C-19 Functional Steroids. X.[1a] 17β-Hydroxy-1β,19-cyclo-5α-androstan-2-one and Related Compounds[1b]

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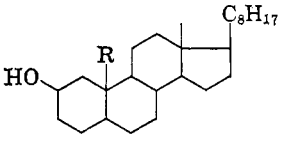
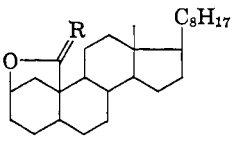
Photolysis of the nitrite ester derived from 5α-cholestan-2β-ol gave 19-oximino-5α-cholestan-2β-ol which on treatment with nitrous acid gave 2β,19-epoxy-5α-cholestan-19-ol. Reduction with lithium aluminum hydride formed 5α-cholestane-2β,19-diol. Selective oxidation of this diol with N-bromosuccinimide furnished 19-hydroxy-5α-cholestan-2-one which with methanesulfonyl chloride in pyridine solution produced 1β,19-cyclo-5α-cholestan-2-one. Wolff–Kishner reduction of this ketone gave 1β,19-cyclo-5α-cholestane. Related experiments in the androstane series are described. Attempts to obtain 3-substituted 1β,19-cyclo-5α steroids failed.

In order to obtain further information regarding the effect of the cyclopropane ring on the biological activity of steroids,[2] the synthesis of compounds having the cyclopropane ring fused to the 1β,10β position was required. Analogous 12β,18-cyclo steroids have been described by Kerwin, *et al.*,[3] and other structures involving C-19 in a cyclopropane ring are the 5β,19-cyclo steroids[4] and the 9β,19-cyclo steroids.[5] The present 1β,19-cyclo-2-oxo steroids may be viewed as inverted ring A derivatives of conventional 3-keto-Δ^4steroids having a cyclopropane ring in place of the normal conjugated double bond.

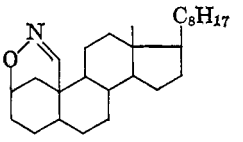
Earlier work from this laboratory[6] had shown that C-19 functionalization could be carried out by photolysis of nitrite esters of 2β-hydroxy steroids or by lead tetraacetate oxidation of such compounds. In the present case, treatment of I[7] with nitrosyl chloride followed by photolysis[8] gave the oxime II, which on treatment with nitrous acid[9] formed the key intermediate III. Compound III could also be obtained, together with IV,[10] by the action of lead tetraacetate and iodine on I. Although the mixture of III and IV was intractable, reduction with sodium borohydride furnished VIII from III, and the resulting mixture of IV and VIII could be separated. Oxidation of III afforded the lactone V, which on lithium aluminum hydride reduction gave VIII. The action of methanol and *p*-toluenesulfonic acid on III gave the ether VI. Hydrolysis of II with hydrochloric acid in acetone at ordinary temperature also yielded III, but when the reaction was carried out in boiling acetone a different product VII was produced. This material had no



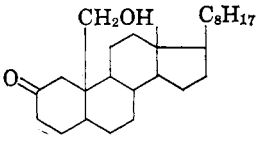
I, R = CH_3
II, R = CHNOH
VIII, R = CH_2OH
IX, R = CN
XI, R = $CH_2OCO_2C_2H_5$



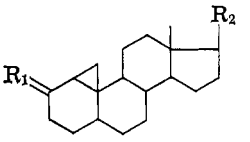
III, R = HO, H
IV, R = H_2
V, R = O
VI, R = CH_3O, H
X, R = NH



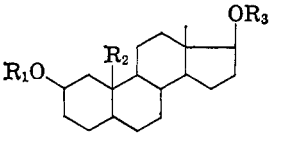
VII



XII



XIII, R_1 = O; R_2 = C_8H_{17}
XIV, R_1 = H_2; R_2 = C_8H_{17}
XX, R_1 = O; R_2 = OH



XV, R_1 = H; R_2 = CH_3; R_3 = H
XVI, R_1 = H; R_2 = CH_3; R_3 = $CO_2C_2H_5$
XVII, R_1 = $CO_2C_2H_5$; R_2 = CH_3; R_3 = $CO_2C_2H_5$
XVIII, R_1 = H; R_2 = CHNOH; R_3 = $CO_2C_2H_5$
XIX, R_1 = H; R_2 = CH_2OH; R_3 = $CO_2C_2H_5$

hydroxyl group as shown by the infrared spectrum; the n.m.r. showed a one-proton singlet at δ 5.62 arising from C-19, a multiplet at 245–265 c.p.s. from the 2α-H, and the C-18 singlet at δ 0.62. Compound VII is formulated as an oxazole on the basis of these spectral data taken together with the analytical results. Oxidation of VII with chromic acid furnished V. Compound V could also be obtained by treatment of II with acetic anhydride to give the nitrile IX which

(1) (a) Paper IX: M. E. Wolff and J. A. Muñoz, *J. Org. Chem.*, **30**, 920 (1965). (b) This investigation was supported by a research grant (AM 05016) from the National Institute of Arthritis and Metabolic Diseases, U. S. Public Health Service. The n.m.r. spectrometer used in this study was provided by a grant (NSF-G 21268) from the National Science Foundation. (c) On leave from Sankyo Co., Ltd., Tokyo, Japan. (d) From the Ph.D. Thesis of T. Morioka, University of California, San Francisco, Calif., 1965.

(2) M. E. Wolff, W. Ho, and R. Kwok, *J. Med. Chem.*, **7**, 577 (1964).

(3) J. F. Kerwin, M. E. Wolff, F. F. Owings, B. B. Lewis, B. Blank, A. Magnani, C. Karash, and V. Georgian, *J. Org. Chem.*, **27**, 3628 (1962); V. Georgian, J. F. Kerwin, M. E. Wolff, and F. F. Owings, *J. Am. Chem. Soc.*, **84**, 3594 (1962); *cf.* M. Akhtar, D. H. R. Barton, and P. G. Sammes, *ibid.*, **86**, 3394 (1964).

(4) D. H. R. Barton and J. M. Beaton, *ibid.*, **83**, 4083 (1961); M. S. Heller, H. Wehrli, K. Schaffner, and O. Jeger, *Helv. Chim. Acta*, **45**, 1261 (1962); K. Heusler, J. Kalvoda, G. Anner, and A. Wettstein, *ibid.*, **45**, 2575 (1962); J. J. Bonet, H. Wehrli, and K. Schaffner, *ibid.*, **45**, 2615 (1962); J. Tadanier and W. Cole, *Tetrahedron Letters*, 1345 (1964); M. Akhtar and D. H. R. Barton, *J. Am. Chem. Soc.*, **86**, 1528 (1964); O. Halpern, P. Crabbé, A. D. Cross, I. Delfin, L. Cervantes, and A. Bowers, *Steroids*, **4**, 1 (1964).

(5) H. Wehrli, M. S. Heller, K. Schaffner, and O. Jeger, *Helv. Chim. Acta*, **44**, 2162 (1961).

(6) R. Kwok and M. E. Wolff, *J. Org. Chem.*, **28**, 423 (1963).

(7) A. Furst and P. A. Plattner, *Helv. Chim. Acta*, **32**, 275 (1949).

(8) D. H. R. Barton, J. M. Beaton, L. E. Geller, and M. M. Pechet, *J. Am. Chem. Soc.*, **82**, 2640 (1960); **83**, 4076 (1961).

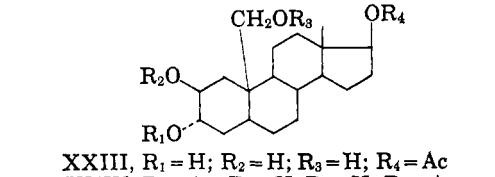
(9) D. H. R. Barton and J. M. Beaton, *ibid.*, **82**, 2641 (1960); **83**, 4083 (1961).

(10) P. N. Rao and J. C. Uroda, *Naturwiss.*, **50**, 548 (1963). These authors state that a 3α-acetate function "negates" preferential 2,19-oxide formation during lead tetraacetate oxidation of 2β-hydroxy steroids, but this was found not to be the case in our prior work in ref. 6.

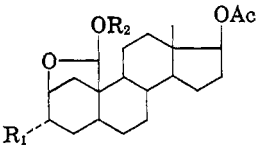
with methanol and hydrogen chloride produced V *via* the intermediate imino ether X.

The primary alcohol group in the diol VIII could be protected by cathylation giving XI, but it was also found that VIII could be oxidized directly to the hydroxy ketone XII with N-bromosuccinimide. This compound on treatment with methanesulfonyl chloride in pyridine solution directly gave the cyclopropane derivative XIII, presumably *via* an intermediate 19-mesylate. The action of *p*-toluenesulfonyl chloride on XII failed to effect cyclization, probably owing to steric effects. Wolff–Kishner reduction of XIII gave the hydrocarbon XIV.

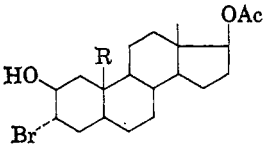
In the androstane series, reduction of 2β,3β-epoxy-5α-androstan-17β-ol[11] with lithium aluminum hydride gave the diol XV which with ethyl chlorocarbonate formed a mixture of the esters XVI and XVII. Photolysis of the nitrite ester of XVI afforded the oxime XVIII, which on nitrous acid degradation followed by borohydride reduction yielded XIX. Without isolation of intermediates, compound XIX successively was oxidized selectively, allowed to react with methanesulfonyl chloride in pyridine solution, and cyclized using sodium methoxide to give the cyclopropane XX.



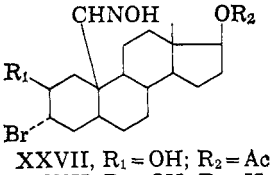
XXIII, R_1 = H; R_2 = H; R_3 = H; R_4 = Ac
XXIV, R_1 = Ac; R_2 = H; R_3 = H; R_4 = Ac
XXV, R_1 = Ms; R_2 = Ms; R_3 = Ms; R_4 = Ac



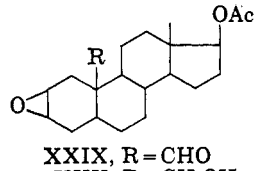
XXI, R_1 = OAc; R_2 = H
XXII, R_1 = OAc; R_2 = Ac
XXVIII, R_1 = Br; R_2 = Ac



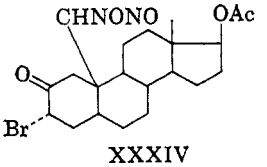
XXVI, R = CH_3
XXXI, R = CH_2OH



XXVII, R_1 = OH; R_2 = Ac
XXXII, R_1 = OH; R_2 = H
XXXIII, R_1 = O; R_2 = Ac



XXIX, R = CHO
XXX, R = CH_2OH



XXXIV

Attempts to obtain 3-substituted 1β,19-cyclo steroids were not successful. Treatment of *syn*-19-oximino-5α-androstane-2β,3α,17β-triol 3,17-diacetate[6] with nitrous acid gave the hemiacetal XXI together with the hemiacetal acetate XXII. Reduction of XXI with sodium borohydride proceeded with concomitant partial saponification giving a mixture of XXIII and XXIV. Attempted selective oxidation of XXIV with N-bromosuccinimide failed; attempted partial mesylation of XXIII gave only the trimesylate XXV. To avoid the presence of a 17-acetate function, 2β,3β-epoxy-5α-androstan-17β-ol[11] was allowed to react with hydrogen bromide, and the nitrite ester derived from the resulting XXVI[12] was photolyzed giving XXVII. The action of nitrous acid on XXVII formed a mixture of XXVIII together with the unexpected epoxide XXIX. Reduction of XXIX gave XXX and this epoxide was opened with hydrogen bromide to afford XXXI. However, an attempt to oxidize this material with N-bromosuccinimide gave XXX. Acid hydrolysis of XXVII furnished only the diol; oxidation of XXVII with N-bromoacetamide[13a] gave XXXIII. Treatment of XXXIII with nitrous acid furnished only the nitrimine XXXIV, indicating that anchimeric assistance by the hydroxyl group plays a role in these nitrous acid degradations.

Compound XX was devoid of anabolic–androgenic (Hershberger test) or estrogenic activity on subcutaneous administration in rats. Compounds XXI, XXIX, and XXX, given subcutaneously, each had 1% of the estrogenic activity of estradiol in castrate female rats.[13]

Experimental[14]

19-Oximino-5α-cholestan-2β-ol (II).—A solution of 10.0 g. (0.026 mole) of I[7] in 30 ml. of pyridine was treated with excess nitrosyl chloride and poured into ice–water. The resulting precipitate was filtered, washed with water, and air dried to afford 8.0 g. of crude 5α-cholestan-2β-ol nitrite, m.p. 50–58°. Under a nitrogen atmosphere, a solution of 8 g. of the crude nitrite ester in 200 ml. of toluene was irradiated for 2 hr. at 0° by means of 200-w. high-pressure mercury arc equipped with a borosilicate filter contained in a quartz immersion well. The course of the reaction was followed by periodic testing for unreacted nitrite by means of a spot plate test with the diphenylamine sulfuric acid reagent. After a negative test was obtained, the solvent was removed under reduced pressure, and the resulting 19-nitroso compound was refluxed in 2-propanol for 1 hr. The solvent was removed under reduced pressure. The residue was washed with petroleum ether and filtered off to afford 2.3 g. of product, m.p. 205–210°. The analytical sample was recrystallized from ethanol and had m.p. 212–214°, $[\alpha]^{27}D$ +12° (*c* 0.55, $CHCl_3$), λ_{max}^{KBr} 3.3 μ (broad).

Anal. Calcd. for $C_{27}H_{47}NO_2$: C, 77.64; H, 11.34. Found: C, 77.88; H, 11.25.

2β,19-Epoxy-5α-cholestan-19-ol (III). **Method A.**—To a stirred solution of 2.0 g. (0.005 mole) of II in 700 ml. of acetic acid there slowly was added 200 ml. of 10% sodium nitrite solution. The mixture was kept at 27° for 30 min. with occasional shaking, diluted with 1 l. of water, and extracted with ether. The ether layer was washed with 10% sodium bicarbonate solution and water, dried over sodium sulfate, and evaporated to dryness under reduced pressure. The residue was chromatographed on 100 g. of neutral alumina; 0.8 g. of product was eluted with ether containing 8% methanol. Recrystalliza-

(11) K. L. Williamson and W. S. Johnson, *J. Org. Chem.*, **26**, 4563 (1961).

(12) The preparation of this compound by another method was recently described by P. D. Klimstra and R. E. Counsell, *J. Med. Chem.*, **8**, 48 (1965).

(13) The biological assays were performed at Endocrine Laboratories, Madison, Wis.

(14) Melting points were determined with a Thomas–Hoover apparatus equipped with a corrected thermometer. Infrared spectra were obtained with a Beckman IR-5 instrument. Microanalyses were performed by the Microanalytical Department, University of California, Berkeley, Calif. Optical rotations were obtained in a 0.5-dm. tube with a Rudolph photoelectric polarimeter. N.m.r. spectra were obtained at a field strength of 60 Mc./sec. on samples in deuteriochloroform solution on a Varian A-60 instrument using tetramethylsilane as internal standard. Resonance positions are reported in δ values (p.p.m.) where possible; unresolved humps are described in c.p.s. units (60 Mc./sec.). It is a pleasure to thank Mr. H. Rolewicz for excellent technical assistance.

tion from aqueous methanol gave the analytical sample, m.p. 136–139°, $[\alpha]^{27}D$ +44° (*c* 0.6, $CHCl_3$), λ_{max}^{KBr} 2.98 and 5.82 μ.

Anal. Calcd. for $C_{27}H_{46}O_2 \cdot 0.5H_2O$: C, 78.78; H, 11.50. Found: C, 79.12; H, 11.37.

From the benzene fractions there was obtained 0.4 g. of material, m.p. 109–111°, which on recrystallization from benzene–methanol gave colorless crystals, m.p. 110–111°, $[\alpha]^{27}D$ +56° (*c* 0.6, $CHCl_3$), λ_{max}^{KBr} 8.95 and 10.1 μ. This material was shown to be VI by comparison with an authentic sample, and presumably is an artifact formed during the isolation procedure.

Anal. Calcd. for $C_{28}H_{48}O_2$: C, 80.71; H, 11.61. Found: C, 80.76; H, 11.37.

Method B.—A mixture of 0.10 g. (0.00025 mole) of II, 5 ml. of benzene, 1 ml. of water, 20 ml. of acetone, and 0.5 ml. of concentrated hydrochloric acid was kept at room temperature for 18 hr. The solvent was evaporated to dryness under reduced pressure, and the crystalline residue was washed with water and dried to afford 0.07 g. of crystals, m.p. 130–135°. Recrystallization from aqueous methanol gave a pure sample, m.p. 135–138°, undepressed upon admixture with an authentic sample from the previous procedure.

2β,19-Epoxy-5α-cholestane (IV).—A mixture of 0.50 g. of calcium carbonate and 1.5 g. of lead tetraacetate in 50 ml. of anhydrous cyclohexane was boiled under reflux for 1 hr. To this mixture, 0.5 g. (0.0013 mole) of I and 0.08 g. of iodine was added, and the suspension was boiled under reflux over a 500-w. incandescent lamp for 30 min. The mixture was cooled and filtered, and the filtrate was washed with 25% sodium thiosulfate solution and water. The residue obtained from evaporation of the dried solution was treated with sodium borohydride and was chromatographed on 25 g. of neutral alumina; 0.20 g. of product, m.p. 76–80°, was eluted by the ether–benzene fraction. Recrystallization from acetone gave the analytical sample, m.p. 90–92°, $[\alpha]^{27}D$ +32° (*c* 1, $CHCl_3$), λ_{max}^{KBr} 9.88 μ; lit.[10] m.p. 91–93°, $[\alpha]^{27}D$ +41° ($CHCl_3$).

Anal. Calcd. for $C_{27}H_{46}O$: C, 83.87; H, 11.99. Found: C, 83.50; H, 11.55.

2β-Hydroxy-5α-cholestan-19-oic Acid 2,19-Lactone (V).—A refluxing solution of 0.10 g. (0.00026 mole) of VII in 50 ml. of benzene and 25 ml. of acetone was treated with excess 8 *N* chromic acid reagent for 5 min., cooled, and kept at 27° for 3 hr. The excess oxidant was decomposed with 2-propanol, and the solvent was removed under reduced pressure. The residue was washed with water, filtered, and dried to afford 0.06 g. of product. Recrystallization from acetonitrile gave the analytical sample: m.p. 142–144°, $[\alpha]^{27}D$ +41° (*c* 0.6, $CHCl_3$), λ_{max}^{KBr} 5.66 and 10.35 μ; lit.[10] m.p. 145–146°, $[\alpha]^{27}D$ +48° ($CHCl_3$).

Anal. Calcd. for $C_{27}H_{44}O_2$: C, 80.94; H, 11.07. Found: C, 81.05; H, 10.90.

2β,19-Epoxy-19-methoxy-5α-cholestane (VI).—A solution of 0.10 g. (0.00025 mole) of III and 10 mg. of *p*-toluenesulfonic acid in 5 ml. of methanol was kept at 50° for 5 min. and filtered. The filtrate was cooled, and the resulting precipitate was collected to afford 0.07 g. of product, m.p. 96–103°. Recrystallization from methanol gave colorless crystals, m.p. 110–112°, identical with the material described in the preparation of III.

***anti*-19-Oximino-5α-cholestan-2β-ol O,N-Ether (VII).**—A solution of 1.0 g. (0.0025 mole) of II and 5 ml. of concentrated hydrochloric acid in 150 ml. of acetone was heated under reflux for 1 hr. The solution was cooled to room temperature, and the resulting precipitate was filtered and dried to afford 0.38 g. of product, m.p. 215–235°. The mother liquor was concentrated further and another 0.35 g. of crystals, m.p. 227–234°, was obtained. Recrystallization from ethanol–benzene gave the analytical sample: m.p. 235–245°; $[\alpha]^{27}D$ +95° (*c* 0.7, $CHCl_3$); λ_{max}^{KBr} 10.35 and 11.58 μ; n.m.r. 0.62 (C-18 methyl), 245–265 c.p.s. (C-2 H), and 5.62 (C-19 H).

Anal. Calcd. for $C_{27}H_{45}NO$: C, 81.14; H, 11.35; N, 3.51. Found: C, 80.84; H, 11.07; N, 3.23.

5α-Cholestane-2β,19-diol (VIII).—A solution of 2.0 g. (0.005 mole) of V and 2.0 g. of lithium aluminum hydride in 150 ml. of anhydrous tetrahydrofuran was boiled under reflux for 3 hr. The excess hydride was decomposed with ethyl acetate under ice-bath cooling, and the mixture was acidified with 20% hydrochloric acid and extracted with ether. After drying over sodium sulfate, the solvent was evaporated. Recrystallization of the residue from acetonitrile gave 1.3 g. of crude product, m.p. 175–185°. The analytical sample had m.p. 186–187°, $[\alpha]^{27}D$ +28° (*c* 0.5, $CHCl_3$), λ_{max}^{KBr} 3.08 μ.

Anal. Calcd. for $C_{27}H_{48}O_2$: C, 80.14; H, 11.96. Found: C, 80.16; H, 12.09.

2β-Hydroxy-5α-cholestane-19-nitrile (IX).—A solution of 0.50 g. (0.00125 mole) of II in 25 ml. of acetic anhydride was boiled under reflux for 2 hr., and poured into 150 ml. of water. It was neutralized with 5% sodium hydroxide solution and extracted with ether. The ether layer was washed with water, dried over sodium sulfate, and evaporated. The gummy residue was dissolved in 10 ml. of ether and added to 1.0 g. of potassium hydroxide and 2 ml. of water in 60 ml. methanol. The resulting solution was kept at 27° for 18 hr. The solvent was evaporated under reduced pressure, and the residue was washed with water and dried to afford 0.30 g. of crystals, m.p. 145–156°. Recrystallization from aqueous methanol gave the analytical sample, m.p. 162–164°, $[\alpha]^{27}D$ +27° (*c* 1, $CHCl_3$), λ_{max}^{KBr} 3.0 and 4.5 μ.

Anal. Calcd. for $C_{27}H_{45}NO$: C, 81.14; H, 11.35; N, 3.51. Found: C, 81.24; H, 11.10; N, 3.62.

5α-Cholestane-2β,19-diol 19-Cathylate (XI).—A solution of 0.20 g. (0.0005 mole) of VIII and 1 ml. of ethyl chloroformate in 10 ml. of pyridine was kept at 27° for 18 hr. It was diluted with 150 ml. of cold 10% hydrochloric acid and extracted with ether. The ether layer was washed with water, dried over sodium sulfate, and evaporated to dryness. The residue was chromatographed on 10 g. of neutral alumina; 0.09 g. of product, m.p. 97–101°, was eluted by ether containing 4% methanol. Recrystallization from acetonitrile gave the analytical sample: m.p. 105–107°; $[\alpha]^{27}D$ +16° (*c* 1, $CHCl_3$); λ_{max}^{KBr} 2.99, 5.81, 7.72, and 8.00 μ.

Anal. Calcd. for $C_{30}H_{52}O_4$: C, 75.58; H, 11.00. Found: C, 75.79; H, 10.87.

19-Hydroxy-5α-cholestan-2-one (XII).—A solution of 1.00 g. (0.0025 mole) of VIII, 0.3 ml. of pyridine, 0.3 ml. of water, and 0.70 g. of N-bromosuccinimide in 30 ml. of *t*-butyl alcohol was kept at 50° for 1 hr. It was diluted with 10% sodium bicarbonate solution, and the resulting precipitate was filtered, washed with water, and dried to afford 0.60 g. of product, m.p. 165–168°. Recrystallization from acetonitrile gave the analytical sample, m.p. 171–173°, $[\alpha]^{27}D$ +38° (*c* 0.8, $CHCl_3$), λ_{max}^{KBr} 3.00 and 5.90 μ.

Anal. Calcd. for $C_{27}H_{46}O_2$: C, 80.54; H, 11.52. Found: C, 80.80; H, 11.30.

1β,19-Cyclo-5α-cholestan-2-one (XIII).—A solution of 0.30 g. (0.00075 mole) of XII and 0.5 ml. of methanesulfonyl chloride in 10 ml. of pyridine was kept at 27° for 8 hr., diluted with 150 ml. of water, and extracted with ether. The ether layer was washed 5% hydrochloric acid and water, and dried over sodium sulfate. The solvent was evaporated to dryness, and the residue was recrystallized from acetonitrile to afford 0.12 g. of product, m.p. 105–110°, which was chromatographed on 10 g. of neutral alumina. The product, eluted with ether containing 1% methanol, was recrystallized from aqueous methanol to give the analytical sample, m.p. 118–122°, $[\alpha]^{27}D$ −18° (*c* 1, $CHCl_3$), λ_{max}^{KBr} 5.98 μ.

Anal. Calcd. for $C_{27}H_{44}O$: C, 84.31; H, 11.53. Found: C, 84.04; H, 11.32.

1β,19-Cyclo-5α-cholestane (XIV).—A mixture of 1 g. of potassium hydroxide, 1 ml. of 95% hydrazine, and 0.10 g. (0.00021 mole) of XIII in 10 ml. of anhydrous diethylene glycol was heated under reflux for 1 hr. The hydrazine was distilled from the mixture, and the solution was heated under reflux for an additional 3 hr. It was cooled, diluted with 100 ml. of water, acidified by addition of concentrated hydrochloric acid, and extracted with ether. The ether layer was dried over sodium sulfate and evaporated, and the residue was chromatographed on 5 g. of neutral alumina; 0.04 g. of product, m.p. 55–57°, was obtained from the petroleum ether fraction. The analytical sample, recrystallized from aqueous methanol had m.p. 55–57°, $[\alpha]^{29}D$ + 10° (*c* 1, $CHCl_3$).

Anal. Calcd. for $C_{27}H_{46}$: C, 87.49; H, 12.51. Found: C, 87.38; H, 12.37.

5α-Androstane-2β,17β-diol (XV).—A solution of 3.0 g. (0.0103 mole) of 2β,3β-epoxy-5α-androstan-17β-ol[11] and 1.5 g. of lithium aluminum hydride in 300 ml. of anhydrous ether was heated under reflux for 1 hr. The excess lithium aluminum hydride was decomposed by addition of ethyl acetate under ice-bath cooling. The mixture was diluted with 200 ml. of 10% hydrochloric acid and extracted with ether. The ether extract was washed with water, and after drying over sodium sulfate, the solvent was evaporated under reduced pressure to afford 2.8 g. of crude product. The crystals were recrystallized from acetonitrile to

furnish 2.0 g. of material, m.p. 170–175°. Further recrystallization gave the analytical sample, m.p. 181–183°, $[\alpha]^{27}D$ +23° (*c* 1, $CHCl_3$), λ_{max}^{KBr} 3.02 μ.

Anal. Calcd. for $C_{19}H_{32}O_2$: C, 77.10; H, 11.03. Found: C, 76.79; H, 10.98.

5α-Androstane-2β,17β-diol 17-Cathylate (XVI).—To a solution of 3.7 g. (0.013 mole) of XV in 150 ml. of pyridine there was added dropwise 8.0 g. of ethyl chloroformate under ice-bath cooling. The solution was kept for 24 hr. at 27°, diluted with 500 ml. of water, and extracted with ether. The ether layer was washed with 5% hydrochloric acid and water and dried over sodium sulfate. The solvent was evaporated under reduced pressure, and the gummy residue was chromatographed on 100 g. of neutral alumina; 1.5 g. of product was eluted by ether containing 4% methanol. Recrystallization from aqueous methanol gave the analytical sample: m.p. 129–130°; $[\alpha]^{27}D$ +11° (*c* 1.1, $CHCl_3$); λ_{max}^{KBr} 3.02, 5.72, and 7.98 μ.

Anal. Calcd. for $C_{22}H_{36}O_4$: C, 72.49; H, 9.96. Found: C, 72.27; H, 9.75.

5α-Androstane-2β,17β-diol dicathylate (XVII) was obtained from the benzene–ether fraction in the chromatography described for the preparation of XVI; 1.5 g. of eluted product was recrystallized from aqueous methanol to afford the analytical sample: m.p. 117–121; $[\alpha]^{27}D$ +1° (*c* 0.5, $CHCl_3$); λ_{max}^{KBr} 5.78, 7.85, and 8.00 μ.

Anal. Calcd. for $C_{25}H_{40}O_6$: C, 68.77; H, 9.24. Found: C, 68.50; H, 9.08.

***syn*-19-Oximino-5α-androstane-2β,17β-diol 17-Cathylate (XVIII).**—A solution of 0.80 g. (0.0022 mole) of XVI in 3 ml. of pyridine was treated with excess nitrosyl chloride and poured into ice water. The precipitate was filtered, washed with water, and air dried to afford 0.70 g. of crude nitrite ester, m.p. 88–93°. A solution of 0.70 g. of the crude nitrite ester in 200 ml. of toluene was irradiated as described for II. The resulting 19-nitroso compound was isomerized in 2-propanol. The residue was chromatographed on 40 g. of neutral alumina; 0.25 g. of oxime, m.p. 230–236°, was eluted by ether containing 8% methanol. Recrystallization from aqueous methanol gave the analytical sample: m.p. 230–236°; $[\alpha]^{27}D$ −25° (*c* 0.8, $CHCl_3$); λ_{max}^{KBr} 3.17, 3.25, 5.78, and 7.94 μ.

Anal. Calcd. for $C_{22}H_{25}NO_5$: C, 67.14; H, 8.99. Found: C, 67.40; H, 8.75.

5α-Androstane-2β,17β,19-triol 17-Cathylate (XIX).—To an ice-cold solution of 1.0 g. (0.0025 mole) of XVIII in 200 ml. of acetic acid there slowly was added 80 ml. of 10% sodium nitrite solution. The solution was kept at 27° for 3 hr. with occasional shaking, diluted with 300 ml. of water, and extracted with ether. The ether layer was washed with 10% sodium bicarbonate solution and water, dried (Na_2SO_4), and evaporated. The gummy residue was chromatographed on 50 g. of neutral alumina; 0.60 g. of the 19-aldehyde was eluted by ether containing 4% methanol. A solution of 1.2 g. of sodium borohydride in 100 ml. of methanol was added slowly to a solution of this material in 100 ml. of methanol under ice-bath cooling. The mixture was kept for 2 hr. at 15° and diluted with 500 ml. of water. The water was saturated with sodium chloride and the resulting precipitate was filtered and dried. The crystals were recrystallized from methanol–hexane to afford 0.30 g. of product, m.p. 155–165°. The analytical sample had m.p. 167–170°; $[\alpha]^{27}D$ +4° (*c* 0.5, $CHCl_3$); λ_{max}^{KBr} 3.05, 5.75, and 7.95 μ.

Anal. Calcd. for $C_{22}H_{36}O_5$: C, 69.44; H, 9.54. Found: C, 69.49; H, 9.29.

17β-Hydroxy-1β,19-cyclo-5α-androstan-2-one (XX).—To a warm solution of 0.30 g. (0.0008 mole) of XIX, in a mixture of 0.25 ml. of pyridine, 0.25 ml. of water, and 10 ml. of *t*-butyl alcohol, was added 0.30 g. of N-bromosuccinimide, and the mixture was kept at 80° for 1 hr. The mixture was cooled and diluted with 30 ml. of 10% sodium bicarbonate solution. The product was extracted with ether, and the ether layer was washed with water, dried over sodium sulfate, and evaporated. The gummy residue was chromatographed on 20 g. of neutral alumina. The fraction (0.15 g.) obtained with ether containing 4% methanol was dissolved in 5 ml. of pyridine and treated with 0.2 ml. of methanesulfonyl chloride. The solution was kept for 3 hr. at 27° and diluted with 20 ml. of ice–water. The resulting solution was extracted with ether, and the ether layer was washed with water and dried (Na_2SO_4), and the solvent was evaporated. The gummy residue was chromatographed on 5 g. of neutral alumina. The fraction (0.05 g.) obtained with ether containing 2% methanol was dissolved in 10 ml. of methanol and boiled under reflux for 2 hr. in the presence of 0.10 g. of sodium methoxide. The solution was diluted with 50 ml. of water, acidified with 5% hydrochloric acid, and saturated with sodium chloride. The resulting precipitate was filtered and dried to afford 0.03 g. of crude material which was chromatographed on 5 g. of neutral alumina. The product was eluted with ether containing 4% methanol. Recrystallization from aqueous methanol gave 8 mg. of analytical sample, m.p. 184–187°, $[\alpha]^{27}D$ −37° (*c* 0.5, $CHCl_3$), λ_{max}^{KBr} 2.98 and 6.02 μ.

Anal. Calcd. for $C_{19}H_{28}O_2$: C, 79.12; H, 9.79. Found: C, 78.89; H, 9.74.

2β,19-Epoxy-5α-androstane-3α,17β,19-triol 3,17-Diacetate (XXI).—A solution of 10 g. of sodium nitrite in 80 ml. of water was added slowly to a solution of 2.6 g. of *syn*-19-oximino-5α-androstane-2β,3α,17β-triol 3,17-diacetate[6] in 150 ml. of acetic acid. The solution was kept at 27° for 2 hr., diluted with 500 ml. of water, and extracted with ether. The ether layer was washed with 10% sodium bicarbonate solution and dried over sodium sulfate. The solvent was evaporated and the gummy residue was chromatographed on 100 g. of neutral alumina; 1.5 g. of gummy material was eluted with ether containing 4% methanol. Crystallization from hexane gave 700 mg. of product, m.p. 125–132°. The analytical sample had m.p. 128–132°; $[\alpha]^{27}D$ +29° (*c* 0.8, $CHCl_3$); λ_{max}^{KBr} 2.95, 5.79, and 8.03 μ.

Anal. Calcd. for $C_{23}H_{34}O_6$: C, 67.85; H, 8.43. Found: C, 67.71; H, 8.37.

2β,19-Epoxy-5α-androstane-3α,17β,19-triol triacetate (XXII, 0.30 g.) was eluted by benzene–ether in the chromatographic separation described in the preparation of XXI. The analytical sample, obtained from methanol, had m.p. 210–213°; $[\alpha]^{27}D$ +42° (*c* 0.6, $CHCl_3$); λ_{max}^{KBr} 5.80 and 8.15 μ (broad); n.m.r., δ 0.75 (C-18 methyl), 2.07, 2.15 (acetate methyl), 260–300 c.p.s. (C-17, 2,3-H), and 6.22 (C-19 H).

Anal. Calcd. for $C_{25}H_{36}O_7$: C, 66.84; H, 8.09. Found: C, 66.66; H, 7.92.

5α-Androstane-2β,3α,17β,19-tetraol 17-Acetate (XXIII).—A solution of 1.5 g. (0.0037 mole) of XXI and 3.0 g. of sodium borohydride in 80 ml. of ethanol was kept at 27° for 10 hr. It was diluted with 500 ml. of water, and the resulting precipitate was filtered and dried. Recrystallization from aqueous methanol afforded 0.50 g. of crystals, m.p. 255–260°. The analytical sample had m.p. 259–261°; $[\alpha]^{27}D$ +15° (*c* 0.7, 95% EtOH); λ_{max}^{KBr} 3.03 (broad), 5.82, and 8.05 μ.

Anal. Calcd. for $C_{21}H_{34}O_5$: C, 68.82; H, 9.35. Found: C, 69.07; H, 9.36.

5α-Androstane-2β,3α,17β,19-tetraol 3,17-Diacetate (XXIV).—A solution of 0.50 g. of sodium borohydride in 30 ml. of methanol was added slowly to a solution of 1.0 g. (0.0025 mole) of XXII in 50 ml. of methanol under ice-bath cooling. The solution was kept at 5° for 1 hr., diluted with 200 ml. of water, and acidified with 5% hydrochloric acid. The resulting precipitate was filtered, dried, and chromatographed on 50 g. of neutral alumina; 0.50 g. of crude material was eluted by ether containing 8% methanol. Recrystallization from aqueous methanol gave 0.30 g. of product, m.p. 154–158°. The analytical sample had m.p. 159–162°; $[\alpha]^{27}D$ +31° (*c* 0.5, $CHCl_3$); λ_{max}^{KBr} 2.98, 5.75, and 5.85 μ.

Anal. Calcd. for $C_{23}H_{36}O_6$: C, 67.62; H, 8.88. Found: C, 67.63; H, 8.56.

5α-Androstane-2β,3α,17β,19-tetraol 17-Acetate 2,3,19-Trimethanesulfonate (XXV).—A solution of 0.07 g. (0.00010 mole) of XXIII and 0.6 ml. of methanesulfonyl chloride in 3 ml. of pyridine was kept at 27° for 10 hr. The solution was diluted with ice–water and extracted with ether. The ether layer was washed with water and dried over sodium sulfate, and the solvent was evaporated to dryness. The residue was chromatographed on 5 g. of neutral alumina; 0.04 g. of product was eluted by ether containing 4% methanol. Recrystallization from aqueous ethanol gave the analytical sample: m.p. 188–190° (sinters at 183°); $[\alpha]^{27}D$ +2° (*c* 1, $CHCl_3$); λ_{max}^{KBr} 5.80, 7.40, and 8.50 μ.

Anal. Calcd. for $C_{24}H_{40}O_{11}S_3$: C, 47.82; H, 6.71. Found: C, 48.03; H, 6.63.

3α-Bromo-5α-androstane-2β,17β-diol 17-Acetate (XXVI).—A solution of 13.0 g. (0.0401 mole) of 2β,3β-epoxy-5α-androstan-17β-ol acetate[6] in 600 ml. of anhydrous ether was saturated with a slow stream of hydrogen bromide. The solution was kept at 27° for 18 hr., and evaporated under reduced pressure to afford 12.0 g. of product. Recrystallization from aqueous methanol gave 11.0 g. of colorless crystals, m.p. 160–167°. Further re-

crystallization gave the analytical sample: m.p. 167–168°, $[\alpha]^{27}D$ +46° (*c* 1, $CHCl_3$), λ_{max}^{KBr} 2.98 and 5.88 μ; lit.[12] m.p. 145–147°, $[\alpha]^{25}D$ + 46.5° ($CHCl_3$).

Anal. Calcd. for $C_{21}H_{33}BrO_3$: C, 61.01; H, 8.05. Found: C, 61.15; H, 7.91.

3α-Bromo-*syn*-19-oximino-5α-androstane-2β,17β-diol 17-Acetate (XXVII).—A solution of 11.0 g.(0.0266 mole) of XXVI in 100 ml. of pyridine was treated with excess nitrosyl chloride and poured into ice–water. The gummy precipitate was extracted with 150 ml. of toluene, and the solvent was washed with water three times. The solution was dried over anhydrous sodium sulfate and filtered. Under a nitrogen atmosphere the filtrate was irradiated for 1.5 hr. The resulting precipitate was filtered and recrystallized from aqueous isopropyl alcohol to afford 2.70 g. of crystals, m.p. 180–195°. The toluene filtrate was evaporated under reduced pressure and the residual gum was washed with benzene. The insoluble residue was recrystallized from aqueous isopropyl alcohol to afford an additional 0.80 g. of crystals, m.p. 180–193°. Recrystallization from ethanol gave the analytical sample: m.p. 183–195°; $[\alpha]^{27}D$ +31° (*c* 1, tetrahydrofuran); λ_{max}^{KBr} 3.18, 3.26, 5.79, and 8.02 μ.

Anal. Calcd. for $C_{21}H_{32}BrNO_4$: C, 57.01; H, 7.29. Found: C, 56.89; H, 7.21.

3α-Bromo-2β,19-epoxy-5α-androstane-17β,19-diol diacetate (XXVIII, 0.20 g.) was eluted by ether containing 2% methanol in the chromatographic separation described in the preparation of XXIX. Recrystallization from aqueous ethanol gave the analytical sample: m.p. 180–184°; $[\alpha]^{27}D$ +51° (*c* 1, $CHCl_3$); λ_{max}^{KBr} 5.79, 8.00, and 8.18 μ; n.m.r., δ 0.7 (C-18 methyl), 1.98, 2.10 (acetate methyls), 240–280 c.p.s. (2α-H, 3β-H, 17α-H), and 6.13 (C-19 H).

Anal. Calcd. for $C_{25}H_{33}BrO_5 \cdot 0.5H_2O$: C, 57.74; H, 7.16. Found: C, 57.78; H, 7.13.

2β,3β-Epoxy-19-oxo-5α-androstan-17β-ol Acetate (XXIX).—A solution of 2.5 g. (0.00566 mole) of XXVII in 300 ml. of glacial acetic acid, prepared with the aid of heat, was cooled to 40°, and a solution of 10 g. of sodium nitrite in 50 ml. of water was added slowly. After being kept for 1.5 hr. at 40° with occasional shaking, the mixture was poured into 1 l. of ice–water and the resulting precipitate was filtered and dried. The crude material (2.2 g.) was chromatographed on 100 g. of neutral alumina; 0.20 g. of product was eluted from ether containing 8% methanol. Recrystallization from aqueous ethanol gave the analytical sample: m.p. 164–168; $[\alpha]^{27}D$ +33° (*c* 0.8, $CHCl_3$); λ_{max}^{KBr} 3.71, 5.80, 5.85, and 8.02 μ; n.m.r., δ 0.67 (C-18 methyl), 1.97 (acetate methyl), 3.10 (2α-H, 3β-H), 255–280 c.p.s. (17α-H), and 9.67 (C-19 H).

Anal. Calcd. for $C_{21}H_{30}O_4$: C, 72.80; H, 8.73. Found: C, 72.81; H, 8.57.

2β,3β-Epoxy-5α-androstane-17β,19-diol 17-Acetate (XXX). A. From XXIX.—A solution of 0.10 g. of sodium borohydride in 10 ml. of methanol was added slowly to an ice-cold solution of 0.10 g. (0.0002188 mole) of XXIX in 20 ml. of methanol. The mixture was kept at 5° for 1 hr. and diluted with water, and the resulting precipitate was collected. Recrystallization from aqueous ethanol gave 0.05 g. of product, m.p. 150–157°. Further recrystallization gave the analytical sample: m.p. 154–158°; $[\alpha]^{27}D$ +32° ($CHCl_3$); λ_{max}^{KBr} 3.01, 5.79, and 8.09 μ.

Anal. Calcd. for $C_{21}H_{32}O_4$: C, 72.38; H, 9.26. Found: C, 72.43; H, 9.31.

B. From XXVII.—A solution of 0.25 g. (0.000566 mole) of XXVII was prepared in 30 ml. of glacial acetic acid with the aid of heat. The solution was cooled to below 3°, and a cold solution of 1.0 g. of sodium nitrite in 5 ml. of water was added slowly. The mixture was kept below 5° for 1 hr. with occasional shaking and diluted with water, and the resulting precipitate was filtered and dried. To a solution of these crystals in 20 ml. of methanol, was added 0.30 g. of sodium borohydride in 5 ml. of methanol under cooling. The mixture was kept at room temperature for 1 hr. and diluted with water, and the resulting precipitate was collected to give 0.10 g. of product, identical with that from method A by melting point, mixture melting point, infrared spectrum, and thin layer chromatography.

C. From XXXI.—A solution of 0.10 g. (0.00023 mole) of XXXI, 0.15 g. of N-bromoacetamide and 0.1 ml. of pyridine in 20 ml. of 95% ethanol was kept at 70° for 1 hr. The solution was cooled and poured into 200 ml. of ice–water. The resulting precipitate was filtered, dried, and chromatographed on 10 g. of neutral alumina; 0.06 g. of material was eluted by the methanol in ether fractions. This product, m.p. 151–154°, was identical with the previous samples.

2β,17β,19-Trihydroxy-3α-bromoandrostane 17-Acetate (XXXI).—A solution of 0.30 g. (0.00089 mole) of XXX in 40 ml. of anhydrous ether was saturated with hydrogen bromide gas, and the solution was kept at room temperature for 18 hr. The solvent was evaporated, and the residue was recrystallized from aqueous methanol to afford 0.17 g. of crystals, m.p. 154–158°. The analytical sample had m.p. 159–161°; $[\alpha]^{29}D$ +51° (*c* 1, $CHCl_3$); λ_{max}^{KBr} 3.2 (broad), 5.79, 8.02, and 9.59 μ.

Anal. Calcd. for $C_{21}H_{33}BrO_4$: C, 58.74; H, 7.75. Found: C, 58.97; H, 7.87.

3α-Bromo-19-oximino-5α-androstane-2β,17β-diol (XXXII).—A solution of 0.10 g. (0.000226 mole) of XXVII in 20 ml. of concentrated hydrochloric acid was kept at 27° for 18 hr. The solution was poured into ice–water, and the resulting precipitate was collected and dried to afford 0.07 g. of product. Recrystallization from aqueous ethanol gave a pure sample which did not melt sharply: m.p. 137–155°, $[\alpha]^{27}D$ +54° (*c* 1, 95% EtOH), λ_{max}^{KBr} 3.15 (broad).

Anal. Calcd. for $C_{19}H_{30}BrNO_3$: C, 57.00; H, 7.50. Found: C, 57.26; H, 7.58.

3α-Bromo-17β-hydroxy-19-oximino-5α-androstan-2-one Acetate (XXXIII).—A solution of 0.20 g. (0.000221 mole) of XXVII, 0.2 ml. of pyridine, and 0.10 g. of N-bromoacetamide in 30 ml. of 95% ethanol was kept at 70° for 30 min. The solution was cooled and diluted with water, and the resulting precipitate was collected and dried. The material was chromatographed on 10 g. of neutral alumina; 0.12 g. of product, m.p. 118–127°, was eluted by ether containing 8% methanol. The melting point of the compound was not sharp and varied after each recrystallization. The analytical sample had m.p. 92–120°; $[\alpha]^{27}D$ −34° (*c* 1, $CHCl_3$); λ_{max}^{KBr} 2.93, 5.80, and 5.98 μ.

Anal. Calcd. for $C_{21}H_{30}BrNO_4$: C, 57.44; H, 6.86. Found: C, 57.17; H, 6.79.

3α-Bromo-17β-hydroxy-19-nitrimino-5α-androstan-2-one Acetate (XXXIV).—To a solution of 0.15 g. (0.00034 mole) of XXXIII in 30 ml. of glacial acetic acid there was added slowly a solution of 0.50 g. of sodium nitrite in 5 ml. of water. The solution was kept at 27° for 1 hr. and poured into ice–water; the resulting precipitate was collected and dried. The product was chromatographed on 10 g. of neutral alumina; the material from the ether fraction was recrystallized from aqueous ethanol to give 0.04 g. of analytical sample: m.p. 203–210° dec.; $[\alpha]^{27}D$ −43° (*c* 1, $CHCl_3$); λ_{max}^{KBr} 2.93, 5.80, 5.98, and 6.39 μ.

Anal. Calcd. for $C_{21}H_{29}BrN_2O_5$: C, 53.73; H, 6.23. Found: C, 53.63; H, 6.11.