Competing Reactions in the Peroxy-acid Oxidation of 3-Alkoxy-steroidal 3,5-Dienes

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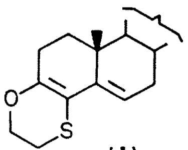
Summary 3-Alkoxy-3,5-dienes (II) are oxidised by peroxy-acid mainly at the 3,4-bond under anhydrous conditions, but at C-6 in the presence of water.

THE recent observation[1] that oxidation of cholesta-3,5-dieno[3,4-*b*]-1,4-oxathian (I) can involve either the Δ^3- or the Δ^5-double bond, according to reaction conditions, prompts us to report closely related findings with the dienol ethers (II).

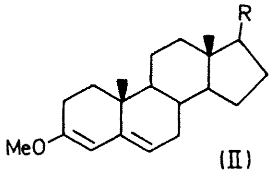
Extending our study[2] of the preparation of 6β-hydroxy-steroids (III), we re-investigated the reaction between some dienol ethers (II) and peroxy-acid, using *m*-chloroperbenzoic acid. Previously reported[3] yields of 6β-hydroxy-steroids by this method have generally been low.

Working in either the cholestane (IIa) or androstane series (IIb or c) the major products were the 3,4-seco-aldehyde-ester (IVa) or the 6β-hydroxy-4-en-3-one (III). Their proportions depended both upon the solvent and upon the method of mixing the reactants. Anhydrous solutions (dioxan, carbon tetrachloride, dichloromethane, *etc.*) and immediate addition of an excess of peroxy-acid, favour the aldehyde-ester (IVa) (up to 80%), whereas aqueous-organic solvents, and gradual addition of peroxy-acid to the steroid, favour the 6β-hydroxy-compound (III) (*ca.* 50%). As a preparative method, the yield of 6β-hydroxy-derivative may be raised to 90% in favourable cases when the oxidation is carried out by gradual addition (2 hr) of an excess of peroxy-acid, buffered by first being half-neutralised with sodium hydroxide, to the dienol ether (each reactant in aqueous dioxan; proportions not critical).

The structure of the aldehyde-ester (IVa) follows from spectral data, *e.g.* in the cholestane series: λ_{max} (EtOH) 232 nm; ν_{max} (gum) 2700 (CHO), 1740 (CO_2Me), 1691, and 1633 cm^{-1} (C=C-CHO); τ (CCl_4) 0·96 (C*H*O), 3·42 (d, *ca.* 4Hz, 6-*H*), 6·50 (CO_2Me), 8·92 (10β-Me), and 9·32 (13β-Me): 2,4-dinitrophenylhydrazone, m.p. 185—186°, λ_{max} (EtOH) 376 nm (ϵ 25,700),[4] λ_{max} (1·0N-KOH–EtOH)[5] 455 nm (e 34,500). Reduction with sodium borohydride gave the hydroxy-ester (IVb) (ν_{max} 1740, no aldehyde bands; no

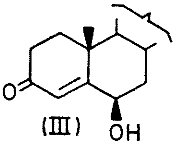


(I)

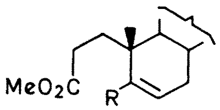


(II)

a; R = C_8H_{17}
b; R = β - OAc
c; R = O



(III)



(IV)

a; R = CHO
b; R = CH_2OH
c; R = CO_2H

λ_{max} above 215 nm), from which the aldehyde (IVa) was regenerated by 2,3-dichloro-5,6-dicyanobenzoquinone.[6] Air-oxidation gave the known[7] 3-mono-ester (IVc), m.p. 124—125°, of "Diels' acid," which afforded "Diels' acid"[7] (m.p. 290—295°) on hydrolysis.

Both the dienol ether (II) and the oxathian (I) are oxidised preferentially at the 3,4-bond in the absence of water, but at C-6 when water is present. This behaviour appears attributable to the dienol ether system, irrespective of any effect due to sulphur at C-4.[1] It is, moreover, almost unique among the known reactions of 3,5-dienol ethers[8] (and esters),[9] which are normally attacked at C-6 by electrophilic reagents. The reasons for the dichotomy in this particular case are under investigation.

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