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CLEAVAGE REACTIONS OF SOME STEROIDAL EPOXIDES

G.A. Morrison* and J.B. Wilkinson

Dept. of Organic Chemistry, The University, Leeds LS2 9JT

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Epoxide migration, in which interconversion of vicinal hydroxy-epoxides occurs by intramolecular nucleophilic attack of an oxy-anion upon an adjacent epoxide, is well documented in the carbohydrate field.[1] We wish to describe some novel cis-cleavage reactions of steroidal epoxides[2] which involve a similar process.

Treatment of 4α,5-epoxy-3β-methoxy-5α-cholestan-6β-ol (7a) [obtained by saponification under mild basic conditions of the corresponding acetate (7b), itself prepared by epoxidation of the olefin (3a)[3] with m-chloroperbenzoic acid] with aqueous perchloric acid in acetone gave a mixture of 3β-methoxy-5α-cholestan-4α, 5,6β-triol (6a) and the derived acetonide (9). Structure (6a) was confirmed by an independent preparation of the compound from the olefin (3a) by successive hydroxylation with osmium tetroxide and saponification. Similar cis-cleavage of the oxirane ring occurred when the epoxide (7a) was treated with formic acid or with acetic acid, when the diformate (6b) and the acetate (6c) respectively were formed. The likeliest pathway for these unusual cis-cleavage reactions involves an initial epoxide migration of compound (7a) to form the isomeric hydroxy-epoxide (10a), the oxirane ring of which then undergoes normal diaxial cleavage to yield products with 4α- and 5α- substituents. In the reaction of (7a) with acetic or formic acids the initial product of such a sequence would be a tertiary ester (6d or 6e), which would then rearrange, via a 4α,5α-orthoester, to the more stable secondary equatorial acetate (6c) or the corresponding formate which would then undergo esterification to the diformate (6b).

In accord with this view, treatment of (7a) with boron trifluoride etherate gave the fluorohydrin (6f), the structure which followed from its ^{1}H and ^{19}F n.m.r. spectra and those of the derived monoacetate (6g). Epoxide migration was also achieved by treatment of the α-epoxide (7a) with hot methanolic potassium hydroxide which brought about rearrangement to the isomeric β-epoxide (10a). As expected, the epoxide (10a) upon treatment with formic acid gave the diformate (6b).

In all these cases the inductive effect of the 3-methoxy group, by inhibiting cleavage of the C_4 - O bond, permits the alternative reaction pathway involving epoxide migration to compete effectively. The same factor operates in the case of the 3α-epimer

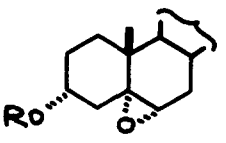
(7c), obtained from epicholesterol epoxide (1a)[4] by treatment with acetic acid, followed by dehydration of the resulting acetate (4) with thionyl chloride to give the olefin (3b), which was oxidised with acetyl hypobromite; treatment of the reaction mixture with base then afforded, among other products, the epoxides (7c) and (10b). Each of these, upon suitable base treatment, gave a mixture of the two, and, as expected, both gave the same triol (6h) when hydrolysed in acetone solution with aqueous perchloric acid.

4α,5-Epoxy-5α-cholestan-6β-ol (7d), which lacks the inductive influence of a 3-methoxy group, has been reported[5] to undergo unexceptional diaxial cleavage with methanolic toluenesulphonic acid to give the triol (2a). We now report, in broad agreement with that observation, that hydrolysis with aqueous perchloric acid in acetone gives, as major products, the triol (2a) and the derived 4β,6β-acetonide (2b), together with a small amount (ca.7%) of the triol (6i) arising by an epoxide migration pathway. However, when the epoxide (7d) is treated with boron trifluoride etherate the fluoro-diol (6j), the structure of which follows from its ^{1}H and ^{19}F n.m.r. spectra and those of the derived monoacetate (6k), is the major product. It would appear therefore that, in the absence of a strong external nucleophile, neighbouring group participation of the adjacent hydroxy group may determine the course of the reaction even when there is no vicinal methoxy group.

Treatment of 3β,6β-dimethoxycholest-4-ene (3c)[6] with m-chloroperbenzoic acid gave the α-epoxide (7e) in which cleavage of either of the C-O bonds of the oxirane ring is inhibited by the inductive effect of the vicinal methoxy groups. Hydrolysis with aqueous perchloric acid in acetone proceeded very slowly to give both the normal trans-diaxial cleavage product (2c) (52%) and the product of cis-cleavage (6l) (29%), arising via an intermediate 5β,6β-methyloxonium ion formed by intramolecular nucleophilic attack of the 6β-methoxy group at C_5. When treated with acetic acid, the epoxide (7e) underwent overall cis-cleavage to give the acetate (6m) (28%).

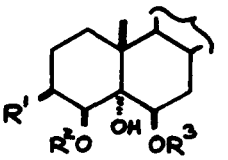
Even in the absence of a 6β-hydroxy or methoxy group to serve as an internal nucleophile, attack of an external nucleophile at C_4 of a 4α,5α-epoxide is still inhibited by a 3-methoxy group. Thus, 4α,5-epoxy-3β-methoxy-5α-cholestane (7f) reacts with aqueous perchloric acid to give 3β-methoxy-5β-cholestane-4α,5-diol (8a). Dehydration of the derived acetate (8b) with thionyl chloride affords the allylic acetate (5b); the corresponding alcohol (5a) has previously been obtained[7] by treatment of the epoxide (7f) with aqueous sulphuric acid.

The 3-methoxy group of the keto-epoxide (11a), obtained by oxidation of the corresponding alcohol (7a), has a profound effect upon the course of its reaction with acetic acid. Thus, whereas the desmethoxy analogue (11b)[5] reacts unexceptionally to give the diaxial cleavage product (14), compound (11a), in which cleavage of the C_4-O bond is inhibited, reacts with cleavage of the C_5-O bond by cine substitution of the



1 (a); R = H

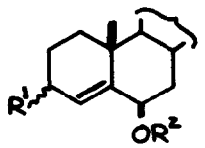
(b); R = Me



2 (a); $R^1 = R^2 = R^3 = H$

(b); $R^1 = H$, $R^2R^3 = >CMe_2$

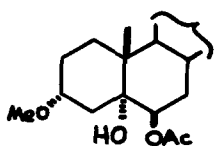
(c); $R^1 = OMe$, $R^2 = H$, $R^3 = Me$



3 (a); R^1 = β-OMe, R^2 = Ac

(b); R^1 = α-OMe, R^2 = Ac

(c); R^1 = β-OMe, R^2 = Me



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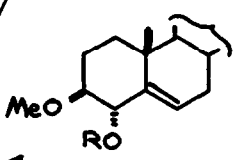
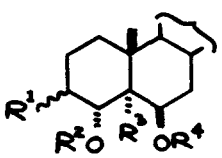


5 (a); R = H

(b); R = Ac



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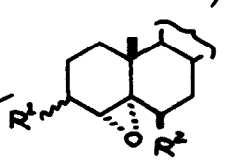
	R^1	R^2	R^3	R^4
(a)	β-OMe	H	OH	H
(b)	β-OMe	CHO	OH	CHO
(c)	β-OMe	Ac	OH	H
(d)	β-OMe	H	OAc	H
(e)	β-OMe	H	OCHO	H
(f)	β-OMe	H	F	H
(g)	β-OMe	Ac	F	H
(h)	α-OMe	H	OH	H
(i)	H	H	OH	H
(j)	H	H	F	H
(k)	H	Ac	F	H
(l)	β-OMe	H	OH	Me
(m)	β-OMe	Ac	OH	Me



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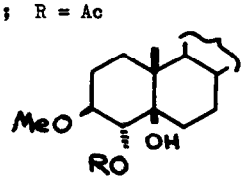
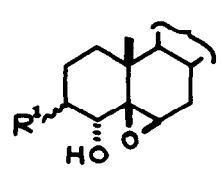
	R^1	R^2
(a)	β-OMe	OH
(b)	β-OMe	OAc
(c)	α-OMe	OH
(d)	H	OH
(e)	β-OMe	OMe
(f)	β-OMe	H



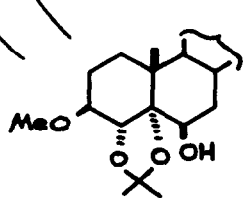
8 (a); R = H

(b); R = Ac



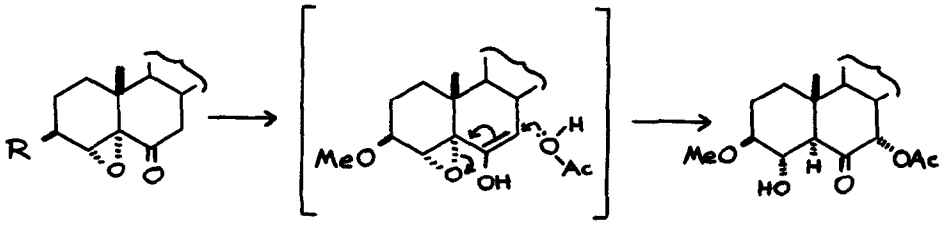
10 (a); R = β-OMe

(b); R = α-OMe



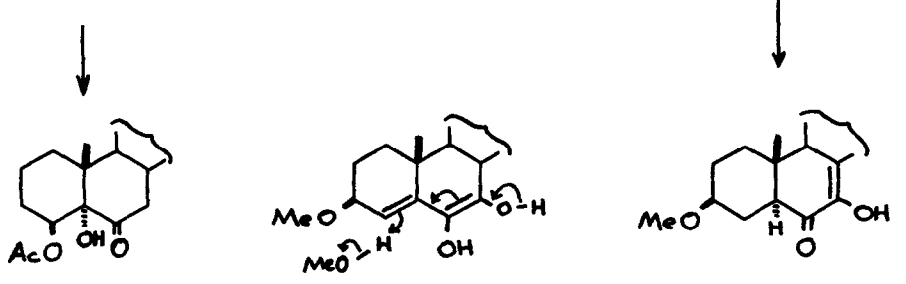
derived enol (12) to give 7α-acetoxy-4α-hydroxy-3β-methoxy-5α-cholestan-6-one (13).[8] The structure of compound (13) followed from its spectra, and from the fact that attempted saponification gave the enolic α-diketone (16). Formation of the last-named compound may be rationalised as involving dehydration of the initial saponification product, and rearrangement of the resulting enolone in its dienolic form (15).

Satisfactory microanalyses and spectra were obtained for all the new compounds described.



11 (a); R = OMe 12 13

(b); R = H



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