269. *Polyterpenoid Compounds. Part I. Betulic Acid from* Cornus florida, *L.*

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An unsaturated monobasic hydroxy-acid of the triterpene series, isolated from the bark of *Cornus florida*, L., has been shown to be identical with betulic acid, an oxidation product of betulin. The identity of the two products has been confirmed by comparison of a number of their derivatives, including the dihydro-compounds. By the action of hydrogen bromide in acetic acid, betulic acid gives rise to the acetate of a saturated stable lactone, and with bromine *O*-acetylbetulic acid yields *O*-acetylbromo- and *O*-acetyldibromo-lactones, reactions common to known unsaturated hydroxytriterpene acids.

In the course of experiments carried out in 1935 on the isolation of the glucoside cornin (verbenalin) from the bark of *Cornus florida*, L., by a modification of Bourdier's method (*Arch. Pharm.*, 1908, **246**, 272) a monobasic triterpene acid, m. p. above 300°, was obtained from the water-insoluble fraction of an alcoholic extract of the bark. Subsequently, having elaborated a satisfactory method for its quantitative extraction and purification, we undertook, in conjunction with a series of researches on cognate topics, a detailed investigation of the chemistry and constitution of this compound and have now found it to be identical with betulic acid, an oxidation product of betulin * (Ruzicka and co-workers, *Helv. Chim. Acta*, 1938, **21**, 1706). Owing to a discrepancy between the melting points of the acid from *Cornus florida*, L., and of that (m. p. 297°) given in the literature for betulic acid and because of the fact that we were at first unable to hydrogenate the acetate or the esters of our product this identity was not at first apparent. However, direct comparison of the acid from *Cornus florida*, L., with that obtained from betulin and of a number of their derivatives (see experimental section) has clearly shown that the two substances are identical.

In agreement with the view that the carboxyl group in betulic acid is attached to a tertiary carbon atom in an angular position (Ruzicka and co-workers, *loc. cit.*) it has been observed that the acid cannot be esterified by the usual methods and that methyl and *ethyl betulate*, formed by means of diazomethane and diazoethane respectively, are remarkably resistant to hydrolysis with alkaline reagents. Although these esters behave normally on acylation, it has been found that acetylation of the parent acid gives rise to a mixed *anhydride* of *O*-acetylbetulic acid and acetic acid, in which the absence of a free carboxyl group was decisively demonstrated by the failure of the product to react with diazomethane. This behaviour, which is shared by other isomeric triterpene acids, *e.g.*, oleanolic and ursolic acid (van der Haar, *Rec. Trav. chim.*, 1928, **47**, 585; Sando, *J. Biol. Chem.*, 1931, **90**, 477; Winterstein and Hämmerle, *Z. physiol. Chem.*, 1931, **199**, 55), has been observed to occur when betulic acid is treated with *p*-nitrobenzoyl chloride in pyridine, but, probably owing to its being considerably less stable, the mixed anhydride was not obtained analytically pure. On hydrolysis this product gave the p-*nitrobenzoate* of the acid.

Treatment of betulic acid (I; $R = H$, $R_1 = H$) or its acetate (I; $R = H$, $R_1 = Ac$) with a solution of hydrogen bromide in acetic acid gave rise to a lactone *acetate* (II, $R = Ac$), which on deacetylation furnished the saturated *lactone* (II, $R = H$), $C_{30}H_{48}O_3$, isomeric with the parent acid and designated lactone (A). On acetylation this compound, which is highly resistant to hydrolysis with alcoholic sodium hydroxide, regenerated the acetate (II, $R = Ac$). In this respect betulic acid closely resembles analogous hydroxytriterpene acids, which, largely owing to the work of Winterstein and his co-workers (*Z. physiol. Chem.*, 1931, **199**, 37, 56), have been shown to form acetates of hydroxy-lactones under the same conditions in which the lactone ring is remarkably resistant to the action of hydrolytic agents. The acetate of the lactone (II; $R = Ac$) was also obtained when acetylbetulic acid (I; $R = H$, $R_1 = Ac$) was heated with formic acid, the action of which was primarily investigated in the course of attempts to shift the position of the double bond in betulic acid or its derivatives. With the latter reagent, however, betulic acid and its methyl ester (I; $R = Me$, $R_1 = H$) were converted into the *formate* of a highly stable *lactone* (B) isomeric with lactone (A). The formation of the acetate (II, $R = Ac$) in this manner affords evidence that the hydroxyl group is not involved in the isomerisation of the acid to the lactone, and the high degree of stability exhibited by both lactones (A) and (B) indicates that in all probability they are of the γ-type and hence are stereoisomerides. Further, on the assumption that migration of the double bond does not take place in the process of lactonisation it seems probable, by analogy with the behaviour of βγ- and γδ-

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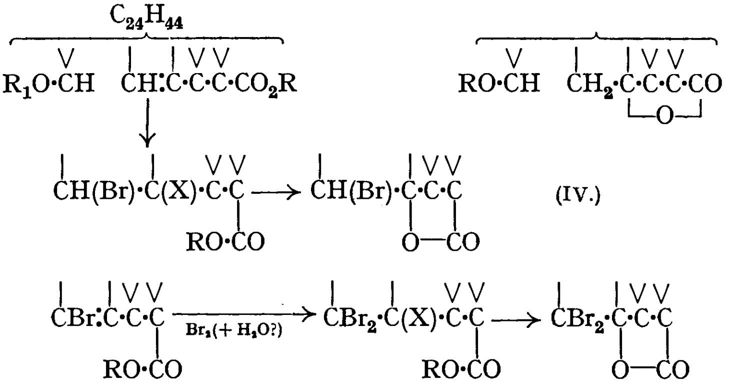
* The major part of the work described in the present communication was contained in a thesis presented in 1938 by Dr. G. Soliman for the degree of Ph.D. of this University before the publication of the paper by Ruzicka and his collaborators. In this thesis the acid was designated cornolic acid.

unsaturated acids in forming γ-lactones, that the ethylenic linkage in betulic acid is in the βγ- or γδ-position to the carboxyl group (compare Ruzicka and co-workers, *loc. cit.*).

The absorption of bromine by betulic acid was accompanied by the evolution of hydrogen bromide and the product appeared to consist of a mixture of bromo-derivatives which could not be separated. With bromine, *O*-acetylbetulic acid (I; R = H, R_1 = Ac), dissolved in ether–acetic acid, yielded the *acetate* of a saturated bromo-lactone, type (IV), together with an inseparable mixture, but when the reaction was carried out in aqueous acetic acid the acetate (I; R = H, R_1 = Ac) and its methyl ester (I; R = Me, R_1 = Ac) furnished the *acetate* of a saturated dibromo-lactone, type (VII); under the same conditions



(I.) (II.) (III.) (IV.) (V.) (VI.) (VII.)

methyl betulate gave rise to a polybromo-lactone which we have not been able to obtain analytically pure. Although the mechanism of the formation of the lactones (IV) and (VII) is somewhat obscure, we consider that, under the conditions employed, (IV) is formed from type (I; R = H, R_1 = Ac) by way of (III), where it is not clear whether X = Br or X = OH; in the latter case the hypobromous acid would arise from traces of moisture present in the reaction mixture. On the other hand, when the reaction is carried out in the presence of water, the addendum is probably hypobromous acid and (VII) may well be formed from (I; R = H, R_1 = Ac) or (I; R = Me, R_1 = H) by way of the stages (III), (V) and (VI, X = OH) (compare Kitasato and Sone, *Acta Phytochim.*, 1932, **6**, 179).

EXPERIMENTAL.

(*With* H. I. KING) *Betulic Acid.*—Powdered bark of *Cornus florida*, L., (1 kg.), which had been extracted three times with water (1 l.) at room temperature for 24 hours and then washed with 95% alcohol (1·5 l.), was extracted four times with boiling 95% alcohol (2 l.) for 5—7 hours, and the combined extracts concentrated under diminished pressure until an orange-yellow solid began to separate. After having been kept at 0° for several hours, the solid was collected, and the filtrate evaporated in a vacuum, leaving a further quantity of solid. The combined products were thoroughly extracted with water, dried, and triturated with much light petroleum (b. p. 40—60°) for 2 hours to remove lipoidal material, and then with ether to extract a yellow colouring matter, finally giving the acid as a reddish amorphous powder.

From the ethereal washings of the crude material, which had been concentrated to a small volume, a further quantity (small) of the acid was obtained, part as a white gelatinous precipitate which separated and the remainder as the insoluble sodium salt which was formed by agitating the ethereal residue with 1% aqueous sodium hydroxide. After the separation of the sodium betulate the colouring matter was precipitated from the filtered alkaline extract by means of carbon dioxide and is being retained for further investigation.

In this way 15 kg. of bark yielded 300 g. of crude acid and 200 g. of dark oil soluble in light petroleum.

Repeated crystallisation of the crude product from alcohol (charcoal) finally gave betulic acid in plates or needles, m. p. 316—318°, containing solvent of crystallisation, only part of which was removed when the substance was dried at 105° in a high vacuum, $[\alpha]_{5461}^{22^\circ}$ + 7·89° in pyridine (*c*, 3·076 g. of anhydrous material in 100 c.c.; *l* = 1) [Found in material dried in a high vacuum at 120° for 8 hours: C, 78·9, 78·9; H, 10·6, 10·6; CO_2H (by titration in alcohol), 9·6, 9·6, 9·6; *M*, 469, 470. Calc. for $C_{29}H_{47}O(CO_2H)$: C, 78·9; H, 10·6; CO_2H, 9·7%; *M*, 456·4].

O-Acetylbetulic acid (0·3 g.), prepared by the oxidation of betulin monoacetate (Ruzicka and co-workers, *loc. cit.*), was boiled with alcohol (30 c.c.), containing potassium hydroxide (2 g.), for 1½ hours, the solution acidified and diluted with water, and the resulting acid isolated with ether and repeatedly crystallised from methyl and then ethyl alcohol, forming needles, m. p. 315°, undepressed by admixture with a specimen from *Cornus florida*, L.

The purification of the crude acid from alcohol was found to be wasteful and the material recovered from the alcoholic filtrates was dissolved in the minimum amount of 5% aqueous-alcoholic potassium hydroxide (3 parts of water and 7 parts of alcohol) and after being treated with animal charcoal the solution was filtered and acidified with hydrochloric acid. In this manner a white flocculent product was obtained which was purified from alcohol without serious loss.

Betulic acid, which is readily soluble in pyridine and sparingly soluble in alcohol, acetone, ethyl acetate, chloroform, or benzene, forms a sodium salt which is almost insoluble in water. When a solution of the acid (1 g.) in ether (100 c.c.) was agitated with 2N-sodium hydroxide (30 c.c.), a flocculent precipitate, *sodium betulate*, separated and on isolation formed glistening rectangular plates from warm 70% alcohol, containing solvent of crystallisation (Found in a specimen dried in a high vacuum at 120°: Na, 4·7, 4·8. $C_{30}H_{47}O_3Na$ requires Na, 4·8%).

The following colour reactions were given by betulic acid: When a crystal of the compound was covered with a drop of concentrated nitric acid, and the mixture evaporated to dryness, the pale yellow residue became orange-coloured on exposure to gaseous ammonia; in the Liebermann–Burchardt reaction, a reddish-violet layer was formed and, on shaking, the mixture became blue- and then red-violet; in Lifschütz's reaction, a red-violet ring was formed and, on shaking, the mixture became pink; Tschugajeff's reaction gave a violet-red colour; Rosenheim's reaction was negative.

O-Acyl Derivatives of Betulic Acid.—A solution of the acid (1 g.) in a mixture of acetic anhydride (6 c.c.) and pyridine (4 c.c.) was kept at room temperature for 2—3 days, and the solvent distilled in a vacuum; the residual mixed *anhydride* of *O*-acetylbetulic acid and acetic acid separated from light petroleum (b. p. 60—80°) in clusters of prisms, m. p. 194—196°, which did not react with ethereal diazomethane [Found: C, 75·8; H, 9·7; $CH_3{\cdot}CO$, 18·4. $C_{30}H_{46}O_3(CH_3{\cdot}CO)_2$ requires C, 75·5; H, 9·7; $CH_3{\cdot}CO$, 15·2%]. The same product was formed when the acid (1 g.) was refluxed with acetic anhydride (8 c.c.), containing sodium acetate (2 g.), for 1 hour, and the excess of acetic anhydride decomposed with water at room temperature. A solution of this product in boiling 70% alcohol, on cooling, deposited the acetate of betulic acid in large plates, m. p. 289—291° after recrystallisation, $[\alpha]_{5461}^{22^\circ}$ + 7·70° in chloroform (*c*, 5·07 g. in 100 c.c.; *l* = 1), identical with a specimen prepared from betulin, m. p. 288—290°, $[\alpha]_{5461}^{20^\circ}$ + 8·6° in chloroform (*c*, 3·53 g. in 100 c.c.; *l* = 1) (Ruzicka and co-workers, *loc. cit.*, give $[\alpha]_D$ + 20·1° in chloroform) [Found: C, 76·9; H, 9·9; $CH_3{\cdot}CO$, 8·4; CO_2H (by titration), 9·05. Calc. for $C_{29}H_{46}O(CH_3{\cdot}CO)(CO_2H)$: C, 77·1; H, 10·1; $CH_3{\cdot}CO$, 8·4; CO_2H, 9·0%]. Treatment of this acetate with acetic anhydride and pyridine at room temperature or with boiling acetic anhydride containing sodium acetate regenerated the mixed anhydride, m. p. 194° after purification.

p-Nitrobenzoyl chloride (4 g.) was added to betulic acid (2 g.) dissolved in pyridine, and the resulting brown-red solution kept at 40—50° for 4 days and then poured on ice; the precipitate was triturated with aqueous sodium bicarbonate for two hours, collected, washed, and dried. On being once crystallised from chloroform–alcohol, this material (3·4 g.) gave pale straw-coloured needles (2·5 g.), m. p. 160°, but after having been recrystallised eight times the m. p. of the product fell to 154—155° (Found in a specimen dried in a high vacuum at 105°: C, 68·0; H, 7·1; N, 4·3. Calc. for $C_{44}H_{54}O_9N_2$: C, 70·0; H, 7·2; N, 3·7%). When a solution of this compound (0·8 g.) in pyridine (20 c.c.) was heated on the water-bath for 15 minutes and then gradually treated with water (2 c.c.), the p-*nitrobenzoate* of betulic acid separated in small plates, m. p. above 320°, after having been recrystallised from aqueous pyridine (Found: C, 73·5; H, 8·3; N, 2·4. $C_{37}H_{51}O_6N$ requires C, 73·3; H, 8·5; N, 2·3%).

Esters of Betulic Acid.—Methyl sulphate (20 c.c.) was gradually added to a solution of the acid (15 g.) in alcohol (200 c.c.) and aqueous potassium hydroxide (20 g. in 150 c.c. of water) maintained at 40° and, after the addition of more alkali, a further portion of methyl sulphate was added. Two hours later the crystalline ester, m. p. 220°, was collected, washed, and recrystallised from methyl alcohol, forming needles, m. p. 223—224°, identical with a specimen prepared by the action of excess of ethereal diazomethane on the acid during 20 minutes, $[\alpha]^{22^\circ}_{5461} + 8{\cdot}01^\circ$ in chloroform (*c*, 4·11 g. in 100 c.c.; $l = 1$), soluble in ether, chloroform or benzene and sparingly soluble in light petroleum [Found: C, 78·9; H, 10·7; OMe, 6·7. Calc. for $C_{30}H_{47}O_2(OMe)$: C, 79·1; H, 10·7; OMe, 6·6%] (Ruzicka and co-workers give $[\alpha]_D + 5{\cdot}0^\circ$). Treatment of this ester with acetic anhydride and pyridine at room temperature during 3 days gave the acetate, which formed prisms, m. p. 201—202°, from alcohol, $[\alpha]^{22^\circ}_{5461} + 18{\cdot}06^\circ$ in chloroform (*c*, 6·756 g. in 100 c.c.; $l = 1$), identical with the product formed by the action of excess of diazomethane on *O*-acetylbetulic acid and with a specimen, m. p. 201—202° prepared from betulin [Found: C, 77·3; H, 10·1; OMe, 5·8. Calc. for $C_{32}H_{49}O_3(OMe)$: C, 77·3; H, 10·3; OMe, 6·1%] (Ruzicka and co-workers, *loc. cit.*, give $[\alpha]_D + 17{\cdot}1^\circ$). Deacetylation of this compound with 5% alcoholic potassium hydroxide at room temperature for 2 days re-formed methyl betulate.

The interaction of methyl betulate (1 g.) and *p*-nitrobenzoyl chloride (1 g.) in pyridine (25 c.c.) at 40—50° for 3 days gave rise to the p-*nitrobenzoate* of the ester, which separated from benzene–alcohol in almost colourless plates, m. p. 232—233° [Found in a specimen dried in a high vacuum at 120°: C, 73·7; H, 8·7; N, 2·3; OMe, 5·1. $C_{37}H_{50}O_5N(OMe)$ requires C, 73·6; H, 8·6; N, 2·3; OMe, 5·0%].

Prepared by the same method, the p-*toluenesulphonate* of the methyl betulate formed colourless plates, m. p. 172—174° (decomp.), from benzene–alcohol, sparingly soluble in acetone or methyl alcohol (Found: C, 73·0; H, 8·9; S, 5·2. $C_{38}H_{56}O_5S$ requires C, 73·0; H, 9·0; S, 5·1%).

Esterification of betulic acid with an excess of ethereal diazoethane gave rise to the *ethyl* ester, which separated from alcohol in needles, m. p. 201—202°, $[\alpha]^{22^\circ}_{5461} + 11{\cdot}44^\circ$ in chloroform (*c*, 4·588 g. in 100 c.c.; $l = 1$) [Found: C, 79·2; H, 10·95; OEt, 9·1. $C_{30}H_{47}O_2(OEt)$ requires C, 79·3; H, 10·8; OEt, 9·3%]. Prepared by the pyridine method, the *acetate* formed prisms, m. p. 185—186°, $[\alpha]^{22^\circ}_{5461} + 14{\cdot}33^\circ$ in chloroform (*c*, 2·198 g. in 100 c.c.; $l = 1$), from alcohol [Found: C, 77·4; H, 10·4; OEt, 8·8. $C_{32}H_{49}O_3(OEt)$ requires C, 77·5; H, 10·3; OEt, 8·6%]. The same compound, m. p. and mixed m. p. 185—186°, was formed by esterification of *O*-acetylbetulic acid with ethereal diazoethane.

Dihydrobetulic Acid and its Derivatives.—*O*-Acetylbetulic acid (0·5 g.), dissolved in alcohol or acetic acid (50 c.c.), was hydrogenated with hydrogen (1 mol. absorbed) and a platinum oxide catalyst (0·05 g.) in the course of ½ hour and the product, m. p. 290—304°, left on evaporation of the filtered solution was crystallised from methyl alcohol, giving the dihydro-compound in monoclinic prisms, m. p. 305—307°, after sintering at 295°, which, on being dried in a vacuum over phosphoric oxide, had m. p. 307—310° (Found: C, 76·9; H, 10·4. Calc. for $C_{32}H_{52}O_4$: C, 76·8; H, 10·4%) (Ruzicka and co-workers, *loc. cit.*, give m. p. 307°, but do not record analyses for the product obtained from betulin).

On treatment with excess of ethereal diazomethane this compound gave methyl *O*-acetyldihydrobetulate, which formed small prisms, m. p. 236—237, identical with a specimen prepared by the hydrogenation of methyl *O*-acetylbetulate (2 g.), dissolved in alcohol (120 c.c.), with hydrogen (approx. 1 mol. absorbed) and a platinum oxide catalyst (0·1 g.); $[\alpha]^{22^\circ}_{5461} = -3{\cdot}31^\circ$ in chloroform (*c*, 5·37 g. in 100 c.c.; $l = 1$) (Found in material dried in a high vacuum at 120°: C, 77·0; H, 10·5. Calc. for $C_{33}H_{54}O_4$: C, 76·9; H, 10·6%) (Ruzicka and co-workers, *loc. cit.*, give m. p. 238—239°). This compound gave a negative tetranitromethane reaction.

A solution of *O*-acetyldihydrobetulic acid in 95% alcohol (60 c.c.) containing potassium hydroxide (4 g.) was boiled for 1½ hours and acidified with acetic acid (10 c.c.). On cooling, the hydrolysate deposited dihydrobetulic acid in well-defined needles, m. p. 316—320°, unchanged on repeated crystallisation from methyl and ethyl alcohol. The same compound was obtained when betulic acid (0·5 g.), dissolved in acetic acid (100 c.c.), was hydrogenated with hydrogen (1 mol. absorbed) and a platinum oxide catalyst (0·05 g.) and on purification had m. p. 316—320°. Acetylation of this material re-formed *O*-acetyldihydrobetulic acid (Found: C, 76·7; H, 10·4%).

Esterification of dihydrobetulic acid obtained from either source with excess of diazomethane yielded the same *methyl dihydrobetulate*, m. p. 238°, which separated from alcohol in long needles, m. p. 238—240° [Found in a specimen dried in a high vacuum at 120°: C, 78·7; H, 11·2; OMe, 6·3. $C_{30}H_{49}O_2(OMe)$ requires C, 78·7; H, 11·1; OMe, 6·6%].

In a similar manner hydrogenation of ethyl *O*-acetylbetulate gave *ethyl* O-*acetyldihydrobetulate*, which separated from alcohol in small prisms, m. p. 205° (Found in material dried at 205°: C, 77·2; H, 10·6. $C_{34}H_{56}O_4$ requires C, 77·2; H, 10·7%), and on deacetylation by boiling 5% alcoholic potassium hydroxide during 45 minutes gave *ethyl dihydrobetulate*, which formed needles, m. p. 208°, from methyl alcohol (Found : C, 78·8; H, 10·9. $C_{32}H_{54}O_3$ requires C, 78·9; H, 11·2%). A mixture of the ester and its acetate melted at about 180°.

Oxide of Methyl O-*Acetylbetulate.*—Estimation of the number of double bonds in methyl *O*-acetylbetulate, dissolved in chloroform, by means of a standard solution of perbenzoic acid (Levy and Lagrave, *Bull. Soc. chim.*, 1925, **37**, 1598) according to the usual procedure gave oxygen number 0·99, 0·98; the time required for oxidation was 7 days and control experiments were carried out. After having been washed with aqueous sodium bicarbonate and then water, the chloroform solution, left on titration of the excess of perbenzoic acid, was dried and evaporated in a vacuum, leaving the *oxide* as a glassy residue, which gradually crystallised in contact with a little alcohol and then separated from dilute alcohol in rectangular plates, m. p. 202° (Found: C, 74·8; H, 9·9. $C_{33}H_{52}O_5$ requires C, 74·8; H, 9·9%). When this compound (0·3 g.) was heated with a solution of hydroxylamine acetate (0·6 g.) in alcohol (20 c.c.) and water (6 c.c.) for 3 hours on the steam-bath and then cooled, a product separated in plates, m. p. 214°, which after repeated crystallisation from dilute alcohol had m. p. 222° and gave a negative test for nitrogen. The amount of material was too small for further investigation.

By the perbenzoic acid method *O*-acetylbetulic acid gave an oxygen number 1·07 and 1·06.

Lactone (*A*) *of Betulic Acid.*—The gradual solution of dried betulic acid (1 g.) in acetic acid (10 c.c.) saturated with hydrogen bromide was accompanied by the production of a violet and finally a blue coloration; after 4 days the viscous mixture was treated with excess of water and the resulting grey precipitate was collected, washed, and dried. Alcohol (30 c.c.) was added to a filtered solution of the product (1·1 g.) in boiling chloroform (20 c.c.) (charcoal) and on being kept at below 0° the mixture gradually deposited plates, m. p. 328°, which contained bromine (Found : C, 76·9; H, 9·8; Br, 2·2%). On being crystallised twice from benzene, this material gave the *acetate* of the lactone in slender needles, m. p. above 350° after sintering at 335°, readily soluble in chloroform or carbon tetrachloride and sparingly soluble in alcohol or ethyl acetate (Found in material dried in a high vacuum at 120° : C, 77·2; H, 10·1. $C_{32}H_{50}O_4$ requires C, 77·1; H, 10·1%). The same compound was obtained by the interaction of *O*-acetylbetulic acid and hydrogen bromide in acetic acid during 4 days and formed needles, m. p. above 330°, on crystallisation from benzene.

On being boiled with 98—100% formic acid (25 c.c.) for 5 hours, *O*-acetylbetulic acid gave rise to the acetate of the lactone, which formed needles from benzene, m. p. above 330° (Found in material dried in a high vacuum at 120° : C, 77·1; H, 10·2%).

This acetate was recovered unchanged after having been heated with acetic anhydride and pyridine on the steam-bath for 1 hour or on prolonged treatment with excess of diazomethane.

5% Alcoholic potassium hydroxide (50 c.c.) was added to a solution of the acetate (0·5 g.) in benzene (50 c.c.), the mixture heated on the steam-bath for ½ hour, the solvent distilled, and, after the addition of water, the residue extracted with chloroform. Crystallisation of the product left on evaporation of the chloroform extracts gave the *lactone* (A) in needles, m. p. above 320°, $[\alpha]_{5461}^{22^\circ} + 75{\cdot}18^\circ$ in chloroform (*c*, 1·37 g. in 100 c.c.; $l = 1$), sparingly soluble in ether, ethyl acetate or light petroleum (Found : C, 78·9; H, 10·7. $C_{32}H_{48}O_3$ requires C, 78·9; H, 10·6%).

Lactone (*B*) *of Betulic Acid.*—On being boiled with formic acid (60 c.c.) for 5 hours, betulic acid (2 g.) gave rise to the *formate* of lactone (B), which was precipitated from the reaction mixture with water, extracted with boiling alcohol (100 c.c.) to remove unchanged material, and crystallised from chloroform–alcohol and then from chloroform–benzene, forming small plates, m. p. above 350°, sparingly soluble in the usual solvents except chloroform and carbon tetrachloride (Found : C, 76·9; H, 10·1. $C_{31}H_{48}O_4$ requires C, 76·8; H, 10·0%). The same compound (0·6 g.) was formed when methyl betulate (1 g.) was boiled with formic acid (30 c.c.) for 2 hours. With tetranitromethane this lactone gave a negative reaction.

A mixture of the formate (0·5 g.), benzene (50 c.c.), and 5% alcoholic potassium hydroxide (40 c.c.) was refluxed for 30 minutes, the resulting solution evaporated in a vacuum, and after the addition of water the product was isolated from the alkaline liquor by means of chloroform. Crystallised from benzene, *lactone* (B) formed needles, m. p. above 330°, $[\alpha]_{5461}^{22^\circ} + 59{\cdot}05^\circ$ in chloroform (*c*, 2·10 g. in 100 c.c.; $l = 1$), which did not react with ethereal diazomethane and gave a negative tetranitromethane reaction (Found in material dried at 120° in a high vacuum : C, 79·0; H, 10·6. $C_{30}H_{48}O_3$ requires C, 78·9; H, 10·6%). A mixture of this compound and lactone (A), m. p. above 320°, melted at 320—330°.

Lactone of O-*Acetylbromobetulic Acid.*—A 5% solution of bromine in absolute acetic acid (10 c.c.) was gradually added to *O*-acetylbetulic acid (1 g.) in dry ether (20 c.c.) and 3 hours later the crystalline precipitate (0·4 g.) was collected, drained, and recrystallised from chloroform–alcohol, giving the *bromo*-compound in slender needles, m. p. 290° (decomp.), which gave a negative reaction with tetranitromethane and with diazomethane (Found in material dried in a high vacuum at 100° : C, 66·0; H, 8·6; Br, 14·6. $C_{32}H_{49}O_4Br$ requires C, 66·5; H, 8·6; Br, 13·9%). Evaporation of the residual ethereal solution left a product which appeared to be a complex mixture.

Lactone of O-*Acetyldibromobetulic Acid.*—*O*-Acetylbetulic acid (2 g.), dissolved in acetic acid (180 c.c.) and water (10 c.c.), was treated with an excess of a 5% solution of bromine in acetic acid (15 c.c.) and 4 hours later the product was precipitated with water, washed with sulphurous acid, and dried. Crystallised from acetic acid and then from chloroform–alcohol, the *dibromo*-derivative formed slender needles, m. p. 290—295° (decomp.), sparingly soluble in alcohol, acetone, or light petroleum and readily soluble in benzene or ethyl acetate (Found in a specimen dried in a high vacuum at 120° : C, 58·5; H, 7·3; Br, 24·2. $C_{32}H_{48}O_4Br_2$ requires C, 58·5; H, 7·4; Br, 24·4%). This product did not react with tetranitromethane or with diazomethane.

The same compound was obtained when *O*-acetylbetulic acid was replaced by its methyl ester in the foregoing mixture; m. p. and mixed m. p. 290—295° (decomp.) after purification (Found : C, 58·3; H, 7·3; Br, 24·3%). This specimen did not contain a methoxyl group.

Bromination of methyl betulate under similar conditions gave a saturated product which after repeated purification from chloroform–alcohol had m. p. above 320° (decomp.) and did not contain a methoxyl group (Found in material dried in a high vacuum at 120° : C, 50·1; H, 6·1; Br, 41·5%).

The authors are indebted to Imperial Chemical Industries, Limited, for a grant.

UNIVERSITY OF LIVERPOOL.

[*Received, June 14th,* 1939.]