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] $[\alpha]_D^{20}$ + 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, $[\alpha]_D^{30}$ +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), $[\alpha]_D^{25}$ +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), $[\alpha]_D^{27}$ −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), $[\alpha]_D^{30}$ +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°, $[\alpha]_D^{30}$ + 134.4° (*c*, 0.95), $\lambda_{max}^{Ethanol}$ 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

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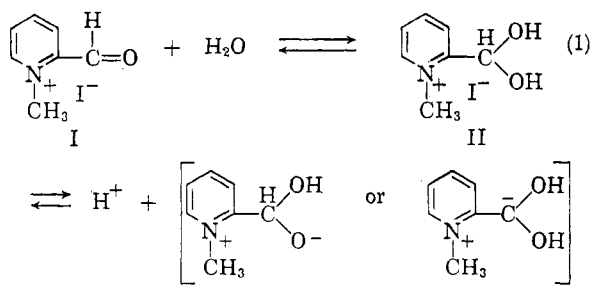
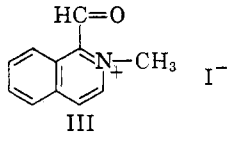
It was observed recently that potentiometric titration of 2-formyl-1-methylpyridinium iodide (I) with aqueous alkali gave a smooth titration curve corresponding to that of a weak acid of

pK_a 9.8–10.0.[1] It was concluded that the titration was due to a neutralization equilibrium (Equation 1) and not a decomposition of the aldehydic function. The ability of I to form a stable *gem*-



(1)

glycol (II) as well as the acid character of II were attributed to the strong electron-withdrawing character of the pyridinium ring. Subsequently, it was found that 1-formyl-2-methylisoquinolinium iodide (III) (in which it would be expected that the



III

π-electron density of the ring at the position of the carbonyl group is markedly lower than in the 2-position of I)[2] was decomposed rapidly during a titration with 0.1*N* alkali at 3–5°. Back titration indicated the presence of a conjugate base of a weak acid of pK_a 4.0. It is reasonable to assume that either the Cannizzaro reaction or cleavage (loss of —CHO as formic acid) occurred. In any case, the discovery that III is attacked by dilute alkali at such a rapid rate is interesting and may stimulate a more thorough investigation.

EXPERIMENTAL

1-Formyl-2-methylisoquinolinium iodide. To 0.97 g. (6.2×10^{-3} mole) of 1-isoquinoline carboxaldehyde (m.p. 53°; reported[3] 55–55.5°) dissolved in acetone and contained in a carbonated beverage bottle was added 8.8 g. (0.062 mole) of methyl iodide. The bottle was capped and heated in an oven at 60° for six days. The reaction mixture was cooled and filtered to give 0.48 g. (26%) of a red crystalline solid (needles) m.p. 203–205° dec. An infrared absorption spectrum was determined in potassium bromide and the curve exhibited a strong absorption band at 5.86 μ in carbonyl stretching region. Ultraviolet absorption maxima in water, 2.5×10^{-5} *M*, mμ (log ϵ): *p*H 6.5, 341(3.65), 282(3.41); *p*H 12.0, 334 (3.65), 272(3.63).

Anal. Calcd. for $C_{11}H_{10}INO$: C, 44.1; H, 3.4; O, 5.3. Found: C, 43.5; H, 3.4; O, 5.6.

Potentiometric titration of 1-formyl-2-methylisoquinolinium iodide (III). Potentiometric titration of III (100 mg. in 10 ml. distilled water) with standard 0.1*N* sodium hydroxide, either at 3–5° or room temperature, gave curves which indicated a pK_a value between 9 and 10 and a neutralization equivalent of 299 ± 5 (calcd. 299). Immediate back titration with 0.1*N* hydrochloric acid indicated a function of pK_a 4.0 and a neutralization equivalent of 600. This neutralization equivalent corresponds to one mole of acid from two moles of carboxaldehyde as would be expected from a Cannizzaro reaction. A Beckmann Model H2 *p*H meter was used in this work.

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(1) G. M. Steinberg, E. J. Poziomek, and B. E. Hackley, Jr., *J. Org. Chem.*, **26**, 368 (1961).

(2) This is based on a qualitative correlation of electron densities of various heterocyclic rings. H. C. Longuet-Higgins and C. A. Coulson, *Trans. Faraday Soc.*, **43**, 87 (1947).

(3) R. S. Barrows and H. G. Lindwall, *J. Am. Chem. Soc.*, **64**, 2430 (1942).

Cortical Steroids as Acetal-Forming Compounds with Aldehydes and Ketones

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The recent communication by Tanabe and Bigley[1] on the 17α,21-isopropylenedioxy steroids has prompted us to report the results of our independent work on the cyclic acetals of steroids with a dihydroxy acetone side chain.

We have prepared several 17α,21-cyclic acetals (Table I) by an acid catalyzed interchange reaction[2] between cortical steroids and lower alkyl acetals of aliphatic, cycloaliphatic, or arylaliphatic aldehydes or ketones.[3] By our procedure (see Experimental) yields were often as high as 90%, particularly in the cases of the cyclopentanone and benzaldehyde derivatives.[4]

When a β-oriented hydroxyl group is present at C-11, this also undergoes the interchange reaction; in this instance, in addition to the expected acetal I,

(1) M. Tanabe and B. Bigley, *J. Am. Chem. Soc.* **83**, 756 (1961).

(2) Nonsteroidal acetals have already been prepared in a similar way. *Cf.* M. Delépine, *Bull. soc. chim. France* (3) **25**, 574 (1901); *Ann. Chim.* (7) **23**, 378 (1901).

(3) Steroids with dihydroxyacetone side chain do not react directly with aldehydes and ketones, or they do so in a quite different manner as in the case of formaldehyde. See R. E. Beyler, R. M. Moriarty, F. Hoffman, and L. H. Sarett, *J. Am. Chem. Soc.* **80**, 1517 (1958).

(4) Benzaldehyde, as well as many other carbonylic compounds, should give two epimeric acetals due to formation of a new asymmetric carbon atom. Up to now, however, we have been able to obtain only one derivative.