lized from absolute ethanol to give 70 mg. (70%) of colorless plates, m.p. 121–127°. Repeated recrystallization from absolute ethanol raised the melting point to 130–131.5°.

*Anal.* Calcd. for $C_{31}H_{55}N$: C, 84.28; H, 12.55; N, 3.17. Found: C, 84.0; H, 12.5; N, 3.2.

(b) **Diborane–Acetic Acid Reduction.**—A solution of 120 mg. of 3-N-pyrrolidylcholestene,[6] m.p. 100–110°, in 5.0 ml. of anhydrous tetrahydrofuran was treated, under nitrogen, with 1.0 ml. of 0.3 *M* diborane in tetrahydrofuran. The solution was stirred at room temperature for 1 hr., cautiously treated with 2.0 ml. of glacial acetic acid, and heated at reflux for 1 hr. The product was isolated as described above to afford a yellow oil which was chromatographed on 10 g. of alumina. Elution with 2% ether in hexane afforded 52 mg. of crude solid. Recrystallization from absolute ethanol gave 37 mg. (31% yield), m.p. 130–132°. The infrared spectrum of this material was identical with that of the specimen prepared as described above in part a of this experiment. A mixture of these substances melted at 130–132°.

(c) **Catalytic Hydrogenation.**—The procedure of Haworth and co-workers[10] was used. A solution of 60 mg. of 3β-N-pyrrolidylcholestene-5, m.p. 166–173°, in 3 ml. of acetic acid was hydrogenated over 50 mg. of platinum oxide (Engelhard Industries Inc.) at 45 p.s.i. for 12 hr. The catalyst was removed by filtration, and the filtrate was made basic with 10% sodium hydroxide and extracted with ether. The combined ether layers were washed with water, saturated brine, and dried over anhydrous sodium sulfate. The solvent was removed, and the residue crystallized from absolute ethanol, affording 50 mg. (83% yield) of colorless plates, m.p. 130–132°, undepressed on admixture with the specimens described above in parts a and b of this experiment. The infrared spectra of all these specimens were identical.

**Acknowledgment.**—The authors wish to thank the U. S. Public Health Service and the National Science Foundation for supporting this work.

# C-19 Functional Steroids. III.[1] 2,19-Disubstituted Androstane and Cholestane Derivatives[2]

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The synthesis of 2,19-disubstituted androstane and cholestane derivatives is described. Photolysis of the nitrite ester of 5α-androstane-2β,3α,17β-triol 3,17-diacetate gave *syn*-19-oximino-5α-androstane-2β,3α,17β-triol 3,17-diacetate, the structure of which was established by its n.m.r. spectrum. Further chemical modification of the oxime ultimately resulted in the preparation of 3,17-dioxo-2β-hydroxy-5α-androstan-19-oic acid 2,19-lactone. Lead tetraacetate oxidation of 5α-androstane-2β,3α,17β-triol 3,17-diacetate afforded 2β,19-epoxy-5α-androstane-3α,17β-diol diacetate which, through a series of steps, formed 2β,19-epoxy-17β-hydroxy-5α-androstan-3-one.

The preparation of steroids having favorable myotrophic/androgenic ratios, relative to testosterone itself, has been accomplished by a variety of structural alterations of the testicular hormone.[4] The purpose of the work described in the present paper was to prepare steroids for pharmacological evaluation of the effects of introduction of lactone and cyclic ether functions involving C-19 and C-2 in androstane derivatives[5]; the resulting final compounds are analogs of 2-hydroxymethylene-17α-methyl-17β-hydroxy-5α-androstan-3-one (oxymetholone), a clinically useful anabolic agent.

Access to the C-19 functional steroids was gained by the use of selective intramolecular reactions. Prior work[6] has shown that intramolecular attack from 6β and 11β oxygen functions can be used to operate on C-19. Since 2,19-disubstituted steroids were sought in the present work, the use of 2β-hydroxy steroid starting materials, in which the hydroxyl group is in a 1,3-diaxial relationship to the C-19 angular methyl group, was investigated.

After a number of orienting experiments in the cholestane series, which are described in the Experimental section,[7] 2α-bromoandrostan-3-one[8] was reduced with $LiAl(t\text{-}BuO)_3H$ in tetrahydrofuran[9] to afford excellent yields of I, which on treatment with alkali, gave the pure β-epoxide III. In both the cholestane and androstane series, it was found that the use of $LiAl(t\text{-}BuO_3)H$ gave stereochemically homogeneous 2α-bromo-3β-ols, in contrast to the mixture of epimeric alcohols obtained[10,11] in the cholestane series by the use of sodium borohydride. The 17-hydroxy group in III was blocked by acetylation to form IV. An attempt was made to benzoylate III using benzoyl chloride in pyridine solution. It was hoped ultimately to secure compounds having a benzoate group at C-17 and an acetate at C-3 so that a selective hydrolysis could be carried out. However, the epoxide was cleaved by pyridinium chloride and only 3α-chloro-5α-androstane-2β,17β-diol dibenzoate was obtained.

(1) Paper II, R. Kwok, and M. E. Wolff, *Chem. Ind.*, (London), 1194 (1962).

(2) Preliminary accounts of portions of this work have been presented in ref. 1 and at the 141st National Meeting of the American Chemical Society, Washington, D. C., March, 1962, p. 43N. This investigation was supported by a PHS research grant (A-5016) from the National Institute of Arthritis and Metabolic Diseases, U. S. Public Health Service.

(3) From the Ph.D. thesis of R. Kwok, University of California, 1963.

(4) For a recent review, see B. Camerino and G. Sala, "Progress in Drug Research," Vol. 2, E. Jucker, ed., Interscience Publishers, Inc., New York, N. Y., 1960, pp. 71–134.

(5) Some of the compounds resulting from this and other work are currently being evaluated biologically, and the results of these tests will be presented separately.

(6) The following basic routes for C-19 functionalization in steroids have been developed: Ultraviolet irradiation of 6β-nitrites, D. H. R. Barton, J. M. Beaton, L. E. Geller, and M. M. Pechet, *J. Am. Chem. Soc.*, **82**, 2640 (1960); ultraviolet irradiation of 6β-hypochlorites, M. Akhtar and D. H. R. Barton, *ibid.*, **83**, 2213 (1961), and J. S. Mills and V. Petrow, *Chem. Ind.*, (London), 946 (1961); lead tetraacetate oxidation of 6β-hydroxy steroids, A. Bowers, L. C. Ibañez, M. E. Cabezas, and H. J. Ringold, *Chem. Ind.*, (London), 1299 (1960); lead tetraacetate oxidation of 11β-hydroxy steroids in presence of iodine, Ch. Meystre, K. Heusler, J. Kalvoda, P. Wieland, G. Anner, and A. Wettstein, *Experientia*, **17**, 475 (1961); ultraviolet irradiation of 11-oxo steroids, H. Wehrli, M. S. Heller, K. Schaffner, and O. Jeger, *Helv. Chim. Acta*, **44**, 2162 (1961).

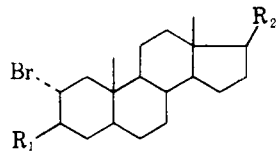
(7) After the completion of this phase of our work, the preparation of VI by a similar method was reported: K. L. Williamson and W. S. Johnson, *J. Org. Chem.*, **26**, 4563 (1961).

(8) A. Butenandt and H. Dannenberg, *Ber.*, **71**, 1681 (1938).

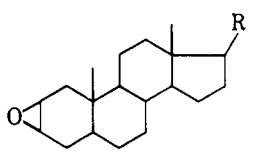
(9) J. Fajkos, *Collection Czech. Chem. Commun.*, **24**, 2284 (1959).

(10) E. J. Corey, *J. Am. Chem. Soc.*, **75**, 4832 (1953).

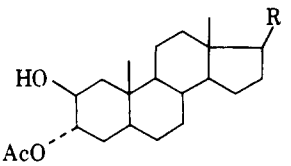
(11) L. F. Fieser and W. Y. Huang, *ibid.*, **75**, 4837 (1953).



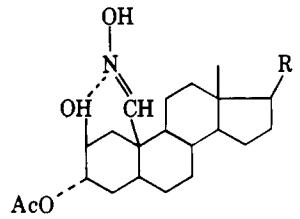
I. $R_1$ = OH, $R_2$ = OAc
II. $R_1$ = OAc, $R_2$ = OAc



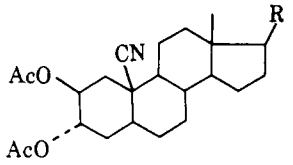
III. R = OH
IV. R = OAc



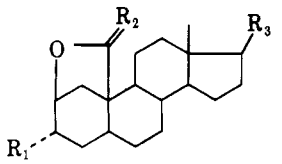
V. R = OAc
VI. R = $C_8H_{17}$



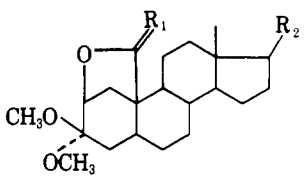
VII. R = OAc
VIII. R = $C_8H_{17}$



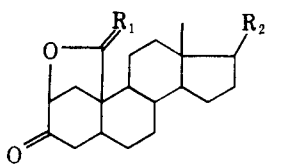
IX. R = OAc
X. R = $C_8H_{17}$



XI. $R_1$ = OH, $R_2$ = $NH_2^+Cl^-$, $R_3$ = OH
XII. $R_1$ = OH, $R_2$ = $NH_2^+Cl^-$, $R_3$ = $C_8H_{17}$
XIII. $R_1$ = OH, $R_2$ = O, $R_3$ = OH
XIV. $R_1$ = OH, $R_2$ = O, $R_3$ = $C_8H_{17}$
XV. $R_1$ = OAc, $R_2$ = $H_2$, $R_3$ = OAc
XVI. $R_1$ = OH, $R_2$ = $H_2$, $R_3$ = OH
XVII. $R_1$ = OH, $R_2$ = $H_2$, $R_3$ = $C_8H_{17}$



XVIII. $R_1$ = O, $R_2$ = O
XIX. $R_1$ = O, $R_2$ = OH
XX. $R_1$ = $H_2$, $R_2$ = O
XXI. $R_1$ = $H_2$, $R_2$ = OH
XXII. $R_1$ = O, $R_2$ = O



XXIII. $R_1$ = O, $R_2$ = OH
XXIV. $R_1$ = O, $R_2$ = $C_8H_{17}$
XXV. $R_1$ = $H_2$, $R_2$ = OH
XXVI. $R_1$ = $H_2$, $R_2$ = OH
XXVII. $R_1$ = $H_2$, $R_2$ = $C_8H_{17}$

By treatment of IV with warm glacial acetic acid for one hour, the oxide was opened to afford the *trans* hydroxy diacetate V. Acetylation of V gave the corresponding triacetate, m.p. 186–187°, which on hydrolysis gave the triol, m.p. 260–262°. These compounds are evidently identical with the "2,3,17-trihydroxyandrostane" (m.p. 261–264°) and its triacetate (m.p. 188°) obtained by treatment of androst-2-en-17-one with hydrogen peroxide in acetic acid followed by reduction utilizing sodium in propanol, by Marker and Plambeck.[12] Since the structural formulas in the article by Marker and Plambeck show the compounds as *cis* 2β,3β-diols (although the possibility of a "3-epi" compound is recognized in the text), the authentic *cis* compound was also prepared.

(12) R. W. Marker and L. Plambeck, Jr., *J. Am. Chem. Soc.*, **61**, 1332 (1939).

Treatment of II with silver acetate in moist acetic acid[13] and subsequent saponification gave 5α-androstane-2β,3β,17β-triol, m.p. 231–233°, which on acetylation with acetic anhydride in the presence of *p*-toluenesulfonic acid gave the corresponding triacetate, m.p. 198–199°. These compounds are clearly different from the substances described by Marker and Plambeck. The possibility of selective acetylation of the 3β and 17β-hydroxyl functions in the *cis* triol was investigated, with the hope of using the resulting diacetate, rather than V, as the main starting material. Suitable conditions could not be developed, however.

The free hydroxyl group in V was then converted, by means of nitrosyl chloride in pyridine solution, to the corresponding 2β nitrite ester. By irradiation of the nitrite[14] in toluene solution with a high pressure mercury arc, the 19-nitroso derivative was readily obtained. The course of the photolysis could be conveniently monitored by periodic testing for unchanged nitrite ester utilizing the diphenylamine–sulfuric acid spot test.[15] Heating the 19-nitroso derivative in 2-propanol caused rearrangement to furnish *syn*-19-oximino-5α-androstane-2β,3α,17β-triol 17-acetate VII which was purified by chromatography and obtained in 28% yield from V. If direct recrystallization without prior chromatography was employed for the purification of VII or VIII, only poor yields of products contaminated by starting material were obtained. It is noteworthy that this photolysis was successful, since it was reported,[16] subsequent to this experiment, that in a nitrite vicinally substituted by an oxygen-bearing moiety, photolytic oxidative fission occurs in competition with, and perhaps to the exclusion of, intramolecular hydrogen abstraction. The neighboring groups reported to be susceptible to such a side reaction are ketones, alcohols, and acetates. At least two explanations are at hand to explain the present results. First, if hydrogen abstraction and oxidative fission both occur, it is possible that only the product of abstraction was isolated. The rather low yield of product is in support of this possibility. Alternatively, the *trans* diaxial geometry of the vicinal oxygen moieties in V may in some fashion inhibit the fission reaction relative to hydrogen abstraction. Another interesting point is that no product resulting from epimerization of the nitrite was isolated, since epimerization of nitrite esters during photolysis has been observed.[17] The axial disposition of the 2-hydroxyl group in VII and VIII was shown clearly by the n.m.r. spectra as well as by the structure of various products made from these oximes.

Although the photolysis of organic nitrites[18] has been in considerable use since its discovery, an unanswered question[19] arising from such studies is whether the hydroxy oximes which the photolysis affords exist as such or in the form of cyclized hydroxy amino tauto-

(13) This hydroxylation is an extension of the *cis*-hydroxylation of olefins using iodine, silver acetate, and wet acetic acid described by R. B. Woodward and F. V. Brutcher, *ibid.*, **80**, 209 (1958).

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

(15) F. Feigl, "Spot Tests in Organic Analysis," Elsevier Publishing Co., New York, N. Y., 1960, p. 178.

(16) A. L. Nussbaum, C. H. Robinson, E. P. Oliveto, and D. H. R. Barton, *J. Am. Chem. Soc.*, **83**, 2400 (1961).

(17) A. Nickon, J. R. Mahajan, and F. J. McGuire, *J. Org. Chem.*, **26**, 3617 (1961).

(18) A. L. Nussbaum and C. H. Robinson, *Tetrahedron*, **17**, 35 (1962).

(19) *Cf.* D. H. R. Barton and J. M. Beaton, *J. Am. Chem. Soc.*, **84**, 199 (1962), footnote 6.

mers. In the present case, this was investigated with n.m.r. spectrometry.[1] A singlet at 7.78 p.p.m., in the n.m.r. spectrum of VII, shows the presence of an aldoxime[20] function at C-19. A low field multiplet centered on 7.60 p.p.m. is due to an intramolecularly hydrogen bonded[21] hydroxyl proton (2β-OH), whereas the oxime hydroxyl proton resonance is observed as a singlet at 10.91 p.p.m.; these signals vanished when the exchangeable protons were replaced with deuterium by treatment with deuterium oxide. On steric grounds only the *syn* isomer of VII can exist in the required quasicyclic, hydrogen bonded conformation. The *syn* configuration was confirmed by acetylation to *syn*-19-acetoxyimino-5α-androstane-2β,3α,17β-triol 2,3,17-triacetate which, on melting, formed the nitrile IX. This facile pyrolysis is due to *cis* elimination of the elements of acetic acid.[22] In larger scale preparations of IX, it was more convenient to reflux VII in acetic anhydride for an hour and a half to dehydrate the oxime.

For the production of a 2β,19-lactone, attempts were first made in the cholestane series at alkaline hydrolysis of the nitrile X. In harmony with the hindered character of the nitrile function in X, saponification proved unsuccessful, and only 2β,3α-dihydroxy-5α-cholestan-19-nitrile was obtained. This diol, however, on treatment with ethereal hydrogen chloride, readily underwent cyclization to the imino ether XII which subsequently was easily hydrolyzed in refluxing 2*N* hydrochloric acid to form the lactone XIV.[23] Alternatively, the nitrile triacetate IX, on treatment with hydrogen chloride in methanol, directly formed the imino ether hydrochloride XI, which without purification, was hydrolyzed to the lactone XIII in an over-all yield of 63%. Oxidation of XIII with chromic acid in acetone[24] gave the diketone XXII. For the production of testosterone analogs, reduction of the 17-keto group selectively was necessary. Selective protection of the 3-ketone was achieved in excellent yield by formation of the dimethyl ketal XVIII using methanol and *p*-toluene sulfonic acid.[25] Reduction with LiAl(*t*-BuO)$_3$H then gave the 17β-alcohol which, on deketalization, formed the desired XXIII.

The 2β,19-ether derivatives were prepared by lead tetraacetate oxidation[26] of the 2β-hydroxy compounds V and VI. Thus, in the androstane series, treatment of V with lead tetraacetate for three days in refluxing benzene solution gave, after chromatography, the ether XV, albeit in low yield. The other products of the reaction formed a gummy mixture, which was not investigated further. Removal of the acetate groups by alkaline hydrolysis gave the diol XVI, which was oxidized with chromic acid in acetone to afford the dione XXV. By reactions similar to those already described, selective ketalization furnished XX, which was reduced to form XXI. Removal of the blocking groups then gave XXVI.

The n.m.r. spectra of these bridged ring steroids present interesting examples of spin coupling and spin-uncoupling which are owing to the geometry of the ring systems. These features, which are being further investigated with double irradiation techniques, will form the subject of a separate communication.

## Experimental[27]

**2α-Bromo-5α-androstane-3β,17β-diol 17-Acetate (I).**—A solution of 3.0 g. (0.0073 mole) of 2α-bromo-17β-hydroxy-5α-androstan-3-one 17-acetate[8] and 6.0 g. (0.017 mole) of LiAl(*t*-BuO)$_3$H in 36 ml. of tetrahydrofuran was kept at 0° for 15 min. and then treated with 350 ml. of 5% acetic acid. The product was extracted with ether and the ether solution was washed with 10% sodium bicarbonate solution and water. The residue from evaporation of the dried ether solution was recrystallized from methanol to afford 2.2 g. (73%) of colorless crystals, m.p. 193–195°. The analytical sample had m.p. 198–199°; $[\alpha]^{22}D$ −3° (*c*, 1% in $CHCl_3$).

*Anal.* Calcd. for $C_{21}H_{33}BrO_3$: C, 61.00; H, 7.98; Br, 19.30. Found: C, 61.01; H, 8.17; Br, 19.41.

**2α-Bromo-5α-androstane-3β,17β-diol Diacetate (II).**—A solution of 3.0 g. (0.0073 mole) of I, 0.30 g. of *p*-toluenesulfonic acid and 6 ml. of acetic anhydride in 30 ml. of glacial acetic acid was kept at 27° for 5 hr. The reaction mixture was diluted with water and the resulting precipitate was filtered and washed with water. One recrystallization from methanol afforded 2.75 g. (84%) of product, m.p. 178–181°. The analytical sample had m.p. 185–186°; $[\alpha]^{22}D$ −21° (*c*, 1% in $CHCl_3$).

*Anal.* Calcd. for $C_{23}H_{35}BrO_4$: C, 60.65; H, 7.72; Br, 17.52. Found: C, 60.66; H, 7.64; Br, 17.58.

**5α-Androstane-2β,3β,17β-triol.**—A solution of 2.0 g. (0.0036 mole) of II, 1.55 g. of silver acetate, and 16.5 ml. of acetic acid containing 1% water in 40 ml. of acetic acid was stirred and refluxed for 6 hr. The reaction mixture was cooled, treated with excess sodium chloride, and filtered. The filter cake was washed with hot benzene, and the dried ($Na_2SO_4$) combined filtrates were evaporated under reduced pressure. The residue was allowed to react with 50 ml. of 10% potassium hydroxide in methanol for 16 hr. The reaction mixture was poured into ice-water and the resulting precipitate was filtered and washed with water. The product was dissolved in hot ethanol and filtered through 5 g. of alumina to remove traces of silver chloride. Evaporation of the ethanol afforded 1.1 g. (81.5%) of product, m.p. 225–228°. The analytical sample, recrystallized from aqueous methanol, had m.p. 231–233°; $[\alpha]^{22}D$ +34° (*c*, 1% in ethanol).

*Anal.* Calcd. for $C_{19}H_{32}O_3$: C, 73.98; H, 10.46. Found: C, 73.90; H, 10.70.

**5α-Androstane-2β,3β,17β-triol Triacetate.**—A solution of 0.30 g. (0.00098 mole) of 5α-androstane-2β,3β,17β triol, 0.10 g. of *p*-toluenesulfonic acid, and 1 ml. of acetic anhydride in 5 ml. of acetic acid was kept at 27° for 10 hr. It was diluted with water and the resulting precipitate was filtered, washed with water, and dried. There was obtained 0.43 g. (98%) of material m.p. 196–198°. The analytical sample, recrystallized from aqueous methanol, had m.p. 198–199°, $[\alpha]^{22}D$ +24° (*c*, 1% in $CHCl_3$), n.m.r.: 0.80 (C-19–H), 0.99 (C-18–H), 2.01, 2.03, 2.08 (acetate methyls), 270–300 c.p.s. (broad hump) (3α-H, 17α-H), 5.3 (multiplet) (2α-H).

*Anal.* Calcd. for $C_{25}H_{38}O_6$: C, 69.09; H, 8.81. Found: C, 69.23; H, 8.66.

**2β,3β-Epoxy-5α-androstan-17β-ol (III).**—A solution of 8.0 g. (0.14 mole) of potassium hydroxide and 1.0 g. (0.0024 mole) of I in 150 ml. of 2-propanol was maintained at 55° for 1.5 hr. The product crystallized from the reaction mixture after addition of water and cooling, and was recrystallized from methanol to

(20) W. D. Phillips, *Ann. N. Y. Acad. Sci.*, **70**, 817 (1958).

(21) 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, chap. 15.

(22) D. Ambrose and O. L. Brady, *J. Chem. Soc.*, 1243 (1950).

(23) Shortly after these experiments were completed, the formation of 20,18 imino ethers and lactones from C-18 nitriles was described in the full paper of ref. 14.

(24) C. Djerassi, R. R. Engle, and A. Bowers, *J. Org. Chem.*, **21**, 1547 (1956).

(25) M. M. Janot, X. Lusinchi, and R. Goutarel, *Bull. soc. chim., France*, 2109 (1961).

(26) G. Cainelli, M. Lj. Mehailovic, D. Arigoni, and O. Jeger, *Helv. Chim. Acta*, **42**, 1125 (1959).

(27) Melting points were determined with a Thomas–Hoover apparatus and are corrected. Microanalyses were performed by the Microanalytical Department, University of California, Berkeley. 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. on samples in deuteriochloroform solution on a Varian A-60 instrument using tetramethylsilane as internal standard. Resonance positions are reported in δ (p.p.m.) values where possible; unresolved humps are described in c.p.s. units (60 Mc.).

afford 0.4 g. (50%) of colorless crystals m.p. 142–144°. The analytical sample, obtained from 60% methanol, had m.p. 145–146°; $[\alpha]^{22}D$ +40° (*c* 1% in $CHCl_3$), $\mu_{max}^{KBr}$ 2.81, 9.38, 12.29.

*Anal.* Calcd. for $C_{19}H_{30}O_2$: C, 78.57; H, 10.41. Found: C, 78.64; H, 10.49.

**2β,3β-Epoxy-5α-androstan-17β-ol Acetate (IV).**—A solution of 1.0 g. (0.035 mole) of III and 2 ml. of acetic anhydride in 10 ml. of pyridine was kept at 27° for 18 hr. and diluted with water. The resulting precipitate was filtered, washed with water, and recrystallized from methanol to give 0.90 g. (80%) of needles, m.p. 168.5–170°. The analytical sample had m.p. 169–170°; $[\alpha]^{22}D$ +35° (*c*, 1% in $CHCl_3$), $\mu_{max}^{KBr}$ 5.77, 8.00, 9.50, 12.29.

*Anal.* Calcd. for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 75.60; H, 9.35.

**3α-Chloro-5α-androstane-2β,17β-diol Dibenzoate.**—A solution of 0.40 g. (0.00138 mole) of III and 0.5 ml. of benzoyl chloride in 3 ml. of pyridine was kept at 50° for 30 min. and then at 27° for 3 hr. It was poured into 30 ml. of 5% sodium bicarbonate solution. The precipitate was filtered, washed with water, and air dried. It was recrystallized once from ethanol to afford 0.20 g. (37%) of colorless fine crystals, m.p. 160–165°. The analytical sample had m.p. 168–169°.

*Anal.* Calcd. for $C_{33}H_{39}ClO_4$: C, 74.01; H, 7.28; Cl, 6.63. Found: C, 73.69; H, 7.32; Cl, 6.80.

**5α-Androstane-2β,3α,17β-triol 3,17-Diacetate (V).**—A solution of 7.0 g. (0.0216 mole) of IV in 70 ml. of acetic acid was maintained at 70° for 1 hr., cooled, and diluted with water. The resulting precipitate was recrystallized from acetonitrile to afford 4.9 g. (61%) of colorless crystals m.p. 173–176°. The analytical sample had m.p. 177–179°; $[\alpha]^{22}D$ +31° (*c*, 1% in $CHCl_3$), $\mu_{max}^{KBr}$ 2.88, 5.79, 8.00, n.m.r.: 0.70 (C-19–H), 0.92 (C-18–H) 1.91, 1.95 (acetate methyls), 3.72 (broad) (2α-H), 4.41 (broad) (17α-H), 4.72 (3β-H).

*Anal.* Calcd. for $C_{23}H_{36}O_5$: C, 70.37; H, 9.24. Found: C, 70.36; H, 9.03.

**5α-Androstane-2β,3α,17β-triol Triacetate.**—A solution of 0.5 g. (0.0013 mole) of V, 1 ml. of acetic anhydride, and 0.10 g. of *p*-toluenesulfonic acid in 30 ml. of acetic acid was kept at 27° for 18 hr. The reaction mixture was diluted with water and the resulting precipitate was filtered and washed with water. It was recrystallized from aqueous methanol to afford 0.49 g. (90%) of product, m.p. 185–187°. The analytical sample had m.p. 186–187°; $[\alpha]^{22}D$ +38° (*c*, 1% in $CHCl_3$), n.m.r.: 0.78 (C-19–H), 0.93 (C-18–H), 2.03, 2.04 (acetate methyls), 4.61 (broad) (17α-H), 4.94 (2α-H, 3β-H).

*Anal.* Calcd. for $C_{25}H_{38}O_6$: C, 69.09; H, 8.81. Found: C, 69.53; H, 8.67.

**5α-Androstane-2β,3α,17β-triol.**—A solution of V in methanol containing 5% potassium hydroxide was kept at 27° for 18 hr. The reaction mixture was diluted with water and the resulting precipitate was filtered and washed with water. It was recrystallized from aqueous methanol to afford the product, m.p. 260–262°. The analytical sample had m.p. 261–262°; $[\alpha]^{22}D$ +29° (*c*, 0.8% in ethanol).

*Anal.* Calcd. for $C_{19}H_{32}O_3$: C, 73.98; H, 10.46. Found: C, 73.67; H, 10.40.

***syn*-19-Oximino-5α-androstane-2β,3α,17β-triol 3,17-Diacetate (VII).**—A solution of 6.0 g. of V in 30 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 6.0 g. of crude 5α-androstane-2β,3α,17β-triol 3,17-diacetate 2-nitrite which was unstable. Under a nitrogen atmosphere, purified by passage through potassium pyrogallate solution, a solution of 6 g. of the crude nitrite ester in 200 ml. of toluene was irradiated for 1.7 hr. at 0° by means of a 200-watt 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[15] 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 4 hr. The solvent was removed under reduced pressure giving a gummy residue which was chromatographed on 200 g. of neutral alumina; 1.7 g. (28%) of oxime was eluted by ether containing 8% methanol. Recrystallization from acetonitrile gave the analytical sample, m.p. 207–208°; $[\alpha]^{22}D$ +8.6° (*c*, 1% in $CHCl_3$), $\mu_{max}^{KBr}$ 3.10 broad, 5.75, 8.00, $\mu_{max}^{Chf}$ 2.85 (sharp) (oxime OH) 3.15–3.30 (2β OH) 5.82, 8.03, n.m.r.: 0.77 (C-18–H), 2.03, 2.05 (acetate methyls), 3.83 (broad) (2α-H), 4.58 (broad) (17α-H), 4.88 (3β-H), 7.60 (2β-OH), 7.78 (C-19–H), 10.91 (NOH).

*Anal.* Calcd. for $C_{23}H_{35}NO_6$: C, 67.53; H, 8.37; N, 3.32. Found: C, 67.56; H, 8.43; N, 3.19.

***syn*-19-Oximino-5α-cholestane-2β,3α-diol 3-Acetate (VIII).**—This compound was obtained from VI[7] in 30% yield in a manner similar to that used in the preparation of VII. The product was eluted by 8% methanol in ether. The analytical sample, recrystallized from acetonitrile had m.p. 171–172°; $[\alpha]^{22}D$ +36° (*c*, 1% in $CHCl_3$).

*Anal.* Calcd. for $C_{29}H_{49}NO_4$: C, 73.22, H, 10.38. Found: C, 73.16, H, 10.40.

***syn*-19-Acetoxyimino-5α-androstane-2β,3α,17β-triol Triacetate.**—A solution of 0.23 g. (0.00055 mole) of VII, 0.20 g. of *p*-toluenesulfonic acid, and 2 ml. of acetic anhydride in 10 ml. of glacial acetic acid was kept at 27° for 16 hr. The reaction mixture was diluted with water and the resulting precipitate was filtered and washed with water to afford 0.23 g. (83.5%) of product, m.p. 123–125°, resolidified, m.p. 190°. The analytical sample recrystallized from aqueous methanol had m.p. 127–128 and 199–200°; $[\alpha]^{22}D$ +52° (*c*, 1% in $CHCl_3$), $\mu_{max}^{KBr}$ 5.8, 8.0, 8.3, n.m.r.: 0.75 (C-18–H), 2.00, 2.05, 2.10, 2.18 (acetate methyls), 4.60 (broad) (17α-H), 4.87 (2α-H, 3β-H), 7.80 (C(19)-H).

*Anal.* Calcd. for $C_{27}H_{39}NO_8$: C, 64.14; H, 7.78. Found: C, 64.48; H, 7.81. When the melting procedure was repeated on a larger scale, the second melting point was found to be owing to the formation of IX.

**2β,3α,17β-Trihydroxy-5α-androstane-19-nitrile Triacetate (IX).**—A solution of 1.0 g. (0.0024 mole) of VII in 50 ml. of acetic anhydride was refluxed for 1.5 hr., cooled, and poured into water. There was obtained 1.0 g. (94.5%) of product m.p. 191–193°, which was recrystallized from 50% methanol to afford the analytical sample, m.p. 201–202°; $[\alpha]^{22}D$ +55° (*c*, 1% in $CHCl_3$), $\mu_{max}^{KBr}$ 4.48, 5.75, 8.1, 8.3.

*Anal.* Calcd. for $C_{24}H_{35}NO_6$: C, 67.39; H, 7.92; N, 3.14. Found: C, 67.84; H, 7.85; N, 2.96.

**2β,3α-Dihydroxy-5α-cholestane-19-nitrile Diacetate (X).**—This compound was obtained in 95% yield from VIII in a manner similar to that used in the preparation of IX. The product was recrystallized from aqueous methanol to afford the analytical sample m.p. 99–101°; $[\alpha]^{22}D$ +71°, (*c*, 1% in $CHCl_3$).

*Anal.* Calcd. for $C_{31}H_{49}NO_4$: C, 74.51; H, 9.88. Found: C, 74.46; H, 10.01.

**2β,3α-Dihydroxy-5α-cholestane-19-nitrile.**—A solution of 2.0 g. (0.004 mole) of X, 6.0 g. of potassium hydroxide, and 4 ml. of water in 120 ml. of methanol was kept at 27° for 18 hr. It was diluted with water and the resulting precipitate was filtered and recrystallized once from methanol to afford 1.30 g. (78%) of colorless crystals, m.p. 245–246°. The analytical sample had m.p. 249–250°; $[\alpha]^{22}D$ +24° (*c*, 0.23% in $CHCl_3$). When a solution of this product was refluxed for 18 hr. in methanol containing 10% potassium hydroxide, the compound was recovered unchanged.

*Anal.* Calcd. for $C_{27}H_{45}NO_2$: C, 78.02; H, 10.91; N, 3.37. Found: C, 78.30; H, 11.07; N, 3.51.

**2β,19-Epoxy-3α-hydroxy-19-iminium-5α-cholestane Chloride (XII).**—A solution of 0.70 g. of 2β,3α-dihydroxy-5α-cholestane-19-nitrile in 800 ml. of ether was treated with a stream of dry hydrogen chloride for 35 min. and kept at 27° for 18 hr. Evaporation of the solvent gave 0.55 g. (75%) of crystalline product, which was recrystallized from ethyl acetate–methanol to afford the analytical sample, m.p. 203–205°; $[\alpha]^{22}D$ +23° (*c*, 1% in ethanol), $\mu_{max}^{KBr}$ 3.05–3.2, 5.95, 9.60.

*Anal.* Calcd. for $C_{27}H_{46}ClNO_2$: C, 71.75, H, 10.03. Found: C, 71.60, H, 10.28.

**2β,3α,17β-Trihydroxy-5α-androstan-19-oic Acid 2,19-Lactone (XIII).**—A solution of 1.0 g. (0.0022 mole) of IX in 50 ml. of methanol was treated with a stream of dry hydrogen chloride for 5 min. and kept at 27° for 1 hr. Evaporation of the solvent gave crude crystalline 3α,17β-dihydroxy-2β,19-epoxy-19-iminium-5α-androstane chloride XI which was water soluble and was not purified. A solution of the crude iminium salt in 60 ml. of 2 *N* hydrochloric acid was refluxed for 18 hr. and cooled, and the precipitated product was filtered to afford 0.45 g. (63%) of product m.p. 239–240°. The analytical sample was recrystallized from aqueous methanol, m.p. 240–241°; $[\alpha]^{22}D$ +41° (*c*, 1% in ethanol), $\mu_{max}^{KBr}$ 2.95, 5.65 (sh.), 5.71.

*Anal.* Calcd. for $C_{19}H_{28}O_4$: C, 71.22; H, 8.81. Found: C, 70.89; H, 8.89.

**2β,3α-Dihydroxy-5α-cholestan-19-oic Acid 2,19-Lactone (XIV).**—This compound was obtained in 80% yield from XII in a manner similar to that used in the preparation of XIII. The analyti-

cal sample, recrystallized from aqueous methanol, had m.p. 184.5–186.5°; $[\alpha]^{22}D$ +45° (*c*, 1% in $CHCl_3$), $\mu_{max}^{KBr}$ 3.05, 5.62.

*Anal.* Calcd. for $C_{27}H_{44}O_3$: C, 77.83; H, 10.65. Found: C, 77.82; H, 10.88.

**3,17-Dioxo-2β-hydroxy-5α-androstan-19-oic Acid 2,19-Lactone (XXII).**—A solution of 0.60 g. (0.0019 mole) of XIII in 50 ml. of acetone was treated with excess 8 *N* chromic acid solution.[24] The excess chromic acid was decomposed with 2-propanol and the solvent was removed under reduced pressure. The residue was washed with water and recrystallized from acetone–hexane to afford 0.40 g. (64%) of colorless crystals m.p. 200–203°. The analytical sample was a hydrate m.p. 203–204°; $[\alpha]^{22}D$ +105° (*c*, 1% in acetone), $\mu_{max}^{KBr}$ 2.98, 5.63, 5.79. The anhydrous material could be obtained by vacuum sublimation as evidenced by disappearance of the band at 2.9 μ, but the product was hygroscopic and readily reformed the hydrate.

*Anal.* Calcd. for $C_{19}H_{24}O_4 \cdot H_2O$: C, 68.24; H, 7.84. Found: C, 67.95; H, 8.02.

**3,3-Dimethoxy-2β-hydroxy-17-oxo-5α-androstan-19-oic Acid 2,19-Lactone (XVIII).**—A solution of 0.60 g. (0.0018 mole) of XXII and 0.05 g. of *p*-toluenesulfonic acid in 30 ml. of methanol[25] was refluxed for 30 min., cooled, made alkaline with sodium methoxide, diluted with water, and extracted with ether. The ether solution was washed with water, dried ($Na_2SO_4$), and evaporated. The residue was chromatographed on 30 g. of neutral alumina; 0.60 g. (92.5%) of product m.p. 209–211° was eluted with 2% methanol in ether. The analytical sample was recrystallized from methanol, m.p. 210–211°; $[\alpha]^{22}D$ +55° (*c*, 0.73% in $CHCl_3$), $\mu_{max}^{KBr}$ 5.62, 5.75, 8.88, 9.21, 9.54, 10.05.

*Anal.* Calcd. for $C_{21}H_{30}O_5$: C, 69.58; H, 8.34. Found: C, 69.35; H, 8.28.

**2β,17β-Dihydroxy-3,3-dimethoxy-5α-androstan-19-oic Acid 2,19-Lactone (XIX).**—A solution of 0.40 g. (0.001 mole) of XVIII and 0.80 g. of LiAl (*t*-BuO)$_3$H in 15 ml. of tetrahydrofuran was kept at 0° for 30 min., poured into 20 ml. of 5% acetic acid, and extracted with ether. The ether solution was washed with 10% sodium bicarbonate solution and water, and the dried ($Na_2SO_4$) solution was evaporated to afford 0.28 g. (70%) of product m.p. 215–220°. Recrystallization from acetone–hexane gave the analytical sample m.p. 228–229°; $[\alpha]^{22}D$ +42° (*c*, 1% in $CHCl_3$) $\mu_{max}^{KBr}$ 2.90, 5.64, 8.95, 9.57.

*Anal.* Calcd. for $C_{21}H_{32}O_5$: C, 69.20; H, 8.85. Found: C, 69.06; H, 8.65.

**2β,17β-Dihydroxy-3-oxo-5α-androstan-19-oic Acid 2,19-Lactone (XXIII).**—A solution of 0.20 g. (0.00057 mole) of XIX in a mixture of 10 ml. of methanol and 5 ml. of 2 *N* HCl was refluxed for 3 hr., cooled, diluted with water, and extracted with ether. The ether solution was washed with water, dried ($Na_2SO_4$), and evaporated. The residue was chromatographed on 10 g. of neutral alumina; 0.16 g. (91.5%) of product, m.p. 182–183°, was eluted by the 16% methanol in ether fractions. The analytical sample was obtained, as a hemihydrate, from acetone–hexane, m.p. 182.5–183.5°; $[\alpha]^{22}D$ +145° (*c*, 1% in $CHCl_3$), $\mu_{max}^{KBr}$ 2.96, 5.65, 5.73.

*Anal.* Calcd. for $C_{19}H_{26}O_4 \cdot 1/2\ H_2O$: C, 69.75; H, 8.33. Found: C, 70.12; H, 8.23.

**2β-Hydroxy-3-oxo-5α-cholestan-19-oic Acid 2,19-Lactone (XXIV).**—This compound was obtained in 72% yield from XIV in a manner similar to that used in the preparation of XXII. The analytical sample, recrystallized from acetonitrile, had m.p. 190–191°; $[\alpha]^{22}D$ +138° (*c*, 1% in $CHCl_3$), $\mu_{max}^{KBr}$ 5.60, 5.73.

*Anal.* Calcd. for $C_{27}H_{42}O_3$: C, 78.21; H, 10.21. Found: C, 78.05; H, 10.02.

**2β,19-Epoxy-5α-androstane-3α,17β-diol Diacetate (XV).**—A solution of 6.15 g. (0.0157 mole) of V and 13 g. (0.0294 mole) of lead tetraacetate in 250 ml. of dry benzene[26] was refluxed for 72 hr. with stirring. The reaction mixture was poured into 250 ml. of a 10% solution of potassium iodide and then extracted with ether. The ether solution was washed with 10% sodium thiosulfate solution and then with water and dried ($Na_2SO_4$). The solvent was removed under reduced pressure and the gummy residue was chromatographed on 250 g. of neutral alumina. The product was eluted by ether containing 1% and 2% methanol. Recrystallization from ether gave 0.70 g. (11.7%) of colorless crystals, m.p. 160–164°. The analytical sample had m.p. 165–166°; $[\alpha]^{22}D$ +18° (*c*, 1% in $CHCl_3$), $\mu_{max}^{KBr}$ 5.70, 8.02, 9.64.

*Anal.* Calcd. for $C_{23}H_{34}O_5$: C, 70.74; H, 8.78. Found: C, 70.52; H, 8.76.

**2β,19-Epoxy-5α-androstane-3α,17β-diol (XVI).**—A solution of 0.60 g. (0.0015 mole) of XV in 100 ml. of methanol and 5 ml. of 20% potassium hydroxide solution was refluxed for 2.5 hr. The solvents were removed under reduced pressure to afford 0.45 g. (96%) of product. The analytical sample was recrystallized from methanol, m.p. 244–245°; $[\alpha]^{22}D$ +24° (*c*, 1% in ethanol), $\mu_{max}^{KBr}$ 3.00, 9.50, 9.65.

*Anal.* Calcd. for $C_{19}H_{30}O_3$: C, 74.47; H, 9.87. Found: C, 74.26; H, 9.59.

**2β,19-Epoxy-5α-cholestan-3α-ol (XVII).**—2β,19-Epoxy-5α-cholestan-3α-ol acetate was prepared from VI in a manner similar to that used for the synthesis of XV. The crude acetate was saponified as in the preparation of XVI and the product was chromatographed on neutral alumina. Elution with 2% methanol in ether gave the pure product in 24% yield from VI. The analytical sample, recrystallized from acetone, had m.p. 192–193; $[\alpha]^{22}D$ +36° (*c*, 1% in $CHCl_3$).

*Anal.* Calcd. for $C_{27}H_{46}O_2$: C, 80.54; H, 11.52. Found: C, 80.33; H, 11.22.

**2β,19-Epoxy-5α-androstane-3,17-dione (XXV).**—A solution of 0.40 g. (0.0013 mole) of XVI in 50 ml. of acetone was treated with excess 8 *N* chromic acid reagent.[24] The excess oxidant was decomposed with 2-propanol and the solvent was removed under reduced pressure. The gummy residue was dissolved in ether, and the ether solution was washed with water, dried ($Na_2SO_4$), and evaporated. The residue was recrystallized from acetone–hexane to afford 0.28 g. (71%) of material, m.p. 135–143°. Further recrystallization gave the analytical sample, m.p. 144–146°; $[\alpha]^{22}D$ +96° (*c*, 1% in $CHCl_3$); $\mu_{max}^{KBr}$ 5.75, 5.82, 9.51.

*Anal.* Calcd. for $C_{19}H_{26}O_3$: C, 75.46; H, 8.67. Found: C, 75.63; H, 8.70.

**2β,19-Epoxy-5α-cholestan-3-one (XXVII).**—This compound was obtained in 85% yield from XVII in a manner similar to that used for the preparation of XXV. The analytical sample, recrystallized from acetonitrile, had m.p. 111–112°; $[\alpha]^{22}D$ +112° (*c*, 1% in $CHCl_3$).

*Anal.* Calcd. for $C_{27}H_{44}O_2$: C, 80.94; H, 11.07. Found: C, 80.81; H, 11.09.

**3,3-Dimethoxy-2β,19-epoxy-5α-androstan-17-one (XX).**—A solution of 0.25 g. (0.00083 mole) of XXV and 0.05 g. of *p*-toluenesulfonic acid in 20 ml. of methanol[25] was refluxed for 30 min. The reaction mixture was cooled and diluted with water. It was extracted with ether and the ether solution was washed with sodium bicarbonate solution and water, dried ($Na_2SO_4$), and evaporated to dryness. The solid residue was chromatographed on 10 g. of neutral alumina; 0.26 g. (90%) of product m.p. 184–186° was obtained from the 2% and 4% methanol in ether fractions. The analytical sample, recrystallized from acetonitrile, had m.p. 186–188°; $[\alpha]^{22}D$ +100° (*c*, 1% in $CHCl_3$), $\mu_{max}^{KBr}$ 5.79, 9.00, 9.59, 10.45, 12.41.

*Anal.* Calcd. for $C_{21}H_{32}O_4$: C, 72.38; H, 9.26. Found: C, 72.16; H, 8.99.

**3,3-Dimethoxy-2β,19-epoxy-5α-androstan-17β-ol (XXI).**—A solution of 0.24 g. (0.0007 mole) of XX and 0.48 g. of LiAl(*t*-BuO)$_3$H in 30 ml. of tetrahydrofuran was kept at 0° for 30 min. Reaction mixture was diluted with 20 ml. of 5% acetic acid. It was extracted with ether and the ether solution was washed with sodium bicarbonate solution and water, dried ($Na_2SO_4$), and evaporated. The residue was chromatographed on 10 g. of neutral alumina; from the 4% and 8% methanol in ether fractions there was obtained 0.17 g. (70%) of material, m.p. 202–204°. The analytical sample was recrystallized from acetonitrile and had m.p. 206–208°; $[\alpha]^{22}D$ +39° (*c*, 1% in $CHCl_3$), $\mu_{max}^{KBr}$ 2.88, 9.02, 9.59, 9.71, 10.51, 12.40.

*Anal.* Calcd. for $C_{21}H_{34}O_4$: C, 71.96; H, 9.78. Found: C, 71.87; H, 9.62.

**2β,19-Epoxy-17β-hydroxy-5α-androstan-3-one (XXVI).**—A solution of 0.25 g. (0.00071 mole) of XXI and 5 ml. of 2 *N* HCl in 20 ml. of methanol was refluxed for 1.5 hr. The reaction mixture was diluted with water and extracted with ether. The ether solution was washed with sodium bicarbonate solution and water, dried ($Na_2SO_4$), and evaporated. The crude product was chromatographed on 15 g. of neutral alumina; 0.20 g. (70%) of product was obtained from the ether containing 4% methanol fractions, m.p. 192–193°. The analytical sample, recrystallized from acetonitrile, had m.p. 193–194°, $[\alpha]^{22}D$ +127° (*c*, 1% in $CHCl_3$), $\mu_{max}^{KBr}$ 2.91, 5.82, 9.79.

*Anal.* Calcd. for $C_{19}H_{28}O_3$: C, 74.96; H, 9.27. Found: C, 74.74; H, 9.01.