A Thesis

entitled

" Studies in the Terpenoid Field "

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by S.G. McGeachin, B.Sc.

Chemistry Department

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ProQuest LLC.
789 East Eisenhower Parkway
P.O. Box 1346
Ann Arbor, MI 48106 – 1346

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Part I

The Chemistry of Cedrelone.

The C_{26} Modified Triterpenes

The following section of this thesis describes the chemistry of the natural product cedrelone, and its rationalisation in terms of the expression (A 1). Inspection of this structure points to a close biogenetic relationship with limonin (A 2), and by way of background, therefore, a brief review of this small, but growing, class of C_{26} modified triterpenes is initially presented.

The structure of limonin was deduced simultaneously from the elegant chemical work of Arigoni, Barton, Corey, Jeger and their collaborators[1], and by an X-ray study of epilimonol iodoacetate (A 8; R = O.$COCH_2I$; R' = H), which in addition gave the relative stereochemistry of the molecule.[2] The absolute stereochemistry as shown in (A 2) was based on the similarity of the optical rotatory dispersion curve of limonin to that of a 7-oxo steroid.

More recently the bitter principles obacunone (A 3) and nomilin (A 4) have been related to limonin by the conversion of each to a common degradation product in the following manner.[3] Limonin on Meerwein-Ponndorf reduction gave limonol (A 8; R = H; R' = OH), which had an axial hydroxyl group in keeping with its mode of formation. Whereas epilimonol was recovered unchanged from treatment with aqueous base, limonol underwent a profound rearrangement, with loss of β-furfuraldehyde and the formation of merolimonol (A 9). This novel reaction, peculiar to the axial alcohol, has been rationalised by postulating

opening of the epoxide ring to give the trimethylene oxide (A 16), sterically possible only for the α-epimer. This then undergoes base-catalysed loss of β-furfuraldehyde as shown, with the formation of the hydroxy-acid (A 17), which lactonises to merolimonol on acidification. Dehydration, followed by catalytic hydrogenation of the product led to tetrahydroanhydromerolimonol (A 10). Vigorous treatment of this with barium hydroxide opened the ring A lactone with concomitant epimerisation at C_1 to give the hydroxy-acid (A 11). This epimerisation is envisaged as occurring by β-elimination to form the αβ-unsaturated acid (A 18) followed by recyclisation to the more stable epimer (A 19). The hydroxymethyl group at C_{10} was converted to a methyl group by a series of standard reactions, which involved formation of the C_{10} methanesulphonate, treatment of this with sodium iodide, and hydrogenolysis of the resulting iodo-compound with zinc in acetic acid to give (A 12). By a similar sequence of reactions isopropyl epi-isoobacunolate (A 13), the Ponndorf reduction product from methyl epi-isoobacunoate (A 14; R = Me), which was formed from obacunone as shown, was degraded to methyl tetrahydroanhydroepi-meroobacunolate. This proved to be identical with (A 12) from which followed the structure of obacunone as (A 3), where only the configuration at the poim of attachment of the furan ring remains to be determined. Since nomilin loses acetic acid on treatment with a tertiary amine to give obacunone, it must therefore have the structure (A 4).

Two other compounds for which structures have been reported in this as yet small class of natural products are gedunin[4, 5], and khivorin[6]

These occur in the West African timbers Entandrophragmin angolense and Khaya ivorensis respectively, both of which belong to the Meliaceae.

Gedunin, $C_{28}H_{34}O_7$, is an αβ-unsaturated ketone. On sodium borohydride reduction it affords a tetrahydro derivative, in which the enone function has been reduced to the saturated alcohol. A recent X-ray crystallographic examination of the corresponding iodoacetate has defined the structure (A 20; R = H) for this alcohol, dihydrogedun-3β-ol.[4] It therefore follows that gedunin has the structure (A 21). The absolute stereochemistry depicted was deduced from the observation that the molecular rotation difference for the conversion of gedunin to deoxygedunin (A 22) by chromous chloride, was close in value to the corresponding change for reduction of limonin to deoxylimonin.[5]

Khivorin, $C_{32}H_{42}O_{10}$, possessed the infra-red and ultra-violet characteristics of a furan, and had no hydroxyl groups. After steam-distillation from alkali β-furfuraldehyde and a hydroxy-lactone, khivol $C_{21}H_{32}O_5$, were isolated. If khivorin has three acetoxyl groups, a furan ring, an epoxide , and a δ-lactone then it must be tricarbocyclic, and in conjunction with the above reaction it was postulated to have the part structure (A 23), in which only two of the acetoxyl groups remain to be placed. The " merolimonol " reaction is dependent among other things on the presence of the epoxide ring, and on hydrolysis of deoxykhivorin, the chromous chloride reduction product, a trisdeacetyl derivative was obtained. This, on oxidation, afforded a triketone whose ultra-violet characteristics indicated that two of the carbonyl groups were β with respect to one another. This permitted the

placing of the remaining two acetoxyl groups at C_1 and C_3 on the normal tetracyclic triterpene skeleton. The structures (A 24, 25, 27, and 28) for khivorin, trisdeacetyldeoxykhivorin, khivol, and the triketone followed. Support for this structure for khivorin was obtained by ozonolysis of trisdeacetyldeoxykhivorin (A 25) to the trisnor-acid (A 26).

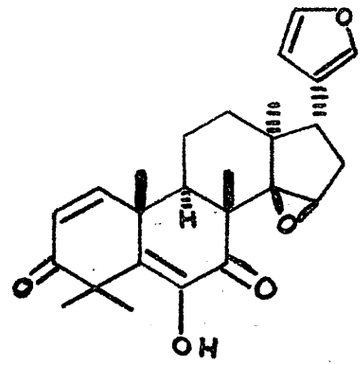
Recently in these laboratories a lactone, cedrelide $C_{26}H_{30}O_6$, has been isolated from Cedrela mexicana.[7] The infra-red and ultra-violet spectra, and the close resemblance of the relevant portions of the nuclear magnetic resonance spectrum to that of cedrelone suggest that it has the structure (A 7), and is yet another C_{26} modified triterpene. The structures assigned to khivorin and cedrelide cannot be said as yet to have been rigorously established. It would, however, be difficult to find alternative structures for either which would both accomodate the chemical observations, and the presumed biogenetic relationship to limonin.

It can be seen that those members of this class of natural products whose structures have been precisely defined, namely limonin, obacunone, nomilin, gedunin, and cedrelone have certain structural and stereochemical features in common. Thus they all have a β-substituted furan ring, a β-epoxide ring between C_{14} and C_{15}, a β-methyl group at C_8, and an oxygen substituent attached to C_7. From a consideration of the constitution and stereochemistry of limonin, Barton has been led to propose that it is biogenetically derived from a precursor possessing the carbon skeleton and stereochemistry of euphol .[8] This skeleton

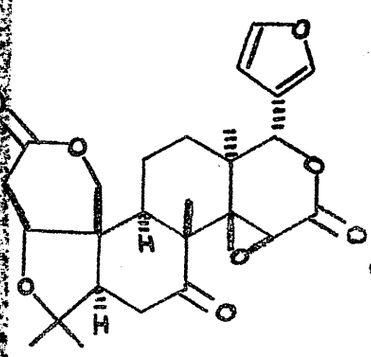
and stereochemistry are believed to originate in cyclisation of all trans squalene in its chair-chair-chair-boat conformation, as shown. The cyclisation is initiated by the attack of OH^+, or its equivalent, and proceeds in a synchronous trans-anti-planar fashion to the final carbonium ion (A 30). This is then stabilised by interaction with the solvent medium, or by a series of consecutive 1,2-shifts of suitably aligned trans-anti-parallel methyl groups and hydrogen atoms, which terminates in the eventual loss of a proton from C_9 to give euphol, or from C_7 to give butyrospermol. Similar cyclisations for other conformations of squalene, followed by the appropriate Wagner-Meerwein migrations have been postulated to lead to all the known skeletal types in triterpenes. Evidence for the synchronous nature of the cyclisation and its initiation through the medium of OH^+, or its equivalent, has been obtained from the tracer studies carried out on the cyclisation of squalene to lanosterol.[10] Attack at C_7 in a derivative of butyrospermol (A 31) by OH^+ then leads to the intermediate (A 32) by means of a methyl migration from C_{14} to C_8 with concomitant loss of a proton from C_{15}. A chemical analogy for this is to be found in the observed formation of 7-oxoapoeuphenyl acetate (A 34) by oxidation under mild conditions of dihydrobutyrospermyl acetate (A 33).[11] The intermediate (A 32) has the requisite functionality for its conversion to any of the known C_{26} triterpenes by biologically unexceptional pathways. Thus allylic oxidation at C_{16}, followed by a Baeyer-Villiger reaction and epoxidation of the double bond gives rise to the common epoxy-δ-lactone function. Cleavage of the side-chain between C_{23} and

C_{24}, followed by oxidative cyclisation of the remainder leads to the furan ring. Further oxidation in ring A leads to gedunin and khivorin. Alternatively cleavage of ring A, which has its precedents in the structures of nyctanthic[12, 13] and dammarenolic[12] acids (A 35 and A 36 respectively) followed by oxidative cyclisation of C_3 on to C_{19}, and of C_4 to C_1 provides limonin.

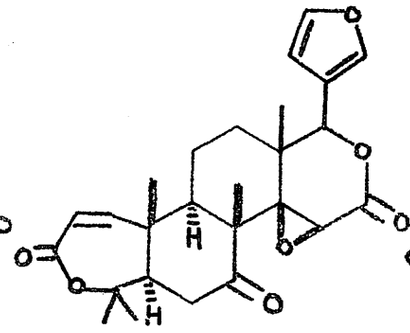
Biogenetically cedrelone is of some interest in that it is the sole member of the class to possess an intact ring D. It is also novel in being a diosphenol, a structural feature of rare occurrence in nature.



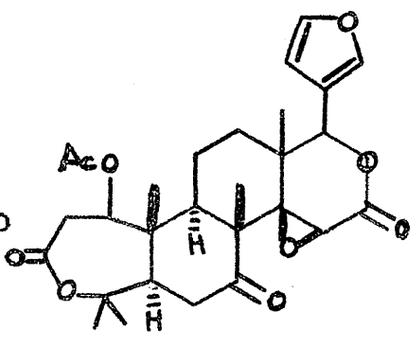
Cedrelone (A1)



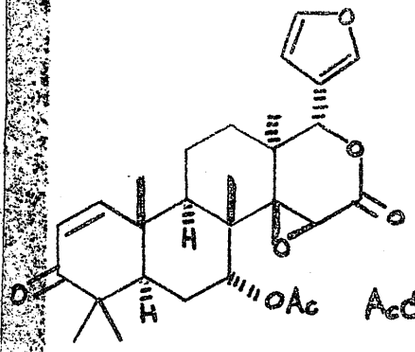
Limonin (A 2)



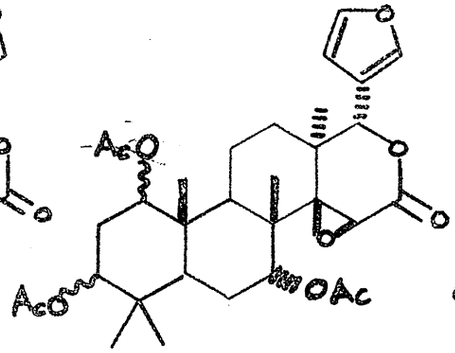
Obacunone (A 3)



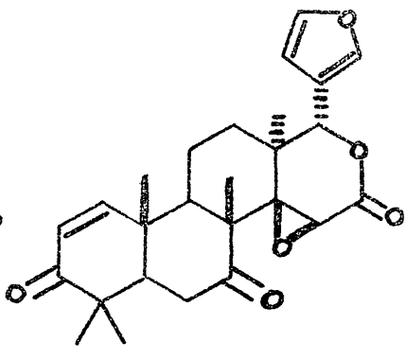
Nomilin (A 4)



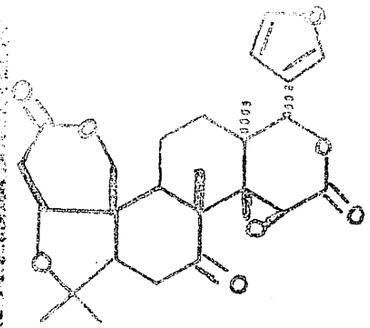
Gedunin (A 5)



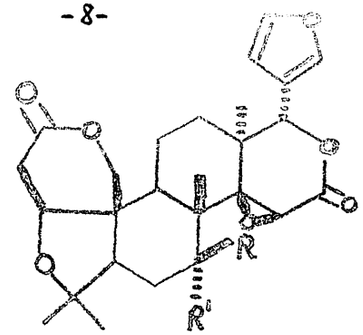
Khivorin (A 6)



Cedrelide (A 7)



Limonin



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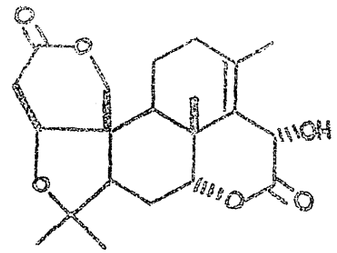

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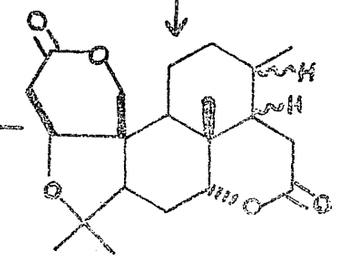

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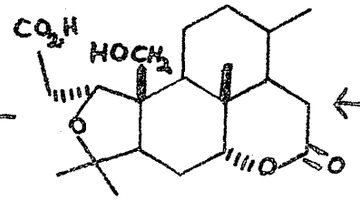

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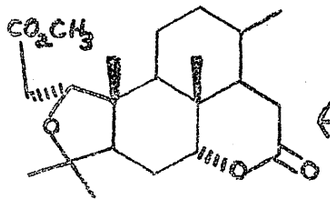

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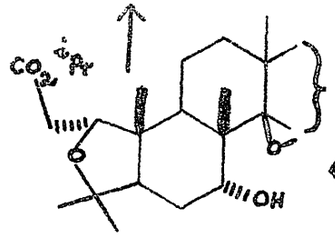

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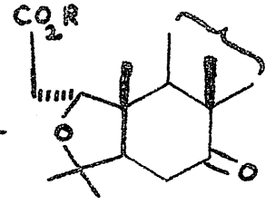

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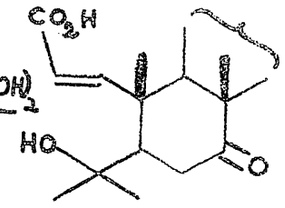

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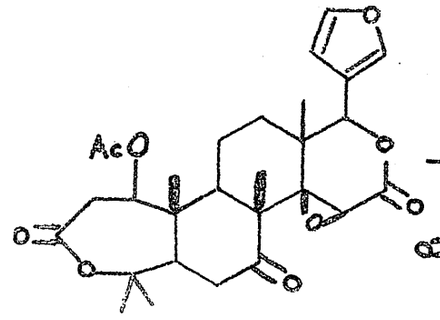
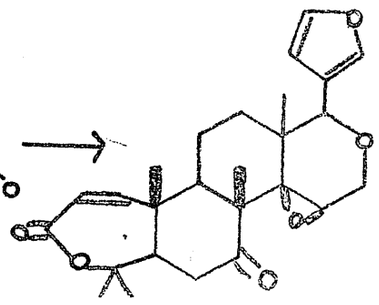
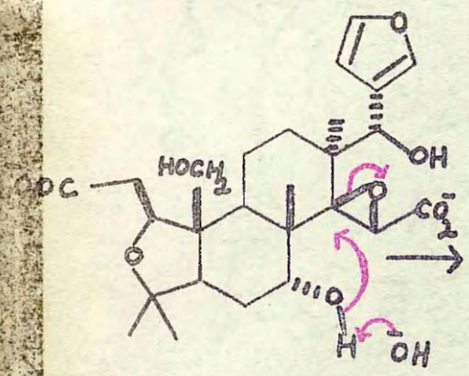


Nomilin



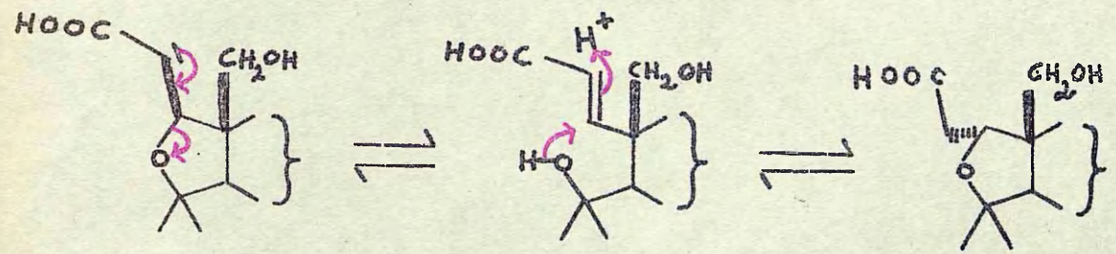
Obacunone



Limonol in base

(A 16)

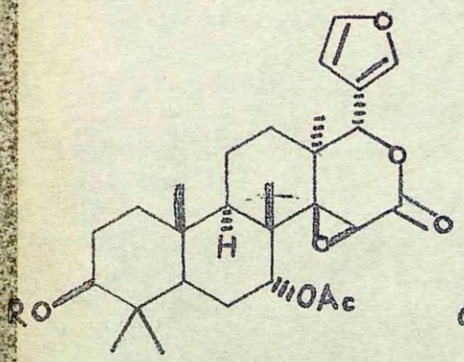
(A 17)



Tetrahydroanhydro-merolimonol (A 10) in base

(A 18)

(A 19)



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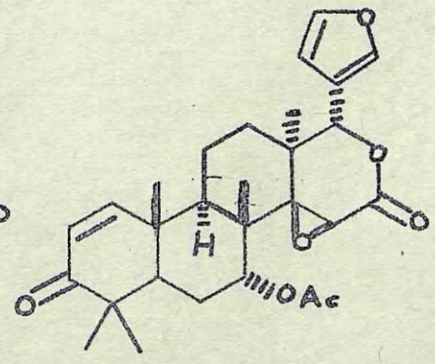
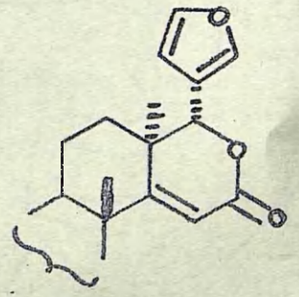


Gedunin (A 21)



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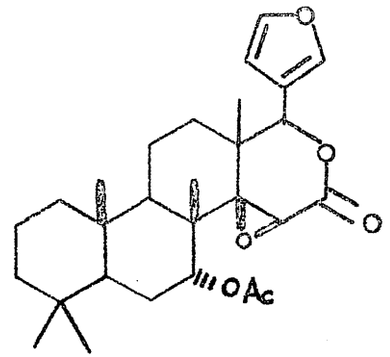

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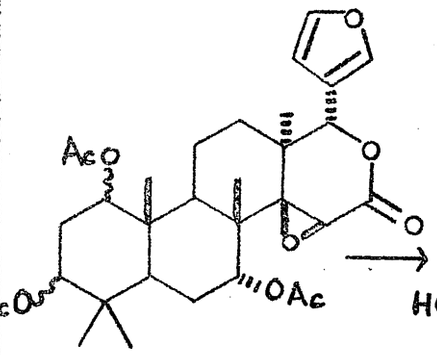
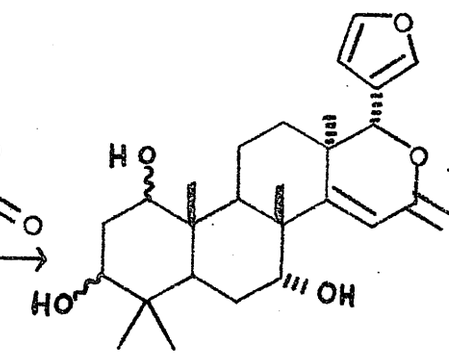
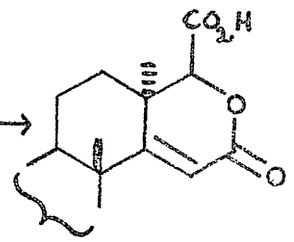


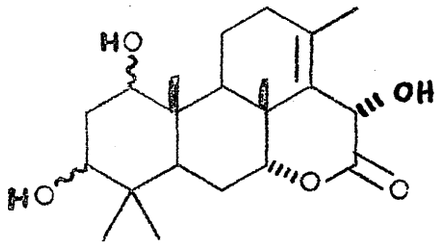




Khivorin (A 24)

(A 25)

(A 26)



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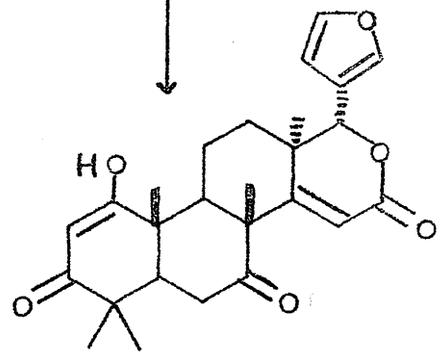

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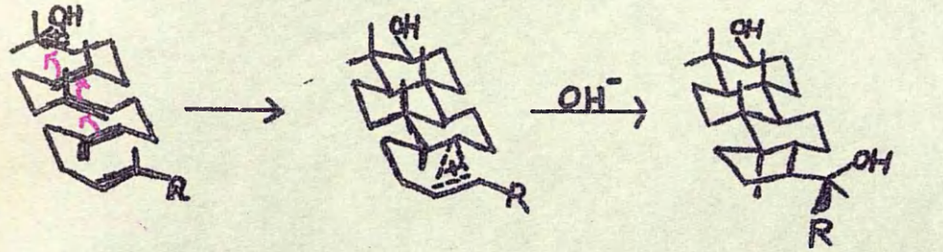
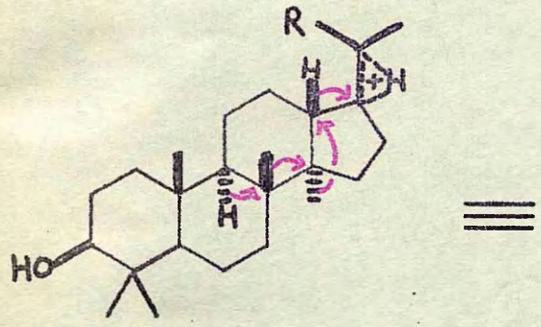
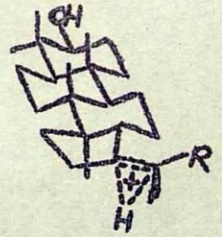


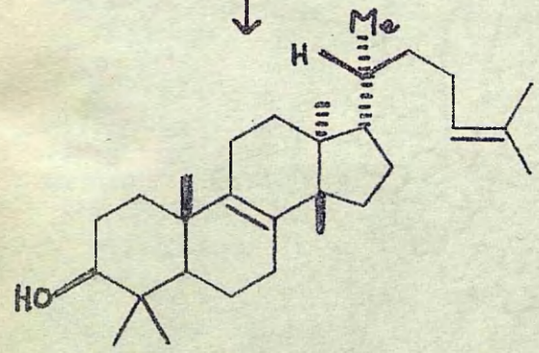
(A 29)

(A 30)

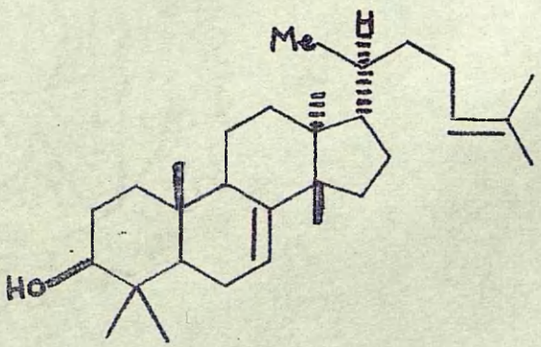
Dammarendiol II



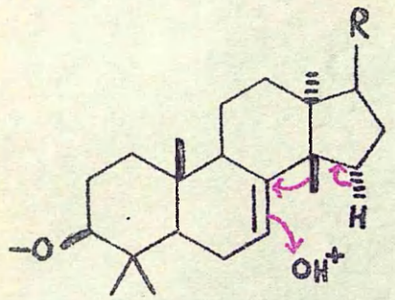




Euphol



Butyrospermol



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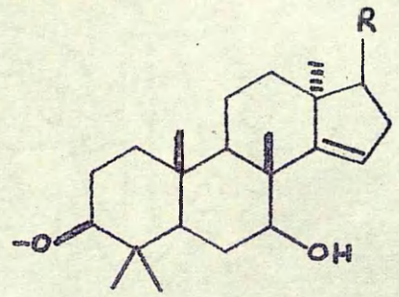

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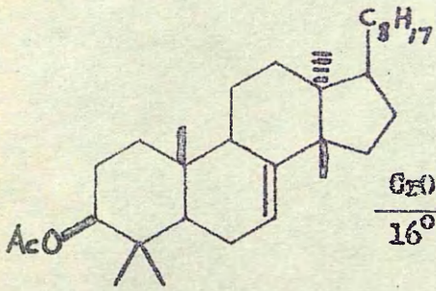

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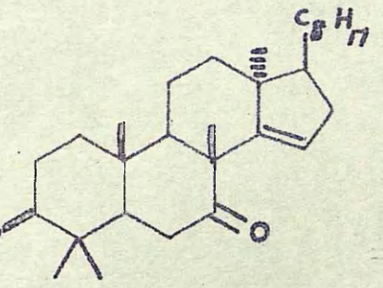

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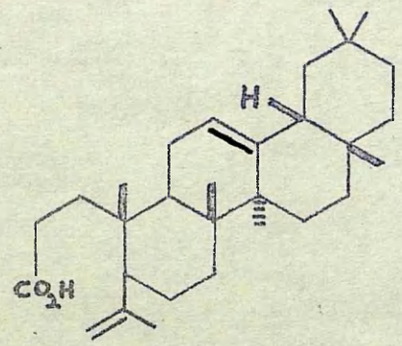
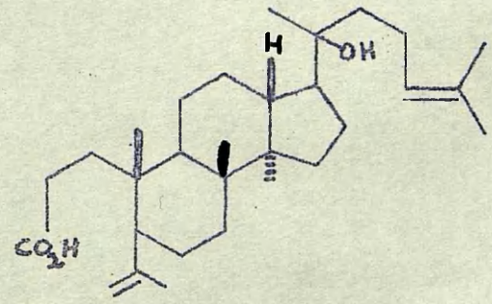


Nyctanthic Acid (A 35)



Dammarenolic Acid (A 36)

The Chemistry of Cedrelone

The isolation of the natural product, cedrelone, was first reported by Parihar and Dutt, who obtained it along with an essential oil by benzene extraction of the heartwood of Cedrela toona Roxb.[14] This species, belonging to the natural order of Meliaceae, is a tree of mahogany type which occurs abundantly in the foot-hills of the Himalayas, and is extensively used in India for the manufacture of furniture. The above workers assigned the formula $C_{25}H_{30}O_5$ to cedrelone. On the basis of some colour tests, and the formation of an acetate, an oxime, and a dibromide they considered it to be phenolic and to possess a ketonic carbonyl group, an ethylenic double bond, and a $\beta\gamma$-unsaturated lactone ring.

Repetition of the Indian workers' isolation procedure gave cedrelone without difficulty as a highly crystalline colourless substance which, in contrast to the analogously constituted " bitter principles ", is quite tasteless. Elemental analysis and an accurate mass-spectrometric determination of the molecular weight immediately showed that the previous molecular formula had to be amended to $C_{26}H_{30}O_5$.

The spectral properties of cedrelone and its simple derivatives were in good agreement with the functional groups present, and are described in some detail since they provided values, characteristic of certain functional groups, which were of considerable use in determining the structures of many of the transformation products. Thus, in the infra-red spectrum, three bands at 3130w, 1505w, and 878s $cm.^{-1}$

characteristic of the furan ring were present. A peak in the carbonyl region at 1678 cm.$^{-1}$, carrying an inflection at 1685 cm.$^{-1}$ indicated the two unsaturated carbonyl groups in the molecule. In addition, the presence of a hydroxyl group was shown by a band at 3425 cm.$^{-1}$ The position of this band and its insensitivity to dilution indicated that the diosphenol hydroxyl was intramolecularly hydrogen bonded to the adjacent carbonyl function. The ultra-violet spectrum of cedrelone had $\lambda_{max.}$ 217 mμ (ε 11,800) consistent with a summation of furan and ring A enone chromophores, and a maximum at 279 mμ (ε 9,100) shifting in base to 327 mμ (ε 5,530) which was particularly characteristic for the diosphenol function. The position and intensities observed for cedrelone and other diosphenols in the series were in good agreement with those observed for diosphenol (B 1), [$\lambda_{max.}$ 274 mμ (ε 11,000)][15] and limonin diosphenol (B 2), [$\lambda_{max.}$ 278 mμ (ε 10,000), shifting in base to 336 mμ (ε 6,150)][8], in which the diosphenol has an environment similar to that in cedrelone.

On acetylation cedrelone readily gave a monoacetate (B 5; R = Ac) and similarly a chloroacetate. Cedrelone acetate had bands in the infra-red at 1770 cm.$^{-1}$, highly characteristic for the enol acetate carbonyl, and 1702 cm.$^{-1}$, associated with the two enone carbonyls. The shift to higher frequency of the diosphenol carbonyl after acetylation can be attributed mainly to removal of the hydrogen bonding. The ultra-violet spectrum had maxima at 222 mμ (ε 16,400) with an inflection at 245 mμ (ε ca. 8,000), and 320 mμ (ε 170), in agreement with the normal neutralisation of the bathochromic effect of the hydroxyl in a

α-hydroxyenone after acetylation.[16] The successful hydrolysis of cedrelone acetate back to cedrelone was found to be very dependent upon the reaction conditions, owing to the lability of cedrelone itself in base (vide infra). The ready chloroacetate formation led in turn to the preparation of the crystalline iodoacetate which was submitted to the X-ray department for structural examination while the chemical work was proceeding. This led rapidly to the determination of the structure and relative stereochemistry of cedrelone as (B 5; R = H).[17] The chemistry of cedrelone as described herein was fully consistent with this constitution.

On treatment with dimethyl sulphate and alkali cedrelone afforded the corresponding methyl ether (B 5; R = Me).

Catalytic hydrogenation of cedrelone under mild conditions led to to the formation of a dihydro-derivative (B 3; R = H), [$\lambda_{max.}$ 210 mμ (ε 6,100) and 279 mμ (ε 9,938), $\nu_{max.}$ 1712, 1677 cm.$^{-1}$], in which the double bond in ring A had been saturated. The ultra-violet subtraction curve of dihydrocedrelone from cedrelone had $\lambda_{max.}$ 225 mμ (ε 8,100) which is the contribution of the enone chromophore in ring A to the total ultra-violet absorption of cedrelone. By the use of platinum in acetic acid hydrogenation proceeded farther to a hexahydro-derivative (B 4; R = H) in which the furan ring was also reduced.

The diosphenol function in cedrelone was found to be completely resistant to quinoxaline formation under a variety of conditions. A number of attempts were made to cleave it to the dicarboxylic acid (B 6) by the use of reagents, standard for the oxidative cleavage

of α-diketones. Cedrelone was recovered unchanged from treatment with sodium periodate. With lead tetra-acetate it afforded a yellow, crystalline compound, which proved to be unstable on standing and for which no satisfactory analysis was ever obtained. On the basis of its spectral properties, and the known behaviour of the reagent we have very tentatively assigned the structure (B 7) to it. Thus its infra-red spectrum showed no hydroxyl absorption and had bands at 1744 and 1240 cm.$^{-1}$ (acetate C:O and C.O respectively), a broad intense band centred at 1690 cm.$^{-1}$ (-CO.CO- and enone carbonyl), bands at 3100, 1500 and 874 cm.$^{-1}$ (furan ring), and one at 680 cm.$^{-1}$ (cis double bond). Its ultra-violet spectrum, [$\lambda_{max.}$ 215 mμ (ε 11,500), 273 mμ (ε 5,100), and 433 mμ (ε 34)], with the exception of the maximum at 273 mμ . was consistent withe presence of the furan and enone chromophores, and with that of an unenolised α-diketone.[18] Whereas cedrelone had completely reacted within two minutes with a little over one molecular proportion of the reagent, cedrelone acetate was recovered unchanged after one day. Acetoxylation α to a carbonyl group by lead tetra-acetate is not unprecedented.[19]

Attempted cleavage of the diosphenol by the action of hydrogen peroxide and alkali led to the isolation of a neutral compound, $C_{26}H_{30}O_6$. This was formulated as the epoxide (B 8; R = H), since its ultra-violet spectrum, [$\lambda_{max.}$ 201 mμ (ε 7,200), and 276 mμ (ε 10,700)], established the retention of the diosphenol function but loss of the ring A enone. The infra-red spectrum with carbonyl bands at 1719 (α-oxygenated cyclohexanone), 1681 cm.$^{-1}$ (diosphenol), and no absorption

below 700 $cm.^{-1}$ confirmed this. Subtraction of the ultra-violet spectrum from that of cedrelone gave $\lambda_{max.}$ 225 mμ (ε 7,300), in good agreement with the previous value estimated for this chromophore.

Parihar and Dutt reported the formation of a crystalline oxime from cedrelone on treatment with hydroxylamine hydrochloride and sodium acetate in refluxing acetic acid. In our hands this procedure afforded only amorphous solids which decomposed on attempted purification, and which had a number of the infra-red characteristics of the acid-catalysed rearrangement product from cedrelone (vide infra). However, oximation in pyridine-ethanol solution gave a nitrogen containing derivative, $C_{26}H_{33}NO_6$, whose formula showed it to be an adduct with hydroxylamine and not an oxime. It decomposed at the melting point with reformation of cedrelone and this, in conjunction with the spectral properties, [$\lambda_{max.}$ 211 mμ (ε 7,000) and 281 mμ (ε 9,300), $\nu_{max.}$ (Nujol) 3450s (hydroxyl), 3300 (N-H), 1695 (hydrogen bonded cyclohexanone), 1678 $cm.^{-1}$ (diosphenol)], indicated the structure (B 9) for it. The formation of β-hydroxylamino-oximes from αβ-unsaturated ketones on oximation is well known,[20] and the above adduct requires little further comment. It is, however, of interest to note that the carbonyl group at C_3 was resistant to oximation even after prolonged treatment with the reagent. A rather similar reaction, reported by Arigoni et al., is the base-catalysed addition of methanol to the enone system with formation of the methoxy-derivative (B 10).[21] This ready addition of nucleophiles to the enone system with saturation of the double bond may have its origin in the resulting reduction of the

strain inherent in the A-B ring system. An entirely analogous, and possibly unique reaction is to be found in the reduction of cedrelone with excess sodium borohydride at room temperature in aqueous dioxan, to the same dihydro-derivative as is obtained by catalytic hydrogenation. Reduction of the double bond in conjugated systems by sodium borohydride has been previously observed. The butenolide system of iresin (B 12) was reduced to the butanolide in dihydroiresin (B 13),[22] and conjugated nitro-alkenes give the saturated nitro-compounds.[23] In other cases known to us saturation of the double bond in an enone by sodium borohydride was accompanied by concomitant reduction of the carbonyl grouping. Thus, cholest-1-en-3-one gave cholestan-3β-ol, and androst-1,4-dien-3,17-dione gave androst-4-en-3,17-diol.[24] The system most closely comparable to cedrelone occurs in gedunin (B 14), which gives dihydrogedunol (B 15) on treatment with sodium borohydride under conditions in which only the double bond of cedrelone is reduced.[5] Drastic reduction of cedrelone to the triol (B 16) by borohydride has been reported.[21]

The failure of the ring A carbonyl of dihydrocedrelone to oximate, and its considerable resistance to borohydride reduction contrast strongly with the normal reactivity of the carbonyl function in 3-oxo-triterpenes, which readily undergo both of these reactions. The reasons for this are probable steric in origin. Ring A of cedrelone iodoacetate (B 5; R = $CO.CH_2I$) was observed to exist in the boat-like conformation rather than in the half-chair also available to it.[17] Although intermolecular forces in the crystal may play some part in

this, it is likely that this conformation is preferred since non-bonded interactions between the methyl groups on C_4 and the bulky substituent at C_6 are minimised. In the half-chair the C_4 α-methyl group eclipses this substituent.

A model of dihydrocedrelone shows that ring A can adopt either a chair (B 17) or one of two boat conformations (B 18 and B 19). A consideration of the non-bonded interactions associated with each of these suggests that much the preferred conformation will be the boat (B 18), since only in it is the severe eclipsed interaction between the C_4 α-methyl and the C_6 substituent absent. In this conformation the carbonyl group is shielded from attack on the β-face by the C_{10} methyl, and on the α-face by the pseudo-axial C_4 α-methyl group. Also, nucleophilic addition to the carbonyl would be energetically unfavourable as it requires that C_3 become tetrahedral, and the resulting intermediate would have a severe non-bonded interaction of the 1,4-" boat-flagpole " type between the C_3 β-substituent and the C_{10} methyl. Nucleophilic addition to the carbonyl group when ring A is in the chair conformation would be free from these objections, but, as has already been stated, this conformation is energetically the less favourable.

In contrast, Ourisson et al. have recently interpreted dipole measurements on some pentacyclic triterpene derivatives as indicating an equilibrium between chair and boat conformations for ring A in a ratio of about seven to three.[25] This would suggest that in general the chair conformation is slightly the more favoured in a normal 3-oxotriterpene. In this conformation there is easy access to the α-face of

the carbonyl group, and the tetrahedral intermediate produced by nucleophilic addition is of a strain-free chair cyclohexane type.

Treatment of cedrelone acetate with boron trifluoride etherate yielded an isomeric compound, isocedrelone acetate. Examination of its infra-red and ultra-violet spectra, [$\lambda_{max.}$ 210 mμ (ε 23,100), and 238 mμ (ε 26,300), $\nu_{max.}$ ($CHCl_3$) 3415, (hydrogen bonded hydroxyl) 1764 (diosphenol acetate), 1696 (cyclohexanone), 1667 (diosphenol carbonyl) $cm.^{-1}$], and comparison with those of cedrelone acetate established that the diosphenol and enone functions were still present, and that a hydroxyl group and a new chromophore had been introduced. Subtraction of the ultra-violet spectrum of cedrelone acetate from that of isocedrelone acetate showed this chromophore to have $\lambda_{max.}$ 242 mμ (ε 13,200). The hydroxyl group failed to acetylate under mild conditions but did so in refluxing acetic anhydride-sodium acetate solution, which suggested that it was a tertiary or hindered secondary alcohol. The latter was favoured on the basis of a new peak in the infra-red spectrum at 1061 $cm.^{-1}$, incompatible with the carbon-oxygen single bond stretching vibration of a tertiary alcohol. That this was correct was shown by comparison of the nuclear magnetic resonance spectra of cedrelone and isocedrelone acetates. These were fairly similar, but the former had a peak at τ 6.36 which had moved downfield in the latter to τ 5.42. This peak had been assigned to the epoxide proton on C_{15} in cedrelone acetate. Its position, ca. 1 τ lower than the literature value for such a proton, [26] is explicable in terms of

deshielding by the nearby carbonyl function at C_7. In isocedrelone acetate it was compatible with a similarly deshielded proton on a carbon bearing a hydroxyl group.

The above spectral observations combined with the mode of formation indicated the structure (B 20; R = H) as the most probable. This arises through acid-catalysed cleavage of the epoxide ring with concomitant methyl migration from C_{13} to C_{14}, and the placing of a double bond in conjugation with the furan ring. The stereochemistry of cedrelone is such that ring C of necessity exists in a boat conformation, whereas it becomes a chair in isocedrelone acetate. It is considered that the driving force for the rearrangement derives from the attendant relief of steric strain. Excellent analogy for this exists in the conversion of the stereochemically similar hexahydrolimoninic acid (B 21) to the γ-lactone (B 22) by the action of hydrochloric-acetic acid mixture.[8]

The new chromophore at 242 mμ was assigned to the substituted β-vinylfuran. The spectra of 3-vinylfuran and its derivatives have not been reported; 2-vinylfuran, however, has $\lambda_{max.}$ 260 mμ (ε 16,600).[27] That the observed chromophore is consistent with the β-vinylfuran formulation is borne out by comparison with the spectra of p-chlorophenylfurans.[28] The 2-isomer has $\lambda_{max.}$ 287 mμ (ε 20,600) whereas the 3-isomer has $\lambda_{max.}$ 262 mμ (ε 13,200). This relationship of the chromophore to the position of the substituent is in agreement with the observation that an equivalent of two ethylenic linkages is contributed to the K-band of a conjugated system by a furan ring.[16]

Thus 2-p-chlorophenylfuran has absorption similar to that of phenylbutadiene, [$\lambda_{max.}$ 280 mμ (ε 24,400)], and the cross-conjugated 3-isomer to styrene, [$\lambda_{max.}$ 262 mμ (ε 13300)]. On this basis the observed value for the β-vinylfuran chromophore in isocedrelone acetate seems reasonable when compared with a trisubstituted butadiene, expected to absorb maximally somewhere around 235 mμ. Analogous rearrangement products were obtained from dihydrocedrelone and acetate, and from epoxycedrelone.

It has been recently reported by Aghoramurthy et al. that cedrelone on treatment with acetic anhydride in the presence of p-toluenesulphonic acid gave a diacetate, m.p. 245-247°, which they formulated as the compound (B 23) on no evidence.[29] The reaction conditions employed would have been expected to give isocedrelone diacetate (B 20; R = Ac) but this, however, has m.p. 195-200°. We have reinvestigated this compound, and found that it analysed as a triacetate of cedrelone. Its infra-red spectrum, [$\nu_{max.}$ (CCl_4) 1767, 1742, 1699, 1688 cm.$^{-1}$], clearly showed by comparison with that of isocedrelone diacetate, [$\nu_{max.}$ (CCl_4) 1766, 1742, 1698 cm.$^{-1}$], that it was a derivative of the latter in to which a third acetyl group had been introduced. The ultra-violet spectrum, [$\lambda_{max.}$ 223 mμ (ε 20,400) and 276 mμ (ε14,010)], provided the clue as to the position of this acetyl group, by indicating that the vinylfuran chromophore had undergone extended conjugation. This required that a Friedel-Crafts acylation of the furan had taken place, and thus structure (B 24) or (B 25) for the product. That this was so was proved by the appearance of

only one α-furan proton, (multiplet at τ 2.44) and one β-proton, (multiplet at τ 3.04) in the nuclear magnetic resonance spectrum. A decision between the two structures has not been conclusively reached. However, the well-known sensitivity of the Friedel-Crafts reaction to steric hindrance would support the 23-acetyl derivative rather than the 21-acetyl isomer. This acetylation of the furan ring is quite unexceptional. Furan, itself, gives in moderate yield 2-acetylfuran on treatment with acetic anhydride and p-toluenesulphonic acid.[30]

The maximum at longest wavelength in the ultra-violet is little different from that of 2-acetylfuran, [$\lambda_{max.}$ 226 mμ (ε 2,400) and 270 mμ (ε 14,000)].[31] This can be rationalised as before, on the basis that the cross-conjugated system of a 2-acetyl-3-vinylfuran would be expected to have an ultra-violet spectrum approximately equivalent to the summation of the chromophores for 2-acetylfuran and 3-vinylfuran respectively. In support of this one may observe that 2,5-diphenylfuran has an ultra-violet spectrum similar to that of 1,4-diphenylbutadiene, whereas the spectrum of the 2,4-isomer is in agreement with a summation of those for styrene and phenylbutadiene.[32]

In addition to the above product there was isolated, in an amount too small to permit complete characterisation, a second compound, whose ultra-violet and infra-red spectra, [$\lambda_{max.}$ 227 mμ (ε 24,240), 256 mμ (ε 19,230) and 282 mμ (ε 15, 630), $\nu_{max.}$ (CCl_4) 1767, 1744, 1697, and 1682 $cm.^{-1}$], would be in agreement with its being the 21-acetyl-furan isomer (B 25).

Treatment of cedrelone with aqueous-alcoholic potassium hydroxide under reflux afforded in moderate yield an acid, $C_{26}H_{32}O_6$. That it was a monocarboxylic acid was shown by its solubility in aqueous sodium hydrogen carbonate solution, and the formation of a neutral monomethyl ester on treatment with diazomethane. The acid had bands in its solid state infra-red spectrum at 3550, 3540, 3250, 1706, 1672, and 875 $cm.^{-1}$ The peaks at 1672 and 875 $cm.^{-1}$ indicated that the ring A enone and furan ring respectively had been retained. Those at 3604 and 3525 $cm.^{-1}$ in the ester established that it was a derivative of a mono- or dihydroxyacid. That the latter was correct was proved by the conversion of the ester to an acetate, (unfortunately non-crystalline, but shown to be pure by its behaviour on a silica-chromatoplate), which still had a hydroxyl band in the infra-red. The presence of two hydroxyl groups, the furan ring, and the enone function in ring A, taken in conjunction with the molecular formula of the acid indicated that the epoxide ring could no longer be intact. The same conclusion was also reached from the observation that the acid was stable to boron trifluoride etherate.

The ultra-violet spectrum of the acid, [$\lambda_{max.}$ 235 mμ (ε 20,000), unaltered in base], confirmed the removal of the diosphenol function, and suggested that the epoxide had been opened in the same manner as in isocedrelone acetate, with the attendant formation of a vinylfuran. This was confirmed by its near identity to the ultra-violet subtraction curve of hexahydrocedrelone acetate (B 4; R = Ac) from isocedrelone acetate, which had $\lambda_{max.}$ 236 mμ (ε 18,000), the contribution of the

ring A enone and vinylfuran chromophores to the ultra-violet spectrum of isocedrelone acetate.

The above evidence strongly indicated that the acid had the structure (B 26; R = H), formed by benzilic acid rearrangement of the diosphenol moiety, and opening of the epoxide ring as previously. Further support for this structure came from two sources. Firstly, similar hydrolysis of isocedrelone acetate gave the same acidic product. Secondly, oxidation of the acid, henceforth referred to as isocedrelonic acid, by lead tetra-acetate in dioxan-benzene at room temperature afforded a neutral compound, $C_{25}H_{30}O_4$. That this was the norketone (B 27; R = H) expected on the basis of structure (B 26) for the acid was shown by its ultra-violet spectrum, identical to that of the acid, and bands at 3470 (hydrogen bonded hydroxyl), 1718 (hydrogen bonded cyclopentanone), 1691 (ring A enone) $cm.^{-1}$ in its infra-red spectrum. The norketone on acetylation gave a monoacetate (B 27; R = Ac), [$\nu_{max.}$ (CCl_4) 1739 with an inflection at 1745 $cm.^{-1}$, and 1690 $cm.^{-1}$], in which the cyclopentanone carbonyl absorption had moved up to a more normal value.

The probable stereochemistry assigned to isocedrelonic acid results from the following observations. The hydroxyl group on C_{15} must be β since the same acid results from hydrolysis of isocedrelone acetate. The norketone was obtained from the acid by a very mild reaction (vide supra), during which quantitative epimerisation at C_5 would appear unlikely to occur. It was shown to be the more stable epimer since it was recovered unchanged from refluxing in 10% aqueous-

alcoholic alkali. Inspection of stereo-models of the cis and trans A:B fused ketones (B 29) and (B 30) respectively, showed that the latter is much the less stable, since it is the more strained and has serious 1,3-non-bonded interactions between the β-methyl groups at C_4, C_{10}, and C_8. By comparison the cis epimer can adopt a conformation in which there is no interaction between the C_4 β-methyl group and that at C_{10}, and in which the interaction between the C_8 methyl and that at C_{10} is diminished. The stereochemistry indicated at C_6 was established through the formation of a lactone (B 28), described in more detail later. Molecular models indicate that for either a cis or trans A:B fused ring junction, lactonisation can take place only if the carboxyl group is placed α on C_6. Consideration of the mechanism of the benzilic acid rearrangement provided some support for the assignment of configurations at C_5 and C_6.

It is of some interest to enquire into the reasons and mechanism for the opening of the epoxide ring during formation of isocedrelonic acid. Under even forcing conditions of hydrolysis dihydrocedrelone and isodihydrocedrelone acetates were converted to the corresponding deacetyl compounds, with only trace formation of acidic byproducts. Arigoni *et al.* have reported that epoxycedrelone behaved similarly, and concluded that the epoxide in ring D is not susceptible to $S_N 2$ cleavage by the attack of external base.[21] From these observations they were led to propose that the epoxide ring is cleaved by an internal attack of the carboxylate anion present in the benzilic acid rearrangement product (B 31) to give, as an intermediate, one of the lactones (B 32)

or (B 33). The known stereochemistry at C_{15} in the acid negates the former possibility. The latter, were it an intermediate, would be hydrolysed to the trihydroxyacid (B 34), and one must then postulate either that this undergoes a base-catalysed Wagner-Meerwein, [(B 34 - B 35)], actuated by removal of the weakly activated proton from C_{17}, or that it undergoes an acid-catalysed dehydration with concomitant methyl migration on acidification of the reaction mixture. The latter pathway cannot be entirely excluded but seems unlikely for the following reasons. As has already been mentioned, the driving force for opening of the epoxide with methyl migration lies in relief of the strain associated with the boat conformation of ring C. This strain is absent in the structure (B 34), in which ring C is now a chair. In addition the hydroxyl group to be eliminated and the migrating methyl group are cis to one another, a situation which would prevent an energetically favourable concerted migration from taking place.

The former possibility was eliminated by isolating the potassium salt from the reaction mixture, and measuring its ultra-violet spectrum. This had $\lambda_{max.}$ 220 mμ (ε 9,700), consistent with the presence of the ring A and furan chromophores only, and on acidification of the solution it changed immediately to the spectrum of isocedrelonic acid.

It would therefore seem highly probable that the epoxide ring is unaffected during the benzilic acid rearrangement per se, but undergoes an extremely facile opening on acidification, owing to the very considerable strain inherent in a boat ring C fused trans to two five membered rings. A number of attempts were made to prove this by forming derivatives

which could be analysed. Thus, the above potassium salt, under conditions which formed a p-nitrobenzyl ester from isocedrelonic acid, gave only solvolysis products of the reagent in the neutral fraction, and none of the ester (B 36; R = $CH_2C_6H_4NO_2$). Similarly, an attempt to oxidise it, by means of chromium trioxide in pyridine, to the norketone (B 37) also failed.

As previously mentioned, dihydro- and isodihydrocedrelone cannot be induced to undergo the benzilic acid rearrangement, behaviour which contrasts markedly with that of cedrelone The reasons for this are not at all obvious. The currently accepted mechanism for the benzilic acid rearrangement is as shown in (B 38 - 41).[33] In this, hydroxide ion adds reversibly to the carbonyl group to form an adduct (B 39), which then undergoes a rate-determining rearrangement to form a second intermediate (B 40), rapidly converted to the benzilate anion by the appropriate proton transfers. By an entirely similar mechanism, benzilic acid esters can be obtained under catalysis by those alkoxide ions, which are not readily oxidised.

The above mechanism indicates that for rearrangement to occur in dihydrocedrelone, initial attack must take place on the cis or trans A:B fused unenolised α-diketone tautomers (B 42; β-H and α-H), present at low concentration in equilibrium with the form (B 43). In the trans alternative the β-face is shielded from attack by the methyls at C_8 and C_{10}. Addition to C_6 from the α-face will be less favoured than to C_7, since in the resulting intermediate two additional 1,3-interactions arise between the β-substituent at C_6 and the C_8 and C_{10}

methyl groups, whereas in the C_7 case the same two interactions are between the α-C_7 substituent and the α-hydrogen atoms at C_5 and C_9. It would thus appear that the necessary intermediate for rearrangement should be capable of forming. The reason for its failure to undergo rearrangement may be because the energy required to form the trans A:B fused acid is prohibitive. In both conformations available to it, (B 44) and (B 45) the acid is severely destabilised by non-bonded interactions between the methyls at C_4, C_8, and C_{10}, and the hydroxyl and carboxyl groups attached to C_6. An exactly similar argument applies to cedrelone, as substitution of a double bond between C_1 and C_2 makes negligible alteration to the steric relationships of the groups mentioned. Hence, since dihydrocedrelone does not form a trans A:B: fused acid neither should cedrelone. By contrast, the cis A:B fused dihydroacid can adopt a conformation (B 46) relatively free from interactions between the methyl groups and the C_6 substituents, and it differs from the corresponding cedrelone derivative in having an additional interaction of the 1,4 " flagpole-type " between a methyl at C_4 and a hydrogen on C_1. One might therefore deduce that, if the necessary intermediate were available, there should be little barrier to its rearrangement to the cis A:B fused dihydroacid. An examination of the possible conformations open to the cis A:B fused diketo tautomer of dihydrocedrelone and cedrelone reveals that for each of these, either access to the carbonyls by hydroxide ion is hindered from both sides of the molecule, or that the intermediate formed is seriously destabilised by 1,3-interactions. It therefore seems probable that the failure to

isolate any cis A:B fused dihydroacid lies in the difficulty involved in forming the first intermediate. By the same argument cedrelone itself should not form the analogous acid. A possible explanation for its so doing may be the following. As has been previously observed, the ring A enone is highly susceptible to nucleophilic attack, and in aqeous methanolic alkali the 1α- and 1β-hydroxy-1,2-dihydrocedrelones will exist in equilibrium with cedrelone. In the case of the 1α-cis A:B fused diketo tautomer (B 47) internal addition of the anion generated by base on the hydroxyl group at C_1 to the carbonyl group at C_6 would lead to the intermediate (B 48 = B 52), which could then undergo rearrangement to the α-hydroxyacid (B 51), of the same stereochemistry deduced on other grounds, by way of either the intermediate (B 49) or (B 50 = B 53). Such a mechanism is of course precluded when the ring A double bond has been removed.

On refluxing in benzene in the presence of dicyclohexylcarbodiimide, isocedrelonic acid afforded two products, readily separable by chromatography. The more polar substance, $C_{26}H_{30}O_5$, had an ultraviolet spectrum identical to that of the acid, and peaks in the infrared at 3593 (hydrogen bonded hydroxyl), 1753 (δ-lactone), and 1686 (ring A enone) $cm.^{-1}$ The spectral data, and the reconversion of the compound to isocedrelonic acid on hydrolysis indicated formulation as the lactone (B 28). The less polar substance was shown to be the norketone (B 27; R = H), by a direct comparison of its physical properties with those of the product resulting fron oxidation of isocedrelonic acid. The lactone was observed to decompose on melting

with evolution of a gas, and the decomposition product proved to be once again the norketone. Rather surprisingly, however, the lactone, when refluxed with more of the reagent in benzene, did not yield any of the norketone, thus indicating that under the reaction conditions employed it was not an intermediate in the formation of the norketone. The formation of the norketone during the diimide reaction may have the following explanation. Benzilic acid, treated under the same conditions, gave a neutral product, judged to be the lactide (B 54) on the basis of its infra-red spectrum, but no benzophenone. Lactides are known to undergo a synchronous double decarbonylation on pyrolysis.[34] Thus, the spirolactide (B 55) gives two molecules each of carbon monoxide and cyclohexanone as shown. If a lactide were formed from two molecules of isocedrelonic acid, as an alternative to lactonisation, then it would seem reasonable that this lactide (B 56) (B 56), highly destabilised by non-bonded interactions between the two linked molecules, might undergo a particularly facile double decarbonylation with the consequent formation of the norketone.

The mother-liquors, from crystallisation of crude isocedrelonic acid, on evaporation gave a mixture of acids. Treatment of this with lead tetra-acetate, followed by chromatography of the resulting neutral fraction, afforded a norketone isomeric with that obtained from isocedrelonic acid. The ultra-violet spectrum, [$\lambda_{max.}$ 220 mμ (ε 12,500)], consistent with enone and furan chromophores, coupled with the absence of hydroxyl absorption and the presence of a sharp peak at 1751 $cm.^{-1}$ in the infra-red spectrum indicated structures

(B 57) or (B 58) as likely. The complete stability of the compound in boron trifluoride etherate showed the former to be correct. This arises from the alternative, and more usual mode of epoxide opening. Attempts to cyclise this 1;4-diketone to a dihydropyridazine (B 59) by the action of hydrazine failed, probably because of the strain involved in such a structure.

The isomeric methyl ester (B 60), corresponding to this new diketone was also obtained through methylation and chromatography of the crystallisation residues.

To conclude this section on the chemistry of cedrelone some mention of the data obtained from solution infra-red studies seems desirable.

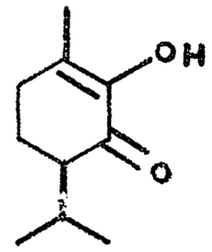
The diosphenol function.

Intramolecular hydrogen bonding between the hydroxyl and the adjacent carbonyl group was observed for all the diosphenols in the series; the hydroxyl absorption being constant between 3425 and 3435 cm.$^{-1}$, and that for the carbonyl falling between 1681 and 1675 cm.$^{-1}$ for chloroform solutions. In isocedrelone (B 61) and isodihydrocedrelone (B 62) an interesting example of double hydrogen bonding of the carbonyl to the diosphenol and ring D hydroxyls was observed, in which the diosphenol carbonyl appeared at 1620 cm.$^{-1}$, nearly 30 cm.$^{-1}$ below the absorption at 1658 cm.$^{-1}$ for the double bond. Similarly, hydrogen bonding between the C_{15} hydroxyl group and the carbonyl in ring B was observed for isocedrelone and isodihydrocedrelone acetates,

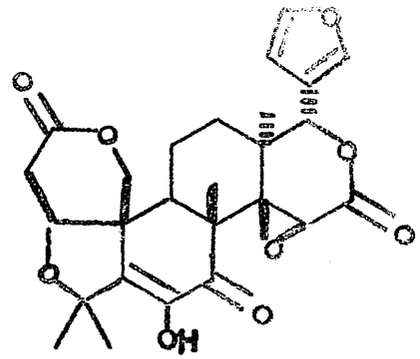
where the diosphenol carbonyl absorbed at 1677 and 1672 $cm.^{-1}$, a shift to lower frequencies of about 30 $cm,^{-1}$ from the normal value of 1702 $cm.^{-1}$, as observed in cedrelone acetate. The above examples, of intramolecular hydrogen bonding , including that of the norketone (B 27) are of interest since a seven membered ring occurs.

Ring A enone function

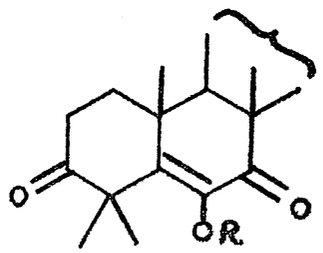
The absorption frequency associated with this function varied over a wider range of values, from 1677 to 1696 $cm.^{-1}$ For the majority of compounds it appeared close to 1685 $cm.^{-1}$ in chloroform, and to 1688 $cm.^{-1}$ in carbon tetrachloride. The precise values for each compound are given in the Experimental Section.



Diosphenol (B 1)



Limonin Diosphenol (B 2)



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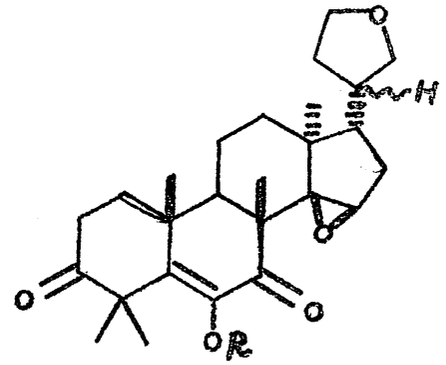

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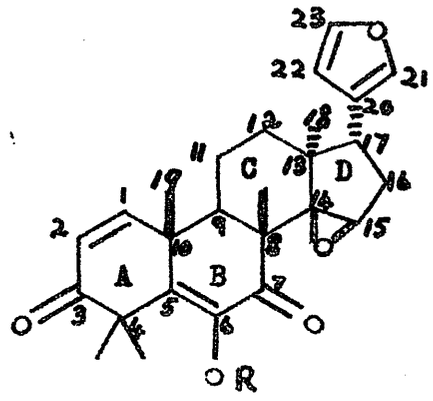

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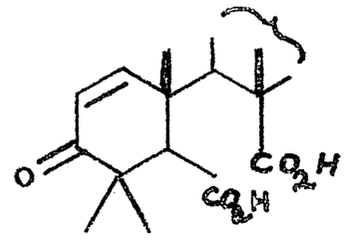

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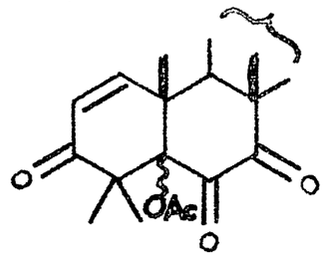

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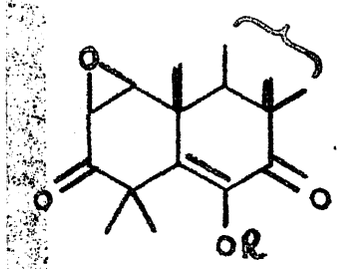

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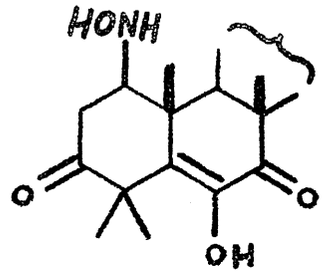

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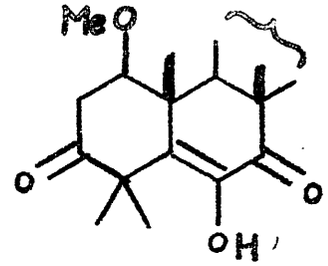

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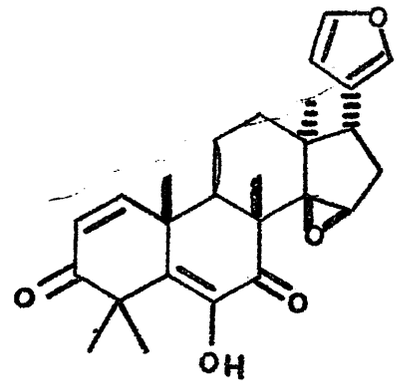
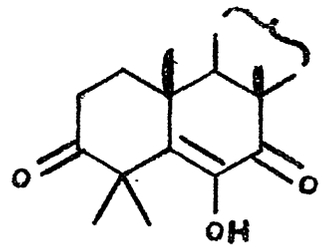
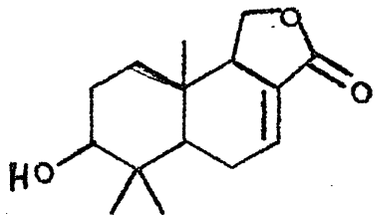
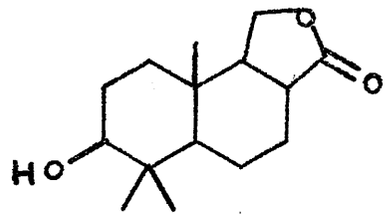




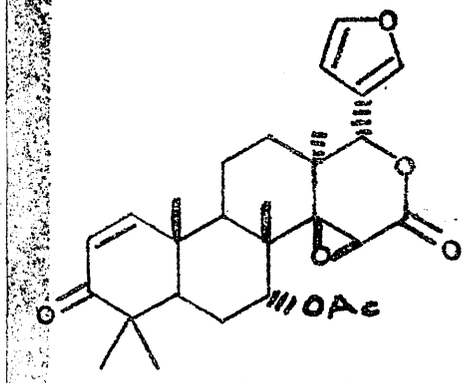
Cedrelone (B 11)



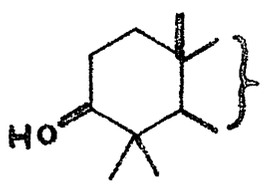
Iresin (B 12)



Dihydroiresin (B 13)



Cedunin (B 14)



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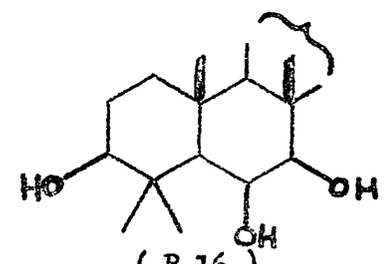
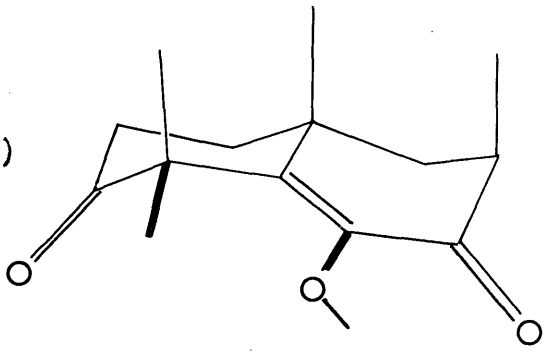


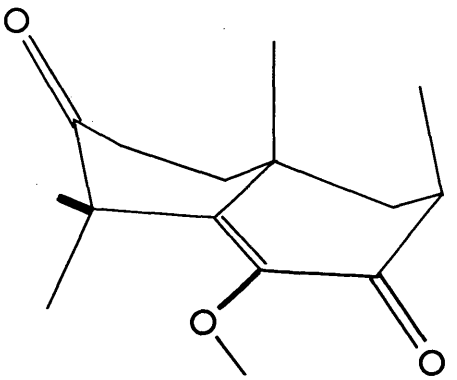
(B 16)

Conformations available to ring A

in dihydrocedrelone

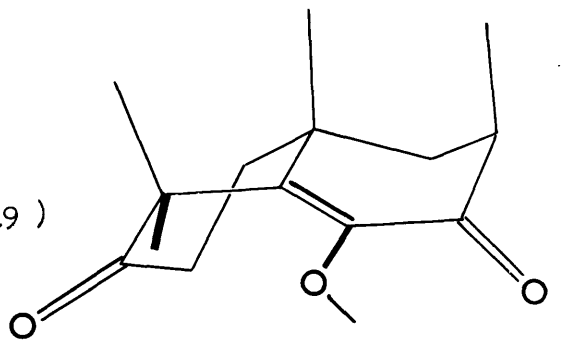
Chair (B 17)

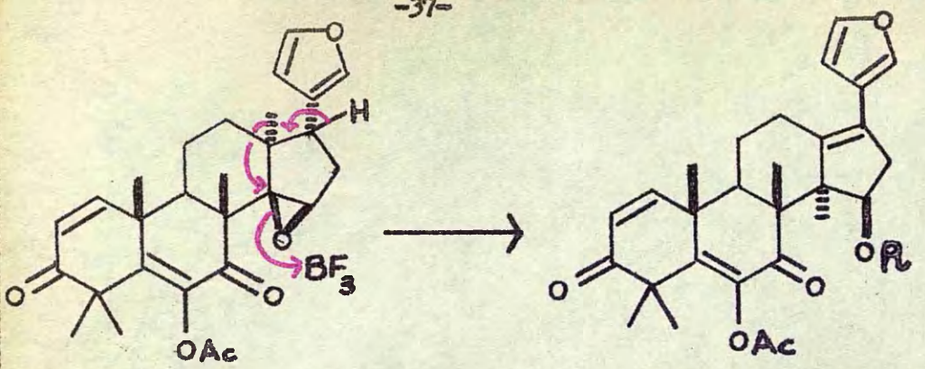




Boat (B 18)

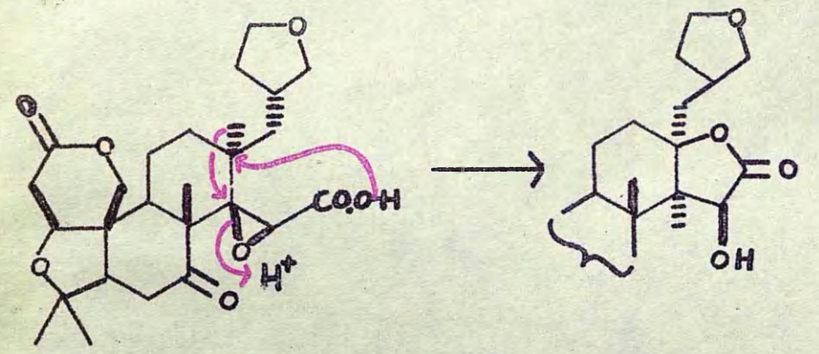
Boat (B 19)





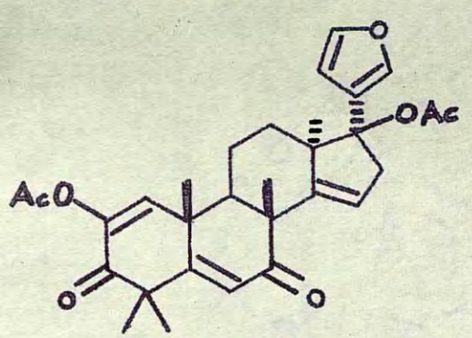
Cedrelone Acetate

Isocedrelone Acetate (B 20)



Hexahydrolimoninic Acid (B 21)

(B 22)



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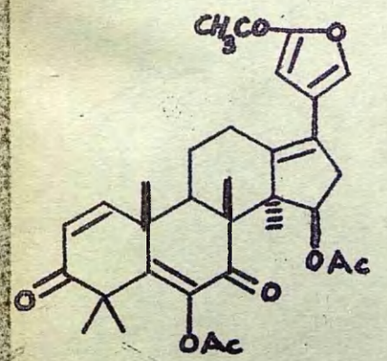

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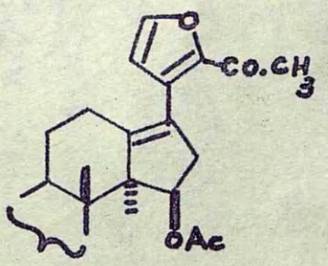

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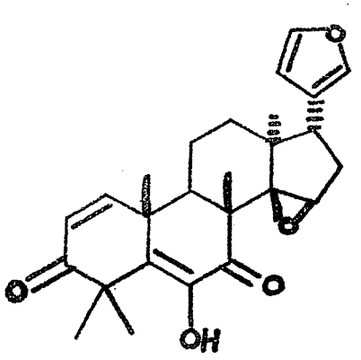
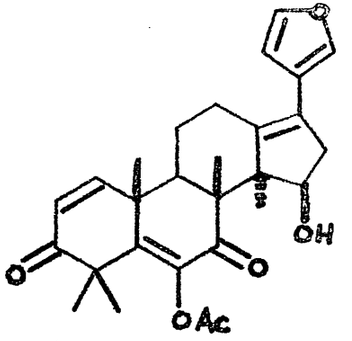
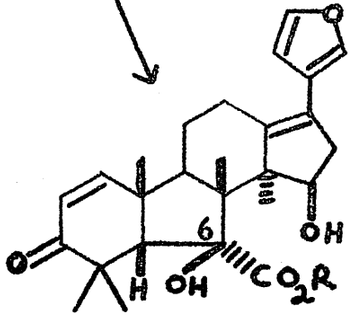


Cedrelone



Isocedrelone Acetate



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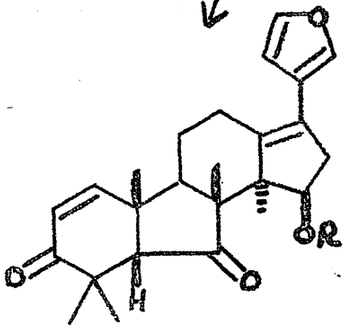

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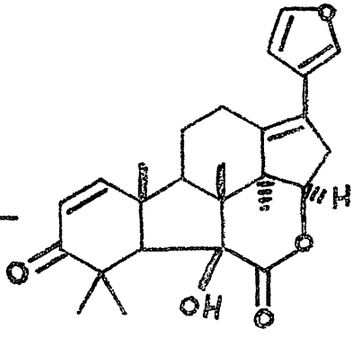

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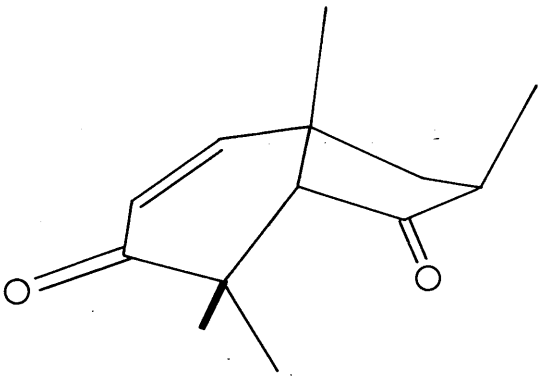

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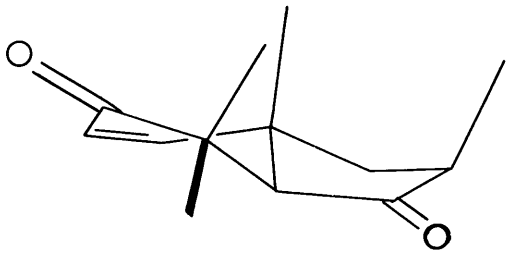

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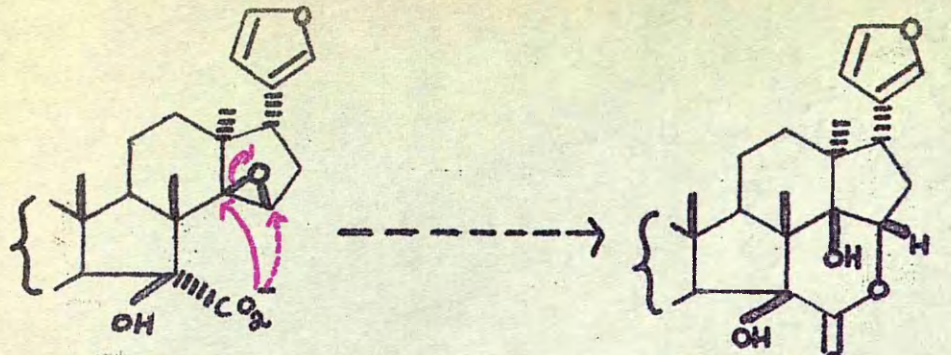

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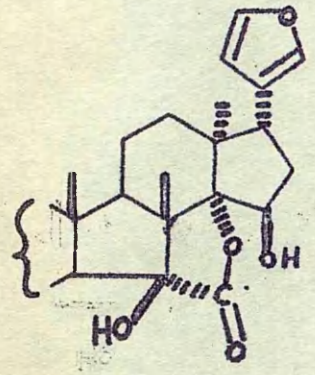

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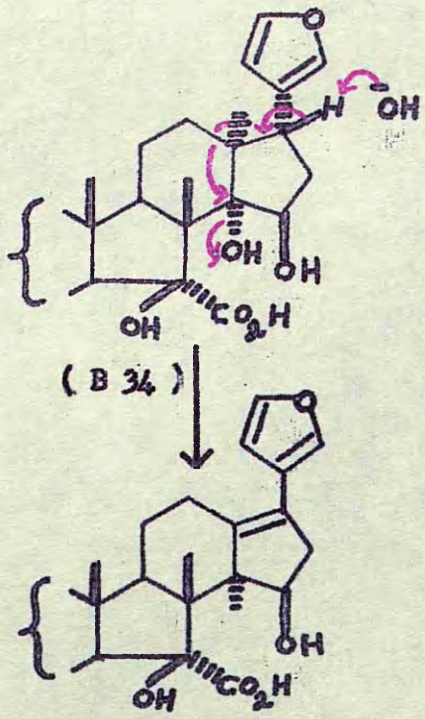

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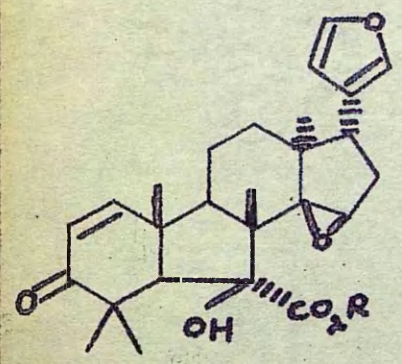

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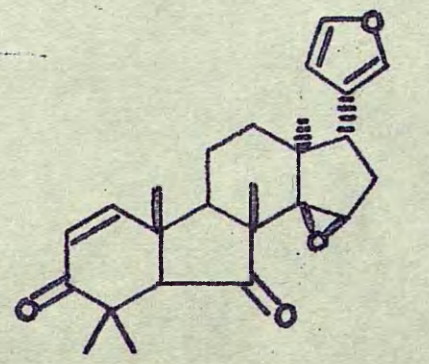

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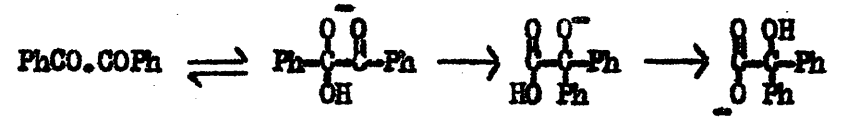

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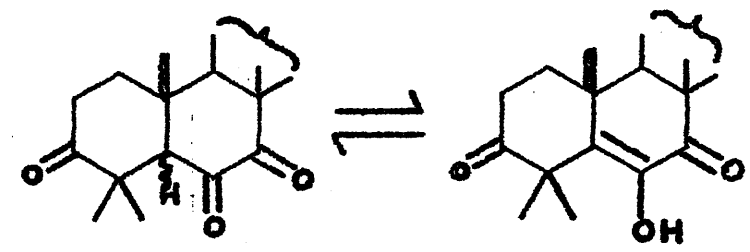

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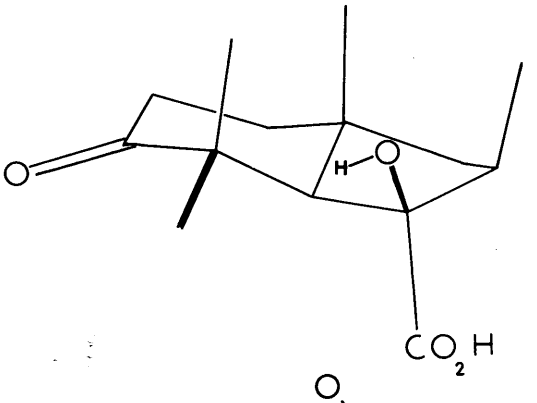

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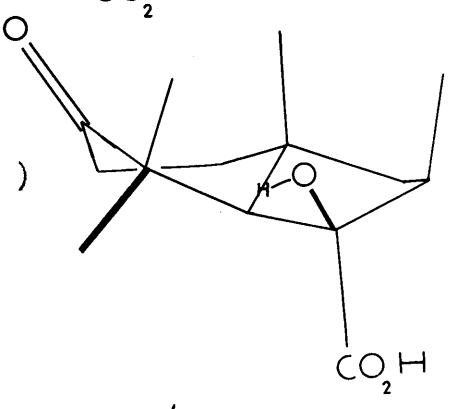

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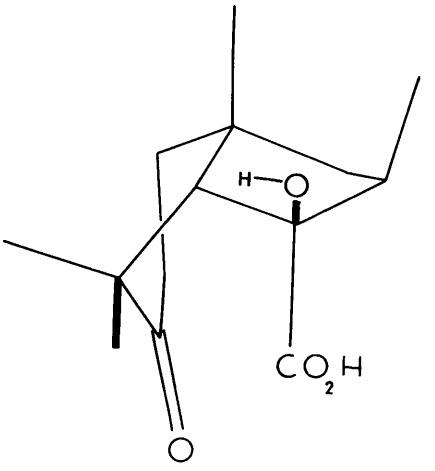

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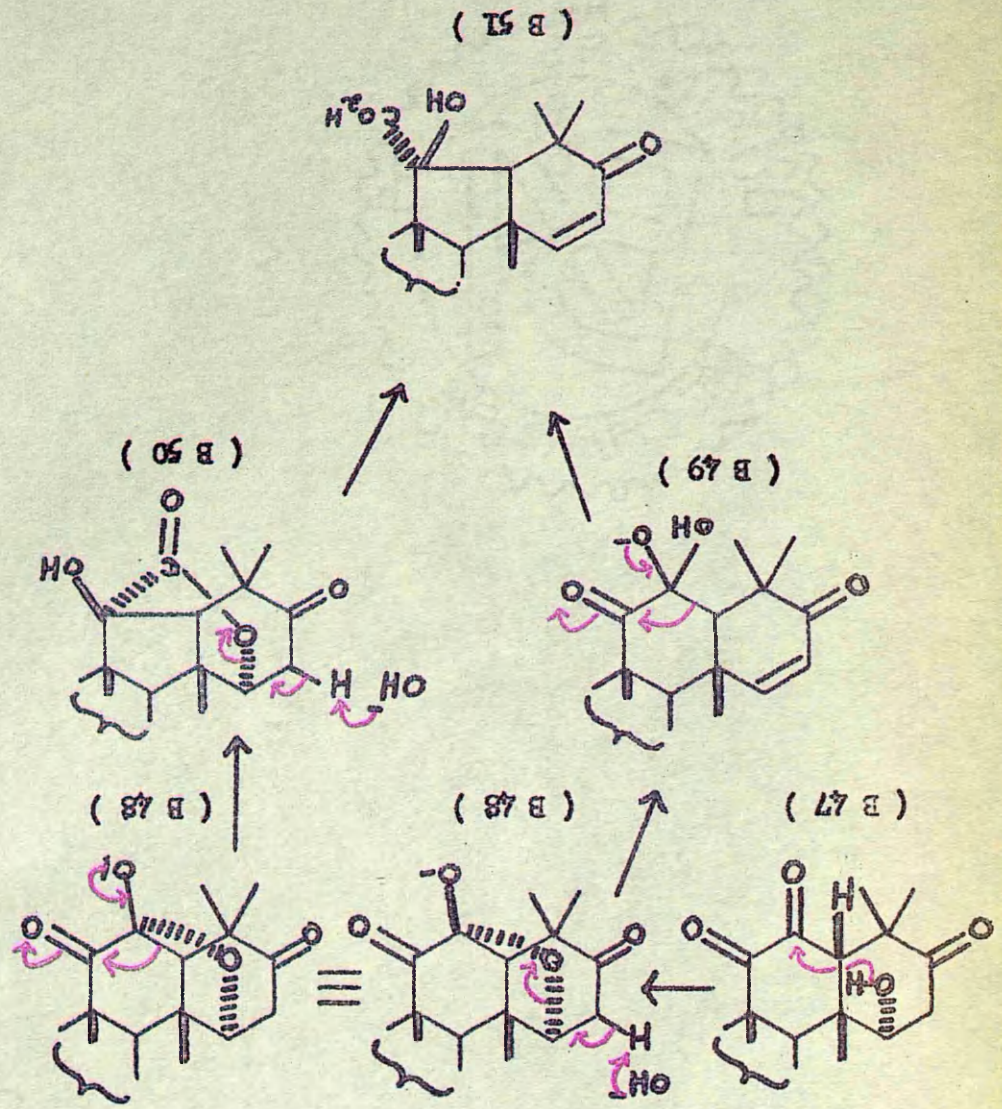
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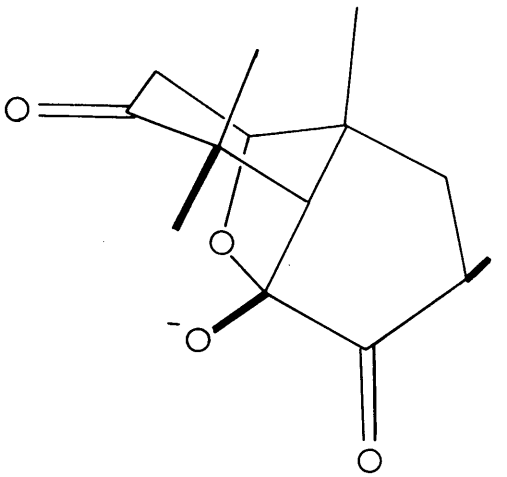
(B 52)



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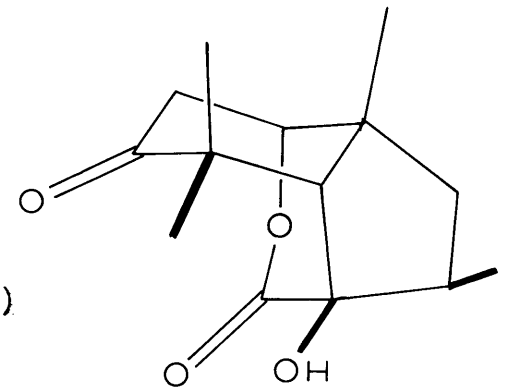

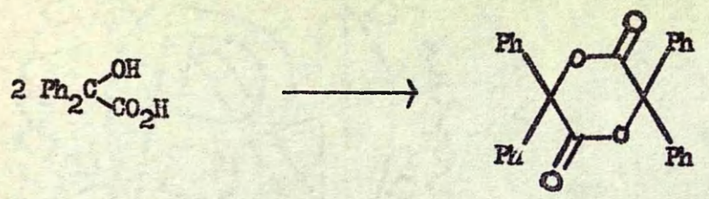

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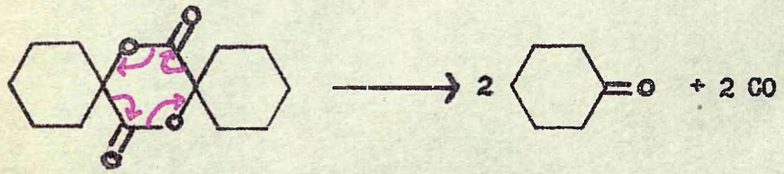

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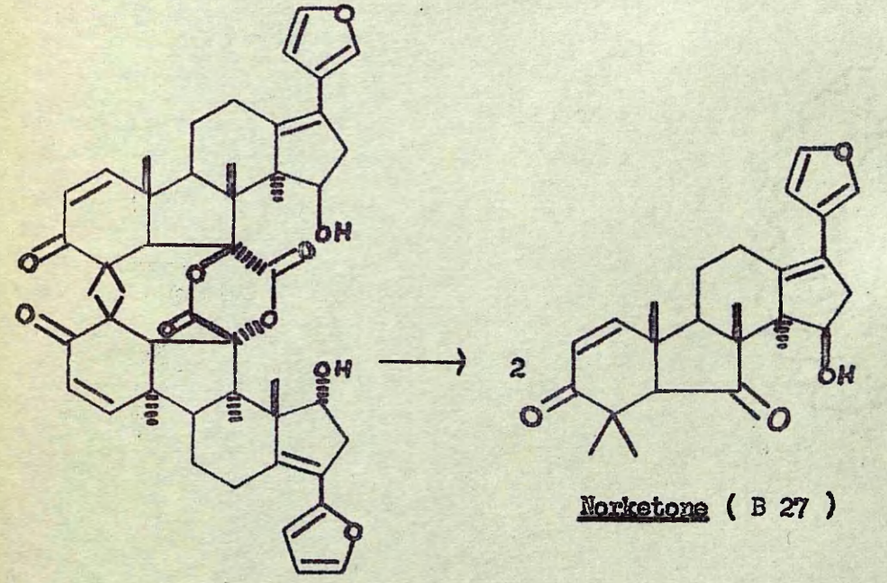
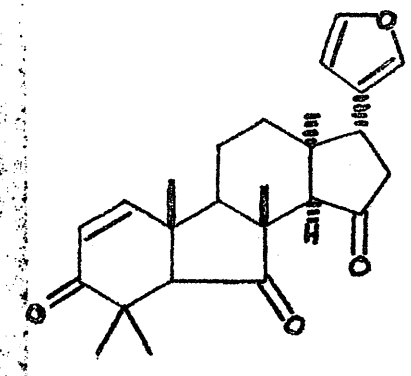


(B 56)

Norketone (B 27)



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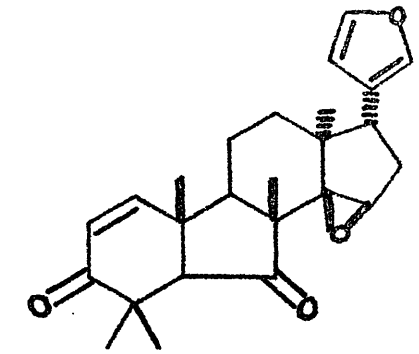

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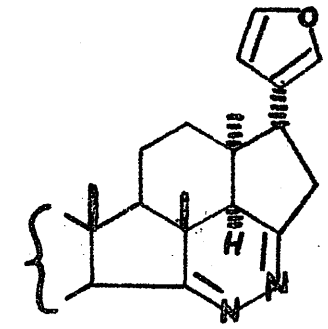

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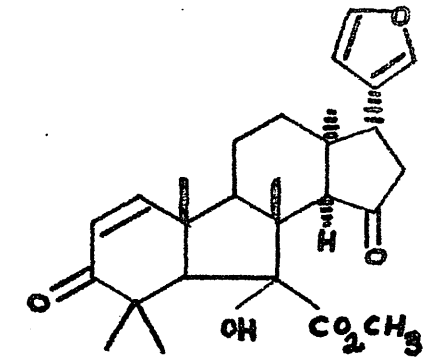

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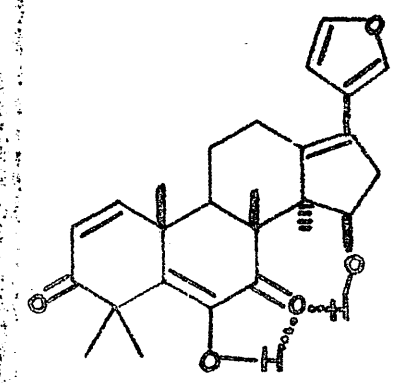
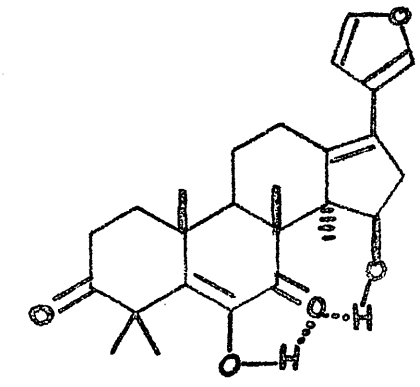


Isocedrelone (B 61)



Isodihydrocedrelone (B 62)

Experimental

M.p.s were determined on the Kofler block. Specific rotations are for chloroform solutions at room temperature, unless otherwise specified. Infra-red solution spectra were recorded on the Unicam SP 100 Mark II, with a prism grating monochromator, and operated with evacuated optics; Nujol spectra were obtained from a Perkin Elmer " Infracord " spectrophotometer. Ultra-violet maxima below 215 mμ were recorded from the Hilger " Uvispek " photoelectric spectrophotometer, and above 215 mμ on the Perkin Elmer U.V. Recording Spectrophotometer (Model 137), both for ethanol solutions. Microanalyses were by Mr. J.M.L. Cameron and his associates. Brockmann standardised alumina was used for chromatography.

Extraction of Cedrelone:- Dry powdered heartwood of Cedrela toona Roxb. was extracted continuously with benzene in a Soxhlet apparatus. Addition of light petroleum to the extract, after concentration in vacuo, precipitated crude cedrelone (0.4% on the weight of dried wood). This on recrystallisation several times from chloroform-ethanol afforded pure cedrelone as rhombs, m.p. 209-214°, $[\alpha]_D$ -64.5° (c 1.0), $\lambda_{max.}$ 217 mμ (ε 11,800) and 279 mμ (ε 9,100) shifting in base to 327 mμ (ε 5,530), $\nu_{max.}$ ($CHCl_3$) 3425 (hydroxyl), 1678 with a shoulder at 1685 (αβ-unsaturated ketones) $cm.^{-1}$, (Nujol) 3130, 1505, 878 (furan) $cm.^{-1}$, (Found: C, 74.1; H, 7.42. Calc. for $C_{26}H_{30}O_5$: C, 73.91; H, 7.16 %). It gave a dark-green coloration with alcoholic

ferric chloride.

Cedrelone Acetate (B 5; R = Ac):- Cedrelone (2 g.) was acetylated in acetic anhydride (2 ml.) and pyridine (2 ml.) at room remperature for 24 hr. The solution was poured into water and ether extracted. The extract was washed with dilute sulphuric acid, sodium hydrogen carbonate solution, and water in succession. Removal of the solvent and crystallisation of the residue from 80% aqueous ethanol gave cedrelone acetate(2 g.) as plates, m.p. 156-159°, $[\alpha]_D$ -56° (c 0.99), $\lambda_{max.}$ 222 mμ (ε 16,400), shoulder at 245 mμ (ε ca. 8,000), $\nu_{max.}$ (CCl_4) 1770 (enol acetate), 1702 (αβ-unsaturated carbonyls) $cm.^{-1}$, (Found: C, 72.52; H, 7.04. Calc. for $C_{28}H_{32}O_6$: C, 72.39; H, 6.94 %).

Hydrolysis of Cedrelone Acetate to Cedrelone:- Cedrelone acetate (20 mg.) was dissolved in dioxan (0.5 ml.) and N. potassium hydroxide solution (0.2 ml.) and kept at room temperature for 2 days. The solution was diluted with water and ether extracted to give cedrelone (13 mg.).

Cedrelone Chloroacetate (B 5; R = $CO.CH_2Cl$):- Cedrelone (100 mg.) and chloroacetic anhydride (97 mg.; 2.4 equiv.) were dissolved in benzene (1 ml.) containing pyridine (0.02 ml.) at room temperature. After standing overnight the solution was poured into water and the product isolated by ether extraction. Removal of the solvent and crystallisation from chloroform-ethanol gave cedrelone chloroacetate (114 mg.) as needles, m.p. 171.5-173°, $[\alpha]_D$ -39° (c 1.1), $\lambda_{max.}$ 222 mμ (ε 15,900), 320 mμ (ε 442), $\nu_{max.}$ (Nujol) 1769, 1702 $cm.^{-1}$, (Found: C, 67.19; H, 6.35. $C_{28}H_{31}ClO_6$ requires C, 67.39; H, 6.26 %).

Cedrelone Iodoacetate (B 5; R = $CO.CH_2I$):- Cedrelone chloroacetate (100 mg.) and sodium iodide (200 mg.) were refluxed under nitrogen in " AnalaR " acetone (8 ml.) for 8 hr. After concentration, the solution was poured into water and the product isolated by ether extraction. Crystallisation from aqeous ethanol afforded cedrelone iodoacetate as plates, m.p. 149-149.5°, $[\alpha]_D$ -24° (c 1.0), $\lambda_{max.}$ 223 mμ (ε 15,610), shoulder at 250 mμ (ε ca. 8,500), (Found: C, 56.70; H, 5.13. $C_{28}H_{31}IO_6$ requires C, 56.94; H, 5.29%).

Cedrelone Methyl Ether (B 5; R = Me):- Cedrelone (1g.) and dimethyl sulphate (2 ml.) were dissolved in dioxan (25 ml.) Small quantities (2.5 ml. in each case) of N. potassium hydroxide solution were added at intervals sufficient to maintain the yellow colour of the solution. When addition of alkali no longer re-established the colour a further quantity (10 ml.) was added to hydrolyse the excess dimethyl sulphate. The precipitate, after filtration through Grade II alumina in 50% benzene-chloroform, gave cedrelone methyl ether (800 mg.). This crystallised as prisms from chloroform-ethanol, m.p. 207-210°, $[\alpha]_D$ -13.4° (c 0.97), $\lambda_{max.}$ 216 mμ (ε 13,180), 262 mμ (ε 9,000), $\nu_{max.}$ ($CHCl_3$) 1692 $cm.^{-1}$, (Found: C, 74.18; H, 7.51. $C_{27}H_{32}O_5$ requires C, 74.28; H, 7.39%).

The Lead Tetra-acetate Oxidation Product from Cedrelone (B 7):- Cedrelone (550 mg.) in benzene (10 ml.) was shaken at room temperature with lead tetra-acetate (630 mg.; 1.05 equiv.) and the resulting mixture, after dilution with ether, was thoroughly washed with dilute sodium hydroxide solution and water. Removal of the solvent and crystallisation of the residue from ethyl acetate-petrol afforded the

oxidation product, which gave one spot on a silica-chromatoplate, m.p. 212°, $[\alpha]_D$ -12.8 (c 1.25), $\lambda_{max.}$ 215 mμ (ε 11,570), 273 mμ (ε 5,176), 433 mμ (in chloroform) (ε 34), $\nu_{max.}$ (Nujol) 3100, 1500, 874 (furan, 1744, 1240 (acetate), 1690 (enone and α-diketone) 690 (cis double bond) $cm.^{-1}$ After standing for a day the product showed several additional spots when examined on a silica-chromatoplate.

Dihydrocedrelone (B 3; R = H):- By hydrogenation. Cedrelone (38.8 mg.) in " AnalaR " ethyl acetate (10 ml.) was hydrogenated over 5% palladium-charcoal (11 mg.) until the uptake of hydrogen (2.41 ml.; theoretical for 1 mol. = 2.25 ml.) ceased. The product was chromatographed over Grade II alumina. Elution with 15% chloroform in benzene gave dihydrocedrelone, prisms from chloroform, m.p. 211-214° (sealed capillary), $[\alpha]_D$ -60° (c 0.97), $\lambda_{max.}$ 210 mμ (ε 6,100) 279 mμ (ε 9,938), $\nu_{max.}$ ($CHCl_3$) 3430, 1712.5, 1677, 1636w $cm.^{-1}$, (nujol) no band at 690 $cm.^{-1}$, (Found: C, 73.23; H, 7.58. $C_{26}H_{32}O_5$ requires C, 73.56; H, 7.60%).

Dihydrocedrelone on acetylation with 1:1 acetic anhydride-pyridine (1 ml.) at room temperature for 24 hr. gave dihydrocedrelone acetate (B 3; R = Ac), plates from aqueous ethanol, m.p. 176-180°, $[\alpha]_D$ -76° (c 0.84), $\lambda_{max.}$ 217 mμ (ε 8,470) 245 mμ (ε 9,040), $\nu_{max.}$ ($CHCl_3$) 1764, 1714, 1702.5, 1610w $cm.^{-1}$, (Found: C, 71.86; H, 7.50. $C_{28}H_{34}O_6$ requires C, 72.08; H, 7.35%).

Hexahydrocedrelone (B 4; R = H):- Cedrelone (1 g.) in " AnalaR " acetic acid (180 ml.) was hydrogenated over prereduced platinum oxide (250 mg.). Hydrogenation was complete after 1.5 hr. during which 214 ml. had been absorbed (theoretical for 3 mol. uptake

= 175 ml.). The product was absorbed from benzene on Grade IV alumina (50 g.). Elution with benzene gave hexahydrocedrelone (700 mg.) as a mixture of epimers at C_{20}. Repeated crystallisation from chloroform-ethanol afforded one isomer, pure, as needles, m.p. 222-225°, $[\alpha]_D$ -44.5° (c 0.86), $\lambda_{max.}$ 279 mμ (ε 11,000) shifting in base to 329 mμ (ε 7,500), $\nu_{max.}$ ($CHCl_3$) 3435 (hydroxyl), 1712 (cyclohexanone), 1676 (diosphenol), 1624w (diosphenol double bond) $cm.^{-1}$, (Found: C, 73.10; H, 8.57. $C_{26}H_{36}O_5$ requires C, 72.86; H, 8.47%). Hexahydrocedrelone (145 mg.) on acetylation as for dihydrocedrelone gave hexahydrocedrelone acetate (B 4; R = Ac), as plates from aqueous ethanol, m.p. 185-190°, $[\alpha]_D$ -44.5° (c 0.92), $\lambda_{max.}$ 245 mμ (ε 9,400) $\nu_{max.}$ (CCl_4) 1770.5 (enol acetate), 1720.5 (cyclohexanone), 1705 (diosphenol) $cm.^{-1}$, (Found: C, 71.57; H, 7.90. $C_{28}H_{38}O_6$ requires C, 71.46; H, 8.14%).

1,2-Epoxycedrelone (B 8; R = H):- Cedrelone (150 mg.) was dissolved in dioxan (20 ml.). 30% Hydrogen peroxide (5 ml.) and N. Sodium hydroxide solution (5 ml.) were added, and the solution was allowed to stand 36 hr. at room temperature. The product was isolated by chloroform extraction of the solution after dilution with water. 1;2-Epoxycedrelone crystallised from chloroform-ethanol as needles, m.p. 222-228°, $[\alpha]_D$-10.6° (c 0.71), $\lambda_{max.}$ 201 mμ (ε 7,200) 276 mμ (ε 10,700), $\nu_{max.}$ ($CHCl_3$) 3428 (hydroxyl) 1719 (α-oxygenated cyclohexanone) 1681 (diosphenol) 1630w (diosphenol double bond) $cm.^{-1}$ (Found: C, 71.24; H, 6.78. $C_{26}H_{30}O_6$ requires C, 71.21; H, 6.90%). Acetylation as for dihydrocedrelone gave 1,2-epoxycedrelone acetate,

plates from aqueous ethanol, m.p. 213-217°, $[\alpha]_D$ -26° (c 0.88), $\lambda_{max.}$ 217 mμ (ε 8,900) 244 mμ (ε 9,910), $\nu_{max.}$ (CCl_4) 1769 (enol acetate), 1722 (α-oxygenated cyclohexanone), 1707.5 (diosphenol) $cm.^{-1}$ (Found: C, 69.92; H, 6.97. $C_{28}H_{32}O_7$ requires C, 69.98; H, 6.71%).

1-Hydroxylamino-1,2-dihydrocedrelone (B 9):- Cedrelone (200 mg.) hydroxylamine hydrochloride (220 mg.) were dissolved in pyridine (4 ml.) and ethanol (2 ml.), and the solution was allowed to stand at room temperature for 9 days. Addition of water precipitated the product in crystalline form. 1-Hydroxylamino-1,2-dihydrocedrelone formed prisms from dioxan-petrol, m.p. 188-190° (decomp.), $[\alpha]_D$ -24° (c 0.9 in dioxan), $\lambda_{max.}$ 211 mμ (ε 6,930) 281 mμ (ε 9,280), $\nu_{max.}$ (Nujol) 3450 (hydroxyl), 3300 (N-H), 1695 (hydrogen bonded cyclohexanone), 1678 (diosphenol) $cm.^{-1}$, (Found: C, 68.55; H, 7.14; N; 3.30. $C_{26}H_{33}NO_6$ requires C, 68.55; H, 7.30; N, 3.08%).
A sample was melted under nitrogen and kept at 200° for 5 min. The resulting red gum was absorbed from benzene on silica. Elution with 10% chloroform in benzene afforded cedrelone (I.R. and mixed m.p.). The same adduct resulted from refluxing cedrelone with hydroxylamine hydrochloride in pyridine-methanol solution.

Dihydrocedrelone (B 3; R = H):- By sodium borohydride reduction. Cedrelone (100 mg.) dissolved in dioxan (1.5 ml.) and water (0.15 ml.) was treated with sodium borohydride (10 mg.; 11 mol.) at room temperature for 1.5 hr. Addition of water precipitated crystalline dihydrocedrelone, identical with the product obtained by hydrogenation of cedrelone.

Isocedrelone Acetate (B 20; R = H):- Cedrelone acetate (100 mg.) in ether (4 ml.) was treated with boron trifluoride etherate (4 ml.) for 2 hr. The solution was diluted with ether and washed with dilute sodium hydrogen carbonate solution and water. Removal of the solvent afforded a gum which was purified by filtration through Grade IV alumina in benzene-ether (9:1), followed by crystallisation from chloroform-ethanol. Isocedrelone acetate formed plates, m.p. 223-227° (decomp.), $[\alpha]_D$ -61° (c 0.98), $\lambda_{max.}$ 210 mμ (ε 23,100) 238 mμ (ε 26,300), $\nu_{max.}$ ($CHCl_3$) 3606w (unbonded hydroxyl), 3415 (hydroxyl), 1764 (enol acetate), 1696 (cyclohexenone), 1667 (diosphenol), (Found: C, 72.41; H, 6.89. $C_{28}H_{32}O_6$ requires C, 72.39; H, 6.94%).

Isocedrelone Diacetate (B 20; R = Ac):- Isocedrelone acetate was refluxed in acetic anhydride (5 ml.) containing anhydrous sodium acetate (300 mg.) for 3 hr. Removal of the acetic anhydride under reduced pressure left a residue which was taken up in ether-water. The ether layer was thoroughly washed with dilute aqueous sodium hydrogen carbonate to remove any unchanged acetic anhydride. Removal of the solvent gave a gum which was purified by filtration through Grade II alumina in benzene-ether (9:1), followed by crystallisation from chloroform-ethanol. Isocedrelone diacetate formed plates, m.p. 195-200°, $[\alpha]_D$ -8.7° (c 0.86), $\lambda_{max.}$ 238 mμ (ε 26,860), $\nu_{max.}$ (CCl_4) 1766 (enol acetate), 1743 (normal acetate), 1698 (enone and diosphenol) $cm.^{-1}$, (Found: C, 71.37; H, 6.49. $C_{30}H_{34}O_7$ requires C, 71.13; H, 6.77%).

Isodihydrocedrelone Acetate:- This was prepared from dihydrocedrelone acetate (B 3; R = Ac) exactly as for isocedrelone acetate. Isodihydrocedrelone acetate crystallised as plates from chloroform-ethanol, m.p. 221-223°, $[\alpha]_D$ -73.8° (c 1.0), $\lambda_{max.}$ 212 mμ (ε 15,200) 242 mμ (ε 20,700), $\nu_{max.}$ (CCl_4) 1772, 1721, 1672 $cm.^{-1}$, (Found: C, 72.23; H, 7.61. $C_{28}H_{34}O_6$ requires C, 72.08; H, 7.35%).

Isodihydrocedrelone (B 62):- This was prepared from dihydrocedrelone (B 3; R = H) as for isocedrelone acetate, with the modification that the reaction was allowed to proceed for 12 hr. Isodihydrocedrelone crystallised from benzene-petrol as fine needles, m.p. 115-118°, $[\alpha]_D$ -45° (c 1.03), (Found: C, 75.41; H, 7.48. $C_{26}H_{32}O_5.\frac{1}{2}C_6H_6$ requires C, 75.16; H, 7.56%), and after sublimation had m.p. 168-172° $\lambda_{max.}$ 239 mμ (ε 13,900) 287 mμ (ε 11,400) shifting in base to 345 mμ (ε 7,000), $\nu_{max.}$ ($CHCl_3$) 3418 (hydroxyl), 1712.5 (cyclohexanone), 1658w (diosphenol double bond), 1620s (diosphenol carbonyl) $cm.^{-1}$, (Found: C, 73.40; H, 7.69. $C_{26}H_{32}O_5$ requires C, 73.56; H, 7.60%).

Isocedrelone (B 61):- This was prepared from cedrelone as for isodihydrocedrelone but was unfortunately not crystalline, $\nu_{max.}$ ($CHCl_3$ 1684 (cyclohexenone), 1659w (diosphenol double bond), 1619s (diosphenol carbonyl) $cm.^{-1}$

23-Acetylisocedrelone Diacetate (B 24):- Cedrelone (60 mg.) and p-toluenesulphonic acid (30 mg) were refluxed in acetic anhydride (3 ml.) for 6 hr. After removal of the acetic anhydride under reduced pressure the residue was dissolved in ether and washed with

dilute sodium hydroxide solution and water. Examination of the crude product on a silica-chromatoplate showed that it contained no isocedrelone diacetate. The product, a black gum, was absorbed on Grade II alumina from benzene. Elution with benzene-ether (1:1) gave 21 mg. which showed one spot and a trace of a second on a silica-chromatoplate. This fraction was crystallised from ethanol to give needles, m.p. 245-252°, $[\alpha]_D$ -12.5° (c 0.65), $\lambda_{max.}$ 223 mμ (ε 20,400) 276 mμ (ε 14,010), $\nu_{max.}$ (CCl_4) 1767 (enol acetate), 1742 (normal acetate), 1699 (cyclohexenone and diosphenol), 1688 (furan acetyl) $cm.^{-1}$, (Found: C, 69.98; H, 6.37. $C_{32}H_{36}O_8$ requires C, 70.05; H, 6.61%).

Elution with ether gave a second fraction (9 mg.). This crystallised from ethanol as fine needles, m.p. 237-241°, $\lambda_{max.}$ 227 mμ (ε 24,240) 256 mμ (ε 19,220) 282 mμ (ε 16,630), $\nu_{max.}$ (CCl_4) 1767, 1744, 1697, 1692 $cm.^{-1}$, and is believed to be 21-acetylisocedrelone diacetate.

Isocedrelonic acid (B 26):- Cedrelone (5 g.) was suspended in methanol (200 ml.). A solution of potassium hydroxide (100 g.) in water (150 ml.), which had been deoxygenated by the passage of nitrogen for 0.5 hr., was added. The resulting solution was refluxed under nitrogen for 7 hr. After cooling it was extracted with ether (2 x 200 ml.) and then poured slowly into ice-cold conc. hydrochloric acid (200 ml.) and methanol (200 ml.). The resulting solution was allowed to stand overnight and was then diluted to 2 l. with water, to give the product in an easily filterable form. Crystallisation from chloroform-methanol afforded isocedrelonic acid (2.136 g.) as

prisms, m.p. 295-300° (decomp.), $[\alpha]_D$ -50° (c 0.5 in 1:1 chloform-ethanol), $\lambda_{max.}$ 235 mμ (ε 20,000) unchanged by the addition of base, $\nu_{max.}$ (Nujol) 3550, 3450 (hydroxyls), 3250 (carboxyl), 1706 (carboxyl), 1672 (cyclohexenone) $cm.^{-1}$, (Found: C, 70.78; H, 7.56. $C_{26}H_{32}O_6$ requires C, 70.89; H, 7.32%). Concentration of the mother liquors gave a further quantity of pure (chromatoplate) isocedrelonic acid (400 mg.). The mother liquors, after evaporation to dryness yielded a mixture of acids (500 mg.) used for the preparation of the norketone (B 57). Extraction of the aqueous filtrate with chloroform gave a foam (800 mg.), which was not further examined. Isocedrelonic acid was suspended in ether and treated with excess ethereal diazomethane to give in the usual manner methyl isocedrelonate (B 26; R = Me). This crystallised as platesfrom chloroform-benzene, m.p. 270-272°, $[\alpha]_D$ -49° (c 1.25), $\lambda_{max.}$ 236 mμ (ε 20,460), $\nu_{max.}$ ($CHCl_3$) 3604 (hydroxyl), 3525 (hydroxyl), 1703 (ester), 1677 (cyclohexenone) $cm.^{-1}$, (Found: C, 71.47; H, 7.68. $C_{27}H_{34}O_6$ requires C, 71.34; H, 7.54%).

Norketone (B 27; R = H):- A solution of isocedrelonic acid (550 mg.) in dry dioxan (10 ml.) was added to lead tetra-acetate (800 mg.) in benzene (15 ml.), and the resulting solution was allowed to stand for 3 hr. at room temperature. After dilution with ether it was washed with dilute sodium hydroxide solution and water. Crystallisation of the residue, after removal of the solvent, afforded the norketone (B 27 R = H) as rhombs from chloroform-ethanol, m.p. 206-208°, $[\alpha]_D$ -87° (c 1.0), $\lambda_{max.}$ 234 mμ (ε 19,000), $\nu_{max.}$ (CCl_4)

3470, 1718 (hydrogen bonded cyclopentanone), 1691 (cyclohexenone) cm.$^{-1}$, (Found: C, 75.86; H, 7.58. $C_{25}H_{30}O_4$ requires C, 76.11; H, 7.67%). The norketone (50 mg.) treated with hydroxylamine hydrochloride (50 mg.) in pyridine (0.5 ml.) for 3 hr. on the steam-bath gave a mono-oxime (ring B), prisms from methanol-benzene, m.p. 240-243°, $[\alpha]_D$ +60.7° (c 0.65 in dioxan), $\lambda_{max.}$ 210 mμ (ε 25,900) 237 mμ (ε 27,450), $\nu_{max.}$ (Nujol) 3380 (N-H and OH), 1696 (cyclohexenone) cm.$^{-1}$, (Found: N, 3.53. $C_{25}H_{31}NO_4$ requires N, 3.42%).

The norketone (40 mg.) was refluxed with anhydrous sodium acetate (300 mg.) in acetic anhydride (5 ml.). The product was isolated by removal of the acetic anhydride under reduced pressure, ether extraction of the residue, and filtration through Grade I alumina in benzene-ether (1:1). The norketone acetate (B 27; R = Ac) formed prisms from ether-petrol, m.p. 133-136°, $[\alpha]_D$ -27° (c 1.35), $\lambda_{max.}$ 234 mμ (ε 17,340), $\nu_{max.}$ (CCl_4) 1739 with an inflection at 1745 (acetate and cyclopentanone), 1690 (cyclohexenone) cm.$^{-1}$, (Found: C, 74.32; H, 7.08. $C_{27}H_{32}O_5$ requires C, 74.28; H, 7.39%).

The norketone was refluxed in ethanol (1.6 ml.) and 50% aqueous potassium hydroxide (0.4 ml.) for 1.5 hr. Isolation of the product by ether extraction and examination of it on a silica-chromatoplate indicated that it contained only starting material.

Hydrolysis of Isocedrelone Acetate:- A solution of isocedrelone acetate (B 20; R = H) (160 mg.) in methanol (5 ml.) and 50% aqueous potassium hydroxide (5 ml.) was refluxed under nitrogen for 4 hr. The solution, after ether extraction, was acidified and the

acids isolated by chloroform extraction. This, upon crystallisation, gave an acid (130 mg.) identical with isocedrelonic acid (m.p., I.R.) and a methyl ester, on treatment with ethereal diazomethane in the usual way, identical with methyl isocedrelonate (m.p., mixed m.p. and I.R.).

Hydrolysis of Dihydrocedrelone Acetate (B 3 R = Ac):- Dihydrocedrelone acetate (100 mg.), 50% aqueous potassium hydroxide (4 ml.) and methanol (4 ml.) were refluxed under nitrogen for 15 hr. The methanol was removed under reduced pressure and the neutral fraction was isolated by ether extraction. Crystallisation from chloroform-ethanol afforded dihydrocedrelone (83 mg.) identical with previous samples. Acidification of the aqueous solution, followed by chloroform extraction yielded only a trace of gum, which was not further examined. Hydrolysis as above by employing 60% aqueous-methanolic potassium hydroxide for 24 hr., gave somewhat less pure dihydrocedrelone.

Hydrolysis of Isodihydrocedrelone Acetate:- Hydrolysis of iso-dihydrocedrelone acetate (100 mg.), under the same manner as for dihydrocedrelone acetate, in 25% aqueous-methanolic potassium hydroxide for 18 hr. gave isodihydrocedrelone (85 mg.).

Examination of the Intermediate Potassium Salt in the Hydrolysis of Cedrelone:- Cedrelone (0.5 g.) was hydrolysed as in the preparation of isocedrelonic acid. The solution, after ether extraction, was diluted with water till cloudy, clarified by warming, and allowed to cool slowly to give the potassium salt (244 mg.), which, after drying under high vacuum at 50° for 2 days, had $\lambda_{max.}$ 220 mμ (ε 9,700),

$\nu_{max.}$ 3445-3455 (hydroxyl), 1678 (cyclohexenone), 1580 (carboxylate anion) $cm.^{-1}$

This salt (55 mg.) and p-nitrobenzyl bromide (25 mg.) were refluxed for 16 hr. in methanol (2 ml.) containing 0.5 N. potassium hydroxide (3 drops). The neutral fraction (12 mg.), isolated by ether extraction, showed only a very small ester carbonyl peak in the infra-red, and was not further examined.

The salt(49 mg.) was treated with chromium trioxide (40 mg.) in pyridine (2 ml.) for 3 days. On work up no neutral fraction was obtained.

p-Nitrobenzyl Isocedrelonate (B 26; R = p-nitrobenzyl):- Isocedrelonic acid (50 mg.) in methanol (2 ml.) was neutralised by the addition of sufficient 5% aqueous potassium hydroxide to make the solution just alkaline to litmus. p-Nitrobenzyl bromide (29 mg.) was added and the solution was refluxed for 24 hr. Crystallisation of the neutral fraction, isolated by ether extraction, afforded p-nitrobenzyl isocedrelonate (47 mg.) as plates from ethanol, m.p. 240-242.5°, $[\alpha]_D$ -28° (c 1.0), $\lambda_{max.}$ 241 mμ (ε 22,000), $\nu_{max.}$ (Nujol) 1700 (ester), 1666 (cyclohexenone), 1505s and 1340 (nitro group) $cm.^{-1}$, (Found: C, 68.82; H, 6.33. $C_{33}H_{37}NO_8$ requires C, 68.85; H, 6.48%).

Isocedrelonic Acid Lactone (B 28):- A solution of isocedrelonic acid (300 mg.) and dicyclohexylcarbodiimide (300 mg.) in benzene (15 ml.) was refluxed for 14 hr. After removal of the solvent the residue was adsorbed on Grade IV alumina (30 g.) from chloroform (5 ml.)

Elution with benzene (3 x 15 ml.) gave unchanged dicyclohexylcarbodiimide. Further elution with benzene (3x 30 ml.) and crystallisation of the product gave the norketone (B 27; R = H) (87 mg.), identical to material obtained by oxidation of isocedrelonic acid (m.p., mixed m.p., I.R. and silica-chromatoplate). Elution with 5 and 10% ether in benzene (60 ml. of each) gave dicyclohexylurea. Elution with 20% ether in benzene (100 ml.) and crystallisation of the product from ethanol gave isocedrelonic acid lactone (140 mg.) as fine needles, m.p. 219-221° (decomp.), $[\alpha]_D$ -90° (c 0.8), $\lambda_{max.}$ 236 mμ (ε 23,300), $\nu_{max.}$ (CCl_4) 3593 (hydroxyl), 1753 (δ-lactone), 1686 (cyclohexenone) $cm.^{-1}$, (Found: C, 73.91; H, 6.99 $C_{26}H_{30}O_5$ requires C, 73.91; H, 7.16%).

The lactone on farther reaction with dicyclohexylcarbodiimide was recovered unchanged.

The lactone was completely hydrolysed to isocedrelonic acid (m.p. and I.R.) on refluxing with 25% aqueous-methanolic potassium hydroxide solution for 12 hr.

The lactone (19 mg.) was heated under nitrogen in an oil-bath at 240° until gas evolution had ceased. The product, after filtration through Grade IV alumina in benzene-ether (95:5) and crystallisation from ethanol, gave the norketone (B 27 R = H) (10 mg.)

Norketone (B 57):- This was obtained by oxidation of the contents of the mother-liquors from crystallisation of isocedrelonic acid. Acid mixture (200 mg.) in dioxan (5 ml.) was treated with lead tetra-acetate (400 mg.) in benzene (10 ml.) for 2 hr.

The neutral fraction was isolated as before, and was absorbed on Grade II alumina (20 g.) from benzene. Elution with 5, 10, and 15% ether in benzene (20 ml. of each) followed by crystallisation gave the norketone (B 27; R = H). Elution with benzene-ether (1:1) gave the isomeric norketone (B 57) which formed prisms from chloroform-ethanol, m.p. 229-231°, $[\alpha]_D$ -35° (c 1.0), $\lambda_{max.}$ 220 mμ (ε 12,620), $\nu_{max.}$ ($CHCl_3$) 1751.5 (cyclopentanone), 1683 (cyclohexenone) $cm.^{-1}$ (Found: C, 76.33; H, 7.86. $C_{25}H_{30}O_4$ requires C, 76.11; H, 7.67%). The norketone was recovered unchanged from treatment with boron trifluoride etherate under the conditions used to form isocedrelone acetate.

Methyl Ester (B 60; R = Me):- In a similar fashion, methylation with ethereal diazomethane of the crystallisation residues (1.5 g.) from preparation of isocedrelonic acid gave a mixture of esters, (chiefly methyl isocedrelonate and one other as judged from the behaviour on a silica-chromatoplate). This was chromatographed over Grade III alumina (100 g.), and elution with 40% chloroform in benzene (100 ml.) gave the new ester, contaminated with a little methyl isocedrelonate. Rechromatography of this fraction (436 mg.) afforded the new methyl ester (B 60) which crystallised from ethanol as plates, m.p. 180-185° $\lambda_{max.}$ 210 mμ (ε 11,200), $\nu_{max.}$ ($CHCl_3$) 3520, 1735 (ester and cyclopentanone), 1683 $cm.^{-1}$, (Found: C, 71.63; H, 7.63. $C_{27}H_{34}O_6$ requires C, 71.34; H, 7.54%). Hydrolysis gave the corresponding acid, needles, m.p. 135-137° from aqueous ethanol. The acid on lead tetra-acetate oxidation gave a neutral product which consisted of the norketone (B 57) and an impurity (silica-chromatoplate).

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Part II

Synthetic Approaches to β-Vetivone.

Some Constituents of Vetiver Oil

Oil of Vetiver is the essential oil obtained by steam-distillation of the roots of Vetiver grass, Vetiveria zizanioides, Stapf. The plant is cultivated principally in Java and Reunion, but has also been developed in India and Ceylon as a source of the oil which finds extensive use in soap manufacture and perfumery.

Prior to 1939 it was known, thanks to the work of Ruzicka and others[1], that the oil contained di- and tricyclic sesquiterpene hydrocarbons and alcohols, and a tricyclic acid, but no attempts had been made to isolate any single compound and open structural investigations. The only mention up to this date in the literature of the presence of ketones appeared in a patent of 1902, which reported their isolation as semicarbazones, and regeneration by acid hydrolysis.[2] The first significant isolation and examination of the ketonic fraction of the oil was performed by Sabetay and Trabaud.[3] They employed the recently developed Girard P reagent[4] to give them a mixture of ketones, which they purified roughly by conversion to the semicarbazone, melting point 210° after several recrystallisations, followed by hydrolysis and distillation of the recovered ketone. They designated their compound as a ketone since the alcohol, obtained by sodium in ethanol reduction, did not form a trityl derivative. Shortly following this, two accounts appeared of degradative work on the ketonic constituents of Vetiver oil by Pfau and Plattner.[5] They isolated the ketones, either by the procedure of Sabetay and Trabaud, or by repeated fractional

distillation, and separated two of them by fractional crystallisation of the crude semicarbazone. The dextrorotatory ketone they named α-vetivone, and the laevo they named β-vetivone. They restricted their investigations to β-vetivone, and accorded it the structure (C 1) on the basis of the following.

The molar refractivity of β-vetivone, $C_{15}H_{22}O$, suggested that it was a bicyclic ketone with two double bonds. That one of these double bonds was in conjugation with the carbonyl group was shown both by the molar refractivity and by the sodium in ethanol reduction of β-vetivone to a mixture of dihydro-β-vetivols (C 6), in which the carbonyl group and one double bond had been reduced. This mixture on dehydration, followed by selenium dehydrogenation gave the known naphthalene, vetivalene (C 5), vetivazulene (C 3), the structure of which was proved by synthesis,[6] and traces of eudalene (C 4). β-Vetivone, itself, afforded on dehydrogenation vetivazulene and a naphthol, believed to be the hydroxyeudalene (C 2). These results established the bicyclic nature of the ketone, and the presence of two methyl groups. Ozonolysis of β-vetivone and of dihydroβ-vetivol gave one molecular proportion of acetone, thereby indicating that the unconjugated double bond was present in an isopropylidene group.

Whereas sodium in alcohol reduction of β-vetivone led to a mixture of dihydro-β-vetivols, catalytic hydrogenation gave only one isomer, which proved to be optically inactive. That this was due to the introduction of a plane of symmetry into the molecule and not to coincidence was confirmed by the formation from this optically inactive

dihydro-β-vetivol of, in all ten optically inactive degradation products and derivatives (C 6 - C 10) The presence of only one -CH(OH)- grouping, and one isopropylidene group in dihydro-β-vetivol requires that these lie in the plane of symmetry. Similarly, the two methyl groups must be opposed symmetrically, and the remaining eight carbon atoms must be divided into two groups of four, one on each side of this plane of symmetry. These requirements, taken in conjunction with the bicyclic nature of the molecule and the known structure of vetivazulene, clearly indicated the cis-fused structure (C 6) for dihydro-β-vetivol, and (C 1) for β-vetivone itself, on the reasonable assumption that epimerisation at the ring junction would not take place during hydrogenation over a nickel catalyst. A piece of confirmatory evidence came from oxidation of tetrahydro-β-vetivone (C 10) to the dicarboxylic acid (C 11). This acid was cyclised by heating with acetic anhydride to the cyclohexanone (C 12), which gave an indanol (C 13), identified by synthesis, on dehydrogenation.

Naves and Perrotet then reinvestigated α- and β-vetivone.[7] They confirmed for the most part the findings of the previous workers with regard to β-vetivone, and discovered the very close similarity in chemical and physical properties which exists between the two ketones. On selenium dehydrogenation α-vetivone gave vetivazulene and the same hydroxyeudalene (C 2) as β-vetivone. This suggested that it had the same carbon skeleton and a similarly placed carbonyl function. On ozonolysis α-vetivone also gave one molecular proportion of acetone, and on catalytic hydrogenation it afforded a mixture of optically

inactive tetrahydro-α-vetivols (C 9), which on oxidation yielded a single tetrahydro-α-vetivone (C 10). These facts, coupled with considerable similarity in the Raman spectra of the two compounds, allowed these authors to propose that α- and β-vetivone were structurally identical and differed only in the configuration of the secondary methyl group. They observed that the physical constants, boiling point, refractive index, and density, were slightly higher for certain compounds (e.g. α- and β-vetivone and α- and β-tetrahydrovetivone) in the α-series than for the corresponding β-vetivone derivatives. On the basis of the Auwers-Skita rule they therefore formulated α-vetivone as having the stereochemistry (C 14) in which the methyl group and the ring junction hydrogen atoms are all cis, and β-vetivone as having the stereochemistry (C 15) in which the methyl group is trans to the ring junction hydrogen atoms. This highly dubious assignment of configuration is made even more uncertain by the fact that a recent determination of the physical constants of the same compounds by Romanuk and Herout has in several cases reversed the above mentioned order.[8] It seems fair to say that although the structures of α- and β-vetivone have been rigorously established, the stereochemistry, save for the presence of a cis ring junction in both, is still uncertain.

A number of the other constituents of Vetiver oil have been subjected to chemical degradation in recent years by Chiurdoglu and his collaborators. They have assigned the structures (C 16) and (C 17) to the primary alcohols, bicyclovetivenol and tricyclovetivenol, obtained via acetylation of the alcohol fraction of oil from

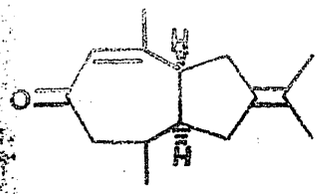
the Belgian Congo.[9] The structures of two tertiary alcohols were determined by examination of their respective dehydration products, bicyclovetivene and veticadinene, and shown to be (C 18) and (C 19).[10] Finally these workers have proved the structure (C 20) for a tricyclic hydrocarbon substituent.[11]

Only one instance appears to have been reported of the isolation of a sesquiterpene of the vetivane type from any natural source other than Vetiver oil. This is the unsaturated tertiary alcohol hinesol, $C_{15}H_{26}O$, which occurs as a mixed-crystal with eudesmol in the essential oil from Atractylodes lancea de Candolle. Two groups have established the vetivane skeleton for this alcohol, and shown that the hydroxyl group is on the side-chain. They differed, however, in their placing of the double bond, (known to be trisubstituted from the infra-red spectrum), one group preferring the structure (C 21),[12] and the other the structure (C 22),[13] both on inconclusive evidence.

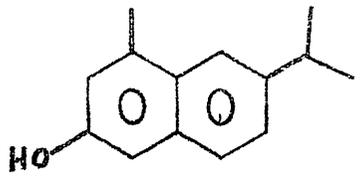
The postulates of Ruzicka and his collaborators on the biogenesis of the triterpenes by conformationally different cyclisations of all-trans-squalene[14] have been adapted by Hendrickson to provide an equivalent scheme for the sesquiterpenes.[15] These are considered to arise by cyclisation of a farnesol precursor with a trans central double bond and either a cis or trans terminal double bond, (C 23) and (C 30) respectively. These, by loss of hydroxide ion or its equivalent, and interaction of the resulting carbonium ion with any suitably juxtaposed double bond, lead to a series of monocyclic carbonium ions (C 24 - C 29). By consideration of the relative probability of

formation of each, its preferred conformation, and the possibilities for occurrence of further cyclisation, Hendrickson has been able to derive plausible pathways for the genesis of all the known sesquiterpene skeletons, except the bicyclofarnesols. These last require cyclisation similar in nature to that occurring with squalene.

The vetivane skeleton can be envisaged as arising by an anti-Markownikoff trans-anti-planar cyclisation of the alcohol (C 31), formed from the carbonium ion (C 28) by solvation, and a migration of one of the double bonds. The product from this cyclisation is the alcohol (C 32) which, by oxidation allylic to the double bond and dehydration involving the tertiary hydroxyl group, would lead to β-vetivone (C 33).



(C1)



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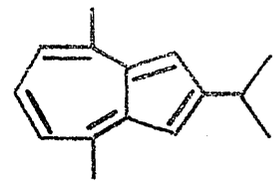

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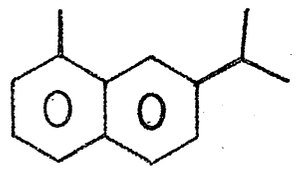

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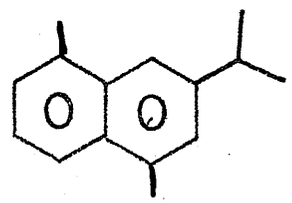
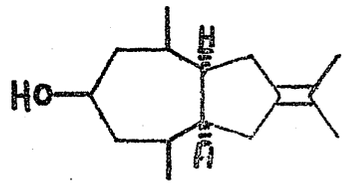
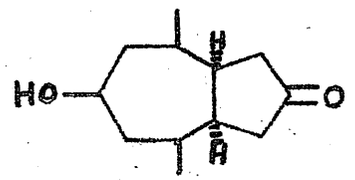


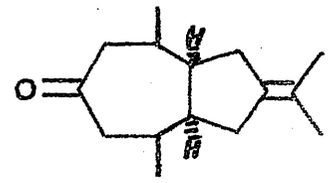
(C5)



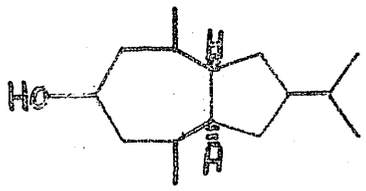
(C6) + dinitrobenzoate



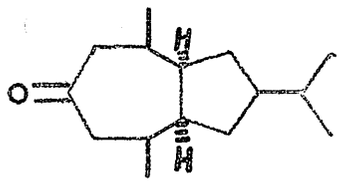
(C7) + semicarbazone



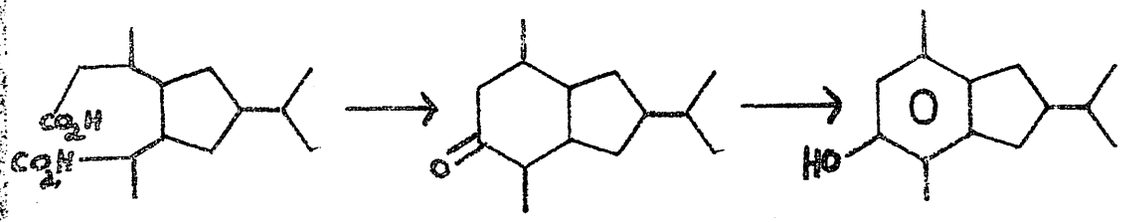
(C8) + dibenzylidene derivative



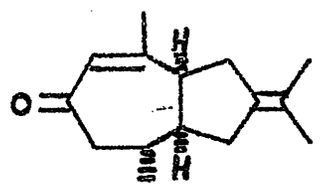
(C9) + dinitrobenzoate



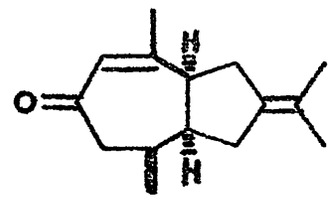
(C10) + dibenzylidene derivative



(C 11)　　(C 12)　　(C 13)



(C 14)



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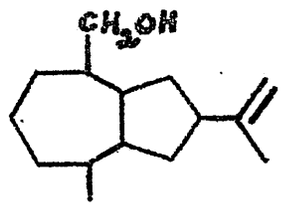
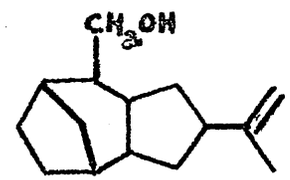


(C 16)



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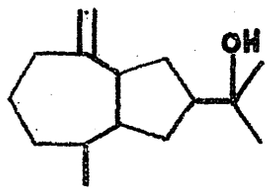

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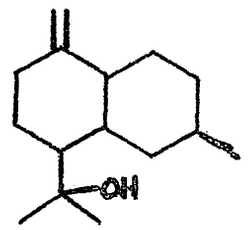

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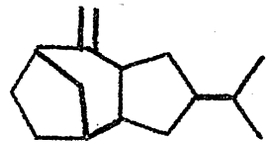

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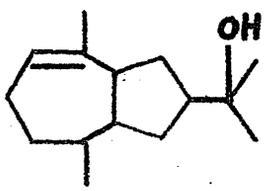

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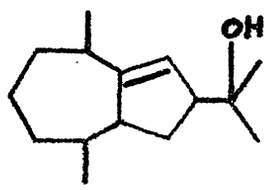

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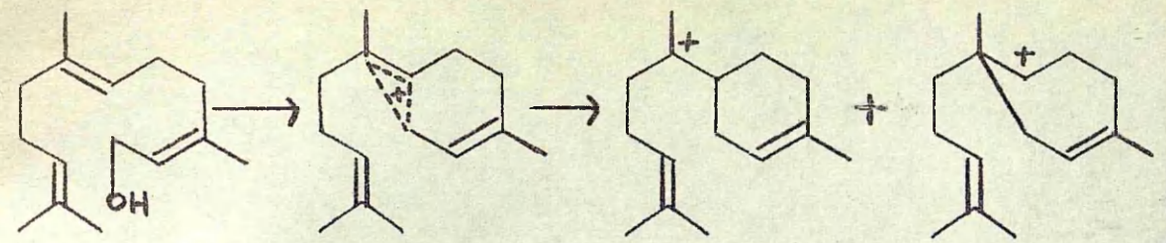
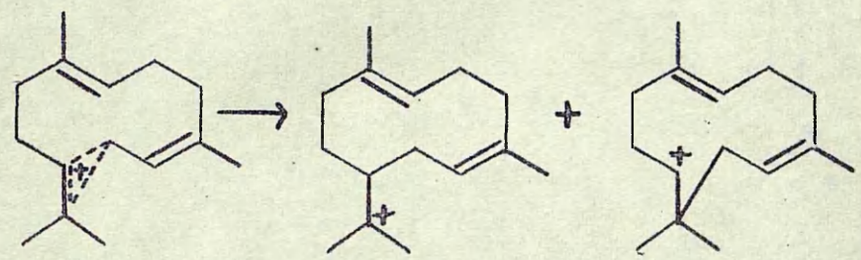


(C 23)

(C 24)

(C 25)



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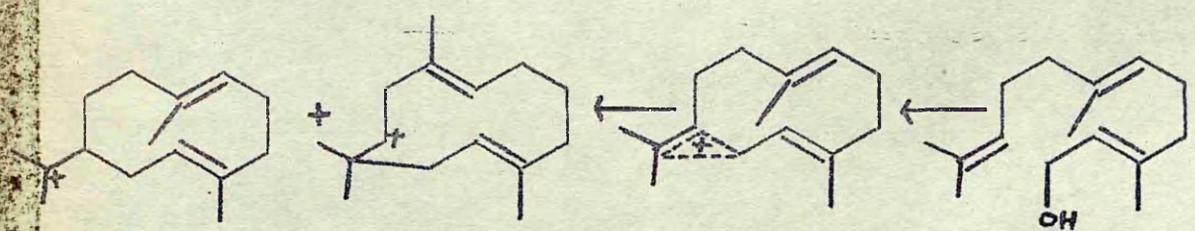
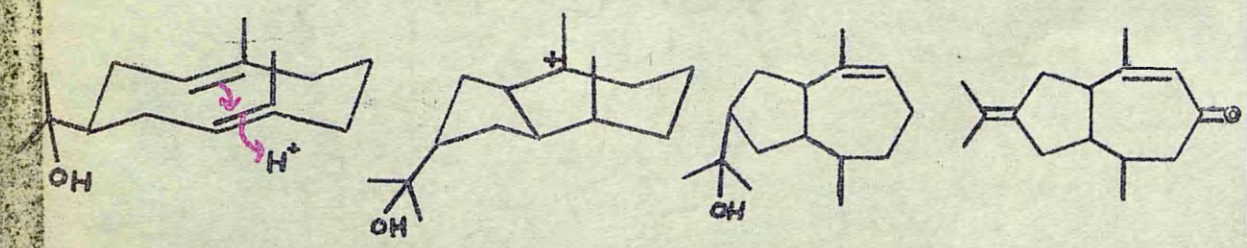
(C 27)



(C 28)

(C 29)

(C 30)



(C 31)

(C 32)

(C 33)

Synthetic Approaches to β-Vetivone

In considering the total synthesis of hydroazulenoid sesquiterpenes the skeletal symmetry of α- and β-vetivone renders them an attractive proposition. As described in the preceding section, the stereochemistry of α- and β-vetivone as a pair of epimers has been assigned, but which of them corresponds to the structure (D 1), and which to (D 2) has not been established. In the incomplete synthesis to be detailed below unambiguous stereochemical control of the three asymmetric centres in the vetivone skeleton was achieved, and the resulting vetivone would have been that of structure (D 1), β-vetivone according to Naves and Perrotet.[7]

The synthetic route employed falls into two sections. The first of these involved the synthesis of the hydrindane derivative (D 5; R = H) by a sequence of standard reactions. This intermediate possessed the necessary functionality for obtention of the cycloheptenone ring, and for addition of an isopropylidene side-chain to the five membered ring.

The synthesis of the hydrindane commenced with the Diels-Alder addition of maleic anhydride to hexa-trans,trans-2,4-diene to give the adduct (D 3). This particular Diels-Alder reaction has been very fully studied by Alder and Vogt.[16] They showed that potassium bisulphate dehydration of hex-2-en-4-ol (D 12) from addition of ethyl magnesium bromide to crotonaldehyde, gave a mixture of dienes (D 13). Reaction of this mixture with maleic anhydride led to the formation of

two easily separated adducts (D 15 = D 3) and (D 17), whose carbon skeletons were identified by dehydrogenation, followed by oxidation of the resulting products to benzene-1,2,3,4-tetracarboxylic acid (D 14) and benzene-1,2,3-tricarboxylic acid (D 18) respectively. The unreacted component of the diene mixture was shown to be hexa-cis,-trans-2,4-diene (D 16), since under forcing conditions it gave an isomeric adduct (D 21) with maleic anhydride, and the adduct (D 15) after it (the diene) had been isomerised with iodine. That the methyl groups in the adduct (D 21) were trans was proved by the formation of two stereoisomeric trans-diacids (D 22 and D 24), from addition of fumaryl chloride to the cis, trans-diene. Similarly, the methyl groups in the adduct (D 15) must have been cis since only one trans-diacid (D 19) resulted on epimerisation of the dihydroacid with concentrated hydrochloric acid at 180°, and a second cis-diacid (D 20) was obtained on heating to 240°. The epimerisations described were carried out on the corresponding dihydro-acids to obviate any change in the configurations of the methyl groups, brought about by double bond migrations under the reaction conditions employed. The initial adduct of hexa-trans,trans-2,4-diene (D 15) was assigned the all-cis stereochemistry, rather than that of the cis-adduct (D 20), on the basis of the " Alder Rules ",[17] which require that the dienophile should add to the diene in that steric sense which allows maximum orbital overlap between the π-bond systems of the two reactants in the transition state.

The next step in the synthesis of the hydrindane derivative lay in the reduction by lithium aluminium hydride of the adduct (D 3) to the diol (D 4; R = H). The configuration at each of the four asymmetric centres in the diol was taken to be the same as in the adduct. The basis for this lies in the well established stereospecificity of lithium aluminium hydride reductions, in which asymmetric centres, adjacent to carbonyl groups do not undergo epimerisation.[18] Thus, in the " closed circuit " transformation, (-)-menthone to menthol followed by oxidation to (-)-menthone, the reduction step was achieved by lithium aluminium hydride without any change in the specific rotation of the menthone.[19] Since no further reactions were performed on, or adjacent to these asymmetric centres the configuration of the final vetivone should have been that of the structure (D 1).

The diol (D 4; R = H) was converted to the corresponding di-p-toluenesulphonate and dimethanesulphonate by reaction with the appropriate acid chlorides in pyridine. A side-reaction in the formation of these derivatives was the formation of the tetrahydrofuran (D 7), by cyclisation of the intermediate mono-ester (D 6). A similar finding has been reported by Alder and Roth, who observed formation of the cyclic ether (D 9) on attempted ditosylation of the diol (D 8).[20] The amount of this byproduct formed can be kept to a minimum by the use of a large excess of reagent, and slow addition of the diol to it.

The double alkylation of malonic ester by either of these sulphonyl derivatives proved to be difficult. Reaction of the methanesulphonate with sodio-malonic ester in ethanol, containing a catalytic amount

of sodium iodide, furnished a small amount of the ester (D 5; R = Et). The yield, however, was found to be improved by employing a higher reaction temperature, and a moderately good yield was eventually obtained through the use of isopentanol with potassium isopentoxide as condensing agent. The use of this combination resulted in partial transesterification of the ethoxycarbonyl groups, and hence the crude ester was hydrolysed directly to the malonic acid (D 5; R = H), characterised as its dimethyl ester. The cyclisation of the bisdesmethyl di-p-toluenesulphonate (D 10) to (D 11) by sodiomalonic ester in ethanol has been reported as proceeding in high yield, (87%).[21] There seemed to be no obvious reason why the di-p-toluenesulphonate (D 4; R = $SO_2C_7H_7$) should not have been transformed equally successfully, but under these conditions it was recovered unchanged.

The method selected to effect expansion of the cyclohexene ring in the intermediate (D 5) to the cycloheptenone ring of β-vetivone was by cleavage of a dichlorocyclopropane, formed by addition of dichlorocarbene to the double bond in a suitable derivative. It is therefore appropriate at this point to review those features of dichloro carbene chemistry relevant to the synthesis.

Dichlorocarbene is one of a number of electron-deficient species of the general formula, $:CR_1R_2$. Its existence was first suspected by Hine who postulated it as an intermediate in the alkaline hydrolysis of chloroform.[22] Proof of this soon followed by the isolation and characterisation of its addition products with alkenes, the gem-dichloro-

cyclopropanes.[23,24] Since dichlorocarbene is rapidly solvolysed in aqueous or alcoholic media its preparation as an intermediate in organic chemistry is preferably done under aprotic conditions. A number of mechanistically similar ractions are available for its preparation, (D 25 - D 28), all of which involve formation of the CCl_3^- ion, which in turn loses chloride ion to give dichlorocarbene.

The opening of a simple alkyl-substituted gem-dichlorocyclopropane ring (D 29) can be envisaged as occurring in several possible ways; (a) by protonation of the ring to give a carbonium ion (D 29a); (b) by loss of halogen with the formation of an allene (D 29b); (c) by heterolysis, catalysed or uncatalysed, of the carbon-halogen bond leading to a cyclopropyl carbonium ion (D 29c), which could then rearrange to the resonance-stabilised allylic carbonium ion (D 29d). The first of these has not been reported; the second has been induced by the action of lithium alkyls.[29] With regard to the third possibility, Skell and Sandler reported, without experimental details, that the cyclopontene adduct (D 30; X = Cl, Br) reacted rapidly with alcoholic silver nitrate to give the ether (D 31; X = Cl, Br), and onshaking with aqueous silver nitrate to give the alcohol (D 32; X = Cl, Br), and that the cyclohexene adduct (D 33; X = Cl), which was about two hundred times less reactive, gave the corresponding cyclo heptene derivatives (D 34; R = OEt, OH; X = Cl).[30] In contrast, Doering and Hoffmann recorded that the cyclohexene adduct (D 33; X = Cl, Br) did not react with bromine or permanganate, was recovered unchanged from 50% potassium hydroxide in refluxing ethylene glycol, from alcoholic

silver nitrate at room temperature, from silver oxide suspension in ethanol, and in 62% yield from seven days' reflux with sodamide in benzene.[23]

On the other hand, where there is an electron-releasing substituent attached to the cyclopropane ring, which can stabilise the carbonium ion formed, or where formation of an aromatic ring results, then opening of a dichlorocyclopropane by path (c) occurs fairly readily. The dichlorocyclopropane from indene, (D 37) underwent solvolysis in methanolic potassium hydroxide with the production of 2-chloronaphthalene (D 38).[31] Similar sequences probably operate in the ring expansion by chloroform and alkali, of pyrroles and indoles to chloropyridines and quinolines respectively.[32] The keten acetal lost methyl chloride at 180° to give the ester (D 40).[33] The dihydropyran adduct(D 41) was converted by the action of quinoline at 140° to the oxepin derivative (D 42),[34] and other similar examples are known.[35]

It was considered that if this reaction, whereby the cyclohexene adduct (D 33; X = Cl) gave a substituted cycloheptene, could be applied to the dichlorocyclopropane from a derivative of the hydrindane (D 5), then the resulting hydroxyl group and vinyl chloride function could be employed as precursors of the double bond and carbonyl group respectively of β-vetivone. In view of the disparity between the results of Skell and Sandler and of Doering and Hoffmann it was considered desirable to re-examine the silver ion catalysed opening of 7,7-dichlorobicyclo-[4,1,0]-heptane (D 33; X = Cl), and investigate its opening by means

of other reagents. In the preparation of this compound, and of others to be described below, dichlorocarbene was prepared by the method of Parham and Schweitzer, by the action of sodium methoxide on methyl trichloroacetate in pentane at room temperature in the presence of the alkene substrate.[26]

In our hands the cyclohexene adduct (D 33; X = Cl) was found to be stable to silver nitrate in aqueous dioxan for two days at room temperature, and to refluxing with siver nitrate in methanol. It was also recovered unchanged from treatment with boron trifluoride etherate, p-toluenesulphonic acid in benzene under reflux, perchloric acid in acetic acid at room temperature, collidine at 110°, and quinoline at 140°. On refluxing with silver acetate in acetic acid for five days a 40% conversion, as estimated by Gas-Liquid-Chromatography, to the acetate (D 32; R = Ac; X = Cl) was achieved. Separation from unchanged starting material was obtained by hydrolysing the mixture and isolating the alcohol (D 32; R = H; X = Cl) by chromatography over alumina. The alcohol was characterised by the preparation of a 3,5-dinitrobenzoate, and by conversion to the cycloheptenone (D 35), isolated as its 2,4-dinitrophenylhydrazone. Dehydration of the alcohol by phosphorus pentoxide in petrol gave a volatile and unstable diene (D 36), [$\lambda_{max.}$ 274 mμ]. Owing to the low over-all yield in the preparation of the alcohol and the instability and volatility of the diene, it was decided to prepare some gem-dichlorocyclopropanes from alkenes of much higher molecular weight.

The method was first applied to cholesterol tetrahydropyranyl ether (D 43) which was recovered unchanged. The reason for this was attributed to steric hindrance in the adduct, by virtue of non-bonded interactions between one of the chlorine substituents on the cyclopropane ring and the pseudo-axial hydrogen atoms at C_7 and C_9 in the rigid ring B. That this was probably so was borne out by the preparation, under the same reaction conditions, of the adduct (D 44) from cholest-2-ene, in which ring A can adopt a conformation which does not have non-bonded interactions comparable in magnitude with those present in an adduct from cholesterol. This adduct from cholest-2-ene was judged not very suitable for studies of ring opening, since this could take place in two approximately equivalent ways, with the consequent formation of product mixtures. The more useful adduct in this respect, from β-amyra2,12-diene (D 45) did not form, and this may again be due to steric hindrance caused by interactions of the chlorine atoms with the α- or β-methyl group at C_4.

The reaction sequence when performed on isophyllocladene (D 46) resulted in the formation of a chlorine containing derivative. This analysed as $C_{21}H_{31}Cl$, had $\lambda_{max.}$ 243 mμ (ε 18,000) in the ultra-violet spectrum, and bands in the infra-red spectrum at 1617w, 1588m (conjugated double bond C:C stretching vibrations), 890s (exomethylene), 875s (trisubstituted double bond), 822s (vinylic chlorine) $cm.^{-1}$ The ultra-violet spectrum indicated that it was a heteroannular diene, and this, in conjunction with the infra-red spectrum, suggested the chlorodiene (D 48) as the probable structure. Proof of this followed

from the formation, by controlled ozonolysis, of an α-chloroketone (D 49), $C_{20}H_{29}ClO$, [$\lambda_{max.}$ 257 mμ (ε 6,790), $\nu_{max.}$ (CCl_4) 1697.5 cm.$^{-1}$]. The abnormally high position of the maximum in the ultra-violet spectrum of this αβ-disubstituted enone is consistent with that observed for the parent system (D 50),[36] which had $\lambda_{max.}$ 241 mμ (ε 7,800). The formation of the diene can be rationalised as proceeding via the desired dichlorocyclopropane (D 47), from which hydrogen chloride has been eliminated in precisely the same manner as occurred with the adduct from indene. Attempts to isolate the supposed intermediate cyclopropane by carrying out the reaction in the presence of a large excess of methyl trichloroacetate over sodium methoxide failed.

Investigation of this chlorodiene was then commenced with a view to finding a method for hydrolysing the vinyl chloride function to a carbonyl, as would be required at some stage in the proposed synthesis of β-vetivone. The method sought was required either to be very mild, or to give the carbonyl group in a protected form, since the vetivones are sensitive to alkali and mineral acids. The chlorodiene was found to be stable to sodium methoxide in refluxing diethylene glycol dimethyl ether for 15 hr., and to sodium acetate in refluxing acetic anhydride for 24 hr. Success, however, attended the use of sodamide in piperidine under reflux,[37] which gave an oily product whose infra-red spectrum, [$\nu_{max.}$ 1611w, 1578m, 889s, and 859s cm.$^{-1}$], indicated retention of the same conjugated diene system, but loss of the vinylic chlorine. That this compound was the enamine (D 51) was shown by its solubility in dilute hydrochloric acid, and the formation

of a crystalline picrate, which analysed correctly for $C_{32}H_{44}N_4O_7$ as required.

The hydrolysis of the enamine was accomplished by a dilute buffered solution of acetic acid in methanol, a procedure which has been successfully employed for the hydrolysis of steroidal enamines.[38] This gave, after chromatography, a crystalline solid in low yield. This analysed as the desired αβ-unsaturated ketone (D 52), but its physical properties were at variance with its possessing this structure. It had no ultra-violet absorption above 220 mμ, and had a band in the infra-red spectrum at 1719 $cm.^{-1}$ (cyclohexanone). The clue to its structure came from the unexpectedly high melting point of 252°, [cf. the enone (D 50), m.p. 115°, and the chloroenone (D 49), m.p. 123-126°], and from the failure to obtain a mass-spectrometric determination of the molecular weight on account of its involatility. These data, and the known peculiarities of the exomethylene cyclohexanone system indicated formulation as the dimer (D 53). This arises from a Diels-Alder reaction of the exomethylene double bond of one molecule of (D 52) with the enone grouping of a second. The structure of the dimer (D 54) resulting from attempted preparation of 2-methylenecyclohexanone has been unambiguously determined by the degradative work of Mannich.[39] The stereochemistry assigned to the dimer (D 53) is that predicted on the basis of the " Alder Rules " of endo addition from the least hindered face (in this case the α-face) of both molecules. That these rules apply to this type of Diels-Alder was established by the dimerisation of the (±)-ketone (D 55)

in this steric fashion, (D 56), to furnish as the major product the (±)-dimer (D 57). This could be given the stereochemistry shown, since it was subsequently converted to (+)-onoceran-8,8'-diol (D 58).[40]

The conversion of a cycloalkene to the homologated cycloalkenone, by way of a dichlorocyclopropane intermediate, had now been shown to be feasible, and attention was therefore directed to effecting the same transformation on a suitable derivative of the hydrindane (D 5). The dicarboxylic acid (D 5; R = H) was decarboxylated at 220° to give the monocarboxylic acid (D 59; R = H). It had earlier been ascertained that an all cis-3,4,5,6-tetrasubstituted cyclohexene would give an adduct with dichlorocarbene, by conversion of the methyl ester (D 60), obtained from the anhydride (D 3) in the usual manner, to the corresponding dichlorocyclopropane derivative (D 61). The methyl ester (D 59; R = Me) confirmed this by furnishing the adduct (D 62; R = Me), characterised by hydrolysis to the parent acid. Reaction of this ester with methyl Grignard reagent afforded the alcohol (D 63). This, after dehydrationby phosphorus oxychloride in pyridine, provided a mixture of two olefins, as determined by Gas-Liquid-Chromatography. The infra-red spectrum of the mixture clearly showed that one of the constituents was the isopropenyl derivative (D 65), by virtue of bands at 1633w and 887m $cm.^{-1}$ The second olefin, present in much larger amount, was obtained pure by repeated crystallisation, and was formulated as the isopropylidene isomer (D 66) on the following basis. Its nuclear magnetic resonance spectrum

indicated the absence of ethylenic protons. Its oxidation, by the Lemieux method, afforded a ketone which from its analysis as $C_{12}H_{16}Cl_2O$ and a band in the infra-red spectrum at 1747.5 cm.$^{-1}$ was clearly the cyclopentanone (D 67).

Dehydration of the alcohol by refluxing it with p-toluenesulphonic acid in benzene gave a different prod uct, which did not crystallise. Examination of this by Gas-Liquid-Chromatography showed it to be one compound, containing only trace amounts of the above two olefins. These, in turn, were converted to this new compound on treatment with p-toluenesulphonic acid under identical conditions, which suggested their being intermediates in its formation. This new compound proved to be unstable on standing, and an analysis completely satisfactory for its formulation as an isomer of the olefins was not obtained. However, from the mode of formation one would predict that the most likely structure for this compound would be that of the endocyclic isomer (D 64), formed by prototropic rearrangement of the double bond in the olefins (D 65 and D 66). The spectra of the compound lent considerable support to this structural assignment. The infra-red spectrum was similar to that of the olefin (D 66), thereby indicating retention of the dichlorocyclopropane ring, but possessed several additional peaks, including one at 856 cm.$^{-1}$, consistent with there being a trisubstituted double bond. The nuclear magnetic resonance spectrum confirmed this by showing the presence of one ethylenic proton, τ 4.88 split as a doublet (J = 10 cps.) by the adjacent proton on the ring junction, and by having two doublets, τ 8.79

(J = 9 cps.) and τ 8.47 (J = 9 cps.) assignable to two pairs of secondary methyl groups, one slightly deshielded by the nearby double bond. In support of this, one may quote the work of Turner and Garner,[41] who suggested, on the basis of heats of hydrogenation, that, in the isomeric pairs, methylenecyclopentane, 1-methylcyclopentene, and ethylidenecyclopentane, 1-ethylcycl opentene, the endocyclic isomer is the more stable, and who showed that treatment of ethylidenecyclopentane with p-toluenesulphonic acid in acetic acid at 100° gave a mixture in which the endo isomer greatly predominated.

With the isolation and positive identification of the olefin (D 66) the necessary intermediate for the final stages of the synthesis was now to hand. Initial attempts to cleave the dichlorocyclopropane ring centred around the use of sodamide in piperidine, which, it was hoped, would perform in one reaction firstly the base-catalysed elimination of hydrogen chloride to give the chlorodiene (D 68), and secondly replacement of the vinylic chlorine in this, with formation of the required enamine (D 69). This failed completely. Reaction, under conditions which gave the enamine (D 51) from the chlorodiene (D 48), produced from the olefin (D 66) intractable polymer. A similar result was obtained on attempted opening of the dichlorocyclopropane from cholest-2-ene (D 44).

It was therefore decided to investigate opening of the ring by the action of siver acetate in acetic acid, which had proved successful in the case of the cyclohexene adduct (D 33; X = Cl). After 4 days' reflux with these reagents the olefin (D 70 = D 66) furnished

an oil which showed weak acetate absorption in the infra-red spectrum. Filtration through alumina in petrol removed the small percentage of acetate present and gave a chlorine containing hydrocarbon, which Gas-Liquid-Chromatography showed to be one compound, containing only a trace of starting material. This compound also proved to be unstable on standing, but the analysis of a distilled sample, although not completely satisfactory, did indicate that loss of hydrogen chloride from the starting material had occurred. First thought suggested that the dichlorocyclopropane had opened in the expected manner to give the conjugated chlorodiene (D 68), however, the absence of absorption above 220 mμ in the ultra-violet spectrum eliminated this possibility. The infra-red spectrum, [$\nu_{max.}$ 1630m, 1611m, 886s (exomethylene), 843s (vinylic chlorine) $cm.^{-1}$], indicated the presence of two double bonds, one an exomethylene, and a vinylic chlorine. A peak in the nuclear magnetic resonance spectrum at τ 4.7 (1 proton), and two at τ 5.19 and 5.27 (each 1 proton) established that the second double bond was trisubstituted and confirmed the exomethylene group respectively. In addition, the spectrum revealed the presence of two secondary methyl groups, [doublets at τ 8.91 (J = 3) and τ 9.03 (J = 2)], and one methyl group attached to a double bond, τ 8.18. The formula, the presence of a minimum of two double bonds, and the reasonable assumption that the compound is at least bicyclic indicate that there must be a third ring or a third double bond, tetra-substituted in character. With regard to the latter possibility there is no structure, based on (D 70) as starting material, which is

consistent with all the facts. With regard to the former there is only one structure (D 73) which will accomodate the known facts, and for which a simple mechanism can be proposed for its derivation from (D 70).

This structure could arise by the silver-catalysed opening of the dichlorocyclopropane ring in the normal manner to give the carbonium ion (D 71), which could then interact with the isopropylidene side-chain to form a second carbonium ion (D 72), stabilised by the loss of a proton. The formation of the second carbonium ion could, however, be a concerted process, in which opening of the ring is anchimerically assisted by the isopropylidene double bond. For this to occur the stereochemistry of the adduct would require to be as shown in (D 70), which is the stereochemistry predicted on the assumption that, in common with other electrophiles, dichlorocarbene adds to double bonds from the least hindered side of the molecule. Some circumstantial evidence for a concerted process comes from comparison of the extent of reaction of the isopropylidene derivative with the methyl ester (D 62). After four days the former had completely reacted to give one product, whereas, under the same conditions, only about 50% of the latter had done so, and a mixture of products resulted.

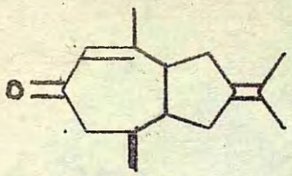
It was hoped that in the case of the methyl ester (D 62) the dichlorocyclopropane ring might open in the normal manner and provide either the chlorodiene (D 74) or the epimeric acetates (D 75). As mentioned above a mixture of products resulted, which was separated by alumina-chromatography into two pairs of compounds, as revealed by

Gas-Liquid-Chromatography and chromatoplate examination. The major component of the first pair was the starting ester (D 62), and the minor component may have been the chlorodiene (D 74), since the mixture had $\lambda_{max.}$ 253 mμ . The second pair was more polar and had no ultra-violet absorption above 220 mμ . It may have been the required acetates since prolonged treatment with methyl Grignard reagent, followed by hydrolysis of the product, gave a glass with intense hydroxyl absorption in the infra-red spectrum but no carbonyl . This, which should have been the diol (D 76) was dehydrated with phosphorus oxychloride in pyridine at 0°. The hydroxyl free product, after filtration in petrol through alumina was found to consist of at least sixteen compounds on Gas-Liquid-Chromatographic examination This experiment terminated our endeavours to synthesise β-vetivone.

Although the use of a dichlorocyclopropane ring intermediate was unsuccessful in elaborating the cyclohexene ring to that of a cycloheptenone it is possible that a similar intermediate, formed with chloromethoxy carbene,[42] might be suitable in that its silver-catalysed opening could well lead to the readily hydrolysed enol ether of a cycloheptenone.

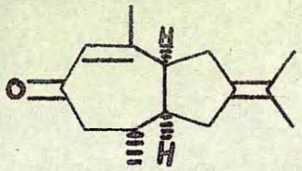
An alternative future route to β-vetivone which does not involve the use of a cyclopropane intermediate has also been considered. This would require the synthesis of the methoxyhydrindane derivative (D 77) by a route analogous to that for the intermediate (D 59), and possessing the same stereochemical advantages. Introduction

of the isopropylidene group, as previously described, followed by hydrolysis of the enol ether function , and bromoacetic ester alkylation of the resulting cyclohexanone should lead to the product (D 78). A Baeyer-Villiger reaction performed on this ester would furnish the lactone (D 79), which, on base treatment, would undergo β-elimination to form the acid (D 80). This, after esterification, could be cyclised by the Dieckmann procedure to a vetivone (D 81) of the same stereochemistry as in the previous synthesis.

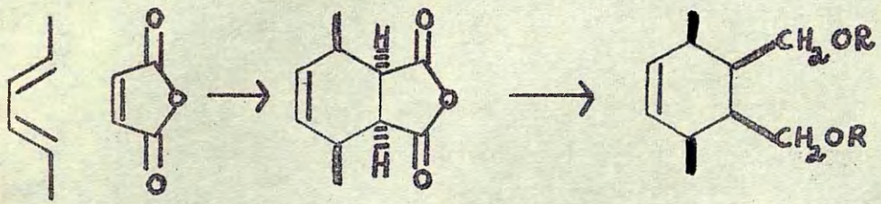


(D 1)

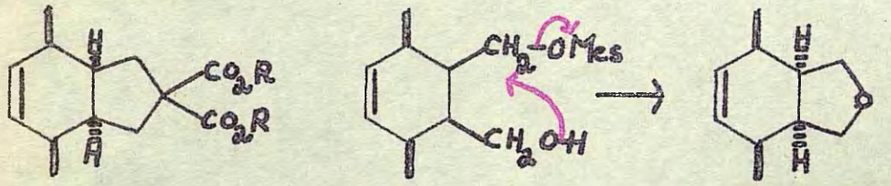
α- and β-Vetivones



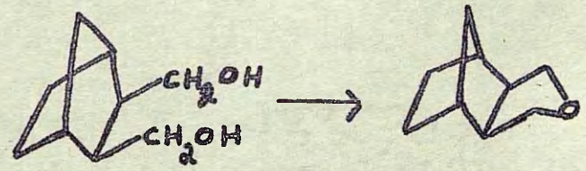
(D 2)



(D 3) (D 4)

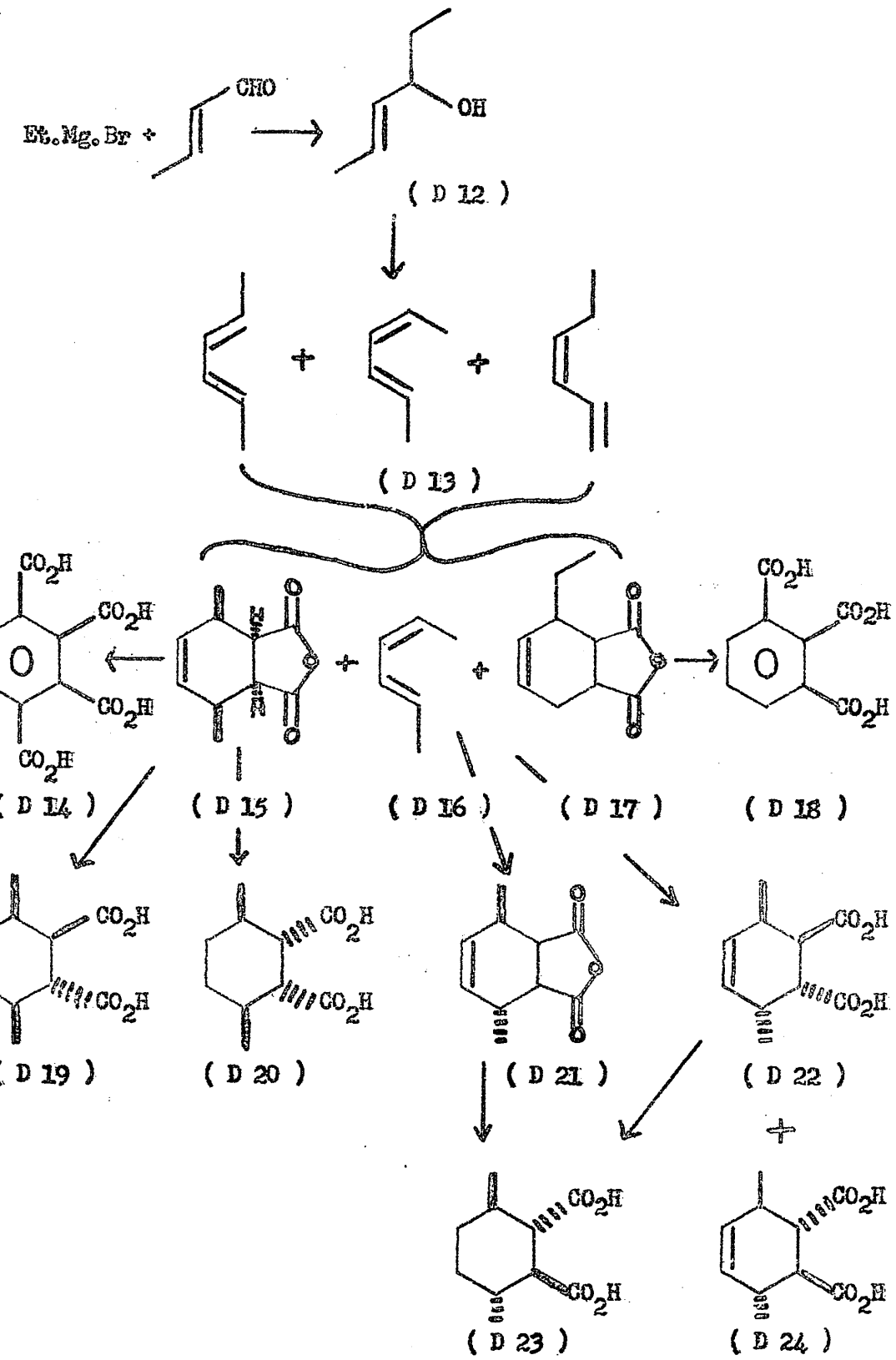


(D 5) (D 6) (D 7)



(D 8) (D 9)

(D 10) (D 11)


Et.Mg.Br +
CHO
OH
(D 12)
(D 13)
CO2H
(D 14)
(D 15)
(D 16)
(D 17)
(D 18)
(D 19)
(D 20)
(D 21)
(D 22)
+
(D 23)
(D 24)

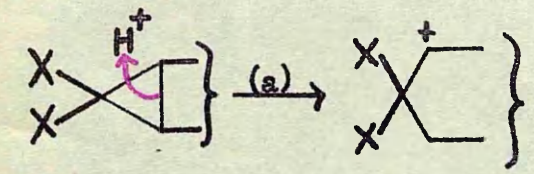
(D 25) $CHCl_3 + O^tBu$ [25]

(D 26) $Cl_3C.COOEt + OR \longrightarrow Cl_3C-C(O^-)(OR)-OEt$ [26]

(D 27) $Cl_3C.CO.CCl_3 + OR \longrightarrow Cl_3C-C(O^-)(OR)-CCl_3$ [27]

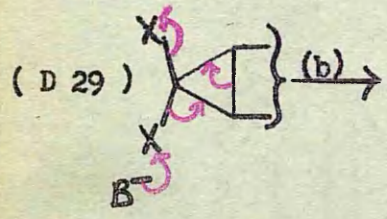
(D 28) $Cl_3C-C(=O)-O^-\ Na^+$ [28]

$CCl_3^- \xrightarrow{-Cl^-} :CCl_2$

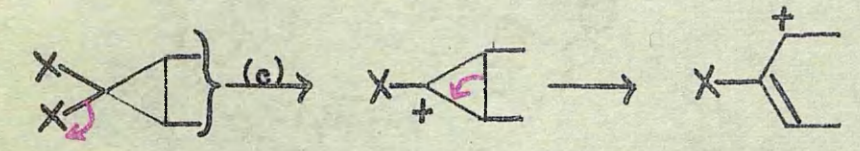


(D 29a)

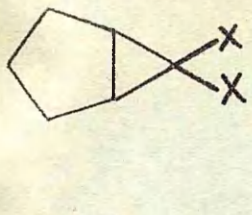
(D 29)



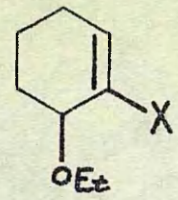
(D 29b)



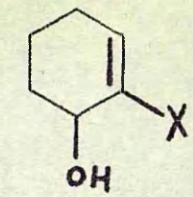
(D 29c) (D 29d)



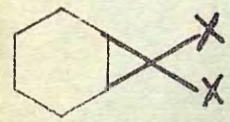
(D 30)



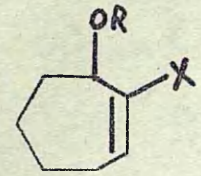
(D 31)



(D 32)



(D 33)



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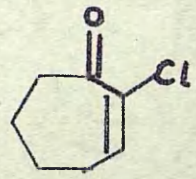

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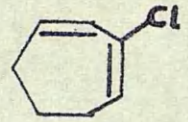

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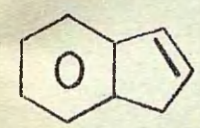

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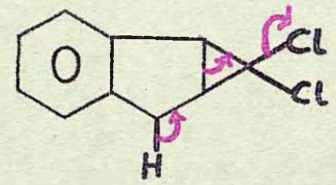

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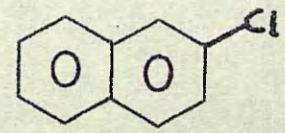

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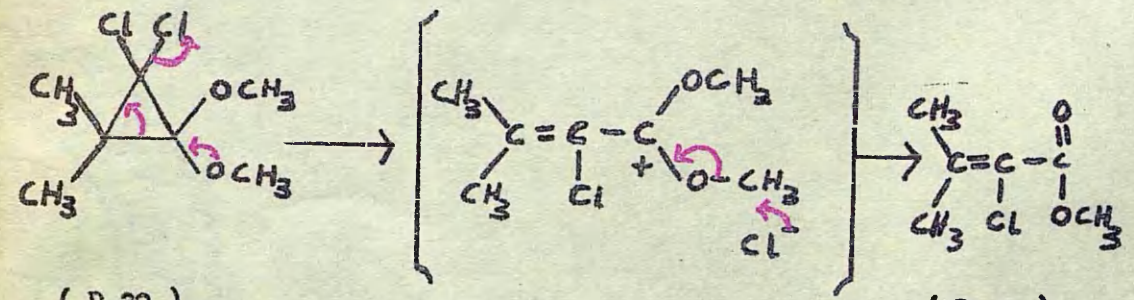

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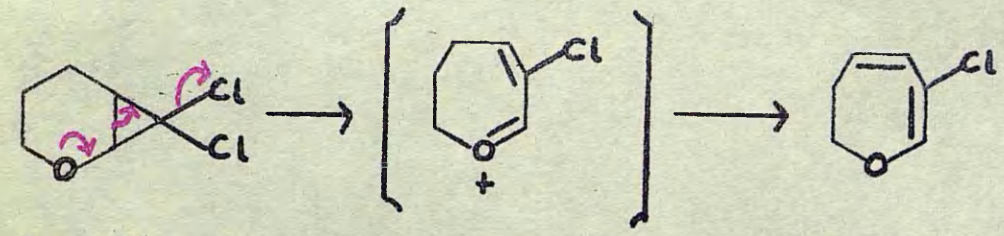

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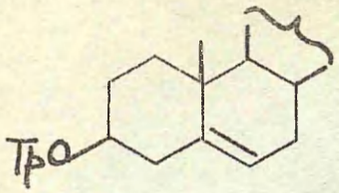

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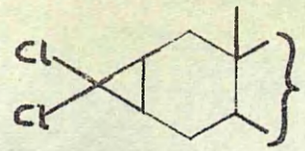

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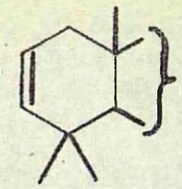

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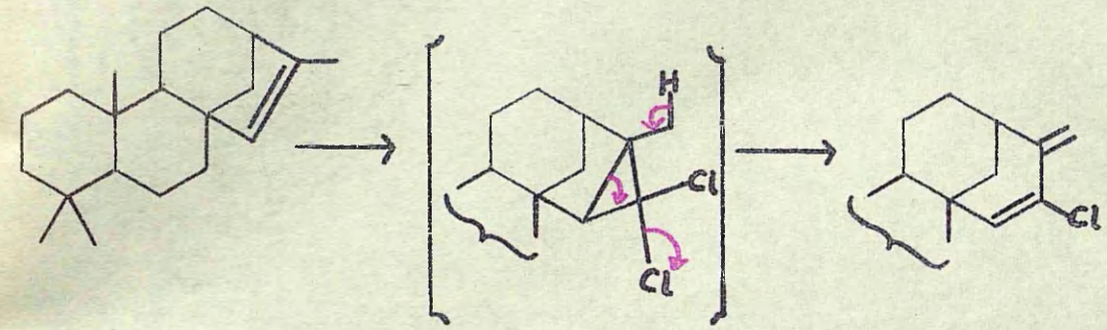

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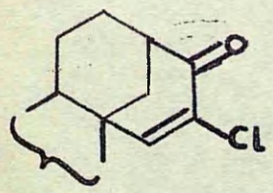
(D 47)

(D 48)



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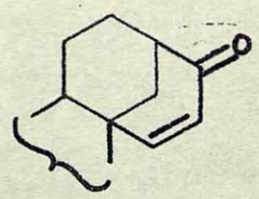

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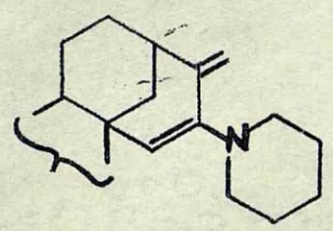

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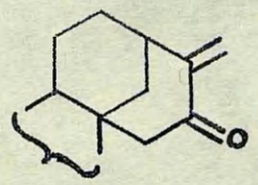

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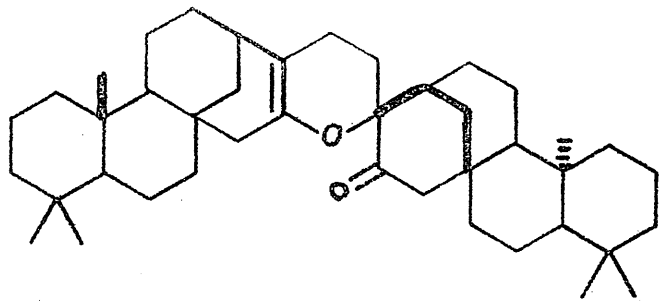

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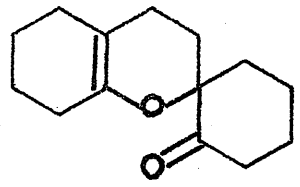

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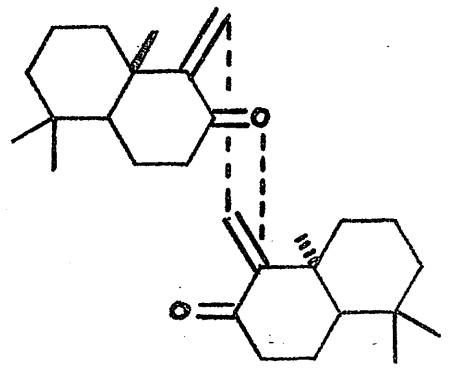

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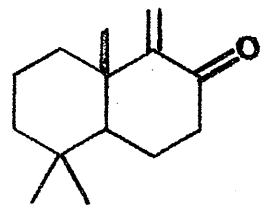

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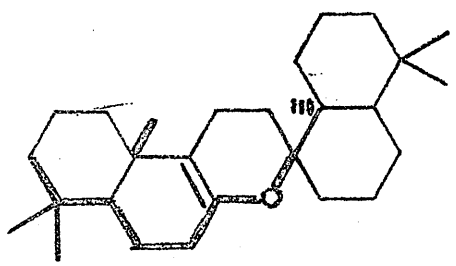

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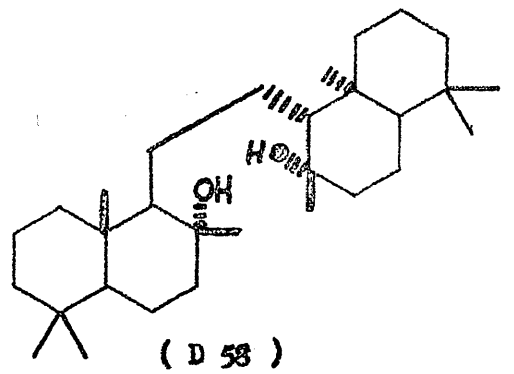

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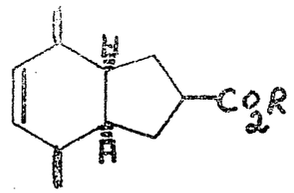

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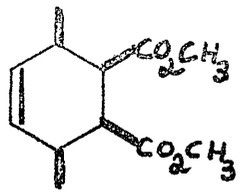

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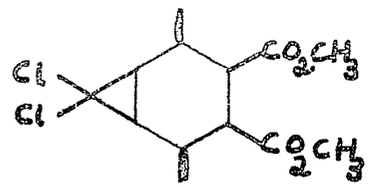

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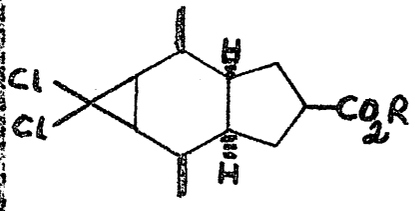

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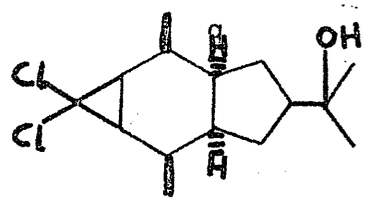

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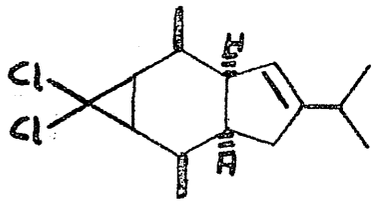

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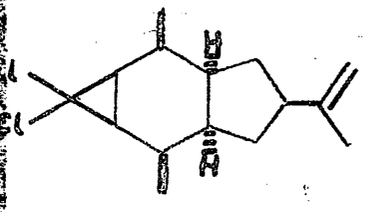

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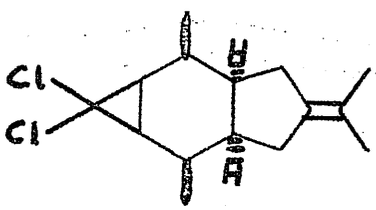

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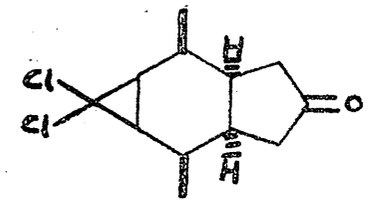

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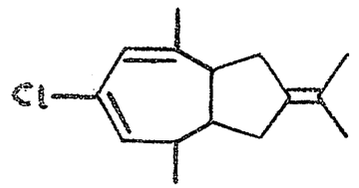

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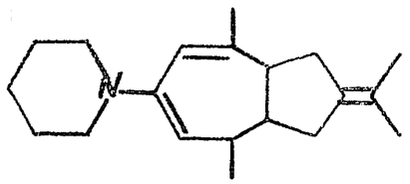

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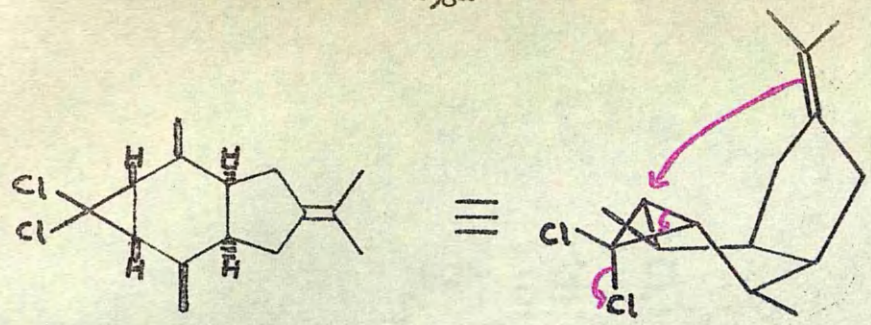

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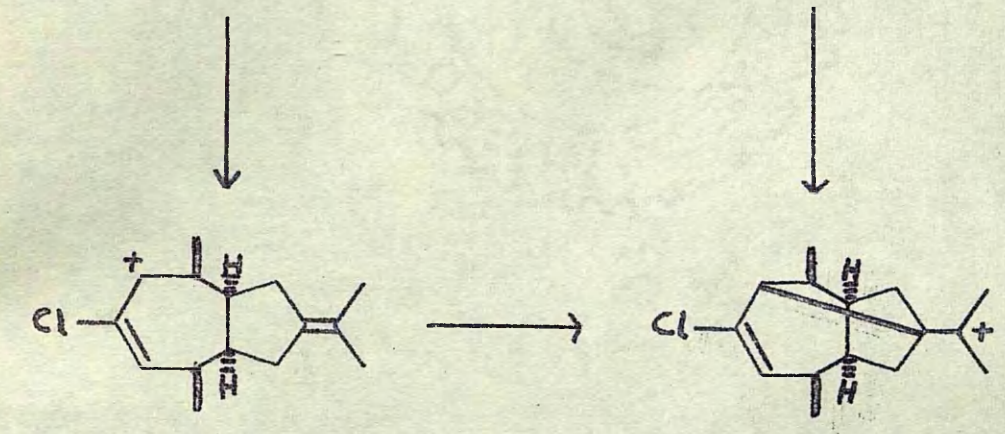

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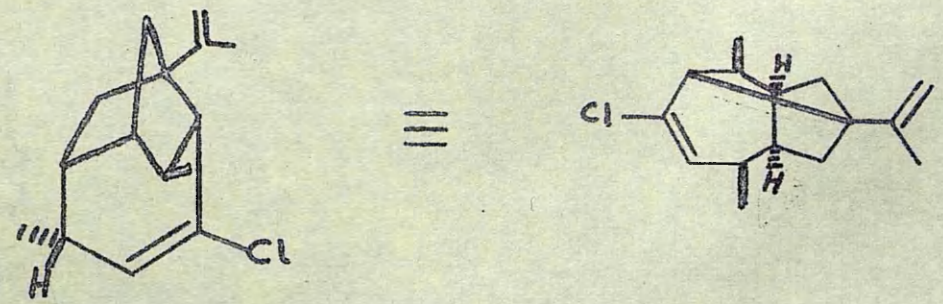

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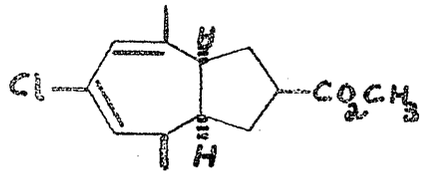

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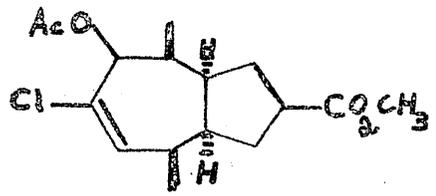

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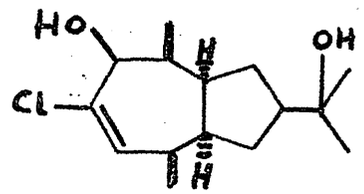

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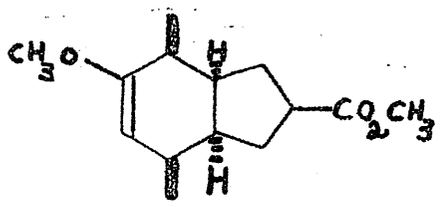

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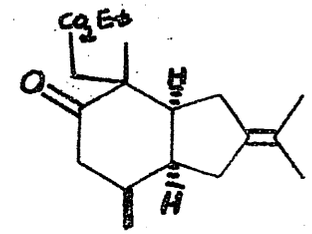

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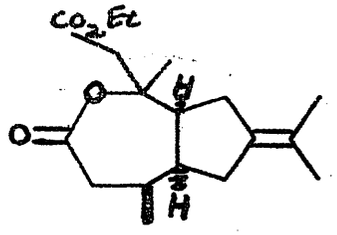

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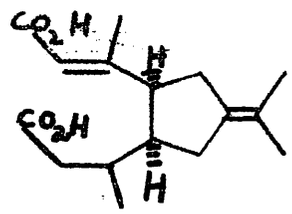

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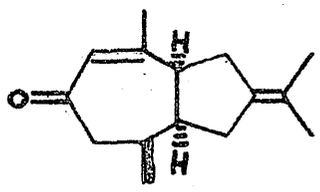

(D 81)

Experimental

For general experimental procedures see p. 47.

The Diene Mixture from Dehydration of Hex-2-en-4-ol:- Hex-2-en-4-ol was prepared in 78% yield by the method of Adams and Geissmann.[43] The product had b.p. 60-62°/ 30 mm., [lit.[43] b.p. 55°/ 15 mm.] The alcohol (180 g.) and p-toluenesulphonic acid (10 g.) were heated in an oil-bath at 110-120°. The distillate was passed up a small fractionating column, and collected with ice-cooling. The organic layer was separated and washed with satd. sodium chloride solution and dried over anhydrous calcium chloride. Distillation gave the mixture of hexadienes (80 g.; 61%).

3,6-Dimethylcyclohexene-4,5-dicarboxylic Acid Anhydride:- This was prepared by the procedure of Alder and Vogt[16], and had m.p. 93-96°, (lit.[16] m.p. 93°).

3,6-Dimethyl-4,5-dihydroxymethylcyclohexene (D 4; R = H):- 3,6-Dimethylcyclohexene-4,5-dicarboxylic acid anhydride (3 g.) in ether (100 ml.) was added dropwise to a stirred solution of lithium aluminium hydride (1.61 g.; 100% excess) in ether (40 ml.). The resulting mixture was refluxed for 8 hr., cooled, and treated with excess ethyl acetate in ether (1:1) to remove unreacted lithium aluminium hydride. The ether layer was separated, after addition of dil. sulphuric acid to the mixture, washed with sodium hydrogen carbonate solution, water and dried. Removal of the ether, and crystallisation of the residual oil from chloroform-petrol gave 3,6-dimethyl-4,5-

dihydroxymethylcyclohexene (2.45 g.; 86%), m.p. 77-78°, (Found: C, 70.36; H, 10.42; C-methyl, 16.80. Calc. for $C_{10}H_{18}O_2$ C, 70.54; H, 10.66; C-methyl, 17.65%), (lit.[44] reports this compound as an oil).

3.6-Dimethyl-4,5-di-p-toluenesulphonyloxymethylcyclohexene (D 4; R = $SO_2C_7H_7$):- A solution of the above diol (1 g.) in pyridine (10 ml.) was added dropwise to ice-cold p-toluenesulphonyl chloride (2.6 g.) in pyridine (10 ml.). The resulting mixture, after 4 days at 0°, was poured into dil. sulphuric acid and the product isolated by ether extraction. Crystallisation from ethanol gave the di-p-toluenesulphonate (1.3 g.) as prisms, m.p. 95-97.5°, (Found: C, 60.40; H, 6.11; S, 13.18. $C_{24}H_{30}O_6S_2$ requires C, 60.24; H, 6.32; S, 13.41%).

3.6-Dimethyl-4.5-dimethanesulphonyloxymethylcyclohexene (D 4; R = SO_2CH_3):- A solution of the above diol (36.5 g.) in 1:1 pyridine-ether (100 ml.) was added dropwise over 4 hr. to a stirred, ice-cold solution of redistiliied methanesulphonyl chloride (100 ml.) in pyridine (100 ml.). After standing 2 days at room temperature, the mixture was poured into excess ice-cold dil. sulphuric acid and the product extracted into ether. The combined ether extracts were washed with dil. hydrochloric acid, 5% sodium hydroxide solution until the washings were alkaline to litmus, and water, then dried. Removal of the solvent, and crystallisation of the residual oil from methanol (75 ml.) afforded the dimethanesulphonate (60 g.; 86%), m.p. 73-75°, (Found: C, 44.40; H, 6.70. $C_{12}H_{20}O_6S_2$ requires C, 44.17; H, 6.80%).

2,5-Dimethylbicyclo[4.3.0]non-3-en-8.8-dicarboxylic Acid (D 5; R = H):- A solution of potassium isopentoxide, from potassium (13.16 g.; 1% excess over theory) and isopentanol (300 ml.) was added dropwise over 3 hr. to a vigorously stirred refluxing solution of the dimethanesulphonate (54 g.), sodium iodide (2 g.) and diethyl malonate (26 ml.; 5% excess) in xylene (60 ml.) and isopentanol (40 ml.) under nitrogen. The resulting solution was refluxed for a further 18 hr. during which potassium methanesulphonate precipitated. The solution was then cooled and poured into water (3 l.) This was acidified by the addition of 6N. sulphuric acid, and the crude product was isolated by petrol extraction (3×400 ml.). After removal of the solvent the mixture was flash-distilled, b.p. 115-140°/ 4×10^{-4} mm. The crude ester thus obtained was hydrolysed with potassium hydroxide (100 g.) in methanol (200 ml.) and water (200 ml.) under reflux for 1.5 hr. The methanol was taken off under reduced pressure, and the remaining solution, after dilution to 1 l. with water, was ether-extracted and then poured into ice-cold conc. hydrochloric acid (200 ml.) to give the dicarboxylic acid. This crystallised from aqueous ethanol as needles (22 g.; 56%), m.p. 197-197.5° (decomp.), $\nu_{max.}$ (Nujol) 1706, 1685 (carboxyls), 925 (carboxyl OH deformation), 689 (cis double bond) $cm.^{-1}$, (Found: C, 65.43; H, 7.56. $C_{13}H_{18}O_4$ requires C, 65.53; H, 7.61%).

The dimethyl ester (D 5; R = Me) prepared in the usual way from the action of ethereal diazomethane, formed plates from aqueous methanol, m.p. 59-61°, (Found: C, 67.64; H, 8.02. $C_{15}H_{22}O_4$ requires C, 67.64;

H, 8.33%).

7,7-Dichlorobicyclo[4,1,0]heptane (D 33; X = Cl):- This was prepared by the method of Parham and Schweitzer,[26] with the modification that methyl trichloroacetate was used instead of the ethyl ester. The product had b.p. 76-78°/ 12 mm., n_D^{20} 1.5015, (lit.[26] b.p. 81.5-82.5°/ 16 mm., n_D^{25} 1.5004)

2-Chlorocyclohept-2-enol (D 34; R = H; X = Cl):- A mixture of 7,7-dichlorobicyclo[4,1,0]-heptane (12 g.) and silver acetate (30 g.) in glacial acetic acid (150 ml.) was refluxed with stirring and under nitrogen for 5 days. Most of the acetic acid was distilled off at atmospheric pressure, and the remaining suspension was diluted with ether and filtered. The filtrate was washed with dil. sodium hydroxide, water and dried. Removal of the ether gave a yellow oil (10 g.) consisting of the dichlorobicycloheptane and 2-chloro-cyclohept-2-enyl acetate in the ratio of 6:4, as determined by G.L.C. The product was hydrolysed by refluxing in 10% methanolic potassium hydroxide solution (25 ml.) for 1 hr. The methanol was taken off under reduced pressure, and the neutral fraction isolated by extraction into petrol. The mixture of starting material and alcohol obtained was separated by chromatography over Grade I alumina (50 g.). Petrol elution gave starting material (4 g.) and elution with petrol-ether (1:1) gave the alcohol (D 34; R = H; X = Cl). This was characterised as its 3,5-dinitrobenzoate, which was prepared by the method of Brewster and Ciotti.[45] The alcohol (137 mg.), 3,5-di-nitrobenzoic acid (407 mg.) and p-toluenesulphonyl chloride (376 mg.)

were dissolved in pyridine (5 ml.) and kept for 1 hr. at 0°. The ester was isolated by diluting the solution with ether, and washing this with dil. hydrochloric acid, sodium carbonate solution, and water in succession. 2-Chlorocyclohept-2-enyl 3,5-dinitrobenzoate crystallised as plates from petrol, m.p. 99-101°, (Found: C, 49.38; H, 3.54; N, 8.07. $C_{14}H_{13}ClN_2O_6$ requires C, 49.34; H, 3.84; N, 8.22%).

Oxidation of this alcohol (40 mg.) in acetone (4 ml.) with 8N. chromic acid[46] gave the corresponding ketone (D 35), which was isolated as its 2,4-dinitrophenylhydrazone. 2-Chlorocyclohept-2-enone 2,4-dinitrophenylhydrazone crystallised as plates from ethyl acetate-petrol, m.p. 157-161°, $\lambda_{max.}$ 371 mμ (ε 26,500) in chloroform, (Found: C, 48.28; H, 4.19; N, 17.09. $C_{13}H_{13}ClN_4O_4$ requires C, 48.08; H, 4.03; N, 17.26%).

The alcohol (250 mg.) in pentane (10 ml.) was shaken for 3 hr. at room temperature with excess phosphorus pentoxide. The pentane solution was diluted, washed with sodium carbonate, water, and dried. Removal of the solvent left a pale yellow oil with the characteristics of the diene (D 36), [$\lambda_{max.}$ 274 mμ, $\nu_{max.}$ (liquid film) 1642m, 1620m (conjugated double bonds) $cm.^{-1}$

The Adduct of Dichlorocarbene and Cholest-2-ene (D 44):- Cholest-2-ene was prepared by the method of Fieser and Dominguez.[47] A solution of methyl trichloroacetate (10.1 g.; a large excess) in pentane (40 ml.) was added dropwise over 3 hr. to a mixture, stirred under nitrogen, of cholest-2-ene (990 mg.) and dry sodium methoxide (3.4 g.) in pentane (40 ml.). The reaction mixture was stirred for

a further 12 hr. and worked up by washing the filtered pentane solution with water. Removal of the solvent gave a red oil, which, after filtration through Grade I alumina in petrol, followed by crystallisation from chloroform-ethanol gave the dichlorocarbene adduct(810 mg.) as needles, m.p. 107-108.5°, $[\alpha]_D$ +44° (c 0.91), $\nu_{max.}$ (Nujol) 808s (chlorine substituents on the cyclopropane ring) $cm.^{-1}$, (Found: C, 74.03; H, 9.94. $C_{28}H_{46}Cl_2$ requires C, 74.20; H, 10.16%). The bisdechloro-adduct, prepared by sodium in liquid ammonia reduction of the above adduct, crystallised from acetone-methanol as needles, m.p. 105-106.5°, $[\alpha]_D$ +31° (c 0.8), (Found: C, 87.34; H, 12.27. $C_{28}H_{48}$ requires C, 87.42; H, 12.58%).

The dichlorocarbene adduct was recovered unchanged from 48 hr. reflux in quinoline, and from 24 hr. reflux in morpholine. On refluxing with an excess of sodium amide in piperidine for 0.5 hr. the adduct gave an intractable polymer.

Attempts to form a dichlorocarbene adduct from cholesterol tetrahydropyranyl ether[48], under the above conditions failed.

Performing the reaction in hexane under reflux similarly furnished a product which, after hydrolysis and chromatography afforded only cholesterol.

Attempts to prepare an adduct from β-amyra-2,12-diene, obtained by pyrolysis of β-amyrin benzoate, also gave only unchanged starting material.

The Chlorodiene (D 48) from the Action of Dichlorocarbene on Isophyllocladene:- A solution of methyl trichloroacetate (1 g.) in pentane (10 ml.) was added to a mixture, stirred under nitrogen

of isophyllocladene (197 mg.) and sodium methoxide (475 mg.) in pentane (15 ml.). Stirring was continued for 24 hr. and the mixture was diluted with pentane and washed with water. Removal of the solvent afforded an oil. This was filtered through Grade I alumina in petrol to give the chlorodiene (150 mg.), which crystallised from chloroform-ethanol as needles, m.p. 103-104.5°, $[\alpha]_D$ -19.2° (c 0.73), $\lambda_{max.}$ 243 mμ (ε 18,000), $\nu_{max.}$ (Nujol) 1617w, 1588m (conjugated double bonds), 890s (exomethylene), 875s (trisubstituted double bond), 847s (vinylic chlorine) $cm.^{-1}$, (Found: C, 79.32; H, 9.74. $C_{21}H_{31}Cl$ requires C, 79.14; H, 9.74%).

Ozonolysis of the Chlorodiene:- Ozonised oxygen was passed through a solution of the chlorodiene (170 mg.) in ethyl acetate (25 ml.) at -80° till the appearance of the pale-violet colour. The residue, after removal of the solvent in vacuo at 30°, was heated on the steam-bath for 5 min. with acetic acid (2 ml.) and 30% hydrogen peroxide (0.5 ml.). Ether extraction, followed by washing the extract with dil. sodium hydroxide solution separated the neutral fraction (150 mg.). This was filtered through Grade I alumina (5 g.) in ether and crystallised from ethanol to give the α-chloroketone (D 49), (80 mg.) as needles, m.p. 123-126°, $[\alpha]_D$ -72° (c 0.95), $\lambda_{max.}$ 257 mμ (ε 6,800), $\nu_{max.}$ (CCl_4) 1697.5 $cm.^{-1}$, (Found: C, 74.66; H, 8.88. $C_{20}H_{29}ClO$ requires C, 74.92; H, 9.05%).

The Action of Sodamide in Piperidine on the Chlorodiene:- The chlorodiene (95 mg.) and sodamide (600 mg.) were refluxed in dry, redistilled piperidine (10 ml.) under nitrogen for 2 hr.

The piperidine was removed under reduced pressure and the excess sodamide was destroyed by the addition of ether containing some ethanol. The ethereal solution was washed with water and dried. Removal of the solvent left the enamine (D 51) (70 mg.) as an oil, [$\nu_{max.}$ 1611w, 1578m (conjugated double bonds), 889 (exomethylene), 859 (trisubstituted double bond) cm.$^{-1}$].

This on treatment with ethanolic picric acid afforded a picrate, as plates from ethanol, m.p. 179-183° (decomp.), (Found: C, 64.48; H, 7.68; N, 9.17. $C_{32}H_{44}N_4O_7$ requires C, 64.41; H, 7.43; N, 9.39%).

Hydrolysis of the Enamine (D 51):- The enamine (60 mg.) was taken up in methanol (10 ml.) and acetic acid (1 ml.) containing sodium acetate (1.5 g.), and was refluxed for 3 hr. The methanol was removed in vacuo, and the neutral products were isolated by ether extraction from the mixture after acidification with dil. hydrochloric acid. The product was adsorbed from petrol on Grade I alumina (5 g.). Elution with petrol (15 ml.), 20% benzene in petrol (10 ml.), and 40% benzene in petrol (10 ml.) gave gums (in all 20 mg.), none of which crystallised. Elution with 60% benzene in petrol (15 ml.) gave a crystalline fraction (10 mg.). This, the dimer (D 53), formed fine needles from ethanol, m.p. 252°, $\nu_{max.}$ (CCl_4) 1719 (cyclohexanone), 1697m (double bond), (Found: C, 83.83; H, 10.37. $(C_{21}H_{32}O)_2$ requires C, 83.94; H, 10.73%).

2,5-Dimethylbicyclo[4.3.0]non-3-en-8-carboxylic Acid (D 59; R = H):- The corresponding dicarboxylic acid (D 5; R = H) (10.4 g.) underwent decarboxylation on being heated at 220° under nitrogen for 6 min.

to give the monocarboxylic acid (8.5 g.). This formed needles from chloroform-petrol, m.p. 130-133°, (Found; C, 74.20; H, 9.06. $C_{12}H_{18}C_2$ requires C, 74.19; H, 9.34%).

Treatment of the acid with ethereal diazomethane in the usual manner afforded the methyl ester (D 59; R = Me), which crystallised as needles from methanol, m.p. 64°, (Found: C, 74.78; H, 9.49. $C_{13}H_{20}O_2$ requires C, 74.96; H, 9.68%).

Methyl 4,4-dichloro-2,6-dimethyltricyclo[5,3,0,$0^{3,5}$]decan-9-carboxylate (D 62; R = H):- A solution of methyl trichloroacetate (42 g.) in pentane (90 ml.) was added dropwise over 1 hr. to a mixture, cooled to 5° under nitrogen, of the methyl ester (D 59; R = Me) (9 g.), sodium methoxide (15 g.) and pentane (130 ml.). After complete addition, the cooling was removed and the mixture was stirred for a further 12 hr. at room temperature, was then diluted with pentane and washed with water. Removal of the solvent left the crude product, and G.L.C. examination of this indicated that only a trace of starting ester remained unreacted. Distillation gave methyl 4,4-dichloro-2,6-dimethyl-tricyclo[5,3,0,$0^{3,5}$]decane-9-carboxylate (7.5 g.), b.p. 126-128°/ 0.01 mm., which formed rhombs from methanol m.p. 119-119.5°, $\nu_{max.}$ (Nujol) 1725 (ester), 830-820 (chlorines on cyclopropane ring) cm.$^{-1}$, (Found: C, 57.69; H, 7.00. $C_{14}H_{20}Cl_2O_2$ requires C, 57.73; H, 6.92%). Redistillation of a slightly higher boiling fraction yielded a further quantity of the same ester (1.5 g.). The ester (100 mg.) was refluxed in 10% methanolic potassium hydroxide solution for 45 min. The residue, after removal of the methanol

in vacuo, was diluted with water and washed with ether. The solution was then acidified and chloroform extraction afforded 4,4-dichloro-2,6-dimethyltricyclo[5,3,0,$0^{3,5}$]decane-9-carboxylic acid (D 62; R = H), which formed plates from petrol, m.p. 166-167.5°, (Found: C, 56.36; H, 6.60. $C_{13}H_{18}Cl_2O_2$ requires C, 56.31; H, 6.55%).

Dimethyl 7,7-dichloro-2,5-dimethylbicyclo[4,1,0]heptane-3,4-dicarboxylate (D 60):- The Diels-Alder adduct (D 3) was hydrolysed to the acid by dissolution in hot aqueous sodium carbonate followed by acidification. The dimethyl ester of this acid was prepared in the usual manner with ethereal diazomethane, and formed stout needles from aqueous methanol, m.p. 50-51°, (Found: C, 63.63; H, 8.29. Calc. for $C_{12}H_{18}O_4$ C, 63.70; H, 8.02%), (lit.[49] reports this as an oil.). A solution of methyl trichloroacetate (1.32 g.) in pentane (15 ml.) was added over 1 hr. to the above dimethyl ester (105 mg.) and sodium methoxide (500 mg.) in pentane (15 ml.). The solution was stirred at room temperature for 4 hr. and the pentane solution was then washed with water and evaporated to give the crude product. This was adsorbed from petrol on Grade I alumina (10 g.). Elution with petrol (30 ml.), 5%. 10%, and 20% benzene in petrol (30 ml. of each) brought off chiefly methyl trichloroacetate. Elution with 30% and 50% benzene in petrol (60 ml. and 30 ml; respectively) gave crystalline material (115 mg.). This was crystallised from methanol to give dimethyl 7,7-dichloro-2,5-dimethylbicyclo[4,1,0,]-heptane-3,4-dicarboxylate as prismatic needles, m.p. 105-106°, $\nu_{max.}$ (Nujol) 1734 (esters), 870m, 828s, 817s, 800w, 779 $cm.^{-1}$,

(Found: C, 50.75; H, 5.88. $C_{13}H_{18}Cl_2O_4$ requires C, 50.49; H, 5.83%). When the reaction was repeated as above, but with stirring for 15 hr., an isomeric dimethyl ester was obtained, probably owing to epimerisation of one of the carboxyl groups under the basic reaction conditions employed. This isomer formed needles from aqueous methanol, m.p. 75.5-76°, $\nu_{max.}$ (Nujol) 1725, 1713 (ester carbonyls), 806s, 798m, 782m, 735m $cm.^{-1}$, (Found: C, 50.24; H, 5.71. $C_{13}H_{18}Cl_2O_4$ requires C, 50.49; H, 5.83%).

4,4-Dichloro-2,6-dimethyl-9-isopropylidenetricyclo[5.3.0.$0^{3,5}$]-decane (D 66):- The methyl ester (D 62) (2 g.) in ether (15 ml.) was added over 20 min. to a stirred solution of methyl magnesium iodide, from magnesium (488 mg.), methyl iodide (2.88 g.) and ether (10 ml.). The resulting mixture was refluxed for 0.5 hr., then cooled to 0° and the Grignard complex was hydrolysed by the addition of satd. ammonium chloride solution (20 ml.). The aqueous phase was extracted with ether, and the combined ether layer and extracts were washed with water. Removal of the solvent gave the alcohol (D 63). This was taken up in pyridine (16 ml.), cooled to 0°, and phosphorus oxychloride (5 ml.) was added. The solution was allowed to stand at 0° for 24 hr., and was then diluted with petrol (200 ml.) and washed cauticusly with water (2×30 ml.), 6N. hydrochloric acid (30 ml.), sodium carbonate solution and water in succession. Removal of the solvent afforded an oil which had no hydroxyl absorption in its infra-red spectrum. The oil was filtered through Grade I alumina in petrol. The resulting product, which partly crystallised

[$\nu_{max.}$ (liquid film) 1633m, 887m (exomethylene) cm.$^{-1}$], was examined by G.L.C. (5% Apiezon L on " Embacel " at 190°) and found to consist of two compounds in the approximate ratio of 4:1. Repeated crystallisation from chloroform-methanol gave pure 4,4-dichloro-2,6-dimethyl-9-isopropylidenetricyclo[5,3,0,$0^{3,5}$]decane, m.p. 110-112°, $\nu_{max.}$ (Nujol) 1189s, 828s (chlorines on the cyclopropane ring) 792m cm.$^{-1}$, (Found: C, 65.83; H, 8.33. $C_{15}H_{22}Cl_2$ requires C, 65.92; H, 8.12%).

4,4-Dichloro-2,6-dimethyltricyclo[5,3,0,$0^{3,5}$]decan-9-one (D 67):- A solution of the isopropylidene alkene (D 66) (90 mg.) in dioxan (5 ml.) was treated with excess aqueous sodium periodate and a trace of osmium tetroxide at room temperature for 3 days. The organic products, isolated by petrol extraction, were adsorbed from petrol on Grade I alumina (10 g.). Elution with petrol gave back unchanged starting material (62 mg.), and with ether 4,4-dichloro-2,6-dimethyltricyclo[5,3,0,$0^{3,5}$]decan-9-one (20 mg.), which crystallised from methanol as prisms, m.p. 99-100°, $\nu_{max.}$ (CCl_4) 1747.5 cm.$^{-1}$, (Found: C, 57.99; H, 6.76. $C_{12}H_{16}Cl_2O$ requires C, 58.29; H, 6.52%).

Dehydration of the Alcohol (D 63) with p-Toluenesulphonic Acid:- The alcohol was refluxed with p-toluenesulphonic acid (58 mg.) in benzene (13 ml.) for 0.5 hr. The solution was washed with aqueous sodium carbonate and water. The product, after removal of the solvent, was filtered through Grade I alumina in petrol and furnished an oil, which G.L.C. examination showed to consist of one compound with trace amounts of impurities. A sample was distilled twice, b.p. 95°/0.015 mm.,

and then had $\nu_{max.}$ (liquid film) 1648w (double bond), 1206 m, 856m (trisubstituted double bond), 828s (chlorines on the cyclopropane ring) $cm.^{-1}$, (Found: C, 64.42; H, 7.62; Cl, 25.53. $C_{15}H_{22}Cl_2$ requires C, 65.92; H, 8.12; Cl, 26.0%)

Treatment of the mixture of olefins, from phosphorus oxychloride-pyridine dehydration, under identical conditions with p-toluenesulphonic acid in benzene gave a product identical to the above oil in its infra-red spectrum, and behaviour on G.L.C. Treatment of the olefin mixture with refluxing acetic acid for 12 hr. gave material containing only a trace of this acid-catalysed rearrangement product.

Action of Sodamide in Piperidine on the Isopropylidene Alkene (D 66):- The alkene (150 mg.) was refluxed under nitrogen with sodamide (200 mg.) in piperidine (5 ml.) for 0.5 hr. Methanol was added to destroy the excess sodamide, and the product, isolated by petrol extraction of the remainder, was an intractable gum, soluble only in chloroform.

Action of Silver Acetate in Acetic Acid on the Isopropylidene Alkene (D 66):- The alkene (650 mg.) and silver acetate (1.1 g.) were refluxed in acetic acid (15 ml.) under nitrogen for 5 days. The solution was cooled, filtered, and the silver acetate well washed with petrol. The petrol washings and filtrate were combined and evaporated *in vacuo* to dryness. The residue was taken up in petrol, filtered, and the filtrate was washed with dil. sodium hydroxide and water. Removal of the solvent and filtration of the remainder through Grade I alumina in petrol afforded a colourless oil, which

G.L.C. examination showed to be one compound containing only a trace of impurity. A sample of this was distilled, b.p. 88-90°/ 0.1 mm., and had $\nu_{max.}$ (liquid film) 1630s 1611m (double bonds), 886s (exomethylene), 843s (vinylic chlorine) $cm.^{-1}$, (Found: C, 75.70; H, 9.44. $C_{15}H_{21}Cl$ requires C, 76.15; H, 8.88%).

Attempted Preparation of the Chlorodiene (D 74):- The methyl ester (D 62; R = Me) (2 g.) and silver acetate (3.6 g.) were refluxed in acetic acid (20 ml.) under nitrogen for 4 days. The mixture was cooled and worked up as before to give a pale green oil Examination of this on a silica-chromatoplate showed it to consist of 4 compounds, grouped into 2 pairs of different polarity. The product was chromatographed over Grade I alumina (100 g.). Elution with 10% and 15% ether in petrol gave the first pair (245 mg.); further elution with increasing percentages of ether in petrol afforded the second pair. This latter was taken up in ether (15 ml.) and added to excess methyl Grignard reagent. After 4 hr. reflux the complex was hydrolysed by the addition of satd. ammonium chloride solution, and the product isolated by ether extraction. The product still showed some carbonyl absorption in the infra-red spectrum and was hydrolysed by refluxing in 10% methanolic alkali. The neutral fraction was isolated by ether extraction of the residue after removal of the methanol in vacuo. It was dissolved in pyridine (15 ml.), cooled to 0° and treated with phosphorus oxychloride (3 ml.) The solution was worked up as previously, and found to consist of at least sixteen compounds on G.L.C. examination.

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