Aromatization of Steroidal Dienones

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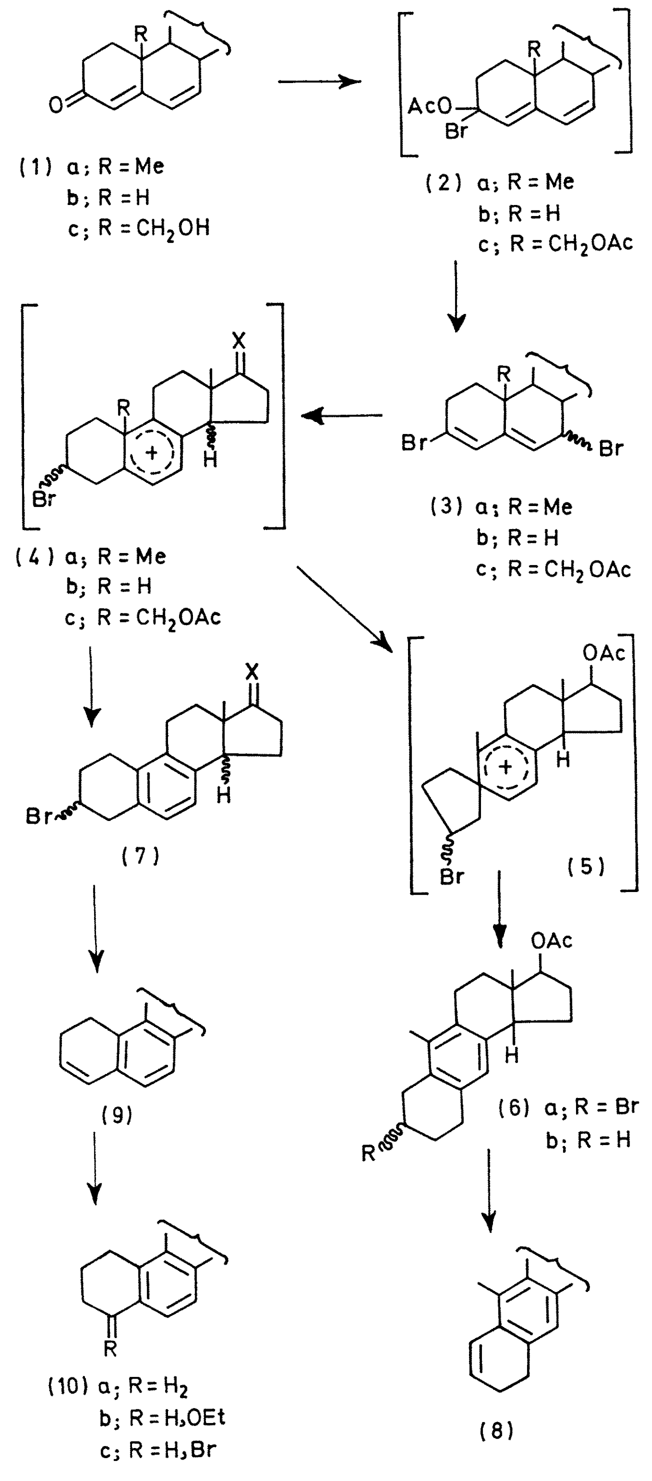
Summary Steroidal 3-oxo-$\Delta^{4,6}$-dienones in both 10-methyl- and 19-nor-series readily undergo aromatization with acetyl bromide at room temperature: the former rearrange to anthrasteroids, while the latter give ring-B-aromatic steroids.

Δ^4-3-OXO-STEROIDS undergo aromatization when heated at 85° with acetyl bromide and hydrogen bromide, resulting mainly in ring-A-aromatized steroids.[1] We now find, that $\Delta^{4,6}$-3-oxo-steroids aromatize even when treated with acetyl bromide alone at room temperature yielding ring-B-aromatized derivatives.

Thus, overnight treatment of the dienone (1a) (17β-OAc) at room temperature with a *ca.* 10-fold molar excess of acetyl bromide resulted in 71% yield of the bromo-anthrasteroid (6a).† Chromatography on silica, or heating with

† This compound was not crystalline, and may consist of a mixture of two epimeric bromides.

ethanolic sodium hydroxide, converted (6a) into the olefin (8), which on hydrogenation over palladium on charcoal gave (6b) and the latter after hydrolysis and yielded the known 17-keto derivative.[2]



Similar treatment of the 19-nor-dienone (1b) (17β-OAc) with acetyl bromide at room temperature for 16 h gave the 3-bromide (7) (14α-H)† as the main product. Chromatography of the reaction mixture yielded (7) (14α-H) and its dehydrobromination product, the olefin (9) (14α-H), in 35 and 21% yields, respectively (from 1b). Olefin (9) (14α-H) was also obtained from the bromide (7) (14α-H) in quantitative yield on treatment with base. Hydrogenation of (9) (14α-H) over palladium on charcoal gave the known benzene derivative (10a) (14α-H).[3]

Reaction of the 17-keto-dienone (1b) (17-ketone) with acetyl bromide followed by heating with ethanolic sodium hydroxide gave the expected 17-keto-olefin (9) (14α-H) as the major product (61%) which was accompanied by its 14-epimer (9) (14β-H) and a 1 : 1 mixture of 4-epimeric ethoxy-derivatives (10b) (14α-H) in 13, 3·5, and 3·5% yields, respectively (all 17-ketones). Addition of hydrogen bromide to the olefin (9) (14α-H) and subsequent treatment with ethanolic sodium hydroxide of the resulting 4-bromide (10c) (14α-H)† gave also a 1 : 1 mixture of the two 4-epimeric ethoxy-derivatives (10b), indicating that the 4-bromide (10c) accompanies the 3-bromides (7), as a minor product in the aromatization of the dienone (1b).

Treatment of the dienones (1a) and (1b) (17β-OAc) with acetyl bromide at room temperature for a shorter period of time (4 h) results in formation of the dibromo-dienes (3a) (7β-Br) and (3b) (7β-Br) respectively. The formation of these dienes indicates their intermediacy in the aromatization reaction. The aromatization path may thus involve an addition of acetyl bromide to the carbonyl group of the dienone (1), to give the geminal derivative (2), which is followed by substitution at C-7. The dibromo-dienes (3) thus formed undergo a series of rapid eliminations and additions of hydrogen bromide, to give the ring-B benzenonium ion (4). Deprotonation of the benzenonium ion (4b) (in the 19-nor-series) gives the aromatic steroid (7), while the rearrangement of (4a) (in the 10-methyl series) *via* the spiranic intermediate (5) by successive 1 : 2 shifts of the C-1–C-10 bond to C-6, results in the anthrasteroid (6a).

The epimerization at C-14, which occurs in the 10-methyl series and also to a small extent in the 19-nor-series, probably proceeds through a $\Delta^{8(14)}$-olefin whose protonation will lead to the more stable C/D-*cis* ring junction.[5]

Reaction of 19-hydroxy-dienone (1c) (17-ketone) with acetyl bromide at room temperature for 16 h yielded no aromatic products but instead, two 7-epimeric dibromo-dienes (3c) were formed. Aromatization of (1c) was achieved after heating at 70° with acetyl bromide and propan-2-ol as described previously for Δ^4-3-ketones.[1] This reaction gave, after dehydrobromination with base a mixture of 17-keto-olefins (9) (14α-H) and (9) (14β-H) in 5 and 30% yields, respectively. Apparently, in this case the expulsion of the CH_2OAc group from the benzenonium ion (4c) to give ring-B-aromatized compounds[6] is more favourable than the formation of a spiran intermediate the precursor of anthrasteroid derivatives.

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