$[\Phi]_{208}$ 0°; λ_{max} 252 mμ (log ε 4.16); ν_{max} 1740, 1720, 1680, and 1250 cm^{-1}; nmr 0.70 (s, H-18), 1.11 (s, H-19), 2.03 (s, H-17α-acetoxy), 2.11 (s, H-21), and 6.14 ppm (s, H-4).

Anal. Calcd for $C_{24}H_{30}O_4Cl_2$: C, 63.57; H, 6.67; Cl, 15.64. Found: C, 63.50; H, 6.72; Cl, 15.70.

The 17 alcohol **10c** (50 mg) gave the following data: mp 259–260° (from acetone); $[\alpha]_D$ +107°; λ_{max} 251 mμ (log ε 4.09); ν_{max} 3460, 1710, 1670, and 1660 cm^{-1}; nmr 0.56 (s, H-18), 1.07 (s, H-19), 2.09 (s, H-21), and 6.00 ppm (s, H-4).

Anal. Calcd for $C_{22}H_{28}O_3Cl_2$: C, 64.23; H, 6.86. Found: C, 64.37; H, 6.91.

Reaction of 17α-Acetoxy-3,3-cycloethylenedioxypregna-4,6-dien-20-one (8c) with Phenyl(trichloromethyl)mercury.—A solution of **8c** (830 mg) and phenyl(trichloromethyl)mercury (950 mg) in benzene (210 ml) was heated under reflux for 120 hr. Since tlc analysis showed the presence of starting **8c**, an additional 950 mg of the mercurial reagent was added and the solution was boiled again for 72 hr. Purification of the crude product by preparative tlc afforded **10b** (360 mg), mp 188°, identical in all respects with a sample of **10b** obtained from the preceding experiment, and the ketal adduct **10d** (235 mg): mp 166–167° (from acetone–hexane); $[\alpha]_D$ +58°; ν_{max} 1740, 1720, and 1250 cm^{-1}; nmr 0.67 (s, H-18), 0.95 (s, H-19), 2.01 (s, H-17α-acetoxy), 2.06 (s, H-21), 4.01 (s, cycloethylenedioxy H), and 5.71 ppm (s, H-4).

Anal. Calcd for $C_{26}H_{34}O_5Cl_2$: C, 62.77; H, 6.89; Cl, 14.25. Found: C, 62.54; H, 7.16; Cl, 14.08.

Treatment of ketal **10d** with methanol containing concentrated hydrochloric acid for 15 min at room temperature furnished the Δ^4-3 ketone **10b**.

Registry No.—Phenyl(trichloromethyl)mercury, 3294-57-3; **2a**, 23367-44-4; **2c**, 23330-50-9; **3a**, 23367-45-5; **3b**, 23330-51-0; **5**, 23330-52-1; **9**, 23330-53-2; **10b**, 23157-28-0; **10c**, 23330-55-4; **10d**, 23330-56-5.

Acknowledgment.—The authors wish to thank Dr. J. H. Fried for helpful discussions.

Steroidal β-Lactams

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Received September 16, 1969

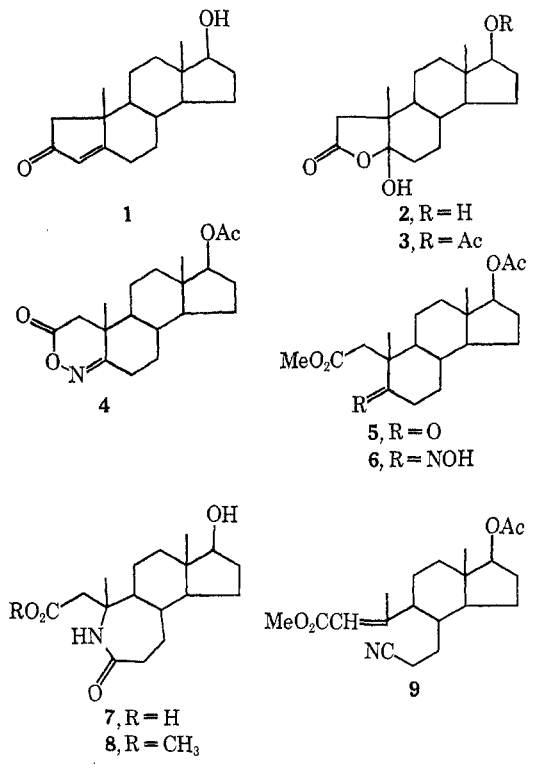
The multistep conversion of A-nortestosterone into a new B-homo steroidal ring system possessing a fused β-lactam as ring A is described. The deshielding effect of the nitrogen atom on the C-19 methyl signal in the nmr spectra of the 5-aza steroidal compounds prepared in this study is discussed briefly.

In this paper, the conversion of A-nortestosterone (**1**)[1] into a new steroidal ring system possessing a fused β-lactam as ring A[2] will be described.[3] The synthesis of this novel structure was of interest to us from both a chemical and biological point of view.

The synthetic scheme for the preparation of the steroidal β-lactam can be divided into three parts. The first stage involves the removal of a carbon atom from ring A of **1** to give a seco compound bearing a two-carbon side chain attached to C-10, the terminal carbon atom of the side chain being oxygenated. The next problem concerns the positioning of a nitrogen atom into ring B in a β relationship to the oxygen-bearing carbon atom of the side chain. Lastly, the modified steroid skeleton must be transformed into a β-amino acid that can then be cyclized to the β-lactam.

The removal of carbon atom 3 from **1** could be achieved by hydroxylation of the conjugated double bond with osmium tetroxide, followed by oxidative cleavage with periodic acid to afford the lactonol **2**.[4] Our synthesis required large amounts of **2**, and it was more conveniently prepared in one step by use of the periodate–permanganate combination.[5] Reaction of **2** with acetic anhydride in pyridine at room temperature resulted in selective acetylation at C-17 to give **3**. Acetylation of the hydroxyl at C-5 is possible, if this reaction is conducted at reflux temperature.

In our initial attempt to introduce the nitrogen atom into ring B in the form of an oxime, we treated **3** with hydroxylamine hydrochloride in pyridine at reflux temperature. The product did not exhibit any hydroxyl or carboxyl bands in the ir spectrum, but showed two carbonyl bands at 5.68 and 5.80 μ. This compound was assigned the cyclic structure **4**, which was confirmed by elemental analysis and the presence of an AB quartet at τ 7.26 and 7.76 (J = 16 cps) in the nmr spectrum for the C-1 methylene hydrogens. In order to circumvent the undesired cyclization of the oximino



(1) F. L. Weisenborn and H. E. Applegate, *J. Amer. Chem. Soc.*, **81**, 1960 (1959).

(2) A ring-A γ-lactam was an intermediate in the synthesis of A-nor-B-homo-5-aza cholestane: W. J. Rodewald and J. Wicha, *Rocz. Chem.*, **40**, 837 (1966).

(3) Presented in part at the 155th National Meeting of the American Chemical Society, San Francisco, Calif., March 1968. A preliminary communication has appeared: S. D. Levine, *Chem. Commun.*, 580 (1968).

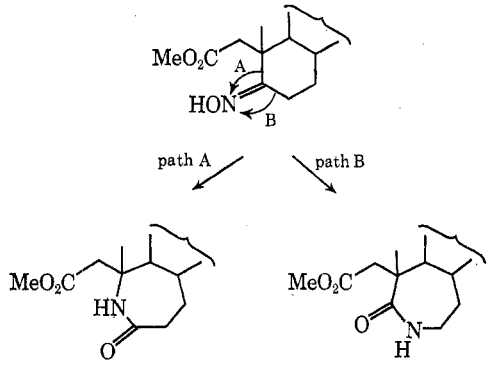
(4) S. D. Levine, *J. Med. Chem.*, **8**, 537 (1965).

(5) M. E. Wall and S. Serota, *J. Org. Chem.*, **24**, 741 (1959).

acid, we treated **3** with diazomethane to open the lactonol and form the keto ester **5**. This oily product was then treated with hydroxylamine hydrochloride in pyridine at room temperature to yield an oxime (**6**) in quantitative yield. Evidence that **6** was actually a single compound, and not a mixture of oxime isomers, was based on the following observations: (a) the nmr spectrum exhibited only one signal for the C-19 methyl group; and (b) tlc revealed only one spot. The orientation of the oxime will be discussed in more detail later.

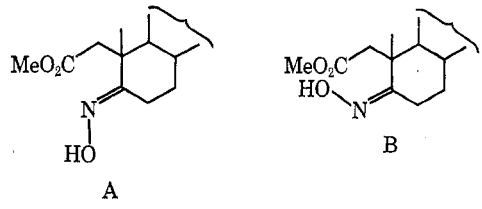
The Beckmann rearrangement of **6** was then investigated under various conditions to find the most efficient route to a ring-B lactam. Among the experimental conditions examined were the use of thionyl chloride as both the solvent and acid catalyst at temperatures of 0 to −20°, and thionyl chloride in dioxane at 10° for varying time intervals. The condition of choice was the addition of thionyl chloride to the oxime in dioxane at 10° and a reaction time of 7–10 min. After hydrolysis with aqueous potassium hydroxide solution, the lactam acid **7** was obtained in 70–80% yield. This compound was characterized by elemental analysis and its ir spectrum, which showed broad bands in the hydroxyl region, a band at 5.86 μ (–CO_2H), and a band at 6.09 μ (–NHCO). The insolubility of **7** in $CDCl_3$ precluded an nmr spectrum in that solvent. Methylation of **7** with diazomethane gave the oily ester **8**, the purity and structure of which were confirmed by tlc and nmr. The C-19 methyl signal appeared at τ 8.58, and this pronounced downfield shift will be discussed further in a separate section.

That the Beckmann rearrangement product resulted from migration of the more substituted α-carbon atom (path A), rather than one in which the less substituted α-carbon atom migrated (path B), was in accord with the results of Rodewald and Wicha for the rearrangement of a related system.[2] Additional evidence for the operation of this pathway was the ultimate formation of the β-lactam.



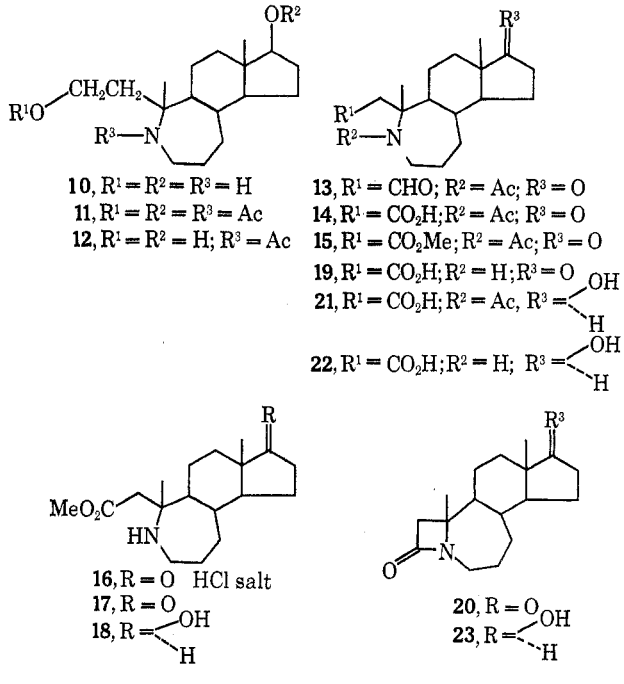
We were unable to isolate any cyclic lactam from the reaction mixture, which would have formed *via* path B; however, a small amount of an oily product was isolated after chromatography of the neutral fraction on alumina. The ir spectrum did not show any hydroxyl bands, but exhibited a peak at 4.45 μ (–CN), a broad carbonyl band at 5.80 μ (–OAc, –CO_2Me), and a band at 6.10 μ (conjugated double bond). The only structure compatible with these results was **9**, which would be formed as a result of an abnormal Beckmann rearrangement. In accord with this structure, the nmr spectrum exhibited the C-18 methyl at τ 9.13, but did not exhibit a signal for the C-19 methyl group. Instead, there were signals at τ 7.84 and 8.12 that could be assigned to vinyl methyl groups, two signals at *ca.* τ 6.3 for methoxyl groups, and a broad signal at τ 4.27 for vinyl protons. Thus it would appear that **9** was a mixture of *cis* and *trans* isomers.

Based on the results from the Beckmann rearrangement, it is tempting to assign oxime **6** the *syn*[6] stereochemistry, as shown in A, rather than the *anti* form depicted in B.



Mazur, in his work on the Beckmann rearrangement of oximes of testosterone derivatives,[7] showed, however, that under these reaction conditions (thionyl chloride in dioxane) the products obtained were not necessarily related to the stereochemistry of the initial oxime. Hence we refrain from making a definite assignment based on the evidence available in our case.

The next step required reduction of the lactam carbonyl. Attempted lithium aluminum hydride reduction of the free acid **7** in tetrahydrofuran led to a poor yield of the dihydroxy amine **10**. Further investigation revealed that this was due to the poor



solubility of **7** in tetrahydrofuran. This was obviated by conducting the reduction on the methyl ester **8** instead, and in this case the reduction product **10** could be obtained in 60–70% yield. Since the presence of nitrogen in a molecule as an amine usually leads to difficulties when attempting oxidations with chromium trioxide,[8] the amine nitrogen was protected as an

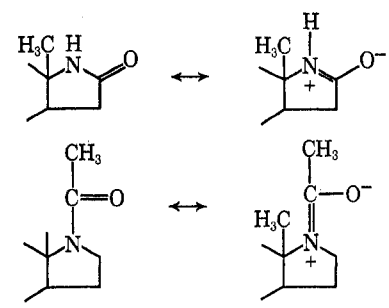
(6) In this case, *syn* and *anti* refers to the relationship of the oxime hydroxyl to the C_6–C_7 bond.
(7) R. H. Mazur, *J. Org. Chem.*, **28**, 248 (1963).
(8) M. Heller and S. Bernstein, *ibid.*, **32**, 3978 (1967).

amide.[9] This was accomplished by first preparing the N-acetyl diacetate **11** under normal acetylation conditions. Selective room-temperature hydrolysis of **11** with potassium carbonate in methanol gave the N-acetyldiol **12**. We next turned our attention to the oxidation of the C-2 hydroxyl group to a carboxylic acid. Oxidation of **12** with Jones reagent led to smooth oxidation of the hydroxyls at both C-2 and C-17; however, the oxidation of the primary alcohol proceeded only to the aldehyde stage. This was quite apparent from the nmr spectrum of the product **13**, which displayed a signal for the aldehyde proton at τ 0.28 (J = 1.8 cps). Treatment of **13** with silver oxide in the dark at room temperature for 4 hr gave the N-acetyl amino acid **14** in 50% yield, and additional oxidation product could be obtained in the form of its methyl ester **15** after treatment of the mother liquor with diazomethane and subsequent chromatography on alumina.

The penultimate synthetic step required hydrolysis of the N-acetyl group of **14** to afford an amino acid. The pilot experiments were conducted on the ester **15** and indicated that acid hydrolysis at room temperature (HCl–methanol or HCl–ethanol) did not cleave the amide bond. After **15** was refluxed overnight in 10% methanolic HCl, evaporation of the solvents gave a chloroform-soluble amine hydrochloride **16** as an oil which was conveniently purified and converted into the free amine **17** as an oil by chromatography on alumina. In an attempt to obtain a crystalline derivative, **17** was reduced with sodium borohydride to the 17β-hydroxy compound **18**, but this too was obtained as an oil. Hydrolysis of the methyl ester of **17** with sodium hydroxide in ethanol and removal of the solvent gave an amino acid containing residue. Electrophoresis indicated that the amino acid **19** was essentially neutral at pH 4.5–6.0.[10] Attempts to extract **19** into organic solvents from aqueous solutions at pH levels within this range were unsuccessful; this behavior could be explained by assuming that the amino acid was very soluble in water. In the next experiment, the free acid **14** was refluxed in acidic dioxane. After removal of the solvents, the aqueous phase was adjusted to pH 5.1 and extracted with chloroform to remove organic material other than the amino acid. The aqueous phase was then brought to pH 5.5 and evaporated, and the white residue was extracted with chloroform to afford, after removal of the solvent, the oily amino acid **19**, identified by ir and nmr. The cyclization of **19** was conducted at room temperature in nitromethane employing dicyclohexylcarbodiimide (DCC). At the end of the reaction, the bulk of the dicyclohexylurea was removed by filtration. Alumina chromatography easily removed excess DCC, but the remaining dicyclohexylurea had an R_f value similar to that of the β-lactam **20**, and it was necessary to repeat the chromatography to achieve good separation. The β-lactam structure was supported by microanalysis, its molecular ion (m/e 275), and the following spectral data. The carbonyl region in the infrared spectrum exhibited a peak at 5.74 μ (17-one) with a shoulder at 5.70 μ (β-lactam carbonyl), while the nmr spectrum showed the following diagnostic signals: τ 9.09 (C-18 Me), 8.56 (C-19 Me), 7.35 (C-1 CH_2), and 6.66 (C-6 CH_2).

A β-lactam bearing a hydroxyl group at C-17 was prepared in the following manner. Sodium borohydride reduction of **14** gave the 17β-hydroxy compound **21**, which was hydrolyzed and the resultant amino acid isolated in the same manner as described previously for **19**. In this case, the amino acid **22** was obtained as a high-melting, crystalline material, which was quite insoluble in nitromethane and other organic solvents; therefore, the cyclization of **22** was carried out in aqueous dioxane using diisopropylcarbodiimide,[11] and the β-lactam **23** was isolated in low yield after chromatography on alumina.

Nmr Spectra.—The nmr spectra of some 17-aza steroids have been discussed recently.[12] The observed deshielding effect of the nitrogen atom on the C-18 methyl protons was close to that predicted when the substituent on nitrogen was either hydrogen or alkyl. When a carbonyl group was present adjacent to the C-17 nitrogen atom, however, the observed deshielding became greater than that predicted. The authors explained these results on the basis of the contribution of charged species as shown below. The charged nitrogen atom would be expected to deshield the adjacent angular methyl group. The 5-aza steroids prepared in this investigation showed a similar pattern. For compounds in which a carbonyl group was adjacent to the C-5 nitrogen atom, the observed chemical shift of the C-19 methyl group was in the τ 8.4–8.6 range, while for those in which the nitrogen atom was not flanked by a carbonyl the signal appeared at τ >8.8. It would appear that charged species analogous to those shown above satisfactorily explain the results obtained in our study.



Experimental Section

Melting points were taken on a Fisher-Johns melting point apparatus and are uncorrected. Values of $[\alpha]_D$ have been approximated to the nearest degree and were taken on a Perkin-Elmer Model 141 polarimeter in 95% ethanol. Infrared spectra were determined on a Perkin-Elmer Model 21 spectrometer in pressed potassium bromide pellets (unless otherwise indicated), and nmr spectra were determined on a Varian A-60 spectrometer in $CDCl_3$ (unless otherwise indicated) with $(CH_3)_4Si$ as internal standard. All evaporations were carried out *in vacuo*, and organic solutions were dried over sodium sulfate. Alumina refers to neutral alumina, activity V. Tlc was carried out on alumina and the compounds were detected with iodine vapor.

3-Oxa-5β,17β-dihydroxy-A-norandrostan-2-one (2)[4].—A suspension of potassium carbonate (10 g), potassium permanganate (1.3

(9) In a subsequent experiment, oxidation of **12** with Jones reagent gave a crude reaction product which showed the presence of at least five components (tlc). This justifies the necessity of protecting the amino group prior to oxidation.

(10) The author wishes to thank Mr. O. Kocy for this determination.

(11) J. C. Sheehan and K. R. Henery-Logan, *J. Amer. Chem. Soc.*, **84**, 2983 (1962).

(12) S. Rakhit, T. Wittstruck, and M. Gut, *Steroids*, 135 (1967).

g), and sodium periodate (41 g) in water (1 l.) was added to a solution of A-nortestosterone (6.6 g)[1] in *t*-butyl alcohol (1 l.) and stirred at room temperature for 1 day. The mixture was filtered, and the filtrate was diluted with water and acidified to pH 2 with concentrated HCl. The acidic solution was extracted with chloroform. The chloroform extracts were washed with water and 8% salt solution, dried, and evaporated. Crystallization of the residue from ethyl acetate–isopropyl ether gave **2** (4.5 g), mp 177–178°).

3-Oxa-5β-hydroxy-17β-acetoxy-A-norandrostan-2-one (3).—A solution of **2** (100 mg) in pyridine (1.6 ml) and acetic anhydride (0.8 ml) was left at room temperature for 4 hr. The reaction mixture was diluted with water and the product was collected by filtration to give **3** (73 mg), mp 183–185°. Recrystallization from chloroform–isopropyl ether gave the analytical sample: mp 187.5–188.5°; $[\alpha]^{25}D$ +24°; λ 3.07, 5.69, and 5.79 μ; nmr τ 9.18 (s, 18-Me), 8.87 (s, 19-Me), 7.97 (s, 17β-acetate), and 5.48 (m, 17α-H).

Anal. Calcd for $C_{19}H_{28}O_5$: C, 67.83; H, 8.39. Found: C, 67.65; H, 8.41.

3-Oxa-4-aza-17β-acetoxy-4-androsten-2-one (4).—A solution of **3** (500 mg) and hydroxylamine hydrochloride (500 mg) in pyridine (15 ml) was refluxed for 2.5 hr. Dilution with water gave a precipitate which was collected by filtration to yield **4** (248 mg), mp 186–188°. Recrystallization from chloroform–isopropyl ether gave the analytical sample: mp 203–205°; $[\alpha]^{27}D$ +51°; λ 5.68 and 5.80 μ; nmr τ 9.16 (s, 18-Me), 8.85 (s, 19-Me), 7.94 (s, 17β-OAc), 7.76 and 7.26 (q, J = 16 cps, 2-CH_2), and 5.41 (m, 17α-H).

Anal. Calcd for $C_{19}H_{27}NO_4$: C, 68.44; H, 8.16. Found: C, 68.37; H, 8.25.

5-Oxo-17β-acetoxy-2,5-seco-3,4-bisnorandrostan-2-oic Acid 2-Methyl Ester (5).—A solution of **3** (1.0 g) in methanol (10 ml) and ether (25 ml) was treated with an excess of diazomethane in ether. After 45 min at room temperature, acetic acid was added and the solvents were evaporated. The residue was dissolved in chloroform and this solution was washed with 8% salt solution, dried, and evaporated to afford **5** (1.0 g) as a homogeneous oil (tlc): λ^{CHCl_3} 5.80 μ; nmr τ 9.15 (s, 18-Me), 8.8 4(s, 19-Me), 7.97 (s, 17β-acetate), 6.38 (s, 2-OCH_3), and 5.39 (m, 17α-H).

5-Oximino-17β-acetoxy-2,5-seco-3,4-bisnorandrostan-2-oic Acid 2-Methyl Ester (6).—A solution of **5** (1.0 g) and hydroxylamine hydrochloride (1 g) in pyridine (20 ml) was left at room temperature for 3 days. The reaction mixture was diluted with ice–water and the product was collected by filtration to give **6** (860 mg), mp 150–152.5°. Recrystallization from chloroform–isopropyl ether gave the analytical sample: mp 155–157°; λ^{CHCl_3} 2.95 and 5.80 μ; nmr τ 9.18 (s, 18-Me), 8.81 (s, 19-Me), 7.97 (s, 17β-acetate), 6.38 (s, 2-OCH_3), and 5.39 (m, 17α-H).

Anal. Calcd for $C_{20}H_{31}NO_5$: C, 65.73; H, 8.55. Found: C, 65.93; H, 8.59.

6-Oxo-17β-hydroxy-2,5-seco-3,4-bisnor-5-aza-B-homoandrostan-2-oic Acid (7).—A solution of **6** (9.2 g) in dioxane (130 ml) was cooled to 10° in an ice bath. Thionyl chloride (9.2 ml) was added, the ice bath was removed, and the reaction mixture was stirred for 7 min. The reaction mixture was then added to 25% aqueous potassium hydroxide solution (725 ml), stirred and heated to 80°. After cooling, the reaction mixture was extracted with ether. The aqueous layer was acidified with concentrated HCl and diluted with ice–water. The precipitate was collected by filtration to give **7** (1.28 g), mp 268.5–269.5°. The filtrate was extracted with chloroform. The chloroform extracts were washed with 8% salt solution, dried, and evaporated. The residue was crystallized from methanol–isopropyl ether to give additional **7** (5.12 g), mp 271–272.5°. Recrystallization from methanol–isopropyl ether gave the analytical sample: mp 275–276°; $[\alpha]^{28}D$ +30°; λ 3.00, 3.08, 5.86, and 6.09 μ.

Anal. Calcd for $C_{17}H_{27}NO_4$: C, 65.99; H, 8.80; N, 4.53. Found: C, 66.10; H, 8.82; N, 4.63.

The ether extract from the Beckmann rearrangement of **6** (800 mg) was washed with water, dried, and evaporated to give a 113-mg residue. Plate chromatography on alumina using chloroform–hexane (3:1) as the developing solvent and elution of the least polar band with ethyl acetate gave, after evaporation, **9**: λ^{CHCl_3} 4.45, 5.80, and 6.10 μ; τ nmr 9.13 (s, 18-Me), 8.12, 7.84 (s, 10-Me), 7.97 (s, 17β-acetate), 6.33, 6.31 (s, 2-OCH_3), 5.39 (m, 17α-H), and 4.27 (s, 1-H).

6-Oxo-17β-hydroxy-2,5-seco-3,4-bisnor-5-aza-B-homoandrostan-2-oic Acid 2-Methyl Ester (8).—A solution of **7** (3.1 g) in methanol (100 ml) and ether (360 ml) was treated with an excess of diazomethane in ether. After 45 min at room temperature, acetic acid was added and the reaction mixture was evaporated. The residue was dissolved in chloroform, washed with water, dried, and evaporated to afford **8** as a homogeneous oil (tlc): λ^{CHCl_3} 2.75, 2.95, 5.78, and 6.08 μ; nmr τ 9.23 (s, 18-Me), 8.58 (s, 19-Me), 6.4 (m, 17α-H), and 6.38 (s, 2-OCH_3).

2,17β-Dihydroxy-2,5-seco-3,4-bisnor-5-aza-B-homoandrostane (10).—A solution of **8** (1.29 g) in tetrahydrofuran (150 ml) was treated with lithium aluminum hydride (2 g) and refluxed for 60 hr. Excess hydride was destroyed with ethyl acetate. The reaction mixture was treated with 25% aqueous sodium hydroxide solution and the layers were separated. The aqueous phase was extracted with additional chloroform. The combined organic fractions were washed with 8% salt solution, dried, and evaporated. The residue was crystallized from chloroform–isopropyl ether to give **10** (617 mg), mp 168–169.5°. Recrystallization from chloroform–isopropyl ether gave the analytical sample: mp 170.5–171°; $[\alpha]^{25}D$ −16°; λ 3.02 μ; nmr τ 9.25 (s, 18-Me) and 8.82 (s, 19-Me).

Anal. Calcd for $C_{17}H_{31}NO_2$: C, 72.55; H, 11.10; N, 4.98. Found: C, 72.65; H, 11.08; N, 4.98.

N-Acetyl-2,17β-diacetoxy-2,5-seco-3,4-bisnor-5-aza-B-homoandrostane (11).—A solution of **10** (2.56 g) in acetic anhydride (17 ml) and pyridine (17 ml) was left at room temperature overnight. The reaction mixture was diluted with water and the product was collected by filtration to give **11** (3.40 g), mp 136–137°. Recrystallization from isopropyl ether gave the analytical sample: mp 139–140°; $[\alpha]^{26}D$ −41°; λ 5.78 and 6.11 μ; nmr τ 9.20 (s, 18-Me), 8.63 (s, 19-Me), 7.97 (s, 17β-acetate and 2-acetate), 7.93 (s, 5-N-acetyl), and 5.42 (m, 17α-H).

Anal. Calcd for $C_{23}H_{37}NO_5$: C, 67.78; H, 9.15; N, 3.44. Found: C, 67.70; H, 9.16; N, 3.35.

N-Acetyl-2,17β-dihydroxy-2,5-seco-3,4-bisnor-5-aza-B-homoandrostane (12).—A solution of **11** (4.55 g) in methanol (550 ml) was treated with 10% potassium carbonate solution (90 ml) and stirred overnight at room temperature. The solution was concentrated, diluted with water, and neutralized with acetic acid. The product was collected by filtration to give **12** (0.93 g), mp 166.5–167.5°. The aqueous phase was extracted with chloroform and the chloroform extracts were washed with 8% salt solution, dried, and evaporated. The residue was crystallized from acetone–isopropyl ether to give additional **12** (1.97 g), mp 169–170°. Recrystallization from acetone–isopropyl ether gave the analytical sample: mp 172–172.5°; $[\alpha]^{23}D$ −47°; λ 2.93, 3.12, and 6.23 μ; nmr τ 9.25 (s, 18-Me), 8.60 (s, 19-Me), 7.93 (s, 5-N-acetyl) and 6.5 (m, 2-CH_2, 6-CH_2, and 17α-H).

Anal. Calcd for $C_{19}H_{33}NO_3$: C, 70.55; H, 10.28; N, 4.33. Found: C, 70.31; H, 10.29; N, 4.43.

N-Acetyl-17-oxo-2,5-seco-3,4-bisnor-5-aza-B-homoandrostan-2-al (13).—A solution of **12** (1.0 g) in acetone (100 ml) was cooled to 3.5° and treated with an excess of Jones reagent. After 2 hr at 3.5°, methanol was added to decompose excess oxidant and water was added. The organic solvents were evaporated and the aqueous phase was extracted with chloroform. The chloroform extracts were washed with water and 8% salt solution, dried, and evaporated. The residue was crystallized from ethyl acetate–isopropyl ether to give **13** (590 mg), mp 171.5–172.5°. Recrystallization from ethyl acetate–isopropyl ether gave the analytical sample: mp 172–173°; $[\alpha]^{24}D$ +60°; λ 3.55, 3.68, 5.75, 5.84, and 6.07 μ; nmr τ 9.12 (s, 18-Me), 8.54 (s, 19-Me), 7.92 (s, 5-N-acetyl), and 0.28 (t, J = 1.8 cps, 2-CHO).

Anal. Calcd for $C_{19}H_{29}NO_3$: C, 71.44; H, 9.15; N, 4.39. Found: C, 71.22; H, 8.96; N, 4.67.

N-Acetyl-17-oxo-2,5-seco-3,4-bisnor-5-aza-B-homoandrostan-2-oic Acid (14).—A solution of silver nitrate (725 mg) in water (7.5 ml) was added to a solution of **12** (695 mg) in 95% ethanol (15 ml). This solution was treated dropwise with a solution of sodium hydroxide (700 mg) in water (12.5 ml) and the resulting suspension was stirred in the dark for 4 hr. The precipitate was removed by filtration and washed with water, and the filtrate was extracted with chloroform. The aqueous phase was acidified and extracted with chloroform. The chloroform extracts were washed with 8% salt solution, dried, and evaporated. The residue was crystallized from acetone–isopropyl ether to give **14** (348 mg), mp 178.5–179.5. Recrystallization from acetone–isopropyl ether gave the analytical sample: mp 180.5–181.5°; $[\alpha]^{28}D$ −2°; λ 2.8–3.2, 5.78, and 6.28 μ; nmr τ 9.12 (s, 18-Me), 8.44 (s, 19-Me), and 7.91 (s, 5-N-acetyl).

Anal. Calcd for $C_{19}H_{29}NO_4$: C, 68.05; H, 8.71; N, 4.18. Found: C, 68.29; H, 8.42; N, 4.28.

N-Acetyl-17-oxo-2,5-seco-3,4-bisnor-5-aza-B-homoandrostan-2-oic Acid 2-Methyl Ester (15).—The mother liquor from the crystallization of **14** in the previous example was dissolved in ether (5 ml) and methanol (2 ml) and treated with an excess of diazomethane for 10 min. Acetic acid was added, and the solution was evaporated. Plate chromatography of the residue on alumina using chloroform as the developing solvent gave a major band which was eluted with ethyl acetate. Evaporation and crystallization from isopropyl ether gave **15** (81 mg), mp 131–132°. Recrystallization from isopropyl ether gave the analytical sample: mp 131.5–132.5°; λ 5.79 and 6.15 μ; nmr τ 9.12 (s, 18-Me), 8.46 (s, 19-Me), 7.94 (s, 5-N-acetyl), and 6.41(s, 2-OCH_3).

Anal. Calcd for $C_{20}H_{31}NO_4$: C, 68.74; H, 8.94; N, 4.01. Found: C, 68.69; H, 8.78; N, 3.77.

Hydrolysis and Reduction of 15.—A solution of **15** (80 mg) in water (0.5 ml) and 10% methanolic HCl (10 ml) was refluxed overnight and then evaporated to give crude 17-oxo-2,5-seco-3,4-bisnor-5-aza-B-homoandrostan-2-oic acid 2-methyl ester hydrochloride (**16**) as an oil: nmr τ 9.13 (s, 18-Me), 8.48 (broad s, 19-Me), and 6.25 (s, 2-OCH_3).

Plate chromatography of **16** on alumina using chloroform as the developing solvent gave a major band which was eluted with ethyl acetate. Evaporation gave 17-oxo-2,5-seco-3,4-bisnor-5-aza-B-homoandrostan-2-oic acid 2-methyl ester as an oil (**17**, 44 mg): nmr τ 9.13 (s, 17-Me), 8.82 (s, 19-Me), and 6.36 (s, 2-OCH_3); λ^{CHCl_3} 3.0 and 5.78 μ.

A solution of **17** (40 mg) was dissolved in methanol (3 ml), treated with sodium borohydride (30 mg), and stirred at room temperature for 35 min. The methanol was evaporated and the residue was diluted with water and extracted with chloroform. The chloroform extracts were washed with 8% salt solution, dried, and evaporated. The residue was plate chromatographed on alumina using chloroform–methanol (99:1) as the developing solvent. Elution of the major band with ethyl acetate and evaporation gave 17β-hydroxy-2,5-seco-3,4-bisnor-5-aza-B-homoandrostan-2-oic acid 2-methyl ester as an oil (**18**, 24 mg): nmr τ 9.26 (s, 18-Me), 8.84 (s, 19-Me), 6.4 (m, 17α-H), and 6.33 (s, 2-OCH_3).

17-Oxo-2,5-seco-3,4-bisnor-5-aza-B-homoandrostan-2-oic Acid (19).—A solution of **14** (200 mg) in water (0.3 ml), concentrated HCl (5 ml), and dioxane (15.5 ml) was refluxed for 17 hr and then evaporated. The residue was dissolved in water, the pH of the solution was adjusted to 5.1 with sodium bicarbonate solution, and 8% salt solution was added. This aqueous solution was extracted with chloroform. The aqueous layer was then adjusted to pH 5.5 and evaporated. The residue was treated with several portions of chloroform. The chloroform layers were dried and evaporated to give **19** (150 mg) as an oil: nmr τ 9.14 (s, 18-Me) and 8.63 (s, 19-Me); λ^{CHCl_3} 2.92, 5.78, and 6.23 μ.

3,4-Bisnor-5-aza-B-homoandrostane-2,17-dione (20).—A solution of **19** (452 mg) in nitromethane (15 ml) was treated with dicyclohexylcarbodiimide (270 mg) and stirred at room temperature or 45 hr. The N,N′-dicyclohexylurea was removed by filtration and the filtrate was evaporated. The residue was plate chromatographed on alumina, using chloroform–hexane (1:1) as the developing solvent. The plate was developed twice and the major band was eluted with ethyl acetate. Evaporation and crystallization from ethyl acetate–isopropyl ether gave **20** (181 mg), mp 157.5–158.5°. Recrystallization from acetone–isopropyl ether gave the analytical sample: mp 158–159°; $[\alpha]^{24}D$ + 117°; λ 5.70 (sh) and 5.75 μ; nmr τ 9.09 (s, 18-Me), 8.56 (s, 19-Me), 7.35 (s, 1-CH_2), and 6.66 (m, 6-CH_2).

Anal. Calcd for $C_{17}H_{25}NO_2$: C, 74.14; H, 9.15; N, 5.09. Found: C, 74.38; H, 9.35; N, 5.08.

N-Acetyl-17β-hydroxy-2,5-seco-3,4-bisnor-5-aza-B-homoandrostan-2-oic Acid (21).—A solution of **14** (50 mg) in methanol (5 ml) was treated with sodium borohydride (30 mg) and stirred at room temperature for 1 hr. The reaction mixture was concentrated, diluted with water, acidified to pH 2, and extracted with chloroform. The chloroform extracts were washed with 8% salt solution, dried, and evaporated. The residue was crystallized from acetone–isopropyl ether to give **21** (43 mg), mp 186–187°. Recrystallization from acetone–isopropyl ether gave the analytical sample: mp 188–188.5°; $[\alpha]^{24}D$ −71°; λ 2.8–4.0 (br), 5.83, and 6.20 μ.

Anal. Calcd for $C_{19}H_{31}NO_4$: 67.62; H, 9.26; N, 4.15. Found: C, 67.91; H, 9.44; N, 4.06.

17β-Hydroxy-2,5-seco-3,4-bisnor-5-aza-B-homoandrostan-2-oic Acid (22).—A solution of **21** (275 mg) in water (0.3 ml), concentrated HCl (4 ml), and dioxane (15 ml) was refluxed overnight. The same procedure described for the isolation of **19** was followed. Crystallization of the residue from methanol–ethyl acetate gave **22** (100 mg), mp 233–234°. Recrystallization from methanol–ethyl acetate gave the analytical sample: mp 233.5–234.5°; $[\alpha]^{23}D$ 0°; λ 2.85–2.95, 6.17, and 6.25 μ; nmr (DMSO) τ 9.35 (s, 18-Me) and 8.82 (s, 19-Me).

Anal. Calcd for $C_{17}H_{29}NO_3$: C, 69.11; H, 9.90. Found: C, 69.09; H, 9.81.

17β-Hydroxy-3,4-bisnor-5-aza-B-homoandrostan-2-one (23).—A solution of **22** (143 mg) in water (1 ml) and dioxane (2 ml) was treated with a solution of diisopropylcarbodiimide (0.085 ml) in dioxane (1 ml). The mixture was stirred at room temperature for 3 days. The mixture was evaporated and the residue was treated with water and extracted with chloroform. The chloroform extracts were washed with 8% salt solution, dried, and evaporated. The residue was treated with ethyl acetate and filtered to remove N,N′-diisopropylurea, and the filtrate was plated on alumina using chloroform as the developing solvent. The major steroid band was eluted with ethyl acetate and evaporated to give **23** (9 mg). Recrystallization from acetone–isopropyl ether gave the analytical sample: mp 208–209°; λ 2.90 and 5.78 μ; nmr τ 9.21 (s, 18-Me), 8.58 (s, 19-Me), 7.37 (s, 2-CH_2), and 6.35 (s, 17α-H).

Anal. Calcd for $C_{17}H_{27}NO_2$: C, 73.60; H, 9.81. Found: C, 73.99; H, 9.72.

Registry No.—**1**, 1154-01-4; **2**, 23327-88-0; **3**, 19508-55-5; **4**, 23327-90-4; **5**, 19508-56-6; **6**, 19508-57-7; **7**, 19508-58-8; **8**, 23327-94-8; **9**, 23327-95-9; **10**, 20711-47-1; **11**, 20711-48-2; **12**, 20711-49-3; **13**, 19508-62-4; **14**, 19508-63-5; **15**, 19508-64-6; **16**, 23328-02-1; **17**, 23328-03-2; **18**, 23367-39-7; **19**, 19508-65-7; **20**, 19746-47-5; **21**, 23330-26-9; **22**, 23330-27-0; **23**, 23330-28-1.

Acknowledgment.—The author wishes to thank Dr. A. I. Cohen for the nmr spectra and Mr. J. Alicino and his staff for the microanalyses.