

## 245. The Reduction of Some 1,2-Epoxides with Lithium Aluminium Hydride

Preliminary Communication

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*Summary.* The factors influencing the ease of the lithium aluminium hydride reduction of various 1,2-epoxycycloalkanes and 1,2-epoxyalkanes are described and discussed.

Epoxidation of an olefinic double bond followed by reductive cleavage of the epoxide ring with lithium aluminium hydride (hereafter referred to as LAH) in refluxing diethyl ether represents a convenient and useful method for the introduction of a hydroxyl group into organic compounds [1]. However, certain 1,2-epoxides, particularly in the steroid and terpene series, either require more vigorous conditions (higher boiling solvents and/or longer reaction times) in order to be reduced or are resistant to LAH [1]. Since the steric factors influencing the LAH reduction of epoxides have not been hitherto studied systematically, we have now investigated the ease of the LAH reduction of a number of unsubstituted 1,2-epoxycycloalkanes in function of ring size, stereochemistry (*cis-trans*), reaction temperature and amount of reducing agent, and of some 1,2-epoxyalkanes in function of the configuration (*cis-trans*) and size of the alkyl substituents attached to the oxirane ring. The results obtained are summarized in Tables 1, 2 and 3.

As can be seen from Table 1, the ease of LAH reduction of 1,2-epoxycycloalkanes in refluxing diethyl ether (with a 1:2 molar ratio of epoxide to LAH) diminishes slowly from C<sub>5</sub> to C<sub>7</sub> (common rings), decreases sharply for C<sub>8</sub> (medium ring), has the lowest value for C<sub>10</sub>, and then increases, particularly when passing from medium (C<sub>11</sub>) to large rings (C<sub>12</sub> and C<sub>15</sub>)<sup>2)</sup>. In all cases the *cis*-epoxides are reduced faster than the *trans*-isomers, but the difference is relatively small for C<sub>8</sub> and C<sub>10</sub> and then increases when one goes to C<sub>11</sub>, C<sub>12</sub> and C<sub>15</sub>. Table 2 shows that the rate of reduction of 1,2-epoxycycloalkanes containing a medium ring increases by increasing the relative amount of LAH and, particularly, the reaction temperature (*i.e.* by using refluxing tetrahydrofuran as solvent instead of diethyl ether). In the 1,2-epoxyalkane series

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2) A few cases have been reported describing the difficult LAH reduction of some 1,2-epoxycycloalkane derivatives which contain a 9-membered [2], 10-membered [3], and 11-membered ring [4].

Table 1. Ease of reduction of 1,2-epoxycycloalkanes with lithium aluminium hydride in refluxing diethyl ether, using a 1:2 molar ratio of epoxide to LAH

1,2-Epoxycycloalkane <sup>a)</sup>	Unchanged epoxide (in %) <sup>b)</sup> after x hours:								
	x = 0.5	1	2	3	4	6	12	24	48
1,2-Epoxycyclopentane	0								
1,2-Epoxycyclohexane	7	0							
1,2-Epoxycycloheptane	41	11	1	0.3	0				
<i>cis</i> -1,2-Epoxycyclooctane						89	73	48	24
<i>trans</i> -1,2-Epoxycyclooctane						99	98	97.7	96.5
<i>cis</i> -1,2-Epoxycyclodecane						93	83	81	76
<i>trans</i> -1,2-Epoxycyclodecane						99	97.7	97.3	96.6
<i>cis</i> -1,2-Epoxycycloundecane				85	82	77	71	63	50
<i>trans</i> -1,2-Epoxycycloundecane						92.5	83	81	77
<i>cis</i> -1,2-Epoxycyclododecane				42	25	12	2.5	0	
<i>trans</i> -1,2-Epoxycyclododecane			93	90	87	83	66	49	28
<i>cis</i> -1,2-Epoxycyclopentadecane	24	22	17	13	11	5.5	1	0	
<i>trans</i> -1,2-Epoxycyclopentadecane		90	80	75.5	61.5	28	12	4	0

<sup>a)</sup> The reductions were performed in the usual way, with 1 mmol of epoxide and 2 mmol of LAH in 15 ml of solvent at reflux temperature.

<sup>b)</sup> Calculated from GL.-chromatograms.

Table 2. Lithium aluminium hydride reduction of the *cis*-1,2-epoxides of cyclooctane and cyclodecane, under various reaction conditions

1,2-Epoxycycloalkane <sup>a)</sup>	Unchanged epoxide (in %) <sup>b)</sup>							
	in diethyl ether (35°)					in tetrahydrofuran (66°)		
	after 24 h							
	1:0.5 <sup>c)</sup>	1:1	1:2	1:8	1:16	1:2	1:8	1:2
<i>cis</i> -1,2-Epoxycyclooctane	80	74	48	38	30	14	0	2
<i>cis</i> -1,2-Epoxycyclodecane	93	91	81	80	79	–	– <sup>d)</sup>	–

<sup>a)</sup> <sup>b)</sup> See the corresponding footnotes in Table 1.

<sup>c)</sup> Molar ratio epoxide/LAH.

<sup>d)</sup> It was reported previously [3a] that after 65 h in refluxing tetrahydrofuran and by using a 1:6.5–7.5 molar ratio of substrate to LAH, *cis*-1,2-epoxycyclodecane was quantitatively reduced, while the isomeric *trans*-1,2-epoxide underwent reductive cleavage only to the extent of 6–9%.

(Table 3), the primary-secondary 1,2-epoxyhexadecane is reduced readily in refluxing diethyl ether, while the dissecondary epoxides require longer reaction times for complete reduction, the decrease of reactivity being particularly important when the alkyl groups attached to the oxirane ring are branched, *i. e.* when methyl substituents are present in the  $\beta$ -positions. Here also the *cis*-epoxides are reduced faster than the corresponding *trans*-isomers.

The LAH reduction of 1,2-epoxides, which requires stoichiometrically 0.25 mol of LAH per mol of epoxide, is considered [1] as an  $S_N2$  type displacement, involving nucleophilic back-side attack (on the oxirane ring) by a series of complex anions (which act as carriers for the hydride ion),  $Al(O-\overset{|}{\underset{|}{C}H}-\overset{|}{\underset{|}{C}H_2})_nH_{4-n}^-$ , where  $n$  progresses

Table 3. Ease of reduction of some epoxyalkanes with lithium aluminium hydride in refluxing diethyl ether, using a 1:2 molar ratio of epoxide to LAH

Epoxyalkane <sup>a)</sup>	Unchanged epoxide (in %) <sup>b)</sup> after x hours:					
	x = 0.5	1	2	6	24	30
1,2-Epoxyhexadecane	0 <sup>e)</sup>					
<i>cis</i> -2,3-Epoxyhexane	7.5	0 <sup>d)</sup>				
<i>trans</i> -2,3-Epoxyhexane	50.5	25	2.5	0 <sup>e)</sup>		
<i>cis</i> -2,5-Dimethyl-3,4-epoxyhexane				45	3	0
<i>trans</i> -2,5-Dimethyl-3,4-epoxyhexane				63	9	3

<sup>a)</sup> <sup>b)</sup> See the corresponding footnotes in Table 1.

<sup>e)</sup> Products obtained: 2- and 1-hexadecanol, in a ratio of 95:5.

<sup>d)</sup> Products obtained: 3- and 2-hexanol, in a ratio of 58:42.

<sup>c)</sup> Products obtained: 3- and 2-hexanol, in a ratio of 52:48.

from 0 to 3 as the reduction proceeds (the last intermediate in this sequence,  $n = 4$ , affording, upon hydrolysis, the final alcohol product(s)). All these intermediate species ( $n = 0-3$ ) are similar in their nucleophilic action, but their steric requirements increase markedly with the number of coordinated alkoxide groups. For that reason, an increase in the LAH/epoxide ratio will increase the amount of the smallest ion,  $AlH_4^\ominus$ , thus facilitating hydride ion transfer in the reduction of sterically hindered epoxides (Table 2).

Inspection of models reveals that in 1,2-epoxycycloalkanes a medium-sized ring, irrespective of its conformation, exerts strong hindrance to back-side attack of LAH, while a larger ring ( $C_{12}$  and particularly  $C_{15}$ ), because of increased conformational flexibility, allows easier approach of the reducing agent (Table 1). Models also show that in all cases the rear side of the oxirane ring in *cis*-1,2-epoxycycloalkanes is, or can become by a small conformational change, more accessible to LAH than in the *trans*-isomers (Table 1). The methyl groups in the stable conformations of *cis*- and *trans*-2,5-dimethyl-3,4-epoxyhexane protect the carbon atoms of the oxirane ring from back-side attack, this screening effect being stronger in the *trans*-isomer (Table 3).

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