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Terpenoids. VI.[1] Dumortierigenin, a New Triterpene Lactone from the Cactus *Lemaireocereus dumortieri*[2]

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The isolation and characterization of a new dihydroxy triterpene lactone, dumortierigenin ($C_{30}H_{46-48}O_4$), from the cactus *Lemaireocereus dumortieri* is described.

The present investigations in our laboratory on the constituents of certain cacti of the sub-tribe *Cereanae* have demonstrated that many of them represent abundant sources of new triterpenes. The genus *Lemaireocereus* seems particularly noteworthy in this respect and we have already recorded the isolation of two new triterpenes, thurberogenin from *L. thurberi*,[4] and longispinogenin from *L. longispinus*.[5] The former appears to be an unusual lactone of the lupeol group,[6] whereas the latter is a member of the β-amyrin series since its structure has been shown to be Δ^{12}-18β-oleanene-3β,16β,28-triol.[7] We should now like to describe the chemical examination of still another species of the genus *Lemaireocereus, L. dumortieri*. This tree-like cactus reaches up to 45 ft. in height and occurs in the central plateau of Mexico, especially in the State of Hidalgo.[8,9] The presently employed specimens were collected by one of the authors together with Dr. Alberto Sandoval near Zimapan and Meztitlan, Hidalgo, and were identified botanically by Prof. Helia Bravo[9] of the Instituto de Biologia in Mexico City. When processed in the customary manner,[4,5] this cactus, just like the related *L. thurberi* and *L. longispinus*, was found to be essentially devoid of alkaloids but quite rich in glycosides, and acid hydrolysis furnished a new triterpene aglycone (m.p. 292–295°) which we have named "dumortierigenin."

Analyses of dumortierigenin (I) and a variety of transformation products (II–VI) do not differentiate between the empirical formulas $C_{30}H_{46}O_4$ and $C_{30}H_{48}O_4$, and we have so far been unable to establish unequivocally which formulation is the correct one. The infrared spectrum (chloroform solution)[10] of dumortierigenin shows bands at 3570 and 1754 cm.$^{-1}$ corresponding to hydroxyl, and five-membered lactone absorption and the presence of two hydroxyl groups was established by the formation of a diacetate and dibenzoate. Additional information concerning these two hydroxyl groups was secured as follows.

Dumortierigenin diacetate is formed readily at room temperature, indicating the presence of two easily acylable hydroxyl groups. Of consequence is the observation that the acetate band at 5.80 μ is partially resolved (shoulder at 5.76 μ) and that the C–O stretching absorption between 8.0–8.2 μ is complex and typical of steroidal type B acetates.[11] In our hands, ordinary 3β-acetoxytriterpenes (methyl oleanolate acetate (VIIb), erythrodiol diacetate, maniladiol diacetate) with equatorial acetoxy groups show only type A bands in the 8μ region. Saponification of dumortierigenin diacetate with potassium carbonate—under conditions where the model methyl oleanolate acetate VIIb was recovered in over 50% yield—furnished a monoacetoxy lactone III which in addition to infrared hydroxyl (2.78 μ), lactone (5.68 μ) and acetate (5.81 μ) absorption showed a sharp type A band at 8.0 μ. This monoacetate III was unaffected by chromium trioxide–pyridine[12] but could be oxidized with chromium trioxide–sulfuric acid[13] to an acetoxyketo lactone IV still showing the single type A band at 8.0 μ. Of interest is the fact that the infrared lactone band has been shifted to 5.59 μ and that the acetate (shoulder at 5.80 μ) and ketone (5.86 μ) carbonyl bands were not very well resolved (see below for contrasting behavior of II). The position of the ketone band indicates that it is attached to a six-membered ring and this, *ipso facto*, applies to the secondary alcoholic function of the precursor III.

Another important difference in the behavior of the two hydroxyl groups of dumortierigenin (I) was observed upon oxidation. Treatment with the chromium trioxide–pyridine complex[12] resulted in the oxidation of only one hydroxyl group yielding a ketohydroxy lactone II with infrared bands at 2.80, 5.68 and 5.90 μ (six-membered ketone). Acetylation furnished a ketoacetoxy lactone II, *different* from that (IV) obtained *via* the partial saponification–oxidation route (I → III → IV) described above. This new ketoacetoxy lactone again showed the complex type B acetate band in the 8 μ region, observed originally in dumortierigenin diacetate, and excellent resolution (in contrast to IV)

(1) Paper V, C. Djerassi, P. Sengupta, J. Herran and F. Walls, THIS JOURNAL, **76**, 2966 (1954).

(2) We are grateful to the Rockefeller Foundation and to the Division of Research Grants of the U. S. Public Health Service (grant No. G-3863) for financial support of this project.

(3) Postdoctorate research fellow at Wayne University.

(4) C. Djerassi, L. E. Geller and A. J. Lemin, THIS JOURNAL, **75**, 2254 (1953).

(5) C. Djerassi, R. M. McDonald and A. J. Lemin, *ibid.*, **75**, 5940 (1953).

(6) E. Farkas, unpublished observations.

(7) C. Djerassi, L. E. Geller and A. J. Lemin, *Chemistry and Industry*, 161 (1954).

(8) N. L. Britton and J. N. Rose, "The Cactaceae," Carnegie Institution of Washington, Vol. II, p. 102.

(9) H. Bravo, "Las Cactaceas de Mexico," Mexico D. F., 1937, pp. 270–271.

(10) Infrared bands given in wave numbers (cm.$^{-1}$) were obtained with Perkin-Elmer instruments through the courtesy of Dr. R. Norman Jones (National Research Council, Ottawa), and Srta. Paquita Revaque (Syntex, S. A., Mexico City), while those given in wave length units (μ) were measured on a Baird double beam instrument at Wayne University.

(11) R. N. Jones, P. Humphries, F. Herling and K. Dobriner, THIS JOURNAL, **73**, 3215 (1951).

(12) G. I. Poos, G. E. Arth, R. E. Beyler and L. H. Sarett, *ibid.*, **75**, 422 (1953).

(13) *Cf.* R. G. Curtis, I. Heilbron, E. R. H. Jones and G. F. Woods, *J. Chem. Soc.*, 461 (1953).

in the carbonyl region with bands at 5.63, 5.78 and 5.90 μ corresponding to the three carbonyl-containing groups (lactone, acetate, ketone). On the assumption that dumortierigenin possessed the 3β-hydroxy-4,4-dimethyl moiety in ring A typical of all other known pentacyclic triterpenes (*e.g.* VII), then it is this 3β-hydroxy function which was oxidized by chromium trioxide–pyridine. This is supported by the following arguments: (1) the model oleanolic acid lactone VIIIa[14] was converted smoothly to the corresponding 3-keto-lactone VIIIb demonstrating the lability of the 3β-hydroxyl group toward this reagent; (2) the monoacetate III, in which the hydroxyl group oxidizable by chromium trioxide–pyridine is protected by acetylation, shows the type A band (8.0 μ) typical of 3β-acetoxytriterpenes (*e.g.*, VIIb); (3) sodium borohydride reduction of the ketohydroxy lactone II followed by acetylation yields dumortierigenin diacetate indicating that the hydroxyl group formed by reduction of the carbonyl group must be equatorial[15]; (4) the position of the infrared carbonyl band of II at 5.90 μ demonstrates that the hydroxyl group must be attached to a six-membered ring; (5) the x-keto-y-hydroxylactone II gave a Zimmerman color reaction[15a] identical over the entire region (300–700 mμ) with that exhibited by a typical 3-keto triterpene, β-amyrone.[15b] On the other hand, the x-acetoxy-y-ketone IV gave no color under the same conditions.[15a] The hypsochromic shift in the infrared lactone band of the y-monoketone IV and the x,y-diketone V (but not of the x-monoketone II) might indicate that the y-keto group is located in the proximity of the lactone ring.

When dumortierigenin (I) was oxidized with the chromium trioxide–sulfuric acid reagent,[13] both hydroxyl groups were affected and the diketone V, further characterized as the dioxime, could be isolated. Sodium borohydride reduction of this dione V followed by acetylation also furnished dumortierigenin diacetate. In summary, these experiments demonstrate that both hydroxyl groups of dumortierigenin are attached to six-membered (or possibly larger) rings, that one of them is easily saponified but not attacked by chromium trioxide–pyridine, and that the other hydroxyl group behaves like a typical 3β-hydroxyl function in that it is easily oxidized with chromium trioxide–pyridine, while its acetate is not very readily hydrolyzed by potassium carbonate. From the fact that the diketone V possesses two reactive carbonyl groups and is reducible to the parent dumortierigenin (I), one can conclude tentatively that both hydroxyl groups are equatorial[15] and that certain subtle steric factors are responsible for the observed differences in the rates of saponification and oxidation. This fortuitous difference should permit the selective removal of either one of the two hydroxyl functions and it is contemplated that subsequent degradation experiments will take advantage of this fact.

A number of model experiments were carried out in the oleanolic acid series (VIIa) in order to shed some light upon the nature of the lactone ring of dumortierigenin. Barton and Holness[14] have shown that treatment of a chloroform solution of oleanolic acid (VIIa) with hydrogen chloride leads to an equilibrium mixture consisting of 24% lactone VIIIa and 76% recovered acid, this equilibrium being attainable from either side. When glacial acetic acid–concentrated hydrochloric acid is employed,[16] a high yield of a stable 18-isoöleanolic acid lactone acetate is obtained, which cannot be reconverted to oleanolic acid and which differs from oleanolic acid lactone VIIIa in possessing the more stable D/E *trans* juncture.[14] At the time that the present work was initiated, no infrared data were available on these lactones and the pertinent information was, therefore, collected by us[17] in order to have available reliable comparison values. These are summarized in Table I.

TABLE I

Compound	Infrared lactone carbonyl band, cm.$^{-1}$ CS_2	$CHCl_3$
Oleanolic acid lactone	1775	1754
18-Isoöleanolic acid lactone acetate	..	1750
Thurberogenin (ref. 4)	1781	1768
Dumortierigenin	..	1754

Recently, Barton and de Mayo[18] reported bands (in CS_2) at 1774 and 1770 cm.$^{-1}$ for oleanolic acid lactone and isoöleanolic acid lactone acetate, respectively. It is clear, therefore, that there is a shift of about 20 cm.$^{-1}$ in these 5-membered lactones in changing from chloroform to carbon disulfide and that dumortierigenin appears to be a simple, five-membered lactone. When treated with chloroform–hydrogen chloride under conditions where oleanolic acid lactone (VIIIa) is reconverted chiefly to oleanolic acid (VIIa), dumortierigenin (I) was recovered unchanged. These results indicate that dumortierigenin (I) cannot have the lactone system (with rings D/E *cis*) found in oleanolic acid lactone (VIIIa) and they also exclude the presence of a reactive cyclopropane ring.[19] In order to exclude the possibility that the lactone ring in dumortierigenin is of the type found in isoöleanolic acid lactone and is produced as an artifact during the acidic hydrolysis conditions of dumortierigenin glycoside, oleanolic acid was subjected to these same conditions and was recovered in good yield. Further comparison of the lactone rings was carried out by studying the course of the lithium aluminum hydride reductions.

Reduction of oleanolic acid lactone (VIIIa) with lithium aluminum hydride followed by careful hydrolysis of the complex smoothly yielded a triol IXa, further characterized by its diacetate IXb.

(14) D. H. R. Barton and N. J. Holness, *J. Chem. Soc.*, 78 (1952).

(15) The basis for this conformational argument is summarized by D. H. R. Barton, *ibid.*, 1027 (1953).

(15a) Kindly carried out by Miss I. E. Broadbent and Dr. W. Klyne (Postgraduate Medical School, London) according to the procedure presented by them before the Biochemical Society in London on January 16, 1954.

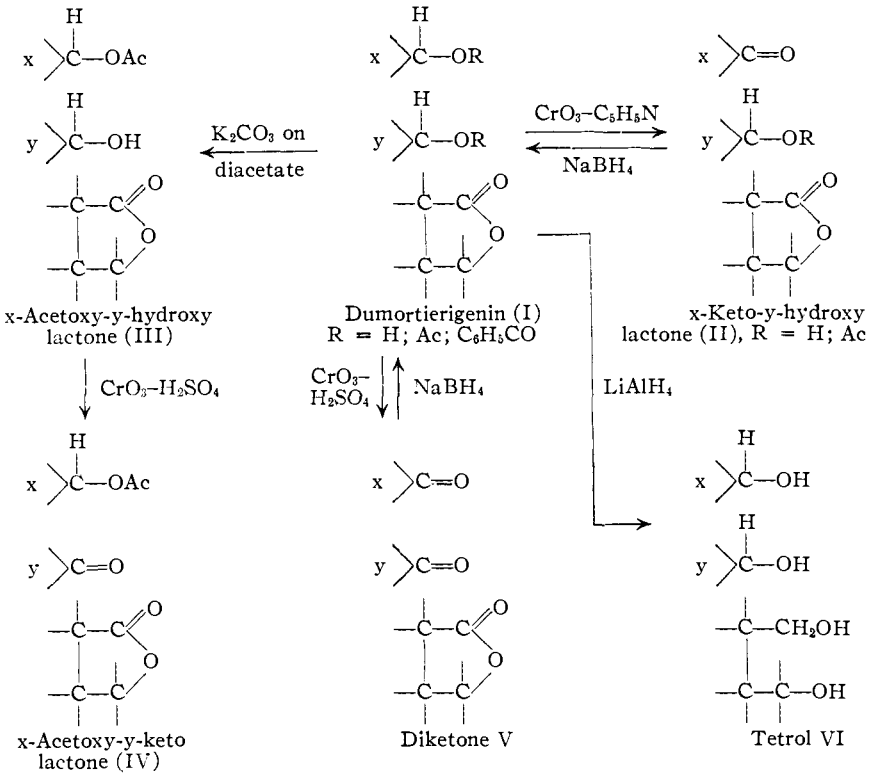
(15b) A positive reaction appears so far to be specific for 3-ketones in the triterpene series (*cf.* D. H. R. Barton and P. de Mayo, *J. Chem. Soc.*, 887 (1954)).

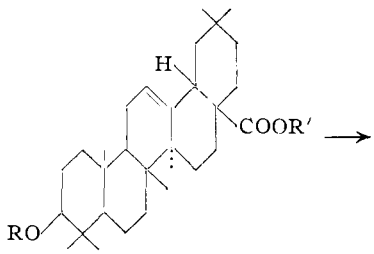
(16) A. Winterstein and G. Stein, *Z. physiol. Chem.*, **199**, 64 (1931).

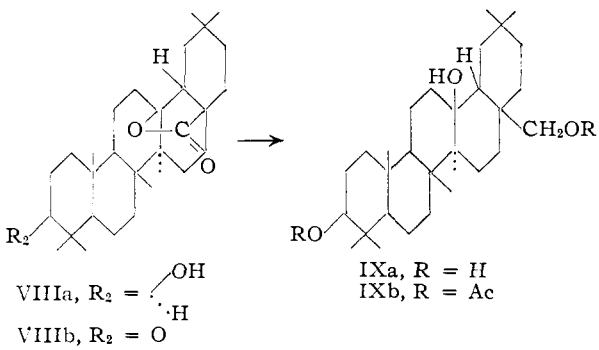
(17) We are greatly indebted to Dr. R. Norman Jones of the National Research Council, Ottawa, for measuring some of these spectra on a high precision instrument.

(18) D. H. R. Barton and P. de Mayo, *J. Chem. Soc.*, 3111 (1953).

(19) D. H. R. Barton and P. de Mayo (*ibid.*, 2178 (1953)) have shown that these conditions are sufficient to open a cyclopropane ring such as is found in the triterpene phyllanthol.







Under comparable conditions, dumortierigenin (I) furnished a tetrol VI which on acetylation gave mixtures that have not as yet been separated. However, the acetate mixture in contrast to dumortierigenin diacetate, gave a strong color with tetranitromethane suggesting that under the acetylating conditions used (acetic anhydride–pyridine) some dehydration had occurred. A study of the dehydration of these lithium aluminum hydride reduction products (IXb, VI) is contemplated in order to determine whether this can be accomplished without rearrangement of the carbon skeleton.

Only circumstantial evidence has so far been adduced in support of the presence of a double bond. Although dumortierigenin does not give any color with tetranitromethane, its diacetate does show a weak yellow color, and although no perbenzoic acid was consumed, dumortierigenin and its diacetate showed high terminal ultraviolet absorption similar to that observed with α- and β-amyrin.[20] Oleanolic acid lactone (VIIIa) and thurberogenin[4] (a lactone of the lupeol group[6]) showed no increased ultraviolet absorption in that region. As pointed out earlier, the analytical results do not differentiate between the formulations $C_{30}H_{46}O_4$ or $C_{30}H_{48}O_4$. If one accepts the presence of a double bond in dumortierigenin, the first formula would lead to the conclusion that dumortierigenin is hexacyclic while the second one requires a pentacyclic structure. Purely on the basis of analogy to the known pentacyclic triterpenes, the $C_{30}H_{46}O_4$ formula might be favored (5 carbocyclic rings plus lactone ring) but a definite decision can be reached only by correlating dumortierigenin with a known triterpene or degradation product thereof.

Acknowledgment.—We are indebted to Dr. Alberto Sandoval of the Instituto de Química de la Universidad National Autónoma de Mexico for organizing the plant collections.

Experimental[21]

Isolation of Dumortierigenin from *Lemaireocereus dumortieri*.—Plant specimens, collected either at km. 180 of the Mexico–Laredo highway near Zimapan, Hidalgo, or near the "Barranca de los Venados" on the Pachuca–Meztitlan road, have been examined and gave essentially identical results. The fresh stems (10 kg.) were cut into smaller pieces, the central woody core having been discarded, and ground in a Waring blendor in portions with a total of 25 l. of methanol. Such treatment greatly facilitated the subsequent extraction since it resulted in the coagulation of much mucilaginous material and removal of considerable quantities of water. The liquid portions were filtered and the remaining solid was then extracted thoroughly with hot methanol. The methanol extracts were combined with the original 25 l. filtrate and flash evaporated yielding 346 g. of residue in which form the material was stored (up to one year), suitable aliquots being used for the subsequent isolation of pure dumortierigenin.

In a representative example, 346 g. of alcoholic residue was dried completely by the repeated addition and distilla-

(20) T. G. Halsall, *Chemistry and Industry*, 867 (1951).

(21) All melting points were determined on the Kofler block. Unless noted otherwise, rotations and infrared spectra (*cf.* ref. 10) were measured in chloroform, and ultraviolet absorption spectra in 95% ethanol. The microanalyses were carried out by Mr. Joseph F. Alicino (Metuchen, N. J.) and by Geller Microanalytical Laboratories (Hackensack, N. J.).

tion of benzene and it was then extracted several times with 4–5 l. of ether. Evaporation of the ether solution yielded 11.5 g. of brown semi-solid which gave a negative test for alkaloids with Mayer reagent. The ether-insoluble, glycosidic portion (246 g., the loss in weight compared to the initial extract being due to removal of water by codistillation with benzene) was hydrolyzed by refluxing for 3 hours with 1800 cc. of methanol and 400 cc. of concentrated hydrochloric acid and then poured into a large volume of water. Thorough extraction with ether, followed by washing with 10% sodium hydroxide, 10% hydrochloric acid and, finally, 10% sodium chloride solution followed by drying and evaporation of the ether furnished 21 g. of crude dumortierigenin with m.p. 280–285°. Several recrystallizations from ethanol yielded the analytical sample with m.p. 292–295°, $[\alpha]^{30}D$ −18.6°, $\lambda_{max}^{CHCl_3}$ 3570 and 1754 cm.$^{-1}$, λ^{EtOH} 220 mμ, log ε 2.73, λ^{EtOH} 225 mμ, log ε 2.29, no perceptible color with tetranitromethane.

Anal. Calcd. for $C_{30}H_{46}O_4$: C, 76.55; H, 9.85; $C_{30}H_{48}O_4$: C, 76.22; H, 10.24. Found: C, 76.22; H, 9.88.

In order to determine whether lactonization of oleanolic acid (VIIa) can occur under the conditions of the acid hydrolysis, 0.487 g. of oleanolic acid (isolated from *Lemaireocereus longispinus*[5]) was refluxed for 3 hours with 60 cc. of methanol and 12 cc. of concd. hydrochloric acid; 0.372 g. of unchanged starting material was recovered.

In a quantitative perbenzoic acid titration experiment, dumortierigenin (in chloroform solution) did not consume any peracid in 48 hours and was recovered unchanged after isolating the remaining material. By comparison, methyl oleanolate acetate (VIIb) consumed 27% of the calculated amount of perbenzoic acid.[22]

Dumortierigenin diacetate, prepared by the acetic anhydride–pyridine method, crystallized from methanol as needles with a variable melting range. The needles were desolvated by codistillation with benzene to give the diacetate m.p. 318–321°, $[\alpha]^{26}D$ −10°, $\lambda_{max}^{CHCl_3}$ 5.66, 5.76 (inflection), 5.80 μ and broad type B[11] band between 7.95–8.3 μ, λ^{EtOH} 220 mμ, log ε 2.89, λ^{EtOH} 225 mμ, log ε 2.58. The diacetate gave a faint yellow color with tetranitromethane.

Anal. Calcd. for $C_{34}H_{50}O_6$: C, 73.61; H, 9.09; $C_{34}H_{52}O_6$: C, 73.34; H, 9.41; acetyl, 15.47. Found: C, 73.55; H, 9.18; acetyl, 15.98.

Dumortierigenin dibenzoate (benzoyl chloride–pyridine, 8 hours at room temperature) was purified by chromatography on alumina (deactivated with 2% of a 10% aqueous acetic acid solution), elution with benzene and recrystallization from methanol–chloroform; m.p. 288–291°, $[\alpha]^{30}D$ +4.4°, $\lambda_{max}^{CHCl_3}$ 3.66, 5.88 and 7.88 μ.

Anal. Calcd. for $C_{44}H_{54}O_6$: C, 77.84; H, 8.02; $C_{44}H_{56}O_6$: C, 77.61; H, 8.29. Found: C, 77.45; H, 7.90.

Oleanolic Acid Lactone (VIIIa).—Oleanolic acid (VIIa) was treated with hydrogen chloride–chloroform in the prescribed manner[14]; recrystallization of the neutral fraction from methanol–chloroform yielded 15% of the lactone with m.p. 280–283°, $[\alpha]^{30}D$ +8.6°, $\lambda_{max}^{CHCl_3}$ 1754 cm.$^{-1}$, $\lambda_{max}^{CS_2}$ 1775 cm.$^{-1}$; reported[14] m.p. 278°, $[\alpha]D$ +11°.

18-Isoöleanolic acid lactone acetate was obtained in high yield by treatment of oleanolic acid (VIIa) with glacial acetic acid and concd. hydrochloric acid[16] and recrystallized from methanol–chloroform; m.p. 347–350° dec., $\lambda_{max}^{CHCl_3}$ 1750 and 1736 cm.$^{-1}$; reported[14] m.p. 340–345° dec. and 350–353° dec.

Stability of Lactones to Chloroform–Hydrogen Chloride.—Through a sample (0.166 g.) of the lactone in 40 cc. of chloroform was passed hydrogen chloride gas for 2 hours and the product was separated into acidic and neutral material. In agreement with Barton and Holness,[14] oleanolic acid furnished about 80% of oleanolic acid; 18-isoöleanolic acid lactone acetate and dumortierigenin were recovered unchanged under those conditions.

3-Keto Oleanolic Acid Lactone (VIIIb).—A solution of 0.25 g. of the lactone VIIIa in 5 cc. of anhydrous pyridine was added at 0° to a previously prepared mixture of 0.3 g. of chromium trioxide in 8 cc. of pyridine.[12] After standing at room temperature for 7 hours, water was added, the product was extracted with ether and washed well with dilute acid, sodium carbonate, water, dried and evaporated. Recrystallization from methanol–chloroform gave 0.17 g. of the keto lactone as needles with m.p. 261–264°, $[\alpha]^{25}D$ +31°, $\lambda_{max}^{CHCl_3}$ 5.68 and 5.86 μ.

Anal. Calcd. for $C_{30}H_{46}O_3$: C, 79.25; H, 10.20. Found: C, 78.75; H, 10.45.

18β-Oleanane-3β,13β,28-triol (IXa).—To a stirred suspension of 2 g. of lithium aluminum hydride in 70 cc. of anhydrous ether was added dropwise a solution of 0.22 g. of oleanolic acid lactone (VIIIa) in 30 cc. of tetrahydrofuran and the mixture was refluxed for 3 hours. The excess reagent was destroyed with ethyl acetate and a saturated aqueous solution of sodium sulfate was added dropwise until the inorganic salts coagulated at which point anhydrous sodium sulfate was added and the mixture allowed to stand for 15 minutes. The supernatant ethereal solution was decanted and the residue was washed repeatedly with fresh solvent. The combined ether solutions were washed with water, dried, evaporated and the crystalline residue was recrystallized from methanol to give 0.17 g. of the triol IXa with m.p. 253–257°, $[\alpha]^{20}D$ +14.1 (pyridine), no carbonyl absorption in the infrared, negative color with tetranitromethane.

Anal. Calcd. for $C_{30}H_{52}O_3$: C, 78.20; H, 11.38. Found: C, 78.01; H, 11.48.

Acetylation of 0.14 g. of the triol with acetic anhydride–pyridine at room temperature (9 hours) followed by recrystallization from methanol–chloroform led to 0.12 g. of the **diacetate IXb** with m.p. 244–247°, $[\alpha]^{25}D$ +24°, $\lambda_{max}^{CHCl_3}$ 5.82 and 8.00 μ (type A band[11]), negative color with tetranitromethane.

Anal. Calcd. for $C_{34}H_{56}O_5$: C, 74.95; H, 10.36; acetyl, 15.72. Found: C, 74.78; H, 10.45; acetyl, 16.10.

Reduction of Dumortierigenin with Lithium Aluminum Hydride.—The reduction of dumortierigenin (I) (0.2 g.) was carried out exactly as described above for oleanolic acid lactone and yielded 0.09 g. of colorless needles of the tetrol VI with m.p. 287–290°, $[\alpha]^{23}D$ −3.0 (pyridine), no color with tetranitromethane.

Anal. Calcd. for $C_{30}H_{50}O_4$: C, 75.90; H, 10.62. $C_{30}H_{52}O_4$: C, 75.58; H, 10.99. Found: C, 75.84; H, 10.57.

x-Keto-y-hydroxydumortierigenin (II).—Dumortierigenin (I) (123 mg.) was oxidized with chromium trioxide–pyridine exactly as described for VIII; recrystallization from methanol–chloroform gave long, colorless needles (75 mg.) with m.p. 294–296°, $[\alpha]^{26}D$ +18°, $\lambda_{max}^{CHCl_3}$ 2.80, 5.68 and 5.90 μ.

Anal. Calcd. for $C_{30}H_{44}O_4$: C, 76.88; H, 9.46. $C_{30}H_{46}O_4$: C, 76.55; H, 9.85. Found: C, 76.97; H, 9.33.

The **oxime** was prepared by the pyridine–ethanol procedure and recrystallized from methanol; m.p. 262–266°.

Anal. Calcd. for $C_{30}H_{45-47}NO_4$: N, 2.88, 2.90. Found: N, 3.35.

The **x-keto-y-acetoxylactone** (II) was obtained in *ca.* 80% yield, m.p. 239–241°, $[\alpha]^{26}D$ +7°, $\lambda_{max}^{CHCl_3}$ 5.63, 5.78, 5.90 and type B band[11] in the 8 μ region.

Anal. Calcd. for $C_{32}H_{46}O_5$: C, 75.26; H, 9.08; acetyl, 8.44. $C_{32}H_{48}O_5$: C, 74.96; H, 9.44. Found: C, 74.75; H, 9.26; acetyl, 8.86.

Reconversion to Dumortierigenin.—A solution of 197 mg. of the ketohydroxy lactone II in 20 cc. of absolute ethanol was kept at room temperature for one hour with 21 mg. of sodium borohydride. The excess reagent was destroyed by the addition of four drops of acetic acid and much water was added. The product was extracted with chloroform, washed with water until neutral, dried and evaporated yielding a crystalline residue (m.p. 264–270°) which was directly acetylated in the usual manner. Recrystallization from methanol–chloroform gave 88 mg. of dumortierigenin diacetate with m.p. 316–319°, undepressed upon admixture with material derived from the natural product, $[\alpha]^{26}D$ −8°, infrared spectrum completely identical with that of the authentic sample.

Dumortierigenin Dione (V).—Using a slight excess of the standard chromium trioxide–sulfuric acid mixture,[13] 275 mg. of dumortierigenin in 15 cc. of acetone was oxidized for 15 minutes at 5–10°. The mixture was worked up in the usual manner and after recrystallization from methanol yielded 96 mg. of colorless, elongated prisms of the diketone

(22) Approximately 17 days are required before one equivalent is taken up (ref. 14). On the other hand, α-amyrin does not form appreciable amounts of oxide with perbenzoic acid (L. Ruzicka, H. Silbermann and M. Furter, *Helv. Chim. Acta*, **15**, 482 (1932)).

V with m.p. 312–316°, $[\alpha]^{25}D$ +12°, $\lambda_{max}^{CHCl_3}$ 5.59 μ (note similar shift in the infrared lactone band of IV) and broad band at 5.88–5.92 μ; no color with alcoholic ferric chloride. Chromatography of the mother liquors furnished 41 mg. of the keto alcohol II, which was identified as its acetate.

Anal. Calcd. for $C_{30}H_{42}O_4$: C, 77.21; H, 9.07. $C_{30}H_{44}O_4$: C, 76.88; H, 9.46. Found: C, 77.00; H, 9.21.

A portion (68 mg.) of the dione V was reduced in ethanol solution with 11 mg. of sodium borohydride in the above indicated manner. Acetylation of the crude reduction product gave 46 mg. of dumortierigenin diacetate with m.p. 315–318°, $[\alpha]^{25}D$ −11°; identity was confirmed by infrared analysis.

The dioxime was prepared in the standard manner (ethanol–pyridine, hours refluxing) and was recrystallized from methanol; m.p. 274–278°, no ketone carbonyl absorption in the infrared.

Anal. Calcd. for $C_{30}H_{44-46}N_2O_4$: N, 5.62, 5.64. Found: N, 5.19.

Dumortierigenin Monoacetate (III).—The partial hydrolysis[23] was performed by refluxing for 40 minutes 162 mg. of dumortierigenin diacetate with 300 mg. of potassium carbonate in 70 cc. of methanol, 6 cc. of dioxane and 6 cc. of water. The crude material was chromatographed on 10 g. of alumina deactivated with 2% of a 10% acetic acid solution, the bulk of the substance being eluted with 1:1 ether–chloroform. Recrystallization from methanol yielded 60 mg. of colorless needles with m.p. 307–310°, $[\alpha]^{23}D$ −9.0°, $\lambda_{max}^{CHCl_3}$ 2.78, 5.68, 5.81 and 8.0 μ (type A band[11] in contrast to type B band of starting material).

Anal. Calcd. for $C_{32}H_{48}O_5$: C, 74.96; H, 9.44; acetyl, 8.37. $C_{32}H_{50}O_5$: C, 74.67; H, 9.79. Found: C, 74.89; H, 9.60; acetyl, 7.36.

x-Acetoxy-y-ketodumortierigenin (IV).—In an attempt to oxidize 60 mg. of the monoacetate III with chromium trioxide–pyridine by the above described procedure, 39 mg. of the pure starting material was recovered. The oxidation of 55 mg. of the monoacetate III was, therefore, carried out by the use of chromium trioxide–sulfuric acid in essentially the same manner indicated above for the diketone except that the reaction time was extended to 30 minutes at 10°. The crude product was purified by chromatography on deactivated alumina and elution with benzene–ether (9:1); recrystallization from methanol–chloroform furnished 34 mg. of long platelets with m.p. 312–316°, $[\alpha]^{25}D$ −6.8°, $\lambda_{max}^{CHCl_3}$ 5.59 (similar shift in V), 5.80 (shoulder), 5.86 (note contrasting good resolution in this region in the isomer II) and 8.02 μ (type A band).

Anal. Calcd. for $C_{32}H_{46}O_5$: C, 75.26; H, 9.08. $C_{32}H_{48}O_5$: C, 74.96; H, 9.44. Found: C, 74.79; H, 9.55.

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(23) In a model experiment, 290 mg. of methyl oleanolate acetate (VIIb) was refluxed for 40 minutes with 80 cc. of methanol, 12 cc. of dioxane, 8 cc. of water and 400 mg. of potassium carbonate. Chromatography of the product followed by recrystallization gave 157 mg. of recovered starting material with m.p. 215–217°, undepressed when mixed with an authentic specimen.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

Condensations by Sodium. XXXV. The Metalation and Cleavage of Ethers, Principally of Alkyl Phenyl Ethers,[1] by Amylsodium and Sodium

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The addition of amyl chloride to sodium in heptane which contains anisole will produce *o*-sodioanisole, sodium phenoxide or *o*-amylanisole, according to the temperature. At 35° the yield of *o*-sodioanisole is 80%. Sodium phenoxide appears to result from pyrolysis (at 50–80°) of *o*-sodioanisole. Other alkyl phenyl ethers undergo metalation and cleavage in a similar manner and the ease of cleavage is dependent upon the availability and reactivity of hydrogens in the β-position of the alkyl group. Metalation in the cresyl methyl ethers also is limited to the vicinity of the oxygen atom. Cleavage of 2,4,6-triisopropylphenyl isopropyl ether and of dialkyl ethers by amylsodium shows that metalation is not always a prerequisite to cleavage. Di-*n*-butyl ether has enough resistance to amylsodium to be useful as a medium for some reactions with that reagent. Anisole is attacked by sodium alone to give *o*-sodioanisole and sodium phenoxide. All results are interpreted on the basis that amylsodium is a reactive salt with bifunctional character and with initiation of the reaction at the cation but with the ion-pair probably dissociating to radicals, as the active intermediates.

Introduction

The previous work in this Laboratory with amylsodium has been concerned primarily with the metalation of hydrocarbons, reactions of the Wurtz type and polymerization. The present paper on the reaction with ethers began with the intention of studying cleavage. With phenyl alkyl ethers, however, metalation seemed to be the precursor of cleavage and considerable attention has been paid to that phase of the process in the first section. The larger part of the work has been done on anisole. In the second part of this paper, the action on various dialkyl ethers is described and di-*n*-butyl ether is shown to be moderately resistant to amylsodium. In the third section, the action of sodium alone on anisole is reported because sodium may be formed by the decomposition of amylsodium during the reaction. A few side reactions in the metalation of anisole are then mentioned. An explanation, based on radicals instead of ions is favored for these processes.

Amylsodium and Alkyl Phenyl Ethers.—This study began with the supposition that the formation of amylsodium in the presence of anisole in heptane might cause immediate cleavage of that ether to sodium phenoxide, and in order to locate suitable conditions a series of experiments at different temperatures in the absence and in the presence of potassium isopropoxide was first carried out, whereupon three products instead of one were revealed. At 35°, metalation gave *o*-sodioanisole and the maximum yield of *o*-anisic acid by carbonation thereof was 80%, referred to amyl chloride as per equations 1 and 2. Potassium isopropoxide usually lowered this yield a little, but increased the amounts of disproportionations.

$$C_5H_{11}Cl + 2Na \longrightarrow NaCl + C_5H_{11}Na \quad (1)$$

$$C_5H_{11}Na + C_6H_5OCH_3 \longrightarrow o\text{-}NaC_6H_4OCH_3 + C_5H_{12} \quad (2)$$

Between 50 and 80° the sodium phenoxide origi-

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