Cleavage of the Epoxide Ring in *trans*-Epoxy-alcohols by Sodium Borohydride in Methanol

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The epoxide ring in steroidal *trans*-αβ, and βγ-epoxy-alcohols is cleaved by sodium borohydride in refluxing methanol to give the corresponding methoxyhydrins, in contrast to the *cis*-epoxy-alcohols which remain unchanged. The steric requirements of the reaction and a mechanism involving the intermediate formation of a boron complex with the substrate are discussed.

In contrast to lithium aluminium hydride, sodium and lithium borohydride are not commonly used [1] as reagents for the reductive opening of epoxides. The few examples encountered so far include but-1-ene oxide,[2] several *para*-substituted styrene oxides,[2] cyclopentene oxide,[3] and some steroidal epoxides.[4] The presence of minor amounts of sodium or lithium borohydride was

[1] E. L. Eliel in 'Steric Effects in Organic Chemistry,' ed. M. S. Newman, Wiley, New York, 1956, p. 106; E. Schenker in 'Newer Methods of Preparative Organic Chemistry,' ed. W. Foerst, vol. 2, Academic Press, New York, 1968, p. 196.

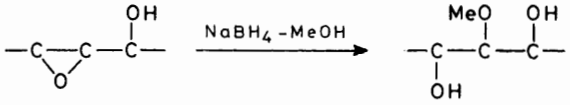
[2] R. Fuchs and C. A. VanderWerf, *J. Amer. Chem. Soc.*, 1954, **76**, 1631.

[3] R. H. Cornforth, *J. Chem. Soc.* (*C*), 1970, 928.

[4] W. J. Adams, D. K. Patel, V. Petrow, and I. A. Stuart-Webb, *J. Chem. Soc.*, 1954, 1825; M. Bharucha, H. Jäger, K. Meyer, T. Reichstein, and O. Schindler, *Helv. Chim. Acta*, 1959, **42**, 1395.

shown to have a major effect on the course of the reduction of several cyclohexene oxides with diborane.[5]

During an investigation of the reaction of steroidal αβ-epoxy-ketones with toluene-*p*-sulphonylhydrazine in methanol solution, in the presence of sodium borohydride as reducing agent, we observed [6] that methoxyhydrins were formed by opening of the epoxide ring. The only previous report of a similar reaction referred to the stereoisomeric tetrahydroxycyclohexene oxides (anhydroinositols).[7] In both instances the reaction is confined to vicinal epoxy-alcohols.

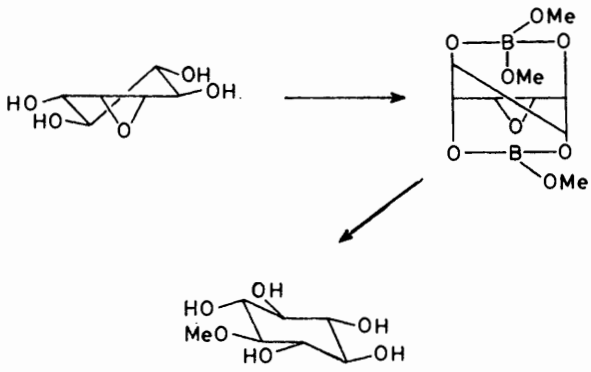


We now present the results obtained with several steroidal epoxy-alcohols, in an attempt to define the scope and limitations of this reaction. Whereas 2α,3α-epoxy-5α-cholestane remains unchanged in the presence of methanolic sodium borohydride at reflux temperature, 1α,2α-epoxy-5α-cholestan-3β-ol (1) is quantitatively transformed into 2β-methoxy-5α-cholestane-1α,3β-diol (15); nevertheless, the isomeric 1α,2α-epoxy-5α-cholestan-3α-ol (2) remains unchanged under similar conditions.[6] No reaction takes place when compound (1) is treated with sodium borohydride in tetrahydrofuran or dioxan; in the presence of ethanol or propan-2-ol a simple reduction of the epoxide ring occurs, leading to 5α-cholestane-1α,3β-diol. The presence of a methanolic solution of borohydride is necessary for the formation of compound (15); the starting epoxy-alcohol (1) remains unchanged even after prolonged heating in methanol (containing a trace of potassium hydrogen carbonate, in order to exclude an eventual reaction catalysed by acidic impurities in the solvent), as well as after heating in methanolic sodium methoxide.

The inertness of compound (2) under these conditions is common to all vicinal *cis*-epoxy-alcohols investigated so far: 1β,2β-epoxy-3β-hydroxy-5α- (4) [8] and 1β,2β-epoxy-3β-hydroxy-5β-cholestane (6),[9] 2α,3α-epoxy-1α-hydroxy- (8) [10] and 2β,3β-epoxy-1β-hydroxy-5α-cholestane (10),[11] and 3α,4α-epoxy-5α-hydroxy- (11) and 3β,4β-epoxy-5β-hydroxy-cholestane (12).[12]

Conversely, methoxyhydrins were obtained from a series of vicinal *trans*-epoxy-alcohols. 1β,2β-Epoxy-5β-cholestan-3α-ol (5) [9] afforded 2α-methoxy-5β-cholestane-1β,3α-diol (16a). 2β,3β-Epoxy-5α-cholestan-1α-ol (9) [11] was first transformed under the slightly alkaline conditions of the reaction into compound (1) which reacted subsequently with sodium borohydride to give the methoxy-diol (15). Transformations like (9) ⟶ (1) are due to an internal nucleophilic displacement of the epoxide by the *trans*-oxyanion and are well known ('epoxide migration') in carbohydrate and cyclitol epoxides.[13] The above conversion does not occur in acidic conditions: treatment of compound (9) with methanol in the presence of toluene-*p*-sulphonic acid results in 3α-methoxy-5α-cholestane-1α,2β-diol (17).

In the stereoisomeric tetrahydroxycyclohexene oxides that reacted with sodium borohydride in methanol,[7] the epoxide ring is *trans* with respect to one of the vicinal hydroxy-groups and to one or both hydroxy-groups in β-positions. According to these authors,[7] the effective reagent might be the tetramethoxyborate anion. The mechanism proposed by Angyal [14] to explain the transformation of 1,2-anhydro-*myo*-inositol into the methyl ether of *scyllo*-inositol involves the intermediate formation of a rigid tetraco-ordinated boron complex in which a methoxy-group is suitably oriented to displace the epoxide ring.



Although this scheme offers an attractive explanation of the above reaction, it seems to be inoperative for the stereoisomeric anhydroinositols [7] in which the hydroxy-groups at positions 3 and 5 or 4 and 6 (with respect to the epoxide) cannot assume the diaxial relationship necessary for the formation of the above bidentate complex; it also leads to the assumption that not one, but two hydroxy-groups are necessary in order to allow the reaction to proceed. According to the results obtained with the simpler steroidal models investigated in the present work, the reaction should involve the initial formation of a tetraco-ordinated boron complex, with participation of the hydroxy-group of the substrate and of one, two, or three methoxy-groups from the solvent. In compound (1), ring A is flexible enough in the tran-

[5] H. C. Brown and N. M. Yoon, *J. Amer. Chem. Soc.*, 1968, **90**, 2686.

[6] M. Weissenberg, D. Lavie, and E. Glotter, *Tetrahedron*, 1973, **29**, 353.

[7] M. Nakajima, H. Kurihara, and T. Ogino, *Chem. Ber.*, 1963, **96**, 619.

[8] H. B. Henbest and R. A. L. Wilson, *J. Chem. Soc.*, 1957, 1958; R. Albrecht and Ch. Tamm, *Helv. Chim. Acta*, 1957, **40**, 2216.

[9] M. Weissenberg and E. Glotter, following paper.

[10] E. Glotter, P. Krinsky, M. Retjö, and M. Weissenberg, *J.C.S. Perkin I*, 1976, 1442.

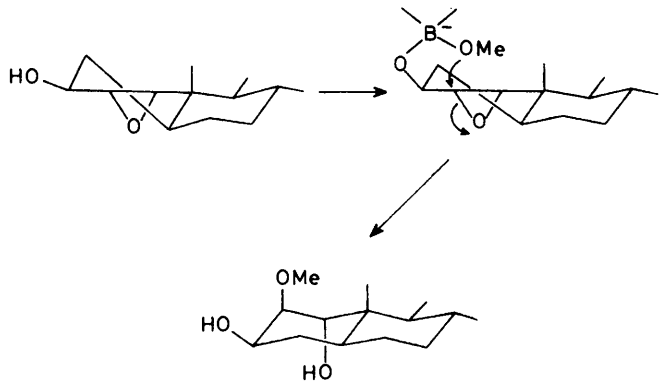
[11] E. Glotter and P. Krinsky, *J.C.S. Perkin I*, 1978, 413.

[12] E. Glotter, S. Greenfield, and D. Lavie, *Tetrahedron Letters*, 1967, 5261.

[13] (*a*) S. J. Angyal, V. Bender, and J. H. Curtin, *J. Chem. Soc.* (*C*), 1966, 798, and references cited therein; see also (*b*) J. G. Buchanan and H. Z. Sable in 'Selective Organic Transformations,' ed. B. S. Thyagarajan, vol. 2, Wiley-Interscience, New York, 1972; (*c*) J. G. Buchanan, *Methods Carbohydrate Chem.*, 1972, **6**, 135.

[14] S. J. Angyal, personal communication to J. G. Buchanan, cited in ref. 13*b*, p. 21.

sition state for this complex to assume the quasidiaxial orientation required for displacement of the epoxide.



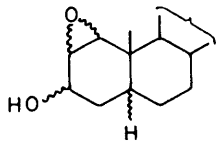
If this orientation is not achieved, the reaction may not occur at all. In fact, 2α,3α-epoxy-5α-cholestan-1β-ol (7) remains unchanged even when treated with methanolic sodium borohydride for longer periods of time. Assuming that the mechanism proposed by us is correct, then the hydroxy-group participating *via* the boron complex in the displacement of the anhydro-inositols [7] should be β with respect to the epoxide ring. To check if indeed a βγ-epoxy-alcohol may behave in the same manner as a vicinal (αβ) epoxy-alcohol, the reaction was attempted with 2β,3β-epoxy-5α-cholestan-5-ol (13).[15] A longer period of time was necessary to bring the reaction to completion, resulting in 3α-methoxy-5α-cholestane-2β,5-diol (18); the corresponding *cis*-epoxy-alcohol (14) remained unchanged under these conditions. Compound (18) was alternatively obtained by acid-catalysed reaction of the epoxy-alcohol (13) in methanol solution. Surprisingly, 1β,2β-epoxy-5α-cholestan-3α-ol (3) [6] remained unchanged even after heating for 20 h with sodium borohydride in methanol.

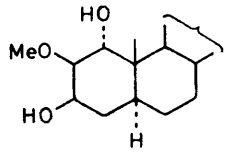
EXPERIMENTAL

M.p.s were taken with a Fisher-Johns apparatus. Optical rotations were recorded with an automatic Perkin-Elmer polarimeter and refer to solutions in chloroform. N.m.r. spectra were determined with a Varian NV-14 instrument (60 MHz) for solutions in deuteriochloroform. T.l.c. was carried out on chromatoplates of silica gel G (Merck) and spots were developed with iodine vapour. Column chromatography was performed on silica gel 60 (Merck; 70—230 mesh). Petroleum refers to the fraction of b.p. 60—80 °C. Analyses were performed in the microanalytical laboratory of the Weizmann Institute, under the direction of Mr. R. Heller.

General Procedure for Treatment of Epoxy-alcohols with Sodium Borohydride.—To a solution of the epoxy-alcohol (100 mg) in methanol (20 ml), sodium borohydride (200 mg) was added over a few minutes. The solution was heated to reflux for 4 h (unless otherwise stated); after cooling it was neutralised with dilute hydrochloric acid, most of the solvent was removed under reduced pressure, and the crude product was collected by filtration or extracted with dichloromethane.

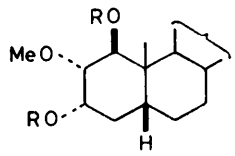
1α,2α-Epoxy-5α-cholestan-3β-ol (1) afforded 2β-methoxy-5α-cholestane-1α,3β-diol (15).[6] The reaction was repeated



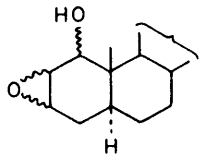


(15)

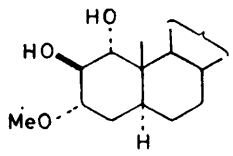
Epoxy		Hydroxy
(1) 5α	α	β
(2) 5α	α	α
(3) 5α	β	α
(4) 5α	β	β
(5) 5β	β	α
(6) 5β	β	β



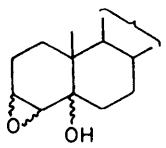
(16) a; R = H
b; R = Ac



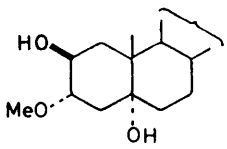
(7)	α	β
(8)	α	α
(9)	β	α
(10)	β	β



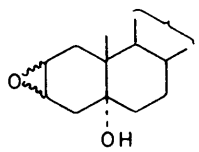
(17)



(11)	α	α
(12)	β	β



(18)



(13)	β	α
(14)	α	α

in 2 : 1 methanol–water (15 ml). The crude product showed two spots on a chromatoplate. According to n.m.r. it was a 1 : 3 mixture of unchanged material (1) and methoxy-diol (15).

1β,2β-Epoxy-5β-cholestan-3α-ol (5) [9] afforded quantitatively 2α-*methoxy*-5β-*cholestane*-1β,3α-*diol* (16a), m.p. 177—178 °C (from methanol); $[\alpha]_D$ +22° (*c* 0.5), δ 1.03 (19-H), 3.4 (narrow m, 2β-H), 3.46 (OMe), 3.85 (br m,

[15] T. Komeno and H. Itani, *Chem. and Pharm. Bull.* (*Japan*), 1970, **18**, 608.

3β-H), and 4.05 (d, *J* 4 Hz, 1α-H) (Found: C, 77.4; H, 11.7. $C_{28}H_{50}O_3$ requires C, 77.35; H, 11.6%). Acetylation with acetic anhydride–pyridine for 48 h at room temperature gave the 1,3-*diacetate* (16b), m.p. 124—126 °C (from methanol); $[\alpha]_D$ +23.5° (*c* 0.4); δ 0.92 (19-H), 2.10 (OAc), 3.5 (narrow m, 2β-H), 3.55 (OMe), 5.15 (br m, 3β-H), and 5.44 (d, *J* 4 Hz, 1α-H) (Found: C, 74.0; H, 10.5. $C_{32}H_{54}O_5$ requires C, 74.1; H, 10.5%).

2β,3β-Epoxy-5α-cholestan-1α-ol (9) [11] afforded quantitatively the methoxy-diol (15), which was isolated by filtration and purified by crystallisation from methanol; m.p. and mixed m.p. 198—200 °C. When the mixture was heated to reflux for only 0.5 h, a mixture of unchanged material (9), epoxy-alcohol (1), and methoxy-diol (15) was obtained. They were identified by t.l.c. and n.m.r. studies of the mixture.

2β,3β-Epoxy-5α-cholestan-5-ol (13) [15] afforded 3α-*methoxy*-5α-*cholestane*-2β,5-*diol* (18), m.p. 173—175 °C (from methanol); $[\alpha]_D$ +12.4° (*c* 0.4); δ 1.15 (19-H), 3.41 (OMe), 3.5 (narrow m, 3β-H), and 4.15 (narrow m, 2α-H) (Found: C, 77.3; H, 11.45. $C_{28}H_{50}O_3$ requires C, 77.35; H, 11.6%). The mixture was heated to reflux for 30 h. The crude product contained *ca.* 60% unchanged material. Separation was achieved by thick-layer chromatography. No reaction occurred when compound (13) was heated to reflux in methanol solution in the absence of sodium borohydride.

Compound (1) (50 mg) showed no reaction under the following experimental conditions:

$NaBH_4$ (mg)	Medium	Reflux time (h)
None	1% $KHCO_3$ in MeOH (10 ml)	4
None	1% $NaOCH_3$ in MeOH (10 ml)	5
100	Dioxan (10 ml)	4
100	Tetrahydrofuran (8 ml) + water (2 ml)	4

Treatment of Compound (1) *with Sodium Borohydride in Propan-2-ol.*—To a solution of compound (1) (250 mg) in propan-2-ol (50 ml), sodium borohydride (500 mg) was added. The solution was heated to reflux for 4 h, cooled, and neutralised with dilute hydrochloric acid. Most of the solvent was removed, water was added, and the crude product was isolated by filtration and acetylated with acetic anhydride and pyridine overnight at room temperature. The product was chromatographed through silica gel (50 g). Elution with petroleum–ether (9 : 1) gave 3β-acetoxy-1α,2α-epoxy-5α-cholestane [6] (40 mg), m.p. and mixed m.p. 118—119 °C. Further elution with the same solvent gave 5α-*cholestane*-1α,3β-*diol diacetate* (190 mg), m.p. 110—112 °C (from methanol); δ 0.90 (19-H), 2.00 and 2.07 (OAc), and 4.7—5.1 (overlap, 1β- and 3α-H). Hydrolysis of this diacetate by heating to reflux with methanolic 2% potassium hydroxide during 0.5 h, gave after work-up 5α-cholestane-1α,3β-diol,[8,16] m.p. and mixed m.p. 154—155 °C. Similar results were obtained when ethanol was used instead of propan-2-ol.

Treatment of Compound (13) *with Methanol in the Presence of Acid.*—To a solution of compound (13) (100 mg) in methanol (50 ml), toluene-*p*-sulphonic acid (10 mg) was added and the solution was heated to reflux for 2 h. After cooling the solution was neutralised with aqueous sodium hydrogen carbonate, most of the solvent was removed, water was added, and the product was collected by filtration. It showed one spot on a chromatoplate, concurrent with that of compound (18). M.p and mixed m.p. 173—175 °C.

Similarly, compound (9) (20 mg) gave a crude product that was isolated by extraction with dichloromethane. It showed one spot on a chromatoplate. 3α-*Methoxy*-5α-*cholestane*-1α,2β-*diol* (17) had m.p. 150—151 °C (from hexane); $[\alpha]_D$ +28° (*c* 0.3); δ 0.95 (19-H), 3.38 (OMe), and 3.1, 3.45, and 4.1 (narrow m) (Found: C, 77.4; H, 11.5. $C_{28}H_{50}O_3$ requires C, 77.35; H, 11.6%).

The following cholestane derivatives remained unchanged when treated with sodium borohydride as described in the general procedure [the solutions were heated to reflux for 8 h; compounds (3) and (7) were heated for 20 h]: 1α,2α-epoxy-3α-hydroxy-5α- (2),[6] 1β,2β-epoxy-3α-hydroxy-5α- (3),[16] 1β,2β-epoxy-3β-hydroxy-5α- (4),[8] 1β,2β-epoxy-3β-hydroxy-5β- (6),[9] 2α,3α-epoxy-1β-hydroxy-5α- (7),[11] 2α,3α-epoxy-1α-hydroxy-5α- (8),[10] 2β,3β-epoxy-1β-hydroxy-5α- (10),[11] 3α,4α-epoxy-5-hydroxy-5α- (11),[12] 3β,4β-epoxy-5-hydroxy-5β- (12),[12] and 2α,3α-epoxy-5-hydroxy-5α- (14).[15]

[7/1468 *Received*, 12*th August*, 1977]

[16] E. Glotter and P. Krinsky, *J.C.S. Perkin I*, 1978, 408.