Preparation and Solvolysis of 6β,19-Oxido-17-ethylenedioxy-3α,5α-cycloandrostane

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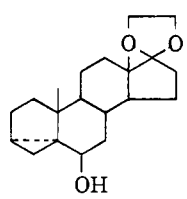
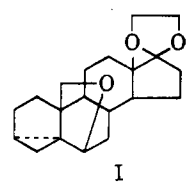
Lead tetraacetate oxidation of 6β-hydroxy-17-ethylenedioxy-3α,5α-cycloandrostane led to the isolation, in 22% yield, of 6β,19-oxido-17-ethylenedioxy-3α,5α-cycloandrostane (I). A study was made of the solvolytic behavior of I under conditions of acid catalysis. The nature of the solvolysis products indicated that the 6β,19-oxide ring is cleaved with C-6 oxygen heterolysis to yield the 19-hydroxyhomoallylic cation, and that the stereochemistry of the reactions of this intermediate at both C-3 and C-6 is analogous to that of related 10-methylhomoallylic cations. Reactions of I were, thus, those anticipated from the solvolysis reactions of 6-substituted 10-methyl-3α,5α-cyclosteroids.

Recently a number of methods[1] have been developed to introduce functional groups at the C-10 and C-13 angular methyl groups of steroids. In each method advantage has been taken of favorable geometric relationships between the angular methyl groups and other functional groups present in the molecules, which have enabled selective, intramolecular reactions. C-19 Oxygenated steroids are of potential value both from the standpoint of their application as intermediates in the synthesis of useful 19-norsteroid hormones[2] as well as the interest in their intrinsic physiological activities. Successful conversions of C-10 methyl steroids to 19-nor derivatives recently have been reported by several groups[3] and have involved lead tetraacetate oxidation of 6β-hydroxy steroids and photolysis of 6β-nitrite esters. The former method has been found to give rise to 6β,19-oxides, the conversions of which have depended on cleavage of the 6β,19-oxide ring.

The present work was undertaken to determine whether lead tetraacetate oxidation of 6β-hydroxy-3α,5α-cyclosteroids would lead to 6β,19-oxide ring formation.[4] From the behavior of 10-methyl-3α,5α-cyclo-6-substituted steroids[5] it was anticipated that 6β,19-oxido-3α,5α-cyclosteroids would react under conditions of mild acid catalysis to yield various 3β-substituted 19-hydroxy-Δ⁵-steroids. It was hoped that the solvolytic behavior of 6β,19-oxido-3α,5α-cyclosteroids would, thus, prove to be of both practical and theoretical interest.

Although the yield of 6β,19-oxido-17-ethylenedioxy-3α,5α-cycloandrostane (I) isolated from the lead tetraacetate oxidation of 6β-hydroxy-17-ethylenedioxy-3α,5α-cycloandrostane was disappointingly low (22%), as yet only preliminary attempts have been made to determine optimum conditions for the reaction. In addition to the 6β,19-oxide (I) about 17% of crude starting material, which was present as the acetate, was isolated. The balance of the product mixture, the composition of which has not yet been examined in detail, showed infrared absorptions which suggested the presence of acetate. It has been reported[1c] that lead tetraacetate oxidation of 3β,17β-diacetoxy-6β-hydroxy-5α-androstane yielded, in addition to the 6β,19-oxide (68%), 7.5% of 3β,17β-diacetoxy-5α-androstan-6-one. Similarly, in the present work, in a preliminary run, a small amount of 17-ethylenedioxy-3α,5α-cycloandrostan-6-one was isolated.





I

Solvolyses of 6β,19-Oxido-17-ethylenedioxy-3α,5α-cycloandrostane (I).—Under conditions of acid catalysis, the 6β,19-oxide ring of I was readily cleaved to yield C-19 substituted products. In each case the conditions were such that conversion of the 17-ethylenedioxy to the 17-keto group occurred.

A. Hydrolysis.—The major product, isolated in 55% yield by acid-catalyzed hydrolysis of I in 1:5 water–tetrahydrofuran (0.3 *M* in *p*-toluenesulfonic acid monohydrate), was 3β,19-dihydroxyandrost-5-en-17-one (II). This material was converted in good yield to 3β,19-diacetoxyandrost-5-en-17-one (IV) by acetylation with acetic anhydride in pyridine.

Chromatography of the product mixture obtained by acid-catalyzed hydrolysis of I in 1:10 water–tetrahydrofuran (0.09 *M* in *p*-toluenesulfonic acid monohydrate) led to the isolation of 6β,19-dihydroxy-3α,5α-cycloandrostan-17-one (III, 15.4% yield) in addition to the 3β,19-dihydroxy isomer (II, 42.5% yield).

B. Acetolysis.—Chromatography of the product mixture obtained by acetolysis of I in glacial acetic acid (0.1 *M* in *p*-toluenesulfonic acid monohydrate) yielded 60% of 3β,19-diacetoxyandrost-5-en-17-one (IV), which proved to be identical with the material obtained by acetylation of 3β,19-dihydroxyandrost-5-en-17-one (II). In addition, 3β-acetoxy-19-hydroxyandrost-5-en-17-one (V) was isolated in 4.6% yield.

(1) (a) E. J. Corey and W. R. Hertler, *J. Am. Chem. Soc.*, **81**, 5209 (1959); (b) D. H. R. Barton, J. M. Beaton, L. E. Geller, and M. M. Pechet, *ibid.*, **82**, 2640 (1960); (c) A. Bowers, E. Denot, L. C. Ibáñez, M. E. Cabezas, and H. J. Ringold, *J. Org. Chem.*, **27**, 1862 (1962); (d) M. Ahktar and D. H. R. Barton, *J. Am. Chem. Soc.*, **83**, 2213 (1961); (e) G. Cainelli, M. Lj. Mihailović, D. Arigoni, and O. Jeger, *Helv. Chim. Acta*, **42**, 1124 (1959); (f) K. Heusler, J. Kalvoda, Ch. Meystre, P. Wieland, G. Anner, A. Wettstein, G. Cainelli, D. Arigoni, and O. Jeger, *ibid.*, **44**, 502 (1961); (g) D. H. R. Barton, J. M. Beaton, L. E. Geller, and M. M. Pechet, *J. Am. Chem. Soc.*, **83**, 4076 (1961); (h) Ch. Meystre, K. Heusler, J. Kalvoda, P. Wieland, G. Anner, and A. Wettstein, *Helv. Chim. Acta*, **45**, 1317 (1962); (i) K. Heusler, J. Kalvoda, Ch. Meystre, G. Anner, and A. Wettstein, *ibid.*, **45**, 2161 (1962).

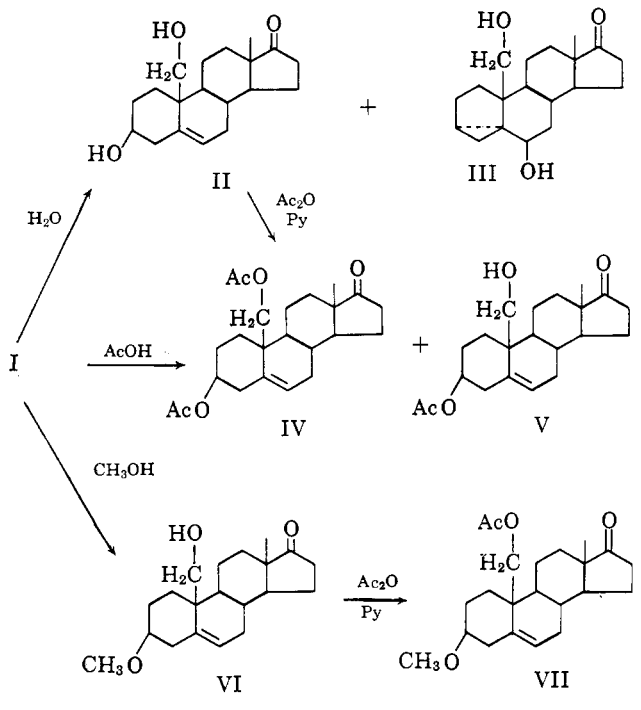
(2) (a) M. Ehrenstein, *J. Org. Chem.*, **9**, 435 (1944); (b) M. Ehrenstein, *ibid.*, **16**, 349 (1951); (c) A. S. Meyer, *Experientia*, **11**, 99 (1955); (d) for configurational assignment at C-10, see C. Djerassi and M. Ehrenstein, *Ann.*, **612**, 93 (1958).

(3) (a) R. Gardi and C. Pedrali, *Gazz. chim. ital.*, **91** (12), 1420 (1961); (b) M. Ahktar and D. H. R. Barton, *J. Am. Chem. Soc.*, **84**, 1496 (1962); (c) A. Bowers, R. Villotti, J. A. Edwards, E. Denot, and O. Halpern, *ibid.*, **84**, 3204 (1962); (d) K. Heusler, J. Kalvoda, Ch. Meystre, H. Ueberwasser, P. Wieland, G. Anner, and A. Wettstein, *Experientia*, **18**, 464 (1962).

(4) Since completion of this work a communication has appeared describing the preparation and solvolysis of 6β,19-oxido-3α,5α-cycloandrostan-17-one. K. Tanabe, R. Takasaki, K. Sakai, R. Hayashi, and Y. Morisawa, *Chem. Pharm. Bull.* (Japan), **10**, 1126 (1962).

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

The crude product mixture obtained by attempted acetolysis of I in 1:10 acetic acid–tetrahydrofuran (0.095 *M* in *p*-toluenesulfonic acid monohydrate) showed infrared absorptions indicative of the presence of *p*-toluenesulfonate ester. This material was chromatographed to yield an oil showing infrared absorptions characteristic of both *p*-toluenesulfonate and acetate. In addition there was isolated 13.1% of 6β,19-dihydroxy-3α,5α-cycloandrostan-17-one (III) and about 20% of 3β,19-dihydroxyandrost-5-en-17-one (II).



The nature of the *p*-toluenesulfonate was not determined but it is presumably 3β-*p*-toluenesulfonoxy-19-hydroxyandrost-5-en-17-one. Further experiments are planned for the isolation and characterization of this product.

C. Methanolysis.—Acid-catalyzed methanolysis (0.106 *M* in *p*-toluenesulfonic acid monohydrate) of the 6β,19-oxide (I) yielded 98.6% of 3β-methoxy-19-hydroxyandrost-5-en-17-one (VI). Acetylation of this material yielded 3β-methoxy-19-acetoxyandrost-5-en-17-one (VII).

Structural Assignments.—The structures of 6β,19-oxido-17-ethylenedioxy-3α,5α-cycloandrostane and its solvolysis products are based primarily on n.m.r. spectra which are summarized in Table I.

A. 6β,19-Oxido-17-ethylenedioxy-3α,5α-cycloandrostane (I).—The n.m.r. spectrum of the 6β,19-oxide (I) in deuteriochloroform showed complex absorption between 0–50 c.p.s. characteristic of the cyclopropyl protons at C-3 and C-4, and the absence of vinyl proton absorption. The spectrum showed only a single, sharp angular methyl absorption at 55.5 c.p.s. The nonequivalent C-19 methylene protons gave rise to the characteristic four-peak absorption of the AB spin system.[6,7] In deuteriochloroform one of the peaks was obscured by the sharp absorption peak[8] of the 17-ethylenedioxy protons, but in pyridine[9] all four peaks were separated from the 17-ethylenedioxy absorption, which in this solvent showed some indication of splitting. Unfortunately the C-6 proton absoption was not observable in either solvent and presumably overlaps that of the 17-ethylenedioxy protons.

B. Solvolysis Products.—The nonequivalent C-19 methylene protons of each of the solvolysis products gave rise to characteristic four-peak absorptions of AB spin systems and only a single angular methyl absorption was present. The presence of C-19 acetoxy and hydroxy substituents apparently effects a paramagnetic shift of the C-6 vinyl proton absorptions. Each of the Δ^5 derivatives showed vinyl proton absorption which occurred at 15–25 c.p.s. lower field than related C-10 methyl steroids such as 3β-acetoxyandrost-5-en-17-one (Table I).

In all known cases rearrangements of 6-substituted 10-methyl-3α,5α-cyclosteroids to Δ^5-3-substituted steroids have given products in which the substituents at C-3 have β-orientations.[5,10] The stereospecificity of reaction at C-3 has been attributed to reactions of nonclassical homoallylic cations. Evidence to be discussed later indicates that the acid-catalyzed solvolyses of the 6β,19-oxide (I) proceed *via* a 19-hydroxyhomoallylic cation. In the absence of an unexpected effect of the 19-hydroxyl group, the stereochemistry of reaction at C-3 of this latter intermediate would be expected to be the same as that of C-10 methylhomoallylic cations. The apparent identity of the diacetate (IV) with the 3β,19-diacetoxyandrost-5-en-17-one recently reported by Heusler and coworkers[3d] provides evidence that IV and the diol (II), from which it could be prepared by acetylation, both have β-oriented substituents at C-3. The stereochemistry of reaction at C-3 of 19-hydroxyhomoallylic cations thus appears to be identical to that of the 10-methylhomoallylic cations, and the substituents at C-3 of the 3,19-disubstituted steroids prepared in the present work are, accordingly, all assigned β-orientations.

The melting point of the diol (II) is in reasonable agreement with that of the product obtained by Mihina[11] by degradation of 17,19,21-trihydroxypregn-4-ene-3,20-dione. In the latter work, the orientation of the hydroxyl group at C-3 of the resulting 3,19-dihydroxyandrost-5-en-17-one was not specified, but was determined by the stereochemistry of an aqueous sodium bromohydride reduction of a 3,19-diacetoxy-3,5-diene. In the C-10 methyl series it nas been established[12] that the Δ^5-3-ols formed in this manner have 3β-hydroxyl groups. The present results, thus, suggest that 19-acetoxyl substituents have no unexpected neighboring group effect on the stereochemistry of

(6) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, New York, N. Y., 1959, p. 89.

(7) 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. 301.

(8) Sharp absorption peaks of the ethylenedioxy protons of steroids in n.m.r. spectra determined in deuteriochloroform have also been observed by W. Wehrli, M. S. Heller, K. Schaffner, and O. Jeger, *Helv. Chim. Acta*, **44**, 2162 (1961).

(9) The use of pyridine as an n.m.r. solvent to change the relative chemical shifts of protons, the absorptions of which overlap in deuteriochloroform, was suggested by G. Slomp and F. MacKellar, *J. Am. Chem. Soc.*, **82**, 999 (1960).

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

(11) J. S. Mihina, U. S. Patent 2,856,415 (October 4, 1958).

(12) (a) B. Belleau and T. F. Gallagher, *J. Am. Chem. Soc.*, **78**, 4458 (1951); (b) W. G. Dauben and J. F. Eastham, *ibid.*, **73**, 4463 (1951); (c) E. Schwenk, M. Gut, and J. Belisle, *Arch. Biochem.*, **31**, 456 (1951).

TABLE I

NUCLEAR MAGNETIC RESONANCE DATA[a]

A. C-19 Oxygenated 3α,5α-cyclosteroids[b]

	C-6	$J_{ae} \simeq J_{ee}$[c]	C-18	O⟨O	H_A—C_{19}—H_B[d] H_A	H_B	$\Delta\nu_{AB}$	$\lvert J_{AB}\rvert$
I	...	...	55.5	234.4[e]	241.4, (234.2)[f]	210.6, 203.4	30.0	7.2
II[g]	...	...	58.4	230.6[h]	243.8, 236.9	213.4, 206.2	29.7	7.0
III	202.0, 198.8, 195.8	3.1	59.6	...	228.3, 217.5[i]	204.8, 194.0	20.9	10.8
III[j]	200.7, 197.5, 194.2	3.2	58.8	...	227.5, 216.7	203.5, 192.5	21.5	10.9

B. C-19 Hydroxy-Δ⁵-3β derivatives

	C-6	C-18	—OCOCH₃	—OCH₃	H_A—C_{19}—H_B[d] H_A	H_B	$\Delta\nu_{AB}$	$\lvert J_{AB}\rvert$
II[k]	350.8	56.9	...	...	241.4, 230.0	223.0, 212.0	14.4	11.2
V	350.0	55.9	121.8	...	241.4, 229.6	222.7, 210.8	14.6	11.8
VI	342.5	57.0	...	202.0	240.2, 229.5	221.6, 210.0	16.1	11.2

C. C-19 Acetoxy-Δ⁵-3β derivatives

	C-6	C-18	—OCOCH₃	—OCH₃	H_A—C_{19}—H_B[d] H_A	H_B	$\Delta\nu_{AB}$	$\lvert J_{AB}\rvert$
IV	344.0	54.0	121.4, 122.5	...	282.2, 269.9	245.2, 233.2	34.8	12.1
VII	340.0	54.8	124.0	202.0	278.2, 267.0	244.0, 232.2	32.5	11.5

D. C-10 Methyl steroids

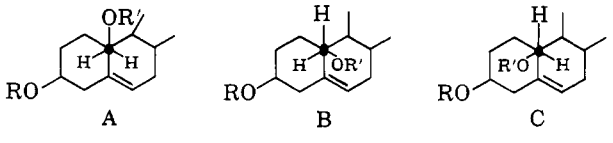
	C-6	$J_{ae} \simeq J_{ee}$[c]	—OCOCH₃	C-18	C-19
6β-Hydroxy-3α,5α-cycloandrostan-17-one	203.5, 200.5, 198.0	2.8	...	56.2	66.5
3β-Acetoxy-androst-5-en-17-one	326.0	...	121.6	53.2	63.3[l]
Cholesterol[m]	321.6				
3α-Acetamidoandrost-5-en-17-one[n]	322.0				
3β-Acetamidoandrost-5-en-17-one[n]	322.0				

[a] The spectra were recorded with a Varian A-60, n.m.r. spectrometer at 60 Mc. Unless otherwise specified, 5–10% solutions in deuteriochloroform were employed using tetramethylsilane as an internal reference. Chemical shifts are reported in c.p.s. from tetramethylsilane (0 c.p.s.) in the direction of decreasing field. J_{AB} is expressed in c.p.s. [b] Complex absorption of the C-3 and C-4 cyclopropyl protons occurred between 0–50 c.p.s. [c] Approximate coupling constants for the interaction of the C-6 proton with C-7 axial and C-7 equatorial protons. [d] H_A and H_B refer to the C-19 methylene protons which absorb at lower and higher field, respectively. [e] Apparent singlet. [f] Overlapped by the ethylenedioxy proton absorption. [g] Determined in 5% pyridine solution using an internal tetramethylsilane reference. [h] Some indication of splitting. [i] Overlapping absorption was present. [j] Added deuterium oxide. The low-field doublet (H_A) was fully resolved. A sharp water peak was present at 276.8 c.p.s. [k] Determined in 2 % deuteriochloroform solution because of limited solubility. [l] R. F. Zürcher, *Helv. Chim. Acta*, **44**, 1380 (1961), has reported 62.8 c.p.s. [m] High Resolution N.m.r. Spectra Catalogue," Varian Associates, Palo Alto, Calif. [n] J. Tadanier and Wayne Cole, *J. Org. Chem.*, **27**, 4624 (1962).

aqueous sodium borohydride reductions of 3-acetoxy-3,5-dienes.

The structures of the unsymmetrical derivatives V, VI, and VII follow from the AB absorption patterns of their C-19 methylene protons. The AB patterns of both the 3β-methoxy-19-ol (VI) and the 3β-acetoxy-19-ol (V) are almost superimposable on that of the 3β,19-diol (II), while the AB pattern of the C-19 methylene protons of the 3β-methoxy-19-acetate (VII), prepared by acetylation of VI, is almost superimposable on that of the 3β,19-diacetate (IV).

It has been established that acetylation of aliphatic alcohols causes a paramagnetic shift in the absorptions of their α-protons. The magnitudes of the shifts are characteristic for primary alcohols (~0.5 p.p.m.) and secondary alcohols (1.0–1.15 p.p.m.), and in steroid molecules the shifts are independent of axial or equatorial orientations.[13] In the present series the paramagnetic shifts resulting from acetylation of the 19-hydroxyl groups differ for the nonequivalent C-19 methylene protons, as is evident from comparison of the chemical shifts for the 19-acetates ($\Delta\nu_{AB}$ = 32.5–34.8 c.p.s.) with the corresponding values for the 19-alcohols ($\Delta\nu_{AB}$ = 14.4–16.1 c.p.s.), Table IB and IC. The large difference between these values may reflect different rotamer populations (A, B, and C) of the acetoxy derivatives and the hydroxy compounds.[14]



The equatorial C-3 substituents of the compounds in question should have little effect on the rotamer population. The small differences in the AB patterns of the hydroxy compounds II, V, and VI, on the one hand, and the acetoxy derivatives IV and VII, on the other, are of the magnitude to be expected of long-range shielding effects of the C-3 substituents on C-19 proton absorptions.[9,15]

To obtain a measure of the paramagnetic shielding effect on the C-19 methylene protons due to acetylation of the C-19 hydroxyl, the mean chemical shifts of the C-19 methylene protons of the 19-hydroxy and 19-acetoxy derivatives in both the 3β-methoxy and 3β-acetoxy series were determined from the difference between the midpoints of their AB patterns. In the case of the 3β-methoxy derivatives the paramagnetic shift thus calculated was 0.50 p.p.m. while for the 3β-acetoxy derivatives the shift was 0.53 p.p.m. These values are, thus, in good agreement with the value, 0.50 p.p.m., cited by Jackman[13] for the paramagnetic

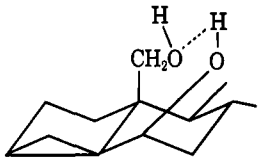
(13) Ref. 6, p. 55.
(14) Ref. 6, pp. 99–103.
(15) Y. Kawazoe, Y. Sato, M. Natsume, H. Hasegawa, T. Okamoto, and K. Tsuda, *Chem. Pharm. Bull.* (Japan), **10**, 338 (1962).

shift of the α-protons of primary alcohols which is effected by acetylation.

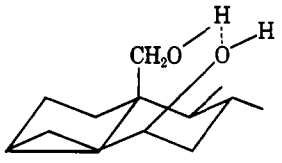
N.m.r. spectra of 6β,19-dihydroxy-3α,5α-cycloandrostan-17-one (III) showed complex absorption between 0–50 c.p.s. characteristic of the cyclopropyl protons at C-3 and C-4 and the absence of vinyl proton absorption. Only a single, sharp angular methyl absorption was present. In dry deuteriochloroform there was complex absorption between 190–230 c.p.s. The high-field portion appeared to consist of a triplet with peaks at 195.8, 198.8, and 202.0 c.p.s. and a doublet with peaks at 194.0 and 204.8 c.p.s. (total integrated area, 1.9 protons). The low-field portion showed peaks at 217.5 and 228.3 c.p.s., but these were overlapped by a broad absorption (total integrated area, 2.3 protons). Since the infrared spectrum of III showed strong hydrogen bonding, it was suspected that the absorption overlapping the low-field doublet was due to absorption of a hydrogen-bonding proton.[16] Accordingly, a small amount of deuterium oxide was added to the solution and the sample was agitated to effect a rapid exchange of the steroid hydroxy protons for deuterons.[17] The n.m.r. spectrum run on the resulting sample showed a sharp water peak at 276.8 c.p.s. The low-field doublet peaks at 216.7 and 227.5 c.p.s. were clearly resolved (integrated area, 0.9 proton) as the low-field doublet of the C-19 methylene AB spin system. The high-field doublet could then be identified directly from the coupling constant determined from the low-field doublet as consisting of the peaks at 192.5 and 203.5 c.p.s. (J_{AB} = |10.9|c.p.s.). The triplet absorption with peaks at 194.2, 197.5, and 200.7 c.p.s. is assigned to the absorption of the C-6 equatorial proton which is coupled to the C-7 equatorial and C-7 axial protons with $J_{ee} \simeq J_{ae} \simeq 3.2$ c.p.s. The total integrated area of the triplet and the high-field doublet was 1.8 protons.

The position of the triplet absorption of the C-6 proton of the diol (III) is close to that of the C-6 proton of 6β-hydroxy-3α,5α-cycloandrostan-17-one which has peaks at 198.0, 200.5, and 203.5 c.p.s. ($J_{ee} \simeq J_{ae} \simeq 2.8$ c.p.s.). Similar triplet absorptions were observed[18] for the C-6 protons of the acetate ($J_{ee} \simeq J_{ae} \simeq 2.7$ c.p.s.) and the *p*-nitrobenzoate ($J_{ee} \simeq J_{ae} \simeq 2.6$ c.p.s.) of 6β-hydroxy-17-ethylenedioxy-3α,5α-cycloandrostane. Since these coupling constants are of the magnitude expected if the dihedral angles between the C-6 protons and the C-7 axial and C-7 equatorial protons are both about 60°,[19] the C-6 protons must be equatorial and the substituents at C-6 were assigned the 6β-axial orientations. A similar argument applies to the C-6 proton absorption of III and thus establishes the 6β-axial orientation of the C-6 hydroxyl.

Independent evidence for the *cis* relationship of the C-6 hydroxyl and the C-10 hydroxymethyl groups of III as well as the 6β-axial orientation of the 6-hydroxyl is furnished by the OH absorptions in the infrared. It has been shown that the difference ($\Delta\nu$) in wave numbers (cm.$^{-1}$) between free and bonded OH absorptions provides a measure of both the strength of the hydrogen bond[20] and the hydrogen bond distance (H - - - O).[21] Infarred spectra of III were determined in carbon tetrachloride solutions at concentrations (0.005 and 0.0025 *M*) at which it has been shown that absorptions due to hydrogen bonded OH are due to intra- rather than intermolecular bonding.[21a] At both concentrations sharp bands due to both free and bonded OH absorptions were observed at 3610 and 3460 cm.$^{-1}$, respectively. At the higher concentration a broad shoulder was present, centered at 3250 cm.$^{-1}$ which indicated that a small amount of intermolecular hydrogen bonding persisted. The large value of $\Delta\nu$ (150 cm.$^{-1}$) indicates strong intramolecular hydrogen bonding and is of the magnitude observed[21a] for *cis*- and *trans*-1,2-bishydroxymethylcyclohexane. In these latter compounds the O - - - H bond distance could not be calculated[21a] since the closest approach of the hydrogen-bonded H and O was found to be less than the length of the covalent OH bond (0.96 Å.). Similarly, in both of the possible hydrogen-bonded species (D and E) with the 6β-axial hydroxyl, the closest approach of the bonding H and O is only 0.4 Å.[22]



D



E

The frequencies measured in the present work with sodium chloride optics were not sufficiently accurate (±15 cm.$^{-1}$) to allow a choice between the two possibilities based on the frequency of the free OH absorption.[21c]

The coupling constants (J_{AB}) for the methylene protons of the 19-hydroxy and 19-acetoxy compounds were almost equal within the experimental error, while that of the 6β,19-oxide (I) was significantly smaller. Although the calculations of Gutowski, Karplus, and Grant[23] predicted that the magnitudes of the coupling constants between geminal protons should be a sensitive function of the H–C–H bond angle, recent work[24] has indicated that the signs of geminal coupling constants are opposite to those predicted by the theory, and that their magnitudes are too sensitive to the effect of substituents to allow an empirical correlation with dihedral angles. Thus, while the small coupling constant of I is presumably related to the strain in the puckered tetrahydrofuran ring, the nature of the effect is not clear.

(16) N.m.r. absorptions of hydrogen-bonded hydroxyl protons occur at lower field than free hydroxyl proton absorptions (ref. 6, p. 66). In the other C-19 hydroxy compounds prepared in this work, no hydroxyl proton peak was observed and these are presumed to absorb at higher field than about 150 c.p.s., which overlaps the complex absorption of the steroid ring protons. Since only the low-field doublet of III was obscured by the overlapping absorption, while both peaks of the low-field doublet appeared to be present, the complexity is believed to be due to overlapping absorption of one bonded hydroxy proton with the low-field doublet rather than to spin–spin coupling of the C-19 methylene protons with the 19-hydroxy proton. This interpretation is consistent with integrated intensities measured before and after addition of deuterium oxide.

(17) This technique was suggested by Jackman, ref. 6, p. 71.

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

(19) See ref. 7, pp. 308–311.

(20) R. F. Badger, *J. Chem. Phys.*, **8**, 288 (1940).

(21) (a) L. P. Kuhn, *J. Am. Chem. Soc.*, **74**, 2492 (1952); (b) L. P. Kuhn, *ibid.*, **76**, 4323 (1954); (c) L. P. Kuhn, *ibid.*, **80**, 5950 (1958).

(22) Calculated from Dreiding Models of 6β,19-dihydroxy-5α-androstane.

(23) H. S. Gutowski, M. Karplus, and D. M. Grant, *J. Chem. Phys.*, **31**, 1278 (1959).

(24) (a) M. Karplus, *J. Am. Chem. Soc.*, **84**, 2458 (1962); (b) P. C. Lauterbur and R. J. Kurland, *ibid.*, **84**, 3405 (1962); (c) F. A. L. Anet, *ibid.*, 3767 (1962); (d) H. J. Bernstein and N. Sheppard, *J. Chem. Phys.*, **37**, 3012 (1962). (The author is indebted to a referee for graciously calling his attention to the latter reference.)

The optical rotations (Table II) of the products are all consistent with the structures assigned. Both the 6β,19-oxide (I) and the 6β,19-diol (III) have high positive rotations characteristic of 3α,5α-cyclo-6-substituted steroids relative to their Δ⁵-3 isomers. The molecular rotation difference, ΔMD, between these

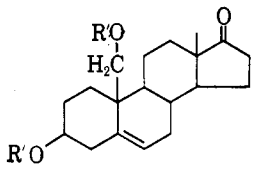
TABLE II

MOLECULAR ROTATIONS

A. 3α,5α-Cyclosteroids

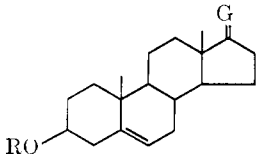
	MD		MD	ΔMD
I	+149°	III	+426°	+277°
6β-Hydroxy-17-ethylenedioxy-3α,5α-cycloandrostane	+39°[a]	6β-Hydroxy-3α,5α-cycloandrostan-17-one	+348°[b]	+309°

B. C-19-Substituted-Δ⁵-3β steroids



R	MD(R' = $COCH_3$)	MD(R' = H)	ΔMD
H	...	+45°	...
$COCH_3$	−138°	+24°	+162°
CH_3	−134°	+32°	+166°

C. C-10-methyl-Δ⁵-3 β Steroids[c]



X	G = 17α-H, 17β-C_8H_{17} MD	G = O MD
H	−150°	+6°
$COCH_3$	−184°	−25°
CH_3	−168°	0°[d]

[a] Calculated from the value reported by S. Julia, C. Neuville, and M. Davis (ref. 31). [b] Calculated from the value for a solution in 95% ethanol, quoted in "Pouvoir Rotatoire Naturel, I. Steroides," by J.-P. Mathieu and A. Petit, Masson and Co., Paris, France, 1956, p. 18. [c] Calculated from values quoted in footnote *b* for chloroform solutions. [d] It has been reported that this material shows no observable rotation in 2.5% chloroform solution. A. Butenandt and W. Grosse, *Ber.*, **69**, 2776 (1936).

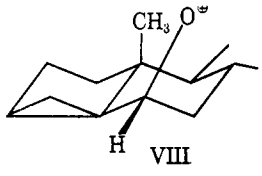
products is almost the same as that between 6β-hydroxy-17-ethylenedioxy-3α,5α-cycloandrostane and 6β-hydroxy-3α,5α-cycloandrostan-17-one (Table IIA) and thus must be due almost entirely to the difference between the 17-ketal and 17-keto functions.

For the Δ⁵-C-19 substituted derivatives, the optical rotations are only slightly sensitive to the nature of the substituent at C-3 as is evident from comparison of the 19-hydroxy compounds (II, V, and VI), on the one hand, and the 19-acetoxy derivatives (IV and VII), on the other. The insensitivity of optical rotation to the nature of the substituent at C-3 is also observed for C-10 methyl steroids (Table IIC). In contrast, a relatively large difference is observed between the rotations of the 19-hydroxy and 19-acetoxy compounds (Table IIB). In both 3β-methoxy and 3β-acetoxy series, the optical rotations of the 19-acetoxy derivatives are much more negative than are those of the 19-hydroxy derivatives.

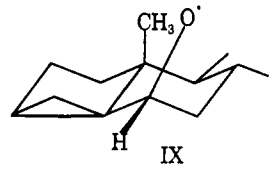
The optical rotations of the 19-hydroxy compounds (II, V, and VI), on the one hand, and the 19-acetoxy compounds (IV and VII), on the other, are almost identical. This is only to be expected if the rotamer populations (A, B, and C) within the C-19 hydroxy series and within the C-19 acetoxy series are the same, and essentially unaffected by the nature of the substituent at C-3. This is in accord with the n.m.r. chemical shift differences ($\Delta\nu_{AB}$) of the two series, described previously.

Discussion

It has been suggested[1e] that the first step in the lead tetraacetate oxidation of the angular methyl groups of hydroxysteroids is the formation of an alkoxylead(IV) derivative. Although, by analogy with the reaction of the *p*-toluenesulfonate of 1,3,3-trimethylcyclohexyl peroxide prepared by Corey and White,[25] this intermediate may undergo subsequent heterolysis to form a cationic species (VIII) followed by proton abstraction from the angular methyl to form the 6β,19-oxide; homolytic cleavage to an alkoxy radical (IX), similar



VIII



IX

to that formed by nitrite ester photolysis,[1g] followed by hydrogen atom abstraction from the angular methyl, has not been excluded. At present, however, in view of the uncertainty with regard to the mechanism of the reaction, and the epimerization which has recently been reported to occur on photolysis of the nitrite ester of "α"-caryophyllene alcohol,[26] formation of the 6β,19-oxide (I) by lead tetraacetate oxidation of 6β-hydroxy-17-ethylenedioxy-3α,5α-cycloandrostane cannot be considered a chemical proof[27] of the configuration of the alcohol. Since the yield of the 6β,19-oxide (I) was relatively low under the conditions employed, an investigation of the behavior of the epimeric 6α-hydroxy-17-ethylenedioxy-3α,5α-cycloandrostane did not seem to offer an unequivocal conclusion.

The evidence for the configurations of C-6 epimeric 6-hydroxy-3α,5α-cyclosteroids, based on the multiplet absorption patterns of the C-6 protons of the acetates and *p*-nitrobenzoates of the C-6 epimeric 6-hydroxy-17-ethylenedioxy-3α,5α-cycloandrostanes, has been previously described.[18] In the present work, the complementary infrared and n.m.r. evidence regarding the configuration of the 6β,19-diol (III), together with the almost identical chemical shifts and multiplet absorption patterns of III and of 6β-hydroxy-3α,5α-cycloandrostan-17-one, provides essentially conclusive evi-

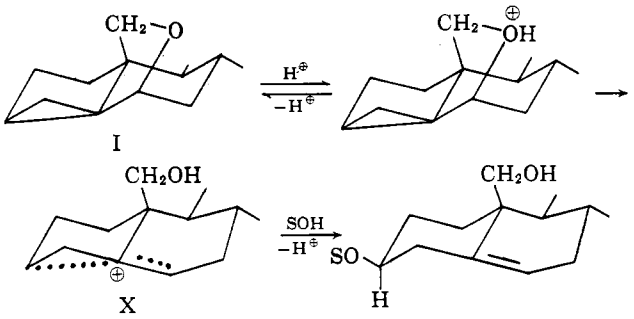
(25) E. J. Corey and R. W. White, *J. Am. Chem. Soc.*, **80**, 6686 (1958).

(26) A. Nickon, J. R. Mahajan, and F. J. McGuire, *J. Org. Chem.*, **26**, 3617 (1961).

(27) As yet there has been no direct chemical proof for the configurations of C-6 epimeric 3α,5α-cyclo-6-ols. See ref. 10, footnote 16.

dence regarding the configurations of 3α,5α-cyclo-6-ols in the C-10 methyl series.[28]

Examination of the solvolytic behavior of 6β,19-oxido-17-ethylenedioxy-3α,5α-cycloandrostane (I) indicates that its reactions are those predictable from the behavior of related 10-methyl-3α,5α-cyclosteroids.[5,10] Under conditions of acid catalysis in each of the solvent systems studied, the major products isolated were Δ^5-3β substituted steroids. Although formation of the symmetrically substituted 3β,19-dihydroxy and 3β,19-diacetoxy compounds (II and IV) by hydrolysis and acetolysis, respectively, furnishes no evidence for the direction of heterolysis of the 6β,19-oxide ring, the isolation of 3β-methoxy-19-hydroxyandrost-5-en-17-one as the sole product from the acid-catalyzed methanolysis provides strong evidence that these reactions all occur *via* C_6–O heterolysis to form the intermediate 19-hydroxyhomoallylic cation (X).



Formation of 3β,19-diacetoxyandrost-5-en-17-one (IV) as the major product of the acid-catalyzed acetolysis in acetic acid seems most probably the result of subsequent esterification of the expected 3β-acetoxy-19-hydroxyandrost-5-en-17-one (V). Although formation of the minor product, V, is conceivably the result of preferential esterification or hydrolysis reactions, this product is significantly that isomer which would be predicted on the basis of reaction of the 19-hydroxyhomoallylic cation (X) with acetic acid.

The isolation of 6β,19-dihydroxy-3α,5α-cycloandrostan-17-one from both the attempted acetolysis in 1:10 acetic acid–tetrahydrofuran (0.095 *M* in *p*-toluenesulfonic acid monohydrate) and the hydrolysis in 1:10 water–tetrahydrofuran, demonstrates that the stereochemistry of reaction of the 19-hydroxyhomoallylic cation at C-6 is identical to that observed for reactions of related 10-methylhomoallylic cations.

Since 6β,19-oxido-3α,5α-cyclosteroids should prove a convenient source of a variety of 3β,19-disubstituted steroids, it is hoped that further studies of the lead tetraacetate oxidation of 6β-hydroxy-3α,5α-cyclosteroids will lead to conditions more favorable for 6β,19-oxide ring formation.

Experimental

The lead tetraacetate used was that of Matheson Coleman and Bell, and was dried over potassium hydroxide prior to use.

Infrared spectra were determined for all compounds and were consistent with functional groups present. The infrared studies on the hydrogen bonding of the 6β,19-diol (III) were carried out with solutions in Mallinckrodt analytical reagent carbon tetrachloride with a Perkin-Elmer, Model 21, spectrophotometer equipped with sodium chloride optics, using a 3.0-cm. cell.

Optical rotations were determined with 1% solutions in Mallinckrodt analytical reagent chloroform using a Hilger and Watts polarimeter.

The tetrahydrofuran used as solvent was purified by the method of Fieser.[29] The neutral activity III alumina used for the chromatographic separations was prepared by the addition of the appropriate amount of water[30] to Woelm, neutral activity I alumina. The petroleum ether used for recrystallizations was a fraction boiling 66–70°.

Unless otherwise specified, melting points were taken in open capillaries and are uncorrected.

A. 6β,19-Oxido-17-ethylenedioxy-3α,5α-cycloandrostane (I).—Two runs were carried out in the following manner. A solution prepared from 5.03 g. (0.0151 mole) of 6β-hydroxy-17-ethylenedioxy-3α,5α-cycloandrostane,[31] 18.7 g. (0.042 mole) of lead tetraacetate, and 300 ml. of benzene was heated under reflux, with stirring, for 24 hr., during which time a white solid separated. At the end of the reaction time the resulting supernatant gave a positive starch iodide test. The excess lead tetraacetate was destroyed by addition of 30 ml. of ethylene glycol, and the resulting two-phase mixture was filtered through a Celite mat. The Celite mat was then washed with 300 ml. of benzene, and the washings were added to the original filtrate. The resulting mixture was washed with 500 ml. of water, and the aqueous phase was separated and extracted with 300 ml. of benzene. The benzene solutions were washed in series with 400 ml. of 5% sodium bicarbonate solution, and six 300-ml. portions of water; then they were combined and dried over anhydrous magnesium sulfate. The benzene was evaporated under reduced pressure, leaving 5.58 g. of a pale yellow glass.

The product mixture was treated with 100 ml. of boiling pentane with vigorous stirring, and the pentane supernatant was separated by decantation. This procedure was repeated five times leaving only a small fraction of the material undissolved. The pentane solutions were combined, swirled to effect homogeneity, and placed on a column of 200 g. of neutral, activity III alumina. The pentane eluate was essentially dry. Elution with 1:15 ether–pentane solution (ten 100-ml. fractions) yielded 1.95 g. of an oil showing medium intensity absorptions indicative of the presence of acetate at 1724 cm.$^{-1}$ (C=O)[32] and 1250 cm.$^{-1}$ (C—O).[32] The corresponding fractions from run II exhibited a similar infrared spectrum and amounted to 2.45 g. of an oil (fractions 1).

Further elution of the column with 1:15 ether–pentane solution (three 100-ml. fractions) yielded 128 mg. of an oil. The remainder of the product was eluted with 1.5 l. of ether. These latter fractions were combined to yield 3.1 g. of a clear, pale yellow oil, the infrared spectrum of which showed strong bands at 1745 cm.$^{-1}$ and 1235 cm.$^{-1}$ and a medium intensity band at 1706 cm.$^{-1}$. This material was not further investigated.

The initial fractions eluted with 1:15 ether–pentane solution, obtained from runs 1 and 2 (fractions 1) were combined (4.4 g. total) and heated under reflux for 2 hr. with 200 ml. of 5% methanolic potassium hydroxide solution. The resulting solution was concentrated to about one-quarter volume under aspirator pressure and poured into 400 ml. of water. The resulting mixture was extracted twice with 300-ml. portions of ether, and the ether solutions were washed in series with six 100-ml. portions of water. The ether solutions were then combined and dried over anhydrous magnesium sulfate. The ether was evaporated, leaving 4.09 g. of a cloudy pale yellow oil. This product showed no absorption in the carbonyl region, but weak absorption, free and bonded, was present in the OH stretching region. This product was placed on a column of 200 g. of neutral, activity III alumina in 50 ml. of pentane solution. Elution with 1:15 ether–pentane solution (fourteen 100-ml. fractions) yielded an oil with a trace of orange coloration. This material was dissolved in pentane, and the pentane solution was treated with carbon and filtered through Celite. The pentane filtrate was colorless. The pentane was evaporated, leaving an oil which crystallized on standing, yielding 2.18 g. (22%) of 6β,19-oxido-17-ethylenedioxy-3α,5α-cycloandrostane (I), m.p. 95–101.5°. For analysis

(28) As described by Kosower and Winstein (ref. 10), 3α,5α-cyclo-6β-ols are formed stereospecifically by hydrolysis of the *p*-toluenesulfonates of their Δ^5-3β-isomers, while the epimeric 3α,5α-cyclo-6α-ols are formed stereospecifically by lithium aluminum hydride reduction of 3α,5α-cyclo-6-ones.

(29) L. F. Fieser, "Experiments in Organic Chemistry," 3rd Ed. D. C. Heath and Co., Boston, Mass., p. 292, 1959.

(30) H. Brockmann and H. Schodder, *Ber.*, **74** (1), 73 (1941).

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

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

1.16 g. was recrystallized from methanol–water solution to yield 992 mg., m.p. 102–103°, $[\alpha]^{24}D$ +45°.

Anal. Calcd. for $C_{21}H_{30}O_3$: C, 76.33; H, 9.15. Found: C, 76.62; H, 9.22.

Elution of the column with ether (1 l.) yielded 1.72 g. (17%) of a pale orange oil which crystallized on standing. The infrared spectrum of this material (7% chloroform solution) was essentially identical to that of the starting material, 6β-hydroxy-17-ethylenedioxy-3α,5α-cycloandrostane. Recrystallization of this material from ether–petroleum ether yielded 1.18 g., m.p. 142–145° (lit.[31] m.p. 142–144°). The melting point of a mixture of this material with authentic 6β-hydroxy-17-ethylenedioxy-3α,5α-cycloandrostane was not depressed.

B. Hydrolysis.—1. A solution prepared from 604 mg. (0.00182 mole) of I, 3 g. (0.02 mole) of *p*-toluenesulfonic acid monohydrate, 10 ml. of water, and 50 ml. of tetrahydrofuran was heated under reflux for 3 hr. The tetrahydrofuran was removed by distillation under reduced pressure, and the residue was shaken with 180 ml. of water and 300 ml. of ether. The aqueous phase was separated and extracted with 250 ml. of ether. The ether solutions were washed in series with 100 ml. of water, 100 ml. of 5% sodium bicarbonate solution, and three 100-ml. portions of water; then they were combined and dried over anhydrous magnesium sulfate. The ether was evaporated leaving 444 mg. of a crystalline solid, m.p. 190–200°. Three recrystallizations from ethyl acetate–petroleum ether yielded 305 mg. (55%) of 3β,19-dihydroxyandrost-5-en-17-one (II), m.p. 212–219° dec., $[\alpha]^{23}D$ +15° (lit.[11] m.p. 204–206°).

Anal. Calcd. for $C_{19}H_{28}O_3$: C, 74.97; H, 9.27. Found: C, 74.69; H, 9.28.

2. A solution prepared from 659 mg. (0.00200 mole) of I, 1 g. (0.005 mole) of *p*-toluenesulfonic acid monohydrate, 5 ml. of water, and 50 ml. of tetrahydrofuran was heated under reflux for 1 hr. and then poured into 400 ml. of water. The resulting aqueous suspension was extracted three times with 250-ml. portions of ether. The ether solutions were washed in series with 100-ml. portions of water, 100 ml. of 5% sodium bicarbonate solution, and three 100-ml. portions of water, then combined and dried over anhydrous magnesium sulfate, after the addition of a few drops of pyridine. The ether was evaporated, leaving a crystalline solid impregnated with an orange impurity (712 mg.).

The product was heated under reflux for 5 min. with 80 ml. of benzene. A small amount of material remained undissolved. The supernatant was separated by decantation, leaving 25 mg. of a white crystalline solid, m.p. 186–192°.

The benzene solution was cooled to room temperature and placed on a column of 50 g. of neutral activity III alumina. The benzene eluate contained 30 mg. of an orange oil. Elution with 1:5 ether–benzene (eight 50-ml. fractions) yielded 115.1 mg. of a crystalline solid, m.p. 146–153°.[33] Two recrystallizations from benzene–petroleum ether yielded 93.4 mg. (15.4%) of 6β,19-dihydroxy-3α,5α-cycloandrostan-17-one (III), m.p. 171–173°. The infrared spectrum of this material (7% chloroform solution) was identical to that obtained from the attempted acetolysis, described below. The melting point of a mixture of these products was not depressed.

Further elution of the column with 1:1 ether–benzene solution (two 50-ml. fractions) gave no more material. Elution with 1:10 methanol–chloroform solution (100 ml.) yielded 302.3 mg. of a white crystalline solid, m.p. 197.5–202°. Recrystallization of this material from ethyl acetate–petroleum ether yielded 258.3 mg. (42.5%) of 3β,19-dihydroxyandrost-5-en-17-one (II), m.p. 213–219° dec. The infrared spectrum of this material (potassium bromide pellet) was identical to that of the material obtained from the acid-catalyzed hydrolysis of I in 1:5 water–tetrahydrofuran solution as described previously. The melting point of a mixture of these products was not depressed.

C. Acetolysis.—1. A solution prepared from 330 mg. (0.00100 mole) of I, 190 mg. (0.0010 mole) of *p*-toluenesulfonic acid monohydrate, and 10 ml. of glacial acetic acid was heated at 60° for 2 hr. Water (2 ml.) was added and heating was continued for 10 min. The reaction product mixture was isolated by ether extraction. The ether solutions were washed with 5% sodium bicarbonate solution and then to neutrality with water, combined, and dried over anhydrous magnesium sulfate. Evaporation of the ether left 372.4 mg. of a deep orange oil.

The product was placed on a column of 25 g. of neutral activity III alumina in 60 ml. of 1:10 ether–pentane solution. Elution with 1:10 ether–pentane (four 50-ml. fractions) yielded 25 mg. of oils. Elution with 1:5 ether–pentane (nine 50-ml. fractions) yielded 233 mg. (60%) of 3β,19-diacetoxyandrost-5-en-17-one (IV), m.p. 106–108.5°. Recrystallization of this material from ether-pentane solution yielded the analytical sample (162 mg.), m.p. 108–109°, $[\alpha]^{21}D$ −35.4° [lit. m.p. 103–105°, $[\alpha]D$ −40° (chloroform)].[3d] The infrared spectrum of this material was identical to that of the product prepared by acetylation of 3β,19-dihydroxyandrost-5-en-17-one (II) as described later. The melting point of a mixture of these samples was not depressed.

Anal. Calcd. for $C_{23}H_{32}O_5$: C, 71.09; H, 8.30. Found: C, 71.05; H, 8.12.

Elution of the column with 1:1 ether–pentane (three 50-ml. fractions) yielded 50 mg. of an oil which crystallized on trituration with 1:1 ether–pentane solution. One recrystallization from methanol–water solution followed by two recrystallizations from ether–petroleum ether solution yielded 16.0 mg. (4.6%) of 3β-acetoxy-19-hydroxyandrost-5-en-17-one (V), m.p. 157–158°,[33] $[\alpha]^{23}D$ +7°.

Anal. Calcd. for $C_{21}H_{30}O_4$: C, 72.81; H, 8.73. Found: C, 72.86; H, 8.59.

2. A solution prepared from 508 mg. (0.00154 mole) of I, 1.0 g. (0.0052 mole) of *p*-toluenesulfonic acid monohydrate, 5 ml. of acetic acid, and 50 ml. of tetrahydrofuran was heated under reflux for 2 hr. Water (10 ml.) was added and reflux was continued for 15 min. The reaction solution was poured into 400 ml. of water and the resulting white suspension was extracted with two 250-ml. portions of ether. The ether solutions were washed in series with two 100-ml. portions of water, 100 ml. of 5% sodium bicarbonate solution, and three 100-ml. portions of water, then combined, and dried over anhydrous magnesium sulfate. The ether was evaporated leaving 603 mg. of a white glass. The infrared spectrum of this material (7% chloroform solution) showed bands at 3584 and 3413 cm.$^{-1}$ [(w), OH free and bonded],[34] 1736 cm.$^{-1}$ (OAc and 17-keto carbonyls),[32] 1603 cm.$^{-1}$ [(w), aromatic ring],[35] 1237 cm.$^{-1}$ (C–O of acetate),[32] doublet 1173 (s), 1183 (w) cm.$^{-1}$, and 1357 cm.$^{-1}$, (–O–SO_2– of *p*-toluenesulfonate).[36]

The product mixture was placed on 50 g. of neutral, activity III alumina in benzene solution and chromatographed as described. Fifty-milliliter fractions were collected.

Fractions	Eluent	Content
1–5	Benzene	Trace amounts of oils
6–10	1:20 Ether–benzene	40 mg. of oils
11–15	1:10 Ether–benzene	Trace amounts of oils
16–21	1:4 Ether–benzene	175 mg., clear, pale green oil
22–23	1:1 Ether–benzene	88 mg., crystalline solid
24–27	1:1 Ether–benzene	Dry
28–32	Chloroform	Dry
33–35	1:10 Methanol–chloroform	91.3 mg., crystalline solid
36–37	1:10 Methanol–chloroform	Dry

The infrared spectrum of combined fractions 16–21 (7% chloroform solution) showed the bands present in the original crude sample described.

The combined fractions 22–23 (m.p. 152–155°) were recrystallized three times from benzene–petroleum ether to yield 61.2 mg. (13.1%) of 6β,19-dihydroxy-3α,5α-cycloandrostan-17-one (III), m.p. 172–174°,[33] $[\alpha]^{25}D$ +140°.

Anal. Calcd. for $C_{19}H_{28}O_3$: C, 74.97; H, 9.27. Found: C, 74.80; H, 9.23.

The material obtained from fractions 33–35, m.p. 175–190° (19.5%), was not further characterized, but its chromatographic behavior indicated that it was impure II.

D. Methanolysis.—A solution prepared from 715 mg. (0.00216 mole) of I, 710 mg. (0.00373 mole) of *p*-toluenesulfonic acid monohydrate, and 35 ml. of absolute methanol was heated under reflux for 2 hr. Water (3.5 ml.) was added and reflux was continued for 15 min. The major portion of the methanol was

(33) Melting point was determined on a *Fisher-Johns block and is uncorrected.*

(34) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1958, p. 95.

(35) Ref. 34, p. 64.

(36) Ref. 34, p. 364.

then evaporated under reduced pressure on the steam bath with a rotatory evaporator. The residue was shaken with a mixture of 250 ml. of ether and 100 ml. of water. The aqueous phase was separated and extracted with 200 ml. of ether. The ether solutions were washed in series with 100 ml. of water, 100 ml. of 5% sodium bicarbonate solution, and three 100-ml. portions of water; they were then combined and dried over anhydrous magnesium sulfate. The ether was evaporated leaving 679 mg. (98.6%) of 3β-methoxy-19-hydroxyandrost-5-en-17-one (VI), m.p. 143–146°. Recrystallization of this material from methanol–water solution yielded 574 mg., m.p. 147–149°. For analysis 272.9 mg. of this latter sample was recrystallized from methanol–water solution to yield 241 mg., m.p. 147.5–149°, $[\alpha]^{23}D$ +10.2°.

Anal. Calcd. for $C_{20}H_{30}O_3$: C, 75.44; H, 9.50. Found: C, 75.64; H, 9.50.

E. Acetylation of 3β,19-Dihydroxyandrost-5-en-17-one (II).—A solution prepared from 151 mg. (0.00050 mole) of II, 2 ml. (0.02 mole) of acetic anhydride, and 6 ml. of pyridine was allowed to stand at room temperature for 23 hr. The resulting solution was shaken with a mixture of 150 ml. of ether and 100 ml. of water. The aqueous phase was separated and extracted with 100 ml. of ether. The ether solutions were washed in series with 100 ml. of water, 100 ml. of 1 *N* hydrochloric acid, two 50-ml. portions of water, 100 ml. of 5% sodium bicarbonate solution, and three 50-ml. portions of water; they were then combined and dried over anhydrous magnesium sulfate. The ether was evaporated leaving 191 mg. (99%) of 3β,19-diacetoxyandrost-5-en-17-one (IV) as an oil which crystallized on cooling in a Dry Ice–acetone bath, m.p. 104–107°. For analysis this material was recrystallized from ether–petroleum ether solution to yield 164 mg., m.p. 109–110°.

Anal. Calcd. for $C_{22}H_{32}O_5$: C, 71.09; H, 8.30. Found: C, 71.22; H, 8.50.

F. Acetylation of 3β-Methoxy-19-hydroxyandrost-5-en-17-one (VI).—A solution prepared from 302 mg. (0.00095 mole) of VI, 4 ml. (0.04 mole) of acetic anhydride, and 12 ml. of pyridine was allowed to stand at room temperature for 23 hr. The product was isolated as described previously for the acetylation of 3β,19-dihydroxyandrost-5-en-17-one (II), to yield 332 mg. (97%) of 3β-methoxy-19-acetoxyandrost-5-en-17-one (VII), m.p. 66–67.8°. For analysis this material was recrystallized from ether–petroleum ether solution to yield 272 mg., m.p. 67–68°, $[\alpha]^{21}D$ −37.3°.

Anal. Calcd. for $C_{22}H_{32}O_4$: C, 73.29; H, 8.95. Found: C, 73.27; H, 9.09.

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Synthesis of Amitriptyline and Related Substances. Hydroboration of 5-Allylidene-5*H*-dibenzo[*a*,*d*]-10,11-dihydrocycloheptene

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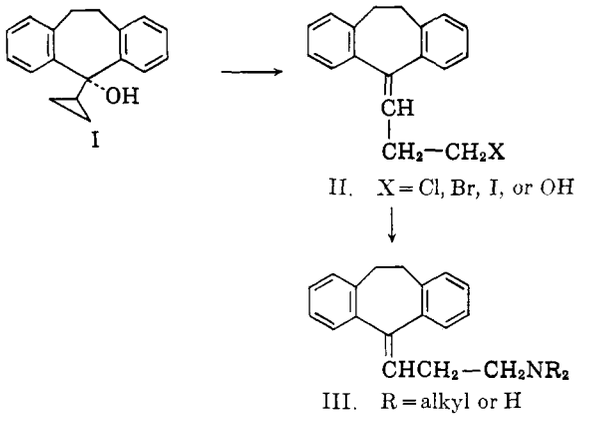
A new route to 5-(γ-dimethylaminopropylidene)-5*H*-dibenzo[*a*,*d*]-10,11-dihydrocycloheptene and related systems by way of hydroboration of a butadiene intermediate has been realized.

Synthesis of the psychotherapeutic drug, amitriptyline (XI), has been accomplished heretofore in the main by way of simple Grignard coupling of γ-dimethylaminopropylchloride with 5*H*-dibenzo[*a*,*d*]-10,11-dihydrocyclohepten-5-one followed by dehydration.[1]

Recently we showed[2] that the carbinol (I), derived from 5*H*-dibenzo[*a*,*d*]-10,11-dihydrocyclohepten-5-one (IV) and cyclopropylmagnesium bromide, rearranges quantitatively to 5-(γ-halopropylidene) (II. X = Cl or Br) and 5-(γ-hydroxypropylidene)-5*H*-dibenzo-10,11-dihydrocycloheptene (II. X = OH) in the presence of anhydrous halogen acids or aqueous mineral acids, respectively. The γ-halo[3] as well as the γ-hydroxy systems, moreover, possess the distinct advantage of providing not only a direct route to amitriptyline, but also to nearly any γ-substituted derivative through choice of the appropriate nucleophile.

A new route to the key γ-halopropylidene and γ-hydroxypropylidene derivatives, II, has now been realized and constitutes the subject of the present report.

The allylcarbinol V formed from 5*H*-dibenzo[*a*,*d*]-10,11-dihydrocyclohepten-5-one (IV) and allylmagnesium bromide is a somewhat unstable compound and readily loses water; for example, by refluxing a cyclohexane solution of this carbinol with a trace of *p*-toluenesulfonic acid, there is afforded the unstable diene 5-allylidene-5*H*-dibenzo-10,11-dihydrocycloheptene (VI) absorbing at 268 mμ (17,200). The same diene is obtained from amitriptyline by Hofmann degradation by way of the quarternary methiodide (VII).



The diene VI exhibits a pronounced tendency toward polymerization. Samples stored in closed containers slowly deteriorate with the production, to a limited extent, of formaldehyde as ascertained by

(1) (a) Belgian Patent 584,061, Merck & Co., Inc; *Cf.* E. Jucker, "Chemie der Psychotropen Pharmaka," *Chimia*, **15**, 267 (1961); (b) British Patents, 858,187; 858,188, Hoffmann-LaRoche A.G.; (c) Belgian Patent 609,095, Kefelas A/S; (d) M. Protiva, V. Hnevsova-Seidlova, Z. J. Vejdelek, F. Jerkovsky, Z. Votava, and J. Metysova, *J. Med. Pharm. Chem.*, **4**, 411 (1961); (e) see also F. J. Villani, C. A. Ellis, C. Teichman and C. Bigos, *ibid.*, **5**, 373 (1962); and South African Patent R611/1889, Kefalas A/S.

(2) R. D. Hoffsommer, D. Taub, and N. L. Wendler, *J. Org. Chem.*, **27**, 4134 (1962).

(3) Compare also S. O. Winthrop, M. A. Davis, G. S. Meyers, J. G. Gavin, R. Thomas, and R. Barber, *ibid.*, **27**, 230 (1962).