reaction mixture was poured into 1.5 l. of cold water containing 6 g of sodium sulfite and the precipitate which formed was collected, dried, and recrystallized from methanol to give 3.0 g (46% yield) of the 3-keto derivative **21**, mp 211–212°. One further recrystallization from methanol furnished the analytical sample: mp 215–216°; $[\alpha]D$ +14.3°; λ_{max} 3.10, 5.85 μ.

Anal. Calcd for $C_{22}H_{36}O_3$: C, 75.81; H, 10.41. Found: C, 75.98, H, 10.48.

The 12α-Acetyl Derivative 22.—**22** was prepared with acetic anhydride and pyridine and purified by recrystallization from acetone–hexane: mp 126–128°; $[\alpha]D$ + 83.3°; λ_{max} 2.80, 5.81, and 7.94 μ.

Anal. Calcd for $C_{24}H_{38}O_4$: C, 73.80; H, 9.81. Found: C, 74.03; H, 9.94.

Chromium Trioxide–Pyridine Oxidation of 17β-Propyl-5β-androstane-3α,12α,17α-triol (16).—To the chromium trioxide–pyridine complex prepared by adding 5.8 g of chromium trioxide to 60 ml of pyridine was added a solution of 2.9 g (8.3 mmoles) of triol **16** in 20 ml of pyridine and the resulting mixture stirred for 20 hr at room temperature. The reaction mixture was diluted with hot benzene and filtered through Celite, and the filter cake was rinsed with two portions of hot benzene. The combined filtrates were diluted with ether, washed successively with water, 2 *N* hydrochloric acid, 2 *N* sodium hydroxide, water, and saturated salt solution, and dried over powdered magnesium sulfate, then concentrated to dryness. Recrystallization of the residue from acetone–hexane afforded 1.8 g (63% yield) of the 3,12-diketo derivative **23**, mp 159–160°. One further recrystallization from the same solvent mixture gave the analytical sample: mp 160–162°; $[\alpha]D$ + 46.1° (1% in acetone); λ_{max} 2.85, 5.77, and 5.93 μ; $\lambda_{max}^{CHCl_3}$ 5.83 and 5.91μ.

Anal. Calcd for $C_{22}H_{34}O_3$: C, 76.26; H, 9.89. Found: C, 76.21; H, 9.93.

17β-Allyl-17α-hydroxy-5β-androstane-3,12-dione (24).—To the chromium trioxide–pyridine complex prepared by adding 9 g of chromium trioxide to 90 ml of pyridine was added a solution of 4.5 g (13 mmoles) of triol **14** in 30 ml of pyridine and the mixture stirred at room temperature for 24 hr. The reaction mixture was diluted with 350 ml of hot benzene and filtered through Celite, and the filter cake was washed with two portions of hot benzene. The filtrate was diluted with ether, washed successively with water, 2 *N* hydrochloric acid, water, and saturated salt solution, dried over powdered magnesium sulfate, decolorized with charcoal, and then concentrated to a white crystalline residue. Recrystallization from acetone–hexane afforded 2.4 g (54% yield) of title compound, mp 156–158°. A second recrystallization from acetone–hexane produced the analytical sample which had the melting point unchanged; $[\alpha]D$ +31.8°; λ_{max} 2.84, 3.28, 5.77, 5.93, and 6.09 μ.

Anal. Calcd for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36. Found: C, 76.55; H, 9.23.

Sodium Borohydride Reduction of 17β-Allyl-17α-hydroxy-5β-androstane-3,12-dione (24).—To 0.20 g (0.58 mmole) of diketone **24** in 5 ml of methanol was added 50 mg of potassium hydroxide and 0.20 g of sodium borohydride in 1 ml of water and the solution was refluxed for 6 hr. The reaction mixture was poured into water and the product separated by extraction with methylene dichloride to give, after recrystallization from acetone–hexane, 0.07 g (35% yield) of 17β-allyl-5β-androstane-3α,12α,17α-triol (**14**), mp 213–218°, undepressed upon admixture with a sample prepared by the Grignard reaction described above; the infrared spectra of the two samples were identical.

Acknowledgment.—The author wishes to thank Dr. Robert L. Clarke for helpful discussions during the course of this work. Analyses were carried out by Mr. K. D. Fleischer and staff and spectral determinations by Dr. F. C. Nachod, Miss Catherine Martini, and Mr. M. Priznar.

Homoallylic Rearrangements of 19-Substituted Steroids[1]

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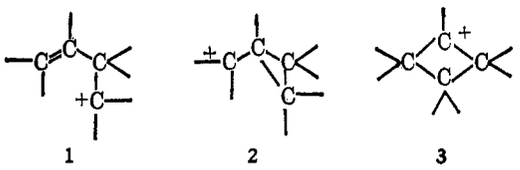
Received February 8, 1966

Homoallylic rearrangements of 19-substituted steroids in elimination reactions and in nucleophilic substitution reactions lead to products the nature of which require the intervention of two discrete, interconvertible, homoallylic cations. Reactions of these cations under conditions of both kinetic and thermodynamic control are described.

The interconversions of homoallylic, cyclopropylcarbinyl and cyclobutyl derivatives in nucleophilic displacement reactions have been the subject of numerous investigations in a variety of systems.[2] Kinetic and stereochemical results have been interpreted to indicate that both the carbonium ion intermediates involved and the transition states leading to them are stabilized by considerable delocalization of positive charge. The charge delocalization in the intermediates has been described in terms of canonical structures such as **1**, **2**, and **3**, and the intermediates have been referred to as homoallylic cations[3] or bicyclobutonium ions,[4] depending on whether there is any significant 1,4 interaction, *i.e.*, whether there is appreciable con-



1 **2** **3**

tribution to the resonance hybrid by **3**.[5] The distinction is governed by the geometry of the system involved.

Perhaps the classic case of rearrangement involving a homoallylic cation is that of the interconversion of Δ^5-3β- and 3α,5α-cyclo-6-substituted steroids.[6] For this system the homoallylic and cyclopropylcarbinyl derivatives are related mechanistically by a homoallylic cation which may be described as a resonance hybrid of the canonical structures **4** and **5**. Formation of the kinetically favored 3α,5α-cyclo steroids occurs by stereospecific β attack of a nucleophile at C_6. A similar

(1) Preliminary communications have appeared in (a) J. Tadanier and W. Cole, *Tetrahedron Letters* 1345 (1964); (b) J. Tadanier, *Experientia*, **21**, 563 (1965). A portion of this material was presented at the Symposium on Steroids Made through Intramolecular Functionalization of the C_{18}- and C_{19}-Methyl Groups, at the 149th National Meeting of the American Chemical Society, Detroit, Mich., April 1965.

(2) For a recent review, see R. Breslow in "Molecular Rearrangements," Part 1, P. de Mayo, Ed., Interscience Publishers, Inc., New York, N. Y., 1963, p 233.

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

(4) R. H. Mazur, W. N. White, D. A. Semenov, C. C. Lee, M. S. Silver, and J. D. Roberts, *ibid.*, **81**, 4390 (1959).

(5) For discussion of this distinction, see S. Winstein and E. M. Kosower, *ibid.*, **81**, 4399 (1959).

(6) (a) L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, p 314; (b) N. L. Wendler, in "Molecular Rearrangements," Part 2, P. de Mayo, Ed., Interscience Publishers, Inc., New York, N. Y., 1964, p 1075; (c) E. M. Kosower and S. Winstein, *J. Am. Chem. Soc.*, **78**, 4347 (1956).

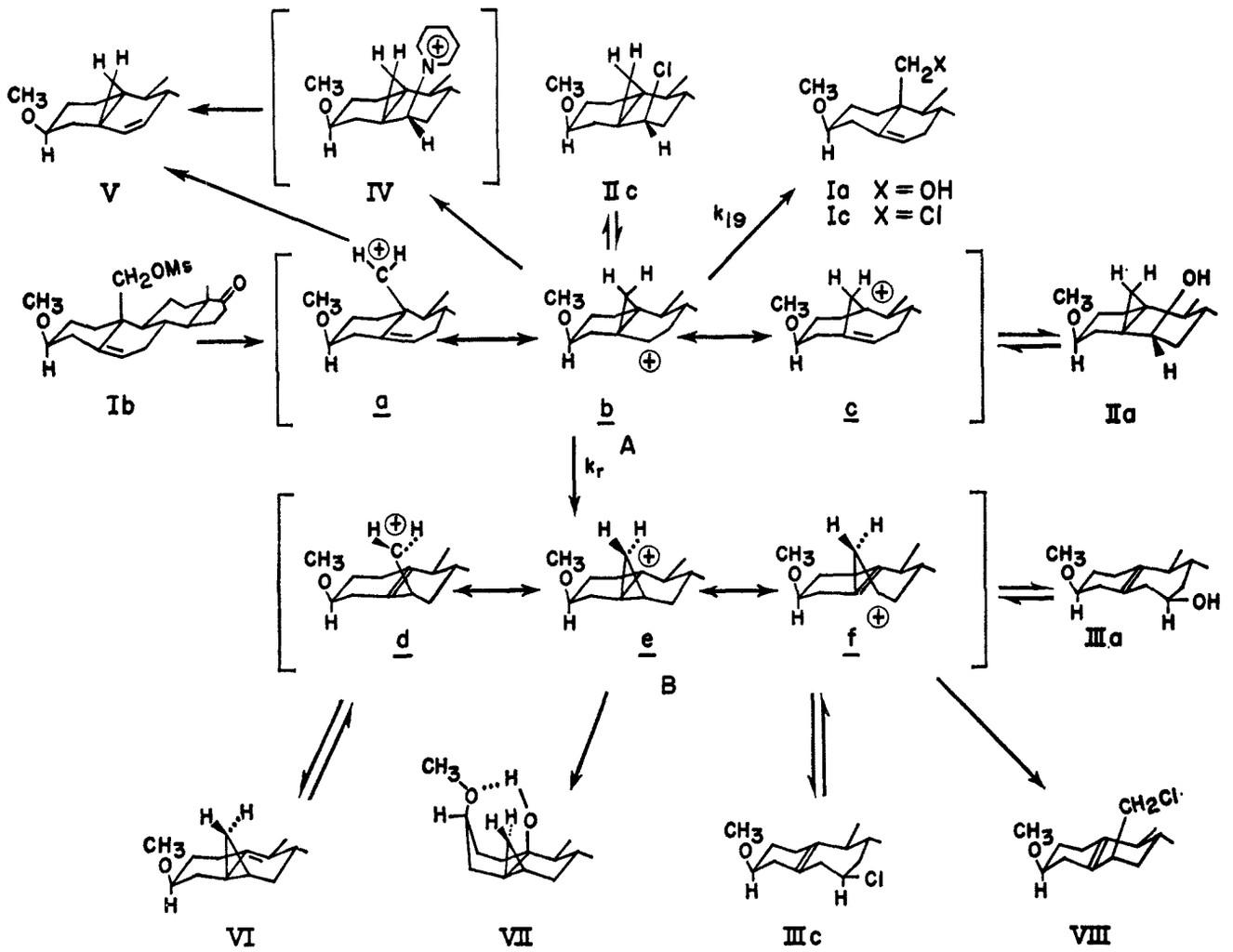
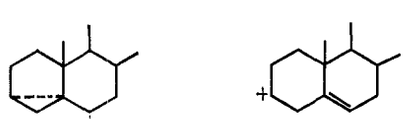


Figure 1.

stereospecificity is evidenced in the formation of Δ^5-3β-substituted products by β attack of nucleophiles at C_3 under conditions of thermodynamic control.



4 5

The recent accessibility of 19-hydroxy-Δ^5 steroids[7] suggested a study of solvolysis reactions of this homoallylic system which might lead to nucleophilic substitution with rearrangement to form 5β,19-cyclo-6-substituted steroids. Previous studies[8] of elimination reactions of Δ^5-19-methanesulfonates, which were found to lead to rearrangement with vinylcyclopropane formation, suggested the intervention of homoallylic cations. It was hoped that the nature and stereochemistry of rearranged substitution products might provide additional insight into the nature of the intermediates involved.

(7) For recent reviews of the available methods, see (a) T. B. Windholz and M. Windholz, *Angew. Chem. Intern. Ed. Engl.*, **3**, 353 (1964); (b) K. Heusler and J. Kalvoda, *ibid.*, **3**, 525 (1964).

(8) (a) J. J. Bonet, H. Wehrli, and K. Schaffner, *Helv. Chim. Acta*, **45**, 2615 (1962); (b) O. Halpern, P. Crabbé, A. D. Cross, I. Delfin, L. Cervantes, and A. Bowers, *Steroids*, **4**, 1 (1964).

Discussion

Hydrolysis of 3β-methoxy-19-methanesulfonoxyandrost-5-en-17-one (Ib) in aqueous acetone containing potassium acetate as a buffer led to the isolation of the 5β,19-cyclo-6β-ol IIa in 60% yield (see Figure 1). This product was characterized by its nmr and infrared spectra and by its oxidation to the cyclopropyl ketone IX. As in the case of the formation of 3α,5α-cyclo-6β-ols in the buffered hydrolyses of Δ^5-3β-*p*-toluenesulfonates, the rearrangement was highly stereospecific giving rise to only one of the two possible C_6-epimeric alcohols.

When treated with aqueous acid under conditions expected to convert cyclopropylcarbinols to their more stable homoallylic isomers, the 5β,19-cyclo-6β-ol was not converted to the parent Δ^5-19-ol Ia, but rather gave the isomeric $\Delta^{5(10)}$-B-homo-7β-ol IIIa. This product was characterized by the absence of vinyl or cyclopropyl proton absorption in the nmr and infrared spectra and by end absorption in the ultraviolet characteristic of tetrasubstituted double bonds.[9] The nmr spectrum showed only a single proton on the carbon bearing the hydroxyl.

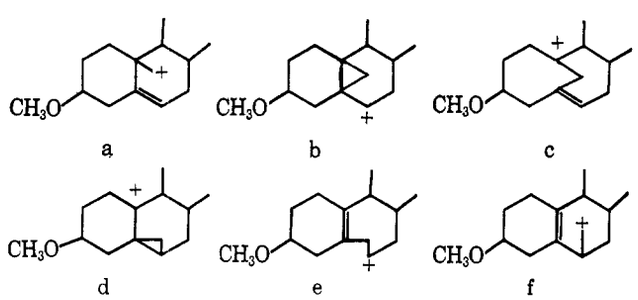
The alcohol IIIa was oxidized to the nonconjugated $\Delta^{5(10)}$-B-homo-7-one XI, the nmr spectrum of which showed a two-proton absorption of the C_6-methylene

(9) L. Dorfman, *Chem. Rev.*, **53**, 47 (1953).

protons at 173 cps ($W_{1/2}$ = 4 cps), characteristic of protons on a methylene group flanked by a double bond and a carbonyl.[10] This product remained unchanged on treatment with 2% methanolic potassium hydroxide solution. A similar reluctance toward conjugation has been observed with β,γ-unsaturated Δ^{4a}-3-keto-A-homo steroids.[10b] The additional resistance toward conjugation in the present system is presumably due to the position of the double bond endocyclic to both rings A and B.

The rearrangement of IIa to IIIa, like that of Ib to IIa, proceeded with a high degree of stereospecificity to produce only one of the two possible C_7 epimers.

The nature and stereospecificities of the rearrangements of Ib to IIa and IIa to IIIa suggested two alternate hypotheses within the framework of current theory regarding the nature of the intermediates involved in homoallylic–cyclopropylcarbinyl interconversions. The first possibility was that only a single intermediate was involved which might be described as a resonance hybrid of the canonical structures a through f. This intermediate ion formed from Ib and IIa would lead to the cyclopropylcarbinol IIa



under conditions of kinetic control and to the $\Delta^{5(10)}$-B-homo-7β-ol IIIa under conditions of thermodynamic control.

Alternately the possibility existed that these rearrangements involved two discrete carbonium ion intermediates, the first (A) a resonance hybrid of canonical structures a through c and the second (B) a hybrid of d through f. Reaction of A with water under conditions of kinetic control would lead to the 5β,19-cyclo-6β-ol IIa, while under conditions of thermodynamic control rearrangement of A would give rise to the isomeric cation B which would react with water to give the B-homo-7β-ol IIIa.

The theoretical distinction between the two possibilities is that, if two intermediates were involved, the internuclear distances in the hybrid described by a through c would differ from those in a hybrid described by d through f. If a single intermediate were involved the canonical structures a through f would describe a single cation and thus refer to a single set of internuclear distances.[11]

Consideration of an intermediate such as B suggested that buffered hydrolysis (kinetic control) of the methanesulfonate of IIIa might lead to the cyclopropylcarbinol VII or to a corresponding elimination product such as the vinylcyclopropane VI. Attempted formation of the methanesulfonate of IIIa with methanesulfonyl chloride in pyridine led to the isolation of the tetrasubstituted vinylcyclopropane VI, the structure of which was established by its spectral characteristics. Both nmr and infrared showed the presence of cyclopropyl protons and the absence of vinyl protons, while the ultraviolet spectrum showed the characteristic absorption of the conjugated vinylcyclopropane chromaphore.

The vinylcyclopropane VI was smoothly converted back to the homoallylic alcohol IIIa under conditions similar to those employed for the rearrangement of IIa to IIIa. It is of interest that the hydration of VI requires a stereospecific α protonation at C_9.

The interconversions of IIIa and VI provide chemical evidence that the alcohol, IIIa, is homoallylic. Since the spectral data of IIIa and VI show that neither has vinyl protons, the relationship of IIIa to the cyclopropylcarbinol IIa and to the tetrasubstituted vinylcyclopropane VI provides convincing evidence for the structures of IIIa and VI. Additional evidence consistent with the structure of the $\Delta^{5(10)}$-B-homo-7β-ol IIIa has been recently reported by Carpio, *et al.*, of the Syntex Laboratories.[12]

Rearrangement of the homoallylic alcohol, chinoventriol, to a vinylcyclopropane on treatment with methanesulfonyl chloride in pyridine at room temperature has been reported by Zürcher, *et al.*[13] The hydration of VI to IIIa is analogous with regard to both structure and stereochemistry to the acid-catalyzed hydration of thujopsene to Widdrol, the mechanism of which was recently elucidated by Dauben and Friedrich.[14]

In contrast to the behavior of IIIa when treated with methanesulfonyl chloride in pyridine, treatment of the Δ^5-19-methanesulfonate Ib with refluxing pyridine led, as anticipated,[8] to the 5β,19-cyclo-6-ene V. To ensure that isolation of this product did not simply reflect the instability of the isomeric 5β,6β-methylen-9-ene VI, a sample of VI was subjected to these reaction conditions (1 equiv of methanesulfonic acid in refluxing pyridine) and recovered unchanged.

Treatment of the cyclopropylcarbinol IIa with methanesulfonyl chloride in pyridine at room temperature (conditions identical with those employed for the conversion of IIIa to VI) led to formation of a water-soluble product which is presumed to be the 5β,19-cyclo-6β-pyridinium salt IV.[15] Continuous extraction of the aqueous solution with chloroform over a period of several days led to the isolation from the chloroform phase of the 5β,19-cyclo-6-ene V. Formation of V from IV most probably occurs *via* a Hofmann-type elimination. The vinylcyclopropane V was inert to the conditions employed for the conversion of the tetra-

(10) (a) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press Inc., New York, N. Y., 1959, p 60, Table 4.11. (b) Infrared, ultraviolet, and nmr spectra are all consistent with those of the structurally related β,γ-unsaturated Δ^{4a}-3-keto-A-homo steroids: *cf.* W. S. Johnson, M. Neeman, and P. S. Birkeland, *Tetrahedron Letters*, 1 (1960); G. Snatzke, B. Zeeh, and Eu. Müller, *ibid.*, 1425 (1963); E. Müller, B. Zeeh, R. Heischkeil, H. Frick, and H. Suhr, *Ann.*, **662**, 38 (1963).

(11) G. H. Wheland, "Resonance in Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y. 1955, p 12.

(12) H. Carpio, A. C. Bazan, M. G. T. Medina, and J. A. Edwards, *J. Org. Chem.*, **30**, 4154 (1965).

(13) A. Zürcher, O. Jeger, and L. Ruzicka, *Helv. Chim. Acta*, **37**, 2145 (1954).

(14) W. G. Dauben and L. E. Friedrich, *Tetrahedron Letters*, 2675 (1964).

(15) Pyridinium salt formation has been reported to occur during attempted preparation of the *p*-toluenesulfonate of 6β-hydroxy-3α,5α-cyclocholestane: see A. F. Wagner, Ph.D. Thesis, Princeton University, May 1951.

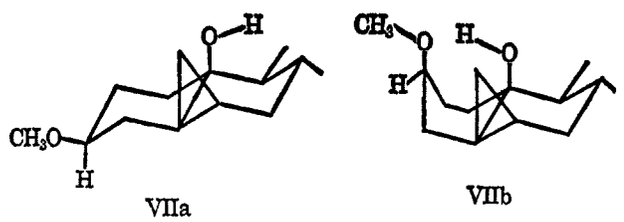
substituted vinylcyclopropane VI to the $\Delta^{5(10)}$-B-homo-7β-ol IIIa.

These results conclusively demonstrate the existence of *two discrete, isomeric carbonium ion intermediates* which give rise to isomeric elimination products. Since the difference between these intermediates must lie in their different internuclear distances and in the orientations of their C_{19}-methylene bridges, these results are consistent with formation of the 5β,19-cyclo-6-ene V from Ib and IIa by loss of a C_7 proton from the intermediate cation A, and formation of the isomeric 5β,6β-methylen-9-ene VI from IIIa by the stereoelectronically favorable loss of the 9α-axial proton from the intermediate cation B (see Figure 1).

The intervention of these ions in the elimination reactions provides a strong argument for their intervention in the substitution reactions. Formation of the cyclopropylcarbinol IIa must result from the kinetically controlled attack of water on the cation A. Under conditions of thermodynamic control, rearrangement of A leads to B which undergoes attack by water leading to the B-homo alcohol IIIa (Figure 1).

Brief treatment of the $\Delta^{5(10)}$-B-homo-7β-ol IIIa with methanesulfonyl chloride in pyridine followed by the addition of water led to the isolation, in low yield, of the desired 3β-methoxy-10β-hydroxy-5β,6β-methylenestran-17-one (VII). This product was characterized by the presence of cyclopropyl protons and the absence of vinyl protons as evidenced by both infrared and nmr spectra. The absorption of the C_3 proton of VII occurred as a complex multiplet at about 212 cps. Because of its overlap with the absorption of the methoxy protons, no accurate measure of its half-width could be obtained. The infrared spectrum in dilute carbon tetrachloride solution showed the presence of strong intramolecular hydrogen bonding between the C_{10}-hydroxyl and the C_3-methoxyl.

Examination of a Dreiding model of VII indicates two possible B-ring conformations. In the first, the substituents on the C_8 and C_9 carbons are staggered while those on the C_7 and C_8 carbons are eclipsed and the B ring exists in a twist-boat form. With the B ring in this form there is no conformation of the A ring which allows close enough approach of the C_{10}-hydroxyl and the C_3-methoxyl groups to permit hydrogen bonding. In the second possible conformation of the B ring the substituents on both the C_7 and C_8 carbons as well as those on the C_8 and C_9 carbons are staggered. The 7α- and 8β-hydrogens and the 8β- and 9α-hydrogens have 1,2-*trans*-diaxial relationships. The unfavorable interaction between the 8β-hydrogen and the hydrogen of the 5β,6β-methylene bridge which lies over the B ring may be partially relieved by a flattening of the B ring at the expense of a certain degree of angle strain. With the B ring in this conformation, two conformations are available to the A ring, a chair form VIIa, in which the C_3-methoxyl is equatorial and a flexible or twist-boat form VIIb, in which the hydrogens on the C_1- and C_2-methylene groups are partially staggered. The conformation VIIb fulfills the requirements necessary for intramolecular hydrogen bonding in that the C_{10}-hydroxyl and the C_3-methoxyl have the necessary *cis*-1,4-diaxial relationship.

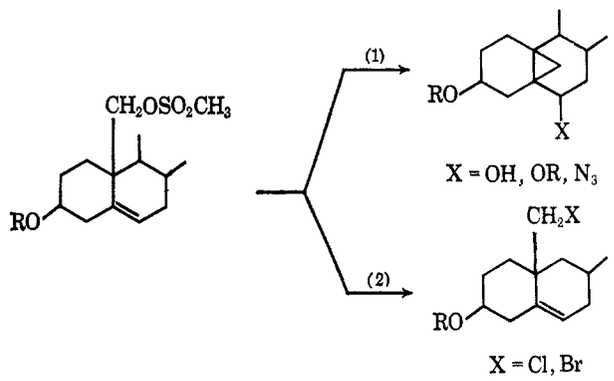


VIIa

VIIb

Although the latter conformation VIIb may be expected to be the less stable of the two based on the relative energies of chair and twist-boat forms in simple cyclohexane systems, the observed intramolecular hydrogen bonding requires that a significant population of molecules with this conformation must be present in this system.

It has been reported[8b] that nucleophilic substitution reactions of Δ^5-19-substituted steroids fall into two classes: (1) those which proceed with homoallylic rearrangement to form 5β,19-cyclo-6-substituted steroids with nucleophiles such as water, alkoxide and azide, and (2) those in which substitution occurs without rearrangement giving rise to Δ^5-19-substituted steroids with halide ions as nucleophiles. Since the



19-substituted steroids are of the neopentyl type, it is unlikely that the reactions with halide ions occur by SN2 processes. Evidence against such direct displacement is provided by the report[16] that 5α-H-19-methanesulfonates are inert to conditions sufficient to convert Δ^5-19 methanesulfonates to the Δ^5-19 halides. Thus, it seemed likely that the substitutions with halide ions also occured *via* the homoallylic cation A.

It has been shown that cyclopropylcarbinyl halides are extremely reactive and readily rearrange to more stable, isomeric, homoallylic isomers.[17] This suggested that isolation of the Δ^5-19 halides by displacement of the 19-methanesulfonate group merely reflected the instability, under the reaction conditions, of the 5β,19-cyclo-6 halides which might be expected as the kinetically favored products.

In order to investigate the stability of 5β,19-cyclo-6 chlorides, 3β-methoxy-6β-chloro-5β,19-cycloandrostan-17-one (IIc) was prepared from the corresponding alcohol IIa with thionyl chloride in ether by the procedure employed by Kosower and Winstein[17] for the conversion of 6β-hydroxy-3α,5α-cyclocholestane to the 6β chloride. The product IIc was characterized by both nmr and infrared spectroscopy. The nmr spectrum taken immediately after the preparation showed the presence of a high-field doublet absorption

(16) C. Djerassi and M. A. Kielczewski, *Steroids*, **2**, 125 (1963).
(17) E. M. Kosower and S. Winstein, *J. Am. Chem. Soc.*, **78**, 4354 (1956).

TABLE I

NMR DATA[a]

Compd	C_{18}–H	OCH_3	OSO_2CH_3	C_6–H	C_{19}–H
Ib	57.0	203	180	345	(246.5, 257.5) (d); (264.7, 275.0) (d)
Ic	57.5	202	...	343	(208.7, 220.7) (d); (229.8, 241.8) (d)

	C_{18}–H	OCH_3	C_6–H	17α-H	C_{19}–H
IIa	52.0	198	250 ($W_{1/2}$ 7.0)	...	(18.8, 23.8) (d); [(47.8, 52.4) (d)][d]
XIIa	44.0	198	245 ($W_{1/2}$ 6.5)	220	(15.2, 20.0) (d); [(52.4; 57.6) (d)][d]
XIIIa	43.5	199	~225	~225	(22.0, 28.0) (d); (30.4, [36.4][e]) (d)
IIc	54.6	197	277 ($W_{1/2}$ 8.0)	...	(33.9, 39.7) (d); [(117.6, 123.4) (d)][d]
XIIb	48.2	198	309 ($W_{1/2}$ 6.5)	275	(20.0, 25.0) (d); [(53.6, 58.4) (d)]
XIIIb	48.2	198	302 ($W_{1/2}$ 18)	270	(25.0, 30.2) (d); (38.0, [43.2][e]) (d)
VII	52.0	198	...	...	15.0 (m)[f]

	C_{18}–H	OCH_3	C_7–H	C_6–H
IIIa	55	202	244 ($W_{1/2}$ 20)	...
IIIb	55	203	307 ($W_{1/2}$ 20)	...
IIIc[b]	58.4	202	263 ($W_{1/2}$ 22)	...
XI	54.1	204	...	173 ($W_{1/2}$ 4.0)[g]

	OCH_3	C_{18}–H	6β-CH_2Cl	6β-CH_3	17-H
VIII	201	54	218 (m)	...	...
Xa	202	46	...	(59.1, 66.0) (d)	214 (m)
Xb[c]	194	51	...	(64.2, 71.0) (d)	297

	OCH_3	C_{18}–H	C_6–H,C_7–H	C_{19}–H	C_8–H
V	199	53.2	[315.5, 325.6; (347.0 / 349.0) (d), (357.0 / 359.2)] (q)	(33.5, 38.2) (d); [(61.7, 66.5) (d)][d]	185 (m)
VI	201	53.4	...	44 (m)	(208.8 / 211.5 / 216.0 / 220.0 / 223.2)[h] (p)

[a] Spectra were determined with a Varian A-60 spectrometer. Solutions were prepared with deuteriochloroform unless otherwise specified. Absorptions are reported in cycles per second from tetramethylsilane used as an internal reference. The following abbreviations are used: d, doublet; m, multiplet; q, quartet; p, pentuplet; $W_{1/2}$, half-band width. [b] From the relative areas of the C_{18}-methyl proton absorptions at 58 and 54 cps it could be estimated that the mixture was composed of 20% of 3β-methoxy-6β-chloromethylestr-5(10)-en-17-one (VIII) and 80% of 3β-methoxy-7β-chloro-B-homoestr-5(10)-en-17-one (IIIc). [c] Run in hexadeuteriobenzene. The absorptions of the C_{18}-methyl protons and the C_6-methyl protons overlapped in deuteriochloroform. [d] Values in brackets were calculated from the coupling constant obtained from the high-field doublet by treating the C_{19}-cyclopropyl protons as an AB system. [e] Value in brackets was determined from the coupling constant obtained from the high-field doublet and the inner peak of the low-field doublet by treating the C_{19}-cyclopropyl protons as an AB system. [f] One proton absorption from the integration curve. The remaining cyclopropyl protons were unresolved from the other ring protons and their absorptions were at lower field than 40 cps. [g] Two proton absorption from the integration curve. [h] The pentuplet was amplified by 49 sweeps with a Varian Model C-1024 computer of average transients. The author is indebted to Dr. Milton Levenberg for carrying out the determination. The relative peak areas were 1:4:6:4:1.

of one of the cyclopropyl protons, and no appreciable vinyl proton absorption (Figure 2a).

The lability of the 5β,19-cyclo-6β chloride was established by the observation that after 24 hr at room temerature the nmr spectrum of the deuteriochloroform solution prepared from 5β,19-cyclo-6β chloride IIc was almost identical with that of pure 3β-methoxy-19-chloroandrost-5-en-17-one (Ic) (Figure 2b). Similar behavior has been observed[17] with 6β-chloro-3α,5α-cyclocholestane which was found to rearrange readily in chloroform solution to the isomeric 3β-chlorocholest-5-ene. The behavior of both cyclopropylcarbinyl chlorides may be interpreted as rearrangement *via* ion-pair return from the corresponding homoallylic cation–chloride ion pairs.

When the 5β,19-cyclo-6 chloride was subjected to the conditions employed for the conversion of the Δ^5-19-methanesulfonates to the Δ^5-19 halides,[8b,16] the Δ^5-19 chloride Ic was isolated in 49% yield. The nmr spectrum of the total crude product showed a small angular methyl absorption at 53 cps, suggesting the presence of some of the 5β,19-cyclo-6-ene V (see Table I).

These results support the hypothesis that the halide substitution reactions proceed *via* the homoallylic cation A, but because of the instability of the 5β,19-cyclo-6 halides give rise only to the thermodynamically favored Δ^5-19 halides.

The nature of the products formed from the 19-substituted steroids in thermodynamically controlled reactions with halide ions, on the one hand, and water on the other, offered an interesting contrast. The thermodynamically controlled halide products formed from Δ^5-19- or 5β,19-cyclo-6-substituted steroids are the Δ^5-19 halides. In contrast, with water as a nucleophile, only the rearranged B-homo-7β-ol IIIa was isolated from the acid-catalyzed hydrolytic rearrangement of the 5β,19-cyclo-6β-ol IIa even though the Δ^5-19-ol Ia was found to be stable under the reaction conditions.

This requires that, in the case of water as a nucleophile, rearrangement of the cation A to cation B must occur more rapidly than attack of water on the C_{19}-methylene bridge of cation A; *i.e.*, $k_r \gg k_{19}$ (Figure 1).

The nature of the thermodynamically controlled product formed in the chloride reactions of the Δ^5-19-methanesulfonate and the 5β,19-cyclo-6β chloride indicates product formation by attack of chloride on the C_{19}-methylene bridge of the cation A. This suggested that with halide ions as nucleophiles k_{19} might be much faster than k_r (Figure 1).

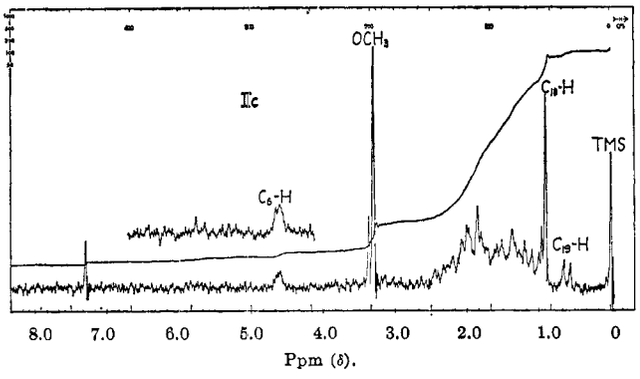


Figure 2a.

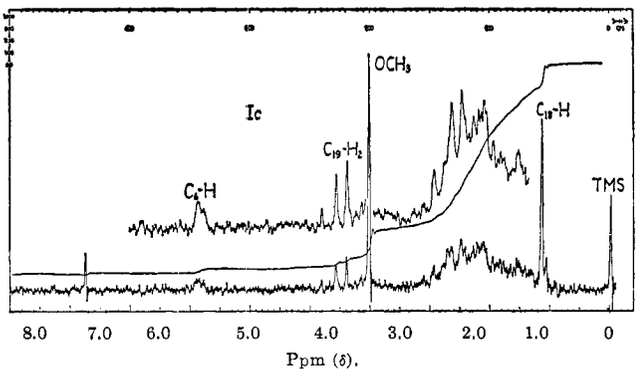


Figure 2b.

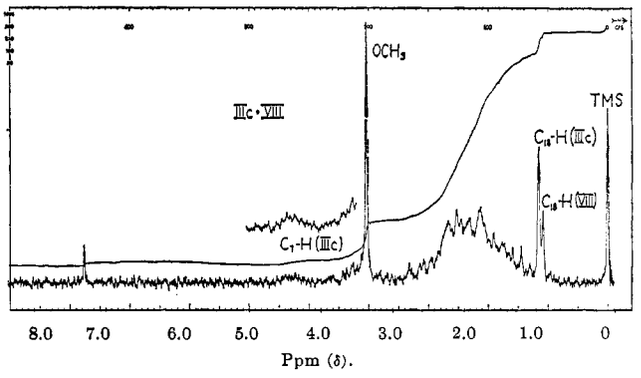


Figure 2c.

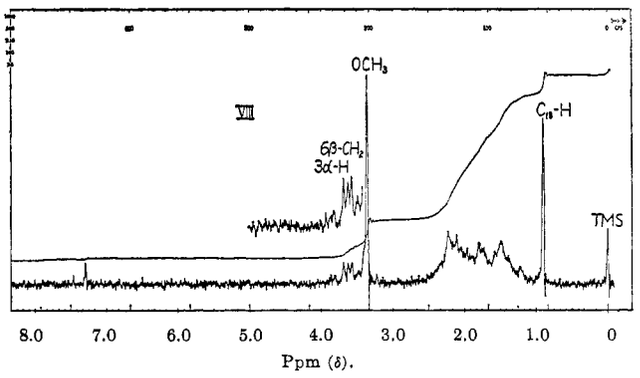


Figure 2d.

In order to investigate this possibility, it was necessary to determine the nature of the products formed by reaction of the cation B and halide ion under the thermodynamically controlled conditions employed for the conversion of the Δ^5-19-methanesulfonates to Δ^5-19 halides. From the reactivity of the $\Delta^{5(10)}$-B-homo-7β-methanesulfonate, which precluded its isolation, it seemed likely that the $\Delta^{5(10)}$-B-homo-7β chloride IIIc, a conceivable substitution product from the cation B, would prove too unstable to permit its isolation under the conditions of the halide reaction in refluxing 2-propanol. The possibility thus existed that, in the absence of the formation of a stable substitution product from the cation B, an equilibrium between cations A and B would result in formation of the Δ^5-19 chloride Ic. This might, alternately, account for the exclusive formation of the Δ^5-19 chloride from both the Δ^5-19-methanesulfonate and the 5β,19-cyclo-6β chloride.

Treatment of the B-homo-7β-ol IIIa with thionyl chloride in ether (conditions used for the preparation of the 5β,19-cyclo-6β chloride from the alcohol IIa) gave a mixture of halides, the major component of which, characterized by the nmr spectrum (Figure 2c) was the B-homo-7β chloride IIIc in about 80% yield. The absorption of the C_7 proton of IIIc appeared at 263 cps with a half-band width ($W_{1/2}$ 22 cps) almost identical with that of the C_7 proton of the $\Delta^{5(10)}$-B-homo-7β-ol IIIa (Table I). The minor component, indicated by the C_{18}-proton absorption at 54.8 cps, was present in about 20% yield. The nmr spectrum of the mixture remained unchanged after the deuteriochloroform solution had stood at room temperature overnight. The mixture gave an immediate precipitate with 2% methanolic silver nitrate solution at room temperature.

Treatment of the mixture with lithium chloride in refluxing 2-propanol led to the isolation of an isomeric homoallylic chloride. The nmr spectrum of the total crude product showed the absence of any B-homo-7β chloride by the absence of C_{18}-proton absorption at 58 cps. The C_{18}-proton absorption of this chloride at 54.5 cps indicated the probability that it constituted the minor (20%) component of the chloride mixture obtained from the B-homo alcohol IIIa on treatment with thionyl chloride in ether. The new chloride was inert to 2% methanolic silver nitrate solution at room temperature.

The isomeric homoallylic chloride was characterized as 3β-methoxy-6β-chloromethyl-estr-5(10)-en-17-one (VIII) by the absence of vinyl or cyclopropyl proton absorption in the nmr (Figure 2d) and the infrared, and by the presence of two protons on the carbon bearing the chloride shown by nmr.

The chloride VIII was reduced with lithium aluminum hydride in diethylene glycol dimethyl ether to 3β-methoxy-6β-methylestra-5(10)-en-17β-ol (Xa) which was characterized as the crystalline *p*-nitrobenzoate Xb. The hydride reduction was carried out by the procedure employed by Djerassi and Kielczewski[16] for the conversion of 3β-acetoxy-19-bromoandrost-5-ene to 3β-hydroxy-19-*d*-androst-5-ene. Both the alcohol Xa and the *p*-nitrobenzoate Xb exhibited doublet absorptions in their nmr spectra due to the 6β-methyl groups split by spin–spin coupling to the 6α protons.

Formation of the 6β-chloromethyl derivative VIII from the B-homo chloride IIIc may be accounted for by attack of chloride ion on the 5β,6β-methylene bridge carbon of the cation B. Thus, formation of the Δ^5-19-chloro steroid IIc from the Δ^5-19-methanesulfonate Ib on the one hand and formation of the 6β-chloro-

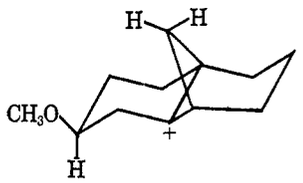
methyl steroid VIII from the B-homo chloride IIIc on the other provides additional evidence, in nucleophilic substitution reactions, for the existence of two discrete, isomeric cations in these systems to add to that obtained in the elimination reactions.

The halide reactions demonstrate that, in contrast to the results with water as a nucleophile, attack of halide on the C_{19}-methylene bridge of cation A is much faster than the rearrangement of cation A to cation B; *i.e.*, $k_{19} \gg k_7$. The greater effectiveness of chloride as compared to water in attacking a homoallylic cation in a thermodynamically controlled process has already been noted by Kosower and Winstein.[17]

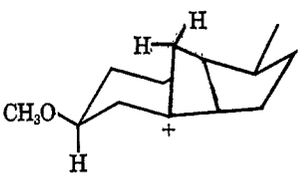
It is of interest that the over-all transformation of the Δ^5-19-hydroxy steroid Ia to the 6β-chloromethyl steroid VIII is analogous to the conversion of presenegenin to senegenin recently reported by Dugan and de Mayo[18a] to be effected on treatment with ethanolic hydrochloric acid and to the conversion of the benzenesulfonate of 10-hydroxymethyl-4-decene, under acetolysis conditions, to 1-acetoxymethyl-9-decene reported by Hikino and de Mayo.[18b]

Stereochemistry

Assignment of configuration at C_6 to the 5β,19-cyclo-6-ols formed in the buffered hydrolysis of Δ^5-19-methanesulfonates has previously been based on the assumption of considerable 6β,19 bonding in the nonclassical, carbonium ion intermediate, *i.e.*, that the canonical structure g made a significant contribution to the resonance hybrid.[1a,8b,19] Such 6β,19 bonding



g

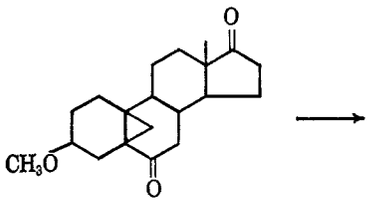


h

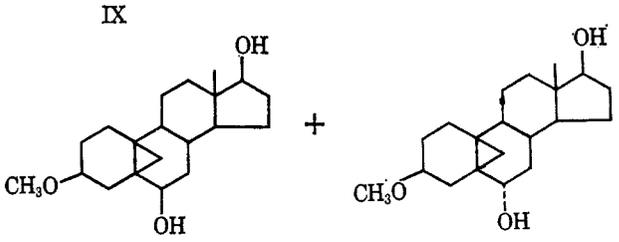
would limit the attacking nucleophile to a 6α attack and lead to formation of the 6α-ol. The assumption of important 6β,19 bonding is not beyond question since, although the additional charge delocalization would have a stabilizing effect, it is difficult to estimate the magnitude of the opposing strain energy in the resulting bicyclobutonium ion. An alternate 1,4 interaction resulting from 6α,10α bonding through a contribution to the cation A by the canonical structure h would lead to prediction of the opposite stereochemistry. Furthermore, the stereospecificity observed does not require control by such a 1,4 interaction since high degrees of stereospecificity are observed in reactions of homoallylic cations in which the geometries preclude 1,4 interaction[6,20] and thus in which stereospecificity is controlled by factors of a quite different nature.

Since nmr has become a powerful tool in the elucidation of the stereochemistry of complex molecules, it was hoped that a study of the nmr spectra of C_6-epimeric 5β,19-cyclo-6-substituted steroids might provide some criteria for configurational assignments.

Sodium borohydride reduction of 3β-methoxy-5β,19-cycloandrostane-6,17-dione (IX) gave a mixture of 5β,-19-cyclo-6,17β-diols, one of which was identical with that obtained by sodium borohydride reduction of the solvolysis product, IIa.



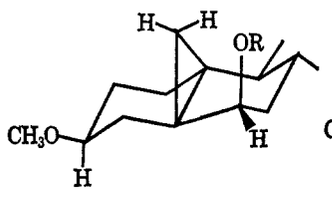
IX



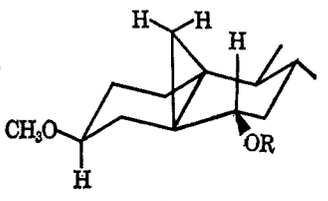
XIIa XIIIa

The C_6-proton absorptions in the nmr spectra of all the 5β,19-cyclo-6-substituted steroids appeared as complex multiplets due to spin–spin coupling with the axial and equatorial protons at C_7. The half-band widths of the C_6 proton of the solvolysis product IIa and its derivatives [3β-methoxy-5β,19-cycloandrostane-6β,17β-diol (XIIa) and 3β-methoxy-6β,17β-diacetoxy-5β,19-cycloandrostane (XIIb)] were all in the range 6–8 cps (Table I), characteristic of equatorial protons.[21] Although the absorption of the C_6 proton of the epimeric diol XIIIa overlapped with the 17α-proton absorption, the C_6-proton absorption of 3β-methoxy-6α,17β-diacetoxy-5β,19-cycloandrostane (XIIIb) was resolved and appeared with a half-band width of 19 cps characteristic of an axial proton.[21]

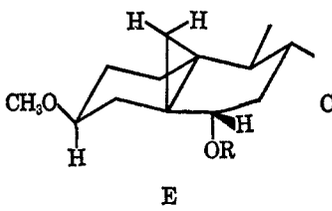
Dreiding models of the 5β,19-cyclo steroids indicate that the B rings may exist either in the half-chair or in the boat conformation. The half-band widths of the C_6 protons of the epimers establish that, in solution, either both have chair-form B rings or both have boat-form B rings.



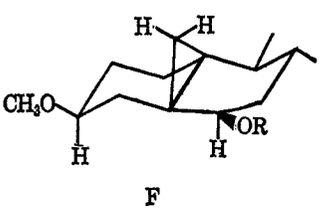
C



D



E



F

In the former case (C and D), the C_6-equatorial proton of the solvolysis product would require a 6β-

(18) (a) J. J. Dugan and P. de Mayo, *Can. J. Chem.*, **43**, 2033 (1965); (b) Y. Hikino and P. de Mayo, *Chem. Commun.*, 550 (1965).

(19) M. Akhtar and D. H. R. Barton, *J. Am. Chem. Soc.*, **86**, 1528 (1964).

(20) (a) S. G. Levene, N. H. Eudy, and E. C. Farthing, *Tetrahedron Letters*, 1517 (1963); (b) W. F. Johns, *J. Org. Chem.*, **29**, 1490 (1964); (c) G. H. Whitham and (in part) J. A. F. Wickramasinghe, *J. Chem. Soc.*, 1965 (1964).

(21) J. I. Musher, *J. Am. Chem. Soc.*, **83**, 1146 (1961).

axial hydroxyl, while the C_6-axial hydrogen of the reduction product would require a 6α-equatorial substituent. If, on the other hand, the epimers possessed boat-form B rings (E and F), the configurational assignments would be reversed.

It has been established that the presence of an electronegative substituent such as a hydroxyl group results in a paramagnetic shift in the absorption of a neighboring proton.[22] Of the two 5β,19-cyclo-6-ols it might be expected that the C_{19}-methylene proton of the 6β-ol which lies over the B ring would be shifted to lower field than in the case of the epimeric 6α-ol. Of the two C_{19}-methylene protons of the 5β,19-cyclo-6-ols, that which lies over the A ring would be least effected by changes in the configuration at C_6.

The cyclopropyl proton absorptions of the C_6-epimeric 5β,19-cyclo-6-ols and their derivatives present a significant contrast which can only be due to the difference in configuration at C_6. Whereas both cyclopropyl protons of the reduction product XIIIa lie in the range 26–32 cps, one cyclopropyl proton of the solvolysis product IIa and the corresponding diol XIIa appears at about 55 cps (Table I) while the other appears at 18 cps. The low-field absorptions at 55 cps of IIa and XIIa may be accounted for as the absorptions of the cyclopropyl protons lying over the B ring which are deshielded by the neighboring 6β-axial hydroxyl (structure C).

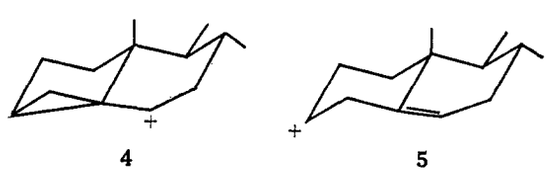
The cyclopropyl proton absorption of 3β-methoxy-10β-hydroxy-5β,6β-methylenestran-17-one (VII) may be accounted for by the same factors which determine that of IIa. In the case of VII the configuration of the C_{10}-hydroxyl is established by the occurrence of intramolecular hydrogen bonding with the C_3-methoxyl. The nmr spectrum of VII, like that of IIa, shows only one high-field cyclopropyl proton absorption which in VII is at 15 cps. Thus one of the cyclopropyl protons of the methylene bridge must lie at lower field, in this case below 50 cps. The low-field absorption of one of the protons of the methylene bridge of VII may be attributed to the paramagnetic shift of the absorption of the methylene bridge proton which lies over the B ring caused by the neighboring C_{10}-hydroxyl.

Further evidence that the C_6 substituents of the solvolysis products are β is provided by the nmr spectrum of the 5β,19-cyclo-6β chloride (IIc). The reaction of the alcohol IIa to form the chloride most probably occurs *via* an SNi process or *via* the same cation which led to the alcohol[17] and thus would be expected to procede with retention (as was found to be the case for the conversion of 6β-hydroxy-3α,5α-cyclocholestane to the 6β chloride[17]). Evidence that the reaction did procede with retention is provided by the half-band width of the C_6 proton (8 cps) which is identical with that of the alcohol IIa (Table I).

It has been established that a chlorine substituent, like a hydroxyl group, causes a paramagnetic shift of the absorption of a neighboring proton, but of a somewhat larger magnitude.[22a] In the present case replacement of a hydroxyl by chloride results in a downfield shift of the high-field doublet of 14 cps, while the downfield shift of the low-field doublet is calculated to be about 70 cps (Table I). The magnitude and nature of these shifts are most compatible with the β configuration of the C_6 substituents.

Correct assignment of configuration to the C_6-epimeric 6α- and 6β-substituted 3α,5α-cyclocholestanes was made by Kosower and Winstein[6c] largely on the basis of optical rotations. In the 3α,5α-cyclo steroids as in 5α-H steroids the 6α epimers have the more positive rotations. In contrast, models indicate that the 5β,19-cyclo steroids are more closely related to 5β-H steroids. Although the difference is small, 6β-hydroxy-5β-cholestane has a slightly more positive rotation ($[\alpha]_D$ +21°) than does 6α-hydroxy-5β-cholestane ($[\alpha]_D$ +18°).[23] This order is in agreement with the observed order of C_6-epimeric 5β,19-cyclo-6-ols: the rotation of 3β-methoxy-6β,17β-dihydroxy-5β,19-cycloandrostane (XIIa, $[\alpha]^{28}_D$ +47°) is more positive than that of 3β-methoxy-6α,17β-dihydroxy-5β,19-cycloandrostane (XIIIa, $[\alpha]^{28}_D$ +10.7°).

Formation of 6β-substituted 5β,19-cyclo steroids by rearrangement of Δ⁵-19-methanesulfonates may be explained by an intermediate homoallylic cation A with negligible C_6–C_{19} interaction. Contribution to the hybrid of canonical structure c, with positive charge on a tertiary carbon, should be much greater than that of a, with positive charge on a primary carbon. The canonical structures b and c (Figure 1) are analogous to the canonical structures **4** and **5** of the stable, homo-



4 **5**

allylic 3α,5α-cyclo cation. Reactions of the latter intermediate at C_6 are known to occur stereospecifically with β attack of a nucleophile which preserves maximum overlap of the p orbitals at C_5 and C_6 in the transition state leading to product.[24] A similar stereoelectronically controlled process operating on a cation with major contributions from canonical structures b and c (Figure 1) would be expected to lead to the 6β-hydroxy-5β,19-cyclo steroid.

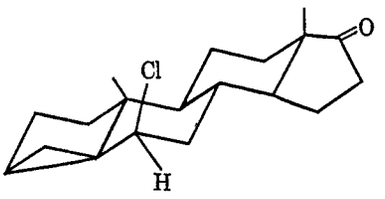
The configuration at C_6 of the 3α,5α-cyclo-6β-chlorides formed by treatment of 3α,5α-cyclo-6β-ols with thionyl chloride in ether has previously been based on correlations of optical rotation.[17] Since nmr has been useful in assigning configurations to C_6-epimeric 3α,5α-cyclo steroids from the multiplet absorption patterns of the 6α-equatorial and 6β-axial protons of 6β- and 6α-substituted epimers, respectively,[25] it was hoped that it would provide a direct correlation of the configurations of the 6β-ols and 6β chlorides. 6β-Hydroxy-3α,5α-cycloandrostan-17-one was converted to the chloride with thionyl chloride in ether by the procedure of Kosower and Winstein.[17] The nmr spectrum of the chloride XIV, recorded immediately after preparation, showed the characteristic

(22) (a) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, Inc., San Francisco, Calif., 1964, pp 20, 21; (b) Y. Kawazoe, Y. Sato, M. Natsume, H. Hasegawa, T. Okamoto, and K. Tsuda, *Chem. Pharm. Bull.* (Japan), **10**, 338 (1962).

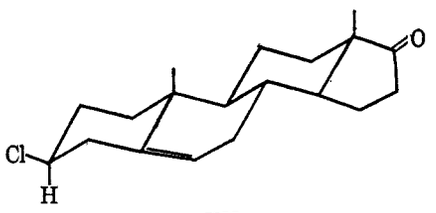
(23) "Selected Constants, Optical Rotatory Power, Ia, Steroids," The Macmillan Co., New York, N. Y., 1965, p 483.

(24) This type of stereoelectronic control is discussed by Whitham in regard to the solvolytic formation of 6β-hydroxy-3β,5β-cyclo steroids from the corresponding cation; see ref 20c.

(25) (a) J. Tadanier and W. Cole, *J. Org. Chem.*, **27**, 4610 (1962); (b) J. Tadanier, *ibid.*, **28**, 1744 (1963).



XIV

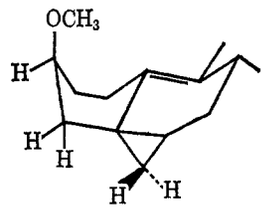


XV

triplet absorption[25] of the 6α-equatorial proton of 6β-substituted 3α,5α-cyclo steroids at 234.5 cps ($J_{ae} \cong J_{ee} \cong 2.7$ cps). This confirms the conclusion of Kosower and Winstein[17] that the substitution occurs with retention. When the spectrum of the product was recorded after 48 hr in deuteriochloroform solution, the spectrum was that of 3β-chloroandrost-5-en-17-one (XV), showing that rearrangement to the homoallylic chloride was essentially complete, in agreement with the previous findings in the cholesteryl system.[17]

Direct evidence that the 5,6-methylene bridge of the vinylcyclopropane VI is β oriented is provided by the nmr spectrum. The C_3-proton absorption occurs as a 1:4:6:4:1 pentuplet with spacings between the peaks of about 4 cps (Table I). The nature of the absorption thus indicates that the C_3 proton is equally coupled to the four vicinal methylene protons. The magnitude of the splitting (J = 4 cps) indicates that the dihedral angles between the C_3 proton and the C_2- and C_4-methylene protons are all about 60°[26] and thus that the C_3 proton is equatorial.

Examination of a Dreiding model of 3β-methoxy-5α,6α-methylenestr-9-en-17-one established that two conformations are available to the A ring: a twist-boat form (6) in which the C_3 proton is equatorial, and a chair form (7) in which the C_3 proton is axial.



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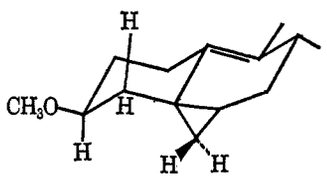
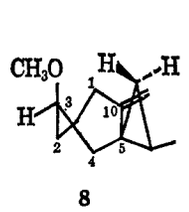


7

Since the chair form may be assumed to be the favored conformation and the axial orientation of the C_3 proton is inconsistent with the nmr spectrum, the possibility that VI may have a 5α,6α-methylene bridge may be excluded.

Of the four possible conformations available to the A ring of 3β-methoxy-5β,6β-methylenestr-9-en-17-one, the half-chair A ring with a C_3-equatorial proton (8) is most consistent with the nmr spectrum. The alternate half-chair form (9) with a C_3-axial proton is



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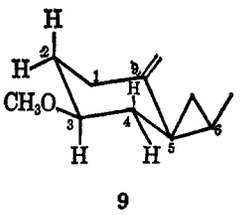

9

presumably less stable since it causes the C_1–C_{10}–C_5 and C_{10}–C_5–C_4 bond angles to increase.

Formation of the 5β,6β-methylen-9-ene is consistent with the mechanistic assumption of its formation from an intermediate cation (B) which maintains significant 5α,6α bonding (canonical structures d and e, Figure 1). The stereochemistry of the $\Delta^{5(10)}$-B-homo-7β-ol IIIa is based on the assumption of its formation from the cation B. By analogy with the stereochemistry of formation of homoallylic derivatives from homoallylic cations in a variety of systems,[6,20a,b] attack of water on the cation B is expected to occur *trans* to the partial 5α,6α bond of the cyclopropanoid ring which is broken in the transition state leading to product.

The configuration at C_7 of the B-homo-7β chloride IIIc is based on the assumption that the reaction of the alcohol IIIa with thionyl chloride in ether proceeds either by an SNi reaction or *via* the same cation which leads to the alcohol IIIa. Replacement of hydroxyl by halide with retention *via* the 3α,5α-cyclo cation is reported in the conversion of cholesterol to cholesteryl chloride.[27]

The same mechanistic assumption which led to the assignment of configuration to the B-homo alcohol IIIa is necessary for the 5β,6β assignment to the methylene bridge of the cyclopropylcarbinol VII and for the 6β-assignment to the chloromethyl group of VIII; *i.e.*, the homoallylic cation intermediate common to all these products retains significant 5α,6α bonding.

Some direct evidence that the cation B has no appreciable C_{10}–C_{19} bonding is provided by the isolation of 3β-methoxy-10β-hydroxy-5β,6β-methylenestran-17-one (VII) as the minor product formed by addition of water to the reaction mixture obtained by treatment of the B-homo-7β-ol IIIa with methanesulfonyl chloride in pyridine.

Summary

The present results establish that two discrete, isomeric cations intervene in the homoallylic rearrangements of 19-substituted steroids. The energy barrier to rearrangement of these ions is sufficient to prevent their interconversion when there is the alternative of reaction with a suitable nucleophile.

The available nmr evidence together with the assumption, derived from examination of models, that the B rings of 5β,19-cyclo steroids exist in half-chair forms leads us to the tentative assignment of the β orientation to the C_6 substituents of the products formed by rearrangement of Δ^5-19-substituted steroids.[28] This

(26) H. Conroy, in "Advances in Organic Chemistry: Methods and Results," Vol. 2, Interscience Publishers, Inc., New York, N. Y., 1960, p 304.

(27) Reference 6a, p 32.

(28) Chemical evidence that the buffered hydrolysis of Δ^5-19-substituted steroids leads to 6β-hydroxy-5β,19-cyclo steroids has recently been obtained by K. Syhora, J. A. Edwards, and A. D. Cross who found that the configuration at C_6 of the rearrangement products is the same as that of a 6β-hydroxy-5β,19-cyclo steroid prepared by the Simmons–Smith addition of methylene to the $\Delta^{5(10)}$ double bond of a 6β-hydroxy-$\Delta^{5(10)}$ steroid. Private communication from Dr. A. D. Cross.

stereochemistry may be explained as resulting from stereoelectronic control effected by a homoallylic cation (A) or by a bicyclobutonium ion with 6α,10α bonding.

Experimental Section

Melting points were determined with a Fisher-Johns block. Optical rotations were determined with a Hilger and Watts polarimeter on 1% solutions in chloroform. Ultraviolet spectra were taken with a Cary Model 11 spectrophotometer with methanol as solvent. Infrared spectra were obtained with a Perkin-Elmer Model 421 grating spectrophotometer.

Woelm alumina activity III was used for all chromatographies. The petroleum ether used for crystallization and chromatography was a fraction boiling 66–70%.

3β-Methoxy-19-methanesulfonoxyandrost-5-en-17-one (Ib).—A solution of 3β-methoxy-19-hydroxyandrost-5-en-17-one (Ia, 2.18 g) in 55 ml of anhydrous pyridine was cooled in an ice bath and 2.18 ml of methanesulfonyl chloride was added. The resulting solution was allowed to stand at room temperature for 2.5 hr and then poured into 500 ml of water. The aqueous suspension was extracted with 200 ml of chloroform. The chloroform solution was washed with 400 ml of water, 400 ml of 5% sodium bicarbonate solution, and three 400-ml portions of water. The chloroform solution was dried over anhydrous magnesium sulfate. The chloroform was evaporated under reduced pressure using a rotary evaporator and the residual pyridine was removed by azeotropic distillation with benzene under reduced pressure. The crude methanesulfonate (2.45 g) melted at 127–132°. The analytical sample, mp 130–133°, was prepared by recrystallization from benzene–petroleum ether: $\tilde{\nu}_{max}$ 1730, 1360, 1172, and 1090 cm^{-1}.

Anal. Calcd for $C_{21}H_{32}O_5S$: C, 63.61; H, 8.20; S, 8.09. Found: C, 63.76; H, 8.07; S, 8.39.

3β-Methoxy-6β-hydroxy-5β,19-cycloandrostan-17-one (IIa).—3β-Methoxy-19-methanesulfonoxyandrost-5-en-17-one (Ib, 1.64 g) was heated under reflux for 16 hr in a solution prepared from 1.6 g of potassium acetate, 30 ml of water, and 100 ml of acetone. The major portion of the acetone was then evaporated under reduced pressure on a steam bath using a rotary evaporator. The residue was shaken with 400 ml of ether and 300 ml of water. The aqueous phase was separated and extracted with 400 ml of ether. The ether solutions were washed in series with 200 ml of 5% sodium bicarbonate solution and three 200-ml portions of water. The ether solutions were combined and dried over anhydrous magnesium sulfate. Evaporation of the ether left 1.35 g of an oil, the infrared spectrum of which showed the presence of acetate and absence of methanesulfonate.

The product was heated under reflux for 1 hr with 100 ml of 5% potassium hydroxide in methanol. The hydrolysis solution was then shaken with a mixture of 400 ml of ether and 1000 ml of water. The aqueous phase was separated and extracted with 400 ml of ether. The ether solutions were washed in series with four 200-ml portions of water, combined, and dried over anhydrous magnesium sulfate. Evaporation of the ether left 1.16 g of a rigid, pale yellow glass.

The product was chromatographed on 100 g of alumina. Elution with 1:15 ether–benzene gave a small amount of yellow oil. Elution with 1:2 ether–benzene yielded 794.4 mg of IIa. The product was crystallized from ether–petroleum ether as dense white prisms, 658 mg, mp 105–106°. For analysis 221 mg was recrystallized from ether–petroleum ether to yield 190.2 mg: mp 105–107°; [α] +126°; $\tilde{\nu}_{max}$ 3599, 1727, and 1084 cm^{-1} ($CHCl_3$); $\tilde{\nu}_{max}$ 3050 cm^{-1} (CCl_4).

Anal. Calcd for $C_{20}H_{30}O_3$: C, 75.44; H, 9.50. Found: C, 75.37; H, 9.59.

3β-Methoxy-5β,19-cycloandrostane-6,17-dione (IX).—To a solution of 258 mg of 3β-methoxy-6β-hydroxy-5β,19-cycloandrostan-17-one (IIa) in 2 ml of pyridine was added a complex prepared from 300 mg of chromic anhydride and 3 ml of pyridine. The resulting suspension was allowed to stand overnight at room temperature and then diluted with 50 ml of ether. The mixture was filtered through a Celite mat. The mat was washed with 50 ml of ether and the washings were added to the original filtrate. The ether solution was washed with 30 ml of water and the aqueous phase was separated and extracted with 80 ml of ether. The ether solutions were washed in series with four 30-ml portions of water, combined, and dried over anhydrous magnesium sulfate. The ether and residual pyridine were evaporated leaving 247 mg of white blades of IX, mp 138–139°. For analysis 218 mg was recrystallized from benzene–petroleum ether to yield 184 mg of white needles: mp 138–139°; $\tilde{\nu}_{max}$ 3072, 3009, 1736, 1672, and 1097 cm^{-1} (CCl_4); λ_{max} 210 mμ (ε 4230); $[\alpha]^{27}D$ +12.6°.

Anal. Calcd for $C_{20}H_{28}O_3$: C, 75.92; H, 8.92. Found: C, 76.14; H, 8.96.

3β-Methoxy-5β,19-cycloandrostane-6β,17β-diol (XIIa).—To a solution of 222 mg of 3β-methoxy-6β-hydroxy-5β,19-cycloandrostan-17-one (IIa) in 26 ml of methanol was added 6 ml of a solution prepared from 850 mg of sodium borohydride in 10 ml of water. The resulting solution was stirred at room temperature for 15 min and then poured into 250 ml of water. The resulting suspension was extracted twice with 200-ml portions of ether and the ether solutions were washed in series with four 100-ml portions of water. The ether solutions were combined and dried over anhydrous magnesium sulfate. Evaporation of the ether left 215 mg of the diol XIIa as a white crystalline solid, mp 183–187°. Recrystallization from acetone–petroleum ether gave the analytical sample, mp 190–192°, $\tilde{\nu}_{max}$ 3604 and 1091 cm^{-1} ($CHCl_3$), $[\alpha]^{28}D$ +47°.

Anal. Calcd for $C_{20}H_{32}O_3$: C, 74.94; H, 10.07. Found: C, 75.19; H, 9.98.

3β-Methoxy-5β,19-cycloandrostane-6α,17β-diol (XIIIa).—To a solution of 411 mg of 3β-methoxy-5β,19-cyclo-androstane-6,17-dione in 50 ml of methanol at 0° was added 1.7 g of sodium borohydride in 20 ml of water. The solution was stirred at room temperature for 30 min and poured into 500 ml of water. The product was isolated by ether extraction in the usual manner to yield 410 mg of a mixture of XIIa and XIIIa. Three recrystallizations from acetone–petroleum ether gave 118 mg of 3β-methoxy-5β,19-cycloandrostane-6β,17β-diol (XIIa), mp 189–192°. Recrystallization of the product obtained from the mother liquors gave 153 mg of 3β-methoxy-5β,19-cycloandrostane-6α,17β-diol (XIIIa), mp 135–139°, $\tilde{\nu}_{max}$ 3602 and 1088 cm^{-1} ($CHCl_3$), $[\alpha]^{28}D$ +10.7°.

Anal. Calcd for $C_{20}H_{32}O_3$: C, 74.94; H, 10.07. Found: C, 74.89; H, 9.94.

3β-Methoxy-7β-hydroxy-B-homoestr-5(10)-en-17-one (IIIa).—To a solution of 3β-methoxy-6β-hydroxy-5β,19-cycloandrostan-17-one (2.15 g) in 135 ml of acetone was added 25 ml of a solution prepared from 2.5 ml of concentrated sulfuric acid and 60 ml of water. The resulting solution was heated under reflux for 2 hr and then poured into 200 ml of water. The major portion of the acetone was evaporated under reduced pressure and the resulting aqueous suspension was diluted by addition of 200 ml of water. The aqueous suspension was extracted three times with 400-ml portions of ether. The ether solutions were washed in series with 300 ml of water, 300 ml of 5% sodium bicarbonate solution, and three 300-ml portions of water, and then combined and dried over anhydrous magnesium sulfate. Evaporation of the ether left an oil (2.02 g), which crystallized on standing and melted at 93–110°.

The product was chromatographed on 150 g of alumina. Elution with 1:20 ether–benzene solution yielded 64 mg of a crystalline solid which was not characterized. Elution with 1:1 ether–benzene solution yielded 1.79 g of 3β-methoxy-7β-hydroxy-B-homoestr-5(10)-en-17-one (IIIa), mp 99–112°. Recrystallization from benzene–petroleum ether gave 1.56 g of IIIa: mp 118–120°; $\tilde{\nu}_{max}$ 3596, 1725, and 1088 cm^{-1} ($CHCl_3$); $\tilde{\nu}_{max}$ 3612 and 3480 cm^{-1} (0.0025 *M* CCl_4); ε 4700 at 210 mμ; $[\alpha]^{25}D$ +50.8°.

Anal. Calcd for $C_{20}H_{30}O_3$: C, 75.44; H, 9.50. Found: C, 75.66; H, 9.30.

3β-Methoxy-B-homoestr-5(10)-ene-7,17-dione (XI).—To a solution of 317 mg of 3β-methoxy-7β-hydroxy-B-homoestr-5(10)-en-17-one in 2.4 ml of pyridine was added 5.0 ml of a complex prepared from 944 mg of chromic anhydride and 8.6 ml of pyridine. The resulting solution was allowed to stand at room temperature for 20 hr. The product was worked up in the usual manner to yield 210 mg of a light green solid, mp 133–143°. The product was eluted through a column of 20 g of alumina with benzene to yield 143 mg of 3β-methoxy-B-homoestr-5(10)-ene-7,17-dione (XI), mp 145–152°. The analytical sample was prepared by recrystallization from methanol–water solution to yield 112 mg: mp 150–152°; $[\alpha]^{28}D$ −112°; $\tilde{\nu}_{max}$ 1740, 1701, and 1092 cm^{-1} (CCl_4); $\tilde{\nu}_{max}$ 287 mμ (ε 387).

Anal. Calcd for $C_{20}H_{28}O_3$: C, 75.92; H, 8.92. Found: C, 76.14; H, 9.11.

Attempted Conjugation of 3β-Methoxy-B-homoestr-5(10)-ene-7,17-dione.—A solution of 3β-methoxy-B-homoestr-5(10)-ene-7,17-dione (60 mg) in 5 ml of 2% potassium hydroxide in methanol, under nitrogen, was heated under reflux for 1 hr and the product isolated by ether extraction. Infrared and ultraviolet spectra of the material obtained were essentially identical with the spectra of the starting material.

3β-Methoxy-5β,19-cycloandrost-6-en-17-one (V). (a) From 3β-Methoxy-19-methanesulfonoxyandrost-5-en-17-one (Ib).—A solution of 1.0 g of 3β-methoxy-19-methanesulfonoxyandrost-5-en-17-one (Ib) in 20 ml of pyridine was heated under reflux for 18 hr. The resulting solution was poured into 100 ml of 10% sodium chloride solution forming a milky white suspension. The suspension was extracted twice with 150-ml portions of ether. The ether solutions were washed in series with 50 ml of 5% sodium bicarbonate solution and three 50-ml portions of water, then combined and dried over anhydrous magnesium sulfate. Evaporation of the solvent left 675 mg of a pale orange solid. This material was eluted through a column of 25 g of alumina with benzene to yield 634 mg of 3β-methoxy-5β,19-cycloandrost-6-en-17-one (V) as a white crystalline solid. Recrystallization from ether–pentane solution gave 512 mg, mp 100–104°, identical in all respects with the product obtained from 3β-methoxy-6β-hydroxy-5β,19-cycloandrostan-17-one as described below.

(b) From 3β-Methoxy-6β-hydroxy-5β,19-cycloandrostan-17-one (IIa). A solution of 511 mg of 3β-methoxy-6β-hydroxy-5β,19-cycloandrostan-17-one (IIa) in 10 ml of pyridine was cooled in an ice bath and 0.52 ml of methanesulfonyl chloride was added with stirring. Stirring was continued with the solution in the ice bath for 10 min; the resulting suspension was allowed to stand at room temperature for 3 hr. The pyridine suspension was poured into 250 ml of water, giving a clear solution. On simple extraction with chloroform or with ether, the product remained in the aqueous phase; the organic extracts contained only trace amounts of oil. To the aqueous solution was added 5 g of sodium chloride and the resulting solution was subjected to continuous extraction with chloroform for 4 days to yield 388 mg of 3β-methoxy-5β,19-cycloandrost-6-en-17-one as an orange solid which was essentially pure by criteria of infrared, nmr, and vapor phase chromatography. This material was eluted through a column of 15 g of alumina with benzene to yield 311 mg of white solid. Recrystallization from ether–pentane solution gave 192 mg of V: mp 100–103°; $\tilde{\nu}_{max}$ 3063, 3025, and 1737 cm^{-1} (CCl_4); λ_{max} 215 mμ (ε 5780); $[\alpha]^{24}D$ +70.5°.

Anal. Calcd. for $C_{20}H_{28}O_2$: C, 79.96; H, 9.39. Found: C, 79.96; H, 9.50.

3β-Methoxy-5β,6β-methylenestr-9-en-17-one (VI).—A solution of 403 mg of 3β-methoxy-7β-hydroxy-B-homoestr-5(10)-en-17-one in 8 ml of pyridine was cooled in an ice bath and 0.42 ml of methanesulfonyl chloride was added with stirring. Stirring was continued in the ice bath for 10 min and the resulting solution was allowed to stand at room temperature for 3 hr. The reaction mixture was shaken with a mixture of 100 ml of ether and 80 ml of water. The aqueous phase was separated and extracted twice with 80-ml portions of ether. The ether solutions were washed in series with 50 ml of water, 50 ml of 5% sodium bicarbonate solution, and three 50-ml portions of water, and then combined and dried over anhydrous magnesium sulfate. Evaporation of solvent left 340 mg of 3β-methoxy-5β,6β-methylenestr-9-en-17-one (VI) as a pale yellow solid which was essentially pure by criteria of infrared, nmr, and vapor phase chromatography. This material (321 mg) was eluted through a column of 14 g of alumina to yield 247 mg of a white crystalline solid. For analysis, this material was recrystallized three times from ether–pentane solution to yield 107 mg, mp 119–122°. A second crop (60 mg), mp 117–122°, was obtained from the mother liquors. The analytical sample melted at 119–122°, $\tilde{\nu}_{max}$ 3067 and 1737 cm^{-1} (CCl_4), λ_{max} 216 mμ (ε 8400), $[\alpha]^{24}D$ +93°.

Anal. Calcd for $C_{20}H_{28}O_2$: C, 79.96; H, 9.39. Found: C, 79.69; H, 9.45.

3β-Methoxy-10β-hydroxy-5β,6β-methylenestran-17-one (VII).—A solution of 3β-methoxy-7β-hydroxy-B-homoestr-5(10)-en-17-one (549 mg) in 11 ml of pyridine was cooled in an ice bath. Methanesulfonyl chloride (0.57 ml) was added and the resulting solution was stirred in the ice bath for 10 min. Water (1.1 ml) was added and stirring was continued in the ice bath for 30 min. The resulting mixture was allowed to stand at room temperature for 30 min and then shaken with a mixture of 150 ml of ether and 80 ml of water. The aqueous phase was separated and extracted with 150 ml of ether. The ether solutions were washed in series with 80 ml of water, 80 ml of 5% sodium bicarbonate solution, and three 80-ml portions of water, then combined and dried over anhydrous magnesium sulfate. Evaporation of solvent left 466 mg of a colorless oil which slowly crystallized on standing.

The product (430 mg) was chromatographed on 15 g of alumina. Elution with benzene gave 271 mg of 3β-methoxy-5β,6β-methylenestra-9-en-17-one (VI) identified by its infrared spectrum. Elution with 1:1 ether–benzene gave 126.2 mg of a colorless oil.

The latter product (116 mg) was rechromatographed on 20 g of alumina. The product eluted with 1:15 ether–benzene was recrystallized from ether–pentane solution to give 31 mg of 3β-methoxy-10β-hydroxy-5β,6β-methylenestran-17-one (VII). For analysis 22 mg was recrystallized from ether–pentane solution to give 18 mg: mp 132–136°; $\tilde{\nu}_{max}$ 3601, 3440, 1725 cm^{-1} ($CDCl_3$); $\tilde{\nu}_{max}$ 3609, 3489, and 3070 cm^{-1} (0.0012 *M* CCl_4); $[\alpha]^{23}D$ +33°.

Anal. Calcd for $C_{20}H_{30}O_3$: C, 75.44; H, 9.50. Found: C, 75.74; H, 9.65.

Hydration of 3β-Methoxy-5β,6β-methylenestr-9-en-17-one.—To a solution of 3β-methoxy-5β,6β-methylenestr-9-en-17-one, (VI, 359 mg) in 25 ml of acetone was added 2.5 ml of a solution prepared from 2.5 ml of concentrated sulfuric acid and 60 ml of water was added. The resulting solution was heated under reflux for 3 hr. The solution was diluted with 25 ml of water and the major portion of the acetone was evaporated under reduced pressure. The product (357 mg of an oily solid) was isolated by ether extraction in the usual manner.

The product (348 mg) was chromatographed on 27 g of alumina. Elution with benzene gave 50 mg of crystals which were not characterized. Elution with 1:1 ether–benzene solution gave 280 mg of 3β-methoxy-7β-hydroxy-B-homoestr-5(10)-en-17-one (IIIa), mp 105–115°. Recrystallization from benzene–petroleum ether gave 244 mg, mp 117–120°, undepressed on admixture with an authentic sample. The infrared spectrum was identical with that of IIIa.

Attempted Hydration of 3β-Methoxy-5β,19-cycloandrost-6-en-17-one.—To a solution of 3β-methoxy-5β,19-cycloandrost-6-en-17-one (V, 407 mg) in 25 ml of acetone was added 4.6 ml of a solution prepared from 2.5 ml of concentrated sulfuric acid and 60 ml of water. The resulting solution was heated under reflux for 3 hr and the product (394 mg) isolated by ether extraction as described above.

The product (385 mg) was eluted through a column of 25 g of alumina with benzene to yield 330 mg of 3β-methoxy-5β,19-cycloandrost-6-en-17-one (V), mp 103–106°, undepressed on admixture with authentic material. The infrared spectrum of the product was identical with that of starting material.

3β-Methoxy-6β-chloro-5β,19-cycloandrostan-17-one (IIc) and 3β-Methoxy-19-chloroandrost-5-en-17-one (Ic).—A suspension of 812 mg of 3β-methoxy-6β-hydroxy-5β,19-cycloandrostan-17-one (IIa) in 16 ml of ether was stirred in an ice bath for 5 min during which time most of the alcohol dissolved. Thionyl chloride (0.4 ml) was added and stirring was continued in the ice bath for 5 min and then at room temperature for 50 min. The solvent was evaporated under reduced pressure at room temperature and the residue dried for 1 hr under high vacuum with a rotary evaporator during which time the product crystallized as a light yellow solid. The yield of 3β-methoxy-6β-chloro-5β,19-cycloandrostan-17-one (IIc) was 881 mg. This material gave an immediate test with 2% methanolic silver nitrate solution and was fully characterized by its nmr spectrum (Table I) taken immediately after its preparation. Infrared showed the absence of OH, $\tilde{\nu}_{max}$ 3064 and 1732 cm^{-1} ($CDCl_3$).

Anal. Calcd for $C_{20}H_{29}ClO_2$: C, 71.30; H, 8.68; Cl, 10.53. Found: C, 71.44; H, 8.69; Cl, 10.77; S, 0.

After standing overnight at room temperature in $CDCl_3$, the nmr spectrum of the product was retaken and found to be almost identical with that of pure 3β-methoxy-19-chloroandrost-5-en-17-one (Ic).

The 5β,19-cyclo-6β chloride (IIc, 791 mg) was heated under reflux for 5 hr with 1.0 g of lithium chloride in 46 ml of 2-propanol and the resulting solution was allowed to stand overnight at room temperature. The solvent was evaporated and the residue was shaken with a mixture of ether and water. The product (756 mg of an oil) was isolated by ether extraction in the usual manner. The nmr spectrum was very similar to that of pure 3β-methoxy-19-chloroandrost-5-en-17-one (Ic) and showed the absence of the 5β,19-cyclo-6β chloride by the absence of cyclopropyl proton absorption.

The product (723 mg) was chromatographed on 70 g of alumina. Elution with 1:1 benzene–petroleum ether gave 622 mg of a pale yellow oil which crystallized from 4 ml of petroleum ether to yield 386 mg of 3β-methoxy-19-chloroandrost-5-en-17-one (Ic), mp 95–97°. The product did not give a test with 2% methanolic silver nitrate solution at room temperature. For analysis, this material was recrystallized from ether–petroleum ether to yield 335 mg, mp 97–98°, $\tilde{\nu}_{max}$ 1733 and 1093 cm^{-1} ($CDCl_3$), $[\alpha]^{24}D$ −7°.

Anal. Calcd for $C_{20}H_{29}ClO_2$: C, 71.30; H, 8.68; Cl, 10.53. Found: C, 71.08; H, 8.79; Cl, 10.32.

6β-Chloro-3α,5α-cycloandrostan-17-one (XIV).—A solution of 502 mg of 6β-hydroxy-3α,5α-cycloandrostan-17-one in 10 ml of ether was cooled in an ice bath and 0.25 ml of thionyl chloride was added with stirring. Stirring was continued in the ice bath for 5 min and then at room temperature for 20 min. The solvent was evaporated under reduced pressure leaving 535 mg of 6β-chloro-3α,5α-cycloandrostan-17-one (XIV) as a crystalline solid, $\tilde{\nu}_{max}$ 3064 and 1732 cm^{-1} ($CDCl_3$).

Anal. Calcd for $C_{19}H_{27}ClO$: Cl, 11.55. Found: Cl, 11.82; S, 0.

The nmr spectrum of the product after 48 hr in deuteriochloroform was that of 3β-chloroandrost-5-en-17-one (XV) (see Table I).

3β-Methoxy-7β-chloro-B-homoestr-5(10)-en-17-one (IIIc) and 3β-Methoxy-6β-chloromethylestr-5(10)-en-17-one (VIII).—A suspension of 1.00 g of 3β-methoxy-7β-hydroxy-B-homoestr-5(10)-en-17-one in 20 ml of ether was cooled in an ice bath and 0.5 ml of thionyl chloride was added with stirring. Stirring was continued with the reaction mixture in the ice bath for 10 min and then at room temperature for 50 min, resulting in a clear solution. The ether and excess thionyl chloride were evaporated under reduced pressure at room temperature leaving an orange oil (1.07 g) which was dried overnight at room temperature under high vacuum. The product gave an immediate test with 2% methanolic silver nitrate solution. The infrared spectrum showed the absence of OH absorption. From the areas of the angular methyl peaks at 54 and 58 cps, respectively, and the area of the C_7-proton absorption at 265 cps, it was estimated that the product was a mixture of about one part of 3β-methoxy-6β-chloromethylestr-5(10)-en-17-one (VIII) and four parts of 3β-methoxy-7β-chloro-B-homoestr-5(10)-en-17-one (IIIc). There was no change in the nmr spectrum after the sample had remained overnight in $CDCl_3$.

Anal. Calcd for $C_{20}H_{29}ClO_2$: Cl, 10.53. Found: Cl, 9.60; S, 0.00.

The product (975 mg) was heated under reflux for 5 hr in a solution prepared from 1.18 g of lithium chloride and 58 ml of 2-propanol. The solvent was evaporated and the residue was shaken with a mixture of 150 ml of ether and 100 ml of water. The aqueous phase was separated and extracted with 150 ml of ether. The ether solutions were washed in series with 100 ml of 5% sodium bicarbonate solution and three 50-ml portions of water, then combined and dried over anhydrous magnesium sulfate. Evaporation of the ether left 962 mg of a red viscous oil. The nmr spectrum showed only a single angular methyl absorption at 54 cps and no vinyl proton absorption.

The product (962 mg) was chromatographed on 90 g of alumina. Elution with 1:2 benzene–petroleum ether gave 691 mg of an oil which gave a single spot on thin layer chromatography. Crystallization occurred on prolonged standing to give 3β-methoxy-6β-chloromethylestr-5(10)-en-17-one (VIII), mp 102–106°, $\tilde{\nu}_{max}$ 1735 and 1095 cm^{-1} ($CDCl_3$), $[\alpha]^{26}D$ +100°.

Anal. Calcd for $C_{20}H_{29}ClO_2$: C, 71.30; H, 8.68; Cl, 10.53. Found: C, 71.61; H, 8.85; Cl, 10.28.

3β-Methoxy-6β-methylestr-5(10)-en-17β-ol (Xa).—3β-Methoxy-6β-chloromethylestr-5(10)-en-17-one (220 mg) was heated under reflux for 5 hr with stirring in a nitrogen atmosphere with a slurry prepared from 3.5 g of lithium aluminum hydride and 50 ml of diethylene glycol dimethyl ether, and the reaction mixture was then stirred overnight at room temperature. The excess lithium aluminum hydride was decomposed by the careful addition of water. Hydrochloric acid (100 ml, 6 *N*) was added with stirring. An additional 300 ml of 6 *N* hydrochloric acid was added and the resulting mixture was extracted twice with 400 ml portions of ether. The ether solutions were washed in series with water and 5% sodium bicarbonate solution followed by three portions of water, then combined and dried over anhydrous magnesium sulfate. Evaporation of the solvent left 200 mg of an oil.

The product (175 mg) was chromatographed on 20 g of alumina. Elution with benzene yielded 16 mg of a yellow oil. Elution with 1:10 ether–benzene yielded 135 mg of 3β-methoxy-6β-methyl-estr-5(10)-en-17β-ol (Xa) as a colorless oil, $\tilde{\nu}_{max}$ 3613 and 3443 cm^{-1} ($CDCl_3$), which was characterized as the crystalline *p*-nitrobenzoate. The product (85 mg) was dissolved in 1.0 ml of pyridine and 120 mg of *p*-nitrobenzoyl chloride was added. The reaction mixture was allowed to stand at room temperature for 3.5 hr and then worked up by ether extraction in the usual manner to yield 123 mg of 3β-methoxy-6β-methylestr-5(10)-en-17β-ol *p*-nitrobenzoate (Xb), mp 159–164°. For analysis the product was recrystallized twice from ether–petroleum ether to yield 64 mg, mp 164–166°, $\tilde{\nu}_{max}$ 1723 and 1531 cm^{-1} ($CDCl_3$), $[\alpha]^{26}D$ +67°.

Anal. Calcd for $C_{27}H_{35}NO_5$: C, 71.50; H, 7.78; N, 3.09. Found: C, 71.69; H, 7.80; N, 3.29.

A second crop (20 mg), mp 158–163°, was obtained from the mother liquors.

Control on the Stability of 3β-Methoxy-5β,6β-methylenestr-9-en-17-one (VI).—A suspension prepared from 0.41 ml of methanesulfonic acid and 50 ml of pyridine was heated in an oil bath at 100° until a clear solution resulted and 8 ml of the resulting solution was added to 301 mg of 3β-methoxy-5β,6β-methylenestr-9-en-17-one. The resulting solution was heated under reflux for 22 hr. The product (212 mg) was isolated by ether extraction in the usual manner and eluted through a column of 12 g of alumina to yield 191 mg of 3β-methoxy-5β,6β-methylenestr-9-en-17-one. The infrared spectrum of this material was identical with that of the starting material.

Control on the Stability of 3β-Methoxy-19-hydroxyandrost-5-en-17-one (Ia).—A solution of 403 mg of 3β-methoxy-19-hydroxyandrost-5-en-17-one, 25 ml of acetone, and 4.65 ml of a solution prepared from 2.5 ml of concentrated sulfuric acid and 60 ml of water was heated under reflux for 3 hr. The solution was then diluted with 25 ml of water and the major portion of the acetone was evaporated under reduced pressure. The product was isolated by ether extraction in the usual manner to yield 403 mg of a white crystlline solid, mp 146–148°, undepressed on admixture with starting material. The infrared spectrum of the product was identical with that of starting material.

Acetylation of Alcohols.—The procedure employed for the acetylation of the alcohols in this work is illustrated by the preparation of 3β-methoxy-6α,17β-diacetoxy-5β,19-cycloandrostane (XIIIb).

The diol (83 mg) was dissolved in 4 ml of pyridine, 1.5 ml of acetic anhyride was added, and the resulting solution was allowed to stand overnight at room temperature. The product was isolated by ether extraction.

Purifications for analyses were by crystallization or chromatography, depending on whether the product was a solid or an oil. Pertinent physical data for the acetates follow: 3β-methoxy-6β,-17β-diacetoxy-5β,19-cycloandrostane (XIIb), oil, $[\alpha]^{24}D$ +33°, $\tilde{\nu}_{max}$ 1722 and 1250 cm^{-1} (*Anal.* Calcd for $C_{24}H_{36}O_5$: C, 71.25; H, 8.97. Found: C, 71.53; H, 8.78.); 3β-methoxy-6α,17β-diacetoxy-5β,19-cycloandrostane (XIIIb), mp 145–152°, $[\alpha]^{24}D$ +24°, $\tilde{\nu}_{max}$ 1722 and 1248 cm^{-1} (*Anal.* Calcd for $C_{24}H_{36}O_5$: C, 71.25; H, 8.97. Found: C, 71.46; H, 8.65.); 3β-methoxy-7β-acetoxy-B-homoestr-5(10)-en-17-one (IIIb), oil, $[\alpha]^{28}D$ +26°, $\tilde{\nu}_{max}$ 1723, 1248, and 1088 cm^{-1} ($CHCl_3$) (*Anal.* Calcd for $C_{22}H_{32}O_4$: C, 73.29; H, 8.92. Found: C, 73.04; H, 8.92.).

Acknowledgment.—The author wishes to thank Drs. Wayne Cole, Leslie A. Freiberg, and Paul Kurath for many helpful discussions of this work. Thanks are due Dr. R. Mattoon and Mrs. Ruth Stanaszek for the nmr spectra, Mr. W. Washburn and associates for the infrared spectra, Mr. O. Kolsto and co-workers for the analyses, and Mr. V. Papendick for the ultraviolet spectra.