Neighbouring Group Effects. Part 2.[1] Effect of Epoxide on the Hydrolysis of Adjacent Acetate Groups

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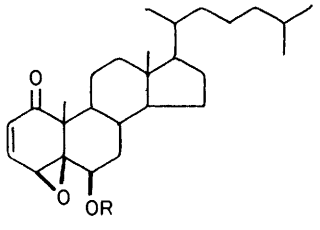
The presence of an epoxide at the 4,5-position of a steroid accelerates the hydrolysis of an acetate group at the 3β- or 6β-positions. This effect is also observed for a 1α-acetoxy-2β,3β-epoxide. A suitable fixed dipole–dipole orientation between the ester group and the adjacent polar group may be an important factor in the rate acceleration, since this neighbouring effect does not occur when a non-rigid side chain is present. Fluorine or bromine substitution at the 5α-position also enhances the rate of hydrolysis of a 6β-acetoxy-group.

In the preceding paper,[1] we reported the effect of α-hydroxy- and α-acetoxy-groups on the ring cleavage of epoxides. We now report the rate enhancement of hydrolysis of an acetyl group by the presence of an adjacent epoxide. In the course of our investigation of the chemistry of steroidal α-hydroxy-epoxides, we found that the acetyl group of 4,5-epoxy-1-oxo-5β-cholest-2-en-6β-yl acetate (1) and of its isomeric 4α,5α-epoxide (3) could be easily hydrolysed with aqueous 10% sodium hydroxide in dimethylformamide at 30 °C to give the hydroxy-epoxides (2) and (4) respectively,[2] while the corresponding Δ^4-analogue (6) and its dihydro-derivative (5) were resistant to hydrolysis under similar conditions. These unusual effects prompted us to carry out further investigation.

It is well known that mild hydrolysis (KOH–MeOH–ether; 0 °C; overnight) of 5α-cholestane-3β,6β-diol diacetate (7) affords the corresponding 6β-monoacetate.[3]



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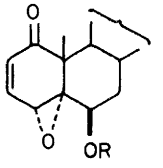
(2) R = H



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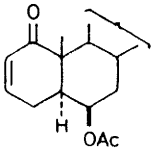

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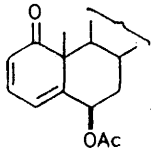
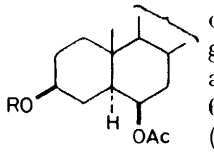


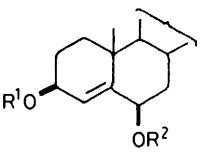
(6)



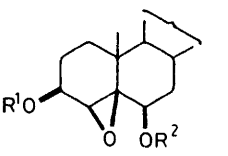
(7) R = Ac
(8) R = H

Cholest-4-ene-3β,6β-diol diacetate (9) is also selectively hydrolysed to its 6β-monoacetate (10). Since the half-height widths of the ^{1}H n.m.r. signals for 6α- and 3α-H of (10) are very different (6 and 16 Hz, respectively), the structure of the monoacetate can be confirmed by the chemical shifts for these protons.

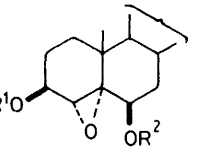
Introduction of an epoxide group at the 4,5-position caused the 6β-acetoxy group to behave differently to that of the diacetate (7) or (9) under the same hydrolysis conditions. Thus the 6β-acetyl group of the diacetoxy-epoxide (12) [or (15)] was readily hydrolysed to afford the 3β,6β-dihydroxy-epoxide (14) [or (17)]. Hydrolysis



(9) $R^1 = R^2 = Ac$
(10) $R^1 = H$, $R^2 = Ac$
(11) $R^1 = R^2 = H$



(12) $R^1 = R^2 = Ac$
(13) $R^1 = H$, $R^2 = Ac$
(14) $R^1 = R^2 = H$

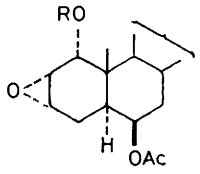


(15) $R^1 = R^2 = Ac$
(16) $R^1 = H$, $R^2 = Ac$
(17) $R^1 = R^2 = H$
(18) $R^1 = Me$, $R^2 = Ac$
(19) $R^1 = Me$, $R^2 = H$

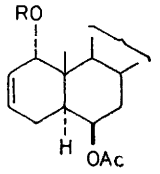
of the 6β-acetyl group of the 6β-acetoxy-3β-methoxy-4α,5α-epoxide (18) was also accelerated to give the 6β-hydroxy-epoxide (19) at a similar rate. By treatment of (15) with a more concentrated base, the 3β-acetyl group of (15) was completely hydrolysed within 0.5 min, and after 2—3 min the dihydroxy-epoxide (17) and the 6β-monoacetate (16) were obtained in equal proportions (as determined from integration of the 3α- and 6α-H n.m.r. signals). In the case of compound (9), it took 15 min for complete hydrolysis of the 3β-acetyl group and *ca.* 15 h to convert the monoacetate (10) into a 1 : 1 mixture of the monoacetate (10) and the diol (11). Thus, 3β-acetyl and 6β-acetyl groups which bear an adjacent 4,5-epoxide group are hydrolysed at *rates* 300—400 times greater than those which have no neighbouring epoxide.

Similar facilitation of hydrolysis of an acetyl group by

an adjacent epoxide was observed with 2α,3α-epoxy-5α-cholestane-1α,6β-diol diacetate (20), synthesized from the allyl alcohol (22) [2] by treatment with *m*-chloroperbenzoic acid followed by acetylation. The half-life



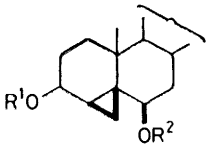
(20) R = Ac
(21) R = H



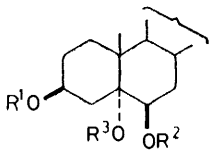
(22) R = H
(23) R = Ac

of hydrolysis of the 1α-acetyl group of (20) to give (21) was 5—10 min, whereas that of the allyl acetate (23) to provide (22) was *ca.* 25 h. In both cases, the 6β-acetyl group was not hydrolysed. The products of hydrolysis were identified by comparison (^{1}H n.m.r. spectra and R_F values) with authentic samples.

To clarify the nature of the ' neighbouring epoxide effect,' compounds having structures similar to the 4,5-epoxide were synthesized. Thus, treatment of the allyl alcohol (11) with zinc–copper couple and methylene iodide [4] and subsequent acetylation afforded the 4β,5β-cyclopropane derivative (25). Hydrolysis of (25) [δ 5.1



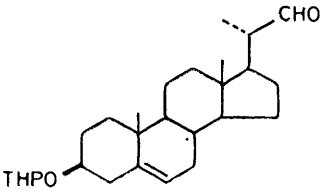
(24) $R^1 = R^2 = H$
(25) $R^1 = R^2 = Ac$
(26) $R^1 = H$, $R^2 = Ac$



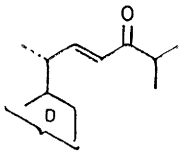
(27) $R^1 = R^2 = Ac$, $R^3 = Me$
(28) $R^1 = R^2 = Ac$, $R^3 = H$
(29) $R^1 = H$, $R^2 = Ac$, $R^3 = Me$
(30) $R^1 = R^2 = H$, $R^3 = Me$
(31) $R^1 = R^3 = H$, $R^2 = Ac$
(32) $R^1 = R^2 = R^3 = H$

(3α-H) and 4.05 (6α-H)] under the conditions used for (12), (15), (20), *etc.*, afforded only the 3β-hydroxy-cyclopropane (26) [δ 4.20 (3α-H) and 4.05 (6α-H)], whereas the 5α-methoxy-diacetate (27) (4.80 p.p.m., 3α-H, 5.00 p.p.m., 6α-H), derived from 5,6β-epoxy-5β-cholestan-3β-ol, was converted into a mixture of the methoxy-diol (30) [δ 3.70 (3α-H) and 3.80 (6α-H)] (30%) and the methoxy-mono-ol (29) [δ 3.70 (3α-H) and 5.00 (6α-H)] (70%) after 24 h. The 5α-hydroxy-diacetate (28), also derived from 5,6β-epoxy-5β-cholestan-3β-ol, was hydrolysed to a 1 : 1 mixture of the triol (32) and the diol (31) after 24 h. Since no acceleration resulting from introduction of the cyclopropane ring was observed, we can exclude the strain effect caused by the presence of the three-membered ring. A slight facilitation of hydrolysis of the 6β-acetyl group in (27) and (28) by the adjacent oxygen function suggested that the polarity of the oxygen could be one of the factors causing the ' neighbouring epoxide effect.'

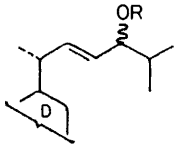
In order to compare the effect of the epoxide in the comparatively rigid AB ring system with that in a non-rigid side chain, the Δ^{22} allyl acetate (36) and the 22,23-epoxy-acetate (38) were synthesized. The enone (34), derived from the 22-aldehyde (33) by Wittig reaction,[5] was reduced with lithium aluminium hydride to the allyl alcohol (35), which was epoxidized with vanadyl acetoacetonate and t-butyl hydroperoxide [6] to the epoxy-



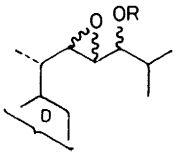
(33)



(34)



(35) R = H
(36) R = Ac
(39) R = Bz
(3—benzoate)



(37) R = H
(38) R = Ac

alcohol (37). Hydrolysis of the 24-acetyl groups of (36) and (38) proceeded at the same rate, showing that the ' neighbouring epoxide effect ' does not occur in a non-rigid side chain. Thus, the observation that hydrolysis of the acetyl group of (38) is not accelerated by the presence of the adjacent epoxide, whereas the hydrolysis of the acetyl groups of the α-epoxy-acetates (12), (15), and (20) is, indicates that the ' neighbouring epoxide effect ' does not operate through carbon–carbon bonds.

The electronic state of the 6β-acetates was investigated by ^{13}C n.m.r. and i.r. spectroscopy. The ^{13}C n.m.r. spectra of the 6β-acetates (8), (10), (13), and (16) showed no significant differences in their 6β-acetyl carbonyl shifts, as shown in Table 1, suggesting that their carbonyl

TABLE 1

^{13}C N.m.r. spectra (in $CDCl_3$) of 6β-acetoxy-compounds (δ values)

Compound	(8)	(10)	(13)	(16)
C-3	71.254	67.766	64.622	65.254
C-4	34.968	131.927	63.230	65.133
C-5	46.356	142.188	66.646	64.083
C-6	73.642	75.741	75.983	74.984
C-19	15.191	21.702	21.288	17.362
Methyl of acetyl group	21.019	20.654	19.898	20.678
Carbonyl of acetyl group	170.670	170.186	170.085	170.280

carbon atoms are electronically similar in the ground state. I.r. absorption maxima for the 6β-acetyl groups are shown in Table 2. Inspection of the position of the carbonyl and C–O absorption frequencies of each

acetoxy-group reveals that the latter shift to low wave number and the former shift to high wave number in the presence of the adjacent epoxide. This polarization of

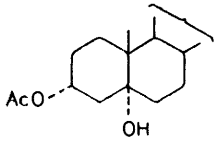
TABLE 2

I.r. absorption maxima (cm^{-1}) of 6β-acetoxy-groups

Compound	
(1)	1 737, 1 225
(3)	1 738, 1 233
(5)	1 728, 1 245
(6)	1 731, 1 249
(7)	1 731, 1 241
(9)	1 734, 1 238
(13)	1 736, 1 244
(16)	1 738, 1 234

acetoxy-groups appears to be similar to that of the 3β-acetoxy-group of (40), reported by Henbest *et al.*[7] Polarization of the acetoxy-group of (40) was ascribed to intramolecular hydrogen bonding between the axial substituents.

Although complete rationalization of the 'neighbouring epoxide effect' is difficult, it is supposed that, as a consequence of a dipole–dipole interaction [8] between the epoxide and acetoxy-group, the oxygen of the alcoholic part of the acetoxy-group would become more negative than that of an acetate having no neighbouring polar group. The effective dipole–dipole interaction between a 4,5-epoxide and a 6β-acetoxy-group could promote a particular orientation of the acetyl group, as postulated in (I).



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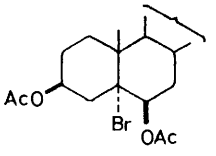
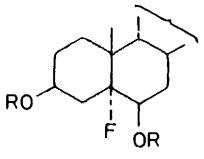
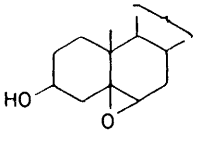


(41)

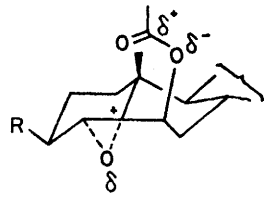


(42) R = Ac
(43) R = H



(44)

Since the 5α-methoxy-group of (27) and the 5α-hydroxy-group of (28) are less effective in orienting the 6β-acetyl group of (27) and (28) in a suitable position than the 4,5-epoxide of (12) and (15), because of their flexibility, it can be assumed that a suitable orientation of acetyl and polar groups will be an important factor for rate enhancement of the ester hydrolysis. In order to confirm this assumption, bromine and fluorine were introduced at C-5 instead of the 4α,5α-epoxide, a carbon–halogen bond being a 'fixed' dipole analogous to an epoxide. The 5α-bromo-diacetate (41) and the 5α-fluoro-di-acetate (42) were prepared from 5,6β-epoxy-5β-cholestan-3α-ol (44) by treatment respectively with aqueous hydrogen bromide and hydrogen fluoride, followed by acetylation. The 5α-bromo-compound (41) was readily hydrolysed to give the 5β,6β-epoxy-alcohol (44). The 5α-fluoro-derivative (42) was also easily hydrolysed to the 5α-fluoro-diol (43) which did not change to the epoxide (44) upon further reaction. The reaction times required for hydrolysis of these compounds are summarised in Table 3.



(I)

TABLE 3

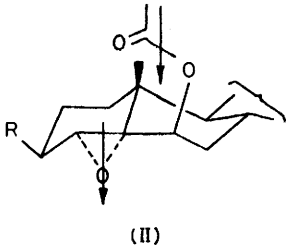
Reaction times for hydrolysis of acetates [a]

Compound	(7)	(9)	(12)	(15)	(20)	(23)	(25)	(27)	(28)	(36)	(38)	(41)	(42)
Reaction time (h)	24	24	1	1	0.5	25	24	24	24	2	2	1	2
Products	(8)	(10)	(14)	(17)	(21)	(22) (23)	(26)	(29) (30)	(31) (32)	(35)	(37)	(44)	(43)

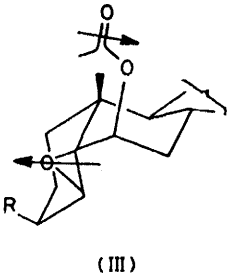
[a] 2.8% KOH–MeOH in ether, at 0 °C.

A kinetic study of neighbouring group effects on the hydrolysis of esters has been reported by Bruice and Fife [9] who measured ΔH and ΔS for the alkaline hydrolysis of esters facilitated by a neighbouring hydroxy-group. They deduced that all the esters which have a neighbouring hydroxy-group owed their greater rates of hydrolysis to a favourable value for $T\Delta S$.

Although there are no quantitative kinetic data on the rate enhancement of hydrolysis of the epoxy-acetates studied in this report, we suppose that a suitable arrangement of dipole–dipole interaction between the epoxide and acetoxy-groups would cause the acetoxy-group to be oriented as shown in (II) and (III), as a



(II)



(III)

consequence of which the reaction system would be entropically activated in the ground state. From this point of view, we can assume that a suitable fixed dipole–dipole orientation between the ester group and an adjacent polar group may be one of the important factors for the rate enhancement of ester hydrolysis.

EXPERIMENTAL

M.p.s were determined with a hot-stage microscope. ^{1}H N.m.r. spectra were run with a Varian T-60 or a Hitachi R-24S spectrometer for solutions in $CDCl_3$ unless otherwise stated, with Me_4Si as a internal reference. ^{13}C N.m.r. spectra were recorded on a JEOL PS/PFT-100 spectrometer. Mass spectra were determined with an LKB-Shimadzu-9000 or a Hitachi RMU-7L instrument at 70 eV. I.r. spectra were taken for Nujol solutions with a Hitachi 215 grating infrared spectrophotometer. Column chromatography was effected using silica gel (Wakogel C-200).

4β,5-Epoxy-1-oxo-5β-cholest-2-en-6β-yl acetate (1), 4α,5-epoxy-1-oxo-5α-cholest-2-en-6β-yl acetate (3), 1-oxo-5α-cholest-2-en-6β-yl acetate (5), 1-oxocholesta-2,4-dien-6β-yl acetate (6), and 5α-cholest-2-ene-1α,6β-diol diacetate (22) were prepared by the method reported previously.[2] 5α-Cholestane-3β,6β-diol 6-acetate (8) was prepared by the method of Pelc,[10] cholest-4-ene-3β,6β-diol diacetate (9) by that of Hallsworth,[11] and cholest-4-ene-3β,6β-diol (11), 4β,5-epoxy-5β-cholestane-3β,6β-diol (14), 4α,5-epoxy-5α-cholestane-3β,6β-diol diacetate (15), and the 3-methoxy-6-acetate (18) by that of Henbest.[12] 5α-Cholestane-3β,5,6β-triol 3,6-diacetate (28) and 5-methoxy-5α-cholestane-3β,6β-diol diacetate (27) were prepared[13] from 5β,6β-epoxy-5β-cholestan-3β-ol with 60% perchloric acid in tetrahydrofuran and in tetrahydrofuran–methanol, respectively. 5-Bromo-5α-cholestane-3β,6β-diol diacetate (41) and 5-fluoro-5α-cholestane-3β,6β-diol (43) were prepared[14] from 5β,6β-epoxy-5α-cholestan-3β-yl acetate with aqueous 48% hydrogen bromide and 48% hydrogen fluoride, respectively, in tetrahydrofuran solution.

General Procedure for Hydrolysis of α-Substituted Esters.—To a solution of the acetate (0.1 mmol) in ether (1.5 ml) was added methanolic potassium hydroxide (2.8%; 0.2 ml) at 0 °C. The mixture was stirred at 0 °C and the reaction monitored by t.l.c.

2α,3α-Epoxy-5α-cholestane-1α,6β-diol 6-Acetate (21).—The allyl alcohol (22) (200 mg, 0.45 mmol) in chloroform was stirred with *m*-chloroperbenzoic acid (200 mg, 1 mmol) at room temperature for 5 h. The chloroform layer was washed with 1N-potassium iodide, 1N-sodium thiosulphate, and saturated sodium hydrogencarbonate solutions, then dried ($MgSO_4$) and evaporated to give the *α-hydroxy-epoxide* (21) as a foam; δ 0.88 (s, 10-Me), 2.0 (s, Ac), 3.2—3.7 (3 H, m, 1β-, 2β-, and 3β-H), and 4.9 (1 H, m, 6α-H) (Found: M^+, 502.183. $C_{31}H_{50}O_5$ requires, *M*, 502.185).

1′,3′-Dihydrocyclopropa[4,5]-*5β-cholestane-3β,6β-diol* (24).—A solution of cholest-4-ene-3β,6β-diol (11) (400 mg, 1 mmol) in ether–THF (3 : 1) (8 ml) was refluxed with methylene iodide (0.28 ml), zinc–copper couple (276 mg), and a small amount of iodine for 4 h. After cooling to room temperature, 1N-HCl was added to the mixture. Extraction with ether, washing with saturated sodium hydrogencarbonate solution, drying ($MgSO_4$), and evaporation afforded the crude product (530 mg). Chromatography on silica gel (16 g), eluting with benzene–ethyl acetate (3 : 1), afforded the amorphous *cyclopropanediol* (24) (147 mg); δ 0.2—0.6 (m, cyclopropyl), 1.1 (s, 10-Me), 2.75 (1 H, m, 6-H), and 4.20 (1 H, m, 3α-H) (Found: M^+, 415.481. $C_{28}H_{48}O_2$ requires *M* 415.484).

3β-Tetrahydropyran-2-yloxycholesta-5,22-dien-24ξ-ol (35).—A solution of the 22-en-24-one (34) [15] (360 mg, 0.75 mmol) in THF (7.5 ml) was added dropwise to a slurry of lithium aluminium hydride (120 mg, 3.1 mmol) in THF (7.5 ml) at 0 °C. This reaction mixture was stirred for 1 h at 0 °C. After addition of 1N-sodium hydroxide, filtration, drying ($MgSO_4$), and evaporation afforded the *allyl alcohol* (35) which showed two spots on t.l.c., m.p. 139—142 °C; δ 0.88 (3 H, s, 13-Me), 1.00 (s, 10-Me), 3.2—3.8 (4 H, m), 4.60 (1 H, m), and 5.30 (3 H, m, 6-, 22-, and 23-H) (Found: C, 79.7; H, 10.8. $C_{32}H_{52}O_3$ requires C, 79.28; H, 10.81).

22ξ,23ξ-Epoxy-3β-tetrahydropyranyloxycholest-5-en-24ξ-ol (37).—A solution of the allyl alcohol (35) (145 mg, 0.3 mmol) in benzene (1.7 ml) was stirred with vanadyl acetyl acetonate (1 mg) and t-butyl hydroperoxide (50 mg) at room temperature for 3 h. Washing with water, drying ($MgSO_4$), and evaporation provided the *epoxy-alcohol* (37), (148 mg), m.p. 96—101 °C; δ 0.68 (3 H, s, 13-Me), 1.02 (s, 10-Me), 2.6—2.9 (m, 22- and 23-H), 3.4—4.0 (4 H, m), 4.70 (1 H, m), and 5.37 (1 H, m, 6-H) (Found: *m/e*, 416.620. $C_{32}H_{52}O_4$ requires $M^+ - 84$, 416.622).

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