Neighbouring Group Effects. Part 1.[1] Effect of α-Hydroxy- and α-Acetoxy-groups on the Ring Opening of Steroidal 4,5-Epoxides

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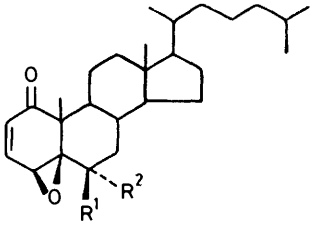
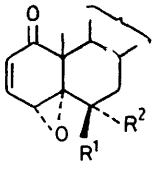
Ring-opening of steroidal 4β,5β-epoxides (1)—(5) and 4α,5α-epoxides (6)—(10) having a hydroxy- or acetoxy-group at C-6 with perchloric acid in tetrahydrofuran occurs at C-4 regioselectively. The reactivity of these epoxides is noticeably affected by the presence of a neighbouring group at the 6-position. A 6β-axial acetoxy-group completely blocks cleavage of the epoxide ring and 6α-equatorial acetoxy- and 6β-hydroxy-groups retard the reaction, while a 6α-equatorial hydroxy-group has no significant effect. Differences in the regioselectivity and reactivity of ring opening of the 4α,5α-epoxide system in (22)—(24) arise from differences in the degree of participation of the 3β- or 6β-acetoxy-group.

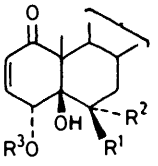
It has been reported that withaferin A and withanolide D, two steroidal lactones having an α-hydroxy-epoxide system adjacent to a cholest-2-en-1-one unit, show antitumour activity for several types of tumours.[2] In the course of our studies on the synthesis of withanolides, we have synthesized eight α-hydroxy-epoxides related to the AB ring systems of withaferin A and withanolide D[3] and have explored their chemical reactivity.



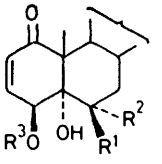
(1) $R^1 = R^2 = H$
(2) $R^1 = OH$, $R^2 = H$
(3) $R^1 = H$, $R^2 = OH$
(4) $R^1 = OAc$, $R^2 = H$
(5) $R^1 = H$, $R^2 = OAc$



(6) $R^1 = R^2 = H$
(7) $R^1 = OH$, $R^2 = H$
(8) $R^1 = H$, $R^2 = OH$
(9) $R^1 = OAc$, $R^2 = H$
(10) $R^1 = H$, $R^2 = OAc$



(11) a; $R^1 = R^2 = H$, $R^3 = H$
b; $R^1 = R^2 = H$, $R^3 = Ac$
(12) a; $R^1 = OH$, $R^2 = H$, $R^3 = H$
b; $R^1 = OAc$, $R^2 = H$, $R^3 = Ac$
(13) a; $R^1 = H$, $R^2 = OH$, $R^3 = H$
b; $R^1 = H$, $R^2 = OAc$, $R^3 = Ac$
(14) a; $R^1 = H$, $R^2 = OAc$, $R^3 = H$
b; $R^1 = H$, $R^2 = OAc$, $R^3 = Ac$



(15) a; $R^1 = R^2 = H$, $R^3 = H$
b; $R^1 = R^2 = H$, $R^3 = Ac$
(16) a; $R^1 = OH$, $R^2 = H$, $R^3 = H$
b; $R^1 = OAc$, $R^2 = H$, $R^3 = Ac$
c; $R^1 = OAc$, $R^2 = H$, $R^3 = H$
(17) a; $R^1 = H$, $R^2 = OH$, $R^3 = H$
b; $R^1 = H$, $R^2 = OAc$, $R^3 = Ac$
(18) a; $R^1 = H$, $R^2 = OAc$, $R^3 = H$
b; $R^1 = H$, $R^2 = OAc$, $R^3 = Ac$

Kupchan and Schubert[4] have reported that ring-opening of the epoxide of triptolide is accelerated by the presence of the hydroxy-group in the β-*syn*-position of the epoxide. They suggest that this rate enhancement would be important with respect to the antitumour activity of the compound. Barton and Houminer[5] have reported the rate enhancement of the ring opening of steroidal 4α,5α-epoxides by the presence of a 7α-hydroxy-group. Recently, the effects of a hydroxy-group at the 4-position of *syn*-1,2-epoxybenzo[*a*]pyrene-3,4-diol on the reactivity of the epoxide with nucleophiles,[6] and on the solvolysis reaction,[7] were reported. Thus, it is clear that the ring cleavage of epoxides can be accelerated by intramolecular assistance of a β-*syn* hydroxy-group.

In the case of α-hydroxy-epoxides, many studies have shown that an α-hydroxy-group affects the regioselectivity of epoxy-ring cleavage.[8] We have already reported that treatment of the β- (1) and α-epoxides (6) with acid gives the 4α,5β- (11a) and 4β,5α-diols (15a), respectively, as a consequence of regioselective ring cleavage at the C-4 position.[3] This result suggested that the system is suitable for examination of neighbouring-group effects on the rate of the ring opening of epoxides having a hydroxy- or acetoxy-group at C-6.

The 4β,5β- (1)—(5) and 4α,5α-epoxides (6)—(10) were treated with 60% perchloric acid in tetrahydrofuran at room temperature to give 4,5-glycols whose structures were mainly deduced from the ^1H n.m.r. spectra of the corresponding 4-acetates. The reactivity of each epoxide was compared through the measurement of the time required for 100% ring opening, as shown in the Table. The ^1H n.m.r. spectra of the glycol 4-acetates

Reaction times of ring opening of epoxides

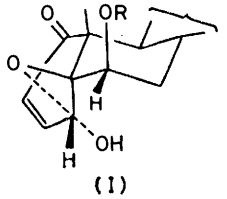
Compound	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)
Reaction time (h)	16	48	20	48 [a]	48 [b]	1.5	18	1.5	48 [a]	20
Products	(11a)	(12a)	(13a)	(14a)	(15a)	(16a)	(17a)	(18a)		

[a] No reaction. [b] 70% of starting material was recovered.

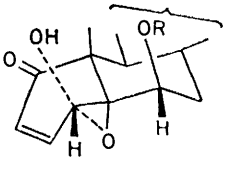
(11b) and (15b) showed significantly different chemical shifts for the 10-methyl protons, signals appearing at higher field for (11b) (δ 1.22) than for (15b) (δ 1.30). The H^1 n.m.r. spectra of the 4,5,6-triol 4,6-diacetates (12b)

and (16b) [obtained from the 6β-hydroxy-4,5-epoxides (2) and (7), respectively] showed a similar tendency: the 10-methyl protons of (12b) (δ 1.33) absorbed at higher field than those of (16b) (δ 1.45). Treatment of (12b) and (16b) with 10% aqueous sodium hydroxide at 0 °C afforded quantitatively the corresponding 6β-acetates of the starting 4,5-epoxides (2) and (7), thus confirming the structures (12b) and (16b). Analogously, the structures of the ring-opened products of (3), (5), (8), and (10) were determined as (13a), (14a), (17a), and (18a), respectively, from the ^{1}H n.m.r. spectra of their acetates.

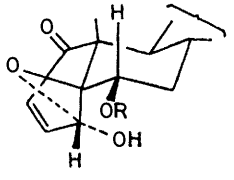
These results indicate that the ring cleavage of the 4,5-epoxides (1)—(3), (5)—(8), and (10) occurs at C-4 regioselectively, but that reactivities are affected by the presence of neighbouring polar groups. The most noticeable effect was observed with compounds (4) and (9), for which no reaction occurred under the reaction conditions used. It can be concluded that a 6β-axial acetoxy-group completely blocks cleavage of the epoxide ring, and that 6α-equatorial acetoxy- [in (5) and (10)]



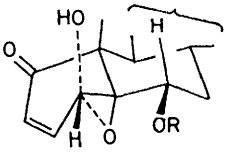
(I)



(II)



(III)

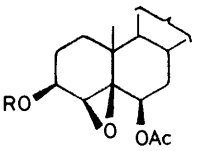


(IV)

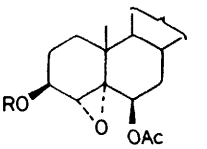
and 6β-hydroxy-groups [in (2) and (7)] retard the reaction, while a 6α-equatorial hydroxy-group [in (3) and (8)] has no significant effect on the reactivity of the 4,5-epoxide.

Retardation of the ring cleavage of 4,5-epoxides by the presence of polar groups (*e.g.* hydroxy or acetoxy) can be explained in terms of a repulsive polar group interaction in the transition state, assuming that the epoxide has partially cleaved and the nucleophile has partially bonded at C-4 as shown in (I)—(IV). There will be a greater repulsive interaction between the axial hydroxy- or acetoxy-group and a polarized epoxide or nucleophile in (I) or (II) than between the equatorial hydroxy- or acetoxy-group and a polarized epoxide and/or nucleophile in (III) or (IV).

Significant deactivation of epoxides towards acid-catalysed ring opening in the presence of the neighbouring acetoxy-group was also observed in other 4,5-epoxy-derivatives containing different functional groups.

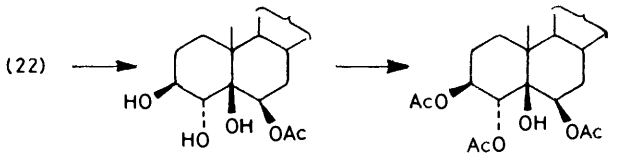


(19) R = H
(20) R = Me
(21) R = Ac

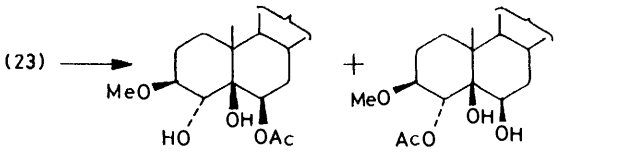


(22) R = H
(23) R = Me
(24) R = Ac

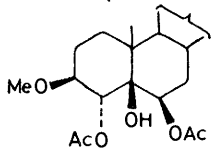
The three 4β,5β-epoxides (19)—(21) were unchanged after treatment with 60% perchloric acid for 48 h, irrespective of the differences in the 3β-oxygen functions. On the other hand, the reactivity of the 4α,5α-epoxides (22)—(24) was highly dependent on the functionality at the 3β-position. Thus, reaction of the 3,6-diacetoxy-4α,5α-epoxide (24) for 5 h gave the isomeric diols (30) and (31), both of which on acetylation yielded the same acetate (32), while 20 h was required for complete reaction of the 3-methoxy derivative (23) giving (27)



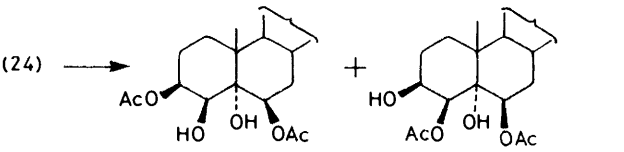
(25) (26)



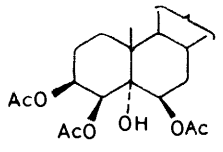
(27) (28)



(29)

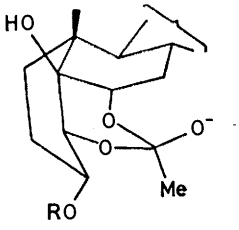


(30) (31)



(32)

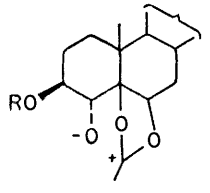
and (28). Acetylation of (27) and (28) afforded the same acetate (29). The structure of the more polar product (27) was established on the basis of its ^{1}H n.m.r. spectrum which showed a typical multiplet for 6α-H at δ 5.00. In addition to these results, 4β-H in the ^{1}H n.m.r. spectrum of the less polar compound appeared at δ 4.91 as a doublet (*J* 3 Hz), suggesting that the acetyl group is present at C-4 [*i.e.* as in (28)]. Although



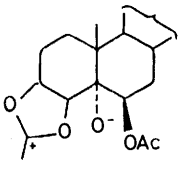
(V)

intramolecular migration of the acetyl group from C-6 to C-4 could be possible *via* a *cis*-fused boat–boat conformation (V) for the AB ring system, the mechanism of this migration is still not clear. An even more sluggish reaction was observed for the 3β-hydroxy-derivative (22): after 48 h the triol (25) was obtained (50%) together with starting material (50%). This triol was converted into the triacetate (26) which showed a similar ^{1}H n.m.r. spectrum to that of (29) and was entirely different from the triacetate (32).

Differences in the regioselectivity and reactivity of ring opening of the 4α,5α-epoxide in compounds (22)—(24) arise from differences in the participation of the 3β- or 6β-acetoxy-groups. In compounds (22) and (23), the 6β-acetoxy-group participates as shown in (VI) yielding the 5β-ols (25), (27), and (28), respectively. In compound (24), the 3β-acetoxy-group participates as shown in (VII) leading to the 5α-hydroxy-compounds (30) and (31). Participation of the 3β-acetoxy-group of (24) should be faster than that of the 6β-acetoxy-group, because formation of the intermediate (VII) is



(VI)



(VII)

via axial attack at C-4, while that of the 6β-acetoxy-group at C-5 requires equatorial attack on ring B. Furthermore, the intermediate (VI) may have greater steric restrictions than (VII). Thus the compound having a 3β-acetoxy-group reacts faster than a corresponding 3-hydroxy- or 3-methoxy-compound.

EXPERIMENTAL

M.p.s were determined with a hot-stage microscope. ^{1}H N.m.r. spectra were obtained with a Varian T-60 or a Hitachi R-24A spectrometer for solutions in $CDCl_3$ unless otherwise stated, with Me_4Si as internal reference. Column chromatography was effected on silica gel (Wakogel C-200).

1-*Oxo*-5β-*cholest*-2-*ene*-4α,5,6β-*triol* 4,6-*Diacetate* (12b).—The 4β,5β-epoxy-6β-alcohol (2) (760 mg, 1.83 mmol) in tetrahydrofuran (THF) (30 ml) was stirred with 60% perchloric acid (0.46 ml) at room temperature for 48 h to afford the crude triol which was acetylated to give the diacetate (885 mg). Chromatography on silica gel (35 g) [benzene–acetone (3 : 1) as eluant] provided the pure *diacetate* (12b) (490 mg), m.p. 126—128.5 °C (from MeOH); δ 1.33 (3 H, s, 10-Me), 2.10 and 2.15 (2 s, 2 Ac), 5.00 (1 H, m, 6-H), 5.43 (1 H, d, *J* 5 Hz, 4β-H), 6.05 (1 H, d, *J* 10 Hz, 2-H), and 6.67 (1 H, dd, *J* 10 and 5 Hz, 3-H) (Found: M^+, 516.340. $C_{31}H_{48}O_6$ requires *M*, 516.344).

1-*Oxo*-5β-*cholest*-2-*ene*-4α,5,6α-*triol* 4,6-*Diacetate* (13b).—The 4β,5β-epoxy-6α-alcohol (3) (140 mg, 0.338 mmol) in THF (5.4 ml) was stirred with 60% perchloric acid (0.09 ml) for 20 h to give the triol, which was converted into the diacetate (13b) (186 mg). Chromatography on silica gel (10 g) [benzene–ether (10 : 1) as eluant] afforded the pure *diacetate* (112 mg) as a foam; δ 1.24 (s, 10-Me), 2.03 and 2.13 (6 H, 2 s, 2 Ac), 3.35br (1 H, s, OH), 5.13 (1 H, m, 6β-H), 5.60 (1 H, d, *J* 5 Hz, 4β-H), 5.99 (1 H, d, *J* 10 Hz, 2-H), and 6.55 (1 H, dd, *J* 10 and 5 Hz, 3-H) (Found: M^+, 516.352).

1-*Oxo*-5α-*cholest*-2-*ene*-4β,5,6β-*triol* 4,6-*Diacetate* (16b).—The 4α,5α-epoxy-6β-alcohol (7) (220 mg, 0.53 mmol) in THF (8.5 ml) was treated with 60% perchloric acid (0.13 ml) at room temperature for 18 h to give the triol which was converted into the diacetate (16b) (208 mg) by acetic anhydride–pyridine. Chromatography on silica gel (10 g) [benzene–ether (20 : 1) as eluant] provided the pure *diacetate* (71 mg) as a foam; δ 1.45 (s, 10-Me), 2.03 and 2.10 (6 H, 2 s, 2 Ac), 2.88br (1 H, s, OH), 5.10 (1 H, m, 6α-H), 5.30 (1 H, d, *J* 4 Hz, 4α-H), 5.93 (1 H, d, *J* 10 Hz, 2-H), and 6.44 (1 H, dd, *J* 10 and 4 Hz, 3-H) (Found: M^+, 516.338).

1-*Oxo*-5α-*cholest*-2-*ene*-4β,5,6α-*triol* 4,6-*Diacetate* (18b).—The 4α,5α-epoxy-6α-alcohol (8) (120 mg, 0.29 mmol) in THF (4.7 ml) was stirred with 60% perchloric acid (0.08 ml) at room temperature for 1.5 h to provide the triol, which was converted into diacetate (18b) (130 mg). Chromatography on silica gel (8 g) [benzene as eluant] afforded the pure *diacetate* (90 mg) as a foam; δ 1.32 (s, 10-Me), 2.00 and 2.05 (6 H, 2 s, 2 Ac), 5.24 (1 H, m, 6β-H), 5.33 (1 H, d, *J* 4 Hz, 4α-H), 5.96 (1 H, d, *J* 10 Hz, 2-H), and 6.40 (1 H, dd, *J* 10 and 5 Hz, 3-H) (Found: M^+, 516.347).

5β-*Cholestane*-3β,4α,5,6β-*tetraol* 3,4,6-*Triacetate* (26).—The 6β-acetoxy-3β-hydroxy-4α,5α-epoxide (22) (110 mg, 0.24 mmol) in THF (3.9 ml) was treated with 60% perchloric acid (0.06 ml) at room temperature for 48 h to give a crude product (120 mg). Chromatography on silica gel (5 g) [benzene–ethyl acetate (5 : 1) as eluant] afforded the pure triol (25) (55 mg), m.p. 191—193 °C (from methanol) (Found: C, 72.85; H, 10.85. $C_{29}H_{50}O_5$ requires C, 72.76; H, 10.53%); a similar amount of starting material was recovered. Acetylation of (25) provided the triacetate (26), m.p. 167—168 °C (from methanol–ether); δ 1.10 (s, 10-Me), 2.08 and 2.13 (9 H, 3 Ac), 2.60br (1 H, s, OH), and 4.80—4.95 (3 H, m, 3α-, 4β-, and 6α-H) (Found: C, 70.65; H, 9.6. $C_{33}H_{54}O_7$ requires C, 70.43; H, 9.67).

3β-*Methoxy*-5β-*cholestane*-4α,5,6β-*triol* 4,6-*Diacetate* (29).—The 6β-acetoxy-3β-methoxy-4α,5α-epoxide (23) (190 mg, 0.4 mmol) in THF (6.4 ml) was treated with 60% perchloric acid (0.1 ml) for 20 h to give a mixture (183 mg)

of two products (t.l.c.). Chromatography on silica gel (7 g) [benzene–ethyl acetate (50 : 1) as eluant] afforded the less polar product (28) (70 mg); δ 1.12 (s, 10-Me), 2.12 (3 H, s, Ac), 3.10br (1 H, s, OH), 3.44 (4 H, s, OMe and 3α-H), 3.64 (1 H, m, 6α-H), 4.25 (1 H, s, OH), and 4.91 (1 H, d, *J* 3 Hz, 4β-H), and further elution with a more polar solvent system [benzene–ethyl acetate (10 : 1)] provided the more polar product (27) (50 mg); δ 1.05 (s, 10-Me), 2.02 (3 H, s, Ac), 2.85 (1 H, m, OH), 3.25 (4 H, s, OMe, 3α-H), 3.80 (2 H, m, OH and 4β-H), and 5.0 (1 H, m, 6α-H).

Acetylation of each diol (27) and (28) afforded the same diacetate (29), m.p. 113—115 °C (from methanol–ether); δ 1.08 (s, 10-Me), 2.05 and 2.09 (6 H, 2 Ac), 3.42 (4 H, s, OMe, 3α-H), 3.92 (1 H, s, OH), and 5.0 (2 H, m, 4β- and 6α-H) (Found: C, 71.6; H, 10.1. $C_{32}H_{54}O_6$ requires C, 71.87; H, 10.18).

5α-*Cholestane*-3β,4β,5,6β-*tetraol* 3,4,6-*Triacetate* (32).—The 3β,6β-diacetoxy-4α,5α-epoxide (24) (208 mg, 0.4 mmol) in THF (6.4 ml) was stirred with 60% perchloric acid (0.1 ml) at room temperature for 5 h to give a mixture (222 mg) of two products (t.l.c.). Chromatography on silica gel (8 g) [benzene–ethyl acetate (10 : 1)] afforded 5α-*cholestane*-3β,4β,5,6β-*tetraol* 3,6-*diacetate* (30) (108 mg); δ 1.39 (s, 10-Me), 2.05 (6 H, s, 2 Ac), 2.80br (1 H, s, OH), 3.05 (1 H, m, OH), 3.95 (1 H, d, *J* 3 Hz, 4α-H), and 5.0—5.20 (2 H, m, 3α- and 6α-H) (Found: C, 71.65; H, 10.15. $C_{31}H_{52}O_6$ requires C, 71.50; H, 10.07); elution with the more polar benzene–ethyl acetate (5 : 1) provided the 4β,6β-diacetoxy-3β,5α-diol (31) (58 mg), as a foam; δ 1.33 (s, 10-Me), 2.02 and 2.12 (6 H, 2 Ac), 2.65br (1 H, s, OH), 3.20 (1 H, s, OH), 4.30 (1 H, m, 3α-H), 4.96 (1 H, m, 6α-H), and 5.13 (1 H, d, *J* 3 Hz, 4α-H).

Acetylation of the both products gave the same *triacetate* (32), m.p. 213—214.5 °C (from methanol); δ 1.35 (s, 10-Me), 1.93, 2.0, and 2.06 (9 H, 3 Ac), 2.50br (1 H, s, OH), 4.85 (1 H, m, 6α-H), 5.20 (1 H, m, 4α-H), and 5.40 (1 H, m, 3α-H) (Found: C, 70.65; H, 9.6. $C_{33}H_{54}O_7$ requires C, 70.43; H, 9.67).

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