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THESIS

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in fulfilment of the
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DEGREE OF DOCTOR OF PHILOSOPHY

by

WILLIAM S. STRACHAN

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STUDIES IN STEROID AND TRITERPENOID CHEMISTRY.

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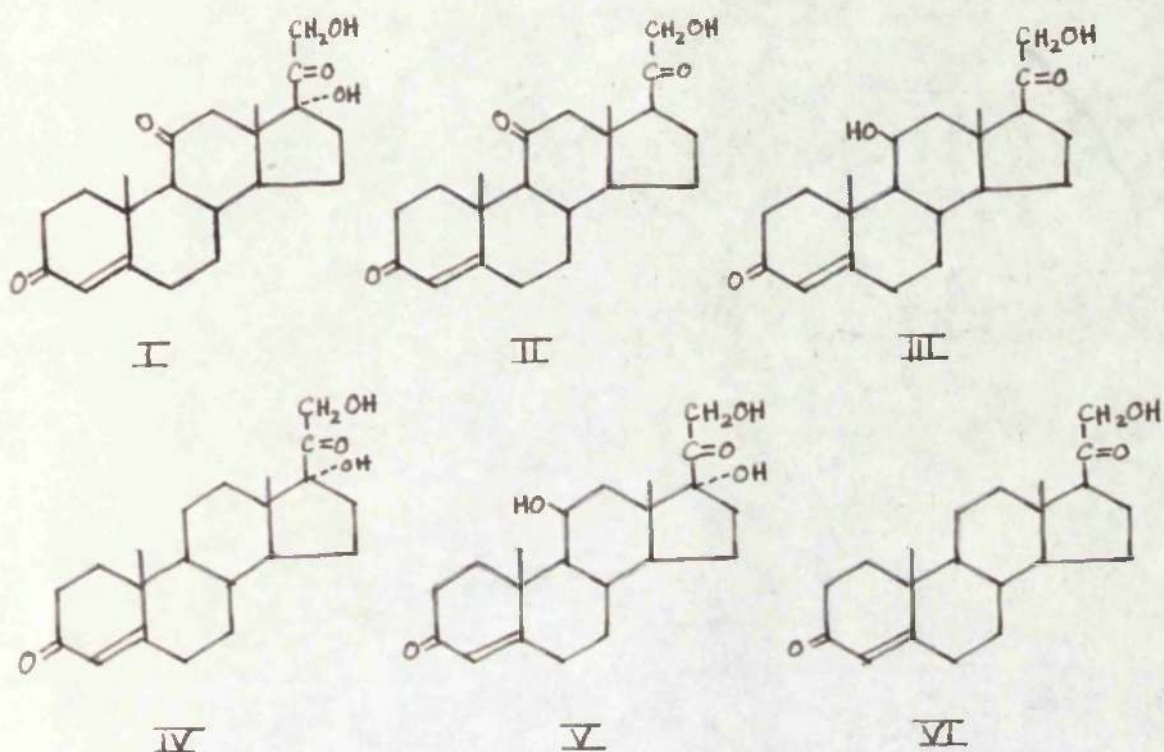
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INTRODUCTORY REVIEW

The investigation of the adrenocortical hormones was initiated by the discovery of Rogoff and Stewart (1) in 1929, that extracts of the cortical tissue would maintain life in adrenalectomised animals. This report was quickly confirmed by Swingle and Pfiffner (2), and Brownell and Hartman (3) in 1930. The active constituent of the cortical tissue extract was then named "cortin" or the "life-maintenance hormone".

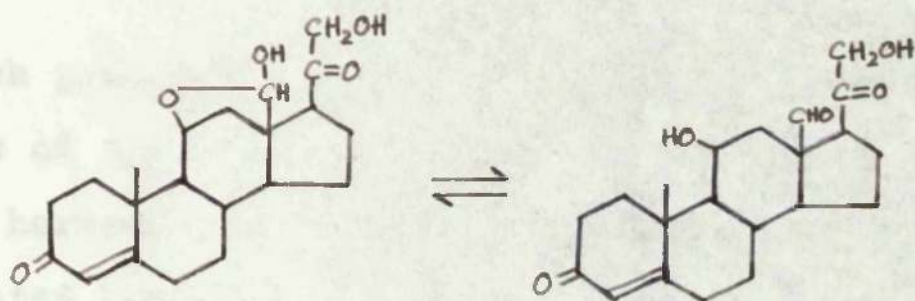
These early reports led to an extensive investigation, mainly by R.C.Kendall, J.J.Pfiffner, T.Reichstein and O.Wintersteiner of the constituents of the cortex. Their investigations resulted finally in the isolation of 28 crystalline steroids from the cortical tissue. The structures of these compounds were elucidated by interconversion into known steroids and also by partial synthesis. Six of them were shown to be capable of maintaining life in adrenalectomised animals.

After removal of all crystalline material, the residual amorphous fraction was found to retain 14-30% of the original activity of the extract, and from



this amorphous fraction there has recently been isolated a 29th steroid (VII) (4), aldosterone (electrocortin), which has a physiological activity about 30-100 times greater than 11-deoxycorticosterone (VI). The structure (VII) has been assigned to this material, and its total synthesis has been described (36).

The physiological activities of the adrenocortical hormones are difficult to define because of the fact that while a substance may show a positive response to one method of assay, it may show a negative response



VII

to another. Thus, in reporting the physiological activity of a substance, it is necessary to specify the method of assay employed. The symptoms following adrenalectomy which provide quantitative assay methods are the following.

- 1) Disturbance of the Na^+ , Cl^- , and water balance (increased excretion) and K^+ (retention).
- 2) Increase of the urea content of the blood.
- 3) Asthenia (inefficiency of muscle)
- 4) Disturbance of the carbohydrate metabolism, leading to a decrease in liver glycogen.
- 5) Reduction in resistance to traumata (cold, shock, etc.).

The isolation of the individual cortical steroids is carried out in the following manner. The minced beef glands are extracted with acetone or alcohol,

which precipitate protein constituents. Use is made of the relatively high water solubility of the hormones (5) to separate certain highly oxygenated hormones by partition between ether or benzene and water. Separation of the reactive ketones from the non-ketonic or inert ketonic material is achieved by means of the Girard procedure (6). The individual steroids are then separated by the chromatography of the more stable acetates.

Mason, Myers and Kendall (7) were the first clearly to associate physiological activity with the crystalline steroid, by proving the effectiveness of cortisone, which they named compound E, in the work performance test of Ingle. This same compound was also isolated by Wintersteiner and Pfiffner (8) who called it compound F, and by Reichstein (6) who called it compound Fa. It was later isolated by Kuizenga and Cartland(9).

Of the steroids isolated from the cortex, almost all are C_{21} -steroids, and those which exhibit cortin activity all have the $\alpha\beta$ -unsaturated ketonic group in

ring A, characteristic of progesterone and testosterone, and possess a ketol grouping in the side chain.

17 α -Hydroxy-11-dehydrocorticosterone, or Kendall's compound E. is of particular importance from the point of view of physiological activity, for it shows a variety of actions reproduced only in part by those cortical steroids lacking the oxygen function at C₁₁ or the hydroxyl group at C₁₇. The $\alpha\beta$ -unsaturated ketone system in ring A, and the ketol grouping in the side chain seem to be necessary for the known physiological actions, and the presence of oxygen at C₁₁ and at C₁₇ appears to enhance the therapeutic value of the compound. The C₁₁ oxygen function is apparently equally effective as the carbonyl or the hydroxyl grouping. Reichstein has shown that all the cortical steroids having the hydroxyl group at C₁₇ are of the same orientation at that centre.

The majority of the inactive substances isolated from the adrenal cortex are saturated in ring A, and appear to be reduction products of the Δ^4 -3-ketosteroids, and are all derivatives of 3 β -hydroxyallo-

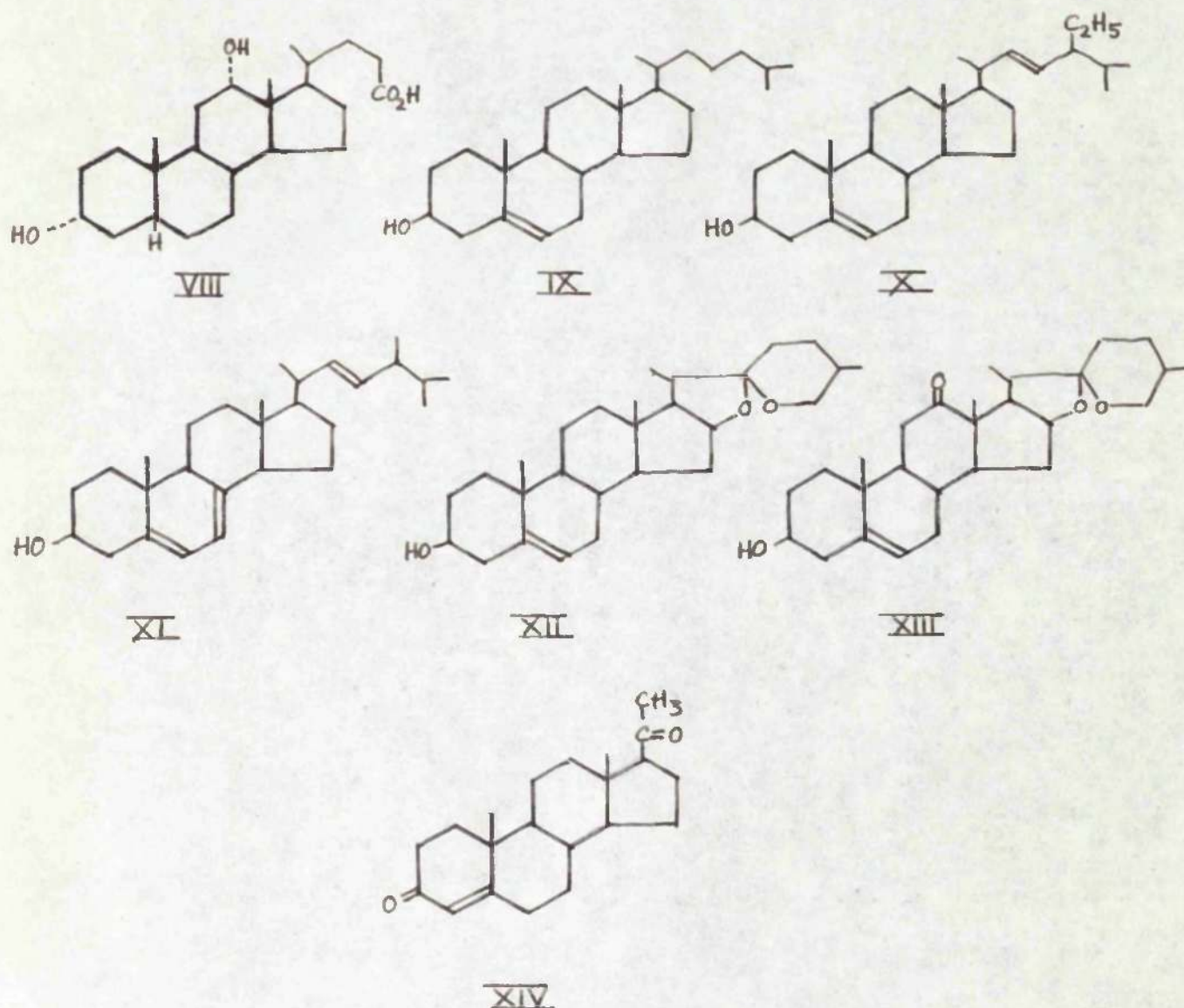
pregnane, in which the A/B ring junction is trans.

The presence of the C₁₁-oxygen function is a distinctive feature characteristic of the more important cortical hormones and of the majority of companion substances. No other naturally occurring steroids, with the exception of sarmentogenin (37), are known to have hydroxyl or carbonyl groups at this position. The oxygen function at C₁₁ is subject to very pronounced steric hindrance from the angular methyl groups at C₁₀ and C₁₃. The carbonyl group at C₁₁ is inert to phenylhydrazine, hydroxylamine, Girard's reagent, and to normal Wolff-Kishner conditions. It is also resistant to hydrogenation in neutral solution, but in acetic acid solution, or by means of lithium aluminium hydride can be reduced to give exclusively the hindered 11 β -hydroxy compound, since the hydrogen attacks the molecule at the unhindered rear face and opens the rear bond of the carbonyl group. Reduction with sodium in amyl alcohol gives, however, the 11 α -hydroxy compound. The 11 β -hydroxyl group is subject to oxidation by chromic acid; it is unusually sensitive to mineral acids, undergoing dehydration with even dilute mineral acid.

Since only minute quantities of the physiologically active cortical steroids could be obtained by the extraction of beef glands, a full clinical evaluation could not be made until they became more readily available. In 1943 Reichstein (10) achieved the important feat of introducing oxygen at the 11-position and succeeded in synthesising a substance identical with natural 11-dehydrocorticosterone (II). In 1946, Sarett (11) completed the synthesis of cortisone, starting from deoxycholic acid (VIII). Shortly after Hench and Kendall announced the anti-arthritic effect of cortisone (12). This effect appears to be specific to cortisone (13), only 17-hydroxycorticosterone having comparable potency. Recent work (14), however, shows that this anti-arthritic effect is not curative, but merely suppresses the symptoms of rheumatoid arthritis.

The apparent anti-arthritic effect of cortisone made it desirable that more economical syntheses should be devised, since the synthesis starting from deoxycholic acid is not economically attractive. Other starting materials were accordingly sought for the

partial synthesis of cortisone. The principal ones considered were ergosterol (XI), cholesterol (IX), stigmasterol (X), and the sapogenins diosgenin (XII), and hecogenin (XIII).



Although there are now methods for converting these steroids into cortisone, certain limitations are enforced by the nature of the steroid used. Apart from hecogenin, all are unsubstituted in ring-C, and the problem of introducing an 11-oxygen function is therefore more difficult. Moreover, cholesterol has a saturated side chain, the degradation of which can only be accomplished with considerable losses. The use of stigmasterol is limited by its relative non-availability. The side chain of diosgenin lends itself to an easy degradation (15) to pregnane derivatives, and this sapogenin is therefore a valuable starting material for ring-C unsubstituted hormones. Progesterone (XIV) can readily be prepared from diosgenin (15), and in view of the recent microbiological hydroxylation (16) of progesterone at C(11), the importance of this sapogenin is increased. Hecogenin, containing a C(12)-keto group, seemed a promising starting material, but its use is limited by the fact that purification of the crude material involves large losses.

The total synthesis of cortisone has been achieved

(17,18,19,20), and this route has now become economically feasible.

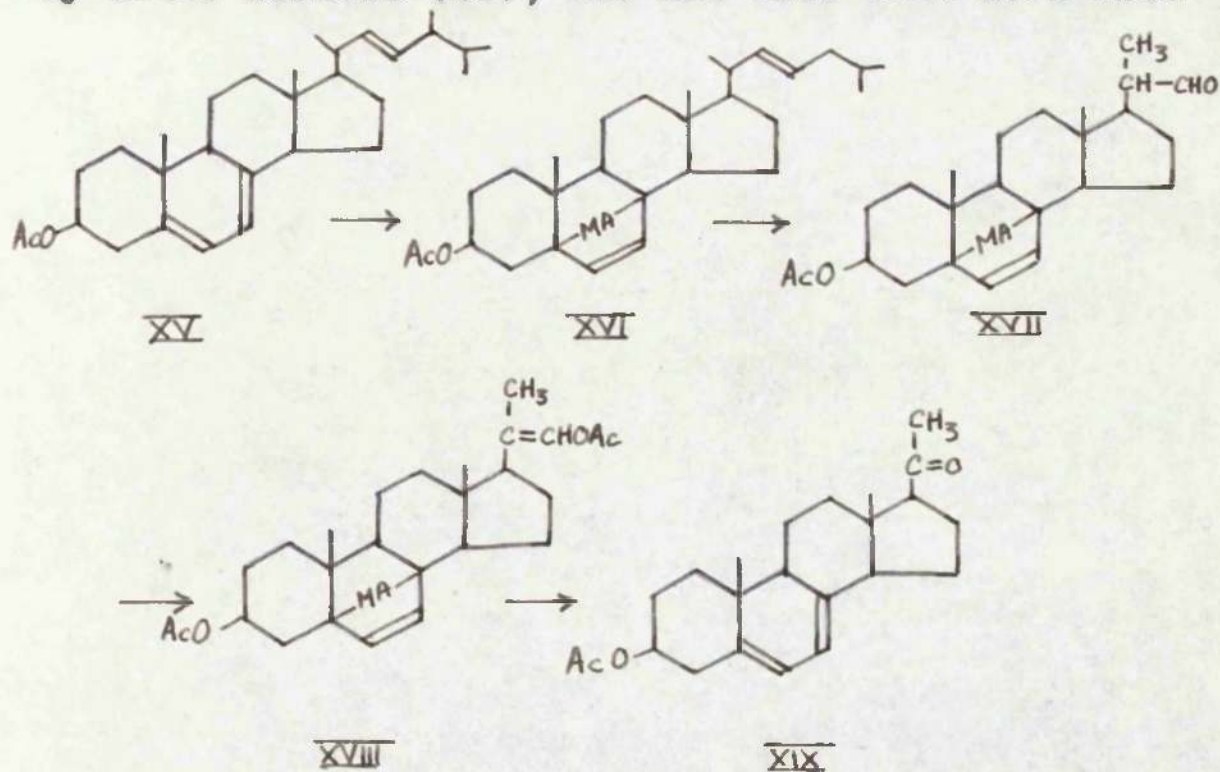
Ergosterol, therefore, appeared to be the most promising starting material for a partial synthesis of cortisone, since it possesses unsaturation in the side-chain which renders it readily convertible into a pregnane derivative, and also since the introduction of the $\Delta^9(11)$ -bond can be readily achieved, thus forming a useful intermediate for the introduction of the necessary C₍₁₁₎-oxygen function.

Ergosterol is the major sterol in the non-saponifiable fraction from yeast, which at present constitutes its main source. Interest in this sterol was first aroused in connection with its relationship to vitamin-D, and consequently its chemistry has been extensively investigated and its structure elucidated.

In 1948, it was suggested by Bergmann and Stevens (21) that ergosterol might be used as a starting material for the syntheses of adrenal cortical hormones. They approached the problem in two different ways. Firstly, they examined the degradation of the side chain

under conditions which left the diene system in ring-B untouched. Secondly, they attempted the introduction of the necessary C(11)-oxygen function before degradation of the side chain.

In both cases, the initial stages met with reasonable success. Addition of maleic anhydride to ergosteryl acetate (XV) gave the adduct (XVI) which was then ozonised preferentially to give the 22-aldehyde (XVII), enolisation of which gave the enol acetate (XVIII). Ozonolysis of the enol acetate, followed by pyrolysis gave 20-oxopregna-5:7-dien-3 β -yl acetate (XIX). This ozonolysis procedure for the degradation of the side chain has been substantiated by later workers (22), and has also been used with

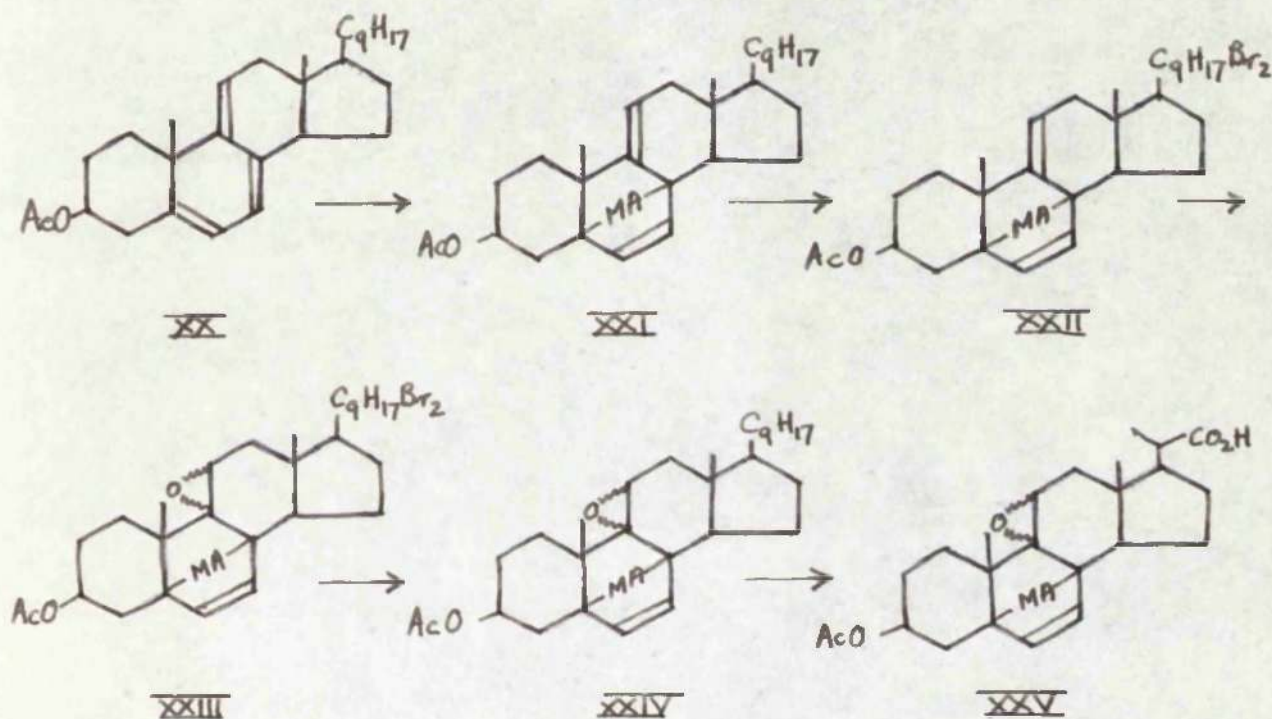


considerable success in the work described in this thesis.

In an attempt to introduce the C₍₁₁₎-oxygen function prior to degradation of the side chain, the maleic anhydride adduct (XXI) of dehydroergosteryl acetate (XX) was prepared and the side chain protected by conversion to the dibromide (XXII). Perbenzoic acid oxidation of this material gave in good yield the 9:11-epoxide (XXIII) which on debromination with zinc dust in acetic acid yielded the adduct (XXIV), ozonolysis of which, followed by oxidation of the resulting aldehyde, yielded the bisnor-acid (XXV). Pyrolysis of this material, however, resulted in aromatisation of ring-B, and in view of the low yields involved, and the difficulty encountered in the elimination of maleic anhydride, from the adducts, the approach was abandoned at this stage.

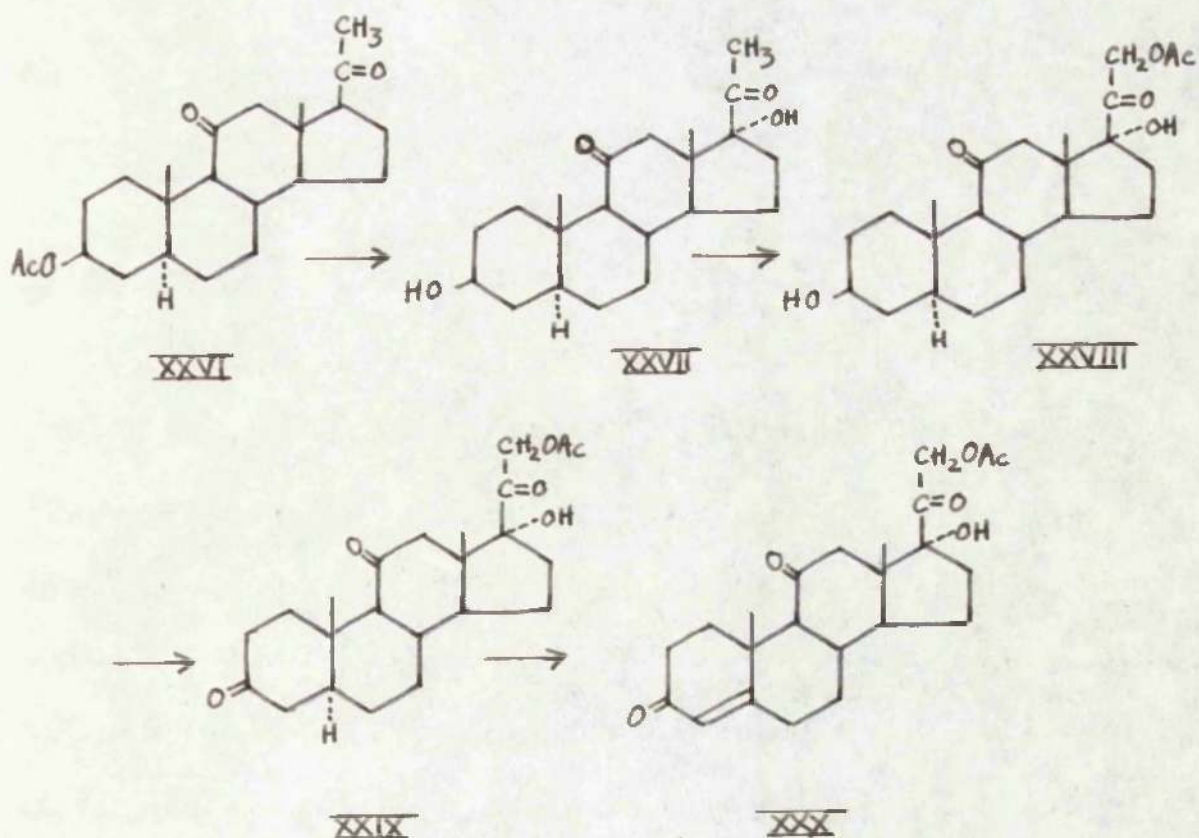
The greatest difficulty in the partial synthesis of cortisone lies in the necessity of obtaining in good overall yield a suitable intermediate possessing the C₍₁₁₎-oxygen function and the pregnane side chain.

Such an intermediate, common to many partial syntheses



of cortisone is 11:20-dioxoallopregnan-3 β -yl acetate (XXVI). The transformation of this to cortisone involves the introduction of hydroxyl groups at C₁₇ and C₂₁, and of the $\alpha\beta$ -unsaturated ketone in ring A. The 11:20-diketone is converted to the enol acetate, using the Gallagher procedure (23). Oxidation of the enol acetate with perbenzoic acid followed by alkaline hydrolysis gives 3 β :17 α -dihydroxy-11:20-

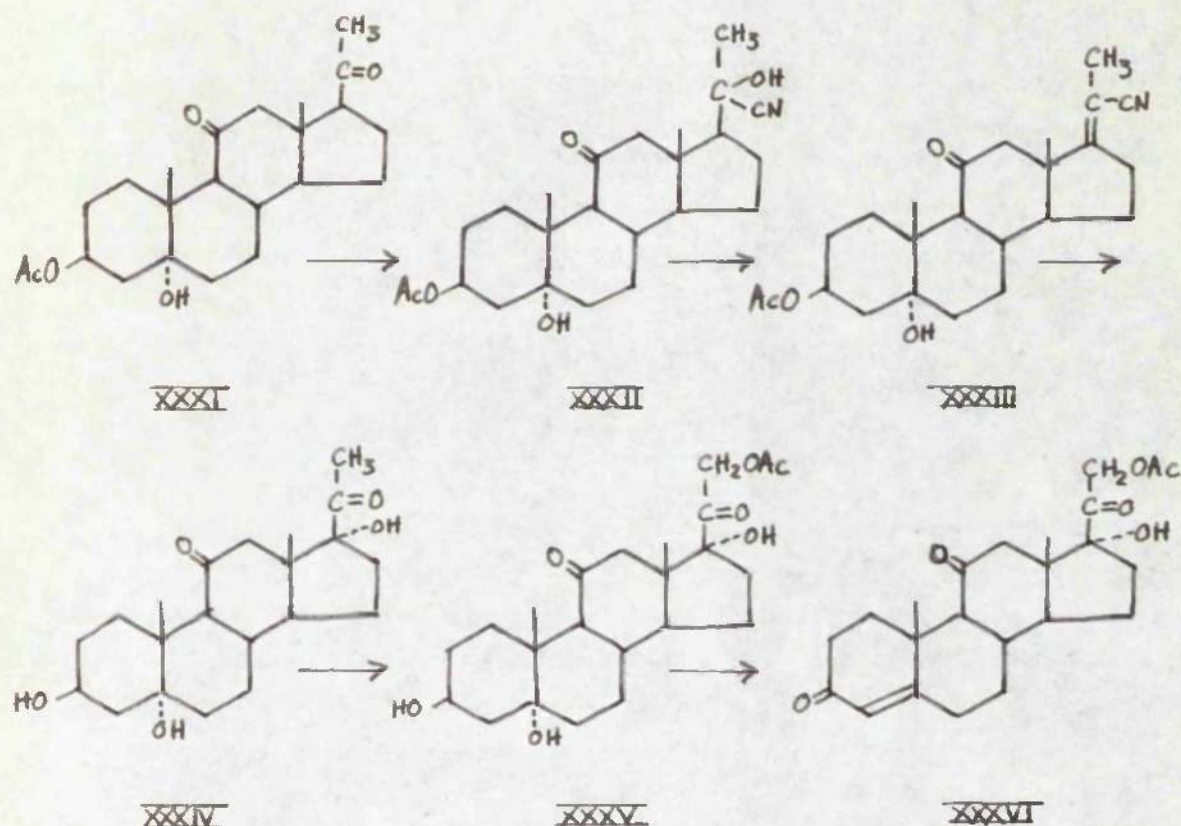
-dioxoallopregnane (XXVII), bromination of which gives the 21-bromo derivative. Treatment of the latter with sodium acetate (24) or with sodium iodide followed by potassium acetate (25) gives 3 β :17 α -dihydroxy-11:20-dioxoallopregnan-21-yl acetate (XXVIII). Oxidation of this with N-bromoacetamide gives 17 α -hydroxy-3:11:20-trioxoallopregnan-21-yl acetate (XXIX) (24,25), bromination of which, followed by dehydrobromination (24) by a method previously used with other 3-keto-allosteroids (26) gives cortisone acetate (XXX)



An alternative method for the introduction of the 17 α - and 21-hydroxyl groups is that of Sarett (26), used for 5 α -hydroxy-11:20-dioxoallopregnan-3 β -yl acetate (XXXI), which under the Gallagher conditions readily dehydrated to give Δ^6 -steroids. The 5 α -hydroxy-11:20-diketone (XXXI) was treated with hydrogen cyanide and the resulting cyanhydrin (XXXII) dehydrated selectively at C₂₀ with phosphorus oxychloride in pyridine to give (XXXIII). Osmium tetroxide oxidation of (XXXIII) gave the 17 α :20-diol, which yielded (XXXIV) on treatment with base. Bromination followed by treatment of the 21-bromo derivative with potassium acetate as described before gave the 21-acetate (XXXV), which on oxidation to the 3-ketone followed by dehydration gave cortisone acetate (XXXVI).

From the above it is evident that 11:20-dioxoallopregnan-3 β -yl acetate (XXVI) is a very important intermediate in a synthesis of cortisone, and correspondingly the work described in this thesis was directed towards the preparation of this compound in the best possible overall yield from a readily available starting material, which in this case was ergosterol. Previous

methods of preparing 11:20-dioxoallopregnan-3 β -yl



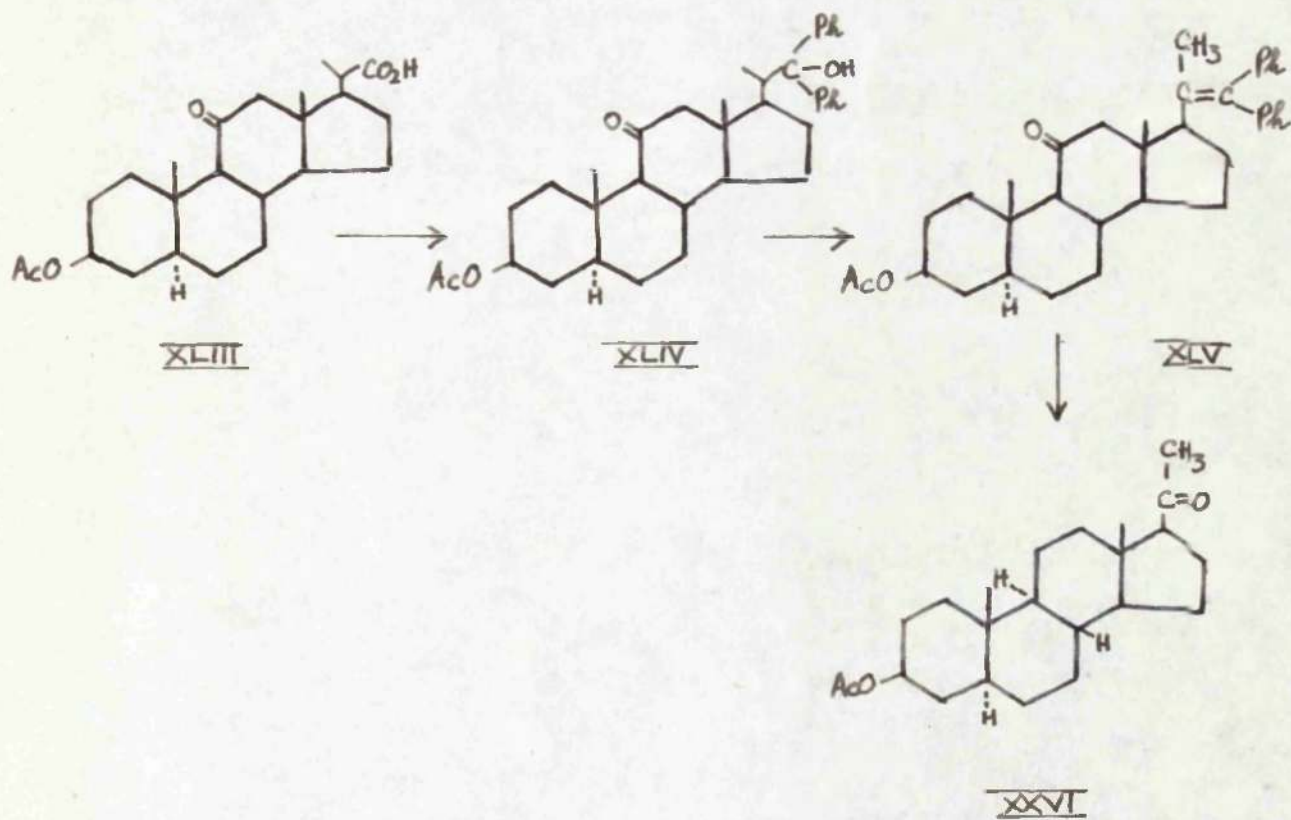
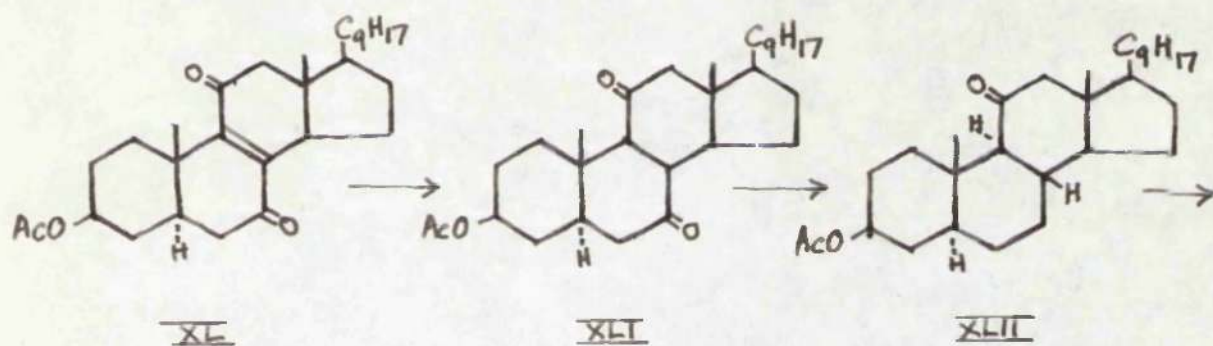
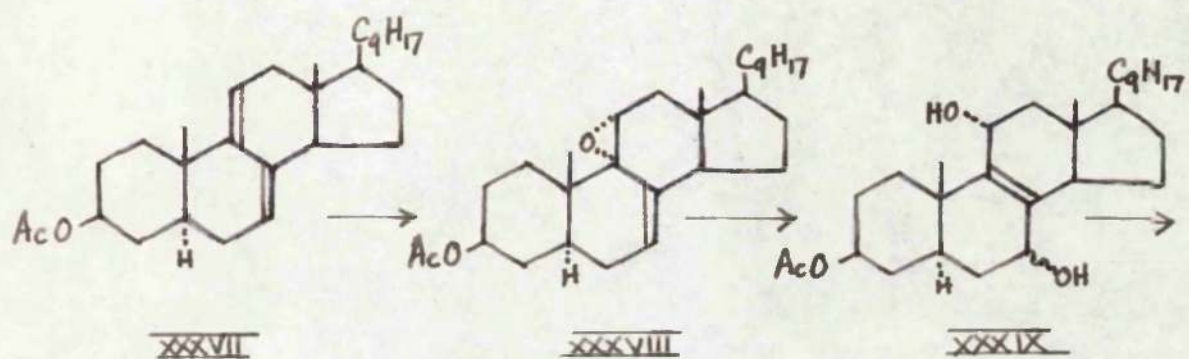
acetate (XXVI) are lengthy, with the result that the overall yield of (XXVI) is poor, which fact indicated the desirability of finding a new and more economically feasible route.

Success in the preparation of an 11-oxygenated steroid from ergosteryl-D-acetate was first achieved in the Merck Laboratories (38). This was immediately

followed by an independent publication (39) by Heusser et al., whose partial synthesis followed essentially the same pattern. Details of this synthesis of 11:20-dioxoallopregnan-3 β -yl acetate (XXVI) are given below.

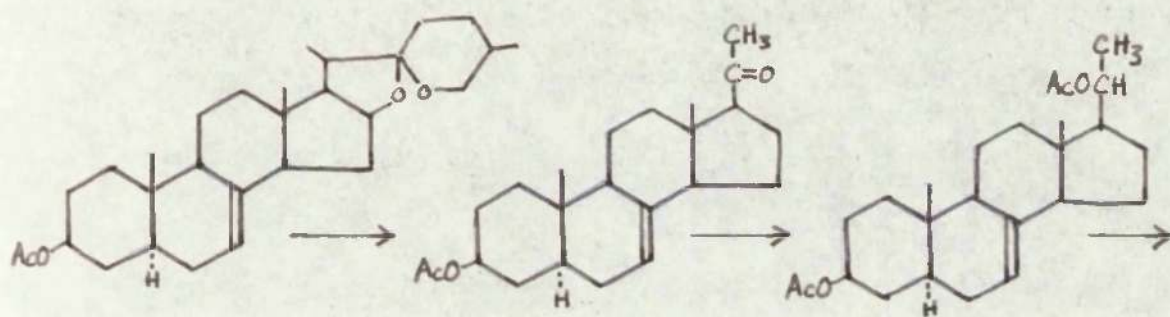
Ergosteryl-D-acetate (XXXVII) was selectively oxidised with perbenzoic acid to give the 9:11-epoxide (XXXVIII), which on treatment with a trace of mineral acid, afforded 3 β -acetoxysterosta-8:22-dien-7 ξ :11 α -diol (XXXIX). Oxidation of this compound with chromic acid led to 7:11-dioxosterosta-8:22-dien-3 β -yl acetate (XL) which when reduced with zinc dust and acetic acid gave 7:11-dioxosterost-22-en-3 β -yl acetate (XLI), further reduced to 11-oxosterost-22-en-3 β -yl acetate (XLII). This latter compound on ozonolysis yielded the acid (XLIII). Treatment of the methyl ester of the acid (XLIII) with phenyl magnesium bromide and dehydration of the resulting diphenyl carbinol (XLIV) yielded the diphenylethylene derivative (XLV), which on ozonolysis gave 11:20-dioxoallopregnan-3 β -yl acetate (XXVI).

The side chain of 11-oxosterost-22-en-3 β -yl acetate (XLII) has also been degraded (40) by the standard method (41), giving (XXVI) in good yield.



In a subsequent publication, Tishler et al., (42) reported a modification of their first route to 11-oxo-ergost-22-en-3 β -yl acetate. They found that preferential reduction of the Δ^8 -bond of 11-oxoergosta-8:22-dien-3 β -yl acetate could be achieved by the use of lithium metal in liquid ammonia.

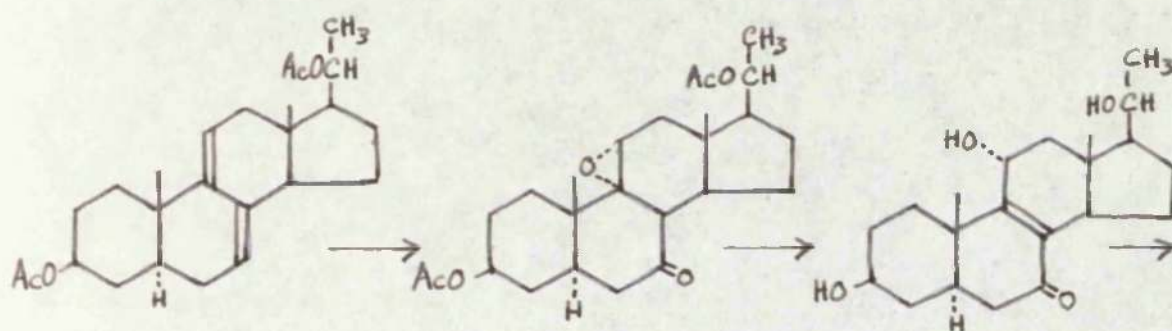
11:20-Dioxoallopregnan-3 β -yl acetate (XXVI) can also be obtained from diosgenin, but the route is lengthy and the overall yield poor. Briefly, the route is as follows. Diosgenin (XII) can be converted by established methods (43) into 22 α -allospirost-7-en-3 β -yl acetate (XLVI), and thence to 20-oxoallopregn-7-en-3 β -yl acetate (XLVII). Djerassi et al. (30) have described the mercuric acetate oxidation of the latter to give 20-oxoallopregna-7 β (11)-dien-3 β -yl acetate, but this reaction proceeds in poor yield. Treatment of (XLVII) with lithium aluminium hydride followed by acetylation gave 3 β :20 β -diacetoxallopregn-7-ene (XLVIII) which was converted to the $\Delta^{7:10}(11)$ -diene (XLIX) by mercuric acetate oxidation. Oxidation of (XLIX) with performic acid gave 3 β :20 β -diacetox-9 α :11 α -epoxyallopregnan-7-one (L) (44), which, on treatment



XLVI

XLVII

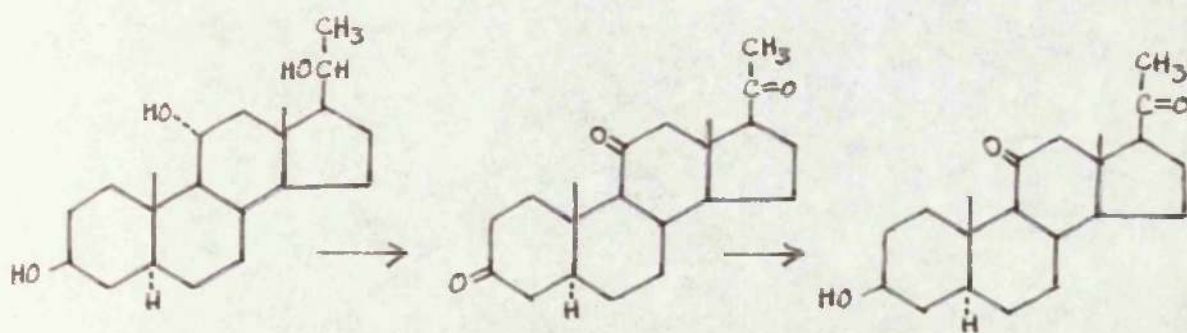
XLVIII



XLIX

L

LI



LII

LIII

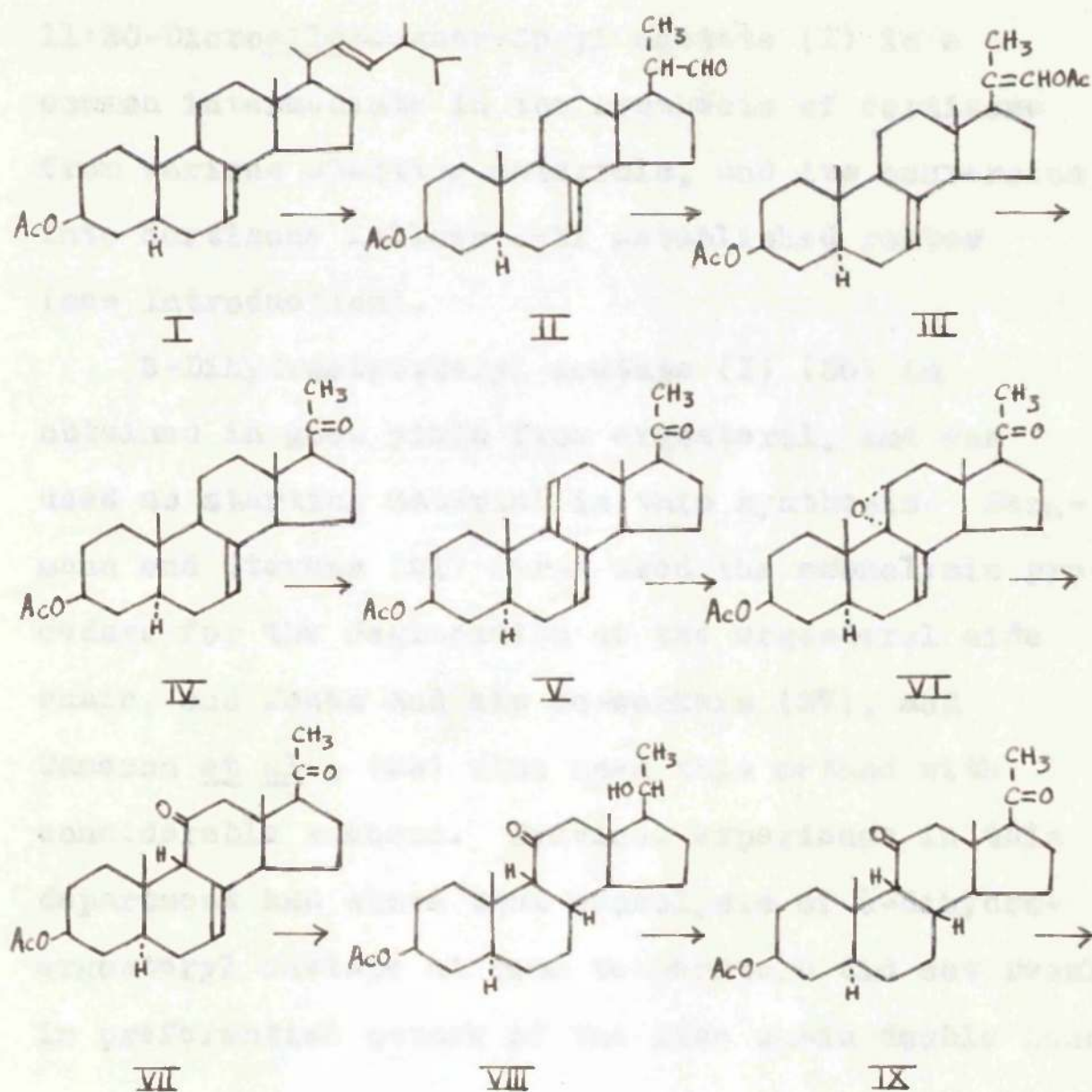
LIV

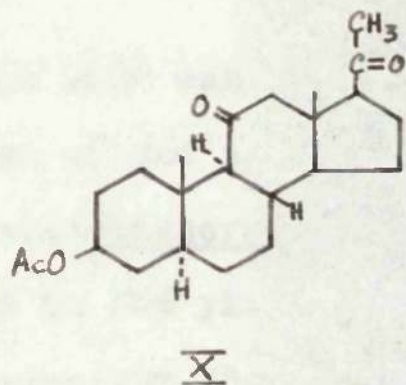
with alkali, isomerised to give $3\beta:11\alpha:20\beta$ -tri-hydroxyallopregn-8-en-7-one (LI). Catalytic hydrogenation of (LI) followed by Wolff-Kishner reduction gave $3\beta:11\alpha:20\beta$ -trihydroxyallopregnane (LII). Chromic acid oxidation of the latter gave the triketone (LIII), which was reduced by Raney nickel hydrogenation to give 11:20-dioxoallopregnan- 3β -ol (LIV).

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The conversion of 5-dihydroergosteryl acetate into 11:20-dioxoallopregnan-3 β -yl acetate (X) has been achieved by the route shown.





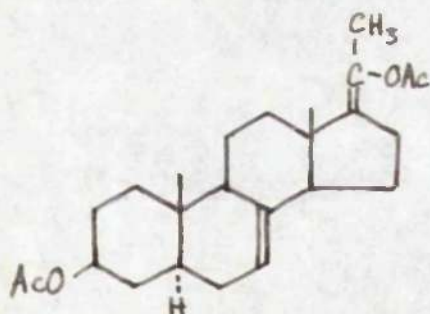
11:20-Dioxoallopregnan-3β-yl acetate (X) is a common intermediate in the synthesis of cortisone from various starting materials, and its conversion into cortisone follows well established routes (see Introduction).

5-Dihydroergosteryl acetate (I) (35) is obtained in good yield from ergosterol, and was used as starting material in this synthesis. Bergmann and Stevens (21) first used the ozonolysis procedure for the degradation of the ergosterol side chain, and Jones and his co-workers (27), and Cameron et al., (28) also used this method with considerable success. Previous experience in this department had shown that ozonolysis of 5-dihydroergosteryl acetate at room temperature did not result in preferential attack of the side chain double bond.

Ozonolysis at -50° was therefore tried, and on decomposition of the ozonide with zinc in acetic acid, 3 β -acetoxybisnorallochol-7-en-22-al (II) was obtained in 85% yield. The ultra-violet absorption spectrum showed the presence of a tri-substituted double bond (29). The aldehyde was characterised by formation of its 2:4-dinitro-phenylhydrazone and also of the dimethyl acetal, which was formed very readily. The aliphatic aldehydic fragment of the side chain degradation was separated by steam distillation and characterised as its 2:4-dinitrophenylhydrazone.

Treatment of the aldehyde (II) with sodium acetate and acetic anhydride gave in good yield, the enol acetate, 3 β :22-diacetoxybisnorallochola-7:20(22)-diene (III), selective ozonolysis of which at -50° gave 20-oxoallopregn-7-en-3 β -yl acetate (IV). This compound has been prepared by Djerassi and his co-workers from diosgenin (30). The alcohol and benzoate of the compound were prepared and the constants were found to be in good agreement with those given by Djerassi.

Since this seemed a suitable point at which to attempt introduction of the 17 α -hydroxy group, the method of Kritchevsky and Gallagher (23) was applied. Following the method of these authors, enol acetylation of 20-oxoallopregn-7-en-3 β -yl acetate was attempted. The product was a gum, which probably consisted of a mixture of the geometrical isomers of the enol acetate of the C₂₈-ketone. Chromatography of the product yielded a low melting crystalline fraction, the analysis of which was in agreement for 3 β :20-diacetoxyallopregna-7:17(20)-diene (XI).



XI

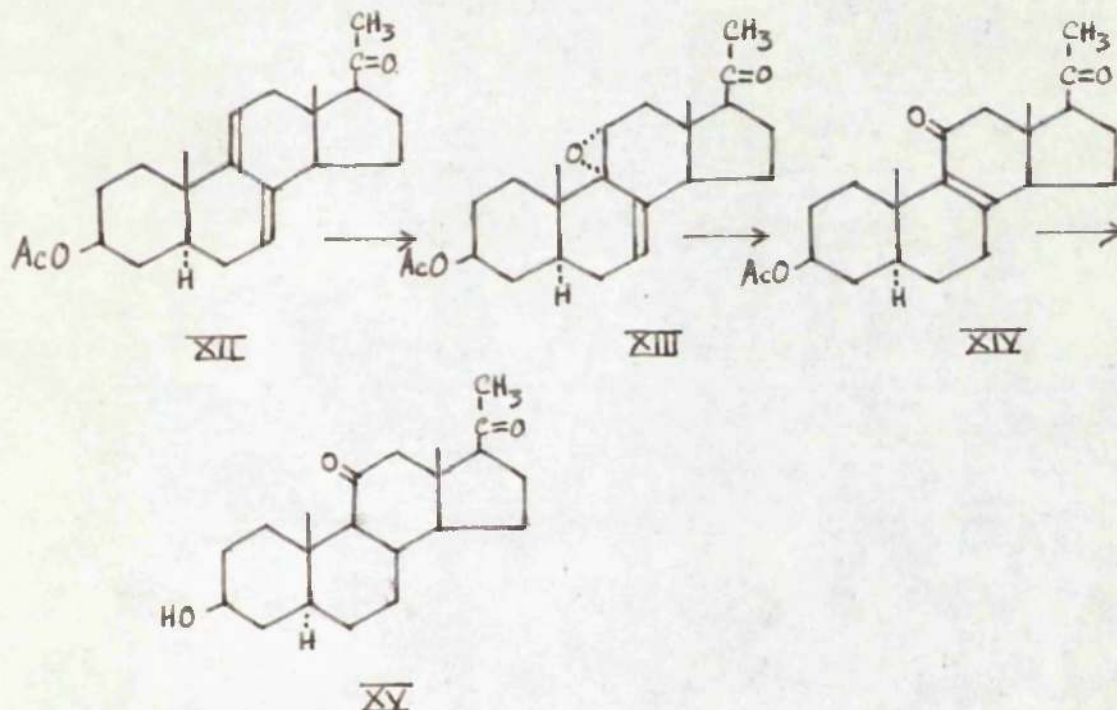
Perbenzoic acid oxidation of the crude material followed by alkaline hydrolysis failed to introduce the 17 α -hydroxy function, 20-oxoallopregn-7-en-3 β -ol being obtained. The use of excess perbenzoic acid

was also unsuccessful, leading only to the formation of a small amount of the $\Delta^{7:9(11)}$ -diene. The introduction of the 17- α -hydroxy function in the 20-ketone by this method has been reported by Djerassi and his co-workers (31), but the product was obtained in very low yield. Since it did not appear to be possible to introduce the 17 α -hydroxy group by a method giving a good yield, the attempt was postponed to a later stage in the synthesis.

The introduction of the $\Delta^{9(11)}$ -bond into 20-oxoallopregn-7-en-3 β -yl acetate (IV) with mercuric acetate, according to the method of Djerassi and his co-workers, was attempted, but the product was obtained in only 10% yield of pure material. The method of Anderson, Stevenson and Spring (32) for oxidation of 5-dihydroergosteryl acetate to ergosteryl-D-acetate was therefore tried, and the yield was thereby greatly improved. Treatment of 20-oxoallopregn-7-en-3 β -yl acetate with bromine at -50° followed by immediate debromination of the product at -50° with zinc dust gave in high yield 20-oxoallopregna-7:9(11)-dien-3 β -yl acetate (V), which shows the characteristic ultra-violet

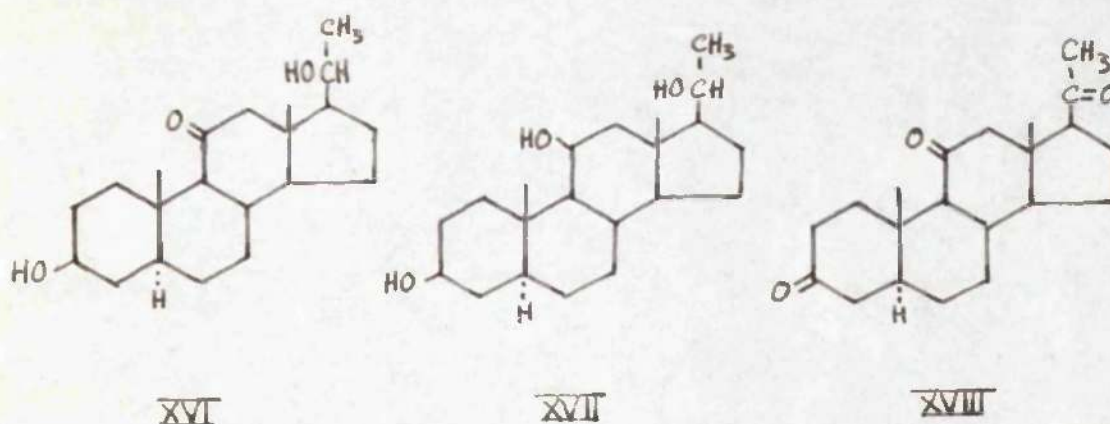
light absorption spectrum of a $\Delta^{7:9(11)}$ -diene.

The introduction of the 11-oxygen function was attempted by two routes. The route described below first suggested itself.



Perbenzoic acid oxidation of 20-oxoallopregna-7:9(11)-dien-3 β -yl acetate (V) at 0° gave 9 α :11 α -epoxy-20-oxoallopregn-7-en-3 β -yl acetate (VI) in good yield. Treatment of the 9:11-oxide (VI) with boron trifluoride-ether complex in benzene solution gave a gum showing relatively low intensity light absorption at 2500 Å. The product could not be

crystallised, and was treated with lithium in liquid ammonia, again yielding an uncrystallisable gum, which by reason of its solubility in methanol, ethanol and ethyl acetate and its relative insolubility in all other common solvents was assumed to be a diol or a triol, or more probably a mixture of these, (XVI, XVII). The product showed no appreciable light absorption intensity above 2000 Å.



The mixture was therefore oxidised with chromic anhydride to give in poor yield a product of m.p. 209-211°, $[\alpha]_D + 125^\circ$, in good agreement with the constants given by Reichstein (33) and Djerassi (45) for 3:11:20-trioxoallopregnane (XVIII). The compound did not depress in melting-point on admixture with an

authentic specimen, prepared by hydrolysis and oxidation of 11:20-dioxoallopregnan-3 β -yl acetate (X), kindly supplied by Dr. B.A.Hems of Glaxo Laboratories. In view of the nature of the products obtained, and the poor yields involved, this route was not investigated further.

The second route, which gave 11:20-dioxoallopregnan-3 β -yl acetate in good yield, was as follows. Treatment of 9 α :11 α -epoxy-20-oxoallopregn-7-en-3 β -yl acetate (VI) with boron trifluoride-ether complex in ether solution using the method of Eladon et al. (34) gave 11:20-dioxo-9 β -allopregn-7-en-3 β -yl acetate (VII). Catalytic hydrogenation of the diketone (VII) yielded 20 β -hydroxy-11-oxo-9 β -allopregnan-3 β -yl acetate (VIII), the structure of which was confirmed by the infra-red absorption spectrum, which showed well resolved hydroxyl, carbonyl, and acetoxyl bands. Selective reduction of the 20-ketone group in 11:20-diketones in the pregnane series (rings A/B cis fused) is reported by Sarett to give mainly the 20 β -isomers. Since the effects of the allopregnane (rings A/B trans fused) or 9 β -hydrogen (rings B/C cis) systems on the reduction of the 20-ketone

have not yet been established, the reduction product (VIII) is provisionally assigned the 20 β -hydroxyl configuration. Oxidation of 20 β -hydroxy-11-oxo-9 β -allopregnan-3 β -yl acetate (VIII) with chromic anhydride gave 11:20-dioxo-9 β -allopregnan-3 β -yl acetate (IX), treatment of which with 20% methanolic potassium hydroxide converted it into 11:20-dioxo-allopregnan-3 β -ol, the identity of which was confirmed by comparison with an authentic specimen prepared by hydrolysis of a sample of 11:20-dioxoallo-pregnan-3 β -yl acetate (X), supplied by Dr. B.A.Hems Acetylation gave 11:20-dioxoallopregnan-3 β -yl acetate (X) which was also identified by comparison with an authentic specimen.

EXPERIMENTAL

3 β -Acetoxybisnorallochol-7-en-22-al. - A solution of 5-dihydroergosteryl acetate (40 g.) in chloroform (600 ml.) at $-45^{\circ} \pm 5^{\circ}$ was treated with a stream of ozonised oxygen until 1.5 mols. ozone had been passed. The solution was allowed to stand for 30 minutes, when glacial acetic acid (200 ml.) and zinc dust (30 g.) were added and the mixture stirred for one hour. After filtration, the solution was steam distilled for 1.5 hr. The gummy residue was extracted with ether, and the extract washed with sodium carbonate solution (5%) and water, dried over sodium sulphate and the ether removed under reduced pressure. The residue was extracted with hot aqueous acetone (3 x 800 ml.; 30%) and the combined extracts concentrated until 3 β -acetoxybisnorallochol-7-en-22-al (27 g.) separated as plates, m.p. $133-134^{\circ}$. After two recrystallisations the material had m.p. $136-138^{\circ}$, $[\alpha]_D - 18^{\circ}$ (c, 2.0).

Light absorption: ϵ_{2100} 5,000.

Found: C, 77.5; H, 10.0

C₂₄H₃₆O₈ requires C, 77.4; H, 9.7%.

The material gives a pale yellow colour with tetranitromethane in chloroform.

The residue from the aqueous acetone extraction was recrystallised from methanol-chloroform to give 5-dihydroergosteryl acetate as plates, m.p. and mixed m.p. 170-173°.

No acid fraction was obtained on acidification of the sodium carbonate washings.

2:4-Dinitrophenylhydrazone of 3 β -acetoxybisnorallochol-7-en-22-al. - A solution of the aldehyde in methanol was treated with Brady's reagent to give the 2:4-dinitrophenylhydrazone which crystallised from ethyl acetate as needles, m.p. 243-244°.

Light absorption: ϵ_{2270} , 14,000, ϵ_{2000} , 21,750.

Found: C, 65.2; H, 7.0

$C_{30}H_{48}O_6N_4$ requires C, 65.2; H, 7.3%.

Dimethylacetal of 3 β -acetoxybisnorallochol-7-en-22-al. - a) The aldehyde (500 mg.) in methanol (50 ml.) was treated with concentrated hydrochloric acid (2 drops) and the solution warmed for a few minutes, when a white solid separated. The precipitate

was filtered off, washed with water and crystallised from methanol-methylene chloride to give the dimethyl-acetal (450 mg.) as plates, m.p. 210-212°, $[\alpha]_D -10^\circ$ (c, 2.4).

Light absorption: t_{2000} , 4,400

Found: C, 74.8; H, 10.3.

$C_{22}H_{42}O_4$ requires C, 74.6; H, 10.1%.

The material gives a pale yellow colour with tetranitromethane in chloroform.

b) Crystallisation of the aldehyde from technical aqueous methanol gave the dimethylacetal, m.p. and mixed m.p. 210-212°, $[\alpha]_D -9^\circ$ (c, 2.5).

2:4-Dinitrophenylhydrazone of Methylisopropyl acetaldehyde. - The steam distillate described above was extracted with chloroform and the extract washed with saturated sodium bicarbonate solution and water, dried over sodium sulphate and the chloroform removed under reduced pressure. The residue was dissolved in methanol and treated with Brady's reagent to give the 2:4-dinitrophenylhydrazone which crystallised from methanol as plates, m.p. 122-123°. (Lit. gives 122-123°).

3 β :22-Diacetoxybisanorallochola-7:20(22)-diene. -
3 β -Acetoxybisanorallochol-7-en-22-al (10 g.) was dissolved in acetic anhydride (40 ml.) and freshly fused potassium acetate (2 g.) added. The mixture was heated at 120-125° for 6 hr. A crystalline solid separated on cooling, and was filtered off, washed well with water, and crystallised from acetone to give 3 β :22-diacetoxybisanorallochola-7:20(22)-diene (5 g.) as plates, m.p. 163-165°, $[\alpha]_D^{25}$ -25° (c, 1.0).

Light absorption: ϵ_{2000} , 5,000.

Found: C, 75.4; H, 9.2.

$C_{28}H_{36}O_4$ requires C, 75.3; H, 9.2%.

The compound gives a pale yellow colour with tetranitromethane in chloroform.

The acetic anhydride mother liquors were treated with water, and extracted with ether. The ether extract was washed with saturated sodium bicarbonate solution, and with water, dried over sodium sulphate and the ether removed under reduced pressure. The gummy residue was crystallised from acetone to yield a further 2.7 g. of the enol acetate.

20-Oxoallopregn-7-en-3 β -yl acetate. - A solution of 3 β :22-diacetox**y**bisnorallochola-7:20(22)-diene (5 g.) in chloroform (400 ml.) at $-45^{\circ} \pm 5^{\circ}$ was treated with a stream of ozonised oxygen until 1.5 mols. ozone had been passed. The solution was allowed to stand for 30 minutes, when glacial acetic acid (150 ml.) and zinc dust (10 g.) were added and the mixture stirred for 1.5 hr. After filtration the solution was concentrated, treated with water and extracted with ether. The ether extract was washed with water, sodium carbonate solution (3%), and water, dried over sodium sulphate and the ether removed under reduced pressure. The residue was crystallised from acetone to give 20-oxoallopregn-7-en-3 β -yl acetate (3 g.) as blades, m.p. $174-176^{\circ}$, $[\alpha]_D + 38^{\circ}$ ($c, 1.0$).

Light absorption: $\epsilon_{2110}, 4,500$

Found: C, 77.0; H, 9.6.

Calc. for $C_{28}H_{34}O_3$: C, 77.05; H, 9.6%.

The compound gives a pale yellow colour with tetranitromethane in chloroform.

Djerassi et al. (30) give m.p. $174-176^{\circ}$, $[\alpha]_D + 39^{\circ}$ for this compound.

20-Oxoallopregn-7-en-3 β -ol. - A solution of 20-oxoallopregn-7-en-3 β -yl acetate in aqueous methanolic potassium hydroxide was refluxed for one hour. The solution was treated with water, extracted with ether and the ether extract washed with dilute hydrochloric acid (2%), saturated sodium bicarbonate solution, water, and dried over sodium sulphate,. The ether was removed under reduced pressure and the residue crystallised from methanol to give 20-oxoallopregn-7-en-3 β -ol as blades, m.p. 213-215°, $[\alpha]_D + 39^\circ$ (c,1.3).

Light absorption: ϵ_{2100} , 5,600.

Found: C,79.4; H,10.3.

Calc. for $C_{21}H_{32}O_2$: C,79.7; H,10.2%.

The compound gives a pale yellow colour with tetranitromethane in chloroform.

Djerassi et al. (30) give m.p. 213-215°, $[\alpha]_D + 41^\circ$.

20-Oxoallopregn-7-en-3 β -yl benzoate. - A solution of the alcohol in pyridine was treated with benzoyl chloride at 100° for 1 hr. The product was isolated in the usual fashion and crystallised from methanol to give 20-oxoallopregn-7-en-3 β -yl benzoate as plates m.p. 186-188°, $[\alpha]_D + 39^\circ$ (c,1.0).

Light absorption: ϵ_{2040} , 10,000; ϵ_{2380} , 17,000.

Found: C, 79.85; H, 8.8.

$C_{25}H_{36}O_3$ requires: C, 80.0; H, 8.6%.

The compound gives a pale yellow colour with tetra-nitromethane in chloroform.

20-Oxoallopregna-7:9(11)-dien-3 β -yl acetate

(c.f. Djerassi et al.). - a) A solution of 20-oxoallopregn-7-en-3 β -yl acetate (1 g.) in chloroform (30 ml.) and glacial acetic acid (30 ml.) was shaken with mercuric acetate (3 g.) for 18 hr. The filtered solution was concentrated, treated with water, and extracted with ether. The washed and dried solution was evaporated to dryness and the residue crystallised from methanol to give plates (300 mg.) m.p. 146-150°, $[\alpha]_D + 53^\circ$, several recrystallisations of which gave 20-oxoallopregna-7:9(11)-dien-3 β -yl acetate (100 mg.) as plates m.p. 157-160°, $[\alpha]_D + 78^\circ$ (c, 1.0).

Djerassi et al. give m.p. 139-141°, $[\alpha]_D + 78.9^\circ$.

b) To a stirred solution of 20-oxoallopregn-7-en-3 β -yl acetate (5 g.) in chloroform (200 ml.) at $-50^\circ \pm 5^\circ$, bromine (5.65 g.; 2.5 mols.) in chloroform (180 ml.) was added dropwise over 2 hr. Glacial acetic acid

(100 ml.) and zinc dust (50 g.) were added and stirring continued at -30° to -50° for 2 hr. The filtered solution was washed with water, saturated sodium bicarbonate solution, and water, dried over sodium sulphate and the chloroform removed under reduced pressure. The solid residue was crystallised from methanol to give 20-oxoallopregna-7:9(11)-dien-3 β -yl acetate (3.9 g.) as elongated plates, m.p. $159-162^{\circ}$, $[\alpha]_D + 81^{\circ}$ ($c, 1.0$).
Light absorption: ϵ_{2300} , 12,500; ϵ_{2400} , 14,200; ϵ_{2500} (sh.) 9,300.

Found: C, 77.2; H, 9.3.

Calc. for $C_{23}H_{32}O_3$ C, 77.5; H, 9.1%.

The compound gives a red-brown colour with tetra-nitromethane in chloroform.

20-Oxoallopregna-7:9(11)-dien-3 β -ol. - A solution of 20-oxoallopregna-7:9(11)-dien-3 β -yl acetate (50 mg.) in ethanolic potassium hydroxide solution (2%; 50 ml.) was allowed to stand overnight. Working up in the usual fashion yielded 20-oxoallopregna-7:9(11)-dien-3 β -ol which crystallised from acetone as plates, m.p. $200-202^{\circ}$, $[\alpha]_D + 73^{\circ}$ ($c, 1.0$).

Light absorption: ϵ_{2300} , 11,000; ϵ_{2420} , 12,750;
 ϵ_{2500} (sh.), 7,800.

The compound gives a red brown colour with tetra-
nitromethane in chloroform.

9a:11a-Epoxy-20-oxoallopregn-7-en-3 β -yl acetate. -
Perbenzoic acid (1.1 mols.) in chloroform (25 ml.) was
added dropwise at 0° over 4 hours to a stirred solution
of 20-oxoallopregna-7:9(11)-dien-3 β -yl acetate (5 g.)
in chloroform (150 ml.), and the solution kept at 0°
overnight. The solution was washed with sodium bi-
carbonate solution, water, and dried over sodium sulphate.
The chloroform was removed under reduced pressure (below
35°), and the residue crystallised from acetone to give
9a:11a-epoxy-20-oxoallopregn-7-en-3 β -yl acetate (3.3 g.)
as plates, m.p. 191-192°, $[\alpha]_D -2^\circ$ (c, 1.4).

Light absorption: ϵ_{2400} , 5,600.

Found: C, 74.3; H, 8.95.

$C_{25}H_{34}O_4$ requires C, 74.2; H, 8.7%.

The compound gives a pale yellow colour with
tetranitromethane in chloroform.

11:20-Dioxo-9 β -allopregn-7-en-3 β -yl acetate. -

A solution of 9a:11a-epoxy-20-oxoallopregn-7-en-3 β -yl acetate (200 mg.) in dry ether (45 ml.) was treated with boron trifluoride-ether complex (0.3 ml.) and the solution kept at room temperature for 16 hours. The solution was washed with water, sodium bicarbonate solution, and with water, dried over sodium sulphate and the ether removed under reduced pressure. The residue was crystallised from acetone-distilled water to give 11:20-dioxo-9 β -allopregn-7-en-3 β -yl acetate (160 mg.) as plates m.p. 119-121°, $[\alpha]_D -110^\circ$ (c, 1.4).

Light absorption: ϵ_{2800} , 5,400.

Found: C, 74.5; H, 9.0.

$C_{23}H_{32}O_4$ requires C, 74.2; H, 8.7%.

The compound gives a pale yellow colour with tetra-nitromethane in chloroform.

20 β -Hydroxy-11-oxo-9 β -allopregnan-3 β -yl acetate. -

A solution of 11:20 dioxo-9 β -allopregn-7-en-3 β -yl acetate (300 mg.) in glacial acetic acid (200 ml.) was added to a freshly reduced suspension of platinum (from 60 mg. PtO_2) and the mixture shaken in an atmosphere of hydrogen for 50 minutes at room temperature.

The filtered solution was concentrated and the product isolated by means of ether. Crystallisation from acetone-light petroleum (b.p. 60-80°) gave 20 β -hydroxy-11-oxo-9 β -allopregnan-3 β -yl acetate (220 mg.) as needles, m.p. 202-203°, $[\alpha]_D + 44^\circ$, +44.5° (c, 1.5, 1.3).

Found: C, 73.7; H, 9.9.

$C_{25}H_{38}O_4$ requires C, 73.4; H, 9.6%.

The compound does not show any high intensity light absorption in the ultra-violet. Infra-red spectrum: peaks at 3500 (hydroxyl), 1726 (ketone), 1720 and 1240 cm.^{-1} (acetate).

11:20-Dioxo-9 β -allopregnan-3 β -yl acetate. - A solution of 11-oxo-9 β -allopregnan-3 β :20 β -diol-3-acetate (109 mg.) in stabilised glacial acetic acid (5 ml.) was treated with chromic anhydride (29 mg.) in acetic acid (1 ml.) and kept at room temperature for 16 hours. The excess oxidising agent was destroyed by treatment with methanol, and the solution concentrated, treated with water, and extracted with ether. The ether extract was washed with sodium bicarbonate solution, water, and dried over sodium sulphate. The ether was removed

under reduced pressure and the residue crystallised from light petroleum (b.p. 60-80°) to give 11:20--dioxo-9 β -allopregnan-3 β -yl-acetate (90 mg.) as plates m.p. 191-193°, $[\alpha]_D + 154^\circ$ (c, 1.6).

Found: C, 73.75; H, 9.3.

$C_{23}H_{34}O_4$ requires C, 73.6; H, 9.15%.

The compound does not give a colour with tetra-nitromethane in chloroform, and does not show any high intensity light absorption in the ultra-violet.

11:20-Dioxoallopregnan-3 β -ol. - A solution of 11:20-dioxo-9 β -allopregnan-3 β -yl acetate (150 mg.) in aqueous methanolic potassium hydroxide (10 ml.; 20%) was refluxed for 6 hours. The cooled solution was treated with water and extracted with ether. The washed and dried ether extract was taken to dryness and the residue crystallised from acetone-light petroleum (b.p. 60-80°) to give 11:20-dioxoallopregnan-3 β -ol (110 mg.) as elongated plates (or prisms, depending on rate of crystallisation), m.p. 194-195°, $[\alpha]_D + 116^\circ$, $+ 118^\circ$, (c, 1.6, 1.3).

Found: C, 75.5; H, 9.7.

Calc. for $C_{21}H_{32}O_3$ C, 75.9; H, 9.7%.

The compound does not give a colour with tetranitromethane in chloroform and shows no high intensity light absorption in the ultra-violet. It did not depress in m.p. on admixture with a specimen m.p. 194-195°, $[\alpha]_D + 117^\circ$ ($c, 1.0$) prepared by hydrolysis of 11:20-dioxoallopregnan-3 β -yl acetate kindly supplied by Dr. B.A.Hems of Glaxo Laboratories.

Stork et al. (44) record m.p. 192-194°, $[\alpha]_D + 99^\circ$.

11:20-Dioxoallopregnan-3 β -yl acetate. - Treatment of the alcohol with acetic anhydride and pyridine at room temperature gave 11:20-dioxoallopregnan-3 β -yl acetate as prismatic needles from aqueous acetone. m.p. and mixed m.p. 143-144°, $[\alpha]_D + 88^\circ$ ($c, 0.5$).

Stork et al. (44) give m.p. 143-144°, $[\alpha]_D + 89^\circ$.

Chamberlin et al. (38) give m.p. 143-144, $[\alpha]_D + 88^\circ$.

Treatment of 9 α :11 α -Epoxy-20-oxoallopregn-7-en-3 β -yl Acetate with Boron Trifluoride-Ether Complex in Benzene Solution. - A solution of 9 α :11 α -epoxy-20-oxoallopregn-7-en-3 β -yl acetate (200 mg.) in dry benzene (17 ml.) was treated with boron trifluoride-ether complex (9 drops), and the solution kept at

room temperature for 3 days. The solution was diluted with ether (25 ml.), washed successively with water, sodium bicarbonate solution and water, and the dried solution evaporated to dryness under reduced pressure. The product was a gum which could not be crystallised, but showed relatively low light absorption intensity at 2500 Å.

Lithium-liquid Ammonia Reduction of the $\alpha\beta$ -unsaturated Ketone. - Lithium (12 mg.) was added to a mixture of dry ether (7 ml.) and liquid ammonia (20 ml.), and the blue solution kept for 10 minutes in a flask with a soda-lime guard tube. A solution of the crude $\alpha\beta$ -unsaturated ketone (115 mg., see above) in dry ether (5 ml.) was added quickly, and lithium (2 mg.) to restore the blue colour. Ammonium acetate was then added to destroy the excess reducing agent, and the ammonia was allowed to evaporate. The product, obtained on working up through ether in the usual fashion, was a solid foam which could not be crystallised, and was hydrolysed using 3% ethanolic potassium hydroxide solution, again yielding a solid foam.

Chromic Acid Oxidation of Lithium-liquid

Ammonia Product. - A solution of the lithium-liquid ammonia product (200 mg.) in stabilised glacial acetic acid (20 ml.) was treated with chromic acid (4 ml., 33.3 g./l.), and the solution kept overnight at room temperature. The product, obtained on working up in the usual fashion, was a gum which was dissolved in light petroleum-benzene (2:1) and chromatographed on alumina. Elution of the column with benzene-light petroleum (2:1) yielded a solid which crystallised from acetone-light petroleum as prisms (20 mg.) m.p. 205-208°, $[\alpha]_D + 122^\circ$ (c , 0.5). On further crystallisation the material had m.p. 209-211°, $[\alpha]_D + 125^\circ$ (c , 0.3), and did not depress in melting-point on admixture with an authentic sample of 3:11:20-trioxoallopregnane.

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PART II
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THE CHEMISTRY OF THE TRITERPENOIDS

α -AMYRIN AND FRIEDELIN

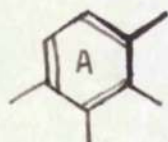
TRITERPENOIDS

Introduction.

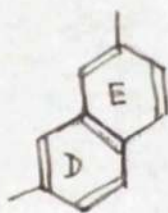
The compounds of the triterpenoid series have wide distribution in Nature, especially in the plant kingdom, where they occur in the resin and sap in the free state, as esters or as glycosides. They are non-nitrogenous materials, containing 30 carbon atoms, the fundamental skeletons of which can be divided into six isoprene ($\text{CH}_2 = \text{CH} - \text{CMe} = \text{CH}_2$) units. On the basis of this view, the parent hydrocarbons should have a molecular formula equivalent to 6 isoprene units i.e. $\text{C}_{30}\text{H}_{48}$, and the fact that many monohydric triterpene alcohols have the formula $\text{C}_{30}\text{H}_{50}\text{O}$ bears out the general validity of this rule.

On dehydrogenation with selenium, the triterpenes give a mixture of aromatic hydrocarbons, particularly naphthalene homologues, and this approach has played a major role in the assignment of the carbon skeletons. The majority of this dehydrogenation work was performed by Ruzicka and his co-workers (1), who found that the main dehydrogenation products of the pentacyclic

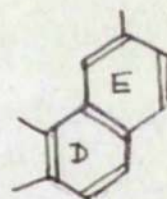
triterpenes were 1:2:3:4-tetramethylbenzene (I), 2:7-dimethylnaphthalene (II), 1:2:7-trimethylnaphthalene (III), 1:2:5:6-tetramethylnaphthalene (IV), 1:5:6-trimethyl- β -naphthol (V), which result from a rupture of the molecule during dehydrogenation. 1:8-Dimethylpicene (VI, R = H) and 1:8-dimethylpicen-2-ol (VI, R = OH) represent the original pentacyclic system.



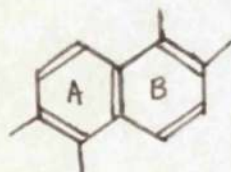
I



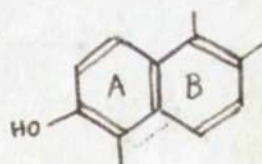
II



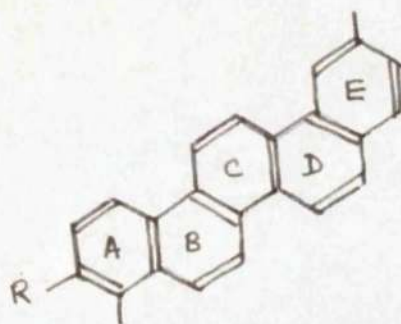
III



IV



V



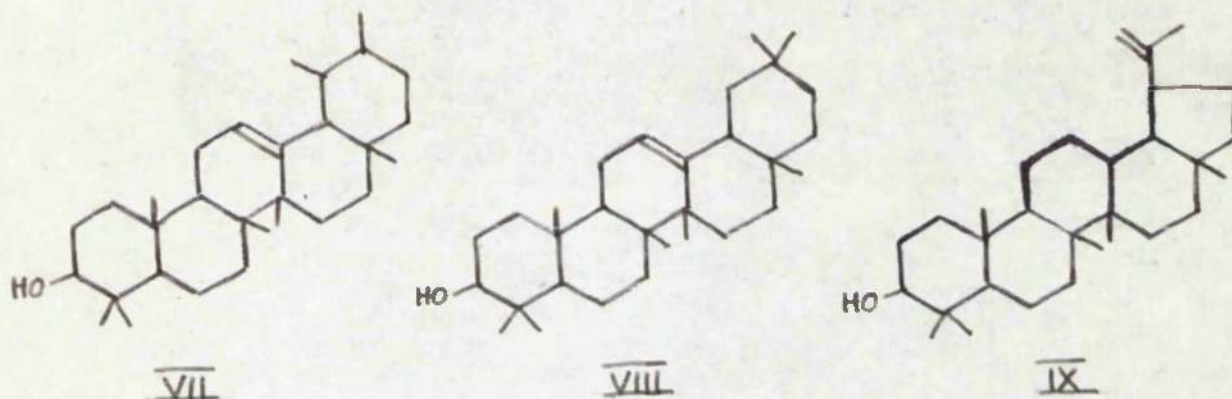
VI

Since 1930, considerable progress has been made in our knowledge of triterpenoids. In this period, the characterisation of the functional groups of the more important members has been achieved, and the elucidation of the molecular formulae and the more important features of their carbon skeletons has led to the postulation of formulae which adequately represent experimental facts.

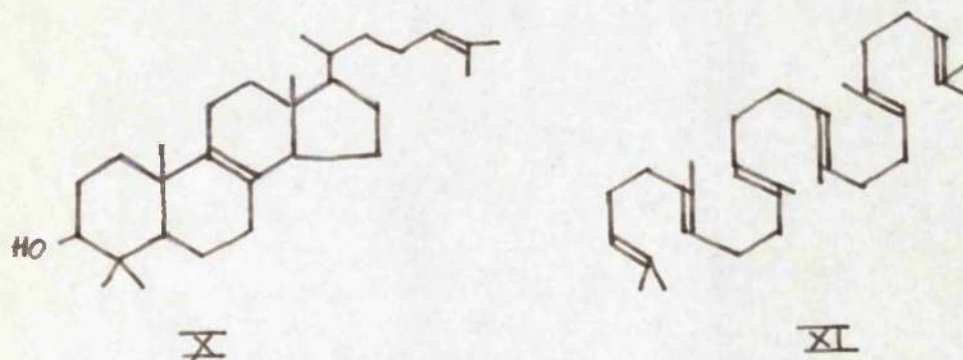
One of the most important advances in the field of triterpenoid chemistry has been the establishment of the relationship between various individual compounds and their assignment to different groups, so that the reactions of any one compound in a given group have a bearing on the structure of all members of the group, and complete determination of structure of one member will establish the constitution of most members of the group.

The triterpenoids can be classified in six groups. The first is the α -amyrin or ursane group, the most important member of which is α -amyrin, hitherto represented by the formula (VII). The second is the β -amyrin or oleanane group, represented by β -amyrin (VIII).

The third is the lupeol group represented by lupeol (IX).



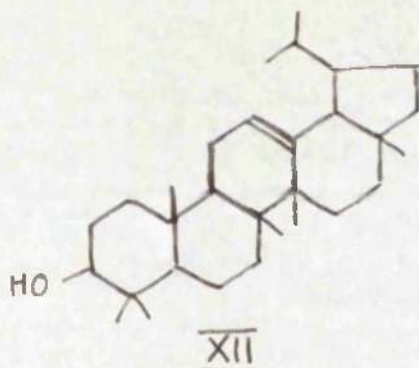
These are all pentacyclic triterpenoids. The fourth group comprises the tetracyclic triterpenes, which may be subdivided into two groups - the lanosterol series and the euphol series, which differ in the fusion of rings C and D. A typical member is lanosterol (X).



The fifth group, the squalene (XI) group, comprises only three members, squalene, ambrein and onocerin.

The last group comprises those triterpenoids which have not yet been assigned to any of the above groups.

The formula (VII) has up till now represented the structure of α -amyrin, but throughout the remainder of this thesis the formula (XII) will be used to denote α -amyrin. The reasons for this formulation are presented in the theoretical section.

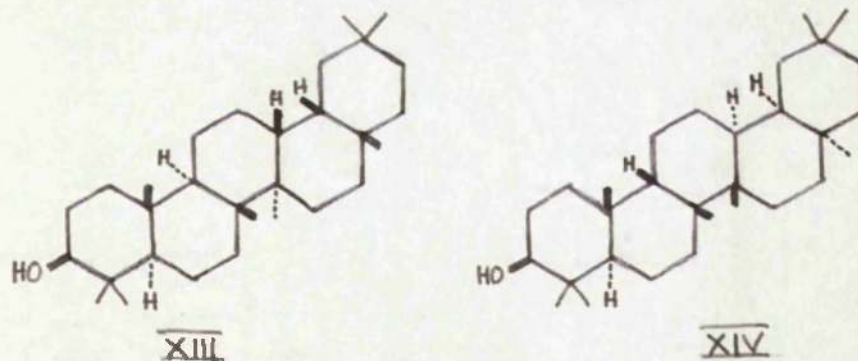


α -Amyrin.

Probably the most abundant of the triterpenes are the amyryns, which were first isolated by Rose (2) in 1839, from Manilla elemi resin. In 1887, Vesterberg (3) separated the amyryns into the α - and β - forms. Since then the amyryns have been found in numerous resins, the latex of many other plants (4) and in shea nut oil (5).

With the solution of some of the structural problems in triterpenoid chemistry, solutions to a number of stereochemical problems have been forthcoming. Since excellent reviews on the subject of triterpenoid chemistry are available (6-13) only a brief outline of the position as regards α -amyrin will be given here.

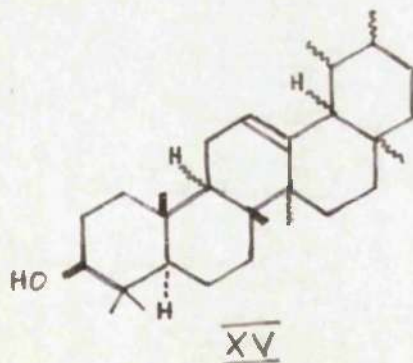
It has been concluded (14) from a wealth of experimental evidence that (XIII) and (XIV) represent the two more probable stereochemical forms of β -amyranol.



Klyne (15) has advanced molecular rotation arguments in favour of (XIII) rather than (XIV), and the structure (XIII) may be taken to represent dihydro- β -amyrin structurally, and stereochemically.

The work of Ruzicka, Jeger and their co-workers

(16-18) has provided evidence that the configurations at positions 3, 5, 8, 10, and probably 9 and 14, are the same in α - and β -amyrin, but in general the stereochemistry of α -amyrin has not been clearly defined - during the last 2 years each of the four theoretically possible arrangements for the locking of rings D and E have been included in the stereochemistry of α -amyrin (19, 20, 21, 22). Thus when the work described in this thesis commenced, α -amyrin was considered to be represented adequately by the formula (XV).



Friedelin.

About 150 years ago the French chemist Chevreul (23) isolated from cork a product which he called "cerine" because of its wax-like nature. Thoms (24), in 1898, was first to report the isolation of a substantially pure product, and this report was closely

followed by that of Istrati and Ostrogovich (25) who discovered that by fractional crystallisation from chloroform, the cork extract could be separated into two distinct compounds which they named cerin and friedelin (in honour of Friedel (27) who had also examined the extract). More recently, Drake and his co-workers (27) attempted to elucidate the structures of friedelin and cerin. Later, Ruzicka and his co-workers continued research on this problem (28). The work of these two groups showed that friedelin is a saturated pentacyclic ketone, $C_{30}H_{50}O$, and that cerin is the corresponding α -hydroxy ketone, $C_{30}H_{50}O_2$. Drake and his associates (27) investigated the selenium dehydrogenation of friedelanol, the related secondary alcohol, and obtained a variety of polynuclear hydrocarbons, all characteristic dehydrogenation products of triterpenoids, thus presenting strong evidence for the view that friedelin is triterpenoid. Ruzicka and his co-workers (28) also concluded from degradation studies that the partial formula

$$\begin{array}{ccccccc} -CH_2 & -CH_2 & -C & -CH & -CH & - & \\ & & || & | & | & & \\ & & O & & & & \end{array}$$

represents the

immediate environment of the carbonyl group. Recent work, however, suggests that this is incorrect (see Theoretical, Section II). The chemistry of friedelin will not be described further here, since it is adequately reviewed elsewhere (27, 28, 29), but those facts relevant to the work described in this thesis will be discussed in the Theoretical section.

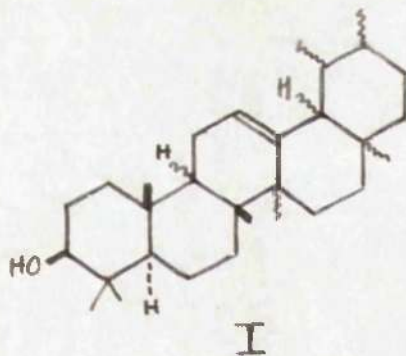
THEORETICAL
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THEORETICAL

Section Ia.

The Structure and Stereochemistry of α -Amyrin

When the work described in this thesis was commenced, the structure of α -amyrin was considered to be represented adequately by the formula (I).



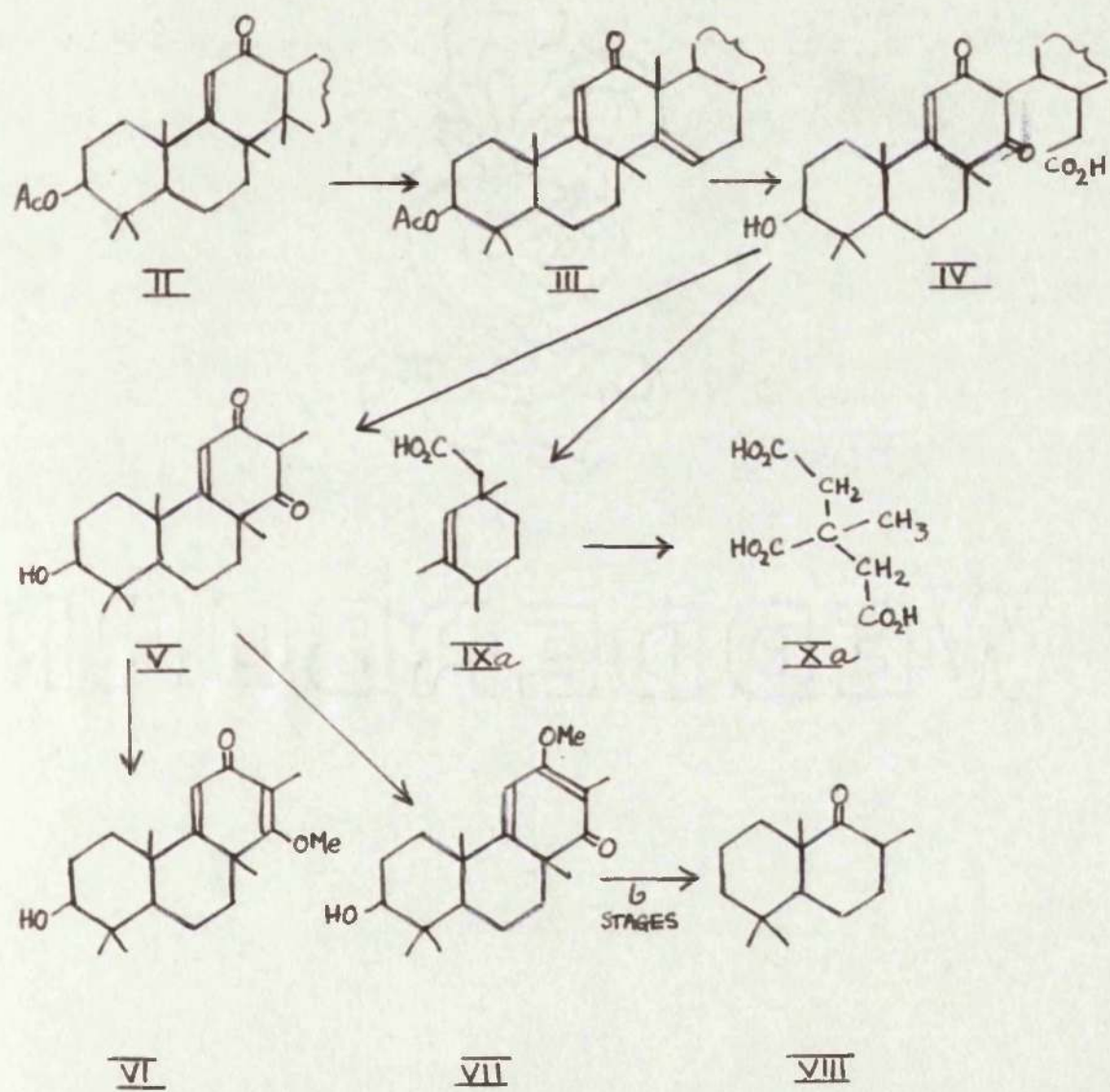
This formula was quite reasonable on the basis of the evidence to hand at the time, although it did not provide a completely satisfactory explanation for the lower reactivity of the double bond in α -amyrin as compared with β -amyrin, and the inert nature of the ketone group in 12-oxoursanyl acetate.

Barton and Jones (30) have suggested that the

molecular rotation differences between α - and β -amyrin derivatives indicate that they are of similar constitution in rings A and B, and this has received confirmation in the experiments of Meisels, Jeger and Ruzicka (16), which also led to the elucidation of the position of the ethylenic linkage in ring C. Ruzicka and his co-workers (18) have shown, by the following series of reactions that rings A, B and C in α - and β -amyrin are similarly constituted.

iso- α -Amyrenonyl acetate (II) was oxidised with selenium dioxide to give iso- α -amyradienonyl-I acetate (III), osmic acid oxidation of which, followed by ring-opening and oxidation of the product gave a di-keto-monocarboxylic acid (IV). Pyrolysis of this acid gave two fractions, volatile and non-volatile. The former consisted of a monobasic acid (IXa), which could be further oxidised to β -methyl-tricarballic acid (Xa), and was considered to arise from ring E of α -amyrin. Treatment of the non-volatile fraction with diazomethane gave two main products (VI-VII). Since these still contained a hydroxyl group, they were considered to come from rings A, B and C of α -amyrin. The ether (VII) was later further degraded to 1:1:6:10-tetramethyl-

-5-keto-trans-decalin.



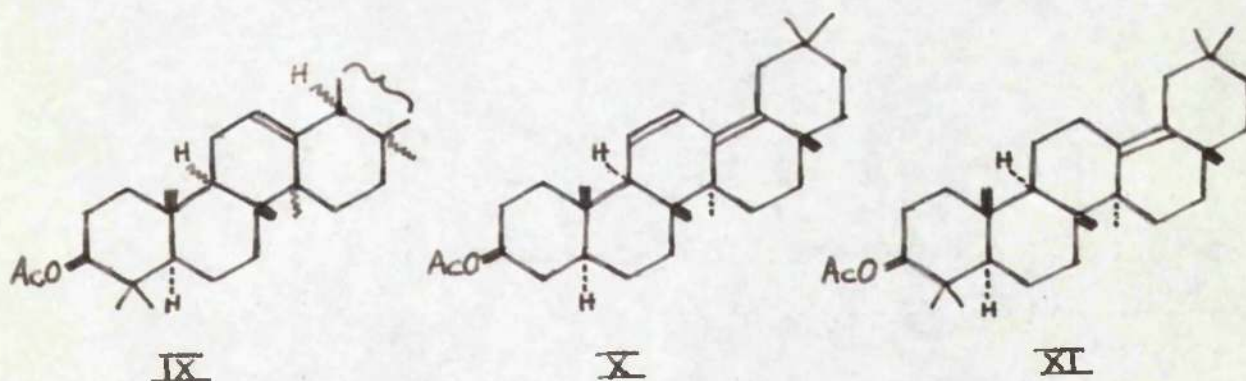
Iso- β -amyradienonyl acetate was subjected to a similar series of experiments, and the same pair of tricyclic compounds (VI) and (VII) was obtained.

The above evidence shows that in α -amyrin the configurations at C₃, C₈, C₉, and C₁₀ are the same as in β -amyrin. In addition, comparative studies on oleanane and ursane derivatives suggested that the configuration at C₉ is identical in both groups (16).

The above summarises the knowledge of the stereochemistry of α -amyrin prior to the commencement of this work. In an attempt to elucidate more fully the stereochemistry of α -amyrin attention was first directed towards C₁₈. That C₁₈ in α -amyrin differed in some way from C₁₈ in β -amyrin is shown by the following facts. 11-Oxo-olean-12-en-3 β -yl benzoate is readily isomerised (and hydrolysed) with strong alkali to give 11-oxo-18 α -olean-12-en-3 β -ol (31), but similar treatment of 11-oxours-12-en-3 β -yl acetate does not change the configuration at C₁₈. From this it may be deduced that either the configuration at C₁₈ in α -amyrin is the more stable arrangement, or there is no hydrogen attached to C₁₈ in α -amyrin (32). Supporting this view

is the related observation that treatment of methyl 11-oxours-12-en-3 β -olate acetate with strong alkali does not cause inversion at C₁₃. An alternative explanation is that enolisation of the $\alpha\beta$ -unsaturated ketone is, for some unspecified reason, directed towards C₉ exclusively.

With a view to solving this problem of the configuration at C₁₃, the chemistry of urs-11:13(18)-enyl acetate and its dihydroderivative urs-13(18)-enyl acetate was studied.



α -Amyrin acetate (IX) in boiling benzyl acetate was treated with selenium dioxide. The bulk of the starting material was recovered unchanged, but a very low yield (1-2%) of a dienyl acetate was obtained on chromatography (33). This compound has properties very similar to those of oleana-11:13(18)-dien-3 β -yl

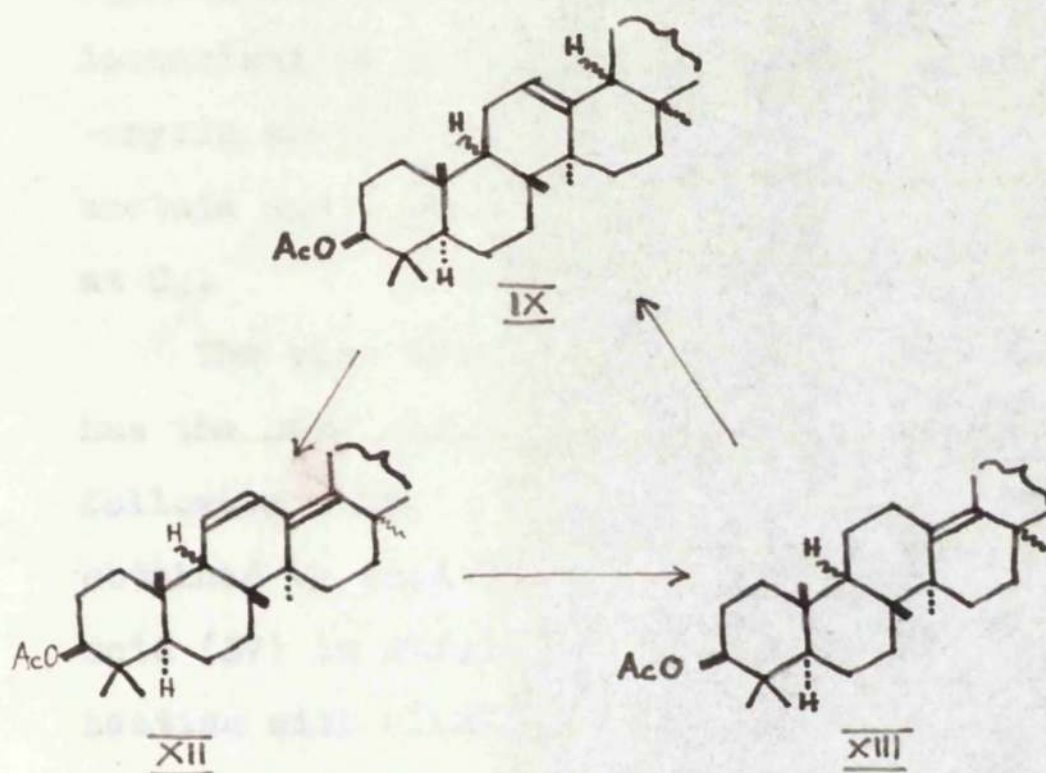
acetate (34) (X). The two dienes have very similar ultra-violet absorption spectra as regards both position and intensity of the maxima. There is a very slight difference in the position of two of the three maxima. The dienyl acetate described above absorbs at 2440, 2510, and 2600 Å., while the corresponding positions for oleana-11:13(18)-dien-3 β -yl acetate are 2420, 2500, and 2600 Å. A more pronounced difference exists in the definition of one of the secondary maxima. In the spectrum of oleana-11:13(18)-dien-3 β -yl acetate (X) there is a well defined minimum at 2560 Å., while in that of the dienyl acetate derived from α -amyrin acetate there is a shoulder and not a minimum at this wavelength. This difference is consistent and provides a ready means of differentiating between the two dienes.

Catalytic hydrogenation of the α -dienyl acetate gave in excellent yield the dihydro-derivative, which again possessed properties similar to those of olean-13(18)-en-3 β -yl acetate (XI) the corresponding dihydro derivative of oleana-11:13(18)-dien-3 β -yl acetate (X). The ultra-violet light absorption of the α -dihydro-derivative (ϵ at 2110 Å. = 5,500) was indicative of the

presence of a tetrasubstituted double bond. The dihydro-derivative from oleana-11:13(18)-dien-3 β -yl acetate has been identified as olean-13(18)-en-3 β -yl acetate (35) (XI).

In view of the forcing conditions employed in the formation of the α -dienyl acetate, and since at that time there was no direct evidence of a hydrogen attached to C₁₈, it was suggested (33) that elimination of a methyl group from C₁₈ might have occurred. In this event, the diene would be norursa-11:13(18)-dien-3 β -yl acetate. The following isomerisation, however, shows that this, in fact, is not the case.

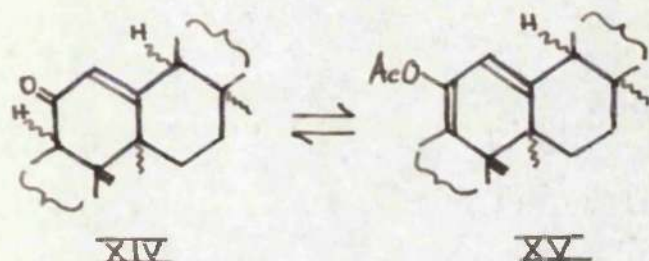
Treatment of the α -dihydro-derivative with sulphuric acid in acetic acid solution at room temperature followed by chromatography of the product, gave α -amyrin acetate (IX), which was further characterised by hydrolysis and benzylation to give α -amyrin benzoate. This proves that no elimination of a methyl group has occurred during treatment with selenium dioxide, and that the dienyl acetate is ursa-11:13(18)-dien-3 β -yl acetate (XII) and the dihydro-derivative urs-13(18)-en-3 β -yl acetate (XIII).



Furthermore, this isomerisation of urs-13(18)-en-3β-yl acetate to urs-12-en-3β-yl acetate proves that α-amyrin has the more stable configuration at C₍₁₈₎ and that in contrast with the relative stabilities of the corresponding oleanane derivatives (36), urs-12-en-3β-yl acetate is thermodynamically more stable than urs-13(18)-en-3β-yl acetate. Jones and his co-workers (36) had previously, by analogy with the acid isomerisation of olean-12-en-3β-yl acetate to olean-

-13(18)-en-3 β -yl acetate, tried without success to equilibrate urs-12-en-3 β -yl acetate. Finally, this isomerisation of urs-13(18)-en-3 β -yl acetate to α -amyrin acetate proves that ursa-11:13(18)-dien-3 β -yl acetate and α -amyrin acetate have the same configuration at C₉.

The view that the hydrogen atom attached to C₉ has the more stable configuration is supported by the following data. 11-Oxours-12-en-3 β -yl acetate (XIV), obtained by oxidation of α -amyrin acetate with chromic acid (37) is recovered unchanged after prolonged heating with alkali followed by reacetylation. A similar observation has been made with the related methyl 11-oxours-12-en-3 β -olate acetate (32). Work done in this department (38) has provided more convincing proof that C₉ in α -amyrin has the more stable configuration. The enol acetate (XV) of 11-oxours-12-en-3 β -yl acetate is strongly dextra-rotatory (+ 275°) and shows an absorption maximum at 2760 Å. (ϵ = 8,000) which is in good agreement for a 9(11):12-diene, since 9(11):12-dienes in both the oleanane and ursane series show similar strong dextrorotation and absorb at approximately 2800 Å. (ϵ ca. 9,000).

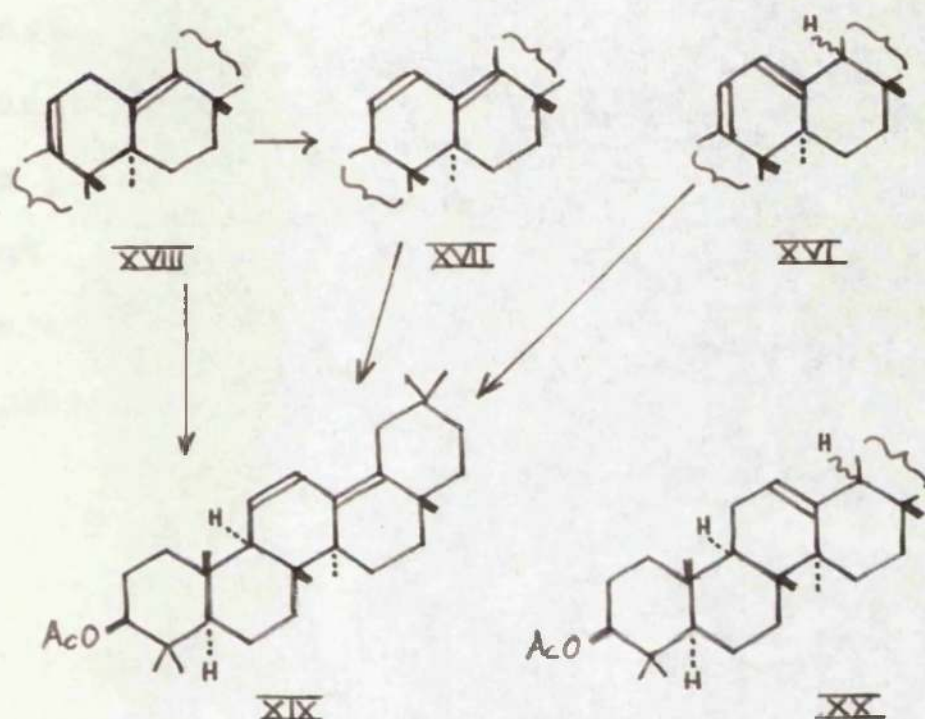


This shows that the enol acetate from 11-oxoursa-12-en-3 β -yl acetate is 3 β :11-diacetoxursa-9(11):12-diene (XV). Hydrolysis of the enol acetate followed by reacetylation gives 11-oxoursa-12-en-3 β -yl acetate (XIV) in good yield.

A final proof that α -amyrin and β -amyrin have the same configurations at C₈, C₉, C₁₀, C₁₃, C₁₄ and C₁₇ was provided by the following rearrangements, which also led to the view that the constitution and stereochemistry of α -amyrin are represented by the formula (XXII). Three ursadien-3 β -yl acetates have been prepared and characterised, and their stabilities studied. These are the homoannular diene ursadien-9(11):12-dien-3 β -yl acetate (XVI) (40), the heteroannular diene ursadien-11:13(18)-dien-3 β -yl acetate (XVII) described above, and the non-conjugated diene ursadien-9(11):13(18)-dien-

-3 β -yl acetate (XVIII) (see Section Ib). These correspond to the analogous 9(11):12-, 11:13(18)- and 9(11):13(18)-dienyl acetates in the oleanane series, where the 11:13(18)-dienyl acetate is thermodynamically the most stable, since it is obtained from either of the other two dienes on treatment with mineral acid (41, 42). In the case of the ursadien-3 β -yl acetates the following interrelationship exists. Treatment of ursa-9(11):13(18)-dien-3 β -yl acetate (XVIII) with hydrochloric-acetic acid mixture gives oleana-11:13(18)-dien-3 β -yl acetate in 30% (crude) and 10% (pure) yield (38). That this isomerisation proceeds through ursa-11:13(18)-dien-3 β -yl acetate (XVII) is shown as follows.

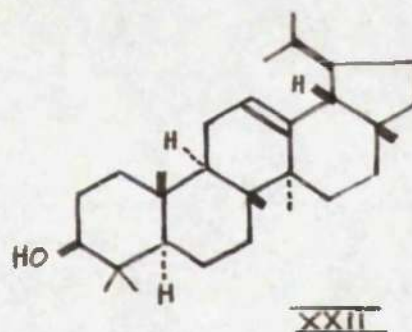
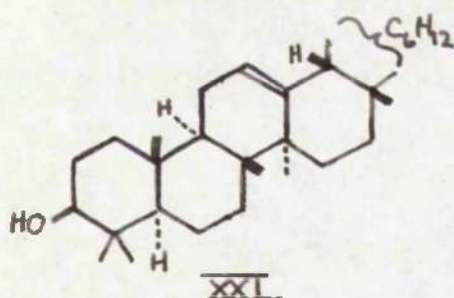
Treatment of ursa-9(11):13(18)-dien-3 β -yl acetate (XVIII) under milder conditions gives ursa-11:13(18)-dien-3 β -yl acetate in low yield (38), and treatment of ursa-11:13(18)-dien-3 β -yl acetate (XVII) with hydrochloric-acetic acid mixture gives oleana-11:13(18)-dien-3 β -yl acetate (XIX) in 10% pure yield. Finally, treatment of the homoannular diene, ursa-9(11):12-dien-3 β -yl acetate (XVI) under the same conditions gives oleana-11:13(18)-dien-3 β -yl acetate (XIX) in similar yield (38).



The conversion of the three ursadien-3 β -yl acetates into oleana-11:13(18)-dien-3 β -yl acetate (XIX) proves that the stereochemistry of α -amyrin is as represented by the formula (XX), and as a result of this the configurations shown in (XVI), (XVII) and (XVIII) represent the stereochemistry of the three ursadienyl acetates.

Allan and Spring (43) give reasons in support of the theory that the C₁₈-hydrogen atom in α -amyrin is β -orientated and that rings D and E are cis- β -fused

as in β -amyrin. Corey and Ursprung (20), from a consideration of the lactones from ursolic and oleanolic acids, came to the same conclusion, and the proof supplied by the above that the C_{17} attachment is β -orientated lends weight to this view. The stereochemistry of α -amyrin may now, therefore, be represented by (XXI).



The final point on the structure and stereochemistry of α -amyrin is the nature of ring E. This is postulated to be 5-membered (38) for the following reasons.

Since, as has been shown above, α -amyrin and β -amyrin are identical in rings A, B, C and D, the conformation of ring-E must be responsible for the differences in reactivity between α - and β -amyrin derivatives, and also for the stability of the cis-fusion

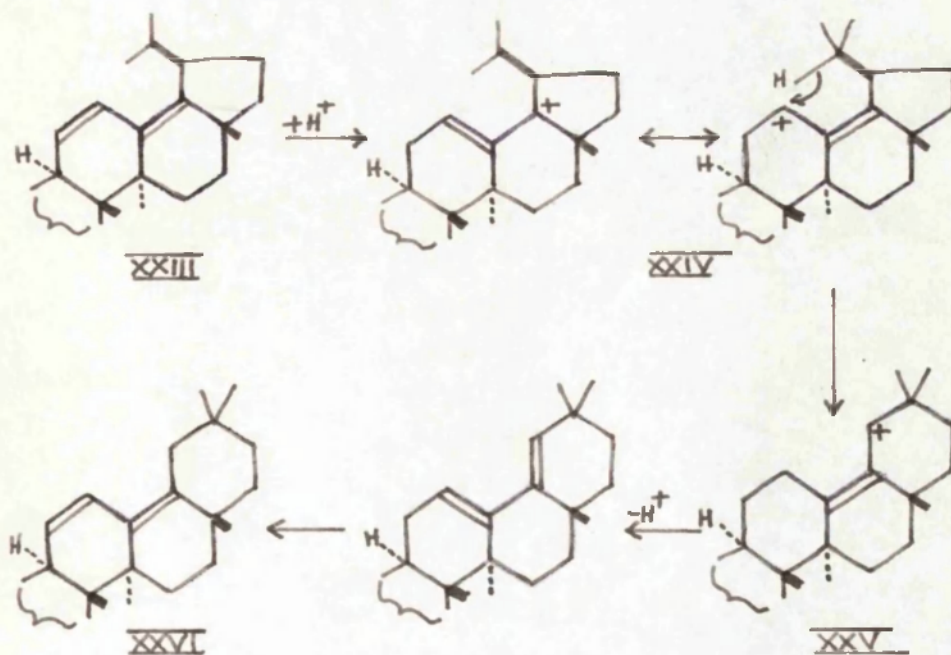
of this ring with ring-D. The fact that rings D and E are cis- β -fused in α -amyrin and that this arrangement is the more stable, as exemplified by the fact that urs-12-en-3 β -yl acetate is thermodynamically more stable than urs-13(18)-en-3 β -yl acetate is best explained if ring-E is 5-membered, since the more stable fusion of a 6-membered ring and a 5-membered ring is the cis-fusion (49).

Also, in ring E must lie the reason for the substantial hindering effect upon the double bond in α -amyrin and on the ketone group in 12-oxoursan-3 β -yl acetate. This, again, is readily explained if ring-E is 5-membered, with an isopropyl group having the β -configuration attached to C₁₀. The β -configuration is assigned to the isopropyl group for two reasons. First, an α -isopropyl group gives a molecular structure in which there is severe interaction between the C₁₀-isopropyl group and the C₁₄-methyl group. Secondly, the β -configuration of the isopropyl group best causes protection of the double bond in α -amyrin and of the ketone group in 12-oxoursanyl acetate, thus affording a reasonable explanation for the inert nature of these functions. Thus the structure and stereochemistry of α -amyrin is

now considered to be represented fully by the formula (XXII) (38).

α -Amyrin has till now been represented as (I), with ring-E 6-membered and possessing methyl groups attached to C₁₀ and C₂₀. The placing of these methyl groups was based on dehydrogenation evidence, and to reconcile the structure (XXII) with this evidence it must be assumed that rearrangement of ring-E occurs during the dehydrogenation.

The rearrangements of the ursadien-3 β -yl acetates to oleana-11:13(18)-dien-3 β -yl acetate (XIX) involving ring enlargement can be explained as depicted below.

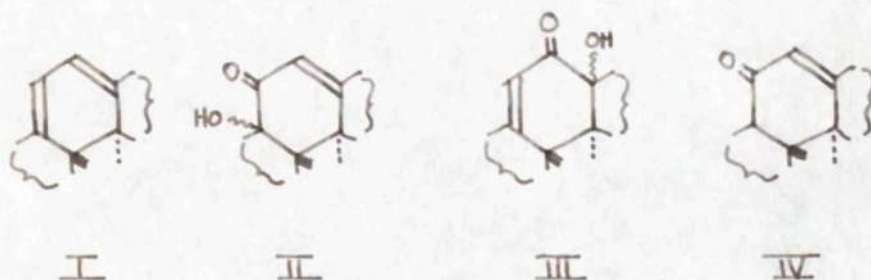


Addition of a proton to (XXIII) gives the ion (XXIV) and the proximity of the C₁₈-proton and the C₂₀-hydrogen allows a transannular hydride shift with synchronous ring enlargement, which gives the ion (XXV) which then loses a proton and rearranges as shown to give oleana-11:13(18)-dien-3 β -yl acetate (XXVI).

Section Ib.

Oxidation of ursa-9(11):12-dien-3 β -yl acetate.

Ursa-9(11):12-dien-3 β -yl acetate (I) is most conveniently prepared from α -amyrin acetate by oxidation with N-bromosuccinimide (44). Beynon, Sharples and Spring (45) reported that oxidation of the homoannular dienyl acetate with chromic acid gives an acetate $C_{32}H_{50}O_4$, in which the presence of an $\alpha\beta$ -unsaturated ketone group and a tertiary hydroxyl group has been established, and which was formulated as (II) or (III).



Ruzicka and his co-workers (17) repeated the oxidation and obtained the same product as above, together with a second acetate $C_{32}H_{48}O_4$, which they suggested contains the grouping $\begin{array}{c} \text{O} \\ \parallel \\ - \text{C} - \text{C} = \text{C} - \text{C} - \\ | \quad | \end{array}$.

It is impossible to accommodate the grouping on the basis of the formula for α -amyrin without assuming molecular rearrangement during the oxidation of the homoannular dienyl acetate.

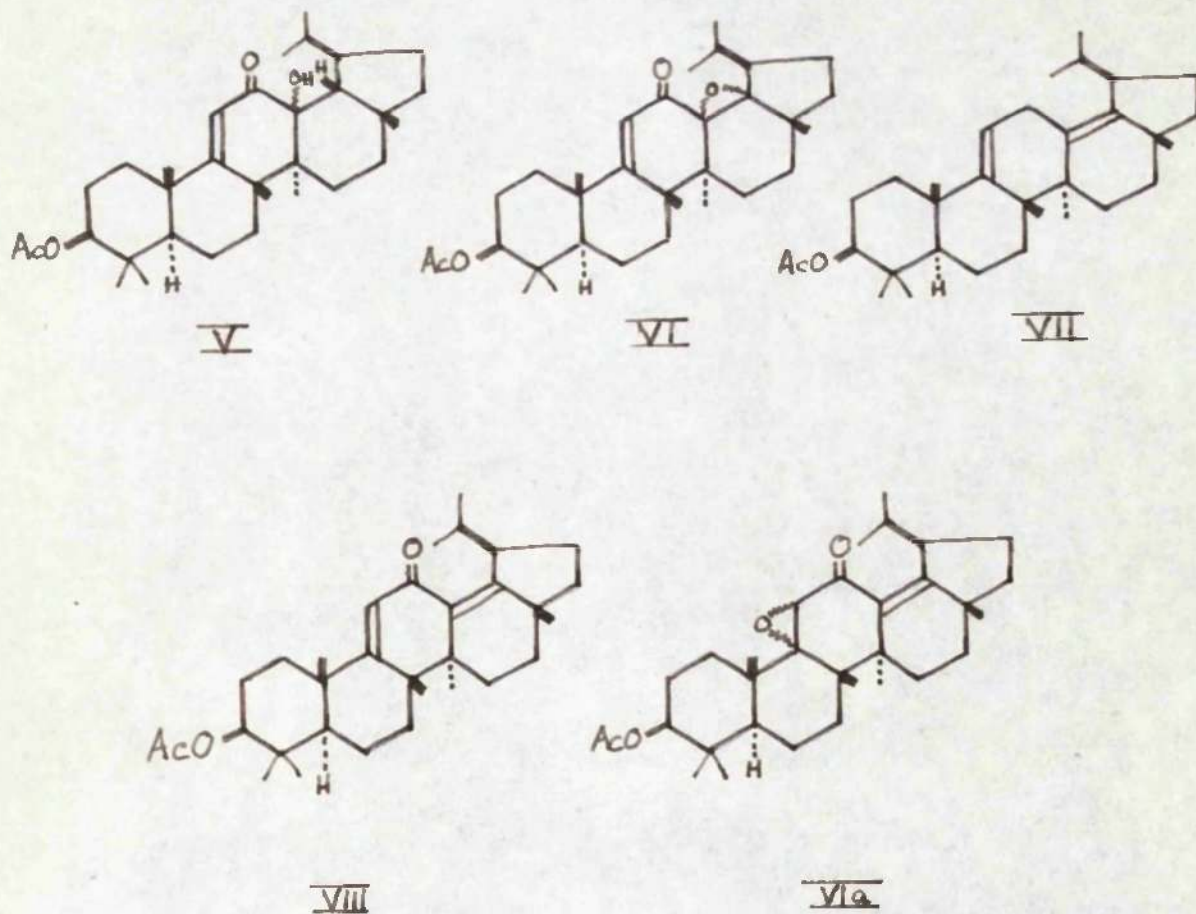
The chromic acid oxidation of urs-9(11):12-dien-3 β -yl acetate has been repeated, and two homogeneous products were isolated. The first was the acetate $C_{32}H_{50}O_4$, treatment of which with zinc dust and acetic acid gave 11-oxours-12-en-3 β -yl acetate (VI) in good yield, from which it follows that the parent acetate is 11-oxours-3 β :9 ξ -diol-3-acetate (39).

The second product, the acetate $C_{32}H_{48}O_4$ was then examined. At first the compound was thought to be 12-oxours-9(11)-en-3 β :13 ξ -diol-3-acetate (V), and was accordingly treated with zinc dust and acetic acid to prove this assumption. The product was, however, a mixture which on chromatography gave in poor yield two homogeneous products formulated as urs-9(11):13(18)-dien-3 β -yl acetate (VII) and 12-oxours-9(11):13(18)-dien-3 β -yl acetate (VIII). The latter compound had the ultra-violet light absorption spectrum characteristic of an enonene with a transoid-cisoid geometry as shown by the analogous

12-oxooleana-9(11):13(18)-dien-3 β -yl acetate (41).

The compound (VIII) shows absorption maxima at 2080, 2620, and 2940 $\overset{\circ}{\text{A}}$. (ϵ , 7,900, 9,300, and 7,700).

The corresponding oleanane derivative shows absorption maxima at 2080, 2600 and 2950 $\overset{\circ}{\text{A}}$. (ϵ , 9,000, 9,250 and 8,450).



It was then found that the second oxygen in the acetate $C_{32}H_{48}O_4$ is an oxidic function, because the infra-red absorption spectrum of the compound includes bands attributable to the acetate group and the $\alpha\beta$ -unsaturated ketone group, but it does not include bands due to the presence of either a hydroxyl or an isolated ketone group.

In assigning a structure to the acetate $C_{32}H_{48}O_4$, preference was given to the formulation (VI) rather than (VIa), for the following reasons. Treatment of the acetate $C_{32}H_{48}O_4$ with hydrochloric-acetic acid mixture (39) resulted in the material being recovered unchanged, and it is unlikely that a 9:11-epoxide would survive this treatment. Also the intensity of the ultra-violet absorption band at $2570 \overset{\circ}{\text{\AA}}$ of the acetate $C_{32}H_{48}O_4$ does not agree well with the presence of a cisoid $\alpha\beta$ -unsaturated ketone as shown in (VIa). Thus the second acetate, $C_{32}H_{48}O_4$, obtained by oxidation of ursa-9(11):12-dien-3 β -yl acetate with chromic acid is 13 ξ :18 ξ -epoxy-12-oxours-9(11)-en-3 β -yl acetate (VI).

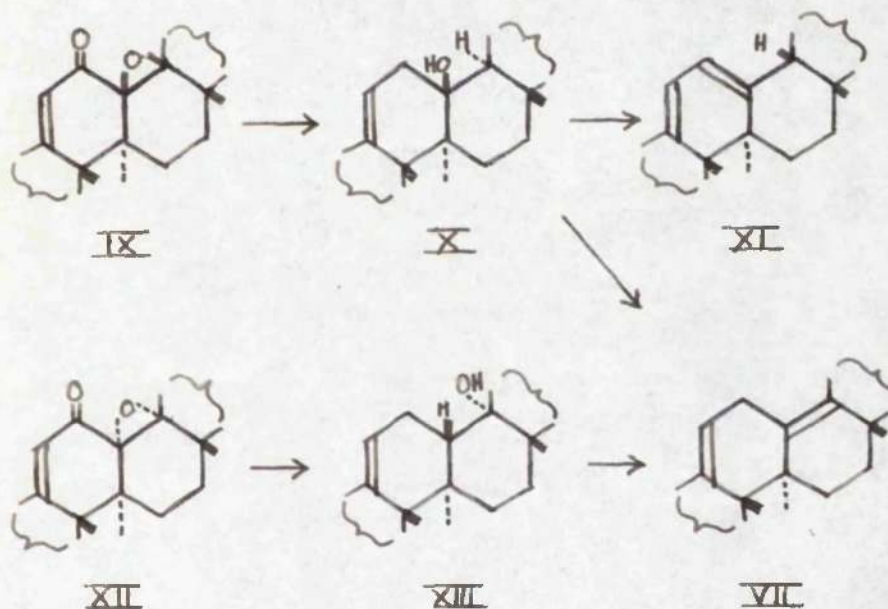
The second product obtained by treatment of (VI) with zinc and acetic acid had the absorption spectrum of a non-conjugated diene (ϵ at $2140 \overset{\circ}{\text{\AA}}$ = 9,150), and

was accordingly formulated as ursa-9(11):13(18)-dien-3 β -yl acetate (VII). This was confirmed by hydrogenolysis of 12-oxoursa-9(11):13(18)-dien-3 β -yl acetate (VIII), which gave the non-conjugated diene in excellent yield (39).

Catalytic hydrogenolysis of 13 ξ :18 ξ -epoxy-12-oxoursa-9(11)-en-3 β -yl acetate (VI) gave a product which was initially insoluble in chloroform, but after two crystallisations from non-redistilled methanol was soluble in chloroform and crystallised from chloroform-methanol to give ursa-9(11):13(18)-dien-3 β -yl acetate (VII).

If the oxide is considered to be a β -oxide, as in (IX), then trans-diaxial fission would yield (X), which could then dehydrate to give ursa-9(11):13(18)-dien-3 β -yl acetate (VII). Against this formulation is the fact that (X) would be more likely to dehydrate to give the homoannular diene (XI). Similar fission of the α -oxide (XII) would yield (XIII), which would be expected to give ursa-9(11):13(18)-dien-3 β -yl acetate (VII) on dehydration. Without further evidence it is not possible to decide between these two possibilities, but on the whole, the latter is

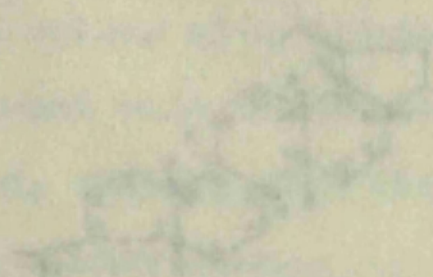
considered the more probable explanation.



12-Oxoursa-9(11):13(18)-dien-3 β -yl acetate is also obtained in excellent yield when 13 ξ :18 ξ -epoxy-12-oxours-9(11)-en-3 β -yl acetate (VI) is reduced with zinc in ethanol solution, and, surprisingly, the same reduction can be effected using lithium in liquid ammonia (39).

The importance of ursa-9(11):13(18)-dien-3 β -yl acetate (VII) is dealt with in Section Ia, where its stability under acid conditions is discussed.

As a basis for a systematic nomenclature for the products described in this section, the hydrocarbon $C_{28}H_{44}$, having the constitution and stereochemistry represented by (I) is called *ursadiene*.

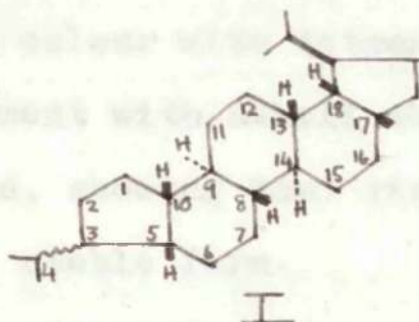


Treatment of *ursadiene* (II) with phosphorus pentachloride yields "4-*ursadiene*" (46) which does not show selective absorption of high intensity above 2200 Å. (47). This compound has been shown to be 8:10:14-trimethyl-5 β -norborn-3(4):12-diene (XII), in the following way. "4-*ursadiene*" is obtained from 8:10:14-trimethyl-11-oxo-5 β -norborn-3(4):12-diene (IV) (30) by Wolff-Fishner reaction (48).

Section Ic.

The Dehydration of urs-12-en-3 β -ol and
ursa-9(11):12-dien-3 β -ol.

As a basis for a systematic nomenclature for the products described in this section, the hydrocarbon $C_{27}H_{48}$, having the constitution and stereochemistry represented by (I) is called novursane.

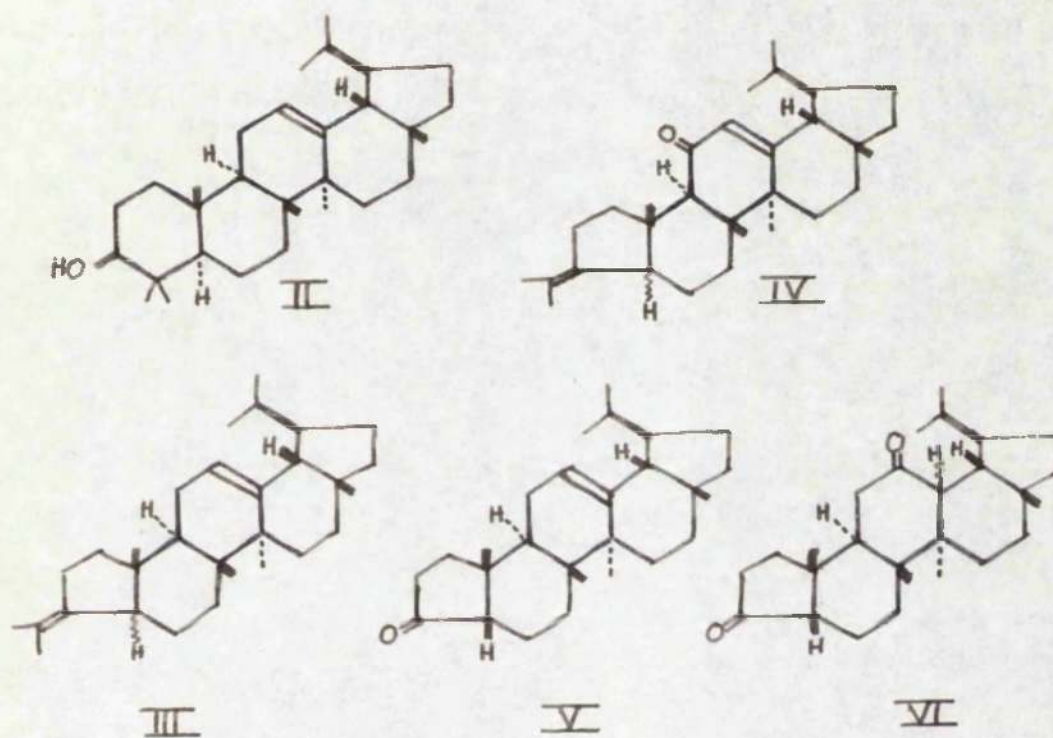


Treatment of α -amyrin (II) with phosphorus pentachloride yields "d- α -amyradiene" (46) which does not show selective absorption of high intensity above 2200 \AA . (47). This compound has been shown to be 8:10:14-trimethyl-5 ξ -novursa-3(4):12-diene (III), in the following way. "d- α -Amyradiene" is obtained from 8:10:14-trimethyl-11-oxo-5 ξ -novursa-3(4):12-diene (IV) (50) by Wolff-Kishner reduction (48).

Also, ozonolysis of "d- α -myradiene" at -35° yielded acetone as the volatile fragment after decomposition of the ozonide, and a mixture of a compound $C_{27}H_{42}O$, together with a very small amount of a compound $C_{27}H_{42}O_2$. The compound $C_{27}H_{42}O$ has been formulated as (V), since its infra-red absorption spectrum includes a band at 1740 cm.^{-1} (in carbon tetrachloride), showing that it contains a ketone group in a 5-membered ring. In agreement with this formulation it gives a yellow colour with tetranitromethane in chloroform. On treatment with alkali the ketone (V) was recovered unchanged, showing that rings A and B are fused in the more stable form.

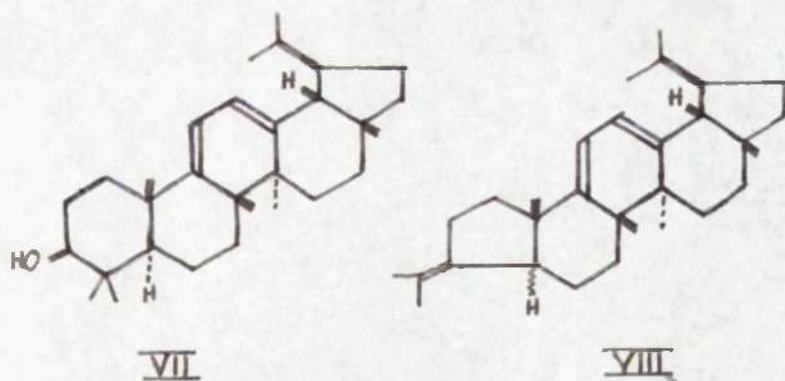
The conversion of α -amyrin (II) into the ketone (V) is accompanied by a change in $[M]_D$ of $+450^{\circ}$.

This change in $[M]_D$ accords very well with the values observed for comparable reactions (15) and proves that rings A and B in (V) are cis- β -fused. The second oxidation product $C_{27}H_{42}O_2$, which does not give a colour with tetranitromethane was not obtained in sufficient quantity to permit of any fuller investigation, but it is considered that it might possibly be the diketone (VI).



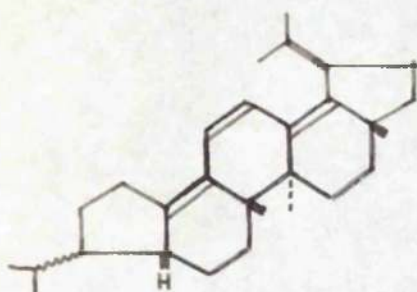
Ewen et al.(47) report that treatment of ursa-9(11):12-dien-3 β -ol (VII) with phosphorus pentachloride yields a dichloro- α -amyradiene, which on treatment with zinc yields "d- α -amyratriene", the ultra-violet absorption spectrum of which shows that the double bond introduced by dehydration is remote from the diene system in ring C. On repetition of this experiment, however, following the method of Ewen, it was found that treatment of ursa-9(11):12-dien-3 β -ol with phosphorus pentachloride gave "d- α -amyratriene" directly. This discrepancy was not more

fully investigated, but it was assumed that it was caused by slight changes in the reaction conditions. The constitution of "d- α -amyratriene" has now been established as 8:10:14-trimethyl-6 ξ -novursa-3(4):9(11):12-triene (VIII) since it is formed from 8:10:14-trimethyl-11-oxo-6 ξ -novursa-3(4):12-diene (IV) by reduction with lithium aluminium hydride, followed by treatment of the reaction product with phosphorus oxychloride in pyridine (48). From this it follows that the dichloro-compound is the 3:4-dichloride of (VIII).

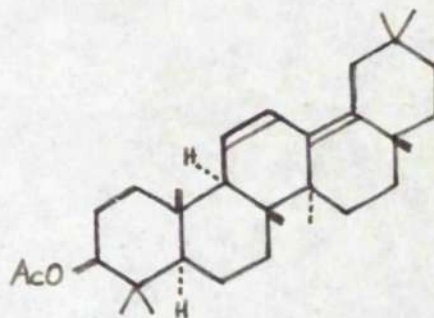


"1- α -Amyradiene" is prepared by treatment of α -amyrin with hydriodic-acetic acid mixture (45). By analogy, it was decided to try this method for the preparation of "1- α -amyratriene", instead of the normal method involving treatment with phosphorus

pentoxide (47). "1- α -amyratriene" has now been shown to have the structure (IX) (48). Treatment of urs-9(11):12-dien-3 β -ol (or 3 β -yl acetate) with hydriodic-acetic acid mixture yielded a gum, which was chromatographed. The major product, eluted with petrol, was a gum which showed the characteristic ultra-violet absorption spectra of a transoid heteroannular diene and of a conjugated triene (2950 Å) of approximately equal intensities. The two components of this mixture could not be separated, but are considered to be dehydration products. Further elution with petrol-benzene yielded some starting material, together with a small amount (ca.10%) of olean-11:13(18)-dien-3 β -yl acetate (X).



IX



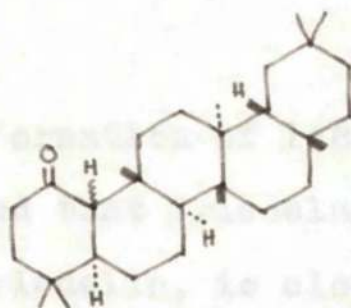
X

The appearance of (X) from this reaction was surprising at the time, but is now fully explained in light of the work described in Section Ia.

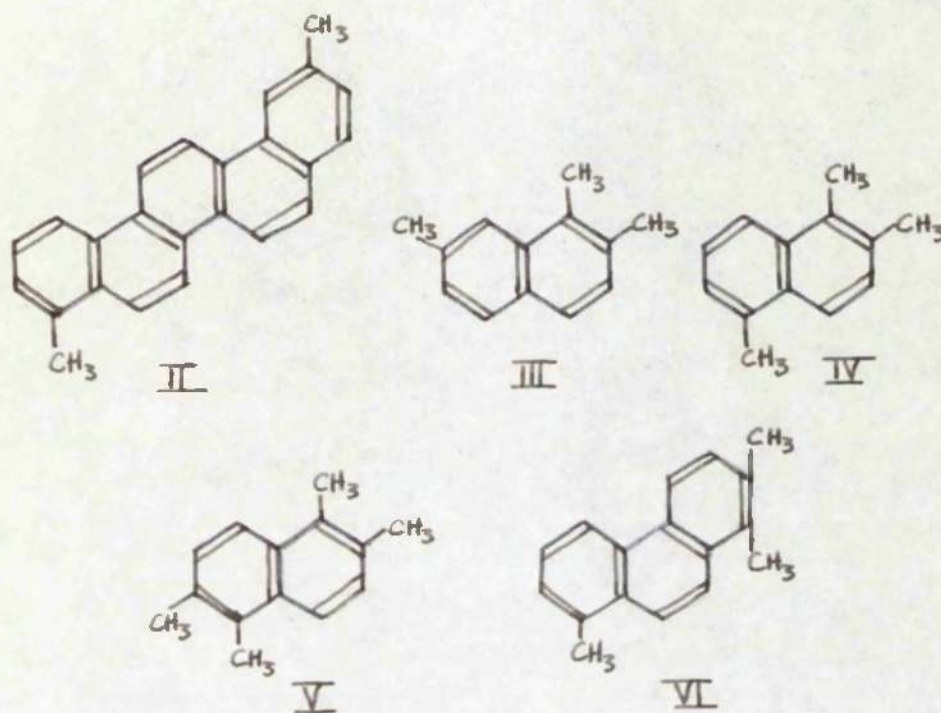
Section II.

The Constitution and Stereochemistry of Friedelin.

As mentioned in the Introduction, the work of Drake and his co-workers (27), and of Ruzicka and his co-workers (28) showed that friedelin is a saturated pentacyclic ketone, $C_{30}H_{50}O$, and that cerin is the corresponding α -hydroxy ketone. The present work has led to the initial postulation of the structure (I) for friedelin (49), as outlined below.



Dehydrogenation of the secondary alcohol, friedelanol, gives a variety of polynuclear hydrocarbons (27), viz. 1:8-dimethylpicene (II), 1:2:7-trimethylnaphthalene (III), 1:2:5-trimethylnaphthalene (IV), 1:2:5:6-tetramethylnaphthalene (V) and 1:2:8-trimethyl phenanthrene (VI).



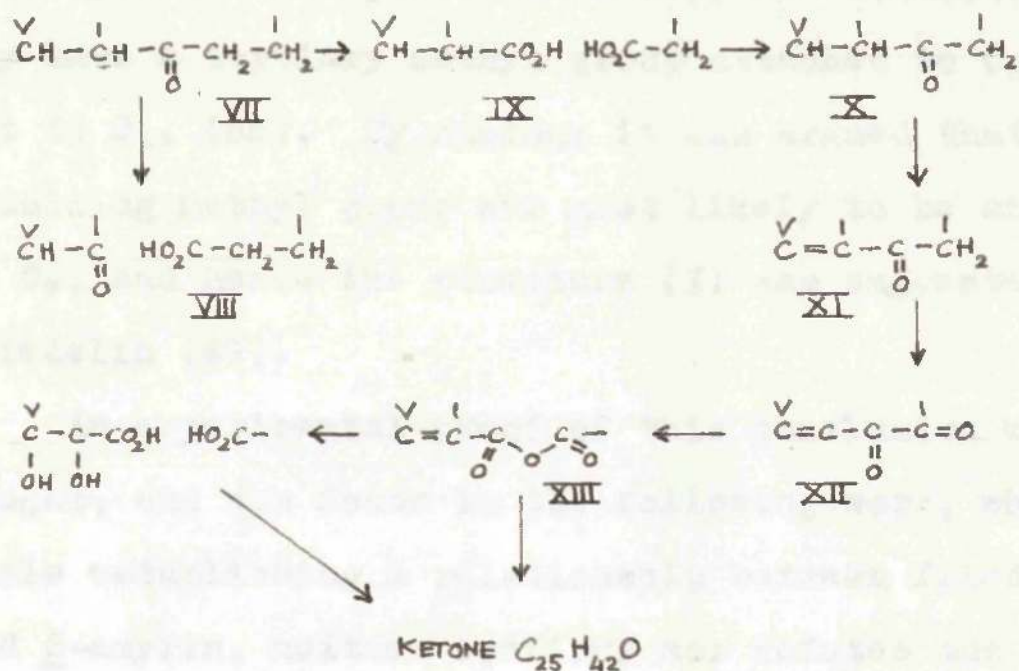
From the formation of 1:8-dimethylpicene (II) it may be argued that friedelane, the hydrocarbon derived from friedelin, is closely related to oleanane, and that the two hydrocarbons differ in the position of one or more of the tertiary methyl groups. The fact that 1:2:8-trimethylphenanthrene (VI) is also formed during the dehydrogenation supports this view, and suggests that two of the tertiary methyl groups are attached to C₁₃ and C₁₄.

Ruzicka et al. (28) established that the ketone group of friedelin is in a terminal ring of a per-

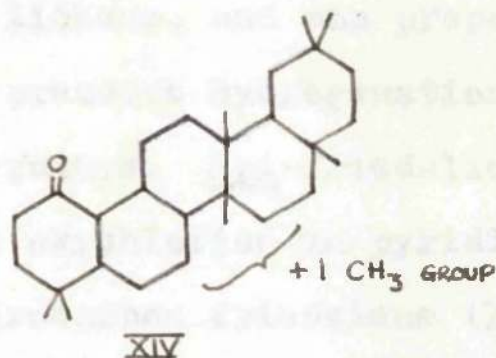
hydropicene homologue and degradation reactions of friedelin (28) have been interpreted as proof of the presence of the grouping $-CH_2 - CH_2 - \overset{O}{\underset{||}{C}} - \underset{|}{CH} -$
 $- \underset{|}{CH} -$. Assuming this to be true, and in light of the fact that friedelene can be isomerised to clean-13(18)-ene (see later), then the carbonyl group of friedelin must be at C₁, and friedelane cannot have a tertiary methyl group at C₁₀. Since these degradation reactions are important later in the discussion, a brief outline will be given at this juncture.

Oxidation of friedelin (VII) with chromic acid gives friedonic acid (VIII) (27) or friedelindioic acid (IX) (28), depending on the conditions of reaction. On heating, the anhydride of the latter (28) gives nor-friedelanone (X) which on oxidation with selenium dioxide in acetic acid yields nor-friedelenone (XI) (28). Further oxidation of nor-friedelenone with selenium dioxide in dioxan at 180° gives norfriedelenedione (XII) treatment of which with hydrogen peroxide or lead tetra-acetate gives norfriedelenedioic acid anhydride (XIII). This,

on ozonolysis, or by treatment with osmic acid followed by cleavage of the glycol with lead tetraacetate, yields a saturated ketone $C_{25}H_{42}O$. (28).

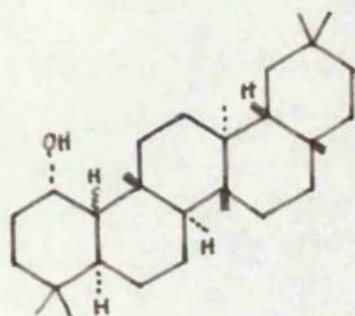


On the basis of the above evidence, the formula (XIV) was suggested for friedelin (49).

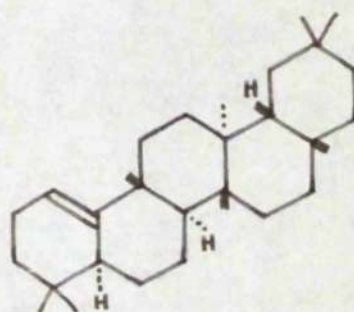


In assigning the position of the remaining methyl group, use was made of the recent discovery in these laboratories that butyrospermol, unlike other tetracyclic triterpenes of established constitution, may have a tertiary methyl group attached to C₉ and not to C₁₀ (55). By analogy it was argued that the remaining methyl group was most likely to be situated at C₉, and hence the structure (I) was suggested for friedelin (49).

An experimental proof of this conclusion was sought, and was found in the following work, which, while establishing a relationship between friedelin and β -amyrin, neither confirms nor refutes the constitution of ring-A suggested above. Treatment of friedelanone (friedelin, I) with lithium aluminium hydride gave in good yield epifriedelanol (XV), which has been isolated by Bruun (50) and Jeffries (51) from different lichens, and was prepared by the latter by high pressure hydrogenation of friedelin at a high temperature. Epi-friedelinol was treated with phosphorus oxychloride in pyridine to yield the unsaturated hydrocarbon friedelene (XVI).



XIV

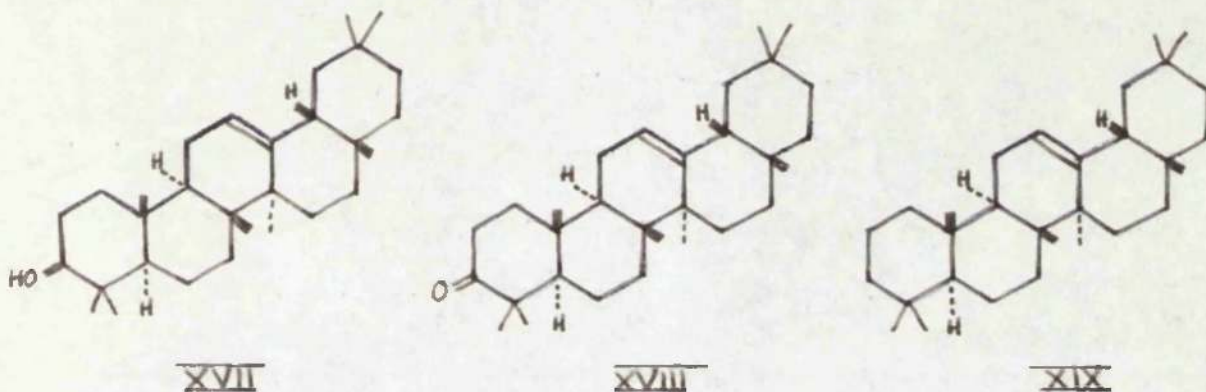


XVI

Treatment of friedelene (XVI) with concentrated hydrochloric-acetic acid mixture (1:5) under reflux gave a product of m.p. 186-187°, $[\alpha]_D - 20^\circ$. It was noted that these constants are very close to those given in the literature for olean-13(18)-ene. The quoted values vary considerably. Takeda (52) gives m.p. 189-190°, $[\alpha]_D - 20.5^\circ$. Jones and his co-workers (36) give m.p. 191.5-192° (Kofler), $[\alpha]_D - 33.5^\circ$. Jeger and his co-workers (53) give m.p. 185-186°, $[\alpha]_D - 27^\circ, -24^\circ$.

In view of these variations in the quoted values for the constants of olean-13(18)-ene, this compound was prepared by a number of different routes. The first method attempted involved oxidation of β -amyrin

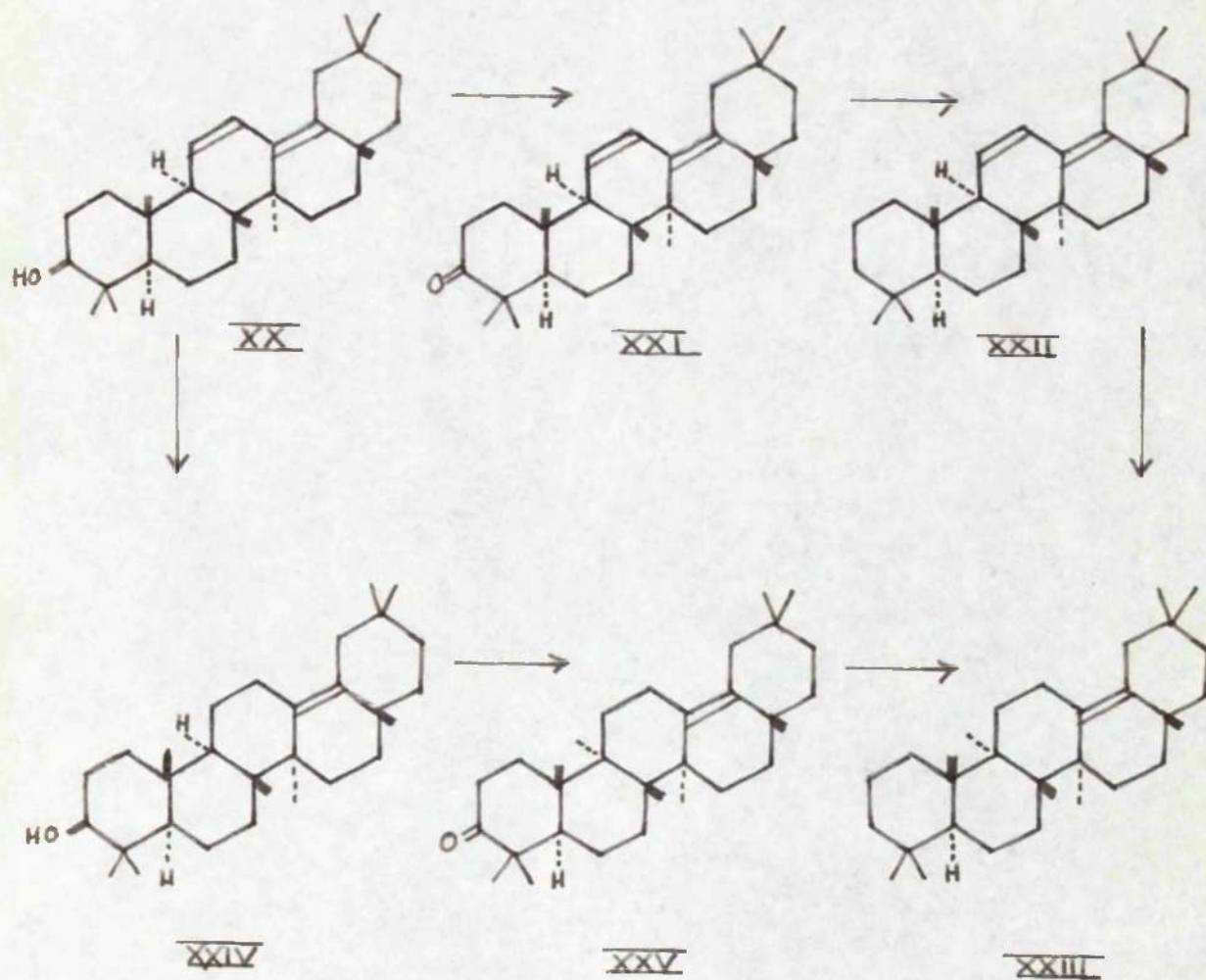
(XVII) to give 3-oxo-olean-12-ene (XVIII), which on Wolff-Kishner reduction yielded the unsaturated hydrocarbon olean-12-ene (XIX).



Treatment of the latter with concentrated hydrochloric-acetic acid mixture (1:5) gave a product m.p. 186-187°, $[\alpha]_D -20^\circ$, identical with the product obtained by treatment of friedelene with acid under the same conditions. It was realised that since the last stage in this preparation involved an acid isomerisation, it was possible that the product was an equilibrium mixture. Accordingly, other methods which did not involve the use of mineral acid in the final stage were sought.

The first method involved chromic acid oxidation of oleana-11:13(18)-dien-3 β -ol (XX) to give 3-oxo-

-oleana-11:13(18)-diene (XXI), Wolff-Kishner reduction of which gave the hydrocarbon oleana-11:13(18)-diene (XXII). Hydrogenation of the latter over platinum gave olean-13(18)-ene (XXIII), m.p. 186-187°, $[\alpha]_D -48^\circ$ (54).



In the second method, hydrogenation of oleana-11:13(18)-dien-3 β -ol (XX) yielded olean-13(18)-en-3 β -ol (XXIV), oxidation of which, followed by Wolff-Kishner reduction of the product 3-oxo-olean-13(18)-ene (XXV) yielded olean-13(18)-ene (XXIII) (54), having the same constants as the product obtained by the first method.

In the third method, Wolff-Kishner reduction of 3-oxo-olean-12-ene (XVIII) gave the hydrocarbon olean-12-ene (XIX), which was oxidised with selenium dioxide to give oleana-11:13(18)-diene (XXII), catalytic hydrogenation of which gave, as before, oleana-13(18)-ene (XXIII), again with m.p. 186-187°, $[\alpha]_D$ -48°. Takeda (52) and Koller (53) both report the formation of olean-13(18)-ene from oleana-11:13(18)-diene by hydrogenation, using slightly different conditions from the above, but they quote the specific rotation as -20.5° and -27° respectively. It must be assumed, as the following experiment indicates, that these discrepancies were due to partial equilibration caused by traces of mineral acid.

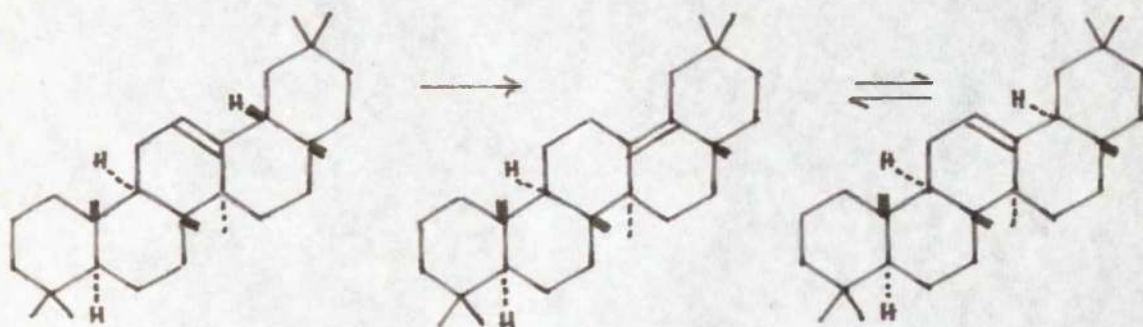
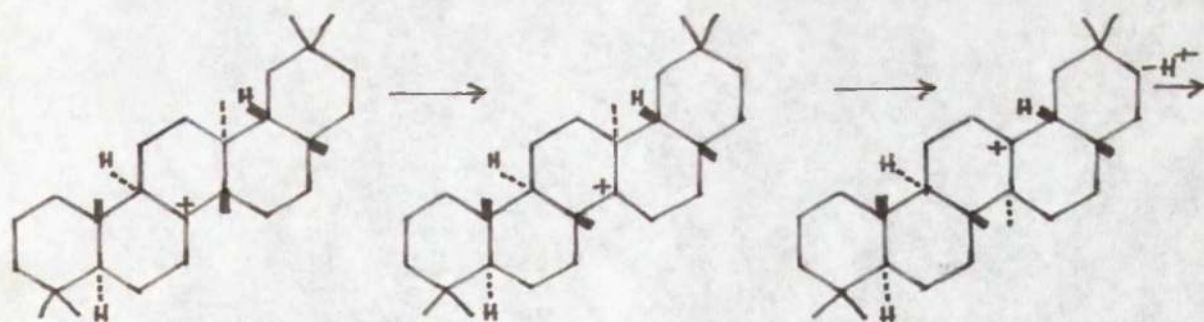
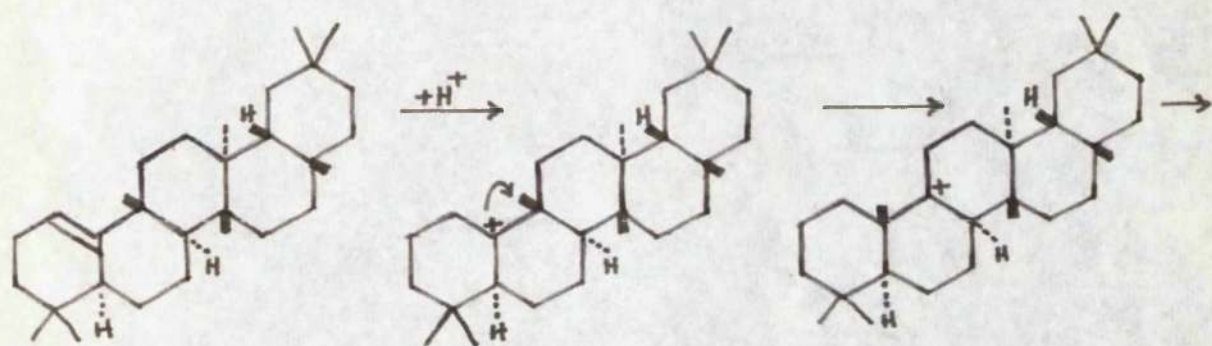
It was found that treatment of olean-13(18)-ene (m.p. 186-187°, $[\alpha]_D$ -48°) with hydrochloric-acetic

acid mixture under the same conditions as employed above for the isomerisation of friedelene, yielded a product, m.p. 186-187°, $[\alpha]_D -20^\circ$, which did not depress in melting-point on admixture with a sample obtained either from the acid rearrangement of friedelene or from the acid rearrangement of olean-12-ene.

The nature of the equilibrium mixture $[\alpha]_D -20^\circ$, was next considered. It is known that rings D and E in oleanane are cis-fused, but this is not the thermodynamically more stable union (32). Under suitable conditions, oleanane derivatives can be converted to 18 α -oleanane derivatives by treatment with acid or alkali, thus giving the more stable trans-D/E fusion (32). Considering the above experimental data, one may reasonably assume that olean-12-ene is an intermediate in the acid rearrangement of friedelene. Under the reaction conditions, this should rearrange completely to olean-13(18)-ene, since this is thermodynamically more stable. Conditions then favour equilibration of the 13(18)-double bond to the 12-position, resulting in the formation of 18 α -olean-

-12-ene, and the position of the equilibrium will be determined by the relative stabilities of these two isomers. If this assumption is correct, and the two isomers are of similar thermodynamic stability, then 18- α -olean-12-ene should be capable of isomerisation to give the same equilibrium mixture, m.p. 186-187°, $[\alpha]_D$ -20°, and this, in fact, has been done (59). To further substantiate this theory a synthetic mixture of 18 α -olean-12-ene and olean-13(18)-ene (1:2) was prepared and crystallised (59) to give a product of m.p. 185-186°, $[\alpha]_D$ -21°, which was identical with the equilibrium mixture obtained from the acid rearrangement of friedelene, olean-12-ene or olean-13(18)-ene.

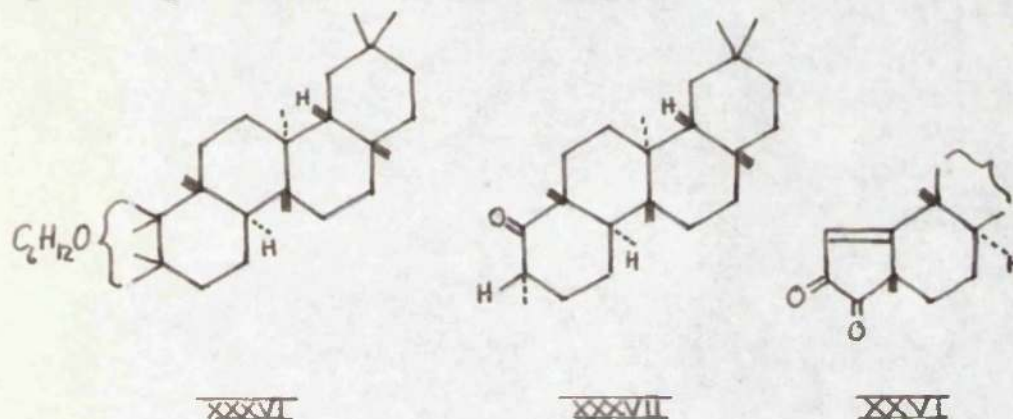
On the basis of the structure (I) for friedelin, the conversion of friedelene into the equilibrium mixture comprising olean-13(18)-ene and 18 α -olean-12-ene may be explained by the series shown below, involving the migration of one axial hydrogen and three axial methyl groups.



In an attempt to stop the isomerisation at the 12-position, friedelene was treated with mineral acid under milder conditions, namely with dry hydrogen chloride in chloroform solution, but the product obtained proved to be the hydrochloride, which on dehydrochlorination with collidine yielded friedelene.

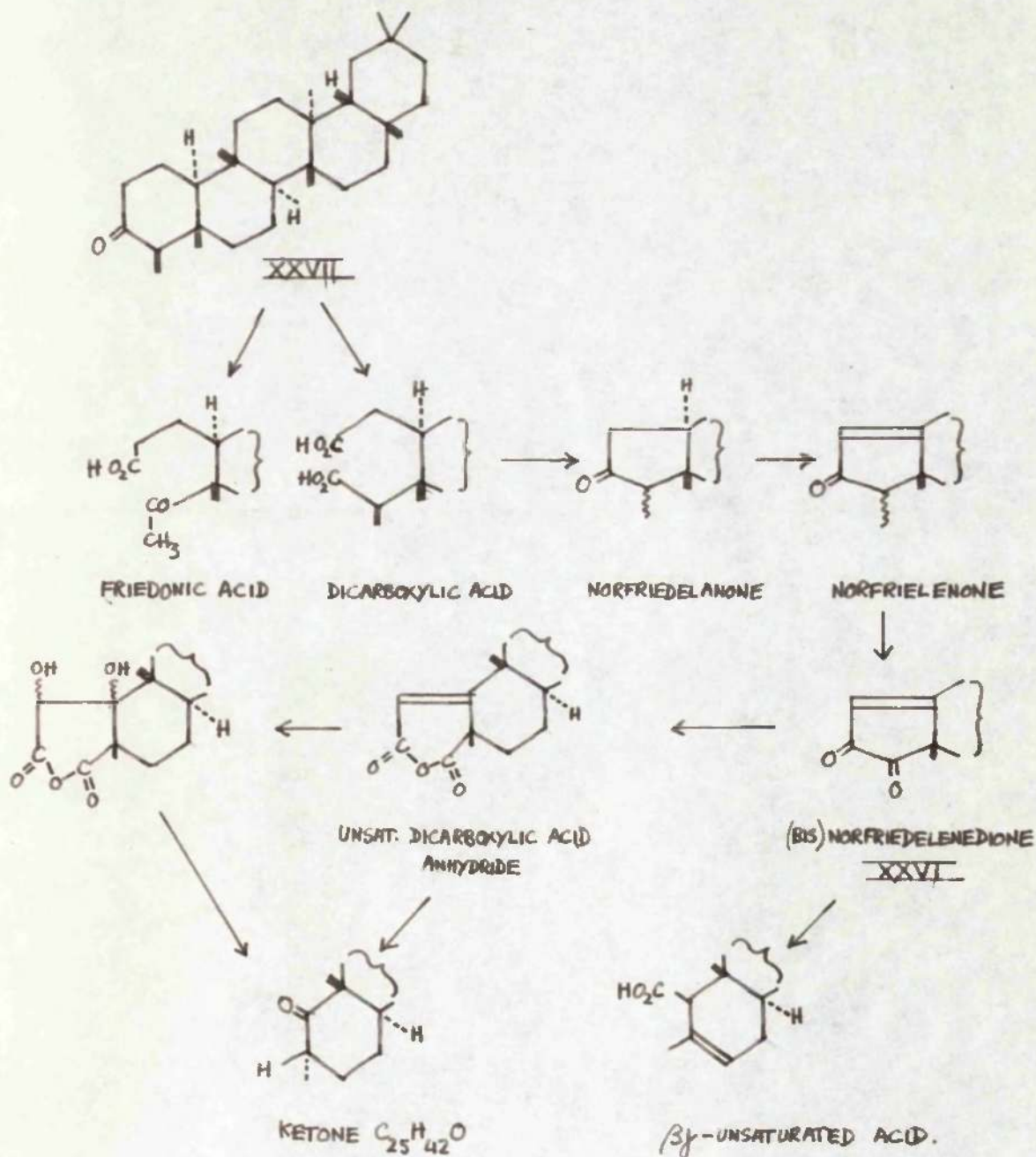
Since the proposal of the structure (I) for friedelin, it was shown by Ourisson and Takahashi (56) that friedonic acid (VIII), obtained by chromic acid oxidation of friedelin (27), is a methyl ketone, and also that the saturated tetracyclic ketone $C_{28}H_{48}O$ (28) has only one α -hydrogen atom. These authors also accept the view that friedelin contains the fragment $-CH_2 - CH_2 - \overset{O}{\underset{|}{C}} - \underset{|}{CH} - \underset{|}{CH} -$, and thence deduce alternative partial formulae for friedelin. These formulae must, however, be rejected, since they are not compatible with the conversion of friedelene into olean-13(18)-ene. In order to accommodate this new evidence, the original assumption that the grouping $-CH_2 - CH_2 - \overset{O}{\underset{|}{C}} - \underset{|}{CH} - \underset{|}{CH} -$ is present in ring-A, has to be discarded, and a new formulation for ring-A sought to fit these facts.

The rearrangement of friedelene into olean-
-13(18)-ene proves that friedelin can be represented
by the partial formula (XXXVI).

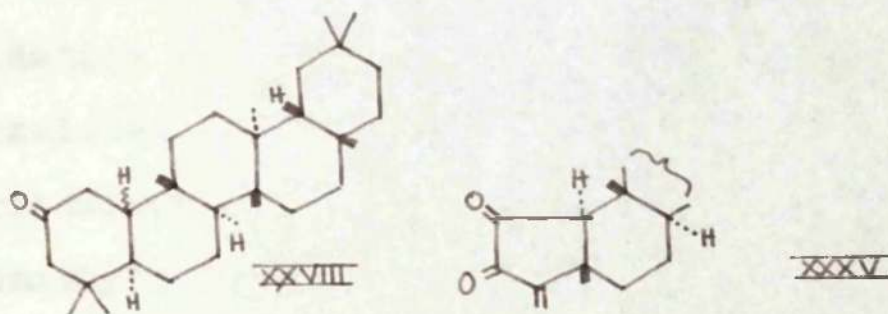


The structure of the ketone $C_{25}H_{42}O$, which was shown by Ourisson and Takahashi to have only one α -hydrogen atom, must therefore be represented by (XXXVII), from which it follows that the structure of norfriedelenedione must be as represented by (XXVI). As a result of this formulation for norfriedelenedione it follows that the carbonyl group in friedelin cannot be attached to C_1 , since the degradation reactions of friedelin to the structure (XXVI) could not then be accommodated. The carbonyl group must therefore be attached to C_2 or C_3 , and consequently, friedelin cannot contain the grouping $-CH_2 - CH_2 - \overset{O}{\parallel} C - \underset{|}{CH} - \underset{|}{CH} -$.

The two possibilities (i.e. carbonyl group attached to C_2 or to C_3) were next considered. If the carbonyl group is attached to C_3 , as in (XXVII), then the degradation products of friedelin may be represented adequately as shown below.



On the basis of this structure (XXVII) for friedelin it is obvious that formation of norfriedelenedione (XXVI) must involve the extrusion of one carbon atom, and accordingly (XXVI) should be named bisnorfriedelenedione; the analytical data (25) for this compound and its derivatives support the molecular formula proposed. Also Ourisson (60) has recently confirmed this by proving by density measurements that bisnorfriedelenedioic acid anhydride has the molecular formula $C_{28}H_{42}O_5$. Corey and Ursprung (58) formulate norfriedelenedione as (XXXV), but in view of the above evidence this appears unlikely.

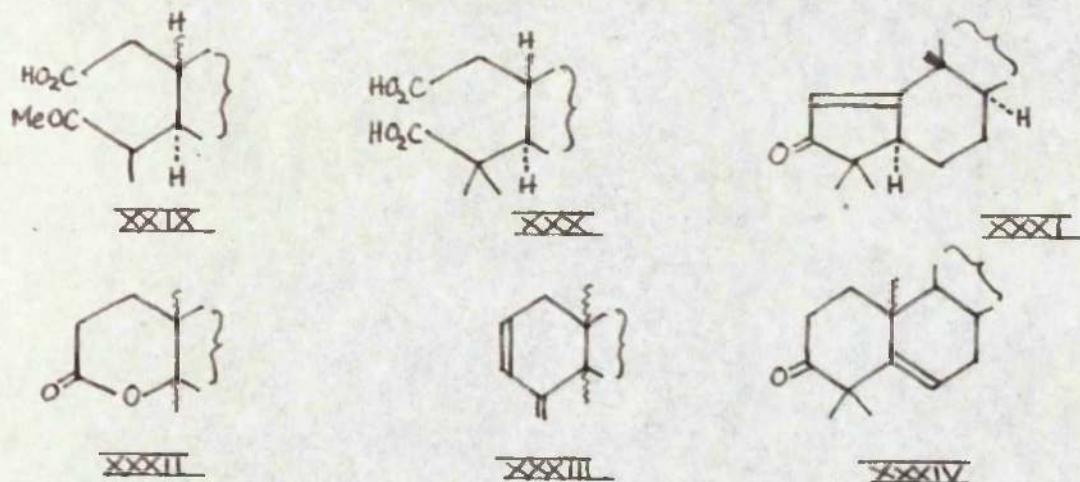


If friedelin has a carbonyl group attached to C_3 it must be formulated as (XXVIII), and its conversion into friedonic acid (XXIX), shown to be a methyl ketone (56), must therefore involve a molecular rearrangement. On the basis of this formulation for friedelin, the dicarboxylic acid is (XXX) and norfriedelenedione is (XXXI). It must also be assumed that the oxidation of

norfriedelenone (XXXI) to norfriedelenedione (XXVI) is accompanied by methyl group migration and methyl group extrusion.

Although these two possibilities (XXVII) and (XXVIII) were suggested (57), it was not possible to decide definitely which was correct without further experimental evidence.

The work of Corey and Ursprung (58) has recently supplied this necessary evidence, which strongly favours the formulation (XXVII) for friedelin, as these authors suggest. Briefly, the evidence they put forward is as follows. Firstly, three-stage oxidation of friedelin gives a C_{28} , 6-membered lactone, formulated as (XXXII). Secondly, bromination of Δ^8 -friedelene followed by dehydrobromination gives the exomethylenic diene which they formulate as (XXXIII).



Also, 4-bromofriedelin, obtained by bromination of friedelin enol benzoate, is readily dehydrobrominated to give an unsaturated, unconjugated ketone which cannot be isomerised to the conjugated structure. This product they formulate as (XXXIV), assuming that migration of a methyl group has occurred during dehydrobromination.

This new evidence can best be accommodated if friedelin has the structure (XXVII) i.e. with the carbonyl group attached to C₃. Corey and Ursprung (58) also present evidence for trans-fusion of rings A and B, and show that the saturated tetracyclic ketone C₂₈H₄₆O has only one α-hydrogen atom (cf. 58). They also show the presence of a hydrogen atom attached to C₁₀ by further degradation of the βγ-unsaturated acid obtained from norfriedelenedione with alkaline peroxide. Their final proof for the structure (XXVII) for friedelin is the acid rearrangement of friedelanol to the equilibrium mixture.

Thus the experimental evidence, both that described in this section and that of Corey and Ursprung (58), strongly favours the view that the structure and stereochemistry of friedelin is as

represented by the formula (XXVII).

EXPERIMENTAL
=====

Experimental

Ursa-11:13(18)-dien-3 β -yl acetate. - A solution of α -amyrin acetate (40 g.) in boiling benzyl acetate (500 ml.; redist.) was treated with selenium dioxide (48 g.) for 24 hours. The solution was filtered, and concentrated to approximately 150 ml. under reduced pressure at 130° (oil-bath). The remainder of the benzyl acetate was removed by steam distillation. The dark gummy residue was dissolved in ether, washed with potassium cyanide solution (3%, 500 ml.), water, and the ether extract dried over sodium sulphate. The residue obtained on removal of the solvent was crystallised from chloroform-methanol to give α -amyrin acetate (20 g.), m.p. and mixed m.p. 220-222°. Concentration of the mother liquors gave a second crop (5 g.) of α -amyrin acetate. These crops were combined and recrystallised until no heteroannular diene absorption was observed. The total mother liquors were combined and evaporated to dryness, dissolved in benzene-light petroleum (b.p. 60-80°, 1:9) and chromatographed on alumina (650 g.). Elution with the same solvent mixture (1700 ml.) gave α -amyrin

acetate (4.5 g.) m.p. 223-225°. Elution with benzene-light petroleum (b.p. 60-80°, 4:1), benzene, and benzene-ether (5%) gave fractions of m.p.'s ranging from 190° to 200° (2.5 g.). These fractions were combined and rechromatographed. Elution of the column with benzene-light petroleum (1:2) gave α -amyrin acetate (1.1 g.). Elution with benzene-ether (5%) gave urs-11:13(18)-dien-3 β -yl acetate (500 mg.) which crystallised from chloroform-methanol as needles m.p. 204-206°, $[\alpha]_D^{25} -76^\circ$ (c, 1.0). Light absorption in ethanol: ϵ_{2440} 26,000; ϵ_{2510} 29,000; ϵ_{2800} 18,400. The residues from the latter chromatography showing heteroannular diene absorption were combined and rechromatographed, yielding a further 200 mg. of urs-11:13(18)-dien-3 β -yl acetate. The compound gave a red-brown colour with tetranitromethane in chloroform.

Urs-13(18)-en-3 β -yl acetate. - A solution of urs-11:13(18)-dien-3 β -yl acetate (400 mg.) in ethyl acetate (80 ml.) and stabilised glacial acetic acid (90 ml.) was added to a freshly reduced suspension of platinum (from 200 mg. PtO₂), and the

mixture shaken with hydrogen for 21 hours. The filtered solution was evaporated to dryness, and the crystalline product was crystallised from chloroform-methanol to give urs-13(18)-en-3 β -yl acetate as needles (350 mg.) m.p. 213-215°, $[\alpha]_D$ -22° (c,1.1). Light absorption in ethanol: ϵ_{2110} 5,500.

Easton, Manson and Spring (33) give m.p. 214-216°, $[\alpha]_D$ -22° and ϵ at 2150 Å. = 5,100 for this compound. The compound gave a yellow colour with tetranitromethane in chloroform.

Urs-13(18)-en-3 β -ol. - A solution of urs-13(18)-en-3 β -yl acetate (100 mg.) in ethanolic potassium hydroxide (3%; 50 ml.) was heated under reflux for 2.5 hours. The product, obtained by working up in the usual fashion, was a solid which was crystallised from methanol to give urs-13(18)-en-3 β -ol as blades (90 mg.) m.p. 201-202°, $[\alpha]_D$ -37°, -37.3° (c,1.0, 1.4). To check that the product was homogeneous, it was reacetylated in the usual fashion and the acetylated material crystallised from chloroform-methanol as needles m.p. 211-212°, $[\alpha]_D$ -22°. This material was dissolved in light petroleum (b.p. 60-80°) and

chromatographed on alumina. The column was eluted with the same solvent (600 ml.); three fractions (ca. 200 ml. each) were collected and crystallised separately. The constants of these were

1. m.p. 212-213°, $[\alpha]_D -21^\circ$
2. m.p. 211-212°, $[\alpha]_D -22^\circ$
3. m.p. 211-213°, $[\alpha]_D -21.7^\circ$

Isomerisation of Urs-13(18)-en-3 β -yl Acetate to α -Amyrin Acetate. - A solution of urs-13(18)-en-3 β -yl acetate (150 mg.) in benzene (3 ml.) and acetic acid (30 ml.) was treated with concentrated sulphuric acid (5.7 ml.), the mixture heated at 80° for 5 minutes and kept at room temperature for 14 days. The crystalline solid (30 mg.) which separated was collected. The filtrate was diluted with water, the mixture extracted with ether, washed with sodium bicarbonate solution, water, and the ether extract dried over sodium sulphate. On removal of the ether there was obtained a gum which was dissolved in benzene-light petroleum (b.p. 60-80°; 1:4) and chromatographed on alumina. Elution with the same solvent mixture gave a crystalline fraction (53 mg.)

which was combined with the previously collected solid (30 mg.), dissolved in light petroleum, and again chromatographed on alumina. Elution with light petroleum (150 ml.) gave a crystalline fraction (35 mg.) which, after two recrystallisations from chloroform-methanol, yielded α -amyrin acetate as plates, m.p. 224-225°, $[\alpha]_D + 78^\circ$. A mixture of this with an authentic sample of α -amyrin acetate, m.p. 226-227°, $[\alpha]_D + 76^\circ$ (c, 1.9), was undepressed in melting-point.

The product (15 mg.) from the isomerisation was hydrolysed with 3% aqueous ethanolic potassium hydroxide solution. Working up in the usual fashion yielded a gum which was benzoylated and worked up in the usual fashion. Crystallisation of the product from methanol gave α -amyrin benzoate as needles, m.p. and mixed m.p. 193-195°.

Rearrangement of Ursa-11:13(18)-dien-3 β -yl
Acetate to Oleana-11:13(18)-dien-3 β -yl Acetate. - A solution of ursa-11:13(18)-dien-3 β -yl acetate (200 mg.) in glacial acetic acid (70 ml.) and concentrated hydrochloric acid (5 ml.) was heated on the steam-bath for

17 hours. The mixture was evaporated under reduced pressure, the residue dissolved in light petroleum (40 ml.) and chromatographed on alumina (12 g.).

Elution with light petroleum (300 ml.) gave an uncrystallisable gum (50 mg.). Further elution with light petroleum (400 ml.) and light petroleum-benzene (20:1, 400 ml.; 10:1, 250 ml.) gave fractions (48 mg.) which crystallised from chloroform-methanol as plates m.p. 219-222°. Recrystallisation of the compound fractions gave oleana-11:13(18)-dien-3 β -yl acetate as plates (20 mg.), m.p. and mixed m.p. 225-226°, $[\alpha]_D -61^\circ$ (c , 1.0).

Light absorption in ethanol: ϵ_{2320} 23,500; ϵ_{2500} 26,500; ϵ_{3000} 16,800.

Chromic Acid Oxidation of Ursa-9(11):12-dien-3 β -yl Acetate. - A solution of chromic acid (15 g.) in water (15 ml.) and glacial acetic acid (150 ml.) was added over 30 minutes with stirring to a solution of ursa-9(11):12-dien-3 β -yl acetate (15 g.) in glacial acetic acid (500 ml.). After refluxing for 2 hours, methanol was added to destroy excess oxidising agent, the solution concentrated under reduced pressure and

diluted with water. On ether extraction there was obtained an ether-insoluble fraction, which was removed by filtration and crystallised from chloroform-methanol to give 11-oxours-12-en-3 β :9 ξ -diol 3-acetate as blades (2.54 g.), m.p. 315-317°, $[\alpha]_D^{+55}$ (c, 2.2). Light absorption in ethanol: ϵ_{2500} 13,500. The compound does not give a colour with tetranitromethane in chloroform. Ruzicka and his co-workers (17) give m.p. 316° (high vac.), $[\alpha]_D^{+62}$ for this compound.

The ether extract was evaporated to dryness and the residue crystallised from chloroform-methanol to give 11-oxours-12-en-3 β :9 ξ -diol 3-acetate (500 mg.), m.p. and mixed m.p. 315-317°. Concentration of the mother liquors yielded a further, slightly impure, crop of the diol monoacetate. Further concentration of the mother liquors yielded 13 ξ :18 ξ -epoxy-12-oxours-9(11)-en-3 β -yl acetate, which, after recrystallisation from the same solvent, separated as plates (600 mg.) m.p. 269-271°, $[\alpha]_D^{+71}$ (c, 1.0). Light absorption in ethanol: ϵ_{2570} 13,000.

The compound does not give a colour with tetranitro-

methane. (Found: C, 77.7; H, 9.6. $C_{32}H_{44}O_4$ requires C, 77.4; H, 9.7%).

Infra-red absorption: bands at 1250 and 1722 cm^{-1} (acetate), 1603 and 1652 cm^{-1} ($\alpha\beta$ -unsaturated ketone), no hydroxyl band. Ruzicka and his co-workers (17) give m.p. 258° , $[\alpha]_D + 70^\circ$ for a compound $C_{32}H_{44}O_4$ obtained by the same method.

Treatment of 13 ξ :18 ξ -epoxy-12-oxours-9(11)-en-3 β -yl Acetate with Zinc in Acetic Acid. - To a solution of 13 ξ :18 ξ -epoxy-12-oxours-9(11)-en-3 β -yl acetate (500 mg.) in acetic acid (250 ml.) was added zinc dust (10 g.), and the mixture refluxed for 5 hours. After filtration, the solution was evaporated to dryness and the residue crystallised from chloroform-methanol to give a material (250 mg.) m.p. 208° , $[\alpha]_D + 23^\circ$. Light absorption in ethanol: ϵ_{2000} 8,500; ϵ_{2200} 7,100; ϵ_{2400} 4,450. The material was dissolved in light petroleum (b.p. $60-80^\circ$; 75 ml.) and chromatographed on alumina (10 g.). Elution of the column with the same solvent (600 ml.) gave a product which crystallised from aqueous methanol to give urs-9(11):13(18)-dien-3 β -yl acetate (see later) as plates

(70 mg.), which after two recrystallisations had m.p. 192-194°, $[\alpha]_D + 74^\circ$ (c, 1.0). Light absorption in ethanol: ϵ_{2150} 11,000. The compound gave a deep yellow colour with tetranitromethane in chloroform. Elution of the column with light petroleum-benzene (1:4, 250 ml.) gave material, m.p. 239-242° (32 mg.). Light absorption: ϵ_{2050} 4,200; ϵ_{2150} 9,300; ϵ_{2240} 2,300. Further elution with light petroleum-benzene (2:1, 300 ml.; 1:1, 300 ml.) gave mixtures of decreasing m.p., and showing an increase in intensity of light absorption at 2950 Å. Light petroleum-benzene (1:2, 200 ml.) eluted material (30 mg.) which crystallised from aqueous methanol to give 12-oxoursa-9(11):13(18)-dien-3 β -yl acetate as pale yellow plates, m.p. 210-212°, $[\alpha]_D -44^\circ$ (c, 0.5). Light absorption in ethanol: ϵ_{2050} 8,300; ϵ_{2150} 8,800; ϵ_{2250} 6,900. (Found: C, 79.84; H, 10.04. $C_{22}H_{42}O_3$ requires C, 79.95; H, 10.07%).

12-Oxoursa-9(11):13(18)-dien-3 β -yl acetate. - Zinc dust (10 g.) activated by warming with ammonium chloride solution) was added to a solution of 13 ξ :18 ξ -epoxy-12-oxours-9(11)-en-3 β -yl acetate (400 mg.) in

ethanol (250 ml.) and the mixture refluxed for 6 hours. The solution was filtered and the solvent removed under reduced pressure, leaving a yellow solid which crystallised from methanol as pale yellow plates, m.p. 202-204°, $[\alpha]_D -42^\circ$ ($c, 1.0$). Recrystallisation from the same solvent yielded 12-oxoursa-9(11):13(18)-dien-3 β -yl acetate as pale yellow plates (300 mg.), m.p. 203-205°, $[\alpha]_D -42^\circ$ ($c, 1.5$). Light absorption in ethanol: $\epsilon_{max} 7,900$; $\epsilon_{max} 9,300$; $\epsilon_{max} 7,700$. A mixture with 12-oxo-oleana-9(11):13(18)-dien-3 β -yl acetate, m.p. 205-207°, had m.p. 172-179°.

Catalytic Hydrogenation of 13 ξ :18 ξ -epoxy-12-oxours-9(11)-en-3 β -yl Acetate. - A solution of 13 ξ :18 ξ -epoxy-12-oxours-9(11)-en-3 β -yl acetate (200 mg.) in stabilised glacial acetic acid (75 ml.) was added to a freshly reduced suspension of platinum (from 100 mg. PtO $_2$) in acetic acid (15 ml.), and the mixture shaken with hydrogen for 18 hours. Working up in the usual way yielded a solid which was insoluble in chloroform, but crystallised from methanol (non-redistilled) as needles, m.p. 184-187°. The needles so obtained were

found to be soluble in chloroform, and on further recrystallisations yielded needles (100 mg.), m.p. 190-192°, $[\alpha]_D + 75^\circ$. Light absorption in ethanol: ϵ_{2120} 10,000. The compound gives a deep yellow colour with tetranitromethane in chloroform. A mixture of the compound with a sample of urs-9(11):13(18)-dien-3 β -yl acetate was undepressed in melting-point. Chromatography of a specimen yielded material which crystallised as plates, m.p. 190-192°.

8:10:14-Trimethyl-5 ξ -novursa-3(4):12-diene. -

A suspension of α -amyrin (22 g.) in light petroleum (b.p. 60-80°; 200 ml.) was shaken with phosphorus pentachloride (15 g.) until all the material was in solution (20 minutes), and the solution then refluxed for 2 minutes. After cooling, the excess phosphorus pentachloride was destroyed by cautious addition of water, and the solution washed with water, dried over sodium sulphate, and the solvent removed under reduced pressure. The product, which was a gum, crystallised from ether-methanol as prisms (11.5 g.), m.p. 133-135°, $[\alpha]_D + 110^\circ$. Light absorption in ethanol: ϵ_{2060} 8,800.

Ozonolysis of 8:10:14-Trimethyl-5 ξ -novursa-
-3(4):12-diene. - A solution of 8:10:14-trimethyl-
-5 ξ -novursa-3(4):12-diene (1.0 g.) in chloroform
(200 ml.) was treated at -35° with a stream of
ozonised oxygen (equivalent to 2 moles of ozone).
After attaining room-temperature, the mixture was
stirred with zinc dust (3 g.) and acetic acid (50 ml.)
for 1 hour. The filtered solution was washed with
water (5 x 250 ml.; see later). The chloroform
solution was washed with sodium bicarbonate solution,
water, dried over sodium sulphate and the solvent
removed under reduced pressure. After two cry-
stallisations from methanol, the gummy residue
yielded a mixture (350 mg., m.p. $164-172^{\circ}$), a solution
of which in light petroleum (b.p. $60-80^{\circ}$) was chromato-
graphed on alumina. Light petroleum eluted a fraction
(250 mg., m.p. $153-155^{\circ}$, $[\alpha]_D + 205^{\circ}$) which, after
three recrystallisations from methanol, gave the
ketone, $C_{27}H_{42}O$ as needles, m.p. $152-155^{\circ}$, $[\alpha]_D + 210^{\circ}$.
Light absorption in ethanol: $t_{2.0\%} 4,000$. (Found:
C, 84.9; H, 11.1. $C_{27}H_{42}O$ requires C, 84.75; H, 11.1%).
The compound gave a yellow colour with tetranitromethane
in chloroform. The fraction eluted from the column

with benzene-light petroleum (1:2) was crystallised from methanol to give the diketone $C_{27}H_{42}O_2$ as plates m.p. 204-206°, $[\alpha]_D + 184^\circ$. (Found: C, 81.8; H, 10.6. $C_{27}H_{42}O_2$ requires C, 81.35; H, 10.6%). The compound did not give a colour with tetranitromethane in chloroform.

The water washings (see above) were adjusted to pH7 and distilled. The first fraction (200 ml.) was treated with 2:4-dinitrophenylhydrazine hydrochloride solution to give acetone 2:4-dinitrophenylhydrazone (25 mg.), m.p. and mixed m.p. 121-124°.

Treatment of the Ketone m.p. 153-155° with Alkali. - A solution of the ketone $C_{27}H_{42}O$ (60 mg.) in 5% aqueous ethanolic potassium hydroxide solution (50 ml.) was heated under reflux for 2.5 hours. The product, obtained in the usual fashion, was crystallised from methanol to give needles, m.p. 145-147°, $[\alpha]_D + 201^\circ$ and showed no depression in m.p. on admixture with a sample of starting material.

8:10:14-Trimethyl-5 ξ -novursa-3(4):9(11):12-triene.

- A solution of ursa-9(11):12-dien-3 β -ol (3.0 g.) in

light petroleum (b.p. 60-80°; 80 ml.) was shaken with phosphorus pentachloride (1.47 g.) for 1.5 hours. After refluxing for 2 minutes, the mixture was treated with water and the product isolated in the usual way. Crystallisation from chloroform-methanol gave 8:10:14-trimethyl-5 β -novursa-3(4):9(11):12-triene as needles, m.p. and mixed m.p. 132-134°, $[\alpha]_D + 439^\circ$ (c, 0.9). Light absorption in ethanol: ϵ_{2000} 8,250; ϵ_{2750} 9,500. (Found: C, 88.4; H, 11.5. Calc. for $C_{30}H_{46}$: C, 88.6; H, 11.4%). Ewen et al. (45) give m.p. 131-133°, $[\alpha]_D + 439^\circ$ for "d-a-amyratriene".

Treatment of Ursa-9(11):12-dien-3 β -yl Acetate with Hydriodic-Acetic acid mixture. - A solution of ursa-9(11):12-dien-3 β -yl acetate (1 g.) in glacial acetic acid (25 ml.) and hydriodic acid (4 ml.) was refluxed for 2 hours. The solution was diluted with water and extracted with ether. The ether extract was washed successively with water, sodium thiosulphate solution, hydrochloric acid (3%), and water. The dried extract was evaporated to dryness, leaving a gummy residue which was dissolved in light petroleum and chromatographed on alumina. Elution with light

petroleum (100 ml.) yielded a gum (450 mg.). Light absorption: Maxima at 2420, 2500, 2600 Å. (hetero-annular diene) and at 2950 Å. (triene) of approximately equal intensities. Further elution of the column with light petroleum yielded a small amount (ca. 70 mg.) of starting material. Benzene-light petroleum (1:3) eluted a crystalline fraction (ca. 90 mg.), which, after three recrystallisations from chloroform-methanol yielded oleana-11:13(18)-dien-3 β -yl acetate as plates, m.p. and mixed m.p. 224-226°, $[\alpha]_D$ -64°. Light absorption in ethanol: ϵ_{2420} 22,100; ϵ_{2500} 25,000; ϵ_{2600} 15,500.

Ursa-9(11):12-dien-3 β -ol was treated similarly, with almost exactly the same results. The fact that oleana-11:13(18)-dien-3 β -yl acetate (and not the 3 β -ol) was obtained, must be attributed to acetylation by the hydriodic-acetic acid mixture.

Extraction and Isolation of Friedelin (Friedelanone). - Extraction of cork (20 lb.) with ethyl acetate (20 l.) in a Soxhlet extractor yielded, on evaporation of the solvent, a crystalline mixture. The mixture was treated with hot chloroform (4 l.)

and the chloroform-insoluble cerin removed by filtration. Evaporation of the filtrate gave a crystalline solid which was dissolved in benzene (rejecting any benzene-insoluble material) and chromatographed on alumina (1500 g.). Elution of the column with benzene (15 l.) yielded fractions which crystallised from chloroform-methanol to give friedelin (27 g.) as needles, m.p. 258-264°, $[\alpha]_D -24^\circ$ (c, 1.1).

Lithium Aluminium Hydride Reduction of Friedelanone. - Friedelanone (500 mg.) in dry ether (250 ml.) was treated with lithium aluminium hydride (500 mg.), and the mixture kept at +4° overnight. The excess lithium aluminium hydride was destroyed with ice, the ether decanted from the sludge and washed with water, dried over sodium sulphate, and the solvent removed under reduced pressure. The product was crystallised from chloroform to give epi-friedelinol as blades (370 mg.), m.p. 279-284°. A further crop was obtained by treatment of the mother liquors with methanol. On recrystallisation, the material had m.p. 287-288°, $[\alpha]_D + 22^\circ$ (c, 0.3).

Acetylation of epi-Friedelinol. - Epi-friedelinol (170 mg.) was dissolved in hot pyridine, and the solution heated at 100° for 1 hour. Working up in the usual fashion, followed by filtration of a benzene solution of the product through alumina yielded the acetate, which crystallised from chloroform-methanol as plates, m.p. 288-290°, $[\alpha]_D + 34^\circ$ (c, 0.75).

Dehydration of epi-Friedelinol. - Epi-friedelinol (250 mg.) was dissolved in hot pyridine (120 ml.) and allowed to cool. To the cooled solution was added phosphorus oxychloride (15 ml.). The solution was kept overnight at room temperature, then heated at 100° for half an hour. The cold reaction mixture was added dropwise to iced water, and extracted with a large volume of light petroleum-chloroform. The extract was washed with water, dried, and the solvent removed under reduced pressure. The product crystallised from chloroform to give friedelene as blades (140 mg.) m.p. 250-258° (261-264°, vac.) $[\alpha]_D + 53^\circ$ (c, 0.5). Light absorption in cyclohexane: ϵ_{2040} 4,600.

Treatment of Friedelene with Hydrochloric-Acetic Acid Mixture. - To a refluxing solution of friedelene (350 mg.) in acetic acid (450 ml.) was added concentrated hydrochloric acid (100 ml.). After refluxing for 18 hours, the solution was taken to dryness under reduced pressure, the product dried, dissolved in light petroleum (b.p. 60-80°) and filtered through a column of alumina. Elution with light petroleum yielded a fraction (290 mg.) which crystallised from chloroform-methanol as blades, m.p. 184-185°, $[\alpha]_D -9.5^\circ$ (c, 0.8). After four further crystallisations from chloroform-methanol the material had m.p. 186-187°, $[\alpha]_D -20^\circ$ (c, 1.0). Light absorption in ethanol: ϵ_{2000} 6,400.

Treatment of Friedelene with dry Hydrogen Chloride.
- A solution of friedelene (200 mg.) in dry chloroform (200 ml.) at 0° was treated with a stream of dry hydrogen chloride for 2 hours. Solid sodium carbonate was added to neutralise the acid present, and the solution washed with water, dried over sodium sulphate, and the solvent removed under reduced pressure. The product was recrystallised from

n-hexane to give the hydrochloride as needles (140 mg.), m.p. 188-191° (decomp.), $[\alpha]_D + 2^\circ$ (c, 2.0). (Found: C, 80.3; H, 11.5. $C_{30}H_{51}Cl$ req. C, 80.6; H, 11.4%).

Dehydrochlorination of Friedelene Hydrochloride.

- A solution of friedelene hydrochloride (100 mg.) in collidine (10 ml.) was refluxed for 2 hours. The crystalline solid which separated on cooling was collected and recrystallised from chloroform-methanol to give needles (60 mg.), m.p. 250-255°, $[\alpha]_D + 52^\circ$ (c, 0.3). The product did not depress in melting-point on admixture with a sample of friedelene.

3-Oxo-olean-12-ene. [cf. Ruzicka and Wirz (61)].

- To a solution of β -amyrin (10 g.) in stabilised glacial acetic acid (500 ml.) and benzene (100 ml.) was added a solution of chromic acid (1.73 g.) in water (4 ml.) and acetic acid (50 ml.), and the solution kept overnight at room temperature. Working up in the usual fashion followed by crystallisation of the product from chloroform-methanol yielded 3-oxo-olean-12-ene as needles (6.1g.), m.p. 177-179°, $[\alpha]_D + 110^\circ$. The compound gave a yellow colour with

tetranitromethane in chloroform.

Olean-12-ene (β -Amyrene-II). - 3-Oxo-
-olean-12-ene (600 mg.), 100% hydrazine hydrate (5 ml.)
and sodium ethoxide (600 mg. sodium in 15 ml. ethanol)
were heated together in an autoclave for 18 hours at
200°. The mixture was poured into water and extracted
with ether. The washed and dried ether extract was
evaporated to dryness, and the product crystallised
from chloroform-methanol to give olean-12-ene as blades
(413 mg.), m.p. 159-161°, $[\alpha]_D + 94^\circ$ ($c, 0.5$). The
compound gave a yellow colour with tetranitromethane
in chloroform.

Oleana-11:13(18)-diene. - A solution of olean-
-12-ene (400 mg.) in glacial acetic acid (150 ml.)
was refluxed with selenium dioxide (400 mg.) for 30
minutes. The crude product, obtained by working up
in the usual fashion, was dissolved in light petroleum
(b.p. 60-80°) and filtered through a column of alumina.
Elution of the column with the same solvent yielded
a fraction which crystallised from chloroform-methanol
as blades (300 mg.), m.p. 218-219°, $[\alpha]_D - 65^\circ$ ($c, 0.9$).

The compound gave red-brown colour with tetranitromethane in chloroform.

Olean-13(18)-ene. - A solution of oleana-11:13(18)-diene (240 mg.) in cyclohexane (50 ml.) and stabilised glacial acetic acid (150 ml.) was added to a freshly reduced suspension of platinum (from 150 mg. PtO_2) in glacial acetic acid (20 ml.), and the mixture shaken with hydrogen for 17 hours. Working up in the usual fashion, followed by crystallisation of the product from chloroform-methanol yielded olean-13(18)-ene as blades (190 mg.) m.p. 186-187°, $[\alpha]_D -48^\circ$, -48.5° ($c, 1.4, 1.2$). Light absorption in ethanol: ϵ_{2100} 7,000. (Found: C, 88.0; H, 12.3. $\text{C}_{30}\text{H}_{50}$ requires C, 87.73; H, 12.27%).

Treatment of Olean-13(18)-ene with Hydrochloric-Acetic Acid Mixture. - A solution of olean-13(18)-ene (110 mg.) in glacial acetic acid (120 ml.) and hydrochloric acid (20 ml.) was heated under reflux for 18 hours. The solution was taken to dryness under reduced pressure, the product dried, dissolved in light petroleum (b.p. 60-80°) and filtered through a column of alumina. Elution of the column with light

petroleum yielded a fraction (90 mg.) which crystallised from chloroform-methanol as blades, m.p. 186-187°, $[\alpha]_D -14.7^\circ$ ($c, 1.0$). After two recrystallisations the product had m.p. 186-187°, $[\alpha]_D -19.5^\circ$ ($c, 1.4$), and did not depress in melting-point on admixture with a sample, m.p. 186-187°, $[\alpha]_D -20^\circ$ ($c, 1.0$) obtained by treatment of friedelene with hydrochloric-acetic acid mixture.

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2. and P.

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3. and G.

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6. Venter

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