Hydrogen Bromide Induced Anthrasteroid Rearrangements

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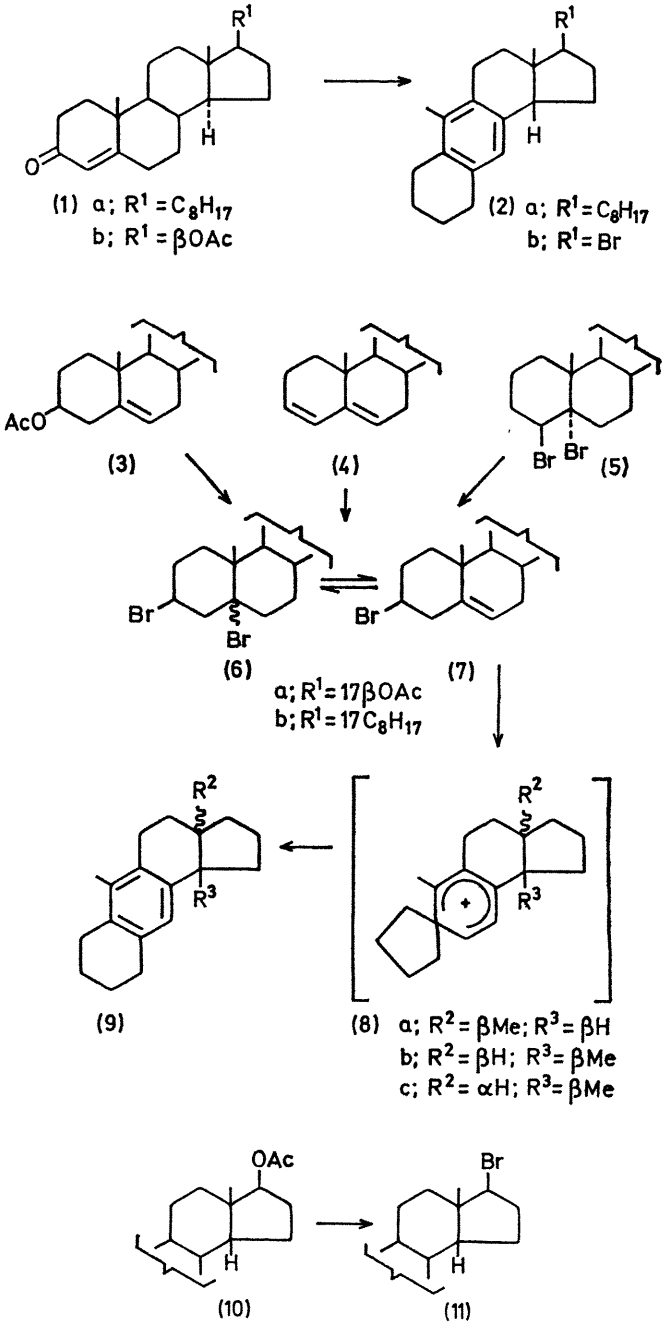
Summary 17β-Acetoxy-androstane derivatives containing two potential sites of unsaturation in rings A and B undergo rearrangement to anthrasteroids on treatment with acetyl bromide and hydrogen bromide generated *in situ* from acetyl bromide and propan-2-ol.

WE reported in the preceding communication[1] that treatment of steroids possessing three potential sites of unsaturation in rings A and B with acetyl bromide and HBr results in mixtures of aromatic products, composed predominantly of 4-methyloestra-1,3,5(10)-triene derivatives. The minor products formed in these reactions were anthrasteroids. Thus cholestenone (**1a**) and testosterone acetate (**1b**) gave in addition to the above oestratriene derivatives the anthrasteroids (**2a**) (25%) and (**2b**)† respectively.

Similar treatment of steroids possessing two sites of unsaturation in rings A and B, and a third one in ring D, gave anthrasteroids, lacking functional groups in ring D. Thus heating of either (**3a**), (**4a**), or (**5a**) with acetyl bromide and propan-2-ol in a sealed ampoule, under the conditions described in the preceding communication, gave in each case the same mixture of anthrasteroids in about 40% yield which was separated into (**9a**), (**9b**), and (**9c**). Analogous cholestane derivatives (**3b**), (**4b**), and (**5b**) did not yield aromatic compounds under these conditions, indicating, that the third site of unsaturation in ring D is essential for this aromatization to occur.

When (**3a**), (**4a**), or (**5a**) were submitted to the above reaction conditions for shorter periods, the dibromide (**6a**) was isolated as the main product in each case. (**6a**) was readily dehydrobrominated to the monobromide (**7a**), which is probably an intermediate in the formation of the anthrasteroids (**9a**), (**9b**), and (**9c**).‡ This transformation involves [(**7a**) → (**9**)] epimerization at C-14 followed by elimination of the 17β-acetoxy group. The resulting double bond migrates from ring D by a series of HBr additions and eliminations giving the benzenonium ion (**8a**) having at C-14 the thermodynamically more stable β-configuration. The formation of anthrasteroids (**9b**) and (**9c**) may be explained by an additional rearrangement involving either a 1,2-migration of the C-18 methyl group from C-13 to C-14, or two 1,2-migrations (C-12→ C-14 and C-8→C-13) to give benzenonium ions (**8b**) and (**8c**). Ring B benzenonium ions were postulated previously to be the intermediates in the acid catalysed "anthrasteroid rearrangement" of $\Delta^{5,7,9(11)}$ trienes observed in the cholestane and ergostane series.[3,4]

The 17β-acetoxy group undergoes elimination followed by HBr addition only when rings C/D are *cis* fused and the acetoxy group assumes a quasi-axial conformation. Thus



† The formation of 17-oxo-anthrasteroid from androst-4-en-3,17-dione by acetyl bromide and α-bromopropionic acid has been reported previously.[2]

‡ It is possible that (**7**) preceeds (**6**) in these rearrangements.

treatment of 3β,17β-diacetoxy-5α,14β-androstane (**10**) with acetyl bromide and propan-2-ol gave the 17β-Br analogue (**11**).§ 3β,17β-Diacetoxy-5α,14α-androstane was recovered unchanged on similar treatment and in the anthrasteroid (**2b**) the 17β-acetoxy substituent (quasi-axial conformation) was replaced by a bromine atom.

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§ This bromo-derivative was also formed by HBr addition to the $\Delta^{16,17}$ olefin obtained by the elimination of 17β-acetoxy group from (**10**).

[1] J. Libman and Y. Mazur, preceding communication.
[2] J. Schmitt, J. J. Panouse, M. Pluchet, A. Hallot, P. J. Cornu, and P. Comoy, *Compt. rend.*, 1964, **259**, 1652; *Bull. Soc. chim. France*, 1965, 1934.
[3] K. Tsuda and R. Hayatsu, *J. Amer. Chem. Soc.*, 1955, **77**, 3089; K. Tsuda, R. Hayatsu, J. A. Steele, D. Tanaka, and E. Mosettig, *ibid.*, 1963, **85**, 1126; J. A. Steele, L. A. Cohen, and E. Mosettig, *ibid.*, **1963**, **85**, 1134; O. Tanaka and E. Mosettig, *ibid.*, 1963, **85**, 1131.
[4] N. L. Wendler, "Rearrangements in Steroids," Vol. 2, Ed. P. DeMayo, J. Wiley, New York, 1964, pp. 1063—1067.