Attempts to hydrolyze the trimethylsilyl ether in a pyridine–ethanol–water mixture and in dimethylformamide were unsuccessful.

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Synthesis of Some Derivatives of Ursolic Acid[1]

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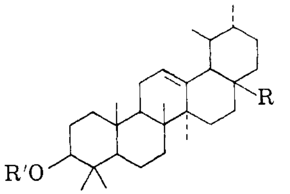
Mention of several new derivatives of ursolic acid (I. R′ = H, R = COOH) in a forthcoming publication,[3] which deals with the far ultraviolet absorption spectra of triterpenoids and steroids, makes a description of the synthesis and properties of these compounds timely.

Ursolic acid was isolated from bearberry leaves (*Arctostaphylos uva-ursi*) by the method of Bilham *et al.*,[4] with some modifications. Acetyl methyl ursolate (I. R′ = CH_3CO—, R= $COOCH_3$) was smoothly converted in 79% yield to the saturated, acid labile ketene[5a,b] II (R = $COOCH_3$) by means of peroxytrifluoroacetic acid in the presence of sodium carbonate.[6] Substitution of triethylammonium trifluoroacetate[7] for the carbonate buffer afforded a product different from the desired dihydroketone II (R = $COOCH_3$). This reaction product[8] was only partially characterized and the reaction has not been investigated further.

Conversion of the dihydroketone into the Δ^{12}-enol diacetate III (R = $COOCH_3$) (66% yield) was brought about by the well known sodium acetate–acetic anhydride method.[9] On the other hand, the acid catalyzed reaction of the same unstable dihydroketone with isopropenyl acetate[10] afforded the isomeric Δ^{11}-enol diacetate IV in 83% yield, probably without C-13 epimerization (see ref. 5b for a pertinent discussion of the α-amyrin analogues).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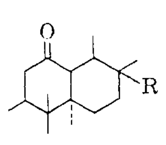
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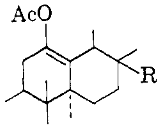
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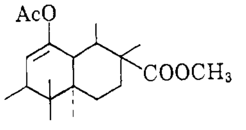
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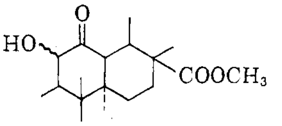
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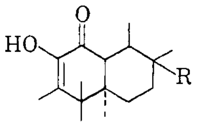
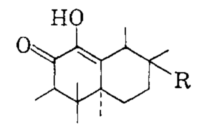

VIa


VIb

Proton magnetic resonance spectra of the two enol diacetates, taken at 60.0 mc. in deuterated chloroform, were provided by Dr. Robert L. Lundin. That for IV showed a broad singlet having a τ value of 4.58 which is typical of olefinic protons, whereas III showed no such peak.

Oxidation of the highly hindered 12,13-double bond of III (R = $COOCH_3$) with peroxytrifluoroacetic acid in the presence of disodium hydrogen phosphate[6] was not successful. Under similar conditions the Δ^{11}-enol diacetate IV could be readily oxidized to the α-hydroxyketone V. That V was indeed a ketol was established from the infrared spectrum and by oxidation with bismuth oxide in acetic acid to an α-diketone. A study of the ultraviolet and infrared spectra as well as

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(2) Present address: Western Regional Research Laboratory, U. S. Department of Agriculture, Albany 10, Calif.

(3) R. A. Micheli and T. H. Applewhite, to be published.

(4) P. Bilham, G. A. R. Kon, and W. C. J. Ross, *J. Chem. Soc.*, 35 (1942).

(5) (a) J. L. Simonsen and W. C. J. Ross, *The Terpenes*, Cambridge University Press, London, 1957; see Vol. V, p. 128. The similarity of melting point and optical rotation values make it difficult to distinguish the C-13 epimeric ketones II (R = $COOCH_3$). There seems little doubt that the product from this reaction corresponds to the known unstable ketone since α-amyrin acetate (I. R = CH_3, R′ = CH_3CO—) also affords the analogous acid labile ketone with peroxytrifluoroacetic acid–sodium carbonate; (b) I. A. Kaye, M. Fieser, and L. F. Fieser, *J. Am. Chem. Soc.*, **77**, 5936 (1955), discuss the epimeric α-amyrin compounds.

(6) W. D. Emmons and A. S. Pagano, *J. Am. Chem. Soc.*, **77**, 89 (1955).

(7) W. D. Emmons, A. S. Pagano, and J. P. Freeman, *J. Am. Chem. Soc.*, **76**, 3472 (1954).

(8) It has been reported that simple olefins yield hydroxytrifluoroacetates and occasionally ditrifluoroacetates.[7] The crude reaction product from acetyl methyl ursolate gave a negative tetranitromethane color test after 1 or 48 hr. at room temperature; infrared (CS_2), no hydroxyl, 5.56 (CF_3COO—), 5.71 (broad), and 8.04 μ. Hydrolysis was accomplished with potassium bicarbonate in methanol [A. Lardon and T. Reichstein, *Helv. Chim. Acta*, **37**, 388 (1954)]; infrared (CS_2), 2.86 (hydroxyl), 5.72 (broad), and 8.05 μ. In some preliminary studies on Δ^5- and Δ^7-sterols, however, the products appeared to be hydroxytrifluoroacetates; typical infrared (CS_2), 2.9–3.0, 5.60–5.65, 5.78–5.82, and 8.0–8.1 μ. The hydroxyls are readily acetylated at room temperature with acetic anhydride and pyridine.

(9) (a) L. Ruzicka and O. Jeger, *Helv. Chim. Acta*, **24**, 1178 (1941); (b) L. Ruzicka, O. Jeger, J. Redel, and E. Volli, *Helv. Chim. Acta*, **28**, 199 (1945).

(10) H. J. Hagemeyer and D. C. Hull, *Ind. Eng. Chem.*, **41**, 2920 (1949).

positive ferric chloride and tetranitromethane tests proved that the latter exists in one of the monoenol forms VIa or VIb (R = $COOCH_3$). Ruzicka *et al.*[9b] reported the preparation of a similar derivative in the α-amyrin series (I. R = CH_3, R′ = H) by chromic acid oxidation of the corresponding dihydroketone II (R = CH_3) or the Δ^{12}-enol diacetate III (R = CH_3). Although the physical properties such as molecular rotation and ultraviolet spectra are similar, the relationship of the monoenol reported here to the products from chromic acid oxidation[9b] has not been firmly established.

EXPERIMENTAL[11]

Isolation of ursolic acid (I. R = COOH, R′ = H). Four kg. of bearberry leaves[12] was extracted with a methanol solution (12 l.) of potassium hydroxide (320 g.) at room temperature for 24 hr. with occasional stirring. The filtrate from the above was acidified (hydrochloric acid), concentrated to 3 l., and the pale green precipitate was collected and dissolved in 5 l. of chloroform–ether (2:1). Treatment of this solution with an equal volume of 10% aqueous sodium hydroxide deposited the crude sodium ursolate. *Ursolic acid* (25 g.) was obtained after acidification and three crystallizations from ethanol as colorless needles, m.p. 288–289.5°.[13,14] *Acetyl methyl ursolate* was prepared in the usual manner with acetic anhydride–pyridine and diazomethane; m.p. 246–247.5°,[15] $[\alpha]^{20}_D$ + 62.5° (*c*, 1.12).

Methyl ursan-3β-ol-12-one-28-oate acetate (II. R = $COOCH_3$). To 13.5 g. of acetyl methyl ursolate in 200 ml. of dichloromethane and a suspension of 65 g. of anhydrous sodium carbonate was added a solution of peroxytrifluoroacetic acid (from 5 ml. of 90% hydrogen peroxide and 28 ml. of trifluoroacetic anhydride[16] in dichloromethane) with stirring over 0.75 hr. The mixture then was refluxed 0.5 hr., filtered, and the product crystallized from methanol as white needles; yield 11.0 g. (79%). A sample was recrystallized twice from ethanol to constant rotation, $[\alpha]^{30}_D$ +28.6° (*c*, 1.94); infrared, 5.78, 5.91, and 8.07 μ. The material melted with sintering 245–251° (open capillary) and 259–262° (evac. capillary).[5a]

Anal. Calcd. for $C_{33}H_{52}O_5$: C, 74.96; H, 9.91. Found: C, 74.57; H, 9.92.

Methyl Δ^{12}-ursene-3β,12-diol-28-oate diacetate (III. R = $COOCH_3$). Five grams of II (R = $COOCH_3$) and 2.5 g. of freshly fused sodium acetate in 200 ml. of acetic anhydride were refluxed for 48 hr., diluted with ice water and extracted with ether. The residue, after evaporation of the solvent, crystallized from methanol as straw colored needles; yield 3.5 g. (66%). One recrystallization from aqueous methanol afforded the analytical sample as colorless needles; m.p. 175–179° (with sintering), $[\alpha]^{25}_D$ +50.6° (*c.*, 1.01), infrared 5.71, 5.78, 5.97 (weak), and 8.07 μ, and a yellow color with tetranitromethane.

Anal. Calcd. for $C_{35}H_{54}O_6$: C, 73.64; H, 9.54. Found: C, 73.66; H, 9.61.

Methyl Δ^{11}-ursene-3β,12-diol-28-oate diacetate (IV). A solution of 6.0 g. of II (R = $COOCH_3$) and 0.9 g. of *p*-toluene sulfonic acid in 120 ml. of isopropenyl acetate was refluxed and slowly distilled for 24 hr. and then concentrated to 50 ml. Ether and water were added and the ethereal extract was washed, dried, and evaporated *in vacuo* on the steam bath. The residue crystallized from methanol as pale tan needles and weighed 5.3 g. (83%); m.p. 219–221°. A sample was filtered through a plug of acid-washed alumina (Merck) and crystallized once from methanol (colorless needles), m.p. 220.5–221.5° (219–220° open capillary), $[\alpha]^{27}_D$ −48.6° (*c*, 1.37), infrared 5.71, 5.82, 6.00 (weak), and 8.08 μ, and a yellow color with tetranitromethane.

Anal. Calcd. for $C_{35}H_{54}O_6$: C, 73.64; H, 9.54. Found: C, 73.42; H, 9.69.

Methyl ursan-3β,11ξ,-diol-12-one-28-oate 3-acetate (V). A solution of peroxytrifluoroacetic acid (2 ml. of 90% hydrogen peroxide, 11 ml. of trifluoroacetic anhydride) in 10 ml. of dichloromethane was added over a 15-min. period to a mixture of anhydrous disodium hydrogen phosphate (25 g.), dichloromethane (50 ml.) and Δ^{11}-enol diacetate IV (0.90 g.). The mixture was refluxed for 0.5 hr. and then filtered. The filtrate was washed, dried, and evaporated and the residue crystallized from aqueous methanol. The yield was 0.38 g. (43%) of colorless crystals which gave no color with tetranitromethane but did give a positive bismuth oxide test (black precipitate after a few minutes refluxing in acetic acid). The analytical sample, which was obtained as stout crystals from a small amount of methanol, m.p. 237–242° (with sintering), $[\alpha]^{30}_D$ +1.3° (*c*, 5.04) and infrared 2.91, 5.77, 5.91, and 8.07 μ.

Anal. Calcd. for $C_{33}H_{52}O_6$: C, 72.75; H, 9.62. Found: C, 72.57; H, 9.65.

Monoenol of methyl 3β-acetoxy-11,12-diketo-28-ursanic acid (VIa *or* VIb. R = $COOCH_3$). Bismuth oxide (500 mg.) was added to a hot solution of V (380 mg.) in glacial acetic acid (15 ml.). After refluxing for 0.25 hr., the mixture was partitioned between dichloromethane and water. The organic phase was worked up in the usual manner, and the product was crystallized from aqueous methanol; yield, 270 mg. (71%) of pale yellow needles which melted by 210° with sintering. The material was filtered through a plug of acid-washed alumina and recrystallized twice from a small volume of methanol (stout, colorless crystals); m.p. 229–231.5°, $[\alpha]^{30}_D$ + 134.4° (*c*, 0.95), $\lambda^{\text{Ethanol}}_{\text{max}}$ 290 mμ (ε 9850) and infrared 2.93, 5.76, 5.97, 6.09, and 8.06 μ. The product gave a typical enol test (blue-grey color) with ferric chloride in methanol and a yellow color with tetranitromethane.

Anal. Calcd. for $C_{33}H_{50}O_6$: C, 73.03; H, 9.29. Found: C, 73.21; H, 9.44.

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(11) Melting points were taken in evacuated capillaries unless otherwise stated. Optical rotations were run in chloroform and infrared spectra were taken in carbon disulfide. Analyses by S. M. Nagy and associates.

(12) This material, previously extracted with 50% alcohol, was generously donated by the S. B. Penick Co.

(13) *Elsevier's Encyclopedia of Organic Chemistry*, Elsevier Publishing Co., Amsterdam, 1940–1952, Vol. 14 and 14S; pp. 565 and 1092S.

(14) Ref. 5, Vol. V, p. 134.

(15) Ref. 13, p. 566.

(16) Aged reagent gave poorer results.

1-Formyl-2-methylisoquinolinium Iodide

EDWARD J. POZIOMEK

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It was observed recently that potentiometric titration of 2-formyl-1-methylpyridinium iodide (I) with aqueous alkali gave a smooth titration curve corresponding to that of a weak acid of