Anal. Calcd. for $C_{29}H_{21}FN_2O_3S$: C, 70.15; H, 4.26; N, 5.64; S, 6.46. Found: C, 70.42; H, 4.24; N, 5.27; S, 6.07.

N-Phenyl-α-S-[1-(2-acetamidonaphthyl)]mercaptosuccinimide. *N*-Phenylmaleimide, m.p. 89.5–90° (reported m.p. 90–91°[22]), prepared in the usual manner from *N*-phenylmaleamic acid (kindly provided by the American Cyanamid Co.), was allowed to react with *N*-2-(α-thiolnaphthyl)-acetamide in acetone giving 83% of addition compound, m.p. 201.5–202.5°.

Anal. Calcd. for $C_{22}H_{18}N_2O_3S$: C, 67.67; H, 4.65; N, 7.18; S, 8.21. Found: C, 67.50; H, 4.63; N, 7.42; S, 8.54.

SEATTLE 5, WASH.

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF SYNTEX, S. A.]

Steroids. CLXIII.[1] Studies in Cyanosteroids. II.[2] The C_5-Cyano Analogs of Dihydrotestosterone and Dihydroprogesterone[3]

A. BOWERS

Received August 19, 1960

The addition of hydrogen cyanide to testosterone and progesterone leads to complex reaction mixtures. Nitriles and amides, epimeric at C_5, are amongst the products obtained. Some transformations of 5α-cyanodihydroallotestosterone are discussed.

As a continuation of the studies from these laboratories of the effect of electronegative groups on the biological activity of steroid hormones[4] the preparation of some C_5- cyanosteroids was undertaken.

Although it has been known for several decades that α,β-unsaturated ketones undergo Michael type addition of hydrogen cyanide[5] it was not certain that nucleophilic attack by cyanide ion at the angular C_5 position of a steroidal Δ^4-3-ketone would occur readily. However, the reaction proceeded easily. Testerosterone acetate (Ib), for example, after treatment with an excess of potassium cyanide in 95% ethanol under reflux for five hours no longer displayed maximum absorption in ultraviolet at 240–242 m μ. Only the very low intensity absorption of an isolated carbonyl group could be detected. The product was divided into benzene soluble and insoluble fractions and chromatography of the former over neutral alumina gave two main fractions differing widely in their polarity toward alumina. Crystallization of the least polar fraction gave a nitrogen containing compound in an overall yield of 27% which had an analysis agreeing with $C_{20}H_{29}O_2N$ and which readily formed a mono acetate (IIb). It did not show any selective absorption in the ultraviolet other than a broad band at 276–292 mμ, ε 31. In the infrared (potassium bromide disk) it displayed bands at 3350 (−OH), 2240 (−CN) and 1720 cm.$^{-1}$ (>C=O). These data were clearly consistent with the product being 5-cyanodihydrotestosterone and the nitrile group was assigned the 5α-stereochemistry (IIa) when it was seen that its rotatory dispersion curve was only compatible with a *trans*- ring junction for rings A and B.[6] The mother liquors from the purification of IIa probably contained some of the 5β-epimer since the crude product direct from the chromatogram and prior to crystallization had $[\alpha]_{312.5}^{\text{dioxane}} + 350°$.[7]

However, fractional crystallization or careful chromatography of this mixture did not lead to any of the pure 5β-isomer.

The more polar products from the chromatogram were combined with the benzene insoluble fraction and acetylated with acetic anhydride and pyridine. Chromatography of the acetylated material afforded as the least polar product 5α-cyanodihydrotestosterone acetate (IIb) identical with the product obtained from 5α-cyanodihydrotestosterone (IIa). The second product was isomeric with IIb and in the infrared it exhibited bands at 2220, 1723 (broad), and 1250 cm.$^{-1}$ Its rotatory dispersion curve in dioxane solution displayed a negative Cotton effect. On the basis of these data it was formulated as 5β-cyanodihydrotestosterone acetate (III). The shapes of the rotatory dispersion curves (see Experimental section) are in agreement with the 5α- and 5β-stereochemistry assigned to II and III, respectively.[6]

---

(1) Part CLXII, A. Bowers, L. C. Ibañez, M. E. Cabezas, and H. J. Ringold, *Chem. & Ind. (London)*, 1299 (1960).

(2) Part I. A. Bowers, E. Denot, M. B. Sanchez, L. M. Sanchez-Hidalgo, and H. J. Ringold, *J. Am. Chem. Soc.*, 81, 5233 (1959).

(3) Through the courtesy of Dr. Carl Djerassi and Dr. Ken'ichi Takeda we learned that a similar investigation with cholestenone had been carried out in the Shionogi Laboratories; *cf.* W. Nagata, S. Hirai, H. Itazaki, and K. Takeda, *J. Org. Chem.*, in press. We thank Dr. Takeda for a copy of this paper prior to publication.

(4) *Cf.* ref. (2) and references cited therein.

(5) *Cf.* C. K. Ingold, *Structure and Mechanism in Organic Chemistry*, Cornell University Press, New York, 1953, p. 690. For some more recent examples *cf.* ref. (3), footnote 8.

(6) C. Djerassi, *Optical Rotatory Dispersion*, McGraw-Hill Book Co., Inc., New York, 1960, pp. 49–51.

(7) *Cf.* 5α-cyanodihydrotestosterone, $[\alpha]_{312.5}^{\text{dioxane}}$ +1147° and 5β-cyanodihydrotestosterone acetate $[\alpha]_{312.5}$ −484°.

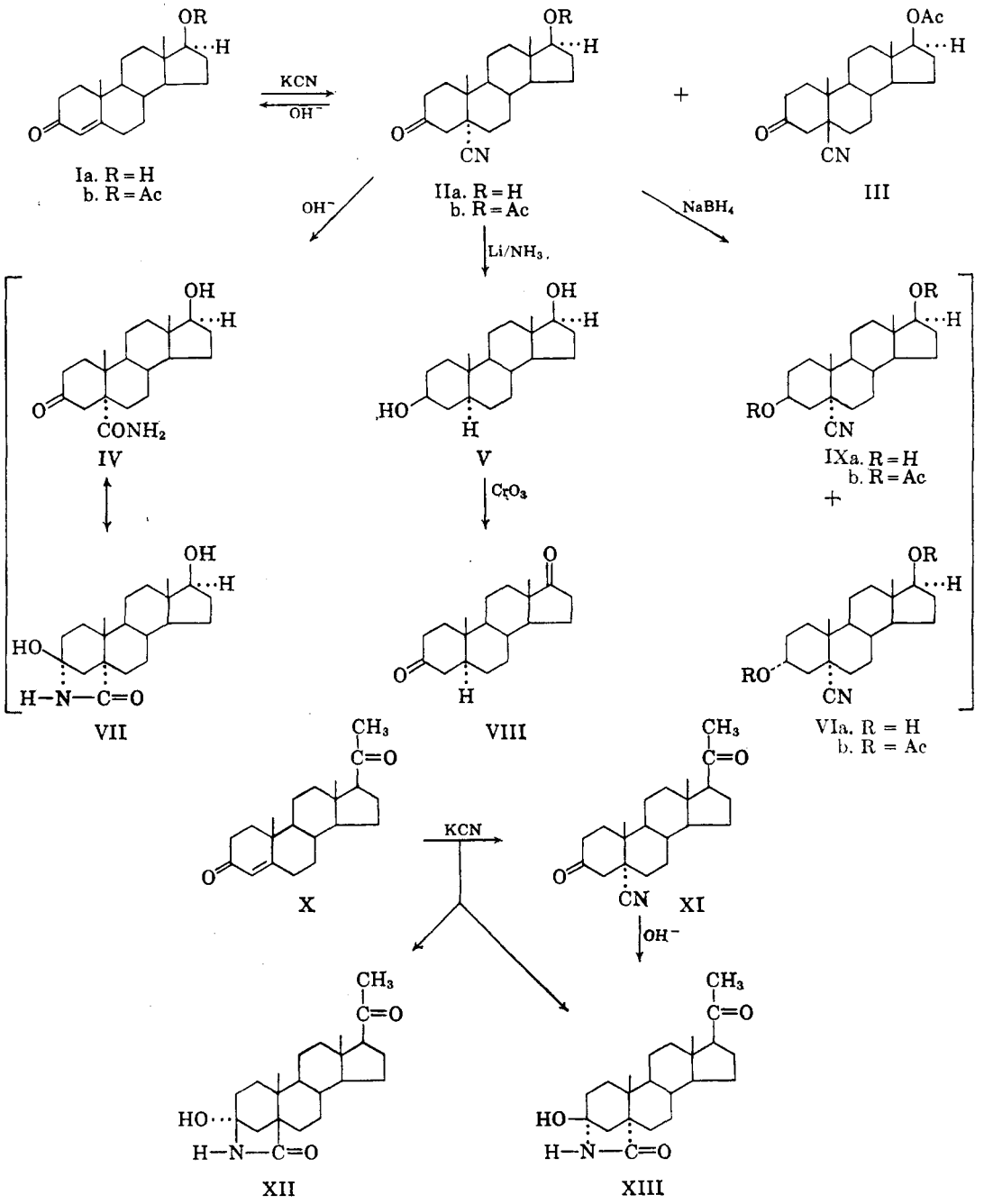

Figure 1

A third product considered to be a dimer was then eluted from the chromatogram. It had m.p. 300° and a molecular weight determination by Rast's method gave a value of 606, a figure which can only be compatible with a dimeric steroid. Insufficient evidence is available to advance a structure for this compound, although it should be noted that certain suggestions have been made by the Japanese workers for the structure of a similar dimer derived from cholestenone.[3] Finally, from the most polar fractions of the chromatogram an acetoxy amide of unknown structure was isolated which displayed bands in the infrared at 3330, 1730, 1670, and 1250 cm.$^{-1}$ and which did not exhibit selective absorption in the ultraviolet between 215 and 350 mμ.

In accord with expectation the addition of hydrogen cyanide to testosterone was shown to be reversible. Strong alkali treatment of 5α-cyanodihydrotestosterone (IIa) led to testosterone (Ia). However, under milder reaction conditions in addition to testosterone the 5α-carboxyamide (IV) was obtained in 28% yield. This compound was characterized by strong bands in the infrared at 3330 and 1680 cm.$^{-1}$ (broad) and it did not exhibit any strong selective absorption in the ultra-

violet. The rotatory dispersion curve of IV is anomalous (see Experimental section) but it is similar to the rotatory dispersion curve exhibited by the 5α-carboxyamide of cholestan-3-one.[3] This finding supports the conclusions of the Japanese group that the 3-keto-5α-carboxyamide moiety exists mainly in the carbinolamide form (VII).

Lithium in ammonia reduction of 5α-cyanodihydrotestosterone (IIa) with methanol as the proton source smoothly afforded androstane-3β,17β-diol (V) identical with an authentic sample. It was further characterized by oxidation to androstane-3,17-dione (VIII) which also proved to be identical with an authentic sample. Presumably the first stage of this reaction is the elimination of the nitrile group under the influence of the strong base (lithium methoxide) to furnish testosterone which then undergoes the expected reduction to the saturated diol (V).

Sodium borohydride reduction of 5α-cyanodihydrotestosterone (IIa) led to the isolation by chromatography over alumina of the corresponding 3α-alcohol (VIa) in 18% yield and the 3β-alcohol (IXa) in 55% yield. The unusually high proportion of the 3α-epimer clearly reflects the increased hindrance caused by the 5α-cyano group to approach of the reagent from the α-side. An analogous case, namely the sodium borohydride reduction of a 5α-hydroxy 3-ketone has also been shown to result in an unusually high yield of the 3α-alcohol.[2] The stereochemistry at C-3 for VI and VII was deduced from their relative polarities towards alumina (IXa more polar than VIa), and the percentage composition of the reaction mixture. Acetylation of the crude sodium borohydride reduction product followed by chromatography led to the isolation of the corresponding 3α,17β- and 3β,17β-diacetates, VIb and IXb, respectively.

Hydrogenation of 5α-cyanodihydrotestosterone with a platinum catalyst in ethyl acetate led mainly to the 5α-cyano-3α,17β-diol (VIa). This result indicates that the 5α-nitrile group (axial) inhibits absorption of the steroid by the catalyst on the α-face.

The analogous reaction of potassium cyanide on progesterone (X) in ethanol was then studied. After two hours under reflux four products were isolated and separated by alumina chromatography. Progesterone was recovered in 26% yield and 5-cyanodihydroprogesterone (XI) was formed in 19% yield. Only one C_5 nitrile was isolated and by analogy with the results noted for testoterone and with the Japanese work[3] the nitrile group was assigned the α-configuration at C_5.[8] Two additional products, each being more polar towards alumina than the nitrile (XI) were isolated. They were epimeric, had an analysis which agreed with $C_{22}H_{33}O_3N$ and did not show any selective absorption in the ultraviolet. In the infrared neither compound showed a nitrile band but instead both compounds displayed strong bands around 1710 and 1675 cm.$^{-1}$. Accordingly they were formulated as the epimeric C_5 amides of dihydroprogesterone XII and XIII respectively (hemiketal forms). The least polar of the two amides towards alumina was assigned the α-configuration at C_5, a finding which was confirmed when it was observed that this amide (XIII) was also obtained by a mild alkali treatment of 5α-cyanodihydroprogesterone (XI). The more polar amide thus has the β-configuration at C_5.

It is noteworthy that when the reaction time was extended from two to five hours it was not possible to recover any progesterone (X) or isolate any 5α-cyanodihydroprogesterone (XI). The only recognizable products were the 5α- and 5β-amides which were isolated in 40% and 16% yield respectively.

The successful angular introduction of a cyano group into a polycyclic ring system indicated certain possibilities for new approaches to the introduction of angular carboxyl, formyl, hydroxymethyl or methyl groups in natural product syntheses. However, since these possibilities are being fully explored by the Japanese workers, no work along these lines is contemplated in our laboratories.

EXPERIMENTAL

Melting points are uncorrected. Rotations were measured in chloroform solution unless stated otherwise and the ultraviolet absorption spectra in 95% ethanol solution. The rotatory dispersion measurements were obtained with a Rudolph Spectropolarimeter in dioxane solution using a xenon arc lamp (250–350 mμ) and a zirconium arc lamp (350–700 mμ). We are grateful to Dr. L. J. Throop and his staff for these measurements and for the infrared spectra which were obtained with a Perkin Elmer model 21 spectrophotometer with a sodium chloride prism. The elemental analyses were carried out by Dr. A. Bernhardt, Mulheim (Ruhr), Germany.

Treatment of testosterone acetate (Ib) *with potassium cyanide.* Potassium cyanide (75 g.) was added to a solution of testosterone acetate (Ib) (50 g.) in 95% ethanol (2.5 l.) and heated under reflux for 5 hr. The potassium cyanide did not dissolve completely. Addition of a saturated sodium chloride solution and extraction with ethyl acetate gave a product which was heated with benzene (1 l.) to afford an insoluble portion (17.5 g.) fraction A, m.p. 175–180° and a benzene solution of the soluble products, fraction B. This solution was adsorbed onto neutral alumina (1.5 kg.). Elution with benzene-ether (70:30 and 50:50; 11.5 l.) afforded a product (14.7 g.) m.p. 223–230°. One crystallization from ethyl acetate gave 5α-cyanoandrostane-17β-ol-3-one (IIa) (9.8 g.) m.p. 238–241°, raised by several crystallizations from ethyl acetate to 240–242°, $[\alpha]_D$ +39°, λ_{max} 276–292 mμ, ε 31; λ_{max}^{KBr} 3500, 2240, and 1720 cm.$^{-1}$; rotatory dispersion curve (*c*, 0.068 in dioxane): $[\alpha]_{700}$ +10°; $[\alpha]_{589}$ + 32°; $[\alpha]_{312.5}$ +1147° $[\alpha]_{307.5}$ +868°.

Anal. Calcd. for $C_{20}H_{29}O_2N$: C, 76.15; H, 9.27; N, 4.44. Found: C, 75.82; H, 9.18; N, 4.46.

The mother liquors from the crystallizations of 5α-cyanoandrostane-17β-ol-3-one (Ia) probably contained some of the 5β-epimeric nitrile. However, neither fractional crystalliza-

(8) For conformational reasons, *cf.* ref. (3), the 5β-nitrile is much more susceptible to further hydrolysis to the amide than is the 5α-epimer and hence the isolation of only one C_5 nitrile strongly indicates that it has the α-configuration at C_5.

tion or rechromatography led to a pure 5β-epimer. The mixture had $[\alpha]_{3.25}^{\text{dioxane}}$ +350°.

Acetylation of IIa with acetic anhydride in pyridine at room temperature for 18 hr. afforded 5α-cyanoandrostane-17β-ol-3-one acetate (IIb), m.p. 230–231°, $[\alpha]_D$ +40°, λ_{max}^{KBr} 2210, 725 (sh), 1710, and 1237 cm.$^{-1}$.

Anal. Calcd. for $C_{22}H_{31}O_3N$: C, 73.91; H, 8.74; N, 3.92. Found: C, 73.97; H, 8.75; N, 4.09.

Further elution with ether-acetone (50:50, 3 l.) afforded a gum (12.3 g.) fraction C, which resisted all attempts to induce crystallization.

Fractions A and C were then combined in pyridine (300 cc.) containing acetic anhydride (40 cc.) and heated at 90° for 1 hr. After cooling, the mixture was poured onto ice water and the product extracted with ethyl acetate. The combined extracts were washed with 2*N* hydrochloric acid and water and then dried over anhydrous sodium sulfate. Removal of the solvent afforded a product which was adsorbed from benzene onto neutral alumina (1 kg.). Elution with benzene-ether (80:20; 1.2 l.) furnished a product, m.p. 190–195° which after one crystallization from ethyl acetate gave 5α-cyanoandrostane-17β-ol-3-one acetate (IIb) (1.77 g.) m.p. 231–233°, $[\alpha]_D$ +44°. The melting point was undepressed upon admixture with an authentic sample and the infrared spectra were identical.

Further elution with benzene-ether (70:30; 2.4 l.) gave 5β-cyanoandrostane-17β-ol-3-one acetate (III) (1.05 g.) m.p. 184–189°, raised by crystallizations from ethyl acetate to 195–197°, $[\alpha]_D$ +11°. λ_{max}^{KBr} 2210 and 1700 cm.$^{-1}$; rotatory dispersion curve (*c*, 0.063 in dioxane): $[\alpha]_{700}$ −16°, $[\alpha]_{589}$ −6°, $[\alpha]_{315}$ −495°, $[\alpha]_{270}$ +48°.

Anal. Calcd. for $C_{22}H_{31}O_3N$: C, 73.91; H, 8.74; O, 13.43; N, 3.92. Found: C, 74.10; H, 8.55; O, 13.69; N, 3.86.

Further elution with ether-acetone (95:5, 1800 cc.) afforded the dimer (1.06 g.) m.p. >300°. After four crystallizations from methanol the analytical sample had m.p. >300°, $[\alpha]_D$ +2°. λ_{max}^{KBr} 3550, 1740, 1715 and 1250 cm.$^{-1}$; rotatory dispersion curve (*c*, 0.070 in dioxane): $[\alpha]_{700}$ −40°, $[\alpha]_{589}$ −10°; $[\alpha]_{320}$ +50°, $[\alpha]_{270}$ −679°.

Found: C, 74.10; H, 8.61; N, 4.15; Mol. wt. 606 (Rast).

Further elution with ether-acetone (90:10, 600 cc.) gave a fraction which after one crystallization from methanol had m.p. >300° (1.2 g.). The analytical sample (four further crystallizations from methanol) had m.p. >300°, $[\alpha]_D$ +41°. λ_{max}^{KBr} 3330, 1730, 1670, and 1250 cm.$^{-1}$.

Found: C, 73.95; H, 8.32; 0, 13.57; N, 4.13.

Treatment of 5α-cyanodihydrotestosterone with alkali. (a) 5α-Cyanoandrostane-17β-ol-3-one (IIa) (2.8 g.) in ethanol (100 cc.) containing potassium hydroxide (4.0 g.) was heated under reflux for 1 hr. After neutralizing with acetic acid the solution was concentrated to approximately 30 cc. Addition of water and filtration afforded a product (2.33 g.) m.p. 125–134°. One crystallization from benzene afforded androstane-17β-ol-3-one-5α-carboxamide (IV) (320 mg.) m.p. 293–296° raised by crystallizations from acetone to 308–310°, $[\alpha]_D$ +8°, λ_{max}^{KBr} 3330 and 1680 cm.$^{-1}$ (broad).

Anal. Calcd. for $C_{20}H_{31}O_2N$: C, 72.03; H, 9.37; O, 14.39; N, 4.20. Found: C, 72.02; H, 9.42; O, 14.59; N, 4.38.

The mother liquors from the benzene crystallization were adsorbed onto neutral alumina (100 g.). Elution with methylene dichloride (1.2 l.) afforded testosterone (Ia) (1.3 g.) m.p. 147–151°, raised by crystallization to 150–151°, λ_{max} 240–242 mμ; ε, 16, 200; the m.p. was undepressed on admixture with an authentic sample and the infrared spectra were dentical.

(b) When 5α-cyanoandrostane-17β-ol-3-one (IIb) was heated at 170° for 12 hr. in a sealed tube with 1.5% sodium hydroxide in 50% aqueous methanol only testosterone (Ia) could be isolated.

(c) Repetition of experiment (a) using 95% ethanol led to a 28% yield of the amide (IV) by direct crystallization of the product instead of 12% obtained in the absence of added water. The yield of testosterone (Ia) in this experiment was 33%.

Reduction of 5α-cyanoandrostane-17β-ol-3-one (IIa) *with lithium in ammonia.* 5α-Cyanoandrostane-17β-ol-3-one (IIa) (2.3 g.) in dry dioxane (230 cc.) was added with stirring to a solution of lithium (1.0 g.) in liquid ammonia (1.75 l.). Methanol was then added dropwise until the blue color was discharged. Evaporation of the ammonia, addition of water, and isolation with ethyl acetate afforded a product which was adsorbed from benzene onto alumina (100 g.). Elution with benzene-ether (85:15; 1200 cc.) and one crystallization from ethyl acetate afforded androstane-3β,17β-diol (V) (1.03 g.) m.p. 161–163° unchanged after three further crystallizations from the same solvent, $[\alpha]_D$ +10°, The melting point was undepressed upon admixture with an authentic sample and the infrared spectra were identical; lit.[9] reports m.p. 164° and $[\alpha]_D$ +4° (alcohol) for V.

Oxidation of V with 8*N* chromic acid in acetone solution afforded androstane-3,17-dione (VIII) m.p. 128–130°, $[\alpha]_D$ +98°. The melting point was undepressed upon admixture with an authentic sample and the infrared spectra were identical; lit.[10] reports m.p. 132–134°, $[\alpha]_D$ +100° (ethanol).

Reduction of 5α-cyanoandrostane-17β-ol-3-one (IIa) *with sodium borohydride.* (a) Sodium borohydride (300 mg.) in water (1.0 cc.) was added to a solution of 5α-cyanoandrostane-17β-ol-3-one (IIa) (1.0 g.) in dioxane (30 cc.). After 45 min. at room temperature addition of water and isolation with ethyl acetate gave a product which did not display a carbonyl band in the infrared. A solution in benzene was adsorbed onto alumina (60 g.). Elution with benzene-ether (70:30; 500 cc.) afforded 5α-cyanoandrostane-3α-17β-diol (VIa) (180 mg.) m.p. 246–250°, raised by crystallizations from acetone to 255–257°, $[\alpha]_D$ +10°; λ_{max}^{KBr} 2245 cm.$^{-1}$

Anal. Calcd. for $C_{20}H_{31}O_2N$: C, 75.67; H, 9.84; N, 4.41. Found: C, 75.97; H, 9.94; N, 4.35.

Further elution with benzene-ether (70:30; 1.5 l.) afforded 5α-cyanoandrostane-3β,17β-diol (IXa) (550 mg.) m.p. 233–237°, raised by crystallizations from ethyl acetate to 239–241°, markedly depressed on admixture with the 3α-epimer (VIa); $[\alpha]_D$ +9°; λ_{max}^{KBr} 2240 cm.$^{-1}$

Anal. Calcd. for $C_{20}H_{31}O_2N$: C, 75.67; H, 9.84; N, 4.41. Found: C, 74.92; H, 9.42; N, 4.76.

(b) Experiment (a) was repeated but the crude product was treated with an excess of acetic anhydride in pyridine at room temperature for 24 hr. Isolation of the mixture of acetates and chromatography over alumina afforded 5α-cyanoandrostane-3α,17β-diol diacetate (VIb) m.p. 204–206°, $[\alpha]_D$ +42°.

Anal. Calcd. for $C_{24}H_{35}O_4N$: C, 71.79; H, 8.79; N, 3.49. Found: C, 71.42; H, 8.86; N, 3.37.

The more polar 5α-cyanoandrostane-3β,17β-diol diacetate (IXb) had m.p. 195–196°, depressed on admixture with VIb, $[\alpha]_D$ +32°.

Anal. Calcd. for $C_{24}H_{35}O_4N$: C, 71.79; H, 8.79; N, 3.49. Found: C, 71.60; H, 8.60; N, 3.50.

Hydrogenation of 5α-cyanoandrostane-17β-ol-3-one (IIa). Adams' catalyst (platinum oxide) (150 mg.) was added to a solution of 5α-cyanoandrostane-17β-ol-3-one (IIa) (500 mg.) in ethyl acetate (30 cc.). After stirring in an atmosphere of hydrogen for 6 hr. the catalyst was removed by filtration and the filtrate evaporated to dryness. The product was adsorbed from benzene onto alumina (30 g.). Elution with benzene-ether (70:30; 750 cc.) afforded 5α-cyanoandrostane-3α,17β-diol (VIa) (240 mg.) m.p. 247–250°, raised by crystallization from acetone to 251–253°, undepressed upon admixture with the product from the sodium borohydride reduction experiment. The infrared spectra of the two products were identical.

Treatment of progesterone (X) *with potassium cyanide.* (a) Potassium cyanide (7.5 g.) was added to a solution of

(9) L. F. Feiser and M. Fieser, *Steroids*, Reinhold, New York, 1959, p. 519.

(10) C. W. Shoppee, *Helv. Chim. Acta*, **23**, 740 (1940).

progesterone (X) (5.0 g.) in 95% ethanol (250 cc.) and heated under reflux for 2 hr. Addition of water and isolation with ethyl acetate afforded a product which was adsorbed from benzene (200 cc.) onto alumina (200 g.) (chromatogram A). Elution with benzene (1.2 l.) and benzene-ether (90:10; 600 cc.) gave a product (3.06 g.) which was dissolved in hexane-benzene (80:20; 150 cc.) and rechromatographed over alumina (120 g.) (chromatogram B). Elution with hexane-benzene (80:20; 300 cc.) and (70:30; 300 cc.) gave progesterone (X) (1.32 g.) m.p. 112–117°, raised by crystallization from hexane to 118–120° undepressed on admixture with an authentic sample. Further elution of chromatogram B with hexane-benzene (1:1, 300 cc.) and benzene (300 cc.) furnished 5α-cyanopregnane-3,20-dione (XI) (960 mg.) m.p. 212–234°, raised by crystallizations from acetone-hexane to 239–241°, $[\alpha]_D$ +113°; λ_{max} 286–288 mμ, ε 60. λ_{max}^{KBr} 2250, 1725, and 1708 cm.$^{-1}$

Anal. Calcd. for $C_{22}H_{31}O_2N$: C, 77.37; H, 9.15; O, 9.37; N, 4.10. Found: C, 77.19; H, 9.05; O, 9.76; N, 4.17.

Continued elution of chromatogram A with ether (600 cc.) and ether-acetone (90:10; 600 cc.) afforded pregnane-3,20-dione-5α-carboxamide (XIII) (500 mg.) m.p. 225–230°, raised by crystallizations from acetone to 243–245°, $[\alpha]_D$ +73°. λ_{max} 280–288 mμ, ε 63. λ_{max}^{KBr} 3330, 1705, and 1680 cm.$^{-1}$

Anal. Calcd. for $C_{22}H_{33}O_3N$: C, 73.50; H, 9.25; O, 13.35; N, 3.90. Found: C, 73.72; H, 9.10; O, 13.52; N, 4.13.

Further elution (chromatogram A) with ether-acetone (80:20, 1500 cc.) gave pregnane-3,20-dione-5β-carboxamide (XII) (900 mg.) m.p. 190–210°, raised by one crystallization from acetone to 230–237°. The analytical sample from acetone had m.p. 243–245°, depressed to 215–230° on admixture with the 5α-epimer (XIII); $[\alpha]_D$ +83°; λ_{max} 280–290 mμ ε 51. λ_{max}^{KBr} 3300, 1710, and 1670 cm.$^{-1}$.

Anal. Calcd. for $C_{22}H_{33}O_3N$: C, 73.50; H, 9.25; N, 3.90. Found: C, 73.77; H, 9.04; N, 4.17.

(b) When the reflux time was extended to 5 hr., no progesterone (X) was recovered, nor could any 5α-cyanopregnane-3,20-dione (XI) be isolated. The 5α-carboxamide (XIII) was isolated in 40% yield and the 5β-carboxamide (XII) in 16% yield.

Alkaline hydrolysis of 5α-cyanopregnane-3,20-dione (XI) (with E. Denot). Potassium hydroxide (500 mg.) was added to a solution of 5α-cyanopregnane-3,20-dione (XI) (150 mg.) in ethanol (12.5 cc.). After heating under reflux for 1 hr. water (25 cc.) was added and the solution acidified with dilute sulfuric acid. Filtration afforded the pregnane-3,20-dione-5α-carboxamide (XIII) (130 mg.) m.p. 215–218°, raised by one crystallization from acetone-hexane to 240–241°, undepressed on admixture with the sample described above. The infrared spectra of the two samples were identical. The m.p. was depressed (187–194°) on admixture with the 5β-carboxamide (XII).

APARTADO POSTAL 2679
MEXICO City, D. F., MEXICO

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF SYNTEX, S.A.]

Steroids. CLXIV.[1] Preparation of 6α,16α-Dimethylprogestational and Cortical Hormone Analogs

JOSE IRIARTE AND MARIA LUISA FRANCO

Received September 8, 1960

Synthetic routes for the preparation of 6α,16α-dimethylprogesterone, 6α,16α-dimethyl-17α-acetoxyprogesterone and 6α,16α-dimethylhydrocortisone are described.

During recent years considerable interest has been attached to the synthesis of steroidal hormone analogs and amongst the more interesting variations in the progestational and cortical hormone series have been the introduction of halogen, hydroxyl, or methyl groups at various positions throughout the steroid molecule. Syntheses involving the latter group have been effected at C-2,[2] C-4,[3] C-6,[4] C-7,[5] C-9,[6] C-17,[7] and C-16[8,9] and of these, the preparation of the 6α-methyl and 16α-methyl analogs have been of special interest. As specific examples, the enhanced progestational activity in the 6α-methyl-17α-acetoxyprogesterone

(1) Paper CLXIII, A. Bowers, *J. Org. Chem.*, in press.

(2) J. A. Hogg, F. H. Lincoln, R. W. Jackson, and W. P. Schneider, *J. Am. Chem. Soc.*, **77**, 6401 (1955).

(3) (a) N. G. Steinberg, R. Hirschmann, and J. M. Chemerda, *Chem. & Ind. (London)*, 975 (1958); (b) W. J. Adams, D. K. Patel, V. Petrow, I. A. Stuart-Webb, and B. Sturgeon, *J. Chem. Soc.*, 4490 (1956).

(4) (a) G. B. Spero, J. L. Thompson, B. J. Magerlein, A. R. Hanze, H. C. Murray, O. K. Sebek, and J. A. Hogg, *J. Am. Chem. Soc.*, **78**, 6213 (1956); (b) H. J. Ringold, E. Batres, and G. Rosenkranz, *J. Org. Chem.*, **22**, 99 (1957); (c) J. C. Babcock, E. S. Gutsell, M. E. Herr, J. A. Hogg, J. C. Stucki, L. E. Barnes, and W. E. Dulin, *J. Am. Chem. Soc.*, **80**, 2904 (1958); (d) H. J. Ringold, J. Pérez Ruelas, E. Batres, and C. Djerassi, *J. Am. Chem. Soc.*, **81**, 3712 (1959); (e) A. David, F. Hartley, D. R. Millson, and V. Petrow, *J. Pharm. and Pharmacol.*, **9**, 929 (1957).

(5) R. E. Beyler, A. E. Oberster, F. Hoffman, and L. H. Sarret, *J. Am. Chem. Soc.*, **82**, 170 (1960) and references therein.

(6) F. Hoffman, R. E. Beyler, and M. Tishler, *J. Am. Chem. Soc.*, **80**, 5322 (1958).

(7) R. E. Beyler, F. Hoffman, and L. H. Sarret, *J. Am. Chem. Soc.*, **82**, 178 (1960) and references therein.

(8) (a) G. E. Arth, J. Fried, D. B. R. Johnston, D. R. Hoff, L. H. Sarret, R. H. Silber, H. C. Stoerk, and C. A. Winter, *J. Am. Chem. Soc.*, **80**, 3161 (1958); (b) E. P. Oliveto, R. Rausser, L. Weber, A. L. Nussbaum, W. Gebert, C. T. Coniglio, E. B. Hershberg, S. Tolksdorf, M. Eisler, P. L. Perlman, and M. M. Pechet, *J. Am. Chem. Soc.*, **80**, 4431 (1958); (c) D. Taub, R. D. Hoffsommer, H. L. Slates, and N. L. Wendler, *J. Am. Chem. Soc.*, **80**, 4435 (1958); (d) E. P. Oliveto, R. Rausser, A. L. Nussbaum, W. Gebert, E. B. Hershberg, S. Tolksdorf, M. Eisler, P. L. Perlman, and M. M. Pechet, *J. Am. Chem. Soc.*, **80**, 4428 (1958); (e) E. P. Oliveto, R. Rausser, H. L. Herzog, E. B. Hershberg, S. Tolksdorf, M. Eisler, P. L. Perlman, and M. M. Pechet, *J. Am. Chem. Soc.*, **80**, 6687 (1958).

(9) R. D. Hoffsommer, H. L. Slates, D. Taub, and N. L. Wendler, *J. Org. Chem.*, **24**, 1617 (1959).