magnesium sulfate. A pinch of 10% palladium-on-carbon catalyst was also added to ensure the decomposition of any peroxidic material.

Claisen-distillation gave 70 g. of crude product, b.p. 47–53° (20 mm.). Redistillation through the spiral-packed column afforded 61.2 g. (70% yield) of 2-methyl-3,4-epoxybutan-2-ol (I), b.p. 69–70° (50 mm). See Table II for analyses.

Isomerization of *trans*-2-Methyl-3,4-epoxypentan-2-ol (VII).—The following procedure was a general one for the isomerization of epoxy alcohols.

A 32.8-g. sample (0.28 mole) of *trans*-2-methyl-3,4-epoxypentan-2-ol (VII) was treated with 150 ml. of 0.5 *N* sodium hydroxide previously cooled to about 5°. The solution was allowed to warm to room temperature and remain there for 1 hr. After saturation with 100 g. of ammonium sulfate, the solution was extracted with three 50-ml. portions of chloroform. The combined chloroform was washed with 25 ml. of half-saturated ammonium sulfate, dried over magnesium sulfate, and concentrated on the steam bath to an internal temperature of 80–85°. Gas chromatographic (GLC) analysis of the concentrate was made by means of a 2.5-m. column packed with DC-710 on Fluoropak 80. The temperature was 100° and a flow rate of 60 cc./min. of helium was used. Emergence times of 9 and 15 min., respectively, were observed for the starting material (45%) and its isomer, *erythro*-4-methyl-3,4-epoxypentan-2-ol (VIII, 55%).

The crude mixture of products was distilled through the glass spiral-packed column at 20 mm. pressure to give the following fractions: (A) 12.2 g., b.p. 57–64°; (B) 2.0 g., b.p. 64–80°; (C) 13.6 g., b.p. 80–81°; $n^{25}D$ 1.4249. GLC analysis of (C) indicated it to be essentially free of impurities. Analysis was in agreement with *erythro*-4-methyl-3,4-epoxypentan-2-ol (VIII) as the structure (see Table II).

A 4.8-g. sample of (C) was isomerized as above in 25 ml. of base. GLC analysis of the chloroform concentrate indicated a 43:57 mixture of *trans* to *erythro* compounds.

Sodium Hydride Isomerization of 2-Methyl-3,4-epoxybutan-2-ol.—To a stirred suspension of 4.7 g. (0.10 mole) of 50.9% sodium hydride in 200 ml. of purified tetrahydrofuran held at 5–10° was added 10.2 g. (0.10 mole) of 2-methyl-3,4-epoxybutan-2-ol (I). A 1940-ml. volume of gas was collected over 20 min. The resulting clear solution was allowed to stir at 10° for 1.5 hr.

After washing with 50 ml. of saturated ammonium sulfate, the organic layer was dried over magnesium sulfate and concentrated on the steam bath to an internal temperature of 85°. GLC analysis indicated a 98:2 ratio of starting material to 3-methyl-2,3-epoxybutan-1-ol (II). In another experiment, a 70% recovery of epoxy alcohol was secured by distillation.

Sodium hydride isomerization of 3-methyl-2,3-epoxybutan-1-ol (II) was attempted using the above procedure. GLC analysis of the crude product indicated that little or no isomerization had occurred.

Acknowledgment.—The author wishes to express his thanks to Dr. F. H. Newth for helpful discussions.

The Synthesis of 17β-Amino-17α-(2′-carboxyethyl)androstane Lactams[1]

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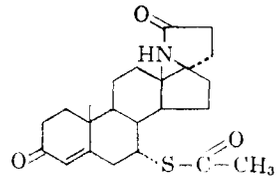
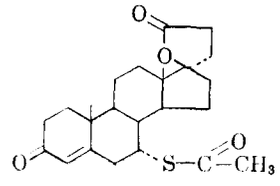
Received April 9, 1962

The synthesis of 17-nitroandrostanes is described from the corresponding oximes. The addition of methyl acrylate to these nitro derivatives, followed by reduction, leads to spirolactams.

As part of our program on steroidal aldosterone antagonists, we decided to prepare 17-spirolactams such as I because of their close similarity to spirolactone antagonists such as II.[2] It seemed to us



I



II

that the unique feature of the spirolactones as a class was the spiro structure at C-17. If so, then changes in this element might be fruitful in altering intrinsic activity in response to the type of cellular bonding which is involved. We were not alone in the selection of this objective since Burtner and Nysted[3] of the Searle group have also synthesized several C-17 spirolactams.

Of various ways of preparing this function, we were attracted by the procedure which is based on a Michael addition α- to a nitro group. We were guided in this selection by recent publications of Hill[4] which draw attention to and develop this method.

We probed three procedures for the synthesis of 17-nitro steroids and decided to base our work on Iffland's oxidation of oximes.[5] We are not in a position to rule out the ultimate applicability of two other methods, the peracid oxidation of 17-

(1) First presented by one of us (A.A.P.) at the Gordon Research Conference on Steroids and Other Natural Products, New Hampton, New Hampshire, August, 1961.

(2) For the chemistry and some of the biology of the spirolactones see J. A. Cella, E. A. Brown, and R. R. Burtner, *J. Org. Chem.*, **24**, 743 (1959); J. A. Cella and R. C. Tweit, *ibid.*, **24**, 1109 (1959); E. A. Brown, R. D. Muir, and J. A. Cella, *ibid.*, **25**, 96 (1960) and N. W. Atwater, R. H. Bible, E. A. Brown, R. R. Burtner, J. S. Mihina, Z. W. Nysted, and P. B. Sollman, *ibid.*, **26**, 3097 (1961).

(3) R. R. Burtner and L. N. Nysted, U.S. Patent 3,001,986 (September 26, 1961).

(4) R. K. Hill, *J. Org. Chem.*, **22**, 830 (1957); R. K. Hill and R. T. Conley, *J. Am. Chem. Soc.*, **82**, 645 (1960).

(5) D. C. Iffland, G. X. Criner, M. Koral, F. J. Lotspeich, Z. B. Papanastassiou, and S. M. White, *J. Am. Chem. Soc.*, **75**, 4044 (1953); D. C. Iffland and G. X. Criner, *ibid.*, **75**, 4047 (1953); and D. C. Iffland and T.-F. Yen, *ibid.*, **76**, 4083 (1954).

oximes[6] or the direct nitration[7,8] of a 17(20)-enol acetate with acetyl nitrate followed by acetyl cleavage. However, in preliminary probes with these two procedures, we had a great deal of trouble in isolating a pure 17-nitro compound despite considerable nitro absorption in the crudes at about 6.5 μ. The Searle[3] procedure for synthesizing the 17-nitro group is a perbenzoic acid oxidation of the 17β-amino group.

We investigated the nitro synthesis of Iffland, *et al.*,[5] using as a starting material the oxime of 3β-hydroxy-5-androstene-17-one 3-acetate. Hypobromite in the presence of air has been known for a long time to convert oximes to α-bromonitro compounds.[9] Iffland, *et al.*, made a number of improvements in the original process including the use of N-bromosuccinimide instead of bromine, the control of pH with sodium bicarbonate and the oxidation of the bromonitroso to the bromonitro intermediate with nitric acid or bromine water instead of air. They also made a major improvement in the reductive removal of bromine in the α-bromonitro compound by using sodium borohydride instead of hydroxide, iodide, or sodium thiosulfate. We found all of these changes applicable to our steroid process with one exception. The nitric acid oxidation was capricious in our hands and ultimately we eliminated this step in favor of stirring the oxime vigorously in dioxane–aqueous potassium bicarbonate with three moles of N-bromosuccinimide for two days (Figure 1). The entire crude at this stage was reduced with sodium borohydride to afford a yield of 50–60% of the desired 3β-hydroxy-17β-nitro-5-androstene 3-acetate.

The stereochemistry of the 17-nitro group is assigned β- since both kinetic and thermodynamic arguments lead to this same prediction. The factors controlling the protonation of the *aci*-nitro and nitro anion groups have been reviewed and further defined by Zimmerman and Nevins.[10] Furthermore, n.m.r. supports a 17β- assignment to the nitro group since the C-17 proton in this compound which is found at 5.62 τ is split into a triplet by the adjacent C-16 methylene group. This is the usual finding for an α- C-17 hydrogen atom. On the other hand, the 17β-hydrogen in, for example, 17-epitestosterone is only split into a doublet.[11]

The Michael addition of methyl acrylate to C-17 proceeded in excellent yield under room temperature conditions in the presence of Triton B. Despite exhaustive chromatography of mother liquors, we were unable to isolate a second isomer and hence it was impossible to prepare both of the possible spirolactams at C-17. We prefer to ascribe this marked stereoselectivity to a kinetically controlled Michael addition to the least hindered side at C-17. To examine the alternate possibility of thermodynamic control, we resubmitted the adduct to the original Michael conditions except that the methyl acrylate was replaced by *t*-butyl alcohol. There was considerable hydrolysis of the acetate and methyl ester, but none of the original 3β-hydroxy-17β-nitro-5-androstene 3-acetate could be detected by thin layer chromatography. We, therefore, propose that the Michael addition is not reversible under the conditions used and hence that the addition was kinetically controlled to the 17α-position.

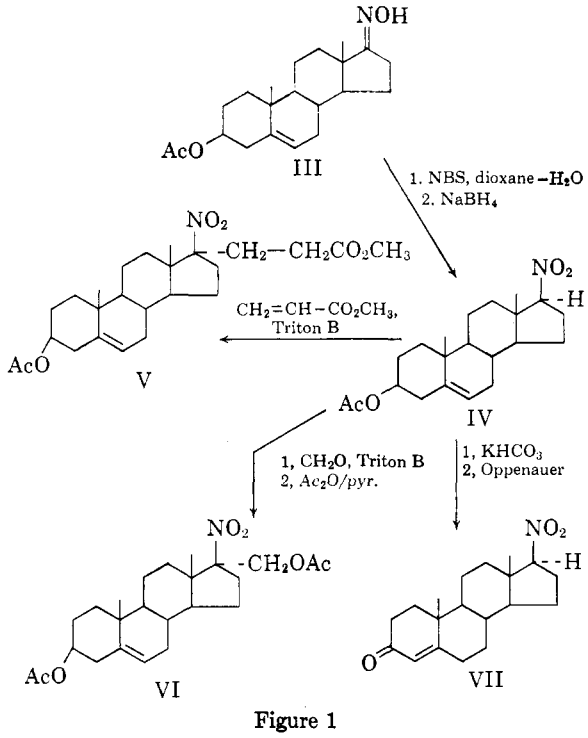


Figure 1

In support of this assignment, the n.m.r. locations of the C-19 methyl hydrogens are at 9.22 τ in the parent nitro compound and 9.19 τ in the Michael adduct. This is at least consistent with the 17-nitro function having the same stereochemistry in both compounds. Furthermore, the optical rotatory dispersion curves are both positive and of similar shape as indicated in Figure 2.[12]

In agreement with the literature, the alkyl halide C-alkylation of nitro compounds is a very poor reaction in sharp contrast with the easy C-alkylation which is possible *via* the Michael addition. We attempted to methylate 3β-hydroxy-17β-nitro-5-androstene 3-acetate with methyl iodide and

(6) W. D. Emmons and A. S. Pagano, *J. Am. Chem. Soc.*, **77**, 4557 (1955).

(7) G. B. Bachman and T. Hokama, *J. Org. Chem.*, **25**, 178 (1960).

(8) F. G. Bordwell and E. W. Garbisch, *J. Am. Chem. Soc.*, **82**, 3588 (1960).

(9) M. O. Forster, *J. Chem. Soc.*, **75**, 1141 (1899); *ibid.*, **77**, 254 (1900).

(10) H. E. Zimmerman and T. E. Nevins, *J. Am. Chem. Soc.*, **79**, 6559 (1957).

(11) We are most indebted to Dr. Nelson Trenner and Mr. Byron Arison for recording and interpreting the n.m.r. data which are reported in this publication. The spectra were recorded in deuterochloroform on a 60 megacycle Varian Associates Model 4300 B high resolution spectrometer and are expressed in τ units as defined by G. V. D. Tiers, *J. Phys. Chem.*, **62**, 1151 (1958).

(12) We are very much indebted to Dr. D. E. Williams of Merck & Co., Inc. for the determination of these curves.

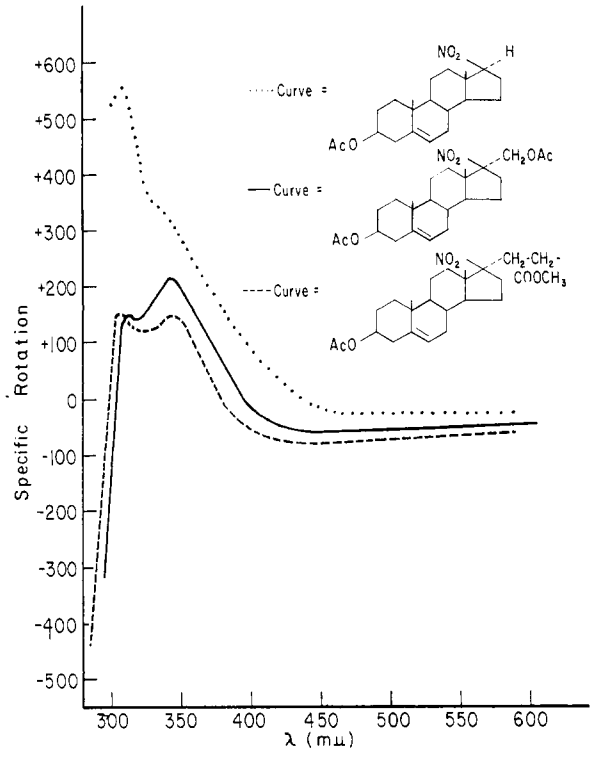


Figure 2

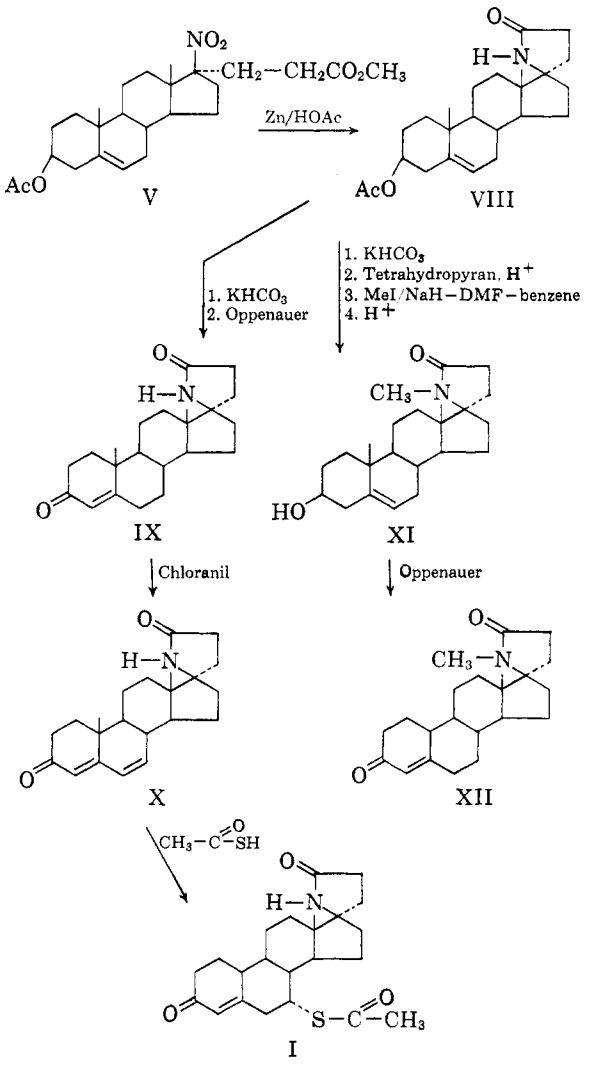


Figure 3

sodium hydride in dimethylformamide–benzene but no new nitro steroid could be isolated after extensive chromatography. However, a one carbon fragment could be added at C-17 *via* the substitution of formaldehyde for methyl acrylate in the Michael procedure. It may be that these reactions are reversible on oxygen whereas alkyl halide reactions are not. The isolated formaldehyde adduct is thought to have a 17β-nitro group since its optical rotatory dispersion curve resembles the parent compound and the Michael adduct.

A further conversion of 3β-hydroxy-17β-nitro-5-androstene 3-acetate was its bicarbonate hydrolysis and Oppenauer oxidation to 17β-nitro-4-androsten-3-one. The yield was only moderate; nevertheless, the nitro group appears to be stable to Oppenauer conditions. We also attempted to convert 3β-hydroxy-17β-nitro-5-androstene 3-acetate into its Δ^{16}-derivative to determine if this would solve the C-alkylation problem. However, this is still an unattained objective. Solvolysis of the crude bromonitro intermediate in dimethylformamide with lithium chloride and lithium carbonate at 110° was not successful as judged by ultraviolet nor was selenium dioxide oxidation in refluxing *t*-butyl alcohol with either acetic acid or pyridine as catalyst.

Returning to the lactam syntheses, the Michael adduct (VIII) was smoothly converted to the corresponding spirolactam by zinc and acetic acid and this in turn could be hydrolyzed at C-3 and converted by the Oppenauer oxidation to the 3-keto-Δ^4-analog (Figure 3). Burtner and Nysted[8] have also described this compound and their m.p. 286–290° is in good agreement with our finding of 288–293°. The 3-keto-Δ^4-spirolactam was further oxidized by chloranil to the $\Delta^{4,6}$ analog and thiolacetic acid was added at C-7 to yield (I).

The preparation of N-methyllactams was smoothly accomplished on the 3-tetrahydropyranyl ether derivative using sodium hydride in dimethyl formamide–benzene followed by tetrahydropyran removal and then an Oppenauer oxidation. The reduction of the spirolactam function was unreliable with lithium aluminum hydride in ether but the spiroamine could be isolated in good yield when dioxane was used as the solvent (Figure 4). This amine was further converted to the 3-keto-Δ^4-analog and to the corresponding N-acetyl derivative. It is noteworthy that the hydrogens of the C-18 methyl are found at 9.15 τ in VII and 9.08 τ in XV. This small but significant displacement is considered to be consistent with proposed stereochemistry at C-17.

The synthesis of 11-oxygenated lactams is sum-

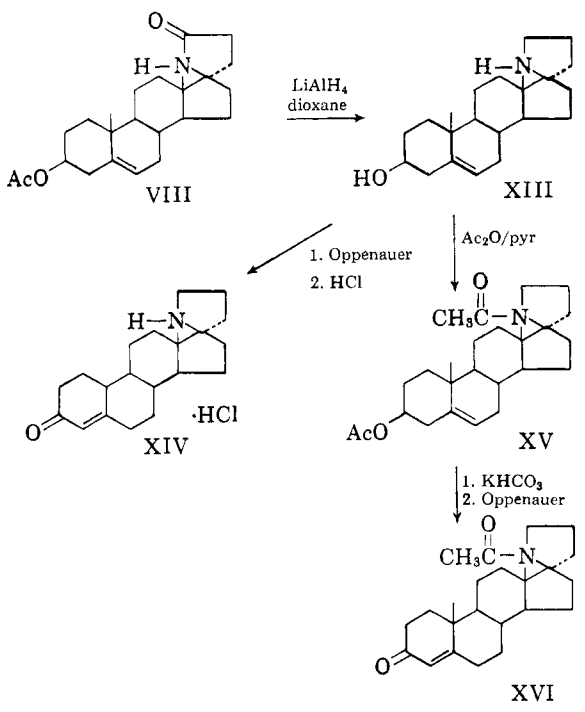


Figure 4

marized in Figure 5 beginning with the known[13] 3α-hydroxy-5β-androstane-11,17-dione 3-acetate. The preparation of the nitro group and the formation of the spirolactam proceeded smoothly as did the remaining elaborations of the 3-keto-Δ^4- and 9α-fluoro-11β-hydroxy functions.

Experimental

Melting points were determined on a hot stage and are uncorrected. We wish to thank Mr. R. N. Boos and his staff for the elemental analyses. The optical rotations were taken under the supervision of Dr. D. E. Williams. Ultraviolet spectra were determined in ethanol by Mr. A. Kalonsky.

3β-Hydroxy-17β-nitro-5-androstene 3-Acetate (IV).—A vigorously stirred suspension was prepared of 39.2 g. of finely powdered N-bromosuccinimide in 125 ml. of water and 125 ml. of dioxane. A solution of 21.8 g. of potassium bicarbonate in 125 ml. of water was added followed by a solution of 25 g. of the oxime of dehydroepiandrosterone acetate[13] in 250 ml. of dioxane. The resulting suspension was stirred vigorously for 2 days. The mixture gradually became green, but at the end of 2 days the suspended globules were brown. Water was added and the product was extracted into ether. The solvent was washed with water and with dilute ferrous sulfate solution and taken to dryness *in vacuo*. The residual foam was taken up in 425 ml. of purified tetrahydrofuran and 85 ml. of water. A stirring bar was inserted and a condenser was put in place. Sodium borohydride (8.5 g.) was added in small portions over 15 min. This caused a gentle reflux during the addition. After 1 hr. at room temperature, an additional 2.5 g. of sodium borohydride was added and then after an additional 1.5 hr. the reaction mixture was acidified with 50 g. of hydroxylamine hydrochloride in water. The product was extracted into ether, washed, and dried. Removal of the solvent and crystallization from ethyl acetate afforded 12.65 g. (yield: 55%) of 3β-hydroxy-17β-nitro-5-androstene 3-acetate of m.p. 210–212° with infrared absorption at 5.78 and 6.52 μ, and $[\alpha]_D$ −29.7° (*c* 0.47 in dioxane).

Anal. Calcd. for $C_{21}H_{29}NO_4$: C, 70.17; H, 8.13; N, 3.90. Found: C, 70.03; H, 8.35; N, 3.80.

17β-Nitro-4-androsten-3-one (VII).—A solution of 1.5 g. of 3β-hydroxy-17β-nitro-5-androstene 3-acetate in 125 ml. of methanol and 12 ml. of water was refluxed for 3 hr. with 3 g. of potassium bicarbonate. Most of the methanol was removed *in vacuo*, aqueous hydroxylamine hydrochloride was added and the product was extracted into ethyl acetate.

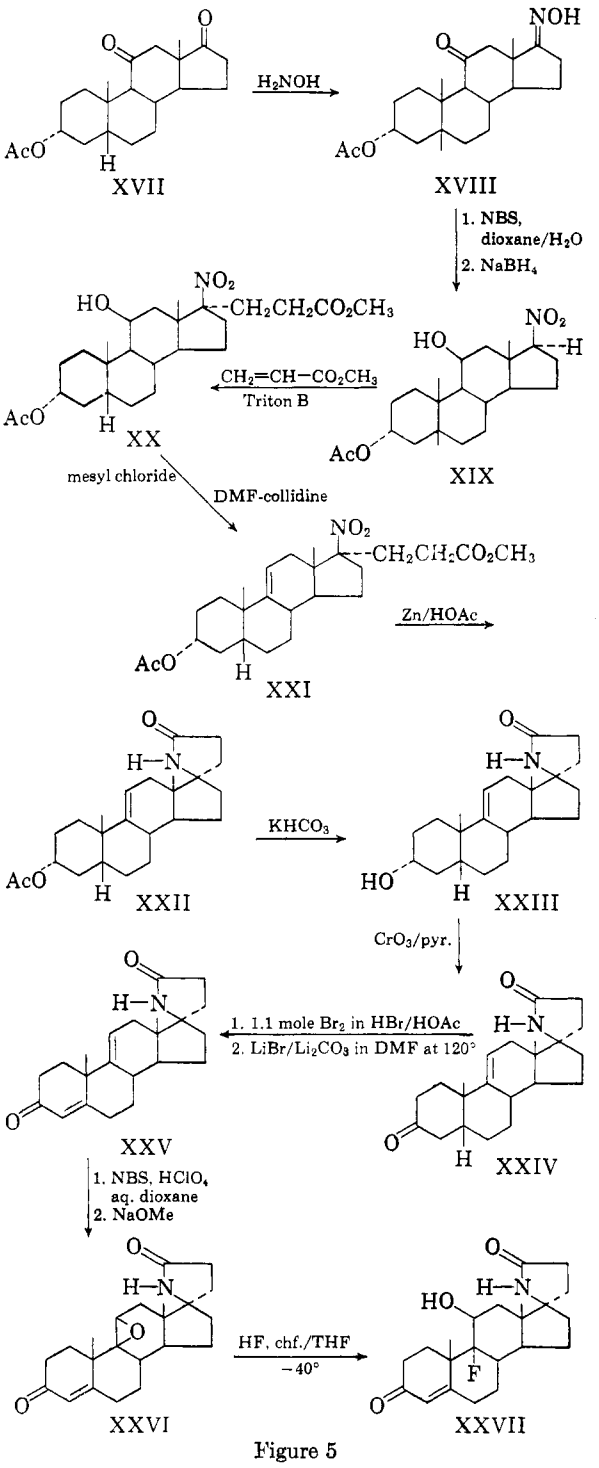


Figure 5

(13) L. H. Sarett, *J. Biol. Chem.*, **162**, 601 (1946).
(14) E. B. Hershberg, *J. Org. Chem.*, **13**, 542 (1948).

Removal of the dried solvent left 17β-nitro-5-androstene-3β-ol of sufficient purity for the next step.

About 15 ml. of toluene was distilled from a solution of 1 g. of 17β-nitro-5-androsten-3β-ol in 16 ml. of cyclohexanone and 150 ml. of toluene. Then 5 ml. was added of a 20% solution of aluminum isopropoxide in toluene and the mixture was refluxed for 1.5 hr. with Drierite protection. Some water was added and the organic layer was decanted, filtered and concentrated *in vacuo*. Chromatography on neutral alumina afforded 300 mg. of product from the ether and ether–chloroform (9:1) fractions. Recrystallization from methanol–ether gave analytically pure 17β-nitro-4-androsten-3-one of m.p. 152–155°, ultraviolet λ_{max} 240 mμ, E%, 448 and $[\alpha]_D$ +137° (*c* 1.0 in chf.).

Anal. Calcd. for $C_{19}H_{27}NO_3$: C, 71.89; H, 8.57. Found: C, 71.65; H, 8.56.

3β-Hydroxy-17β-nitro-17α-(2-carbomethoxyethyl)-5-androstene 3-Acetate (V).—A partial suspension was prepared of 20 g. of 3β-hydroxy-17β-nitro-5-androstene 3-acetate in 150 cc. of *t*-butyl alcohol and 290 cc. of methyl acrylate. Thirty cubic centimeters of methanolic Triton B was added slowly with magnetic stirring whereupon all of the steroid went into solution. After 18 hr. at room temperature, the reaction mixture was poured onto iced dilute hydrochloric acid and it was extracted with ethyl acetate. Removal of the washed and dried solvent, finally at high vacuum, left a semicrystalline residue. Crystallization from ether and petroleum ether afforded 12.86 g. of product, m.p. 130–132°. The analytical sample from the same solvent had m.p. 133–134°, $[\alpha]_D$ −57° (*c* 1.01 in dioxane).

Anal. Calcd. for $C_{25}H_{37}NO_6$: C, 67.09; H, 8.33; N, 3.13. Found: C, 66.90; H, 8.38; N, 2.95.

3β-Hydroxy-17β-nitro-17α-acetoxymethyl-5-androstene 3-acetate (VI).—A mixture of 100 mg. of 3β-hydroxy-17β-nitro-5-androstene 3-acetate, 5 ml. of dioxane, 1 ml. of water, 1 ml. of 37% formaldehyde, and 0.1 ml. of methanolic Triton B was heated in the steam bath for 1 hr. Most of the solvent was removed on the rotating evaporator, dilute hydrochloric acid was added, and the product was extracted into ethyl acetate. The crude material after removal of the dried solvent was acetylated at room temperature overnight with 1 ml. of pyridine and 1 ml. of acetic anhydride. Work-up in the usual manner gave a semicrystalline residue which after several crystallizations from ether had m.p. 210–212°, $[\alpha]_D$ − 47° (*c* 0.51, dioxane).

Anal. Calcd. for $C_{24}H_{35}NO_6$: C, 66.49; H, 8.14. Found: C, 66.15; H, 8.16.

3-(3β-Hydroxy-17β-amino-5-androsten-17α-yl)-propionic Acid Lactam 3-Acetate (VIII).—Two grams of 3β-hydroxy-17β-nitro-17α-(2-carbomethoxyethyl)-5-androstene 3-acetate was dissolved in 150 ml. of glacial acetic acid and heated under reflux with stirring with 2 g. of zinc dust for 72 hr. An additional 1 g. of zinc dust was added at each 24-hr. interval of heating. The reaction mixture was then filtered, washed with warm glacial acetic acid, and concentrated to dryness *in vacuo*. The residue was extracted with ethyl acetate and water, and the solvent was dried and evaporated to yield 1.9 g. of crude 3-(3β-hydroxy-17β-amino-5-androsten-17α-yl)propionic acid lactam 3-acetate. Recrystallization from acetone–ether gave 1.6 g. of product, m.p. 309–311°; infrared absorption at 3.16, 5.78, 5.85, and 8.1 μ; $[\alpha]_D$ −68° (*c* 1.04 in chf.).

Anal. Calcd. for $C_{24}H_{35}NO_3$: C, 74.76; H, 9.15; N, 3.63. Found: C, 74.82; H, 9.30; N, 3.67.

3-(17β-Amino-4-androsten-3-one-17α-yl)propionic Acid Lactam (IX).—3-(3β-Hydroxy-17β-amino-5-androsten-17α-yl)propionic acid lactam 3-acetate (1.6 g.) was refluxed for 2 hr. with 3 g. of potassium bicarbonate in 300 ml. of methanol and 30 ml. of water. Most of the solvent was then removed *in vacuo*, water was added, and the crystalline product was filtered off. The yield was 1.2 g., m.p. 290–300° (from methylene chloride–methanol), and infrared absorption at 2.95, 3.10, and 5.86 μ.

A solution of 1.00 g. of 3-(3β-hydroxy-17β-amino-5-androsten-17α-yl)propionic acid lactam in 16 ml. of cyclohexanone and 150 ml. of toluene was dried by distilling 20 ml. Then 5.0 ml. of a 20% aluminum isopropoxide solution in toluene was added. After a 2.5-hr. reflux, *n*-butyl alcohol was added to the cooled mixture and this solution was extracted with dilute hydrochloric acid and water. Most of the dried solvent was removed *in vacuo*, finally at 100° at the oil pump. The semicrystalline residue was rubbed with petroleum ether and collected; yield, 706 mg.; m.p. 284–288°. Further crystallization from methylene chloride–ether and from methylene chloride–acetone afforded an analytical sample, m.p. 288–293°; infrared, 2.9, 3.1, 5.9, 6.0, and 6.2 μ; ultraviolet λ_{max} 240, E% 455 and $[\alpha]_D$ +93° (*c* 1.0 in chf.).

Anal. Calcd. for $C_{22}H_{31}NO_2$: C, 77.37; H, 9.15; N, 4.10. Found: C, 77.58; H, 9.18; N, 4.19.

3-(17β-Amino-4,6-androstadien-3-one-17α-yl)propionic Acid Lactam (X).—A solution of 500 mg. of 3-(17β-amino-4-androsten-3-one-17α-yl)propionic acid lactam and 1.0 g. of chloranil in 75 ml. of *t*-butyl alcohol was refluxed overnight. The mixture was cooled to room temperature, filtered, and the *t*-butyl alcohol was removed *in vacuo*. The residue was dissolved in chloroform which was then washed three times with dilute sodium hydroxide and then with water. Removal of the dried solvent left material which was crystallized two times each from methylene chloride–acetone and from methylene chloride–ether. The yield of product was 122 mg., m.p. 316–318°. Further crystallizations from methylene chloride–acetone afforded the analytical sample, m.p. 318–320°, ultraviolet λ_{max} 282, E% 744 and $[\alpha]_D$ +26° (*c* 1.0 in chf.).

Anal. Calcd. for $C_{22}H_{29}NO_2$: C, 77.84; H, 8.61. Found: C, 77.52; H, 8.41.

3-(17β-Amino-7α-acetylthio-4-androsten-3-one-17α-yl)-propionic Acid Lactam (I).—A solution of 75 mg. of 3-(17β-amino-4,6-androstadien-3-one-17α-yl)propionic acid lactam in 0.5 ml. of redistilled thioacetic acid was heated on the steam bath for 1 hr. in the absence of moisture. The excess thioacetic acid was blown off at room temperature with nitrogen and the residue was washed two times with small amounts of ether. Trituration with cold methanol afforded crystals. After a second trituration, the product was collected; yield, 46 mg. After two crystallizations from methanol–ether the acetylthio analog (I) was characterized by m.p. 222–226°, ultraviolet λ_{max} 238, E% 469 and $[\alpha]_D$ +7° (*c* 1.0 in chf.).

Anal. Calcd. for $C_{24}H_{33}NO_3S \cdot CH_3OH$: C, 67.09; H, 8.33. Found: C, 66.83; H, 7.91.

3-(3β-Hydroxy-17β-methylamino-5-androsten-17α-yl)-propionic Acid Lactam (XI).—Five hundred milligrams of 3-(17β-amino-3β-hydroxy-5-androsten-17α-yl)propionic acid lactam reacted at room temperature for 18 hr. with 50 ml. of dry dihydropyran and 150 mg. of *p*-toluenesulfonyl chloride. This mixture was then diluted with 5% sodium bicarbonate solution and the crystalline precipitate was collected; yield, 300 mg.

A solution was prepared of 250 mg. of this tetrahydropyranyl ether in 8-ml. of dimethylformamide and 16 ml. of benzene. Eight milliliters of benzene was distilled to insure dryness. After the addition of 80 mg. of sodium hydride, a yellow anion developed. Two milliliters of methyl iodide was added and the mixture was stirred overnight under nitrogen and then it was refluxed for 1 hr. The mixture was diluted with benzene, washed with water, dried, and evaporated to yield 192 mg. of crude 3-(3β-hydroxy-17β-methylamino-5-androsten-17α-yl)propionic acid lactam 3-tetrahydropyranyl ether.

The reversal of the ether at C-3 was accomplished by 20 mg. of *p*-toluenesulfonic acid in 10 ml. of ethanol. After 18 hr. at room temperature, some of the ethanol was removed on the rotator, water was added, and the product was extracted into ethyl acetate. The solvent was washed with dilute sodium bicarbonate, dried, and evaporated. Recrystallization of the residue from methylene chloride–ether

yielded 140 mg. of 3-(3β-hydroxy-17β-methylamino-5-androsten-17α-yl)propionic acid lactam, m.p. 255–260°.

Anal. Calcd. for $C_{23}H_{35}NO_2$: C, 77.26; H, 9.87. Found: C, 77.20; H, 9.65.

3-(17β-Methylamino-4-androsten-3-one-17α-yl)-propionic Acid Lactam (XII).—About 10 ml. of solvent was distilled from a solution of 500 mg. of 3-(3β-hydroxy-17β-methylamino-5-androsten-17α-yl)propionic acid lactam in 8 ml. of cyclohexanone and 75 ml. of toluene. Then 2.5 ml. of a 20% solution of aluminum isopropoxide in toluene was added and the mixture was refluxed for 3 hr. A small amount of water was added to the cooled solution which was filtered and evaporated to dryness. Elution from neutral alumina with ether and ether chloroform (1:1) afforded 311 mg. of 3-(17β-methylamino-4-androsten-3-one-17α-yl)propionic acid lactam. It was recrystallized from methylene chloride–ether to m.p. 217–220°, infrared absorption at 5.95, 6.0, and 6.2 μ and ultraviolet λ_{max} 240, E% 448.

Anal. Calcd. for $C_{23}H_{33}NO_2$: C, 77.70; H, 9.36. Found: C, 77.45; H, 9.60.

3β-Hydroxy-5-androstene-17-spiro-2′-pyrrolidine-(17β-N) (XIII).—One gram of 3-(3β-hydroxy-17β-amino-5-androsten-17α-yl)propionic acid lactam was refluxed with 3 g. of lithium aluminum hydride in 400 ml. of purified dioxane for 90 hr. Ether and saturated aqueous sodium potassium tartrate were added carefully to the cooled solution. This mixture was filtered through Supercel and then concentrated *in vacuo* to remove most of the dioxane. Dilute sodium hydroxide was added and the desired amine was brought into ethyl acetate with several extractions. Removal of the washed and dried solvent left 820 mg. of 3β-hydroxy-5-androstene-17-spiro-2′-pyrrolidine-(17β-N). It was recrystallized from methanol–ethyl acetate to m.p. 195–198°, infrared absorption at 3.18 μ.

Anal. Calcd. for $C_{22}H_{35}NO$: C, 80.19; H, 10.71; N, 4.25. Found: C, 80.34; H, 10.62; N, 3.99.

4-Androsten-3-one-17-spiro-2′-pyrrolidine-(17β-N) Hydrochloride (XIV).—The Oppenauer oxidation of 3β-hydroxy-5-androstene-17-spiro-2′-pyrrolidine-(17β-N) was conducted in the same manner as that reported for the above 3-(3β-hydroxy-17β-methylamino-5-androsten-17α-yl)-propionic acid lactam. The yield of 4-androsten-3-one-17-spiro-2′-pyrrolidine-(17β-N) was 310 mg. from 500 mg. of the alcohol. A hydrochloride was prepared by dissolving the free base in a small amount of methanol to which a 20–40 fold quantity of ether was added. After centrifuging off impurities, hydrogen chloride gas was added to precipitate the salt. This was recrystallized several times from methanol–methyl ethyl ketone, m.p. >350°; infrared absorption at 3.69, 3.81, 4.05, 5.98, 6.21, and 6.30 μ; ultraviolet λ_{max} 239.5, E% 446; $[\alpha]_D$ +85° (*c* 1.07 in chf.).

Anal. Calcd. for $C_{22}H_{34}NOCl$: C, 72.59; H, 9.41; N, 3.85. Found: C, 72.35; H, 9.22; N, 3.46.

3β-Hydroxy-5-androstene-17 spiro-2′-pyrrolidine-(17β-(N)-1′-acetyl 3-Acetate (XV).—The diacetylation of 250 mg. of 3β-hydroxy-5-androstene-17-spiro-2′-pyrrolidine-(17β-N) was accomplished with 2.5 ml. of acetic anhydride and 2.5 ml. of pyridine. This mixture was heated on the steam bath under nitrogen for 1.5 hr. It was then taken to dryness on the rotating evaporator and the residue was crystallized from methylene chloride–ether. The analytical sample was of m.p. 208.5–210°; infrared absorption at 5.78 and 6.10 μ.

Anal. Calcd. for $C_{29}H_{39}NO_3$: C, 75.40; H, 9.66. Found: C, 75.50; H, 9.51.

4-Androsten-3-one-17-spiro-2′-pyrrolidine-(17β-N)1′-acetyl (XVI).—A solution of 298 mg. of 3β-hydroxy-5-androstene-17-spiro-2′-pyrrolidine-(17β-N)1′-acetyl 3-acetate in 35 ml. of methanol, 3.5 ml. of water, and 600 mg. of potassium bicarbonate was refluxed for 3 hr. Most of the methanol was removed *in vacuo*, water was added, and essentially pure 3β-hydroxy-5-androstene-17-spiro-2′-pyrrolidine-(17β-N)1′-acetyl was recovered by ethyl acetate extraction. It weighed 200 mg. and had infrared absorption at 2.91 μ and 6.14 μ.

This material was azeotropically dried in a solution of 16 ml. of toluene, 8 ml. of dioxane, 8 ml. of benzene, and 3.2 ml. of cyclohexanone. After most of the benzene had distilled, 1 ml. of a 20% aluminum isopropoxide solution in toluene was added. Reflux was maintained for 3 hr. and then a small amount of water was added to the cooled solution. Filtration and removal of solvent under vacuum afforded a crystalline residue. An analytical sample was prepared from ethyl acetate, m.p. 223.5–225.5°, $[\alpha]_D$ +23° (*c* 1.0 in chf.), infrared 6.00, 6.11, and 6.20 μ and ultraviolet 240, E% 419.

Anal. Calcd. for $C_{24}H_{35}NO_2$: C, 78.00; H, 9.55; N, 3.79. Found: C, 78.11; H, 9.59; N, 3.63.

3α-Hydroxy-5β-androstane-11,17-dione-17-oxime 3-Acetate (XVIII).—A solution of 75 g. of 3α-hydroxy-5β-androstane-11,17-dione 3-acetate, 17.2 g. of hydroxylamine hydrochloride, and 500 ml. of pyridine was heated on a steam cone at 90° for 2.5 hr. The solution was cooled and diluted with 300 ml. of water. The precipitate was collected on a filter, rinsed well with water, and air dried to yield 68 g. A sample for analysis melted at 190–193° after crystallization from methanol, $[\alpha]_D$ +59° (*c* 0.98 in chf.).

Anal. Calcd. for $C_{21}H_{31}NO_4$: C, 69.77; H, 8.65; N, 3.88. Found: C, 69.60; H, 8.43; N, 3.97.

3α,11β-Dihydroxy-17β-nitro-5β-androstane 3-Acetate (XIX).—To a slurry of 110 g. of N-bromosuccinimide in 350 ml. of dioxane and 350 ml. of water there was added simultaneously 65 g. of oxime (XVIII) in 700 ml. of dioxane and 61 g. of potassium bicarbonate in 350 ml. of water. The mixture was stirred for 18 hr., diluted with water, and extracted with ethyl acetate. The ethyl acetate was washed successively with a saturated ferrous sulfate solution (two times), water, 10% sodium bisulfite (two times) and again with water. After drying over anhydrous sodium sulfate, the ethyl acetate was removed under vacuum leaving a solid residue. This was dissolved in 1.8 l. of an 80% tetrahydrofuran–water solution and 31 g. of sodium borohydride was added over a 40-min. period with vigorous stirring. The mixture was stirred for 2.5 hr. and 80 g. of hydroxylamine hydrochloride in 1.2 l. of water was added slowly. The solution was extracted with ether and washed successively with water, ferrous sulfate, water, sodium bisulfite, and water. Concentration of the ether afforded 13.0 g. of 3α,11β-dihydroxy-17β-nitro-5β-androstane 3-acetate. Chromatography over 900 g. of acid washed alumina yielded an additional 7 g. of product. The analytical sample had m.p. 180–183°.

Anal. Calcd. for $C_{21}H_{33}NO_5$: C, 66.46; H, 8.79; N, 3.69. Found: C, 66.31; H, 8.32; N, 3.63.

3α,11β-Dihydroxy-17β-nitro-17α-(2-carbomethoxyethyl)-5β-androstane 3-Acetate (XX).—To 19.2 g. of 3α,11β-dihydroxy-17β-nitro-5β-androstane 3-acetate in 290 ml. of methyl acrylate and 145 ml. of *t*-butyl alcohol there was added 29 ml. of methanolic Triton B. The solution was left overnight in a stoppered flask and it was then poured into 100 ml. of 2.5 *N* hydrochloric acid and an equal volume of ice.

The organic materials were extracted into ether which was washed once with 50 ml. of saturated potassium bicarbonate solution and two times with water. The dried solvent was evaporated *in vacuo* until crystallization began. The crystals were collected on a filter, washed with cold ether, and air-dried to yield 20.7 g. of 3α,11β-dihydroxy-17β-nitro-17α-(2-carbomethoxyethyl)-5β-androstane 3-acetate, m.p. 214–220°.

A sample for analysis, after crystallization from ethyl acetate, melted at 220–222° $[\alpha]_D$ +46° (*c* 1.03 in chf.).

Anal. Calcd. for $C_{25}H_{39}NO_7$: C, 64.49; H, 8.44; N, 3.01. Found: C, 64.48; H, 8.58; H, 3.16.

3α-Hydroxy-17β-nitro-17α-(2-carbomethoxyethyl)-9(11)-5β-androstene 3-Acetate (XXI).—A solution consisting of 17.1 g. of 3α,11β-dihydroxy-17β-nitro-17α-(2-carbomethoxyethyl)-5β-androstane 3-acetate, 102 ml. of dimethylformamide, and 51 ml. of collidine was cooled to 10°. Twenty milliliters of methanesulfonyl chloride was added

and the reaction flask was immersed immediately in an oil bath maintained at 35°. After 20 min. the reaction mixture was poured into 1.5 l. of cold water and the solid was collected by filtration. Crystallization from methanol yielded 11.7 g. of 3α-hydroxy-17β-nitro-17α-(2-carbomethoxyethyl)-9-(11)-5β-androstene 3-acetate, m.p. 127–130°. The mother liquor was chromatographed over 300 g. of acid washed alumina and the 50% petroleum ether–ether eluates yielded an additional 2.8 g. The analytical sample from methanol had m.p. 129–130°, $[\alpha]_D$ +28° (*c* 0.57 in chf.).

Anal. Calcd. for $C_{25}H_{37}NO_6$: C, 67.09; H, 8.33; N, 3.13. Found: C, 66.90; H, 8.24; N, 2.90.

3-[3-Hydroxy-17β-amino-5β-androst-9(11)-en-17α-yl]propionic Acid Lactam 3-Acetate (XXII).—To 12.2 g. of 3α-hydroxy-17β-nitro-17α-[2-carbomethoxyethyl]-5β-androst-9-(11)-ene 3-acetate in 300 ml. of glacial acetic acid there was added 12.2 g. of zinc dust in small portions over a 65-min. period. After 1 hr. 12.2 g. of zinc was again added and the mixture was stirred for 18 hr. The mixture was filtered and the filtrate was evaporated under reduced pressure. Dilution with water and filtration yielded 9.74 g. of 3-(3β-hydroxy-17β-amino-5β-androst-9(11)-en-17α-yl)propionic acid lactam 3-acetate, m.p. 230–235° (crystal change at 220°). A sample for analysis melted at 238–240° after crystallization from ethyl acetate, $[\alpha]_D$ +20° (*c* 0.87 in chf.).

Anal. Calcd. for $C_{24}H_{35}NO_3$: C, 74.76; H, 9.15; N, 3.63. Found: C, 74.71; H, 9.33; N, 3.31.

3-[3α-Hydroxy-17β-amino-5β-androst-9(11)-en-17α-yl]-propionic Acid Lactam (XXIII).—To a solution of 3 g. of 3-[3α-hydroxy-17β-amino-5β-androst-9(11)-en-17α-yl]propionic acid lactam 3-acetate in 94 ml. of methanol there was added a solution of 6.5 g. of potassium bicarbonate in 36 ml. of water. The solution was refluxed for 4 hr., cooled, poured into water, and extracted with ethyl acetate. The ethyl acetate solution was washed with water, dried over anhydrous sodium sulfate and concentrated *in vacuo*. The crude product was crystallized from ethyl acetate to yield 2.71 g. of 3-[3α-hydroxy-17β-amino-5β-androst-9(11)-en-17α-yl] propionic acid lactam, m.p. 179–183°. A sample for analysis melted at 181–183° after recrystallization from ethyl acetate.

Anal. Calcd. for $C_{22}H_{33}NO_2$: C, 76.92; H, 9.63; N, 4.08. Found: C, 76.83; H, 9.63; N, 4.03.

3-[17β-Amino-5β-androst-9(11)-en-3-one-17α-yl]propionic Acid Lactam (XXIV).—A solution of 3.5 g. of 3-[3α-hydroxy-17β-amino-5β-androst-9(11)-en-17α-yl]propionic acid lactam in 20 ml. of pyridine was added slowly with stirring to a pyridine–chromic acid complex prepared from 3.5 g. of chromium trioxide and 20 ml. of pyridine. After 18 hr. at room temperature the dark brown solution was poured into water and extracted two times with ethyl acetate. The ethyl acetate was washed two times with dilute hydrochloric acid, three times with water, and dried over sodium sulfate. The solvent was evaporated *in vacuo* and the residue was crystallized from ethyl acetate to yield 2.42 g. of 3-[17β-amino-5β-androst-9(11)-en-3-one-17α-yl]propionic acid lactam, m.p. 245–250°. The analytical sample was crystallized from methanol, m.p. 255–258°, $[\alpha]_D$ −23° (*c* 0.62 in chf.).

Anal. Calcd. for $C_{22}H_{31}NO_2$: C, 77.37; H, 9.15; N, 4.10. Found: C, 77.56; H, 8.95; N, 3.85.

3-[17β-Amino-4,9(11)-androstadien-3-one-17α-yl]propionic Acid Lactam (XXV).—A solution of 1.26 g. of 3-[17β-amino-9(11)-5β-androsten-3-one-17α-yl]propionic acid lactam, 21 ml. of chloroform, 5 ml. of glacial acetic acid, and 0.5 ml. of hydrobromic acid-acetic anhydride reagent was stirred at 0°. The latter solution was prepared by adding 0.5 ml. of 48% hydrobromic acid to 2 ml. of cold acetic anhydride. To the reaction mixture there was added dropwise over a 1-hr. period 14 ml. of glacial acetic acid containing 670 mg. of bromine and 2 ml. of the hydrobromic acid-acetic anhydride reagent. After stirring for an additional 45 min., the reaction was quenched by the addition of 4 g. of potassium acetate. The mixture was poured into water, extracted with chloroform, and the chloroform layer was washed with water, dried over sodium sulfate, and concentrated *in vacuo*.

The crude product (1.6 g.) was heated in an oil bath at 120° for 2 hr. with 30 ml. of dimethylformamide, 1.6 g. of lithium bromide, and 1.6 g. of lithium carbonate. The reaction mixture was cooled, diluted with water, and extracted with ethyl acetate. The organic layer was washed with water, dried over sodium sulfate, and concentrated *in vacuo*. Crystallization from ethyl acetate yielded 560 mg. of 3-[17β-amino-4,9(11)-androstadien-3-one-17α-yl]propionic acid lactam, m.p. (decomp.) 288–294°. The analytical sample was crystallized from methanol, m.p. (decomp.) 294–298°, ultraviolet absorption λ_{max} 238 mμ, E% 460.

Anal. Calcd. for $C_{22}H_{29}NO_2$: C, 77.84; H, 8.61; N, 4.13. Found: C, 77.54; H, 8.20; N, 3.94.

3-(17β-Amino-9β,11β-epoxy-4-androsten-3-one-17α-yl)-propionic Acid Lactam (XXVI).—Perchloric acid (0.71 ml., 0.2*N*) was added with stirring to a suspension of 200 mg. of 3-[17β-amino-4,9(11)-androstadien-3-one-17α-yl]propionic acid lactam, 135 mg. of *N*-bromosuccinimide, and 4 ml. of dioxane at 5°. This mixture was left in the refrigerator for 3.5 hr. and was then diluted carefully with water until a precipitate occurred. The crystals were collected on a filter, washed two times with water, and dried to yield 176 mg. of crude 3-(17β-amino-9α-bromo-11β-hydroxy-4-androsten-3-one-17α-yl)propionic acid lactam.

To a suspension of 176 mg. of this bromohydrin in 5 ml. of dry methanol there was added 0.5 ml. of a 1*N* sodium methoxide solution and the mixture was stirred at room temperature for 10 min. The reaction was terminated by the addition of glacial acetic acid and ice water. After cooling, the crystalline precipitate was collected, washed with water, and dried *in vacuo* to yield 120 mg. of 3-(17β-amino-9β,11β-epoxy-4-androsten-3-one-17α-yl)propionic acid lactam. Two crystallizations from ethyl acetate afforded the analytical sample, m.p. (decomp.) 282–286°, ultraviolet absorption λ_{max} 243 mμ, E% 400 and $[\alpha]_D$ −7.5° (*c* 0.52 in chf.).

Anal. Calcd. for $C_{22}H_{29}NO_3$: C, 74.33; H, 8.22; N, 3.94. Found: C, 74.07; H, 8.50; N, 4.04.

3-(17β-Amino-9α-fluoro-11β-hydroxy-4-androsten-3-one-17α-yl)propionic Acid Lactam (XXVII).—A hydrogen fluoride solution was prepared at −60° from 10.4 g. of anhydrous hydrogen fluoride, 14.3 ml. of tetrahydrofuran, and 7.5 ml. of chloroform. One and one-half cubic centimeters of this solution was kept at −60° and to it was added 54 mg. of 3-(17β-amino-9β,11β-epoxy-4-androsten-3-on-17α-yl)-propionic acid lactam in 0.75 ml. of chloroform likewise chilled at −60°. The reaction mixture was maintained at −40° for 2.5 hr. and then it was added to a well agitated mixture of aqueous potassium carbonate, chloroform and ice. The organic layer was washed two times with water, dried over sodium sulfate, and concentrated *in vacuo*. Crystallization from ethyl acetate yielded 30 mg. of 3-(17β-amino-9α-fluoro-11β-hydroxy-4-androsten-3-on-17α-yl)-propionic acid lactam, m.p. (decomp.) 346–348° with ultraviolet absorption at λ_{max} 238 mμ, E% 425 and $[\alpha]_D$ +90° (*c* 0.5 in chf.).

Anal. Calcd. for $C_{22}H_{30}FNO_3$: C, 70.37; H, 8.05; N, 3.72. Found: C, 70.68; H, 8.20; N, 3.80.

Acknowledgment.—The authors wish to thank Dr. L. H. Sarett and Dr. N. L. Wendler for a number of helpful suggestions.