600. *The Chemistry of the Triterpenes. Part X.* The Structures of Some Isomerisation Products from Betulin and Betulinic Acid.*

By G. S. Davy, T. G. Halsall, E. R. H. Jones, and G. D. Meakins.

The structures suggested in the preceding paper for the keto-lactone obtained from betulinic acid, and for its lithium aluminium hydride reduction product have been confirmed. A relationship between the lactone and *allo*-betulin has been established and the structure of *allo*betulin is now formulated for the first time.

The stereochemistry of rings D and E of the keto-lactone and the triol derived from it has been elucidated.

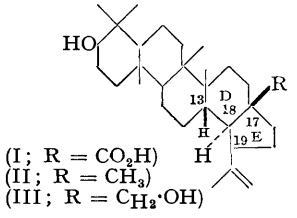
A preliminary account of part of this work has already been published (Davy, Halsall, and Jones, *Chem. and Ind.*, 1951, 233).

In Part IX of this series,* the conversion of betulinic acid (I) into a keto-lactone (IV) has been described. The lactone was reduced with lithium aluminium hydride to a triol (V) which, on vigorous acetylation, underwent dehydration giving the diacetate of moradiol (VI). Structure (V) for the triol followed from the known structure (VI) (Barton and Brooks, *J.*, 1951, 257) provided that no rearrangement of the carbon skeleton accompanied or followed dehydration, a possibility which, however, could not immediately be excluded in view of the employment of powerful acidic catalyts (boron trifluoride and perchloric acid).

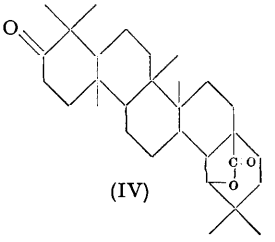
In order to confirm structure (V) a study of the properties of the triol diacetate, formed by acetylation with acetic anhydride–pyridine, was begun. On dehydration of this diacetate with phosphorus oxychloride in pyridine at 100° moradiol diacetate was again formed. The two easily acetylated hydroxyl groups of the triol must be those located at $C_{(2)}$ and $C_{(28)}$, the readily eliminated hydroxyl group not being acetylated. This lack of reactivity suggests that

* Part IX, preceding paper.

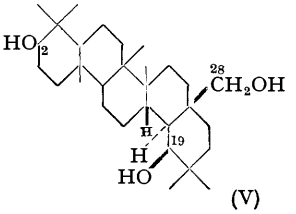
this hydroxyl group is either tertiary, or secondary but sterically hindered. A tertiary hydroxyl group could be accommodated by formulating the triol as (VIII), but this is excluded



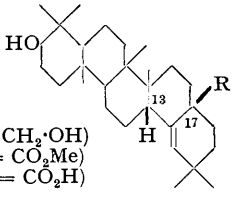
(I; R = CO_2H)
(II; R = CH_3)
(III; R = CH_2·OH)



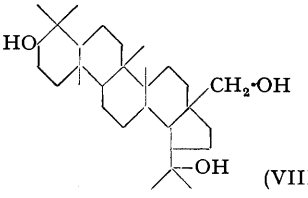
(IV)



(V)



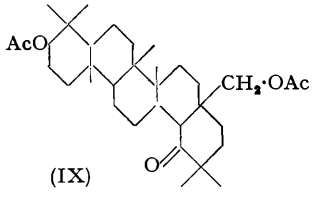
(VI; R = CH_2·OH)
(VII; R = CO_2Me)
(VIIa; R = CO_2H)



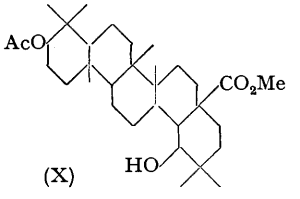
(VIII)

since the triol diacetate can be oxidised by chromic acid to the keto-diacetate (IX) which, in turn, can be reduced back to the parent triol by lithium aluminium hydride as described below.

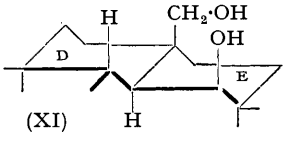
Dehydration of the triol diacetate may be carried out with both boron trifluoride–acetic anhydride at 20° (rather than at 100°) *and* the milder reagent, phosphorus oxychloride in pyridine at 100°, moradiol diacetate again being produced in both cases. The smooth dehydration under the latter conditions tends to discount the possibility of rearrangement following dehydration. An analogous elimination of a $C_{(19)}$ hydroxyl group with phosphorus oxychloride in pyridine has been described by Barton, Brooks, and Holness (*J.*, 1951, 278), who report the conversion of methyl dihydrosiaresinolate acetate (X) into the acetate of methyl morolate (VII). The structure of the triol (V) has been confirmed still further by the preparation of both its diacetate and the keto-diacetate (IX) by the alternative route discussed below.



(IX)



(X)



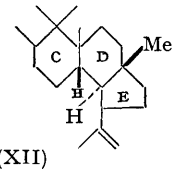
(XI)

The ease of dehydration, the resistance to acetylation, and the relative ease of oxidation of the hydroxyl group at $C_{(19)}$ indicate that it is polar (Barton, *Experientia*, 1950, **6**, 316). Further, the ease and method of dehydration indicate that the hydroxyl group at $C_{(19)}$ and the hydrogen atom at $C_{(18)}$ eliminated with it are *trans* to one another. The formation of the triol by lithium aluminium hydride scission of the lactone ring of (IV) leads to the conclusion that in the triol the primary alcohol group at $C_{(17)}$ must be *cis* to the hydroxyl group at $C_{(19)}$, *i.e.*, also polar. Hence, the primary alcohol group is *trans* to the hydrogen atom at $C_{(18)}$, *i.e.*, rings D and E in the triol (V) [cf. (XI)], and hence in the lactone (IV), are *trans*-fused.

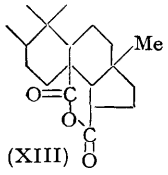
Provided that the formation of the keto-lactone (IV) from betulinic acid (I) does not involve the D–E ring fusion, it may be concluded that in this acid, and hence in the lupeol group of triterpenes [lupeol (II); betulin (III)], rings D and E are *trans*-fused, with the substituent at $C_{(17)}$ polar, in contrast to the *cis*-linking of rings D and E in the β-amyrin series (see below). On the basis of present knowledge this conclusion is believed to be correct, but further evidence is being sought in order to establish it rigorously.

Barton and Brooks (*loc. cit.*) have shown that in moradiol (VI) the primary alcohol group at $C_{(17)}$ is *cis* relative to the hydrogen atom at $C_{(13)}$. A similar relation must hold in the triol (V), and consequently in the lupeol group of triterpenes the substituent at $C_{(17)}$ is *cis* to the hydrogen atom at $C_{(13)}$. The stereochemistry of rings D and E of the lupeol group can therefore be represented provisionally by (XII), that of rings A and B being already known

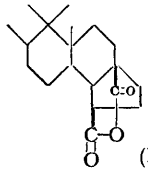
(cf. Barton, *loc. cit.*; Gutmann, Jeger, and Ruzicka, *Helv. Chim. Acta*, 1951, **34**, 1154). The configuration of the *iso*propenyl group is not indicated as it is not yet regarded as being definitely established. The degradation of the *iso*propenyl side chain of betulinic acid to a carboxyl group, and the interaction of this group with that originally present leading to anhydride formation, have been described by Ruzicka and Rey (*Helv. Chim. Acta*, 1943, **25**,



(XII)



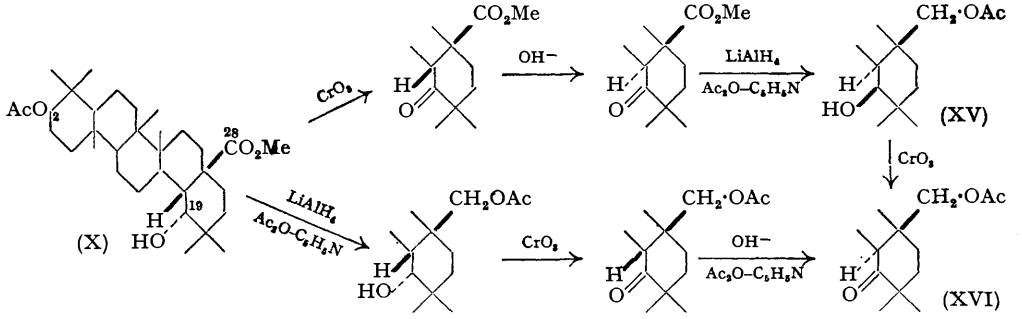
(XIII)



(XIV)

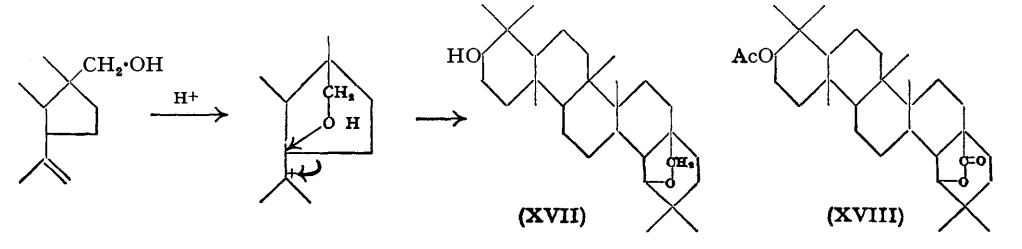
2143). The anhydride was originally formulated as (XIII) but must now be (XIV) with the two carboxyl groups *cis* to one another. This might be taken to indicate that the *iso*propenyl group of the lupeol series (I, II, and III) must be *cis* relative to the polar substituent at $C_{(17)}$, *e.g.*, the $C_{(17)}$ carboxyl group of betulinic acid. There is, however, a possibility of inversion at $C_{(19)}$ (cf. Gutmann, Jeger, and Ruzicka, *loc. cit.*) either during degradation or anhydride formation and, in fact, evidence has been obtained recently that this possibility may represent the truth and that the *iso*propenyl group is probably *trans* to the $C_{(17)}$ substituent.

While the work described above was in progress Dr. Barton kindly disclosed to us his results concerning the *cis*-fusion of rings D and E of the β-amyrin group and, in particular, of siaresinolic acid (Barton and Holness, *Chem. and Ind.*, 1951, 233). On consideration of these results it became clear that still further confirmation of the structure (V) deduced above for the triol could be obtained since its 2 : 28-diacetate and the 19-keto-derivative of this diacetate (IX) should be produced from methyl dihydrosiaresinolate acetate (X) by the following series of reactions.



Compounds (XV) and (XVI) prepared by Barton and Holness (*loc. cit.*) according to the above scheme have fulfilled this prediction, proving to be identical with the triol 2 : 28-diacetate and (IX), as shown by their identical constants and by mixed melting-point determinations.

The elucidation of the nature of the lactones formed when betulinic acid and its derivatives are treated with strong acids suggested that the production of the saturated ether, *allo*betulin, by formic acid isomerisation of betulin (Schulze and Pieroh, *Ber.*, 1922, **55**, 2332) might take place in an analogous manner :



This leads to structure (XVII) for *allo*betulin. The oxidation of *allo*betulin acetate with nitric acid (Dischendorfer and Polak, *Monatsh.*, 1929, **51**, 43) or chromic acid (Schulze and Pieroh, *loc. cit.*) gives the so-called oxy*allo*betulin acetate (m. p. >335°; $[\alpha]_D$ +60° in chloroform), in

which two hydrogen atoms have been replaced by an oxygen atom. Dr. Barton drew our attention to this compound and suggested that it might be identical with the acetoxy-lactone (XVIII) (m. p. >350°; $[\alpha]_D$ +57° in chloroform) obtained from betulinic acid acetate. As pointed out by Davy, Halsall, and Jones (preceding paper) the most suitable compound for comparison is the lower-melting keto-lactone (IV). The corresponding derivative from oxy*allo*betulin acetate, oxy*allo*betulone, has been prepared by a method similar to that of Dischendorfer and Juvan (*Monatsh.*, 1930, **56**, 242) and shown to be identical with the keto-lactone (IV). Structure (XVII) for *allo*betulin is thus confirmed, oxy*allo*betulin arising by oxidation of the CH_2 group adjacent to the ethereal oxygen atom of *allo*betulin.

Experimental.

All m. p.s were determined on a Kofler block and are corrected. Rotations were determined in chloroform. Light petroleum refers to the fraction with b. p. 40—60° unless otherwise stated. The alumina used for chromatography had an activity of I—II.

Treatment of the Triol Diacetate with Boron Trifluoride–Acetic Anhydride.—The triol diacetate (100 mg.) was dissolved in acetic anhydride (30 c.c.), and boron trifluoride–acetic acid complex (0·5 c.c.) was added dropwise with shaking. After 18 hours at 20°, the solution was added to excess of water. The product (127 mg.), isolated by extraction with benzene–ether (1 : 1), was adsorbed from light petroleum–benzene (30 c.c.; 2 : 1) on a column of alumina (13 g.). Elution with light petroleum–benzene (1 : 1; 25 c.c.) gave a crystalline fraction (27 mg.) which was crystallised from chloroform–methanol, yielding moradiol diacetate, m. p. 274·5—276° undepressed with an authentic specimen (m. p. 277—278°). Elution with benzene (50 c.c.) gave a gum (61 mg.) which could not be crystallised but was probably the triol triacetate.

Action of Phosphorus Oxychloride in Pyridine on the Triol Diacetate.—The triol diacetate (100 mg.) was dissolved in dry pyridine (15 c.c.) and phosphorus oxychloride (3 c.c.) added. The solution was heated at 100° for 1½ hours, then cooled, and cautiously added to excess of water. The product (90 mg.), isolated by ether-extraction, was adsorbed from *n*-pentane–benzene (10 c.c.; 1 : 1) on a column of alumina (10 g.). The following fractions were eluted with *n*-pentane–benzene (1 : 1) (4 × 25 c.c.); (i) trace, (ii) 24 mg., m. p. 276·5°, (iii) 40 mg., m. p. 269·5—274°, and (iv) 4 mg. A further fraction (v), 42 mg., m. p. 240—244°, was eluted with ether (50 c.c.). Crystallisation of (ii) and (iii) from chloroform–methanol gave moradiol diacetate, m. p. 276·5—277·5°, undepressed with an authentic specimen (m. p. 277—278°). Crystallisation of fraction (v) from chloroform–methanol gave unchanged triol diacetate.

Oxidation of the Triol Diacetate.—The triol diacetate (477 mg.) was dissolved in chloroform (22 c.c.), and a solution of chromic acid (220 mg.) in acetic acid (15 c.c.), acetone (30 c.c.), and water (2·5 c.c.) was added slowly with shaking. After 45 minutes at 20°, the mixture was diluted with water, and the product isolated by extraction with benzene–ether (1 : 1). Crystallisation of the product from methanol afforded undefined crystals, m. p. 221—340° (decomp.). Concentration of the mother-liquors gave material (80 mg.) as flakes, m. p. 215—220°. Recrystallisation of these from methanol gave the *keto-diol diacetate* (IX), m. p. 220—222·5° undepressed on admixture with the sample of m. p. 222—224°, $[\alpha]_D$ +41° (*c*, 1·13), prepared by Barton and Holness (*loc. cit.*), $[\alpha]_D^{20}$ +37° (*c*, 0·90) (Found: C, 75·25; H, 10·25. $C_{34}H_{54}O_5$ requires C, 75·25; H, 10·05%). Light absorption in ethanol: Max. 2940—2980 Å; $\varepsilon = 34$.

*Oxy*allo*betulone* (IV).—To a boiling solution of *allo*betulin acetate (663 mg.) in acetic acid (70 c.c.), chromic acid (823 mg.) in acetic acid (60 c.c.) was slowly added. After boiling under reflux for 15 minutes the mixture was cooled and diluted with water. The product (493 mg.) obtained by chloroform-extraction was adsorbed from light petroleum–benzene (1 : 1) (150 c.c.) on a column of alumina (50 g.). The fractions eluted with benzene (400 c.c.) and benzene–ether (1 : 1) (750 c.c.) were combined and crystallised from chloroform–methanol, to give oxy*allo*betulin acetate as plates (350 mg.), m. p. >360°.

The acetate (220 mg.) was dissolved in benzene (120 c.c.) and boiled under reflux for 2 hours with a solution of potassium hydroxide (5 g.) in 95% ethanol (100 c.c.). The reaction mixture was diluted with water, and the product (156 mg.), isolated by chloroform-extraction, was dissolved in chloroform (20 c.c.) and added to a solution of chromic acid (100 mg.) in acetic acid (100 c.c.). After 18 hours at 20° the mixture was diluted with water. The neutral product, isolated by chloroform extraction, was adsorbed from benzene on a column of alumina (10 g.). The fraction (70 mg.) eluted with benzene was crystallised several times from chloroform–methanol, giving oxy*allo*betulone as rods (45 mg.), m. p. 333—334° undepressed on mixing with a specimen of the keto-lactone-A from betulonic acid, $[\alpha]_D^{20}$ +84·7° (*c*, 1·05) (Found: C, 79·0; H, 9·8. Calc. for $C_{30}H_{46}O_3$: C, 79·2; H, 10·2%). During the melting-point determination a change of crystal form (rods ⟶ needles) occurs at *ca.* 230°. Dischendorfer and Juvan (*loc. cit.*) report a rotation of $[\alpha]_D$ −6° in benzene for oxy*allo*betulone.

Thanks are offered to Mr. E. S. Morton and Mr. H. Swift for microanalyses and to Miss E. Fuller for the ultra-violet absorption spectra. One of the authors (G. S. D.) thanks the University of Manchester for a post-graduate scholarship.

The University, Manchester, 13. [*Received, July 5th*, 1951.]