Remote Hydroxylation of a Steroid D-Ring by a Free-radical Process

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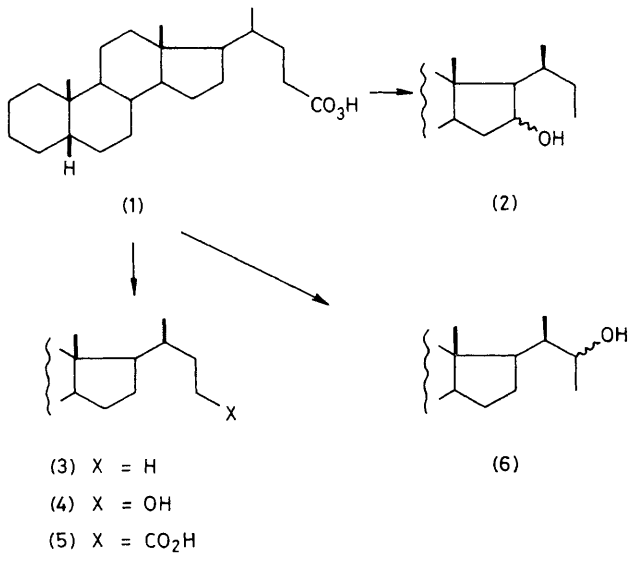
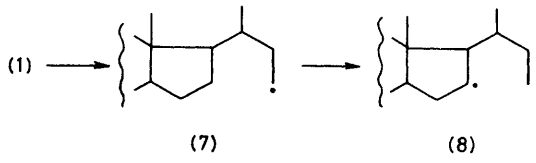
Summary The thermal decarboxylation of peroxycholanic acid (**1**) leads, by a radical chain reaction, to the epimeric 16-hydroxy norcholanes (**2**) in >35% yield; this regioselective D-ring functionalization is the result of an intramolecular homolytic 1,5-hydrogen shift.

REMOTE homolytic functionalization is generally effected by means of heteroatomic (alkoxy or amino) radicals; carbon radicals have rarely been employed for this purpose. Carbon radicals can, however, also give rise to selective 1,5- and 1,6-hydrogen shifts,[1] and their use for the intramolecular, regioselective hydroxylation of steroids therefore appeared to offer a useful complement both to the classical radical routes and to the cationic route[2] for intramolecular functionalization. Here we report a homolytic D-ring hydroxylation starting from a bile acid; radical reactions of bile acid derivatives generally lead to functionalization at C-20.[3]

The thermal decarboxylation of peroxy-acids constitutes an excellent route to carbon radicals, which then afford alcohols *via* a chain reaction with the peroxy-acid.[1] Applied to peroxycholanic acid (**1**) {m.p. 108 °C (decomp.), $[\alpha]_{546}^{24.5}$ 33·7°}, prepared in a 95% yield by stirring cholanic acid and H_2O_2 (85% in $MeSO_3H$) for 4 h at 25 °C, this reaction leads to hydroxylation of the D-ring at C-16. Thus, refluxing a 10^{-3} M solution of (**1**) in n-octane for 0·5 h afforded the mixture (**2a**, **b**) of 16-hydroxynorcholanes ($\alpha:\beta$ *ca.* 3:1 by ^{1}H n.m.r.); (**2a**) (α-OH) δ ($CDCl_3$) 4·0 (t-like, $W_{\frac{1}{2}}$ 8 Hz); (**2b**) (β-OH) δ ($CDCl_3$) 4·31 (m, $W_{\frac{1}{2}}$ 17 Hz), accompanied by other products (Scheme 1); the compounds (**2**); (**3**),[5] m.p. 105—106 °C, $[\alpha]_D^{24}$ 23° (*c* 5·0, CH_2Cl_2); (**4**),[6] m.p. 151 °C, $[M]_D^{27}$ +92° (*c* 1, $CHCl_3$); (**6**) (2 epimers); and cholanic acid (**5**) were produced as a 33:32:9:11:15 mixture (by g.l.c.), respectively. The D-ring alcohols (**2**) were identified by ^{1}H and ^{13}C n.m.r spectroscopy: (**2a**), $[\alpha]_{546}^{22}$ +4·3° (*c* 2·7, CH_2Cl_2); (**2b**), $[\alpha]_{546}^{22}$ +26·9° (*c* 1·2, CH_2Cl_2), and by oxidation[7] to the corresponding ketone, m.p. 64 °C, $[\alpha]_{578}^{25.5}$ −130·5° *c* 2·2, CH_2Cl_2), which has a characteristic mass spectrum.[8] The 22-hydroxy-norcholanes (**6**), the mechanism of the formation of which has not been elucidated,† were identified by comparison with authentic samples of 22-keto-norcholane {m.p. 89—92 °C, $[\alpha]_{578}^{22}$ −8° (*c* 2·2, CH_2Cl_2)} prepared from Δ^{22}-norcholene.[9]



SCHEME 1



SCHEME 2

† Two processes are possible to explain the formation of 22-hydroxynorcholanol: one is a homolytic 1,4-hydrogen shift (C-22 to C-16); the other is that the primary radical (**7**), initially formed, rearranges by a 1,6-hydrogen shift to the C-18 primary radical, which again rearranges by a 1,5-hydrogen shift to the C-22 secondary radical (**8**). However, 18-hydroxynorcholane was not detected.

Homolytic 1,5-hydrogen shifts are known to occur with great ease,[1] and the 16-hydroxy compounds (**2**) presumably arise by the mechanism shown in Scheme 2: the primary radical (**7**), initially formed by thermal decarboxylation of the peroxy-acid (**1**), rearranges by a 1,5-hydrogen shift to the secondary radical (**8**), which then reacts with another molecule of peroxyacid (**1**), leading to the alcohols (**2**) and at the same time regenerating (after decarboxylation) the primary radical (**7**).

We conclude that the reactions of carbon radicals can be as selective, and as synthetically useful,‡ as those of their heteroatomic counterparts. The presence of a peroxy-acid function in the molecule allows the direct hydroxylation of an unactivated methylene group with an entirely different regioselectivity from that observed in bimolecular processes.[10]

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‡ The reaction is satisfactory in the presence of other functional groups; details will be published elsewhere.

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