Experimental

cis-4-*t*-Butylcyclohexanecarboxamide.—Pure *cis*-4-*t*-butylcyclohexanecarboxylic acid,[16] m.p. 117–118°, 6.7 g. (0.036 mole), was added to thionyl chloride and the mixture was stirred overnight at room temperature. The excess thionyl chloride was removed on a rotary film evaporator, and the residue was cooled in Dry Ice–acetone. Rapid addition of 60 ml. of concentrated ammonium hydroxide gave a slurry which was allowed to warm slowly with stirring. The mixture was filtered, and the resultant solid was dissolved in boiling ethanol. This solution was filtered while hot, and water was added dropwise to the cloud point. After cooling, 5.0 g. (75%) of the *cis* amide, m.p. 162.7–163.9° (lit.,[16] 161°) was collected.

trans-4-*t*-Butylcyclohexanecarboxamide.—Similar treatment of the pure *trans* acid,[16] m.p. 174.2–175.8°, 3.7 (0.02 mole), gave on recrystallization from cyclohexane 3.3 g. (90%) of the *trans* amide, m.p. 134.2–135.8° (lit.,[16] 134–135°).

Dehydration with Phosphorus Pentoxide.—In a typical experiment, 1.00 g. (0.0054 mole) of *cis*-4-*t*-butylcyclohexanecarboxamide was thoroughly dispersed in 1.2 g. of phosphorus pentoxide in a simple distillation apparatus. The system was subjected to reduced pressure (20–25 mm.), and placed in an oil bath preheated to 145°. Distillation commenced rapidly to yield 0.83 g. (93%) of the pure crystalline *cis* nitrile, m.p. 56.3–57.3.°

Dehydration with Thionyl Chloride.—*cis* Amide, 0.70 g. (0.0038 mole), was dissolved in 1.0 ml. of thionyl chloride, and the mixture was refluxed for 1 hr. The excess thionyl chloride was removed on a rotary film evaporator; distillation (6 mm.) gave 0.61 g. (97%) of product, m.p. 52–55.2.°

Dehydration with Phosphorus Oxychloride.—A sample of the same *cis* amide, 0.70 g. (0.0038 mole), used in the above procedures, was added to 2.0 ml. of phosphorus oxychloride and the mixture was refluxed for 1.5 hr. Ten milliliters of methylene chloride and 50 ml. of water were added and the mixture extracted. The aqueous phase was extracted with another portion of methylene chloride, and the combined organic extracts were washed with water, then heated on a steam bath with water until the methylene chloride boiled. After cooling the mixture was neutralized with dilute sodium hydroxide, the organic phase separated, dried, and evaporated. Distillation of the residue (6 mm.) gave 0.50 g. (80%) of product, m.p. 47–54.°

cis-4-*t*-Butylcyclohexanecarbonitrile, a nitrile sample collected by v.p.c., had a melting point of 56.3–57.3.°

Anal. Calcd. for $C_{11}H_{19}N$: C, 79.94; H, 11.59. Found: C, 80.14; H, 11.48.

Trans-4-*t*-Butylcyclohexanecarbonitrile, a nitrile sample collected by v.p.c., had a melting point of 33.4–34.7°.

Anal. Found: C, 80.05; H, 11.55.

(16) H. H. Lau and H. Hart, *J. Am. Chem. Soc.*, **81**, 4897 (1959).

Configurational Assignment to C-6 Epimeric 3α,5α-Cyclosteroid Alcohols and Amines by Means of N.m.r.

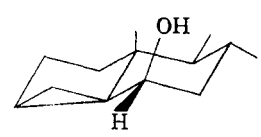
JACK TADANIER AND WAYNE COLE

Organic Chemistry Department, Research Division, Abbott Laboratories, North Chicago, Illinois

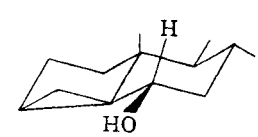
Received July 9, 1962

Interpretation by the first order approximation of the multiplet absorption patterns of the C-6 protons of acetoxy and *p*-nitrobenzoyloxy derivatives of the C-6 epimeric 6-hydroxy-17-ethylenedioxy-3α,5α-cycloandrostanes provides strong evidence for their configurations. These products have been related to the C-6 epimeric 6-hydroxy-3α,5α-cyclocholestanes by the methods of preparation and correlations of optical rotation. The 3α,5α-cyclo-6-substituted steroids provide an example of an exception to the generalization that, for rigid six-membered ring systems, axial ring protons absorb at higher field than the epimeric equatorial protons. Configurational assignments have been made to the C-6 epimeric 6-amino-3α,5α-cycloandrostan-17-ones based on the chemical shifts of the C-6 protons of acetamido and *p*-nitrobenzamido derivatives.

The criteria on which the accepted configurations of the epimeric 6-hydroxy-3α,5α-cyclocholestanes have been based are described in detail by Kosower and Winstein.[1] These authors concluded from examination of models that the 3α,5α-cyclo bond does not greatly affect the conformation of the B-ring and, thus, that both of the epimers have chair-form *B*-rings. From relationships of optical rotation, chromatographic behavior, and relative rates of solvolysis of derivatives, it was deduced that the epimer (*i*-cholesterol) resulting from hydrolysis of the *p*-toluenesulfonate of 3β-hydroxycholest-5-ene (cholesterol) has the 6β-axial hydroxyl (I), while the epimer (epi-*i*-cholesterol) resulting from reduction of 3α,5α-cyclocholestan-6-one has the 6α-equatorial hydroxyl group (II). Further evidence for these assignments was reported by Evans and Summers,[2] who found that *i*-cholesterol was epimerized to the extent of 37% on treatment with sodium ethoxide in ethanol at 190°, while no change occurred on similar treatment of epi-*i*-cholesterol. The results were interpreted as reflecting the greater stability of the 6α-equatorial hydroxyl of II.



I



II

By analogy with the configurations assigned to 3α,5α-cyclo 6-alcohols obtained by hydrolysis of steroid Δ^5-3β *p*-toluenesulfonates, the 3α,5α-cyclo 6-amines formed by ammonolysis have been assigned the 6β-amino configuration.[3] It was reported[2] that sodium–ethanol reduction of 6-oximino-

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

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

(3) R. D. Haworth, L. H. C. Lunts, and J. McKenna, *ibid.*, 986 (1955).

TABLE I[a,b]

R		M.p.	[α]D		M.p.	[α]D		M.p.	[α]D
H	Ia[d]	144–146°	+15°	IIa	...	...	IIIa	100–101°	+112°
—COCH3	Ib	112–112.5°	+18.5°	IIb	111–113°	+69°	IIIb	140–141°	+79.2°
—CO—C6H4—NO2	Ic	187–189°	+16.8°	IIc	168–170°	+60.5°	IIIc	247–249° dec.	+66°

		M.p.	[α]D
IVa		70–72°	+160.5°
IVb		117–134°[c]	+163.5°
IVc		165–168°	+101°

[a] Melting points were taken in open capillaries and are uncorrected. [b] Rotations were taken in chloroform (c = 1%). [c] Pure by vapor phase chromatography.[5] [d] Literature, m.p. 142–144°, [α]D + 11.6° (chloroform), see ref. 4.

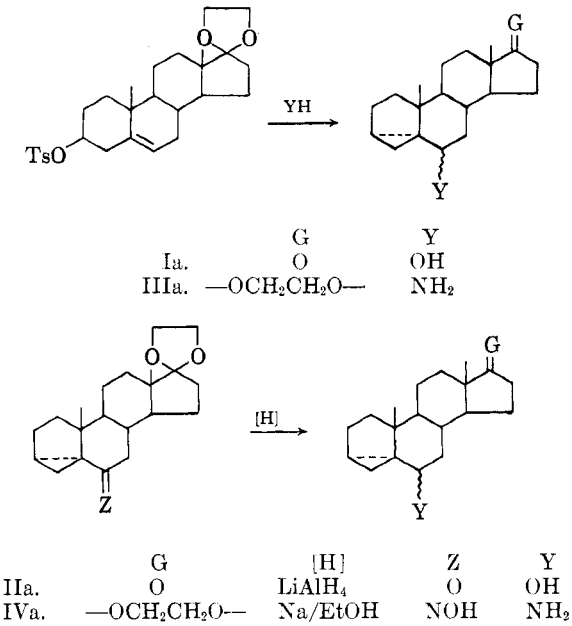


Fig. 1.—Formation of C-6 epimers.

3α,5α-cyclocholestane led to 6α-amino-3α,5α-cyclocholestane. These assignments were consistent with the optical rotations of the epimeric amines, since in both amine and alcohol series, the optical rotations of the products assigned the 6β-configuration are less positive than are those of the epimers[1,2] (Table II).

This report deals with the application of n.m.r. spectroscopy as an independent means of determination of the configurations of C-6 epimeric 3α,5α-cyclo 6-alcohols and amines which further serves to relate directly the configurations of the alcohol and amine series.

The epimeric 6-hydroxy-17-ethylenedioxy-3α,5α-cycloandrostanes and 6-amino-3α,5α-cycloandrostan-17-ones were prepared by methods developed in the cholesteryl system[1,2] which are outlined in Fig. 1. The procedures used for the preparation of the amines as well as that used for the preparation of 6-oximino-17-ethylenedioxy-3α,5α-cycloandrostane will be described in detail in another paper.[4] Elemental analyses, obtained for all new products, were satisfactory and infrared spectra were consistent with functional groups present.

The preparation of the 6-hydroxy-17-ethylenedioxy-3α,5α-cycloandrostane, Ia, and its oxidation to 17-ethylenedioxy-3α,5α-cycloandrostan-6-one have been described by Julia.[5] The epimeric alcohol, IIa, was obtained as a glass by lithium aluminum hydride reduction of 17-ethylenedioxy-3α,5α-cycloandrostan-6-one. The alcohols Ia and IIa were characterized as the acetates, Ib and IIb, and the *p*-nitrobenzoates, Ic and IIc. The physi-

(4) J. Tadanier and W. Cole, *J. Org. Chem.*, **27**, 4624 (1962).

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

Fig. 2.—Absorption envelopes of the C-6 protons of the epimeric acetates, Ib and IIb.[6]

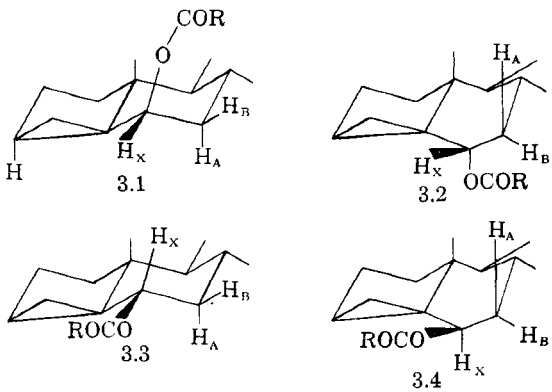


Fig. 3.—Possible conformations of the C-6 epimeric 3α,5α-cyclosteroids.

cal properties of the products are recorded in Table I. The relationship of the alcohols Ia and IIa to the epimeric 6-hydroxy-3α,5α-cyclocholestanes is supported by correlations of optical rotation and analogous methods of preparation. In both series, the rotations of the acetate and *p*-nitrobenzoate derivatives of the products formed by hydrolysis of the Δ^5-3β *p*-toluenesulfonates are much less positive than are those of the derivatives of the alcohols prepared by reduction of the 3α,5α-cyclo-6-ones (Tables I and II).

TABLE II

MOLECULAR ROTATIONS OF C-6 EPIMERIC 3α,5α-CYCLOSTEROIDS[a,b]

	MD		ΔMD
	6α	6β	(6α–6β)
6-Hydroxy-3α,5α-cyclocholestane	+293°	+193°	+100°
6-Acetoxy-3α,5α-cyclocholestane	+419°	+205°	+214°
6-*p*-Nitrobenzoyloxy-3α,5α-cyclocholestane	+370°	+300°	+70°
6-Acetoxy-17-ethylenedioxy-3α,5α-cycloandrostane	+258°	+69°	+189°
6-*p*-Nitrobenzoyloxy-17-ethylenedioxy-3α,5α-cycloandrostane	+291°	+81°	+210°
6-Amino-3α,5α-cyclocholestane	+237°	+134°	+103°
6-Amino-3α,5α-cycloandrostan-17-one	+462°	+322°	+140°
6-Acetamido-3α,5α-cycloandrostan-17-one	+536°	+260°	+276°
6-*p*-Nitrobenzamido-3α,5α-cycloandrostan-17-one	+440°	+289°	+151°

[a] All rotations were taken in chloroform solutions. [b] Molecular rotations of the 6-hydroxy-3α,5α-cyclocholestanes and their derivatives were calculated from the data of Kosower and Winstein, (ref. 1). Molecular rotations of the 6-amino-3α,5α-cyclocholestanes are from the data of Evans and Summers (ref. 2).

Ammonolysis of the *p*-toluenesulfonate of 3β-hydroxy - 17 - ethylenedioxyandrost - 5 - ene, followed by acid hydrolysis of the ketal linkage of the resulting ketal amine, led to the 6-amino-3α,5α-cycloandrostan-17-one, IIIa. The epimeric keto amine, IVa, was obtained by hydrolysis of the ketal linkage of the ketal amine which resulted from sodium–ethanol reduction of 6-oximino-17-ethylenedioxy-3α,5α-cycloandrostane. The epimeric amines IIIa and IVa were characterized as the acetamides, IIIb and IVb, and the *p*-nitrobenzamides IIIc and IVc (Table I). The relationship of the epimeric 6-amino-3α,5α-cycloandrostan-17-ones to the epimeric 6-amino-3α,5α-cyclocholestanes is based on the analogous methods of preparation[2] and correlations of optical rotation (Table II).

The n.m.r. studies were carried out with ester and amide derivatives, respectively, of the epimeric alcohols and amines. The spectra of these derivatives were characterized by complex absorption between 0 and 50 c.p.s.[6] due to absorption by the cyclopropyl portons, and the absence of vinyl proton absorption.

The protons (H_X) at C-6 of the acetates Ib and IIb constitute the *X*-atoms of *ABX* systems[7] in which H_A and H_B may be designated the axial and equatorial protons, respectively, at C-7. Because of spin–spin coupling with H_A and H_B, the absorptions of the C-6 protons of Ib and IIb occur as multiplets (Fig. 2) which may be treated on the basis of the first order approximation[8] since, for both isomers, the chemical shifts $|\nu_A - \nu_X|$ and $|\nu_B - \nu_X|$ are large compared to the coupling constants J_{AX} and J_{BX}.

The absorption of the C-6 proton (H_X) of the acetate Ib, derived from the alcohol Ia, appears as a pseudo triplet (Fig. 2) with peaks at 265.2, 268.0, and 270.6 c.p.s. Simple analysis indicates that $J_{AX} \simeq J_{BX} \simeq 2.7$ c.p.s. The magnitudes and approximate equality of the coupling constants indicates that the dihedral angles $H_XC - CH_A$ and $H_XC - CH_B$ must both be about 60°[9] and thus H_X must be equatorial.

The absorption of the C-6 proton of the acetate IIb (Fig. 2), prepared from IIa, appears as a quartet with peaks at 295.9, 300.1, 307.8, and 312.2 c.p.s. Analysis by the first order approximation indicates that $J_{AX} \simeq 12$ and $J_{BX} \simeq 4.3$ c.p.s. Thus the dihedral angle $H_XC - CH_B$ must be about

(6) The n.m.r. spectra were determined at 60 M.c. in deuteriochloroform using tetramethylsilane as an internal reference. Chemical shifts are reported in c.p.s. measured from tetramethylsilane (0 c.p.s.) in the direction of decreasing field.

(7) (a) L. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, 1959, pp. 90, 91. (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., 1960, pp. 304, 305.

(8) Ref. 7b, p. 293.

(9) For a discussion of the relationship between the coupling constants between vicinal protons and their dihedral angle, see ref. 7b, pp. 308–311.

180° while $H_XC - CH_B$ must be about 60°. This requires that H_X be axial.

Consideration of the possible *B*-ring conformations of the epimeric 3α,5α-cyclosteroids (Fig. 3) indicates only two ways in which the C-6 proton of Ib can be equatorial while that of IIb can be axial. Either both of the epimers must have the chair-form *B*-ring, in which case Ib and IIb would have 6β-axial and 6α-equatorial acetoxyl groups, respectively (Fig. 3, 3.1 and 3.3), or both isomers must have the boat-form *B*-ring in which case Ib and IIb would have 6α-axial and 6β-equatorial acetoxyl groups, respectively (Fig. 3, 3.2 and 3.4). In the case of the 6β-acetoxy derivative, relief of the 1,3-diaxial interaction between the C-10 methyl and the acetoxyl group might tend to favor the boat-form *B*-ring. In the case of the epimeric 6α-acetoxy derivative, however, there can be little doubt of the greater stability of a chair-form *B*-ring with 6α-equatorial acetoxyl (Fig. 3, 3.3). Consequently, both isomers must have chair-form *B*-rings and Ib and IIb must be 6β-acetoxy-17-ethylenedioxy-3α,5α-cycloandrostane and 6α-acetoxy-17-ethylenedioxy-3α,5α-cycloandrostane, respectively.

Although the C-6 protons of the *p*-nitrobenzoates Ic and IIc were found to absorb at slightly lower field than did those of the corresponding acetates, similar multiplet absorptions resulted. The 6α-equatorial proton of Ic occurred as a triplet with peaks at 283.1, 286.0, and 288.3 c.p.s. ($J_{AX} \simeq J_{BX} \simeq 2.6$ c.p.s.) while the 6β-axial proton absorption of IIc occurred as a quartet with peaks at 311.8, 316.2, 323.8, and 328.2 c.p.s. ($J_{AX} \simeq 11.5$ c.p.s., $J_{BX} \simeq 4.4$ c.p.s.).

In a wide variety of rigid six-membered ring systems it has been established that axial ring protons absorb at higher fields than do the epimeric equatorial protons.[10] These chemical shifts (δ_{AE}) have their origin in a long-range shielding effect associated with the diamagnetic anisotropies of the carbon–carbon single bonds bearing a 2,3-relationship to the absorbing protons. Recently, however, several exceptions to this rule have been reported. Williamson and Johnson, in a study of a series of α-acetoxy ketones, found that equatorial protons attached to the carbon bearing the acetoxy group absorb at higher fields than do the axial protons of the epimers.[11] Campaigne, Chamberlin, and Edwards have reported that the axial protons of α-trithioacetaldehyde absorb at lower field than the equatorial proton and suggest that the anisotropy of the carbon–sulfur single bond is opposite in sign to that of the carbon–carbon single bond.[12] The 3α,5α-cyclosteroids offer another example of an anomalous chemical shift between axial and equatorial protons since the 6α-equatorial protons of the acetate, Ib, and *p*-nitrobenzoate, Ic, absorb at much higher field than do the 6β-axial protons of the epimers, IIb and IIc. In this latter case, the abnormal shifts (δ_{AE}) are presumably the consequence of differential shielding by the 3,4,5-cyclopropyl ring.

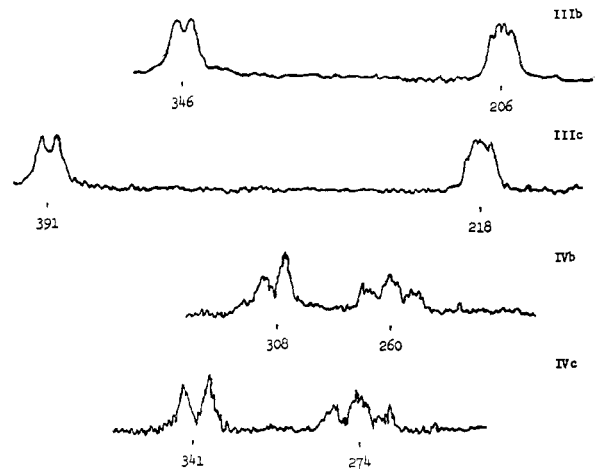


Fig. 4.—Absorption envelopes of the C^6—H (high field) and NH (low field) protons of the epimeric acetamides, IIIb and IVb, and *p*-nitrobenzamides, IIIc and IVc.[6] Half-widths of the C-6 protons are: IIIb and IIIc (13 c.p.s.), IVb and IVc (29 c.p.s.).

In the case of the acetamides IIIb and IVb, and the *p*-nitrobenzamides IIIc and IVc, a simple interpretation of the C-6 proton absorptions is not feasible. These absorptions occur as complex multiplets because of the additional coupling of the C-6 protons with the protons on nitrogen, the absorptions of which occur as poorly resolved doublets (Fig. 4).[13] If it is assumed that the amides, like the esters, have chair-form *B*-rings, the configurations of the amides may be assigned from the chemical shifts of their C-6 proton absorptions since the spectra of the acetates Ib and IIb and the *p*-nitrobenzoates Ic and IIc indicate that the 6α-equatorial protons of 3α,5α-cyclosteroids absorb at higher fields than do the corresponding 6β-axial protons. Thus IIIb and IIIc must be the 6β-acetamido and 6β-*p*-nitrobenzamido derivatives, respectively, the 6α-equatorial protons of which absorb at higher field than do the 6β-axial protons of the 6α-acetamido and 6α-*p*-nitrobenzamido derivatives, IVb and IVc. These assignments are consistent with the widths of the bands at half their height (Fig. 4)[14] since the broader bands are expected for the 6β-axial protons of IVb and IVc because of their strong coupling with the vicinal 7α-axial protons.

The absorptions of the methyl protons of both the acetoxyl groups of the acetates, Ib and IIb, and

(10) Ref. 7a, pp. 115–119.

(11) K. L. Williamson and W. S. Johnson, *J. Am. Chem. Soc.*, **83**, 4623 (1961).

(12) E. Campaigne, N. F. Chamberlin, and B. E. Edwards, *J. Org. Chem.*, **27**, 135 (1962).

(13) Most nitrogen-containing compounds such as amides do not show N^{14} splitting, although there is a recent report of its occurrence with isonitriles. See, for example, I. D. Kuntz, Jr., P. Von R. Schleyer, and A. Allerhand, *J. Chem. Phys.*, **35**, 1533 (1961).

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

the acetamido groups of the acetamides IIIb and IVb occur as sharp singlets. In both acetoxy and acetamido series, the methyl protons of the axial acetoxy and acetamido groups absorb at lower field than those of the equatorial epimers. The acetate absorptions occur at 121 c.p.s. for Ib and 117 c.p.s. for IIb, whereas the absorptions of the acetamido protons of IIIb and IVb occur at 119 c.p.s. and 116 c.p.s., respectively. These results are consistent with those of Lemieux, Kullnig, Bernstein, and Schneider,[14] who reported that the methyl protons of axial acetoxyl groups of various acetylated inositols and sugar pentaacetates absorbed at lower field than did the equatorial epimers. In the present series, however, the differences between axial and equatorial methyl proton absorptions are small and recall the relative insensitivity to configuration which has been observed with other epimeric acetoxy steroids.[15]

In view of the recent reports[16] concerning the effect of ring substituents on the chemical shifts of the protons of the angular methyl groups of steroids, it was anticipated that the stereochemistry of the C-6 epimeric 3α,5α-cyclosteroids would be reflected in chemical shift differences between the C-19 methyl protons of 6α- and 6β - epimers. Shielding effects on the C-19 methyl protons by 6β-substituents would be expected to be greater, because of the 1,3-*cis* diaxial relationship of the groups, than by 6α-substituents. Shielding of the C-18 methyl protons by C-6 substituents would be expected to be small due to the large separation between the groups, and thus for a given C-17 substituent, the C-18 methyl proton absorptions should remain relatively constant. The chemical shifts of the C-18 and C-19 methyl proton absorptions of the C-6 epimeric acetates, acetamides, *p*-nitrobenzoates, and *p*-nitrobenzamides are recorded in Table III; the higher field absorptions in each case are assigned as the C-18 methyl proton absorptions in accord with the order normally observed.[15,17] Differences in the chemical shifts of the C-18 proton absorptions of the 17-keto and 17-ketal series were small. No appreciable chemical shift differences between the C-19 methyl proton absorptions of the 6α- and 6β-acetates (IIb and Ib) and acetamides (IVb and IIIb) were observed and these were approximately the same as the chemical shifts of the 6α-*p*-nitrobenzoate (IIc) and 6α-*p*-nitrobenzamide (IVc). The chemical shifts of the C-19 methyl protons of the 6β-*p*-nitrobenzoate (Ic) and 6β-*p*-nitrobenzamide (IIIc), on the other hand, suggest small paramagnetic shielding effects by the 6β-*p*-nitrobenzoyloxy and 6β-*p*-nitrobenzamido groups.

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

(16)(a) G. Slomp, Jr., and B. R. McGarvey, *ibid.*, **81**, 2200 (1959). (b) R. F. Zürcher, *Helv. Chim. Acta*, **44**, 1380 (1961). (c) Y. Kawazoe, Y. Sato, M. Natsume, H. Hasegawa, T.Okamoto, and K. Tsuda, *Chem. Pharm. Bull.* (Japan), **10**, 338 (1962).

(17) Exceptions to this order have been noted. See ref. 16b.

TABLE III

ANGULAR METHYL PROTON ABSORPTIONS[6]

A. 17-Ethylenedioxy esters

	Ib	IIb	Ic	IIc
C_{18}	54	51	54	51
C_{19}	60	57	68	58

B. 17-Keto amides

	IIIb	IVb	IIIc	IVc
C_{18}	54	53	52	55
C_{19}	62	60	69	62

Thus n.m.r., in agreement with previous assignments,[1-3] offers strong evidence that 1) both 6α- and 6β-substituted 3α,5α-cyclosteroids normally have chair-form *B*-rings, and 2) hydrolysis and ammonolysis of Δ^5-3β-*p*-toluenesulfonates lead to 3α,5α-cyclo-6β alcohols and amines while reduction of 3α,5α-cyclo-6-ketones and oximes leads to 3α,-5α-cyclo 6α-alcohols and amines.

The stereospecific formation of 3α,5α-cyclo 6β-alcohols by hydrolysis of Δ^5-3β halides or *p*-toluenesulfonates has been attributed to product formation from homoallylic carbonium ion intermediates.[1] Formation of the 6β-amines by ammonolysis indicates that product formation must similarly result from reaction of homoallylic carbonium ion intermediates and thus that the mechanism of ammonolysis must be closely related to that of hydrolysis.

Experimental[18]

6β-Hydroxy-17-ethylenedioxy-3α,5α-cycloandrostane (Ia) and 17-ethylenedioxy-3α,5α-cycloandrostan-6-one were prepared as described by Julia.[5]

6β-Acetoxy-17-ethylenedioxy-3α,5α-cycloandrostane (Ib).—A solution prepared from 789 mg. of 6β-hydroxy-17-ethylenedioxy-3α,5α-cycloandrostane, 4.0 ml. of acetic anhydride, and 20 ml. of pyridine was heated on a steam bath for 4 hr. The solution was cooled to room temperature and shaken with 200 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 six 150-ml. portions of water, combined, and dried over anhydrous magnesium sulfate. The ether was evaporated on a steam bath and the residual pyridine was removed under aspirator pressure on a steam bath using a rotary evaporator. The residue was dissolved in 20 ml. of pentane and the resulting solution was treated with carbon to remove an orange coloration. The pentane was evaporated and the residue was recrystallized from methanol–water solution to yield 722 mg. of 6β-acetoxy-17-ethylenedioxy-3α,5α-androstane, m.p. 110–111°. For analysis, a portion of this material (237 mg.) was recrystallized from methanol–water solution to yield 218 mg., m.p. 112–112.5°, $[\alpha]^{22}D$ +18.5° (1% chloroform).

Anal. Calcd. for $C_{23}H_{34}O_4$: C, 73.75; H, 9.15. Found: C, 73.88; H, 9.14.

6β-*p*-Nitrobenzoyloxy-17-ethylenedioxy-3α,5α-cycloandrostane (Ic).—*p*-Nitrobenzoyl chloride (458 mg.) was added to a solution of 404 mg. of 6β-hydroxy-17-ethylenedioxy-3α,5α-cycloandrostane in 5 ml. of pyridine. The reaction mixture was allowed to stand at room temperature for 5 hr. and then poured into 50 ml. of water. The crystalline solid which separated was collected on a sintered glass funnel.

(18) Melting points were taken in open capillaries and are uncorrected.

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

JACK TADANIER AND WAYNE COLE

Organic Chemistry Department, Research Division, Abbott Laboratories, North Chicago, Illinois

Received July 9, 1962

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.