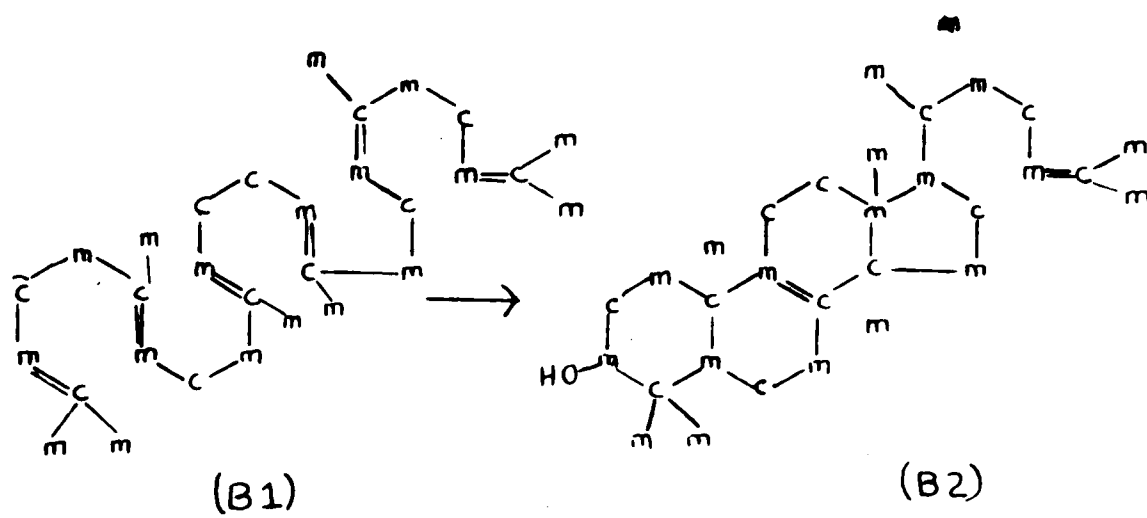
Ourisson has proposed that the nomenclature of the triterpenes be based on the structures: lanostane, ambrane, onocerane, oleanane (A28), ursane (A29), lupane (A30) and gammacerane (A46), each with precise stereochemical implications. Modifications of these basic skeletons are defined by prefixes as, for example, friedo- for the friedelin type of structure.

The Biogenesis of Terpenes and Steroids.

Pioneering work^{87,88}, especially by Bloch⁸⁸, in the use of isotopically labelled precursors, showed that acetic acid is incorporated by enzyme systems into both squalene and

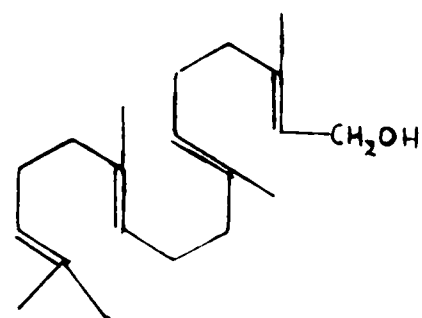
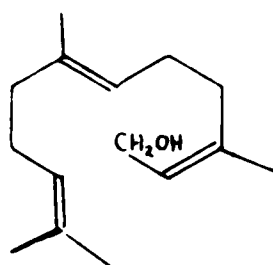
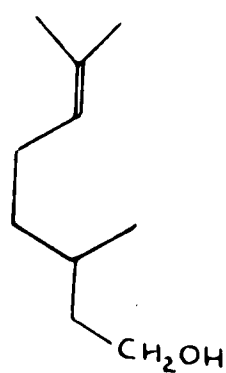
cholesterol according to a definite distribution pattern of 'methyl'(m) and 'carboxyl'(c) carbon atoms. In 1953⁸⁹ Woodward and Bloch proposed that lanosterol (B2) is a biogenetic precursor of cholesterol (B3), and is formed by the cyclisation of squalene, in a specific conformation (B1), accompanied by the migration of two methyl groups. In a mechanism previously proposed by Robinson⁹⁰, the required folding of the squalene molecule⁽³⁴⁾ was such as to require no methyl shifts for the generation of the cholesterol skeleton. Experimental support for Woodward and Bloch's hypothesis has been provided by the elucidation of the complete distribution patterns of squalene (B1)⁹¹ and cholesterol (B3)⁹², and the proof that lanosterol is biosynthesised from both acetate⁹³ and squalene⁹⁴.

The importance of a triterpene in steroid biogenesis led Ruzicka⁹⁸ to formulate analogous biogenetic schemes for all terpenes. An expression of Ruzicka's hypothesis is the biogenetic isoprene rule which defines the terpenes as compounds obtainable by cyclisation and, in certain cases, rearrangement mechanisms from aliphatic substances, such as geraniol (B5), farnesol (B6), geranylgeraniol (B7) and squalene, which are formed by the combination of isoprene units. This hypothesis has been further amplified



(B4)

(B3)



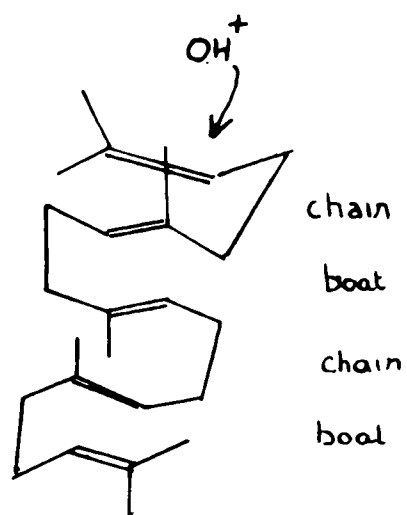
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(B6)

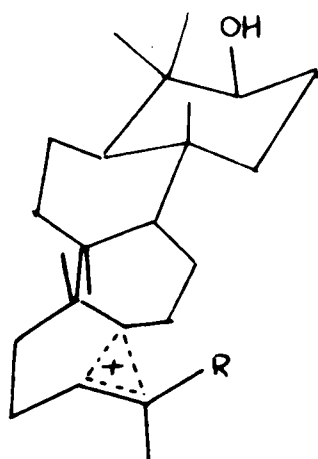
(B7)

with respect to triterpene biogenesis to define, not only gross carbon skeletons, but also their complete stereochemistry^{99,100}, by postulating the cyclisation of all-trans squalene in different conformational modes. In all such cyclisations it is envisaged that attack by a cationic species, probably $(OH^+)^{94}$, on one of the terminal double bonds of squalene initiates a fully concerted⁹⁴ series of anti-planar additions and rearrangements. The stereo-specificity of these processes requires configurational stability of the cationic intermediates, for which Ruzicka's bridged cation structures (cf. B8 -B5) are convenient pictorial representations.

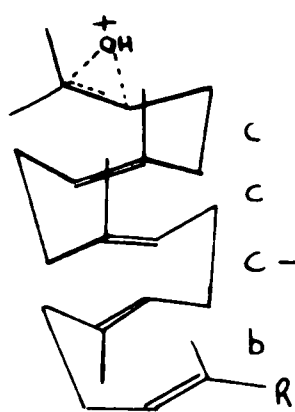
The biogenesis of lanosterol requires the cyclisation of squalene in the chair-boat-chair-boat conformation (B8) to give, in the first place, a tricyclic cation (B9). The concerted processes (cf. Scheme 1) responsible for the formation of the dammarenediols, euphol, tirucallol and those pentacyclic triterpenes in which rearrangement of the squalene skeleton has occurred, are all initiated by a cyclisation in the chair-chair-chair-boat conformation (B10) to give the cation (B11). The tetracyclic cationic precursor (B13) of the pentacyclic triterpenes no longer contains the carbon sequence of squalene as a result of the rearrangement.



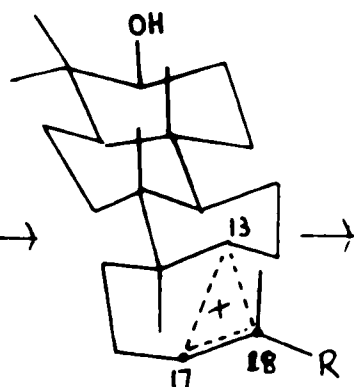
(B8)



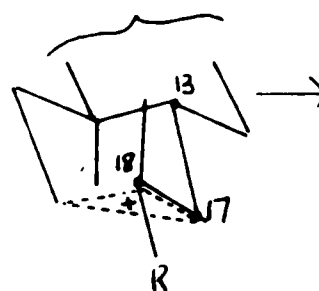
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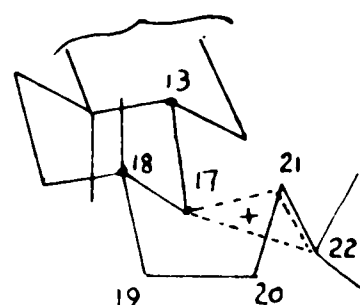
(B10)



(B11)

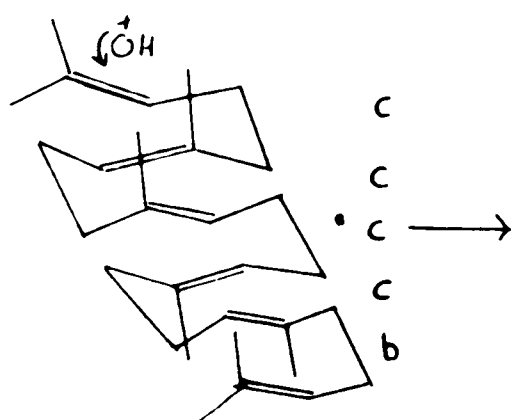


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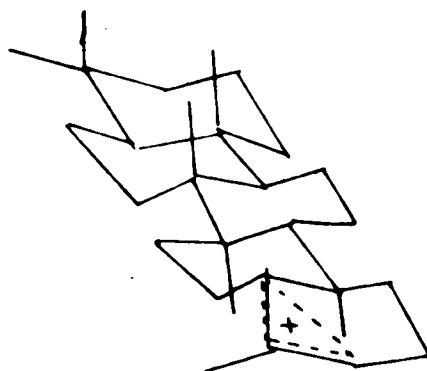


(B13)

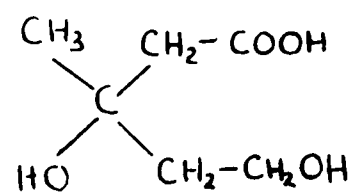
SCHEME 1



(B14)



(B15)



(B16)

implicit in the conformational change of ring D from a boat to a chair form (B11-B12). If however the initial cyclisation of squalene were to occur with ring D in a chair conformation (B14), a pentacyclic system preserving the original carbon sequence could be formed. This theoretically predicted type of structure has now been found in hydroxy-hopanone (A22).

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The demonstration by Arigoni⁹⁵ that mevalonic acid (B15) (see below) is a biogenetic precursor of soyasapogenol-A provided the first direct experimental data on the biogenesis of the pentacyclic triterpenes. Previous experimental work had been confined to the more easily studied squalene-lanosterol-cholesterol sequence (cf. refs. 87-94).

An important advance in the knowledge of earlier stages of squalene biogenesis was the discovery that mevalonic acid (B16)⁹⁶ is the source of the 5-carbon unit, being incorporated into polyprenoid structures^{95,97} with loss of the carboxyl group. Other probable intermediates in the conversion of mevalonic acid into squalene have been isolated,¹⁰¹ and Cornforth and Popjak¹⁰² have put forward a detailed mechanism for this conversion.

Many important aspects of terpene and steroid biogenesis¹⁰³ are discussed in a recent symposium¹⁰³, which includes

a review of work on the acid catalysed cyclisations of polyenes. The latter provide a possible laboratory analogy for the enzymatic cyclisations of biogenetic processes.

Approaches to the Synthesis of the Higher Terpenes.

Reference has already been made to syntheses of the acyclic squalene and of the tetracyclic triterpenes.

Tsutsui and Tsutsui³¹ have reviewed work on the synthesis of naturally occurring triterpenes and of related structures. In the majority of these syntheses the starting materials have been, either suitably substituted naphthalenes, or a substituted cyclohexanone and a methoxyphenylacetylene. Thus ($\pm$)-dehydroabietic acid (C5) has been obtained from 2-isopropyl-6-hydroxynaphthalene (C1) as shown (C1-C5)¹⁰⁴. ($\pm$)-6-Methoxypodocarpene (C6)¹⁰⁵ and ($\pm$)-ferruginol (A10)¹⁰⁶ have been synthesised by analogous routes.

Starting materials of the second type have been used in syntheses of ($\pm$)-ferruginol (A10)²⁸ and ($\pm$)-podocarpic acid (A9)²⁷, and of the ketone (C10)¹⁰⁷ and the keto ester (C11)¹⁰⁸, both versatile synthetic intermediates. The synthesis of (C10) is outlined (C7-C10): (C7) was obtained by condensation of sodio-m-methoxyphenylacetylene and 2,2,6-trimethylcyclohexanone. Catalytic reduction

followed by cyclisation with polyphosphoric acid gave a tri-cyclic system (C9) which was converted into the ketone (C10) by metal-ammonia reduction. This ketone has been converted into $(\pm)$ -totarol (A11)³⁰ and into $(\pm)$ -ambreinolide (C12)¹⁰⁹, a degradation product of ambrein³⁶; $(+)$ -sclareol (A8)²⁵ has been synthesised from $(+)$ -ambreinolide. The possible significance of (C10) as regards triterpene synthesis will be discussed elsewhere in this thesis.

The keto-ester (C11) is a possible starting material¹⁰⁸ for the synthesis of resin acids not containing an aromatic ring.

A third general approach to the bicyclofarnesol skeleton of diterpenes utilises the stereospecific acid-catalysed cyclisation of polyenes or related structures. An early application of this method was in Dietrich and Lederer's synthesis of ambreinolide (C12) by the cyclisation of the acid (C13) obtained from farnesyl bromide³⁷. A recent example is the cyclisation of the olefinic alcohol (C14) to a mixture of two podocarpatrienes (C15, C16)¹¹⁰, one of which (C15) has been converted into the racemate of the methyl ether of nimbiol (C17), a naturally occurring diterpene¹¹¹.

Paper syntheses of the pentacyclic triterpenes can be constructed starting either from a previously synthesised steroid, or from simple alicyclic starting materials, but only the latter route has been investigated experimentally.

Halsall and Thomas¹¹², in 1956, proposed a synthetic route in which a bicyclic intermediate (C19) was to be linked, with nucleophilic displacement of X, to the bicyclic ketone (C20) activated at C-*. The adjacent carbonyl group would ensure attachment of (C19) in the stable equatorial configuration to give a mixture of two racemates (C21a, C21b). The ketone (C21b) could be easily transformed into a tetracyclic structure (C22) which, there was reason to suppose, would undergo an acid catalysed cyclisation to 3-hydroxyolean-13(18)-ene (δ -amyrin) (C23). All subsequent synthetic approaches to the pentacyclic triterpenes have envisaged routes of this general form, involving the coupling of moieties representative of the A and B and of the D and E rings, followed by closure of ring C. The stereochemical problems in such syntheses are greatly simplified in comparison with routes requiring a ring-by-ring construction of a pentacyclic structure starting from ring A.

The crux of the synthetic route outlined by Halsall and Thomas is the final cyclisation to give a trans-anti-trans-

anti arrangement of rings A,B,C and D. A possible analogy was the cyclisation of derivatives of α -onocerin (A17) to those of γ -onocerin (A20) (viz. p.6)³⁸. The position of the double bond in the cyclisation product (C23) is predicted by the known isomerisation¹¹³, under acidic conditions, of the 12(13)-double bond of β -amyrin into the 13(18)- position. The validity of the original proposal has now been demonstrated by the use of a cyclisation of this type in Corey's recent synthesis¹¹⁴ of olean-11(12),13-diene (D11) (viz. p.21).

The synthesis of the bicyclic intermediates (C19) and (C20) presents no great stereochemical difficulties. In a synthesis of the A-B rings (C20), the key step would be the formation of the trans-fused ring junction; and for the D-E intermediate (C19) either the pure cis (C19;18 β -H) or the pure trans (C19;18 α -H) isomer is required. Halsall¹¹² and Thomas described the synthesis of the hydroxy-ketone (C18), a precursor of (C19). More recently (C20)¹¹⁵, and (C19)¹¹⁶ with the ring junction trans (18 α -H), have been prepared by Halsall's group.¹¹⁷

King, Ritchie and Timmons¹¹⁷ proposed a modification of the route discussed above, in which the C-11 and C-12 carbon atoms are attached to the A-B rings. The postulated intermediates (C24) and (C25) were to be linked by an aldol

condensation to give the tetracyclic ketone (C26). Work by Halsall and Thomas suggests that reaction would occur at α' (C25) and protection at this position would therefore be necessary prior to the condensation.

As a result of the proposals outlined above attention was directed towards the preparation of bicyclic systems and, in particular, interest centred on intermediates representing rings A and B of the pentacyclic triterpenes. An alternative use for such intermediates was the preparation of structures of the onocerane type, in which synthetic problems are simplified by virtue of the unique symmetry of the molecule.

The synthesis of the A-B intermediates poses problems similar to those encountered in the synthesis of diterpenes in which the same bicyclofarnesol skeleton is found. Work in the two fields is therefore closely related and the possibility arises of utilising, in triterpene syntheses, degradation products of naturally occurring diterpenes (and also ambreinolide) which have previously been synthesised. The use of such relays is limited by the absence of the 2-oxygen function. An exception to this limitation is cassaic acid (C27)¹¹⁸ obtained by hydrolysis of the Erythro-¹¹⁹phleum alkaloid casseine. Recently a degradation product¹¹² of cassaic acid has been synthesised (viz. p.22) (C28).

In 1957 three methods were described for the linking of two molecules of a bicyclic intermediate to give an onocerane structure.

Corey and Sauers⁵¹ obtained (+)(8S,8S')-onocerane-8,8-diol (32a) by the electrolytic coupling of two molecules of the ammonium salt of the acid (C31). Cyclisation of this diol with perchloric acid in benzene-acetic acid gave pentacyclosqualene (A20) identical with the γ -onocerane obtained by Barton and Overton³⁸. The (-)lactone (30a), from which the acid (C31) was derived, was obtained in racemic admixture with its (+) antipode by the acid catalysed cyclisation of α - or β - monocyclofarnesic acid (C29)¹²¹. An alternative route involved the oxidation of sclareol to a lactone (C30b)¹²¹ which readily isomerised to (C30a) in the presence of acid. From the diastereoisomeric lactone (C30b) was obtained the diol (32b). Phosphorus oxybromide-pyridine dehydration of (C31b) and (C31a) gave α - (C33b) and β - (C33a) onocera-diene respectively, as would be predicted from the assigned orientations of the hydroxyl groups.

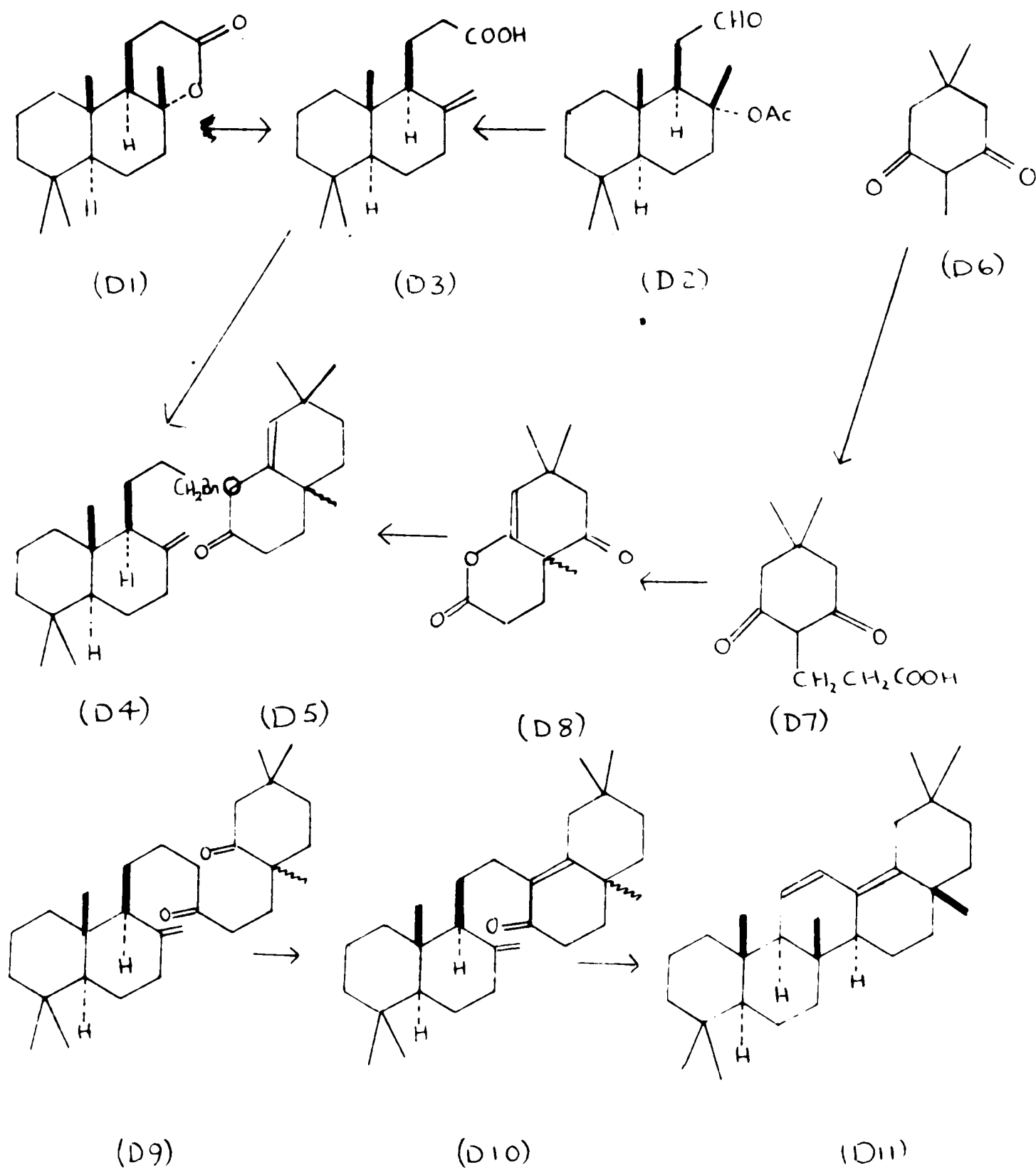
The tetracyclic diol (C32a) was also obtained by Eschenmoser and his co-workers^{124,126}. Stereoselective dimerisation of the α -methylene ketone (C36) gave a ketone (C37); reduction of this ketone yielded a diol which was

resolved and the correct enantiomorph (C38) converted to (32a). The methylene ketone (C36) was obtained from the hydroxy-acid (C35) which is formed by the cyclisation of bicyclofarnesic acid (C34)¹²⁵. An attempt¹²⁶ was also made to prepare a tetracyclic precursor of the oleanane series by cross dimerisation of (C36) and (C39). A ketone, possibly (C40), was obtained but its structure has not been proved.

Sondheimer and Elad^{127,128} have described a third approach to tetracyclic structures of the onocerane type, in which 1-decalones such as (C42) are the bicyclic starting materials and the two extra carbon atoms are provided by an acetylene molecule. Thus, treatment of the decalone (C42) with sodium acetylide in liquid ammonia gave the acetylenic carbinol (C45) which, after reaction^{with} sodamide in liquid ammonia, was condensed with a second molecule of decalone to give a mixture of the meso- (46a) and racemic (C46b) glycols. Dehydration and catalytic hydrogenation of the latter gave ($\pm$)dinoronocerane (C47)¹²⁹. The ketone (C42), which is also a possible intermediate for the synthesis of a degradation product (C48) of labdanolic acid¹²⁹, was obtained¹²⁷ from the readily accessible 9-methyl- Δ -octalin-3,8-dione (C41)¹³⁰. This starting material has also

been used for three independent syntheses of the decalone
 (C43)¹³¹⁻¹³³, which has been converted into the racemate of
 a degradation product (C44)¹³⁴ of α -amyrin^{131,132}. Haynes
 and Timmons¹³⁵ have reported a different route to (C44) which
 is also a possible precursor of the aldehydic intermediate
 (C24) (viz. p.16). The ethynyl carbinol (C49), which
 was prepared from (C44) by Sondheimer and Elad¹³¹, is a
 potentially useful intermediate for the synthesis either
 of the onocerins, or of the oleanane skeleton. Sondheimer
 and Rosenthal¹³⁶ have discussed such an approach to the
 β -amyrin series, in which the ethynyl carbinol (C49) would
 be condensed with the decalone (C50). As model compounds,
 the cis- and trans- decalones (C51b,C51a) have been
 synthesised from the decalol (C52). This decalol was
 prepared from (C53) by an interesting application of the
 Brown hydration reaction¹³⁷.

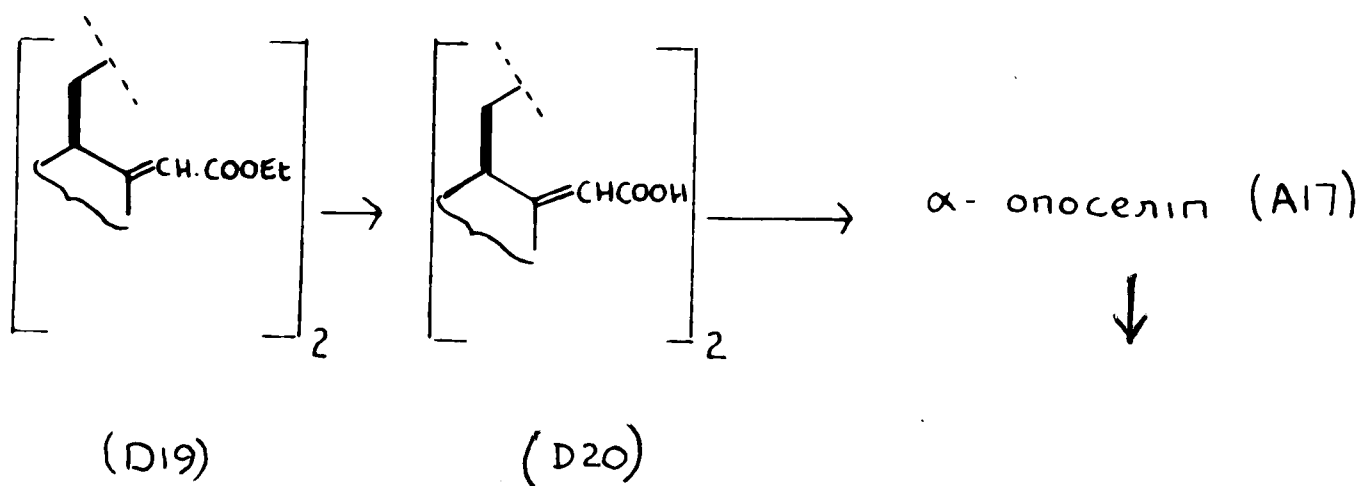
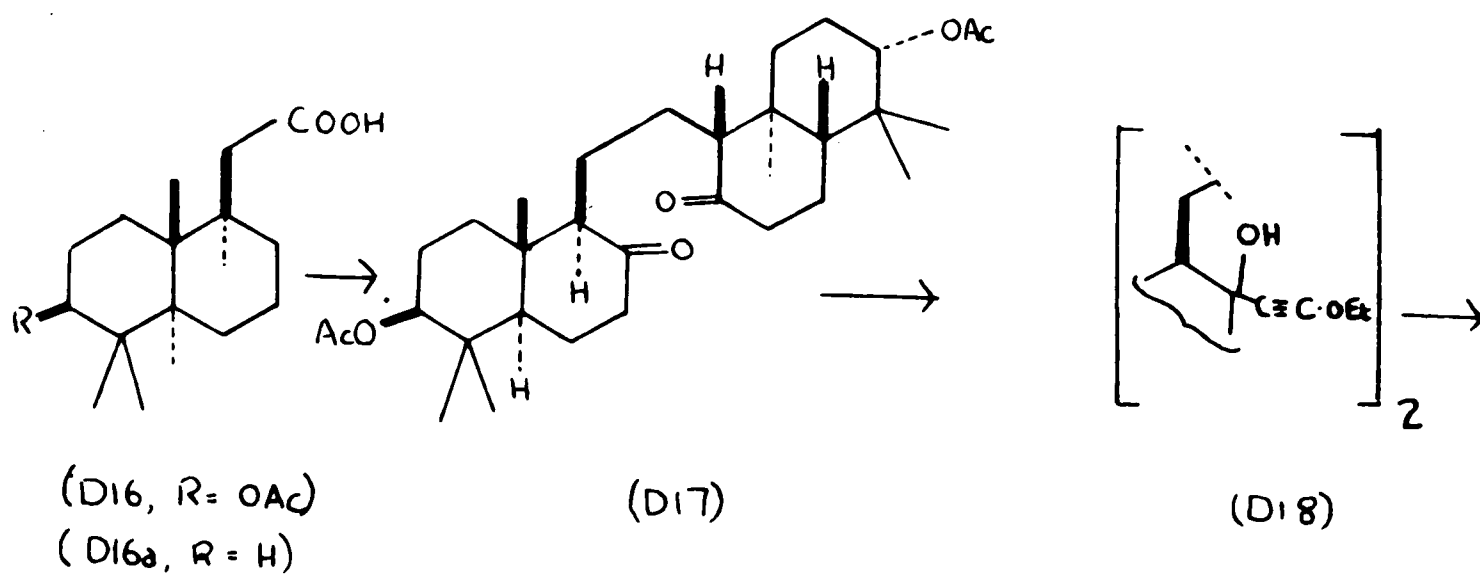
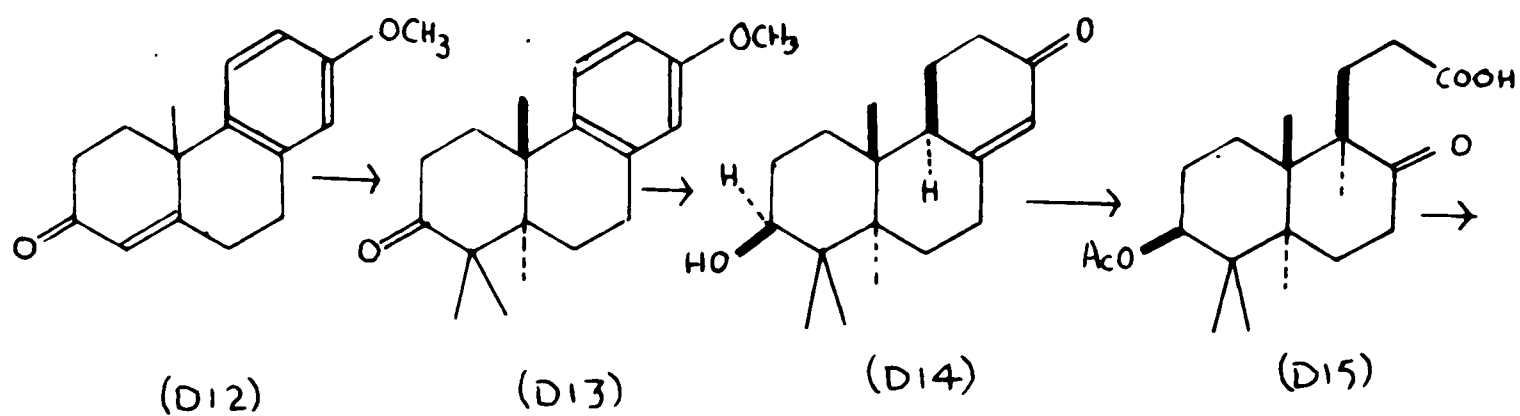
A major advance toward the solution of the still out-
 standing synthetic problems was made in 1959 when syntheses
 of α -onocerin¹³⁸ and of olean-11(12),13(18)-diene¹¹⁴ were
 described. The main stages of Corey, Hess and Preskow's
 synthesis¹¹⁴ of the latter are shown in Scheme 2 (D1-D11).
 The (+)bromide (D4), representing rings A and B, was obtained
 by four-stage reaction sequences both from ($\pm$) ambreinolide



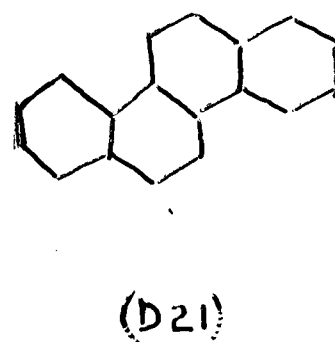
SCHEME 2

(D1), and from the acetoxy-aldehyde (D2) previously prepared by Corey and Sauers⁵¹. Reaction of the Grignard derived from the (+)bromide with the (+)enol lactone (D5) gave a tricyclic diketone (D9). Closure of ring D by an aldol condensation yielded a mixture of two ketones (D10) epimeric at C-17. Treatment of this mixture with lithium methyl, and final cyclisation of the resulting tertiary alcohol with hydrochloric acid/acetic acid gave, after careful chromatography, a 2% yield of the required stereoisomer (D11). Though the yield in the final stage was very low, the isolation of (D11) was facilitated by the intense and characteristic ultraviolet absorption of the diene chromophore.

Stork, Davies and Meisels' synthesis of α -onocerin also constitutes a synthesis of a naturally occurring pentacyclic skeleton since α -onocerin has been cyclised to γ -onocerin (A20a)³⁸ and the latter converted to hopenone-1 (D21)¹⁴⁰. The synthetic route to α -onocerin is outlined in Scheme 3, (D12-D21). Two molecules of the (+)keto-acid (D16) were coupled by the electrolytic method of Corey and Sauers⁵¹ (viz p.18) to give the tetracyclic diketone (D17); the keto groups were converted into exocyclic methylene groups as shown (D18-D20). The tricyclic starting material (D12)



SCHEME 3



was obtained by the method of Howell and Taylor¹³⁹. The unsaturated ketone (D14) was easily prepared from (D12) and on ozonolysis gave the keto-acid (D15); the derived methyl ester was ketalised and the carbomethoxy group was converted into a diphenylethylene which, after oxidation and removal of the dioxalan protecting group, gave the ($\pm$)keto-acid (D16). The resolution of (D16) was achieved by fractional crystallisation of the strychnine salt of the half phthalic ester of the derived alcohol (D16a).

The unsaturated ketone (D14) was also obtained by a similar route to that outlined above by Turner and his co-workers¹²⁰ as an intermediate for the synthesis of a cassaic acid degradation product (C28) (viz. p.17).

An independent synthesis of the intermediate (D12),¹³⁹ by a route almost identical with that of Howell and Taylor, has been achieved in the present work and is described in Section 1 of this thesis.

This thesis describes the investigation of a synthetic route to pentacyclic structures having an oxygen function at C-24 as is found in oleanolic acid (A32). In the envisaged route the tetracyclic intermediate (E7) was to be synthesised by the alkylation of the octalone (E6a) with an alkyl halide (E5a, R=OH or H), which would provide the

potential A and B rings of the pentacyclic system.

Mr. I.D. Rushton has carried out parallel investigations into the synthesis of a β -amyrin structure using the octalone (E6b) as a source of the D and E rings. A number of aspects of the latter investigation are closely related to the present work and will therefore be discussed in this thesis.

(Diagrams (E5) - (E7) are placed at the end of Section 1)

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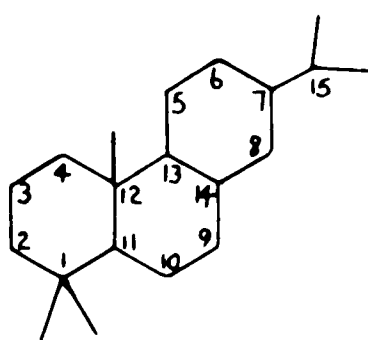
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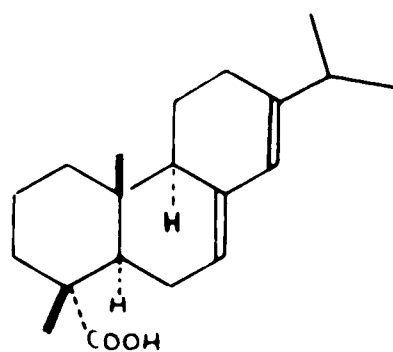
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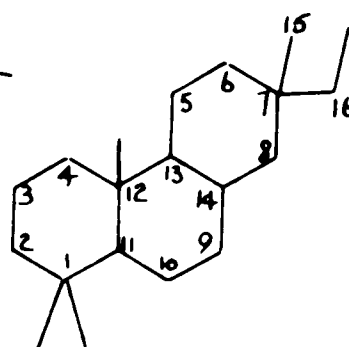
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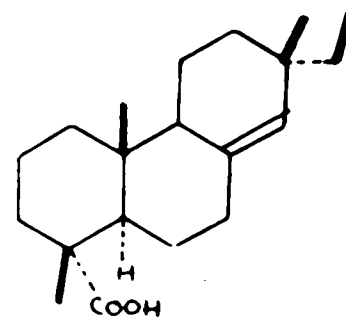
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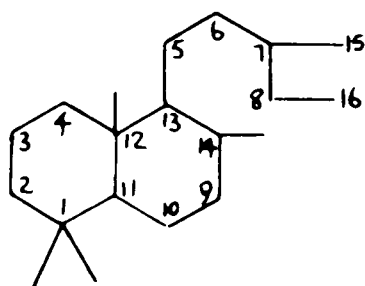
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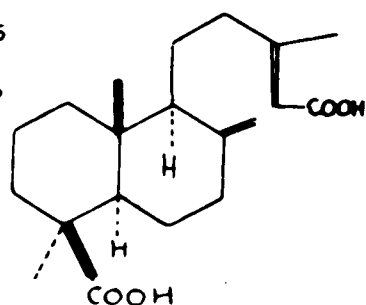
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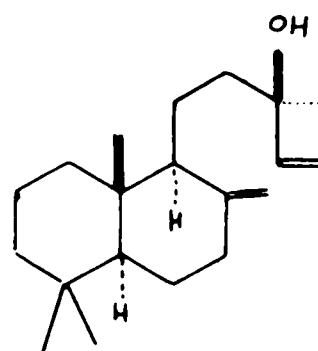
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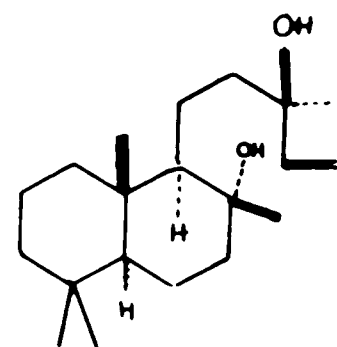
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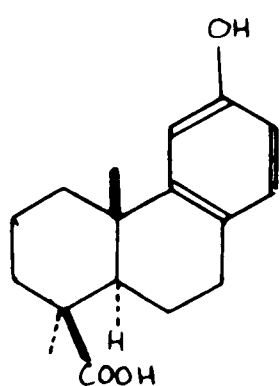
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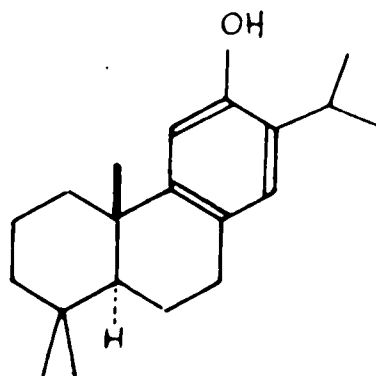
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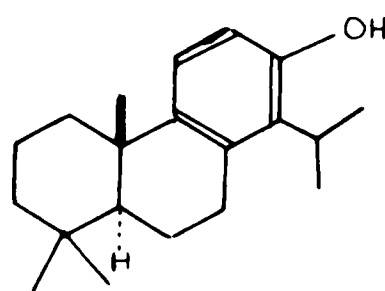
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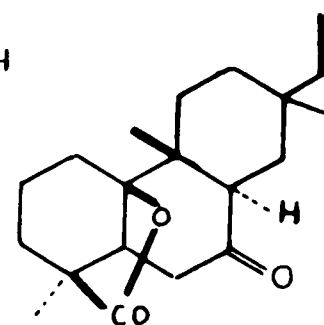
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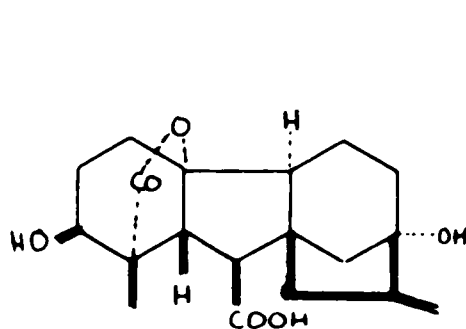
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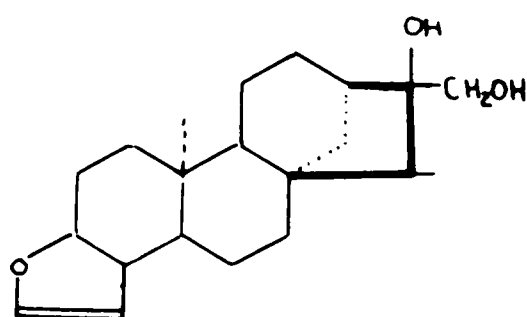
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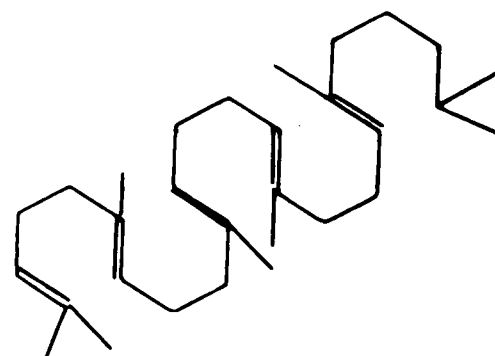
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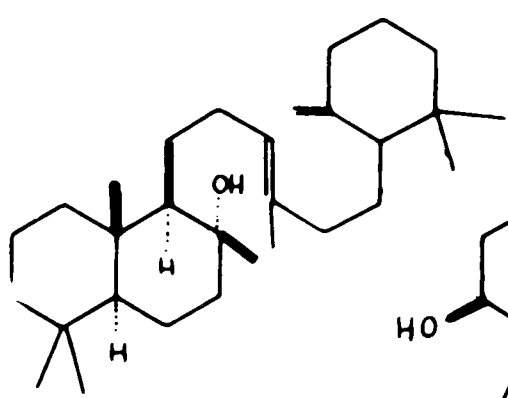
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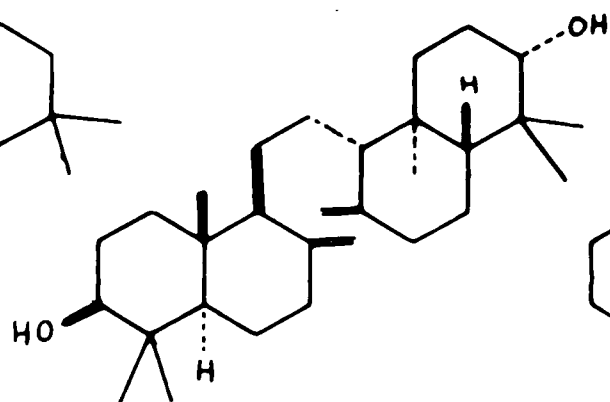
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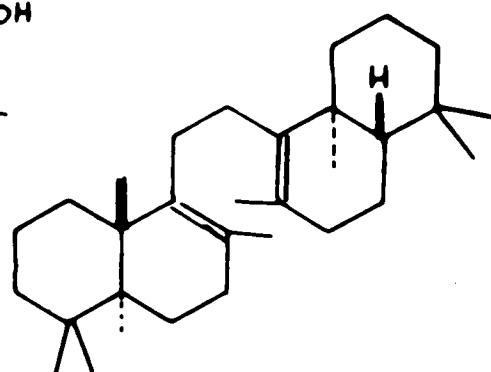
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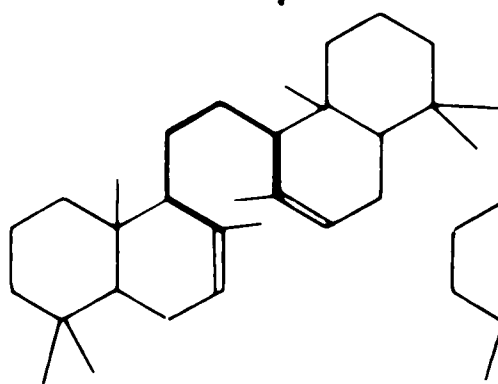
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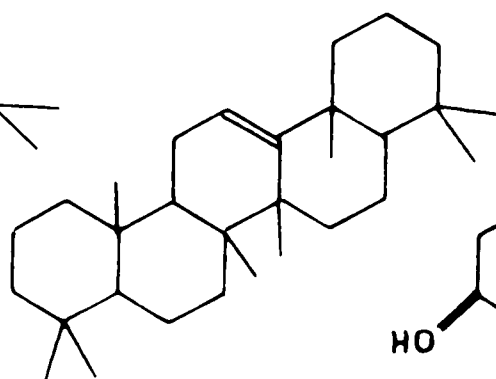
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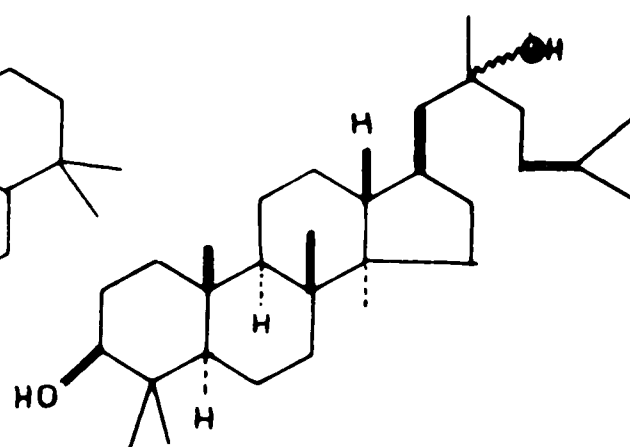
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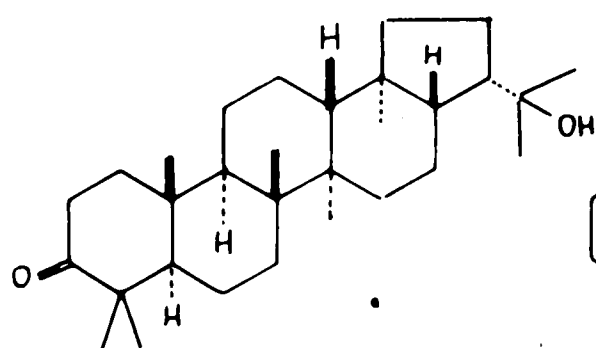
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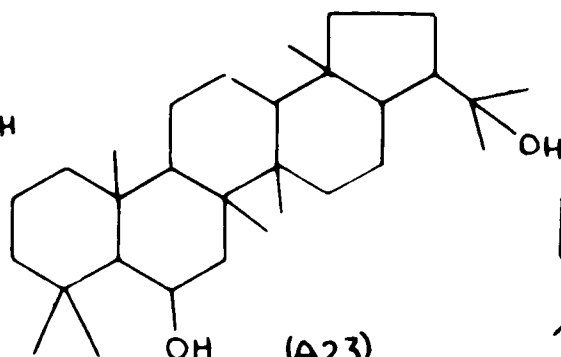
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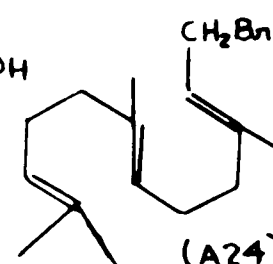
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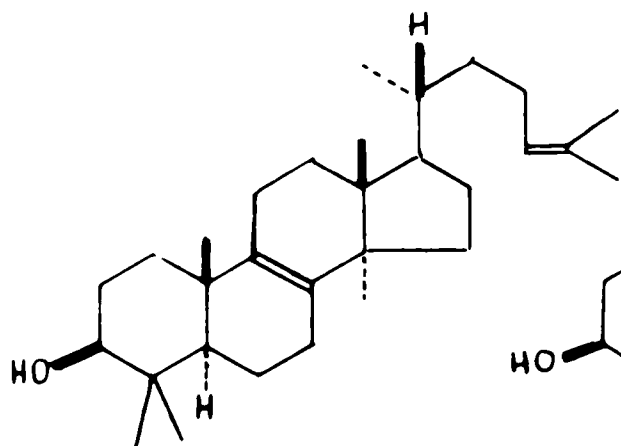
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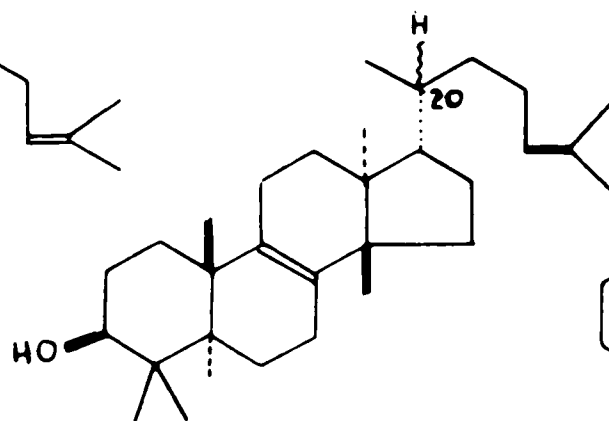
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(A24)

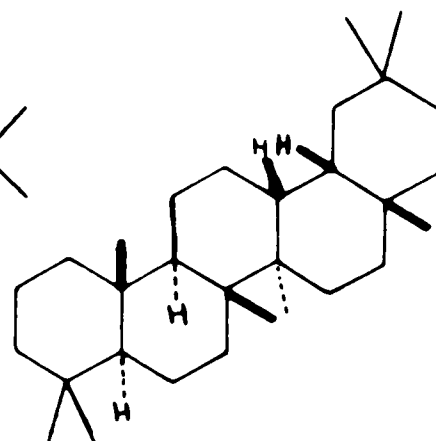


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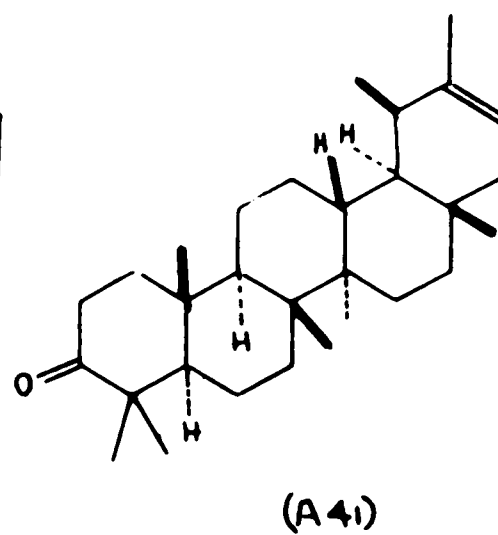
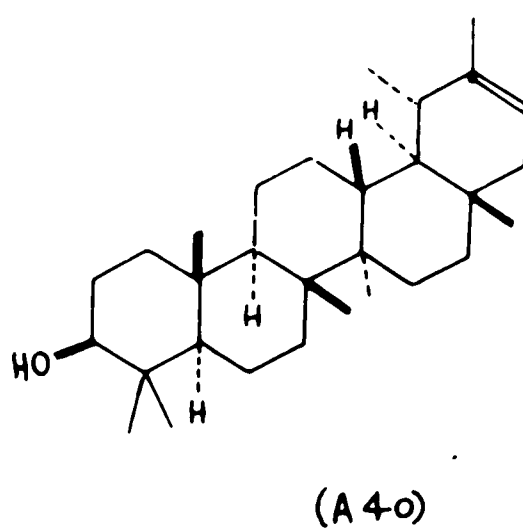
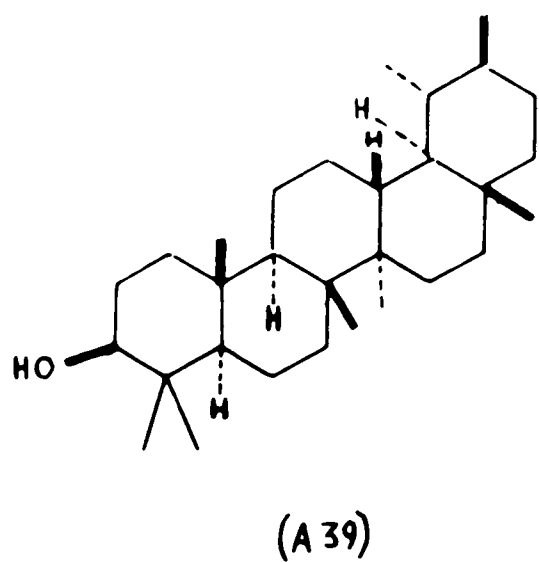
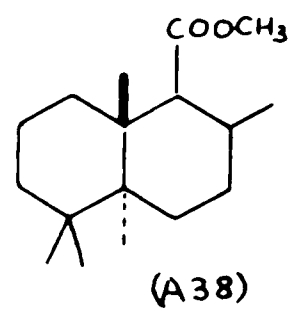
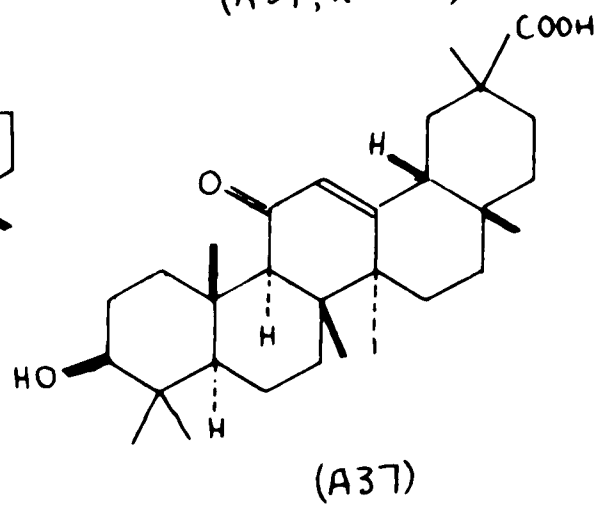
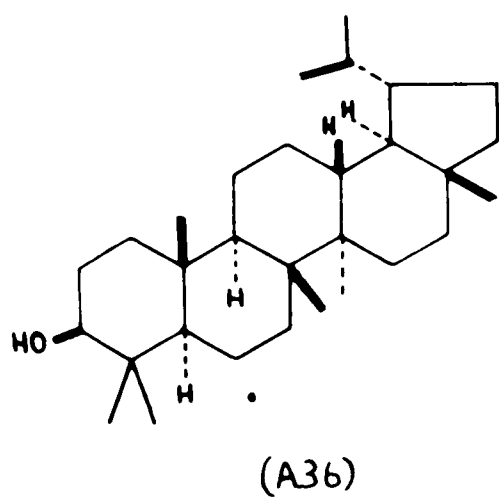
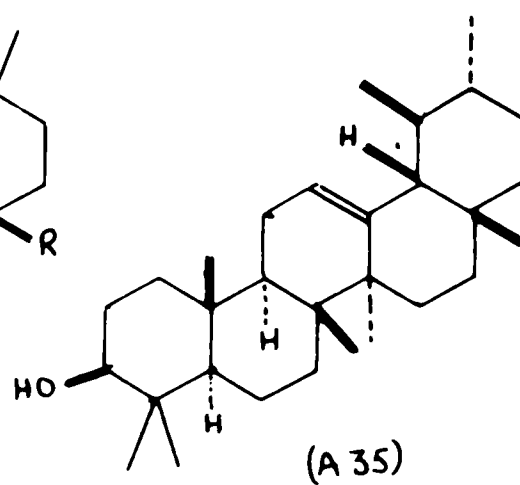
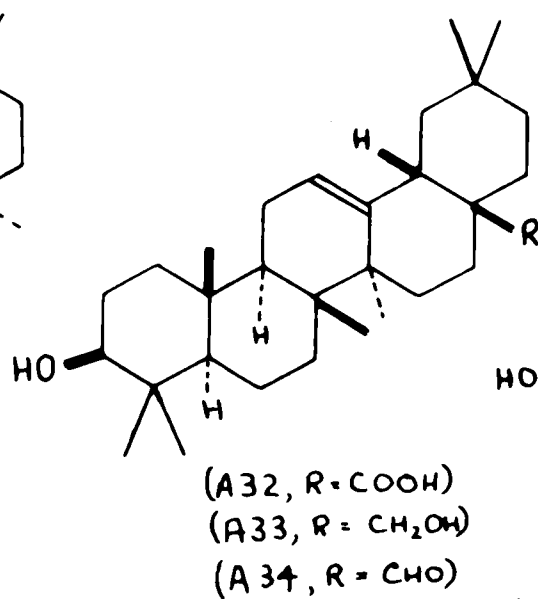
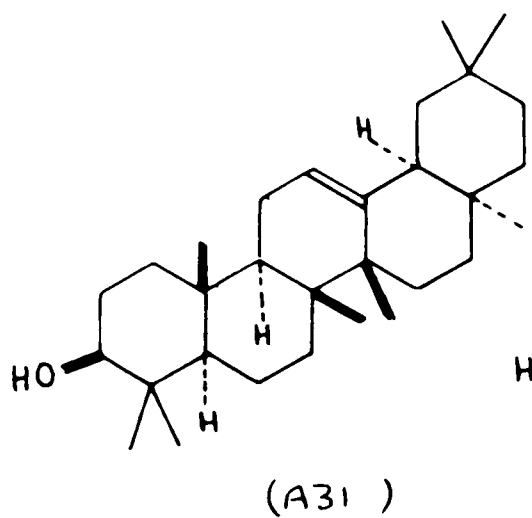
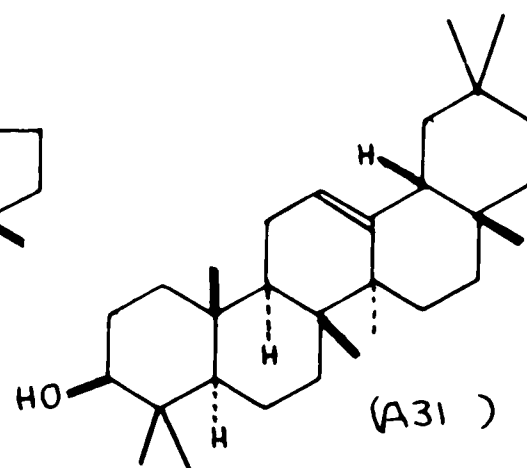
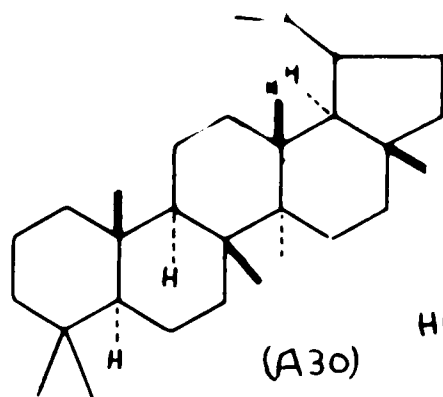
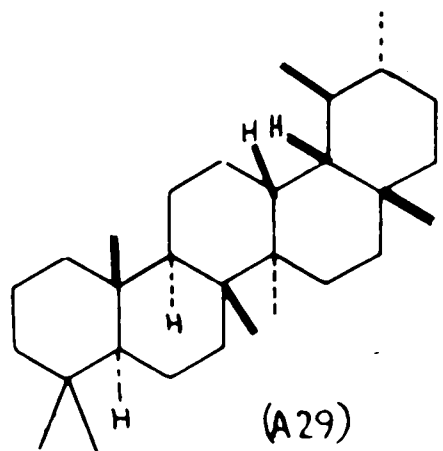


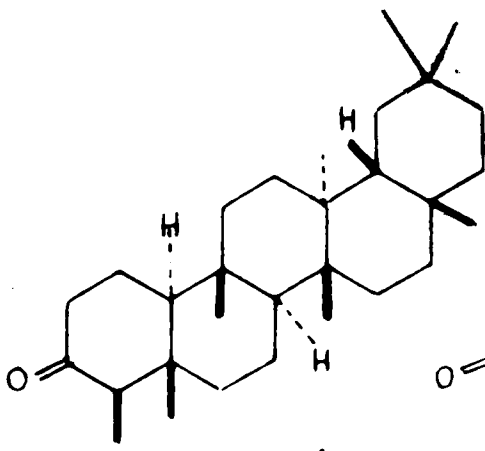
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(A27, 20α-H)

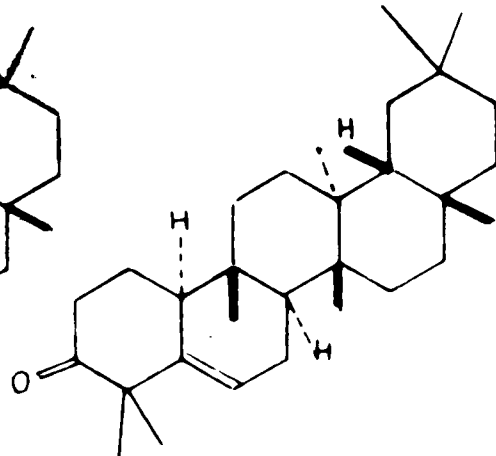


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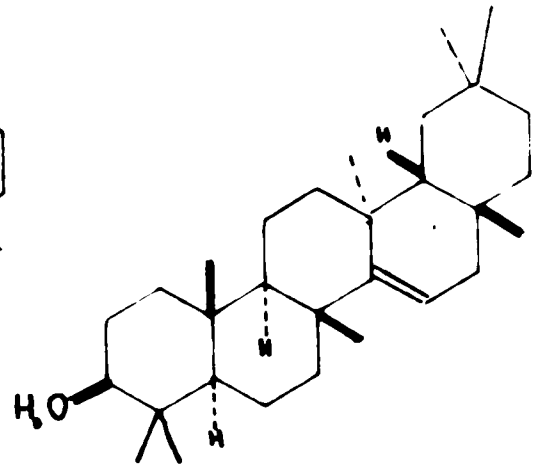




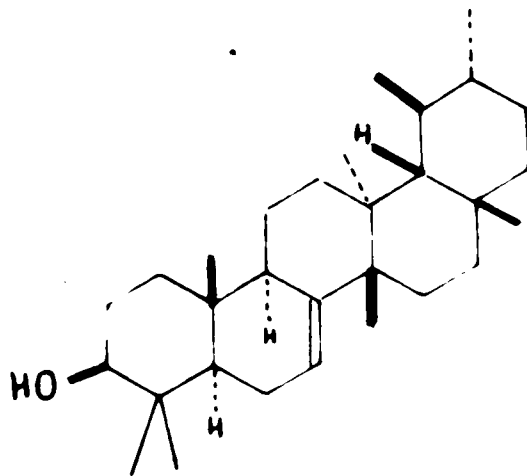
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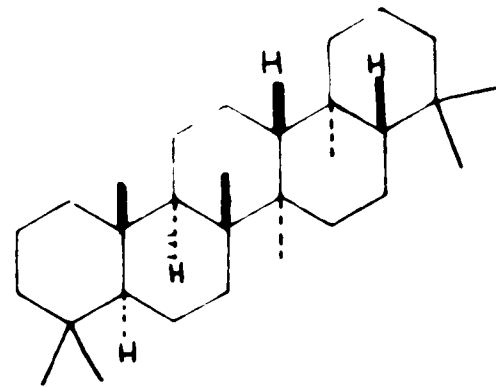
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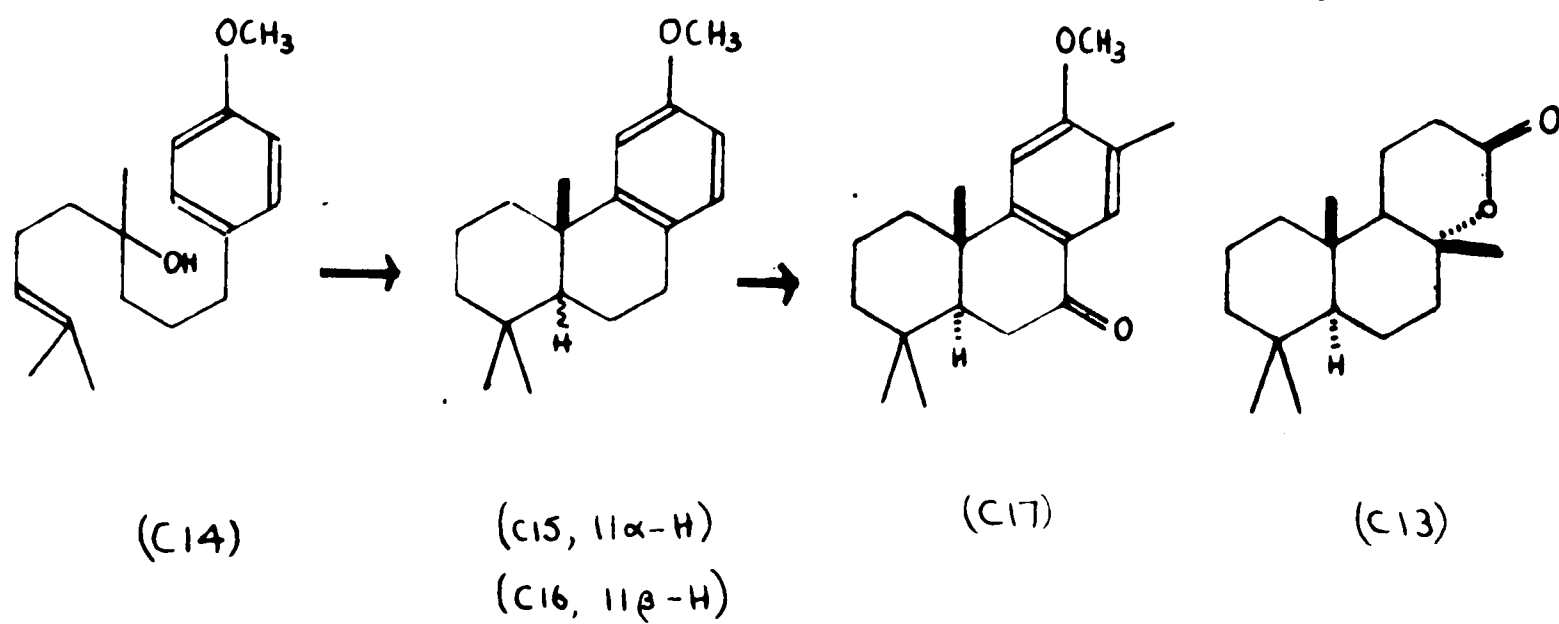
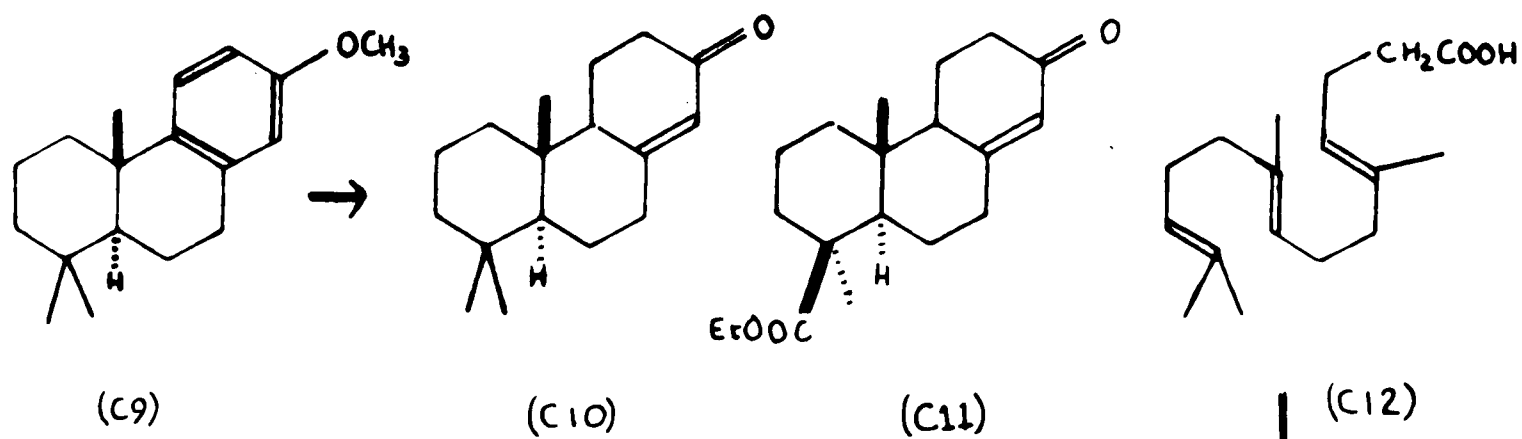
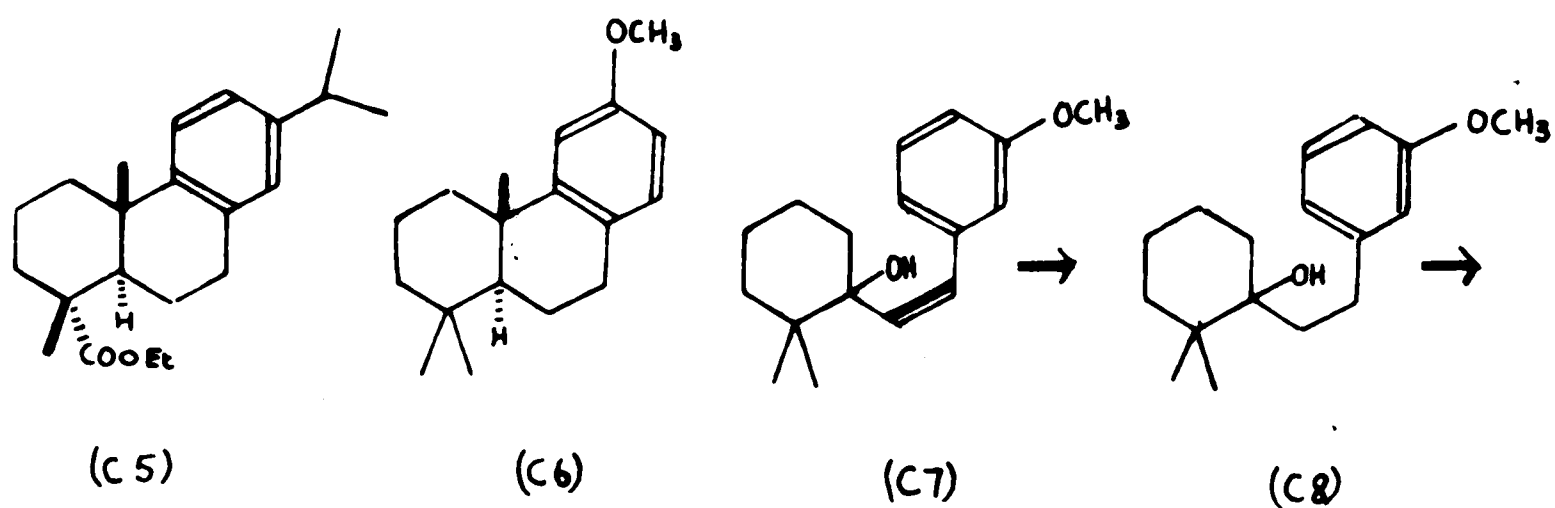
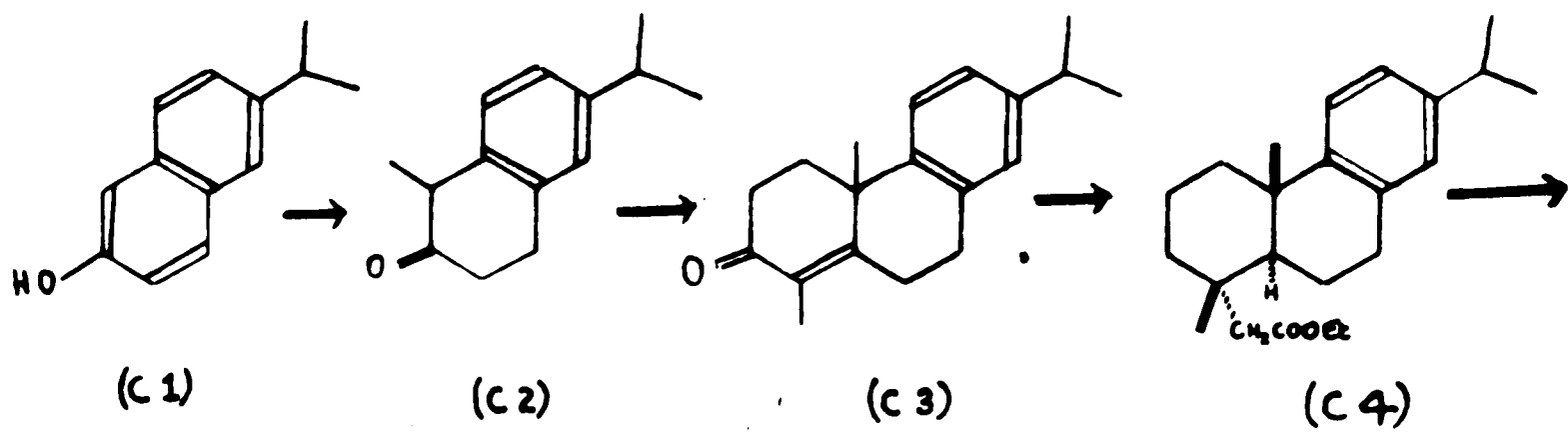
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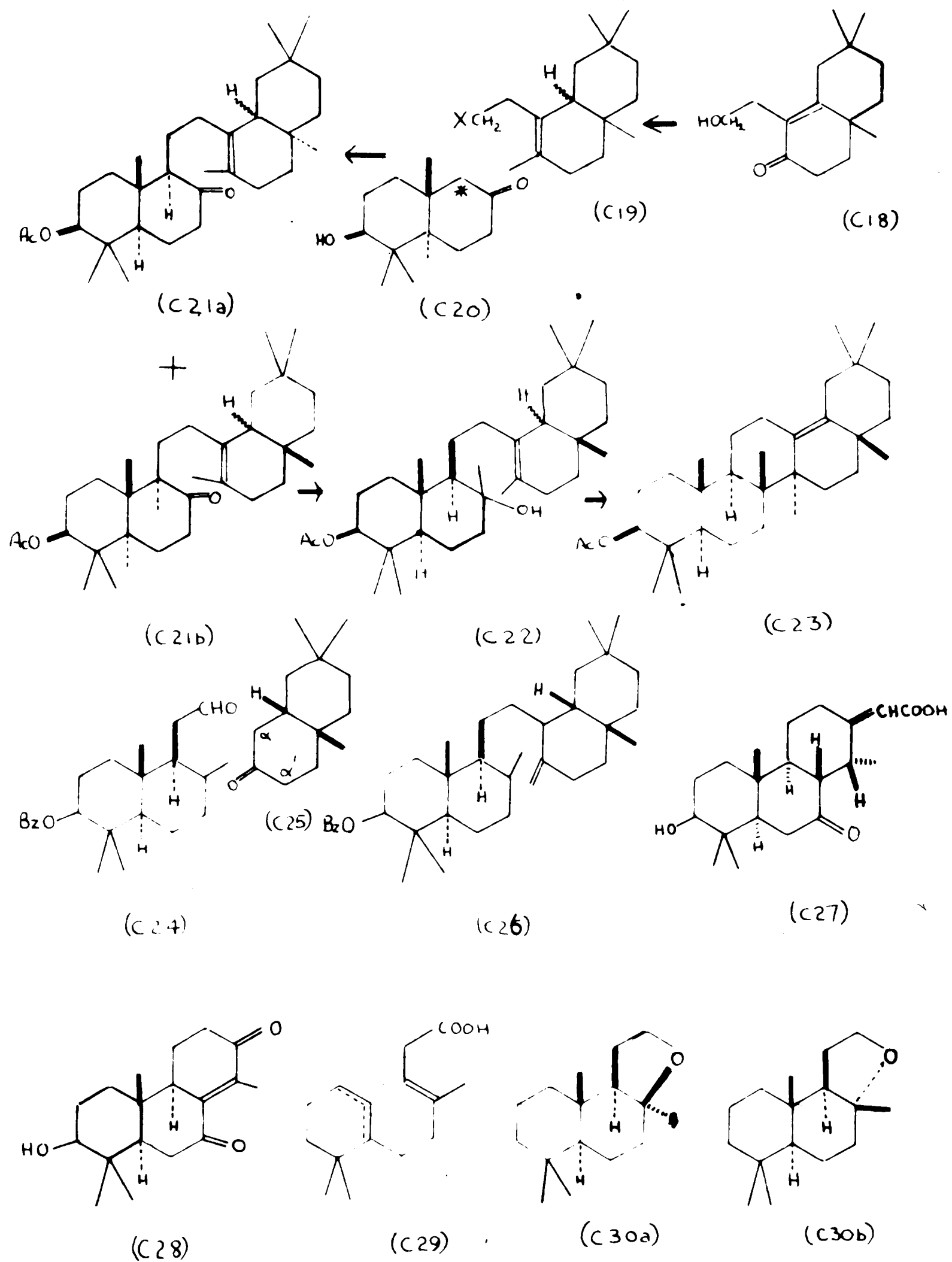


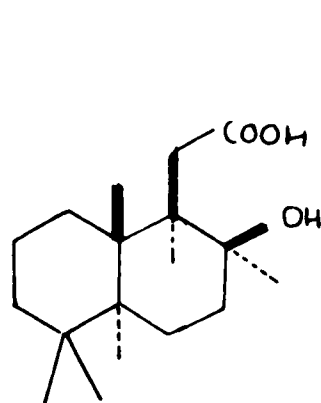
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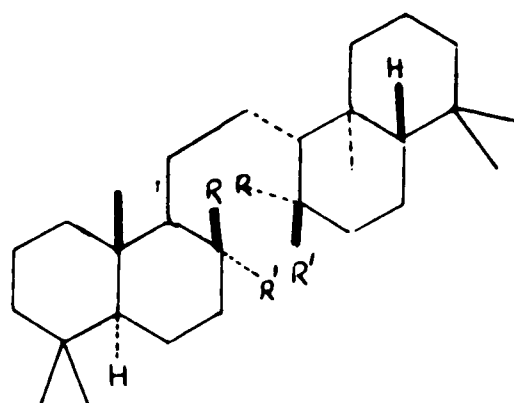
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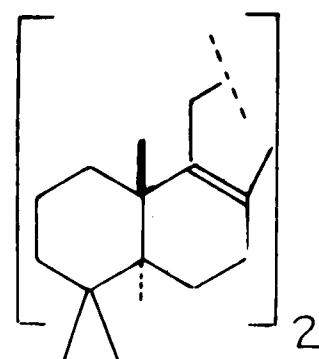


(C31)

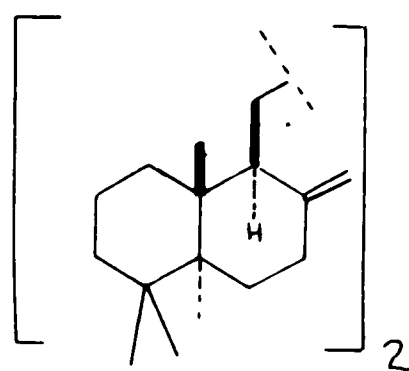


(C32a, $R=OH, R'=H$)

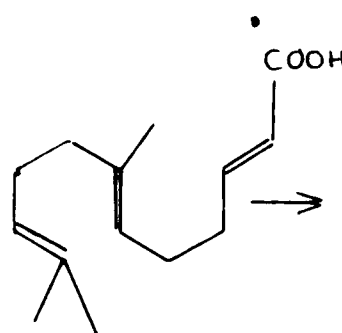
(C32b, $R'=OH, R=H$)



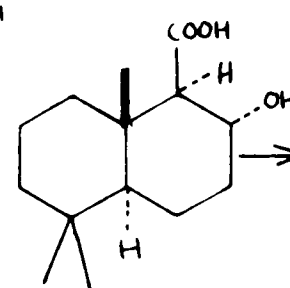
(C33a)



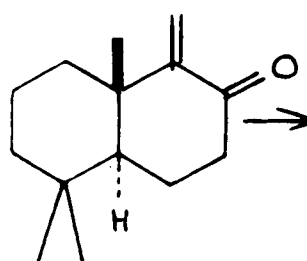
(C33b)



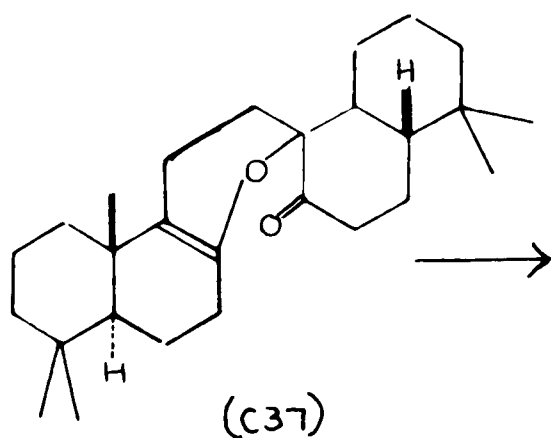
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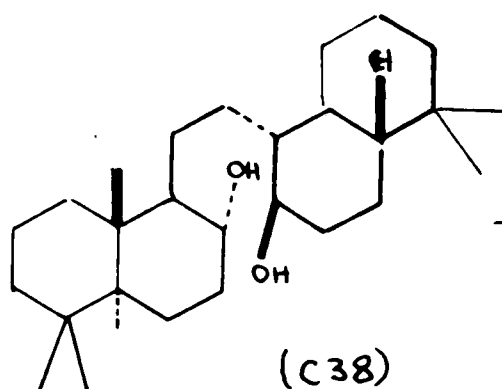
(C35)



(C36)



(C37)

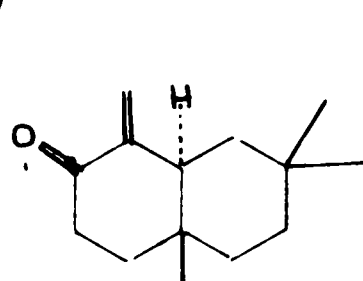


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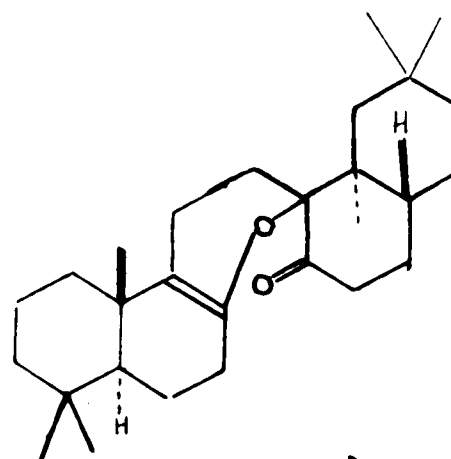
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(C36)

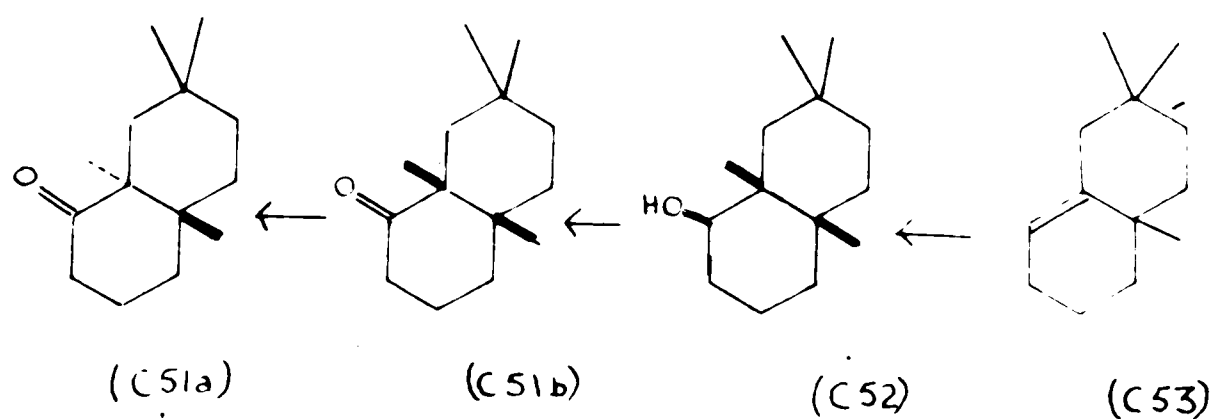
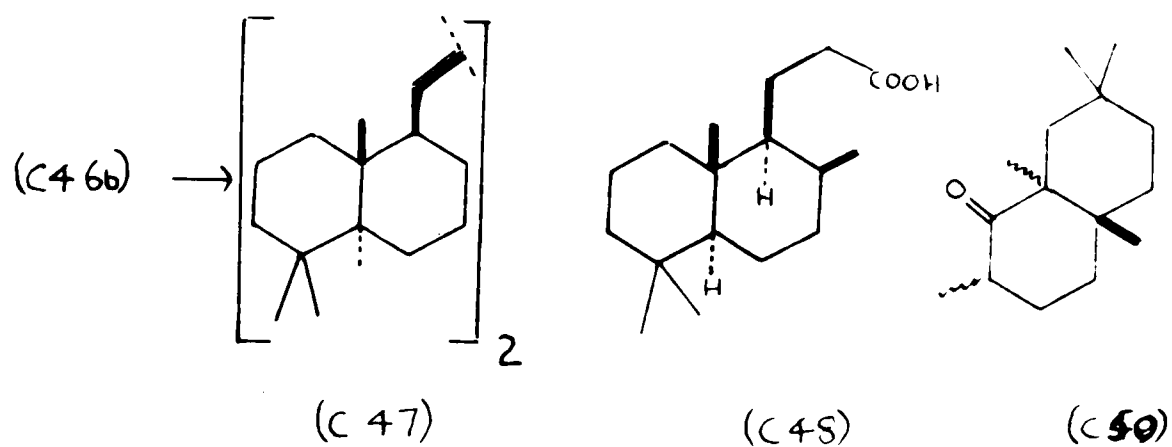
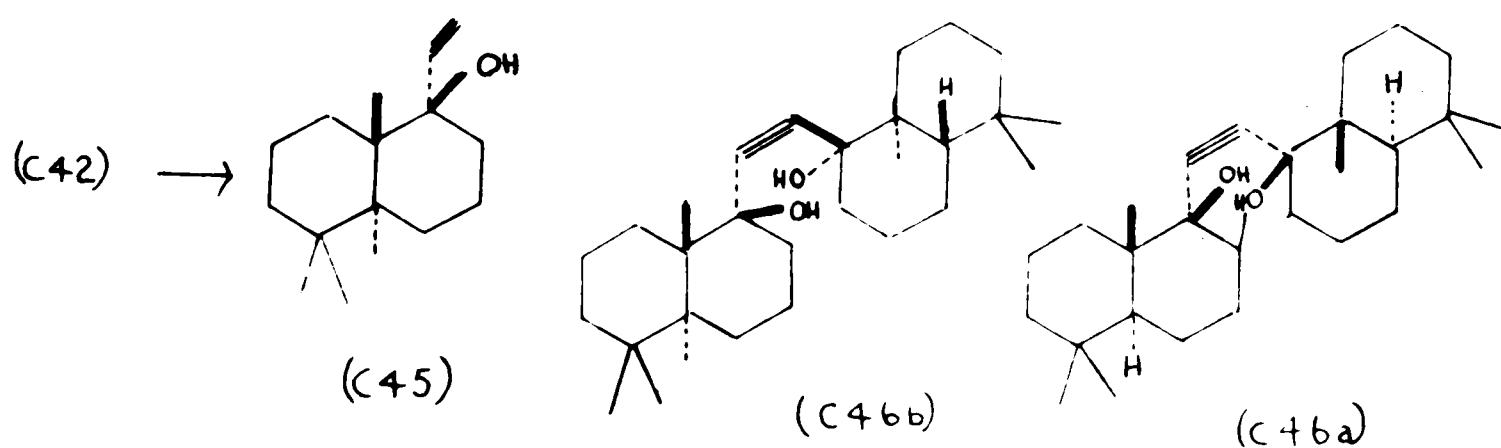
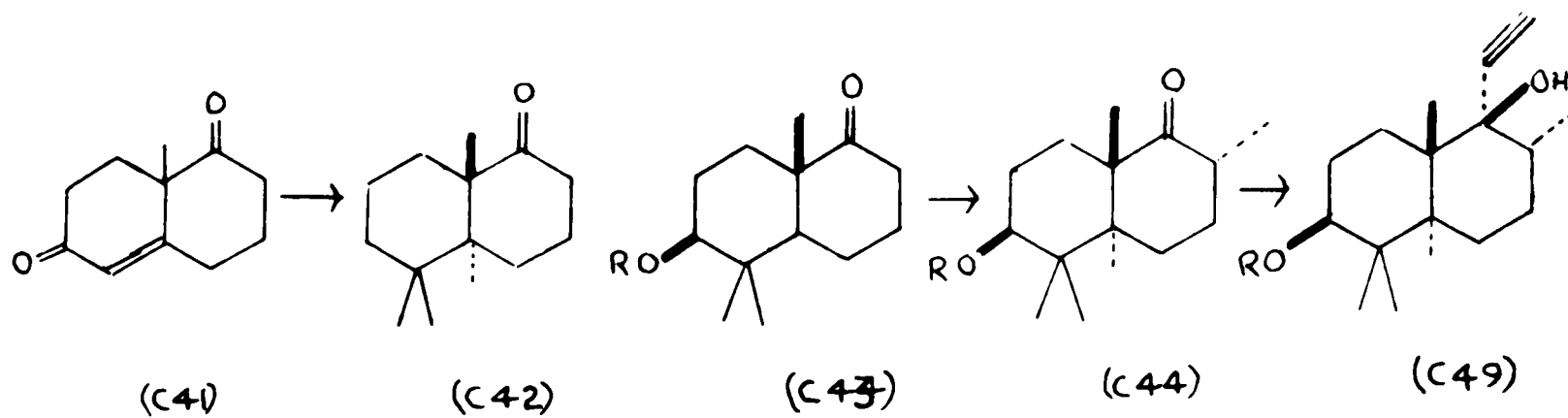
+



(C39)



(C40)



The synthesis of the synthetic route which has been outlined (Fig. 1) is outlined in a consideration of possible synthetic routes for 2,3-dihydro-2H-pyran (23, 24), which has been prepared by various methods (Fig. 2-15), and for related structures.

2,3-Dihydro-2H-pyran (23, 24) has been given, in high yield, a number of different syntheses, and has been used, in the synthesis of many, new compounds. The synthesis of 2,3-dihydro-2H-pyran (23, 24) is outlined in Fig. 2, and has already been discussed. The synthesis of 2,3-dihydro-2H-pyran (23, 24) is also a possible synthesis of 2,3-dihydro-2H-pyran (23, 24).

DISCUSSION

SECTION 1

It represents a possible route of the synthesis of 2,3-dihydro-2H-pyran (23, 24), which has been given in a previous section of the synthesis of 2,3-dihydro-2H-pyran (23, 24). The synthesis of 2,3-dihydro-2H-pyran (23, 24) would require a transformation of the starting material into a homologous acid (25, 26) and the replacement of the ester group by a -OH group. A possible route for this transformation is suggested by the synthesis of 2,3-dihydro-2H-pyran (23, 24) as an example of a transformation of the starting material into the ester group. The proposed route is a possible route which could also utilize the starting material (25, 26) to obtain the ester group in the transformation of the starting material. It is thought that the characteristic infrared absorption of the ester group could be used to identify the starting material.

The inspiration for the synthetic route which has been outlined (viz. p.22) originated in a consideration of possible synthetic uses for the intermediate ($E2, R=H$), which had been prepared by Barltrop and Rogers^{1,2} (viz. p.13), and for related structures.

Ozonolysis^{2,3} of ($E2, R=H$) had given, in high yield, a keto-acid ($E3, R=H$) which had also been obtained, as its methyl ester, from ambreinolide⁴. The subsequent successful applications of ($E2, R=H$) and ($E3, R=H$) in diterpene syntheses have already been discussed. The keto-acid ($E3, R=H$) was also a possible intermediate for a triterpene synthesis as it represented a potential source of the methylene halide ($E5a, R=H$), which would provide the A and B rings of the triterpene structure. To synthesize ($E5a, R=H$) from ($E3, R=H$) would require a transformation of the latter into the homologous acid ($E4, R=H$) and the replacement of the $-COOH$ group by a $-CH$ X function. At some point in this sequence an exocyclic methylene group must be introduced in place of the keto group. The proposed route to a pentacyclic system could also utilise the halide ($E5b, R=H$) in which the double bond is in the tetrasubstituted position. However it was thought that the characteristic infrared absorption of the exocyclic methylene function would be invaluable in

identifying the presence of the A-B ring system. This supposition was amply justified by later work which is described in Section 11 of this thesis.

The usefulness of the halide (E5a, R=H) would be limited to the synthesis of 3-desoxy-triterpenes. It also seemed probable that this halide could be more easily obtained by elaboration of a previously synthesised diterpene. A convenient synthesis of the bromide (E5a, R=~~H~~^{X=Bn}) by such a method has now been realised, chiefly through the work of Rushton, and will be described later in this section.

A more ambitious synthetic objective would be the methylene halide (E5a, R=OH) which could be used for the synthesis of a pentacyclic system containing the all-important 3-hydroxyl function. A synthesis of (E5a, R=OH) by a route analogous to that outlined for the corresponding desoxy-compound (E5a, R=H) would require the unsaturated ketone (E2, R=OH) as starting material. This ketone would also be a possible intermediate for syntheses of cassaic acid and α -onocerin. The first object of the present work was the synthesis of 2-hydroxy-7-methoxypodocarpa-5,7,13(14)-triene (E1, R=OH) for which the ketone (E2, R=OH) could be obtained by metal-ammonia reduction.

1

The method used by Barltrop and Rogers for the

synthesis of (E1,R=H) could not be reapplied to the synthesis of (E1,R=OH) as there was no obvious method for preparing 3-hydroxy-2,2,6-trimethylcyclohexanone which would be required as starting material (cf. p.13).

A possible route to (E1,R=OH) was suggested by Raman and Rao's synthesis of the 6-methoxy-2-oxo-podocarpatriene (E12)⁵; the application of a Robinson ring extension reaction to 7-methoxy-2-tetralone (E10) yielded the tricyclic ketone (E11); dimethylation of this ketone followed by palladium-carbon hydrogenation gave (E12) with the required trans A/B ring junction. It was expected that the tricyclic ketone (E28) could be obtained from 6-methoxy-1-methyl-2-tetralone (E25) by a similar sequence of reactions. Reduction of the keto group of (E28) would give the required alcohol (E1,R=OH). This route to (E1,R=OH) and the methods investigated for the preparation of the 2-tetralone (E25) are outlined in Scheme 4 (E13-E28).

An obvious starting material for the preparation of the 2-tetralone (E25) is 2,6-dihydroxynaphthalene (E16). The corresponding dimethyl ether (E17) has been reduced with sodium and ethanol to an enol ether which on treatment with acid, rearranged to the 2-tetralone (E19)⁶. Mono-methylation of (E19) by Stork's enamine procedure⁷ would give (E25).

2-Naphthol-6-sulphonic acid (Schaeffer's acid) (E13) had been made available as a gift by I.C.I. The alkali fusion of this acid (or its sodium salt) is the normal method of preparing 2,6-dihydroxynaphthalene, either in large quantities in the laboratory, or on a commercial scale. The fusion temperature is somewhat higher than is required in similar fusions of other naphthalene sulphonic acids. Fusion of both the acid and its sodium salt were carried out under a variety of experimental conditions at temperatures up to 340°. From none of these fusions was the dihydroxynaphthalene isolated, though in one reaction β -naphthol was identified as a product in low yield. To obviate the possibility of oxidation of the dihydroxynaphthalene formed, a number of these fusions were carried out under nitrogen and sodium hydrosulphite was added to the reaction mixture. It was concluded that, with the apparatus available, this method was not practicable.

An attempt was made to obtain 6-methoxy-2-naphthol (E18b) by a Baeyer-Villiger oxidation of 6-acetyl-2-methoxynaphthalene (E14) with perbenzoic acid, followed by treatment with alkali to hydrolyse any of the acetate (E18a) formed. Friess and Soloway have achieved yields of 50-80% of the corresponding acetates in analogous oxidations of substituted

acetophenones. In the case of the ketone (E14), however, the reaction gave almost entirely unchanged starting material containing a small amount of phenolic material which was not isolated. This method was not further investigated.

A known route¹⁴ for the preparation of 6-methoxy-2-naphthol is through the oxidation of the Grignard derivative of 2-bromo-6-methoxynaphthalene¹⁵ by the method of Kharasch¹⁶. This method was not attempted and the approach to the 2-tetralone (E25) from 2,6-dihydroxynaphthalene (or its methyl ethers) was abandoned in favour of a route utilising the readily available 6-methoxy-1-tetralone (E21). This route (E20-E25) will now be described.

¹⁷Stork has shown that hydrogenation of 2-methoxynaphthalene in the presence of acid gives predominantly 2-methoxytetralin (E20), identified by oxidation to 6-methoxy-1-tetralone. In the present work the hydrogenation was performed at a much lower initial hydrogen pressure (75 atmos.) than that used by Stork (210 atmos.) and a longer reaction time was therefore necessary. A vapour phase chromatogram showed that the product was a mixture of three major components designated A, B and C. A comparison of retention times suggested that component A was probably tetralin. Component B, which represented 50% of the product, was

identified as 2-methoxytetralin from a consideration of the oxidation of the mixture. Distillation of the products of this oxidation gave 6-methoxy-1-tetralone (E21) and a lower boiling non-ketonic fraction; a vapour phase chromatogram showed that the latter contained only components A and C of the starting material. The formation of these large amounts of byproducts in the hydrogenation can be ascribed to the low hydrogen pressure used. It was found that an increased proportion (55-60%) of 6-methoxytetralin resulted when a higher hydrogen pressure (120 atmos.) was used.

A number of experimental procedures have been described for the selective oxidation of 6-methoxytetralin (E20) at C-1^{17,18.} with chromic acid in acetic acid. These procedures differ with respect to the solvent system and the method used for isolating the product. A number of oxidations¹⁷ were carried out by the method of Stork, but it was found that a more convenient procedure, for use on a large¹⁹ scale, was that described by Rao and Dev for the oxidation of 4-isopropyl-6-methoxytetralin.

The conversion of 6-methoxy-1-tetralone (E21) into the 2-tetralone (E25) was achieved by the application of the⁵ reactions used by Raman and Rao to prepare the 2-tetralone (E10) from 7-methoxy-1-tetralone (E8). In the latter synthesis

the dihydronaphthalene (E9) was obtained by reaction of the 1-tetralone (E8) with methyl magnesium iodide and dehydration of the resulting tertiary alcohol²¹. Treatment of this dihydronaphthalene with red lead and acetic acid gave a diacetate which, with ethanolic sulphuric acid, rearranged to the 2-tetralone (E10)²². Newhall has also applied this method to the synthesis of the 2-tetralone (E29) from the corresponding dihydronaphthalene.

The tertiary alcohol (E22) formed by the reaction of 6-methoxy-1-tetralone (E21) with methyl magnesium iodide was not isolated; distillation of the reaction product in presence of a catalytic amount of p-toluenesulphonic acid gave a completely dehydrated product. When first obtained, this product was assumed to be homogeneous but later examination showed it to be a mixture containing ca. 75% of the dihydronaphthalene (vide infra). This dehydration product was converted to the diacetate (E24) and the latter was rearranged to the 2-tetralone (E25) by the experimental procedures already outlined.

A considerable amount (ca. 20%) of unreacted material (vide infra) was isolated in the preparation of the 2-tetralone (E25) from the corresponding dihydronaphthalene; the yield of the tetralone, though calculated in respect of reacted

starting material, was very low (30%). This was in contrast to the high yields reported by Raman and Rao⁵ for the method. Furthermore great difficulty was experienced in isolating the pure tetralone, free from coloured impurities; unless obtained pure, the tetralone rapidly discoloured and redistillation resulted in losses of material due to tar formation.

The ring extension of the tetralone (E25) by the method of Cornforth and Robinson²³ gave the tricyclic unsaturated ketone (E26). This compound was subsequently prepared by Howell and Taylor²⁴ by a similar route to that of the present work. A small scale dimethylation of the ketone (E26), with methyl iodide and potassium t-amylate²⁵, was attempted. Infrared evidence suggested that the crude reaction product contained approximately equal amounts of the unreacted $\alpha\beta$ -unsaturated ketone (E26) and of the 1,1-dimethyl- $\beta\gamma$ -unsaturated ketone (E27), but the latter was not isolated.

At this stage in the work it was decided to reinvestigate two aspects of the synthesis as so far described: the purity of the dehydration product (denoted as Y) of the tertiary alcohol (E22); and the method of converting this product into the 2-tetralone (E25).

The dehydration product (Y) had at first been assumed to be the pure dihydronaphthalene (E23) but it was found that

its ultraviolet absorption spectrum differed significantly from that of the 'unreacted material' (X) which was isolated in the preparation of the 2-tetralone (E25) (vide supra). Vapour phase chromatograms showed that the dehydration product (Y) was a mixture of three components A (ca. 15%), B (ca. 75%) and C (ca. 10%); and that the unreacted material (X) contained only components A and C.

From previous work²⁶ on dihydronaphthalenes it seemed probable that dehydration of the tertiary alcohol (E22) had been accompanied by partial dismutation and that components A and C were the tetralin (E36) and the naphthalene (E37).²⁶ Jacques and Kagan have shown that a variety of 1-substituted dihydronaphthalenes undergo dismutations of this type; these hydrogen transfer reactions are catalysed both by acids and by heterogeneous catalysts such as Raney nickel. In particular it was shown that dehydration of the tetralol (E22), with four times its weight of formic acid, gives, not the dihydronaphthalene (E23), but a mixture of the tetralin (E36) and the naphthalene (E37); the latter was isolated as its picrate. Though most of the dismutations investigated involved the use of powerful acidic catalysts such as aluminium chloride and formic acid, it was found that partial dismutation occurred in the dehydration of

the 1-ethyl-1-tetralol (E30) in the presence of potassium hydrogen sulphate at 124-130 °.

In the present work it was found that, from the mixture of components A and C, there could be isolated 6-methoxy-1-methylnaphthalene. The latter was characterised as a picrate, identical with that obtained by Jacques and Kagan²⁶, and also obtained in low yield from the dehydration product (Y). This naphthalene corresponded to component C of the mixture.

Methods for dehydrating the tetralol (E22) to give the pure dihydronaphthalene (E23) were now investigated. It was found that this could be achieved, using p-toluenesulphonic acid as a dehydrating agent, providing that the temperature was carefully controlled and that the acid was removed before distillation. Alternatively, as was found by Jacques and Kagan²⁶, dehydration without an acid catalyst, but at higher temperatures, gave a homogeneous product. Distillation of this product was, however, accompanied by rather more polymerisation than was observed with the products from acid catalysed dehydrations at lower temperatures, and the distillate had a persistent green colour.

While this work was in progress Howell and Taylor²⁴ reported their synthesis of the tricyclic ketone (E26) (vide supra). In this synthesis the tertiary alcohol (E22)

had been dehydrated with potassium hydrogen sulphate. A dehydration was therefore performed under conditions apparently identical with those of Howell and Taylor. It was found that the resulting material contained ca. 30% of the dismutation products. This finding is consistent with the results reported by Jacques and Kagan²⁶ for the analogous dehydration of the tetralol (E30) which has already been discussed.

A considerable number of dehydrations were carried out under the various conditions defined above. It was found that the composition of the products of such reactions was not completely predictable. It was necessary therefore to analyse the products from each reaction, either by vapour phase chromatography, or by ultraviolet spectroscopy.

In all the dehydrations performed polymeric material was obtained; vapour phase chromatography of such material resulted in depolymerisation, as the peaks on the resulting chromatograms corresponded to the monomeric dihydronaphthalene and its dismutation products. A dimeric structure (E35) can be postulated for this polymer by analogy with the dimer (E32) isolated by Woodward and Eastmann²⁷ as the main product of the dehydration of 6-methoxy-1-tetralol (E31) under strongly acidic conditions.

Acid -catalysed hydrogen transfer reactions between unlike donors and acceptors are well-known^{28,29} and the dismutation of dihydronaphthalenes may be considered as a special case of this type of reaction. A possible mechanism for such dismutations will now be discussed.²⁷ This mechanism represents an extension of that proposed to account for the formation of the dimer (E32); it is also closely analogous to the mechanism, put forward by Ipatieff²⁸ Pines and Oldberg, for the reduction of olefines by aromatic hydrocarbons. Braude and Linstead²⁹ have suggested a similar mechanism, based on kinetic data, for the aromatisation of dihydroaromatic compounds by quinones.

It is assumed that the first step in the acid-catalysed dehydration of the alcohol (E22) is the loss of water from the conjugate acid (E33) to give the 'carbonium ion' (E34) (vide Scheme 5). This carbonium ion may:

- a) expel a proton to form the dihydronaphthalene (E23); in the presence of acids this step is reversible and a reservoir of carbonium ions is provided.
- b) attack the dihydronaphthalene at the double bond; loss of a proton from the resulting cation (E35a) will give the dimer (E35).
- c) extract H^- from (say) the 4-position of the

dihydronaphthalene to give the tetralin (E36) and the conjugate acid (E37a); expulsion of a proton from the latter will give the naphthalene (E37).

In the case of 1-hydroxy-1-methyl-6-methoxytetralin, steps (b) and (c) will be kinetically favoured due to stabilisation of the carbonium ion (E34) by the mesomeric effect of the 6-methoxyl group and the hyperconjugative effect of the 1-methyl group. Results obtained by Jacques and Kagan²⁶ support the view that 1-substituents facilitate dismutation: (This is an over-simplification of the effect of structure on the course of reaction as thermodynamic control, depending on the relative free energies of the dihydronaphthalene and its dismutation products, will also operate).

The synthesis of 3,4-dihydronaphthalenes by acid-catalysed dehydration of 1-tetralols has been frequently reported³⁰. As is pointed out by Jacques and Kagan²⁶, the occurrence of dismutation in such reactions (even, as shown in the present work, under relatively mild conditions) throws suspicion on the nature of the products obtained in these syntheses.

Attention was now directed toward possible alternative methods for converting the dihydronaphthalene (E23) into the 2-tetralone (E25). Howell and Taylor²⁴ reported that treatment of the dihydronaphthalene with perbenzoic acid in chloroform

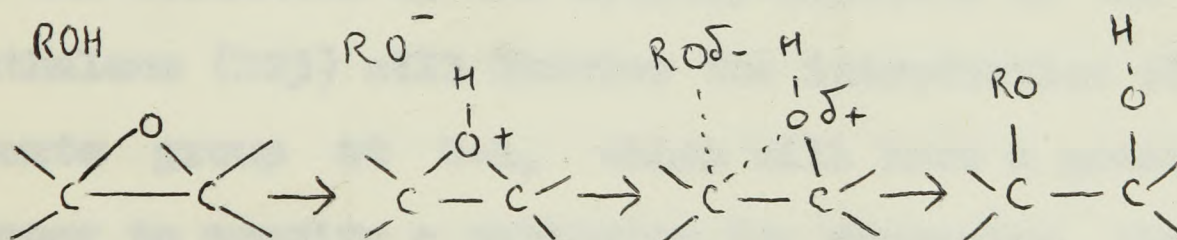
and rearrangement of the product with ethanolic sulphuric acid gave a 50% yield of the 2-tetralone. This work was repeated, using pure dihydronaphthalene, but no more than a 30% yield of the tetralone could be achieved. This yield was not increased by the use of perbenzoic acid in ether and benzene solutions, nor by the use of monoperphthalic acid in ether.

Spectroscopic data indicated that the product of the perbenzoic acid treatment was a hydroxy-benzoate; treatment with monoperphthalic acid appeared to give mainly the glycol. In no case could the epoxide be isolated. The rearrangement of the hydroxy-benzoate was also effected with boron trifluoride etherate; the yield of the 2-tetralone was similar to that obtained by rearrangement with sulphuric acid.

A crystalline hydroxy-benzoate was isolated, in low yield, from the crude reaction product and was formulated as 1-benzoyloxy-2-hydroxy-6-methoxy-1-methyltetralin (E38). The reasons for the choice of this formulation in preference to the isomeric 2-benzoyloxy-1-hydroxy structure will be made clear in the following discussion.

The formation of a hydroxy-benzoate rather than an epoxide has been observed in the reaction of perbenzoic acid with

a number of olefins³¹, including the cis- and trans- p-methoxy-
 stilbenes^{32,33}, which are close electronic analogues of³³
 the dihydronaphthalene (E23). Recent experiments³³, using
 isotopically-labelled benzoic acid, have provided strong
 evidence that the hydroxy-benzoates are obtained by the attack
 on an initially formed epoxide by a molecule of benzoic acid.
³⁴Brewster had previously discussed the mechanism of the
 acid-catalysed opening of oxide rings with particular reference
 to α -aryl substituted epoxides. A number of factors can
 facilitate the opening of the epoxide ring (see diagram)³⁴.
 Thus contributions to the driving force of the reaction will
 made by the strain inherent in the epoxide ring, by the
 protonation of the oxygen atom, by the attack of an anionoid
 reagent at C-1, and by the development of partial carbonium
 ion character on this carbon atom. The importance of the



latter effect will be greatly enhanced by aryl substituents
 at C-1 and in such systems the anionoid strength of the
 attacking group will be of secondary importance as a driving

force in the ring fission. This will be specially marked if p-methoxy or similar substituents are present, and thus the epoxides derived from the p-methoxy-stilbenes and the 6-methoxy-dihydronaphthalene (E23) undergo ring opening even with the weakly nucleophilic benzoate anion. By contrast, trans-stilbene³³, p-chloro-trans-stilbene³⁵, and p-methyl-trans-stilbene³³ give epoxides and not hydroxybenzoates.

A comparison of the reactions of 6-methoxy-1-methyl-3,4-dihydronaphthalene (E23) and 1-methyl-3,4-dihydronaphthalene with perbenzoic acid provides a further indication of the importance of the 6-methoxyl group in determining the course of the reaction. The latter compound has been found³⁶ to give the corresponding tetralone in 84% yield; neither the benzoate nor the epoxide have been isolated.

If the above arguments are valid, then it is obvious that the formation of the hydroxy-benzoate of the dihydronaphthalene (E23) will involve the introduction of the benzoate group at C-1, which will have a greater tendency to acquire a carbonium ion character than C-2. The resulting hydroxy-benzoate will therefore be the postulated 1-benzoyloxy-2-hydroxy derivative (E38).

The latter is an analogue of an ester of a benzyl alcohol and esters of this type are known to undergo ready hydrogenolysis, the benzyl group being eliminated as toluene (or the appropriate substituted toluene)³⁹. It might be expected therefore that the hydroxy-benzoate (E38) could be converted to the 2-tetralol (E42) by this means. However preliminary attempts to achieve this hydrogenolysis, in the presence of a palladium-carbon catalyst, gave completely negative results and this possibility was not further investigated.

The work so far carried out suggested that it would be possible to obtain reasonable quantities of the 2-tetralone (E25), and therefore the tricyclic ketone (E26), by the rearrangement either of the diacetate (E24) or of the hydroxy-benzoate (E38). This would be a laborious process due to the large amounts of starting materials necessitated by the low yields of the 2-tetralone. Other methods for the preparation of this tetralone were therefore considered. With one exception these methods utilised the dihydronaphthalene (E23) as the starting material, but one route was considered which would utilise the benzyldene derivative (E39) of 6-methoxytetralone.

It was envisaged that treatment of the benzal-

tetralone (E39) with methyl magnesium iodide would give the tertiary alcohol (E40); ozonolysis of the latter would then afford the α -ketol (E41) which, it was hoped, could be reduced to the required 2-tetralone, with zinc dust and acetic acid⁴⁰. It was found that the benzal-tetralone reacted very slowly, even in the presence of an excess of reagent, both with methyl magnesium iodide and with lithium methyl. Furthermore no alcohol could be detected in the reaction product. The nature of this product was not investigated though it was possible that a 1,4 addition reaction had occurred.

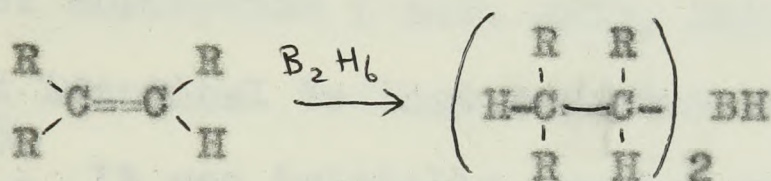
The reaction of performic acid with the dihydronaphthalene was now investigated. This reagent is known to react with olefines to give high yields of hydroxy-formates, which are very easily hydrolysed to the corresponding glycols⁴¹. (It was assumed that, under the experimental conditions used, the dismutation of the dihydronaphthalene would not be a significant reaction). The dihydronaphthalene was treated with performic acid, prepared in situ from formic acid and hydrogen peroxide, at 40°.

The infrared spectrum of the product showed bands at 3350cm⁻¹, characteristic of an alcohol, and at 1700 cm⁻¹, characteristic of a saturated ketone rather than a formate ester. The

former designation for this band was confirmed by the fact that treatment of the crude reaction product with ethanolic potassium hydroxide gave a spectroscopically unchanged material. This material was also unaffected by treatment with acids, under conditions which had effected the rearrangement of the hydroxy-benzoate (E38), and no 2-tetralone could be isolated from such reactions. Tituration of the crude product with ether afforded a solid which had an infrared spectrum almost identical with that of the crude material. This suggested that the main product from the formic acid reaction was a hydroxy-ketone, possibly the α -ketol (E41), though analytical data in support of this hypothesis could not be obtained, nor is it clear how such a product could be formed. Examples are known of the reduction of α -ketols⁴² and their vinylogues⁴⁰, and α -acetoxy-ketones⁴³, with zinc dust in boiling acetic or hydrochloric acid. No reduction of the above product was achieved by treatment with zinc dust in boiling acetic acid and this problem was not further investigated as it had become obvious that a convenient preparation of the 2-tetralone (E25) could not be achieved by this route.

A possible route to the 2-tetralol (E42) was suggested by the publication⁴⁴ of a method for the anti-Markownikoff

hydration of olefines by the use of organoborane derivatives. The 'Brown hydration' reaction, as it has come to be known, depends on the reaction of diborane or aluminium borohydride with olefines to give organoboranes in which the boron atom is attached to the least substituted carbon atom:



The organoboranes can be oxidised to borate esters, which are readily hydrolysed to the free alcohols. The dihydronaphthalene (E23) was made to react with aluminium borohydride, prepared in situ from aluminium chloride and sodium borohydride in diglyme. The resulting organoborane was oxidised with alkaline hydrogen peroxide to give a clean product from which the hydroxylic material could be isolated in good yield by chromatography. Examination of the non-hydroxylic material isolated from the reaction product indicated that some dismutation of the dihydronaphthalene had been effected by the aluminium chloride. However, the amount of unreacted material was small, and this side-reaction did not therefore present a serious problem. It was almost

certain that the main product of the hydration reaction was a secondary alcohol, presumably the 2-tetralol (E42), and not the tertiary alcohol (E22) as no dehydration was observed on distillation, which gave an analytically pure product. The infrared spectrum (CS solution) of this product showed a single sharp band in the hydroxyl region at 3600 cm^{-1} . The ultraviolet absorption (λ_{max} . 2785, 2835 Å; ϵ 2250, 2130) was almost identical to that reported for 6-methoxy-2-tetralol⁴⁵. It was initially assumed therefore that the product of the hydration reaction was the expected 6-methoxy-1-methyl-2-tetralol (E42). Surprisingly the 2,4-dinitrobenzoate was obtained as an oil and repeated attempts to recrystallise this derivative were unsuccessful.

In order to obtain the required 2-tetralone (E25), the oxidation of the '2-tetralol' was investigated. From the results of this investigation, it seems probable that the hydration product, contrary to the earlier assumption, is a mixture of two tetralols. Thus it was found that treatment with 8N-chromic acid in acetone gave a mixture of a saturated and an unsaturated ketone, containing a slightly higher proportion of the former. The two ketones were separated by chromatography and the saturated ketone identified as the previously prepared 2-tetralone (E25).

The infrared spectrum of the unsaturated ketone (bands at 1672, 1602, and 1560 cm^{-1}) was consistent with the carbonyl group being conjugated with the aromatic nucleus. The ultraviolet absorption, which had maxima at 2530 Å (ϵ 7900) and 3230 Å (ϵ 2300), was markedly different from that of 6-methoxy-1-tetralone which showed a single maximum at 2755 Å (ϵ 18600). It is of interest that α -tetralone shows similar maxima (at 2370, 2860 Å; ϵ 11450, 1550) though shifted to shorter wavelengths. From this evidence, as a working hypothesis, the ketone has been formulated as 6-methoxy-1-methyl-4-tetralone (E43a) though evidence to substantiate this formulation has not been obtained. It seems possible⁴⁵ that the introduction of a methoxyl group para to the ketonic function would produce a more marked effect on the ultraviolet absorption of α -tetralone than would the introduction of the same group in the meta position (as in E43a).

It is unlikely that the ketone (E43a) could result from the oxidation of the pure 2-tetralol (E42). It appears therefore that hydration of the dihydronaphthalene (E23), under the conditions described, affords a mixture of the expected 2-tetralol and (probably) the 4-tetralol (E43), but no mechanism can be devised to account for this behaviour, though it may be of significance, that, as already discussed,

aluminium chloride facilitates hydrogen transfer reactions involving the dihydronaphthalene (E23).

Small scale oxidations of the 'tetralol' were also conducted with chromium trioxide in acetic acid, and with the chromium trioxide-pyridine complex.⁴⁶ Under the conditions used, only a part of the hydroxylic material was oxidised. With these reagents more of the unsaturated than the saturated ketone was formed. This was particularly so with chromium trioxide-pyridine, when the unsaturated ketone was formed almost exclusively. It would appear that, with somewhat selective oxidising agents, the 4-tetralol (E43), in which the hydroxyl function is adjacent to the aromatic nucleus, is preferentially oxidised.

Oxidation of the 'tetralol' was attempted under Oppenauer conditions to eliminate the possibility that the formation of the unsaturated ketone was the result of an anomalous reaction of the chromic acid reagents with the 2-tetralol (E42). No significant amount of ketonic material was formed in the oxidation of the tetralol by the normal Oppenauer procedures,⁴⁸ using acetone in benzene or cyclohexanone in toluene. Partial oxidation was achieved by carrying out the reaction at the boiling temperature of xylene⁴⁹, using cyclohexanone as the hydrogen acceptor. The same mixture of ketones was obtained

as in the chromic acid oxidations.

At this point a synthesis of the tricyclic ketone (E2, R = OH) was reported⁵⁰ by a route almost identical with that intended in the present work (see pp.17, 22). At the same time information was received by private communication concerning the work of Stork, Davies and Meisels (see p.21) on the synthesis of the keto-acid (E4, R=OAc). The present work in this field was therefore abandoned.

In order to investigate the utility of the proposed route to a pentacyclic system, it was decided to prepare the (+)bromide (E5a, R=H, X=Br) from sclareol by a route which had already been used by Rushton and which was based partly on previous work by Stoll and Hinder.^{51,52}

The oxidation of sclareol with potassium permanganate was first investigated by Ruzicka et al.⁵³, and has been more recently studied by Barltrop, Bigley and Rogers⁵⁴. This oxidation affords either the enol ether (E44) or the hydroxyketone (E45), depending on the conditions used. Under the conditions used in the present work the main product was the enol ether, contaminated with varying amounts of the hydroxyketone. The pure enol ether was conveniently obtained by dissolving the crude product in petrol and shaking with dilute hydrochloric acid to accomplish the facile dehydration of the

hydroxy-ketone. Chromatography then gave the pure enol ether in good yield. It was found, however, that good yields of the enol ether depended on the efficient stirring of the oxidation mixture and the use of finely ground potassium permanganate.

Ozonolysis of the enol ether and decomposition of the ozonide with Raney nickel gives a complex mixture from which Stoll and Hinder⁵¹ isolated a number of compounds, including the acetoxy-acid (E46) and the acetoxy-aldehyde (E47). The same workers investigated the reduction, both of these products and of the ozonide itself, to give the glycol (E48). In the present work ozonolysis was allowed to proceed for twice the reaction time necessary to produce the blue colour indicating an excess of ozone. The infrared spectrum of the product suggested that the acetoxy-acid (E46) was the major component. No attempt was made to isolate pure substances from this product which, without further purification, was reduced with an excess of lithium aluminium hydride to give the glycol (E48) in 50-55% overall yield from the enol ether.

Treatment of this glycol with phosphorus pentabromide in pyridine accomplished both the replacement of the primary alcohol group by bromine, and the dehydration of the tertiary alcohol to give the methylene bromide (E5a, R=H, X=Br). The course of this dehydration to give an exocyclic double bond is

predictable from the known equatorial orientation of the hydroxyl groups. The geometrical requirement of four coplanar centres can only be achieved by using a hydrogen atom of the methyl group.⁵⁵

At a later stage in this work, for reasons outlined in section II of this thesis, it was necessary to prepare the iodide (E5 a, R=H, X=I). Treatment of the bromide with ^{sodium} ~~lithium~~ iodide in boiling methyl ethyl ketone gave a mixture of the two halides. Analytical data indicated that the iodide formed at least 90% of the mixture and was sufficiently pure for its use in the alkylation described in section II.

EXPERIMENTAL

for

SECTION 1.

Alkali fusion of 2-methyl-5-polyphosphoric acid (Lapworth's acid) and of its sodium salt

Notes on experimental

Melting points were determined on a Kofler block and are corrected.

Optical rotations were done in a 1-dm tube; $c = 0.5-2.0$.

Unless otherwise stated:- (a) 'alumina' means Grade H alumina deactivated by shaking with 5% of its volume of 10% (v/v) acetic acid; (b) petrol means petroleum ether b.p. $60-80^{\circ}$.

Alkali fusion of 2-naphthol-6-sulphonic acid (Schaeffer's
acid) and of its sodium salt ^{8,9,10} .

Both the sodium salt and the free acid were fused, under a variety of conditions, with potassium and with sodium hydroxides and also with equimolecular mixtures of both; in most of the fusions sodium hydrosulphite was added. The fusions were effected in both open vessels and in autoclaves flooded with nitrogen at temperatures varying between 270° and 340° . In no case was 2,6-dihydroxy-naphthalene isolated. The experimental procedure in one such fusion is described below.

An intimate mixture of 2-naphthol-6-sulphonic acid (63g.), potassium hydroxide (200g.) and sodium hydrosulphite (10g.) was heated at 320-340 for 4½ hours in a rocking autoclave flooded with nitrogen. The melt was poured into concentrated hydrochloric acid (2 litres) and ice (1kg.). Filtration gave a brown solid. The normal procedure from this point is described under (a); in one fusion the procedure described under (b) was used.

a) The brown solid obtained above was heated under reflux with water for 6 hours. The resulting aqueous solution was heated under reflux for a further 6 hours with animal charcoal, filtered and the volume reduced to 700 c.c. On cooling

potassium 2-naphthol-6-sulphonate separated as a brown solid. Concentration of the filtrate gave further quantities of this compound but no 2,6-dihydroxynaphthalene could be isolated.

b) The precipitate, obtained on pouring the melt into acid, was dissolved in potassium hydroxide solution and treated with dimethyl sulphate. Steam distillation of the reaction mixture gave a solid which was recrystallised from ether to give 2-methoxynaphthalene, m.p. and mixed m.p. 72°.

2-Acetyl-6-methoxynaphthalene

2-Methoxynaphthalene (186g.) was acetylated under Friedel-Crafts conditions as described by Robinson and Rydon¹² to give 2-acetyl-6-methoxynaphthalene (84g., 37%), m.p. 106°. (The oxime, recrystallised from methanol, had m.p. 174° (Robinson and Rydon¹² give m.p. 169-170°).

Perbenzoic acid oxidation of 2-acetyl-6-methoxynaphthalene

The experimental procedure is that used by Friess and Soloway¹³.

A solution of perbenzoic acid in chloroform (0.2M, 160c.c.) was added to 2-acetyl-6-methoxynaphthalene (5.1g.) in chloroform (50c.c.). After standing for 11 days at 0° with occasional shaking, excess perbenzoic acid was destroyed.

by addition of sodium thiosulphate solution. The chloroform solution was washed repeatedly with sodium bicarbonate solution and was then evaporated to give a dark coloured oil which solidified on standing. The infrared absorption spectrum was almost identical with that of the starting material but had a weak band at 3560 cm^{-1} corresponding to a phenolic hydroxyl group.

6-Methoxytetralin

This preparation was carried out as described by Stork¹⁷ but, of necessity, lower hydrogen pressures had to be used and, as a result, large amounts of by-products were formed.

A suspension of 2-methoxynaphthalene (154g.) in dry ethanol (450c.c.) containing acetic acid (3c.c.) was hydrogenated in the presence of Raney nickel (10g.). The initial hydrogen pressure was 75 atmos. Hydrogenation was complete after $2\frac{1}{2}$ hours at $120-130^{\circ}$. The product distilled over a range $120-145^{\circ}/20\text{mm}$.

Vapour phase chromatograms showed that:

1) the distillate contained three major components designated A(25%), B(25%) and C(50%) in order of increasing retention times. A fractional distillation achieved only partial separation of the three components.

(11) no unreacted 2-methoxynaphthalene was present.

(111) component A had the same retention time as tetralin.

(1V) only components A and B were present in the low boiling, non-ketonic material recovered from the oxidation of the hydrogenation product by the method described in the next experiment.

The hydrogenation was repeated using initial hydrogen pressures of 100 and of 125 atmos. The products contained slightly higher proportions (55-60%) of component C (6-methoxy-tetralin).

17,18,19

6-Methoxy-1-tetralone

The product from the above hydrogenation (at 75 atmos.)²⁰ was oxidised by the procedure described by Rao and Dev .

Sodium dichromate (410g.) in glacial acetic acid (2 litres) was added during 6 hours to a well-stirred, ice-cooled solution of the hydrogenation product (104g.) in benzene (1 litre). The mixture was stood at room temperature for 24 hours. Excess chromic acid was destroyed by cautious addition of ethyl alcohol. Water (5 litres) was added and the benzene layer separated. The aqueous layer was extracted with benzene-ether (50/50) (5 times 600c.c.). The residue obtained

by evaporation of the combined extracts was distilled and three fractions collected:

(I) b.p. 110-160°/20mm. (40g.) (The vapour phase chromatogram of this fraction is discussed in the previous experiment)

(II) b.p. 160-170°/20mm. (7.0g.)

(III) b.p. 170-190° (50g.)

Fraction (III) solidified to give 6-methoxy-1-tetralone which, after recrystallisation from methanol, had m.p. 80-81° (Stork¹⁷ gives m.p. 78-79°). Light absorption in ethanol: $\lambda_{\text{max.}} 2755\text{\AA}$ (ϵ , 18,600). The semicarbazone prepared in methanol containing pyridine, and recrystallised from methanol, had m.p. 233-234° (Stork¹⁷ gives 236-7°). The yield of 6-methoxy-tetralone, allowance being made for the recovered starting material, was 80%.

6-Methoxy-1-methyl-3,4-dihydronaphthalene (E23)

A solution of 6-methoxy-1-tetralone (15g.) in ether (300c.c.) was added in portions to methyl magnesium iodide prepared from magnesium (3.8g.) and methyl iodide (18c.c.) in ether (20c.c.). The mixture was stirred for 12 hours and refluxed for a further hour. The Grignard complex was decomposed with ice-cold N-sulphuric acid. The ethereal layer was separated and well washed with sodium bisulphite

solution. Evaporation gave a dark coloured oil which was probably a mixture of 1-hydroxy-1-methyl-6-methoxytetralin (E22) and its dehydration product. Dehydration was completed by distillation from a crystal of p-toluenesulphonic acid to give a yellow oil (11.8g., 78%), b.p. 149-159°/20mm. which was redistilled at 82-90°/0.05mm. to give a colourless oil (Y). A vapour phase chromatogram showed that the product (Y) was a mixture of three components which were designated (A(15%) B(75%) and C(10%) in order of increasing retention times. B and C were identified as 6-methoxy-1-methyl-3,4-dihydronaphthalene (E23) and 6-methoxy-1-methylnaphthalene (E37) respectively by subsequent experiments (vide infra). The product X gave a low yield (ca. 5%) of 6-methoxy-1-methyl-²⁶naphthalene picrate, m.p. 102° (Jacques and Kagan give m.p. 105°). (Found: N, 10.4%; calculated for C₁₈H₁₇N₃O₈: N, 10.4%).

Investigation of the dehydration of the product from the above Grignard reaction.

Conditions were required for the preparation of the pure dihydronaphthalene (E23) (component B), uncontaminated with A or C. A series of dehydrations were therefore effected.

The conditions used and the composition of the products formed are defined in Table 1. The general experimental procedure was as follows:

The Grignard product was dehydrated under the conditions defined and then taken up in benzene. The benzene solution was washed with sodium carbonate solution and water, dried and evaporated. The residue was distilled at 0.05mm. and the distillate was analysed by vapour phase chromatography.

Catalyst	Temperature and time of heating	Product
Toluene sulphonic acid	2hr./100° and 2hr./110°	Pure B
"	3hr./150°	50-60% B
Potassium bisulphate	2hr./130°	70% B ^a
"	2hr./110°	90% B
no catalyst	3hr./180°	Pure B ^b

Table 1.

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Notes: a) cf. method used by Howell and Taylor .

b) Product had a persistent green colour.

The pure 6-methoxy-1-methyl-3,4-dihydronaphthalene had
 n_D^{20} , 1.5818 (Jacques and Kagan give n_D^{26} , 1.5810).
 Light absorption in ethanol: λ_{max}^{20} 2710A (ϵ 17,400).
 (Found: C, 82.71; H, 8.24; calculated for $C_{11}H_{14}O$: C, 82.75;
 H, 8.03%).

In all the above dehydrations polymeric material was formed; the vapour phase chromatogram of this material showed peaks of retention times identical with those of the monomeric components A, B and C.

6-Methoxy-1-methyl-2-tetralone, Method A: by rearrangement of 1,2-diacetoxy-6-methoxy-1-methyltetralin.

The experimental procedure is that of Newhall et al. ²²

The 'dihydronaphthalene' used in the following experiment was a mixture of components A, B and C as defined in the previous experiment. The yield of the tetralone is calculated on the assumption that this starting material contained 75% of the dihydronaphthalene (E23). A similar yield was achieved in subsequent experiments using the pure dihydronaphthalene.

The 'dihydronaphthalene' (4.7g.), acetic anhydride (12c.c.) and a crystal of sodium acetate were heated under reflux

for 1 hour. Acetic acid (45c.c.) and red lead (24.5g.) were added with frequent shaking and cooling. The mixture was stood overnight at room temperature and then refluxed for 1 hour. Half the acetic acid was evaporated and the residue was poured into water. Chloroform extraction gave a red oil; the infrared spectrum showed a very intense band at 1740 cm^{-1} with a weak shoulder at 1704 cm^{-1} . Without further purification this product was rearranged as described below.

Rearrangement of the diacetate.

The above product was heated under reflux for 1 hour with water (10c.c.), ethanol (10c.c.) and concentrated sulphuric acid (1.7c.c.), poured into water and extracted with ether. The ethereal solution was evaporated and the residue distilled to give a red oil, b.p. $135-160^{\circ}$ (air bath)/0.02mm., which was chromatographed on alumina:

(1) Elution with petrol gave a colourless oil (0.8g.); the vapour phase chromatogram showed this product to be a mixture of the components A and C of the starting material.

Component B was therefore identified as 6-methoxy-1-methyldihydronaphthalene, which had been completely removed by the above reaction. Tituration of this product with ether gave 6-methoxy-1-methylnaphthalene, m.p. $44-46^{\circ}$ (Jacques

and Kagan²⁶ give m.p. 48°). Light absorption in ethanol: λ_{max} . 2240 (ϵ 20,000), 2750, 2850, 3155 and 3300 Å. (The absorption spectrum in the ultraviolet region was almost identical with that reported by Jacques and Kagan²⁶ and closely resembled the absorption spectrum of 2-methoxynaphthalene). The picrate from ethanol had m.p. 102°.

(11) Elution with petrol/50% benzene gave a yellow oil which distilled at 120-132°/0.05mm. to give 6-methoxy-1-methyl-2-tetralone (1.5g., 38%). Light absorption in ethanol: λ_{max} . 2790 Å (ϵ 4000). (Found: C, 75.51; H, 7.12. Calculated for C₁₂H₁₄O : C, 75.76; H, 7.42%). The semicarbazone from ethanol had m.p. 212-214° (Howell and Taylor²⁴ give m.p. 218-220°). (Found: C, 62.57; H, 6.81; N, 16.6. Calculated for C₁₃H₁₇N₃O : C, 63.14; H, 6.93; N, 17.9%).

7-Methoxy-12-methyl-2-oxo-2,3,4,9,10,12-hexahydrophenanthrene²⁵

The procedure was that of Cornforth and Robinson²⁵; diethylaminobutanone was prepared as described by Wilds and Shunk²³ and had n_D^{18} , 1.4350, b.p. 71°/15mm. (Wilds and Shunk²³ give n_D^{20} , 1.4333 b.p. 70-70.5°/11mm)

Diethylaminobutanone (1.28g.) was swirled gently in a 100 c.c. flask at -5° during the addition of dry redistilled methyl iodide (1c.c.) in portions (10 minutes).

The swirling was regulated so as to obtain an even coating of crystalline methiodide on the walls of the flask. When no more liquid remained the temperature was allowed to rise slowly to 15°. The tetralone (E25) (1.65g.) in dry benzene (8c.c.) was added, air was expelled by dry nitrogen and a solution of potassium (0.54g.) in dry ethanol (10c.c.) was added with ice cooling during 5 min. The flask was swirled until all the methiodide had dissolved (35 min.). After standing at 0° for 1 hour the mixture was refluxed for 15 min. Excess 2N-sulphuric acid and benzene (10c.c.) were added and the benzene layer was separated. The aqueous layer was twice extracted with ether and the combined extracts were dried and evaporated. The residue was distilled and the distillate chromatographed on alumina. Elution with petrol 40% benzene gave 7-methoxy-12-methyl-2-oxo-2,3,4,9,10,12-hexahydro-phenanthrene, slightly contaminated with unreacted tetralone, as a yellow oil (450mg., 23%). The pure ketone which separated as a white crystalline solid on standing at 0°, after two recrystallisations from ether, had m.p. 109° (Howell and Taylor²⁴ give m.p. 106-108°). Light absorption in ethanol: λ_{max} . 2315Å; 2750Å; 2840Å (inflexion) (ϵ 22,500; 2600; 2200). (Found: C, 79.38; H, 7.85. Calculated for C₁₆H₁₈O : C, 79.33; H, 7.43%). The dinitrophenylhydrazine was recrystallised

from methanol-ethylacetate and had m.p. 145-150°. (Found: C, 63.1; H, 5.6; N, 12.9. C H N O requires: C, 62.56; H, 5.2; N 13.27%).
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Dimethylation of 7-methoxy-12-methyl-2-oxo-2,3,4,9,10,13-hexahydronaphthalene.

A standardised solution of sodium t-amylate in benzene (C.74M, 7c.c.) was added to the ketone (E26) (250 mg.) and methyl iodide (2c.c.) in benzene (5c.c.). The mixture was stood under nitrogen at room temperature for 2 hours, and then heated under reflux for 20 min. After addition of 2N-sulphuric acid, ether extraction gave a red viscous oil. The infrared spectrum showed bands at 1703⁻¹cm and 167⁻¹cm of equal intensity indicating the presence of the unreacted unsaturated ketone (E26) and, probably, of 7-methoxy-2-oxo-1,1,12-trimethyl-1,2,3,4,9,12-hexahydrophenanthrene (E27). The latter was not isolated.

6-Methoxy-1-methyl-2-tetralone: Method B

The tetralone was prepared by the rearrangement, under acidic conditions, of the product from the peracid treatment of the dihydronaphthalene (E23).

(1) Peracid oxidation of 6-methoxy-1-methyl-3,4-dihydronaphthalene.

The procedure for the reaction of the dihydronaphthalene with perbenzoic acid is described. In other reactions perbenzoic acid in ether and in chloroform, and permonophthalic acid in ether were used, but no improvement in the yield of tetralone resulted. In none of these reactions was the epoxide of the dihydronaphthalene isolated.

The perbenzoic solutions were prepared by the method of Kergomard and Bijou³⁷ and the solutions of permonophthalic acid in ether by the method of Fieser³⁸. These solutions were standardised by adding excess sodium iodide and titrating the liberated iodine with N/10-sodium thiosulphate solution. The consumption of peracid during the reaction was followed by similar titrations of aliquots removed at regular intervals.

The dihydronaphthalene (5.0g., 0.029g.m.) was treated with a solution of perbenzoic acid (0.06g.m.) in benzene (300c.c.) at 0°. After 14 hours at 0°, 95% of the theoretical amount of perbenzoic acid had been consumed. The solution was well washed with aqueous sodium carbonate and water, dried and evaporated to give a dark-red, viscous oil. The infrared spectrum had bands at 3,500(s), 1720(s) and 1704cm⁻¹ (w) and

suggested that the product was mainly a hydroxy-benzoate together with a small amount of the 2-tetralone (E25). This product was rearranged to the 2-tetralone as described below, without further purification.

In a subsequent experiment an attempt was made to purify this product by chromatography on alumina. Elution with benzene and benzene-ether gave the bulk of the product as a red oil, but one fraction crystallised from ethanol to give a low yield of a brown solid, m.p. 126°, probably 1-benzoyloxy-2-hydroxy-6-methoxy-1-methyltetralin (E38). (Found C, 72.24; H, 6.27. $\begin{smallmatrix} C & H & O \\ 19 & 20 & 4 \end{smallmatrix}$ requires: C, 73.08; H, 6.41%). The infrared spectrum had the same bands as found in the crude product.

(11) Rearrangement of the crude hydroxy-benzoate.

(a) With boron trifluoride etherate.

The crude product from the previous reaction was shaken with boron trifluoride etherate (7.2g.) in benzene (50c.c.) at room temperature for 20 min. The benzene solution was washed with sodium carbonate solution and water, dried and evaporated. Distillation of the residue gave 6-methoxy-1-methyl-2-tetralone (1.6g., 30%).

(b) With ethanolic sulphuric acid.

The perbenzoic acid reaction described under (1) was repeated and the product heated under reflux with

ethanol (40c.c.), water (40c.c.) and concentrated sulphuric acid (9c.c.) for 3 hours. The yield of the 2-tetralone was similar to that obtained in the rearrangement with boron trifluoride.

2-Benzal-6-methoxy-1-tetralone.

6-Methoxy-1-tetralone (4.1g.) was heated under reflux for 1½ hours with benzaldehyde (2.5g.) and 4% aqueous potassium hydroxide (20c.c.), then treated with acetic acid and water. The precipitate crystallised from methanol to give 2-benzal-6-methoxy-1-tetralone (3.9g., 63%), m.p. 99°. (Found: C, 82.00; H, 6.14. C₁₈H₁₆O₂ requires: C, 81.81; H, 6.06%). Light absorption in ethanol: λ_{max} 2300, 3,200 Å (ϵ 15,200, 24000).

Reaction of 2-benzal-6-methoxy-1-tetralone with methyl magnesium iodide.

2-Benzal-6-methoxy-1-tetralone (2.9g.) in ether (250 c.c) was added to the Grignard reagent prepared from magnesium (1.1g.) and methyl iodide (10g.) in ether (10c.c.). The reaction mixture was stirred under nitrogen for 12 hours, refluxed for 4 hours and worked up by the usual procedure to give a red oil. The infrared spectrum showed a weak carbonyl band at 1670 cm⁻¹ and no hydroxyl band. The absence

of a hydroxyl band was confirmed by the infrared spectrum in CS solution.

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The same result was obtained when the reaction was conducted with lithium methyl.

Reaction of 6-methoxy-1-methyl -3,4-dihydronaphthalene with performic acid.

Hydrogen peroxide solution (30% v/v, 7.05g.) was added to the deep green solution of the dihydronaphthalene (10.0g.) in formic acid (98%, 50c.c.). The temperature was maintained at 40° by water cooling during the initial exothermic reaction, and then by warming for a further hour (titration showed that all the active oxygen had been consumed). The reaction mixture was poured into water; ether extraction gave a red oil which had bands in the infrared spectrum at 3350cm⁻¹ (hydroxyl) and 1700cm⁻¹ (saturated ketone) and a very weak band at 1670cm⁻¹. Tituration of a part of this product with ether gave a solid (200mg.) which, after recrystallisation from petrol/ether, had m.p. 77°. The infrared spectrum of this solid showed strong bands at 3350cm⁻¹ and 1670cm⁻¹ and was almost identical with that of the crude material.

A series of reactions were carried out on the crude

product (denoted as A) of the above reaction.

(I) Treatment with base.

In order to confirm that the band at 1700 cm⁻¹ in the infrared spectrum represented a keto group and not a formate ester, the product (A) (1g.) was heated under reflux with potassium hydroxide (1.0g.) in 90% ethanol (50c.c.). Ether extraction gave a product which had an infrared spectrum identical to that of product (A).

(II) Treatment with acid.

Product (A) (5g.) was treated with concentrated hydrochloric acid (10c.c.) in methanol (150c.c.) for 1½ hours at reflux temperature and, subsequently, with concentrated sulphuric acid in 80% ethanol (130c.c.) for 3 hours at reflux temperature. The products isolated from both treatments had infrared spectra almost identical to that of Product (A).

(III). Treatment with zinc dust and acetic acid.

From the infrared spectrum it seemed possible that the product (A) was an α -ketol. This product (3g.) was therefore heated under reflux with acetic acid (40c.c.) and dry zinc dust (3.0g.) for 15 hours. The reaction mixture was worked up by the normal procedure to give a very dark coloured oil.

The infrared spectrum was essentially the same as that of the starting material (A).

Anti-Markownikoff hydration of 6-methoxy-1-methyl-3,4-dihydronaphthalene.

The procedure is that of Brown and Rao⁴⁴.

Sodium borohydride was purified by a Soxhlet extraction with freshly distilled isopropylamine. The solvent was evaporated and the residual sodium borohydride dried at 100-120°/0.5mm for 6 hours.

Diethylene glycol dimethyl ether (diglyme) was dried by standing over sodium wire followed by distillation from lithium aluminium hydride.

Aluminium chloride (1.4g.) in diglyme (14c.c.) was added to a well stirred mixture of diglyme (28c.c.), sodium borohydride (1.5g.) and 6-methoxy-1-methyl-3,4-dihydronaphthalene (9.1g.) under nitrogen. The mixture was stirred at room temperature for 3 hours and at water bath temperature for a further hour. Half the volume of diglyme was removed at 0.5mm., N/2-hydrochloric acid (100c.c.) was added, and the mixture extracted with ether. The ethereal solution was washed repeatedly with N/2-hydrochloric acid and with brine. The ether was evaporated and the residue dissolved in

a solution of potassium hydroxide (1.1g.) in methanol (50c.c.). Hydrogen peroxide solution (30% v/v. 5 g.) was added over 5 min.: a white precipitate formed and much heat was evolved when the initial reaction had moderated, the mixture was refluxed for 15 min. After addition of water, ether extraction yielded a yellow oil which was chromatographed on alumina: elution with petrol gave unchanged 'starting material' (1.55g.). The ultraviolet spectrum of the latter showed the presence of significant amounts of the dimerization products of the dihydronaphthalene. Elution with benzene gave a mixture of the 6-methoxy-1-methyl-2 and 4-tetralols (6.4g., 77%)²⁴, b.p. 100-110°/0.02mm. n_D^{20} , 1.5534. (Found: C, 74.58; H, 8.49; O requires: C, 75.00; H, 8.33%). Light absorption in ethanol: λ_{max} 2785, 2855 Å (ϵ 2250, 2130). The infrared spectrum (CS solution) had a single, sharp hydroxyl band at 3600 cm⁻¹. A 2,4-dinitrobenzoate was prepared from the above mixture of tetralols as an oil, identified by its infrared spectrum, which could not be crystallised nor obtained analytically pure.

Chromic acid oxidations of the mixture of tetralols.

(A) Using 8N-Chromic acid in acetone.

8N-Chromic acid solution (2.2c.c.) was added dropwise

to a solution of the mixture of tetralols (0.7g.) (cf. previous experiment) in acetone (100c.c.) until a red colour persisted. The solution was stirred for a further 15 min., water was added and the product was isolated with ether. Distillation gave a light yellow oil, b.p. 110-120^o (air bath)/0.01mm.. The infrared spectrum had bands at 3400(w), and at 1704(s) and 1670(s) cm⁻¹ of which the former was the more intense.

This distillate was chromatographed on alumina:

(1) Elution with petrol/20% benzene gave a colourless oil (100mg.) formulated as 6-methoxy-1-methyl-4-tetralone.

(Found: C, 75.85; H, 7.90. C₁₂ H₁₄ O requires: C, 75.76;

H, 7.42%). Light absorption in ethanol: λ max. 2530, 3230 Å

(ϵ 8000, 2700). The infrared spectrum had bands at 1672(s),

1602(m) and 1560(w) cm⁻¹. The 2,4-dinitrophenylhydrazone

recrystallised from ethanol as bright red plates and had

m.p. 223-4^o. (Found: N, 15.3. C₁₈ H₁₈ O N requires: N, 15.2%).

(11) Elution with petrol/50% benzene gave 6-methoxy-1-methyl-2-tetralone (200mg.) identical in all respects with the authentic material.

(B) Using chromium trioxide in acetic acid.

The reagent for this reaction was prepared by dissolving chromium trioxide (2.15g.) in 95% acetic acid (100c.c.).

The mixture of tetralols (0.7g.) was dissolved in acetic acid (20c.c.) and treated with this solution (12c.c.) for 30min. at room temperature. The product was isolated by ether extraction. The infrared spectrum had bands at 3450(m) 1704(m) and 1670(s) cm^{-1} .

(C) With chromium trioxide in pyridine.

The tetralol (150mg.) in pyridine (6c.c.) was treated with a slurry prepared from chromium trioxide (1g.) and pyridine (10c.c.). After standing for 18 hours at room temperature the reaction mixture was poured into water and extracted with ether. The ethereal solution was well-washed with 2N-hydrochloric acid and water, dried and evaporated. The infrared spectrum of the product had bands at 3450(m), 1704(w) and 1670(s) cm^{-1} .

Attempted Oppenauer oxidations of the mixture of tetralols.

The following procedure for an Oppenauer oxidation in xylene is that described in Witkop⁴⁹. Oxidations were also attempted, by the standard procedures, with acetone in benzene and cyclohexanone in toluene. In both reactions the yield of ketonic material was negligible.

The mixture of tetralols (1.85g.) was dissolved in xylene (200c.c.) and 30c.c. of the solvent evaporated. The solution was heated under reflux and cyclohexanone (35g.) and a solution of aluminium isopropoxide (4.0g.) in xylene (50c.c.) were added. After refluxing for 2 hours, the solution was washed with dilute sulphuric acid and water, and xylene and cyclohexanone were removed by steam distillation. The residue was taken up in ether and the ethereal solution washed, dried and evaporated. The infrared spectrum of the residue had bands at 3450(m), 1704(m) and 1670(w) cm^{-1} . After treatment of this product with saturated sodium bisulphite solution for 48 hours, the bands at 1704 and 1670 cm^{-1} were of equal intensity.

Oxidation of sclareol

This preparation is based on the work of Ruzicka et al⁵³ and of Bigley⁵⁴.

Sclareol was obtained from Permenich et Cie., Geneva and had m.p. 100-102°.

'Analar' Acetone was purified by distilling from potassium permanganate.

Finely ground 'Analar' permanganate (88g.) was added in small portions during 8 hours to a very efficiently stirred solution of sclareol (50g.) in acetone (2½ l.) at -5°. After stirring for a further 2½ days at -5°, the slight excess of permanganate was destroyed by the addition of sodium bisulphite. The manganese dioxide was collected, washed with hot acetone (2 × 1 litre) and then refluxed with acetone (1 litre) for 1 hour. The combined acetone extracts were evaporated and the residual oil dissolved in ether, washed with aqueous sodium carbonate and water, dried and evaporated. The infrared spectrum showed the product to be mainly the enol ether (E44) plus a small quantity of the hydroxy-ketone (E45). A solution of this product in light petroleum was shaken with hydrochloric acid and chromatographed on alumina. Elution with petrol gave the enol ether (E44), (24g. 56%), m.p. 42°, b.p. 116-118°/0.05mm. $[\alpha]_D^{20} = +7(\pm 2)$.

Ruzicka et al. give m.p. $45-6^{\circ}$, b.p. $120-125^{\circ}/0.03\text{mm.}$,
 $[\alpha]_D^{25} = +5(\pm 2)$. The infrared spectra had a band at 1680 cm^{-1} .

5-(Hydroxyethyl)-6(e)-hydroxy-1,1,6,10-tetramethyl-trans-decalin (E48).

This method is similar to that used by Stoll and Hinder .
 (1) Ozonolysis of the enol ether (E44).

Ethyl acetate was purified by standing over potassium carbonate solution and distilling.

A solution of the enol ether (22g.) in ethyl acetate (350c.c.) was cooled to -45° and ozone (5%, 15 l./hr.) was bubbled through the solution until a blue colour persisted (6 hr.) and then for a further 5 hours. The solution was poured on to Raney nickel (15g.) at -15° and the mixture heated under reflux for 30min. and filtered. The catalyst was washed with ethyl acetate (300c.c.) and the ethyl acetate solution dried and evaporated to give a viscous oil. The infrared spectrum showed a diffuse band in the region $2500 - 3500\text{ cm}^{-1}$ and bands at $1710(\text{s})(\text{broad})$ and 1755 cm^{-1} . This product was used in the following reaction without further purification.

(11) Lithium aluminium hydride reduction.

The ozonolysis product was treated with lithium aluminium hydride (15g.) in dry ether (700c.c.) at reflux temperature for 4 hours. After decomposition of the excess lithium aluminium hydride with wet ether, the mixture was filtered and the residue washed with ether. The ethereal solution was washed with water, dried and evaporated to give a gum which crystallised from petrol to yield 5-(2'-hydroxy-ethyl)-6(e)-hydroxy-1,1,6,10-tetramethyl-trans-decalin. (E48). (12.0g., 52%) as a white crystalline solid which, after recrystallisation from petrol, had m.p. 129-131°. (Hinder and Stoll⁵¹ give m.p. 131-132°), $[\alpha]_D^{25} = -17^\circ$. (Found: C, 75.29; H, 11.73. Calculated for C₁₆H₃₀O₂: C, 75.53; H, 11.86%).

5-(2'-Bromoethyl)-6-methylene-1,1,10-trimethyl-trans-decalin.

Phosphorous oxybromide: acetic acid (11c.c.) was added dropwise during 1 hour to phosphorous pentabromide (65g.). Distillation of the product gave phosphorous oxybromide (28g.) as an almost white solid which was used immediately in the following reaction.

The glycol (E48) (5.5g.) in dry pyridine (200c.c.) was slowly added to an ice-cooled solution of phosphorous

oxybromide (28g.) in pyridine (400c.c.). After standing for 15 hours at room temperature the mixture was poured into water, extracted with ether. The ethereal solution was washed repeatedly with N-hydrochloric acid, then with sodium carbonate solution, water and brine, dried and evaporated. The residue was chromatographed on alumina: elution with petrol gave 5-(2'-bromoethyl)-6-methylene-1,1,10-trimethyl-trans-decalin (E5a). as a colourless oil, $(\alpha)_D^{20} = +50$. (Found: C, 64.50; H, 9.04; Br, 26.4. $\begin{matrix} \text{C} & \text{H} & \text{Br} \\ 16 & 27 & \end{matrix}$ requires: C, 64.21; H, 9.03; Br, 26.77%). The infrared spectrum had bands at 1650(m) and 893(s) cm^{-1} .

5-(2'-Iodoethyl)-6-methylene-1,1,10-trimethyl-trans-decalin.

The corresponding bromide (F5a, X=Br) (0.8g.) was treated with a solution of sodium iodide (0.8g.) in redistilled methyl ethyl ketone (15c.c.) at reflux temperature for 20 hours. Water and a crystal of sodium thiosulphate were added. Ether extraction afforded an almost colourless oil (0.78g.) consisting of a mixture of 5-(2'-iodoethyl)-6-methylene-1,1,10-trimethyl-trans-decalin and a small amount of the unchanged bromide. (Found: 1, 32.15%. $\begin{matrix} \text{C} & \text{H} & \text{I} \\ 16 & 27 & \end{matrix}$ requires 1, 36.70%). This material was used in the alkylations reactions described in Section 11 of this thesis.

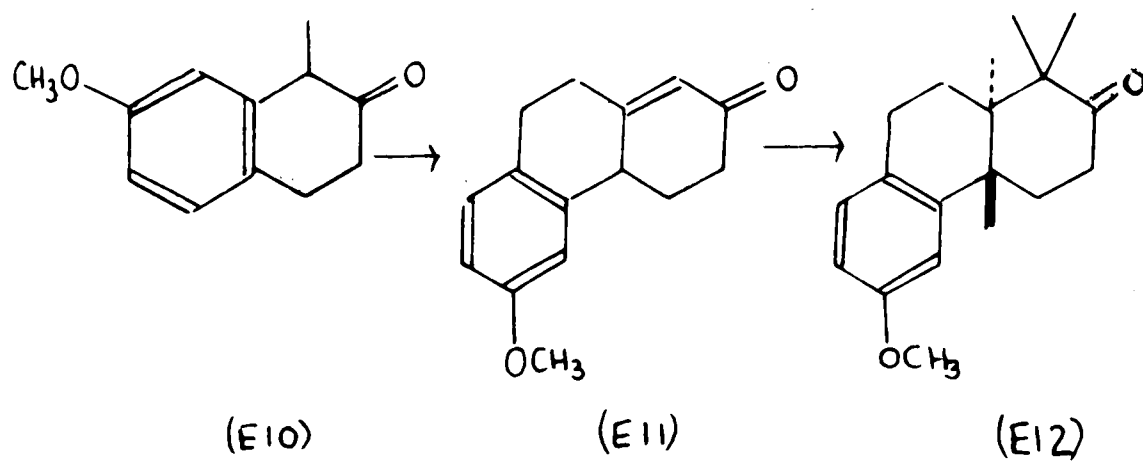
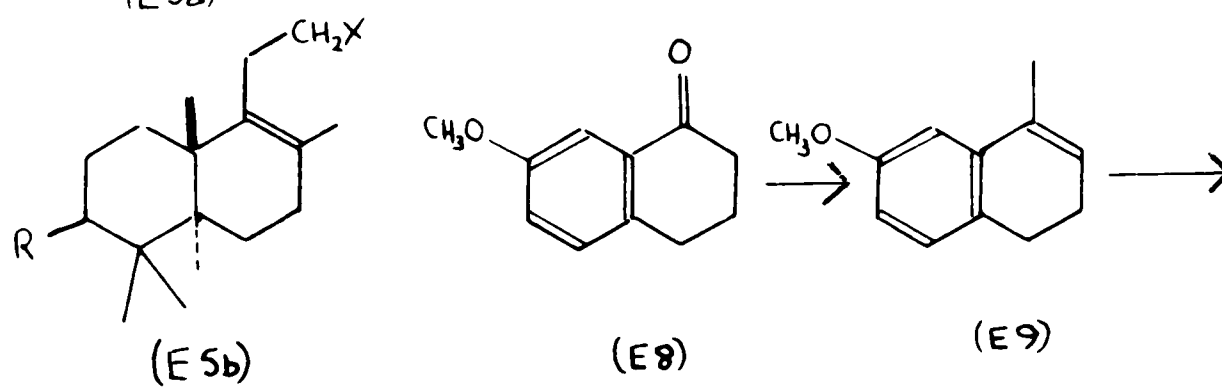
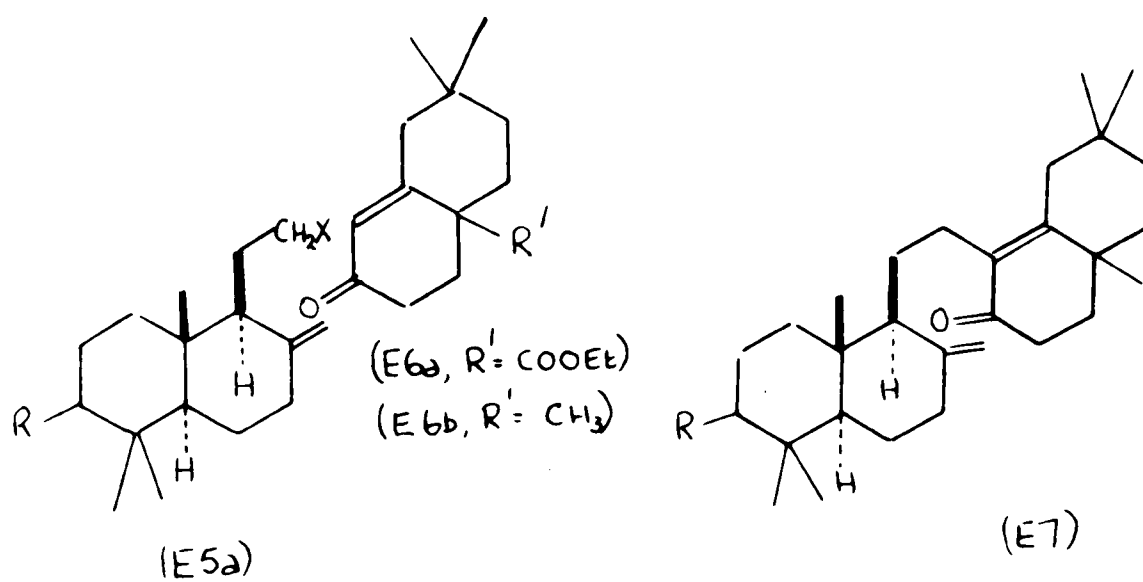
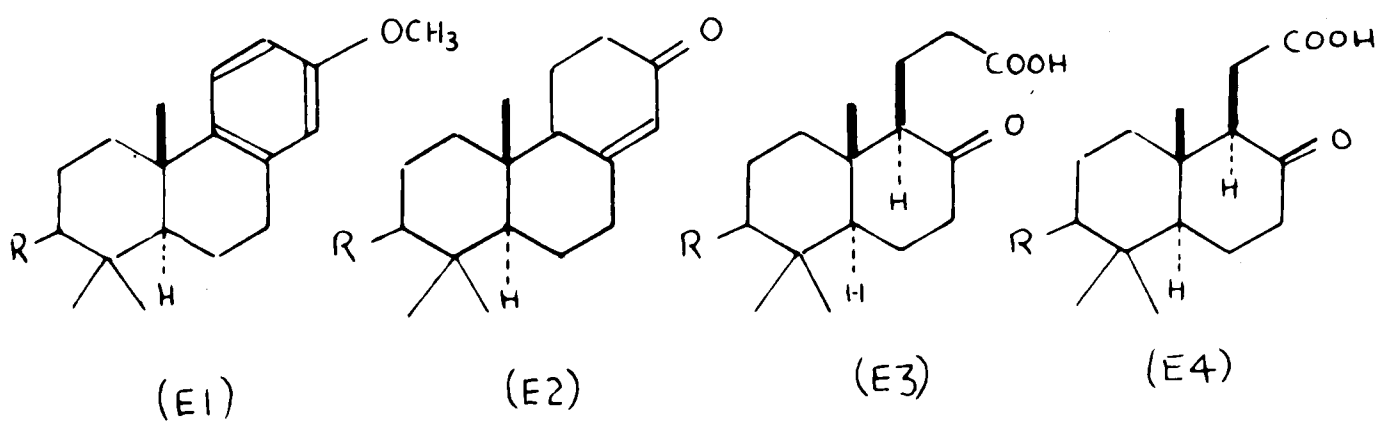
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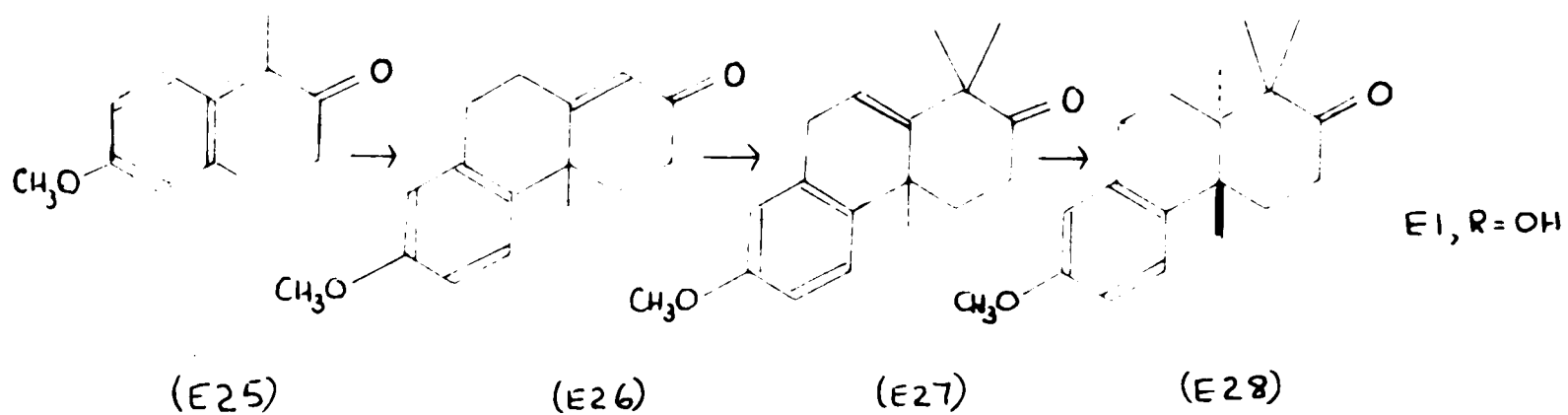
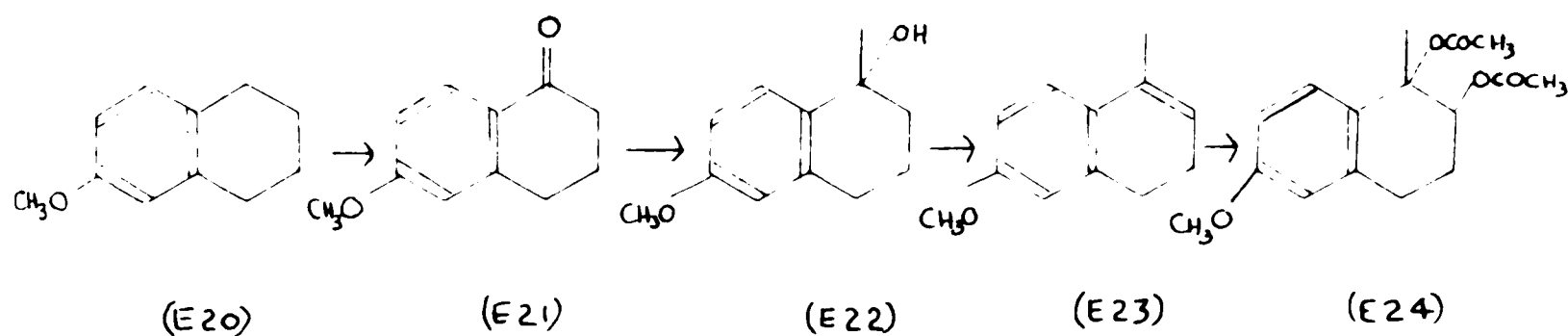
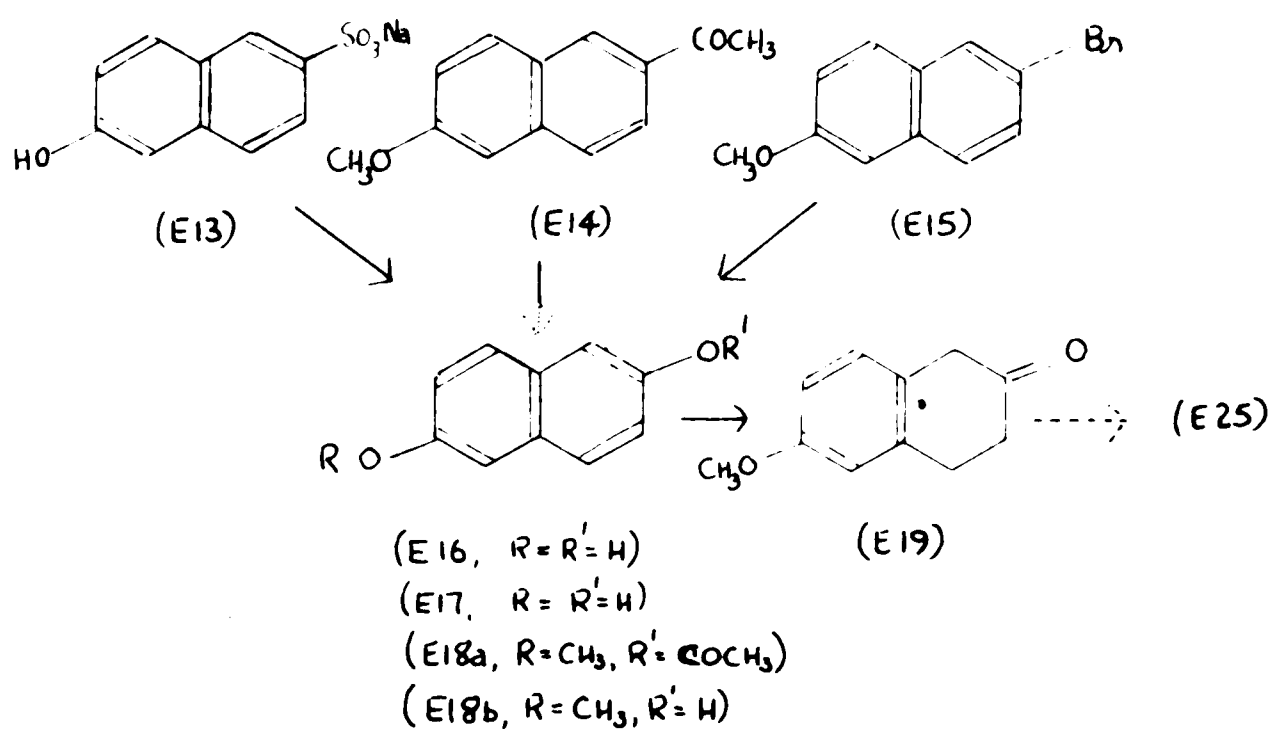
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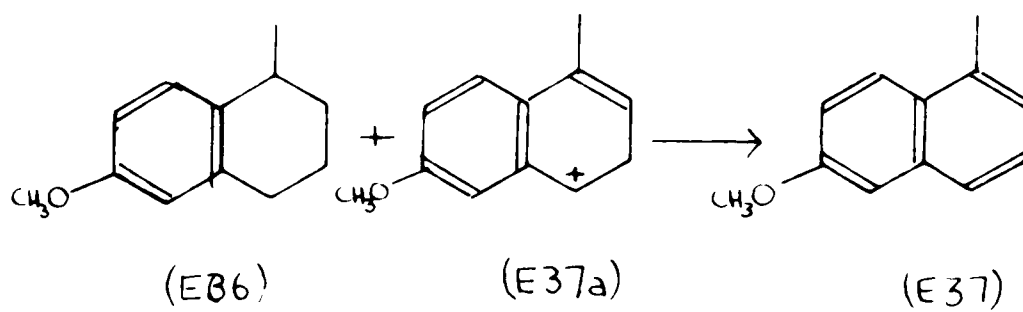
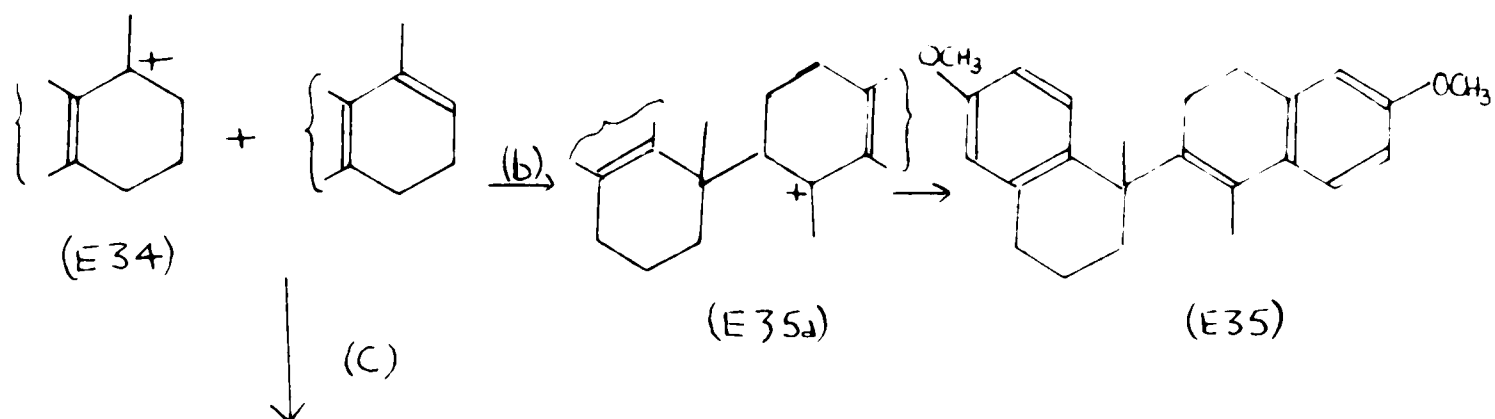
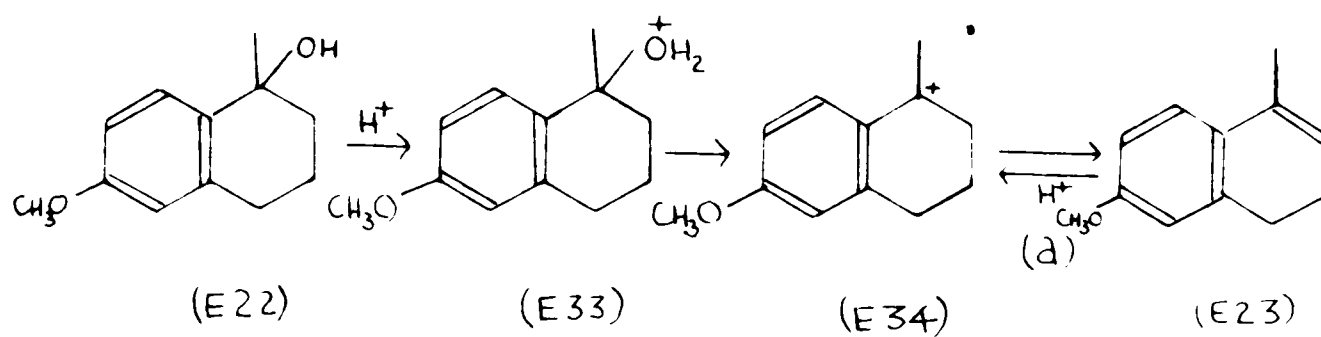
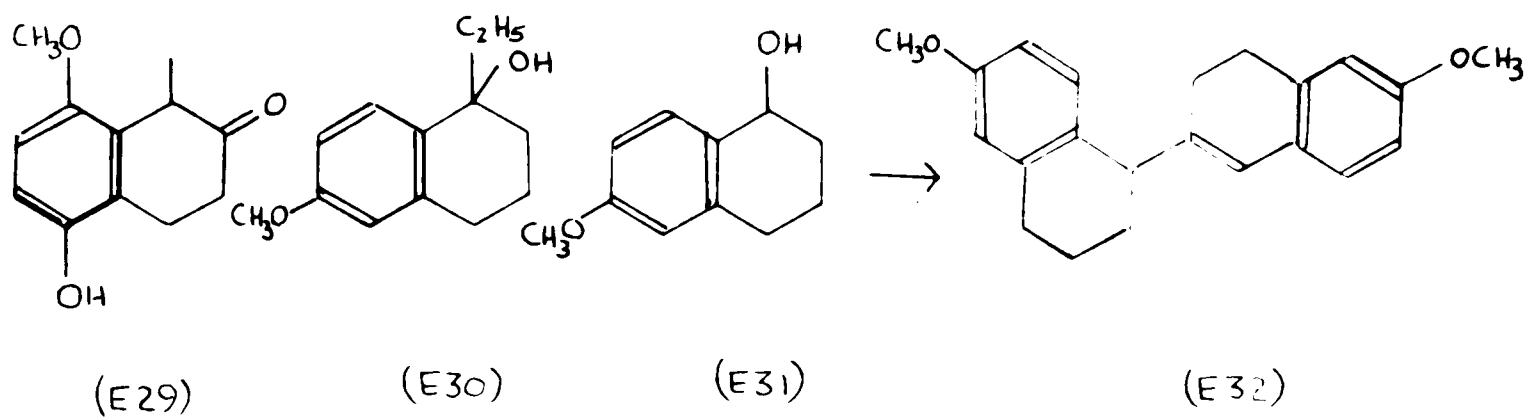
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SCHEME 4



Section 1 of this thesis described the successful synthesis of a bicyclic (+)methylene bromide (and the corresponding iodide) intended as the potential A and B rings in a synthesis of an oleanane type structure lacking the 3-hydroxyl function. It is convenient at this point to consider in some detail the later stages of the envisaged synthesis (scheme 5).

It was proposed to utilise the (+)bromide in the synthesis of a pentacyclic system having an angular carbethoxy group at C-17 and therefore related to oleanolic acid. To achieve this objective would require the attachment of the (+)bromide (F1), by means of an alkylation reaction involving nucleophilic displacement of bromine, at the 1-position of either the carbethoxy-octalone (F13) or the corresponding cis- or trans decalone (F8 or F9). Thus alkylation of the ($\pm$)octalone (F13) in this manner would give two ketones (F2,F3), diastereoisomeric at C-17 (triterpene numbering). The correct diastereoisomer (F3) could then be elaborated by the method¹ proposed by Halsall and Thomas and realised experimentally by Corey, Hess and Proskow in the synthesis of olea-11(12),13(18)-diene which has already been described in detail (viz. p.19). In the present case, treatment of the ketone (F3) with lithium methyl (or methyl magnesium iodide) should give the tertiary alcohol (F4); an acid catalysed cyclisation of the latter would

give ethyl 3-desoxy-olean-12(13),18(19)-dienolate (F5).

Alternatively a lithium-ammonia reduction of the unsaturated ketone (F3) would give the ketone (F6) which could then be elaborated to give ethyl 3-desoxy- δ -oleanolate (F7). (Whether the ketone (F6) has a cis or a trans D/E ring junction is not significant as the asymmetry at C-19 is destroyed in the final cyclisation).

The ketone (F6) could also be obtained, with the D/E ring junction defined as cis (19 β -H) or trans (19 α -H), as one of two diastereoisomers, by alkylation of either the cis-decalone (F8) or the trans-decalone (F9). By analogy with the steroids cholestanone and coprostanone, it would be expected that the cis and trans-decalones (F8 and F9) would enolise toward C-1 and C-3 respectively. The alkylation of the trans-decalone (F9) would therefore require the prior protection at C-3, whereas the cis-isomer would undergo direct alkylation at C-1. However Halsall and Thomas have shown that the 10-methyl-¹cis-₁decalone (F19) enolises towards C-3. The reasons given to explain this behaviour appear to be equally applicable to the 10-Carbethoxy-cis-decalone (F8) and therefore alkylation of the latter at C-1 would also require the protection of the C-3 position.

The investigation of the synthetic routes outlined above

required, as a first objective, the synthesis of the 10-carbethoxy-octalone (F13). The synthesis of this compound by the ring-extension of 2-carbethoxy-5,5-dimethylcyclohexanone (F¹²₁) will now be discussed.

The β -keto-ester (F12) has been prepared by Adams et al² by the condensation of 3,3-dimethylcyclohexanone (F11) with diethyl oxalate and pyrolysis of the resulting α -ketoester. Crossley and Rensuf³ had previously prepared the ketone (F11) by reduction of the enol chloride (F10) with zinc dust and acetic acid.

The enol chloride (F10) was prepared by treatment of dimedone with phosphorous trichloride; lithium-ammonia reduction then gave a mixture of the cyclohexanone (F11) and the corresponding alcohol. Chromic acid oxidation of this mixture afforded the pure ketone (F11). The experimental conditions for these initial stages of the synthesis were almost identical with those used by Halsall and Thomas¹ in the synthesis of 1,4,4-trimethylcyclohexanone (F17) from the dione (F15). In the latter synthesis the lithium-ammonia reduction of the enol chloride (F16) gave 70% yield of the ketone (F17). Under similar conditions the yield of the ketone (F11) was only 30% and a large amount of red polymeric material was formed. No increase in the yield of ketone (F11) was achieved by using

a shorter reaction time for the reduction. It is of interest that Crossley and Renouf³ (vide supra) reported the formation of a higher proportion of polymeric material, identified as the pinacol (F20), in their reduction of the enol chloride (F10).

Catalytic methods for the reduction of the enol chloride⁴ were now investigated. Steiner and Willhalm report that hydrogenation of a similar enol chloride (F21) with a palladium-on-charcoal catalyst in the presence of pyridine gave the keto-¹ester (F22) in high yield. Halsall and Thomas found that, under similar conditions, the enol chloride (F16) was not reduced, but that the enol chloride (F10) gave the ketone (F11); the experimental details for the latter hydrogenation are not given. Surprisingly, in the present work, it was found that, in the presence of pyridine, the enol chloride (F10) absorbed hydrogen extremely slowly at atmospheric pressure and, when the hydrogenation was conducted at a pressure of 5 atmospheres, the main product was dimedone.

Recently Moyle⁵ and Sondheimer and Wolfe⁶ have prepared the ketone (F17) in high yield, by hydrogenation of the corresponding enol chloride with a palladium-on-charcoal catalyst in the absence of pyridine. Under similar conditions the initial hydrogenation of the enol chloride (F10) proceeded very rapidly, but the reaction stopped abruptly when

approximately half the calculated theoretical quantity of hydrogen had been absorbed.

Further hydrogenations of the enol chloride were conducted in the presence of both potassium hydroxide and ammonia. With potassium hydroxide the rate of hydrogen absorption was very slow and hydrogenation was incomplete; the ketone (F11) was isolated in 30% yield by fractional distillation. A high yield (ca. 70%) of this ketone was eventually obtained by carrying out the hydrogenation with a palladium-on-charcoal catalyst in the presence of ammonia.

The β -keto-ester (F12) was prepared from the ketone (F11) as described by Adams et al.² (vide supra). This keto-ester was ring-extended by a procedure described by Dreiding and Tomasewski⁸; condensation of the keto-ester (F12) with rigorously purified methyl vinyl ketone in the presence of triton B gave an almost quantitative yield of the diketo-ester (F13a) which was cyclised with sodium ~~hydride~~^{ethoxide} to the octalone (F13) in 80% yield.

⁸
Dreiding and Tomasewski isolated a significant amount (ca. 13%) of the carboxy-octalone (F23) in a similar synthesis of the carbethoxy-octalone (F24). A much smaller amount of a high-melting acidic material (1%) was isolated in the present reaction and by analogy was formulated as the

carboxy-octalone (F14). This formulation is supported by analytical data but it is difficult to explain the anomalous spectroscopic properties of the compound. The extinction coefficient of the ultraviolet absorption maximum at $2425\text{\AA}$ is abnormally low (7400) in comparison with the corresponding intensities for the carbethoxy-octalone (F13) (17400) and the carboxy-octalone (F24) (12300).⁸ The infrared spectrum (nujol) showed the expected broadening of the C-H stretching band in the $3500\text{--}2500\text{ cm}^{-1}$ region, but also showed a sharp intense band at 3420 cm^{-1} . Assuming that the proposed structure is correct this suggests that a high proportion of the acid exists in the monomeric form. A possible, though speculative, explanation is that the monomer is energetically favoured relative to the dimeric form due to an unusually large steric hindrance of the carboxyl group.

It was found that, under appropriate conditions, the diketo-ester (F13a) could be cyclised with triton B. The procedure described above was therefore modified to afford an almost quantitative yield of the octalone (F13) in a single stage process which did not involve the isolation of the diketo-ester (F13a). The investigation of this modified experimental procedure was facilitated by the very characteristic infrared spectrum of the β -keto-ester (F12), the diketoester (F13a) and

the octalone (F13) which provided a convenient means for following the progress of the condensation and cyclisation steps.

Under the optimum conditions defined above this synthetic route afforded a 30% overall yield of the octalone (F13) from dimedone.

It was decided to investigate the catalytic hydrogenation and chemical reduction of the octalone (F13) to the corresponding decalones in the hope that conditions could be found for the preparation of the cis-decalone (F8). The possibility of protecting the C-3 position of the analogous 10-methyl-cis-decalone (F19) was meanwhile being investigated by Rushton.

It is known that catalytic hydrogenation, in neutral solution, of the 7,7,10-trimethyl-octalone (F18) and the 10-methyl-octalone (F30) gives predominantly the corresponding cis-decalones. However, it has been shown that, contrary to an earlier assumption, hydrogenation of the 10-carbethoxy-octalone (F24) affords the trans-decalone. The reason for this stereochemical difference is not apparent, though it has been attributed to catalyst hindrance by the larger grouping at the ring junction. Apart from the synthetic objective, it was of interest to discover whether

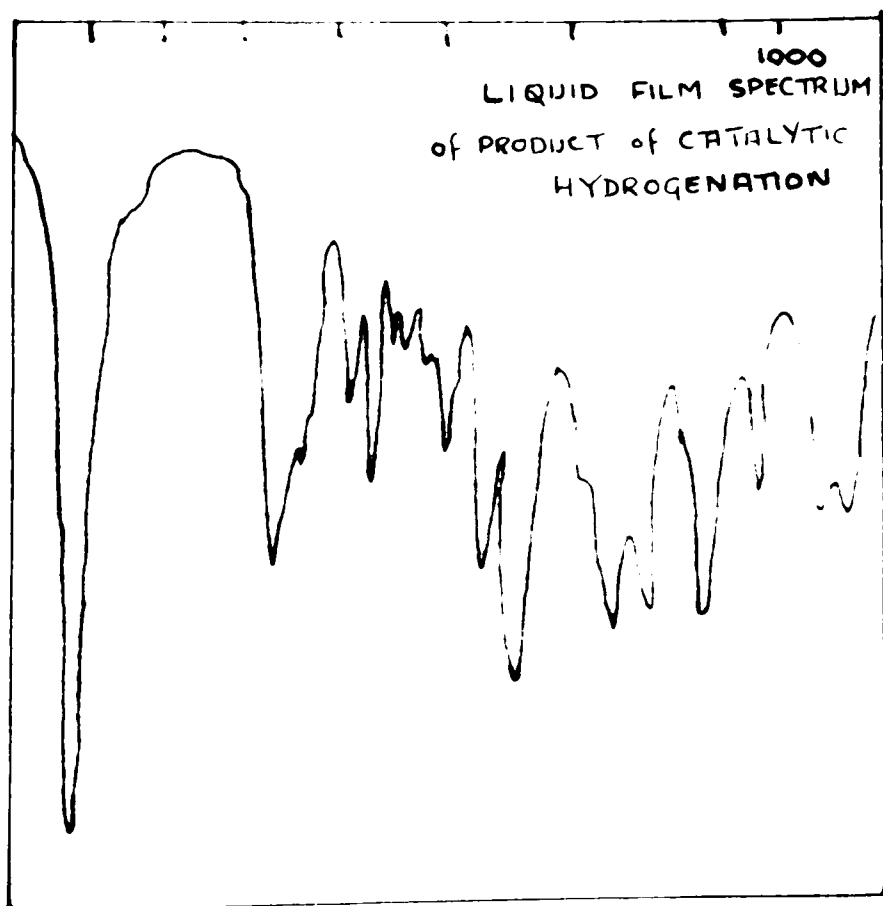
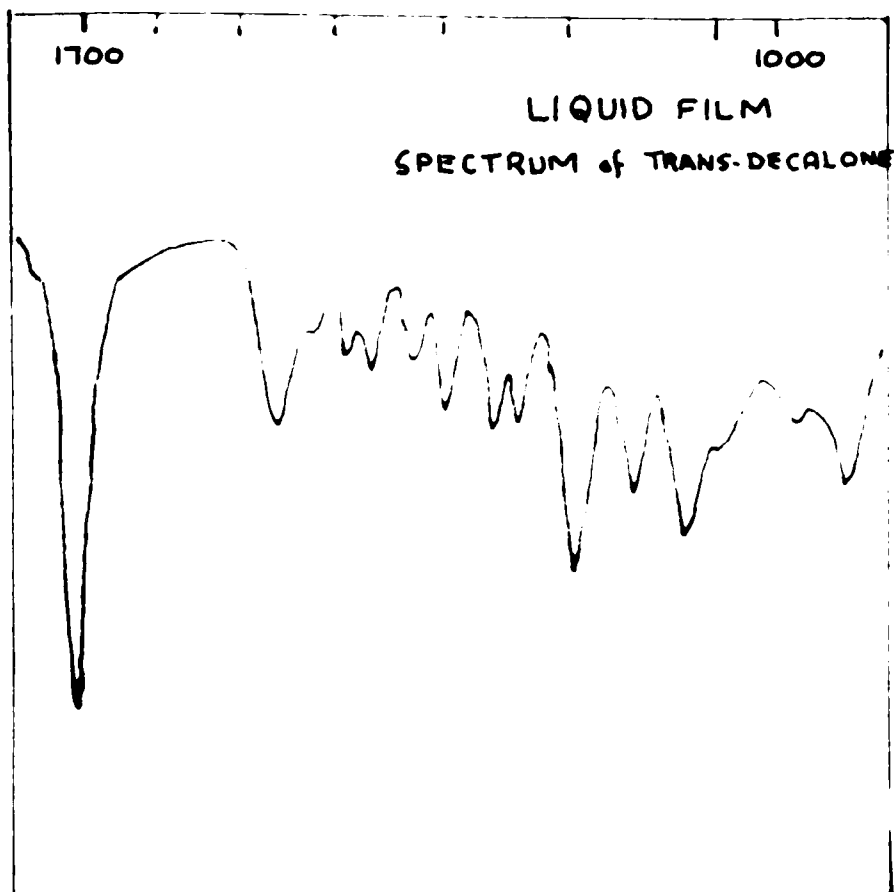
this effect operated in the case of the carbethoxy-octalone (F13). However, while this investigation was in its early stages, Rushton reported that the cis-decalone (F19) could not be effectively protected at C-3. Attempts to obtain the cis-decalone (F8) were therefore discontinued. The results which had been obtained at this stage will now be discussed.

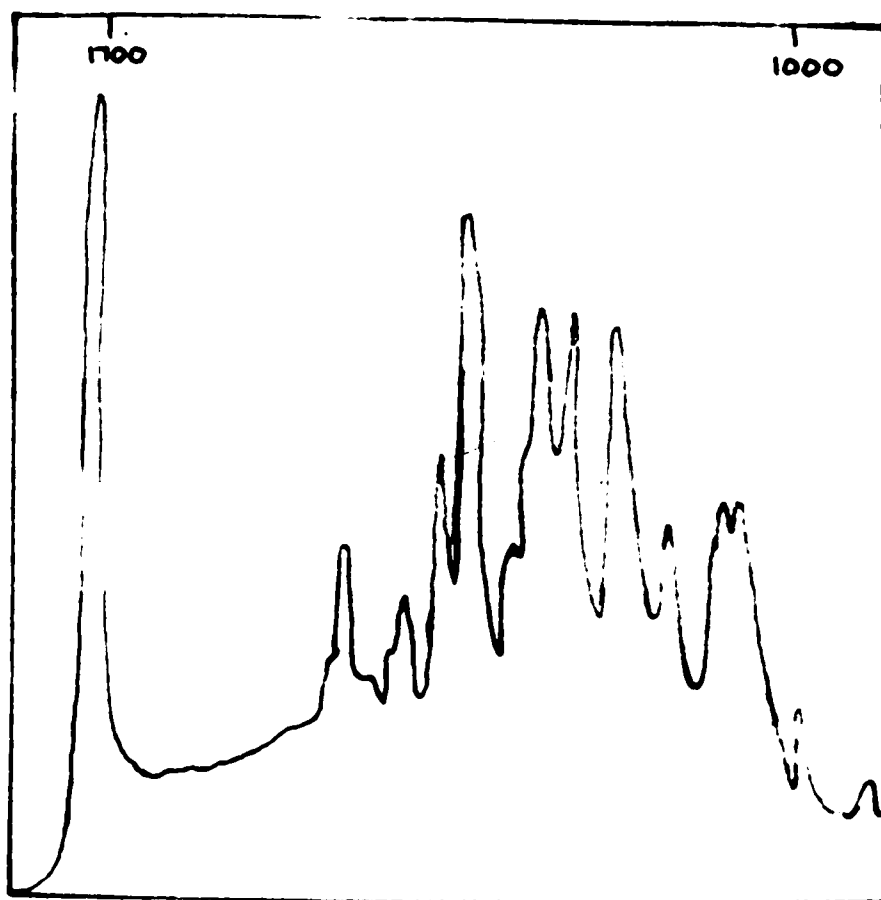
The octalone (F13) was hydrogenated, using platinum oxide, to give a product which showed an intense band at 1710 cm^{-1} in the infrared spectrum, presumably due to the two coincident bands representing the carbethoxyl and the saturated ketone groups, respectively. Careful chromatography of this product gave a series of fractions with identical infrared spectra; these were combined for further investigation. The behaviour of the crystalline derivatives of this decalone suggested that it was a mixture of the cis- and trans-isomers, in spite of the fact that these could not be separated by chromatography. The semicarbazone, although analytically pure, melted over a range of 5° . The 2,4-dinitrophenylhydrazone, as first prepared, also had an indefinite m.p., but was recrystallised to constant m.p. - thus providing, it was assumed, a derivative of either the pure cis- or the pure trans-decalone (F8 or F9). Attempts

to isolate a second, more sharply melting dinitrophenylhydrazone corresponding to the other stereoisomer, assumed to be present, were unsuccessful.

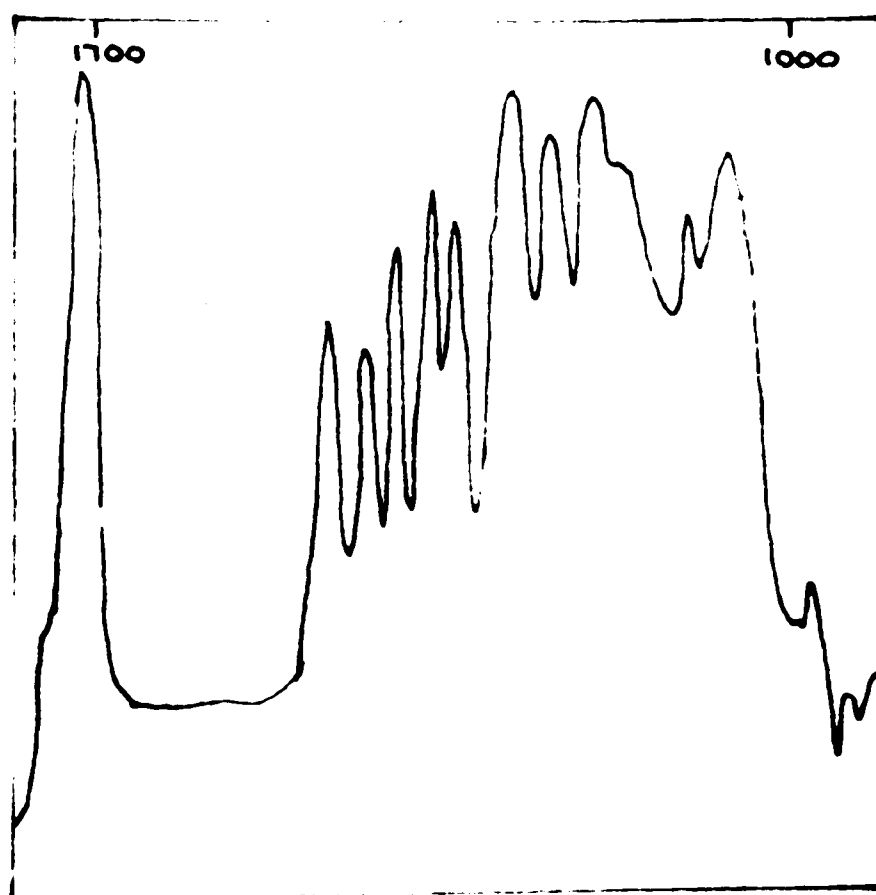
To provide farther information regarding the constitution of the above decalone, the octalone (F13) was reduced with lithium in liquid ammonia. Such reductions are known to give compounds with the thermodynamically more stable ring junction,^{12,13} in this case almost certainly the trans-decalone (F9). Unfortunately, reduction of the octalone (F13) by this method was complicated by the presence of a carbethoxyl group, which is also attacked by the reagent. Thus, although infrared spectra of the reduction product of the octalone (F13) showed that the unsaturated ketone group was not completely reduced, much hydroxylic material was nevertheless formed. Treatment with chromic acid effected only a partial oxidation of the hydroxylic material and, surprisingly intensified those absorption bands in the infrared region characteristic of unsaturated ketones. A very small quantity of the trans-decalone (F9) was isolated from the oxidation product by chromatography; it was characterised by spectroscopic and analytical data.

It appears that, in the above reaction, reduction of the carbethoxy group to a hydroxymethylene group occurs to a considerable extent. The 10-hydroxymethylene-octalone (F14a)





SPECTRUM IN CS_2 SOLUTION of
CATALYTIC HYDROGENATION PRODUCT



SPECTRUM IN CS_2 SOLUTION
of TRANS DECALONE

has been recently prepared by Rushton, who was unable to oxidise the angular hydroxymethylene group. This agrees with the fact that most of the hydroxylic material obtained in the reduction with lithium in ammonia, referred to above, could not be oxidised with chromic acid. The infrared spectra (of liquid films and carbon disulphide solutions) of the trans-decalone (F9) and of the decalone obtained by catalytic hydrogenation show marked differences in the region $1000-1500\text{ cm}^{-1}$ (see Fig.1). This suggests that catalytic hydrogenation of the octalone (F13) gives at least a high proportion of the cis-decalone (F8). To confirm this conclusion one would be required to prepare crystalline derivatives of the trans-compound and, more preferable still, to convert the decalone obtained by hydrogenation into the corresponding 10-methyl-decalone, the cis- (F19) and trans-forms of which have been fully characterised.¹

A realisation of the proposed synthesis now depended on the use of the octalone (F13). The resolution of this octalone and the determination of the absolute configuration of the two enantiomorphs would enable the ketone (F3) to be synthesised, thereby avoiding the necessity of separating two diastereoisomers at a later stage in the synthesis. A possible way of resolving the octalone (F13) was to use derivatives of either the carbonyl

function or the corresponding carboxylic acid (F14); the latter method would require a method for preparing the acid (F14) in good yield from the carbethoxy-octalone (F13).

The carbethoxy-octalone (F13) was unaffected by treatment with potassium hydroxide in aqueous ethanol under mild conditions. This was to be expected, in view of the sterically hindered nature of the carbethoxyl group. More vigorous conditions resulted mainly in decarboxylation of the octalone, which can be considered as the vinylogue of a β -keto-ester, and hence subject to relatively easy decarboxylation.

Recently ¹⁴ Elsinger et al. have described the preparation of free acids from sterically hindered methyl esters, including methyl O-acetyl oleanolate, using lithium iodide in collidine. When the carbethoxy-octalone (F13) was treated under similar conditions, only the starting material was obtained; the method is perhaps restricted to methyl esters.

The use of (-)-menthyl-N-aminocarbamate ((-)-menthhydrazide) for resolving carbonyl compounds was introduced by Woodward ¹⁵ et al. . It was found that the (-)-menthhydrazone of the octalone (F13) could be prepared in high yield by the method of Woodward ¹⁵ et al. , and that the ketone could be conveniently ¹⁶ regenerated by treatment with pyruvic acid. Unfortunately,

no solvent could be found which effected a significant separation of the two diastereoisomeric menthhydrazones by recrystallisation.

Resolution of the octalone (Fl3) was achieved by using the (-)brucine salt of the p-carboxyphenylhydrazone. The p-carboxyphenylhydrazone was prepared by the procedure of Anchel and Scoenheimer¹⁷, the yield being increased to 95% by carrying out the reaction under nitrogen. Both this compound and its brucine salt, which was prepared in ethyl methyl ketone, were unstable in the presence of oxygen, and even under nitrogen it was difficult to obtain a pure, crystalline material free from tarry matter. However, by taking the first crops from successive recrystallisations under nitrogen from ethyl methyl ketone, acetone and ether/petrol, a brucine salt of constant rotation was obtained.

Because of this instability, the octalone (Fl3) was regenerated directly from the brucine salt by treatment with pyruvic acid¹⁶, the yield being low. It had a rotation of -100° ; its 2,4-dinitrophenylhydrazone had a rotation of -300° . Decomposition of the mother-liquors from the recrystallisation of the brucine salt gave an octalone with a rotation of $+60^{\circ}$.

A sample of the laevorotary octalone has been sent to Prof. Djerassi in order that its absolute configuration may be determined.

In view of the difficulties experienced in the resolution of the octalone (F13), the alkylation of the racemic form was studied.

Using Rushton's conditions (sodium t-amylate in boiling toluene), which were suitable for the alkylation of the octalone (F18) with the bromide (F1), considerable amounts of hydroxylic material were obtained, and no tetracyclic compounds were isolated from the product. To conserve the methylene halide (F1), model experiments were carried out using n-propyl iodide and a weaker base, potassium isopropoxide. With either benzene or isopropanol as solvent three products were obtained, P, Q and R.

The major product (P), obtained in 30% yield, was the monoalkylated material (F25). The band in the ultra-violet due to the $\alpha:\beta$ -unsaturated ketone group was displaced to longer wavelengths, as expected; and that at 860 cm^{-1} in the infrared, characteristic of ^{tri}unsubstituted double bonds, had disappeared.

Product Q was probably the dialkylated compound (F26). The band at 1670 cm^{-1} in the infrared had disappeared, and no 2,4-dinitrophenylhydrazones could be prepared (whereas the monoalkylated product formed one readily).

Product R had no band in the infrared characteristic of the carbethoxyl group, but alkylation had presumably taken place, since the band at 860 cm^{-1} had disappeared.

Using the bromide (F1) under these conditions, alkylation was not achieved, probably because of the low reactivity of the bromide and the ready decomposition of the octalone at elevated temperatures and under basic conditions. The more reactive iodide (F1), prepared as discussed in section I, was therefore used and gave under the above conditions small yields of three products, A, B and C, which will be discussed below. Zook and Russo have recently reported¹⁸ greatly increased rates of alkylation of carbanions, using diglyme or triglyme as solvents.

The minor product from this last reaction (B) was formulated as the carbethoxylated tetracyclic ketone (F28), on the basis of analytical data; the absorption at 2500 Å in the ultra-violet; ~~and~~ the presence of a band at 890 cm^{-1} in the infrared characteristic of exocyclic methylene groups; and the absence of bands due to ester groups and trisubstituted double bonds.

The analytical data pointed to product C being mono-alkylated, and its high rotation ($[\alpha]_D = +150^\circ$) indicated that substantial resolution had taken place. The infrared spectrum contained bands characteristic both of exocyclic methylene groups and of unsaturated ketones; the band due to methylene was split ($\nu = 900, 880\text{ cm}^{-1}$), presumably owing to interaction between the methylene and carbonyl groups. The ultra-violet spectrum showed the expected shift to longer wavelengths (λ_{max}

2480 Å), compared with the absorption of the octalone (F13) (λ_{max} 2375 Å).

Product A was not completely characterised, but it was assumed from the analytical data that it was monoalkylated tetracyclic compound. A and C are perhaps the enantiomorphous ketones (F2) and (F3), a view supported by the different rotations (A had $[\alpha]_D = -36^\circ$). However, the spectra of A and C differ in two respects. In product A the bands in the infrared ascribed to exocyclic methylene are at 869 and 890 cm^{-1} ; and the position of maximum absorption in the ultra-violet is at 2410 Å. Moyle⁵ found that the product (F29) of alkylation of the 10-methyl-octalone (F18) with bromoacetic ester exhibits a similar small shift in the ultra-violet absorption band. In the present case the shift may be explained in terms of different non-bonded interactions between the exocyclic methylene and the carbonyl groups in the two enantiomorphs. An alternative structure of the product A, however, would be that alkylated at C-3.

Attempts to raise the yield of the tetracyclic material, using the iodide (F1) in diglyme, will be the subject of further research in this field. It should then be possible to establish unambiguously the structures of these substances. Confirmatory evidence may come from alkylation of the resolved octalone (F13).

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

Commercial dimedone (5,5-dimethylcyclohexa-1,3-dione) (B.D.H.) was recrystallised from acetone and had m.p. 149°.

Treatment of the purified dimedone (125g.) with phosphorus trichloride (45 c.c.) by the procedure described by Halsall and Thomas¹ gave 3-chloro-5,5-dimethylcyclohex-2-en-1-one (100g., 71%), b.p. 90°/20mm., n_D^{20} , 1.4943. (Found: C, 60.73; H, 7.05; Cl, 22.15. Calculated for $C_8H_{11}OCl$: C, 60.56; H, 6.94; Cl, 22.39%). Light absorption in ethanol: λ_{max} 2370 Å (ϵ 17560).

3,3-Dimethylcyclohexanone

Method A: Lithium-ammonia reduction of 3-chloro-5,5-dimethylcyclohex-2-en-1-one.

The experimental procedure is similar to that of Halsall¹ and Thomas.

The enol chloride (89g.) in dry ether (250c.c.) was added during 1½ hours, with vigorous stirring, to lithium (20g.) in liquid ammonia (2 l.). After the mixture had been stirred for a further 45min., the lithium complex was decomposed with ethanol, the ammonia was evaporated and water was added. Ether extraction gave a dark red oil which on distillation gave a mixture of 3,3-dimethylcyclohexanone and 3,3-dimethyl-

cyclohexanol (26g.) as a colourless oil, b.p. 81-86° / 18mm.. A large amount of red, polymeric material remained in the distillation flask; the infrared spectrum of this material showed a broad intense hydroxyl band and a complex of ill-defined bands in the carbonyl region. The distillate obtained above was dissolved in acetone (60c.c.) at room temperature and 8N-chromic acid solution was added dropwise until the orange colour persisted. Ether extraction gave a product which was distilled to give 3,3-dimethylcyclohexanone (21g., 30%), b.p. 66-68° / 14mm., n_D^{22} , 1.4462. The 2,4-dinitro-phenylhydrazone recrystallised from petrol/5% benzene as orange needles, m.p. 123-126°. (Found: C, 54.63; H, 5.44; N, 18.6. C H N O requires: C, 54.89; H, 5.92; N, 18.29%).
 14 18 4 4

An attempt was made to cut down the amount of red polymeric material formed in the reduction: the total reaction time, from the addition of the enol chloride to the discharge of the blue colour of the reaction mixture, was reduced to 45 min. No significant decrease in the amount of polymeric material formed was observed and the low boiling material which was obtained contained unchanged enol chloride (ca. 10%).

Method B; Catalytic reduction of 3-chloro-5,5-dimethylcyclohex-2-en-1-one.

The enol chloride was hydrogenated with 10% palladium-on-charcoal and with 2½% palladium-on-calcium carbonate, both in neutral solutions and in the presence of bases. In all the reactions carried out in neutral solution, hydrogenation stopped when half the theoretical quantity of hydrogen had been absorbed. The procedure described below gave the best yield of 3,3-dimethylcyclohexanone of all the methods investigated.

(1) The enol chloride (42g.) in dry ethanol (500c.c.) was hydrogenated at atmospheric pressure in the presence of 10%-palladium-on-charcoal, (10g.), with vigorous shaking. Rapid absorption of hydrogen (5½ l.) occurred during 30min.; the rate of absorption of hydrogen then slowed abruptly. Ammonia (s.g. 0.88, 10c.c.) was added and a further absorption of hydrogen (5½ l.) occurred during 1 hour. After a further 30 min. during which the rate of absorption was very slow, the solution was filtered and the catalyst well washed with ether. The total volume of the filtrate was made up to 2 l. with ether and the ethereal solution well-washed with water and brine and stood over an excess of calcium chloride.

Evaporation of the solvent and distillation of the residue gave 3,3-dimethylcyclohexanone (25g., 70%).

(11) The hydrogenation was conducted under similar conditions but using a 2½% palladium-on-calcium carbonate catalyst, prepared by the method of Vogel⁷. A slightly lower yield of the cyclohexanone was obtained.

(111) Hydrogenation was conducted with 2½%-palladium-on calcium carbonate in the presence of potassium hydroxide; the absorption of hydrogen was very slow and hydrogenation was incomplete. The yield of 3,3-dimethylcyclohexanone was ca. 35%.

(1V) Hydrogenation in the presence of pyridine (cf.ref.14)

The enol chloride (5.8g.) in ethanol (70c.c.) containing pyridine (3c.c.) was hydrogenated with 2½% palladium-on-calcium carbonate (2.5g.) at atmospheric pressure. During 12 hours 350c.c. (ca. 20% of the calculated theoretical amount) of hydrogen was absorbed. A further amount of catalyst (1.0g.) was added and hydrogenation continued for 6 hours at 5 atmospheres pressure. The crude product was isolated as described under (1) and, on standing, there crystallised out 5,5-dimethylcyclohexan-1,3-dione (1.0g.), m.p. and mixed m.p. 149 °.

2-Carbethoxy-5,5-dimethylcyclohexanone.

3,3-Dimethylcyclohexanone (16.4g.) was carbethoxylated by the method of Adams ² et al. to give 2-carbethoxy-5,5-dimethylcyclohexanone (15.5g., 60%), b.p. $140^{\circ}/20\text{mm.}$, n_D^{18} , 1.4732. (Adams ² et al. give b.p. $125-128^{\circ}/14\text{mm.}$, n_D^{20} , 1.4716). (Found: C, 66.39; H, 9.09. Calculated for $C_{11}H_{18}O_2$: C, 66.65; H, 9.15%). Light absorption in ethanol: $\lambda_{\text{max.}}$ $2560 \text{ \AA}$ (ϵ 10000). The infrared spectrum had bands at 1725, 1700, 1645 and 1610 cm^{-1} .

10-Carbethoxy-7,7-dimethyl- $\Delta^{1(9)}$ -octalin-2-one (F13).

The following experimental procedure is similar to that of Dreiding and Tomasewski ⁸.

Methyl vinyl ketone was purified by refluxing with acetic anhydride for $2\frac{1}{2}$ hours and distilling through a Vigreux column.

An aqueous solution of benzyltrimethylammonium hydroxide (triton B) (40% w/w, 2c.c.) was freed from water by azeotroping with benzene/ethanol.

2-Carbethoxy-5,5-dimethylcyclohexanone (30g.) was added to the solution of Triton B in benzene/ethanol (12c.c.) prepared as described above. The mixture was cooled in an ice bath and methyl vinyl ketone (13.0g.) in benzene (15c.c.)

was added during $2\frac{1}{2}$ hours with vigorous stirring. After stirring for a further 12 hours at room temperature the reaction mixture was taken up in ether and the ethereal solution was washed with water, N/5-hydrochloric acid, sodium carbonate solution and brine. Evaporation gave 2-(3'-keto-1'-n-butyl)-2-carbethoxy-5,5-dimethylcyclohexanone (39g., 96%) as a light yellow oil. The infrared spectrum showed a single broad band in the carbonyl region at ca. 1715 cm^{-1} . A small amount was distilled for analysis, b.p. 150° (air bath)/3mm. (Found; C, 67.45; H, 9.38. C H O requires C, 67.13; H, 9.02%).
15 24 4

Without further purification the diketoeester (Fl3a) (30g.) was treated with a solution of sodium (3.1g.) in ethanol (400c.c.) at room temperature under an atmosphere of nitrogen during $1\frac{1}{2}$ hours. After acidification with acetic acid the mixture was concentrated under reduced pressure and then taken up in benzene. The benzene solution was washed with sodium carbonate solution and water, dried and evaporated. Distillation of the residue gave 10-carbethoxy-7,7-dimethyl- $\Delta^{(9)}$ -octalin-2-one (22.5g., 81%), b.p. $135-140^{\circ}$ /0.2mm. as a colourless oil which, solidified on standing overnight at 0° and, after recrystallisation from ether at 5° , had m.p. $31-32^{\circ}$. (Found: C, 71.60; H, 8.85. C H O requires:
15 22 3

C, 71.97; H, 8.86%). Light absorption in ethanol: λ max. 2375⁰A (ϵ 17400). The infrared spectrum showed bands of equal intensity at 1725 and 1675 cm.⁻¹ (s) and a weaker band at 1625 cm.⁻¹ (m). The semicarbazone, recrystallised from ethanol, had m.p. 200-210⁰ (dec.). (Found: C, 62.36; H, 8.14; N, 13.48; C H N O requires: C, 62.52; H, 8.20; N, 13.67%). The 2,4-dinitrophenylhydrozone from ethanol had m.p. 166⁰. (Found: C, 58.35; H, 6.23; N, 13.35. C H N O requires: C, 58.59; H, 6.09; N, 13.02 %). Light absorption in ethanol: λ max. 3810⁰A (ϵ 32700).

The carbonate washings from the above reaction were acidified and extracted with ether to give 10-carboxy-7,7-dimethyl- $\Delta^{1(9)}$ -octalin-2-one (220 mg.), as a white solid which, after recrystallisations from methylene dichloride had m.p. 214-215⁰. (Found: C, 70.52; H, 8.13. C H O requires: C, 70.24; H, 8.16%). Light absorption in ethanol: λ max. 2425⁰A (ϵ 7400). The infrared spectrum showed the diffuse band in the 3500-2500 cm.⁻¹ region, characteristic of carboxylic acids, and had sharp bands at 3450(s), 1712(s), 1670(s) and 1620cm.⁻¹.

A modification of the above method for the preparation of the octalone (F13).

The β -keto-ester (F12) (28g.) was condensed with methyl vinyl ketone as described in the previous experiment, but the diketo-ester (F13a) was not isolated. Instead, after the reaction mixture had been stirred for 12 hours, there was added a further amount of triton B in benzene ethanol (15c.c.) (prepared from the 40% aqueous solution (5c.c.) as described above). After 12 hours the reaction mixture was worked up as in the previous experiment to give the almost pure octalone (F13) (32.5g., 96%).

Hydrogenation of 10-carbethoxy-7,7-dimethyl- $\Delta^{(9)}$ -octalin-2-one with platinum oxide.

The octalone (2.18g.) in dry ethanol (30c.c.) was hydrogenated in the presence of platinum oxide (0.36g.) at atmospheric pressure. One mole of hydrogen was absorbed in 15 min. after which absorption became very slow. After a further 10 min. the catalyst and the solvent were removed and the residual oil (2.0g.) chromatographed on alumina (180g.). Elution with petrol and then petrol/10% benzene and collection of one column volume fractions gave a series of oils which had identical infrared spectra and were therefore combined

to yield, it was assumed, a mixture of cis- and trans-
10-carbethoxy-7,7-dimethyldecalin-2-one (1.3g.). (Found:

C, 71.83; H, 9.73. $\begin{smallmatrix} C & H & O \\ 15 & 24 & 3 \end{smallmatrix}$ requires C, 71.39; H, 9.59 %).

The infrared spectra (liquid film and CS solution) are

shown in fig. 1(p.). The 2,4-dinitrophenylhydrazone
 of this product (80mg.) was prepared and allowed to crystallise
 from a dilute solution in ethanol. The first crop (A) (27mg.)

of orange crystals had m.p. 148-150°; concentration of the
 mother liquor gave a second crop (B) (82mg.) which had m.p.
 140-5°, mixed m.p. with (A), 144-6°. (B) was recrystallised
 from ethyl acetate to constant m.p. 150-2°. (Found: C, 57.84;

H, 6.19; N, 12.96. $\begin{smallmatrix} C & H & O & N \\ 21 & 28 & 6 & 4 \end{smallmatrix}$ requires: C, 58.32; H, 6.53;

N, 12.95 %). The semicarbazone from aqueous methanol had

m.p. 191-5°. (Found: n, 13.85. $\begin{smallmatrix} C & H & O & N \\ 16 & 27 & 3 & 3 \end{smallmatrix}$ requires: N

N, 13.58%).

Lithium-ammonia reduction of 10-carbethoxy-7,7-dimethyl-¹⁽⁹⁾
octalin-2-one. Δ -

The octalone (550 mg.) in dry ether (50c.c.) was added
 dropwise with stirring to a solution of lithium (55mg.) in
 liquid ammonia (125c.c.). The mixture was stirred for a
 further 10 min. and excess ammonium chloride was added. The
 reaction mixture was worked up by the normal method to give

a yellow oil (450 mg.). The infrared spectrum of this had bands at 3450(s), 1710(s), 1670(w) and 1620(vw) cm^{-1} .

The above product was dissolved in acetone (5 c.c.) and treated with 8N-chromic acid by the normal procedure. The product of this reaction showed the same bands in the infrared region as the starting material, but with the band at 3450 cm^{-1} reduced in intensity, and those at 1670 and 1620 cm^{-1} increased in intensity; it also showed a very weak band at 1780 cm^{-1} .

The mixture was chromatographed on alumina. Elution with petrol/10% benzene gave 10-carbethoxy-7.7-dimethyl-trans-decalin-2-one as a colourless oil (20 mg.) (Found: C, 71.00; H, 9.31; $\text{C}_{15}\text{H}_{24}\text{O}_3$ requires C, 71.39; H, 9.59%). The infrared spectra (liquid film and CS_2 solution) differed in the region 1500-1000 cm^{-1} from those of the product of catalytic hydrogenation, as shown in Fig.1.

Attempted preparation of 10-carboxy-7.7-dimethyl- $\Delta^{1(9)}$ -octalin-2-one from the corresponding ethyl ester (F13).

(a) The ester (F13) (300 mg.) was treated with potassium hydroxide (0.4 g.) in 95% ethanol (10 c.c.) for 12 hours at room temperature, and a further $1\frac{1}{2}$ hours at the boiling temperature. The reaction mixture was worked up to give unchanged starting material.

(b) The ester (1.0g.) was treated with potassium hydroxide (1.9g.) in ethanol (30c.c.) and water (5c.c.) at reflux temperature for 5 hours. The product was separated into neutral and acidic fractions. The latter (50mg.) was a brown, tarry solid. The neutral material (750mg.) probably consisted of mainly 7,7-dimethyl- $\Delta^{1(9)}$ -octalin-2-one. The infrared spectrum had bands at 1670 cm^{-1} (s) and 1620 cm^{-1} (w), but only a very weak band at 1715 cm^{-1} .

(c) Treatment with lithium iodide in collidine (cf. Elsinger et al.¹⁴)

The ester (0.9g.) was treated with lithium iodide (3.4g.) in collidine (85c.c.) at reflux temperature under nitrogen for 5 hours. The reaction mixture was poured into 2N-hydrochloric acid (600c.c.) and extracted with ether/methylene dichloride. The organic extracts were well washed with 2N-hydrochloric acid and water, dried and evaporated. The product had an infrared spectrum identical with that of the starting material.

An attempted resolution of 10-carbethoxy-7,7-dimethyl- $\Delta^{1(9)}$ -octalin-2-one using (-)-menthyl-N-aminocarbamate ((-)-menthydrazone)

The procedure for the preparation of the menthydrazone is that described by Woodward et al.¹⁵

(-)-Menthydrazone was prepared by Mr. W. Smith in this laboratory and, after recrystallisation from petrol (b.p. 80-100°), had m.p. 101.5-102°, M_D^{EtOH} -177°. (Woodward et al. give m.p. 101.5-102°, M -171°).

The ($\pm$)octalone (2.0g.) and (+)-menthydrazone (1.7g.) were dissolved in the minimum volume of a solution prepared by dissolving acetic acid (1c.c.) and sodium acetate (2g.) in 95% ethanol (100c.c.) and the mixture was heated under reflux for 48 hours. The solution was concentrated and, on cooling, a mixture of almost equal amounts of the (+)octalone-(-)methydrazone and the (-)octalone-(-)menthydrazone separated a very small white needles (fraction A, 1.4g.), m.p. 125-135°. $[\alpha]_D^{EtOH}$ -200°. Concentration of the mother liquor gave a further crop of crystals (B, 1.6g.), m.p. 129-135°, $[\alpha]_D^{EtOH}$ -17°, and on final evaporation of the mother liquor, there was obtained an amorphous solid which, after recrystallisation from methanol, had m.p. 135-136°, $[\alpha]_D^{EtOH}$ -18°. Two recrystallisations of

A and B from methanol gave:

(A1), m.p. 140-141°, $[\alpha]_D^{EtOH}$ -27°.

(B1), m.p. 136-137.5°, $[\alpha]_D^{EtOH}$ -18°.

Further recrystallisations of (A1) and (B1) from petrol did not alter either the m.p. or the optical rotations of the two products.

(Found: C, 69.51; H, 9.14; N, 6.40. C H O N requires:
26 42 4 2
C, 69.92; H, 9.48; N, 6.27%.)

The octalone was regenerated from (A1) (0.7g.) by heating under reflux for 2 hours with glacial acetic acid (20c.c.), water (5c.c.) and 50% pyruvic acid (3c.c.) and had $[\alpha]_D^{EtOH}$ -4(±2)°.

Resolution of 10-carbethoxy-7,7,-dimethyl-¹⁽⁹⁾Δ-octalin-2-one using the (-) brucine salt of the p-carboxyphenylhydrazone.

The procedure for the preparation of the p-carboxyphenylhydrazone is that of Anchel and Scoenheimer.¹⁷

All the reactions described below were conducted in an atmosphere of nitrogen; the evaporation of solvents was achieved by bubbling through a rapid stream of nitrogen, where possible, at room temperature.

(1) A solution of the (±)octalone (10.5g.) and p-carboxyphenylhydrazine (8.0g.) in 95% ethanol (400c.c.) containing acetic acid (2c.c.) was heated under reflux for 3 hours.

The volume of the solution was then reduced to 80c.c. and the alcoholic suspension was distributed between 4% potassium carbonate solution (300c.c.) and ether (150c.c.). Acidification of the aqueous phase with 2N-hydrochloric acid precipitated the p-carboxyphenylhydrazine (16.0g., 95%) which, after recrystallisation from ethanol and drying at 50°/14mm. for 3 hours, had m.p. 226-228°. (Found: C, 68.19; H, 7.47; N, 7.12. $\begin{smallmatrix} \text{C} & \text{H} & \text{O} & \text{N} \\ 22 & 28 & 4 & 2 \end{smallmatrix}$ requires: C, 68.72; H, 7.34; N, 7.29%). Light absorption in ethanol: λ_{max} . 3345Å (ϵ 57500).

(2) (-)Brucine was purified by recrystallisation from acetone.

The p-carboxyphenylhydrazine (8.1g.) was added to suspension of (-)brucine (8.25g.) in methyl ethyl ketone (40c.c.) at reflux temperature. After one minute, a homogeneous solution was obtained. The volume of the solution was reduced to 20c.c. Three crops (A, B and C) of the solid (-)brucine salt were obtained as follows:

1st Crop (A). The above solution was stood overnight at 0°. The Brucine salt separated as a light yellow solid, m.p. 137-140°, $[\alpha]_D^{25}$ -190°. (Found: N, 6.85%. $\begin{smallmatrix} \text{C} & \text{H} & \text{N} & \text{O} \\ 45 & 54 & 4 & 8 \end{smallmatrix}$ requires: N, 7.2%). Light absorption in ethanol; λ_{max} . 3445Å (ϵ 42500). The infrared spectrum showed no diffuse band in the region 2500-3500cm⁻¹, but had bands at

1720(m), 1650(m) and 1600(s) cm^{-1} .

2nd Crop (B). After evaporation of most of the methyl ethyl ketone from the filtrate, a further amount of solid (1.51g.) optically identical with (A), separated from acetone.

3rd Crop (C). The filtrate was again evaporated and the residue crystallised from petrol/ether to give a salt which had $[\alpha]_D^{20} 0$, m.p. 141-3°.

No further solid material could be isolated from the mother liquor remaining after the third crop of brucine salt had separated. This mother liquor (designated as X) was red-black in colour, probably due to decomposition of the carboxyphenylhydrazone anion.

The recrystallisation of the combined fractions A and B from acetone did not change the optical rotation; the octalone was regenerated from the product (D, 3.0g.) of this recrystallisation as described below.

(3) Regeneration of the octalone.

The brucine salt (D, 3.0g.) was distributed between hydrochloric acid and ether and the ethereal layer was washed with hydrochloric acid and evaporated. The residue was heated under reflux for 5 hours with pyruvic acid (8.0c.c.) in ethanol (70c.c.). The reaction mixture

was poured into water and extracted with ether. Evaporation of the ethereal solution gave the crude octalone (500mg.) which was distilled at 0.05mm. to give a sample of pure octalone having $[\alpha]_D^{EtOH} -100^\circ$. The 2,4-dinitrophenylhydrazone from ethanol had m.p. 159-161 $^\circ$, $[\alpha]_D^{EtOH} -300^\circ$.

The mother liquors (X) were treated in a similar manner to give crude octalone (900mg.) which on distillation gave pure octalone having $[\alpha]_D^{EtOH} +60^\circ$.

Alkylation of 10-carbethoxy-7,7-dimethyl- Δ -octalin-2-one¹⁽⁹⁾ with n-propyl iodide.

Isopropanol was dried by standing over potassium carbonate, heating under reflux for 6 hours over calcium turnings and then fractional distillation. The fraction b.p. 79-80 $^\circ$ was used in the following experiment.

The procedure detailed below was also used in all the other attempted alkylations of the octalone which are described in subsequent experiments.

(a) Potassium (0.253g.) was dissolved in isopropanol (10c.c.) under nitrogen and the excess alcohol distilled off; the last traces of alcohol were removed by heating at 120 $^\circ$ /14mm. for 40min. The potassium isopropoxide so

obtained was dissolved in dry benzene (40c.c.), 10-carbethoxy-7,7-dimethyl- $\Delta^{(9)}$ -octalin-2-one (1.53g.) was added and the solution heated at reflux temperature under nitrogen for 30min. during which a cloudy red colour developed. Dry, freshly distilled n-isopropyl iodide (1.07g.) was added and the mixture maintained at reflux temperature for a further 24 hours. Acetic acid (1c.c.) and benzene (50c.c.) were added and the benzene solution washed with sodium carbonate solution and water. Acidification of the carbonate washings and extraction with ether yielded only a small quantity of acidic material (50mg.) which was not further investigated. Evaporation of the benzene layer gave a red oil (1.55g.). Light absorption in ethanol: $\lambda_{\text{max.}} 2440\text{\AA}^{\circ}$ (ϵ 12000).

(b) A second alkylation of the octalone (1.05g.) with n-propyl iodide (0.65g.) was carried out, using the conditions described above with the exception that the octalone in benzene (2c.c.) was added immediately after the dissolution of the potassium (0.19g.) in isopropanol (10c.c.) without removal of the excess isopropanol. The subsequent reaction was therefore conducted in isopropanol at reflux temperature. The resulting product showed light absorption in ethanol: $\lambda_{\text{max.}} 2240\text{\AA}^{\circ}$ (ϵ 12000).

The combined products of reactions (a) and (b) were chromatographed on alumina:

(1) Elution with petrol/20% benzene gave a colourless oil (77mg.), probably 7,7-dimethyl-1-(n-propyl)- $\Delta^{(9)}$ -octalin-2-one. The infrared spectrum had bands at 1670cm⁻¹ (s) and 1610cm⁻¹ (m) but no bands at 1710cm⁻¹ and 860cm⁻¹.

(11) Further elution with petrol/20% benzene gave 10-carbethoxy-7,7-dimethyl-1-di(n-propyl)- $\Delta^{(9)}$ -octalin-2-one (100mg.) as a colourless oil, b.p. 140° (air bath)/0.01mm. (Found: C, 75.30; H, 10.34. C₂₁H₃₄O requires: C, 75.40; H, 10.25 %). Light absorption in ethanol: no maximum in the range 2300-2500Å. The infrared spectrum had a single intense band in the carbonyl region at 1715cm⁻¹ and a band at 1205cm⁻¹, but no band at 860cm⁻¹. The 2,4-dinitrophenylhydrazone could not be prepared.

(111) Elution with petrol/50% benzene gave 10-carbethoxy-7,7-dimethyl-1-(n-propyl)- $\Delta^{(9)}$ -octalin-2-one (800mg. 33%) (Found: C, 74.53; H, 10.13. C₁₈H₂₈O requires: C, 73.93; H, 9.65 %) Light absorption in ethanol: λ_{max} 2480Å (ϵ 11000). The infrared spectrum had bands at 1715(s), 1665(s) and 1665(s) and 1610(w), but no band at 860cm⁻¹. The 2,4-dinitrophenylhydrazone crystallised from ethanol as bright red plates, m.p. 140-141°, depressed on admixture with the 2,4-dinitrophenylhydrazone

of unalkylated octalone (F13) (Found: C, 60.59; H, 6.91; N, 12.02; $C_{24}H_{32}N_4O_6$ requires: C, 61.00; H, 6.83; N, 11.86%). Light absorption in ethanol: λ_{max} 3835 Å ($\epsilon = 30,500$).

(IV) Further elution with petrol-benzene gave unchanged 10-carbethoxy-7,7-dimethyl- $\Delta^{1(9)}$ -octalin-2-one (550 mg.).

1(9)

Attempted alkylations of 10-carbethoxy-7,7-dimethyl- Δ -octalin-2-one with the methylene bromide (Fl).

a) Using potassium tert-amylate in toluene.

Potassium (0.12 g.) was dissolved in tert-amyl alcohol (10 c.c.) and the excess of alcohol was completely removed at 180 (14 mm.). The remaining potassium tert-amylate was dissolved in toluene (20 c.c.); the octalone (0.72 g.) and the bromide (1.0 g.) were added; and the mixture was boiled under reflux for 14 hours. The product was isolated by the method used in previous alkylations. Its infrared spectrum showed a strong band due to hydroxyl, but only weak bands at 1725 cm⁻¹. Chromatography gave only the bromide (0.6 g.), impure octalone in low yield, and, on elution with ether, hydroxylic material which was not further investigated.

b) Using potassium isopropoxide in benzene.

The octalone (0.56 g.), the bromide (0.65 g.), and potassium isopropoxide (from 0.1 g. potassium) were heated in boiling benzene, the experimental procedure being the same as that for alkylations with n-propyl iodide (vide supra). The crude product in ethanol absorbed at 2375 A ($\epsilon = 10,000$). The infrared spectrum had a strong band at 360 cm⁻¹. Chromatography gave only unchanged starting material. The same result was obtained when the alkylation was carried out

in isopropanol.

Alkylation of 10-carbethoxy-7,7-dimethyl- $\Delta^{1(9)}$ -octalin-2-one with the methylene iodide (F1).

The iodide was obtained as described in section I of this thesis, and probably contained ca. 10% of the corresponding bromide. Using the experimental procedure already described, the octalone (F13) (0.78 g.) was made to react with the iodide (F1) (0.7 g.) in boiling isopropanol (20 c.c.), in the presence of potassium isopropoxide (from 0.15 g. potassium). After 14 hours the product was chromatographed on alumina. Elution with petrol/10% benzene gave three very viscous gums. These were (in the order in which they were eluted):

A. (40 mg.); possibly one of the enantiomorphous tetracyclic ketones (F2) and (F3) (Found: C, 80.62; H, 10.39; $C_{31}H_{48}O_3$ requires: C, 79.49; H, 10.44%). $[\alpha]_D^{EtOH} = -36^\circ$. Light absorption in ethanol: λ_{max} 2410 Å ($\epsilon = 19,000$). The infrared spectrum (liquid film) had bands at 3060, 1725(s), 1640(s), 1625(m), 869(m) and 890 cm^{-1} .

B. (69 mg.), identified as the decarboxylated tetracyclic ketone (F28) (Found: C, 85.34; H, 11.60; $C_{28}H_{44}O$ requires: C, 84.85; H, 11.11%). Light absorption in ethanol: λ_{max} 2500 Å ($\epsilon = 10,000$). The infrared spectrum (CCl_4) showed a

single band in the carbonyl stretching region at 1684 cm^{-1} , and one at 884 cm^{-1} ; the spectrum of a liquid film showed no band at 860 cm^{-1} .

C. (60 mg.); possibly the enantiomorph of A (Found: C, 79.49; H, 10.25; $\text{C}_{31}\text{H}_{48}\text{O}_3$ requires: C, 79.96; H, 10.44%). $[\alpha]_D^{\text{EtOH}} = +150^\circ$. Light absorption in ethanol: $\lambda_{\text{max}} 2480\text{ \AA}$ ($\epsilon = 13,000$). The infrared spectrum showed bands at $3070(\text{w})$, $1725(\text{s})$, $1640(\text{s})$, $1630(\text{shoulder})$, $1590(\text{w})$, $900(\text{m})$ and $880(\text{m})\text{ cm}^{-1}$.

An alkylation of 10-carbethoxy-7,7-dimethyl- $\Delta^{1(9)}$ -octalin-2-one with the bromide (Fl) using diglyme as solvent.

For method see Zook and Russo ¹⁸.

Potassium (0.23 g.) was added to a mixture of t-amyl alcohol (50 c.c.) and diglyme (50 c.c.). When, after 1 hr., all the metal had dissolved, the volume of the solution was reduced by evaporation to 10 c.c. Diglyme (100 c.c.) was added and the solution was warmed to 90° . Addition of the octalone (0.67 g.) gave a deep red colour almost immediately. After 30 min. the bromide (0.83 g.) was added and the mixture was stirred at 100° for 12 hr., during which time potassium bromide was precipitated. Acetic acid (0.5 c.c.) was then added, the solution evaporated under reduced pressure, and

the residue taken up in ether. The ethereal solution was washed repeatedly with N hydrochloric acid, then with sodium carbonate solution and water. Evaporation of the ether left an oil (1.14 g.) which was chromatographed on alumina. The products A, B and C were eluted as in previous experiments, in the following amounts:

A, 320 mg.;

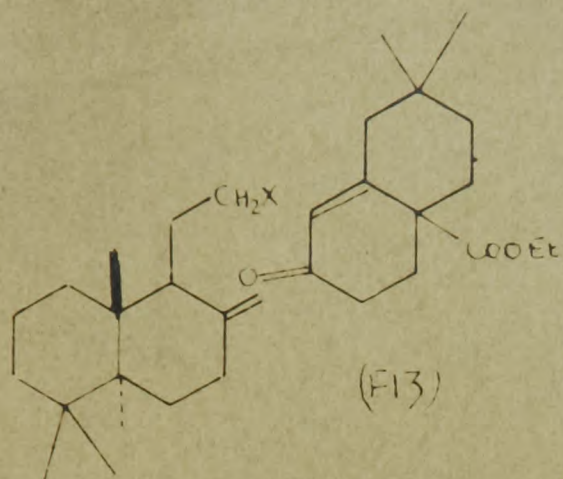
B, 60 mg.;

C, 170 mg.

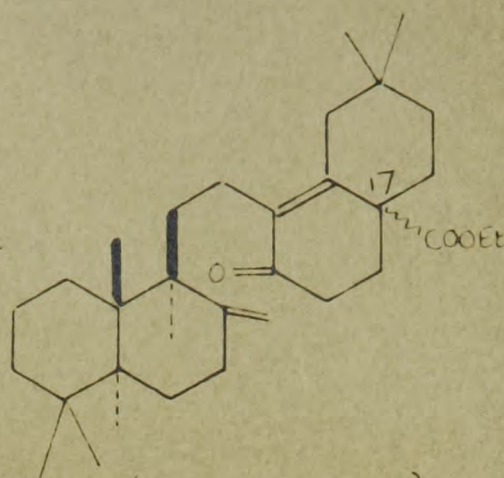
Attempts to prepare the 2,4-dinitrophenylhydrazones and oximes failed.

References to Section II

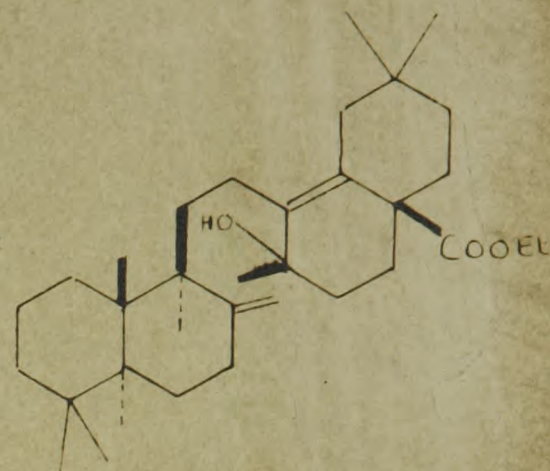
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17. Anchel and Scoenheimer, J.Biol.Chem., 1936, 114, 543.
18. Zook and Russo, J.Amer.Chem.Soc., 1960, 82, 158.



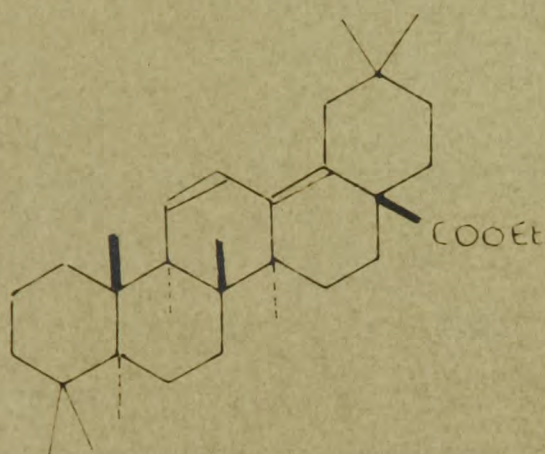
(F1, $\text{X} = \text{Bn}$ or I)



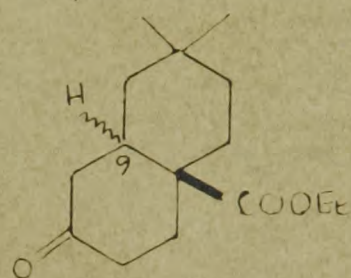
(F2, $17\alpha\text{-COOEt}$)
(F3, $17\beta\text{-COOEt}$)



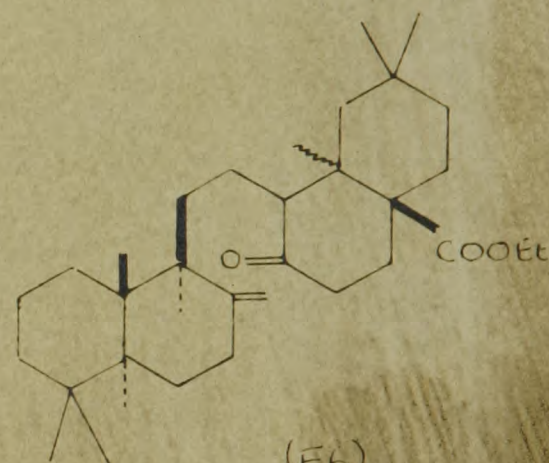
(F4)



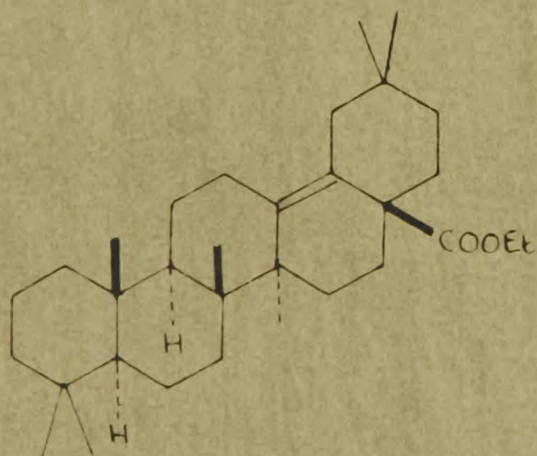
(F5)



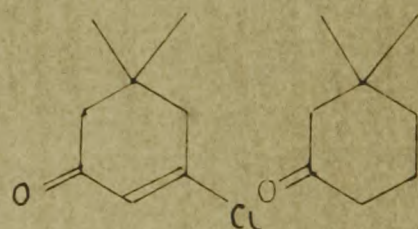
(F8, $9\beta\text{-H-CIS}$)
(F9, $9\alpha\text{-H-TRANS}$)



(F6)



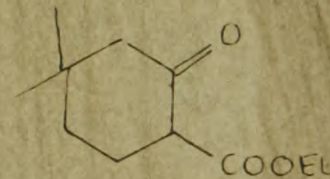
(F7)



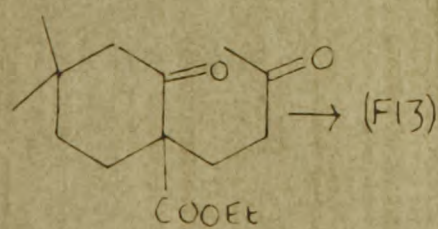
(F10)



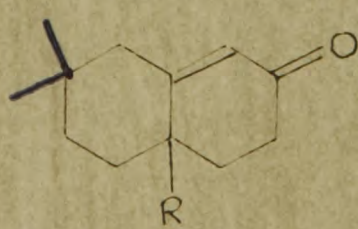
(F11)



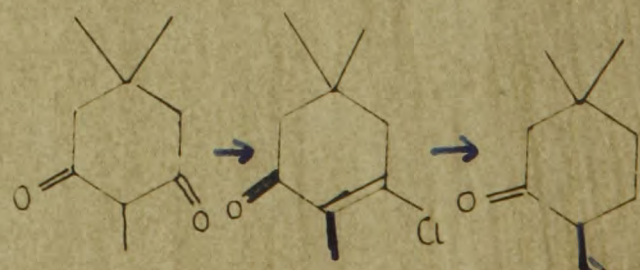
(F12)



(F13A)



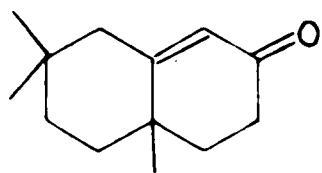
(F14, $\text{R} = \text{COOH}$)
(F14a, $\text{R} = \text{CH}_2\text{OH}$)



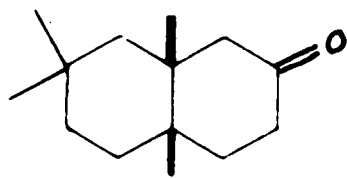
(F15)

(F16)

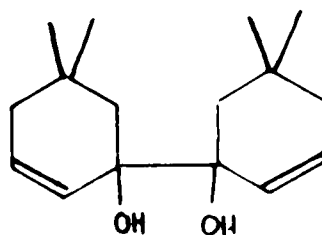
(F17)



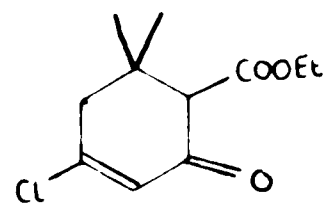
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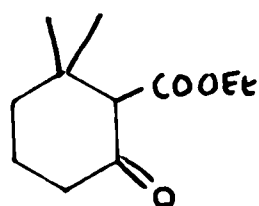
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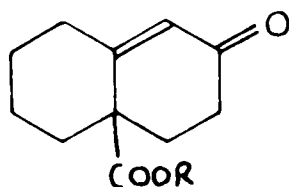
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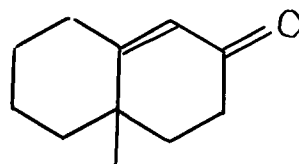
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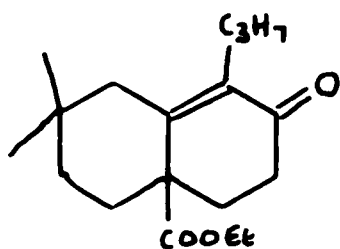
(F22)



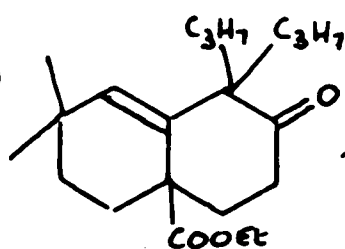
(F23, R = H)
(F24, R = Et)



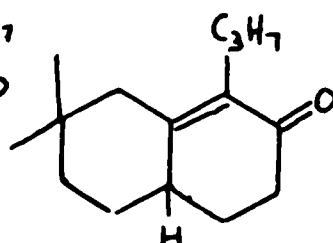
(F30)



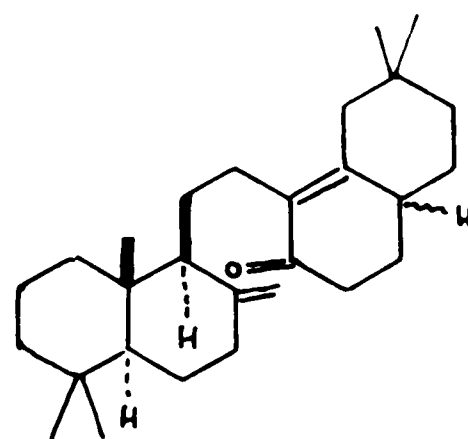
(F25)



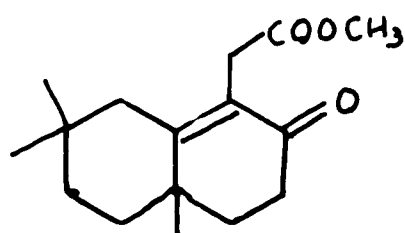
(F26)



(F27)



(F28)



(F29)