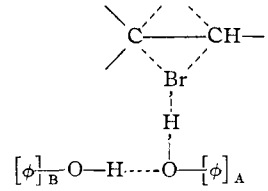
requirement of two moles (or molecular aggregates) of phenol in the catalyzed reaction transition state is most dramatically demonstrated in the crossed experiment. The data here show that a mixture of phenol and *o*-chlorophenol is approximately six times more efficient catalytically than either acting alone. We conclude from this result that each catalyst molecule coöperating in an act of catalysis can perform one of the two required functions *most* ably. *o*-Chlorophenol (the poorer catalyst where autoprotolysis is required in solvation of the halogen) is evidently the better solvator of oxygen. The reverse must be the case for phenol. The higher (apparent) activity of the mixture correlates with the transition state picture VI.

An alternate explanation for the crossed catalyst data may be gleaned from a representation of the



VI; $[\phi]_A$ is the phenol and $[\phi]_B$ is the *o*-chlorophenol

VII; the reverse of VI

transition state as VII. Here, conceivably, the more acidic chlorophenol proton solvates the halogen while the relatively more basic oxygen of the cooperating phenol moiety is acting to reduce the growing charge deficiency at C_6.

A program designed to investigate the generality of these observations and the scope of our conclusions is presently in progress in these laboratories.

NEWARK, DELAWARE

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF ILLINOIS INSTITUTE OF TECHNOLOGY]

17- and 17a-Aza-D-homosteroids[1,2]

BY BERNARD M. REGAN[3] AND F. NEWTON HAYES

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Rearrangement of several 17-ketosteroid oximes gave lactams which were shown by two independent methods to be 17a-aza-D-homosteroids, in agreement with a previous report. Rearrangement of a 16-oximino-17-ketosteroid gave a 17-aza-D-homosteroid imide, which was identified by hydrolysis to the corresponding, known dicarboxylic acid. Lithium aluminum hydride reduction of the lactams and imide provided 17a- and 17-aza-D-homosteroid amines, respectively, in excellent yield. Hydrolysis of the lactam function (in part) to an aminoacid hydrochloride and N-acylation of the lactams in ordinary fashion were accomplished contrary to a previous report.

This work was undertaken with the aim of preparing certain altered steroids, which we hoped would function as hormone antagonists or in fewer capacities than the polybiofunctional steroid hormones themselves. We chose to prepare various aza-D-homosteroids since certain oxa-D-homosteroid lactones[4] were shown to possess interesting physiological properties.

Recently, Beckmann rearrangement of 17-ketosteroid oximes was reported to yield 17a-aza-D-homosteroid lactams on the basis that selenium dehydrogenation of "dehydroisoandrololactam" (Vb) gave 1-azachrysene.[5]

We have found that rearrangement of 17-ketosteroid oximes with thionyl chloride in dioxane gave in general slightly higher yields of the desired lactams than Kaufmann's *p*-acetamidobenzenesulfonyl chloride–pyridine method. In the case of estrone oxime, in which the latter method was reported to yield only intractable tars, our method gave the lactam, 17a-aza-D-homoestrone (Ia), in 90% yield. Also, rearrangement with excess thionyl chloride alone was satisfactory, although more vigorous, but thionyl chloride in pyridine was too drastic and a dark, tarry product resulted.

3β-Acetoxy-5-androsten-16,17-dione 16-oxime rearranged only very slowly with a limited amount of thionyl chloride in dioxane and not at all with *p*-toluenesulfonyl chloride in pyridine at room temperature. However, rearrangement was smooth and rapid with excess thionyl chloride with or without benzene. The rearrangement product IX, isolated in 65% yield, was 3β-acetoxy-16,-17-seco-5-androsten-16,17-dioic 16,17-imide. Another theoretically possible[6] product, isomeric with IX, a cyanocarboxylic acid, *e.g.*, XII, was eliminated on the basis of the neutral nature and infrared spectrum of IX.

Conclusive proof of the imide structure was accomplished by alkaline hydrolysis first to an amido-acid, probably Xa, and then after ten days at 110° to the known[7-9] dicarboxylic acid, 3β-hydroxy-16,17-seco-5-androsten-16,17-dioic acid (Xb).

The 17-amido structure Xa was favored over the alternative 16-amido structure for the partially hydrolyzed imide IX because of the ease of attack by hydroxide ion on IX at the primary carboxyl (C_{16}) compared to the tertiary carboxyl (C_{17}), and because of the very slow hydrolysis of the amido-acid which is typical of C_{17} carboxyl derivatives.[7,10]

(1) This work was supported in part by grants from the U. S. Public Health Service.

(2) Abstracted from the Doctoral dissertation of Bernard M. Regan to the Graduate School of Illinois Institute of Technology.

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(4) R. P. Jacobsen, *et al.*, *J. Biol. Chem.*, **171**, 61, 71, 81 (1947).

(5) St. Kaufmann, THIS JOURNAL, **73**, 1779 (1951).

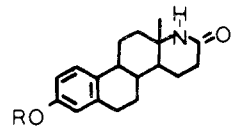
(6) *E.g.*, rearrangement of isonitrosocamphor with phosphorus pentachloride has given "α-camphornitrilic acid"; H. Rupe and I. Splittgerber, *Ber.*, **40**, 4313 (1907).

(7) S. Kuwada, *J. Pharm. Soc. Japan*, **56**, 75 (1936); S. Kuwada and K. Nakamura, *ibid.*, **58**, 835, 841 (1938).

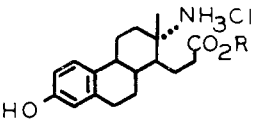
(8) A. Butenandt, J. Schmidt-Thomé, T. Weiss, D. von Dresler and U. Meinerts, *Ber.*, **72**, 417 (1939).

(9) A. Wettstein, H. Fritzsche, F. Hunzicker and K. Miescher, *Helv. Chim. Acta*, **24**, 332E (1941).

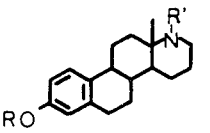
(10) See, *e.g.*, J. Heer and K. Miescher, *ibid.*, **28**, 156 (1945); **29**, 1895 (1946); **30**, 786 (1947); J. Heer, J. R. Billeter and K. Miescher, *ibid.*, **28**, 991 (1945).



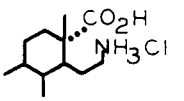
Ia, R=H
b, R=CH_3
c, R=Bz



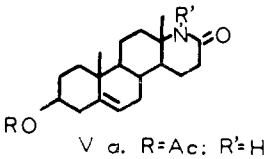
IIa, R=H
b, R=CH_3



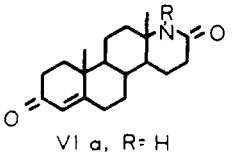
IIIa, R=R'=H
b, R=CH_3; R'=H
c, R=CH_3; R'=Ac



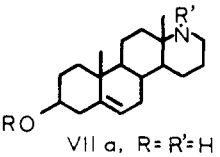
IV



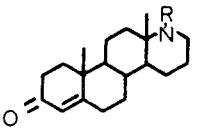
Va, R=Ac; R'=H
b, R=R'=H
c, R=R'=Ac



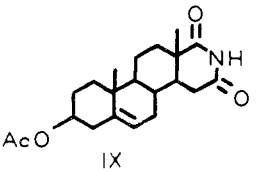
VIa, R=H
b, R=Bz



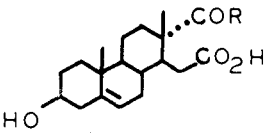
VIIa, R=R'=H
b, R=R'=Ac
c, R=H; R'=Ac



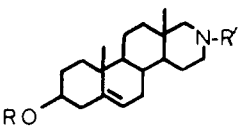
VIIIa, R=H
b, R=Ac
c, R=Bz



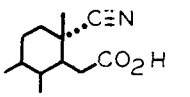
IX



Xa, R=NH_2
b, R=OH



XIa, R=R'=H
b, R=R'=Ac



XII

These results were in part anticipated, since rearrangement of isonitrosoestrone 3-methyl ether with phosphorus pentachloride, followed by strong alkaline hydrolysis for 14 days was reported[11] to yield "marrianolic acid 3-methyl ether." However, none of the intermediates were isolated.

Inasmuch as lactams of 17a-aza structure Ia and the isomeric 17-aza structure were both theoretically possible rearrangement products of estrone oxime, we investigated the structure by first hydrolyzing the lactam with hydrochloric acid in boiling acetic acid. Contrary to Kaufmann's report, acidic hydrolysis was successful. However, only an equilibrium mixture of unchanged lactam and aminoacid hydrochloride was formed within 30 hours. From the foregoing, it is obvious that two aminoacid hydrochloride structures IIa and IV are possible. The former, derived from the 17a-aza lactam Ia, is a primary carboxylic acid, while the latter, derived from the alternative 17-aza lactam, is a tertiary carboxylic acid. By analogy with the known esterification reactions of the primary-tertiary dicarboxylic acid Xb[7] and other similarly unsymmetrical dicarboxylic acids[12,13] we can predict that the aminoacid hydrochloride IIa and not IV would readily esterify with methanol and an acid catalyst.

Since the aminoacid hydrochloride obtained from the hydrolysis described above was completely esterified with 0.9 *M* hydrogen chloride in methanol within three hours at 65°, it, therefore, must be constituted as 3-hydroxy-13α-amino-13,17-seco-1,-3,5(10)-estratrien-17-oic acid hydrochloride (IIa). Consequently, the lactam precursor of IIa has the 17a-aza-D-homosteroid structure Ia.

(11) F. Litvan and R. Robinson, *J. Chem. Soc.*, 1997 (1938).
(12) V. C. E. Burnop and R. P. Linstead, *ibid.*, 720 (1940).
(13) A. Haller and G. Blanc, *Compt. rend.*, **141**, 697 (1905).

Titration of the aminoacid hydrochloride IIa with 0.1 *N* sodium hydroxide required only one equivalent and cyclization to the lactam Ia occurred instantaneously. Careful treatment of IIa with potassium bicarbonate in water and "salting out" gave apparently the free aminoacid, m.p. 373–37°, which was not characterized further.

Opening of the lactam ring with alkali was accomplished by way of the N-benzoyl lactam as has been reported for *trans*-2-aminocyclohexyl-β-propionic acid lactam.[14] Thus, treatment of the lactam VIa with benzoyl chloride and alkali in the cold gave the N-benzoyl lactam VIb. Hydrolysis of the latter with methanolic alkali gave an acid, m.p. 120° with effervescence, which we believe to be 3-oxo-13α-benzoylamino-13,17-seco-4-androsten-17-oic acid.

Lithium aluminum hydride reduction of the lactams Ia and Ib gave 17a-aza-D-homo-1,3,5(10)-estratrien-3-ol (IIIa) and its 3-methyl ether IIIb, respectively. 3β-Hydroxy-13α-amino-13,17-seco-5-androsten-17-oic 13,17-lactam (Vb) and preferably its 3-acetate Va were similarly reduced to 17a-aza-D-homo-5-androsten-3β-ol (VIIa). Moreover, similar reduction of the imide IX gave 17-aza-D-homo-5-androsten-3β-ol (XIa). All of these amines were isolated in very high yield.

There can be no doubt that the isomeric amines VIIa and XIa are different when they are compared together with their hydrochloride and diacetate derivatives. This fact corroborates the structure proofs advanced by Kaufmann and ourselves for the lactam and imide precursors of these amines.

Oppenauer oxidation of the lactam Vb and corresponding amine VIIa gave 3-oxo-13α-amino-13,17-seco-4-androsten-17-oic 13,17-lactam (VIa) and

(14) E. Bamberger and S. Williamson, *Ber.*, **27**, 1458 (1894); *cf.* W. Hückel and F. Stepf, *Ann.*, **453**, 163 (1927).

17a-aza-D-homo-4-androsten-3-one (VIIIa), respectively, in 84–91% yield. This represented a simpler and more efficient route to VIa than was reported previously.[5] Benzoylation of the 3-oxo-Δ^4-amine VIIIa by the Schotten–Baumann technique gave the corresponding N-benzoyl-3-oxo-Δ^4-amine VIIIc.

Kaufmann has indicated that N-acetylation of the 17a-aza-lactam Va required forcing conditions, *i.e.*, boiling acetic anhydride and *p*-toluenesulfonic acid. We find instead that O,N-diacetylation of Va to Vc can be accomplished simply by heating with acetic anhydride in pyridine at 90° for several hours.

As expected, the N-acetylamine function in IIIc and VIIc was stable to mild alkaline hydrolysis. Methylation and benzoylation of the phenolic lactam Ia in aqueous alkali preferentially formed the phenolic derivatives in high yield.

The biological testing of these compounds is under investigation at other laboratories.

Experimental[15]

Preparation of Oximes.—All 17-oximes were made by refluxing for two hours a solution of the appropriate 17-ketone and excess hydroxylamine acetate in ethanol.

When synthetic *d*-estrone (m.p. 260–261°) was used, **estrone oxime** crystallized from the water-diluted reaction mixture as shiny plates (solvated); m.p. 248–250° dec., with loss of solvent between 160–190°. For analysis, a sample was recrystallized from methanol and dried *in vacuo* at 100° over phosphorus pentoxide; m.p. unchanged; $[\alpha]^{27}D$ +74° (*c* 0.742 in dioxane).

Anal. Calcd. for $C_{18}H_{23}O_2N$: C, 75.75; H, 8.12; N, 4.91. Found: C, 75.28; H, 8.11; N, 5.13.

When U.S.P. naturally occurring estrone was used, sometimes this oxime and sometimes another lower melting, 231–233° dec., oxime (solvated) were isolated in the same manner described above. The lower melting oxime was always formed when 95% estrone (100% 17-ketosteroid by Kober assay), m.p. 252–257°, red melt,[16] was employed. Only the lower melting oxime has been reported[17,18] previously.

Either estrone oxime exhibits polymorphism or, more likely, the lower melting oxime is impure. The possibility that the oximes were stereoisomeric forms was not substantiated since both forms were rearranged to the same lactam in high yield (see below).

Methylation[19] of synthetic *d*-estrone and then oximation gave **estrone oxime 3-methyl ether**, which, after recrystallization from methanol, had m.p. 195–196°; $[\alpha]^{27}D$ +72° (*c* 0.757 in dioxane).

Anal. Calcd. for $C_{19}H_{25}O_2N$: C, 76.22; H, 8.42; N, 4.68. Found: C, 76.38; H, 8.43; N, 4.51.

An oxime of estrone methyl ether, m.p. 182–187°, prepared[20] previously was probably impure.

Dehydroepiandrosterone acetate gave an **oxime** as needles from aqueous alcohol; m.p. 177–179° (lit.[5] records m.p. 178–180°).

The isonitroso derivative of dehydroepiandrosterone acetate, **3β-acetoxy-5-androsten-16,17-dione 16-oxime** was prepared exactly as described[21] previously. From 10 g. of **3β-hydroxy-5-androsten-17-one** (m.p. 149–151°) the yield of 16-oxime, m.p. 181–183°, was 6.9 g. (55%) (lit.[21] records m.p. 183–184°). There were indications that the mother liquors contained another stereoisomeric form of this oxime.

Estrane Series

3-Hydroxy-13α-amino-13,17-seco-1,3,5(10)-estratrien-17-oic 13,17-Lactam (Ia) (17a-Aza-D-homoestrone).—A solution of 20.0 g. of estrone oxime (m.p. 248–250° or 231–233°) in 700 ml. of purified, dry dioxane at 40° was stirred as 20 ml. of purified thionyl chloride was added in five minutes. A white precipitate, which became yellow and then light brown, formed as the temperature rose to 49°. After stirring ten minutes longer, the reaction mixture was decomposed and made slightly alkaline by slow addition of 2000 ml. of an aqueous sodium bicarbonate solution. The precipitate was filtered, washed with water and dried. Then it was triturated with methanol to give the lactam Ia as an almost white powder, m.p. 373–377° dec. (sealed tube in a copper block); yield 16.5 g. It sublimed above 300°. Recrystallizations from acetic acid raised the melting point to 383–385° dec. (sealed tube). It was only sparingly soluble in organic solvents.

Anal. Calcd. for $C_{18}H_{23}O_2N$: C, 75.75; H, 8.12; N, 4.91. Found: C, 75.94; H, 8.32; N, 4.92.

This lactam was recently prepared[5] by a similar but circuitous route; m.p. above 360°, subliming at 200° and 0.005 mm.

The **3-benzoate Ic** was prepared from 500 mg. of 17a-aza-D-homoestrone in aqueous alkali by shaking vigorously with benzoyl chloride. The washed and dried precipitate, m.p. 300–310° dec., weighed 565 mg. It was recrystallized from methanol–chloroform; m.p. 320–322° (lit.[5] records m.p. 300–313°).

3-Methoxy-13α-amino-13,17-seco-1,3,5(10)-estratrien-17-oic 13,17-Lactam (Ib).—The oxime of estrone methyl ether was rearranged in the manner described above. From 2.0 g. of oxime, 1.6 g. of the desired lactam Ib was obtained after crystallization from aqueous methanol; m.p. 220–222°. Recrystallization raised the melting point to 222–224°; $[\alpha]^{27}D$ +95° (*c* 0.776 in dioxane); λ_{max} 279, 286 mμ (log ε 3.30, 3.26, resp.).

Anal. Calcd. for $C_{19}H_{25}O_2N$: C, 76.22; H, 8.42; N, 4.51. Found: C, 76.58; H, 8.60; N, 4.73.

This compound was also prepared by methylation of 500 mg. of 17a-aza-D-homoestrone (Ia) in aqueous alkali with dimethyl sulfate. The washed and dried precipitate weighed 505 mg.; m.p. 218–220°.

3-Hydroxy-13α-amino-13,17-seco-1,3,5(10)-estratrien-17-oic Acid Hydrochloride (IIa).—A solution of 5.0 g. of 17a-aza-D-homoestrone (Ia) in 1000 ml. of acetic acid and 250 ml. of concd. hydrochloric acid was refluxed for 30 hours in a nitrogen atmosphere, and then concentrated *in vacuo* to dryness. The solid residue was triturated with methanol–water (4:1) and then filtered to recover 2.2 g. of unchanged lactam. An additional 0.3 g. of Ia was recovered upon concentration of the filtrate until most of the methanol was removed. Then further concentration *in vacuo* to dryness gave a residue which was dissolved in a small amount of methanol. Addition of ether to the methanol solution precipitated the crude aminoacid hydrochloride IIa; yield 2.7 g. It was recrystallized from methanol–ethyl acetate as silky colorless needles with little loss; m.p. 375–380° dec. (sealed tube). Recrystallizations from methanol–ethyl acetate did not alter the melting point; $[\alpha]^{24}D$ +115° (*c* 0.765 in ethanol). The hygroscopic compound was dried to constant weight at 130° just before analysis.

Anal. Calcd. for $C_{18}H_{26}O_3NCl$: C, 63.61; H, 7.71; N, 4.12; Cl, 10.43. Found: C, 63.31; H, 7.91; N, 4.11; Cl, 10.43.

In other experiments, longer hydrolysis periods of 60 and 90 hours also gave Ia and IIa in about the same ratio.

A solution of 136.7 mg. of the amino acid hydrochloride IIa in distilled water was titrated with 0.1182 *N* sodium hydroxide. Only one equivalent (3.30 ml. of a calcd. 3.40 ml.) of alkali was consumed as cyclization to the parent lactam Ia occurred instantaneously.

However, when 100 mg. of IIa in 20 ml. of distilled water was neutralized with 30 mg. of potassium bicarbonate in 3 ml. of water, no immediate precipitation occurred and on standing overnight in the cold only a trace amount of pre-

(15) All melting points are uncorrected, and all ultraviolet spectra were determined in methanol solution using a Beckman model DU quartz spectrophotometer. Microanalyses by Micro-Tech Laboratories, Skokie, Illinois.

(16) Indicative of the presence of equilenin: *Cf.* G. Sandulesco, W. W. Tchung and A. Girard, *Compt. rend.*, **196**, 137 (1933).

(17) A. Butenandt and F. Hildebrandt, *Z. physiol. Chem.*, **199**, 243 (1931).

(18) S. A. Thayer, L. Levin and E. A. Doisy, *J. Biol. Chem.*, **91**, 791 (1931).

(19) A. Butenandt, I. Stormer and A. Westphal, *Z. physiol. Chem.*, **208**, 149 (1932).

(20) G. F. Marrian and G. A. D. Haslewood, *Biochem. J.*, **26**, 25 (1932).

(21) F. H. Stodola, E. C. Kendall and B. F. McKenzie, *J. Org. Chem.*, **6**, 841 (1941).

cipitate formed. The filtered solution was diluted with saturated sodium chloride solution and soon a chloride-free precipitate formed; m.p. 373–377° dec. (sealed tube). It redissolved in water and probably was the free **aminoacid** corresponding to IIa.

Methyl 3-Hydroxy-13α-amino-13,17-seco-1,3,5(10)-estratrien-17-oate Hydrochloride (IIb).—A solution of 500 mg. of aminoacid hydrochloride IIa in 10 ml. of anhydrous methanol containing 0.33 g. of hydrogen chloride was refluxed for three hours in a dry atmosphere. Then the mixture was concentrated *in vacuo* to dryness. The crystalline residue was redissolved in anhydrous methanol and precipitated by the addition of absolute ether; m.p. 375–380° dec. (sealed tube); yield 477 mg. Recrystallization from anhydrous methanol–absolute ether gave the desired methyl ester IIb as colorless needles with no change in m.p.; $[\alpha]^{24}D$ +100° (*c* 0.730 in ethanol).

Anal. Calcd. for $C_{18}H_{28}O_3NCl$: C, 64.48; H, 7.98; N, 3.96; Cl, 10.02. Found: C, 64.24; H, 8.22; N, 4.38; Cl, 9.96.

17a-Aza-D-homo-1,3,5(10)-estratrien-3-ol (IIIa).—In the extraction chamber of a Soxhlet apparatus there was placed 1.30 g. of 17a-aza-D-homoestrone (Ia), which was continuously extracted for 12 hours by refluxing a solution of 1.3 g. of lithium aluminum hydride in 130 ml. of dioxane. As a white precipitate steadily formed, the reaction mixture was refluxed for another 12 hours before it was decomposed by the cautious addition of 4 ml. of water, followed by boiling for 30 minutes. The hot mixture was filtered, and the filter cake washed with hot dioxane. Concentration of the filtrate *in vacuo* gave a white crystalline residue which was recrystallized from isopropyl alcohol. The desired amine IIIa, m.p. 310–315°, was obtained in 78% yield (0.96 g.). It was recrystallized from methanol, m.p. 312–315°.

Anal. Calcd. for $C_{18}H_{25}ON$: C, 79.66; H, 9.29; N, 5.16. Found: C, 79.54; H, 9.36; N, 5.32.

This amine was characterized by the formation of a water-insoluble **hydrochloride**; m.p. above 400°.

This hydrochloride was also prepared by refluxing a solution of 150 mg. of the 3-methoxyamine IIIb in 4 ml. each of concd. hydrochloric and acetic acids for 24 hours. It crystallized abundantly from the reaction mixture as colorless prisms, m.p. above 400°.

17a-Aza-D-homo-1,3,5(10)-estratrien-3-ol 3-Methyl Ether (IIIb).—Two grams of 17a-aza-D-homoestrone 3-methyl ether (Ib) was reduced with 1.0 g. of lithium aluminum hydride using the technique described above. The yield of 3-methoxyamine IIIb, m.p. 128–133°, was 1.81 g. Recrystallization from ether raised the m.p. to 135–136°.

Anal. Calcd. for $C_{19}H_{27}ON$: C, 79.95; H, 9.54; N, 4.91. Found: C, 79.55; H, 9.38; N, 5.25.

The **hydrochloride** of IIIb melted above 340°. A solution of this hydrochloride in water was treated at 5° with sodium nitrite and, after standing overnight in the cold, the **hydronitrite** of IIIb crystallized as shiny plates, m.p. 223–224° dec. Recrystallization from methanol–ethyl acetate raised the melting point to 232–233° dec.; λ_{max} 279, 286 mμ (log ε 3.29, 3.25, resp.). This salt was *basic* to litmus.

Anal. Calcd. for $C_{19}H_{28}O_3N_2$: C, 68.65; H, 8.49; N, 8.43. Found: C, 68.21; H, 8.57; N, 8.00.

The **N-acetyl derivative IIIc** was prepared from 500 mg. of 3-methoxyamine IIIb and 2 ml. of acetic anhydride in 5 ml. of pyridine at room temperature overnight. It was crystallized by cautious addition of water, m.p. 182–187°; yield 0.50 g. Recrystallization from alcohol raised the m.p. to 189–190°.

Anal. Calcd. for $C_{21}H_{29}O_2N$: C, 77.02; H, 8.93; N, 4.28. Found: C, 76.90; H, 8.78; N, 4.48.

This compound was recovered unchanged after boiling with potassium hydroxide in methanol solution for three hours.

Androstane Series

3β-Acetoxy-13α-amino-13,17-seco-5-androsten-17-oic 13,17-Lactam (Va).—A solution of 10.0 g. of 3β-acetoxy-5-androsten-17-one oxime in 175 ml. of dry dioxane was cooled to 15°, stirred and treated dropwise with a solution of 5 ml. of purified thionyl chloride in 25 ml. of dioxane. After 15 minutes, the reaction mixture was diluted with water, neutralized with ammonium hydroxide and extracted with methylene chloride. The washed extract was concentrated until the lactam Va crystallized as shiny plates, m.p. 289–292°; yield 6.45 g. (lit.[5] records m.p. 295–298°). This material was sufficiently pure for subsequent use.

Hydrolysis of 6.00 g. of Va in 90 ml. of methanol with 1.25 g. of potassium hydroxide by refluxing for one hour gave, after acidification with acetic acid and concentration, 5.16 g. of the expected **3β-hydroxy-Δ⁵-lactam Vb**, m.p. 290–295°. Recrystallization from methylene chloride–methanol raised the m.p. to 295–297° (lit.[5] records m.p. 292–295°).

Acetylation of 50 mg. of Vb with 0.5 ml. of acetic anhydride in 2 ml. of pyridine at 0° for 16 hours regenerated the **3-monoacetate Va**, m.p. 288–291°.

Moreover, acetylation of 303 mg. of Vb with 2 ml. of acetic anhydride in 5 ml. of pyridine, by heating on the steam-bath, gave 372 mg. of crude **3,17a-diacetate Vc**, m.p. 158–161°. This product was dissolved in ether, filtered to remove a trace amount of 3-monoacetate Va and then crystallized to yield colorless prisms, m.p. 160–162° (lit.[5] records m.p. 162–165°).

3-Oxo-13α-amino-13,17-seco-4-androsten-17-oic 13,17-Lactam (VIa).—A solution of 2.40 g. of the 3β-hydroxy-Δ⁵-lactam Vb in 24 ml. of cyclohexanone, 100 ml. of dry dioxane and 85 ml. of dry toluene was distilled slowly as a solution of 2.2 g. of aluminum isopropylate in 11 ml. of toluene was added. Distillation was continued for two hours as 60 ml. of toluene was added and 160 ml. of distillate collected. Then the mixture was refluxed for four hours and let stand at room temperature overnight. The mixture was filtered to remove an orange precipitate containing all the aluminum. The almost colorless filtrate was steam distilled, extracted with methylene chloride, and the washed extract was concentrated to dryness. The lactam VIa was crystallized from ethyl acetate; m.p. 255–260°; yield 2.19 g. (91% theory). Recrystallization from ethyl acetate gave colorless prisms of m.p. 261–263°; $[\alpha]^{28}D$ +85° (*c* 0.825 in alcohol); λ_{max} 240 mμ (log ε 4.22).

This lactam was recently prepared[5] by a different route and had m.p. 261–263°, but the reported log ε 4.36 for the 240 mμ maxima was too high.[22]

A solution of 300 mg. of the 3-oxo-Δ⁴-lactam VIa in 3 ml. of methylene chloride was shaken vigorously with 20 ml. of ice-cold 15% sodium hydroxide solution as 2 ml. of benzoyl chloride was added portionwise in an hour with continual cooling. Then the mixture was shaken at room temperature for 30 minutes, *i.e.*, until the characteristic odor of benzoyl chloride disappeared. The neutral product was extracted with methylene chloride and crystallized from ether, m.p. 210–215°; yield 345 mg. It was recrystallized from ethyl acetate; m.p. 213–216°; λ_{max} 240 mμ (log ε 4.40). It was assumed to be the **N-benzoyl 3-oxo-Δ⁵-lactam VIb.**

17a-Aza-D-homo-5-androsten-3β-ol (VIIa).—To a refluxing solution of 1.0 g. of lithium aluminum hydride in 100 ml. of dioxane, there was added a solution of 3.00 g. of the 3β-acetoxy-Δ⁵-lactam Va in 200 ml. of dioxane. A white precipitate steadily formed, so the mixture was refluxed for two days. Then 6 ml. of water was added cautiously and, after refluxing for one hour, the hot mixture was filtered through filter-cel and the filtrate concentrated to dryness *in vacuo*. The crystalline residue was dissolved in 20% hydrochloric acid and the solution filtered to clarify. Neutralization of the filtrate with sodium hydroxide solution produced a voluminous white precipitate of the desired amine VIIa; m.p. 224–228°; yield 2.3 g. (92%). Recrystallization from methanol raised the m.p. to 231–233°.

Anal. Calcd. for $C_{19}H_{31}ON$: C, 78.83; H, 10.80; N, 4.84. Found: C, 78.46; H, 10.87; N, 5.17.

This amine was also made by similar reduction of the corresponding lactam Vb. The **hydrochloride** of VIIa had m.p. 333–336° dec.

Acetylation of 0.59 g. of VIIa with 3 ml. of acetic anhydride in 6 ml. of pyridine at room temperature for five hours gave, upon careful dilution of the mixture with water, the **N-acetyl-3β-acetoxy-Δ⁵-amine VIIb** with m.p. 196–197°; yield 0.72 g. It formed needles (solvated), m.p. 197–198°, from methanol, and, for analysis, was dried at 100° over phosphorus pentoxide *in vacuo*.

Anal. Calcd. for $C_{23}H_{35}O_3N$: C, 73.95; H, 9.44; N, 3.75. Found: C, 73.92; H, 9.87; N, 3.69.

Hydrolysis of 0.37 g. of diacetate VIIb with 1 ml. of 10% sodium hydroxide solution in 10 ml. of refluxing methanol

(22) *Cf.* L. Dorfman, *Chem. Revs.*, **53**, 47 (1953).

for five minutes and another 30 minutes at room temperature gave 0.32 g. of **N-acetyl-3β-hydroxy-Δ⁵-amine VIIc** with m.p. 269–272°. Recrystallization from methanol gave small prisms; m.p. 278–280°.

Anal. Calcd. for $C_{21}H_{33}O_2N$: C, 76.09; H, 10.03; N, 4.23. Found: C, 76.43; H, 9.87; N, 4.03.

17a-Aza-D-homo-4-androsten-3-one (VIIIa).—A solution of 2.00 g. of 3β-hydroxy-Δ⁵-amine VIIa in 20 ml. of cyclohexanone and 180 ml. of dry toluene was slowly distilled as 2.0 g. of aluminum isopropylate in 10 ml. of toluene was added. Distillation was continued for 30 minutes as 40 ml. of distillate was collected. The mixture was refluxed 1.5 hours and then let stand for 12 hours. It was filtered to remove an orange precipitate which contained all of the aluminum. The filtrate was steam distilled and then extracted with ether. The extract was washed with water and then with dilute hydrochloric acid. Neutralization of the acidic washes with sodium hydroxide solution, reextraction with ether and then concentration of the dried extract gave 1.68 g. (84%) of the expected 3-oxo-Δ⁴-amine VIIIa; m.p. 136–138°; λ_{max} 239, 312 mμ (log ε 4.22, 1.94, resp.). It was extremely soluble in methanol from which it was difficult to precipitate even with water.

This amine gave a **hydrochloride** which crystallized from methanol–ethyl acetate as needles (solvated); m.p. 325° dec.; λ_{max} 239 mμ (log ε 4.23). It was dried at 100° over phosphorus pentoxide *in vacuo* for several hours before analysis.

Anal. Calcd. for $C_{19}H_{30}ONCl \cdot {}^1/_2CH_3OH$: C, 68.89; H, 9.49; N, 4.12. Found: C, 68.63; H, 9.42; N, 4.76.

Acetylation of 160 mg. of VIIIa with 0.4 ml. of acetic anhydride in 0.4 ml. of pyridine at room temperature overnight gave, upon careful precipitation with water, 170 mg. of **N-acetyl-3-oxo-Δ⁴-amine VIIIb**; m.p. 155–157°. It was recrystallized from acetone–isopropyl ether with no change in m.p.; λ_{max} 240 mμ (log ε 4.23).

A solution of 144 mg. of VIIIa in 16 ml. of ether and 8 ml. of 5% sodium hydroxide solution was cooled and then shaken vigorously as 0.14 g. of benzoyl chloride in 4 ml. of ether was added during 30 minutes. A precipitate formed which, after additional shaking at room temperature for 30 minutes, was filtered, washed and dried. It weighed 149 mg.; m.p. 230–233°. An additional 39 mg. was isolated from the ethereal filtrate. Recrystallization of the combined crops from methanol gave the **N-benzoyl-3-oxo-Δ⁴-amine VIIIc** with m.p. 234–236°; λ_{max} 240 mμ (log ε 4.34).

3β-Acetoxy-16,17-seco-5-androsten-16,17-imide (IX).—Rearrangement of 4.10 g. of 3β-acetoxy-5-androsten-16,17-dione 16-oxime in 20 ml. of purified thionyl chloride at 0–5° proceeded smoothly with gas evolution. After one hour in the cold and one hour at room temperature, the deep red solution was concentrated *in vacuo* with gentle heating. The residue was dissolved in methylene chloride and washed with sodium bicarbonate solution and then water. The desired imide IX was crystallized from methylene chloride; m.p. 254–259°; yield 2.79 g. It was recrystallized from ethyl acetate as needles, m.p. 257–259°.

Anal. Calcd. for $C_{21}H_{29}O_4N$: C, 70.16; H, 8.13; N, 3.90. Found: C, 70.52; H, 8.50; N, 4.40.

The infrared spectrum (Perkin–Elmer double beam spectrophotometer) of IX (Nujol mull) had principal absorption bands at (cm.$^{-1}$) 3250, 2945 (broad), 1710 (strong), 1680 (strong), 1425, 1405, 1350, 1335, 1300, 1265 (strong), 1245 (strong), 1220, 1195, 1180, 1120 and 1020.

Attempted rearrangement of the α-keto-oxime with *p*-toluenesulfonyl chloride in pyridine solution at 30–35° for 24 hours failed; unchanged starting material was recovered in 96% yield.

3β-Hydroxy-16,17-seco-5-androsten-16,17-dioic Acid 17-Amide (Xa).—A solution of 238 mg. of the 3β-acetoxy-Δ⁵-imide IX in 50 ml. of methanol was treated with 10 ml. of 0.28 *N* sodium hydroxide solution. After standing overnight, the mixture was refluxed for three hours, concentrated *in vacuo*, neutralized with hydrochloric acid and extracted with methylene chloride. The organic extract was washed with 2% sodium carbonate solution. The alkaline wash was acidified to congo red and the desired amide Xa precipitated; m.p. 253–255° dec. with gas evolution; yield 201 mg. (93% theory). For analysis, a sample was recrystallized from alcohol; m.p. 255–257° dec., gas evolution.

Anal. Calcd. for $C_{19}H_{29}O_4N$: C, 68.03; H, 8.71; N, 4.18. Found: C, 68.03; H, 8.71; N, 4.41.

A mixture of 155 mg. of 3β-acetoxy-Δ⁵-imide IX and 3 g. of potassium hydroxide in 9 ml. of water was heated at 110° in an autoclave for 12 days (*cf.* ref. 11). The diluted mixture was filtered; acidification of the filtrate gave 122 mg. of a brown solid precipitate; m.p. 240–245°. The precipitate was decolorized (Norite) and crystallized twice from aqueous methanol to give **3β-hydroxy-16,17-seco-5-androsten-16,17-dioic acid (Xb)** as colorless needles; m.p. 250–251°; neut. equiv. 115 (calcd. 118). It did not depress the m.p. of an authentic sample[9] of "3β-hydroxy-Δ⁵-etiobilienic acid."

17-Aza-D-homo-5-androsten-3β-ol (XIa).—Using a Soxhlet extraction apparatus, 1.6 g. of 3β-acetoxy-Δ⁵-imide IX was reduced with 1.6 g. of lithium aluminum hydride in 320 ml. of ether by continuous extraction for two days, followed by refluxing another day. The mixture was decomposed by cautious addition of 9 ml. of water, then refluxed an hour and filtered. The product was extracted from the filtrate with 1% hydrochloric acid and precipitated by addition of aqueous alkali; m.p. 185–188°; yield 1.21 g. (94%). This amine XIa was recrystallized from aqueous methanol; m.p. 191–193°

The **hydrochloride** of XIa was prepared and crystallized from methanol–ethyl acetate; m.p. 318–320° dec.

Anal. Calcd. for $C_{19}H_{32}ONCl$: C, 70.02; H, 9.90; N, 4.30. Found: C, 69.81; H, 9.99; N, 4.95.

A solution of 260 mg. of amine XIa in 2 ml. each of acetic anhydride and pyridine was allowed to stand 12 hours. The **N-acetyl-3β-acetoxy-Δ⁵-amine XIb** was precipitated by careful addition of water; m.p. 205–209°; yield 322 mg. It was recrystallized from methanol; m.p. 208–210°.

Anal. Calcd. for $C_{23}H_{35}O_3N$: C, 73.95; H, 9.45; N, 3.75. Found: C, 74.40; H, 9.73; N, 3.87.

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