1:1 Molecular Complex of 5,16-Pregnadiene-3β,20α- and 3β,-20β-diol Diacetates (IIa:IIb).—Material from the previous experiment, m.p. 177–179°, was acetylated with acetic anhydride in pyridine to give a product having m.p. 140–141°. Recrystallization from methanol afforded leaflets with m.p. 143–143.5°, $[\alpha]_D$ −57°; for n.m.r. see Table II. This product is the 1:1 mixture of the 20α and 20β epimers. (The reported values for 5,16-pregnadiene-3β,20α-diol diacetate are as follow: lit.[2a] m.p. 137–138°, $[\alpha]_D$ −57°; lit.[2b] m.p. 138–140°, $[\alpha]_D$ −60°.) The M_D increment for conversion of the mixed 20-ols to the acetate complex[10] is as follows: calculated from our data, Δ = +42°; from the data of Ercoli,[2a] Δ = +33°; from the data of Shapiro[2b], Δ = +30°.

Anal. Calcd. for $C_{25}H_{36}O_4$: C, 74.96; H, 9.06. Found: C, 75.22; H, 8.98.

Separation of 5,16-Pregnadiene-3β,20α- and 3β,20β-diols (Ia and Ib).—A pure sample of the 1:1 diacetate mixture, m.p. 143–143.5°, $[\alpha]_D$ −57°, was hydrolyzed with methanolic potassium hydroxide in approximately quantitative yield and the crude product, m.p. 180–182°, $[\alpha]_D$ −72°, was placed on an alumina column (Woelm, neutral, activity III, 50 to 1 ratio) and subjected to gradient elution[5] by gradually enriching the benzene eluant with a solution of 6% ethyl alcohol in benzene. The products were eluted as a plateau by the 0.6 to 0.8% ethyl alcohol–benzene eluants. The early fractions were pooled and evaporated; the product was crystallized from methanol in the form of leaflets, m.p. 186.5–188.5, $[\alpha]_D$ −86°. The yield of pure material was 13%.

Anal. Calcd. for $C_{21}H_{32}O_2$: C, 79.70; H, 10.19. Found: C, 79.68; H, 9.84.

From the n.m.r. spectrum (Table II) and the change in rotation upon acetylation, this compound was assigned the 5,16-pregnadiene-3β,20α-diol structure (Ia).

The 3β,20α-diacetate IIa was prepared from the diol by treatment with acetic anhydride–pyridine. An analytical sample was crystallized from ethyl alcohol, m.p. 139.5–140°, $[\alpha]_D$ −92°.

Anal. Calcd. for $C_{25}H_{36}O_4$: C, 74.96; H, 9.06. Found: C, 75.25; H, 9.06.

From the later fractions of the broad band of material eluted from the chromatographic column, there was obtained in about 20% yield material having identical melting point and infrared spectral properties as an authentic sample of the 3β,20β-diol, prepared by aluminum isopropoxide reduction of 16-dehydropregnenolone acetate followed by alkaline hydrolysis as described by Marker.[3] A sample was crystallized from ethyl acetate–methylcyclohexane, m.p. 169.5–171.5°, $[\alpha]_D$ −66.5° (lit.[3] m.p. 169–171°).

The 3β,20β-diacetate IIb prepared by acetic anhydride–pyridine treatment of the diol, crystallized as leaflets from dilute methanol, m.p. 123.5–125°, $[\alpha]_D$ −29° (lit.[3] m.p. 121°).

20α- and 20β-Hydroxy-5,16-pregnadien-3-one Ethylene Ketal (IIIa and IIIb).—A slurry of 65 g. of 5,16-pregnadiene-3,20-dione 3-ethylene ketal[6] in 7.5 l. of dry ether and 500 ml. of tetrahydrofuran together with 70 g. of lithium aluminum hydride was refluxed for 6 hr. The excess reagent was destroyed with ethyl acetate, and dilute sodium hydroxide solution was added to precipitate the aluminum salts. The ether solution was decanted, dried, and evaporated to dryness. Crystallization from acetone containing a trace of pyridine afforded a 66% yield of material, m.p. 184–188°, $[\alpha]_D$ −55.5°. The melting range could not be narrowed by further recrystallization. The n.m.r. spectrum indicated (see discussion) that the material consisted of 56% of the 20α epimer and 44% of the 20β compound.

The pure epimers were isolated by chromatography of the crude reduction product on Florisil.[11] From the fractions eluted by mixtures of 1 to 2% ether–benzene there was obtained by crystallization from ethyl acetate–methylcyclohexane (pyridine) the pure 20α-hydroxy compound IIIa, m.p. 192.5–195°, $[\alpha]_D$ −58.5°; for n.m.r., see Table II.

Anal. Calcd. for $C_{23}H_{34}O_3$: C, 77.05; H, 9.56. Found: C, 76.94; H, 9.56.

From the fractions eluted by 10% ether–benzene 20β epimer IIIb was obtained as needles from ethyl acetate–methylcyclohexane (pyridine), m.p. 180–182, $[\alpha]_D$ −52.7°.

Anal. Calcd. for $C_{23}H_{34}O_3$: C, 77.05; H, 9.56. Found: C, 77.44; H, 9.65.

20α-Acetoxy-5,16-pregnadien-3-one Ethylene Ketal (IVa).—The 20α-hydroxy compound IIIa was acetylated using acetic anhydride in pyridine to afford the acetate as needles from methylcyclohexane (pyridine), m.p. 170–171°, $[\alpha]_D$ −75°.

Anal. Calcd. for $C_{25}H_{36}O_4$: C, 74.96; H, 9.06. Found: C, 74.76; H, 8.66.

20β-Acetoxy-5,16-pregnadien-3-one Ethylene Ketal (IVb).—The 20β alcohol IIIb was acetylated in the same manner to afford the title compound as blades from methylcyclohexane (pyridine), m.p. 148.5–150°, $[\alpha]_D$ −11°.

Anal. Calcd. for $C_{25}H_{36}O_4$: C, 74.96; H, 9.06. Found: C, 74.99; H, 9.04.

In the early attempts at purification, the crude lithium aluminum hydride reduction product from 5,16-pregnadiene-3,20-dione 3-ethylene ketal was acetylated and crystallized from aqueous methanol. The material had m.p. 136–137°, $[\alpha]_D$ −40°, and had an analysis consistent with an acetoxy ketal. The n.m.r. spectrum showed resonances at 51.3 and 54.3 c.p.s. of equal amplitude but one-half of the amplitude of the single C-19 methyl resonance peak at 63.8 c.p.s. These data and the rotational value are consistent with a 1:1 molecular complex of the 20α and 20β epimers.

(9) For a recent discussion of the configuration of the reduction products of various 20-keto steroids, see S. Rakhit and C. R. Engel, *Can. J. Chem.*, **40**, 2163 (1962); also K. Heusler and A. Wettstein, *Helv. Chim. Acta*, **45**, 347 (1962).

(10) See footnote *a* of Table I.

(11) A synthetic magnesium silicate product of the Floridin Co., Warren, Pa.

Oxidation of 6β-Hydroxy-3α,5α-cycloandrostan-17-one with Lead Tetraacetate. A Route to 19-Norsteroids from *i*-Steroids

PAUL B. SOLLMAN

Division of Chemical Research, G. D. Searle and Company, Skokie, Illinois

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This report describes a route to 19-norsteroids starting with *i*-steroids (3α,5α-cyclosteroids).[1] Intramolecular substitution of the steroidal 19-methyl group initiated by abstraction of hydrogen by a 6β-oxygen radical or cation has had many applications, particularly in the formation of 6β,19-oxides by the action of lead tetraacetate on 6β-hydroxy steroids.[2] Lead tetraacetate oxidation of 3β-acetoxy-5α-bromo-6β-hydroxy steroids afforded an excellent route to 19-norsteroids, as the resulting oxides could be converted to 19-oxygenated steroids from which the C-19 could be eliminated.[3]

It was conceived that the use of *i*-steroids would easily provide the 6β-hydroxyl, would protect the potential 3β-hydroxyl-Δ[5] functions while oxygen was introduced at C-19, and would enable these functions readily to be regenerated prior to elimination of the angular C-19. Dreiding models of 3α,5α-cyclosteroids indicate that the shape of ring B is only slightly changed from its shape in 5α-steroids.[4] Ring B is in the chair

(1) After the present work was completed, three reports of independent investigations similar to this were reported: (a) K. Tanabe, R. Takasaki, K. Sakai, R. Hayashi, and Y. Morisawa, *Chem. Pharm. Bull.* (Tokyo), **10**, 1126 (1962), isolated *ca.* 25% yield of 6β,19-oxido-3α,5α-cycloandrostan-17-one (II); (b) J. Tadanier, *J. Org. Chem.*, **28**, 1744 (1963), obtained the 17-ethylenedioxy derivative of II in 22% yield and studied its solvolysis; (c) R. M. Moriarty and T. D. D'Silva, *J. Org. Chem.*, **28**, 2445 (1963), synthesized and hydrolized 6β,19-oxido-3α,5α-cyclocholestane.

(2) (a) C. Meystre, K. Heusler, J. Kalvoda, P. Wieland, G. Anner, and A. Wettstein, *Experientia*, **17**, 475 (1961); (b) A. Bowers, E. Denot, L. C. Ibanez, M. E. Cabezas, and H. J. Ringold, *J. Org. Chem.*, **27**, 1962 (1962).

(3) A. Bowers, R. Villotti, J. A. Edwards, E. Denot, and O. Halpern, *J. Am. Chem. Soc.*, **84**, 3204 (1962).

(4) J. Tadanier and W. Cole, *J. Org. Chem.*, **27**, 4610 (1962).

form and the axial 6β-hydroxyl and 19-methyl groups are only slightly farther separated than in the 5α-substituted steroids previously used to produce cyclic ethers.

In initial experiments oxidation of 6β-hydroxy-3α,5α-cycloandrostan-17-one (I) in benzene solution with lead tetraacetate followed by chromatography on silica gel gave the 19-hydroxylated product III in 7–15% yields (based on unrecovered starting material) but none of the expected oxide II. Subsequently, by rapid elution with more polar solvent mixtures, a small amount (*ca.* 2%) of II was isolated. A sample of II was then converted to III in 62% yield simply by rechromatographing on silica gel. From this latter column a new product identified by spectra as 19-hydroxy-3α,5α-cyclo-6-androsten-17-one (VII) also was isolated. The ultraviolet maximum of VII was at 207 (ε 10,900); the maximum of 3β,5β-cyclo-6-cholestene is at 207 mμ (ε 12,000).[5c] Compound VII evidently is formed independently from II[5] and not by dehydration of the alcohol III. A solution of III stirred with silica gel produced no detectable amount of VII.

In the n.m.r. spectrum of II the two 19-protons appear as a pair of doublets, one pair of which is at 205 and 212.5 c.p.s. Peaks at 234.5 and 241 representing two protons, are postulated to be composed of a doublet at 233.5 and 241 (symmetrical with the doublet at 205 and 212.5) due to the other 19-proton, and two peaks at 235 and 239.5 c.p.s. representing the 6α-proton coupled with the 7-protons. The separation (4.5 c.p.s.) of the latter peaks, is in excellent agreement with the calculated value of $J_{AX} + J_{BX}$, where X is the C-6 proton and A and B are the C-7 protons.[6] Estimation from a Dreiding model of II of the dihedral angle ϕ made by the 6α-proton with the 7α-proton is 80°, estimated ϕ for the 6α- and 7β-protons is 40°. The calculated[7] coupling constant, J, for the 6α- and 7α-protons is zero; calculated J for the 6α- and 7β-protons is 4.7 c.p.s.

In the relatively unstrained 6β-hydroxy *i*-steroids I and III, the 6α-proton appears as a triplet with J = 2.5 c.p.s., indicating a dihedral angle of 60° between 6α-H and 7α-H, and also between 6α-H and 7β-H.[1b] The 6α-proton was not observable in Tadanier's 6β,19-oxides presumably because it was obscured by the 17-ethylenedioxy protons present in his compounds.[1b]

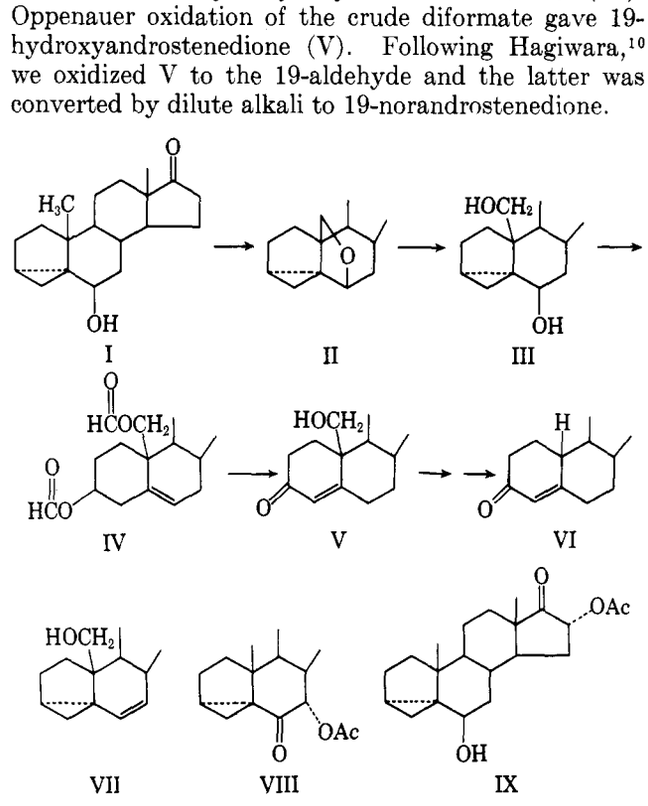
Major side reactions with lead tetraacetate were oxidation of the 6β-hydroxyl to 6-carbonyl, accompanied by acetoxylation at C-7. The configuration of the acetoxyl group in 7α-acetoxy-3α,5α-cycloandrostane-6,17-dione (VIII) was assigned on the basis of the coupling constant (J = 2.5 c.p.s.) of the 7-proton with the axial 8β-proton.

The n.m.r. spectrum of VIII showed absorption due to only one cyclopropane proton in the 0–50-c.p.s. region, instead of the usual three. Presumably this reflects deshielding of two of the cyclopropane protons by the 6-carbonyl group.[8]

A minor side product was 6β,16α-dihydroxy-3α,5α-cycloandrostan-17-one 16-acetate (IX) resulting from acetoxylation alpha to the 17-carbonyl. The configurational assignment at C-16 was on the basis of the ultraviolet maximum at 302 (ε 78); reported[9] for a 16α-acetoxy-17-keto steroid λ_{max} 302 (ε 80), for a 16β-acetoxy-17-ketosteroid λ_{max} 306 mμ (ε 46).

6β,19-Dihydroxy-3α,5α-cycloandrostan-17-one (III) was reduced to the 6β,17β,19-triol; it also was converted by ethynylation followed by reduction to 17α-ethyl-3α,5α-cycloandrostane-6β,17β,19-triol.

Treatment of III with formic acid gave the crude diformate of 19-hydroxydehydroisoandrosterone (IV). Oppenauer oxidation of the crude diformate gave 19-hydroxyandrostenedione (V). Following Hagiwara,[10] we oxidized V to the 19-aldehyde and the latter was converted by dilute alkali to 19-norandrostenedione.



Experimental

Melting points were taken on a Fisher-Johns block and are uncorrected. N.m.r. spectra were obtained on deuteriochloroform solutions using a Varian A-60 spectrometer and are reported in c.p.s. downfield from tetramethylsilane which was used as internal standard. Infrared spectra were obtained with a Beckman IR-4 spectrophotometer. Davidson grade 950, 60–200 mesh-silica gel was used in the chromatograms.

Oxidation of 6β-Hydroxy-3α,5α-cycloandrostan-17-one (I) with Lead Tetraacetate.—A solution of 25.0 g. of I[11] and 82.5 g. (1.9 mole equiv.) of lead tetraacetate (commercial reagent containing about 10% acetic acid) in 2.5 l. of dry benzene was refluxed for 26 hr. Precipitated lead acetate (39 g.) was removed by filtration and the filtrate was washed successively with dilute solutions of sodium bicarbonate, potassium iodide, and sodium thiosulfate. That unchanged lead tetraacetate remained was shown by the appearance of a heavy black precipitate of lead oxide during the

(5) Smooth conversion of 6β-ethers of 3,5-cyclosteroids to 3,5-cyclo-6-dehydrosteroids by activated alumina has been observed: (a) B. Riegel, G. P. Hager, and B. L. Zenitz, *J. Am. Chem. Soc.*, **68**, 2562 (1946); (b) A. Romeo and R. Villotti, *Ann. Chim.* (Rome), **47**, 684 (1957) [*Chem. Abstr.*, **52**, 1194 (1958)]; (c) W. G. Dauben and J. A. Ross, *J. Am. Chem. Soc.*, **81**, 6521 (1959).

(6) J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High-resolution Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc., New York, N. Y., 1959, p. 134.

(7) $J = 8.5 \cos^2 \phi - 0.28$ (c.p.s.): M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959).

(8) We have observed that only one proton peak (centered at 45 c.p.s.) appears in the 0–50-c.p.s. region in the n.m.r. spectra of 3α,5α-cycloandrostane-6,17-dione. The n.m.r. spectrum of 6β-nitro-3α,5α-cycloandrostan-17-one shows no absorption in this region: J. Tadanier and W. Cole, *J. Org. Chem.*, **27**, 4618 (1962).

(9) W. S. Johnson, B. Gastambide, and R. Pappo, *J. Am. Chem. Soc.*, **79**, 1991 (1957).

(10) H. Hagiwara, S. Noguchi, and M. Nishikawa, *Chem. Pharm. Bull.* (Tokyo), **8**, 84 (1960); *Chem. Abstr.*, **55**, 3653 (1961).

(11) A. Butenandt and L. A. Suranyi, *Ber.*, **75**, 591 (1942).

first wash. The organic layer was dried over sodium sulfate and concentrated to 28 g. of oil which was dissolved in benzene. An aliquot (140 ml. of 250 ml. total) representing 14.0 g. of starting *i*-steroid was rapidly chromatographed on 1700 g. of silica gel, using relatively polar eluents (20, 25, and 30% ethyl acetate in benzene).[12]

The first weight peak was 1.37 g. of crude 6β-hydroxy-3α,5α-cycloandrostan-17-one acetate as was shown by infrared.

This was followed by 3.74 g. of a mixture from which crystallizations from ether and from acetone–hexane gave 1.10 g. of crude **7α-hydroxy-3α,5α-cycloandrostane-6,17-dione acetate (VIII)** melting at 190–205°. The analytical sample melted at 209–213°; $\lambda_{max}^{CHCl_3}$ 5.72, 5.85, 8.06 μ; n.m.r. 41 (one cyclopropane proton), 55 (18-methyl), 62 (19-methyl), 124 (acetoxy methyl), and a doublet at 310 and 312.5 (equatorial 7β-proton) c.p.s. The ultraviolet spectrum in 1 *N* methanolic potassium hydroxide indicated a sequence of rearrangements: λ at 240 and at 340 mμ was, respectively, 1200 and 350 initially, 4300 and 6200 after 4 hr., and 6200 and 3100 after 25 hr.

Anal. Calcd. for $C_{21}H_{28}O_4$: C, 73.22; H, 8.19. Found: C, 72.94; H, 8.20.

Remaining in the weight peak after the removal of 1.1 g. of crude VIII was 1.6 g. of amorphous material which evidently contained an isomeric diketo acetate. The infrared spectrum ($\lambda_{max}^{CHCl_3}$ 5.72, 5.83, 8.02 μ) of the amorphous material was very similar in the carbonyl stretching regions to that of VIII. N.m.r. showed all of the peaks due to VIII, which was estimated to comprise 30–40% of the amorphous material; in addition there were peaks at 63 (19-methyl), 129 (acetoxy methyl), and at 297.5 and 308 c.p.s. (doublet, axial proton). These spectra indicated the presence of 7β-hydroxy-3α-5α-cycloandrostane-6,17-dione acetate, the 7-epimer of VIII.

A suspension of 345 mg. (1.00 mmole) of VIII in 20 ml. of methanol was treated with 10.0 ml. of 0.10 *N* sodium hydroxide solution. After 15 min. at room temperature, the resulting solution was diluted with about 60 ml. of water. The product was removed by filtration and recrystallized from ether–hexane, giving 188 mg. of **7α-hydroxy-3α,5α-cycloandrostane-6,17-dione**, m.p. 200–203°; $[\alpha]_D$ +84.5° ($CHCl_3$); $\lambda_{max}^{CHCl_3}$ 2.75, 2.89 (split hydroxyl), 5.72 (17-carbonyl), and 5.90 (6-carbonyl) μ; n.m.r., 44 (cyclopropane proton), 55 (18-methyl), 61 (19-methyl), 202.5 and 206 (split hydroxy proton), and 234 (half-band width approximately 5 c.p.s., equatorial 7β-proton) c.p.s.

Anal. Calcd. for $C_{19}H_{26}O_3$: C, 75.46; H, 8.67. Found: C, 75.77; H, 8.82.

Reacetylation of 15 mg. of this ketol with acetic anhydride and pyridine (2 hr. at room temperature) gave 9 mg. of VIII, m.p. 209–213°, identified by infrared spectrum and mixture melting point.

Further elution, using 25% ethyl acetate in benzene, gave a weight peak of 1.34 g. which was crystallized from acetone–hexane and from aqueous acetone, giving 0.22 g. of **6β,19-oxido-3α,5α-cycloandrostan-17-one (II)**, m.p. 138–140°, lit.[1a] 137–138°; $\lambda_{max}^{CHCl_3}$ 3.41, 3.49, 5.76, 8.02, 9.56, 10.03, 10.81, and 11.06 μ; n.m.r. complex bands centered at 20 and 45 (cyclopropane protons), 57 (18-methyl), 205 and 212.5 (doublet, 1 proton), and 234.5 and 241 (2 protons) c.p.s.

Anal. Calcd. for $C_{19}H_{26}O_2$: C, 79.68; H, 9.15. Found: C, 79.42; H, 8.89.

Continued elution of the column with 25% ethyl acetate in benzene gave 1.40 g. of pure starting compound, m.p. 141–143°.

The first weight peak eluted with 30% ethyl acetate was 0.96 g. from which crystallization from acetone–hexane gave 0.12 g. of **6β,16α-dihydroxy-3α,5α-cycloandrostan-17-one 16-acetate; (IX)**, m.p. 215–222° (unchanged by recrystallization or sublimation), $\lambda_{max}^{95\%\,EtOH}$ 302 mμ (ε 78); $\lambda_{max}^{CHCl_3}$ 2.74, 5.67, 5.71, 7.99 μ; n.m.r., 0–50, 62, 65, 126, 196-199-202 (triplet, 6α-proton) and 321–329 (doublet, 16-proton) c.p.s.

Anal. Calcd. for $C_{21}H_{30}O_4$: C, 72.80; H, 8.73. Found: C, 72.60; H, 8.40.

A solution of 68 mg. of IX in 3 ml. of formic acid was kept at room temperature for 4 hr. Addition of water gave 65 mg. of crystals, m.p. 188–193°. Recrystallization from aqueous acetone and from acetone–hexane gave 54 mg. of **16α-acetoxy-3β-formyloxy-5-androsten-17-one**, m.p. 193–195°, lit.[13] 182°; $\lambda_{max}^{95\%\,EtOH}$ 302 mμ (ε 79); λ_{max}^{KBr} 3.38, 5.72, 5.81, 7.30, 8.10, and 8.53 μ; n.m.r. 59, 64, 127, 282 (broad, 3α-proton), 315–330 (complex envelope, 6- and 16β-protons), and 483 (formate proton) c.p.s.

It was possible to crystallize **6β,19-dihydroxy-3α,5α-cycloandrostan-17-one (III)** from the last weight peak (2.84 g.) using ether; however, direct crystallization was difficult due to an impurity which on thin layer chromatography appeared as a streak running ahead of III. This material was treated with aqueous methanolic sodium hydroxide overnight at room temperature. The hydrolysate was extracted with ether; the ether residue was crystallized from acetone–hexane, giving 0.83 g. of III, m.p. 177–179°; lit.[1] 175–175.5°, 172–174°.

Conversion of II to III and VII on Silica Gel.—A benzene solution of 47 mg. of 6β,19-oxido-3α,5α-cycloandrostan-17-one (II) was chromatographed on 11 g. of silica gel. Nothing was eluted with 100-ml. fractions each of 1, 2, 4, 5, and 8% ethyl acetate in benzene. Material (13 mg.) eluted with 300 ml. of 10% ethyl acetate in benzene was crystallized from aqueous acetone. This gave 4 mg. of 19-hydroxy-3α,5α-cyclo-6-androsten-17-one (VII) as cottony fibers, m.p. 174–177°; $\lambda_{max}^{CHCl_3}$ 2.73 (OH), 5.75 (17 C=O), 6.10 (double bond), 8.02, 9.54, and 9.88 μ; $\lambda_{max}^{95\%\,EtOH}$ 207 mμ (ε 10,900).

Nothing was eluted with 100 ml. of 20% ethyl acetate in benzene. This was followed by 400 ml. of 30% ethyl acetate in benzene, which eluted 29 mg. of III, m.p. 172–178°, identified by infrared and mixture melting point.

A solution of 2 mg. of III in 4 ml. of benzene was stirred for 3 days with 2 g. of silica gel. The solution was diluted with ethyl acetate, filtered, and concentrated to crystals melting 170–178° shown by thin layer chromatography to be unchanged III, containing no detectable amount of olefin VII.

Conversion of III to 19-Norandostenedione (VI).—A solution of 105 mg. of III in 3.0 ml. of 99% formic acid was kept at room temperature for 5 hr. Addition of water caused separation of the crude 3β,19-diformate (IV) as 105 mg. of needles, m.p. 134–136°. The infrared in potassium bromide had strong absorption at 5.75 aud 8.52 μ, and had no band corresponding to hydroxyl.

The crude diformate was refluxed for 30 min. in 5 ml. of toluene and 2 ml. of cyclohexanone containing 125 mg. of aluminum isopropoxide. Addition of 20 ml. of saturated Rochelle salt solution followed by steam distillation, then extraction with ether, gave a crude oil. Crystallization of the oil from acetone–hexane and from ether–hexane gave 15 mg. of 19-hydroxy-4-androstene-3,17-dione (V), m.p. 170–173°, lit.[14] 168–170°.

A solution of 302 mg. of 19-hydroxyandrostenedione (V) in 17 ml. of acetone at 10° under nitrogen was treated with 0.28 ml. of 8 *N* chromic acid. After 2 min., water was added and the product was extracted with methylene chloride. Crystallization from hexane gave 196 mg. of 4-androstene-3,17-dion-19-al, m.p. 134–135°, lit.[15] 129–133°.

A solution of 38 mg. of the 19-aldehyde in 5 ml. of methanol was treated with 1 ml. of 10% sodium hydroxide solution. After 0.5 min. the solution was diluted with 50 ml. of water and concentrated under reduced pressure. The product separated as crystals which, recrystallized from ether–hexane, gave 14 mg. of 19-norandrostenedione VI, m.p. 170–172°, having identical infrared and not depressing the melting point of an authentic sample prepared by Dr. L. J. Chinn of these laboratories using the method of Wilds and Nelson.[16]

6β,17β,19-Trihydroxy-3α,5α-cycloandrostane.—To a solution of 52 mg. of sodium borohydride in 2.2 ml. of methanol containing 0.02 ml. of 10% sodium hydroxide was added 125 mg. of 6β,19-dihydroxy-3α,5α-cycloandrostan-17-one (III). After 1 hr. a drop of acetic acid followed by 25 ml. of water was added. The product (116 mg., m.p. 121–126°) was removed by filtration from the basic solution. Recrystallization from acetone–water gave solvated crystals, m.p. 126–128°; $\lambda_{max}^{CHCl_3}$ 2.75, 2.93, 9.55 μ and small peaks at 2.70 and 6.23 μ representing water.

Anal. Calcd. for $C_{19}H_{30}O_3 + 1/2H_2O$: C, 72.35; H, 9.91. Found: C, 72.23; H, 9.78.

Drying at 140° (0.01 mm.) gave 6β,17β,19-trihydroxy-3α,5α-cycloandrostane as a clear glass, the infrared spectrum of which

(12) The remaining portion of the reaction mixture also was chromatographed on silica gel. It was eluted more gradually with less polar solvent mixtures (2, 5, 10, 15, 20, 25, 30, and 35% ethyl acetate in benzene). Consequently greater volumes of solvent were used and the chromatogram required more time. In this case there was no weight peak corresponding to compound II, and the total absence of II was indicated by infrared spectra of the oils eluted between compounds VIII and I.

(13) V. Sanda and J. Fajkos, *Collection Czech. Chem. Commun.*, **26**, 2734 (1961).

(14) A. S. Meyer, *Experientia*, **11**, 99 (1955).

(15) M. Nishikawa and H. Hagiwara, *Chem. Pharm. Bull.* (Tokyo), **6**, 226 (1958); *Chem. Abstr.*, **53**, 452 (1959).

(16) A. L. Wilds and N. A. Nelson, *J. Am. Chem. Soc.*, **75**, 5366 (1953).

was identical with that of the hydrated sample except that it lacked the two peaks due to water.

Anal. Calcd. for $C_{19}H_{30}O_3$: C, 74.47; H, 9.87. Found: C, 74.50; H, 9.78.

17α-Ethyl-3α,5α-cycloandrostane-6β,17β,19-triol.—A solution of 250 mg. of III in 10 ml. of purified tetrahydrofuran containing 0.60 g. of lithium acetylide–ethylenediamine 1:1 complex was stirred at room temperature for 2 hr. Addition of water gave the product as an oil which crystallized. Several recrystallizations from acetone–hexane gave 84 mg. of almost pure 17α-ethynyl-3α,5α-cycloandrostane-6β,17β,19-triol, melting at 225–235°.

Reduction at room temperature of 55.87 mg. of the ethynyl compound in 4 ml. of 95% ethanol was catalyzed by 6.02 mg. of 5% palladium on charcoal. After 0.5 hr. the hydrogen uptake was 8.00 ml. (theory, 8.03 ml.). Addition of water gave 50 mg. of 17α-ethyl-3α,5α-cycloandrostane-6β,17β-19-triol, m.p. 247–251°. The analytical sample, crystallized from acetone–hexane, had m.p. 248–253°; λ_{max}^{KBr} 2.80, 2.98, 3.13, 6.79, 9.36, 9.52, 9.67, and 9.86 μ.

Anal. Calcd. for $C_{21}H_{34}O_3$: C, 75.40; H, 10.25. Found: C, 75.02; H, 10.03.

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Alkaloids from *Tripterygium wilfordii* Hook. The Chemical Structure of Wilfordic and Hydroxywilfordic Acids

MORTON BEROZA

Entomology Research Division, Agricultural Research Service, U. S. Department of Agriculture, Beltsville, Maryland

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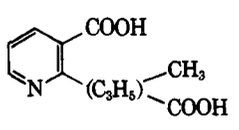
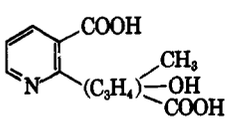
Alkaline saponification of five large insecticidal alkaloids (molecular weights between 826 and 891) isolated from the roots of the perennial twining vine *Tripterygium wilfordii* Hook yielded among other products two pyridine dicarboxylic acids whose structures were not completely identified. One of these ($C_{11}H_{13}NO_4$, m.p. 195–196°), for which the name wilfordic acid is proposed, was obtained from the alkaloids wilforine, wilforgine, and wilforzine.[1] The other ($C_{11}H_{13}NO_5$, m.p. 178–179°), for which the name hydroxywilfordic acid is suggested, was isolated from wilfordine and wilfortrine.[1] The following partial formulas summarize the information on the chemical structures of the acids as established previously by the author.[2]



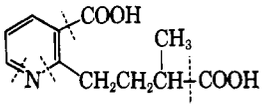
I, wilfordic acid



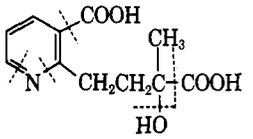
II, hydroxywilfordic acid

These formulas were based on elemental analyses, neutral equivalents, potentiometric titration, and the following data. Permanganate oxidation of both acids gave acetic, oxalic, and quinolinic acids; both acids failed to chelate with ferrous sulfate, indicating there is no carboxyl group *ortho* to the pyridine nitrogen atom. The hydroxyl group of hydroxywilfordic acid was shown to be alpha to a carboxyl group. Decarboxylation of the dibasic acids in quinoline in the presence of basic copper carbonate gave one mole of carbon dioxide for wilfordic acid and two for hydroxywilfordic acid.[3] It was concluded that a methyl group was present in the side chain, since acetic acid was present among the oxidation products.

This note shows that wilfordic acid is 3-carboxy-α-methyl-2-pyridinebutyric acid (III) and that hydroxywilfordic acid is 3-carboxy-α-hydroxy-α-methyl-2-pyridinebutyric acid (IV) (dotted lines of III and IV will be discussed in later section).

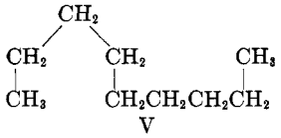


III, Wilfordic acid



IV, hydroxywilfordic acid

Both acids were subjected to analysis by the hydrogenolytic gas chromatography technique described by the author,[4] and each gave nonane (V, written so as to facilitate comparison with III and IV).



V

This chromatographic procedure would be expected to cleave the bonds of III and IV that are severed with dotted lines (for example, α-picoline gives hexane, RCOOH gives RH, and RR'CHOH gives RR'CH_2). Although the position of the methyl group is established from the nonane carbon skeleton, the positions of the hydroxyl and the carboxyl groups are not, since the carboxyl and hydroxyl groups could be attached to the carbons alpha and beta to the ring, and nonane would still be obtained.

Nuclear magnetic resonance spectra of the acids (Fig. 1 and 2) showed III and IV to be the correct structures. (Chemical shift data are given in parts per million from the water peak, taking the high field as positive.) In the wilfordic acid spectrum the methyl peak is a doublet at +3.59 ($J_{\alpha\text{-Me}}$ = 7 c.p.s.), split by a single proton (alpha to the carboxyl group) that appears as a multiplet at +2.15 p.p.m. Were the carboxyl alpha or beta to the ring, the methyl would be a triplet and not a doublet. A sample of 2-methylpentanoic acid run under the same conditions gave the same $J_{\alpha\text{-Me}}$ spin-coupling constant, and the chemical shifts for the peaks of the methyl and α-protons agreed closely (+3.66 and +2.33 p.p.m.) with the shifts of the corresponding structures in wilfordic acid. Splittings of the protons on the β-carbon were not readily resolvable, but those on the γ-carbon (adjacent to the ring) are a triplet at +1.48 ($J_{B\gamma}$ = 5.3 c.p.s.). The protons on the γ-carbon are expected to be furthest downfield since phenyl substituents cause a much larger paramagnetic shift of alkyl frequencies than a carbonyl double bond, and the heteroatom of the ring would be expected to accentuate

(1) M. Beroza, *J. Am. Chem. Soc.*, **73**, 3656 (1951); **74**, 1585 (1952); **75**, 2136 (1953).

(2) M. Beroza, *ibid.*, **75**, 44 (1953).

(3) Aromatic carboxylic and α-hydroxycarboxylic acids give one mole of carbon dioxide per mole of carboxyl group by the procedure of M. Beroza, *Anal. Chem.*, **25**, 177 (1953).

(4) M. Beroza, *ibid.*, **34**, 1801 (1962); **35**, 1353 (1963).