709. *Aza-steroids. Part II.* 3-Aza- and 4-Aza-A-homo-5α- and -5β-androstane, and the Structure of Neosaman.*

By C. W. Shoppee and G. Krueger.

3-Aza- and 4-aza-A-homo-5α-androstane (IX, VIII) have been prepared by various routes from 4,5α-dihydrotestosterone and 5α-androstan-3-one. Similarly, 3-aza- and 4-aza-A-homo-5β-androstane (XVI, XV) have been obtained from 4,5β-dihydrotestosterone or 5β-androstane-3-one. From androst-4-en-3-one there was obtained 3-aza-A-homoandrost-4a-en-4-one, which by hydrogenation gave 3-aza-A-homo-5α- and -5β-androstan-4-one, confirming the structures assigned to the four isomeric aza-steroids, and their precursor ε-lactams.

None of the four aza-steroids (VIII, IX, XIV, XVI) is identical with the aza-A-homoandrostane from cycloneosamandione, isolated by Schöpf from the venom of the fire salamander, *Salamandra maculosa* Laur.

In Part I * the preparation and proofs of structure of 3-aza-A-homo-5α- and -5β-cholestane were described, and a partial bibliography of recent work on aza-steroids was given. To the latter should be added studies on 16-oxo-17-aza- and 17-oxo-16-aza-D-homo-5α-cholestan-3β-yl benzoate by Tsuda and Hayatsu,[1] 11,17a-dioxo-17b-aza-D-bishomo-5α-androstan-3β-yl acetate by Barton, Campos-Neves, and Scott,[2] 2-oxo-3-aza- and 3-oxo-2-aza-5β-cholanic esters and 24-hydroxy-7a-aza-B-homo-5β-cholan-7-one by Hara,[3] 12-oxo-12a-aza-C-homo-5α,22a-spirostan-3β-yl acetate and 12,20-dioxo-12a-aza-C-homo-5α-pregn-16-en-3β-yl acetate by Mazur,[4] and 6-aza-5α-cholestan-7-one by Jacobs and Brownfield.[5] We now deal with the 3-aza- and 4-aza-derivatives of A-homo-5α- and -5β-androstane.

We have used the Beckmann rearrangement of appropriate steroid ketoximes to furnish ε-lactams in which the steroid ring A is rendered seven-membered. The oximes of the saturated steroid ketones were crystalline compounds of relatively sharp m. p. and appeared to be homogeneous (cf. ref. 1); nevertheless *syn*- and *anti*-isomers must have been present, or must have been produced under the reaction conditions, since mixtures of isomeric ε-lactams were formed in every case. The oxime of the only αβ-unsaturated ketone used, androst-4-en-3-one, could not be obtained crystalline, but by contrast gave a single Δ^4-ε-lactam. The Beckmann rearrangement of ketoximes, under the influence of thionyl

(A) $R^1{-}C(=N{\cdot}OH){-}R^2 \longrightarrow R^1{-}C(=N{-}O{-}SO{\cdot}Cl){-}R^2 \longrightarrow R^1{-}C(=N^+){-}R^2 \longrightarrow {}^+C(R^1{-}N){-}R^2 \longrightarrow Cl{\cdot}OS{\cdot}O{-}C(R^1{-}N){-}R^2 \longrightarrow HO{-}C(R^1{-}N){-}R^2$

chloride (or phosphorus pentachloride) has been regarded as proceeding by mechanism (A); this involves hydroxyl ions in the last stage,[6] and it has been shown [7] by use of isotopically labelled water for decomposition of the product from benzophenone and phosphorus pentachloride that there is complete loss of the original oxime-oxygen. Recently, however, another mechanism (B) has been invoked [8] whereby rearrangement occurs in the complete

(B) $(R^1R^2C{=}N{\cdot})_2O \longrightarrow R^1{-}CR^2{=}NH{-}O{-}N{=}CR_1R_2 \longrightarrow R^1{-}N{=}CR^2{-}O{-}N{=}CR^1{-}R_2 \longrightarrow$

$(R^1N{=}CR^2{\cdot})_2O \longrightarrow R^1N{=}CCIR^2 + R^1NH{\cdot}CO{\cdot}R^2$

* Part I, *J.*, 1958, 3458.

[1] Tsuda and Hyatsu, *J. Amer. Chem. Soc.*, 1956, **78**, 4107; Heard, Ryan, and Bolker, *J. Org. Chem.*, 1959, **24**, 172.

[2] Barton, Campos-Neves, and Scott, *J.*, 1957, 2698.

[3] Hara, *Yakagaku Zasshi*, 1958, **78**, 1027, 1030.

[4] Mazur, *J. Amer. Chem. Soc.*, 1959, **81**, 1454; 1960, **82**, 3992.

[5] Jacobs and Brownfield, *J. Amer. Chem. Soc.*, 1960, **82**, 4033.

[6] Lampert and Bordwell, *J. Amer. Chem. Soc.*, 1951, **73**, 2369.

[7] Brodskii and Miklukhin, *Compt. rend. Acad. Sci. U.S.S.R.*, 1941, **32**, 558; *Acta Physiochim. U.S.S.R.*, 1942, **16**, 63.

[8] Stephen and Staskun, *J.*, 1956, 980.

absence of water, so that this mechanism requires there to be complete retention of the original oxime oxygen. Some of our rearrangements were carried out under anhydrous conditions.

We have employed brief treatment of steroid ketoximes with an excess of thionyl chloride at −20°, followed in the case of saturated ketoximes by decomposition with water to yield the ε-lactams, and in the case of αβ-unsaturated ketoximes by decomposition with 4N-potassium hydroxide at 80—100°; for the oxime of A-norcholest-5-en-3-one (to appear in a future communication) treatment with thionyl chloride at −20° followed by use of ice-cold potassium hydroxide led to complete recovery of the unchanged oxime. Prolonged treatment of steroid ketoximes with an excess of thionyl chloride, even at −20° and in presence of pentane or ether as diluent, leads to formation of non-crystalline by-products; we have found reaction times of 1—3 minutes satisfactory, except in the case of the oxime of androst-4-en-3-one, where a single treatment gave only 4% of lactam (increased to 25% by four-fold repetition and to 35% by further four-fold recycling of the product).

Beckmann rearrangement of the oxime of 4,5α-dihydrotestosterone [9] (IV; R = OH) as the oxime by thionyl chloride at −30° gave a moderate yield of the 17β-hydroxy-ε-lactams (V, VI; R = OH). Separation of the isomerides by fractional crystallisation was found to be extremely difficult, and the mixed isomerides were converted by oxidation with chromium trioxide in pyridine to the 17-oxo-ε-lactams (V, VI; R = :O), which were partially separated by fractional crystallisation. Alternatively, and preferably, the oxime of 4,5α-dihydrotestosterone acetate (IV; R = OAc), by Beckmann rearrangement, gave a nearly quantitative yield of 17β-acetoxy-ε-lactams (V, VI; R = OAc) which without separation were hydrolysed by alcoholic potassium hydroxide to the mixed 17β-hydroxy-ε-lactams (V, VI; R = OH) and then oxidised with chromium trioxide in pyridine to the mixed 17-oxo-ε-lactams (V, VI; R = :O). Separation of these 17-oxo-lactams by fractional crystallisation appeared somewhat readier than that of the 17β-hydroxy-lactams (V, VI; R = OH) on account of their greater solubility and lower m. p., but was not pursued in order to conserve time and material. The mixture of the isomerides (V, VI; R = :O) was reduced with hydrazine and sodium hydroxide in diethylene glycol at ~200° to a product containing 3-oxo-4-aza- (V; R = H) and 4-oxo-3-aza-A-homo-5α-androstane (VI; R = H); slow sublimation at 170°/0·001 mm. furnished a molecular compound, m. p. 263—264°, of these substances. This resisted separation by fractional crystallisation and by chromatography, and gave an infrared absorption spectrum different from the spectra of the individual ε-lactams (V and VI; R = H) (see below); attempted separation was complicated by the presence of an unidentified compound, m. p. >315°, possibly a hydrazide arising from cleavage of ring A or less probably a mixture of the 17β-hydroxy-ε-lactams (V, VI; R = OH) formed by partial reduction of the 17-carbonyl group in the Wolff–Kishner reaction. Formation of this by-product was largely avoided, and the yield of ε-lactams improved to 43%, by prior conversion of the mixture of isomeric 17-oxo-lactams (V, VI; R = :O) into the mixed hydrazones and Wolff–Kishner reduction with potassium ethoxide at 180—215°; fractional crystallisation then furnished 3-oxo-4-aza-A-homo-5α-androstane (V; R = H), m. p. 303°, and the molecular compound (V + VI; R = H), m. p. 263—264°.

Subsequently, the following simpler route was found. 3β-Hydroxyandrost-5-en-17-one (I) was hydrogenated [10] and then reduced (Wolff–Kishner) to 5α-androstan-3β-ol,[11] which was oxidised by chromium trioxide in acetic acid at 20° to 5α-androstan-3-one (IV; R = H),

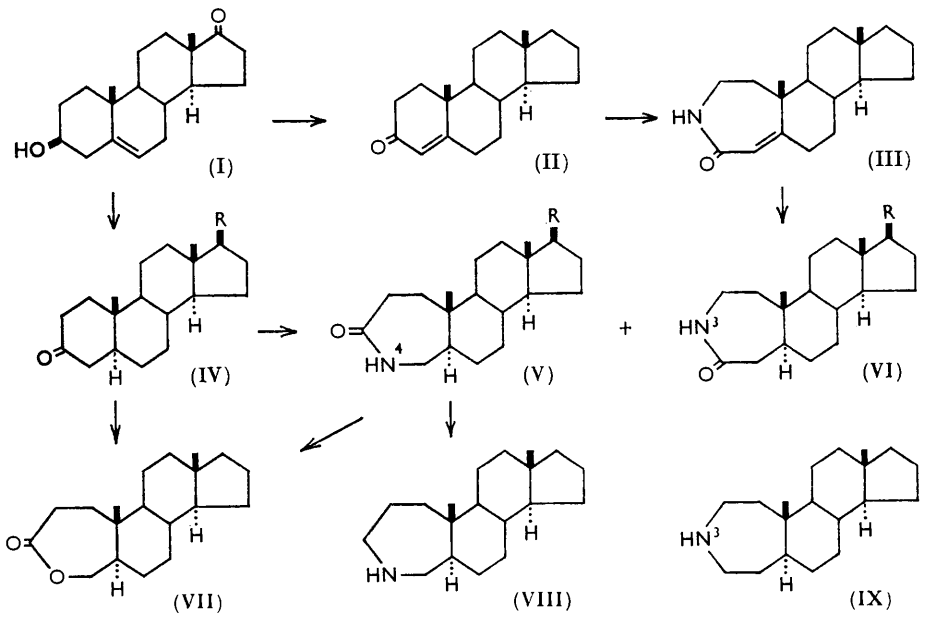
[9] Butenandt, Tscherning, and Hanisch, *Ber.*, 1935, **68**, 2097; Ruzicka and Goldberg, *Helv. Chim. Acta*, 1936, **19**, 99; Butenandt, Tscherning, and Dannenberg, *Z. physiol. Chem.*, 1937, **248**, 205; Ruzicka, Goldberg, and Grob, *Helv. Chim. Acta*, 1941, **24**, 1151.

[10] Reichstein and Lardon, *Helv. Chim. Acta*, 1941, **24**, 955; Wenner and Reichstein, *ibid.*, 1944, **27**, 44.

[11] Heard and McKay, *J. Biol. Chem.*, 1945, **165**, 677, 681; Norymberski, Norymberska, and Olalde, *J. Amer. Chem. Soc.*, 1948, **70**, 1256.

accompanied by 2,3-seco-5α-androstane-2,3-dioic acid.* The oxime of 5α-androstan-3-one (IV; R = H) underwent Beckmann rearrangement nearly quantitatively; careful chromatography followed by extensive fractional crystallisation of the product gave 4-aza-A-homo-5α-androstan-3-one (V; R = H), m. p. 303°, and the molecular compound (V + VI; R = H), m. p. 263—264° [overall yield (I ⟶ V + VI; R = H), 16—17%].

3-Aza-A-homo-5α-androstan-4-one (VI; R = H) was obtained as follows. The ketone (I) was reduced (Wolff–Kishner) to androst-5-en-3β-ol,[11] which by Oppenauer oxidation with aluminium isopropoxide in cyclohexanone in the absence of solvent [12] gave a good yield of androst-4-en-3-one [13] (II). The non-crystalline oxime of this αβ-unsaturated ketone, on Beckmann rearrangement, gave a single ε-lactam (III), existing in two polymorphic forms with the same ultraviolet absorption spectrum [$\lambda_{max.}$ 222 mμ (log ε 4·15) (cf. ref. 4)] and showing infrared absorption spectra different in the solid state but identical in solution. Hydrogenation of either polymorph (III) over palladium–calcium carbonate in ethanol gave 3-aza-A-homo-5α-androstan-4-one (VI; R = H), m. p. 295°; a small quantity of the epimeric 5β-compound (XII), m. p. 245° (see below), was also isolated and the proportion of it was greater on hydrogenation with platinum in acetic acid. An ~1 : 2 synthetic mixture of the lactams (V; R = H), m. p. 303°, and (VI;



R = H), m. p. 295°, furnished the molecular compound, m. p. 263—264°, whose infrared spectrum was identical with that of the product obtained by Beckmann rearrangement of the crystalline oxime of 5α-androstan-3-one (IV; R = H).

The structure of the ε-lactam, m. p. 303°, as 4-aza-A-homo-5α-androstan-3-one (V; R = H) was established by hydrolysis with hydrochloric acid to the related amino-acid

* The anhydride of this acid, on treatment with ammonia in ether, gave a product, which appeared to contain both the possible monoamides; the mixture sublimed unchanged, failing to give the expected imide. Attempted reduction with lithium aluminium hydride in ethyl acetate gave a non-basic, non-crystalline product.

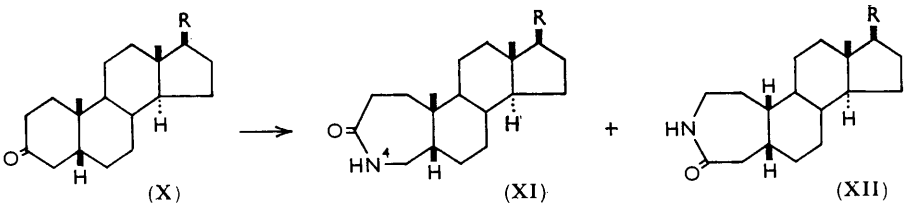
[12] U.S.P. 2,379,832; "Organic Reactions," Wiley and Sons, Inc., New York, Vol. VI, p. 232, footnote 159.

[13] Romo, *Bol. Inst. Quim. Univ. nac. auton. México*, 1952, **4**, 91.

hydrochloride, and deamination of this with dinitrogen trioxide in a two-phase ether–water system to the known ε-lactone (VII), m. p. 185°, $[\alpha]_D$ −38°, obtained from 5α-androstan-3-one (IV; R = H) by oxidation with perbenzoic acid.[14] The structure of the lactam, m. p. 295°, as 3-aza-A-homo-5α-androstan-4-one (VI; R = H) follows by exclusion and is supported by conversion by deamination of the derived amino-acid into the corresponding ε-lactone and reduction of this with lithium aluminium hydride to the crystalline 2,3-seco-5α-androstane-2,3-diol, also obtained from 2,3-seco-5α-androstane-2,3-dioic acid [14] by treatment with lithium aluminium hydride.

Reduction of the ε-lactams (V, VI; R = H) with lithium aluminium hydride in ether at 20°, and treatment of the reaction mixture with water [but not ethyl acetate (see below)] gave, respectively, 4-aza- (VIII) and 3-aza-A-homo-5α-androstane (IX), characterised as the *N*-acetyl derivatives, nitroso-compounds and hydrochlorides.

For the preparation of 3-aza- and 4-aza-derivatives of A-homo-5β-androstane, we first attempted to obtain 5β-androstan-3-one (XIII) from testosterone. Hydrogenation of testosterone with 2% palladium–calcium carbonate in methanol has been reported [9] to give 7% of 4,5α- (IV; R = OH) and 25% of 4,5β-dihydrotestosterone (X; R = OH); repetition with a 10% palladium–calcium carbonate catalyst gave a crude reduction product, m. p. 80—85°, from which the 4,5β-dihydro-ketone was only isolated by extensive fractional recrystallisation. It has been shown [15] that for some Δ^4-3-ketones of the pregnane series hydrogenation in presence of potassium hydroxide favours formation of 5β-pregnan-3-ones; we have found that hydrogenation of testosterone with 10% palladium–calcium carbonate in ethanol in presence of potassium hydroxide gives a crude product, m. p. 122—129°, but extensive fractional crystallisation is required to obtain ~30% of 4,5β-dihydrotestosterone, m. p. 135—140°. A great improvement is effected, however, if testosterone and the reduced catalysts are shaken for 10—15 min. with 0·2N-ethanolic potassium hydroxide in air and then hydrogenated in the usual way; * this procedure affords 80% of a product, m. p. 132—135°, giving on a single recrystallisation pure 4,5β-dihydrotestosterone, m. p. 137—140°. Pyrolysis of the 17β-benzoate (X; R = OBz) proved unsatisfactory (compare the observations of Prelog, Ruzicka, *et al.*[14] on the epimeric 17α-benzoate) for preparation of the Δ^{16}-derivative; the oxime of the 17β-benzoate (X; R = OBz) was therefore subjected to Beckmann rearrangement with thionyl chloride at −20°; it gave a good yield of a mixture of the 17β-benzoyloxy-ε-lactams (XI, XII; R = OBz); attempted elimination of the 17β-benzoyloxy-group by pyrolysis was again unsatisfactory, and the mixed benzoates were hydrolysed with alcoholic potassium hydroxide; this gave a difficulty separable mixture of the 17β-hydroxy-ε-lactams (XI, XII; R = OH), oxidised by chromium trioxide in pyridine to a mixture of the 17-oxo-ε-lactams (XI, XII; R = :O). To avoid losses, the mixture of 17-oxo-ε-lactams was not



separated but was reduced by the Wolff–Kishner technique; the product was treated with dry hydrogen chloride in ether, sublimed, and fractionally recrystallised, affording

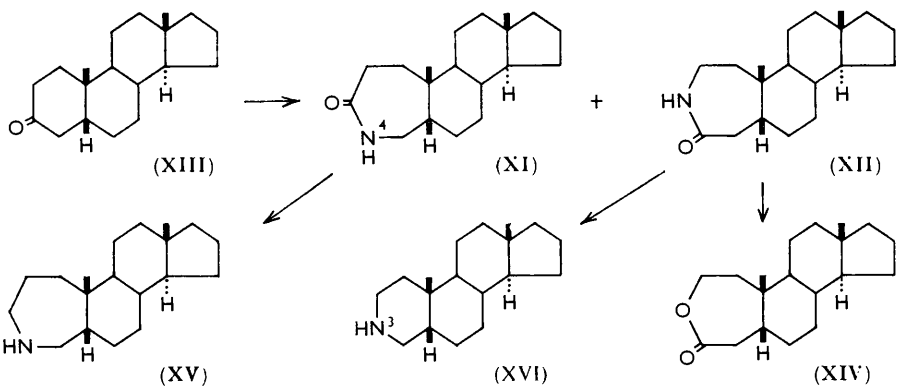
* A possible explanation is suggested by the general theory developed by Brewster [16] for hydrogenation of ketones in presence of metals.

[14] Prelog, Ruzicka, Meister, and Wieland, *Helv. Chim. Acta*, 1945, **28**, 618; Ruzicka, Prelog, and Meister, *ibid.*, p. 1651.
[15] Mancera, Ringold, Djerassi, Rosenkranz, and Sondheimer, *J. Amer. Chem. Soc.*, 1953, **75**, 1286.
[16] Brewster, *J. Amer. Chem. Soc.*, 1954, **76**, 6361.

4-aza-A-homo-5β-androstan-3-one (XI; R = H), m. p. 206°, and 3-aza-A-homo-5β-androstan-4-one (XII; R = H), m. p. 245°.

Subsequently, the following alternative route was found. 3β-Hydroxyandrost-5-en-17-one (I) was converted as previously into androst-4-en-3-one (II), and this was hydrogenated over palladium–barium carbonate in ethanol, after pretreatment with air in the presence of potassium hydroxide, mainly to 5β-androstan-3-one (XIII). The non-crystalline oxime of this ketone, on Beckmann rearrangement, gave a nearly quantitative yield of ε-lactams, separated by fractional crystallisation into 4-aza-A-homo-5β-androstan-3-one (XI), m. p. 206°, and 3-aza-A-homo-5β-androstan-4-one (XII), m. p. 245°. An attempt to hydrolyse the ε-lactam (XI) to the related amino-acid sulphate and to deaminate this with dinitrogen trioxide in ether failed to give 4-hydroxy-3,4-seco-5β-androstan-3-oic acid lactone, m. p. 142°, $[\alpha]_D$ +33° [previously obtained from 5β-androstan-3-one (XIII) by oxidation with perbenzoic acid [14]]; it yielded a non-crystalline unsaturated acid, possibly 3,4-secoandrost-4-en-3-oic acid. The lactam (XII), on hydrolysis and deamination, gave in good yield the new 2-hydroxy-2,3-seco-5β-androstan-3-oic acid lactone (XIV), m. p. 154°. The structure of the lactam (XII), and of the derived lactone (XIV), follows from its formation as the minor product of catalytic hydrogenation of 3-aza-A-homoandrost-4a-en-4-one (III). The structure of the isomeric lactam (XI) follows by exclusion.

Reduction of the ε-lactams (XI, XII) with lithium aluminium hydride in ether at 20° and treatment of the reaction mixture with water (but not with ethyl acetate) gave, respectively, 4-aza- (XV) and 3-aza-A-homo-5β-androstane (XVI), characterised as the *N*-acetyl derivatives, nitroso-compounds, and hydrochlorides.

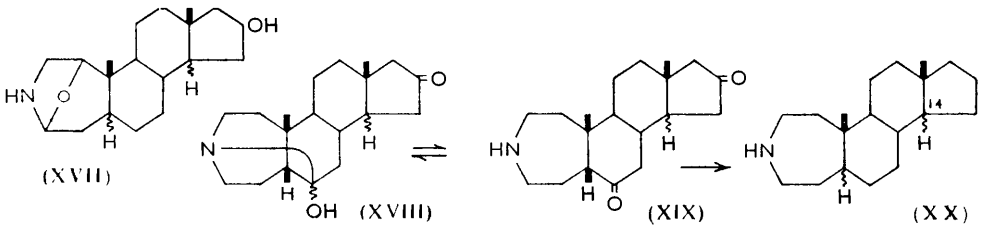


The four isomeric aza-A-homoandrostanes are strong bases, rapidly absorbing carbon dioxide, and difficult to recrystallise; they are best purified by distillation in a high vacuum. All four show infrared absorption bands in the NH region at ~3400 cm.$^{-1}$; compounds (VIII) and (XV) exhibit two peaks in this region, but compounds (IX) and (XVI) give only a single peak. The properties of the four isomeric ε-lactams (which were considered pure only when the m. p. was unchanged on recrystallisation and the material obtained by evaporation of the mother-liquor also had the same m. p.), the four aza-A-homoandrostanes, and their derivatives are summarised in the Table which also contains data for neosaman.[17]

Series	ε-Lactam, m. p.	Aza-steroid, m. p.	Acetyl deriv., m. p.	Nitroso-cpd., m. p.
3-Aza-5α-	(VI) 295°	(IX) 72—73°	113—115°	109—112°
4-Aza-5α-	(V) 303	(VIII) 62—63	136—138/168	136—138
3-Aza-5β-	(XII) 245	(XVI) 52—56	74—76	94—96
4-Aza-5β-	(XI) 205	(XV) 84—85	72—74	106/130
Cycloneosamandione (XIX)...	—	(XX) 105—106	58—59	—

[17] Schöpf and Müller, *Annalen*, 1960, **633**, 127.

Samandarin, $C_{19}H_{31}O_2N$, the related ketone samandarone, $C_{19}H_{29}O_2N$, and cycloneosamandione, $C_{19}H_{29}O_2N$, are steroid alkaloids isolated by Schöpf and Müller [17] from the parotoid and skin glands of the fire salamander, *Salamandra maculosa* Laur. When samandarin is converted into its dihydro-product samandiol, and this is dehydrogenated by selenium, this gives a mixture of 5,6-dialkyl-1,2-cyclopentenonaphthalenes. The structure 1,4-epoxy-3-aza-A-homo-5ξ-androstan-16ξ-ol (XVII) has been proposed for



samandarin on the basis of *X*-ray crystallographic analysis of samandarin hydrobromide and hydriodide; samandarone has the analogous 16-oxo-structure. Whilst samandarin (XVII) and samandarone are secondary bases containing an oxazolidine ring and are masked aldehyde ammonias, cycloneosamandione is a tertiary base containing no oxazolidine ring, and is a ketone ammonia (XVIII) which can react in a tautomeric " open " form neosamandione (XIX). Wolff–Kishner reduction of cycloneosamandione (XVIII ⇌ XIX) gives the 3-aza-A-homo-5ξ-androstane, neosaman (XX).

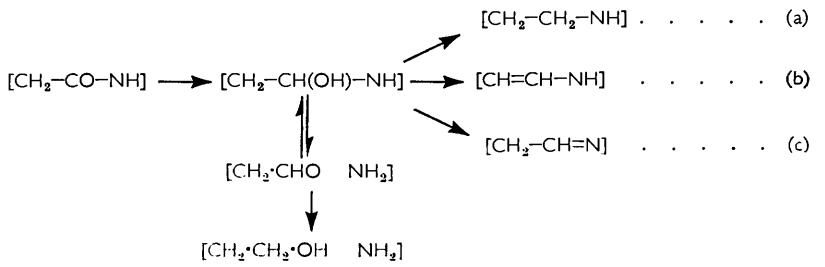
From the Table it is clear that neosaman is isomeric with our synthetic aza-steroids (VIII, IX, XV, XVI); the infrared absorption spectrum of neosaman hydrochloride (prepared from 3 mg. of neosaman kindly supplied by Professor C. Schöpf) is similar to, but not identical with, those of the hydrochlorides of our aza-steroids. A probable source of difference is the 14β-configuration in neosaman (XX).

When the three isomeric ε-lactams (VI, XI, XII) were reduced with lithium aluminium hydride in ether at 20°, and the excess of the reagent was decomposed by addition of ethyl acetate,[18] three new bases were obtained, giving water-insoluble hydrochlorides but showing no NH bond in their infrared absorption spectra and incapable of acetylation. Although reduction of 1-azacycloheptan-2-one with lithium aluminium hydride gives an almost quantitative yield of azacycloheptane (hexamethyleneimine),[19] according to Gaylord [20] carbinolamines appear to be intermediates in the process: ·NH·CO· ⟶ NH·CH_2·; thus 2-piperidone affords, in addition to piperidine, 4% of the carbinolamine in the tautomeric form of δ-aminovaleraldehyde.[21] It also appears that, according to stereoelectronic circumstances, carbinolamines may undergo elimination (b,c) rather than further reduction (a).[20] Compounds of type (b) are excluded by their character as secondary bases; and cyclic Schiff's bases of type (c) would be expected to be reduced by lithium aluminium hydride to saturated secondary bases of type (a) [22] whereas our tertiary bases resist such reduction and also hydrogenation over platinum oxide in ethanol.

The addition of ethyl acetate to a mixture of a secondary amine and lithium aluminium hydride has recently been shown [23] to result in alkylation of the amine; formulation of the new tertiary bases as the *N*-ethyl derivatives of the three aza-A-homoandrostanes (IX, XV, XVI) is confirmed by reduction of the *N*-acetyl derivative of the aza-steroid (XVI) with lithium aluminium hydride to 3-ethyl-3-aza-A-homo-5β-androstane (as XVI), identical

[18] Brown, " Organic Reactions," Wiley and Sons, Inc., New York, 1951, Vol. VI, p. 488; Barnes, *Chem. Eng. News*, 1954, **32**, 2424.
[19] Ruzicka, Kobelt, Häfliger, and Prelog, *Helv. Chim. Acta*, 1949, **32**, 544.
[20] Gaylord, " Reduction with Complex Metal Hydrides," Interscience Publ. Inc., New York, 1956, pp. 600, 619.
[21] Galinovsky, Wagner, and Weiser, *Monatsh.*, 1951, **82**, 551.
[22] Gaylord, ref. 20, p. 796.
[23] Wright, *J. Org. Chem.*, 1960, **25**, 1033.

with the product of reduction of the ε-lactam (XII) by lithium aluminium hydride and ethyl acetate.



Experimental

For general experimental directions see *J.*, 1959, 345. Thionyl chloride was purified by successive distillation from quinoline and linseed oil. M. p.s were determined on a Kofler block; $[\alpha]_D$ are for $CHCl_3$ solutions (c ~1·0). Ultraviolet absorption spectra were measured for EtOH solutions by a Hilger Uvispek or a Perkin–Elmer Spectrochord; infrared absorption spectra were measured for Nujol suspensions by an Infrachord and for CCl_4 solutions by a Perkin–Elmer model 21 spectrophotometer.

Oxime of 17β-*Hydroxy*-5α-*androstan*-3-*one* (IV; R = OH).—The hydroxy-ketone (m. p. 178°; 945 mg.) was refluxed with hydroxylamine hydrochloride (3·45 g.) and sodium acetate trihydrate (4·4 g.) in 90% methanol for 2·5 hr.; hot water (50 ml.) was added, and the mixture refluxed for 5 min. and allowed to cool. Filtration, washing with water, and drying gave the oxime (895 mg.), m. p. 205—210°; recrystallisation from methanol yielded plates, m. p. 210° (lit.,[9] 209°).

3-*Oxo*-5β-*androstan*-17α-*yl Acetate* (IV; R = OAc).—The hydroxy-ketone (3 g.), acetic anhydride (3 ml.), and pyridine (15 ml.) were left at 23° for 16 hr., then diluted with water (150 ml.), and shaken for 15 min. The precipitate was collected, washed with 2N-hydrochloric acid and with water, dried, and recrystallised from methanol, to give the acetoxy-ketone (3 g.), m. p. 155—157° (lit.,[9] 157°). The oxime (2·8 g.), prepared as described above, had m. p. 195—197° (lit.,[9] 197°).

17β-*Hydroxy*-4-*aza*-A-*homo*-5α-*androstan*-3-*one and* 17β-*Hydroxy*-3-*aza*-A-*homo*-5α-*androstan*-4-*one* (V, VI; R = OH).—(*a*) To 17β-hydroxy-5α-androstan-3-one oxime (50 mg.), purified thionyl chloride (0·5 ml.; cooled to −20°) was added. After 3 min., the solution was poured into an excess of 4N-potassium hydroxide, and the precipitate was filtered off, washed with water, and dried; it had m. p. 320—350° (decomp.) (Found: S, 1·3%) but was contaminated with chlorosulphites. The mixed ε-lactams were practically insoluble in methanol and in chloroform, and sublimed appreciably only above 280°/0·001 mm. to give material of m. p. >340°. Brief hydrolysis with hot ethanolic 2N-potassium hydroxide did not alter these properties.

(*b*) To 3-oxo-5α-androstan-17β-yl acetate oxime (2·82 g.) was added, in one portion, purified thionyl chloride (25 ml.) at −20°; immediately after dissolution the almost colourless solution was added in 5 ml. portions to 4N-potassium hydroxide (230 ml.) at 20°. The suspension was neutralised with 2N-hydrochloric acid, and the precipitate was collected, washed with water, and dried; the product (2·52 g.) sublimed readily and completely at ~190°/0·001 mm., to yield a mixture of 3-oxo-4-aza- (V; R = OAc) and 4-oxo-3-aza-A-homo-5α-androstan-17β-yl acetate (VI; R = OAc), m. p. 280—290°, as thin hexagonal plates. The mixed 17β-acetoxy-ε-lactams (9·76 g.) were suspended in boiling 95% ethanol (180 ml.), and a hot solution of potassium hydroxide (29·5 g.) in 95% ethanol (90 ml.) was added. The solid dissolved, but after ~ 1 min. precipitation began; the mixture was refluxed for 2 hr., then left overnight at 10°, and the product was filtered off, and washed with water, 2N-hydrochloric acid, and again with water. The colourless product (6·15 g.) sublimed at 280°/0·001 mm. to yield a mixture of hydroxy-lactams (V and VI; R = OH) as compact square crystals, m. p. >340°, $\nu_{max.}$ (in Nujol) 3400s, 3290s, 3200sh (NH,OH), 1670 and 1625 cm.$^{-1}$ (CO·NH) (Found: C, 74·8; H, 10·4; N, 4·55. Calc. for $C_{19}H_{31}NO_2$: C, 74·7; H, 10·2; N, 4·55%). Dilution of the mother-liquor gave material

(1·2 g.), which commenced to sublime above 200°/0·001 mm. again to give compact square crystals, m. p. 310—338°, and was oxidised separately (see below).

4-Aza-A-homo-5α-androstane-3,17-dione and 3-Aza-A-homo-5α-androstane-4,17-dione (V, VI; R = :O).—The mixed 17β-hydroxy-lactams (V and VI; R = OH; m. p. >340°; 6·15 g.), dry powdered chromium trioxide (6·15 g.), and dry pyridine (61·5 ml.) were shaken together at 23° for 18 hr., and the solution filtered through a column of aluminium oxide (125 g.) prepared in pyridine. Elution with pyridine (4 × 100 ml.) gave slightly yellow material (4·218 g.), m. p. 255—263°; further elution with pyridine (12 × 100 ml.) gave a second fraction (988 mg.), m. p. 325—355° after transformation to compact rectangular prisms at 280—300°, and a third fraction (362 mg.), m. p. 325—335° after similar transformation. The first fraction, on recrystallisation from chloroform–ether, gave the mixed 17-oxo-ε-lactams (V, VI; R = :O) (4·0 g.), m. p. 255—260°; a small portion by sublimation at 190—220°/0·001 mm. gave needles, m. p. 258—260°, $\nu_{max.}$ (in Nujol) 3405, 3040 (NH), 1735 (5-ring CO), 1665 and 1639sh cm.$^{-1}$ (CO·NH) [Found: C, 74·95; H, 9·9; N, 4·7. Calc. for $C_{19}H_{29}NO_2$: C, 75·2; H, 9·65; N, 4·6%). Fractions 2 and 3 were reoxidised, and the products recrystallised from chloroform–ether to yield the mixed 17-oxo-ε-lactams (V and VI; R = :O) (338 mg.).

Material (1·2 g.) from the mother-liquor was oxidised and chromatographed similarly; elution with pyridine (6 × 100 ml.) gave a product (1·02 g.), which by recrystallisation from chloroform–ether yielded the mixed 17-oxo-lactams (433 mg.), m. p. 255—260°, and unchanged mixed hydroxy-lactams (400 mg.). Reoxidation of the latter gave a further quantity (176 mg.) of the mixed oxo-lactams.

4-Aza-A-homo-5α-androstan-3-one and 3-Aza-A-homo-5α-androstan-4-one (V, VI; R = H).—(A) (*a*) The mixed oxo-lactams (V, VI; R = :O) (m. p. 258—260°; 4 g.) were heated with hydrazine hydrate (16 ml.) and ethanol (120 ml.) in a sealed tube at 100° for 2 hr.; complete evaporation at 100° in a vacuum gave the mixed 17-hydrazones, m. p. >300°, $\nu_{max.}$ (in Nujol) 3335, 3220, 3060 (NH), 1670 and 1625 cm.$^{-1}$ (CO·NH), no peak at 1735 cm.$^{-1}$.

Potassium (2·9 g.) was dissolved in ethanol (50 ml.; dried with magnesium), the mixed hydrazones (3·45 g.) were added, and the mixture was heated with exclusion of moisture. At 125° (bath-temperature) effervescence commenced, and after 20 min. the temperature was raised to 140°, slow distillation setting in; the temperature was then kept at 155° for 10 min., 180° for 10 min., and 200—225° for 30 min. A vacuum was gradually created and the mixture kept at ~225°/1 mm., for 30 min., during which it solidified. After cooling, ether (50 ml.) saturated with dry hydrogen chloride was added, and the mixture shaken with intermittent cooling; methanol (150 ml.) was then added and the mixture refluxed for 30 min. to digest the precipitate of sodium chloride, cooled, and filtered. The filtrate was concentrated to ~10 ml. and left at 0°. The product was filtered off and washed with ice-cold methanol (6 × 1 ml.); the filtrate was evaporated and the residue treated with 50% aqueous-methanolic 1·5N-sodium hydroxide; this gave more crystals. Repeated recrystallisation of the combined products from chloroform–ether finally gave colourless material (1·34 g.), subliming at 170°/0·001 mm., m. p. 245—280°, and yielding by fractional crystallisation (i) the lactam (V; R = H) as rhombic prisms, m. p. 300—303°, giving no depression and an identical infrared absorption (in Nujol) with a pure sample, m. p. 303°, prepared from 5α-androstan-3-one oxime (see below), and (ii) a molecular compound of the lactams (V + VI; R = H), m. p. 262—263°, mixed m. p. 264°, and infrared absorption spectrum (in Nujol) identical with the specimen prepared from 5α-androstan-3-one oxime (see below). A quantity of chloroform-insoluble material (346 mg.), m. p. 310—322°, was also isolated but not further examined.

(*b*) The mixed oxo-lactams (V, VI; R = :O) were reduced with hydrazine hydrate in diethylene glycol at 200° under nitrogen or in a vacuum. Acidification of the solution with dry hydrogen chloride and dilution with water gave only a ~20% yield of an almost colourless product; if acidification was omitted, no precipitate was formed on dilution. The product consisted mainly of chloroform-insoluble material, m. p. >315°, $\nu_{max.}$ (in Nujol) 3450 (NH or OH?), 2230, 1670, 1645 (CO·NH), 780, 767, 710 cm.$^{-1}$, showing little tendency to sublime; fractional sublimation at 170—180°/0·001 mm. gave some of the molecular compound (V + VI; R = H), m. p. and mixed m. p. 263—264°.

5α-Androstan-3-one (IV; R = H).—3β-Hydroxy-5α-androstan-17-one (m. p. 175°) (4 g.), hydrazine hydrate (13 ml.), and sodium hydroxide (716 g.) in diethylene glycol (130 ml.) were heated to 130—140° for 1·5 hr.; the temperature was then slowly raised to 190—200° and kept thereat for 4 hr. The cooled mixture was diluted with water (8 vol.), acidified with

2N-hydrochloric acid, and extracted with ether (1 vol.). The usual working up gave material (3·5 g.), m. p. 143—148°, which on recrystallisation from methanol gave 5α-androstan-3β-ol (3·2 g.), m. p. 147—148° (lit.,[24] 147·5—148°). This alcohol (3 g.) in 92% acetic acid (130 ml.) at 5° was treated with chromium trioxide (2·5 g.) in 92% acetic acid at 5°; after 4 days at 5°, the mixture was diluted with water (12 vol.), and the product extracted with ether. The usual isolation procedure gave 5α-androstan-3-one (2·1 g.), m. p. 96—100° (after washing with a little ice-cold pentane) (lit.,[14] 104—105°); acidification of the alkaline extract gave 2,3-seco-5α-androstane-2,3-dioic acid (300 mg.), m. p. 225—235° (from ether–pentane), raised by repeated recrystallisation from acetic acid to 237° (lit.,[14] 237—238°). Androstan-3β-ol (4·0 g.), m. p. 149—150°, was also prepared from androst-5-en-3β-ol (4·4 g.) by hydrogenation over platinum oxide in acetic acid.

The ketone (2·35 g.) in methanol (47 ml.) was refluxed with a solution of hydroxylamine hydrochloride (2·35 g.) and sodium acetate trihydrate (3·3 g.) in water (47 ml.) for 4 hr.; dilution and a single crystallisation of the product from methanol gave the *oxime* (2·2 g.), m. p. 184—188°. For analysis, a sample was recrystallised from methanol and sublimed at 155—165°/1 mm., then having m. p. 189—190° (Found: C, 78·8; H, 10·65; N, 4·9. $C_{19}H_{31}NO$ requires C, 78·85; H, 10·8; N, 4·8%).

4-Aza-A-homo-5α-androstan-3-one and 3-Aza-A-homo-5α-androstan-4-one (V, VI; R = H).—(B) *From 5α-androstan-3-one* (IV; R = H). To the ketoxime (m. p. 184—188°; 250 mg.) was added in one portion thionyl chloride (2·5 ml.) at −20°; after dissolution, the colourless mixture was poured into ice-cold 4N-sodium hydroxide. The precipitated lactams were collected, washed with water, and dried (240 mg.); they melted at 255—262°, some crystals disappearing only at 274°. A series of preparations (5·4 g.) was combined and subjected to triangular fractional crystallisation from chloroform–ether combined with repeated sublimation at ~190°/0·001 mm., yielding rhombic prisms (1·21 g.) of pure *4-aza-A-homo-5α-androstan-3-one* (V: R = H), m. p. 303°, $\nu_{max.}$ (in Nujol) 3150, 3074 (NH), 1675 and 1625 cm.$^{-1}$ (CO·NH), (in CCl_4) 1680 cm.$^{-1}$ (almost insoluble in CCl_4) (Found: C, 78·7; H, 10·7. $C_{19}H_{31}NO$ requires C, 78·85; H, 10·8%) (also 410 mg. of this ketone, m. p. 295—300°), and hexagonal prisms (2·1 g.) of a molecular *compound*, m. p. 262—264°, $\nu_{max.}$ (in Nujol) 3310, 3180, 3080 (NH), 1675 cm.$^{-1}$ (CO·NH), $\nu_{max.}$ (in CCl_4) 1680 cm.$^{-1}$ (almost insoluble in CCl_4), of the isomers (V and VI; R = H) (Found: C, 78·65; H, 10·65%), plus residues of m. p. >235°. The mother-liquor from the fractions containing the pure molecular compound contained only material of m. p. 262—264°.

A 1 : 2 synthetic mixture of the lactams (V; R = H), m. p. 303°, and (VI; R = H), m. p. 295° (see below), on crystallisation from chloroform–ether furnished the molecular compound, m. p. 263—264°, with infrared bands as before.

Chromatography on aluminium oxide failed to resolve the molecular compound.

(C) *From Androst-4-en-3-one* (II). (i) 3β-Hydroxyandrost-5-en-17-one (m. p. 153°; 11 g.), hydrazine hydrate (8·7 ml.), and sodium hydroxide (23·2 g.) in diethylene glycol were heated in nitrogen at 140° for 1·5 hr.; the temperature was then raised to 190° and the pressure reduced to 10 mm. rapidly to remove the excess of hydrazine; the mixture was kept at 190—200° for 4 hr., cooled, and diluted with water (4 vol.), and the precipitate extracted with ether (2 l.). The ethereal extract was washed thrice with water (2 l.), dried, and evaporated to give androst-5-en-3β-ol (10·2 g.), m. p. 133—136° (lit.,[11] 135—136°); this procedure is a marked improvement on the methods listed in Elsevier's " Encyclopaedia of Organic Chemistry," Vol. XIV, Series III, p. 1504S. Androst-5-en-3β-ol (10 g.) was dissolved in cyclohexanone (100 ml.) and xylene (40 ml.), and the mixture slowly distilled until 40 ml. of distillate had been collected; aluminium isopropoxide (2·5 g.) was then added; the solution became yellow, and slow distillation was continued for 10 min. After cooling, a concentrated solution of sodium potassium tartrate was added and the mixture shaken for 10 min. to give two almost colourless layers. The mixture was steam-distilled until 2·5 l. of distillate had been obtained; the residue solidified on cooling and was collected, dried, and recrystallised from methanol, to afford androst-4-en-3-one (7·5 g.), m. p. 103—106° (lit.,[11] 104—106°). The oxime, prepared as described above, was amorphous (m. p. 75—85°); it was dissolved in ether, washed twice with water to remove hydroxylamine salts, dried, and recovered as a glass. The oxime (1·5 g.) was dissolved in ether (5 ml.) and cooled to −15°, and thionyl chloride (12 ml.; also cooled to −15°) was added; the mixture was at once poured into an excess of hot (80—100°) 4N-potassium hydroxide; after cooling,

[24] Prelog, Ruzicka, and Wieland, *Helv. Chim. Acta*, 1944, **27**, 66.

the product was extracted with ether, and the ethereal extract evaporated to an oil which was dried at 25°/1 mm. for 30 min. and subjected to the same treatment. After recycling four times, the sparingly ether-soluble crystals were filtered off (440 mg.; m. p. 225—228°) and recrystallised from chloroform–ether to give 3-*aza*-A-*homoandrost*-4a-*ene*-4-*one* (III) (271 mg.), m. p. 233—236°, $\lambda_{max.}$ 222 mμ (log ε 4·15), $\nu_{max.}$ (in Nujol) 3290, 3178, 3050 (NH), 1668, 1636, 1602 [C:C·CO], $\nu_{max.}$ (in $CHCl_3$) 3420 (NH), 1643, 1603 cm.$^{-1}$ [C:C·CO]; the analytical specimen was sublimed at 200°/0·01 mm. and had m. p. 236—238° (Found: C, 79·2; H, 10·2. $C_{19}H_{29}NO$ requires C, 79·4; H, 10·2%). The ethereal filtrate and the mother-liquors were combined, evaporated, and dried in a high vacuum for 0·5 hr.; the resultant material was recycled four times, with half-quantities of reagents and solvent, to give a brownish product (181 mg.), m. p. 246—250° (from ether–benzene). The product (150 mg.) was chromatographed on aluminium oxide (4 g.) in pentane, and the column eluted with pentane, chloroform–pentane (60—90% of chloroform), and with chloroform; the chloroform–pentane fractions were combined after infrared spectroscopic examination to give a *polymorph* of 3-aza-A-homoandrost-4a-ene-4-one (III) (90 mg.), m. p. 246—250°, $\lambda_{max.}$ 222 mμ (log ε 4·15), $\nu_{max.}$ (in Nujol) 3168, 3062 (NH), 1665, and 1575 (broad), whose infrared absorption spectrum in $CHCl_3$ solution was identical with that of the form, m. p. 233—236°, described above (Found: C, 78·6; H, 10·0%). This lactam was unchanged by N-sodium ethoxide at 100° for 5 min. or by concentrated sulphuric acid at 50° for 5 min., the product obtained by dilution having in both cases the same infrared spectrum as the starting material.

Attempted rearrangement of the oxime (115 mg.) with toluene-*p*-sulphonyl chloride (140 mg.) in pyridine (0·5 ml.) at 25° for 3 days (cf. ref. 4) failed to give a crystalline product.

(ii) 3-Aza-A-homoandrost-4a-ene-4-one (III), m. p. 233—236° (271 mg.), 10% palladium–calcium carbonate, and ethanol (67 ml.) were shaken in hydrogen for 29 hr. Filtration from the catalyst, dilution with water (8 vols.), and collection and drying of the precipitate gave a product (270 mg.), m. p. 270—288°. Repeated recrystallisation from chloroform–ether gave 3-aza-A-homo-5α-androstan-4-one (VI; R = H) (160 mg.), m. p. 295°, $\nu_{max.}$ (in Nujol) 3270, 1650, and 1615 cm.$^{-1}$; when this preparation (20 mg.) was mixed with 4-aza-A-homo-5α-androstan-3-one (V; R = H) (20 mg.), the mixture crystallised from chloroform–ether, and the material from the mother-liquor recrystallised and sublimed slowly at 170°/1 mm., the molecular compound (V + VI; R = H), m. p. 263—264°, was obtained having an infrared absorption spectrum identical with that of the specimen obtained by Beckmann rearrangement of 5α-androstan-3-one oxime. The material from the mother-liquor of the recrystallised reduction product was repeatedly recrystallised from chloroform–ether; it yielded 3-aza-A-homo-5β-androstan-4-one (XII; R = H), m. p. and mixed m. p. 245°, $\nu_{max.}$ (in Nujol) 3205, 3005, 1670, and 1600 (broad) cm.$^{-1}$, identical with a specimen obtained by Beckmann rearrangement of 5β-androstan-3-one oxime (see below).

(iii) The Δ^4-ε-lactam (III) (m. p. 236—238°; 50 mg.), platinum oxide (40 mg.), and acetic acid (10 ml.) were shaken in hydrogen for 36 hr. Filtration from the catalyst, dilution with water (8 vol.), and filtration and drying of the precipitate gave a product (35 mg.), m. p. 225—270°. Recrystallisation from chloroform–ether gave 3-aza-A-homo-5α-androstan-4-one (VI; R = H) (18 mg.), m. p. 295°, $\nu_{max.}$ (in Nujol) 3270, 1650, and 1615 cm.$^{-1}$. The residue from the mother-liquor had m. p. 224—240°, and further recrystallisation of this from chloroform–ether gave slightly impure 3-aza-A-homo-5β-androstan-4-one (XII; R = H) (4 mg.), m. p. 237—244°, whose infrared absorption spectrum in Nujol was identical with that of a genuine specimen, m. p. 245°, except for a small additional peak at 1612 cm.$^{-1}$ due to a trace of the 5α-epimer (VI; R = H).

(iv) 3-Aza-A-homoandrost-4a-en-4-one (III) (polymorph, m. p. 246—250°; 10 mg.) did not absorb hydrogen in presence of 10% palladium–calcium carbonate in ethanol (2·5 ml.) overnight; the infrared spectrum of the product was identical with that of the starting material. The recovered lactam (6 mg.) was shaken with hydrogen and platinum oxide (3 mg.) in acetic acid (1 ml.) overnight. Removal of the catalyst and isolation by dilution gave material (5·5 mg.), m. p. 230—270°. Recrystallisation from chloroform–ether–pentane gave 3-aza-A-homo-5α-androstan-4-one (VI; R = H), m. p. 294—297°, whose infrared spectrum (in Nujol) was identical with that of an authentic specimen, but entirely different in the finger-print region from the spectra of the starting material and of 3-aza-A-homo-5β-androstan-4-one (XII; R = H). The material from the mother-liquor, when twice recrystallised from chloroform–pentane, gave 3-aza-A-homo-5β-androstan-4-one (XII; R = H), m. p. 242° after softening from 232°, whose

infrared absorption spectrum (in Nujol) was identical with that of a genuine specimen but entirely different in the finger-print region from the spectra of the starting material and of 3-aza-A-homo-5α-androstan-4-one (VI; R = H).

(v) The lactam (III) (polymorph, m. p. 245—248°; 45 mg.), platinum oxide (36 mg.), and acetic acid (9 ml.) were shaken in hydrogen for 72 hr. Removal of the catalyst and isolation by dilution gave material (22 mg.), m. p. 250—283°. Recrystallisation from chloroform–ether gave 3-aza-A-homo-5α-androstan-4-one (VI; R = H) as a polymorph, m. p. 304—305°, whose infrared absorption spectrum in Nujol was different in the NH and CO·NH stretching region, $\nu_{max.}$ (in Nujol) 3280, 3170, 3080, and 1670, 1625 cm.$^{-1}$, closely similar between 1400 and 1200 cm.$^{-1}$, and identical below 1200 cm.$^{-1}$, with that of its polymorph, m. p. 295°; it was not analysed but was converted into 2,3-seco-5α-androstane-2,3-diol (see below). Further recrystallisation yielded the polymorph (8 mg.), m. p. 295°. No product melting between 235° and 245° could be isolated, and this may be connected with the long reduction period which led to serious loss of material soluble in ~10% aqueous acetic acid.

4-Hydroxy-3,4-seco-5α-androstan-3-oic Acid Lactone (VII).—4-Aza-A-homo-5α-androstan-3-one (V; R = H) (m. p. 303°; 81 mg.) with concentrated hydrochloric acid (0·8 ml., boiled shortly before use) was cooled to −180°, and the tube was evacuated, sealed, and heated at 100° for 60 hr. (traces of oxygen affect the colour and quality of the derived amino-acid hydrochloride). Water and the excess of hydrogen chloride were removed in a vacuum, to give the hydrochloride of 4-amino-3,4-seco-5α-androstan-3-oic acid. This was dissolved in water (7 ml.), ether (15 ml.) added, and the mixture cooled to 0°, saturated with dinitrogen trioxide, and shaken at 20° for 9 hr. The initial thick precipitate of the amino-acid nitrite gradually dissolved. The ethereal solution was washed with aqueous sodium hydrogen carbonate and with water, dried, and evaporated to give an oil, which crystallised. Recrystallisation from methanol and sublimation at 125°/0·01 mm. gave 4-hydroxy-3,4-seco-5α-androstan-3-oic acid lactone, m. p. and mixed m. p. 185—186° (lit.,[14] 185·5—186°) (correct infrared spectrum) (Found: C, 78·6; H, 10·3. Calc. for $C_{19}H_{30}O_2$: C, 78·6; H, 10·4%). The amino-acid nitrite, obtained as an insoluble precipitate by treatment of the amino-acid hydrochloride with aqueous sodium nitrite solution, when washed and heated at 100° for 4 days, regenerated the lactam (V; R = H), m. p. 303°.

2-Hydroxy-2,3-seco-5α-androstan-3-oic Acid Lactone and 2,3-Seco-5α-androstane-2,3-diol.—(*a*) 3-Aza-A-homo-5α-androstan-4-one (VI; R = H) (m. p. 295°) was resistant to hydrolysis by hot 10N-hydrochloric acid and 65% sulphuric acid; it was therefore heated in a sealed tube with 50% aqueous-ethanolic 6N-hydrochloric acid at 100° as above for 16 hr., and the amino-acid hydrochloride was deaminated with dinitrogen trioxide as above. The resulting non-crystalline lactone (dried at 25°/1 mm. for 6 hr.) was reduced with an excess of lithium aluminium hydride in ether at 36° for 24 hr., to give, after the usual isolation procedure, 2,3-seco-5α-androstane-2,3-diol, m. p. and mixed m. p. 195—197° (from benzene), whose infrared absorption was identical with that of a genuine specimen. The polymorph of (VI; R = H), m. p. 304—305°, likewise gave 2,3-seco-5α-androstane-2,3-diol, m. p. and mixed m. p. 195—197°, with the same infrared spectrum.

(*b*) 2,3-Seco-5α-androstane-2,3-dioic acid (m. p. 235°; 100 mg.) was reduced with lithium aluminium hydride as above to *2,3-seco-5α-androstane-2,3-diol*, m. p. 196—197° (from benzene), $\nu_{max.}$ (in CCl_4) 3265, 1067, 1047, 1024 cm.$^{-1}$, $\nu_{max.}$ (in Nujol) 3290s (OH), 1055s, 1040m, 1020s cm.$^{-1}$ (C·O) [Found (after drying at 100°/1 mm. for 16 hr.): C, 78·2; H, 11·3. $C_{19}H_{34}O_2$ requires C, 78·0; H, 11·05%].

17β-Hydroxy-5β-androstan-3-one (X; R = OH).—10% Palladium oxide–calcium carbonate (250 mg.), suspended in ethanol (12·5 ml.), was reduced by shaking it with hydrogen; testosterone (m. p. 155°; 500 mg.) and 0·44N-ethanolic potassium hydroxide (12·5 ml.) were added, and the mixture was swirled in the air for 15 min. and (after removal of the air) shaken with hydrogen for 30 min. After 20 min. the theoretical amount of hydrogen had been absorbed and uptake had ceased; the catalyst was filtered off, the filtrate diluted with water (10 vols.) and the precipitate collected, washed with water, and dried to yield material (412 mg.), m. p. 132—135°. Recrystallisation from ethyl acetate–hexane gave 17β-hydroxy-5β-androstan-3-one (X; R = OH) (350 mg.), m. p. 137—140° (lit.,[9] 137—140°). The *benzoate*, prepared by using benzoyl chloride and pyridine in methylene chloride in a sealed tube at 65° and recrystallised from hexane, had m. p. 158—160° [Found (after drying at 100°/0·01 mm. for 3 hr.): C, 78·95; H, 8·5. Calc. for $C_{26}H_{34}O_3$: C, 79·15; H, 8·7%]. The oxime, prepared in the usual way from the benzoate

(1·04 g.), was amorphous; it was dissolved in ether, washed with water to remove hydroxylamine salts, dried, and evaporated, but resisted all attempts at recrystallisation; it had m. p. 105—115°.

The pretreatment with molecular oxygen and alkali appears to involve both substrate and catalyst, since pretreatment of testosterone in absence of the catalyst was ineffective; it loses effectiveness at low temperatures (0°, −40°, −70°). The optimum duration appears to vary with the batch of catalyst, but if unduly extended leads to increasing amounts of water-soluble products giving a positive Schiff's test for aldehydes, reducing Fehling's solution, and yielding 2,4-dinitrophenylhydrazones.

3-Oxo-4-aza- (XI; R = OBz) *and 4-Oxo-3-aza-A-homo-5β-androstan-17β-yl Benzoate* (XII; R = OBz).—To the oxime (1·08 g.) of 3-oxo-5β-androstan-17β-yl benzoate was added thionyl chloride (10 ml.) at −20°, and the solution was left at −15° for 1 hr., and then poured into an excess of 2N-sodium hydroxide. The precipitate was filtered off, washed with water, dried, and washed with a little ether, to give a mixture of the 17β-benzoyloxy-lactams (XI, XII; R= OBz) (1·03 g.), m. p. 222—228°. Two sublimations at 200°/0·001 mm. gave a mixture of 3-oxo-4-aza- (XI; R = OBz) and 4-oxo-3-aza-A-homo-5β-androstan-17β-yl benzoate (XII; R = OBz), m. p. 227—228° (Found: C, 76·2; H, 8·6; N, 3·4. Calc. for $C_{26}H_{35}NO_2$: C, 76·3; H, 8·6; N, 3·4%). The mixed products were recovered largely unchanged after attempted pyrolysis at the softening point (~500°) of soda glass at 1 mm. or at 0·001 mm.

17β-Hydroxy-4-aza-A-homo-5β-androstan-3-one (XI; R = OH) *and the Isomer* (XII; R = OH).—The mixed 17β-benzoyloxy-lactams (600 mg.) were refluxed with potassium hydroxide (300 mg.) in ethanol (14 ml.) for 2 hr. Dilution with water (1 vol.) gave a clear solution containing the potassium salts of the appropriate amino-acids; acidification with hydrochloric acid and complete evaporation at 100°/1 mm. gave a product which was slowly sublimed at 220°/0·005 mm. to yield after 5 hr. a mixture of hydroxy-lactams (XI and XII; R = OH) (364 mg.), m. p. 240—244°; resublimation at 220°/0·001 mm. gave the analytical specimen as needles, m. p. 242—244° (Found: C, 74·45; H, 10·2. Calc. for $C_{19}H_{31}NO_2$: C, 75·0; H, 9·9%).

3-Aza-A-homo-5β-androstane-3,17-dione (XII; R = :O) *and the 4-Aza-3,17-dione* (XI; R = :O).—The mixed 17β-hydroxy-lactams (250 mg.) were shaken with a solution of chromium trioxide (250 mg.) in pyridine (2·5 ml.) in a sealed tube at 20° for 16 hr. The dark solution, containing a finely divided black solid, was filtered in succession through two columns of aluminium oxide (2 × 2·5 g.) and evaporated in a vacuum. The residual yellow solid (200 mg.) was chromatographed on aluminium oxide (6 g.) in benzene–hexane (3 : 1). Elution with chloroform (6 × 20 ml.) gave a mixture of dioxo-derivatives (XI and XII; R = :O) (110 mg.), recrystallising from methanol in needles, m. p. 191—210°; two further recrystallisations from methanol gave a specimen, m. p. 195—197° clearing at 210°, $\nu_{max.}$ (in Nujol) 3230, 3120 (NH), 1740 (5-ring CO), 1677, 1665, 1642sh, 1615sh, 1587 cm.$^{-1}$ (CO·NH), $\nu_{max.}$ (in $CHCl_3$) 1735, 1662, 1605 cm.$^{-1}$ [Found (after drying at 80°/0·01 mm. for 3 hr.): C, 75·05; H, 9·5. Calc. for $C_{19}H_{29}NO_2$: C, 75·3; H, 9·6%]. A preliminary oxidation with chromium trioxide in acetic acid at ~5° gave only viscous, insoluble green oils.

4-Aza-A-homo-5β-androstan-3-one (XI; R = H) *and 3-Aza-A-homo-5β-androstan-4-one* (XII; R = H).—(*a*) The mixed 17-keto-lactams (57 mg.), hydrazine hydrate (0·1 ml.), and potassium hydroxide (100 mg.) in diethylene glycol (2 ml.) were heated at 135° for 1 hr., then at 190—200°/10 mm., and finally at 200°/760 mm. for 4 hr. The cooled mixture was treated with a stream of dry hydrogen chloride, and the excess of hydrogen chloride was removed at 10 mm.; the solvent was distilled off at 150°/1 mm., and the dry residue kept at 150°/1 mm. for 2 hr. After repeated trituration with ether, the residue was repeatedly recrystallised from chloroform–pentane and finally from methanol, to give 3-aza-A-homo-5β-androstan-4-one, m. p. and mixed m. p. 244—245° preceded by extensive sublimation to yield large hexagonal plates, whose infrared absorption spectrum was identical with that of the lactam, m. p. 245°, obtained from 5β-androstan-3-one [see (*b*) below]. From the mother-liquors, 4-aza-A-homo-5β-androstan-3-one (XII; R = H) was obtained as needles, m. p. 210°, preceded by sublimation to give needles at 205°.

(*b*) 10% Palladium oxide–calcium carbonate (100 mg.) in 0·22N-ethanolic potassium hydroxide was shaken in hydrogen for 0·5 hr.; androst-4-en-3-one (II) (m. p. 103—106°; 500 mg.) was added and the mixture shaken in air for 15 min. (In a later experiment with a different batch of catalyst, this treatment was omitted without detrimental results.) The

air was replaced by hydrogen and shaking continued for 50 min. When absorption (90% of theory) ceased, the catalyst was filtered off, and the yellow filtrate made slightly acid and colourless with 10N-hydrochloric acid and concentrated at 100°/10 mm. The usual working up yielded 5β-androstan-3-one (XIII) (lit.,[14,25] m. p. 59—60°) as an oil (475 mg.). To conserve material, a portion (130 mg.) only was chromatographed on Davison silica gel (12 g.; 100—200 mesh; from W. R. Grace and Co., Baltimore, Maryland, U.S.A.) in pentane; elution with ether–pentane (1 : 24) gave material (100 mg.), m. p. ~45°, which on rechromatography gave 5β-androstan-3-one, m. p. 50—55°, raised to 59—61° by two quick successive washings of the well-formed crystals with a little pentane. The reduction product and the chromatographed material were converted into oximes in refluxing methanol in the usual way (2·5 hr.); the precipitate obtained on dilution was collected, washed with water, dried, dissolved in ether, washed with water (to remove hydroxylamine salts), dried, and recovered by evaporation at 1 atm. and then at 1 mm. The oxime was amorphous, m. p. 65—75°; thionyl chloride (5·0 ml.) at −20° was added in one portion to the oxime (500 mg.); after 1 hr. at −20° the solution was poured into 4N-potassium hydroxide (50 ml.). The product was extracted with ether to give a mixture of the lactams (XI, XII) (490 mg.), m. p. 175—240°.

These mixed lactams (5·6 g.) on triangular fractionation (about 50 crystallisations) from chloroform–hexane gave 3-*aza*-A-*homo*-5β-*androstan*-4-*one* (XII) (1·31 g.); m. p. 244·5—245·5° after final recrystallisation from methanol, subliming easily above 200°/1 mm. in hexagonal plates, $\nu_{max.}$ (in Nujol) 3200, 3060sh (NH), 1660 (CO·NH), and 1595 cm.$^{-1}$, $\nu_{max.}$ (in CCl_4) 3370, 3180, 3040, and 1660 cm.$^{-1}$ [Found (after sublimation): C, 78·95; H, 10·9; N, 4·9. $C_{19}H_{31}ON$ requires C, 78·85; H, 10·8; N, 4·85%], with slightly less pure material (573 mg.), m. p. 242—245°, and 4-*aza*-A-*homo*-5β-*androstan*-3-*one* (XI) (450 mg.), needles (from methanol), m. p. 206—207°, $\nu_{max.}$ (in Nujol) 3200, 3100 (NH), 1670, and 1635 cm.$^{-1}$ (CO·NH) (Found: C, 79·05; H, 10·8; N, 5·1%), with further material of almost equal purity (150 mg.), m. p. 205—207°. Fractions (i) 372 mg., m. p. >260°, and (ii) 1·38 g., m. p. 180—190°, were also obtained; the former may contain some of the A/B-*trans*-lactam (V and/or VI; R = H), whilst the latter probably consists of a mixture of lactams (XI, XII) but was not subjected to further fractional crystallisation.

2-*Hydroxy*-2,3-*seco*-5β-*androstan*-3-*oic Acid Lactone* (XIV).—3-Aza-A-homo-5β-androstan-4-one (XII) (m. p. 245°; 100 mg.) was hydrolysed in absence of oxygen with a mixture of concentrated sulphuric acid (0·3 ml.) and distilled water (0·3 ml.) at 110° for 14 hr. in a tube which had been evacuated at −180°/1 mm. and sealed. The colourless amino-acid sulphate, which separated, on cooling, in flakes, was filtered off, washed repeatedly with small quantities of water, and deaminated by being shaken at 20° for 4 days in ether (8 ml.) and water (8 ml.), each previously saturated with dinitrogen trioxide. The ethereal layer was separated, washed with sodium hydrogen carbonate and with water, dried, and evaporated. The residue was chromatographed on silica gel (Davison; 3 g.) in pentane. Elution with ether–pentane (1 : 1) gave 2-*hydroxy*-2,3-*seco*-5β-*androstan*-3-*oic acid lactone* (XIV), hexagonal prisms (from benzene–pentane; after sublimation at 130°/1 mm.), m. p. 155—157°, $\nu_{max.}$ (in Nujol) 1730s, 1710s cm.$^{-1}$ (Found: C, 78·6; H, 10·55. $C_{19}H_{30}O_2$ requires C, 78·6; H, 10·4%).

3- *and* 4-*Aza*-A-*homo*-5α-*androstane* (IX, VII) *and* 3- *and* 4-*Aza*-A-*homo*-5β-*androstane* (XVI, XV).—The lactam (V, VI, XI, or XII; R = H), suspended in ether (100 mg. per 5 ml.), was reduced with lithium aluminium hydride in ether (150 mg. per 5 ml.) in sealed tubes at 20° for 2 days; similar results were obtained when the period was 10 days. The reactants were rapidly introduced into tubes constricted for 2 cm. to a diameter of 3 mm., and ether was added; after ~10 min. when evolution of gas had effectively ceased, the orifices were closed with corks bearing long glass tubes (20 cm.), the lower parts of the tubes placed in an ice–salt bath, and the tubes sealed. The sealed tubes, inserted in larger tubes and padded with cotton wool, were then shaken in batches of 4—8. The resulting mixtures were decomposed with a minimum of water, and the precipitates filtered off and washed extensively with ether as quickly as possible to avoid formation of base carbonates; the ethereal filtrates were then evaporated in vacuum-desiccators over potassium hydroxide. The crystalline residues consisted of the almost pure aza-steroids, since conversion into the hydrochlorides, recrystallisation of these from ethanol–ether, and regeneration of the bases hardly altered their m. p. Analytical specimens were prepared by refluxing them in a narrow vertical tube at 170—180°/0·001 mm. for 0·5 hr.; the tube was then swiftly withdrawn from the bath, placed horizontally, disconnected

[25] Mason and Schneider, *J. Biol. Chem.*, 1950, **184**, 593.

from the vacuum-train, and cut on either side of the ring of distillate. The samples used for infrared spectroscopy unavoidably became contaminated with base carbonate during preparation of mulls or solutions.

3-*Aza*-A-*homo*-5α-*androstane* (IX) was obtained as an oil, which when rubbed with a little pentane gave crystals, m. p. 72—73° (Found: C, 82·5; H, 12·2. $C_{19}H_{33}N$ requires C, 82·8; H, 12·1%).

4-*Aza*-A-*homo*-5α-*androstane* (VIII), m. p. 62—63°, $\nu_{max.}$ (in Nujol) 3440 cm.$^{-1}$ (NH), crystallised spontaneously during evaporation in a vacuum of its ethereal solution (Found: C, 82·8; H, 11·9%).

3-*Aza*-A-*homo*-5β-*androstane* (XVI) was obtained as an oil which at 1 mm. solidified to needles, m. p. 50—54°; after being washed with a little cold pentane, these had m. p. 52—56°, $\nu_{max.}$ (in Nujol) 3390sh, 3260 cm.$^{-1}$ (NH) (Found: C, 82·3; H, 12·2%).

4-*Aza*-A-*homo*-5β-*androstane* (XV) crystallised readily and had m. p. 84—85°. The hydrochloride, prepared in ether, recrystallised from ethanol–ether; the base liberated by alkali was refluxed at 170°/0·001 mm.; it then crystallised, having m. p. 84—85°, $\nu_{max.}$ (in Nujol) 3320, 3220 (NH), 1630, 1550 cm.$^{-1}$ (Found: C, 82·55; H, 11·95%). When the aza-steroid was simply distilled at 100°/0·001 mm. the analytical figures were much lower. The hydrochloride, m. p. 280—290° with prior sublimation, had $\nu_{max.}$ (in Nujol) 1615, 1590 cm.$^{-1}$.

N-*Acetyl derivatives*. The aza-steroid (VIII, IX, XV, or XVI; 100 mg.) was treated with acetic anhydride (0·5 ml.) and pyridine (1 ml.) at 23° for 16 hr. The products were isolated by dilution with water and filtration, or by extraction with ether. After drying at 20°/1 mm. for 10 hr., chromatography on Davison silica gel columns (W. R. Grace and Co., Baltimore, Maryland, U.S.A.; 100—200 mesh; 3 g.) prepared in pentane, and elution with ether–chloroform, gave the pure acetyl derivatives, which were very soluble in all the usual solvents. Attempted use of aqueous methanol or ethanol did not afford nicely crystalline precipitates.

The N-*acetyl derivative* of base (IX) was eluted from silica gel with ether–chloroform (4 : 1) and formed needles, m. p. 113—115°, $\nu_{max.}$ (in Nujol) 1625 cm.$^{-1}$ [Found (after drying at 20°/1 mm. for 30 hr.): C, 79·5; H, 11·2. $C_{21}H_{35}NO$ requires C, 79·45; H, 11·1; N, 4·4%].

The N-*acetyl derivative* of base (VIII) was eluted from silica gel with ether–chloroform (2 : 3 and 1 : 3) and crystallised on evaporation of the eluates in needles, double m. p. 134—136°, 138°, $\nu_{max.}$ (in Nujol) 1640, 1630 cm.$^{-1}$ (C=O), no N–H stretching band at ~3400 cm.$^{-1}$ [Found (after drying at 25°/1 mm. for 30 hr.): C, 79·2; H, 11·2; N, 4·5%]. A Nujol mull of a sample which had not been specially dried exhibited a peak at 3450 cm.$^{-1}$ (OH), probably due to moisture.

The N-*acetyl derivative* of base (XVI) crystallised when rubbed with cold pentane and was eluted from silica gel with ether–chloroform (5 : 1 and 3 : 1); the eluted material crystallised as needles, m. p. 74—76°, $\nu_{max.}$ (in Nujol) 1640, 1625 cm.$^{-1}$ (C=O), no band at ~3400 cm.$^{-1}$ [Found (after drying at 15°/1 mm. for 40 hr.): C, 79·45; H, 10·9%].

The N-*acetyl derivative* of base (XV) was eluted from silica gel with ether–chloroform (3 : 1); it formed plates, m. p. 72—74°, $\nu_{max.}$ (in Nujol) 1645, 1610 cm.$^{-1}$ (C=O), no peak at ~3400 cm.$^{-1}$ [Found (after drying at 30°/1 mm. for 48 hr.): C, 79·25; H, 11·05%]. A Nujol mull prepared in a room without air-conditioning showed a peak at 3450 cm.$^{-1}$ (OH), probably due to traces of water.

N-*Nitroso-derivatives*. The aza-steroids (VIII, IX, XV, or XVI; 50 mg.) were dissolved in ether (5 ml.) saturated with distilled water, and shaken with a saturated solution of dinitrogen trioxide in distilled water at 20°. A precipitate of the base nitrite, often in the form of long needles, appeared almost immediately and dissolved after ~0·5 hr.; after 14 hr., the aqueous phase was removed, and the ethereal solution washed with sodium hydrogen carbonate and with water, dried (Na_2SO_4) and evaporated in a vacuum-desiccator over sulphuric acid. The *nitroso-derivatives*, obtained in nearly quantitative yield, were purified by chromatography on Davison silica gel columns prepared in pentane, and eluted with ether–pentane ($\nu_{max.}$ refer to Nujol mulls):

(IX), eluted with ether–pentane (1 : 4), needles, m. p. 109—112°, $\nu_{max.}$ 1410s, 1360, 1135 cm.$^{-1}$ (N=O), no N–H stretching band at ~3400 cm.$^{-1}$.

(VIII), eluted with ether–pentane (1 : 4), needles, m. p. 136—138°, $\nu_{max.}$ 1415s, 1370, 1145, 1140 cm.$^{-1}$ (N=O), no peak at ~3400 cm.$^{-1}$ [Found (after drying at 25°/1 mm. for 30 hr.): C, 75·15; H, 10·3. $C_{19}H_{32}N_2O$ requires C, 74·95; H, 10·6; N, 9·2%].

(XVI), eluted with ether–pentane (1 : 3 and 2 : 5), needles, m. p. 94—96°, $\nu_{max.}$ 1410s, 1295, 1110 cm.$^{-1}$ (N=O), no peak at ~3400 cm.$^{-1}$ [Found (after drying at 20°/1 mm. for 48 hr.): C, 75·3; H, 10·5; N, 9·0%].

(XV), eluted with ether–pentane (1 : 3), plates, that after being washed with a little cold pentane had a double m. p. 105—106°/128—130°, $\nu_{max.}$ 1410s, 1165, 1140 cm.$^{-1}$, no peak at 3400 cm.$^{-1}$ [Found (after drying at 20°/1 mm. for 48 hr.): C, 75·2; H, 10·15%].

N-*Ethyl derivatives*. The ε-lactam (VI, XI, or XII; R = H) was reduced for 2 days with lithium aluminium hydride in ether as described above, but the mixtures were decomposed with ethyl acetate. The usual procedure gave colourless oils, yielding, on addition of 10N-hydrochloric acid to their solutions in aqueous acetic acid, crystalline hydrochlorides which were recrystallised from ethanol–ether. The bases were then regenerated by alkali and extracted with ether. They formed carbonates only slowly and they were unattacked by acetic anhydride–pyridine at 20°. Infrared absorption spectra of the hydrochlorides, taken in potassium chloride discs, showed no features useful for identification above 1600 cm.$^{-1}$, apart from a broad band at 2610—2625 cm.$^{-1}$ which we cannot assign. The base from (XVI) had no characteristic band above 1360 cm.$^{-1}$.

From base (VIII). The lactam (V; R = H) (m. p. 303°, 100 mg.) furnished after reduction a hydrochloride, m. p. ~280° preceded by much sublimation, which yielded 4-*ethyl*-4-*aza*-A-*homo*-5α-*androstane* (60 mg.), m. p. 33—36° after long storage at −10° [Found (after distillation at 150°/1 mm.): C, 82·6; H, 12·1. $C_{21}H_{37}N$ requires C, 82·85; H, 12·05%].

From base (XVI). (*a*) The lactam (XII; R = H) (m. p. 245°; 100 mg.) afforded a hydrochloride as needles, m. p. 270° preceded by much sublimation, giving 3-*ethyl*-3-*aza*-A-*homo*-5β-*androstane* (55 mg.), needles, m. p. 58—62° [Found (after distillation at 150°/1 mm., and solidification of the distillate in a vacuum-desiccator over potassium hydroxide): C, 82·95; H, 12·25%].

(*b*) 3-Acetyl-3-aza-A-homo-5β-androstane (as XVI) (m. p. 74—76°; 20 mg.) was reduced with lithium aluminium hydride (30 mg.) in ether (2 c.c.) in a sealed tube at 100° for 5 hr. The mixture was decomposed with water, and the product isolated by extraction with ether; the resultant oil crystallised immediately on inoculation with preparation (*a*) in needles, m. p. 58—62°. This material was purified by chromatography on a column of Davison silica gel (0·6 g.), prepared in pentane; elution with pentane containing 5—15% of ether gave 3-ethyl-3-aza-A-homo-5β-androstane (18 mg.), m. p. and mixed m. p. 62—63°, identical in infrared spectrum with the product obtained as in (*a*).

From base (XV). The lactam (XI) (m. p. 205°; 100 mg.) yielded a hydrochloride, m. p. ~280°, which crystallised from ethanol–ether in rectangular prisms; this by basification gave 4-ethyl-4-aza-A-homo-5β-androstane as a colourless oil.

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Department of Organic Chemistry,
The University of Sydney.

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