600. *The Chemistry of the Triterpenes and Related Compounds. Part XX.* The Stereochemistry of Ring* E *of Betulin and Related Compounds.*

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The stereochemical course of the conversion of betulin into the anhydride (VI) has been investigated and clarified.

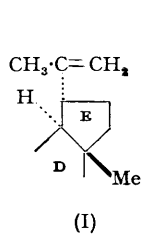
The stereochemistry of ring E of lupeol has recently been shown to be represented by the partial formula (I) (Halsall, Jones, and Meakins, *J.*, 1952, 2862) with the *iso*propenyl group at $C_{(19)}$ and the hydrogen atom at $C_{(18)}$ both *trans* to the $C_{(17)}$ methyl group. β-Amyrin has now been shown to be (II) (olean-12-en-3β-ol) † (Barton and Holness, *J.*, 1952, 78; Klyne, *J.*, 1952, 2916; Dauben, Dickel, Jeger, and Prelog, *Helv. Chim. Acta*, 1953, **36**, 325). Structure (III) follows for germanicol (olean-18-en-3β-ol) (Barton and Brooks, *J.*, 1951, 257) and hence (IV; R = H, R′ = Me) for lupeol (Ames, Halsall, and Jones, *J.*, 1951, 450; Halsall, Jones, and Meakins, *loc. cit.*). In turn betulin and betulinic acid (Davy, Halsall, and Jones, *J.*, 1951, 2696) must be (IV; R = H, R′ = CH_2·OH) and (IV; R = H, R′ = CO_2H) in which the *iso*propenyl group is *trans* to both the hydroxymethyl and the carboxyl group.

Ruzicka and Rey (*Helv. Chim. Acta*, 1943, **26**, 2143) studied the degradation of the *iso*propenyl group of betulinic acid to a carboxyl group (·CMe:CH_2 ⟶ ·CO_2H) and isolated the resulting dicarboxylic acid. One route to the acid involved oxidation of the *iso*propenyl group of acetylbetulinic acid (IV; R = Ac, R′ = CO_2H) with selenium dioxide, followed by vigorous chromic acid oxidation of the resulting aldehyde (V). In

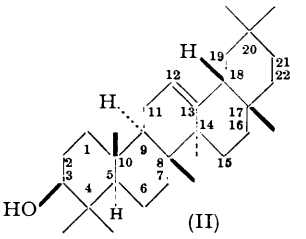
* Part XIX, preceding paper.

† With the agreement of Professor L. Ruzicka and of British triterpene chemists, the numbering of rings A and B of the pentacyclic triterpenes is to be the same as that of rings A and B of the steroids [cf. (II)].

addition to the dicarboxylic acid, a C_{28}-anhydride was obtained which must be (VI), in which the two carbonyl groups are *cis* to one another. An alternative structure for the anhydride involving inversion of the $C_{(17)}$ carboxyl group is extremely unlikely. It was originally concluded, on the basis of this evidence, that the *iso*propenyl group of lupeol was *cis* to the $C_{(17)}$ methyl group (Davy, Halsall, and Jones, *Chem. and Ind.*, 1951, 233), but this conclusion had to be abandoned after consideration of the mechanism of the



(I)



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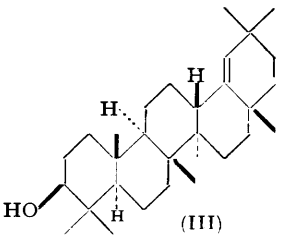

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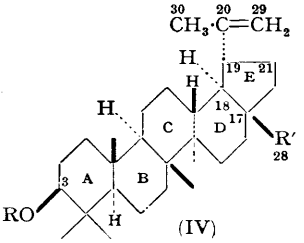
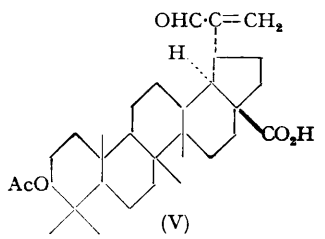


(IV)

dehydrochlorination of lupeol hydrochloride (19α-chloro-18α-oleanan-3β-ol) (Halsall, Jones, and Meakins, *loc. cit.*). Since inversion at $C_{(17)}$ is excluded, the *cis*-relationship can only arise by an inversion at $C_{(19)}$ at some stage during the oxidation of the *iso*propenyl group and the formation of the anhydride. The investigations now reported have confirmed this view and the step at which inversion occurs has been elucidated.

The naming of the compounds arising from the degradation of the *iso*propenyl group is based on the C_{27}-hydrocarbon (VII), trisnorlupane, and such systematic names are used in the Experimental section.

Betulin diacetate was oxidised with selenium dioxide to the αβ-unsaturated aldehyde, 3β : 28-diacetoxylup-20(29)-en-30-al, ozonolysis of which gave the bisnor-acid (VIII).



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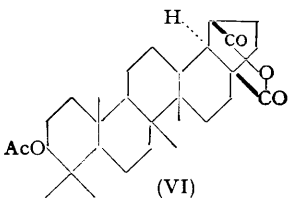
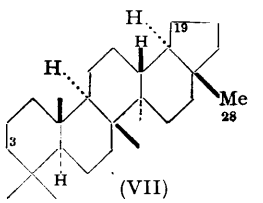


(VI)

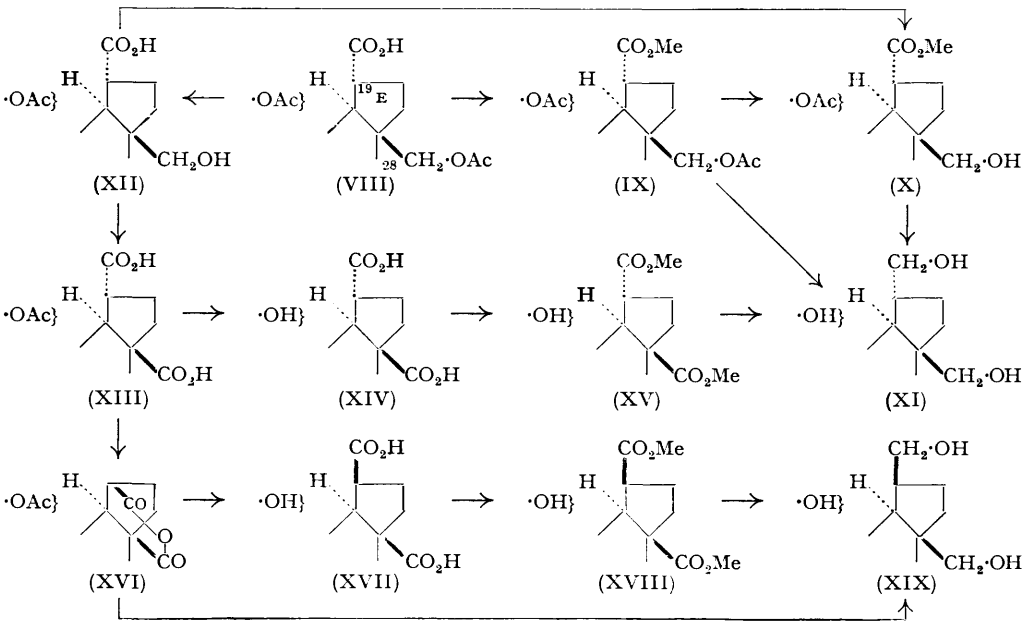


(VII)

The acid was characterised as its methyl ester (IX), partial hydrolysis of which with alkali gave the 3β-monoacetate (X). Reduction of the methyl esters (IX) and (X) with lithium aluminium hydride led to the triol (XI). Partial hydrolysis of the crude diacetoxy-acid (VIII) gave rise, in good yield, to the 3β-monoacetate (XII), oxidation of which gave the dicarboxylic acid (XIII). Compound (XIII) was hydrolysed to (XIV) which was converted into the dimethyl ester (XV) and then reduced to the triol (XI).

When compound (XIII) was heated under reflux in acetic anhydride in an attempt to convert it into an anhydride it was recovered unchanged. The anhydride (VI ≡ XVI) was only obtained when compound (XIII) was heated under reflux in acetic anhydride in the presence of toluene-*p*-sulphonic acid. This result suggested that inversion at $C_{(19)}$ occurred at this stage, being catalysed by the acidic reagent. Evidence in support of the

view that inversion occurs during the anhydride formation is provided by hydrolysis of the anhydride to the hydroxy-dicarboxylic acid (XVII) which was characterised as its dimethyl ester (XVIII). This was not identical with the dimethyl ester (XV) derived from the precursor of the anhydride. Reduction of the ester (XVIII) with lithium aluminium hydride gave the triol (XIX) which was also obtained by direct reduction of the anhydride.



The group next to the brace (·OAc}, ·OH}) represents the 3β-substituent.

This triol was different from the triol (XI). From these results it is clear that inversion at $C_{(19)}$ does not occur during the degradation of the *iso*propenyl side chain or before the anhydride formation.

Experimental

M. p.s were determined on a Kofler block and are corrected. Rotations were determined in chloroform, unless otherwise stated. The alumina used for chromatography had an activity of I–II unless otherwise indicated.

Oxidation of Betulin Diacetate with Selenium Dioxide.—Betulin diacetate (10 g.) was heated under reflux in benzene–acetic acid (400 c.c.; 1 : 3) for 2 hr. with selenium dioxide (3 g.). After filtration and evaporation the residue was dissolved in ether, and the solution was washed with 20% sodium hydroxide solution and water. The solid (10 g.) obtained by evaporation of the solution was adsorbed from benzene on deactivated alumina (300 g.). Elution with benzene (900 c.c.) gave a fraction (6 g.) which was decolorised with charcoal in ethyl acetate solution and then crystallised from ethyl acetate–ethanol, giving 3β : 28-*diacetoxylup*-20(29)-*en*-30-*al* (V; CH_2·OAc in place of CO_2H) as fine needles (4·5 g.), m. p. 237—240°, raised by further recrystallisation from acetone to 239—241°, $[\alpha]_D$ +9° (*c*, 1·8) (Found: C, 75·2; H, 9·8. $C_{34}H_{52}O_5$ requires C, 75·5; H, 9·65%). Light absorption in ethanol: Max., 2250 Å; ε = 7000.

Ozonolysis of 3β : 28-*Diacetoxylup*-20(28)-*en*-30-*al.*—The aldehyde (4 g.) in glacial acetic acid (250 c.c.) was treated with a stream of ozonised oxygen for 4 hr. The solution was diluted with water and evaporated to dryness under reduced pressure, and the residue was dissolved in ether. The acidic fraction (3·25 g.) was isolated by extraction with sodium hydroxide solution.

The crude acid (3β : 28-diacetoxytrisnorlupane-19α-carboxylic acid; VIII) (1 g.) in acetone (25 c.c.) was treated with ethereal diazomethane. The resulting ester was adsorbed from benzene on alumina (50 g.). Elution with benzene–ether (19 : 1) (200 c.c.) gave 3β : 28-*diacetoxy*-19α-*methoxycarbonyltrisnorlupane* (IX) (400 mg.) which crystallised from methanol as needles, m. p. 161—164°, $[\alpha]_D$ −15·5° (*c*, 0·96) (Found: C, 73·0; H, 9·65. $C_{33}H_{52}O_6$ requires

C, 72·9; H, 9·6%). Elution with benzene–ether (1 : 1) (200 c.c.) gave a fraction (200 mg.) which crystallised from chloroform–methanol as prisms, m. p. 265—275°. It was probably 3β-acetoxy-28-hydroxy-19α-methoxycarbonyltrisnorlupane (see below).

Partial Hydrolysis of 3β : 28-*Diacetoxy*-19α-*methoxycarbonyltrisnorlupane*.—The ester (400 mg.) in methanol (25 c.c.) was treated at 20° with potassium hydroxide (45 mg.; 1·05 mol.) for 16 hr. The solution was neutralised with dilute sulphuric acid and then evaporated to half volume; crystallisation then occurred. After separation the crystals were recrystallised several times from chloroform–methanol, to give 3β-*acetoxy*-28-*hydroxy*-19α-*methoxycarbonyltrisnorlupane* (X) as prisms, m. p. 270—275°, $[\alpha]_D$ −14° (*c*, 1·12) (Found: C, 74·0; H, 10·1. $C_{31}H_{50}O_5$ requires C, 74·0; H, 10·0%).

Reduction of 3β : 28-*Diacetoxy*-19α-*methoxycarbonyltrisnorlupane*.—The ester (140 mg.) in anhydrous ether (20 c.c.) was refluxed for 3 hr. with a solution of lithium aluminium hydride in ether (14 c.c.; 0·5M). Excess of reagent was destroyed, and the complex decomposed, with dilute sulphuric acid. The product (100 mg.) obtained by ether-extraction crystallised from aqueous methanol as needles, m. p. 254—257°. Further recrystallisations from methanol gave 3β : 28-*dihydroxy*-19α-*hydroxymethyltrisnorlupane* (XI) as needles, m. p. 258—261°, $[\alpha]_D$ −23° (*c*, 0·86 in pyridine) (Found: C, 77·4; H, 11·3. $C_{28}H_{48}O_3$ requires C, 77·7; H, 11·2%). The triol (210 mg.) was acetylated in pyridine (10 c.c.) with acetic anhydride (20 c.c) at 100° for 1 hr., to give 3β : 28-*diacetoxy*-19α-*acetoxymethyltrisnorlupane*, which crystallised from methanol as needles, m. p. 162—164°, $[\alpha]_D$ −21° (*c*, 1·17) (Found: C, 73·0; H, 9·85. $C_{34}H_{54}O_6$ requires C, 73·1; H, 9·75%).

Partial Hydrolysis of 3β : 28-*Diacetoxy*-19α-*carboxytrisnorlupane*.—The crude acid (2·5 g.) in ether (100 c.c.) was shaken with sodium hydroxide solution (100 c.c., 10%) for 1 hr. The aqueous layer was acidified and extracted with ether. The residue from the extract crystallised from methanol, to give 3β-*acetoxy*-19α-*carboxy*-28-*hydroxytrisnorlupane* (XII) as needles (2 g.), m. p. 280—295°, raised by further recrystallisation from chloroform–methanol to 300—303°, $[\alpha]_D$ −23° (*c*, 0·72) (Found: C, 73·35; H, 9·85. $C_{30}H_{48}O_5$ requires C, 73·7; H, 9·9%). This acid was esterified with diazomethane to give the methyl ester (X) previously described.

Oxidation of 3β-*Acetoxy*-19α-*carboxy*-28-*hydroxytrisnorlupane*.—The acid (1·5 g.) in acetic acid (20 c.c.) was kept at 90° for 15 min. with chromic acid solution (2 c.c.; 8N). The mixture was then diluted with water and extracted with ether. From the ethereal solution the acidic fraction was isolated by extraction with sodium hydroxide solution. The crude product (3β-acetoxy-19α-carboxytrisnorlupan-28-oic acid; XIII) was used without further purification.

Hydrolysis of 3β-*Acetoxy*-19α-*carboxytrisnorlupan*-28-*oic Acid*.—The acid (500 mg.) in dioxan (25 c.c.) was heated under reflux with 10% methanolic potassium hydroxide (25 c.c.) for 2 hr. The mixture was acidified and extracted with ether, and the acid obtained by sodium hydroxide extraction of the ethereal solution. The crude acid (19α-carboxy-3β-hydroxytrisnorlupan-28-oic acid; XIV) was dissolved in acetone (20 c.c.) and treated with ethereal diazomethane. The resulting ester was adsorbed from benzene on alumina (20 g.) and eluted with benzene–ether (1 : 1) (200 c.c.), to give methyl 3β-hydroxy-19α-methoxycarbonyltrisnorlupan-28-oate (XV) which crystallised from methanol as needles (200 mg.), m. p. 210—212°, $[\alpha]_D$ −26° (*c*, 1·08) (Found: C, 73·6; H, 9·9. Calc. for $C_{30}H_{48}O_5$: C, 73·7; H, 9·9%). Ruzicka and Rey (*loc. cit.*) give m. p. 210°, $[\alpha]_D$ −13°.

Anhydride Formation.—3β-Acetoxy-19α-carboxytrisnorlupan-28-oic acid (2·2 g.) in acetic anhydride (130 c.c.) was heated under reflux with toluene-*p*-sulphonic acid (200 mg.) for 8 hr. The mixture was poured into water and extracted with ether. After being washed with sodium hydroxide solution and water, the ethereal extract was evaporated to give a solid (1·1 g.) which was crystallised from methanol, and from methanol–chloroform, to give the anhydride (XVI) of 3β-acetoxy-19β-carboxytrisnorlupan-28-oic acid as needles (1·0 g.), m. p. 345—350° (in sealed tube), $[\alpha]_D$ +36° (*c*, 1·19). Ruzicka and Rey (*loc. cit.*) give m. p. 352°, $[\alpha]_D$ +32°.

Attempted Anhydride Formation.—3β-Acetoxy-19α-carboxytrisnorlupan-28-oic acid (1·2 g.) was heated under reflux in acetic anhydride for 6 hr. The mixture was then diluted with water and extracted with ether. After removal of the acidic fraction (1·1 g.) by extraction with sodium hydroxide solution, evaporation of the ethereal extract yielded only a small amount of neutral material as a yellow gum (50 mg.) which could not be crystallised.

Hydrolysis of the Anhydride.—The anhydride (550 mg.) in dioxan (25 c.c.) was heated under reflux with 10% methanolic potassium hydroxide for 2 hr. The mixture was acidified, diluted with water, and extracted with ether. The extract was separated into an acidic fraction (275 mg.) and a neutral fraction (50 mg.). The latter after acetylation with acetic anhydride and pyridine yielded starting material. The acidic fraction was crystallised several times from

acetone, to give 19β-*carboxy*-3β-*hydroxytrisnorlupan*-28-*oic acid* (XVII) as needles, m. p. above 350°, $[\alpha]_D$ +63° (*c*, 0·93) (Found: C, 73·25; H, 9·65. $C_{28}H_{44}O_5$ requires C, 73·5; H, 9·65%).

The acid (250 mg.) in acetone was treated with ethereal diazomethane. The resulting ester was adsorbed from benzene on alumina (10 g.) and eluted with benzene–ether (9 : 1) (200 c.c.) to give *methyl* 3β-*hydroxy*-19β-*methoxycarbonyltrisnorlupan*-28-*oate* (XVIII) as needles (from methanol), m. p. 208—210°, $[\alpha]_D$ +69° (*c*, 0·97) (Found: C, 73·55; H, 9·95. $C_{30}H_{48}O_5$ requires C, 73·7; H, 9·9%).

Reduction of Methyl 3β-*Hydroxy*-19β-*methoxycarbonyltrisnorlupan*-28-*oate* (XVIII).—The ester (275 mg.) in anhydrous ether (100 c.c.) was heated under reflux with lithium aluminium hydride (200 mg.) for 3 hr. Excess of reagent was destroyed with water, and the complex was decomposed with dilute sulphuric acid. Ether-extraction yielded 3β : 28-dihydroxy-19β-hydroxymethyltrisnorlupane (XIX) (220 mg.), which was crystallised three times from methanol as needles, m. p. 265—270°, $[\alpha]_D$ +39° (*c*, 0·64 in pyridine).

Reduction of the Anhydride (XVI).—The anhydride (90 mg.) was dissolved in di-*n*-butyl ether (30 c.c.), and an ethereal solution of lithium aluminium hydride (0·5M; 15 c.c.) was added. The diethyl ether was distilled off and then the remaining solution was heated under reflux for 3 hr. The mixture was then worked up as described above, yielding 3β : 28-dihydroxy-19β-hydroxymethyltrisnorlupane (50 mg.) which crystallised from methanol as needles, m. p. 265—270°, undepressed on admixture with the triol prepared from methyl 3β-hydroxy-19β-methoxycarbonyltrisnorlupan-28-oate (XVIII).

Reduction of Methyl 3β-*Hydroxy*-19α-*methoxycarbonyltrisnorlupan*-28-*oate* (XV).—The ester n anhydrous ether (25 c.c.) was heated under reflux with ethereal lithium aluminium hydride (0·5M; 10 c.c.) for 3 hr. The mixture was worked up in a similar manner to that in previous experiments. The product (100 mg.) which crystallised from methanol as needles, m. p. 255—259°, $[\alpha]_D$ −22° (*c*, 0·78 in pyridine), was identical with 3β : 28-dihydroxy-19α-hydroxymethyltrisnorlupane (XI) prepared from (IX).

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