hydride was then destroyed by the addition of about 2 cc. of acetic acid followed by water until gas evolution ceased. The mixture was evaporated in a 50° bath, and the wet residue was distributed between methylene chloride and water. The organic phase was washed with water and saturated saline solution and was dried and evaporated. The residue was dissolved partially in 10 cc. of 50% acetic acid, and the stirred mixture was heated on the steam bath for 30 min. when all of the solid had dissolved. The solution was evaporated and the residue was dissolved in methylene chloride and water. The organic phase was washed with a little water and was dried and evaporated. The residue was crystallized from ethyl acetate; 88 mg. (49%), m.p. 190–192°. One recrystallization from ethyl acetate gave a sample with m.p. 218–219°; $[\alpha]^{25}D$ +88.5° (*c* 0.521); λ_{max} 2.87 μ (m), 4.44 μ (w), 5.96 μ (s) broad band, 6.16 μ (m); λ_{max} 240 mμ (ϵ 16,170) in methanol, 247 mμ (ϵ 15,680) in base.

Anal. Calcd. for $C_{20}H_{27}O_2N$: C, 76.64; H, 8.63; N, 4.43. Found: C, 76.18; H, 8.80; N, 4.44.

16ξ-Cyanoestrone 3-Methyl Ether (XXIV).—The reaction of 1.7 g. (5.45 mmoles) of 16-hydroxymethyleneestrone 3-methyl ether (XV)[22] with 1.22 g. of II in 54 cc. of benzene and 1.63 cc. of pyridine was carried out as described for the preparation of III. The product was crystallized from ether to afford 1.16 g. (69%), m.p. 149–153°. Several recrystallizations from methylene chloride–ether gave material with m.p. 138–148°; $[\alpha]^{25}D$ +189° (*c* 0.99); λ_{max} 4.43 μ (w), 5.68 μ (s), 6.17 μ (m), 6.32 μ (w).

Anal. Calcd. for $C_{20}H_{23}O_2N \cdot {}^1/_4H_2O$: C, 76.53; H, 7.54; N, 4.46. Found: C, 76.64; H, 7.90; N, 4.90.

16ξ-Cyanoestradiol 3-Methyl Ether (XXV).—A solution of 1.56 g. (5.05 mmoles) of XXIV in 150 cc. of tetrahydrofuran was reduced with 360 mg. of lithium borohydride for 3 hr. at room temperature. Acetic acid was added carefully and then water until the solution was homogeneous. Removal of most of the solvents under reduced pressure left a residue which was triturated with water and filtered. The precipitate was washed with water and was dissolved in methylene chloride. The solution was washed with a little water and was dried and evaporated to afford 1.5 g. of product which was recrystallized from methylene chloride–ether; 1.17 g. (74%), m.p. 194–200°. For analysis, a sample was recrystallized from ethyl acetate, m.p. 197–200°; $[\alpha]^{25}D$ +54° (*c* 1.39); λ_{max} 2.86 μ (s), 4.47 μ (m), no absorption in the carbonyl region.

Anal. Calcd. for $C_{20}H_{25}O_2N \cdot {}^1/_4H_2O$: C, 76.01; H, 8.14; N, 4.43; H_2O, 1.43. Found: C, 76.08; H, 8.30; N, 4.06; H_2O, 1.10.

Acknowledgment.—The authors wish to thank Mr. W. Fulmor and staff for spectrophotometric and polarimetric data, Mr. L. Brancone and staff for microanalyses and Dr. H. Arlt, Jr., and staff of the Chemical Preparations Laboratory for the large-scale preparation of certain intermediates.

Steroidal Aldosterone Antagonists. VI[1]

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The synthesis of several steroidal 17-spirolactams analogous to physiologically active spirolactones is described.

There are numerous examples of physiologically important compounds which contain a lactam moiety. Our experience with the steroidal spirolactones as aldosterone antagonists[2] suggested the investigation of the corresponding spiro-γ-lactams.[3] The conventional method for converting γ-lactones to γ-lactams by treatment with an appropriate amine was unsuccessful in our hands. Thus, the treatment of 3-methoxy-17α-(2-carboxyethyl)-17β-hydroxy-1,3,5(10)-estratriene lactone[2] with ammonia, methylamine, or aniline under forcing conditions yielded only the corresponding amides. We therefore chose the sequence of reactions shown on the following page.

Smilagenin was degraded to 3β-acetoxy-16-pregnen-20-one by the procedure of Mueller.[4] The reduced product was converted to the oxime which was subjected sequentially to Beckmann rearrangement and saponification to yield 3β-hydroxy-17β-amino-5β-androstane (Ib).[5] Selective monoacetylation and oxidation afforded the 17-nitro compound which condensed smoothly with methyl acrylate in the presence of tetramethylguanidine. It should be noted that when either Triton B or sodium alkoxide was used the yield was only 10%.

The configuration of the Michael adduct is based upon the following:

(1) Oxidation of the 17β-amino group under *acidic* conditions should produce the 17β-nitro derivative. (2) Because of the flatness of the *aci*-nitro anion, approach from the rear by an entering group should be favored. Only one adduct was found. (3) The o.r.d. curves are similar and positive for the 17β-nitro compound (IIb) and the Michael adduct (IIIb). This would not be true had inversion occurred during addition.

Catalytic hydrogenation afforded the spirolactam (IVb) which was saponified and oxidized to the ketone (VIb). Bromination followed by dehydrobromination with the lithium bromide–dimethylformamide method gave the desired 17α-(2-

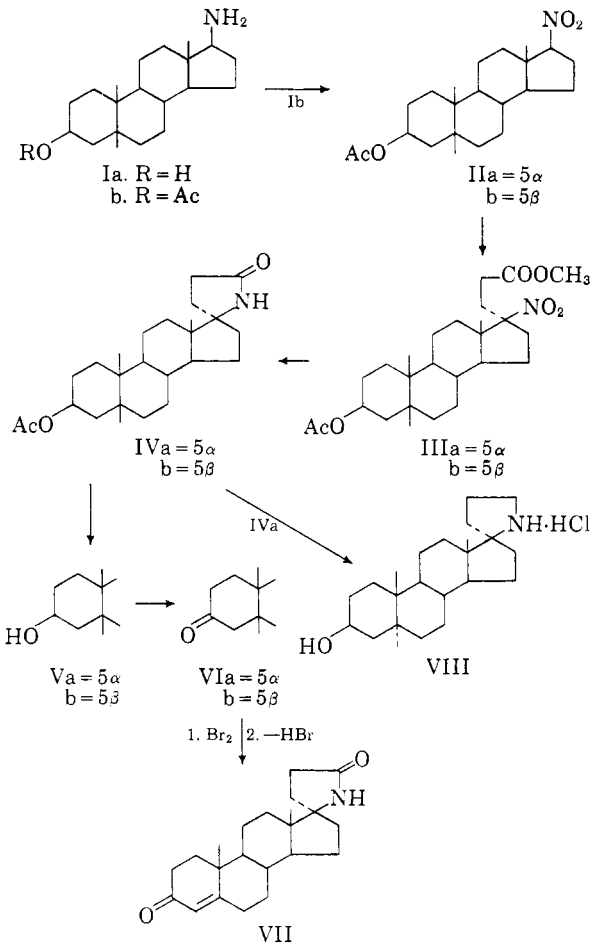
(1) Paper V, R. C. Tweit, F. B. Colton, N. L. McNiven, and W. Klyne, *J. Org. Chem.*, **27**, 3325 (1962).

(2) J. A. Cella, E. A. Brown, and R. R. Burtner, *ibid.*, **24**, 743 (1959).

(3) The lactams and certain intermediates described herein are the subject of U.S. Patent 3,001,986 issued September 26, 1961, to R. R. Burtner and Leonard Nysted.

(4) G. P. Mueller, *Nature*, **181**, 771 (1958).

(5) German Patent 871,010 (1953); *Chem. Zentr.*, 6938 (1953); J. Schmidt-Thomé, *Ber.*, **88**, 895 (1955).



carboxyethyl)-17β-aminoandrost-4-en-3-one lactam (VII).

Starting with 3β-acetoxy-17β-amino-5α-androstane (Ib, 5α) the same sequence was followed to produce 17α-(2-carboxyethyl)-17β-amino-5α-androstan-3-one lactam (VIa). An attempt to convert VIa to the 1,4-diene by bromination and dehydrobromination was unsuccessful. Reduction of the lactam (IVa) with lithium aluminum hydride gave the pyrrolidine derivative (VIII).

The aldosterone antagonizing properties of these compounds were studied by Dr. Charles Kagawa and Mr. Robert Jacobs of our Biological Research Department. They will publish their results elsewhere.

Experimental[6]

3β-Acetoxy-17β-amino-5β-androstane (Ib).—A solution of 4.5 g. of 3β-hydroxy-17β-amino-5β-androstane[5] (Ia) in 22 ml. of acetic acid and 3 ml. of 12 *M* hydrochloric acid was treated with 14.5 g. of acetic anhydride (cooling). After the solution was stirred for 24 hr. at room temperature, the acetic acid was removed under vacuum. The residue was dissolved in water and this solution was washed several times with ether. Addition of an excess of 5% sodium hydroxide liberated the base which was taken up in ether, washed with water, and dried. Removal of the solvent under nitrogen gave 4.1 g. of a crystalline product (Ib), m.p. 115–118°, λ_{max}^{KBr} 5.78, 7.95, and 8.05 μ. This product was oxidized to IIb without further purification.

3β-Acetoxy-17β-amino-5α-androstane (Ib,5α).—3β-Acetoxy-5α-androstan-17-one (50 g.) and 140 g. of ammonium acetate were dissolved in 900 ml. of 95% alcohol and then shaken with 25 g. of 10% palladium on charcoal under hydrogen at atmospheric pressure for 24 hr. After removal of the catalyst and vacuum distillation of the solvent, the solid residue was suspended in 1 l. of water and made strongly alkaline with sodium hydroxide. The mixture was extracted with a total of 1500 ml. of ether, and the extract was washed with water and dried. Evaporation of the solvent gave the crude amine which was dissolved in 500 ml. of hexane and then treated with 12 ml. of acetic acid. The precipitated acetate, m.p. 225–230°, of Ib was collected on a funnel, rinsed with hexane, and dried. This material was converted to the nitro compound (IIa) without further purification. The yield of crude product was 46 g.

The amine base melted at 122–125°.

Anal. Calcd. for $C_{21}H_{35}NO_2$: C, 75.63; H, 10.58. Found: C, 75.52; H, 10.42.

3β-Acetoxy-17β-nitro-5β-androstane (IIb).—A solution of 288 ml. of 1.24 *N* perbenzoic acid in benzene was added at room temperature during a 2-hr. period to a stirred suspension of 20.5 g. of the amine (Ib) in 150 ml. of redistilled ethylene dichloride. The mixture was heated and stirred at 75° for 1.5 hr. and then diluted to 1 l. with ether. This solution was washed successively with 3% sodium sulfite, 5% potassium bicarbonate, 3% hydrochloric acid, 5% potassium carbonate, and water. Vacuum evaporation of the dried solution yielded the crude nitro compound (IIb) which, after crystallization from a mixture of ethanol and hexane, weighed 10.7 g. and melted at 194–196°, λ_{max}^{KBr} 5.75, 6.47, 8.0, and 9.75 μ.

Anal. Calcd. for $C_{21}H_{33}NO_4$: C, 69.33; H, 9.12; N, 3.82. Found: C, 69.61; H, 9.14; N, 3.90.

The 5α-isomer (IIa) prepared in the same manner melted at 189–191° and exhibited infrared spectrum congruent with that of the 5β-isomer.

Anal. Calcd. for $C_{21}H_{33}NO_4$: C, 69.33; H, 9.12; N, 3.82. Found: C, 69.41; H, 8.99; N, 4.02.

3β-Acetoxy-17α-(2-carbomethoxyethyl)-17β-nitro-5β-androstane (IIIb).—A mixture of 7.5 g. of the nitro steroid (IIb), 50 ml. of redistilled methyl acrylate, and 5 ml. of tetramethylguanidine in 150 ml. of benzene was stored at room temperature for 5 days. The pale yellow solution was decanted from a small amount of oil which had separated, and the latter was washed with a small amount of benzene. The combined benzene solutions were evaporated in vacuum to an oil which was diluted with water and further distilled to remove residual benzene. The residual white solid was collected on a funnel, dried, and recrystallized from a mixture of ether and hexane to yield 7.8 g. of condensation product (IIIb) melting at 143–145°, λ_{max}^{KBr} 5.73, 5.78, 6.50, 7.8, and 8.02 μ.

Anal. Calcd. for $C_{25}H_{39}NO_6$: C, 66.79; H, 8.74; N, 3.12. Found: C, 66.69; H, 8.76; N, 3.08.

The 5α-isomer (IIIa) was obtained in the same manner and melted at 156–158°. Its infrared spectrum (KBr) was almost indistinguishable from that of the 5β-isomer.

Anal. Calcd. for $C_{25}H_{39}NO_6$: C, 66.79; H, 8.74; N, 3.12. Found: C, 66.73; H, 8.70; N, 3.03.

Saponification of IIIa gave 3β-hydroxy-17α-(2-carboxyethyl)-17β-nitro-5α-androstane, m.p. 290–295°, after crystallization from methylene chloride–ethanol, λ_{max}^{KBr} 2.88, 3.6–3.9, 5.79, 6.48, and 8.2 μ.

Anal. Calcd. for $C_{22}H_{33}NO_5$: C, 67.66; H, 8.23. Found: C, 67.39; H, 8.61.

Acetylation of this acid (350 mg.) with acetic acid (25 ml.) saturated with hydrogen chloride at room temperature afforded the 3-monoacetoxy derivative (290 mg.) melting at

(6) Melting points were determined on a Fisher-Johns block and are reported uncorrected. We are indebted to Dr. Robert Dillon and his associates of these laboratories for the microanalyses and optical determinations.

221–223° when crystallized from a mixture of ether and hexane.

Anal. Calcd. for $C_{24}H_{37}NO_6$: C, 66.17; H, 8.10. Found: C, 66.00; H, 8.32.

3β-Acetoxy-17α-(2-carboxyethyl)-17β-amino-5β-androstane Lactam (IVb).—A solution of 7.5 g. of the nitro derivative (IIIb) in 100 ml. of ethanol was treated with hydrogen at 1000 p.s.i. and 100° in the presence of 1.0 g. of W-5 Raney nickel catalyst[7] for 5 hr. After removal of catalyst and stripping of solvent the residue was crystallized from a mixture of ethanol and water, yielding 5.2 g. of the lactam, m.p. 230–233°, λ_{max}^{KBr} 3.01, 3.2, 5.74, 5.84, and 8.0 μ.

The 5α-isomer (IVa) similarly obtained melted at 308–312° and exhibited congruent infrared spectrum.

Anal. Calcd. for $C_{24}H_{37}NO_3$: C, 74.32; H, 9.64. Found: C, 74.17; H, 9.42.

3β-Hydroxy-17α-(2-carboxyethyl)-17β-amino-5β-androstane Lactam (Vb).—A solution of 1.5 g. of the acetate (IVb) and 2.0 g. of potassium carbonate in 80 ml. of methanol and 20 ml. of water was stirred at room temperature for 24 hr. Addition of 200 ml. of water and collection of the solid precipitate on a funnel gave 1.3 g. of Vb melting at 224–230°, λ_{max}^{KBr} 2.9–3.1, 3.2, 5.83 with a shoulder at 5.9 μ.

Anal. Calcd. for $C_{22}H_{35}NO_2$: C, 76.47; H, 10.21. Found: C, 76.36; H, 10.25.

The 5α-isomer (Va) possessed an infrared spectrum essentially identical with the above and melted at 330–335°.

17α-(2-Carboxyethyl)-17β-amino-5β-androstan-3-one (VIb).—A rapidly stirred solution of 2.0 g. of the alcohol (Vb) in 50 ml. of acetic acid was treated during a 2-min. period with 1.6 ml. of 8 *M* chromic acid in aqueous sulfuric acid. After an additional 2 min., 5 ml. of isopropyl alcohol was added and then the acetic acid was distilled in vacuum. A suspension of the residue in 120 ml. of 10% sodium hydroxide was extracted with chloroform and the extract was washed with water. Removal of the solvent and crystallization of the residue from a mixture of chloroform and hexane afforded 1.8 g. of the ketone (VIb), m.p. 259–261°, λ_{max}^{KBr} 3.15, 3.25, 5.85, and 5.90 μ.

(7) Subsequent experiments have shown this reduction to be equally successful when conducted at room temperature and atmospheric pressure using T-1 Raney nickel as the catalyst.

Anal. Calcd. for $C_{22}H_{33}NO_2$: C, 76.92; H, 9.68. Found: C, 76.74; H, 9.44.

The 5α-isomer (VIa) melted at 310–320° and exhibited infrared spectrum similar to that of the 5β-derivative.

Anal. Calcd. for $C_{22}H_{33}NO_2$: C, 76.92; H, 9.68. Found: C, 76.72; H, 9.69.

17α-(2-Carboxyethyl)-17β-aminoandrost-4-en-3-one Lactam (VII).—A stirred solution of 1.75 g. of the ketone (VIb) in 40 ml. of acetic acid was treated with 5 ml. of 1 *N* hydrobromic acid in acetic acid. Water (5 ml.) was added to dissolve the precipitate which formed. Bromine (1.8 g.) in 18 ml. of acetic acid was added dropwise during a 10-min. period. Dilution with 150 ml. of water gave a solid which was collected and crystallized from a mixture of methanol and water. The 4-bromo ketone weighed 1.1 g. and melted at 202–204°, λ_{max}^{KBr} 3.0, 5.75–5.95 μ (doublet).

A mixture of 500 mg. of the 4-bromo ketone and 500 mg. of lithium bromide in 15 ml. of dimethylformamide was heated at 100° for 2 hr. Water was added slowly to the point of crystallization and the solid was collected. Recrystallization from a mixture of chloroform and ethyl acetate yielded 240 mg. of the conjugated ketone (VII) melting at 286–290°, λ_{max}^{KBr} 3.1, 3.22, 5.8, 5.92, 6.17 μ, $\lambda_{max}^{CH_3OH}$ 241 mμ, 15,500.

Anal. Calcd. for $C_{22}H_{31}NO_2$: C, 77.37; H, 9.15. Found: C, 77.23; H, 9.20.

3β-Hydroxy-5α-androstan-17-spiro-2′-pyrrolidine-(17β-N) Hydrochloride (VIII).—A solution of 2.5 g. of the lactam (IVa) in 50 ml. of tetrahydrofuran (THF) was added dropwise to a refluxing suspension of 4.0 g. of lithium aluminum hydride in 200 ml. of THF. After a 5-hr. reflux period, 4 ml. of water, 3 ml. of 20% sodium hydroxide, and finally 14 ml. of water were added successively. The precipitate was suspended in 200 ml. of a 1:1 solution of THF in ether and the insoluble material was removed by filtration. The dried amine weighed 2.0 g. Crude amine (1 g.) dissolved in the minimum volume of methanol was treated with one equivalent of methanolic hydrogen chloride. The warm solution was diluted with ether until crystallization began. The crystalline hydrochloride (VIII) was washed well with ether and dried in vacuum. It weighed 0.75 g. and melted above 300°, λ_{max}^{KBr} 2.94, 3.6–4.1, 6.28 μ.

Anal. Calcd. for $C_{22}H_{38}ClNO$: C, 71.80; H, 10.41. Found: C, 72.20; H, 10.45.

Cyclizations Leading to 3-Anilinohydantoin[1]

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3-Anilinohydantoin is formed in the base-catalyzed cyclization of S-benzylthiocarboxyglycine phenylhydrazide, carboethoxyglycine phenylhydrazide, and N-carboxyphenylhydrazidoglycine ethyl ester. Carboethoxyglycine phenylhydrazidd reacts with alcoholic potassium hydroxide to give the potassium salt of N-carboxyphenylhydrazidoglycine. The evidence indicates that this rearrangement proceeds though an 3-anilinohydantoin intermediate.

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We recently reported a reaction in which S-benzylthiocarboxyglycine phenylhydrazide[3] (I) was

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(2) Portion of a thesis presented by Duane W. Fish in partial fulfillment of the requirements for the degree of Doctor of Philosophy, Washington State University.

(3) H. B. Milne, S. L. Razniak, R. P. Bayer, and D. W. Fish, *J. Am. Chem. Soc.*, **82**, 4582 (1960).