*Anal.* Calcd. for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59. Found: C, 71.29; H, 9.65.

The *methyl ester* (*21*) of this acid, obtained by treatment with diazomethane, melted at 71–72° after crystallization from petroleum ether (b.p. 30–60°) at −78°.

*Anal.* Calcd. for $C_{16}H_{26}O_3$: C, 72.14; H, 9.84. Found: C, 72.23; H, 9.91.

*Enol-lactone* (*22*). Following the procedure of Woodward,[21] a solution of 138 mg. (0.55 mmole) of the keto acid (*20*) in 5 ml. of acetic anhydride was refluxed 1.5 hr. under nitrogen and then 26 mg. of sodium acetate was added. Reflux was continued for 2.5 hr. most of the acetic anhydride removed at reduced pressure, and the residue taken up in 1:1 benzene–ether. The organic solution was washed with 10% aqueous potassium bicarbonate, water, and saturated salt solution and dried ($Na_2SO_4$). The residue obtained after evaporation of the solvents at reduced pressure was chromatographed on 10 g. of Florisil. Elution with 200 ml. of 1% ether–benzene afforded 100 mg. (78%) of the enol-lactone (*22*), m.p. 90–92°. Crystallization from petroleum ether (b.p. 60–75°) afforded the analytical sample, m.p. 91.5–92.5°; infrared: $\lambda_{max}^{HCCl_3}$ 5.72 $\mu$ (>C=O), 8.60 $\mu$ (—C—O—C).

*Anal.* Calcd. for $C_{15}H_{22}O_2$: C, 76.87; H, 9.46. Found: C, 77.00; H, 9.54.

*Methyl 2-keto-5,5,9-trimethyl-trans-decal-1β-ylacetate* (*23*). To a stirred solution of 51 mg. (0.22 mmole) of the enol-lactone (*22*) in 2 ml. of dry methanol in a nitrogen atmosphere was added 3 ml. of a solution of 87 mg. (0.45 mg.-atom) of sodium in 25 ml. of dry methanol, and the mixture was refluxed for 2.5 hr. Most of the methanol was removed at reduced pressure, water was added, and the product isolated by ether extraction in the usual manner. The crystalline residue obtained after evaporation of the ether was chromatographed on 10 g. of Florisil. Elution with 200 ml. of 2% ether–benzene and crystallization from petroleum ether (b.p. 30–60°) at −78° afforded 38 mg. (66%) of the keto ester (*23*), m.p. 61–63°. Two further crystallizations from the same solvent afforded the analytical sample, m.p. 63–64°.

*Anal.* Calcd. for $C_{16}H_{26}O_3$: C, 72.14; H, 9.84. Found: C, 72.17; H, 9.90.

A mixture of this ester, m.p. 63–64°, and the keto ester (*21*), m.p. 71–72°, softened at 35° and melted over the range 41–55°.

*Acknowledgment.* The authors gratefully acknowledge the support of the Research Corporation and are indebted to Prof. Stork and Dr. Meisels for providing a sample of the keto acid (*12*). We are indebted, also, to the Parke, Davis and Co. Spectral Laboratory for making their facilities available to us.

ANN ARBOR, MICH.

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

# Steroids. CLXXXI.[1] 11a-Aza- and 11a-Oxa-C-homo Steroidal Hormone Analogs

JOHN A. ZDERIC,[2] HUMBERTO CARPIO, AND DINORAH CHÁVEZ LIMÓN

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The preparation of a number of steroids possessing either 11a-aza or 11a-oxa structures are described. Among these are compounds related to progesterone, prednisone, and certain androgens.

Recently the preparations of 11a-aza-C-homotigogenin and 11a-oxa-C-homotigogenin-11-one 3-acetate (11,12-secotigogenin-11-oic-12-ol 3-acetate (11→12) lactone) were reported.[3] This present paper now describes their conversion to a variety of hormone analogs.

Aside from these modifications other reports have appeared concerning the introduction of nitrogen and oxygen into various positions of the steroid molecule. Mazur,[4] for example, has described the preparation of several 12a-aza-C-homo steroids whereas Jacobs and Brownfield[5] have synthesized steroids containing nitrogen and oxygen in ring B. In addition to these previous reports and the references they contain, the preparation of several 9α-aza-C-homo steroids has also been achieved[6] by means of Beckmann rearrangements of 11-oximino steroids.

For the synthesis of the nitrogen analogs, 11a-aza-C-homotigogenin 3-acetate *N*-acetate[3] (I) was subjected to the usual side chain degradation sequence, with the exception that a 55-minute acetolysis period was employed.[7] The resulting $\Delta^{16}$-pregnene derivative II was epoxidized with *t*-butyl hydroperoxide[8] to provide III which was then transformed to the bromohydrin IVa. In contrast to most 16β-bromo-17α-ols which readily undergo reductive debromination, the removal of bromine from IVa proved initially difficult. For

(1) Paper CLXXX. A. D. Cross, J. A. Edwards, and A. Bowers, *Tetrahedron Letters, in press.*

(2) Present address, Syntex Institute for Molecular Biology, Palo Alto, Calif.

(3) J. A. Zderic, H. Carpio, D. Chávez Limón, and A. Ruiz, *J. Org. Chem.*, **26**, 2842 (1961).

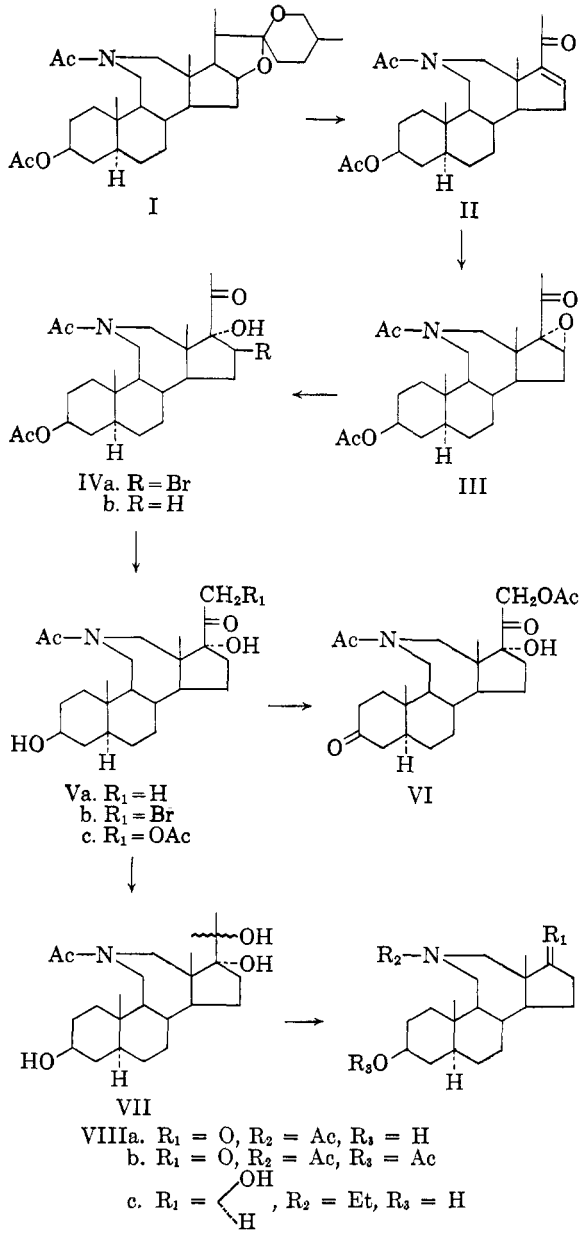
(4) R. H. Mazur, *J. Am. Chem. Soc.*, **81**, 1454 (1959); **82**, 3992 (1960).

(5) T. L. Jacobs and R. B. Brownfield, *J. Am. Chem. Soc.*, **82**, 4033 (1960). This paper contains a lengthy list of references to the substitution of nitrogen and oxygen at other positions of the steroid nucleus.

(6) J. A. Zderic and J. Iriarte, *J. Org. Chem. in press.*

(7) For examples of other sapogenins which undergo rapid furostene formation see ref. 3 and J. A. Zderic, H. Carpio, and C. Djerassi, *J. Am. Chem. Soc.*, **82**, 446 (1960).

(8) N. C. Yang and R. A. Finnegan, *J. Am. Chem. Soc.*, **80**, 5845 (1958).




example when IVa was treated with either fresh Raney nickel or hydrogen in the presence of 2% palladium-carbon, debromination proceeded only with concomitant reformation of the epoxide ring to yield III. With older samples of Raney nickel[9] or with 2% palladium-carbon in the presence of large quantities of sodium acetate, debromination could be smoothly effected in a reproducible fashion to give the expected 17a-hydroxy-20-ketone IVb.

After hydrolysis of the C-3 acetate function the resultant compound Va was subjected to the action of bromine in a variety of solvent media in order to effect C-21 bromination. Under these conditions, *e.g.*, bromine in chloroform, tetrahydrofuran or acetic acid, rapid decolorization of the bromine was observed. In each case however, the only solid product that could be recovered was the starting material Va. On the other hand when phenyltrimethylammonium perbromide[10] was used, a new crystalline compound could be isolated. While satisfactory analytical results were not obtained for this substance, its nature was evident since displacement with potassium acetate led to the 21-acetate Vc. As would be expected, Vc gave a positive TPTZ test and its analytical data was in accord with the proposed structure.

Following oxidation at C-3, the ketone VI was obtained. Attempts to introduce the $\Delta^{1,4}$-diene system into this compound either by bromination-dehydrobromination sequence[11] or dehydrogenation with selenium dioxide[12] were unsuccessful. Similar results have been observed in the attempted introduction of the $\Delta^{1,4}$-dienone system into a 9a-aza steroid.[6] With dicyanodichloroquinone[13] however there was obtained in very low yield a new substance with the following characteristics. *A.* The ultraviolet spectrum exhibited a maximum at 240 m$\mu$ and the infrared spectrum possessed a band at 6.02 $\mu$. The position of these bands is consistent with a $\Delta^{1,4}$-dienone system. *B.* The possibility that VI possessed instead a $\Delta^{4}$-3-one system was eliminated by the fact that VI did not give the strong fluorescent test associated with this type of grouping.[14] *C.* The infrared spectrum in addition to the above band also possessed absorption peaks at 5.75 $\mu$, 5.81 $\mu$, and 6.18 $\mu$ which may be assigned to the 21-acetate, the 20-ketone, and the *N*-acetate respectively. *D.* The compound gave a positive TPTZ test thereby indicating that the cortical type side chain was still intact. In spite of these points, however, the nature of the reaction product remains unknown. Repeated combustion analyses gave widely varying values none of which were in accord with the expected product.

Several derivatives in the androstane series which contained the 11a-aza structure were also prepared. As an entry to these compounds, Va was reduced with sodium borohydride to produce the 20-ol VII. This compound was then subjected to lead tetraacetate cleavage of the C-17:C-20 glycol thereby yielding 11a-aza-C-homo-5$\alpha$-androstane-3$\beta$-ol-17-one *N*-acetate (VIIIa). Attempts to effect reduction of VIIIa with lithium aluminum hydride were only partially successful presumably due to the insolubility of VIIIa in tetrahydrofuran. The acetate VIIIb, however, was found to react normally and moderate yields of *N*-ethyl-11a-aza-

(9) Estimated 6 months to one year old.

(10) A. Marquet and J. Jacques, *Tetrahedron Letters*, No. 9, 24 (1959).

(11) G. Rosenkranz, J. Pataki, St. Kaufmann, J. Berlin, and C. Djerassi, *J. Am. Chem. Soc.*, **72**, 4081 (1950).

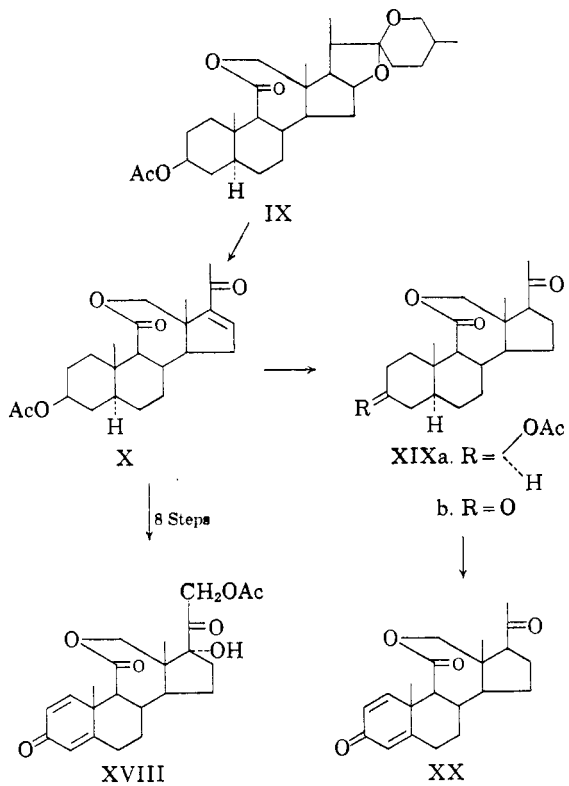
(12) Ch. Meystre, H. Frey, W. Voser, and A. Wettstein, *Helv. Chim. Acta*, **39**, 734 (1956); S. A. Szpilfogel, T. A. Posthumus, M. S. de Winter, and D. A. Van Dorp, *Rec. Trav. Chim.*, **75**, 475 (1956).

(13) D. Burn, D. N. Kirk, and V. Petrow, *Proc. Chem. Soc.*, 14 (1960).

(14) I. E. Bush, *Recent Progr. in Hormone Research*, **9**, 326 (1954).

C-homo-5α-androstane 3β,17β-diol VIIIc could be obtained.

An over-all reaction sequence similar to I → VI was employed in the preparation of 11a-oxa-C-homo-pregna-1,4-diene-17α,21-diol-3,11,20-trione 21-acetate (XVIII) and only a few of the steps bear comment.




In contrast to the rapid acetolysis previously mentioned for 11a-aza-c-homotigogenin (I), the acetolysis of 11a-oxa-C-homotigogenin-11-one 3-acetate (IX) proceeded only during reaction periods of eight to ten hours. Moreover in our hands, the yield of the $\Delta^{16}$-20-ketone X was variable and lower than the aza example.

A marked difference was also noted in the hydrogenolysis of the bromine in XII. Whereas in IVa recyclization to the epoxide III occurred readily, normal hydrogenolysis was observed with XII and the corresponding 17α-hydroxy-20-ketone XIII was obtained in good yield.

In completing the synthesis of the prednisone analog XVIII, no further difficulties were experienced. Indeed, the final step of introducing the $\Delta^{1,4}$-diene system proceeded normally with dicyanodichloroquinone.[13] This finding stands in contrast to the results observed in the aza series.

The synthesis of the progesterone analog XX was achieved by catalytic reduction of X followed by hydrolysis of the 3-acetate. While this latter product could never be obtained crystalline, upon oxidation it provided the well characterized diketolactone XIXb. Dehydrogenation of this compound with dicyanodichloroquinone[13] then gave 11a-oxo-C-homopregna-1,4-diene-3,11,20-trione (XX).

Mazur in his paper[4] on 12a-aza steroids noted that molecular models do not indicate any significant change in the stereochemical environment of the $\Delta^{16}$-double bond. Furthermore, on the basis of these molecular models he suggested that the configuration of C-17 would be the same as in normal ring-C steroids. We concur in these opinions for the presently described compounds and feel that the multisteps conversion of II to VIIIa offers support for these views.

If the conversion of II to III had proceeded by beta face attack, the resultant epoxide, when treated with hydrogen bromide, should have led to a 16β-hydroxy-17α-bromo-20-ketone.[15] Upon debromination such a compound would lead to a 16β-hydroxy-20-ketone. After reduction at C-20 this compound would provide a diol resistant to lead tetraacetate cleavage.

As previously noted, treatment of VII with lead tetraacetate resulted in a rapid reaction from which the 17-ketone VIIIa was isolated. This fact then dictates that VII contained a hydroxy group in the 17α-position and that epoxidation of the $\Delta^{16}$-double bond must have proceeded by alpha face attack. On the basis of these results and observations the configuration of all 11a-oxa compounds may be similarly assigned.

## EXPERIMENTAL[16]

*11a-Aza-C-homo-$\Delta^{16}$-5α-pregnene-3β-ol-20-one 3-acetate N-acetate* (II). A sealed tube containing 10 ml. of acetic anhydride and 1.5 g. of 11a-aza-C-homotigogenin[3] was heated at 200° for 55 min. After this time the tube was cooled and the excess acetic anhydride was hydrolyzed by the addition of 100 ml. of water. The liquid phase was then decanted from the separated semisolid. This material was dissolved with stirring in 12.5 ml. of acetic acid, 12.5 ml. of dichloroethane and to it was added 0.48 g. of chromium trioxide dissolved in 8.5 ml. of 90% aqueous acetic acid. After 2 hr. at room temperature the solution was diluted with 100 ml. of water and extracted with ethyl acetate (4 × 25 ml.). The combined extracts were washed with water and evaporated. The residue was then placed in 15 ml. of acetone containing 0.75 g. of potassium hydroxide and 6 ml. of water. After 30 min. at reflux temperature, the mixture was cooled and diluted with 30 ml. of water. The resultant precipitate was collected and allowed to stand at room temperature overnight with pyridine (5 ml.) and acetic anhydride (5 ml.). Dilution with water and several recrystallizations of the resultant crystals from acetone-hexane provided pure II (0.3 g.) m.p. 180–186°, $[\alpha]_D$ +68°, $\lambda_{max}^{EtOH}$ 236 mμ, log ε 3.98, $\lambda_{max}^{KBr}$ 5.79 μ, 6.01 μ, 6.15 μ, and 8.10 μ.

*Anal.* Calcd. for $C_{25}H_{37}NO_4$: C, 72.25; H, 8.98; O, 15.40; N, 3.37. Found: C, 72.42; H, 8.77; O, 15.76; N, 3.48.

(15) For an example of this type synthesis see B. Löken, S. Kaufmann, G. Rosenkranz, and F. Sondheimer, *J. Am. Chem. Soc.*, 78, 1738 (1956).

(16) All melting points are uncorrected and the rotations have been recorded in chloroform. The authors are indebted to Dr. J. Matthews and his staff for the determination of all rotations and the recording of spectra.

*16α,17α-Oxido-11a-aza-C-homo-5α-pregnane-3β-ol-20-one 3-acetate N-acetate* (III). To 1.2 ml. of dry benzene containing 0.12 ml. of *t*-butyl hydroperoxide and 0.1 ml. of Triton B[17] was added 0.2 g. of II. After 18 hr. at room temperature the solution was diluted with water (5 ml.) and ethyl acetate (20 ml.). The organic phase was washed with water, dried over sodium sulfate, and evaporated to leave a residue. Repeated recrystallization from acetone-hexane gave 80 mg. of crystals, m.p. 207–209°, $[\alpha]_D$ +45°, $\lambda_{max}^{KBr}$ 5.79 μ, 5.92 μ, and 8.14 μ.

*Anal.* Calcd. for $C_{25}H_{37}NO_5$: C, 69.57; H, 8.64; O, 18.54; N, 3.25. Found: C, 69.83; H, 8.52; O, 18.08; N, 3.64.

*16β-Bromo-11a-aza-C-homo-5α-pregnane-3β,17α-diol-20-one 3-acetate N-acetate* (IVa). Acetic acid (8 ml.) containing 0.80 g. of III was allowed to stand at room temperature for 1.15 hr. with 1.6 ml. of acetic acid saturated with hydrogen bromide. The solution was then poured into water and the resultant crystals collected. Three recrystallizations from acetone-hexane yielded the analytical sample, m.p. 236–238° dec., $[\alpha]_D$ −23°, $\lambda_{max}^{KBr}$ 3.00 μ, 3.30 μ, 5.84 μ, 6.14 μ, and 8.09 μ.

*Anal.* Calcd. for $C_{25}H_{38}BrNO_5$: C, 58.59; H, 7.47; N, 2.73. Found: C, 59.33; H, 7.41; N, 2.60.[18]

*11a-Aza-C-homo-5α-pregnane-3β,17α-diol-20-one 3-acetate N-acetate* (IVb). To 40 ml. of methanol containing 0.75 g. of prereduced 2% palladium-carbon and 1.0 g. of sodium acetate was added 1.0 g. of IVa dissolved in 100 ml. of methanol and 10 ml. of acetic acid. This mixture was then stirred in a hydrogen atmosphere. When the hydrogen uptake had ceased, the solids were filtered and the filtrate was evaporated to dryness. Several crystallizations from methanol gave the pure sample 700 mg., 178–180°, $[\alpha]_D$ −80°, $\lambda_{max}^{KBr}$ 3.05 μ, 5.81 μ, 5.90 μ, 6.20 μ, and 8.09 μ.

*Anal.* Calcd. for $C_{25}H_{39}NO_5$: C, 69.25; H, 9.07; O, 18.45. Found: C, 69.68; H, 9.29; O, 18.26.

*11a-Aza-C-homo-5α-pregnane-3β,17α-diol-20-one N-acetate* (Va). A solution (12 ml.) of perchloric acid in methanol (2.5%) containing 0.50 g. of IVb was maintained at room temperature for 18 hr. At the end of this period the reaction was diluted with water and the resultant crystals, 0.40 g., m.p. 213–216° were collected. Purification was effected by several recrystallizations from acetone-hexane, m.p. 235–236°, $[\alpha]_D$ −78°, $\lambda_{max}^{KBr}$ 3.12 μ, 5.90 μ, and 6.24 μ.

*Anal.* Calcd. for $C_{23}H_{37}NO_4$: C, 70.55; H, 9.53; N, 3.58. Found: C, 70.47; H, 9.44; N, 3.95.

*21-Bromo-11a-aza-C-homo-5α-pregnane-3β,17α-diol-20-one N-acetate* (Vb). Tetrahydrofuran (40 ml.) containing 0.30 g. of Va was treated with 0.3 g. of phenyltrimethylammonium perbromide. After 3 hr. at room temperature the original orange color of the solution had completely disappeared and the reaction was diluted with water (100 ml.). Following extraction with ethyl acetate (4 × 25 ml.) the extracts were combined, washed with water, dried over sodium sulfate, and evaporated. The residue was then crystallized from acetone to provide 0.22 g. of crystals, m.p. 226–228° dec. raised by further recrystallization from the same solvent to m.p. 235–236° dec., $[\alpha]_D$ +24° (pyridine). This substance gave a rapid positive test with TPTZ and was homogeneous by paper chromatography.[18]

*11a-Aza-C-homo-5α-pregnane-3β,17α,21-triol-20-one 21-acetate N-acetate* (Vc). A mixture of acetone (50 ml.), sodium iodide (80 mg.), potassium acetate (800 mg.), and 220 mg. of Vb was kept at reflux temperature for 15 hr. The acetone was then removed by evaporation and the residue was diluted with water (25 ml.). After ethyl acetate extraction, the extracts were washed with water, dried over sodium sulfate, and evaporated. Crystallization from acetone–hexane gave 110 mg. of crystals m.p. 128–130° which were pure after two further crystallizations, m.p. 131–133°, $[\alpha]_D$ −76°, $\lambda_{max}^{KBr}$ 3.15 μ, 5.73 μ, 5.83 μ, 6.13 μ, and 8.19 μ. TPTZ—positive.

*Anal.* Calcd. for $C_{25}H_{39}NO_6$: C, 66.79; H, 8.75; N, 3.12. Found: C, 66.63; H, 8.81; N, 3.12.

*11a-Aza-C-homo-5α-pregnane-17α,21-diol-3,20-dione 21-acetate N-acetate* (VI). Acetone (5 ml.) containing 0.36 g. of Vc was treated at room temperature with 0.36 ml. of 8*N* chromium trioxide solution.[19] After dilution with water (10 ml.) there were obtained 250 mg. of crystals m.p. 95–98°.

Repeated recrystallization from methanol-ether provided the analytical sample m.p. 119–120°, $[\alpha]_D$ −61°, $\lambda_{max}^{KBr}$ 3.18 μ, 5.75 μ, 5.89 μ, 6.24 μ, and 8.15 μ.

*Anal.* Calcd. for $C_{25}H_{37}NO_6$: C, 67.09; H, 8.33; O, 21.45; N, 3.13. Found: C, 66.73; H, 8.55; O, 21.27; N, 3.32.

*Treatment of* VI *with dicyanodichloroquinone.* Dioxane (4 ml.) containing 200 mg. of VI and 0.31 g. of dicyanodichloroquinone was heated at reflux temperature for 20 hr. At the end of this time, the solution was evaporated to dryness and residue in 10 ml. of acetone was passed through a column containing 25 g. of neutral alumina. Continued elution with acetone gave 90 mg. of crystals m.p. 78–80°. After four recrystallizations from acetone-hexane, the melting point was constant at m.p. 85–87°, $[\alpha]_D$ −88° $\lambda_{max}^{EtOH}$ 240 mμ, log ε 4.10, $\lambda_{max}^{CHCl_3}$ 5.75 μ, 5.81 μ, 6.02 μ, and 6.18 μ. This material was TPTZ positive.[18]

*11a-Aza-C-homo-5α-pregnane-3β,17α,20-triol N-acetate* (VII). Sodium borohydride (20 mg.), 100 mg. of Va and 1 ml. of methanol containing 0.3 ml. of dioxane were stirred for 1.5 hr. at room temperature. Dilution with water gave 85 mg. of crystals, m.p. 120–145° which were raised by three crystallizations from acetone to m.p. 238–240°, $[\alpha]_D$ −38° (pyridine), $\lambda_{max}^{KBr}$ 3.05 μ and 6.22 μ.

*Anal.* Calcd. for $C_{23}H_{39}NO_4 + C_3H_6O$: C, 69.14; H, 10.04; O, 17.71; N, 3.10. Found: C, 69.20; H, 9.67; O, 17.88; N, 3.38.

*11a-Aza-C-homo-5α-androstane-3β-ol-17-one N-acetate* (VIIIa). A solution of 4 ml. of acetic acid, 200 mg. of VII and 400 mg. of lead tetraacetate was kept for 20 min. at room temperature. After dilution with water (20 ml.) the mixture was extracted with methylene chloride (4 × 15 ml.). The combined extracts were then washed with water, dried over sodium sulfate and evaporated to dryness to leave a crystalline mass. Four recrystallizations from acetone gave pure VIIIa, m.p. 279–280°, $[\alpha]_D$ +172°, $\lambda_{max}^{KBr}$ 3.10 μ, 5.80 μ, and 6.20 μ.

*Anal.* Calcd. for $C_{21}H_{33}NO_3$: C, 72.58; H, 9.57; N, 4.03. Found: C, 72.70; H, 9.17; N, 3.94.

*11a-Aza-C-homo-5α-androstane-3β-ol-17-one 3-acetate N-acetate* (VIIIb). To 30 ml. of pyridine containing 3.0 g. of VIIIc was added 5 ml. of acetic anhydride and the resulting solution was left at room temperature for 15 hr. Dilution with water followed by extraction with methylene chloride eventually provided 2.7 g. of crystals m.p. 155–158°. Two recrystallizations from acetone-hexane led to the analytical sample, m.p. 162–164°, $[\alpha]_D$ +146°, $\lambda_{max}^{KBr}$ 5.76 μ and 6.10 μ doublet.

*Anal.* Calcd. for $C_{23}H_{35}NO_4 + {}^1/_2C_3H_6O$: C, 70.30; H, 9.15; N, 3.35. Found: C, 70.29; H, 8.79; N, 3.83.[20]

*N-Ethyl-11a-aza-C-homo-5α-androstane-3β,17β-diol* (VIIIc). One liter of anhydrous tetrahydrofuran containing 4 g. of lithium aluminum hydride and 3.0 g. of VIIIb was heated at reflux temperature for 18 hr. After decomposition of the excess hydride with ethyl acetate and saturated aqueous sodium sulfate, the mixture was diluted with 2 l. of ethyl acetate and filtered. Evaporation of the filtrate then gave 3 g. of gum which was crystallized from acetone-hexane to yield 0.8 g. of crystals m.p. 138–140°. Repeated recrystallization from this same solvent pair gave pure VIIIc, m.p. 147–149°, $[\alpha]_D$ +9°, $\lambda_{max}^{KBr}$ 3.01 μ.

(17) Eastern Chemical Corporation, Newark, N. J.

(18) Satisfactory analytical data could not be obtained for this compound.

(19) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).

(20) Repeated attempts to obtain this material free of solvent of crystallization were unsuccessful.

*Anal.* Calcd. for $C_{21}H_{37}NO_2$ + $^1/_2$ $C_3H_6O$: C, 74.12; H, 11.06; O, 10.97; N, 3.84. Found: C, 74.37; H, 11.03; O, 10.63; N, 4.23.[20]

*11a-Oxa-C-homo-$\Delta^{16}$-5α-pregnen-3β-ol-11,20-dione 3-acetate* (X). By the method described in the conversion of I to II, but employing acetolysis periods of 8–9 hr., 6.00 g. of IX was degraded to X, 1.10 g., recrystallized from acetone hexane, m.p. 220–222°, [α]D +38°, $\lambda_{max}^{EtOH}$ 226 mμ, log ε 3.88, $\lambda_{max}^{KBr}$ 5.86μ, 6.00 μ and 8.06 μ.

*Anal.* Calcd. for $C_{23}H_{32}O_5$: C, 71.10; H, 8.30. Found: C, 71.05; H, 8.20.

*16α,17α-Oxido-11a-oxa-C-homo-5α-pregnane-3β-ol-11,20-dione 3-acetate* (XI). When 0.20 g. of X was treated with *t*-butyl hydroperoxide as reported above, 0.18 g. of crude epoxide, m.p. 275–277° was obtained. One crystallization from ethyl acetate gave crystals with constant melting point, m.p. 281–282°, [α]D ±0°, $\lambda_{max}^{KBr}$ 5.82 μ, 5.86 μ, and 8.00 μ.

*Anal.* Calcd. for $C_{23}H_{32}O_6$: C, 68.29; H, 7.98; O, 23.73. Found: C, 68.33; H, 8.09; O, 24.00.

*16β-Bromo-11a-oxa-C-homo-5α-pregnane-3β,17α-diol-11,-20-dione 3-acetate* (XII). Treatment of XI (100 mg.) with saturated hydrogen bromide–acetic acid solution (*vide supra*) gave 100 mg. of XII m.p. 192–195°. Recrystallization from methanol led to pure XII m.p. 205–206°, [α]D −47°, $\lambda_{max}^{KBr}$ 2.96 μ, 5.81 μ, and 8.04 μ.

*Anal.* Calcd. for $C_{23}H_{33}O_6Br$: C, 56.91; H, 6.85. Found: C, 56.99; H, 6.92.

*11a-Oxa-C-homo-5α-pregnane-3β,17α-diol-11,20-dione 3-acetate* (XIII). To 120 ml. of methanol containing 8 g. of Raney nickel was added 630 mg. of XII. After 2 hr. at reflux temperature the mixture was filtered and the filtrate was evaporated to dryness leaving a semisolid residue. A single crystallization from methanol then gave 420 mg. of crystals m.p. 191–193°. Two further crystallizations from the same solvent gave XIII m.p. 194–195°, [α]D −77°, $\lambda_{max}^{KBr}$ 2.92 μ, 5.79 μ, 5.90 μ, and 8.06 μ.

*Anal.* Calcd. for $C_{23}H_{34}O_6$: C, 67.95; H, 8.43; O, 23.62. Found: C, 68.11; H, 8.38; O, 23.85.

*11a-Oxa-C-homo-5α-pregnane-3β,17α-diol-11,20-dione* (XIV). Methanol (3 ml.) containing 270 mg. of XIII was saturated with dry hydrogen chloride and left at room temperature for one hr. Dilution with water (15 ml.) provided 160 mg. of crystals, m.p. 260–262°, which were obtained pure by two recrystallizations from methanol, m.p. 281–282°, [α]D −71°, $\lambda_{max}^{KBr}$ 2.96 μ, 3.04 μ, 5.82 μ, and 5.92 μ.

*Anal.* Calcd. for $C_{21}H_{32}O_5$: C, 69.20; H, 8.85. Found: C, 69.35; H, 8.98.

*21-Bromo-11a-oxa-C-homo-5α-pregnane-3β,17α-diol-11,20-dione* (XV). To a solution of chloroform (25 ml.) and 0.25 g. of XV containing 2 drops of concd. hydrogen bromide–acetic acid solution was added dropwise 0.12 g. of bromine in 10 ml. of chloroform. The resultant solution was then extracted with 5% aqueous sodium bicarbonate and washed with water. After drying over sodium sulfate and evaporation there remained 0.31 g. of crystals, m.p. 240–243° dec. A single recrystallization from chloroform provided material with a constant melting point, m.p. 248–250°, [α]D −29° (pyridine), $\lambda_{max}^{KBr}$ 2.99 μ and 5.85 μ.

*Anal.* Calcd. for $C_{21}H_{31}BrO_5$: C, 56.88; H, 7.05; Br, 18.03. Found: C, 56.25; H, 6.78; Br, 21.13.[18]

*11a-Oxa-C-homo-5α-pregnane-3β,17α,21-triol-11,20-dione 21-acetate* (XVI). A mixture of acetone (50 ml.) sodium iodide (90 mg.) and 150 mg. of XV was heated at reflux temperature for 1.5 hr. The acetone was then evaporated and the solid residue was suspended in 10 ml. of water. This suspension was extracted with methylene chloride (3 × 15 ml.) and the combined extracts were evaporated to dryness. The residue was then dissolved in 50 ml. of acetone containing 1.0 g. of anhydrous potassium acetate. After being maintained at reflux temperature for 4 days the mixture was worked up by the previously described procedure. The residue thus obtained was chromatographed over 3.0 g. of silica gel. Elution with benzene-ether (80:20) gave 65 mg. of crystals which were obtained pure after 3 crystallizations from acetone-hexane, m.p. 112–117°, [α]D −32°, $\lambda_{max}^{KBr}$ 3.00 μ, 5.80 μ, 5.88 μ, 5.94 μ, and 8.14 μ.

*Anal.* Calcd. for $C_{23}H_{34}O_7$ + $C_3H_6O$: C, 64.98; H, 8.39; O, 26.63. Found: C, 64.93; H, 8.23; O, 26.98.[20]

*11a-Oxa-C-homo-5α-pregnane-17α,21-diol-3,11,20-trione-21-acetate* (XVII). By the method employed in the preparation of Vd, 210 mg. of XVI provided 200 mg. of crude crystals, m.p. 237–242°, raised to m.p. 247–251° by two crystallizations from acetone; m.p. 247–251° [α]D −30°, $\lambda_{max}^{KBr}$ 2.96 μ, 5.76 μ, 5.92 μ, and 8.14 μ.

*Anal.* Calcd. for $C_{23}H_{32}O_7$ + $C_3H_6O$: C, 65.25; H, 8.00. Found: C, 64.78; H, 7.64.[20]

*11a-Oxa-C-homo-pregna-1,4-diene-17α,21-diol-3,11,20-trione 21-acetate* (XVIII). Dehydrogenation was effected by the use of dicyanodichloroquinone as previously described. Under these conditions, 90 mg. of XVII gave 40 mg. of crude crystals, m.p. 247–249°, after a single crystallization from ethanol. Two further recrystallizations from this same solvent gave pure XVIII, m.p. 251–253°, [α]D −13°, $\lambda_{max}^{EtOH}$ 238–240 mμ, log ε 4.16, $\lambda_{max}^{KBr}$ 2.92 μ, 5.80 μ, 5.90 μ, 6.03 μ, 6.16 μ, 6.24 μ, and 8.12 μ.

*Anal.* Calcd. for $C_{23}H_{28}O_7$: C, 66.33; H, 6.78. Found: C, 66.08; H, 6.76.

*11a-Oxa-C-homo-5α-pregnane-3β,ol-11,20-dione 3-acetate* (XIXa). To a mixture of prereduced 5% palladium/carbon (200 mg.) in methanol (50 ml.) was added 500 mg. of X. After stirring in a hydrogen atmosphere for 15 min., the solution was filtered and evaporated. The residue upon crystallization from methanol gave 350 mg. of crystals, m.p. 159–160°, whose melting point was unchanged upon further crystallization, [α]D −7°, $\lambda_{max}^{KBr}$ 5.86 μ and 8.07 μ.

*Anal.* Calcd. for $C_{23}H_{34}O_5$: C, 70.74; H, 8.78; O, 20.48. Found: C, 70.66; H, 8.93; O, 20.26.

*11a-Oxa-C-homo-5α-pregnane-3,11,20-trione* (XIXb). Twenty-four milliliters of methanol containing 2.5% of 70% perchloric acid and 600 mg. of XIXa was kept at 0° for 20 hr. The solution was then poured into water (40 ml.) and extracted with methylene chloride (4 × 30 ml.). The extracts were then washed with water, dried over sodium sulfate, and evaporated to leave 570 mg. of clear heavy oil which could not be crystallized. Since the material no longer possessed an acetate function as indicated by its infrared spectrum, it was subjected to oxidation with 8*N* chromium trioxide as described above. The reaction product thus obtained was a mixture of oily crystals (530 mg.) which upon washing with ether gave 200 mg. of crystals m.p. 233–236°. Several recrystallizations from acetone then gave the analytical sample m.p. 253–255°, [α]D +21°, $\lambda_{max}^{KBr}$ 5.82 μ.

*Anal.* Calcd. for $C_{21}H_{30}O_4$: C, 72.80; H, 8.73. Found: C, 72.40; H, 8.70.

*11a-Oxa-C-homo-pregna-1,4-diene-3,11,20-trione* (XX). By the use of dicyanodichloroquinone as previously described, 180 mg. of XIXb led to 75 mg. of oily crystals. Recrystallization first from acetone-ether and then several times from acetone gave XX, m.p. 255–257°, [α]D +15°, $\lambda_{max}^{EtOH}$ 240 mμ, log ε 4.22.

*Anal.* Calcd. for $C_{21}H_{26}O_4$ + $^1/_2C_3H_6O$: C, 72.75; H, 7.86. Found: C, 72.47; H, 7.48.

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