164.5°. For analysis this sample was recrystallized twice from ether–pentane solution to yield 73 mg., m.p. 163.5–165°; $[\alpha]^{25}D$ −13.6° (1% ethanol).

Anal. Calcd. for $C_{19}H_{28}O_2$: C, 79.13; H, 9.78. Found: C, 79.30; H, 9.73.

The remaining material was rechromatographed on neutral, activity III alumina. The latter fractions, eluted with 1:4 ether–pentane solution, were combined and recrystallized first from ether–pentane solution and then from methanol–water solution to yield 50 mg. of isomer *b*, m.p. 155–158°, softening 143–155°; $[\alpha]^{25}D$ + 137 ± 4° (1%, ethanol).

Anal. Calcd. for $C_{19}H_{28}O_2$: C, 79.13; H, 9.78. Found: C, 79.23; H, 9.65.

K. Dehydration of Isomer *a* Isolated from the Products of Deamination of 3α-Aminoandrost-5-en-17-one.—Isomer *a* (20.5 mg.) was dissolved in 3 ml. of glacial acetic acid and 0.2 ml. of concentrated hydrochloric acid was added. The resulting solution was allowed to stand at room temperature for 21 hr. and then shaken with a mixture of 30 ml. of water and 25 ml. of chloroform. The chloroform solution was washed with two 15-ml. portions of water, 15 ml. of 5% sodium bicarbonate solution, and two 10-ml. portions of water and dried over anhydrous magnesium sulfate. The chloroform was evaporated leaving an orange oil which partially crystallized on standing. This material was chromatographed on 2 g. of neutral, activity III alumina. Elution with 1:10 ether–pentane solution yielded 11 mg. of a white crystalline solid which was recrystallized from methanol–water solution to yield 6 mg. of androsta-3,5-dien-17-one, m.p. 89–90°, λ_{max} 234 mμ (ethanol) lit.,[38] m.p. 88–89°, λ_{max} 234 mμ (ether).

Acknowledgment.—The authors thank Mr. W. H. Washburn and associates for infrared determinations, Messrs. Frank Chadde and David Wimer for ultraviolet spectra, and Mr. E. Shelberg and staff for microanalyses, all at Abbott Laboratories. The n.m.r. spectra were run at Battelle Memorial Institute by Mr. T. F. Page.

(38) Elsevier, "Encyclopedia of Organic Chemistry," Springer-Verlag, Berlin, **14s**, 2400s.

Preparation of the Epimeric 3-Aminoandrost-5-en-17-ones and 6-Amino-3α,5α-Cycloandrostan-17-ones. The Mechanism of the Ammonolysis of Steroid-Δ⁵-3β *p*-Toluenesulfonates

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Ammonolysis of the *p*-toluenesulfonate of 3β-hydroxy-17-ethylenedioxyandrost-5-ene yielded 6β-amino-17-ethylenedioxy-3α,5α-cycloandrostane as well as 3α- and 3β-amino-17-ethylenedioxyandrost-5-ene. 6α-Amino-17-ethylenedioxy-3α,5α-cycloandrostane resulted from sodium–ethanol reduction of 6-oximino-17-ethylenedioxy-3α,5α-cycloandrostane. Acid hydrolysis of the ketal groups yielded the corresponding 17-keto amines. Structural and configurational assignments are based on nuclear magnetic resonance and infrared spectra as well as correlations of optical rotations and behavior on vapor phase chromatography. The present results indicate that the 3α,5α-cyclo-6-amines formed by ammonolysis of Δ⁵-3β *p*-toluenesulfonates have the 6β-amino configuration in accord with the assignment of Haworth[1c] and, thus, that the mechanism of the homoallylic rearrangement which occurs on ammonolysis must be closely related to mechanisms of the rearrangements which occur during other types of solvolyses.

It has been reported[1] that ammonolysis of cholesteryl *p*-toluenesulfonate yields 6β-amino-3α,5α-cyclocholestane as the major product together with smaller amounts of both 3α- and 3β-aminocholest-5-ene. Sodium–ethanol reduction of 6-oximino-3α,5α-cyclocholestane was reported to yield the epimeric 6α-amino-3α,5α-cyclocholestane.[2] The configurations of the 6-amino-3α,5α-cyclocholestanes, I and II (R = C_8H_{17}), have been based on the assumption that the ammonolysis of steroid-Δ⁵-3β *p*-toluenesulfonates, like other types of solvolysis such as hydrolysis, acetolysis, and methanolysis, gives rise to the rearranged product with the 6β-substituent.[1c] The optical rotations of the 3α,5α-cyclo-6-amines are consistent with these assignments in that the optical rotations of 3α,5α-cyclo-6β derivatives are, in general, less positive than are those of the 6α epimers,[3] but there has been no convincing direct evidence. Although Evans and Summers[2] have interpreted the deaminations of the 6α- and 6β-amino-3α,5α-cyclocholestanes as providing evidence for the configurations of these amines, their conclusions are based on the minor products of the reactions and have not been found generally applicable.[4]

The present work was initiated with the object of adapting the reactions developed in the cholesteryl series to the preparation of related steroid-Δ⁵-3-amines and 3α,5α-cyclo-6-amines with other functional groups of the types found in naturally occurring hormones. The preparations of the 3α- and 3β-aminoandrost-5-en-17-ones and the 6α- and 6β-amino-3α,5α-cycloandrostan-17-ones were accomplished by protecting the 17-carbonyls as the ethylene ketals during introduction of the amino groups. In the course of this work additional criteria for the configurations of C-6-epimeric

(1) (a) P. L. Julian, A. Magnani, E. W. Meyer, and W. Cole, *J. Am. Chem. Soc.*, **70**, 1834 (1948); (b) R. D. Haworth, J. McKenna, and R. G. Powell, *J. Chem. Soc.*, 1110 (1953); (c) R. D. Haworth, L. H. C. Lunts, and J. McKenna, *ibid.*, 986 (1955).

(2) D. E. Evans and G. H. R. Summers, *ibid.*, 906 (1957).

(3) E. M. Kosower and S. Winstein, *J. Am. Chem. Soc.*, **78**, 4347 (1956).

(4) J. Tadanier and W. Cole, *J. Org. Chem.*, **27**, 4615 (1962).

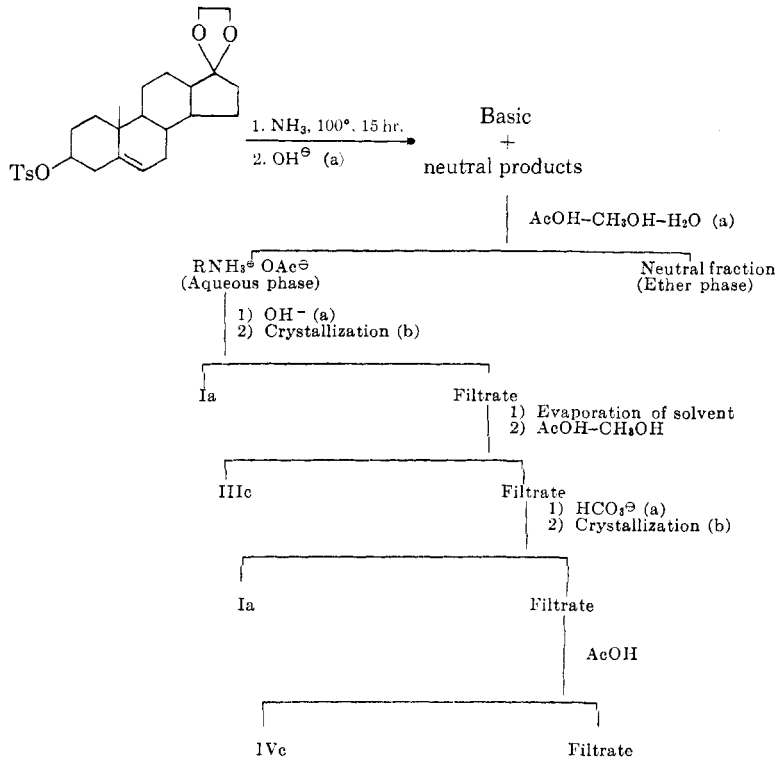
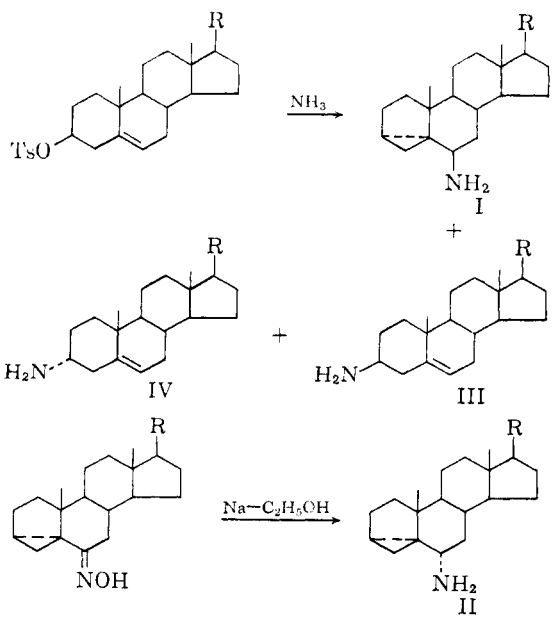


Fig. 1.[c]—Flow sheet—isolation of ammonolysis products.
(a) Ether extraction. (b) From ether–pentane solution.
(c) For structural formulas of the products see Table I.

3α,5α-cyclo-6-amines were obtained which provide a direct comparison of the stereochemistry of the rearrangement which occurs on ammonolysis of Δ^5-3β *p*-toluenesulfonates with that of rearrangements which result from other types of solvolysis.

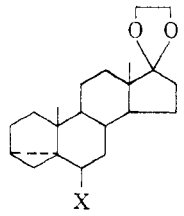
Ammonolysis of the *p*-Toluenesulfonate of 3β-Hydroxy - 17 - ethylenedioxyandrost - 5 - ene.—Treatment of the *p*-toluenesulfonate of 3β-hydroxy-17-ethylenedioxyandrost-5-ene with ammonia at

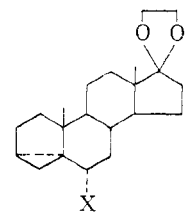


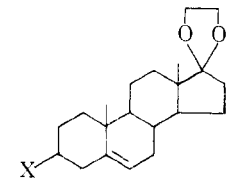
100° for fifteen hours led to a mixture of products from which the basic fraction was separated by extraction as the water-soluble mixture of acetic acid salts. In this manner the neutral and basic fractions were separated without hydrolysis of the 17-ketal. 6β-Amino-17-ethylenedioxy-3α,5α-cycloandrostane (Ia) was separated by crystallization as the free amine. 3β-Amino-17-ethylenedioxyandrost-5-ene (IIIa) and 3α-amino-17-ethylenedioxyandrost-5-ene (IVa) were isolated by fractional crystallization as the acetic acid salts, IIIc and IVc. The procedure used for the isolation of these products is outlined in Fig. 1. The ketal amines, Ia and IIIa, were characterized as the acetamides, Ib and IIIb. The acetic acid salt, IVc, was converted to the free amine, IVa, by treatment with a mixture of 5% sodium carbonate solution and ether. Treatment of the ketal amine, Ia, and the acetic acid salts, IIIc and IVc, with excess hydrochloric acid led to crystallization of the keto amine hydrochlorides which were readily converted to the free keto amines, IA, IIIA, and IVA on treatment with base. The keto amines were characterized as the acetamides, IB, IIIB and IVB, and each amine formed a stable, crystalline acetic acid salt (Table I).

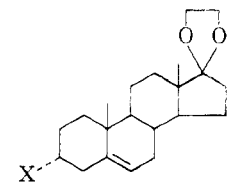
Reduction of 6-Oximino-17-ethylenedioxy-3α,5α-cycloandrostane.—Sodium–ethanol reduction of 6-oximino-17-ethylenedioxy-3α,5α-cycloandrostane was carried out by a procedure similar to that employed by Evans and Summers[2] for the reduc-

TABLE I
PHYSICAL PROPERTIES[a,b]

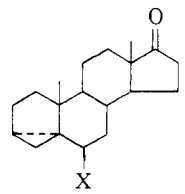


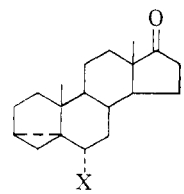


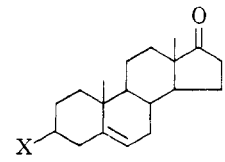


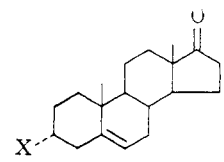


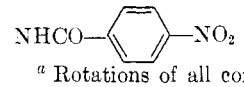
X	M.p., °C.	[α]D	M.p., °C.	[α]D	M.p., °C.	[α]D	M.p., °C.	[α]D
NH_2	Ia 108–110	+18.5	IIa ...	...	IIIa ...	...	IVa 146–148	−87.8
$NHCOCH_3$	Ib 158–160	−19	IIb 198–200	+53	IIIb 218–219	−85	IVb ...	...
$NH_3^{\oplus}OAc^{\ominus}$	Ic ...	...	IIc ...	...	IIIc 218–225	−64	IVc 128–130	...









X	M.p., °C.	[α]D	M.p., °C.	[α]D	M.p., °C.	[α]D	M.p., °C.	[α]D
NH_2	IA 100–101	+112	IIA 70–72	+160.5	IIIA 132–134	+9.2	IVA 176–184	−4.7
$NHCOCH_3$	IB 140–141	+79.2	IIB 117–134[c]	+163.5	IIIB 226.5–227.5	−3	IVB 224.5–226.5	−20.4
$NH_3^{\oplus}OAc^{\ominus}$	IC 125–126	+72.5	IIC dec. >266	+125.6	IIIC dec. >260	+16.6	IVC 154–158 dec.	+9.7
$NH_3^{\oplus}Cl^{\ominus}$	ID 262–264	+81	IID dec. >260	+128.6	IIID dec. >300	...	IVD 270–273 dec.	...
	IE 247–249	+66	IIE 165–168	+101	IIIE ...	...	IVE ...	...

[a] Rotations of all compounds other than the acetic acid salts and the amine hydrochlorides were taken in chloroform solution (*c* 1%). The rotations of the salts were taken in methanol (*c* 1%) on material dried to constant weight under high vacuum and are not corrected for any solvent of crystallization. [b] Melting points were taken in open capillaries and are uncorrected. [c] Purity established by vapor phase chromatography.

tion of 6-oximino-3α,5α-cyclocholestane. The basic fraction was readily separated from the mixture of products as the water-soluble acetic acid salt. The mixture of ketal amines thus isolated was converted to a mixture of ketal acetamides with acetic anhydride in pyridine. 6α-Acetamido-17-ethylenedioxy-3α,5α-cycloandrostane (IIb) separated as a gel from an acetone–ether–pentane solution and was crystallized from methanol–water solution. The 6α- and 6β-acetamido ketals (IIb and Ib) were cleanly separated on both polar and nonpolar columns on vapor phase chromatography (Table II). The vapor phase chromatography allowed the estimate that the reduction of the 3α,5α-cyclo-6 oxime led to a mixture of amines consisting of approximately 75% of the 6α-amine, IIa, and 25% of the 6β-amine, Ia.

Isolation of 6α-amino-3α,5α-cycloandrostan-17-one (IIA) was accomplished by recrystallization of the hydrochloride prepared from the mixture of ketal amines obtained by reduction of the 3α,5α-cyclo-6 oxime. The 3α,5α-cyclo-6α-amine (IIA), obtained from the hydrochloride, formed a crystalline acetic acid salt, IIC, and was characterized as the acetamide, IIB, and *p*-nitrobenzamide, IIE. A sharp melting sample of the acetamide was not obtained, but there was an indication that the product crystallized with ether of solvation. The 6α- and 6β-acetamido ketones, IIB and IB, were cleanly separated by vapor phase chromatography on both polar and nonpolar columns (Table II). The pure 6α-acetamide showed no trace of the epimer.

Structural and Configurational Assignments.—The nuclear magnetic resonance spectra of the keto acetamides clearly distinguished between the 3α,5α-cyclo derivatives, IB and IIB, and Δ^5 isomers, IIIB and IVB, on the basis of vinyl *vs.* cyclopropyl proton absorption. The vinyl protons of IIIB and IVB were characterized by absorption at 322 c.p.s. while the spectra of IB and IIB showed complex absorption between 0–50 c.p.s. because of absorption by the cyclopropyl protons at C-3 and C-4 (Fig. 2).

In the present series, as was found for the corresponding cholesterols[3] and cholesterylamines,[1,2] the optical rotations of the 3α,5α-cyclo derivatives are much more positive than those of the Δ^5 isomers (Table I). For both the 6-amino-3α,5α-cycloandrostan-17-ones and the 6-amino-3α,5α-cyclocholestanes, the optical rotations of the amines formed by ammonolysis of the Δ^5-3β *p*-toluenesulfonates are much less positive than those of the epimers formed by sodium–ethanol reduction

of the 3α,5α-cyclo-6 oximes. These rotations are consistent with those of the epimeric 6-hydroxy-3α,5α-cyclocholestanes prepared by analogous methods since the product (*i*-cholesterol) resulting from hydrolysis of cholesteryl *p*-toluenesulfonate has a rotation less positive than that of the epimer (*epi-i*-cholesterol) formed by reduction of 3α,5α-cyclocholestan-6-one.[3] These correlations, thus, suggest that the 3α,5α-cyclo-6-amines and alcohols formed by the solvolysis reactions have the same configurations at C-6 and that their epimers are formed by reduction of the 3α,5α-cyclo-6 oxime and ketone, respectively.

Although chromatographic behavior is not an unambiguous criterion of configuration,[5] it has been established that on adsorption chromatography, steroids with more highly hindered axial substituents are generally eluted before the equatorial epimers. In the case of the 6-hydroxy-3α,5α-cyclocholestanes, it was found[3] that the hydrolysis product with 6β-axial hydroxyl was eluted before the 6α-equatorial epimer formed by reduction of 3α,5α-cyclocholestan-6-one.

It has recently been established that a similar correlation exists with regard to behavior of axial and equatorial epimers on vapor phase chromatography. Steroids with axial substituents are generally detected before their equatorial epimers.[6] In the present work it was found that a synthetic mixture of the isomeric keto acetamides was cleanly separated on both polar and nonpolar columns. The 3α,5α-cyclo amides were detected before the Δ^5 isomers. Of the 3α,5α-cyclo amides, the keto acetamide IB derived from the ammonolysis product was detected before the amide IIB derived from the reduction product (Table II). This behavior is thus consistent with the 6β-axial and 6α-equatorial acetamido groups of IB and IIB, respectively.

The order of detection of the epimeric 3-acetamidoandrost-5-enes was indicative of 3α-axial and 3β-equatorial acetamide groups of IVB and IIIB, respectively (Table II).

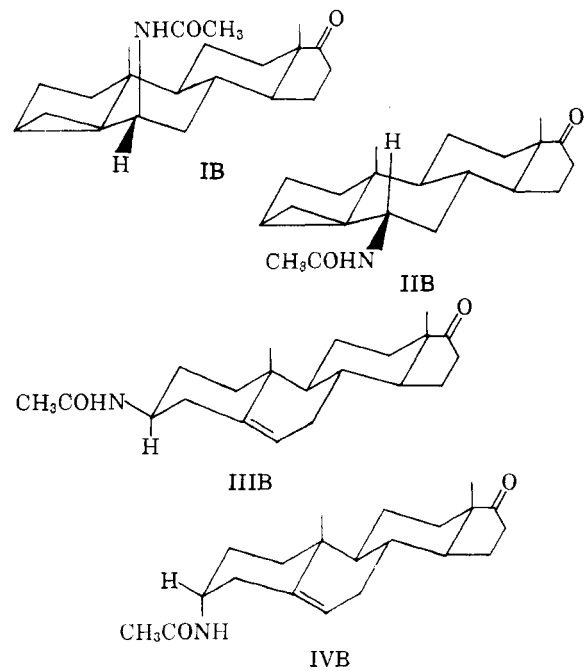


TABLE II

VAPOR PHASE CHROMATOGRAPHY—RELATIVE RETENTION TIMES (t = 222°)[a] (PROGESTERONE = 1.00)

Column	IB	IIB	IVB	IIIB
A. Keto Acetamides				
0.25% QF-1	0.79	1.05	1.29	1.61
.7% SE-30	.74	1.0	1.22	1.58
B. Ketal Acetamides				
Column	Ib	IIb		
4% SE-30	1.22	1.62		
3% F-50	1.19	1.58		

Column Characteristics: (Glass, 6-mm. diameter; flash heater, 250°; solid support Chromosorb W, 60–80 mesh)

Stationary phase[b]	0.25% QF-1	0.7% SE-30	4% SE-30	3% F-50
Column length	8.0 ft.	8.0 ft.	6.0 ft.	8.0 ft.
Inlet pressure, p.s.i.	20	25	20	20
Flow rate, ml./min.	95	95	80	80
Time for progesterone	5.1 min.	6.5 min.	14.1 min.	17.6 min.

[a] Run on Barber–Colman Model 10 gas chromatograph with argon ionization detector. [b] QF-1, a fluorinated alkyl silicone, Dow Corning Corp.; SE-30, a silicone polymer, General Electric Co.; F-50, General Electric Versilube, a chlorophenyl methyl silicone.

Further evidence for these configurations is provided by infrared spectra. As a consequence of the sensitivity of intermolecular hydrogen bonding to steric hindrance, the appearance of the NH stretching regions of the four keto acetamides reveals their axial or equatorial characters. The spectra were all determined with 7% solutions in chloroform.[7] The spectra of the acetamides IB and IVB show only sharp peaks at 3484 cm.$^{-1}$ and 3401 cm.$^{-1}$, respectively, characteristic of free NH absorption.[8] The spectra of IIB and IIIB on the other hand show, in addition to the free NH absorptions at 3401 cm.$^{-1}$ and 3390 cm.$^{-1}$, respectively, broad, bonded NH absorptions centered at 3279 cm.$^{-1}$. These characteristic differences are indicative of the inhibition of intermolecular hydrogen bonding of the hindered axial acetamido groups of IB and IVB.

(5) D. H. R. Barton and G. A. Morrison, "Conformational Analysis of Steroids and Related Products," in "Progress in the Chemistry of Organic Natural Products," Wien, Springer Verlag, 1961, p. 188.

(6) W. J. A. Vandenheuvel, Abstracts of the 140th National Meeting of the American Chemical Society, Chicago, Ill., September 3–8, 1961, p. 68-Q.

(7) A. J. Kammer, W. H. Washburn, and P. Kurath, *Appl. Spectry.* **15**, 178 (1961).

(8) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd ed., John Wiley & Sons, Inc., New York, N. Y., 1958, pp. 203–209.

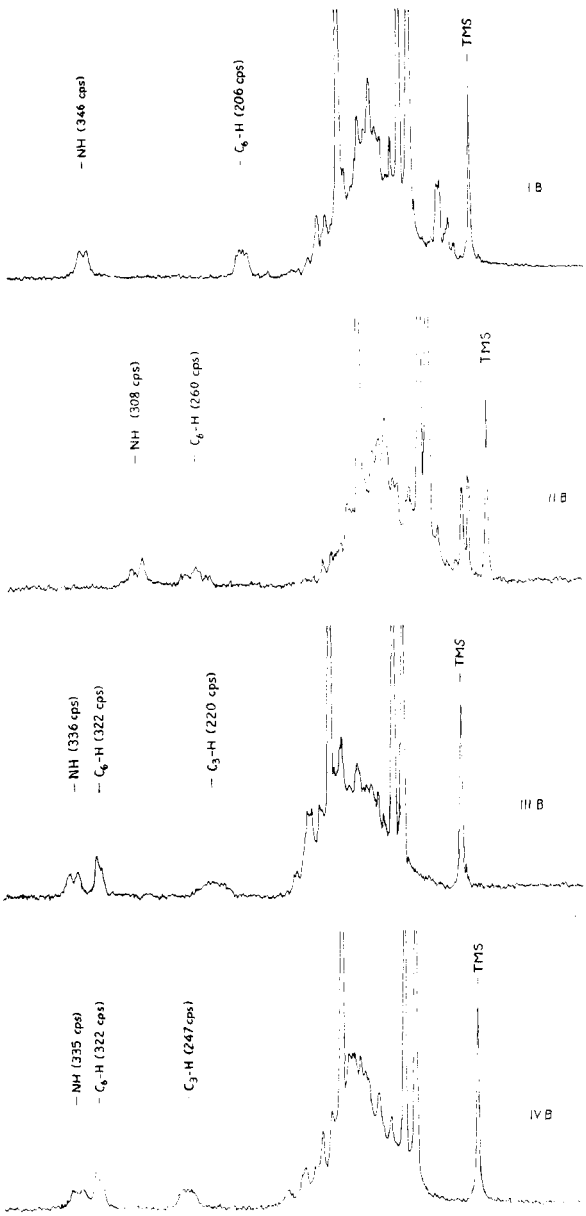


Fig. 2.—N.m.r. spectra of 6β-acetamido-3α,5α-cycloandrostan-17-one (IB), 6α-acetamido-3α,5α-cycloandrostan-17-one (IIB), 3β-acetamidoandrost-5-en-17-one (IIIB), and 3α-acetamidoandrost-5-en-17-one (IVB). Spectra were run at 60 Mc. in deuteriochloroform using tetramethylsilane (TMS) as an internal reference.

Nuclear magnetic resonance (n.m.r.) spectroscopy has become a valuable method for the determination of the stereochemistry of complex molecules, based on criteria of both chemical shift and spin–spin coupling. The absorptions of axial and equatorial protons attached to rigid six-membered rings exhibit different chemical shifts. Axial ring protons have generally been found to absorb at higher field than the corresponding equatorial protons.[9] In addition, the magnitude of the coupling constants between vicinal axial protons is two to three times as great as that between vicinal protons having equatorial–equatorial or equatorial–axial relationships.[10] In those cases where the proton absorptions occur as complex unresolved multiplets, this latter criterion is reflected by the widths of the absorption band measured at half its height.[11] The half-widths are, thus, greater for the absorptions of axial protons than for the absorptions of the corresponding equatorial protons when vicinal axial protons are present.

The absorptions of the C-6 protons of the acetamide, IB, and *p*-nitrobenzamide, IE, prepared from the amine IA, occurred at higher fields than those of the epimers IIB and IIE prepared from the amine IIA (Fig. 2). It has been shown[12] with the *p*-nitrobenzoates and acetates of the epimeric 6α- and 6β-hydroxy-17-ethylenedioxy-3α,-5α-cycloandrostanes that, in the case of 3α,5α-cyclosteroids, the chemical shift between axial and equatorial protons is anomalous since the 6α-equatorial protons absorb at higher field than do the 6β-axial protons. The chemical shifts of the C-6 protons of the amides thus provide strong evidence that the C-6 protons of IA and its derivatives IB and IE must be equatorial while those of the epimers IIA, IIB and IIE must be axial.[12] Therefore, IA and IIA must be the 6β-amino- and 6α-amino-3α,5α-cycloandrostanes, respectively.

The half-widths of the absorption bands of the C-6 protons of IB and IIB (13 and 29 c.p.s.) are consistent with these assignments since the 6β-axial proton of IIB, because of its interaction with the 7α-axial proton, is expected to have a half-width greater than that of the 6α-equatorial proton of IB.

The assignment of 3β-acetamido and 3α-acetamido configurations to the 3-acetamidoandrost-5-en-17-ones, IIIB and IVB, respectively, is supported by the half-widths of the absorption bands of the C-3 protons (IIIB, 33 c.p.s.; IVB, 18 c.p.s.). The broader band is expected for the absorption of the 3α-axial proton of IIIB due to its interaction with the 2β- and 4β-axial protons.

Further evidence for the configurations of the 3-acetamidoandrost-5-en-17-ones is provided by consideration of the relative chemical shifts of the C-3 protons. The effect of long range shielding by isolated double bonds is described by Jackman,[13] whereby the absorption of protons which lie above the plane of a double bond are shifted to higher field (diamagnetic shift) while the absorptions of protons which lie in the plane of the double bond are shifted to lower field (paramagnetic shift). Recently, the

(9) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, New York, N. Y., 1959, pp. 115–119.

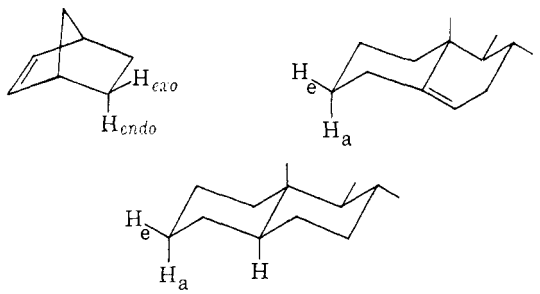
(10) (a) Ref. 9, p. 84; (b) H. Conroy, "Nuclear Magnetic Resonance in Organic Structural Elucidation," in "Advances in Organic Chemistry: Methods and Results," Vol. 2, Interscience Publishers, Inc., New York, N. Y., p. 309.

(11) R. U. Lemieux, R. K. Kullnig, H. J. Bernstein, and W. G. Schneider, *J. Am. Chem. Soc.*, **80**, 6098 (1958).

(12) J. Tadanier and W. Cole, *J. Org. Chem.*, **27**, 4610 (1962).

(13) Ref. 9, p. 129.

effect of the double bond on chemical shifts of the homoallylic *exo* and *endo* protons at C-5 and C-6 in a series of bicyclo[2.2.1]hept-2-enes has been demonstrated by Fraser.[14] The *endo* protons which lie above the plane of the double bond absorb at higher field while the *exo* protons which lie in the plane of the double bond absorb at lower field than to the corresponding protons of the dihydro derivatives. In the case of the Δ^5-3-substituted steroids, examination of models indicates that the 3α-axial protons lie over the plane of the double bond while the 3β-equatorial protons lie approximately in the



plane of the double bond. Consequently, any long range shielding by the Δ^5-double bond should cause the 3α-axial protons to absorb at higher field and the 3β-equatorial protons to absorb at lower field than the corresponding protons in the 5α-H series (A/B *trans*). For epimeric 3-substituted 5α-H steroids, 3α-axial protons absorb at higher field than do the 3β-equatorial protons of the epimers.[9] Thus, in the Δ^5-series 3α-axial protons should also absorb at higher field than the corresponding 3β-equatorial protons. The C-3 protons of IIIB and IVB must, thus, be axial and equatorial, respectively, since the C-3 proton of IIIB absorbs at higher field than does that of IVB (Fig. 2). Accordingly, the acetamides, IIIB and IVB must be 3β-acetamidoandrost-5-en-17-one and 3α-acetamidoandrost-5-en-17-one, respectively, in agreement with the criteria of infrared spectra and vapor phase chromatography described above.

Discussion

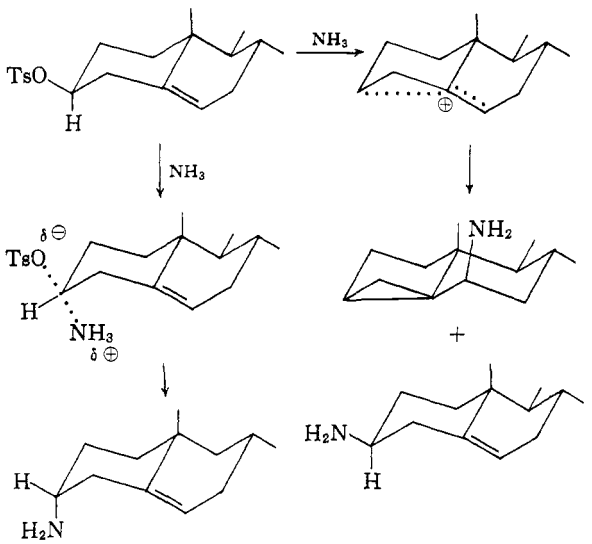
The amines formed by ammonolysis of the *p*-toluenesulfonate of 3β-hydroxy-17-ethylenedioxyandrost-5-ene are analogous to those which have been reported to result from ammonolysis of the *p*-toluenesulfonates of both cholesterol[1] and 3β-hydroxypregn-5-ene.[15] In each case, in addition to a 3α,5α-cyclo-6-amine, both Δ^5-3α- and Δ^5-3β-amines are formed. The present results provide strong evidence that the 3α,5α-cyclo-6-amines formed by the rearrangement have 6β-amino groups in agreement with the assignment of Haworth.[1c]

(14) R. R. Fraser, *Can. J. Chem.*, **40**, 78 (1962).

(15) R. D. Haworth, L. H. C. Lunts, and J. McKenna, *J. Chem. Soc.*, 3749 (1956).

In general, formation of both 3α,5α-cyclo-6β and Δ^5-3β derivatives by solvolysis of Δ^5-3β halides or *p*-toluenesulfonates has been accounted for on the basis of reaction of the homoallylic cation.[3,16] The stereospecific formation of 3α,5α-cyclo-6β-amines by ammonolysis strongly suggests that this intermediate intervenes in the ammonolysis reaction, and, thus, that its reaction may also account for the formation of the Δ^5-3β-amine.

The extent of formation of Δ^5-3α derivatives appears to be strongly dependent on both the strength of the nucleophile and the ionizing power of the medium Thus, reaction of the *p*-toluenesulfonate of 3β-hydroxypregn-5-ene with dimethylamine has been reported to yield 3α-dimethylaminopregn-5-ene as the sole substitution product[1b,15] whereas methanolysis of cholesteryl *p*-toluenesulfonate yields only the 3α,5α-cyclo-6β- and Δ^5-3β-methoxides.[3] It seems likely, therefore, that the formation of Δ^{15}-3α derivatives represents a competing reaction of the homoallylic *p*-toluenesulfonate which does not involve the Δ^5 double bond.[17]



Experimental

Ammonolysis of the *p*-Toluenesulfonate of 3β-Hydroxy-17-ethylenedioxandrost-5-en-17-one.—Two runs were carried out in the following manner: The *p*-toluenesulfonate[18] (15 g.) was heated at 100° for 15 hr. with 60 ml. of liquid ammonia. The ammonia was evaporated and the residue was shaken with 300 ml. of ether and 200 ml. of 5% sodium hydroxide solution. The aqueous phase was separated and extracted with 300 ml. of ether. The ether solutions were washed in series with three 200-ml. portions of water, combined, and dried over anhydrous magnesium sulfate. The ether was evaporated leaving a deep orange, viscous oil (9.8 g. from run I; 9.0 g. from run II).

The ammonolysis product was dissolved in a solution prepared from 30 ml. of methanol and 3 ml. of glacial acetic acid. The resulting solution was shaken with 200 ml. of

(16) L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, pp. 314–318.

(17) M. Simonetta and S. Winstein, *J. Am. Chem. Soc.*, **76**, 18 (1954).

(18) S. Julia, C. Neuville, and M. Davis, *Bull. soc. chim. France*, 297 (1960).

water and 300 ml. of ether. The aqueous phase containing the basic fraction as the amine acetate was separated and extracted with 300 ml. of ether. The ether solutions were washed in series with three 100-ml. portions of water, and the aqueous washings were combined with the aqueous solution containing the basic fraction. The ether solutions were washed in series with 200 ml. of 5% sodium bicarbonate solution and then with three 200-ml. portions of water. The ether solutions were combined and dried over anhydrous magnesium sulfate. The ether was evaporated leaving the neutral fraction (1.44 g. from run I, 1.66 g. from run II).

The aqueous solution containing the basic fraction as the acetic acid salt was shaken with 300 ml. of ether and 200 ml. of 5% sodium hydroxide solution. The aqueous layer was separated and extracted with 300 ml. of ether. The ether solutions were washed in series with six 100-ml. portions of water, combined, and dried over anhydrous magnesium sulfate. The ether was stripped and the residue crystallized on standing as a pale orange solid (6.53 g. from run I, 7.33 g. from run II).

Recrystallization of the combined basic fractions (run I and run II) from pentane yielded 4.8 g. of 6β-amino-17-ethylenedioxy-3α,5α-cycloandrostane (Ia), m.p. 100–110° (run I + run II). Recrystallization of this material from ether–pentane yielded 3.18 g., m.p. 108–110°; $[\alpha]^{23}D$ +18.5° (1% $CHCl_3$).

Anal. Calcd. for $C_{21}H_{33}NO_2$: C, 76.08; H, 10.03; N, 4.23. Found: C, 76.15; H, 9.95; N, 4.58.

The filtrates from the first recrystallizations of the basic fraction from runs I and II were combined and the solvent was stripped. The residue, a deep orange oil, was treated with 20 ml. of 1:10 acetic acid–methanol solution. A white solid crystallized almost immediately. This material was separated by filtration and washed with two 4-ml. portions of methanol to yield 1.92 g. of the acetic acid salt of 3β-amino-17-ethylenedioxyandrost-5-ene (IIIc), m.p. 203–209°. Recrystallization of this material from methanol–ether solution yielded 1.59 g., m.p. 218–225°; $[\alpha]^{23}D$ −64° (1% CH_3OH).

The combined methanol filtrate and washings from the crystallization of the acetic acid salt of 3β-amino-17-ethylenedioxyandrost-5-ene was shaken with 400 ml. of 5% sodium bicarbonate solution and 400 ml. of ether. A small amount of white solid remained suspended in the ether layer.[19] The aqueous phase was separated and the solid (615 mg.) was collected by filtration of the ether layer.

The basic aqueous phase was extracted with 300 ml. of ether and the two ether solutions were washed in series with three 250-ml. portions of water, combined, and dried over anhydrous magnesium sulfate. The ether was stripped leaving a deep orange, viscous oil which slowly crystallized as the last traces of ether were stripped under house vacuum (yield 6.13 g.). This material was dissolved in 60 ml. of ether and the resulting solution treated with carbon and filtered through Celite. The ether was displaced by pentane and the pentane solution concentrated to about 15 ml. A crop of dense white prisms crystallized in about 3–4 hr. at room temperature. At this time a small amount of a poorly crystalline, pale yellow solid began to separate. The supernatant was separated by decantation and the solid washed with 5 ml. of pentane and the washings were added to the supernatant. The solid (2.24 g.) was recrystallized from ether–pentane solution to yield another crop of 6β-amino-17-ethylenedioxy-3α,5α-cycloandrostane (1.57 g.), m.p. 108–110°.

To the combined supernatant and washings recovered from the crystallization of the second crop of 6β-amino-17-ethylenedioxy-3α,5α-cycloandrostane was added 20 ml. of ether and 1 ml. of glacial acetic acid. On standing about 5 hr., dense white crystals of the acetic acid salt of 3α-amino-17-ethylenedioxyandrost-5-ene (IVc) separated. The supernatant was separated by decantation and the crystals were washed with 5 ml. of ether to yield 1.1 g., m.p. 118–125°. Further purification was accomplished by converting the salt to the free amine followed by precipitation of the acetic acid salt from ether–pentane solution by addition of excess glacial acetic acid. In this way there was obtained material melting at 128–130°.

On standing overnight a second crop of 474 mg. of acetic acid salt separated, from which the supernatant was separated by decantation. The supernatant was shaken with 200 ml. of 5% sodium bicarbonate solution and 250 ml. of ether. The aqueous phase was separated and extracted with 200 ml. of ether. The ether solutions were washed in series with three 100-ml. portions of water, combined, and dried over anhydrous magnesium sulfate. The ether was evaporated leaving 2.13 g. of an orange solid. This material was recrystallized from ether–pentane solution to yield 720 mg. of 6β-amino-17-ethylenedioxy-3α,5α-cycloandrostane, m.p. 106–110°.

6β-Acetamido-17-ethylenedioxy-3α,5α-cycloandrostane (Ib).—To a solution of 1.03 g. of 6β-amino-17-ethylenedioxy-3α,5α-cycloandrostane in 25 ml. of pyridine was added 8 ml. of acetic anhydride. The resulting solution was allowed to stand overnight at room temperature and was then shaken with 250 ml. of water and 200 ml. of ether. The aqueous phase was separated and extracted with 200 ml. of ether. The ether solutions were washed in series with three 100-ml. portions of water, combined, and dried over anhydrous magnesium sulfate. The ether was evaporated and the residual pyridine was stripped on the steam bath under aspirator pressure using a rotary evaporator. The residue was crystallized from benzene–petroleum ether (b.p. 68–70°) solution to yield 1.05 g. of 6β-acetamido-17-ethylenedioxy-3α,5α-cycloandrostane, m.p. 158–160°; $[\alpha]^{23}D$ −19° (1%, $CHCl_3$).

Anal. Calcd. for $C_{23}H_{35}NO_3$: C, 73.95; H, 9.45; N, 3.75; O, 12.85. Found: C, 73.76; H, 9.44; N, 3.91; O, 13.05.

6β-Acetamido-3α,5α-cycloandrostan-17-one (IB).—Concentrated hydrochloric acid (1.0 ml.) was added to a solution of 504.5 mg. of 6β-acetamido-17-ethylenedioxy-3α,5α-cycloandrostane in 50 ml. of ether. The resulting solution was stirred at room temperature for 15 min. The ether solution was diluted to 200 ml. and the mixture was shaken with 200 ml. of water. The aqueous phase was separated and extracted with 200 ml. of ether. The ether solutions were washed in series with two 100-ml. portions of water, 100 ml. of 5% sodium bicarbonate solution, and three 100-ml. portions of water. The ether solutions were combined and dried over anhydrous magnesium sulfate. The ether was stripped leaving 446 mg. of a rigid, white glass. This material was crystallized and recrystallized from ether to yield 341 mg. of 6β-acetamido-3α,5α-cycloandrostan-17-one, m.p. 140–141°; $[\alpha]^{23}D$ +79.2° (1% $CHCl_3$).

Anal. Calcd. for $C_{21}H_{31}NO_2$: C, 76.54; H, 9.48; N, 4.25. Found: C, 76.64; H, 9.36; N, 4.48.

6β-Amino-3α,5α-cycloandrostan-17-one (IA).—6β-Amino-17-ethylenedioxy-3α,5α-cycloandrostane (2.0 g.) was dissolved in 40 ml. of ether. Concentrated hydrochloric acid (0.9 ml.) was added and a white solid separated. The supernatant ether was decanted. The ether was stripped from the supernatant leaving a small amount of solid which was added to the main crop. The product was recrystallized from water to yield 2.31 g. of dense white prisms of 6β-amino-3α,5α-cycloandrostan-17-one hydrochloride (ID), m.p. 262–264° dec. (sensitive to rate of heating); $[\alpha]^{23}D$ +81° (1% CH_3OH).

A suspension of the hydrochloride (2.0 g.) in 15 ml. of methanol was shaken with 250 ml. of ether and 200 ml. of 5% sodium carbonate solution. The aqueous phase was separated and extracted with 200 ml. of ether. The ether solutions were washed in series with four 100-ml. portions of water, combined, and dried over anhydrous magnesium

(19) Preliminary investigation indicated that this material was largely the bicarbonate salt of 3β-amino-17-ethylenedioxyandrost-5-ene.

sulfate. The ether solution was concentrated to 15 ml. and 1.0 ml. of glacial acetic acid was added. The solution was allowed to stand in a refrigerator for 2 hr. during which time 1.96 g. of the acetic acid salt (IC) of 6β-amino-3α,5α-cycloandrostan-17-one was deposited, m.p. 125–126°; $[\alpha]^{23}D$ +72.5° (1%, CH_3OH).

The acetic acid salt (405 mg.) was shaken with 70 ml. of ether and 50 ml. of 5% sodium hydroxide solution. The aqueous phase was separated and washed with 50 ml. of ether. The ether solutions were washed in series with three 50-ml. portions of water, combined, and dried over anhydrous magnesium sulfate. The ether was stripped and the product was crystallized from pentane to yield 120 mg. of 6β-amino-3α,5α-cycloandrostan-17-one, m.p. 100–101°; $[\alpha]^{23}D$ +112° (1%, $CHCl_3$).

Anal. Calcd. for $C_{19}H_{29}NO$: C, 79.40; H, 10.17; N, 4.88. Found: C, 79.35; H, 10.03; N, 5.29.

6β-*p*-Nitrobenzamido-3α,5α-cycloandrostan-17-one (IE).—A mixture prepared from 407.2 mg. of the acetic acid salt of 6β-amino-3α,5α-cycloandrostan-17-one 483.1 mg. of *p*-nitrobenzoyl chloride, 10 ml. of benzene, 10 ml. of water, and 20 ml. of 5% sodium hydroxide solution was stirred at room temperature for 30 min. and then allowed to stand at room temperature for 2 hr. The reaction mixture was shaken with 30 ml. of 5% sodium hydroxide solution and 150 ml. of ether. The aqueous phase was separated and extracted with 100 ml. of ether. The ether solutions were washed in series with four 50-ml. portions of water, combined, and dried over anhydrous magnesium sulfate. The ether was evaporated and the residue was recrystallized from benzene-petroleum ether (b.p. 68–70°) solution to yield 348 mg. of 6β-p-nitrobenzamido-3α,5α-cycloandrostan-17-one, m.p. 247–249°; $[\alpha]^{22}D$ +66° (1%, $CHCl_3$).

Anal. Calcd. for $C_{26}H_{32}N_2O_4$: C, 71.54; H, 7.39. Found: C, 71.50; H, 7.47.

3α-Amino-17-ethylenedioxyandrost-5-ene (IVa).—The acetic acid salt of 3α-amino-17-ethylenedioxyandrost-5-ene (336 mg.) was shaken with 5% sodium carbonate solution and ether. The extraction was carried out in the usual manner to yield 212.5 mg. of amine, m.p. 136–144°. Recrystallization from ether-pentane solution yielded 147 mg. of 3α-amino-17-ethylenedioxyandrost-5-ene, m.p. 146–148°; $[\alpha]^{23}D$ −87.8° (1% $CHCl_3$).

Anal. Calcd. for $C_{21}H_{33}NO_2$: C, 76.08; H, 10.03; N, 4.23. Found: C, 76.19; H, 9.86; N, 4.22.

3α-Aminoandrost-5-en-17-one (IVA).—The acetic acid salt (1.1 g.) of 3α-amino-17-ethylenedioxyandrost-5-ene was dissolved in 25 ml. of water and 2.5 ml. of concentrated hydrochloric acid was added. The reaction mixture was allowed to stand at room temperature for 1 hr. and then in a refrigerator for 2 hr. The hydrochloride (pretty white leaflets) was collected by filtration to yield 643.9 mg., m.p. 277–278° dec., charring 240–270°.

The hydrochloride (640 mg.) was dissolved in 10 ml. of methanol and the resulting solution was shaken with 25 ml. of 5% sodium hydroxide solution and 250 ml. of ether. Water (100 ml.) was added and the mixture was again shaken. The aqueous phase was separated and extracted with 200 ml. of ether. The ether solutions were washed in series with three 100-ml. portions of water, combined, and dried over anhydrous magnesium sulfate. The ether solution was concentrated to 5 ml. and the amine crystallized from the boiling ether to yield 460.7 mg. of 3α-aminoandrost-5-en-17-one, m.p. 176–184°; $[\alpha]^{23}D$ −4.7° (1% $CHCl_3$).

Anal. Calcd. for $C_{19}H_{29}NO$: C, 79.40; H, 10.17; N, 4.88. Found: C, 79.27; H, 10.55; N, 5.03.

Work-up of the filtrate from the crystallization of the hydrochloride yielded an additional 97 mg. of amine, m.p. 168–173.2°.

The amine (m.p. 176–184°, 252 mg.) was dissolved in 50 ml. of boiling ether. The solution was cooled to room temperature and 0.5 ml. of glacial acetic acid was added. A finely divided white solid separated almost immediately. The mixture was allowed to stand in a refrigerator for 45 min. and the acetic acid salt of 3α-aminoandrost-5-en-17-one (330.1 mg.) was collected by filtration on a sintered glass funnel; m.p. 154–158° dec.; $[\alpha]^{23}D$ +9.7° (1% CH_3OH).

3α-Acetamidoandrost-5-en-17-one (IVB).—To a solution of 160.1 mg. of 3α-aminoandrost-5-en-17-one in 3 ml. of pyridine was added 1 ml. of acetic anhydride and the resulting solution was allowed to stand overnight at room temperature. The reaction mixture was shaken with 50 ml. of water and 80 ml. of ether. The aqueous phase was separated and extracted with 80 ml. of ether. The ether solutions were washed in series with 50 ml. of water, 50 ml. of 3 *N* hydrochloric acid, 50 ml. of water, 50 ml. of 5% sodium bicarbonate solution, and two 50-ml. portions of water. The ether solutions were combined and dried over anhydrous magnesium sulfate. The ether was stripped leaving a powdery white solid, 187.2 mg., m.p. 222.5–225.5°. This material was recrystallized from ethanol–water solution to yield 158.7 mg., m.p. 224.5–226.5°; $[\alpha]^{23}D$ −20.4° (1% $CHCl_3$).

Anal. Calcd. for $C_{21}H_{31}NO_2$: C, 76.54; H, 9.48; N, 4.25. Found: C, 76.43; H, 9.42; N, 4.45.

3β-Aminoandrost-5-en-17-one (IIIA).—The acetic acid salt of 3β-amino-17-ethylenedioxyandrost-5-ene (598 mg.) was suspended in 80 ml. of boiling water and concentrated hydrochloric acid (4 ml.) was added. The suspension was carefully heated to boiling for 5 min., cooled to room temperature, and allowed to stand in a refrigerator for 3 hr. The hydrochloride was collected on a sintered glass funnel to yield 462 mg. This material darkened and sintered without melting between 300–330°.

A suspension of the amine hydrochloride (456 mg.) in 10 ml. of methanol was shaken with 25 ml. of 5% sodium hydroxide solution and 250 ml. of ether. Water (100 ml.) was added and the mixture was again shaken. The aqueous phase was separated and extracted with 200 ml. of ether. The ether solutions were washed in series with water, combined, and dried over anhydrous magnesium sulfate. The ether was stripped and the product was recrystallized from ether to yield 194 mg. of 3β-aminoandrost-5-en-17-one, m.p. 127–129.5°. Concentration of the filtrate yielded 82 mg., m.p. 120–125°. The analytical sample melted 132–134°; $[\alpha]^{23}D$ +9.2° (1%, $CHCl_3$).

Anal. Calcd. for $C_{19}H_{29}NO$: C, 79.40; H, 10.17; N, 4.88. Found: C, 79.48; H, 10.44; N, 4.65.

The amine prepared from 600 mg. of the hydrochloride was dissolved in 30 ml. of ether and 0.2 ml. of glacial acetic acid was added. The acetic acid salt (IIIC) of 3β-aminoandrost-5-en-17-one (437.6 mg.) separated immediately and was collected on a sintered glass funnel. This salt decomposed above 260°; $[\alpha]^{23}D$ +16.6° (1% CH_3OH).

3β-Acetamido-17-ethylenedioxyandrost-5-ene (IIIb).—A solution prepared from 205 mg. of the acetic acid salt of 3β-amino-17-ethylenedioxyandrost-5-ene, 1.0 ml. of acetic anhydride, and 5 ml. of pyridine was allowed to stand overnight at room temperature. The reaction mixture was worked up by chloroform extraction. The chloroform was evaporated under aspirator pressure using a rotary evaporator. To the residue, which contained a small amount of pyridine, was added 50 ml. of water. The white solid which separated was collected on a sintered glass funnel. The product was taken up in 50 ml. of chloroform, and the resulting solution was dried over anhydrous magnesium sulfate. The chloroform was evaporated leaving 196 mg. of 3β-acetamido-17-ethylenedioxyandrost-5-ene, m.p. 215–218°. Recrystallization from benzene–petroleum ether (b.p. 68–70°) solution raised the melting point to 218–219°; $[\alpha]^{25}D$ −85° (1% $CHCl_3$).

Anal. Calcd. for $C_{23}H_{35}NO_3$: C, 73.95; H, 9.45; N, 3.75. Found: C, 73.92; H, 9.34; N, 3.95.

3β-Acetamidoandrost-5-en-17-one (IIIB).—(a) To a solution of 153 mg. of 3β-aminoandrost-5-en-17-one (IIIA) in 3 ml. of pyridine was added 1 ml. of acetic anhydride. The resulting solution was allowed to stand overnight at room temperature and then worked up as described for 3α-acetamidoandrost-5-en-17-one. The crude product (178

mg.) melted at 223–227°, m.m.p. with 3α-acetamidoandrost-5-en-17-one, 190–200°. The product was recrystallized from ethanol–water solution to yield 123 mg. of 3β-acetamidoandrost-5-en-17-one, m.p. 226.5–227.5°; $[\alpha]^{23}D$ −3° (1%, $CHCl_3$).

Anal. Calcd. for $C_{21}H_{31}NO_2$: C, 76.54; H, 9.48; N, 4.25. Found: C, 76.80; H, 9.43; N, 4.28.

(b) 3β - Acetamido - 17 - ethylenedioxyandrost - 5 - ene (IIIb), 306 mg., was dissolved in 10 ml. of methanol and 2.0 ml. of 6 *N* hydrochloric acid was added. The resulting solution was allowed to stand at room temperature for 1 hr. The product was worked up by chloroform extraction to yield 290.2 mg. of 3β-acetamidoandrost-5-en-17-one, m.p. 224–227°. Recrystallization from benzene–petroleum ether (b.p. 68–70°) raised the melting point to 225–228°. The infrared spectrum of this material was identical to that of the product obtained by acetylation of the keto amine (IIIA).

6-Oximino-17-ethylenedioxy-3α,5α-cycloandrostane.—A solution prepared from 4.8 g. of 17-ethylenedioxy-3α,5α-cycloandrostan-6-one,[18] 5.0 g. of hydroxylamine hydrochloride, and 200 ml. of pyridine was heated on a steam bath for 3 hr. The resulting solution was cooled and shaken with a mixture of 700 ml. of ether and 1200 ml. of water. The aqueous phase was separated and extracted with 700 ml. of ether. The ether solutions were washed in series with four 400-ml. portions of water, combined, and dried over anhydrous magnesium sulfate. The ether was evaporated on the steam bath and the residual pyridine was evaporated under aspirator pressure on the steam bath using a rotary evaporator. The residue was crystallized from ethanol–water solution to yield 4.18 g. of 6-oximino-17-ethylenedioxy-3α,5α-cycloandrostane, m.p. 182–186°. The analytical sample prepared by recrystallization from ethanol–water solution melted 186–187°.

Anal. Calcd. for $C_{21}H_{31}NO_3$: C, 73.00; H, 9.04; N, 4.05. Found: C, 72.75; H, 9.04; N, 4.16.

6α-Amino-3α,5α-cycloandrostan-17-one (IIA).—A solution of 4.1 g. of 6-oximino-17-ethylenedioxy-3α,5α-cycloandrostane in 400 ml. of absolute ethanol was heated under reflux and 36 g. of metallic sodium was added at a rate sufficient to maintain reflux over a period of 1.5 hr. The reaction mixture was allowed to stand for 1 hr. during which time a large amount of white solid separated. Ethanol (200 ml.) was added and most of the solid dissolved. The undissolved solid and the excess sodium were separated by filtration on a sintered glass funnel. The filtrate was cooled by the addition of crushed ice and 2 l. of water was added causing a white turbidity. The mixture was extracted with 750 ml. of ether. The aqueous phase was separated and extracted with 500 ml. of ether. The ether solutions were washed in series with water, combined, and dried over anhydrous magnesium sulfate. The solvent was stripped leaving 4.33 g. of a viscous, pale yellow oil.

The crude product was dissolved in 80 ml. of ether, and 2.5 ml. of glacial acetic acid was added. The resulting solution was diluted to 200 ml. with ether and extracted with 150 ml. of water. The aqueous phase was separated and extracted with 200 ml. of ether. The ether solutions were washed in series with two 150-ml. portions of water and the washings were added to the original aqueous extract.

The aqueous solution containing the basic fraction as the acetic acid salt was treated with 200 ml. of 5% sodium hydroxide solution. The solution became milky-white and a white solid separated. The suspension was extracted twice with 300-ml. portions of ether. The ether solutions were washed in series with two 150-ml. portions of water, combined, and dried over anhydrous magnesium sulfate. The ether was evaporated leaving 2.83 g. of a pale yellow, viscous oil, containing 6α-amino-17-ethylenedioxy-3α,5α-cycloandrostane.

The crude amine (2.8 g.) was dissolved in a solution prepared from 1.5 ml. of glacial acetic acid and 15 ml. of water. Concentrated hydrochloric acid (2.0 ml.) was added. The crystallization mixture was allowed to stand in a refrigerator for 2 hr. and the hydrochloride (2.40 g.) was collected on a sintered glass funnel.

A sample (848 mg.) of the hydrochloride was recrystallized from water to yield 702.6 mg. of 6α-amino-3α,5α-cycloandrostan-17-one hydrochloride (IID) which decomposed above 260°; $[\alpha]^{23}D$ +128.6° (1%, CH_3OH).

The amine hydrochloride (600 mg.) was shaken with 50 ml. of 5% sodium hydroxide solution and 100 ml. of ether. The aqueous phase was separated and extracted with 80 ml. of ether. The ether solutions were washed in series with three 30-ml. portions of water, combined, and dried over anhydrous magnesium sulfate. The ether solution was concentrated to 20 ml. and 0.48 ml. of glacial acetic was added. The acetic acid salt (IIC) of 6α-amino-3α,5α-cycloandrostan-17-one (404 mg.) separated as small white needles, which decomposed above 266°; $[\alpha]^{23}D$ +125.6° (1%, CH_3OH).

The acetic acid salt of 6α-amino-3α,5α-cycloandrostan-17-one (505.3 mg.) prepared as described above, was shaken with a mixture of 200 ml. of ether and 100 ml. of 5% sodium carbonate solution. The aqueous phase was separated and extracted with 200 ml. of ether. The ether solutions were washed in series with three 100-ml. portions of water, combined, and dried over anhydrous magnesium sulfate. The ether was evaporated and the residual oil was crystallized from pentane to yield 390 mg. of 6α-amino-3α,5α-cycloandrostan-17-one, m.p. 67–70°; $[\alpha]^{23}D$ +160.5° (1%, $CHCl_3$).

The analytical sample, prepared by further recrystallization from pentane, melted at 70–72°.

Anal. Calcd. for $C_{19}H_{29}NO$: C, 79.40; H, 10.17; N, 4.88. Found: C, 79.67; H, 9.98; N, 5.18.

6α-Acetamido-3α,5α-cycloandrostan-17-one (IIB).—To a solution of 285 mg. of 6α-amino-3α,5α-cycloandrostan-17-one in 6 ml. of pyridine was added 2.0 ml. of acetic anhydride and the resulting solution was allowed to stand overnight at room temperature. The solution was then shaken with 200 ml. of ether and 100 ml. of water. The aqueous phase was separated and extracted with 200 ml. of ether. The ether solutions were washed in series with 100 ml. of water, 100 ml. of 3 *N* hydrochloric acid, 100 ml. of water, 100 ml. of 5% sodium hydroxide solution, and three 100-ml. portions of water. The ether solutions were combined and dried over anhydrous magnesium sulfate. The ether was evaporated leaving 331 mg. of a white crystalline solid, m.p. 79–118°.

Attempts to recrystallize this material from benzene–or ethyl acetate–petroleum ether (b.p. 68–70°) were unsuccessful. The material oiled out on cooling in a Dry Ice–acetone bath. The material did crystallize from these solutions on addition of a small amount of ether.

The product was recrystallized from acetone–ether solution from which it crystallized as broad blades. On briefly drying under house vacuum (5–10 min.), the product sintered and swelled between 90–95°. On being dried overnight under high vacuum at 78° the product melted 117–134°. Repeated recrystallization did not change the melting point; $[\alpha]^{23}D$ +164° (1% $CHCl_3$).

Anal. Calcd. for $C_{21}H_{31}NO_2$: C, 76.54; H, 9.48; N, 4.25. Found: C, 76.79; H, 9.55; N, 4.42.

6α-*p*-Nitrobenzamido-3α,5α-cycloandrostan-17-one (IIE).—A mixture prepared from 231.2 mg. of the acetic acid salt of 6α-amino-3α,5α-cycloandrostan-17-one, 330 mg. of *p*-nitrobenzoyl chloride, 5 ml. of benzene, 5 ml. of water, and 15 ml. of 5% sodium hydroxide solution was stirred at room temperature for 30 min. and then allowed to stand at room temperature for 1.5 hr. The reaction mixture was shaken with 45 ml. of benzene and 30 ml. of 5% sodium hydroxide solution. The aqueous phase was separated and extracted with 50 ml. of benzene. The benzene solutions were washed in series with three 50-ml. portions of water, combined, and dried over anhydrous magnesium sulfate. The benzene was evaporated and the residue was crystallized and recrystallized from ethanol–water solution to yield 214.0 mg. of

6α-*p*-nitrobenzamido-3α,5α-cycloandrostan-17-one, m.p. 165–168°; $[\alpha]^{22}D$ +101° (1%, $CHCl_3$).

Anal. Calcd. for $C_{26}H_{32}N_2O_4$: C, 71.54; H, 7.39. Found: C, 71.78; H, 7.57.

6α-Acetamido-17-ethylenedioxy-3α,5α-cycloandrostane (IIb).—The ketal amine (1.62 g.), isolated as described above by separation as the water-soluble acetic acid salt from the products obtained by sodium–ethanol reduction of 6-oximino-17-ethylenedioxy-3α,5α-cycloandrostane, was dissolved in 36 ml. of pyridine and 12 ml. of acetic anhydride was added. The resulting solution was allowed to stand overnight at room temperature and then poured into 400 ml. of water. The sticky, white solid which separated was collected on a sintered glass funnel. This product was taken up in 200 ml. of chloroform, and the chloroform solution was dried over anhydrous magnesium sulfate. The chloroform was evaporated leaving a viscous, pale yellow glass. The product separated as a gel from acetone–ether–pentane solution, and was separated by filtration leaving a finely divided white solid, m.p. 157–186°. Two more such separations yielded 839 mg. of 6α-acetamido-17-ethylenedioxy-3α,5α-cycloandrostane, m.p. 192–197°, $[\alpha]^{23}D$ +53° (1%, $CHCl_3$), shown to be free of the 6β-acetamido epimer by vapor phase chromatography. For analysis 104 mg. was recrystallized twice from methanol–water solution to yield 66 mg., m.p. 198–200°.

Anal. Calcd. for $C_{23}H_{35}NO_3$: C, 73.95; H, 9.45; N, 3.75. Found: C, 73.82; H, 9.28; N, 4.02.

The ether–acetone–pentane filtrates from purification of the product were combined and the solvent was evaporated. The residue was dissolved in acetone, and the boiling solution was treated with carbon and filtered through Celite. The acetone was evaporated leaving 684 mg. of a rigid white glass. Vapor phase chromatography on both polar and nonpolar columns showed peaks of approximately equal area with retention times corresponding to those of the 6α- and 6β-acetamido-17-ethylenedioxy-3α,5α-cycloandrostanes (Table II) indicating a mixture of approximately equal amounts of the epimers.

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Notes

New Synthesis of Uric Acid and 1,7-Dimethyluric Acid[1]

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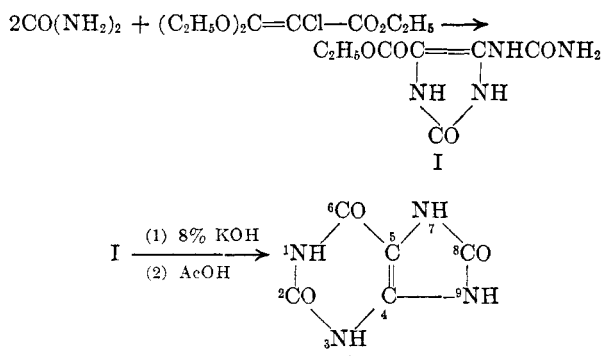
In the course of work on a new synthesis of pyrimidines of possible biological interest,[3] we sought to extend the reaction of ureas and β,β-diethoxyacrylic esters to include ethyl α-chloro-β,β-diethoxyacrylate in the expectation that such a reaction would yield with urea, ethyl α-chloro-β-ethoxy-β-ureidoacrylate, which then could be converted to 5-chloro-6-ethoxyuracil by ring closure. The unexpected occurred, however, and instead, two moles of urea interacted with one of ester to yield an imidazole (I), which by appropriate treatment with alkali followed by acid gave uric acid in good yield. This result affords a convenient tracer method for obtaining uric acid labeled with C^{14} in the 2 and 8 positions, starting with active urea, since the synthesis is conservative in the use of urea.



Two courses are possible, each capable of explaining the final result. One might suppose (1) that the first mole of urea reacting produces an imidazole, which reacts further to give the ureido imidazole, or (2) that the presence of a halogen atom in the acrylic ester promotes double replacement of the β-ethoxy groups followed by ring closure.

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