Triterpenoids. Part XLIV. The Constitution of "* l*-α-Amyradiene."*

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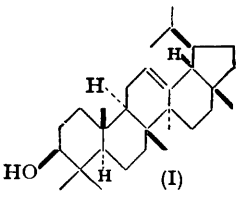
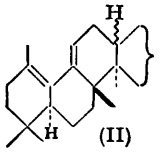
The hydrocarbon, "*l*-α-amyradiene," obtained by dehydration of α-amyrin (I) with either phosphoric oxide or hydriodic acid (or by treatment of α-amyrin acetate with the latter reagent), is shown to be 5 : 8α : 9β-trimethyl-10α-novursa-12 : 14-diene (XIV). Neither the 3(4) : 12-diene (III) nor the 3(5) : 12-diene (III*a*) is an intermediate in the phosphoric oxide reaction since these hydrocarbons are not isomerised by this reagent. The formation of the "*l*-diene" (XIV) from α-amyrin is considered to be a fully concerted reaction and it includes the migration of three axial methyl groups.

Elucidation of the constitution of the "*l*-diene" was facilitated by a study of the action of hydriodic acid on 12-oxoursanyl acetate (VI) which gives an αβ-unsaturated ketone identified as 5 : 8α : 9β-trimethyl-10α-novurs-13-en-12-one (XIII). This αβ-unsaturated ketone is also obtained from the "*l*-diene" and, conversely, it is converted into the "*l*-diene" by reduction with lithium aluminium hydride followed by treatment with mineral acid. The position of the double bond in the αβ-unsaturated ketone (XIII) was disclosed by its optical properties and by its oxidation to the transoid ene-dione, 5 : 8α : 9β-trimethyl-10α-novurs-13-ene-12 : 15-dione (XVII).

Dehydration of α-amyrin (I) by phosphoric oxide in benzene at room temperature gives, in high yield, a hydrocarbon, "*l*-α-amyradiene," in which the two double bonds are conjugated and heteroannular. The diene is also obtained by treatment of α-amyrin or its acetate with hydriodic–acetic acid (Vesterberg, *Ber.*, 1891, **24**, 3835; Ewen, Gillam, and Spring, *J.*, 1944, 28). A structure (II),† provisionally attributed to the hydrocarbon by


(I)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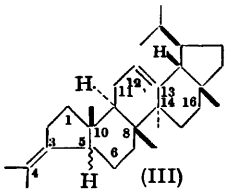
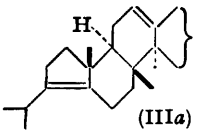
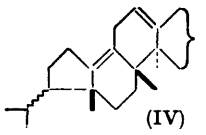
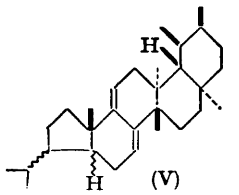

(III)


(III*a*)


(IV)


(V)

Ewen, Gillam, and Spring (*loc. cit.*), became improbable with the subsequent proof that ionic-type dehydrations of 3β-hydroxy-triterpenoids contract ring A (for references see Jeger, "Fortschritte der Chemie organischer Naturstoffe," Springer-Verlag, 1950, Vol. VII, p. 1) and it has since been excluded by the preparation of the "*l*-diene" by the isomerisation of two hydrocarbons, each of which contains a contracted ring A. Treatment of 8 : 10 : 14-trimethyl-5ξ-novursa-3(4) : 12-diene (III)‡ with boron trifluoride and of 5 : 8 : 14-trimethylnovursa-9(10) : 12-diene (IV) with hydrochloric–acetic acid gives the "*l*-diene" (preceding paper). Recently it has been suggested that the constitution of the "*l*-diene" is to be represented by (V) (Beton and Halsall, *Chem. and Ind.*, 1954, 1560).

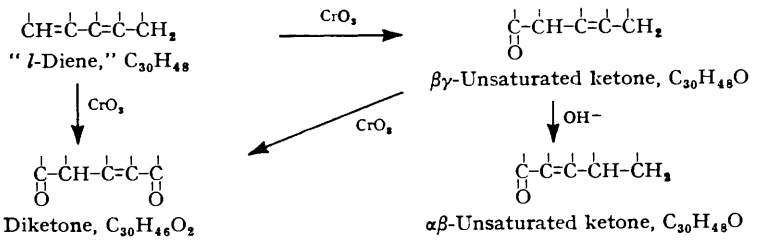
* Part XLIII, preceding paper.

† This formula is translated to correspond with that (I) recently proposed for α-amyrin (Beaton, Spring, Stevenson, and Strachan, *J.*, 1955, 2610).

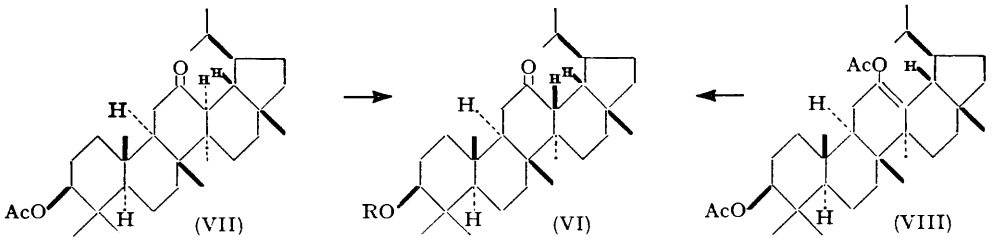
‡ The nomenclature adopted for ring A contracted ursane derivatives is explained in the preceding paper.

Irrespective of the constitution ascribed the ring E, this structure likewise cannot be correct for reasons which will become clear in the sequel.

Oxidation of the "*l*-diene," $C_{30}H_{48}$, with chromic acid (*ca.* 1·5 atoms of oxygen) yields a compound, $C_{30}H_{48}O$, which does not show high-intensity ultraviolet absorption above 2200 Å. The presence of an isolated double bond in the compound is shown by its positive tetranitromethane reaction and by its ultraviolet absorption, the intensity of which suggests that the double bond is of the type $>C{:}CH-$. The infrared absorption spectrum of the compound, $C_{30}H_{48}O$, contains a strong band at 1698 cm.$^{-1}$, thus showing that the oxygen function is an isolated ketone group in a 6-membered ring. Although the compound is stable to acid, when treated with alkali it gives an αβ-unsaturated ketone ($\lambda_{max.}$ 2600 Å, ε 9000). These properties and its origin show that the primary oxidation product of the "*l*-diene" is a βγ-unsaturated ketone. More drastic oxidation of either the "*l*-diene" or the βγ-unsaturated ketone with chromic acid gives a compound $C_{30}H_{46}O_2$, which contains an αβ-unsaturated ketone function ($\lambda_{max.}$ 2500 Å, ε 10,500) and a second isolated carbonyl group. The "*l*-diene" and its oxidation products are therefore represented by the following partial formulæ :



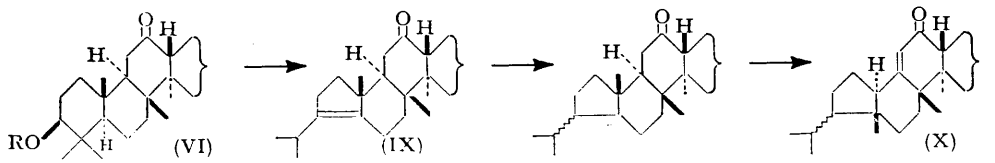
The position of the carbonyl group in the αβ-unsaturated ketone, and consequently in the βγ-unsaturated ketone, was disclosed by an examination of 12-oxoursan-3β-yl acetate (VI; R = Ac) and its relatives. When treated with hydriodic–acetic acid the oxo-acetate (VI; R = Ac) is converted into an αβ-unsaturated ketone, $C_{30}H_{48}O$, identical with that obtained as described above from the "*l*-diene." The αβ-unsaturated ketone is also obtained by the same treatment of either 12-oxo-13α-ursan-3β-yl acetate (VII) (Allan, Spring, and Stevenson, *J.*, 1955, 3072) or the enol acetate (VIII).



The acid-induced isomerisation of 5 : 8 : 14-trimethylnovursa-9(10) : 12-diene (IV) to the "*l*-diene" together with the established relation between the latter and the αβ-unsaturated ketone, $C_{30}H_{48}O$, show that the initial stages of the conversion of 12-oxoursan-3β-yl acetate (VI; R = Ac) into the αβ-unsaturated ketone include A-ring contraction and movement of a methyl group from $C_{(10)}$ to $C_{(5)}$, whereafter a double bond becomes conjugated with the 12-carbonyl group. A simple representation of this reaction includes the intermediate formation of 8 : 10 : 14-trimethylnovurs-3(5)-en-12-one (IX). Approach of a proton to the double bond of (IX) with synchronous (*a*) movement of the $C_{(10)}$-methyl group (β) to $C_{(5)}$, (*b*) movement of the 9-hydrogen (α) to $C_{(10)}$, and (*c*) loss of a proton from $C_{(11)}$ then leads to the αβ-unsaturated ketone (X).* If this reaction mechanism is correct, the "*l*-diene" will be (XI), and the βγ-unsaturated ketone will be (XII). Several

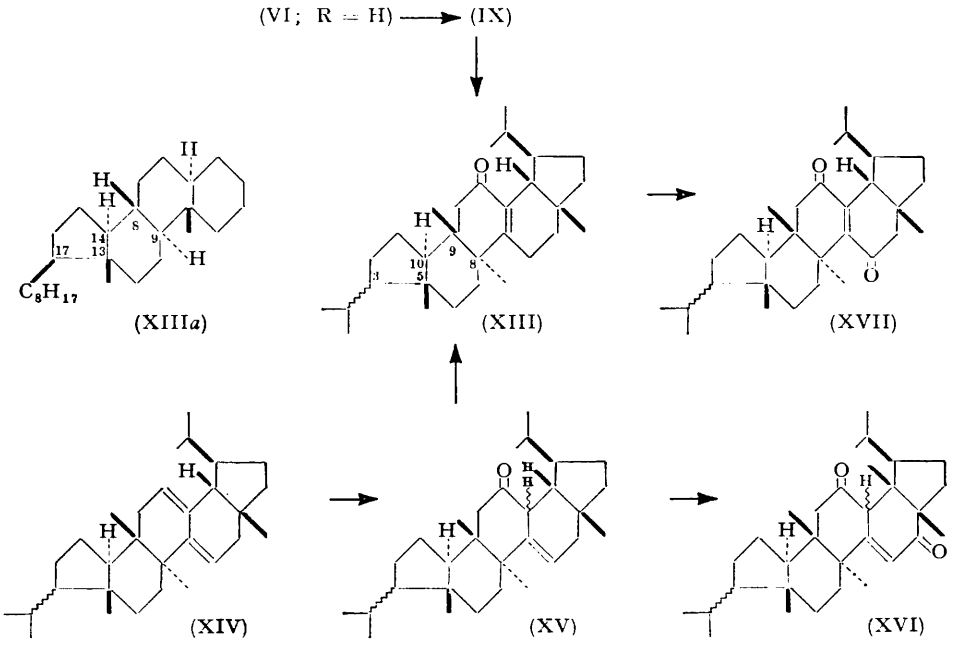
* An attractive reaction path is that in which the proton approaches from the rear (α) side, so affording a fully synchronous reaction. This would require that the *iso*propyl group in (X) is β-orientated; proof of the configuration of this group is however still lacking.

considerations, however, show that the three related formulæ (X), (XI), and (XII) cannot represent the αβ-unsaturated ketone, the "*l*-diene," and the βγ-unsaturated ketone respectively. First, the intensity of absorption in the ethylenic region of the spectrum



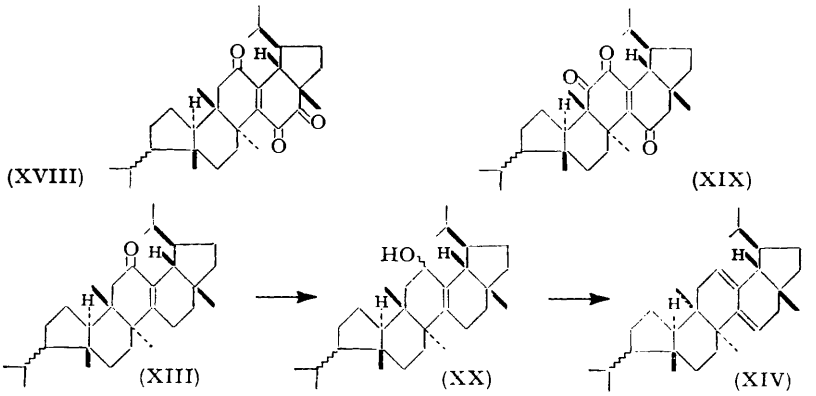
precludes the possibility that the double bond in the βγ-unsaturated ketone is exocyclic to two rings as in (XII). Secondly, the αβ-unsaturated ketone shows maximal absorption at 2600 Å, whereas by analogy with other 12-oxo-9(11)-enes, a compound of structure (X) should show maximal absorption at approximately 2500 Å. Finally, and more important,

oxidation of the αβ-unsaturated ketone with chromic acid gives, in high yield, a bright yellow compound $C_{30}H_{46}O_2$ which shows the ultraviolet absorption of a fully transoid $\overset{\|}{C}-\overset{|}{C}=\overset{|}{C}-\overset{\|}{C}$ system. This behaviour proves that a methylene group is adjacent to the double bond in the αβ-unsaturated ketone.



The exclusion of (X) as the structure of the αβ-unsaturated ketone and the oxidation of this compound to a transoid ene-dione leads inevitably to the conclusion that the double bond in this compound is between $C_{(13)}$ and $C_{(14)}$. The formation of the αβ-unsaturated ketone from 12-oxoursan-3β-yl acetate (VI; R = Ac) must therefore include the movement of the methyl groups attached to $C_{(8)}$ and $C_{(14)}$. The reaction may be represented as

proceeding through 8 : 10 : 14-trimethylnovurs-3(5)-en-12-one (IX), with subsequent attack by a proton at the double bond in (IX) with synchronous (*a*) movement of the $C_{(10)}$-methyl group (β) to $C_{(5)}$, (*b*) movement of the 9-hydrogen (α) to $C_{(10)}$ (*c*) movement of the $C_{(8)}$-methyl group (β) to $C_{(9)}$, (*d*) movement of the $C_{(14)}$-methyl group (α) to $C_{(8)}$, and (*e*) loss of a proton from $C_{(13)}$. The αβ-unsaturated ketone is therefore 5 : 8α : 9β-trimethyl-10α-novurs-13-en-12-one (XIII). Accordingly the " *l*-diene " is 5 : 8α : 9β-trimethyl-10α-novursa-12 : 14-diene (XIV), the βγ-unsaturated ketone is 5 : 8α : 9β-trimethyl-10α-novurs-14-en-12-one (XV), the diketone $C_{30}H_{46}O_2$ is 5 : 8α : 9β-trimethyl-10α-novurs-14-ene-12 : 16-dione (XVI) and the transoid ene-dione is 5 : 8α : 9β-trimethyl-10α-novurs-13-ene-12 : 15-dione (XVII). The concerted reactions detailed above lead to a conformation in which the stereochemistry at positions 5, 10, 9, and 8 coincides with that at positions 13, 14, 8, and 9 in cholestane (XIII*a*) and we suggest that the urge to adopt this conform-



ation is at least part of the force causing the reaction (VI) ⟶ (XIII). As we shall show in a later paper an essential driving force is the *cis*-β-locking of rings D and E.

A mechanism similar to that described above is postulated for the conversion of α-amyrin (I) into the " *l*-diene " (XIV) by treatment with hydriodic acid, with the difference that final proton elimination occurs from $C_{(15)}$.

It is certain that the conversion of α-amyrin (I) into the " *l*-diene " (XIV) by shaking with phosphoric oxide in benzene at room temperature does not include the formation of either 8 : 10 : 14-trimethyl-5ξ-novursa-3(4) : 12-diene (III) or the 3(5) : 12-isomer (III*a*) as discrete intermediates since these two hydrocarbons are unchanged after the same treatment.* The reaction is probably *fully* concerted.

As stated above, oxidation of the αβ-unsaturated ketone (XIII) with chromic acid gives the ene-dione (XVII). More drastic oxidation of the αβ-unsaturated ketone, or of the ene-dione (XVII) with the same reagent, gives two isomeric compounds, $C_{30}H_{44}O_3$, which are considered to be 5 : 8α : 9β-trimethyl-10α-novurs-13-ene-12 : 15 : 16-trione (XVIII) and 5 : 8α : 9β-trimethyl-10α-novurs-13-ene-11 : 12 : 15-trione (XIX). The behaviour of the ene-dione (XVII) and of the two ene-triones on reduction will be reported later.

Reduction of 5 : 8α : 9β-trimethyl-10α-novurs-13-en-12-one (XIII) with lithium aluminium hydride gives a mixture of epimeric allylic alcohols (XX). Treatment of the mixture with either acetic anhydride and pyridine or hydrochloric–acetic acid gives 5 : 8α : 9β-trimethyl-10α-novursa-12 : 14-diene (XIV) identical with the " *l*-diene " obtained by dehydration of α-amyrin with phosphoric oxide.

Experimental

Rotations were measured in $CHCl_3$ and ultraviolet absorption spectra in EtOH solutions. Grade II alumina and light petroleum, b. p. 60—80°, were used for chromatography.

* These experiments were made by Mr. G. G. Allan to whom we express our best thanks.

5 : 8α : 9β-*Trimethyl*-10α-*novurs*-13-*ene*-12-*one* (XIII).—(*a*) A solution of 12-oxo-13α-ursan-3β-yl acetate (VII) (Allan, Spring, and Stevenson, *loc. cit.*) (2·0 g.) in glacial acetic acid (25 c.c.) was refluxed for 16 hr. with hydriodic acid (7 c.c.; *d* 1·7; freshly distilled from hypophosphorous acid). The mixture was diluted with water and extracted with ether, and the extract washed with sodium thiosulphate solution, and evaporated. The residue crystallised from aqueous methanol, to give 5 : 8α : 9β-*trimethyl*-10α-*novurs*-13-*en*-12-*one* as flat needles (400 mg.), m. p. 157—158·5°, $[\alpha]_D$ −41° (*c*, 1·6), $\lambda_{max.}$ 2600 Å (ε 9000) (Found : C, 84·9; H, 11·7. $C_{30}H_{48}O$ requires C, 84·8; H, 11·4%). It does not give a colour with tetranitromethane.

(*b*) A solution of 12-oxo-13α-ursan-3β-yl benzoate (Allan, Spring, and Stevenson, *loc. cit.*) (45 g.) in acetic acid (2 l.) was refluxed for 16 hr. with hydriodic acid (150 c.c.; *d* 1·7; freshly distilled from hypophosphorous acid). The mixture was concentrated, then diluted with water, and the product isolated as described above. A solution of the product in benzene–light petroleum (300 c.c.; 1 : 2) was chromatographed on alumina (1000 g.). Elution with the same solvent (4 l.) gave a fraction which after four recrystallisations from aqueous methanol gave 5 : 8α : 9β-trimethyl-10α-novurs-13-en-12-one (10·0 g.) as flat needles, m. p. 155—157° (no depression), $[\alpha]_D$ −38° (*c*, 1·0), $\lambda_{max.}$ 2610 Å (ε 8600).

(*c*) A solution of 3β : 12-diacetoxyurs-12-ene (VIII) (Allan, Spring, and Stevenson, *loc. cit.*) (1 g.) in acetic acid (15 c.c.) was treated with hydriodic acid (3·5 c.c.) as described under (*a*). The product was purified by chromatography on alumina and thrice crystallised from aqueous methanol, to give 5 : 8α : 9β-trimethyl-10α-novurs-13-en-12-one (550 mg.) as flat needles, m. p. 157—158° (no depression), $[\alpha]_D$ −41° (*c*, 1·8).

(*d*) A solution of 12-oxoursan-3β-yl acetate (VI) (Allan, Spring, and Stevenson, *loc. cit.*) (900 mg.) in acetic acid (18 c.c.) was treated with hydriodic acid (3·5 c.c.) as described under (*a*). The product, purified by chromatography and four recrystallisations from aqueous methanol, gave 5 : 8α : 9β-trimethyl-10α-novurs-13-en-12-one as flat needles, m. p. 158—159° (no depression), $[\alpha]_D$ −39° (*c*, 1·5).

Oxidation of 5 : 8α : 9β-*Trimethyl*-10α-*novursa*-12 : 14-*diene* (XIV) *with Chromic Acid.*—(*a*) A solution of chromium trioxide (540 mg.) in 90% acetic acid (15 c.c.) was added with stirring to a solution of 5 : 8α : 9β-trimethyl-10α-novursa-12 : 14-diene ("*l*-α-amyradiene"; Ewen *et al.*, *loc. cit.*) (2·0 g.) in benzene (20 c.c.) and glacial acetic acid (60 c.c.), and the mixture was kept at 100° for 1 hr. The product was isolated in the usual way and crystallised five times from chloroform–methanol, to give 5 : 8α : 9β-*trimethyl*-10α-*novurs*-14-*en*-12-*one* (XV) as needles (760 mg.), m. p. 218—219°, $[\alpha]_D$ −62° (*c*, 2·2), ε at 2050 Å = 3,500. Infrared absorption (in $CHCl_3$) : strong band at 1698 cm.$^{-1}$ (Found : C, 84·9; H, 11·4. $C_{30}H_{48}O$ requires C, 84·8; H, 11·4%). It gives a yellow colour with tetranitromethane. The ultraviolet spectrum showed the presence of *ca.* 5% of αβ-unsaturated ketone impurity, which could not be removed by crystallisation or chromatography.

(*b*) Chromium trioxide (3·0 g.) in acetic acid (150 c.c.) was added dropwise with stirring to a solution of 5 : 8α : 9β-trimethyl-10α-novursa-12 : 14-diene (3 g.) in glacial acetic acid (1·5 l.) at 100°. After being kept at 100° for 5½ hr. and overnight at room temperature, the mixture was worked up in the usual way. Crystallisation of the residue from chloroform–methanol yielded needles (900 mg.), m.p. 216—220°, $\lambda_{max.}$ 2500 Å (ε 7500), which were chromatographed in benzene–light petroleum (360 c.c.; 1 : 1) on alumina (100 g.). The product eluted with the same solvent (600 c.c.) crystallised from chloroform–methanol to give 5 : 8α : 9β-*trimethyl*-10α-*novurs*-14-*ene*-12 : 16-*dione* (XVI) as needles (320 mg.), m. p. 224—225°, $[\alpha]_D$ −134° (*c*, 1·2), $\lambda_{max.}$ 2500 Å (ε 10,500) (Found : C, 81·85; H, 10·4. $C_{30}H_{46}O_2$ requires C, 82·2; H, 10·5%). It does not give a colour with tetranitromethane.

Action of Alkali on 5 : 8α : 9β-*Trimethyl*-10α-*novurs*-14-*en*-12-*one* (XV).—The βγ-unsaturated ketone (250 mg.) in 5% methanolic sodium hydroxide (200 c.c.) was refluxed for 3 hr. Addition of water precipitated a solid which was recrystallised from aqueous methanol, to give 5 : 8α : 9β-trimethyl-10α-novurs-13-en-12-one (XIII) as needles, m. p. 155—157° (no depression), $[\alpha]_D$ −38° (*c*, 0·9), $\lambda_{max.}$ 2600 Å (ε 8600).

The βγ-unsaturated ketone (XV) was recovered unchanged by treatment with concentrated hydrochloric acid (1 part) in chloroform (2 parts) and acetic acid (5 parts) at 40° for 1 hr.

Oxidation of 5 : 8α : 9β-*Trimethyl*-10α-*novurs*-14-*en*-12-*one* (XV) *with Chromic Acid.*—Chromium trioxide (112 mg.) in acetic acid (5 c.c.) was added to a solution of the ketone (224 mg.) in benzene (3 c.c.) and acetic acid (1·8 c.c.), and the mixture heated at 100° for 1 hr. Crystallisation of the product, isolated in the usual way, from chloroform–methanol gave 5 : 8α : 9β-trimethyl-10α-novurs-14-ene-12 : 16-dione (XVI) as fine needles (93 mg.), m. p. 220—222° (no depression), $[\alpha]_D$ −130° (*c*, 0·8), $\lambda_{max.}$ 2500 Å (ε 10,100).

Oxidation of 5 : 8α : 9β-*Trimethyl*-10α-*novurs*-13-*en*-12-*one* (XIII) *with Chromic Acid.*—Chromium trioxide (4·8 g.) in 90% acetic acid (56 c.c.) was added to a solution of the ketone (8·0 g.) in acetic acid (580 c.c.), and the mixture stirred at 95° for 1 hr. The product, isolated by means of ether in the usual way, in benzene–light petroleum (3 : 7) was chromatographed on alumina. Elution with the same solvent (200 c.c.) gave a yellow solid (2·6 g.) which crystallised from methanol, to give 5 : 8α : 9β-*trimethyl*-10α-*novurs*-13-*ene*-12 : 15-*dione* (XVII) as flat yellow needles, m. p. 176—177°, $[\alpha]_D$ +86° (*c*, 2·7), $\lambda_{max.}$ 2260 and 2760 Å (ε 3400 and 8000) (Found : C, 82·1; H, 10·5. $C_{30}H_{46}O_2$ requires C, 82·1; H, 10·6%). Benzene–light petroleum (1 : 1; 500 c.c.) eluted an orange solid (0·84 g.) which on crystallisation from aqueous methanol yielded 5 : 8α : 9β-*trimethyl*-10α-*novurs*-13-*ene*-11(or 16) : 12 : 15-*trione* (XIX) or (XVIII) as long flat orange needles, m. p. 182—183°, $[\alpha]_D$ +214° (*c*, 1·8), $\lambda_{max.}$ 2220 and 2990 Å (ε 4600 and 5600) (Found : C, 79·4; H, 9·9. $C_{30}H_{44}O_3$ requires C, 79·6; H, 9·8%). Continued elution with the same solvent (200 c.c.) gave an orange solid (0·09 g.) which after six recrystallisations from aqueous methanol furnished 5 : 8α : 9β-*trimethyl*-10α-*novurs*-13-*ene*-12 : 15 : 16(or 11)-*trione* (XVIII) or (XIX) as yellow-orange needles, m. p. 228—230°, $[\alpha]_D$ +378° (*c*, 0·9), $\lambda_{max.}$ 2220 and 2960 Å (ε 3500 and 6000) (Found : C, 79·9; H, 10·1. $C_{30}H_{44}O_3$ requires C, 79·6; H, 9·8%).

Oxidation of 5 : 8α : 9β-*Trimethyl*-10α-*novurs*-13-*ene*-12 : 15-*dione* (XVII) *with Chromic Acid.*—Chromium trioxide (200 mg.) in acetic acid (5 c.c.) was added to the ene-dione (120 mg.) in acetic acid (20 c.c.) and the mixture stirred at 95° for 1 hr. The product, isolated in the usual way, was dissolved in benzene–light petroleum (1 : 1) and filtered through a short column of alumina. Crystallisation of the residue from aqueous methanol gave 5 : 8α : 9β-trimethyl-10α-novurs-13-ene-11(or 16) : 12 : 15-trione (XIX) or (XVIII) as flat needles (30 mg.), m. p. 178—180° (no depression).

5 : 8α : 9β-*Trimethyl*-10α-*novursa*-12 : 14-*diene* (XIV) *from* 5 : 8α : 9β-*Trimethyl*-10α-*novurs*-13-*en*-12-*one* (XIII).—A solution of the αβ-unsaturated ketone (1·0 g.) in dry ether (200 c.c.) was added dropwise to a suspension of lithium aluminium hydride (1·0 g.) in dry ether (200 c.c.), the mixture refluxed for 2 hr. and kept overnight at room temperature. The product, obtained by working up in the usual way, on crystallisation from chloroform–methanol yielded a mixture of the epimeric 5 : 8α : 9β-trimethyl-10α-novurs-13-en-12-ols (XX) as needles and prisms (0·68 g.) which gave a yellow colour with tetranitromethane and were not further purified. Concentrated hydrochloric acid (1 c.c.) was added to the mixture (100 mg.) in chloroform (2 c.c.) and acetic acid (20 c.c.), and the solution heated at 100° for 2 hr. On cooling, the solid which separated was collected and crystallised twice from chloroform–methanol, to yield 5 : 8α : 9β-trimethyl-10α-novursa-12 : 14-diene (80 mg.) as plates, m. p. 195—197° (no depression), $[\alpha]_D$ −112° (*c*, 2·6), $\lambda_{max.}$ 2340, 2410, and 2500 Å (ε 15,200, 16,400, and 10,000).

The mixture of alcohols (XX) (66 mg.) in pyridine (2 c.c.) and acetic anhydride (2 c.c.) was heated at 100° for 1 hr., worked up in the usual way, and the product crystallised several times from chloroform–methanol, to yield 5 : 8α : 9β-trimethyl-10α-novursa-12 : 14-diene (30 mg.), m. p. 194—196° (no depression), $[\alpha]_D$ −111° (*c*, 2·2), $\lambda_{max.}$ 2340, 2410, and 2500 Å (ε 13,300, 15,000, and 8,800).

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