Retropinacol Rearrangement of 1α-Hydroxy Steroids. A New Route to 1β-Methyl 19-Norsteroids

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Received June 8, 1965

Treatment of 1α-hydroxy-5α-androstane-3,17-dione with 2-chloro-1,1,2-trifluoroethyldiethylamine leads to a retropinacol rearrangement of the C-19 methyl group and affords Δ^4-, $\Delta^{5(10)}$-, and Δ^9-1β-methylestrene 3-ketones.

Until very recently[2] no 1-fluoro steroids had been prepared in spite of substantial synthesis activity which led to fluoro steroids substituted at most other nuclear positions. In an attempt to prepare some 1-fluoro steroids *via* the action of 2-chloro-1,1,2-trifluoroethyldiethylamine[3] on 1α-hydroxy-5α-androstane-3,17-dione (V), we obtained in approximately equal amounts, two isomeric ($C_{19}H_{26}O_2$) nonfluorinated diketones VI and VII and trace amounts of a third isomer VIII whose nature as rearranged products was recognized by their characteristic proton n.m.r. spectra.[4] The present study suggests the structure of the rearranged products as 1β-methyl 19-nor-3-ketones and thus offers a fourth major synthesis route to nonaromatic 1-methyl steroids, along with metal–ammonia reductions of dienone phenol rearrangement products,[5] addition of methyl Grignard reagent to Δ^1-3-ketones,[6] and addition of diazomethane to Δ^1-3-ketones with subsequent catalytic reduction.[7]

Synthesis of the requisite starting material proceeded directly from the 1α,2α-epoxide II *via* the 3,17-bis ketal III stereoselectively to the 1α-hydroxy 3,17-bis ketal IV, from which the known 1α-hydroxy-5α-androstane-3,17-dione (V)[8] was obtained (Scheme I). Alternatively, the bromohydrin IXa, obtained by the action of N-bromoacetamide on I, was reduced catalytically to give V, though a poorer over-all yield than the synthesis of V *via* the epoxide.

Separation of the major isomeric products VI and VII was capricious. In an initial experiment VI crystallized spontaneously from VII after chromatography, but repetition on a larger scale led to inseparable mixtures even after multiple chromatography. Treatment of VI with acid led to the third isomeric diketone VIII, which was recognized as a Δ^4-3-ketone by spectral means (ultraviolet, infrared, and proton spectra). Isomer VII was stable to acid treatment. Acid isomerization of VI in mixtures of VI and VII gave mixtures of VII and VIII which were readily separated, thus affording a source of the Δ^4-3-ketone VIII and the isomeric VII.

The acid isomerization of VI to the Δ^4-3-ketone VIII suggested a $\Delta^{5(10)}$-3-ketone structure for VI, which was supported by a broad two-proton resonance at 2.73 p.p.m.[9] characteristic of the two allylic C-4 protons in $\Delta^{5(10)}$-3-ketone systems.[10]

The C-19 methyl proton resonance initially present in V was missing in spectra of VI, VII, and VIII; yet, a new three-proton doublet in the 1.02–1.03-p.p.m. region (J = 5–6.5 c.p.s.) appeared in spectra of the isomers. These spectral data suggested that the tertiary C-19 methyl group of V was now a secondary methyl group in VI, VII, and VIII. Since the usual retropinacol rearrangement in hydroxy steroids proceeds by a simple 1,2 migration of the methyl group, the isomers VI and VII were formulated as 1-methyl 19-norsteroids. The presence of tetrasubstituted unsaturation in VI and VII was indicated by elemental analysis, the previously mentioned proton resonance data for the C-4 protons in VI, and the absence of any vinyl proton signals. Selenium dioxide dehydrogenation of VIII led to 1-methylestrone (X), thus establishing the 1-methyl structure for VI and VIII (assuming no further methyl migration), and by analogy, a 1-methyl structure is suggested for VII.

The configuration of the 1-methyl group in VIII is indicated as 1β, since VIII is not identical with the known 1α-methylestr-4-ene-3,17-dione.[5a,12] Mechanistic arguments of β-face migration of the methyl

(1) To whom requests for reprints should be addressed.

(2) A. D. Cross and A. Bowers, U. S. Patent 3,127,429 (March 31, 1964); D. F. Morrow and M. E. Butler, *J. Org. Chem.*, **29**, 1893 (1964).

(3) For recent use of this reagent for preparation of other fluoro steroids, see (a) D. E. Ayer, *Tetrahedron Letters*, **No. 23**, 1065 (1962); U. S. Patents 3,056,807 and 3,056,808 (Oct. 2, 1962); *J. Med. Chem.*, **6**, 608 (1963); (b) L. H. Knox, E. Velarde, S. Berger, D. Cuadriello, and A. D. Cross, *Tetrahedron Letters*, **No. 26**, 1249 (1962); (c) L. H. Knox, E. Velarde, and A. D. Cross, *J. Am. Chem. Soc.*, **85**, 2533 (1963); (d) L. H. Knox, E. Velarde, S. Berger, D. Cuadriello, and A. D. Cross, *J. Org. Chem.*, **29**, 2187 (1964).

(4) Rearrangements of the Wagner–Meerwein type have been observed with this reagent in other steroid reactions.[3b,3c]

(5) (a) H. J. Ringold, G. Rosenkranz, and F. Sondheimer, *J. Am. Chem. Soc.*, **78**, 2477 (1956); (b) C. Djerassi, A. E. Lippman, and J. Grossman, *ibid.*, **78**, 2479 (1956); (c) J. A. Edwards, P. Crabbé, and A. Bowers, *ibid.*, **85**, 3313 (1963); (d) D. D. Evans, D. E. Evans, and R. W. J. Williams, *J. Chem. Soc.*, 1184 (1964).

(6) (a) H. Mori, *Chem. Pharm. Bull.* (Tokyo), **10**, 386 (1962); (b) D. Bertin and J. Perronnet, *Compt. rend.*, **257**, 1946 (1963); (c) R. Wiechert, U. Kerb, and K. Kieslich, *Chem. Ber.*, **96**, 2765 (1963); (d) W. J. Wechter, *J. Org. Chem.*, **29**, 163 (1964); (e) D. Bertin and J. Perronnet, *Bull. soc. chim. France*, 2782 (1964).

(7) R. Wiechert and E. Kaspar, *Chem. Ber.*, **93**, 1710 (1960); A. Popper and R. Wiechert, *Arzneimittel-Forsch.*, **12**, 213 (1962).

(8) R. M. Dodson, A. H. Goldkamp, and R. D. Muir, *J. Am. Chem. Soc.*, **82**, 4026 (1960).

(9) Six known $\Delta^{5(10)}$-3-ketones exhibited broad two-proton signals in the range 2.70–2.77 p.p.m.

(10) The $\Delta^{5(10)}$ double bond was also demonstrated in a microtest involving bromination–dehydrobromination to give an uncharacterized dienone, isolated from thin layer chromatoplates, with λ_{max} 303 mμ (ε 15,000), 220–240 mμ (ε 4300) (plateau), spectra typical of steroidal $\Delta^{4,9}$-3-ketones.[11]

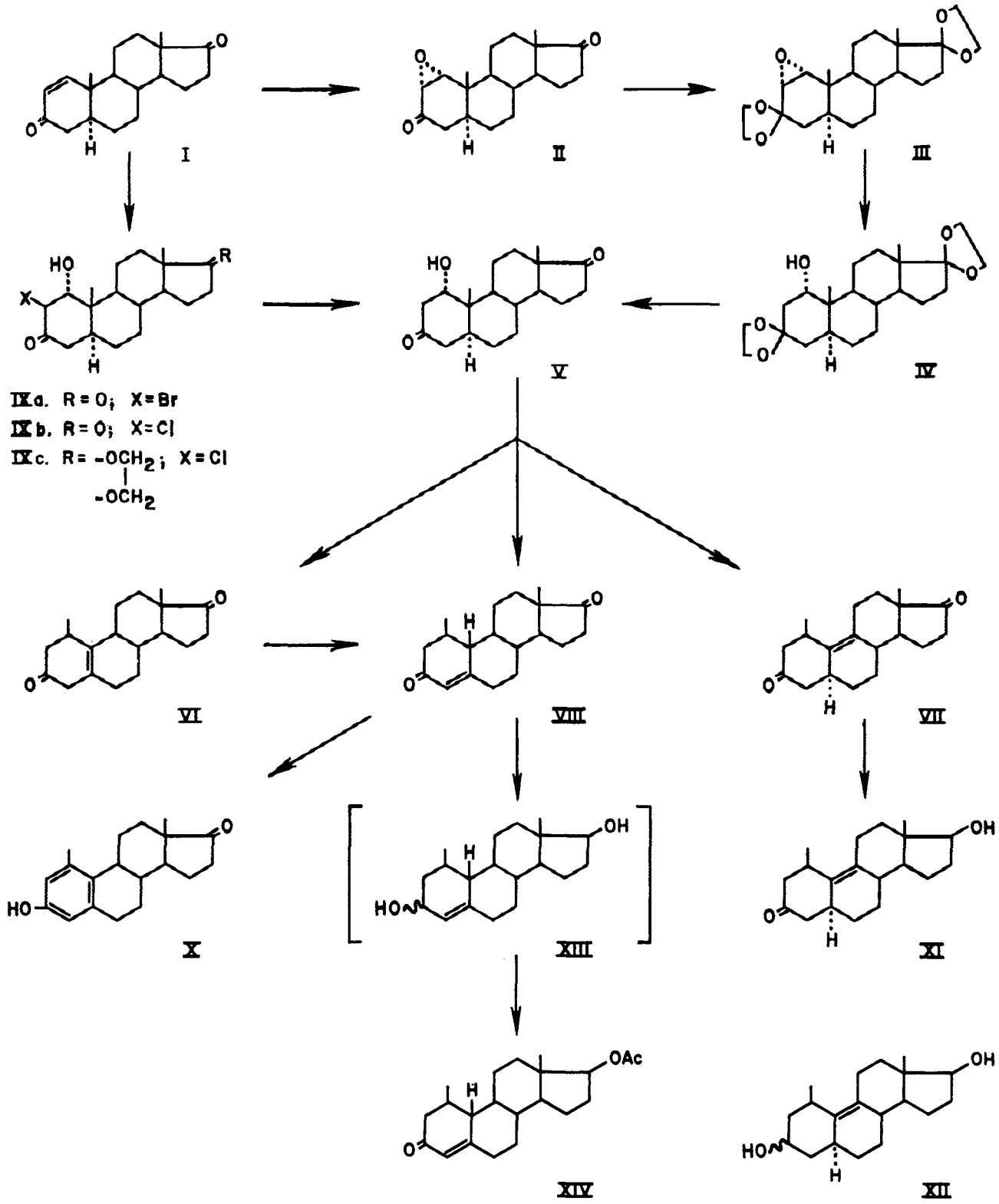
(11) M. Perelman, E. Farkas, E. J. Fornefeld, R. J. Kraay, and R. T. Rapala, *J. Am. Chem. Soc.*, **82**, 2402 (1960); J. H. Fried, T. S. Bry, A. E. Oberster, R. E. Beyler, T. B. Windholz, J. Hannah, L. H. Sarett, and S. L. Steelman, *ibid.*, **83**, 4663 (1961).

(12) Nonidentity of VIII with 1α-methylestr-4-ene-3,17-dione could also arise from isomerization of VI to a 1ξ-methyl 10α-Δ^4-3-ketone. Such unprecedented 10α steroid formation would require that VIII have a more negative specific rotation, since Δ[M]D values for 10α isomerization in Δ^4-3-ketones range from −713 to −1032.[13] The 10α structure is also ruled out on the basis of optical rotatory dispersion data (Figure 1).[13a]

(13) K. Heusler and J. Kalvoda, *Helv. Chim. Acta*, **46**, 2732 (1963).

(13a) NOTE ADDED IN PROOF.—Dr. Eugene Farkas, Lilly Research Laboratories, informs us in private communication of his recent synthesis of 10α-19-nortestosterone derivatives. Optical rotatory dispersion spectra of such 10α-19-nor compounds are virtually identical with the corrected curve of R. Wenger, H. Dutler, H. Wehrli, K. Schaffner, and O. Jeger [*Helv. Chim. Acta*, **45**, 2420 (1962); **46**, 1096 (1963)] for 10α-testosterone. In addition the C-18 protons of 10α-19-nortestosterone derivatives are shielded relative to C-18 protons of the analogous 19-nortestosterone. Comparison of these data with those of VIII definitively eliminate 10α structures for VIII.

SCHEME I



group in retropinacol rearrangements of steroids, together with molecular rotational increments (Table I) also support the 1β-methyl formulation.[14] The 1β-methylΔ⁴- 3-ketone structure of VIII is fully established, however, by these considerations taken with the optical rotatory dispersion spectrum (Figure 1). The dispersion curve of VIII is very similar to published curves of 1β-methyl-19-norprogesterone but decidedly

(14) Note that the $\Delta[M]_D^{1\beta\text{-methyl}}$ values depend on the exact nature of the A ring. 1β-Methyl Δ⁴-3-ketones have strong negative increments (−530 to −407) whereas saturated A-ring 1β-methyl 3-ketones have moderate positive increments (+106 to +271). These differences undoubtedly are consequences of conformational changes necessitated by interactions between the 1β-methyl group and the C-11 methylene protons.[15] The $\Delta^{5(10)}$-3-ketone, VI, exhibits a rotational increment typical of the saturated A-ring series rather than of the Δ⁴-3-ketone class.

(15) (a) C. Djerassi, R. Riniker, and B. Riniker, *J. Am. Chem. Soc.*, **78**, 6377 (1956); (b) C. Djerassi, R. Records, E. Brunnenberg, K. Mislow, and A. Moscowitz, *ibid.*, **84**, 870 (1962); (c) K. Mislow, *Ann. N. Y. Acad. Sci.*, **93**, 459 (1962); (d) C. Djerassi and W. Klyne, *Proc. Natl. Acad. Sci. U. S.*, **48**, 1093 (1962).

TABLE I

MOLECULAR ROTATIONAL DATA FOR 1-METHYL STEROIDS[a]

Steroid	$[\alpha]_D$, degrees	$[M]_D$	$\Delta[M]_D^{1\text{-methyl}}$
1α-Methyl Series			
1α-Methylestr-4-ene-3,17-dione[b]	+132	+378	+2[c]
17β-Hydroxy-1α-methylestr-4-en-3-one[b]	+43	+124	−27[c]
1α-Methyl-19-norpregn-4-ene-3,20-dione[d]	+88	+276	−166
17α-Hydroxy-1α-methyl-19-norpregn-4-ene-3,20-dione[d]	+26	+86	−44[e]
11β,17α,21-Trihydroxy-1α-methylpregn-4-ene-3,20-dione[f]	+182	+685	+88
21-Acetoxy-11β,17α-dihydroxy-1α-methylpregn-4-ene-3,20-dione[f]	+196	+820	+219
17α,21-Dihydroxy-1α-methylpregn-4-ene-3,11,20-trione[f]	+176.3	+660	−103
21-Acetoxy-17α-hydroxy-1α-methylpregn-4-ene-3,20-dione[f]	+154	+620	+48
21-Acetoxy-17α-hydroxy-1α-methylpregn-4-ene-3,11,20-trione[f]	+213	+885	−89
1α-Methylcholest-4-en-3-one[g]	+121	+482	+144
17β-Hydroxy-1α-methylandrost-4-en-3-one[g]	+144	+436	+96
1α-Methyl-5α-estrane-3,17-dione[h]	+115	+331	−50[i]
17β-Hydroxy-1α-methyl-5α-estran-3-one[h]	+46	+133	−30[i]
17β-Acetoxy-1α-methyl-5α-estran-3-one[j]	+16.7	+58	−52
1α-Methyl-5α-cholestan-3-one[g]	+32	+127	−37
1α-Methyl-5β-cholestan-3-one[g]	+28	+110	−30
17β-Hydroxy-1α-methyl-5α-androstan-3-one[g,j]	+12	+37	−50
	+17.6	+54	−33
1β-Methyl Series			
1β-Methyl-19-norpregn-4-ene-3,20-dione[d]	+11	+35	−407
11β,17α,21-Trihydroxy-1β-methylpregn-4-ene-3,20-dione[k]	+25.5[l]	+96	−501
17α,21-Dihydroxy-1β-methylpregn-4-ene-3,11,20-trione[k]	+83.5[l]	+312	−451
17β-Hydroxy-1β-methyl-5α-androstan-3-one[j]	+117.8	+358	+271
17β-Acetoxy-1β-methyl-5α-androstan-3-one[m]	+68[n]	+216	+106
17β-Hydroxy-1β,17α-dimethyl-5α-androstan-3-one[o]	+85	+270	+235
1β-Methylestr-5(10)-ene-3,17-dione (VI)	+346.5	+991	+257[p]
1β-Methylestr-4-ene-3,17-dione (VIII)	−11.2	−32	−408[c]
1β-Methyl-17,20;20,21-bismethylenedioxypregn-4-ene-3,11-dione[q]	−48[l]	−200	−530[r]
11β-Hydroxy-1β-methyl-17,20;20,21-bismethylenedioxypregn-4-en-3-one[q]	−96[l]	−402	−507[s]

[a] Rotations are in chloroform except as noted. Specific rotations of parent steroids are taken as far as possible from J. P. Mathieu and A. Petit, "Pouvoir Rotatoire Naturel. I. Steroides," Masson & Cie., Paris, 1956. [b] Reference 5a. [c] Parent steroid rotation: A. L. Wilds and N. A. Nelson, *J. Am. Chem. Soc.*, **75**, 5366 (1953). [d] Reference 5b. [e] Parent steroid: A. Zaffaroni, H. J. Ringold, G. Rosenkranz, F. Sondheimer, G. H. Thomas, and C. Djerassi, *J. Am. Chem. Soc.*, **76**, 6210 (1954). [f] Reference 6c. [g] Reference 6a. [h] A. Bowers, H. J. Ringold, and E. Denot, *J. Am. Chem. Soc.*, **80**, 6115 (1958). [i] Parent steroid: R. E. Counsell, *Tetrahedron*, **15**, 202 (1961). [j] R. Wiechert, German Patent 1,122,944, (Feb. 1, 1962); *Chem. Abstr.*, **57**, 5994*i* (1962). [k] Reference 6b. [l] In dioxane. [m] From optical rotatory dispersion data: C. Djerassi, E. Lund, and A. A. Akhrem, *J. Am. Chem. Soc.*, **84**, 1249 (1962). [n] In methanol. [o] Parent steroid: H. Hagiwara, *Yakugaku Zasshi*, **80**, 1675 (1960). [p] Reference 6e. [q] R. Wiechert, private communication. [r] Parent steroid: P. F. Beal, R. W. Jackson, and J. E. Pike, *J. Org. Chem.*, **27**, 1752 (1962). [s] Parent steroid: R. E. Beyler, R. M. Moriarty, F. Hoffman, and L. H. Sarett, *J. Am. Chem. Soc.*, **80**, 1517 (1958).

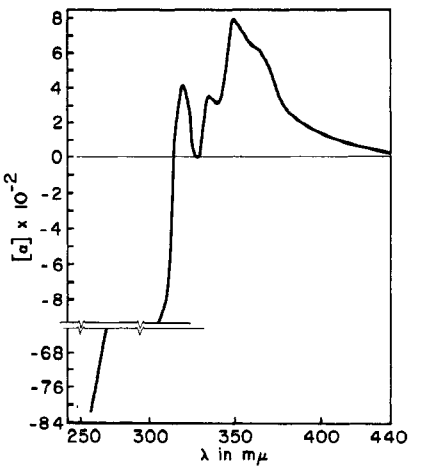


Figure 1.—Optical rotatory dispersion spectra of 1β-methylestr-4-ene-3,17-dione (VIII).

different from published curves for 1α-methyl-19-norprogesterone and 1α-methyl-19-nortestosterone.[15a] Although our dispersion data do not extend below 265 mμ, the short wave length portions agree in shape and magnitude with the published short wave length dispersion data for 1β-methyl-19-norprogesterone but differ substantially from published short wave length dispersion data for the 1α epimer.[15b,15c]

Since, from the proton resonance spectra, the second major isomer VII cannot be the 1(10)-double-bond isomer, the 9(10)-dehydro structure is assigned on the basis of Occam's razor. Reduction of the pyrrolidine enamine derivative of VII afforded the 17β-alcohol XI and as a minor by-product the 3ξ,17β-diol, XII.

Selective reduction of the 17-ketone group of VIII with sodium borohydride gave poor yields of the sought 17β-alcohol. Reduction of both 3- and 17-ketone groups, followed by selective dehydrogenation of the A-ring allylic alcohol, XIII, with dichlorodicyanoquinone, and acetylation, gave the 1β-methyl-19-nortestosterone acetate, XIV. Selective protection of the 3-ketone group by enamine or enol ether formation prior to reduction did not give a crystalline 17β-alcohol, but acetylation of the reduction product gave the crystalline acetate, XIV.

Attempts to cause rearrangement of V under other acidic conditions so as to obviate use of the fluorination reagent were to no avail. Phosphoric acid, acetic anhydride–acetic acid, hydrochloric acid, sulfuric acid, *p*-toluenesulfonic acid, etc., all failed to rearrange V and resulted in simple dehydration to I or to complex mixtures free from rearranged products.

For further attempts at synthesis of 1-fluoro derivatives with the same reagent, the bromohydrin IXa and chlorohydrins IXb and IXc, as well as the 1α-hydroxy bis ketal, IV, were treated with 2-chloro-1,1,2-trifluoroethyldiethylamine. No fluorination occurred, nor did rearrangement take place. With the halohydrins either no reaction was obtained (at reflux in methylene chloride) or dehydration occurred after longer times and at higher temperatures (up to 113 hr. at reflux in dioxane). The halohydrin bis ketal, IXc, was partially hydrolyzed, giving complex mixtures of 3- and 17-monoketones, halohydrin, and 2-chloro-Δ^1 derivatives. The 1α-hydroxy bis ketal, IV, was recovered unaltered from such conditions.

The n.m.r. spectrum of the 2β-chloro 3,17-bis ketal IXc requires comment. The 17-ethylene ketal methylene protons of IXc appear as a sharp singlet at 3.82 p.p.m. in the usual fashion.[16,17] However, the 3-ketal methylene protons, in distinction to those of the 3,17-bis ketal, IV and of 5α-androstane-3,17-dione bis ketal (sharp singlets), appear as an putative A_2B_2 pattern centered about 4.03 p.p.m. No attempt was made at a full analysis of the A_2B_2 pattern because of inadequate resolution and overlap of other proton resonance signals.

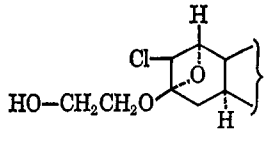
The 2β-chlorine atom in IXc would exert strong 1,3-diaxial interactions with the C-19 methyl group were the A ring in the chair form. In such a case the 2β-chlorine atom would not be sterically situated so as to offer equal shielding to two of the ethylene ketal protons to form an A_2B_2 pattern. However, in the A-ring boat conformation, the 2β-chlorine atom should give equal shielding to two of the 3-ketal methylene protons *cis* to the chlorine atom, thus permitting an A_2B_2 coupling pattern between these two protons and the other set of ketal methylene protons *trans* to the chlorine atom. On the basis of the observed A_2B_2 pattern, we suggest a boat conformation for ring A of the 2β-chloro ketal IXc.[19]

(16) Methylene protons of steroidal ethylene ketals appear at 3.8–4.1 p.p.m. as sharp singlets: *cf.* N. S. Bhacca and D. H. Williams, "Application of NMR Spectroscopy in Organic Chemistry," Holden-Day, Inc., San Francisco, Calif., 1964, pp. 103, 104.

(17) Steroidal ketal methylene proton resonances have been observed which are subject to asymmetric broadening[18a] or which are split into various multiplet patterns.[6d,16,18]

(18) (a) E. Caspi, T. A. Wittstruck, and D. M. Piatak, *J. Org. Chem.*, **27**, 3183 (1962); (b) S. Julia, H. Linarès, and P. Simon, *Bull. soc. chim. France*, 2471 (1963); (c) E. Caspi, H. Zajac, and T. W. Wittstruck, *J. Org. Chem.*, **29**, 640 (1964); (d) J. Tadanier, *ibid.*, **28**, 1744 (1963); (e) K. Heusler, J. Kalvoda, G. Anner, and A. Wettstein, *Helv. Chim. Acta*, **46**, 352 (1962).

(19) An alternate structure i could account for the A_2B_2 pattern in the proton spectra of IXc.[20] This structure can be rejected on the basis of



i

the high strain expected of a 1α,3α-epoxide ring and of the 1,3-diaxial interactions between the 2β-chlorine atom and the C-19 methyl group. Furthermore, the molecular rotational increment for IXc and its 3-ketone parent IXb ($\Delta[M]_D$ −298) agrees well with the increments for 5α-androstane-3,17-dione bisethylene ketal (−355) and for 1α-hydroxy-5α-androstane-3,17-dione bisethylene ketal (−319).

(20) The adjacent methylene protons of the mixed ketal i should have different magnetic environments. Structure i is analogous to the mixed ketals, 3,3-ethylenedioxy-11β,18;18,20-bisepoxy-20-(2′-hydroxyethoxy)-(18*R*)-pregn-5-ene and its O-acetate, which exhibit A_2B_2 and ABCD patterns for the mixed ketal protons.[21a] Other ethylene glycol derivatives having A_2B_2 coupling patterns include ethylene glycol monoesters of steroidal acids[21b] (mixed glycol diesters do not show A_2B_2 patterns[21c]), 20,21-bisethylene ketals,[18c] a glycol monoether of a steroidal enol,[21d] and in our unpublished work, 17,17-ethylenedioxy-3-methoxyestra-1,3,5(10)-trien-16-one and 17,17-ethylenedioxy-3-methoxyestra-1,3,5(10)-trien-16β-ol 16β-acetate.[22] Nonsteroidal ethylene ketals having A_2B_2 patterns are known.[21e,23]

(21) (a) J. Schmidlin and A. Wettstein, *Helv. Chim. Acta*, **46**, 2799 (1963); (b) R. F. Zürcher and J. Kalvoda, *ibid.*, **44**, 198 (1961); (c) M. Amorosa, L. Caglioti, G. Cainelli, H. Immer, J. Keller, H. Wehrli, M. L. Mihailović, K. Schaffner, D. Arigoni, and O. Jeger, *ibid.*, **45**, 2674 (1962); (d) R. D. Youssefyeh, *Tetrahedron Letters*, **No. 32**, 2161 (1964); (e) E. Caspi, T. A. Wittstruck, and D. M. Piatak, *J. Org. Chem.*, **27**, 3183 (1962).

(22) Prepared by Dr. J. F. Fisher of these laboratories, see G. C. Buzby, R. A. Edgren, J. F. Fisher, G. A. Hughes, R. C. Jones, K. Ledig, T. W. Pattison, R. Rees, H. Smith, L. L. Smith, D. M. Teller, and G. R. Wendt, *J. Med. Chem.*, **7**, 755 (1964).

(23) B. Mathiasson, *Acta Chem. Scand.*, **17**, 2133 (1963); G. R. H. Green, J. E. Page, and S. E. Staniforth, *J. Chem. Soc.*, 144 (1964).

(24) Melting points were taken on a calibrated Kofler block under microscopic magnification. Ultraviolet light absorption spectra were obtained on solutions in 95% ethanol. Infrared spectra were obtained on pressed potassium bromide disks. Optical rotation data were obtained on 1% solutions in chloroform. Proton n.m.r. spectra were obtained on a Varian Associates A-60 spectrometer on 10–15% solutions in deuteriochloroform. Chemical shifts (δ) are expressed in parts per million downfield from an internal tetramethylsilane reference. Resonances are singlets except where higher multiplicity is mentioned.

(25) All preparations were shown to be homogeneous on thin layer chromatograms.[26] Detection of the several 1-dehydro-, 1-oxy-, and 1-methyl steroids was best accomplished with a 20% methanolic phosphoric acid spray. The chromatoplates were then heated at 100° for 15–20 min. to bring out maximum intensities. The several androstane derivatives gave violet colors whereas the 1β-methylestrane derivatives gave blue colors. 1-Methylestrone gave an ochre color. Some relative mobilities (R_f) using the solvent system hexane–ethyl acetate (1:1) are: I, 0.40; II, 0.53; III, 0.31; IV, 0.26; V, 0.18; VI and VII, 0.53; VIII, 0.31; X, 0.60.

(26) L. L. Smith and T. Foell, *J. Chromatog.*, **9**, 339 (1962).

(27) W. M. Hoehn, *J. Org. Chem.*, **23**, 929 (1958).

(28) The 1α-hydroxyl proton doublet becomes a sharp singlet in acidified deuteriochloroform solutions.

(29) Dodson, *et al.*,[8] report m.p. 204–206°, $[\alpha]_D$ +114°, and m.p. 211–213.5°, $[\alpha]_D$ +110°, for V derived from fermentation sources.

Experimental Section[24,25]

1α,2α-Epoxy-5α-androstane-3,17-dione 3,3;17,17-Bisethylene Ketal (III).—A mixture of 4 g. of 1α,2α-epoxy-5α-androstane-3,17-dione (II),[27] 200 ml. of benzene, 9.2 ml. of ethylene glycol, and 40 mg. of *p*-toluenesulfonic acid monohydrate was refluxed 5 hr. with continuous removal of water with a Dean–Stark apparatus. The cooled mixture was washed with dilute alkali and with water, the benzene layer was dried and concentrated under vacuum, and the precipitated solids were washed with methanol and dried, yielding 4.32 g., m.p. 150–155°, $[\alpha]_D$ −17.4°.

Anal. Calcd. for $C_{23}H_{34}O_5$: C, 70.74; H, 8.78. Found: C, 70.88; H, 8.66.

1α-Hydroxy-5α-androstane-3,17-dione 3,3;17,17-Bisethylene Ketal (IV).—A solution of 1.0 g. of III in 50 ml. of dry ether was added over 30 min. to a stirred slurry of 500 mg. of lithium aluminum hydride in 50 ml. of dry ether. After adding 150 ml. of ether, the mixture was refluxed for 2.5 hr., and then 10 ml. of water was added dropwise. The ether layer was separated, dried over anhydrous sodium sulfate, and concentrated to incipient crystallization. The crystals, 590 mg., and 73 mg. of product recovered from the mother liquor, consisted of a mixture of two components by thin layer chromatography. One recrystallization from hot methanol gave 450 mg. of pure IV, homogeneous on thin layer chromatograms: m.p. 179–180°; $[\alpha]_D$ +7.1°; λ_{max}^{KBr} 2.86 μ, etc.; δ = 0.77 (C-19 protons), 0.83 (C-18 protons), 3.20 (doublet, J = 10 c.p.s., 1α-hydroxy proton[28]), 3.62 (multiplet, 1β-proton), 3.84 (17-ethylene ketal protons), and 3.93 p.p.m. (3-ethylene ketal protons).

Anal. Calcd. for $C_{23}H_{36}O_5$: C, 70.37; H, 9.24. Found: C, 70.31; H, 9.45.

1α-Hydroxy-5α-androstane-3,17-dione (V). A. From IV.—A solution of 1.4 g. of IV in 70 ml. of methanol and 35 ml. of 50% aqueous acetic acid was refluxed for 1 hr. The mixture was neutralized, and the methanol was removed under vacuum. The solution was extracted with chloroform; the chloroform extract was washed with brine and with water, dried over anhydrous magnesium sulfate, and evaporated under vacuum, giving an oil which was crystallized from benzene: 285 mg.; m.p. 206–207.5°; $[\alpha]_D$ +112°[29]; δ 0.87 (C-18 protons), 1.01 (C-19

protons), 3.02 (doublet, J = 3 c.p.s., 1α-hydroxyl proton), and 4.12 (doublet, J = 3 c.p.s., 1β-proton).

B. From IXa.—IXa (300 mg.) dissolved in 40 ml. of tetrahydrofuran–methanol (1:1) containing 60 μl. of glacial acetic acid and 88 mg. of sodium acetate was catalytically reduced with 100 mg. of prereduced 2% palladium on calcium carbonate and hydrogen. The calculated amount of hydrogen was absorbed after 30 min. The suspension was filtered, the filtrate was evaporated under vacuum, and the residue was taken up in chloroform. The chloroform solution was washed with water, dried, and evaporated under vacuum, yielding 130 mg. of crude V. Preparative thin layer chromatography using silica gel–starch bound plates developed with hexane–ethyl acetate (1:1) gave a single major product zone together with two minor, more mobile zones. Elution of the product zones with chloroform and recrystallization of the residue therefrom with benzene–cyclohexane afforded pure V, m.p. 203–207°, not depressed on admixture with V obtained from IV. Infrared and chromatographic comparisons also established identity of the two samples of V.

1β-Methylestr-5(10)-ene-3,17-dione (VI).—A solution of 2.2 g. of V in 25 ml. of methylene chloride and 2.2 ml. of 2-chloro-1,1,2-trifluoroethyldiethylamine was refluxed for 15 min., after which time thin layer chromatography indicated that no substrate remained. The solution was washed with water, with sodium bicarbonate solution, and with water again, dried over anhydrous sodium sulfate, and evaporated under vacuum to an oil. Thin layer chromatographic examination of the oil indicated the presence of a major product zone (blue color with phosphoric acid) and minor amounts of a more polar, ultraviolet light absorbing zone (blue color with phosphoric acid), together with a violet-colored zones associated with weak ultraviolet light absorption at the same R_f as I. The product mixture was chromatographed on 200 g. of silica gel (prepared in benzene). Elution with 5% ethyl acetate in benzene gave an oil which was crystallized from benzene to yield 463 mg. of VI, m.p. 136°. Recrystallization from benzene–hexane gave 257 mg. of pure VI: m.p. 139–140°; $[\alpha]_D$ +346.5°; λ_{max} no selective absorption; λ_{max}^{KBr} 5.75 and 5.81 μ, etc.; δ = 0.92 (C-18 protons), 1.03 (doublet, J = 5 c.p.s., 1β-methyl protons), and 2.73 p.p.m. (two C-4 protons).

Anal. Calcd. for $C_{19}H_{26}O_2$: C, 79.68; H, 9.15. Found: C, 79.71; H, 9.23.

From the benzene mother liquors from which crude V was crystallized there was recovered 261 mg. of crude VII, m.p. 125–130°, identical with fully characterized VII described later.

Continued elution of the silica gel column (from which mixed VI and VII were obtained) with 5% ethyl acetate in benzene afforded 44 mg. of impure I, m.p. 99–107°, λ_{max} 230 mμ (ε 6600), identified by thin layer chromatography and infrared spectra.

1β-Methylestr-4-ene-3,17-dione (VIII).—A solution of 150 mg. of 1:1 mixture of 1β-methyl isomers VI and VII in 4 ml. of methanol and 0.25 ml. of concentrated hydrochloride acid was stirred under nitrogen for 2 hr. The solution was neutralized with sodium bicarbonate, diluted with water, and extracted with chloroform. The chloroform extract was washed with water, dried over anhydrous magnesium sulfate, and evaporated under vacuum. The resultant oil was chromatographed on six thin layer chromatoplates using hexane–ethyl acetate (1:1). The more polar, ultraviolet light absorbing zone was eluted with acetone, the residue therefrom was recrystallized from acetone–hexane to give 53.0 mg. of the Δ^4-3-ketone, VIII: m.p. 148–149°; $[\alpha]_D$ −11.2°; λ_{max} 244 mμ (ε 15,640); λ_{max}^{KBr} 5.75, 6.02, and 6.16 μ, etc., δ = 0.92 (C-18 protons), 1.03 (doublet, J = 6.5 c.p.s., 1β-methyl protons), and 5.80 p.p.m. (C-4 vinyl proton).

Anal. Calcd. for $C_{19}H_{26}O_2$: C, 79.68; H, 9.15. Found: C, 79.52; H, 8.87.

Optical rotatory dispersion data for VIII in dioxane solution (c 0.0970 over the range 440–310 mμ and 0.0194 over the range 310–265 mμ) were as follows: $[\alpha]_{440}$ +33°, $[\alpha]_{363}$ +635° (inflection), $[\alpha]_{350}$ +795°, $[\alpha]_{341}$ +309°, $[\alpha]_{336}$ +367°, $[\alpha]_{329}$ 0°, $[\alpha]_{320}$ +420°, and $[\alpha]_{265}$ −8180°.

Repetition of the isomerization experiment with a pure sample of VI also gave the Δ^4-3-ketone, VIII.

1β-Methylestr-9-ene-3,17-dione (VII).—Elution of the more mobile zone from the thin layer chromatoplates (detection with phosphoric acid sprayed on a guide strip as a blue color) with acetone gave 41.1 mg. of VII, m.p. 124–126°. Recrystallization from aqueous methanol gave the pure sample: m.p. 124.5–125.0°; $[\alpha]_D$ +316°; λ_{max} no selective absorption; λ_{max}^{KBr} 5.74 and 5.80 μ, etc.; δ = 0.99 (C-18 protons) and 1.02 p.p.m. (doublet, J = 6.5 c.p.s., 1β-methyl protons).

Anal. Calcd. for $C_{19}H_{26}O_2$: C, 79.68; H, 9.15. Found: C, 79.28; H, 9.09.

17β-Hydroxy-1β-methylestr-9-en-3-one (XI).—A solution of 647 mg. of VII in 14 ml. of benzene was refluxed with 0.4 ml. of pyrrolidine and a crystal of p-toluenesulfonic acid monohydrate with continuous removal of water with a Dean–Stark apparatus. After 7.5 hr. the solvents were removed under vacuum, and the residue was crystallized from hexane–benzene, yielding 445 mg. of enamine. The product was dissolved in 10 ml. of benzene and added to a stirred suspension of 450 mg. of lithium aluminum hydride in 60 ml. of dry ether. The mixture was refluxed for 5 min., cooled, and diluted with water, and the solvents were removed under vacuum. The solids were filtered, dried, and dissolved in 10 ml. of 95% ethanol and refluxed 5 min. and evaporated under vacuum. Thin layer chromatography of the residue indicated that three components were present in the crude product. The solids were extracted with chloroform, the chloroform extract was washed with dilute hydrochloride acid and with water, dried over anhydrous magnesium sulfate, and evaporated under vacuum. The product was chromatographed on 40 g. of silica gel. Elution with ethyl acetate–hexane (1:9) gave a homogeneous product which was recrystallized from acetone–hexane to give 100 mg. of pure XI: m.p. 185–186°, $[\alpha]_D$ +226.8°, λ_{max}^{KBr} 2.90 and 5.85 μ, etc.

Anal. Calcd. for $C_{19}H_{28}O_2$: C, 79.12; H, 9.79. Found: C, 79.21; H, 9.76.

From the mother liquor an additional 50 mg. of product, m.p. 180–182°, was recovered.

1β-Methylestr-9-ene-3ξ,17β-diol (XII).—Continued elution of the silica gel column (from which XI was recovered) with ethyl acetate–hexane (1:9) yielded material which was crystallized from acetone–hexane: 34.3 mg.; m.p. 170–196°; λ_{max}^{KBr} 3.07 μ, etc.

Anal. Calcd. for $C_{19}H_{30}O_2 \cdot 0.5C_6H_{14}$: C, 79.22; H, 11.18. Found: C, 79.17; H, 11.15.

Extensive drying under vacuum at 64° did not remove the hexane of solvation.

Anal. Found: C, 79.99, 80.04; H, 10.97, 11.26.

17β-Acetoxy-1β-methylestr-4-en-3-one (XIV).—A solution of 250 mg. of VIII in 4 ml. of absolute ethanol containing 40 mg. of sodium borohydride (under nitrogen) was refluxed and stirred for 2 hr., after which time 0.3 ml. of 50% aqueous acetic acid was added, followed by water and chloroform. The chloroform layer was dried over anhydrous magnesium sulfate and evaporated under vacuum, and the solid product was dissolved in 3 ml. of dioxane and treated with 250 mg. of dichlorodicyanoquinone at room temperature for 16 hr. The reaction mixture was filtered, the solids were washed with methylene chloride, and the combined filtrate and washes were evaporated under vacuum. The crude product was dissolved in 50 ml. of methylene chloride, washed with water until neutral, dried over anhydrous magnesium sulfate, and evaporated under vacuum. The residue was dissolved in pyridine (3 ml.) and 1.0 ml. of acetic anhydride was added. The solution was evaporated under vacuum after 18 hr. and the product was chromatographed on 12 g. of silica gel. Elution with ethyl acetate–hexane (1:19) gave the 17β-acetate XIV, 108 mg., which was recrystallized from acetone–hexane: m.p. 129–131°; λ_{max} 246 mμ (ε 13,600); λ_{max}^{KBr} 5.77, 5.96, and 6.14 μ, etc.

Anal. Calcd. for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15. Found: C, 76.62; H, 9.37.

2β-Bromo-1α-hydroxy-5α-androstane-3,17-dione (IXa).—To a stirred solution of 3.00 g. of 5α-androst-1-ene-3,17-dione (I) in 50 ml. of dioxane containing 10 ml. of water and 1.1 ml. of 70% perchloric acid there was added 1.93 g. of N-bromoacetamide in 50 ml. of dioxane. The solution was stirred for 3 hr. and poured into 2 l. of ice–water containing 10 g. of sodium sulfite; the solids were filtered and dissolved in ether. The ether solution was washed with water, dried, and evaporated, and the solids thereby obtained were recrystallized from methanol, yielding 945 mg. of the pure bromohydrin IXa, homogeneous on thin layer chromatoplates developed with hexane–ethyl acetate (1:1): m.p. 228–236°; $[\alpha]_D$ +49.6°; λ_{max}^{KB} 3.00 and 5.80 μ, etc.; δ = 0.88 (C-18 protons), 1.12 (C-19 protons), 2.47 (doublet, J = 2.5 c.p.s., 1α-hydroxyl proton[30]), 4.15 (broad, 1β-proton), 5.02 p.p.m. (doublet, J = 2.5 c.p.s., 2α-proton).

(30) The 1α-hydroxyl proton is not observed in spectra obtained on pyridine solutions of IXa or in deuteriochloroform solutions equilibrated with deuterium oxide.

Anal. Calcd. for $C_{19}H_{27}BrO_3$: C, 59.53; H, 7.11; Br, 20.85. Found: C, 59.47; H, 7.34; Br, 20.7.

2β-Chloro-1α-hydroxy-5α-androstane-3,17-dione (IXb).—A solution of 5.00 g. of I in 50.0 ml. of dioxane was treated with 7.5 ml. of water, 0.80 ml. of 70% perchloric acid, and finally dropwise with 2.70 g. of N-chlorosuccinimide in 25 ml. of dioxane over 10 min. The mixture was stirred at room temperature for 3 hr., after which time 250 ml. of 10% aqueous sodium sulfite solution was added. Ice water (1000 ml.) was added and the solids were filtered and dried under vacuum at 64° for 2 hr., yielding 3.547 g. of product which was recrystallized several times from methanol in order to obtain 1.610 g. of pure material, homogeneous on thin layer chromatoplates developed with hexane–ethyl acetate (1:1): m.p. 218–222°; $[\alpha]D$ +81.2°; λ_{max}^{KBr} 3.01, 5.75, and 5.81 μ, etc.; δ = 0.80 (C-18 protons), 1.14 (C-19 protons), 2.52 (doublet, J = 2.5 c.p.s., 1α-hydroxyl proton[27]), 4.15 (multiplet, 1β-proton), and 4.84 p.p.m. (doublet, J = 2.5 c.p.s., 2α-proton).

Anal. Calcd. for $C_{19}H_{27}ClO_3$: C, 67.34; H, 8.03; Cl, 10.46. Found: C, 67.77; H, 7.94; Cl, 10.50.

2β-Chloro-1α-hydroxy-5α-androstane-3,17-dione 3,3;17,17-Bisethylene Ketal (IXc).—A mixture of 1.0 g. of IXb, 100 mg. of *p*-toluenesulfonic acid monohydrate, 20 ml. of ethylene glycol, and 125 ml. of benzene was refluxed with continuous removal of water for 13 hr. The cooled mixture was washed with aqueous sodium bicarbonate solution and with water; the benzene layer was dried over anhydrous magnesium sulfate and then evaporated. The residue was crystallized from methanol, yielding 760 mg. of product homogeneous on thin layer chromatoplates: m.p. 224–226°; $[\alpha]D$ −5.1°; λ_{max}^{KBr} 2.88 μ, etc.; δ = 0.84 (C-18 and C-19 protons), 3.06 (doublet, J = 7.5 c.p.s., 1α-hydroxyl proton), 3.68 (doublet, J = 3 c.p.s., 1β-proton), 3.82 (17-ethylene ketal protons), 4.03 (A_2B_2 multiplet, 3-ethylene ketal protons), and 4.28 p.p.m. (doublet, J = 3 c.p.s., 2α-proton).

Anal. Calcd. for $C_{23}H_{35}ClO_5$: C, 64.69; H, 8.26; Cl, 8.35. Found: C, 64.83; H, 8.16; Cl, 8.25.

3-Hydroxy-1-methylestra-1,3,5(10)-trien-17-one (X).—A solution of 50 mg. of VIII in 5 ml. of *t*-butyl alcohol and 0.25 ml. of glacial acetic acid (under nitrogen) was treated with 60 mg. of selenium dioxide, and the mixture was refluxed for 20 hr. The cooled mixture was diluted with ethyl acetate and filtered, and the residue from the evaporated filtrate was chromatographed on six 20 × 20 cm. silica gel thin layer chromatoplates using hexane–ethyl acetate (1:1). The more mobile component (ochre color with phosphoric acid) was eluted with methanol, concentrated, cooled, and diluted with hexane. The crystalline precipitate was filtered, m.p. 243–245°, and identified as 1-methylestrone by thin layer chromatographic and infrared spectral comparisons with authentic material. A second major component (red color with phosphoric acid), more polar than X, was eluted from the chromatoplates. Ultraviolet spectra of this material were essentially the same as spectra of X, but selenium analyses established that the preparation contained organic-bound selenium. This component was not investigated further.

Acknowledgment.—The authors thank Professor Kurt Mislow, New York University, for the optical rotatory dispersion data of VIII.

Studies Related to 2-Keto Steroids

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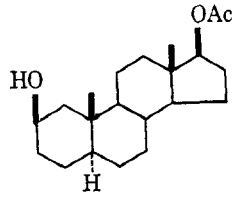
Received February 26, 1965

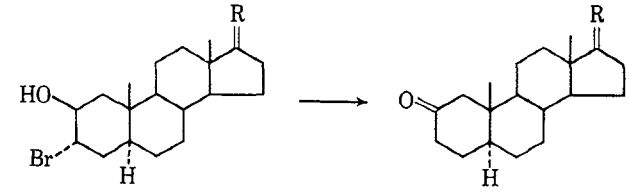
Catalytic debromination of certain steroidal bromohydrins produces ketones instead of the expected alcohols. The rearrangement of 2α-bromo-3-keto steroids to a mixture of 2- and 3-keto steroids has been reported earlier. Applicability of this reaction to certain other steroidal bromo ketones is reported. Several derivatives of 2-keto-androstanes are reported, including a pyrazole and an isoxazole.

A few years ago we desired some 2β(axial)-hydroxy steroids such as 5α-androstane-2β,17β-diol 17-acetate (**1**) for use in preparation of 2,19-oxides, a reaction which has since been reported.[1]



1

An attractive route to **1** appeared to lie through the debromination of 3α-bromo-5α-androstane-2β,17β-diol 17-acetate (**2**).[2] Debromination of this *trans*-diaxial bromohydrin in 95% ethanol with hydrogen in the presence of 30% palladium on strontium carbonate produced, surprisingly, 17β-hydroxy-5α-androstan-2-one acetate (**4**) in 59% yield. These same conditions transformed 3α-bromo-2β-hydroxy-5α-androstan-17-one (**3**)[2] into 5α-androstane-2,17-dione (**5**).[3] Gas

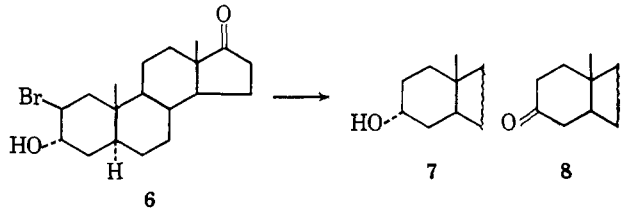


2, R = β-OAc, α-H
3, R = O

4, R = β-OAc, α-H
5, R = O

chromatography indicated that the yield of diketone in this latter reaction was 77%; the yield of purified ketone was 64%. A 4% yield of starting material (**3**) was isolated in pure form as its acetate by careful thick layer chromatography. It appeared that if any normal debromination occurred, the yield of 2β-hydroxy-5α-androstan-17-one was less than 5%.

Another *trans*-diaxial compound, 2β-bromo-3α-hydroxy-5α-androstan-17-one (**6**), was studied, this one with the positions of the hydroxyl and bromine functions simply reversed from those above. Normal de-



6 **7** **8**

(1) *Cf.* R. Kwok and M. E. Wolff, *J. Org. Chem.*, **28**, 423 (1963); K. Heusler, J. Kalvoda, P. Wieland, G. Anner, and A. Wettstein, *Helv. Chim. Acta*, **45**, 2575 (1962); P. N. Rao and J. C. Uroda, *Naturwissenschaften*, **50**, 548 (1963).

(2) P. D. Klimstra and R. E. Counsell, U. S. Patent 3,018,298 (Jan. 23, 1962).

(3) C. Djerassi, R. Yashin, and G. Rosenkranz, *J. Am. Chem. Soc.*, **72**, 5750 (1950).