16-Oxa Steroids

R. W. KIERSTEAD AND A. FARAONE

Chemical Research Department, Hoffmann-La Roche, Inc., Nutley, New Jersey 07110

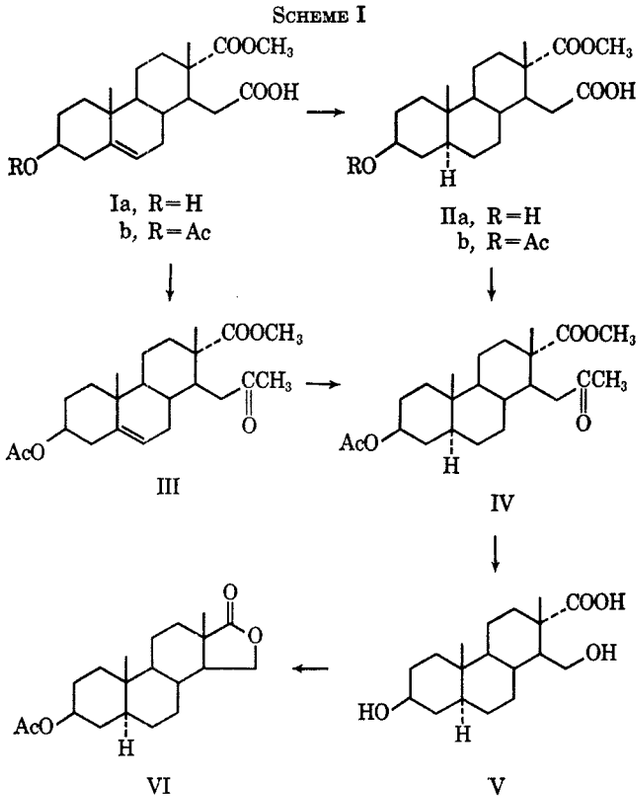
Received July 15, 1966

The preparation of a few 16-oxa steroids is described, utilizing the half-ester (Ia) of 3β-hydroxy-16,17-seco-androst-5-ene-16,17-dioic acid as starting material. In the first method, Ia was converted by standard procedures to the acetate of 1-acetonyltetradecahydro-7-hydroxy-2,4b-dimethyl-2-phenanthrenecarboxylic acid methyl ester (IV). Per acid oxidation of the latter compound, followed by hydrolysis and lactonization gave the acetate of 3β-hydroxy-16-oxa-5α-androstan-17-one (VI). In a more convenient sequence leading to the same class of compounds, the acetate of 2-carbomethoxytetradecahydro-7-hydroxy-2,4b-dimethyl-1-phenanthrene-acetic acid (IIb) was bromodecarboxylated *via* its silver salt and the resulting crude bromide was converted to the corresponding acetate. Hydrolysis of the latter compound followed by lactonization gave 3β-hydroxy-16-oxa-5α-androstan-17-one (VII). The conversion of the latter compound to 17,17-dimethyl-16-oxa-5α-androstan-3-one (XII) and 17ξ-hydroxy-16-oxa-5α-androstan-3-one (XIV) is described.

The insertion of an oxygen atom into the steroid nucleus has led to a variety of structurally modified derivatives,[1] some of which exhibit interesting biological activity.[2] A recent publication[3] on the synthesis of 17-oxa-5α-androstan-3-one prompts us to report our work on the preparation of some 16-oxa steroids.

In our initial studies (Scheme I), half-ester Ia[4] of 3β-hydroxy-16,17-secoandrost-5-ene-16,17-dioic acid was hydrogenated over palladium on carbon to give dihydro derivative IIa which was converted to acetate IIb. Reaction of the latter compound with oxalyl chloride gave the corresponding acid chloride which was treated with dimethyl cadmium[5] to yield methyl ketone IV.

SCHEME I



In an alternate and preferred method leading to IV, original half-ester Ia was acetylated to give known acetate Ib.[4] The latter material was converted to the corresponding acid chloride,[4] which on treatment with dimethyl cadmium gave methyl ketone III. Hydrogenation of III over palladium on carbon gave IV, identical with the sample described previously.

Baeyer–Villiger oxidation of IV with peroxytrifluoroacetic acid[6] followed by hydrolysis of the resulting crude ester gave the dihydroxy acid V. The latter material was cyclized smoothly in boiling acetic anhydride to afford the 16-oxa steroid (VI).

In a far superior procedure leading to these compounds (Scheme II), the silver salt of IIb was allowed to react with bromine under the conditions of the Hunsdiecker reaction.[7] The resulting crude bromide IIc was treated with potassium acetate in dimethyl sulfoxide to give crude acetate IId. Hydrolysis of IId with potassium hydroxide, followed by treatment of the product with dilute hydrochloric acid, gave 3β-hydroxy-16-oxa-5α-androstan-17-one (VII) in 40% over-all yield from IIb.

Chromic acid oxidation of VII gave ketone VIII which was brominated in acetic acid to give the crude 2,4-dibromo ketone. Treatment of the latter material with lithium bromide and lithium carbonate in dimethylformamide[8] gave dienone IX. In another sequence, reaction of ketone VIII with ethylene glycol and *p*-toluenesulfonic acid gave ketal X. The latter compound was treated with methylmagnesium bromide to give dimethylcarbinol XI. Cyclization of XI with *p*-toluenesulfonic acid in benzene followed by hydrolysis of the ketal group gave cyclic ether XII.

Numerous methods were investigated to convert lactone X to corresponding hemiacetal XIII. For example, it is well known that under mild conditions the reduction of lactones with lithium aluminum hydride[9] or sodium aluminum hydride[10] gives rise to the cyclic hemiacetal or the corresponding acyclic hydroxy-

(1) See L. Tokes in "Steroid Reactions," C. Djerassi, Ed., Holden Day, Inc., San Francisco, Calif., 1963, pp 459–502, for leading references.

(2) (a) S. D. Levine, *J. Med. Chem.*, **8**, 537 (1965); (b) R. Pappo and C. J. Jung, *Tetrahedron Letters*, 365 (1962); (c) H. D. Lennon and F. J. Saunders, *Steroids*, **4**, 689 (1964).

(3) S. Rakhit and M. Gut, *J. Org. Chem.*, **29**, 229 (1964).

(4) (a) S. Kuwada and K. Nakamura, *J. Pharm. Soc. Japan*, **58**, 835 (1938); (b) J. Heer and K. Miescher, *Helv. Chim. Acta*, **30**, 786 (1947); (c) E. B. Hershberg, E. Schwenk, and E. Stahl, *Arch. Biochem.*, **19**, 300 (1948); (d) C. von Seeman and G. A. Grant, *J. Am. Chem. Soc.*, **72**, 4073 (1950).

(5) D. A. Shirley, *Org. Reactions*, **8**, 28 (1954).

(6) (a) W. D. Emmons and G. B. Lucas, *J. Am. Chem. Soc.*, **77**, 2287 (1955); (b) H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, Inc., New York, N. Y., 1965, p 123.

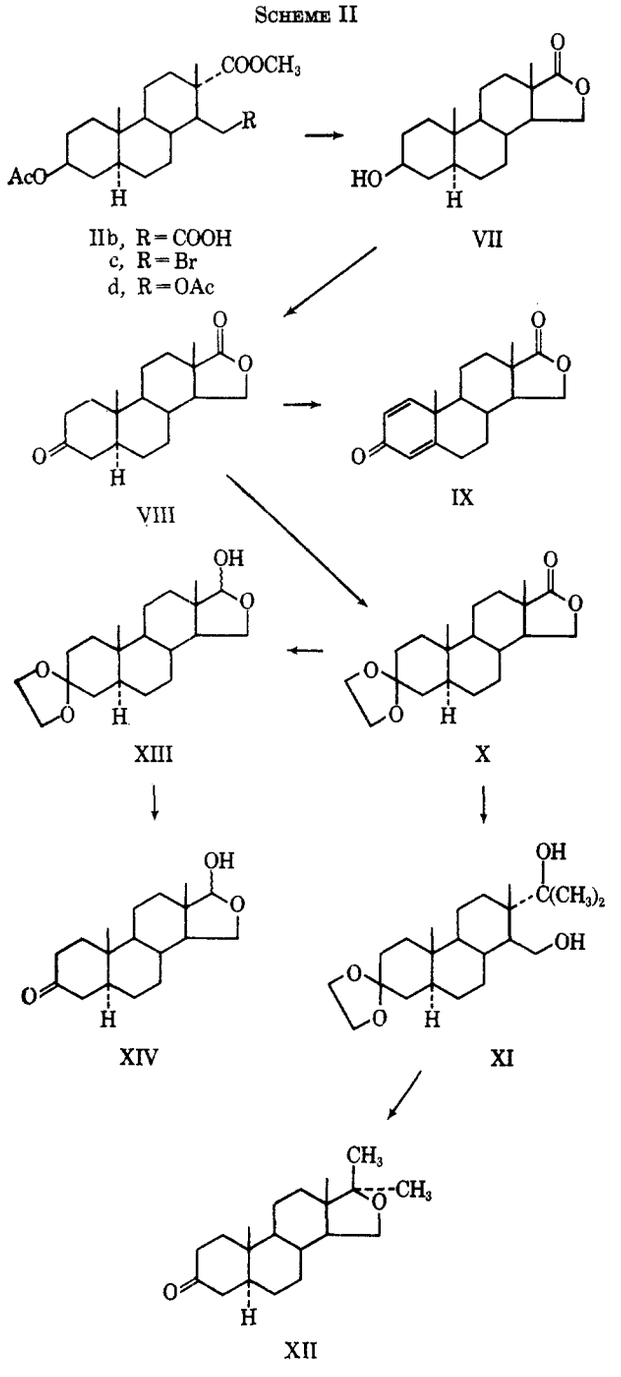
(7) C. V. Wilson, *Org. Reactions*, **9**, 332 (1957).

(8) (a) R. Joly, J. Warnant, G. Nominé, and D. Bertin, *Bull. Soc. Chim. France*, 336 (1958); (b) P. Kurath and W. Cole, *J. Org. Chem.*, **26**, 1939 (1961).

(9) (a) G. E. Arth, *J. Am. Chem. Soc.*, **75**, 2413 (1953); (b) M. Hinder and M. Stoll, *Helv. Chim. Acta*, **37**, 1866 (1954); (c) J. T. Edward, P. F. Morand, and I. Puskas, *Can. J. Chem.*, **39**, 2069 (1961).

(10) L. I. Zakharkin, V. V. Gavrilenko, D. N. Maslin, and I. M. Khorlina, *Tetrahedron Letters*, 2087 (1963).

SCHEME II



aldehyde. The use of these reagents in our case gave only small amounts of desired XIII, accompanied by substantial quantities of diol arising from over reduction of X. No improvement in yield was noted when lithium tri-*t*-butoxyaluminum hydride was employed.

Our best results were obtained with the use of disiamylborane (bis-3-methyl-2-butylborane).[11] Thus, treatment of lactone X with disiamylborane in tetrahydrofuran solution gave hemiacetal XIII in 30% yield. The latter compound showed no carbonyl absorption in the infrared (KBr)[12] and the C_{17} proton exhibited a downfield shift at τ 5.03 in the nmr spectrum, indicating that XIII exists in the cyclic hemiacetal form. Compound XIII was hydrolyzed at room temperature with dilute hydrochloric acid (in tetrahydrofuran solution) to give XIV. In this case, the nmr signal at τ 5.03 appears as a doublet (J = 3.5 cps) owing to coupling with the C_{17}-hydroxyl proton. The configuration of the C_{17} hydroxyl in XIII and XIV is not known.

(11) (a) H. C. Brown and G. Zweifel, *J. Am. Chem. Soc.*, **82**, 3222 (1960); (b) H. C. Brown and D. B. Bigley, *ibid.*, **83**, 486 (1961); (c) H. C. Brown, "Hydroboration," W. A. Benjamin, Inc., New York, N. Y., 1962, Chapter 18.

(12) However, the infrared spectrum in chloroform solution exhibited a weak band at 5.83 mμ, indicating the possible presence (about 2%) of the acyclic γ-hydroxyaldehyde. See also C. D. Hurd and W. H. Saunders, Jr., *J. Am. Chem. Soc.*, **74**, 5324 (1952).

Experimental Section[13]

2-Carbomethoxytetradecahydro-7-hydroxy-2,4b-dimethyl-1-phenanthreneacetic Acid (IIa).—3β-Hydroxy-16,17-secoandrost-5-ene-16,17-dioic acid (mp 246–249° dec) was prepared by the general procedure outlined by Petrow and co-workers.[14] Treatment of the latter compound with diazomethane gave a quantitative yield of the corresponding dimethyl ester (mp 106.5–110°),[4d] which was hydrolyzed readily to half-ester Ia (mp 205–208°).[4]

A solution of 25.0 g of Ia in 500 ml of ethanol was hydrogenated over 5.0 g of 10% palladium on carbon (t = 24°, P = 763 mm). After the absorption of 1 equiv of hydrogen (about 6 hr) the rate of hydrogenation had decreased markedly and the reaction was stopped. The catalyst was removed by filtration and the filtrate was evaporated to dryness under reduced pressure to give an oil. Two crystallizations from ethyl acetate gave 12.02 g (48%) of IIa, mp 180.5–182.5° (vacuum). Crystallization from aqueous methanol gave the analytical sample: mp 180.5–182.5° (vacuum), $[\alpha]^{25}D$ −24.7° (c 1.05, $CHCl_3$), $\lambda_{max}^{CHCl_3}$ 2.96 and 5.76 μ.

Anal. Calcd for $C_{20}H_{32}O_6$: C, 68.15; H, 9.15. Found: C, 68.53; H, 8.99.

Acetate of 2-Carbomethoxytetradecahydro-7-hydroxy-2,4b-dimethyl-1-phenanthreneacetic Acid (IIb). A. By Acetylation of IIa.—To a solution of 11.5 g of IIa in 120 ml of dry pyridine was added 60.0 ml of freshly distilled acetic anhydride and the resulting solution was allowed to stand overnight at room temperature. The reaction mixture was then treated slowly with 60 ml of water, the exothermic reaction being maintained at about 50° by external cooling. The resulting solution was allowed to stand at room temperature for about 30 min and was then poured into 1 l. of water. The resulting mixture was extracted with ether–methylene chloride (3:1) and the organic layers were washed twice with cold 2 N hydrochloric acid solution and once with water. The dried (Na_2SO_4) organic layers were evaporated and the residue was crystallized from ether–hexane to give 9.57 g (74%) of IIb, mp 135–137° (vacuum). One further crystallization from ether–hexane gave the analytical sample: mp 134–136.5° (vacuum), $[\alpha]^{25}D$ −38.8° (c 1.1, $CHCl_3$), $\lambda_{max}^{CHCl_3}$ 5.80 and 7.95 μ.

Anal. Calcd for $C_{22}H_{34}O_6$: C, 66.98; H, 8.69. Found: C, 67.07; H, 8.82.

B. By Catalytic Hydrogenation of Ib.—A solution of 60.0 g of Ib (mp 169–171°)[4] in 1200 ml of ethyl acetate was hydrogenated over 12.0 g of 10% palladium on carbon (t = 24°, P = 761 mm). After the absorption of 1 equiv of hydrogen (about 24 hr) the rate of hydrogenation had decreased markedly and the reaction was stopped. The catalyst was removed by filtration and the filtrate was evaporated to dryness. The residue was crystallized twice from ether–hexane to give 35.7 g (59%) of IIb, mp 135–137°, identical in all respects with the sample described in part A. This material was frequently isolated as a polymorphic mixture, mp 133–141°, otherwise identical in all respects with the sample described above.

Acetate of 1-Acetonyl-1,2,3,4,4a,4b,5,6,7,8,10,10a-dodecahydro-7-hydroxy-2,4b-dimethyl-2-phenanthrenecarboxylic Acid Methyl Ester (III).—The half-ester (Ia)[4] was converted, *via* acetate Ib, to the corresponding acid chloride,[4] mp 133–139°, $\lambda_{max}^{CHCl_3}$ 5.56 and 5.80 μ.

A solution of methylmagnesium bromide was prepared from 3.26 g of magnesium and 20 g of methyl bromide in 300 ml of

(13) Melting points were determined in capillary tubes and are corrected. Infrared spectra were recorded on a Beckman Instrument Model IR-9. Nuclear magnetic resonance spectra were recorded on a Varian A-60 Instrument using tetramethylsilane as internal reference standard.

(14) W. J. Adams, D. K. Patel, V. Petrow, and I. A. Stuart-Webb, *J. Chem. Soc.*, 297 (1956).

ether. To this stirred and cooled (0°) solution was added rapidly 12.7 g of cadmium chloride. The cooling bath was then removed and the reaction was allowed to stir at room temperature for 1 hr, whereupon a negative Gilman test was observed. The ether was removed by distillation and was replaced simultaneously by an equivalent volume of benzene.

To the resulting stirred benzene solution (room temperature) was added, over a 5-min period, a solution of 10.8 g of the acid chloride of Ib in 135 ml of benzene. The reaction mixture was stirred at room temperature for 1 hr and was then heated at 60° for 1 hr. The cooled mixture was treated with 50 g of ice and 300 ml of 1 *N* hydrochloric acid solution. The organic layer was separated and the aqueous layer was extracted three times with ether–methylene chloride (3:1). The organic layers were washed once with 1 *N* hydrochloric acid solution, once with 1 *N* sodium hydroxide solution, and once with water. The combined organic layers were dried (Na_2SO_4) and evaporated to dryness to give 9.7 g of crude solid.

The above material was dissolved in benzene and filtered through a short column of Florisil,[15] eluting with benzene and finally with ether. The eluates were combined and evaporated to dryness. The residue was crystallized twice from ether–hexane to give 6.0 g (58%) of III, mp 109–110°. Crystallization from methylene chloride–hexane gave the analytical sample: mp 109–110°, $[\alpha]^{25}D$ −87.8° (*c* 1.0, $CHCl_3$), $\lambda_{max}^{CHCl_3}$ 5.81 and 8.00 μ.

Anal. Calcd for $C_{23}H_{34}O_5$: C, 70.74; H, 8.78. Found: C, 70.60; H, 8.76.

Acetate of 1-Acetonyltetradecahydro-7-hydroxy-2,4b-dimethyl-2-phenanthrenecarboxylic Acid Methyl Ester (IV). A. From IIb *via* the Acid Chloride and Dimethylcadmium.—To a stirred solution of 9.0 g of half-ester IIb in 80 ml of benzene was added 14 ml of oxalyl chloride and the resulting solution was heated at 68° for 1.5 hr. An additional 3.3 ml of oxalyl chloride was then added and heating was continued for 30 min. The solvent was removed under vacuum and the residue was evaporated twice in the presence of benzene to yield the acid chloride as an oil which was suitable for the next step ($\lambda_{max}^{CHCl_3}$ 5.53, 5.78, and 7.93 μ).

A solution of methylmagnesium bromide was prepared from 2.9 g of magnesium and 18 g of methyl bromide in 180 ml of ether. To this stirred and cooled (0°) solution was added 90 ml of ether followed by the rapid addition of 11.3 g of cadmium chloride. The cooling bath was then removed and the reaction mixture allowed to stir at room temperature for 30 min whereupon a negative Gilman test was observed. The ether was removed by distillation and was replaced simultaneously by an equivalent volume of benzene.

To the resulting solution (room temperature) was added, over a 5-min period, a solution of 9.8 g of the acid chloride of IIb in 120 ml of benzene. The reaction mixture was allowed to stir at room temperature for 2 hr and was heated at 60° for 45 min. The cooled mixture was then treated with 175 g of ice followed by 175 ml of 1 *N* hydrochloric acid solution. The organic layer was separated and the aqueous layer was extracted with ether–methylene chloride (3:1). The organic layers were washed once with dilute hydrochloric acid, once with dilute sodium hydroxide solution, and once with water. The combined organic layers were dried (Na_2SO_4) and evaporated to dryness. The residue was crystallized twice from ether–hexane to give 2.40 g of IV, mp 85–86.5°. An additional 2.45 g (mp 82.5–84°) was recovered from the mother liquors (total yield 54%). Crystallization from ether–hexane gave the analytical sample: mp 84.5–86°, $[\alpha]^{25}D$ −40.9° (*c* 1.0, $CHCl_3$), $\lambda_{max}^{CHCl_3}$ 5.81 and 8.00 μ.

Anal. Calcd for $C_{23}H_{36}O_5$: C, 70.37; H, 9.24. Found: C, 70.22; H, 9.25.

B. By Catalytic Hydrogenation of III.—A solution of 390 mg of III in 8 ml of ethyl acetate was hydrogenated over 78 mg of 10% palladium on carbon (t = 26°, P = 760 mm). After the absorption of 30 ml of hydrogen (theory for 1 equiv = 24.6 ml) the rate of hydrogenation had decreased markedly and the reaction was stopped (about 4 hr). The catalyst was removed by filtration and the filtrate was evaporated to dryness. The residue was crystallized from ether–hexane to give 175 mg of IV, mp 86–87.5°, undepressed upon admixture with the sample prepared by method A. An additional 42 mg (mp 84.5–86°) was recovered from the mother liquors (total yield, 56%).

Tetradecahydro-7-hydroxy-1-hydroxymethyl-2,4b-dimethyl-2-phenanthrenecarboxylic Acid (V).—To a solution of 0.392 g of IV in 7.5 ml of methylene chloride was added 1.0 g of anhydrous disodium hydrogen phosphate. To this stirred mixture was added over a 5-min period a solution containing 0.32 ml of 90% hydrogen peroxide and 1.5 ml of trifluoroacetic anhydride in 10 ml of methylene chloride.[16] The reaction mixture, which had warmed noticeably, was then stirred at room temperature for 2.5 hr. It was then decomposed with ice and water, and the resultant mixture was extracted with ether–methylene chloride (3:1). The organic layers were washed twice with dilute sodium bicarbonate solution and once with brine. The combined organic layers were dried (Na_2SO_4) and evaporated to dryness to give an oil which was dissolved in benzene and filtered through a short column of silicic acid. The benzene and ethyl acetate eluates were evaporated to give 0.391 g of oil which failed to crystallize.

To a solution of the above material (0.391 g) in 4.0 ml of methanol was added a solution of 0.4 g of potassium hydroxide in 0.4 ml of water and the resulting solution was heated under reflux for 90 min. The solvents were then removed under vacuum and the residue was diluted with 15 ml of water. The aqueous solution was washed with ether and then acidified to congo red with 3 *N* hydrochloric acid. The resulting precipitate was filtered, washed with water, and dried. Crystallization from methanol–acetonitrile gave 123 mg (40% yield, based on the methyl ketone IV) of V, mp 182–189° (vacuum). One further crystallization from the same solvent system gave the analytical sample: mp 184.5–189° (vacuum), λ_{max}^{KBr} 2.78, 2.94, and 5.88 μ.

Anal. Calcd for $C_{18}H_{30}O_4$: C, 69.64; H, 9.74. Found: C, 69.69; H, 9.81.

Acetate of 3β-Hydroxy-16-oxa-5α-androstan-17-one (VI).—A solution of 50 mg of V in 2.5 ml of freshly distilled acetic anhydride was heated under reflux for 2 hr. The reaction mixture was then evaporated to dryness and the residue was dissolved in ether and filtered through a short column of Florisil. The eluates were evaporated to dryness and the residue was crystallized from ether–hexane to give 26 mg (48%) of VI, mp 172.5–175°. The sample was identical with the product described below, in which the intermediate (V) was not isolated.

Thus, 2.11 g of the methyl ketone IV was oxidized with peroxytrifluoroacetic acid as described earlier to give 2.5 g of crude product which was hydrolyzed directly with alcoholic potassium hydroxide to give 1.40 g of crude V. The latter material was lactonized directly with acetic anhydride. The crude product was filtered through Florisil (ether) and the resulting material was crystallized three times from ether–hexane to give 481 mg (27% over-all yield from the methyl ketone IV) of VI, mp 172–174° (vacuum). One further crystallization gave the analytical sample: mp 173–174.5° (vacuum); $[\alpha]^{25}D$ +6.5° (*c* 0.5, $CHCl_3$); $\lambda_{max}^{CHCl_3}$ 5.63, 5.80, and 7.96 μ.

Anal. Calcd for $C_{20}H_{30}O_4$: C, 71.82; H, 9.04. Found: C, 71.83; H, 9.03.

3β-Hydroxy-16-oxa-5α-androstan-17-one (VII).[17]—To a solution of 142 g of IIb in 1440 ml of ethanol was added about 3650 ml of 1 *N* sodium hydroxide solution until the solution just gave a pink coloration with phenolphthalein, whereupon the mixture was acidified immediately with a few drops of dilute nitric acid solution. The stirred solution was then diluted with an additional 1440 ml of water, followed by the addition of a solution of 85.4 g of silver nitrate in 1440 ml of water. The resulting voluminous precipitate was filtered, washed well with water, and dried overnight in a vacuum oven at 80° to give 173 g of the silver salt of IIb.

A solution of 54.5 g of bromine in 540 ml of dry carbon tetrachloride was added over a 10-min period, to a vigorously stirred suspension of the above silver salt (173 g) in 1730 ml of dry carbon tetrachloride. The yellow reaction mixture was then heated under reflux for 80 min. The cooled reaction mixture was filtered through a bed of Celite[18] and about 90% of the solvent was removed under vacuum. The residue was diluted with 1400 ml of ether and the organic layer was washed with 10% sodium carbonate solution and water. The combined organic layers were dried (Na_2SO_4) and evaporated to dryness to give 107 g (73%) of crude bromide IIc.

(15) Florisil (Floridin Co.) is a synthetic magnesium silicate adsorbent.

(16) Little or no peroxidation took place when perbenzoic acid was used; see R. B. Turner, M. Perelman, and K. T. Park, Jr., *J. Am. Chem. Soc.*, **79**, 1108 (1957).

(17) The lactone was formed in inferior yield (19%) when the Hunsdiecker reaction was carried out by the modification described by S. J. Cristol and W. C. Firth, *J. Org. Chem.*, **26**, 280 (1961).

(18) Celite (Johns-Manville Co.) is a diatomaceous silica product.

A solution of 107 g of the crude bromide and 214 g of anhydrous potassium acetate in 1 l. of dimethyl sulfoxide was heated on the steam bath for 4 hr. The cooled reaction mixture was poured into 3 l. of water and the resulting mixture was extracted three times with ether–methylene chloride (3:1). The organic layers were washed four times with water. The combined organic layers were dried (Na_2SO_4) and evaporated. The resulting oil was dissolved in benzene and filtered through a short column of Florisil. The benzene (1.5 l.) and ethyl acetate (500 ml) eluates were evaporated to dryness to give 102 g of the crude diacetate IId as a yellow oil.

A solution of the above diacetate (102 g) in 1 l. of methanol was heated under reflux for 2 hr with a solution of 102 g of potassium hydroxide in 102 ml of water. The cooled reaction mixture was then concentrated to near dryness under vacuum. The residue was then dissolved in 4 l. of water and the aqueous solution was washed twice with ether. The aqueous layer was acidified to congo red with 6 *N* hydrochloric acid. The resulting mixture (precipitate) was diluted with an equal volume of methanol and was heated under reflux for 30 min. Most of the methanol was then removed under vacuum and the residue was diluted with 1500 ml of water. The resulting mixture was extracted three times with ether–methylene chloride (3:1) and the organic layers were washed once with 5% sodium bicarbonate solution and once with water. The combined organic layers were dried (Na_2SO_4) and evaporated to dryness. The residue was dissolved in 200 ml of methylene chloride and filtered through a short column of Florisil. The eluates were concentrated to dryness and the residue was crystallized from ethyl acetate to give 35.7 g of VII, mp 181–183° (vacuum). An additional 5.8 g, mp 180–182° (vacuum), was recovered from the mother liquors (total yield, 40% based on the starting acid IIb). Crystallization from ethyl acetate gave the analytical sample: mp 182.5–184° (vacuum), $[\alpha]^{25}D$ +23.8° (*c* 1.0, $CHCl_3$), $\lambda_{max}^{CHCl_3}$ 2.77 and 5.65 μ.

Anal. Calcd for $C_{18}H_{28}O_3$: C, 73.93; H, 9.65. Found: C, 73.83; H, 9.42.

16-Oxa-5α-androstane-3,17-dione (VIII).—To a stirred solution of 20.0 g of VII in 300 ml of acetone was added dropwise 28 ml of 8 *N* chromic acid solution.[19] After the addition was finished, the reaction was stirred at room temperature for an additional 5 min. The excess chromic acid was then decomposed by the addition of 1 ml of isopropyl alcohol. The reaction mixture was then poured into 1.5 l. of water and the resulting mixture was extracted with ether–methylene chloride (3:1). The organic layers were washed once with water and once with 5% sodium bicarbonate solution. The combined organic layers were dried (Na_2SO_4) and evaporated. The residue was crystallized from ether–hexane to give 15.4 g of VIII, mp 187–189° (vacuum). An additional 1.0 g, mp 187–189° (vacuum), was obtained from the mother liquors (total yield, 83%). Crystallization from methylene chloride–ether gave the analytical sample: mp 188–189.5° (vacuum), $[\alpha]^{25}D$ +41.3° (*c* 1.0, $CHCl_3$), $\lambda_{max}^{CHCl_3}$ 5.62 and 5.85 μ.

Anal. Calcd for $C_{18}H_{26}O_3$: C, 74.44; H, 9.03. Found: C, 74.42; H, 9.27.

16-Oxa-1,4-androstadiene-3,17-dione (IX).—To a stirred solution of 3.45 g of VIII in 34.5 ml of glacial acetic acid and 3.45 ml of 33% hydrobromic acid in acetic acid was added dropwise, over a 1-min period, a solution of 3.98 g of bromine in 17 ml of acetic acid. The reaction mixture was allowed to stand at room temperature for 1 hr. The resulting precipitate was filtered and crystallized once from chloroform–methanol to give 3.39 g (64%) of the 2,4-dibromo ketone, mp 192.5–194°, which was used directly for the next step.

A solution of 2.4 g of the above crude dibromo ketone in 32 ml of dry N,N-dimethylformamide was added, over a 10-min period, to a stirred suspension (maintained at 95° on the steam bath) of 3.2 g of lithium bromide and 3.2 g of lithium carbonate in 48 ml of N,N-dimethylformamide.[20] The resulting mixture was stirred at 95° overnight, cooled, and filtered. The filtrate was diluted with 500 ml of 1 *N* hydrochloric acid and was extracted three times with ether–methylene chloride (3:1). The organic layers were washed with water, dried (Na_2SO_4), and evaporated. The residue was dissolved in benzene and filtered through a short column of Florisil. The benzene and ethyl acetate eluates were concentrated and the residue was crystallized twice from methylene chloride–ether to give 1.10 g (72% from the dibromide or 46% over-all from VIII) of IX, mp 213–215° (vacuum). Further crystallization from methylene chloride–ether gave the analytical sample: mp 214–216.5° (vacuum); $[\alpha]^{25}D$ +57.2° (*c* 1.0, $CHCl_3$); $\lambda_{max}^{C_2H_5OH}$ 242 mμ (ϵ 15,880); $\lambda_{max}^{CHCl_3}$ 5.62, 6.01, 6.15, and 6.23 μ.

Anal. Calcd for $C_{18}H_{22}O_3$: C, 75.49; H, 7.74. Found: C, 75.54; H, 7.95.

3-(Cyclic Ethylene Ketal) of 16-Oxa-5α-androstane-3,17-dione (X).—A solution of 10.0 g of VIII, 550 mg of *p*-toluenesulfonic acid, and 55 ml of ethylene glycol in 330 ml of benzene was distilled slowly over a period of 2.5 hr. An additional 15 ml of ethylene glycol, 0.1 g of *p*-toluenesulfonic acid, and 150 ml of benzene were then added and slow distillation was carried out for an additional 2.5 hr. The cooled reaction mixture was then diluted with ether and the organic layer was washed twice with 5% sodium bicarbonate solution and once with water. The dried (Na_2SO_4) organic layer was concentrated and the residue was crystallized from methylene chloride–ether–hexane to give 8.22 g of XI, mp 193–195° (vacuum). An additional 2.6 g, mp 190–192° (vacuum), was obtained from the mother liquors (total yield, 94%). Crystallization from ether–hexane gave the analytical sample: mp 193.5–195° (vacuum), $[\alpha]^{25}D$ +17.9° (*c* 1.1, $CHCl_3$), $\lambda_{max}^{CHCl_3}$ 5.62 μ.

Anal. Calcd for $C_{20}H_{30}O_4$: C, 71.82; H, 9.04. Found: C, 71.93; H, 9.31.

Cyclic Ethylene Ketal of 2,4b-Dimethyl-1-hydroxymethyl-2-(1-hydroxy-1-methylethyl)dodecahydro-7(6H)-phenanthrone (XI).—To a stirred solution of 4.0 g of X in 100 ml of dry tetrahydrofuran was added, over a 10-min period, 100 ml of 1.22 *M* methylmagnesium bromide in ether. The resulting mixture was heated under reflux for 3 hr. It was then cooled, treated with 40 ml of saturated ammonium chloride solution, and was filtered through a bed of Celite. The filtrate was evaporated to near dryness and the residue was dissolved in 300 ml of ether–methylene chloride (3:1). The organic layer was washed with brine, dried (Na_2SO_4), and concentrated to dryness. The residue was crystallized twice (charcoal) from methylene chloride–ether–hexane to give 2.75 g (63%) of XI, mp 182.5–185.5° (vacuum). Crystallization from methylene chloride–ether gave the analytical sample: mp 184–186° (vacuum), $[\alpha]^{25}D$ −37.7° (*c* 1.0, $CHCl_3$), $\lambda_{max}^{CHCl_3}$ 2.76 μ.

Anal. Calcd for $C_{22}H_{38}O_4$: C, 72.09; H, 10.45. Found: C, 72.01; H, 10.61.

17,17-Dimethyl-16-oxa-5α-androstan-3-one (XII).—A solution of 2.5 g of XI and 0.25 g of *p*-toluenesulfonic acid in 100 ml of benzene was distilled slowly over a period of 1.5 hr, the volume being maintained constant by the simultaneous addition of fresh dry benzene. The reaction mixture was then diluted with an equal volume of ether and the organic layer was washed twice with 5% sodium bicarbonate solution and once with brine.

The dried (Na_2SO_4) organic extract was evaporated to dryness and the residue was dissolved in 130 ml of methanol and 15 ml of 3 *N* hydrochloric acid. The resulting solution was allowed to stand overnight at room temperature and was then concentrated to about half its original volume under reduced pressure. The residue was diluted with 150 ml of water and was extracted three times with ether–methylene chloride (3:1). The organic layers were washed with 5% sodium bicarbonate solution and brine, dried (Na_2SO_4), and concentrated. The residue was crystallized once from ether–hexane to give 1.23 g (59%) of XII, mp 134.9–136°. One further crystallization from ether–hexane gave the analytical sample: mp 135–136°, $[\alpha]^{25}D$ −13.9° (*c* 1.0, $CHCl_3$), $\lambda_{max}^{CHCl_3}$ 5.86 μ.

Anal. Calcd for $C_{20}H_{32}O_2$: C, 78.89; H, 10.59. Found: C, 78.70; H, 10.74.

Cyclic Ethylene Ketal of 17ξ-Hydroxy-16-oxa-5α-androstan-3-one (XIII).—A stock solution of disiamylborane[11] was prepared by adding a solution of 15.0 g of 2-methyl-2-butene in 40 ml of dry tetrahydrofuran to 100 ml of cold (0°) 1 *M* borane solution[21] (tetrahydrofuran). The resulting solution was then allowed to stand for 1 hr at room temperature, and a portion was used immediately for the following reaction.

(19) (a) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946); (b) R. G. Curtis, I. M. Heilbron, E. R. H. Jones, and G. F. Woods, *ibid.*, 461 (1953); (c) C. Djerassi, R. R. Engle, and A. Bowers, *J. Org. Chem.*, **21**, 1547 (1956).

(20) Dehydrobromination of the crude dibromide by heating under reflux in *sym*-collidine for 1 hr gave an inferior yield (40%) of IX.

(21) The 1 *M* borane solution was obtained from Metal Hydrides, Inc., Beverly, Mass.

To a stirred solution of 8.0 g of X in 80 ml of dry tetrahydrofuran was added, at room temperature and over a 30-min period, 100 ml of the above disiamylborane stock solution and the resulting mixture was allowed to stir at room temperature for 2 hr. The reaction mixture was then treated with 10 ml of saturated sodium sulfate solution and the precipitated inorganic salts were removed by filtration. The filtrate was evaporated to near dryness and the residue was diluted with 300 ml of ether–methylene chloride (3:1) The organic layer was washed with saturated sodium chloride solution and then with water. The organic solution was dried (Na_2SO_4) and concentrated to dryness to afford a colorless oil which was dissolved in benzene and chromatographed on a column (400 g) of silicic acid (400-ml fractions). The fractions eluted with 30% ethyl acetate–benzene and then pure ethyl acetate were concentrated and dissolved in benzene and chromatographed again using a 250-g column of silicic acid (250-ml fractions). The fractions eluted with 40% ethyl acetate–benzene, followed by pure ethyl acetate, were combined and concentrated. The residue was crystallized once from ether–hexane and then from methylene chloride–ether to give 1.94 g of XIII, mp 166.5–168° (vacuum). The mother liquors were combined and chromatographed as described above. Two crystallizations gave an additional 0.44 g, mp 167.5–169° (vacuum, total yield 30%). Crystallization from ether–hexane gave the analytical sample: mp 167–169° (vacuum), $[\alpha]^{25}D$ −42.2° (*c* 1.0, $CHCl_3$), λ_{max}^{KBr} 2.97 μ (no carbonyl absorption), $\lambda_{max}^{CHCl_3}$ 2.77 and trace (about 2%) carbonyl absorption at 5.83 μ, nmr ($CDCl_3$) τ 5.03 (C_{17} proton) and 6.03 (ethylene ketal protons).

Anal. Calcd for $C_{20}H_{32}O_4$: C, 71.39; H, 9.59. Found: C, 71.60; H, 9.92.

17ξ-Hydroxy-16-oxa-5α-androstan-3-one (XIV).—A solution of 2.25 g of XIII in 225 ml of tetrahydrofuran and 50 ml of 3 *N* hydrochloric acid was allowed to stand at room temperature for 3 days. Most of the solvent was then removed under vacuum and the residue was diluted with 250 ml of water. The resulting mixture was extracted with ether–methylene chloride (3:1) and the organic layers were washed with water, dried (N_2SO_4), and evaporated. The residue was dissolved in benzene and filtered through a short column (20 g) of silicic acid. The fractions eluted with 20% ethyl acetate–benzene and pure ethyl acetate were combined and evaporated. The residue was crystallized twice from methylene chloride–ether–hexane to give 1.04 g of crude XVI, mp 155.5–159° dec (vacuum). An additional 0.221 g, mp 158–160.5° dec (vacuum), was obtained from the mother liquors. Both samples were combined and crystallized once from acetonitrile to give 0.763 g (39%) of XIV: mp 161.5–163° dec (vacuum), $[\alpha]^{25}D$ −28.3° (*c* 1.1, $CHCl_3$), $\lambda_{max}^{CHCl_3}$ 2.77 and 5.85 μ, nmr ($CDCl_3$) τ 5.03 (doublet, J = 3.5 cps; this doublet collapses to a singlet upon addition of D_2O).

Anal. Calcd for $C_{18}H_{28}O_3$: C, 73.93; H, 9.65. Found: C, 73.97; H, 9.91.

Registry No.—IIa, 7785-89-9; IIb, 10022-25-0; III, 7785-90-2; IV, 7785-91-3; V, 7785-92-4; VI, 7785-93-5; VII, 7785-94-6; VIII, 10028-43-0; IX, 7785-95-7; X, 7785-96-8; XI, 7785-97-9; XII, 7785-98-0; XIII, 7785-99-1; XIV, 7786-00-7.

Acknowledgment.—We are indebted to Dr. Al Steyermark and his staff for the microanalyses, and to Dr. V. Toome, Mr. S. Traiman, and Dr. Floie M. Vane for the ultraviolet, infrared, and nmr spectra, respectively. We are also indebted to Mr. R. Vass for technical assistance.

The Absolute Configuration at C-20 in 11-Oxo-3,20,21-trihydroxy Steroids[1]

VERNON R. MATTOX AND WILEY VRIEZE

Section of Biochemistry, Mayo Clinic and Mayo Foundation, Rochester, Minnesota

Received September 26, 1966

The C-11 and C-21 oxygen atoms of 3α,20,21-trihydroxy-5β-pregnan-11-one, mp 233–234.5°, were removed by reactions which did not alter the configuration at C-20. The product was identical with 5β-pregnane-3α,20β-diol, a substance of known absolute configuration at C-20. It follows that the absolute configuration at C-20 in the original compound is β.

In a previous paper,[2] 3α,20-diacetoxy-11-oxo-5β-pregnan-21-oic acid (mp 199–200°) was shown to have the same C-20 configuration as a compound designated 3α,20β,21-trihydroxy-5β-pregnan-11-one[3] (IV). The initial assignment[4] of configuration at C-20 in the latter compound was based in part on application of the rule which states that the acetylation increments in optical rotatory values for 20β-hydroxy steroids are strongly positive and that those for 20α-hydroxy steroids are either negative or weakly positive.[5] Evidence subsequently obtained from several other lines of investigation[5] has been in agreement with the configuration which was assigned originally. By this method of correlation, the C-20 configuration in compound IV appeared to be the same as that in 5β-pregnane-3α,20β-diol.[4]

However, the use of optical rotatory values is not valid for assignment of configuration at the C-20 position in some circumstances.[6]

Consequently, we wished to correlate the C-20 configuration of 3α,20β,21-trihydroxy-5β-pregnan-11-one (IV) (and thus that of 3α,20-diacetoxy-11-oxo-5β-pregnan-21-oic acid,[2,6] mp 199–200°) with that of 5β-pregnane-3α,20β-diol by a direct procedure, independent of correlations derived from measurement of optical rotatory values. The objective was to remove the C-11 and C-21 oxygen functions from compound IV by use of reactions which would not disturb the configuration at C-20 and to determine whether the product was identical with 5β-pregnane-3α,20β-diol. That inversion of configuration at C-20 has not occurred during the process of removal of the oxygen functions at C-11 and C-21 can be assumed if (1) one uses well-known reactions which ordinarily do not cause inversion of configuration at the asymmetric center of interest, (2) one removes each function by two or more different pathways, and (3) the different pathways lead to the same product. This conclusion should then be on as firm a basis as is the absolute configuration which has been assigned to 5β-pregnane-3α,20β-diol[7] through

(1) This investigation was supported in part by Research Grant AM-5452 from the National Institutes of Health, U. S. Public Health Service.

(2) V. R. Mattox and Wiley Vrieze, *J. Org. Chem.*, **29**, 3158 (1964).

(3) L. H. Sarett, *J. Am. Chem. Soc.*, **71**, 1165 (1949).

(4) L. H. Sarett, *ibid.*, **71**, 1175 (1949).

(5) L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, pp 612–618.

(6) M. L. Lewbart and V. R. Mattox, *J. Org. Chem.*, **28**, 1779 (1963).

(7) Reference 5, p 338.