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HOMOALLYLIC REARRANGEMENTS OF 19-SUBSTITUTED STEROIDS

Jack Tadanier and Wayne Cole

Organic Chemistry Department, Research Division,

Abbott Laboratories, North Chicago, Illinois

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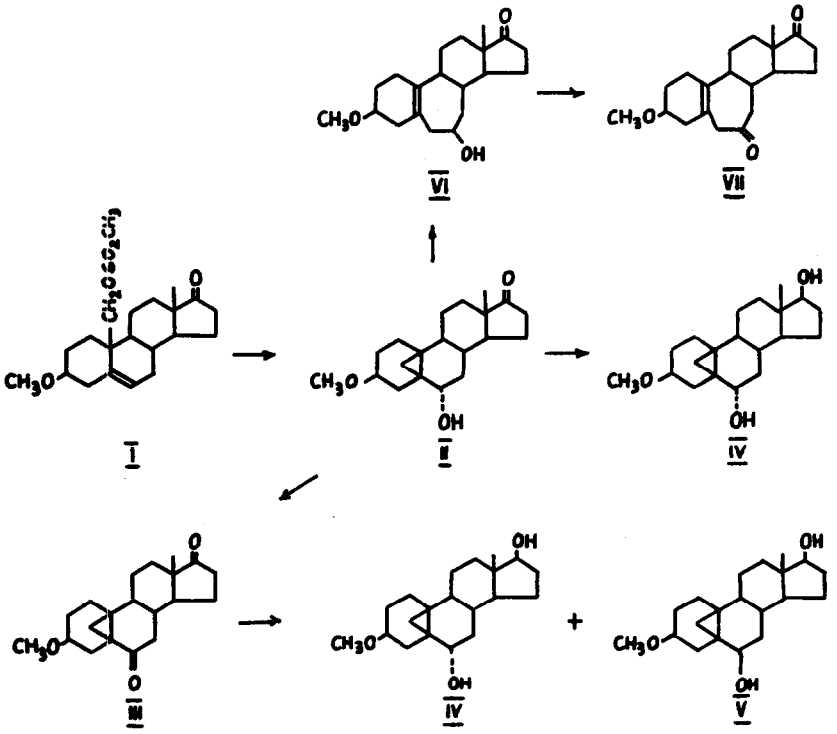
Considerable insight into the steric and electronic requirements for homoallylic rearrangement has been achieved by studies of the solvolysis of Δ^5-3-substituted steroids[1] and more recently $\Delta^{5(10)}$-substituted steroids.[2] The present report concerns the occurrence of homoallylic rearrangement during buffered hydrolysis of Δ^5-19-substituted steroids to form 6-substituted-5β,19-cyclosteroids,[3] and rearrangement of the latter by acid-catalyzed hydrolysis to $\Delta^{5(10)}$-B-homosteroids.

Hydrolysis of the methanesulfonate (I) of 3β-methoxy-19-hydroxyandrost-5-en-17-one[4] in aqueous acetone in the presence of potassium acetate buffer, followed by basic hydrolysis of the crude acetate-containing product, led to the isolation in 60% yield of 3β-methoxy-6α-hydroxy-5β,19-cycloandrostan-17-one (II),[5] m.p. 105-106°, $[\alpha]_D^{27}$ + 126°, $\tilde{\nu}_{max}$ 3599, 1727, 1084 cm^{-1} ($CHCl_3$), 3609 cm^{-1}, and cyclopropyl absorption[6] at 3050 cm^{-1} (CCl_4).

Oxidation of II with chromic anhydride in pyridine led to an essentially quantitative yield of 3β-methoxy-5β,19-cycloandrostane-6,17-dione (III), m.p. 138-139°, $[\alpha]_D^{27}$ + 13°, $\tilde{\nu}_{max}$ 1736, 1672, 1097 cm^{-1} and cyclopropyl absorptions[6] at 3009 and 3072 cm^{-1} (CCl_4), λ_{max} 210 mμ (ε 4230).



Sodium borohydride reduction of the hydroxyketone (II) in aqueous methanol gave 3β-methoxy-5β,19-cycloandrostane-6α,17β-diol (IV) in essentially quantitative yield, m.p. 190-192°, $[\alpha]_D^{28}$ + 47°, $\tilde{\nu}_{max}$ 3604 and 1091 cm^{-1} ($CHCl_3$).

Sodium borohydride reduction of the dione (III) in aqueous methanol yielded a mixture of diols. Fractional crystallization of this product from acetone-petroleum ether yielded 28% of 3β-methoxy-5β,19-cycloandrostane-6α,17β-diol (IV), m.p. 189-192°, identical with the diol described above, and 37% of 3β-methoxy-5β,19-cycloandrostane-6β,17β-diol (V), m.p. 135-139°, $[\alpha]_D^{28}$ + 11°, $\tilde{\nu}_{max}$ 3602 and 1088 cm^{-1} ($CHCl_3$).

Thin layer chromatography of the epimers, IV and V, on silica gel using 1:3 benzene-ethyl acetate eluent showed the 6β-ol (V) to be the more mobile.

Treatment of 3β-methoxy-6α-hydroxy-5β,19-cycloandrostan-17-one (II) with 0.5 N sulfuric acid in 4:1 acetone-water solution for two hours under reflux led to the isolation in 75% yield of an isomeric secondary alcohol, m.p. 116-118°, $[\alpha]_D^{25}$ + 50.8°, $\tilde{\nu}_{max}$ 3596, 1725, and 1088 cm^{-1} ($CHCl_3$); 3612, 3480 cm^{-1} (0.0025 M CCl_4), no cyclopropyl absorption; ϵ 4700 at 210 mμ indicating the presence of a carbon-carbon double bond. N.m.r. showed no vinyl proton absorption. This product has been tentatively identified as 3β-methoxy-7β-hydroxy-B-homoestr-5(10)-en-17-one (VI) on the basis of the evidence cited below. This rearrangement (II to VI) of a bicyclo [4.1.0] heptane to a cycloheptene system is analogous to the rearrangement, under acidic conditions, of thujopsene to the sesquiterpene alcohol widdrol, described by Dauben and Ashcraft.(7)

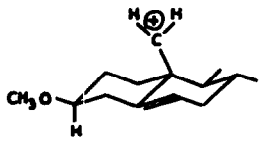
Acetylation of VI with acetic anhydride in pyridine at room temperature gave the acetate as an oil, $[\alpha]_D^{28}$ + 26°, $\tilde{\nu}_{max}$ 1723, 1248, and 1088 cm^{-1} ($CHCl_3$).

Oxidation of VI with chromic anhydride in pyridine at room temperature gave a 46% yield of a non-conjugated, unsaturated diketone, m.p. 150-152°, $[\alpha]_D^{28}$ - 112°, $\tilde{\nu}_{max}$ 1740, 1701, and 1092 cm^{-1} (CCl_4); no cyclopropyl absorption; λ_{max} 287 mμ (ϵ 387). The n.m.r. spectrum showed no vinyl proton absorption. An absorption (2H) was present at 7.02τ, indicative of a methylene group flanked by a carbonyl and a double bond (-C=C-CH_2-CO-).(8,9) The spectral data are consistent with the tentative assignment of structure VII: 3β-methoxy-B-homoestr-5(10)-ene-7,17-dione.(9)

The product recovered after refluxing VII for 1 hr. under nitrogen in 2% methanolic potassium hydroxide solution showed the original carbonyl absorptions in the infrared. The ultraviolet spectrum showed no evidence of conjugated ketone. Reluctance towards conjugation has been observed with the β,γ-unsaturated

Δ^{4a}-3-keto-A-homosteroids.[9] The additional resistance toward conjugation in the present case is presumably due to the position of the $\Delta^{5(10)}$-double bond endocyclic to both rings A and B.[10]

The rearrangements of I to II and II to VI suggest that, as in other types of i-steroid rearrangement,[1] a non-classical, homoallylic cation (or cations) is involved.[11] The configurations at C-6 of the 5β,19-cyclo derivatives as well as the configuration at C-7 of the B-homosteroid, VII, are at present based largely on stereoelectronic arguments. Solvolyses of I and II may lead to a non-classical ion which may be described as a resonance hybrid of the canonical structures 1-5. Alternately, there may be an equilibrium between two non-classical cations, the first a resonance hybrid of structures 1-3 leading to



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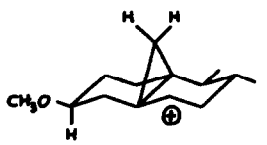

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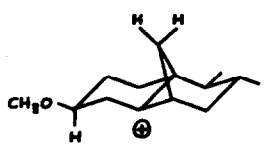

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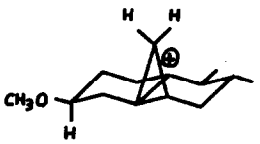

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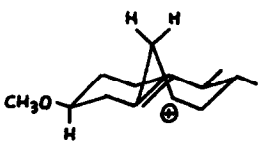

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the 6α-hydroxy-5β,19-cyclosteroid, and the second, a resonance hybrid of structures 4 and 5, leading to the B-homosteroid.[12] In either case, formation of the 5β,19-cyclo derivative from a cation, with breaking of the partial bond between C-6 and C-19 (kinetic control) should occur by α-attack of the incoming nucleophile, while formation of the B-homosteroid, in which

the partial bond between C-5 and C-6 is broken (thermodynamic control) should occur by β-attack of the nucleophile.

Both optical rotations and chromatographic mobilities of the 6α- and 6β-hydroxy-5β,19-cyclosteroids IV and V, are in the same order as those of the 6α- and 6β-hydroxy-3α,5α-cyclosteroids.[13] The n.m.r. spectral data (Table I) thus far obtained, however, are inconclusive with regard to the configurations at C-6. It has been reported that a hydroxyl group effects a long-range, paramagnetic shift of the absorption of a neighboring proton[2b,14] and that a diamagnetic shift of comparable magnitude results when the alcohol is acetylated.[14] In the n.m.r. spectra of the 6-hydroxy-5β,19-cyclosteroids II and IV, which have their stereochemistry at C-6 determined in the solvolysis reaction, one low-field cyclopropyl proton absorption occurred near 9.15 τ (Table I). If the chemical shift of this proton were the result of a paramagnetic interaction of a 6β-hydroxyl group with the cyclopropyl proton lying over the B-ring, a diamagnetic shift would be expected to occur on acetylation. Although limitations in the accuracy of measurement of the areas of the peaks of the observable high-field cyclopropyl proton doublets prevented exact calculation of the chemical shifts of the low-field doublets, it was clear the acetylation of IV caused no appreciable shifts in either the high or low field cyclopropyl proton absorptions. It is anticipated that the n.m.r. spectrum of 3β-methoxy-5β,19-cycloandrostan-17-one will contribute to an understanding of the factors which influence the chemical shifts of the C-19 cyclopropyl protons.

The narrow absorption bands ($W_{1/2}$, 6 c.p.s.) of the C-6 protons of II, IV and IV-diacetate are indicative of equatorial protons, while the broad band ($W_{1/2}$, 19 c.p.s.) of the C-6 proton of V-diacetate is indicative of an axial proton.[2b,15] Dreiding models indicate that the B-rings of 5β,19-cyclosteroids may exist in a half-chair form with 6β- and 7α-axial bonds or in a boat form with 6β- and 7α-equatorial bonds. If the criterion of absorption band width is valid in this system,[16] and the confirgurations at C-6 are

TABLE I[a]

A. 5β,19-Cyclosteroids

Structure	C-6-H		17α-H[b]		18-CH_3[b]	19-CH_2-	
	τ	$W_{1/2}$	τ	$W_{1/2}$	τ	τ	J
II	5.83	6.8	---	---	9.13	9.15[c], 9.65	5.1
IV	5.92	6.0	6.36	16	9.27	9.20[c], 9.70	5.0
IV-diacetate	4.86	6.3	5.36	18	9.20	9.14[c], 9.64	5.3
V	(6.08-6.58)[d]	---	(6.08-6.58)[d]	---	9.28	9.46, 9.56	6.4
V-diacetate	4.97	19	5.37	13	9.24	9.34, 9.53	5.2

B. 8-Homosteroids

Structure	C-7-H		C-6-CH_2		18-CH_3
	τ	$W_{1/2}$	τ	$W_{1/2}$	τ
VI	5.92	14	---	---	9.08
VI-acetate	4.88	15	---	---	9.08
VII	---	---	7.02	3.4	9.10

(a) All spectra were determined in deuteriochloroform at 60 m.c. using a Varian A-60 spectrometer. Chemical shifts were determined using tetramethylsilane as an internal standard and are reported in τ-units. Coupling constants (J) and band widths at half height ($W_{1/2}$) are reported in c.p.s. (b) The chemical shifts of the 17α-protons and the 18-methyl protons are in good agreement with those of testosterone (6.33 and 9.22τ) determined in these laboratories and testosterone acetate (5.38 and 9.20τ) reported by N. S. Bhacca, L. F. Johnson and J. N. Shooler in the "N.M.R. Spectra Catalog", Varian Associates, 1962, Spectrum No. 353. (c) Estimated. Limitations in the accuracy of measurement of the intensities of the peaks of the high-field doublets prevented exact calculation. (d) Broad overlapping absorptions of C-6 and C-17 protons.

those assigned on the basis of the stereoelectronic arguments stated above, the B-rings of the 5β,19-cyclosteroids, in solution, must resemble the boat form. If the B-rings do have the half-chair conformation, the configurational assignments, made above, must be reversed.

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