Steric Course of Reduction with Sodium Borohydride of Steroidal αβ-Epoxy-ketones

By **Martin Weissenberg,*** Department of Organic Chemistry, The Weizmann Institute of Science, Rehovot, Israel
Erwin Glotter,* Faculty of Agriculture, The Hebrew University of Jerusalem, Rehovot 76–100, P.O. Box 12,. Israel

The formation of *cis*- and *trans*-epoxy-alcohols by treatment of steroidal epoxy-ketones with sodium borohydride is analysed in terms of the direction of attack on the corresponding unsubstituted ketones, and the steric hindrance exerted by the epoxide ring.

ALTHOUGH αβ-epoxy-alcohols are easily obtained by reduction of the corresponding epoxy-ketones with sodium borohydride, there are relatively few reports on stereochemical aspects of this reaction. Earlier results obtained by reduction of steroidal αβ-epoxy-ketones, mainly 4,5-epoxy-3-ones [(2c and d) and (4b and c); see Table], led to the view [2,3] that the preferential formation of *trans*-epoxy-alcohols is a general feature of this reduction. The stereochemistry of these, as well as of other similar reductions of related unhindered steroidal epoxy-ketones [compounds (1c), (2a, c, and d),

[1] B. Camerino and D. Cattapan, *Farmaco, Ed. Sci.*, 1958, **13**, 39.

[2] J. M. Coxon, M. P. Hartshorn, and D. N. Kirk, *J. Chem. Soc.*, 1964, 2461.

[3] E. Toromanoff, *Compt. rend.*, 1967, **264**, 1881.

and (4a—c)] has been evaluated by Toromanoff,[4] who suggested that the direction of the kinetic addition of the hydride ion is determined by electronic factors and should take place preferentially from the side of the oxygen atom (or of the methylene group, in the case of αβ-methylene ketones) of the three-membered ring. The predominant products would therefore be *trans*-epoxy-alcohols (or *trans*-methylene-alcohols).

More recently, Chautemps and Pierre[5] proposed a different interpretation of the results obtained by reduction of αβ-epoxy-ketones with sodium borohydride, based on steric and electronic factors. Whenever one of the lone pairs of the epoxidic oxygen and the carbonyl can assume a *cis*-relationship, a chelate with the cation of the complex hydride might be formed ('cyclic model'); consequently the reducing species would attack the carbonyl from the less hindered face, leading largely to a *trans*-epoxy-alcohol. If the formation of such a cyclic model is sterically difficult, mixtures of *cis*- and *trans*-epoxy-alcohols would be formed; their formation could also be rationalised by use of Felkin's model.[6,7]

Reduction of steroidal αβ-epoxy-ketones with sodium borohydride

Compound	Substrate	Epoxide	Ketone	Epoxy-alcohol *trans* (%)	Epoxy-alcohol *cis* (%)	Ref.
AB-*trans*						
(1a)	Cholestane	1α,2α-	3-	60	40	13
(1b)	Androstan-17β-ol	1α,2α-	3-	Major		11
(1c)	Androstan-17-one	1α,2α-	3-	60		12
(2a)	Cholestane	4α,5α-	3-	75		*a*
(2b)	17β-Acetoxyandrostane	4α,5α-	3-	63		*b*
(2c)	Pregnan-20-one	4α,5α-	3-	76		1
(2d)	4-Methylcholestane	4α,5α-	3-	>58		2
(3)	Cholestane	5α,6α-	4-	72	12	*c*
AB-*cis*						
(4a)	Cholestane	4β,5β-	3-	85		*a*
(4b)	Pregnan-20-one	4β,5β-	3-	75		1
(4c)	4-Methylcholestane	4β,5β-	3-	>70		2
(5)	Cholestane	5β,6β-	4-	90		*d*

[a] D. J. Collins, *J. Chem. Soc.*, 1959, 3919. [b] D. Baldwin and J. R. Hanson, *J.C.S. Perkin I*, 1972, 1889. [c] D. Lavie, Y. Kashman, and E. Glotter, *Tetrahedron*, 1966, **22**, 1102. [d] S. Greenfield, E. Glotter, D. Lavie, and Y. Kashman, *J. Chem. Soc.* (*C*), 1967, 1460.

A re-examination of the results in the Table leads to the conclusion that only tri- and tetra-substituted 4,5-epoxy- and 5,6-epoxy-ketones give predominantly *trans*-epoxy-alcohols, whereas disubstituted 1α,2α-epoxy-ketones show only a slight preference for the formation of such derivatives. In 4α,5α-epoxy-3-ones (2) and in 5α,6α-epoxy-4-ones (3), rings A and B are *trans*-fused and the spatial arrangement of the molecule is almost the same as in the unsubstituted 3- and 4-ones (5α-series). In fact, reduction with borohydride of 5α-3-ones and of 5α-4-ones gives mainly 3β- (87—94%)[8] and 4β-alcohols (90%),[9] *i.e.* the major attack of the reducing agent takes place from the rear side of the molecule, irrespective of the presence or absence of the epoxide ring. However, 3β- and 4β-alcohols are obtained from the unsubstituted ketones in higher yields than are *trans*-epoxy-alcohols from the corresponding epoxy-ketones (2) and (3). Similarly, reduction of 5β-3-ones and of 5β-4-ones yields mainly 3α-[8] and 4α-alcohols,[10] the steric course of reduction being the same as for the corresponding epoxy-ketones (4) and (5).

The tendency of a 3-one in the 5α-series to give by hydride reduction the equatorial 3β-ol is diminished in the reduction of 1α,2α-epoxy-3-ones. In the experiments with compounds (1b)[11] and (1c),[12] only the *trans*-epoxy-alcohols are mentioned; in the experiment with compound (1a)[13] a substantial amount of the *cis*-epoxy-alcohol has been isolated.

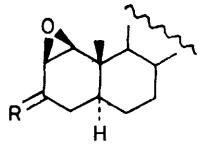
The behaviour of these compounds suggests that electronic factors alone cannot satisfactorily accommodate the results given above and that steric factors should be considered as well. In our view, the outcome of the hydride reduction of αβ-epoxy-ketones in a rigid framework may be interpreted as follows: (i) the main direction of attack of the reducing agent is the same as in the corresponding unsubstituted ketone; and (ii) the epoxide ring may sterically interfere with this attack, leading to various amounts of the stereoisomeric epoxy-alcohol.

A case in point is that of 1β,2β-epoxy-5α-cholestan-3-one (6).[14] By analogy with the behaviour of several αβ-methylene-ketones, Toromanoff predicted[4] that

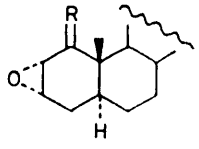
[4] E. Toromanoff, *Bull. Soc. chim. France*, 1968, 2457.
[5] P. Chautemps and J.-L. Pierre, *Tetrahedron*, 1976, **32**, 549.
[6] M. Cherest and H. Felkin, *Tetrahedron Letters*, 1968, 2205; 1971, 383.
[7] For a pertinent discussion on the factors controlling axial or equatorial attack on cyclohexanones, see J. Huet, Y. Maroni-Barnaud, Nguyen Trong Anh, and J. Seyden-Penne, *Tetrahedron Letters*, 1976, 159.
[8] D. M. S. Wheeler and M. M. Wheeler, in 'Organic Reactions in Steroid Chemistry,' eds. J. Fried and J. A. Edwards, Van Nostrand, New York, 1972, vol. 1, pp. 61, 78, and references cited therein.
[9] D. C. Ayres, D. N. Kirk, and R. Sawdaye, *J. Chem. Soc.* (*B*), 1970, 505.
[10] M. Weissenberg and E. Glotter, *J.C.S. Perkin I*, 1977, 988.
[11] W. R. Benn, F. Colton, and R. Pappo, *J. Amer. Chem. Soc.*, 1957, **79**, 3920.
[12] B. Pelc, J. Hodkova, and J. Holubek, *Coll. Czech. Chem. Comm.*, 1966, **31**, 1363.
[13] M. Weissenberg, D. Lavie, and E. Glotter, *Tetrahedron*, 1973, **29**, 353.
[14] (*a*) R. Albrecht and Ch. Tamm, *Helv. Chim. Acta*, 1957, **40**, 2216; (*b*) H. B. Henbest and R. A. L. Wilson, *J. Chem. Soc.*, 1957, 1958.

reduction with borohydride of a 5α-steroidal 1β,2β-methylene-3-one and of the analogous epoxy-ketone should yield predominantly *trans*-methylene- and epoxy-alcohols, respectively. In fact, only the *cis*-epoxy-alcohol (7) is obtained by reduction of the epoxy-ketone (6). In our opinion, the factors outlined above concur to secure the stereospecificity of this reaction: the tendency of the 3-one to give the equatorial 3β-ol by rear-side attack is supported by the hindrance of the β-face of the molecule (epoxide ring, in addition to the angular methyl group), precluding ' top '-side attack.

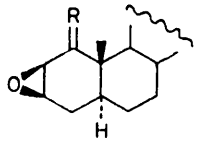
The isomeric 2α,3α-epoxy-5α-cholestan-1-one (8) was prepared by mild oxidation of the epoxy-alcohol (9).[15] Reduction of compound (8) is stereospecific leading to the *cis*-epoxy-alcohol (9). The result agrees with our views, since reduction of 5α-cholestan-1-one with sodium borohydride yields only 1α-hydroxy-5α-cholestane.[10] In compound (8), the tendency, if any, for rear-side attack of the reducing agent is counterbalanced by the hindrance due to the epoxide ring.



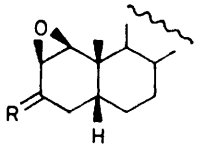
(6) R = O
(7) R = α - H, β - OH



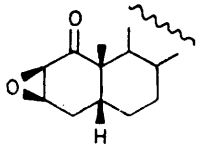
(8) R = O
(9) R = α - OH, β - H



(10) R = O
(11) R = α - OH, β - H
(12) R = α - H, β - OH



(13) R = O
(14) R = α - OH, β - H
(15) R = α - H, β - OH



(16)

Electronic and steric factors should have been anticipated to concur in the reduction of 2β,3β-epoxy-5α-cholestan-1-one (10),[16] leading mainly to the *trans*-epoxy-alcohol (11). In fact a 2 : 1 mixture of *trans*- (11) and *cis*- (12) epoxy-alcohols is obtained.[16] The outcome of this reduction is consistent with the hindrance exerted by the β-oriented epoxide ring, diminishing the propensity for approach of the reducing agent from the ' top ' of the molecule.

Reduction of 1β,2β-epoxy-5β-cholestan-3-one (13) [17] afforded a mixture of *trans*- (14) and *cis*- (15) epoxy-alcohols, roughly in the same ratio as in the reduction of the stereoisomeric epoxy-ketone (1a). Although the orientation of the hydroxy-group in the major product (14) is the same as in the alcohol obtained by reduction of 5β-cholestan-3-one, the propensity to α-attack by the reducing agent [leading to more than 40% of the *cis*-epoxy-alcohol (15)] is remarkable for a ketone in the 5β-series, in which the folding of rings A and B admittedly precludes the rear-side approach of the reagent at C-3.

In 2β,3β-epoxy-5β-cholestan-1-one (16),[18] front-side approach of the reducing agent is difficult owing to hindrance by the epoxide ring, and rear-side approach at C-1 is difficult owing to the folding of rings A and B. In fact compound (16) remained mostly unchanged on attempted reduction with sodium borohydride.

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 A-60 instrument 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). Analyses were performed in the microanalytical laboratory of the Weizmann Institute, under the direction of Mr. R. Heller.

2α,3α-*Epoxy*-5α-*cholestan*-1-*one* (8).—To a solution of 2α,3α-epoxy-1α-hydroxy-5α-cholestane (9) [15] (300 mg) in acetone (50 ml), Jones reagent was added dropwise at 5—10 °C. The excess of oxidising agent was then destroyed with a few drops of methanol and most of the solvent was removed under reduced pressure. The product was extracted with ether; the extract was washed with water, dried, and evaporated. The crude *product* (280 mg) was homogeneous on t.l.c.; m.p. 95—97 °C (from methanol), $[\alpha]_D$ +26.5° (*c* 1.1); δ 3.42 (3β-H, m, $W_{\frac{1}{2}}$ 8 Hz), 3.11 (2β-H, d, *J* 3.5 Hz), and 0.99 (19-H, s) (Found: C, 80.7; H, 11.1. $C_{27}H_{44}O_2$ requires C, 80.95; H, 11.05%).

General Procedure for Reduction of Steroidal αβ-Epoxy-ketones with Sodium Borohydride.—To a solution of the epoxy-ketone (100 mg) in methanol (15—25 ml), sodium borohydride (100 mg) was added over a few minutes. The solution was stirred for 2 h at room temperature, then neutralised with dilute hydrochloric acid; most of the solvent was removed under reduced pressure, water was added, and the crude product was filtered off or extracted with ether, washed with water, and dried. Further purification was carried out as required, by direct crystallisation or by chromatography.

1β,2β-Epoxy-5α-cholestan-3-one (6) [14] afforded (after chromatography; elution with hexane–ether, 4 : 6), 1β,2β-epoxy-3β-hydroxy-5α-cholestane (7) [14] (95 mg), m.p. and mixed m.p. 174—176 °C (from methanol) (lit.,[14a] 175—

[15] E. Glotter, P. Krinsky, M. Rejto, and M. Weissenberg, *J.C.S. Perkin I*, 1976, 1442.
[16] E. Glotter and P. Krinsky, *J.C.S. Perkin I*, 1978, 413.
[17] E. Glotter, M. Weissenberg, and D. Lavie, *Tetrahedron*, 1970, **26**, 3857.
[18] M. Weissenberg, unpublished results.

176 °C); δ 3.98 (3α-H, m, $W_{\frac{1}{2}}$ 18 Hz), 3.25 (1α- and 2α-H, narrow signal), and 0.90 (19-H, s).

2α,3α-Epoxy-5α-cholestan-1-one (8) gave quantitatively 2α,3α-epoxy-1α-hydroxy-5α-cholestane (9),[15] m.p. and mixed m.p. 93—95 °C (from methanol) (lit.,[15] 94—95 °C).

1β,2β-Epoxy-5β-cholestan-3-one (13) [17] gave a crude product which was separated by chromatography into two components. Elution with hexane–ether (7.5 : 2.5) afforded 1β,2β-*epoxy*-5β-*cholestan*-3β-*ol* (15) (45 mg), m.p. 140—142 °C (from methanol), $[\alpha]_D$ +61° (*c*. 0.6); δ 4.11 (3α-H, m, $W_{\frac{1}{2}}$ 10 Hz), 3.3 (1α- and 2α-H, partial overlap), and 1.18 (19-H, s) (Found: C, 80.6; H, 11.4. $C_{27}H_{46}O_2$ requires C, 80.55; H, 11.5%). Further elution with the same solvent gave a mixture of (14) and (15) (5 mg), followed by 1β,2β-*epoxy*-5β-*cholestan*-3α-*ol* (14) (50 mg), m.p. 141—143 °C (from methanol), $[\alpha]_D$ +37° (*c* 0.2); δ 4.02 (3β-H, m), 3.10 (1α- and 2α-H, narrow signal), and 1.14 (19-H, s) (Found: C, 80.4; H, 11.6. $C_{27}H_{46}O_2$ requires C, 80.55; H, 11.5%).

2β,3β-Epoxy-5β-cholestan-1-one (16),[18] m.p. 98—99 °C (from ethanol–chloroform), $[\alpha]_D$ +6.5° (*c* 0.6), remained practically unchanged under similar conditions (t.l.c. and n.m.r. evidence).

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