Tetrahedron, 1965, Vol. 21, pp. 743 to 757. Pergamon Press Ltd. Printed in Northern Ireland

THE PHOTOCHEMICAL REARRANGEMENT OF STEROIDAL 17-NITRITES[1]

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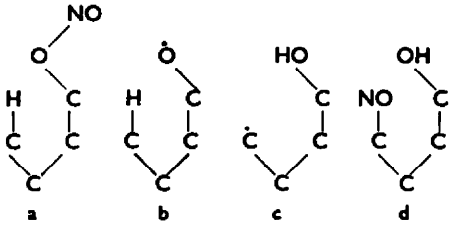
(*Received* 11 *November* 1964)

Abstract—The photolysis, in solution, of steroidal 17-nitrite esters gives rise to the 17a-aza-D-homo-17a-ol 17-one system. This hydroxamic acid grouping is considered to arise *via* carbon-carbon fission of an intermediary alkoxy radical. The isolation, from one and the same photolysis mixture, of two isomeric hydroxamic acids shown to be epimeric at C-13 supports the proposal of ring fission between C-13 and C-17.

THE first communications[4,5] describing the synthetic use of nitrite photolysis involved situations wherein a 6-membered ring transition state for hydrogen abstraction was possible (see below, a → d). In subsequent studies with a variety of systems[6] it has been noted that such a transition state is greatly preferred.



[1] A portion of this work has been the subject of a preliminary communication: C. H. Robinson, O. Gnoj, A. Mitchell, R. Wayne, E. Townley, P. Kabasakalian, E. P. Oliveto and D. H. R. Barton, *J. Amer. Chem. Soc.* **83**, 1771 (1961).

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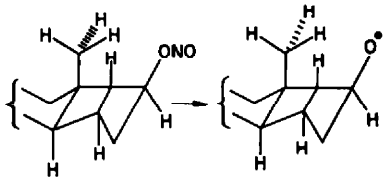
[4] D. H. R. Barton, J. M. Beaton, L. E. Geller and M. M. Pechet, *J. Amer. Chem. Soc.* **82**, 2640 (1960).

[5] D. H. R. Barton and J. M. Beaton, *J. Amer. Chem. Soc.* **82**, 2641 (1960).

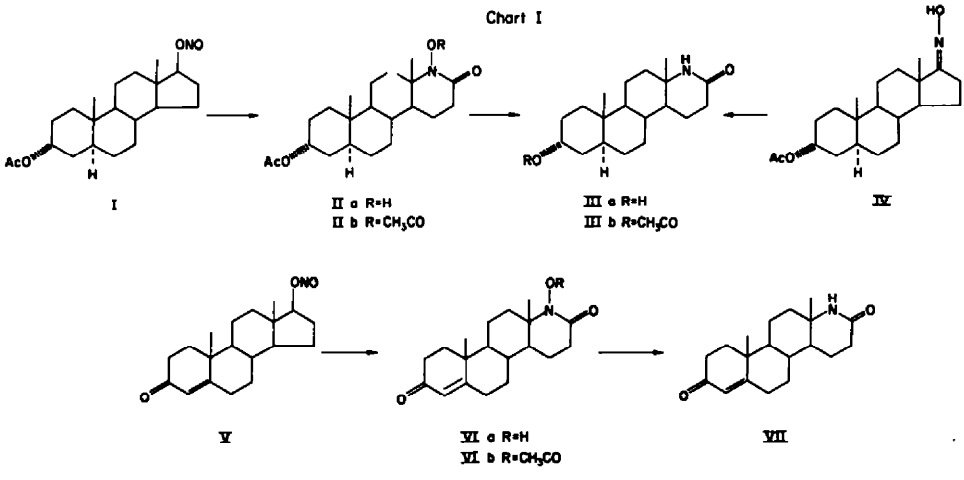
[6] For a review see A. L. Nussbaum and C. H. Robinson, *Tetrahedron* **17**, 35 (1962).

It seemed of interest then to study the steroidal 17-nitrite system, which offered the possibility of a 5- (rather than 6-) membered transition state and which also involved the generation of an alkoxy radical attached to the highly strained D-ring:



As a model series, the preparation and photolysis of 5α-androstane-3α,17β-diol 3-acetate 17-nitrite (I) [Chart I] were accordingly undertaken. A convenient route from androsterone 3α-acetate to 5α-androstane-3α,17β-diol 3-acetate[7] consisted in reduction with sodium borohydride in aqueous dimethylformamide[8] at steam bath temperature. The 3α,17β-diol 3-monoacetate was then converted, using nitrosyl chloride in pyridine, to the 17-nitrite (I) which was irradiated, at 18° in benzene solution under nitrogen, by a 200-watt Hanovia mercury lamp, with pyrex filter. From the resulting mixture a crystalline product could be isolated, in about 20% yield,[9] by direct crystallization. This product IIa gave an instantaneous purple colour with ferric

Chart I



chloride solution, showed the correct analysis for an isomer of the nitrite (Ia) and had IR absorptions (Nujol) at 3·28 (strongly bonded hydroxyl) and 6·12 μ (amide carbonyl) as well as the absorptions due to the 3-acetoxy group (5·77 and 7·92 μ)..

[7] K. Miescher, H. Kagi, C. Scholz, A. Wettstein and E. Tschopp, *Biochem. Z.* **294**, 39 (1937).

[8] D. Taub, R. D. Hoffsommer and N. L. Wendler, *J. Amer. Chem. Soc.* **81**, 3291 (1959).

[9] The other major products were shown by paper chromatography to be 5α-androstane-3α,17β-diol 3-acetate and 5α-androstane-3α-ol-17-one 3-acetate.

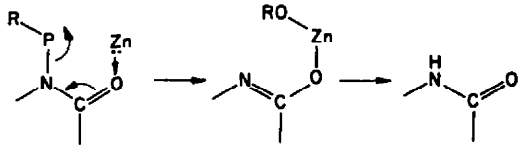
Acetylation of the product (IIa), using pyridine–acetic anhydride at room temperature, produced a new hydroxyl-free compound (IIb) showing a new carbonyl band at 5·58 μ, while the amide carbonyl absorption had shifted to lower wavelength (5·90 μ). This compound had the composition expected for a mono-acetylated derivative of IIa.

The properties outlined above are consistent with those of hydroxamic acids.[10–13] Moreover, it has been pointed out[13] that, while the carbonyl absorptions of cyclic hydroxamic acids are known to appear at higher wavelengths than the corresponding lactam carbonyl absorptions, this shift seems greater for 6-membered than for 5-membered rings, possibly due to the relative effectiveness of intramolecular hydrogen bonding in the two systems. The values recorded (1623 and 1630 cm^{-1}) for the C=O absorptions of six-membered ring hydroxamic acids are very close to that observed (6·12 μ; 1634 cm^{-1}) in the case of our product IIa.

The structure of IIa was then confirmed as follows: reduction of IIa with zinc and acetic acid under reflux gave the known lactam (IIIb), identical in all respects with an authentic sample[14] prepared by Beckmann rearrangement of the 17-oxime (IV). In addition, reduction of the hydroxamic acid (IIa) with 95% hydrazine in boiling ethylene glycol[15] gave the 3α-hydroxy lactam (IIIa), also derived from the authentic 3-acetoxy lactam (IIIb) by hydrolysis with base. These facts, then left no doubt that IIa was indeed 17a-aza-D-homo-5α-androstane-3α,17a-diol-17-one-3-acetate.

Similarly, testosterone 17-nitrite (V) was photolysed as for 1 and the resulting hydroxamic acid (VIa) was isolated by direct crystallization. The presence in the crude photolysis product of testosterone and of Δ^4-androstene-3,17-dione was demonstrated by paper chromatography. Reduction of the hydroxamic acid (LXII) with zinc and acetic acid resulted in the known[16] lactam (VII).

The zinc–acetic reduction of the hydroxamic acid system, by analogy with the reduction of α-ketol systems,[17] may be plausibly rationalized as shown:



[10] D. E. Ames and T. F. Grey, *J. Chem. Soc.* 631 (1955).

[11] R. Bonnett, R. F. C. Brown, V. M. Clark, I. O. Sutherland and Sir Alexander Todd, *J. Chem. Soc.* 2094 (1959).

[12] J. A. Moore and J. Binkert, *J. Amer. Chem. Soc.* **81**, 6029 (1959).

[13] J. T. Edward and P. F. Morand, *Canad. J. Chem.* **38**, 1316 (1960) and Refs. cited therein.

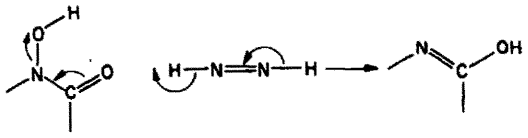
[14] Cf. B. M. Regan and F. N. Hayes, *J. Amer. Chem. Soc.* **78**, 639 (1956).

[15] This represents a convenient modification of the procedure (hydrazine-methanol in a sealed tube) employed by D. W. C. Ramsay and F. S. Spring, *J. Chem. Soc.* 3409 (1950), for reduction of a hydroxamic acid.

[16] S. Kaufmann, *J. Amer. Chem. Soc.* **73**, 1779 (1951). We thank Dr. B. M. Regan for kindly supplying an authentic specimen of the lactam VII for comparison purposes.

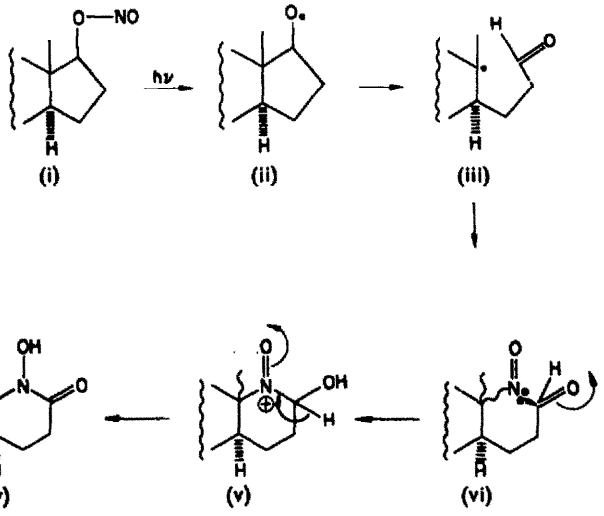
[17] Cf. R. S. Rosenfield and T. F. Gallagher, *J. Amer. Chem. Soc.* **77**, 4367 (1955) and Refs. cited therein.

The hydrazine reduction presumably involves the intervention of diimide,[18] a possible process being illustrated below:



With the structures of the photolysis products well secured, we now turn to the nature of the rearrangement reaction itself. It must be noted, first of all, that the formation of a hydroxamic acid from the 17-nitrite owes nothing to thermal rearrangement. This was shown by *pyrolysis* of steroidal 17-nitrite esters, which generated 17-ketone and 17-alcohol, but no detectable amounts of hydroxamic acid or other nitrogen containing product.

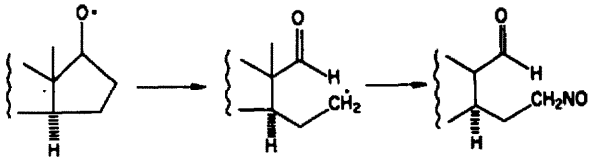
We have already suggested[1] a pathway for the photochemical rearrangement, and this is shown below (i–vi):



Thus, homolysis of the O—NO bond in (i) to give the alkoxy radical (ii) is followed by C–C fission between C-13 and C-17 yielding the tertiary radical (iii). The latter combines with NO, giving the tertiary nitroso compound (iv) which cyclizes and generates the observed product (vi).

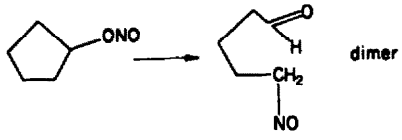
An alternative fragmentation path for the initial alkoxy radical (ii) would involve C–C fission between C-16 and C-17, leading to the nitroso compound (ii → viii; below) and thence to the oxime.

[18] E. van Tamelen, R. Dewey and R. Timmons, *J. Amer. Chem. Soc.* **83**, 3725, 3729 (1961); E. J. Corey, W. Mock and D. Pasto, *Tetrahedron Letters* 347 (1961); S. Hunig, H. Muller and W. Thier, *Ibid.* 353 (1961).



(ii) (vii) (viii)

Indeed it has been shown[19] that cyclopentyl nitrite (ix) suffers ring cleavage on photolysis, furnishing the nitrosoaldehyde (x) and the corresponding oxime.



(ix) (x)

Such products have not been isolated in our work with steroidal nitrites; we attribute this to the highly favoured nature of carbon–carbon cleavage leading to a tertiary rather than to a primary carbon radical. In our cases, the resulting C-13 tertiary nitroso intermediates cannot of course rearrange to oxime, nor presumably can they dimerize for steric reasons. Hence the cyclisation path is possible.

The capture of NO by the tertiary radical could, in principle, lead to loss of stereochemistry at C-13 and we have obtained evidence of such equilibration (*vide infra*).

The reaction of nitroso compounds and aldehydes to give hydroxamic acids has some precedent.[20,21] The cyclization of our postulated nitroso aldehyde intermediate to give a hydroxamic acid can be viewed *a priori* as either a dark or photochemically activated reaction. Recent work[22] suggests that the postulated nitroso-aldehyde cyclization in the nitrite photolysis reaction is likely to be a light-induced process.

Returning now to the studies with steroidal 17-nitrites: it will be recalled that the rearrangement mechanism requires cleavage between C-13 and C-17, with the consequent possibility of equilibration at C-13. We had observed, however, in the two cases mentioned earlier, that the isolated photolysis products (IIa and VIa) retained the 13β-configuration, although 13α-products were undoubtedly also formed.

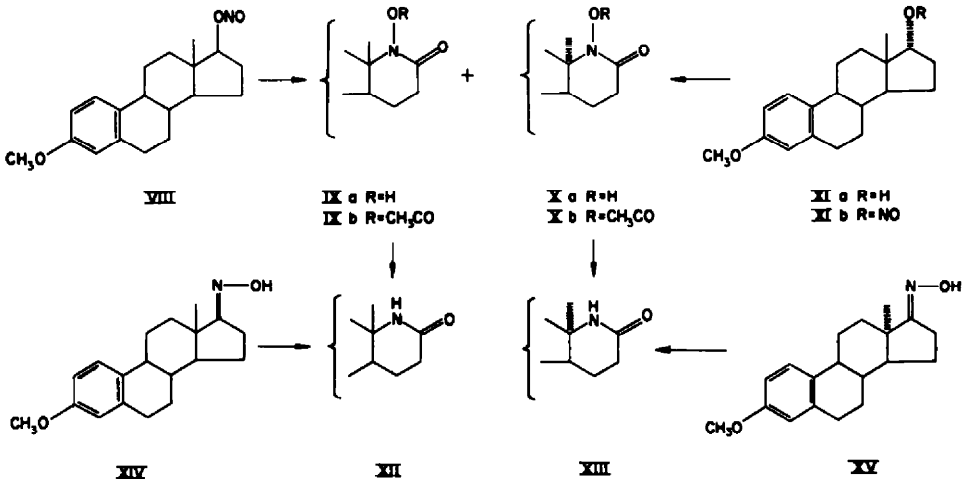
Indeed, when we turned to the photolysis of estradiol 3-methyl ether 17β-nitrite (VIII; Chart II), *two* isomeric hydroxamic acids (IXa and Xa) were isolated by crystallization. These products were characterized as the N-acetoxy compounds (IXb and Xb), and were reduced to the lactams (XII and XIII respectively) using the hydrazine–ethylene glycol procedure. The lactam XII was identical with the known[14]

[19] P. Kabasakalian and E. R. Townley, *J. Org. Chem.* **27**, 2918 (1962).
[20] E. Bamberger and F. Tschirner, *Ber. Dtsch. Chem. Ges.* **32**, 1882 (1899);
[21] J. A. Moore and D. H. Ahlstrom, *J. Org. Chem.* **26**, 5254 (1961).
[22] P. Kabasakalian and E. R. Townley, *J. Org. Chem.* **27**, 3562 (1962).

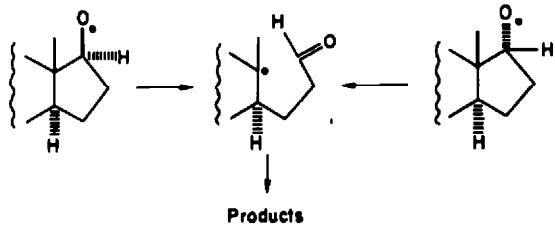
compound, prepared by Beckmann rearrangement of the 17-oxime (XIV). The isomeric lactam (XIII) was shown to possess the 13α-configuration in the following way: 13α-estrone 3-methyl ether[23] was converted to the 17-oxime (XV), which was then subjected to the Beckmann rearrangement, giving a lactam which proved identical with the lactam (XIII).

Having thus demonstrated loss of stereochemistry at C-13 during the nitrite photolysis reaction, we obtained additional evidence for the proposed pathway by photolysing 17-*epi*estradiol 3-methyl ether 17α-nitrite (XIb). The same two hydroxamic

Chart II



acids (IXa and Xa) were isolated from the reaction mixture in approximately the same proportions as those seen for the 17β-nitrite photolysis. These experiments, then, provide compelling evidence for the initial steps proposed earlier:



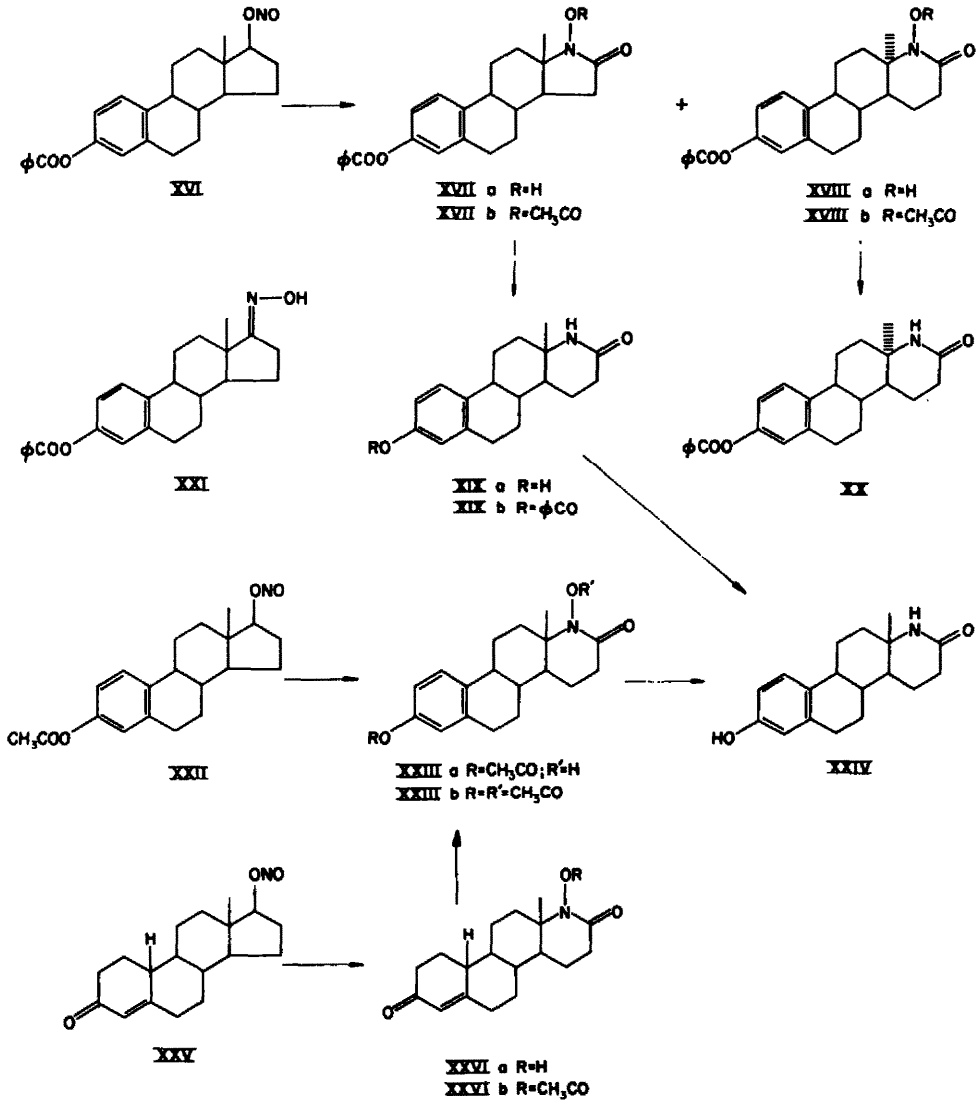
They are also of interest in view of the interesting observation[24] of epimerization at the carbon bearing nitrite during photolysis of α-caryophyllene alcohol nitrite ester.

In complete accord with the results obtained with estradiol 3-methyl ether 17-nitrite (VIII), we observed that estradiol 3-benzoate-17-nitrite (XVI; chart III) gave rise to two isomeric hydroxamic acids (XVIIa and XVIIIa). The structure of XVIIa was secured by reduction to the known[14] lactam (XIXb), thus confirming the configuration at C-13 as β. The isomeric product (XVIIIa) was reduced to the lactam (XX), to

[23] A. Butenandt, A. Wolff and P. Karlson, *Ber. Dtsch. Chem. Ges.* **74B**, 1308 (1941).
[24] A. Nickon, J. R. Mahajan and F. J. McGuire, *J. Org. Chem.* **26**, 3617 (1961).

which was assigned the 13α-configuration by analogy with our previous observations and on the basis of $[M]_D$ comparisons. The $\Delta[M]_D$ value for compound IXa minus compound Xa (Chart II), i.e. $\Delta[M]_D$ (13β–13α), is +252°. The $\Delta[M]_D$ for XVIIa–XVIIIa (Chart III) is +263°.

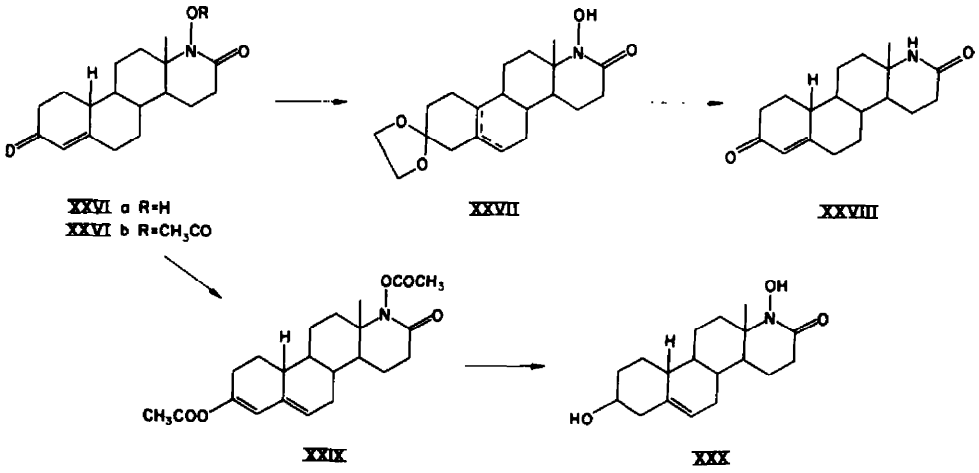
Chart III



However, when estradiol 3-acetate 17β-nitrite (XXII; chart III) was irradiated, we could isolate only one hydroxamic acid (XXIIIa), of the 13β-series as shown by reduction to the known[14] lactam (XXIV).

Finally, as part of a biological screening study, we prepared the hydroxamic acid XXVIa (Chart III) from 19-nortestosterone 17-nitrite, and XXVIa was shown to be

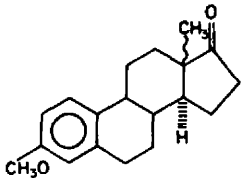
Chart IV



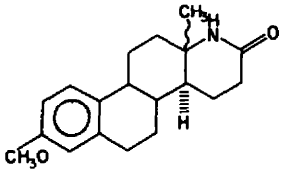
XXVI a R=H
XXVI b R=CH_3CO

XXVII XXVIII XXIX XXX

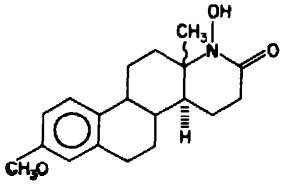
18-Methyl resonance



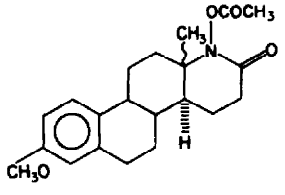
13α	1·05
13β	0·89



13α	1·33
13β	1·19



13α	1·44
13β	1·28



13α	1·41
13β	1·24

of the 13β-series by dehydrogenation (with *C. simplex*[25]) to the estratriene derivative (XXIIIa) of known configuration.

By the sequences shown in Chart IV, the 19-nor derivative (XXVIa) was converted to the lactam (XXVIII), and to the Δ^5-3β-hydroxy compound (XXX) using standard procedures.

In conclusion, we note that the NMR spectra of the pairs of C-13 epimers shown below provide a consistent picture, with the C-18 methyl resonance in the 13α-series shifted downfield relative to the 13β-series in all cases by 0·14–0·17 ppm. (All spectra were run in $CDCl_3$, and all chemical shifts are given in parts per million (ppm) relative to internal tetramethylsilane.)

EXPERIMENTAL

M.ps were taken on the Kofler block. Rotations were measured at 25° in dioxan solution at about 1% concentration, UV spectra were measured in MeOH solution, and IR data refer to Nujol mulls unless otherwise stated. We are indebted to the Physical Chemistry Department, Schering Corporation, for these measurements. Micro-analyses were performed by Mr. E. Conner, Micro-analytical Laboratory, Schering Corporation. We thank Dr. Leon Mandell, Emory University, for the NMR spectra.

5α-*Androstane*-3α,17β-*diol* 3α-*acetate*

To a solution of 5α-androstan-3α-ol-17-one 3α-acetate (2·32 g) in dimethylformamide (252 ml) was added a solution of $NaBH_4$ (1·59 g) in water (63 ml), and the solution was heated on the steam bath for 1 hr. The reaction mixture was then cooled, neutralized with acetic acid, diluted with water, and filtered. The solid residue was washed with water, dried and crystallized from MeOH aq giving the diol monoacetate (1·18 g), m.p. 170–183°. Prolonged drying at 60°, *in vacuo*, changed the m.p. to 180–183°. $[\alpha]_D$ +12° λ_{max}^{Nujol} 2·92, 5·86, 7·88 μ. (Lit.[7] m.p. 183–184°.)

5α-*Androstane* 3α,17β-*diol* 3α-*acetate* 17-*nitrite* (I)

To a stirred solution of the foregoing monoacetate (100 mg) in pyridine (5 ml) at −20° was added, dropwise, a saturated solution of nitrosyl chloride in pyridine until a permanent blue colour was obtained. The solution was stirred for 2 min more, and was then diluted with water, and filtered. The residue was washed with water and dried *in vacuo* at room temp. This material (95 mg) was essentially pure nitrite as judged by paper chromatography. The analytical sample was prepared by crystallization from ether–pentane which furnished 32 mg I, m.p. 177–180° dec, $[\alpha]_D$ −33°. λ_{max}^{Nujol} 5·76, 6·10, 6·25, 7·94 μ. (Found: C, 69·28; H, 9·23; N, 3·98. Calc. for $C_{21}H_{33}NO_4$: C, 69·39; H, 9·15; N, 3·85.)

17α-*Aza*-D-*homo*-5α-*androstane*-3α,17a-*diol*-17-*one* 3α-*acetate* (IIa)

A solution of the 17β-nitrite (I; 500 mg) in benzene (170 ml) was irradiated for 1 hr (at 18° under N_2) using a 200-watt Hanovia mercury lamp (pyrex filter). The solution was then evaporated *in vacuo*, and the residue was crystallized from ether–acetone to give the hydroxamic acid (IIa; 100 mg), m.p. 225–229°. (Instantaneous purple colour with $FeCl_3$aq).

The analytical sample (obtained by recrystallization from acetone–hexane) showed m.p. 229–233°, $[\alpha]_D$ −2°. λ_{max}^{Nujol} 3·28, 5·77, 6·12, 7·92 μ. (Found: C, 69·70; H, 9·17; N, 3·83. Calc. for $C_{21}H_{33}NO_4$: C, 69·39; H, 9·15; N, 3·85%.)

17α-*Aza*-D-*homo*-5α-*androstane*-3α,17α-*diol*-17-*one diacetate* (IIb)

Acetylation of the hydroxamic acid (IIa 90 mg) in pyridine–acetic anhydride (18 hr at room temp) gave the diacetate (IIb; 49 mg), m.p. 173–176° (from acetone–hexane), $[\alpha]_D$ +16°. λ_{max}^{Nujol} 5·58, 5·75, 5·90,

[25] Cf. H. L. Herzog, C. C. Payne, M. T. Hughes, M. J. Gentles, E. B. Hershberg, A. Nobile, W. Charney, C. Federbush, D. Sutter and P. L. Perlman, *Tetrahedron* **18**, 591 (1962).

8·05, 8·12 μ. (Found: C, 68·36; H, 8·73; N, 3·46. Calc. for $C_{22}H_{35}NO_5$: C, 68·12; H, 8·70; N, 3·45%.)

17a-Aza-D-homo-5α-androstan-3α-ol-17-one 3α-acetate (IIIb)

(a) *By Beckmann rearrangement of 17-oximino-3α-acetoxy 5α-androstane* (IV). To a stirred solution of the 17-oxime (IV; 1·0 g) in dioxan (35 ml) at 40° was added, dropwise over 5 min, thionyl chloride (1·0 ml). The reaction mixture was stirred at 40° for 10 min more, and 10% $NaHCO_3$aq was then added slowly to neutralize the mixture. The precipitated solid was filtered off, washed with water, dried *in vacuo* and then crystallized from acetone–hexane to give the lactam (IIIb 320 mg), m.p. 280–284°, $[\alpha]_D$ +18°. λ_{max}^{Nujol} 3·12, 3·24, 5·76, 5·96, 6·22, 7·95 μ. (Found: C, 72·31; H, 9·42; N, 4·21. Calc. for $C_{21}H_{33}NO_3$: C, 72·58; H, 9·57; N, 4·03%.)

(b) *By reduction of the hydroxamic acid* (IIa) *with zinc and acetic acid.* To a stirred solution of the hydroxamic acid (IIa; 50 mg) in glacial acetic acid (10 ml) was added Zn powder (250 mg), and the mixture was stirred, under reflux, for 4 hr. The hot reaction mixture was then filtered, the residue on the filter was washed with a little hot acetic acid, and the combined filtrate and washings were poured into iced water. The aqueous mixture was extracted with methylene chloride, and the organic extract was washed with 10% $NaHCO_3$aq (twice) and then with water. The dried (Na_2SO_4) extract was evaporated *in vacuo* to give an oily residue (45 mg) which crystallized on trituration with ether. The resulting solid was crystallized from acetone–ether to give the lactam IIIb, m.p. 282–284°, identical with authentic IIIb prepared as in (a) above as evidenced by mixed m.p., and IR comparison.

17a-Aza-D-homo-5α-androstan-3α-ol-17-one (IIIa)

(a) *By hydrolysis of the 3α-acetoxylactam* (IIIb). The 3α-acetoxylactam (IIIb; 100 mg) was dissolved in boiling 5% methanolic KOH (15 ml) and reflux was continued for 1 hr. The reaction mixture was then concentrated *in vacuo* and the residue was triturated with water, filtered, washed with water on the filter and dried, giving 75 mg crude IIIa. The analytical sample (from ethyl acetate–MeOH) had m.p. 341–346°, $[\alpha]_D$ +25° (MeOH). λ_{max}^{Nujol} 3·05, 3·22, 6·05 μ. (Found: C, 74·69; H, 10·07; N, 4·50. Calc. for $C_{19}H_{31}NO_2$: C, 74·71; H, 10·23; N, 4·59.)

(b) *By reduction of the hydroxamic acid* (IIa) *with hydrazine.* A solution of the hydroxamic acid (IIa; 100 mg) in ethylene glycol (10 ml) and 95% hydrazine (0·3 ml) was heated under reflux for 4 hr, and was then cooled and poured into aqueous 2 N HCl. The resulting mixture was extracted with methylene chloride, and the extract was washed with water, dried (Na_2SO_4) and evaporated *in vacuo*. The residue was crystallized from ethyl acetate–MeOH, giving the lactam (IIIa; 24 mg), m.p. 338–343°, undepressed on admixture with authentic IIIa prepared as in (a) above. The IR spectrum (Nujol) proved to be identical with the spectrum of authentic IIIa.

Δ⁴-Androsten-17β-ol-3-one 17-nitrite (*V*)

To a cooled (−20°) stirred solution of testosterone (8·35 g) in pyridine (120 ml) was added, dropwise, a saturated solution of nitrosyl chloride in pyridine until a permanent blue colouration resulted. The solution was then diluted with iced water and filtered. The residue was dried *in vacuo* at room temp. This material was homogeneous as judged by paper chromatography (one spot which gave positive diphenylamine reaction), and had m.p. ca. 100° (frothing), $[\alpha]_D$ +63°, λ_{max}^{MeOH} 239 mμ (ε = 17,700). λ_{max}^{Nujol} 5·98, 6·05, 6·22 μ. (Found: N, 4·89. Calc. for $C_{19}H_{27}NO_3$: N, 4·41.)

Attempts to recrystallize this material resulted in decomposition, and satisfactory analytical data could not be obtained. The crude nitrite (V) was therefore put into the photolysis step with further purification.

Photolysis of the 17-nitrite (*V*) *to give 17a-aza-D-homo-4-androsten-17a-ol-3,17-dione* (VIa)

A solution of testosterone nitrite (V; 13·8 g) in benzene (1·8 l.) was irradiated for 1·5 hr (at 18°, under N_2) using a 200-watt Hanovia mercury lamp (pyrex filter). The solution was then evaporated *in vacuo* to give an oily residue which was dissolved in 800 ml acetone. After brief treatment with decolourizing charcoal and filtration, the solution was concentrated until crystallization ensued, chilled and filtered, to give 9·22 g hydroxamic acid (VIa). The analytical sample was prepared by recrystallization twice from acetone, and showed m.p. 222–223°, $[\alpha]_D$ +67°, λ_{max}^{MeOH} 238 mμ (17,900). λ_{max}^{Nujol} 3·05, 5·98, 6·02 μ. (Found: C, 71·91; H, 8·53; N, 4·75. Calc. for $C_{19}H_{27}NO_3$: C, 71·89; H, 8·57; N, 4·41%.)

17a-Aza-D-homo-4-androsten-17a-ol-3,17-dione 17-acetate (VIb)

The hydroxamic acid (VIa; 300 mg) was acetylated using pyridine–acetic anhydride at room temp for 22 hr. The acetylated product was crystallized from acetone–isopropyl ether to give pure VIb (187 mg), m.p. 172–174°, $[\alpha]_D$ +80°, λ_{max}^{MeOH} 239 mμ (17,000). λ_{max}^{Nujol} 5·58, 5·95, 6·18, 8·45 μ. (Found: C, 70·07; H, 8·38; N, 3·83. Calc. for $C_{21}H_{29}NO_4$: C, 70·12; H, 8·13; N, 3·96%.)

17a-Aza-D-homo-4-androstene-3,17-dione by zinc and acetic acid reduction of the hydroxamic acid (VIa)

To a stirred refluxing solution of the hydroxamic acid (VIa; 500 mg), in glacial acetic acid (60 ml) was added Zn dust (5·0 g), and the mixture was stirred and refluxed for 4 hr. The hot reaction mixture was filtered, the residue on the filter was washed with a little hot acetic acid, and the combined acetic acid solutions were evaporated to dryness. The residue was triturated with water, and the mixture was extracted with methylene chloride. The methylene chloride extract was evaporated *in vacuo*, and the residue was crystallized from ethyl acetate–MeOH to give the lactam (VII; 198 mg), m.p. 258–260°, undepressed on admixture with authentic material.[14,16,26] Identity was confirmed by IR comparison.

The use of shorter reaction times resulted in mixtures containing the N-acetoxy compound (VIb), as shown by paper chromatography, the appearance of absorption at 5·58 μ in the IR spectrum, and in one case by isolation of the N-acetoxy compound.

$\Delta^{1,3,5(10)}$-Estratriene-3,17β-diol 3-methyl ether 17-nitrite (VIII)

To a stirred solution of estradiol 3-methyl ether (15 g) in pyridine (100 ml) at −25° was added dropwise a saturated solution of nitrosyl chloride in pyridine until a permanent blue colour was obtained. The solution was then diluted with water, and the mixture was filtered to give the crude 17β-nitrite (VIII) which was washed with water and dried *in vacuo* at room temp (wt: 16·5 g). The analytical sample, prepared by recrystallization from ether, had m.p. 143–145°, $[\alpha]_D$ −13°. λ_{max}^{Nujol} 6·15, 6·22, 6·26, 6·66, 8·14 μ. (Found: C, 71·98; H, 8·13; N, 4·22. Calc. for $C_{19}H_{25}NO_3$: C, 72·35; H, 7·99; N, 4·44%.)

Photolysis of estradiol 3-methyl ether 17-nitrite (VIII)

The 17β-nitrite (VIII; 3·3 g) was dissolved in benzene (180 ml) and the solution was irradiated with a 200-watt Hanovia mercury lamp (pyrex filter) for 1 hr, at 25° under N_2. The solution was then evaporated to dryness *in vacuo*, and the residue was triturated with acetone, and filtered. The insoluble material was crystallized from acetone to give Xa (600 mg), m.p. 160–167°, $[\alpha]_D$ 0°, λ_{max}^{MeOH} 276 mμ (ε = 2,000), 285 mμ (ε = 1,800) λ_{max}^{Nujol} 3·24, 6·10, 6·19, 6·32, 6·66, 8·00 μ. (Found: C, 72·26; H, 8·04; N, 4·49. Calc. for $C_{19}H_{25}NO_3$: C, 72·35; H, 7·99; N, 4·44%.)

The derived 17a-acetate (Xb; pyridine–acetic anhydride, room temp overnight) had m.p. 193–196°, $[\alpha]_D$ −13°, λ_{max}^{Nujol} 5·58, 5·92, 6·20, 6·34, 6·66, 8·0, 8·44 μ. (Found: C, 70·23; H, 7·77; N, 4·28. Calc. for $C_{21}H_{27}NO_4$: C, 70·56; H, 7·61; N, 3·92%.)

The acetone mother liquor from the original trituration of the crude photolysis product was now concentrated until crystallization ensued, and the crystalline material was filtered off (310 mg; $[\alpha]_D$ +2·7°, indicating that the material was 13α-isomer (Xa) contaminated with a small amount of the 13β-compound (IXa)

The filtrate was again concentrated, and gave 740 mg of IXa. The analytical sample (from methylene chloride–hexane) showed m.p. 186–191°, $[\alpha]_D$ +86°, λ_{max}^{MeOH} 276 mμ (ε = 2,000), 285 mμ (ε = 1800). λ_{max}^{Nujol} 3·25, 6·12, 6·22, 6·36, 6·66, 7·98, 8·12 μ. (Found: C, 72·99; H, 8·06; N, 4·45. Calc. for $C_{19}H_{25}NO_3$: C, 72·35; H, 7·99; N, 4·44%.)

The derived 17a-acetate (IXb; pyridine–acetic anhydride acetylation at room temp overnight) showed m.p. 185–189°, $[\alpha]_D$ +59°, λ_{max}^{Nujol} 5·56, 5·96, 6·18, 6·35, 6·66, 8·46 μ. (Found: C, 70·79; H, 7·68. Calc. for $C_{21}H_{27}NO_4$: C, 70·56; H, 7·61%.)

17a-Aza-D-homo-13α-$\Delta^{1,3,5(10)}$-estratrien-3-ol-17-one 3-methyl ether (XIII) *by hydrazine reduction of the hydroxamic acid* Xa

The 13α-hydroxamic acid (Xa; 360 mg) was dissolved in a boiling mixture of ethylene glycol (36 ml) and 95% hydrazine (1·08 ml), and the solution was heated under reflux for 4 hr. The solution

[26] Kindly supplied by Dr. B. M. Regan, to whom our best thanks are due.

was then cooled, diluted with water and filtered, and the washed, dried solid (238 mg) was crystallized from ethyl acetate–MeOH to give the pure lactam (XIII), m.p. 225–229°, $[\alpha]_D$ −2°, λ_{max}^{MeOH} 276 mμ (2,000), 285 mμ (1,300). λ_{max}^{Nujol} 3·16, 3·30, 6·02, 6·22, 6·34, 6·65 μ. (Found: C, 75·98; H, 8·24; N, 4·82. Calc. for $C_{19}H_{25}NO_2$: C, 76·22; H, 8·42; N, 4·68%.) This compound proved identical in all respects with the product obtained by Beckmann rearrangement of 17-oximino-13α-$\Delta^{1,3,5(10)}$-estratrien-3-ol 3-methyl ether. (See below).

17-Oximino-13α-$\Delta^{1,3,5(10)}$-estratrien-3-ol-3-methyl ether (XV) *and the Beckmann rearrangement of* XV

A solution of 13-isoestrone 3-methyl ether (400 mg) in EtOH (40 ml) containing hydroxylamine hydrochloride (1·20 g) and sodium acetate (990 mg) was refluxed for 20 hr. The reaction mixture was cooled, diluted with water and filtered. The dried product was crystallized from methylene chloride–hexane to give pure oxime (XV), m.p. 138–141°, $[\alpha]_D$ +5°. λ_{max}^{Nujol} 3·04, 3·14, 6·18, 6·21, 7·93, 8·01 μ. (Found: C, 76·47; H, 8·68; N, 4·80. Calc. for $C_{19}H_{25}NO_2$: C, 76·22; H, 8·42; N, 4·68%.)

To a solution of the foregoing compound (200 mg) in dioxan (7 ml) at 40° was added, dropwise over 5 min, thionyl chloride (0·2 ml). The reaction mixture was stirred at 40° for 10 min more, and was then cooled and neutralized by the slow addition of 10% $NaHCO_3$aq. The precipitated solid was filtered off, washed with water and dried, and was subjected to partition chromatography on a chromosorb W column, using the toluene–propylene glycol system. The pure lactam (XIII) which resulted had m.p. 228–231° (from ethyl acetate–MeOH), $[\alpha]_D$ −4°. The m.p. was undepressed on admixture with a sample of XIII prepared from the hydroxamic acid (Xa) and the IR spectra were superimposable.

17a-Aza-D-homo-$\Delta^{1,3,5(10)}$-estratrien-3-ol-17-one 3-methyl ether (XII) *by reduction of* IXa

Reduction of the hydroxamic acid (IXa) using exactly the procedure described for Xa gave the known lactam (XII), identified by mg., mixed mp., and IR comparison.

Photolysis of $\Delta^{1,3,5(10)}$-estratrien-3,17α-diol 3-methyl ether 17-nitrite

A solution of the 17α-ol (XIa; 195 mg) in pyridine (1 ml) was converted to the 17α-nitrite ester in exactly the manner described above for the 17β-nitrite (VIII). The crude 17α-nitrite (which showed one diphenylamine-positive spot on paper chromatography) was irradiated in benzene (150 ml) at 20° under N_2 for 1 hr, using a 200-watt Hanovia lamp, and the solution was evaporated *in vacuo*. The residue was triturated with acetone, giving 20 mg of insoluble crystalline material, m.p. 162–165°, $[\alpha]_D$ +2°, IR spectrum (Nujol) identical with that of authentic Xa.

Concentration of the mother liquors gave crystalline material which was a mixture of the 13α- and 13β-epimers (IXa and Xa) as judged by rotation ($[\alpha]_D$ +48°) and IR spectrum.

$\Delta^{1,3,5(10)}$-Estratriene-3,17β-diol 3-benzoate 17-nitrite

To a stirred, cooled (−20°) solution of estradiol 3-benzoate (7·15 g) in pyridine (153 ml) was added a saturated solution of nitrosyl chloride in pyridine until a permanent blue colour was obtained. The reaction mixture was then diluted with water, and filtered. The residue was washed with water, and dried *in vacuo*, giving the 17-nitrite (XV; 7·56 g), m.p. 165–167° dec, $[\alpha]_D$ +8°, λ_{max}^{MeOH} 229 mμ (21,700). λ_{max}^{Nujol} 5·74, 6·1, 6·24, 6·3, 7·9 μ. (Found: C, 74·05; H, 6·71; N, 3·45. Calc. for $C_{25}H_{27}NO_4$: C, 73·94; H, 6·69; N, 3·38%.)

Photolysis of $\Delta^{1,3,5(10)}$-estratrien-3,17β-diol 3-benzoate 17-nitrite (XVI)

A solution of the 17-nitrite (XV; 3·0 g) in benzene (180 ml) was irradiated for 1 hr at 18°, under N_2, using a Hanovia 200-watt mercury lamp (pyrex filter). The reaction mixture was evaporated *in vacuo*, and the residue was crystallized from methylene chloride–MeOH, giving a crystalline mixture (plates and needles). This mixture was then triturated with acetone, in which the plates were soluble, and the needles were insoluble. The acetone-insoluble portion (700 mg) was then crystallized from acetone–methylene chloride to give XVIIa (460 mg) as needles, m.p. 227–232°, $[\alpha]_D$ +63°, λ_{max}^{MeOH} 229 mμ (21,300), 266 mμ (3,900), 274 mμ (3,200). λ_{max}^{Nujol} 3·25, 5·78, 6·12, 6·30, 6·70, 7·96, 8·24 μ. (Found: C, 73·72; H, 6·99; N, 3·29. Calc. for $C_{25}H_{27}NO_4$: C, 74·05; H, 6·71; N, 3·45%.)

The derived 17a-acetate (XVIIb; pyridine–acetic anhydride at room temp overnight) had m.p.

195–197° (from methylene chloride–hexane), $[\alpha]_D$ +43°. λ_{max}^{Nujol} 5·60, 5·76, 5·94, 6·24, 6·30, 6·70, 7·98, 8·45 μ. (Found: C, 72·60; H, 6·42; N, 3·27. Calc. for $C_{27}H_{39}NO_5$: C, 72·46; H, 6·53; N, 3·13%.)

The mother liquor from the acetone trituration of the photolysis product (*vide supra*) was then evaporated to dryness, and the residue was crystallized from acetone-MeOH to give XVIIIa (281 mg) as plates, m.p. 205–210°, $[\alpha]_D$ −5°, λ_{max}^{MeOH} 228 (20,000), 266 (3,700) and 274 mμ (3,200). λ_{max}^{Nujol} 3·26, 5·76, 6·12, 6·22, 6·28, 6·68, 7·92 μ. (Found: C, 74·06; H, 6·88; N, 3·29. Calc. for C, 74·05; H, 6·71; N, 3·45%.)

The derived 17a-acetate (XVIIIb), obtained by the action of pyridine–acetic anhydride at room temp for 18 hr, showed m.p. 220–225° (from methylene chloride–hexane), $[\alpha]_D$ −26° λ_{max}^{Nujol} 5·56, 5·74, 5·96, 6·22, 6·28, 6·66, 7·92, 8·22, 8·42 μ. (Found: C, 72·62; H, 6·63; Calc. for $C_{27}H_{39}NO_5$: C, 72·46; H, 6·53%.)

17a-*Aza*-D-*homo*-$\Delta^{1,3,5(10)}$-*estratrien*-3-*ol*-17-*one* 3-*benzoate by reduction of the hydroxamic acid* (XVIIa)

A solution of the hydroxamic acid (XVIIa; 200 mg) in glacial acetic acid (40 ml) containing Zn dust (1·0 g) was stirred and heated under reflux for 4 hr. The hot reaction mixture was filtered, and the filtrate was diluted with water. The resultant precipitate was washed with water and dried, and was crystallized from methylene chloride–ethyl acetate to give the lactam (XIXb), m.p. 314–320°, $[\alpha]_D$ +76° ($CHCl_3$) [lit., m.p. 320–322° Ref. 14; m.p. 300–313°, $[\alpha]_D$ +90° ($CHCl_3$) Ref.16]. There was no depression of m.p. on admixture with an authentic specimen[27] of XIXb, and the IR spectra were superimposable.

17a-*Aza*-D-*homo*-13α-$\Delta^{1,3,5(10)}$-*estratrien*-3-*ol*-17-*one* 3-*benzoate* (XX) *from the* 13-*isohydroxamic acid* (XVIIIa)

A solution of the 13-isohydroxamic acid (XVIIIa; 100 mg) in glacial acetic acid (20 ml) containing Zn dust (500 mg) was stirred and heated to reflux for 4 hr. The hot reaction mixture was filtered, and the filtrate was diluted with water. The precipitated solid was filtered off, washed with water, dried and crystallized twice from methylene chloride–ethyl acetate, to give the lactam (XX; 20 mg), m.p. 278–285°, $[\alpha]_D$ −17° ($CHCl_3$), λ_{max}^{Nujol} 3·15, 5·77, 6·02, 6·20 μ. (Found: C, 76·89; H, 7·08; N, 3·71. Calc. for $C_{25}H_{27}NO_3$: C, 77·09; H, 6·99; N, 3·60%.)

Photolysis of $\Delta^{1,3,5(10)}$-*estratriene*-3,17β-*diol*-3-*acetate* 17-*nitrite* (XXII) *to give* 17a-*Aza*-D-*homo*-$\Delta^{1,3,5(10)}$-*estratrien*-3,17a-*diol* 17-*one*-3-*acetate* (XXIIIa)

Estradiol 3-acetate (1·5 g) was converted to the 17-nitrite ester (pyridine–nitrosyl chloride at −20° as in the previous cases) and the crude nitrite (XXII) was dissolved in benzene (80 ml) and irradiated for 1 hr, at 18° under N_2, by a 200-watt Hanovia mercury lamp. The solution was then evaporated to dryness *in vacuo*, and the residue was crystallized from ether to give the hydroxamic acid (XXIIIa; 415 mg). Recrystallization from ether–methylene chloride gave the analytical sample, m.p. 185–190°, $[\alpha]_D$ +75°, λ_{max}^{MeOH} 266 mμ (750), 275 mμ (750), λ_{max}^{Nujol} 3·2, 5·68, 6·07, 6·30, 8·18, 8·28 μ. (Found: C, 70·36; H, 7·49; N, 4·11. Calc. for $C_{20}H_{35}NO_4$: C, 69·95; H, 7·33; N, 4·08%.)

The derived N-acetoxy compound (XXIIIb.) had m.p. 185–190° (crystallized from ether–methylene chloride), $[\alpha]_D$ +51°. λ_{max}^{Nujol} 5·60, 5·70, 5·98, 6·20, 6·30; 8·25, 8·5 μ. (Found: C, 68·33; H, 7·04; N, 3·97. Calc. for $C_{22}H_{27}NO_5$: C, 68·55; H, 7·06; 3·63%.)

Conversion of 17a-*aza*-D-*homo*-$\Delta^{1,3,5(10)}$-*estratrien*-3,17a-*diol*-17-*one* 3-*acetate* (XXIII) *to* 17a-*aza*-D-*homo*-$\Delta^{1,3,5(10)}$-*estratrien*-3-*ol*-17-*one* (XXIV)

The hydroxamic acid (XXIIIa; 15 mg) was dissolved in ethylene glycol (1·0 ml) and 95% hydrazine (0·05 ml) and the solution was heated under reflux for 4 hr. After cooling, the solution was then poured into water, filtered, dried *in vacuo* and crystallized from ethyl acetate–MeOH to yield 5·6 mg of the lactam (XXIV) m.p. 322–327° identical with authentic XXIV as judged by mixed m.p. and IR comparison.

[27] We thank Dr. B. M. Regan for kindly supplying us with this sample.

19-Nortestosterone 17β-nitrite (XXV)

To a stirred, cooled (−20°) solution of 19-nortestosterone (4·0 g) in pyridine (40 ml) was added dropwise a saturated solution of nitrosyl chloride in pyridine until a permanent blue colour resulted. The solution was then diluted with water and filtered, and the residue on the filter was washed with water, and dissolved in methylene chloride. The methylene chloride solution was dried (Na_2SO_4) and evaporated *in vacuo* (<40°). The residue was crystallized from ether–hexane, to give the 17-nitrite (XXV), m.p. 84–87°, $[\alpha]_D$ +9°. λ_{max}^{Nujol} 6·0, 6·14 μ. (Found: C, 71·44; H, 8·53; N, 4·42. Calc. for $C_{18}H_{25}O_3N$: C, 71·25; H, 8·31; 4·62%.)

17a-*Aza*-D-*homo*-19-*nor*-Δ⁴-*androsten*-17a-*ol*-17-*one* (XXVIa)

A solution of 19-nortestosterone 17-nitrite (XXV; 4 g) in benzene (150 ml) was irradiated for 1 hr (at 18° under N_2 by a 200-watt Hanovia mercury lamp. The solution was the evaporated *in vacuo* and the residue was crystallized twice from ethyl acetate–MeOH to give the hydroxamic acid (XVIa; 715 mg), m.p. 227–235°, $[\alpha]_D$ +21°, λ_{max}^{MeOH} 237 mμ (18,500). λ_{max}^{Nujol} 3·25, 6·04, 6·14 μ. (Found: C, 71·24; H, 8·33; N, 4·85. Calc. for $C_{18}H_{25}NO_3$: C, 71·25; H, 8·31; N, 4·62%.)

The derived N-acetoxy compound (XXVIb) showed m.p. 185–188° after crystallization from methylene chloride–hexane, $[\alpha]_D$ +39°, λ_{max}^{MeOH} 238 mμ (18,200) λ_{max}^{Nujol} 5·60, 5·90, 6·02, 6·18, 8·45 μ. (Found: C, 69·79; H, 7·76; N, 4·37. Calc. for $C_{20}H_{27}NO_4$: C, 69·54; H, 7·88; N, 4·06%.)

Conversion of 17a-*aza*-D-*homo*-19-*nor*-Δ⁴-*androsten*-17a-*ol*-17-*one* (XXVIa) *to* 17a-*aza*-D-*homo*-Δ¹,³,⁵(¹⁰)-*estratriene*-3,17a-*diol*-17-*one*-3,17-*diacetate* XXIIIb, *using* C. simplex

A solution of the hydroxamic acid (XXVIa 400 mg) in dimethylformamide (12 ml) was incubated for 44½ hr with *C. simplex*, under the conditions defined by Charney *et al.*,[25] and the crude steroidal product was acetylated (pyridine–acetic anhydride, at room temp for 18 hr.) The acetylated product was subjected to partition chromatography on a column of Chromosorb W, using the ligroin–propylene glycol system, and the fractions were checked paper chromatographically *versus* authentic diacetate (XXIIIb). The appropriate fractions were combined (ca. 60 mg) and crystallized twice from methylene chloride–hexane to give pure XXIIIb, m.p. 184–189°, $[\alpha]_D$ +51°, identical with authentic XXIIIb as judged by mixed m.p. and IR comparison.

3-*Ethylene ketal* (XXVII) *of* 17a-*aza*-D-*homo*-19-*nor*-4-*androsten*-17a-*ol*-3,17-*dione* (XXVIa)

A stirred solution of the hydroxamic acid (XXVIa; 250 mg) and *p*-toluenesulphonic acid (2·5 mg) in benzene (25 ml) and ethylene glycol (1·0 ml) was boiled, under a Dean and Stark water separator for 4 hr. The reaction mixture was cooled, pyridine (1 ml) was added, and the benzene layer was separated, washed with water and evaporated *in vacuo*. The residue was triturated with ether, giving a solid (100 mg) which was crystallized from acetone–hexane to give the 3-ethylene ketal (XXVII), m.p. 230–243°, $[\alpha]_D$ +25°, no UV absorption between 220 and 350 mμ. Strong positive $FeCl_3$ reaction. λ_{max}^{Nujol} 3·22, 6·13 μ.

17a-*Aza*-D-*homo*-19-*nor*-4-*androsten*-3,17-*dione* XXVIII

A solution of the foregoing 3-ethylene ketal XXVII; 200 mg) in ethylene glycol (20 ml) and 95% hydrazine (0·6 ml) was heated under reflux for 4 hr. The solution was then cooled, poured into water, and extracted with methylene chloride. Evaporation of the washed methylene chloride extract *in vacuo* gave a solid residue ($FeCl_3$ test negative) which was dissolved in a mixture of MeOH (72 ml), water (8 ml) and concentrated HCl (0·5 ml). This solution was then heated under reflux for 20 min, and was then concentrated *in vacuo* to about 20 ml and diluted with water. Extraction with methylene chloride in the usual way afforded a solid product, which was crystallized from acetone–hexane to give the analytically pure lactam (XXVIII; 26 mg), m.p. 220–230°, $[\alpha]_D$ +35°, λ_{max}^{MeOH} 239 mμ (15,800) λ_{max}^{Nujol} 3·18, 3·33, 6·0, 6·05, 6·2 μ. (Found: C, 75·36; H, 8·07; N, 4·81. Calc. for $C_{18}H_{25}NO_2$: C, 75·22; H, 8·77; N, 4·87%.)

17a-*Aza*-D-*homo*-19-*nor*-Δ³,⁵-*androstadiene*-3,17a-*diol*-17-*one* 3,17-*diacetate* (XXIX).

A solution of the hydroxamic acid (XXVIa; 600 mg) and *p*-toluenesulphonic acid (60 mg) in acetic anhydride (6 ml) was heated on the steam bath for 1 hr. The solution was then cooled, poured into water and was neutralized with $KHCO_3$. The resulting precipitate was filtered, washed with

water and dried *in vacuo*. Two crystallizations from methylene chloride–ethyl acetate gave the pure diacetate (XXIX; 226 mg) m.p. 191–197°, $[\alpha]_D$ −132°, λ_{max}^{MeOH} 234 mμ (19,900) λ_{max}^{Nujol} 5·56, 5·68, 5·94, 6·06, 8·25, 8·44 μ. (Found: C, 68·00; H, 7·54; N, 3·76. Calc. for $C_{23}H_{33}NO_6$: C, 68·19; H, 7·54; N, 3·62%.)

17a-*Aza*-D-*homo*-19-*nor*-5-*androstene*-3β,17a-*diol*-17-*one* (XXX)

A solution of the hydroxamic acid diacetate (XXIX; 970 mg) in MeOH (65 ml), tetrahydrofuran (30 ml) and water (2·5 ml) containing $NaBH_4$ (1·05 g) was left at 25° for 20 hr. The reaction mixture was then poured into water, neutralized with acetic acid and filtered. The residue on the filter was washed with water, dried and crystallized from MeOH–ethyl acetate to give the Δ^5-3β-hydroxy compound, m.p. 212–218°, $[\alpha]_D$ −15°. Positive $FeCl_3$ reaction. No selective UV absorption between 220 and 350 mμ. λ_{max}^{Nujol} 2·91, 3·22, 6·16 μ. (Found: C, 71·05; H, 8·80; N, 4·64. Calc. for $C_{19}H_{27}NO_3$: C, 70·79; H, 8·91; N, 4·59%.)