This material was taken up in 300 ml. of ether and the ether solution was washed with 100 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 5% sodium bicarbonate solution and three 100-ml. portions of water, then combined and dried over anhydrous magnesium sulfate. The ether solution was concentrated to 80 ml. and placed on a column of 20 g. of neutral, activity III alumina. The product was eluted with 200 ml. of ether. The ether was evaporated leaving 564 mg. of 6β-*p*-nitrobenzoyloxy-17-ethylenedioxy-3α,5α-cycloandrostane m.p. 186–189°. For analysis the product was recrystallized twice from benzene–petroleum ether (b.p. 68–70°) to yield 488 mg. m.p. 187–189°, $[\alpha]^{22}D$ +16.8° (1% chloroform).

Anal. Calcd. for $C_{28}H_{35}NO_6$: C, 69.83; H, 7.33. Found: C, 70.03; H, 7.39.

Lithium Aluminum Hydride Reduction of 17-Ethylenedioxy-3α,5α-cycloandrostan-6-one.—A solution of 2.0 g. of 17-ethylenedioxy-3,5-cycloandrostan-6-one in 60 ml. of ether was added over a period of 30 min. to a stirred slurry prepared from 1 g. of lithium aluminum hydride in 80 ml. of ether. After the addition was complete, stirring was continued for 4 hr. and then the reaction mixture was allowed to stand overnight at room temperature. The excess lithium aluminum hydride was decomposed by the addition of a solution prepared from 5 ml. of methanol and 50 ml. of ether. The resulting mixture was shaken with a mixture of 250 ml. of ether and 250 ml. of water. The aqueous phase, containing undissolved metal hydroxides, was separated and extracted with 300 ml. of ether. The ether solutions were washed in series with six 200-ml. portions of water, combined, and dried over anhydrous magnesium sulfate. The ether was evaporated leaving the crude 6α-hydroxy-17-ethylenedioxy-3α,5α-cycloandrostane (IIa) as a white, opaque glass.

6α-Acetoxy-17-ethylenedioxy-3α,5α-cycloandrostane (IIb).—A solution prepared from 1.09 g. of the crude 6α-hydroxy-17-ethylenedioxy-3α,5α-cycloandrostane, 30 ml. of pyridine, and 8 ml. of acetic anhydride was allowed to stand for 20 hr. at room temperature. The product was worked up by ether extraction in the manner described for the preparation of the 6β-epimer. The ether was evaporated and the residue was washed with several portions of water to remove the residual pyridine. The residue was taken up in 250 ml. of ether and the ether solution was dried over anhydrous magnesium sulfate. The ether was evaporated and the residue crystallized on standing to yield 1.2 g. of 6α-acetoxy-17 ethylenedioxy-3α,5α-cycloandrostane, m.p. 105–111°. A mixture with the 6β-acetoxy epimer melted 75–84°. Seed crystals were set aside for use in the recrystallization from ether–pentane solution which yielded a product melting at 111–113°, $[\alpha]^{22}D$ + 69° (1% chloroform).

Anal. Calcd. for $C_{23}H_{34}O_4$: C, 73.75; H, 9.15. Found: C, 73.89; H, 9.42.

6α-*p*-Nitrobenzoyloxy-17-ethylenedioxy-3α,5α-cycloandrostane (IIc).—A solution prepared from 408 mg. of crude 6α-hydroxy-17-ethylenedioxy-3α,5α-cycloandrostane, 462 mg. of *p*-nitrobenzoyl chloride, and 5 ml. of pyridine was allowed to stand at room temperature for 1.5 hr. The product was worked up by ether extraction as described above for the 6β-epimer and eluted through 20 g. of neutral, activity III alumina with 250 ml. of ether. The ether was evaporated and the residue was recrystallized from benzene–petroleum ether (b.p. 68–70°) solution to yield 363 mg. of 6α-*p*-nitrobenzoyloxy-17-ethylenedioxy-3α,5α-cycloandrostane, m.p. 168–169.5°. For analysis, 247 mg. was recrystallized from benzene–petroleum ether (b.p. 68–70°) to yield 179 mg., m.p. 168–170°, $[\alpha]^{26}D$ +60.5° (1% chloroform).

Anal. Calcd. for $C_{28}H_{35}NO_6$: C, 69.83; H, 7.33. Found: C, 70.02; H, 7.36.

Acknowledgment.—The authors thank Mr. W. H. Washburn and associates for infrared determinations, and Mr. E. F. Shelberg and staff for microanalyses. The n.m.r. measurements were obtained from Battelle Memorial Institute. The authors discussed this problem with Mr. T. F. Page at the institute and acknowledge his assistance in preparing the curves and making certain frequency assignments.

Deamination of the Epimeric 3-Aminoandrost-5-en-17-ones and 6-Amino-3α,5α-cycloandrostan-17-ones

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Deaminations of 3β-aminoandrost-5-en-17-one, 6α-amino-3α,5α-cycloandrostan-17-one, and 6β-amino-3α,5α-cycloandrostan-17-one, followed by basic hydrolysis of the products all gave rise to 6β-hydroxy-3α,5α-cycloandrostan-17-one. The stereochemistry of the deamination reactions, thus, corresponds to that found by Kosower and Winstein[11] for the methanolysis of related cholesteryl derivatives. These results indicate that the deaminations, like the solvolyses, must proceed *via* nonclassical homoallylic cations. Deamination of 3α-aminoandrost-5-en-17-one gave rise to a mixture of keto alcohols believed to be the products of the rearrangement of the homoallylic to the allylic system. The conditions employed for the deaminations were similar to those generally employed for deaminations of steroid amines. It was found that nitrite esters could be isolated as the principal products.

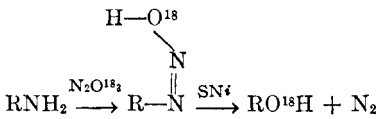
It has frequently been observed that the products obtained by deamination of primary aliphatic amines differ markedly, with regard to both structural isomerism and stereochemistry, from the products obtained by solvolyses of the corresponding alkyl halides or *p*-toluenesulfonates.[1] From the fact that stable, aryl diazonium ions are formed by nitrosation of primary aromatic amine it is believed that nitrosation of primary aliphatic amines similarly leads to formation of aliphatic diazonium ions,[2] which, lacking the stabilizing effect resulting from delocalization of positive charge available to their aromatic counterparts, rapidly undergo subsequent reaction with loss of nitrogen. Although

(1) (a) A. Streitwieser, Jr., *J. Org. Chem.*, **22**, 861 (1957). (b) J. H. Ridd, *Quart. Rev.*, **15**, 418 (1961).

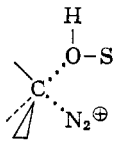
(2) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, p. 295.

a number of theories have been proposed to account for the nature of the products formed, it is generally agreed that the distinctive feature of the deamination reaction, as contrasted to solvolysis, is the low activation energy for heterolysis of the C—N bond of aliphatic diazonium ions relative to that for heterolysis of the C—X bond[1,3-5] of alkyl halides or arylsulfonates (X = Cl, Br, I, OTs). It has been proposed that the products formed by deamination result from competing modes of decomposition of the aliphatic diazonium ion.[1a,3] Alternately, it has been suggested that decomposition of aliphatic diazonium ions leads to higher energy, or "hot" open carbonium ions which lack solvation or charge delocalization effected by participating neighboring groups.[4]

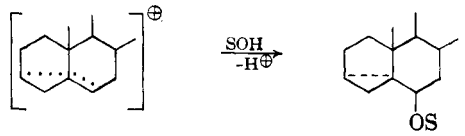
The stereochemistry of deamination of saturated steroidal[6] and decalyl amines[7] is configurationally specific. In both series, equatorial amines undergo deamination with quantitative substitution and essentially complete retention of configuration while deamination of axial amines leads largely to olefin. It has been argued that the high stereospecificity of the deaminations of the equatorial amines is not accounted for by either the competing reactions mechanism or the "hot" carbonium ion theory.[8] Strong evidence that the observed retention does not result from S_Ni reactions of nonpolar diazonium hydroxides was obtained by Boutle and Bunton,[9] who found that the cyclohexanol obtained by deamination of cyclohexylamine with $N_2O^{18}_3$ in aqueous acetic acid contained no O^{18}, although Streitwieser and Coverdale[8] had found that the deamination of *cis*-cyclohexylamine-2*d* occurred with at least 94% retention. It has been suggested that the substitution with retention may be accounted for by a pyramidal



transition state for the decomposition of the aliphatic diazonium ion.[5,6,8,10]



Studies of the solvolysis of steroid Δ^5-3β, 3α,5α-cyclo 6α- and 6β-ester and -halide derivatives have shown that the rate-determining heterolysis occurs with formation of the nonclassical, homoallylic cation, which, under conditions of kinetic control, reacts to form predominantly 3α,5α-cyclo 6β-derivatives.[11] In contrast, the solvolysis of the *p*-toluenesulfonate of 3α-hydroxycholest-5-ene has been found to lead predominantly to cholestadiene.[12]



It was, thus, of interest to investigate the deaminations of the epimeric 3-aminoandrost-5-en-17-ones and 6-amino-3α,5α-cycloandrostan-17-ones to determine whether decomposition of the Δ^5-3β and 3α,5α-cyclo 6α- and 6β-diazonium ions would lead to the homoallylic cation or whether their decomposition might be similar to that of saturated steroid diazonium ions. In addition, it was desired to determine whether the stereospecificity observed in solvolysis of Δ^5-3α and 3β-*p*-toluenesulfonates would also be found for deaminations of the Δ^5-3α and 3β amines.

Although deaminations of the related cholesterylamines have been reported,[6,13] the conditions employed were such that both 3α,5α-cyclo 6-alcohols and ethers underwent considerable rearrangement[13] to Δ^5-3β derivatives and large amounts of starting materials were recovered. The results were interpreted to indicate that the deaminations of 3α,5α-cyclo-6α equatorial amines and 6β-axial amines conform to the pattern found for saturated steroid amines—the axial amine leading to elimination and substitution with retention of configuration, and the equatorial amine giving rise to substitution with retention.[13] For both isomers, however, the major substitution product was found to be cholesterol, and conclusions regarding the stereochemistry of the deaminations were based on the isolation of approximately 7% of 3α,5α-cyclocholest-6-ene and 15% of 3α,5α-cyclocholestan-6β-ol from the 6β-amine and 4% of 3α,5α-cyclocholestan-6α-ol from the 6α-amine.

Deamination of 3β-Aminoandrost-5-en-17-one and 6α- and 6β-Amino-3α,5α-cycloandrostan-17-one.—Deaminations of 3β-aminoandrost-5-en-17-one and both 6α- and 6β-amino-3α,5α-cycloandrostan-17-one with nitrous acid in 1:3 acetic acid–water solution at 0–20°, followed by basic hydrolysis of the

(3) A. Streitwieser, Jr., and W. D. Shaffer, *J. Am. Chem. Soc.*, **79**, 2888 (1957).

(4) (a) L. S. Ciereszko and J. G. Burr, *ibid.*, **74**, 145 (1952). (b) J. D. Roberts and M. Holmann, *ibid.*, **75**, 5759 (1953). (c) D. Y. Curtin and M. C. Crew, *ibid.*, **76**, 3719 (1954). (d) D. J. Cram and J. McCarty, *ibid.*, **79**, 2866 (1957). (e) D. Semenow, Chin-Hua Shih, and W. G. Young, *ibid.*, **80**, 5472 (1958).

(5) R. Huisgen and C. Rüchardt, *Ann.*, **601**, 1 (1956).

(6) C. W. Shoppee, D. E. Evans, and G. H. R. Summers, *J. Chem. Soc.*, 97 (1957).

(7) (a) W. Hückel, *Ann.*, **533**, 1 (1938). (b) W. G. Dauben, R. C. Tweit, and C. Mannerskantz, *J. Am. Chem. Soc.*, **76**, 4420 (1954).

(8) A. Streitwieser, Jr., and C. E. Coverdale, *ibid.*, **81**, 4275 (1959).

(9) D. L. Boutle and C. A. Bunton, *J. Chem. Soc.*, 761 (1961).

(10) J. A. Mills, *ibid.*, 260 (1953).

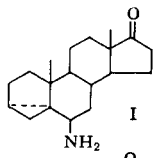
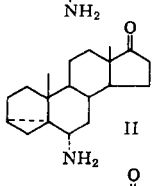
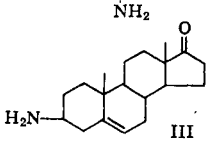
(11) E. M. Kosower and S. Winstein, *J. Am. Chem. Soc.*, **78**, 4347 (1956).

(12) (a) H. Schmid and K. Kägi, *Helv. Chim. Acta*, **35**, 2194 (1952). (b) D. D. Evans and C. W. Shoppee, *J. Chem. Soc.*, 540 (1953). (c) E. J. Becker and E. S. Wallis, *J. Org. Chem.*, **20**, 353 (1955). (d) D. N. Jones, J. R. Lewis, C. W. Shoppee, and G. H. R. Summers, *J. Chem. Soc.*, 2876 (1955).

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

TABLE I

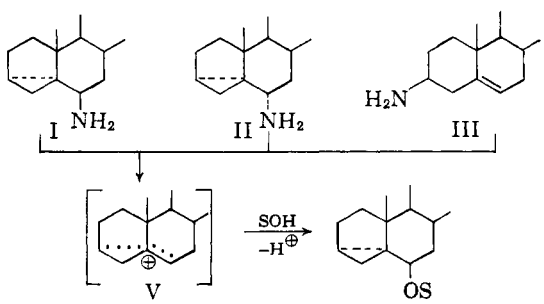
DEAMINATIONS OF 6β-AMINO-3α,5α-CYCLOANDROSTAN-17-ONE (I), 6α-AMINO-3α,5α-CYCLOANDROSTAN-17-ONE (II), AND 3β-AMINOANDROST-5-EN-17-ONE (III). PRODUCT ISOLATED AFTER BASIC HYDROLYSIS

Amine	Solvent	Yield of 6β-hydroxy-3α,5α-cycloandrostan-17-one[a]	Physical data of products M.p.[b,c]	[α]D[d]
 I	1:3 (acetic acid–water)	62%	136–139°	+115°
 II	1:3	62%	138–141°	+118°
 III	1:3	46	135–139°	+114°
	1:1	53	139–141°	+114°

[a] Infrared spectra of the products taken in chloroform solutions were identical to that of authentic 6β-hydroxy-3α,5α-cycloandrostan-17-one. Yields are based on the weights of the acetic acid salts. [b] Melting points were taken in open capillaries and are uncorrected. [c] Mixed melting point of each product with authentic 6β-hydroxy-3α,5α-cycloandrostan-17-one (m.p. 139–141°, [α]D +118°) showed no depression. [d] All rotations were taken in 95% ethanol at $c = 1\%$.

products, all gave 6β-hydroxy-3α,5α-cycloandrostan-17-one (Table I). The formation of a common product by processes of rearrangement, inversion, and retention, respectively, provides strong evidence for the intervention of a common intermediate.

Kosower and Winstein[11] have reported that methanolysis of cholesteryl *p*-toluenesulfonate and of the trichloroacetates of both 6α-and 6β-hydroxy-3α,5α-cyclocholestane, yield, in each case, about 90% of 6β-methoxy-3α,5α-cyclocholestane and have proposed that the near identity of the products results from product formation from the non-classical, homoallylic carbonium ion (V). The similarity in the stereochemical results of the deamination and the solvolysis reactions of Δ5-3β; 3α,5α-cyclo-6α; and 3α,5α-cyclo-6β derivatives indicates that the same type of intermediate must govern the course of both types of substitution reactions in these systems, and thus that the deamination reactions must also occur *via* the homoallylic cation.



Shoppee, Evans, and Summers[6] have reported that deamination of 3β-aminocholest-5-ene with nitrous acid in 50% acetic acid–water solution at room temperature for sixteen hours led to "100% cholesterol." To ensure that this discrepancy with the result of deamination of 3β-aminoandrost-5-en-17-one (III) was not the result of a solvent effect, the deamination of III was carried out in 1:1 acetic acid–water solution between 0–20° for twenty-five minutes. After basic hydrolysis of the product, 6β-hydroxy-3α,5α-cycloandrostan-17-one was isolated in 53% yield.

It is well known[14] that 3α,5α-cyclo-6-ols rearrange under acidic conditions to more stable Δ5-3β isomers, and Evans and Summers[13] have shown that both 3α,5α-cyclocholestan-6α- and 6β-ols undergo considerable rearrangement under the conditions employed for the deaminations of the cholesterylamines. In the present work a similar experiment was carried out with 6β-hydroxy-3α,5α-cycloandrostan-17-one. This alcohol was treated with excess sodium nitrite in 1:1 acetic acid–water solution at room temperature for twenty-six hours. At the end of this time the product was isolated by ether extraction and acetylated with acetic anhydride in pyridine at room temperature. Partial separation of the components of the resulting mixture was achieved by chromatography. Crystallization of the appropriate fractions, as indicated by infrared spectra, yielded 3β-acetoxyandrost-5-en-17-one (29%), a compound A (12%), $C_{19}H_{27}NO_3$, showing infrared absorption characteristic of a nitro compound[15] (1543 cm.$^{-1}$) and a compound *B* (2%) found identical to that obtained in 22% yield on treatment of 6β-hydroxy-3α,5α-cycloandrostan-17-one with sodium nitrite in 3:1 acetic acid–water solution for 19 hr. This latter product, $C_{19}H_{27}NO_4$,

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

(15) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd ed., John Wiley & Sons, Inc., New York, N. Y., 1958, chap. 17, p. 297.

showed infrared absorption characteristic of nitrate esters[16] at 1623 cm.$^{-1}$; doublet 1282, 1271 cm.$^{-1}$; and 864 cm.$^{-1}$.

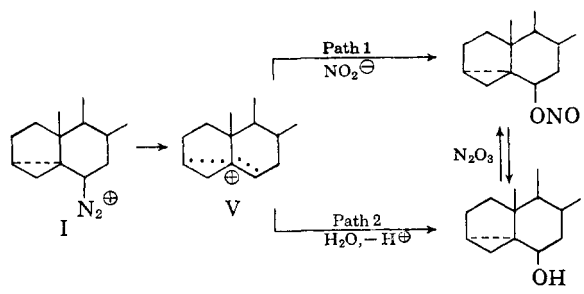
The n.m.r. spectrum[17] of the nitrate ester (*B*) showed vinyl proton absorption at 327 c.p.s. and a broad unresolved absorption at 286 c.p.s. of the type characteristic of absorption by the C-3 protons of cholesteryl and cholestanyl derivatives.[18] Based on this data and the known tendency of 3α,5α-cyclo-6β derivatives to rearrange to Δ^5-3β derivatives,[14] this product is tentatively identified as the nitrate ester of 3β-hydroxyandrost-5-en-17-one. As has been reported to be the case for nitrate esters,[19] this product proved relatively stable toward basic hydrolysis. The preparation of the analogous cholesteryl nitrate has been reported to result from treatment of cholesteryl chloride with silver nitrate in boiling ethanol.[20]

The n.m.r. spectrum of the nitro compound (*A*) showed no absorption in the region characteristic of vinyl protons and is believed to be 6β-nitro-3α,5α-cycloandrostan-17-one, formed by attack, of nitrite ion on the homoallylic carbonium ion. The absence of absorption in the 0–50 c.p.s. region may reflect a paramagnetic effect of the nitro group on the cyclopropyl proton absorption similar to that which appears to be caused by the 11-carbonyl of 3,20 - bisethylenedioxy - 11 - oxo - 9β,19 - cyclo-5α-pregnane.[21] A long range paramagnetic shielding effect by the nitro group has been reported recently by Huitric and Trager for the equatorial C-2 and C-6 protons of *cis*-4-*tert*-butylnitrocyclohexane.[22] In the present case, a quartet with peaks at 233.7, 235, 237, and 238.3 c.p.s. is attributed to absorption of the C-6 equatorial proton which is split by the C-7 methylene protons. The magnitudes of the approximate coupling constants, J = 1.3 c.p.s. and J = 3.4 c.p.s. are close to those expected for coupling between vicinal axial-equatorial and equatorial–equatorial protons.[23] The reason for the apparent difference in this case between J_{ae} and J_{ee}, in contrast to 6β-acetoxy and 6β-*p*-nitrobenzoyloxy derivatives[24] where pseudo triplets indicate that $J_{ae} \simeq J_{ee} \simeq 2.6$ c.p.s., is not clear.

The products obtained from the nitrous acid deamination of aliphatic amines have been shown to include both nitro compounds and nitrite esters.[25] Since the products obtained by deamination of 6α- and 6β-amino-3α,5α-cycloandrostan-17-one and 3β-aminoandrostan-17-one, prior to basic hydrolysis, all showed absorption at 1543 cm.$^{-1}$ and 1630 cm.$^{-1}$ characteristic of nitro compounds and nitrite esters, respectively,[15] it seemed desirable to determine the nature of the products formed directly in the deamination medium by isolation of products without basic hydrolysis. 6β-Amino-3α,5α-cycloandrostan-17-one was deaminated in 1:3 acetic acid–water solution in the usual manner, and the crude product, isolated by ether extraction, was chromatographed on neutral, activity III alumina. The products isolated in this manner included the nitrite ester of 6β-hydroxy-3α,5α-cycloandrostan-17-one (46%), 6β-hydroxy-3α,5α-cycloandrostan-17-one (14%), and a nitro compound (7%) which proved identical to that which was obtained by the rearrangement of 6β-hydroxy-3α,5α-cycloandrostan-17-one with nitrous acid in 1:1 acetic acid–water solution as described above.

The nitrite ester was identified by its infrared[15] and ultraviolet spectra[26] and its hydrolysis with 5% methanolic potassium hydroxide to 6β-hydroxy-3α,5α-cycloandrostan-17-one. Since the major product of deamination was found to be the nitrite ester, while the stereochemistry of the deamination is based on the configuration of the alcohol derived by hydrolysis, the structure of the nitrite ester, and consequently the stereochemistry of the deamination reaction, is based on the studies of Allen,[27] who found that hydrolysis and alcoholysis of a variety of nitrite esters proceed with O—N cleavage.

Although formation of 6β-nitro-3α,5α-cycloandrostan-17-one by deamination of the 6β-amine or nitrosation of the 6β-alcohol requires a nucleophilic displacement reaction, most probably involving the homoallylic cation and the ambident nitrite ion, there are two likely pathways by which the nitrite ester might be formed[25]: (1) attack by nitrite ion on the homoallylic cation, and (2) esterification of 6β-hydroxy-3α,5α-cycloandrostan-17-one by the nitrosating agent.



(16) R. A. G. Carrington, *Spectrochimica Acta*, **16**, 1279 (1960).

(17) N.m.r. spectra were determined with deuteriochloroform solutions at 60 Mc. using tetramethylsilane (TMS) as an internal reference. Chemical shifts are expressed in c.p.s. measured from TMS (0 c.p.s.) in the direction of decreasing field.

(18) J. N. Shoolery and M. T. Rogers, *J. Am. Chem. Soc.*, **80**, 5121 (1958).

(19) R. Boschau, R. Merrow, and R. W. van Dolah, *Chem. Rev.*, **55**, 485 (1955).

(20) Elsevier, "Encyclopedia of Organic Chemistry," Springer-Verlag, Berlin, 14*s*, 1922*s*.

(21) H. Wehrli, M. S. Heller, K. Schaffner, and O. Jeger, *Helv. Chim. Acta*, **44**, 2162 (1961).

(22) A. C. Huitric and W. F. Trager, *J. Org. Chem.*, **27**, 1926 (1962).

(23) 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., 1960, p. 311.

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

(25) A. T. Austin, *Nature*, **188**, 1086 (1960).

(26) R. N. Haszeldine and J. Jander, *J. Chem. Soc.*, 691 (1954).

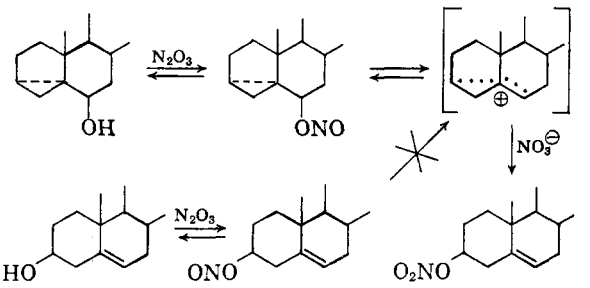
(27) (a) A. D. Allen, *J. Chem. Soc.*, 1968–1974 (1954). (*b*) A. D. Allen, *Nature*, **172**, 301 (1953). (c) A. D. Allen and G. R. Shonbaum, *Can. J. Chem.*, **39**, 940 947 (1961).

Treatment of alcohols with nitrous acid in aqueous acid solution has beem employed as a general method for the preparation of nitrite esters.[28] To determine the relative importance of path 2, it was desired to determine the ease with which 6β-hydroxy-3α,5α-cycloandrostan-17-one is nitrosated under conditions similar to those used for the deaminations. Treatment of 6β-hydroxy-3α,5α-cycloandrostan-17-one with excess sodium nitrite in 3:1 acetic acid–water solution at room temperature for fifteen minutes yielded, after chromatography, 57% of the nitrite ester, the infrared spectrum of which was identical to that of the product obtained by deamination of 6β-amino-3α,5α-cycloandrostan-17-one. As in the case of the deamination, the extent to which hydrolysis of the nitrite ester may have occurred during the workup was not determined. The relative ease of nitrosation of the 3α,5α-cyclo-6β-ol, thus, strongly suggests that at least part of the nitrite ester formed in the deamination reaction is formed by nitrosation of the 3α,5α-cyclo-6β-ol (path 2).

In the hope of gaining insight into the nature of the process by which the nitrate ester of 3β-hydroxyandrost-5-en-17-one was formed on prolonged nitrosation of 6β-hydroxy-3α,5α-cycloandrostan-17-one, nitrosation experiments were carried out with 3β-hydroxyandrost-5-en-17-one. Treatment of 3β-hydroxyandrost-5-en-17-one with excess sodium nitrite in 3:1 acetic acid–water solution for fifteen minutes led to isolation of the Δ^5-3β-nitrite ester in 25% yield. When the reaction was carried out for twenty-three hours, in contrast to the reaction of 6β-hydroxy-3α,5α-cycloandrostan-17-one, there was no formation of the Δ^5-3β-nitrate ester. The infrared spectrum of the product isolated without basic hydrolysis was almost identical to that of 3β-hydroxyandrost-5-en-17-one. There was no absorption at 1642 cm.$^{-1}$ (RONO)[15] and only very weak absorption at 1543 cm.$^{-1}$ (RNO_2)[15] indicating a trace of a nitro compound. Since the formation of the nitrite ester from the alcohol is reversible,[27] the absence of any nitrite ester after twenty-three hours is attributed to diffusion of the nitrosating agent from the open reaction vessel.

The ease of formation of both 3α,5α-cyclo-6β and Δ^5-3β nitrite esters from the corresponding alcohols, and the absence of nitrate ester formation from the latter, excludes the possibility that the Δ^5-3β nitrate ester is formed by oxidation of the Δ^5-3β nitrite ester. Thus the nitrate ester must be formed by attack of nitrate ion on the homoallylic cation, and its formation only from the 3α,5α-cyclo-6β-ol reflects the greater reactivity of 3α,5α-cyclo-6β derivatives compared to the Δ^5-3β isomers.[11] (See top of col. 2.)

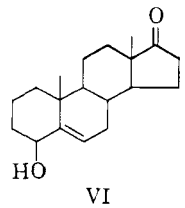
Deamination of 3α-Aminoandrost-5-en-17-one (IV).—The infrared spectrum of the crude product



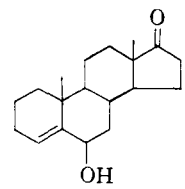
obtained by deamination of 3α-aminoandrost-5-en-17-one showed absorption at both 1631 cm.$^{-1}$ and 1548 cm.$^{-1}$ indicative of a mixture of nitrite esters and nitro compounds.[15] After hydrolysis with 5% methanolic potassium hydroxide, a mixture of keto alcohols was obtained which was only partially separated by chromatography on neutral alumina. Crystallization of the earlier fractions led to isolation of a keto alcohol (isomer *a*), m.p. 163.5–165°, $[\alpha]^{25}D$ −13.6°, while crystallization of the latter fractions yielded a keto alcohol, isomer *b*, m.p. 155–158° (softening 143–155°), $[\alpha]^{25}D$ +137.4°. Treatment of isomer *a* with hydrochloric acid in acetic acid yielded androsta-3,5-dien-17-one. Because of the small amount of material on hand and the fact that the melting range indicated that isomer *b* was not pure, it was not similarly treated.

To the extent that substitution occurs on methanolysis of the *p*-toluenesulfonate of 3α-hydroxycholest-5-ene, there is formed a mixture of 4β-methoxycholest-5-ene and 6β-methoxycholest-4-ene, the structures of which have been established synthetically by Shoppee, *et al.*[12d] These products represent an alternate mode by which the homoallylic system may rearrange.[29] In the case of the *p*-toluenesulfonate of 3α-hydroxycholest-5-ene, the occurrence of this type of rearrangement is apparently due to the *trans* diaxial relationship of the leaving group and the neighboring allylic 4β-proton. Exclusive formation of the isomeric axial allylic alcohols is apparently the result of stereoelectronic control[30] operating on the intermediate allylic cation.

Although the structures of the products resulting from the deamination of 3α-aminoandrost-5-en-17-one were not conclusively established, it is believed that they represent the products, VI and



VI



VII

(28) (a) W. A. Noyes, *Org. Syn.*, **16**, 7 (1936). (b) A. Chrétien and Y. Longi, *Compt. rend.*, **220**, 746 (1945).

(29) (a) M. Simonetta and S. Winstein, *J. Am. Chem. Soc.*, **76**, 18 (1954). (b) J. D. Roberts and R. H. Mazur, *ibid.*, **73**, 2509 (1951). (c) W. C. Wildman and D. R. Saunders, *ibid.*, **76**, 946 (1954). (d) H. L. Goering, R. W. Greiner, and M. F. Sloan, *ibid.*, **83**, 1391 (1961).

(30) (a) E. J. Corey and R. A. Sneen, *ibid.*, **78**, 6269 (1956). (b) A. Nickon and J. F. Bagli, *ibid.*, **83**, 1498 (1961).

TABLE II
MOLECULAR ROTATION CORRELATIONS

Structure	M_D, 17-Keto	M_D, 17-C_8H_{17}	ΔM_D (17-Keto–17-C_8H_{17})
4β-Hydroxy-Δ⁵	−39° (Isomer *a*)	−228°[a]	+189°
6β-Hydroxy-Δ⁴	+396° (Isomer *b*)	+240°[a]	+156°
5α-(no substituents)	+260°[b]	+83°[b]	+177°
3β-Hydroxy-5α-	+261°[b]	+89°[b]	+172°
3β-Hydroxy-Δ⁵	+58°[b]	−150°[b]	+208°
3-Oxo-Δ⁴	+566°[b]	+338°[b]	+228°

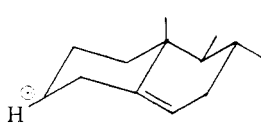
[a] Data calculated from that of Evans and Shoppee, *et al.*, ref. 12b. [b] Data taken from Mathieu and Petit, "Pouvoir Rotatoire Naturel," Part I, Masson and Co., Paris, 1956.

VII, of the rearrangement of the homoallylic to the allylic systems. This assumption is consistent with molecular rotation differences (Table II).

It has been reported that deamination of 3α-aminocholest-5-ene leads exclusively to cholesta-3,5-diene.[6] Since the axial, allylic alcohols 4β-hydroxycholest-5-ene and 6β-hydroxycholest-4-ene are known to be prone to elimination,[12] it seems likely especially in view of the rearrangement of 3α,5α-cyclo-6-ols under similar conditions that any of the allylic alcohols formed might have undergone elimination under the prolonged deamination conditions employed.

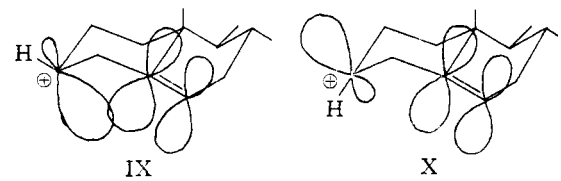
Discussion

Since the nature of the rearrangements observed in the deaminations of the 3-aminoandrost-5-en-17-ones and the 6-amino-3α,5α-cycloandrostan-17-ones indicates that carbonium ion intermediates similar to those formed in solvolysis reactions of analogous ester and halide derivatives must intervene, pyramidal transition states, such as those postulated to account for the stereochemistry of the deamination reactions of saturated steroid amines,[6,8,10] are unlikely in the present series. The stereospecificity observed in the deaminations of the 3α- and 3β-aminoandrost-5-en-17-ones rules out the formation of a common intermediate such as the planar (sp^2) carbonium ion (VIII) by decomposition of the Δ⁵-3α and -3β diazonium ions. Although the rapid deaminations of bridgehead



VIII

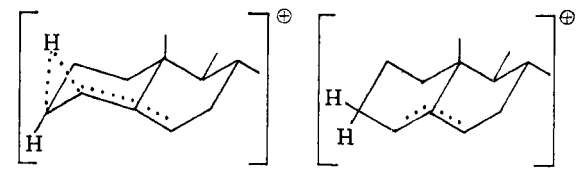
amines[31] suggests that formation of tetrahedral (sp^3) carbonium ions by decomposition of aliphatic-diazonium ions may not be energetically unfavorable, the present results cannot be explained by intermediates such as the epimeric tetrahedral carbonium ions, IX and X, formed by decomposition of the Δ⁵-3α and Δ⁵-3β diazonium ions, respectively. Because of overlap of the α-lobe of the vacant sp^3 orbital at C-3 of IX with the Δ⁵-π



IX X

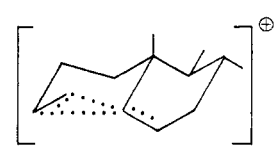
orbital, IX might be expected to lead to the homoallylic cation at least as readily as X.

The most probable mechanism for the decomposition of the Δ⁵-3α diazonium ion would thus appear to be that in which there is considerable charge delocalization in the transition state for the C—N heterolysis, leading directly to a nonclassical intermediate such as XI or XII.



XI XII

Kinetic investigations of solvolysis reactions in the cholesteryl system[11] have indicated that the homoallylic cation is formed directly in the rate-determining heterolyses of Δ⁵-3β and the 3α,5α-cyclo-6α and -6β derivatives. Although the nature of the deamination reaction precludes kinetic investigations of this type, formation of 3α,5α-cyclo-6β derivatives by deamination of 3β-aminoandrost-5-en-17-one indicates that if a localized cation, such as VIII or X, does intervene, its conversion to the homoallylic cation must be much more rapid than direct reaction with solvent. By analogy with the solvolysis reactions, formation of 3α,5α-cyclo-6β derivatives on deamination of the Δ⁵-3β- and the 3α,5α-cyclo-6α- and 6β-amines suggests that the homoallylic cation is formed directly on decomposition of the aliphatic diazonium ions. Formation of the homoallylic cation from both 6α- and 6β-isomers is in accord with the results of Kosower and Winstein[11] for solvolysis reactions, and would be expected if this cation exists as a symmetrical species such as XIII, of the type considered by these authors, and for which further evidence has been recently advanced by Whitham.[32]

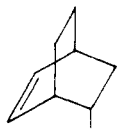


XIII

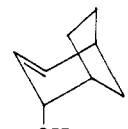
(31) (a) P. D. Bartlett and L. H. Knox, *J. Am. Chem. Soc.*, **61**, 3184 (1939). (b) M. Wilhelm and D. Y. Curtin, *Helv. Chim. Acta*, **40**, 2129 (1957). (c) W. Theilacker and K.-H. Beyer, *Ber.*, **94**, 2968 (1961).

(32) G. H. Whitham, *Proc. Chem. Soc.*, 422 (1961).

Rearrangements of homoallylic systems to both allylic and cyclopropylcarbinyl systems have been observed in deaminations of other homoallylic amines, and the nature of the rearrangment has similarly been found to be dependent on the stereochemistry of the system. While deamination of *endo*-2-aminobicyclo[2.2.2]oct-5-ene (XIV) has been found to lead to *exo*-bicyclo[3.2.1]oct-3-en-2-ol (XV),[29c,d] deamination of *endo*-dehydronorbornylamine (XVI) was found to give rise to both

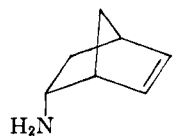


XIV

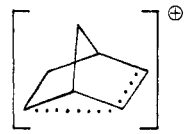


XV

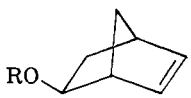
exo-dehydronorbornyl (XVIII) and nortricyclyl (XIX) derivatives, indicating reaction *via* the homoallylic cation (XVII).[33] In the latter system, rearrangement to the allylic system is apparently



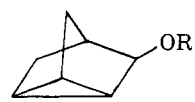
XVI



XVII



XVIII



XIX

inhibited by the strain inherent in formation of the four-membered ring.

Although in the present work the deaminations of the 3-amino- and 6-aminoandrostan-17-ones were relatively rapid (reaction time less than one hour), it was reported that under similar conditions, large amounts of starting materials were recovered after about sixteen hours in the deaminations of the corresponding cholesterylamines.[6,13] The extent to which differences in basicities of the amines would effect the rates of deamination under these conditions has not been established. It has recently been reported,[34] that attempted deamination of 3e-aminofriedelan at room temperature led to isolation of an insoluble, crystalline nitrous acid salt, and in the present work[35] it was found that the acetic acid salt of 3β-amino-17-ethylenedioxyandrost-5-ene was quite insoluble in water. These results suggest that incomplete deamination of high molecular weight amines with nitrous acid in aqueous acetic acid may frequently be due to the formation of insoluble acetic acid salts and/or nitrous acid salts.

(33) J. D. Roberts, C. C. Lee, and W. H. Saunders, Jr., *J. Am. Chem. Soc.*, **77**, 3034 (1955).
(34) G. Drefall and S. Huneck, *Ber.*, **93**, 1961 (1960).
(35) J. Tadanier and W. Cole, *J. Org. Chem.*, **27**, 4624 (1962).

The present results indicate that under the conditions commonly employed for deamination of steroid amines, the principal substitution products formed are nitrite esters. The rearrangements of the 3α,5α-cyclo-6α- and 6β-ols to Δ^5-3β derivatives, under deamination conditions reported by Evans and Summers[13] in the cholesteryl system and also found for 6β-hydroxy-3α,5α-cycloandrostan-17-one, indicate that when labile products are formed in deamination reactions, the stereochemistry of deamination may be obscured by subsequent solvolysis reactions of the deamination products.

Experimental

A. Deamination in 1:3 Acetic Acid–Water Solution. Isolation of Products after Basic Hydrolysis. 1. Deamination of 6β-Amino-3α,5α-cycloandrostan-17-one (I).—A solution prepared by dissolving 413 mg. of the acetic acid salt of 6β-amino-3α,5α-cycloandrostan-17-one in 20 ml. of 1:3 acetic acid–water solution was cooled to 0–5° and a freshly prepared solution of 1.6 g. of sodium nitrite in 20 ml. of 1:3 acetic acid–water solution, at 0–5°, was added. The resulting solution was swirled to effect homogeneity and allowed to stand at room temperature for 45 min. The solution was initially clear, but became slightly turbid within 2 to 3 min. After 10 min. the reaction mixture was milky-white and a white paste had separated.

At the end of the deamination time, the reaction mixture was shaken with 200 ml. of ether and 150 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, two 100-ml. portions of 5% sodium bicarbonate solution, and three 100-ml. portions of water, then combined and dried over magnesium sulfate. The ether was evaporated leaving a deep orange, viscous oil.

The deamination product was dissolved in 12 ml. of 5% methanolic potassium hydroxide solution and the resulting solution was heated under reflux for 1 hr. At the end of this time, the hydrolysis solution was cooled and shaken with 200 ml. of ether and 150 ml. of water. 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 magnesium sulfate. The ether was evaporated leaving 266 mg. of a bright-yellow solid. This material was placed on a column of 26 g. of neutral, activity III alumina in 8 ml. of ether solution. Elution with 1:1 ether–pentane solution yielded 216.5 mg. of crystalline product. This material was dissolved in 20 ml. of ether and treated with carbon to remove a trace of colored impurity, and filtered through Celite. The carbon–Celite mat was washed with 10 ml. of ether and the washings were added to the original ether filtrate. The ether was evaporated leaving 214 mg. of a white crystalline solid, m.p. 136–139°. The mixed melting point with 6β-hydroxy-3α,5α-cycloandrostan-17-one was 136–140°; $[\alpha]^{23}D$ + 115° (1%, 95% ethanol).

2. Deamination of 6α-Amino-3α,5α-cycloandrostan-17-one (II) and 3β-Aminoandrost-5-en-17-one (III).—The same procedure, described above, was employed for deamination of both II and III. In both cases the acetic acid salts dissolved readily in 1:3 acetic acid–water solution. The behavior of the deamination medium in the case of the 3α,5α-cyclo-6α-amine was similar to that observed in the case of the 3α,5α-cyclo 6β-isomer. The initially clear solution gradually became turbid, then milky-white. In the case of the Δ^5-3β amine, a finely divided white precipitate separated immediately on the addition of the sodium nitrite solution, suggesting formation of an insoluble nitrous acid salt. After about 10 min., during which time the reaction mixture was

frequently swirled, the white solid was converted to a white foam.

The results of the deamination reactions are summarized in Table I.

B. Deamination of 3β-Aminoandrost-5-en-17-one (III) in 1:1 Acetic Acid–Water Solution.—A solution prepared by dissolving 506 mg. of the acetic acid salt of 3β-aminoandrost-5-en-17-one in 20 ml. of 1:1 acetic acid–water solution was cooled to 0–5° and a freshly prepared solution of 1.5 g. of sodium nitrite in 20 ml. of 1:1 acetic acid-water solution, at 0–5°, was added. The resulting solution was swirled to effect homogeneity and allowed to stand at room temperature for 25 min. After 15 min. the reaction mixture had become milky-white.

The reaction mixture was worked up as described above and the product subjected to basic hydrolysis with 5% methanolic potassium hydroxide. The resulting product (368 mg. of an orange crystalline solid) was chromatographed on neutral activity III alumina as described above to yield 299 mg. of an orange crystalline solid. This material was dissolved in ether and treated with carbon. The white crystalline solid (271 mg.) recovered from the ether solution melted 132–140°. This material was recrystallized from ethanol–water solution to yield 222 mg. of white crystals, m.p. 139.5–141°, mixed melting point with 6β-hydroxy-3α,5α-cycloandrostan-17-one 139–141°; $[\alpha]^{23}D$ + 114° (1%, 95% ethanol).

C. Deamination of 6β-Amino-3α,5α-cycloandrostan-17-one (I). Isolation of Products without Basic Hydrolysis.—A solution prepared from 1.9 g. of the acetic acid salt of 6β-amino-3α,5α-cycloandrostan-17-one (I) and 100 ml. of 1:3 acetic acid–water solution was cooled to 8° and a freshly prepared solution of 8 g. of sodium nitrite in 100 ml. of 1:3 acetic acid–water solution, at 8°, was added. The resulting solution was allowed to stand at room temperature for 1 hr. during which time the solution became turbid and a white paste separated.

At the end of the deamination time the reaction mixture was shaken with 100 ml. of water and 250 ml. of ether. The aqueous solution was separated and extracted with 200 ml. of ether. The ether solutions were washed in series with three 100-ml. portions of water, four 100-ml. portions of 5% sodium bicarbonate solution, and three 100-ml. portions of water. The ether solutions were combined and dried over anhydrous magnesium sulfate. Evaporation of the ether left 1.53 g. of a clear, viscous, light yellow oil.

The deamination product was placed on a column of 100 g. of neutral, activity III alumina in 12 ml. of ether solution. Elution with 1:20 ether–pentane solution yielded 799 mg. of a pale-green oil which partially crystallized on standing and proved extremely soluble in pentane. For analysis, this material was eluted through a column of 80 g. of neutral, activity III alumina with 1:25 ether–pentane solution to yield 560.2 mg. of a pale green oil identified as the nitrite ester of 6β-hydroxy-3α,5α-cycloandrostan-17-one. Infrared: 1730 cm.$^{-1}$ (17 > C=O),[36] 1629 cm.$^{-1}$ (RONO),[15] (Chloroform). Ultraviolet $\lambda_{m\mu}^{max}$ (ε): 383 (41.3); 370 (61.7); 358 (57.1); 346 (41.3); 336 (28.2); 229 (1740) (Cyclohexane).

Anal. Calcd. for $C_{19}H_{27}NO_3$: C, 71.90; H, 8.58; N, 4.42. Found: C, 71.69; H, 8.36; N, 4.82.

Elution of the original column with 1:1 ether–pentane solution yielded 339 mg. of product. This material was washed with 6 ml. of pentane leaving a white solid (180 mg.), m.p. 168–169°. Recrystallization from ether–pentane solution yielded 6β-nitro-3α,5α-cycloandrostan-17-one (compound A, 116 mg.), m.p. 178–180°. Infrared: 1733 cm.$^{-1}$ (17 > C=O),[36] 1543 cm.$^{-1}$ (RNO_2),[15] (chloroform). For analysis this material was recrystallized from ether–pentane solution.

Anal. Calcd. for $C_{19}H_{27}NO_3$: C, 71.90; H, 8.58; N, 4.42. Found: C, 71.94; H, 8.43; N, 4.22.

(36) R. N. Jones and F. Herling, *J. Org. Chem.*, **19**, 1252 (1954).

Further elution of the original column with 1:1 ether–pentane solution yielded 213.7 mg. of a white crystalline solid, m.p. 136–139°, the infrared spectrum of which was essentially identical to that of 6β-hydroxy-3α,5α-cycloandrostan-17-one.

D. Hydrolysis of the Nitrite Ester of 6β-Hydroxy-3α,5α-cycloandrostan-17-one.—The nitrite ester (193 mg.), obtained by deamination of 6β-amino-3α,5α-cycloandrostan-17-one, was heated under reflux for 1 hr. with 8 ml. of 5% methanolic potassium hydroxide solution. The resulting solution was cooled and shaken with 80 ml. of ether and 80 ml. of water. The aqueous phase was separated and washed with 80 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 leaving 168.2 mg. of a white crystalline solid, m.p. 140.5–142°; $[\alpha]D^{23}$ +117° (1%, 95% ethanol). Mixed melting point with 6β-hydroxy-3α,5α-cycloandrostan-17-one, 139–141.5°. The infrared spectrum of the hydrolysis product was identical to that of 6β-hydroxy-3α,5α-cycloandrostan-17-one.

E. Nitrosation of 6β-Hydroxy-3α,5α-cycloandrostan-17-one.—6β-Hydroxy-3α,5α-cycloandrostan-17-one (804 mg.) was dissolved in 53 ml. of glacial acetic acid. A freshly prepared solution of 2.8 g. of sodium nitrite in 17.6 ml. of water was added, and the resulting solution was allowed to stand at room temperature for 15 min. The solution was then shaken with 200 ml. of ether and 500 ml. of water. The aqueous solution was separated and extracted with 200 ml. of ether. The ether solutions were washed in series with three 100-ml. portions of water, two 150-ml. portions 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 evaporated leaving 858 mg. of a clear, orange, viscous oil. This material was placed on a column of 80 g. of neutral activity III alumina in 10 ml. of ether solution. Elution with 1:25 ether–pentane solution yielded 503 mg. of the nitrite ester of 6β-hydroxy-3α,5α-cycloandrostan-17-one as a pale green oil identified by comparison of its infrared spectrum with that of the nitrite ester obtained by deamination of 6β-amino-3α,5α-cycloandrostan-17-one, as described above.

Further elution of the column with ether yielded 271 mg. of crude 6β-hydroxy-3α,5α-cycloandrostan-17-one, m.p. 132–137°.

F. Treatment of 6β-Hydroxy-3α,5α-cycloandrostan-17-one with Sodium Nitrite in 3:1 Acetic Acid–Water Solution.—6β-Hydroxy-3α,5α-cycloandrostan-17-one (610 mg.) was dissolved in 40 ml. of glacial acetic acid and a freshly prepared solution of 2.12 g. of sodium nitrite in 13.4 ml. of water was added. The solution was swirled to effect homogeneity and allowed to stand at room temperature for 19 hr. The resulting solution was shaken with a mixture of 200 ml. of ether and 400 ml. of water. The aqueous solution was separated and extracted with 200 ml. of ether. The ether solutions were washed in series with three 100-ml. portions of water, two 150-ml. portions 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 evaporated leaving 673 mg. of a pale yellow glass.

The product (660 mg.) was heated under reflux for 1 hr. with 20 ml. of 5% methanolic potassium hydroxide solution. The reaction solution was worked up by ether extraction in the usual manner to yield 590 mg. of a mixture of solid and oil. This material was placed on a column of 80 g. of neutral, activity III alumina in 10 ml. of ether solution. Elution with 1:10 ether–pentane solution yielded 203 mg. of the nitrate ester of 3β-hydroxyandrost-5-en-17-one (Compound B), m.p. 127–130°. Infrared: 1730 cm.$^{-1}$ (17 > C=O)[36] and 1623 cm.$^{-1}$; doublet 1282 and 1271 cm.$^{-1}$; 864 cm.$^{-1}$ ($RONO_2$).[16]

Recrystallization from ether pentane solution yielded 157 mg., m.p. 142–143.5°. For analysis, this material was

recrystallized from ether–pentane solution to yield 100 mg., m.p. 142–143.5°; $[\alpha]^{26}D$ + 1.92° (1%, chloroform).

Anal. Calcd. for $C_{19}H_{27}NO_4$: C, 68.45; H, 8.16; N, 4.20. Found: C, 68.64; H, 8.28; N, 4.08.

G. Treatment of 6β-Hydroxy-3α,5α-cycloandrostan-17-one with Sodium Nitrite in 1:1 Acetic Acid–Water Solution.—6β-Hydroxy-3α,5α-cycloandrostan-17-one (1.52 g.) was dissolved in 150 ml. of glacial acetic acid and a freshly prepared solution of 6 g. of sodium nitrite in 150 ml. of water was added. The resulting solution was swirled to effect homogeneity and allowed to stand at room temperature for 26 hr. The resulting solution was shaken with a mixture of 700 ml. of ether and 700 ml. of water. The aqueous phase was separated and extracted with 700 ml. of ether. The ether solutions were washed in series with two 200-ml. portions of water, three 250-ml. portions of 5% sodium bicarbonate solution, and three 200-ml. portions of water, combined, and dried over anhydrous magnesium sulfate. The ether was evaporated leaving 1.64 g. of an orange glass.

The product was dissolved in 50 ml. of reagent pyridine, 10 ml. of acetic anhydride was added, and the resulting solution was allowed to stand at room temperature for 20 hr. The reaction solution was then shaken with a mixture of 500 ml. of ether and 600 ml. of water. The aqueous phase was separated and extracted with 500 ml. of ether. The ether solutions were washed in series with four 300-ml. portions of water, combined, and dried over anhydrous magnesium sulfate. The ether was evaporated and the residual pyridine was removed under aspirator pressure on the steam bath using a rotary evaporator leaving 1.79 g. of an orange oil.

This product was chromatographed on 160 g. of neutral activity III alumina. The first fractions eluted with ether–pentane solution (206 mg.) showed strong bands at 1730 $cm.^{-1}$ (17 > C=O)[36] and 1623 $cm.^{-1}$; doublet 1282 and 1271 $cm.^{-1}$ and 864 $cm.^{-1}$ ($RONO_2$).[16] This material was heated under reflux for 1 hr. with 8 ml. of 5% methanolic potassium hydroxide solution. The resulting product (145 mg.), isolated by ether extraction in the usual manner, was chromatographed on 20 g. of neutral activity III alumina. Elution with 1:10 ether–pentane solution yielded 44.2 mg. of white solid, m.p. 130–131°. Recrystallization from ether–petroleum ether (b.p. 68–70°) yielded 30 mg. of the nitrate ester of 3β-hydroxyandrost-5-en-17-one, m.p. 145–146°. The melting point was not depressed by addition of the nitrate ester, compound B (described in part F), and the infrared spectra of these products were identical.

Additional elution of the original column with 1:5 ether–pentane solution yielded 680 mg. of a white crystalline solid, m.p. 158–168°. Recrystallization of this material from ether-petroleum ether (b.p. 68–70°) yielded 504 mg. of 3β-acetoxyandrost-5-en-17-one, m.p. 168–171° (lit.,[37] 171–172°). The melting point was not depressed by addition of an authentic sample, and the infrared spectrum was identical to that of 3β-acetoxyandrost-5-en-17-one.

Continued elution of the column yielded 282 mg. of intermediate fractions showing absorption at both 1543 $cm.^{-1}$ (NO_2)[15] and 1250 $cm.^{-1}$ (ester C—O).[15]

Further elution with 1:5 ether–pentane yielded 338 mg. of a white solid, m.p. 173–178°. Recrystallization from benzene–petroleum ether (b.p. 68–70°) yielded 192 mg., m.p. 178–180°; $[\alpha]^{26}D$ + 7.9° (1%, chloroform). The melting point was not depressed by addition of 6β-nitro-3α,5α-cycloandrostan-17-one (compound *A*) obtained by deamination of 6β-amino-3α,5α-cycloandrostan-17-one as described above, and the infrared spectra of the two products were identical.

H. Nitrosation of 3β-Hydroxyandrost-5-en-17-one.—3β-Hydroxyandrost-5-en-17-one (1.0 g.) was dissolved in 60 ml. of glacial acetic acid and a freshly prepared solution of 3 g. of sodium nitrite in 20 ml. of water was added. The resulting solution was allowed to stand at room temperature for 15 min. and then shaken with a mixture of 600 ml. of water and 250 ml. of ether. The aqueous phase was separated and extracted with 250 ml. of ether. The ether solutions were washed in series with three 150-ml. portions of water, two 250-ml. portions of 5% sodium bicarbonate solution and three 100-ml. portions of water, combined, and dried over anhydrous magnesium sulfate. The ether was evaporated leaving 1.08 g. of a light yellow solid.

The product was placed on a column of 110 g. of neutral, activity III alumina in 45 ml. of ether. Elution with 1:10 ether–pentane solution yielded 378 mg. of an orange solid. Recrystallization from ether–pentane solution using decolorizing carbon yielded 270 mg. of the nitrite ester, m.p. 144–146°. Infrared: 1736 $cm.^{-1}$ (17 > C=O);[36] 1642 $cm.^{-1}$ (RONO)[15] (chloroform). Ultraviolet $\lambda_{m\mu}^{max}$ (ϵ); shoulder 388 (41.5); 372 (68.7); 357 (69.0); 346 (53.8); 336 (38.4); 229 (2140) (cyclohexane).

Anal. Calcd. for $C_{19}H_{27}NO_3$: C, 71.90; H, 8.58; N, 4.42. Found: C, 71.71; H, 8.47; N, 4.31.

Elution of the column with 1:1 ether–pentane solution yielded 420 mg. of 3β-hydroxyandrost-5-en-17-one, m.p. 148–150°. The melting point was not depressed by addition of authentic material, and the infrared spectrum was identical to that of starting material.

I. Treatment of 3β-Hydroxyandrost-5-en-17-one with Sodium Nitrite in 3:1 Acetic Acid–Water Solution.—3β-Hydroxyandrost-5-en-17-one (2.0 g.) was dissolved in 132 ml. of glacial acetic acid and a freshly prepared solution of 7.16 g. of sodium nitrite in 44.2 ml. of water was added. The resulting solution was allowed to stand at room temperature for 23 hr. and then shaken with a mixture of 300 ml. of ether and 1 l. of water. The aqueous solution was separated and extracted with 300 ml. of ether. The ether solutions were washed in series with 250 ml. of water, two 250-ml. portions of 5% sodium bicarbonate solution, and three 250-ml. portions of water, combined and dried over anhydrous magnesium sulfate. The ether was evaporated leaving 2.1 g. of a pale-yellow solid. The infrared spectrum of this material was almost identical to that of the starting material except for a weak absorption at 1540 $cm.^{-1}$ suggesting the presence of a trace of a nitro compound. There was no absorption between 1550–1700 $cm.^{-1}$ showing the absence of nitrite and nitrate esters.

J. Deamination of 3α-Aminoandrost-5-en-17-one (IV).—A solution prepared by dissolving 1.5 g. of the acetic acid salt of 3α-aminoandrost-5-en-17-one in 80 ml. of 1:3 acetic acid–water solution was cooled to 8° and a freshly prepared solution of 6.5 g. of sodium nitrite in 80 ml. of 1:3 acetic acid–water solution, at 8°, was added. The resulting solution was swirled to effect homogeneity and allowed to stand at room temperature for 1 hr. during which time a white solid separated.

At the end of the deamination time, the reaction mixture was shaken with 300 ml. of water and 400 ml. of ether. The aqueous phase was separated and extracted with 400 ml. of ether. The ether solutions were washed in series with 200-ml. portions of water, two 200-ml. portions of 5% sodium bicarbonate solution, and three 200-ml. portions of water, combined, and dried over anhydrous magnesium sulfate. The ether was evaporated leaving 1.35 g. of an orange oil which partially crystallized on standing. This material showed strong absorption at 1631 $cm.^{-1}$ (RONO)[15] and a medium absorption peak at 1548 $cm.^{-1}$ (RNO_2).[15]

The deamination product (1.14 g.) was eluted through a column of 130 g of neutral activity III alumina with 500 ml. of 1:1 ether–pentane solution to yield 797 mg. of a yellow oily solid which showed strong absorption at 1631 $cm.^{-1}$ and no absorption at 1548 $cm.^{-1}$. This product was hydrolyzed with 5% methanolic potassium hydroxide solution in the usual manner to yield 563 mg. yellow solid melting between 99–135°. Careful chromatography of this material on neutral activity III alumina failed to effect a clean separation of the products. Recrystallization of the initial fractions eluted with 1:4 ether–pentane solutions from ether–pentane solution yielded 121 mg. of a product (isomer *a*), m.p. 162–

(37) Elsevier, "Encyclopedia of Organic Chemistry," Springer-Verlag, Berlin, **14s**, 2609–2612*s*.

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).

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(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).