Steroids. CLXXVIII.[1] 9a-Aza-C-homo Steroids

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Evidence is presented which shows that Beckmann rearrangement of oximes derived from 11-ketones provides 9a-aza-11-keto-C-homo lactams. The preparations of several steroids possessing this structure are described.

Attention to steroid modifications containing nitrogens has led to a wide variety of positional substitutions.[3] In particular, C-homo substitutions have involved the preparation of 12a-aza[4] and 11a-aza[5] compounds. These researches are now extended by reporting the syntheses of several 9,11-9a-aza-C-homo steroids hereinafter referred to as 9a-aza-C-homo steroids.

In 1958 a Schering group noted the facile preparation of oximes derived from 11-ketones.[6] With this in mind, it appeared that a Beckmann rearrangement of such a compound would readily provide a C-homo lactam. From observation of molecular models, it was considered highly probable that the product of such a reaction would possess the 9a-aza-11-keto structure. This assumption seemed likely since, of the two geometrical isomers possible for the oxime, extreme steric hindrance was associated with the isomer possessing the oxime hydroxyl *syn* to ring A. This implied then that the oxime would preferentially exist in the form with the oxime hydroxyl *anti* to ring A, where no severe steric effects were apparent. Furthermore, on the basis of mechanistic considerations[7] it followed that the rearrangement product from an oxime in this configuration would possess the 9a-aza-11-keto structure. In order to obtain confirmation for these conjectures, lactam formation was first studied in the 11-ketotigogenin acetate series (Ia) where one of the two possible products of lactam reduction, namely, 11a-aza-C-homotigogenin, was already known.[5a]

Upon oximation Ia gave the oxime 3-acetate Ic, which was further characterized by hydrolysis to the oxime Ib. Treatment of the former compound with phosphorus oxychloride in pyridine yielded the lactam IIa. The location of the nitrogen was established by subjecting IIa to lithium aluminum hydride reduction. While such a reduction of 12a-aza-12-keto lactams is very slow,[5a] the lactam IIa proved even more resistant and periods of twenty-three days at reflux temperature were required to effect partial conversion. In any case, since direct comparison of the reduced product IIb with authentic IIa-aza-C-homotigogenin[5a] proved them to be dissimilar, it was evident that IIb could only have the indicated 9a-aza structure. This in turn required the lactam IIa to possess the structure 9a-aza-C-homotigogenin-11-one 3-acetate. With these points established, attention was turned to the preparation of a hormone analog containing this type of structure.

Originally it was thought that a convenient intermediate for such a synthesis should contain in addition to the 11-ketone a Δ^4- or $\Delta^{1,4}$-3-acetate function. These latter groupings would then later serve as routes for generating the Δ^4-3-ketone system present in many steroidal hormones. For these reasons prednisone BMD[8] was chosen as a starting material and its reduction with lithium tri-*t*-butoxyaluminum hydride[9] was investigated. Because of its bulky nature, this reagent was expected to effect reduction of the C-3 ketone without attacking the C-11 ketone. Surprisingly, however, when the reaction was carried out under mild conditions, reduction at C-11 was observed and prednisolone BMD[8] was isolated in 68% yield. Similar reductions may be noted with sodium borohydride although in these cases the yields are somewhat lower.

With sodium borohydride over a prolonged period reduction was effected not only at C-3 and C-11, but also at the Δ^1 double bond as would be expected on the basis of the work by Sondheimer and his co-workers.[10] Following acetylation at C-3 and oxidation at C-11, there was obtained the 3β-acetoxy-11-ketopregn-4-ene derivative IIIa.

The assignment of configuration at C-3 was made on the basis of the large negative molecular

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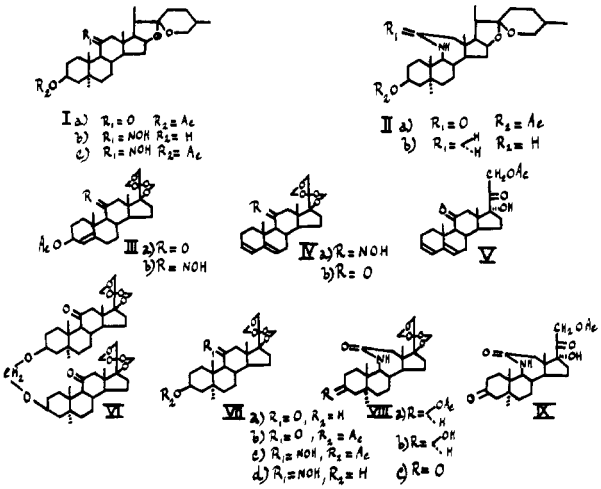

rotation difference, ΔM_D −401°, observed for the conversion of prednisone BMD to IIIa. As has been previously noted,[11] the conversion of Δ^4-3-ketones to the corresponding 3β-acetate is associated with a large negative molecular rotation shift, whereas the conversion to 3α-acetates leads to large positive shifts.

This substance was then treated with hydroxylamine hydrochloride in hot pyridine and by these means there were obtained two new products. One of these was produced in trace amounts and proved to be the expected 11-oximino 3-acetate (IIIb). The other compound on the basis of its ultraviolet spectrum was readily recognized as a pregna-3,5-diene derivative to which structure IVa was assigned. The isolation of this latter derivative also prompted the synthesis of the corresponding 11-keto derivative IVb from IIIa. After hydrolysis of the BMD grouping and acetylation at C-21, there was obtained pregna-3,5-diene-17α,21-diol-11,20-dione 21-acetate (V).

Since the above sequence showed that oximation could not be carried out in the presence of a Δ^4-3-acetoxy system, attention was turned to the use of 5α-pregnane-3β,17α,21-triol-11,20-dione[12] as a starting material. In order to protect the side chain, this substance was treated under the usual conditions for BMD formation.[8] By these means, two new compounds were obtained neither of which exhibited hydroxyl absorption bands in their infrared spectrum. Since it was observed that mild acid hydrolysis of either of these provided the desired BMD derivative VIIa, it appeared that both substances represented products wherein the C-3 hydroxyl had undergone some type of condensation with formaldehyde.

One of these products (VI) possessed a melting point above 300°, a fact which suggested that the product might be a bis steroid. While Rast molecular weight determination was impossible due to solubility problems, the analytical data accorded for the bis steroid methylenedioxy structure VI assigned. The nature of the second product is still in doubt. By its melting point and Rast determination results the product is clearly monomeric, at least in as far as the steroid moiety is concerned. From its analytical data, however, no definite information could be obtained and for the moment the material is considered to be a hemiketal of formaldehyde or possibly a formate ester.

Following conversion of VIIa to its 3-acetate VIIb, oximation gave a mixture from which the pure acetate oxime VIIc could be obtained in yields of up to 50%. Beckman rearrangement of this substance yielded the lactam VIIIa. Hydrolysis of the C-3 acetate function followed by 8 *N* chromium trioxide oxidation[13] led to VIIIc which was then subjected to BMD cleavage and C-21 acetylation. By these means 9α-aza-C-homo-5α-pregnane-17α,21-diol-3,11,20-trione 21-acetate (IX) was obtained.

Having achieved this synthesis repeated attempts were made to introduce a $\Delta^{1,4}$-diene system in IX. Studies involving selenium dioxide[14] and dichlorodicyanoquinone[15] gave either unchanged starting material or noncrystallizable gums which did not exhibit any ultraviolet absorption. When efforts were made to introduce the dienone system by bromination at C-2 and C-4 followed by elimination,[16] the results were equally abortive. Although the bromination proceeded rapidly, the resultant product could never be obtained crystalline. Furthermore, attempts to eliminate the introduced halogens gave materials with only very low extinction coefficients in their ultraviolet spectrum.

Experimental[17]

11-Ketotigogenin Acetate Oxime (Ic).—A solution of 11-ketotigogenin acetate[18] (Ia) (2 g.) and hydroxylamine hydrochloride (3 g.) in aqueous pyridine (pyridine 50 cc., water 2 cc.) was heated for 20 hr. under reflux. The reaction mixture was poured into water and the separated crystalline material was filtered and washed with water. It was then purified by dissolving in ethyl acetate and washing the solution with dilute hydrochloric acid, sodium bicarbonate solution, and water. Evaporation of the solvent and several crystallizations of the residue from benzene–hexane gave 0.5 g. of material Ic with m.p. 238–239° $[\alpha]_D \pm 0°$, ν_{max} 3500, 1720, 1270 cm.$^{-1}$.

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(17) Melting points are uncorrected and the rotations have been determined in chloroform unless otherwise noted. The infrared spectra were determined in potassium bromide pellets. We are indebted to Dr. J. Matthews and his staff for the determination of these latter constants.

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Anal. Calcd. for $C_{29}H_{45}NO_5+C_6H_6$: C, 74.30; H, 9.09; N, 2.48; O, 14.14. Found: C, 73.91; H, 8.89; N, 2.76; O, 14.47.

Additional material with m.p. 228–230° was obtained from the mother liquors.

11-Ketotigogenin Oxime (Ib).—Hydrolysis of 11-ketotigogenin acetate oxime (Ic) (475 mg.) was effected by refluxing with 1% potassium hydroxide (50 cc.) for 1 hr. followed by precipitation with water. Crystallization of the crude material from ether furnished the free oxime Ib (200 mg.) with m.p. 288–290°, $[\alpha]_D$ +5.9° and ν_{max} 3400 cm.$^{-1}$.

Anal. Calcd. for $C_{27}H_{43}NO_4$: C, 72.77; H, 9.73; N, 3.14; O, 14.36. Found: C, 72.90; H, 9.83; N, 3.06; O, 14.48.

9α-Aza-C-homotigogenin-11-one 3-Acetate (IIa).—A solution of 11-ketotigogenin acetate oxime (Ic) (3.2 g.) in anhydrous pyridine (50 cc.) cooled to 0° was treated with phosphorus oxychloride (0.7 cc.) and left 30 min. at room temperature. It was then poured into water, and the brown precipitate which formed was extracted with ethyl acetate. Evaporation of the solvent gave a semicrystalline residue which was purified by chromatography over neutral alumina. The material eluted with ether was recrystallized three times from benzene–hexane using charcoal to remove the color and furnished IIa as needles (1 g.) with m.p. 305–307°, $[\alpha]_D$ −65.4° and ν_{max} 1720, 1660, 1270 cm.$^{-1}$.

Anal. Calcd. for $C_{29}H_{45}NO_5+C_6H_6$: C, 74.30; H, 9.09; N, 2.48; O, 14.14. Found: C, 74.50; H, 8.71; N, 2.59; O, 14.01.

9a-Aza-C-homotigogenin (IIb).—Partial reduction of 9a-aza-C-homotigogenin-11-one 3-acetate (IIa) (1 g.) was effected by prolonged refluxing (23 days) with lithium aluminum hydride (5 g.) in anhydrous tetrahydrofuran (500 cc.). The strong carbonyl absorption band at 1660 cm.$^{-1}$ of the amide grouping never disappeared completely. When the total reaction mixture was worked up in the usual way and the residue was chromatographed on neutral alumina (50 g.), two compounds were isolated. The more polar compound, eluted with benzene–ether (4:1), and crystallized from methylene chloride (180 mg.) had m.p. 285–287°. Inspection of the infrared spectrum showed a strong band at ν_{max} 1660 and it was not further investigated. The less polar compound (IIb) (320 mg.) was eluted with benzene–ether (9:1) and after repeated crystallizations from acetone had m.p. 183–184°, $[\alpha]_D$ −49.7°; ν_{max} in carbonyl region, none.

Anal. Calcd. for $C_{27}H_{45}NO_3$: C, 75.13; H, 10.51. Found: C, 75.23; H, 10.89.

A mixed melting point determination between this compound and authentic 11a-aza-C-homotigogenin[5a] showed a 15° depression.

Prednisolone BMD.—Prednisone BMD[8] (2 g.) dissolved in anhydrous tetrahydofuran (300 cc.) was reduced with lithium tri-*t*-butoxyaluminum hydride[9] (4 g.) at room temperature for 24 hr. It was then poured into a dilute solution of acetic acid and the precipitate was filtered, washed, and dried. In this way pure material (0.75 g.) with m.p. 268–275° was obtained. Extraction of the filtrate with ethyl acetate, washing to neutrality, evaporation of the solvent, and crystallization of the residue from ethyl acetate gave additional material (0.62 g.) with m.p. 265–271°, thereby increasing the total yield to 68.5%. An analytical sample prepared by recrystallization from ethyl acetate showed m.p. 278–279°, $[\alpha]_D$ −29.5° (lit.,[8] m.p. 270–274°, $[\alpha]_D$ −20°), λ_{max} 242–244 mμ, log ε 4.11, ν_{max} 3500, 1660, 1625, 1610 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{33}O_6$: C, 68.63; H, 7.51; O, 23.86. Found: C, 68.62; H, 7.43; O, 23.54.

Pregn-4-ene-3,17α,21-triol-11,20-dione BMD Acetate (IIIa).—Prednisone BMD (17 g.) dissolved in tetrahydrofuran (850 cc.) and methanol (425 cc.) was reduced with sodium borohydride (20 g.) by adding this reagent dissolved in water (100 cc.) to a cooled solution of the steroid. The mixture was maintained for 20 min. at 0 to 5° and then allowed to attain room temperature slowly. After 6 hr. the reaction mixture was left in the ice box (10°) for 5 days. It was then neutralized with acetic acid and water was added. The precipitate formed was collected by filtration, washed, and dried, and the filtrate was extracted with ethyl acetate. The crude product (17 g.) was amorphous with m.p. 105–112° and showed no significant ultraviolet absorption nor infrared carbonyl bands. This material was acetylated by warming on the steam bath for 1 hr. with acetic anhydride (60 cc.) and pyridine (50 cc.) and, after addition of water, the amorphous acetate was isolated by extraction with ethyl acetate. This crude acetate (16 g.) was dissolved in acetone (500 cc.) and oxidized with Jones' reagent[13] at 5°. Water was then added and the material extracted with ethyl acetate which was then washed to neutrality, dried, and evaporated. The residue (16 g.) was chromatographed over neutral alumina. Elution with hexane–benzene (7:3) and crystallization from ether gave crystals (.7 g.) with m.p. 189–194° (IIIa). An analytical sample was prepared by recrystallization from ether–hexane, m.p. 199–201°, $[\alpha]_D$ −39°, ν_{max} 1750, 1710, 1250 cm.$^{-1}$.

Anal. Calcd. for $C_{25}H_{34}O_7$: C, 67.24; H, 7.67. Found: C, 66.81; H, 7.77.

The over-all yield obtained through this sequence of reactions was 21%. In different experiments in which the reduction was carried out at room temperature for 20 hr., the yields were from 17 to 24%. In other experiments with even milder reducing conditions (shorter reaction period or lower temperature) preferential reduction of the 11-ketone grouping took place as evidenced by the isolation of the insoluble prednisolone BMD.

Pregna-3,5-diene-17α,21-diol-11,20-dione-BMD 3-Acetate 11-Oxime (IVa).—This compound was obtained in an attempt to prepare the 11-oxime of pregn-4-ene-3,17α,21-triol-11,20-dione-BMD 3-acetate by refluxing the ketone (IIIa) (1.8 g.) dissolved in aqueous pyridine (125 cc.) with hydroxylamine hydrochloride (5 g.) for 36 hr. After this heating period, the solution was cooled, dilute hydrochloric acid was added and the material was extracted with ethyl acetate. Upon washing with dilute hydrochloric acid and water, the solution was dried and evaporated and the residue was chromatographed on washed alumina. The material, eluted with hexane–benzene (1:1) and with benzene (600 mg.) had m.p. 190–196° and was recrystallized from ether–hexane to give IVa as silky needles (300 mg.) with m.p. 194–196°, $[\alpha]_D$ −127°, λ_{max} 228, 234 mμ, log ε 4.13, 4.15, ν_{max} 3500 cm.$^{-1}$, no carbonyl bands.

Anal. Calcd. for $C_{23}H_{31}NO_5$: C, 68.80; H, 7.78; N, 3.49; O, 19.93. Found: C, 68.96; H, 7.83; N, 3.67; O, 20.18.

From the chromatogram of the free oxime IVa, another more polar compound was isolated by elution with benzene–ether and crystallization from ether–hexane. Only a few milligrams of this material was obtained and to it we have assigned the structure IIIb. It had m.p. 233–236°, $[\alpha]_D$ +8°, ν_{max} 3500, 1730, 1710, 1270 cm.$^{-1}$.

Anal. Calcd. for $C_{25}H_{33}NO_7$: C, 65.34; H, 7.24; N, 3.05; O, 24.37. Found: C, 65.52; H, 7.44; N, 2.99; O, 24.37.

The Reaction of Formaldehyde with Reichstein Compound D, 5α-Pregnane-3β-17α,21-triol-11,20-dione.—Free Compound D[12] (17.8 g.) dissolved in chloroform (1800 cc.) was stirred at room temperature with formaldehyde solution (450 cc., 40%) and concentrated hydrochloric acid (450 cc.) for 66 hr. The chloroform layer was separated, the aqueous upper layer was extracted several times with chloroform, and the combined chloroform solutions were washed to neutrality with sodium bicarbonate and water, dried and the solvent distilled. The residue was partially crystalline, m.p. 232–235°, and after crystallization from methylene chloride–methanol had m.p. 264–267°. The total material was chromatographed on neutral alumina (500 g.) whereby two compounds were isolated. The less polar compound, whose structure remains unknown (10.5 g., m.p. 130–140°) was eluted with hexane–benzene (4:1) and crystallized

from ether–hexane. An analytical sample had m.p. 163–165°, $[\alpha]_D$ −53° and ν_{max} 1700 cm.$^{-1}$.

Anal. Found: C, 66.16, 66.21; H, 8.77, 8.58; O, 25.11. Rast mol. wt., 405.

The more polar material, VI (2.35 g., m.p. 275–285°), was eluted with hexane–benzene (1:4) and with pure benzene; it crystallized from methylene chloride–acetone as a powder with m.p. 327–330°, $[\alpha]_D$ −50.4° and ν_{max} 1715 cm.$^{-1}$.

Anal. Calcd. for $C_{47}H_{68}O_{12}$: C, 68.42; H, 8.31; O, 23.27. Found: C, 68.03; H, 8.30; O, 23.30.

5α-Pregnane-3β,17α,21-triol-11,20-dione Bismethylenedioxy Derivative (VIIa). A.—Acid hydrolysis of the bis steroid VI (0.6 g.) effected by boiling with 80% aqueous acetic acid (60 cc.) during 0.5 hr. followed by precipitation with water gave a crystalline crude product (0.5 g., m.p. 180–185°). This material was collected by filtration, washed with water to neutrality, dried, and recrystallized from acetone. The pure compound was thus obtained as needles with m.p. 222–224°. This material was found to be identical by infrared and mixed melting point comparisons with the compound obtained by acid hydrolysis of the above described unknown compound with m.p. 163–165° (vide infra). The acetate VIIb was prepared by warming the free compound with acetic anhydride–pyridine for 1 hr. on the steam bath. Precipitation with water, filtration, washing, and drying furnished the crude acetate (m.p. 189–195°) which was purified by two crystallizations from ether–hexane, m.p. 204–206°, $[\alpha]_D$ −60.3°, ν_{max} 1740, 1720, 1250 cm.$^{-1}$.

Anal. Calcd. for $C_{25}H_{36}O_7$: C, 66.94; H, 8.09; O, 24.97. Found: C, 66.82; H, 8.17; O, 25.21.

B.—Hydrolysis of the unknown compound (1 g.) m.p. 163–165° described above was achieved by heating with 80% aqueous acetic acid (100 cc.) during 0.5 hr. Following isolation by water precipitation, collection by filtration, washing and drying, there was obtained 0.9 g. of crude material with m.p. 222–224°, $[\alpha]_D$ −58.3°, ν_{max} 3400, 1720 cm.$^{-1}$.

Anal. Calcd. for $C_{29}H_{34}O_6$: C, 67.95; H, 8.43; O, 23.62. Found: C, 67.52; H, 8.73; O, 23.74.

5α-Pregnane-3β,17α,21-triol-11,20-dione-BMD 3-Acetate 11-Oxime (VIIc).—A mixture of 5α-pregnane-3β,17α,-21-triol-11,20-dione-BMD 3-acetate (VIIb) (3 g.), pyridine (150 cc.), water (10 cc.), and hydroxylamine hydrochloride (3 g.) was heated under reflux for 48 hr. Cooling, precipitation with water, and filtration gave a solid (2.4 g.) with m.p. 102–105°. Extraction of the filtrate with ethyl acetate increased (0.3 g.) the recovery very slightly. The total material was chromatographed on neutral alumina (200 g.), whereupon four compounds were isolated: 1) pure starting material (0.46 g.) eluted with hexane–benzene (9:1) and crystallized from ether–hexane, m.p. 200–203°, $[\alpha]_D$ −64.6°, identified by infrared and mixed melting point comparisons. 2) The **oxime 3-acetate, VIIc** (0.47 g.), with m.p. 195–197° which was eluted with hexane–benzene (7:3) and pure benzene and crystallized from ether–hexane. The analytical sample had m.p. 200–202°, $[\alpha]_D$ −26.5°, ν_{max} 3600, 1740, 1650, 1250 cm.$^{-1}$.

Anal. Calcd. for $C_{25}H_{37}NO_7$: C, 64.77; H, 8.05; N, 3.02; O, 24.16. Found: C, 64.88; H, 8.39; N, 2.99; O, 24.38.

3) Elution with benzene–ether (1:4) gave 5α-pregnane-3β,17α,21-triol-11,20-dione-BMD (50 mg.) identified by mixed melting point and infrared spectrum.

4) The most polar compound isolated by elution with benzene–ether (1:4) and pure ether (110 mg.) was **5α-pregnane-3β,17α,21-triol-11,20-dione-BMD oxime (VIId)**, m.p. 260–265°. Crystallization from acetone gave the pure compound with m.p. 288–290°, $[\alpha]_D$ −28.15°, ν_{max} 3550 cm.$^{-1}$.

Anal. Calcd. for $C_{25}H_{35}NO_6$: C, 65.53; H, 8.37; N, 3.32; O, 22.78. Found: C, 65.62; H, 8.39; N, 3.47; O, 22.80.

In experiments with longer heating periods (50–100 hr.) the yields of this free oxime progressively increased (up to 50%) and the yields of acetate oxime VIIc correspondingly diminished. No unchanged ketonic material was isolated from these experiments.

9a-Aza-C-homo-5α-pregnane-3β,17α,21-triol-11,20-dione-BMD 3-Acetate (VIIIa).—Beckmann rearrangement of 5α-pregnane-3β,17α,21-triol-11,20-dione-BMD 3-acetate 11-oxime (VIIc) was effected by addition of phosphorus oxychloride (2 cc.) to a solution of the steroid (14.9 g.) in anhydrous pyridine (125 cc.) at 0°. After 2 hr. at room temperature the mixture was poured into water, acidified with dilute hydrochloric acid, and extracted with ethyl acetate. The organic solution was washed with dilute hydrochloric acid, sodium bicarbonate, and water, dried, and the solvent removed. Direct crystallization of the residue from acetone gave material with m.p. 320–324° (1.2 g.). The remaining semicrystalline material (9.6 g.) was however chromatographed on washed alumina (350 g.). The material (3.6 g.) eluted with hexane–benzene (3:2), was crystallized from ether–hexane, m.p. 200–203°, and identified by infrared and mixed melting point as unchanged oxime acetate VIIc (24%). Elution with ether furnished the crude **Beckmann rearrangement product VIIIa** (2.4 g.) with m.p. 260–265°. Rechromatography on neutral alumina employing elution with ethyl acetate and recrystallization from chloroform–ethyl acetate or acetone–ether gave the pure sample as needles with m.p. 338–341°, $[\alpha]_D$ −71.1°, ν_{max} 1730, 1660, 1250 cm.$^{-1}$, yield 24%.

Anal. Calcd. for $C_{25}H_{37}NO_7$: C, 64.77; H, 8.05; N, 3.02; O, 24.16. Found: C, 64.55; H, 8.04; N, 3.16; O, 24.26.

9a-Aza-C-homo-5α-pregnane-3β,17α,21-triol-11,20-dione-BMD (VIIIb).—Hydrolysis of 9a-aza-C-homo-5α-pregnane-3β,17α,21-triol-11,20-dione-BMD 3-acetate (VIIIa) was effected by refluxing the steroid acetate (1.8 g.) in 1% methanolic potassium hydroxide (50 cc.) for 30 min. Precipitation with water and extraction with ethyl acetate gave the crude compound (1.5 g.) with m.p. 277–280°. An analytical sample was prepared by recrystallization from acetone: needles, m.p. 282–283°, $[\alpha]_D$ −88.9°, ν_{max} 3500, 1660 cm.$^{-1}$.

Anal. Calcd. for $C_{25}H_{35}NO_6$: C, 65.53; H, 8.37; N, 3.32; O, 22.78. Found: C, 65.80; H, 8.47; N, 3.40; O, 22.72.

9a-Aza-C-homo-5α-pregnane-17α,21-diol-3,11,20-trione-BMD (VIIIc).—This compound was obtained by oxidation of the corresponding 3-alcohol (VIIIb) (1.3 g.) in acetone (50 cc.) with chromic acid by Jones' method.[13] Isolation by extraction with ethyl acetate gave a crude product (0.85 g.) with m.p. 315–324°. This material gave a negative test for α ketol groupings with triphenyltetrazolium chloride. Crystallization from ethyl acetate–ether provided an analytical sample with m.p. 321–324°, $[\alpha]_D$ −64.5°, ν_{max} 3450, 1710, 1660 cm.$^{-1}$.

Anal. Calcd. for $C_{25}H_{33}NO_6$: C, 65.85; H, 7.93; N, 3.34; O, 22.88. Found: C, 65.67; H, 8.04; N, 3.19; O, 23,10.

9a-Aza-C-homo-5α-pregnane-17α,21-diol-3,11,20-trione 21-Acetate (IX).—Cleavage of the 17α,20,20-21-bismethylenedioxy protecting group in 9a-aza-C-homo-5α-pregnane-17α,21-diol 3,11,20-trione-BMD (VIIIc) was effected by warming a solution of the steroid (10 g.) in 60% formic acid on the steam bath for 2 hr. under a nitrogen atmosphere. The solution was then kept at room temperature for 65 hr. The formic acid was removed under vacuum, whereafter the residue was extracted with ethyl acetate and the extract washed to neutrality and evaporated. Acetylation of the residue at room temperature with acetic anhydride–pyridine followed by the usual isolation procedure employing extraction with ethyl acetate gave an amorphous product which was chromatographed on silica gel (300 g.). By elution with methylene chloride–acetone (2:1) crystalline material was obtained (3.5 g.) with m.p. 265–270° which was further purified by recrystallization from ethyl acetate (needles) or from acetone (plates). The analytical specimen (IX) had m.p. 268–270°, $[\alpha]_D$ +27.8°, ν_{max} 3550, 1750, 1730, 1660, 1240 cm.$^{-1}$; it gave a positive α-ketol test with triphenyltetrazolium chloride.

Anal. Calcd. for $C_{23}H_{33}NO_6$: C, 65.85; H, 7.93; N, 3.34; O, 22.88. Found: C, 66.05; H, 7.62; N, 3.45; O, 22.78.

Pregna-3,5-diene-17α,21-diol-11,20-dione 21-Acetate (V).—Hydrolysis of the 17α,20,20,21-bismethylenedioxy group and elimination of the 3-acetate from 4-pregnene-3,17α,21-triol-11,20-dione 3-acetate (IIIa) (0.5 g.) was effected by heating with 50% aqueous acetic acid (100 cc.) on the steam bath under a nitrogen atmosphere for 24 hr. After removal of the acid under vacuum and extraction with ethyl acetate, the solution was washed to neutrality and evaporated. The residue was acetylated at room temperature with acetic anhydride and pyridine for 20 hr. Isolation of the crude acetate by extraction with ethyl acetate and chromatography on silica gel (30 g.) furnished two compounds: a) **Pregna-3,5-diene-17α,21-diol-11,20-dione-BMD, IVb** (50 mg., m.p. 150–160°) eluted with benzene–hexane (9:1) and crystallized from ether–hexane to yield needles with m.p. 170–172°, $[\alpha]_D$ −164°, λ_{max} 228, 234 mμ, log ε 4.25, 4.27, and ν_{max} 1710 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{30}O_5$: C, 71.48; H, 7.82. Found: C, 71.44; H, 7.76.

b) **Pregna-3,5-diene-17α,21-diol-11,20-dione 21-Acetate (V)** was isolated by elution with benzene–ether (30 mg.). It had m.p. 154–156°, raised to 173–175° by one additional crystallization, and $[\alpha]_D$ +26°, λ_{max} 228, 234, 290–292 mμ, log ε 4.27, 4.28, 2.13, ν_{max} 3500, 1720, 1260 cm.$^{-1}$. This compound gave a positive α-ketol reaction with triphenyltetrazolium chloride.

Anal. Calcd. for $C_{23}H_{30}O_5$: C, 71.48; H, 7.82; O, 20.70. Found: C, 71.15; H, 7.92; O, 21.06.

The Cleavage Reaction of 16-Oximino-17-keto Steroids[1]

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16-Oximinoandrostane-3β-ol-17-one (Ib) and its 5,6-dehydro analog Ia form oxime acetates, the structures, reactions, and spectral characteristics of which have been determined. Cleavage of the oxime acetates was found to be extremely facile, aqueous solvents giving nitrile acids, anhydrous alcohols yielding nitrile esters. The structure of the products was proved by independent synthesis and chemical conversions. Interpretation of the results to reconcile previously reported data is given. Spectral properties of the oxime acetates are discussed.

Kendall and co-workers[2] and later Regan and Hayes[3] found that the acylation of 16-oximino-5-androstene-3β-ol-17-one (Ia) with acetic anhydride gave a product which was assigned the structure 3β - acetoxy - 16 - oximino - 5 - androstene - 17-one (IIa) on the basis of elemental analysis and conversion with thionyl chloride, conditions for a Beckmann transformation, to a ring D imide XVIa. Recently Heard, Ryan, and Bolker,[4] evidently unaware of the previous work,[2,3] reported that acylation of 16-oximinoandrostane-3β-ol-17-one (Ib), the 5,6-dihydro derivative of Ia, gave a diacetate which was assigned the structure of the Beckmann rearrangement intermediate XVb.[5] This assignment was based[4] on the hypsochromic shift in the ultraviolet absorption maximum on the conversion of the oxime Ib to the acetate XVb, and on the reaction of XVb with base to form a compound, soluble in sodium carbonate, and believed to be the imide XVIb.

In the course of related studies the acylation of 16-oximino-5-androstene-3β-ol-17-one (Ia) was attempted in this laboratory and gave two products A and B which corresponded in analyses to a monoacetate (B) and a diacetate (A). Compound B was identical[6] with the material isolated by Kendall[2] and Regan[3]; compound A was very unstable and was converted readily into compound B by aqueous acid or base, on recrystallization from aqueous solvents or even on standing in air. This explains the failure of these authors[2,3] to isolate A. Compound A was shown to be analogous to the diacetate obtained from Ib by Heard[4] (*vide infra*).

The incorrectness of the assignment of structure IIa to compound B was immediately obvious from the infrared spectrum which showed absorption bands at 2250 cm.$^{-1}$, characteristic of a nitrile group, and at 2600–2700 cm.$^{-1}$ and 1700 cm.$^{-1}$ indicative of a carboxy group. These results and the chemical properties of the material, namely formation of a methyl ester and solubility in aqueous sodium carbonate, suggested the structures VIa or Xa for compound B.

The direct cleavage[7] of Ia or IIIa would be expected to lead to VIa with a primary nitrile function; however, the resistance of the nitrile function of B to hydrolysis required the consideration of structure Xa with a tertiary nitrile.[8] Thus,

(1) Presented in part before the Division of Organic Chemistry at the 138th Meeting of the American Chemical Society, New York, N. Y., September, 1960.

(2) F. H. Stodola, E. C. Kendall, and B. F. McKenzie, *J. Org. Chem.*, **6**, 843 (1941).

(3) B. M. Regan and F. N. Hayes, *J. Am. Chem. Soc.*, **78**, 639 (1956).

(4) R. D. Heard, M. T. Ryan, and H. I. Bolker, *J. Org. Chem.*, **24**, 172 (1959).

(5) These results have subsequently been quoted as evidence for the isolation of a Beckmann rearrangement intermediate, *cf.*, A. R. Surrey, "Name Reactions in Organic Chemistry," 2nd ed., Academic Press, New York, 1961, p. 15.

(6) We are indebted to Dr. Regan for samples of Ia and its acetate used for comparison of melting points and infrared spectra with our materials.

(7) Such reactions have been referred to as "second-order Beckmann rearrangement" (*cf.*, ref. 12, 13), but we feel a more appropriate term is "cleavage of oximes."

(8) Mechanistically it is possible to conceive of a path leading from IIIa to Xa *via* intermediates of type XVa.