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DIMETHYL SULPHOXIDE AS A SOLVENT FOR THE HYDROLYTIC CLEAVAGE OF EPOXIDES. SYNTHESIS OF THE FOUR DIASTEREOISOMERIC 4-tert-BUTYLCYCLOHEXANE-1,2-DIOLS

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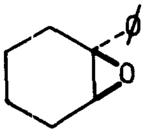
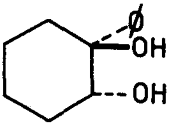
The interesting properties of dimethyl sulphoxide (DMSO) as a solvent and a reagent have led to very extensive investigations of this compound (1). In the course of our work on the stereochemistry of additions to phenyl-substituted epoxides (2) we were looking for a solvent in which alkaline hydrolysis of such compounds could be run at a reasonable rate. Epoxides, and particularly those which have large substituents on the oxirane ring, are very stable towards cleavage by hydroxides and data about such reactions are almost completely absent from the literature. In consideration of the large rate enhancements produced in base-catalyzed reactions by the use of DMSO as a solvent, because of its high polarity and low solvating power for anions (3), we hoped that it would be useful also in our case. The only data we found in the literature about the use of DMSO as a solvent for the hydrolysis of oxiranes were those of Virtanen (4), who reported that ethylene oxide is cleaved by sodium hydroxide at a higher rate in DMSO-water than in dioxane-water.

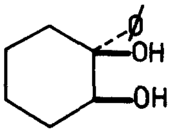
It was possible to achieve 60% hydrolysis of 1-phenyl-



I



II



III

cyclohexene oxide (I) with 0.3N potassium hydroxide in 85% DMSO-water in 6 hr at 100°. The product contained exclusively the trans-glycol II and not even a trace of the cis isomer III. The same reaction, carried out in aqueous dioxane (2b), had given after 48 hr at 150° only a 10% yield of III and no II. A better insight into the stereochemistry of the reaction was obtained with the cis- and trans-4-tert-butylcyclohexene oxides (IV and V), m.p. 67-68° and 64-65.5°, respectively, which were prepared from the olefin with peroxybenzoic acid and separated by column chromatography. The configuration of IV was deduced from its reduction to the known 1-phenyl-cis-4-tert-butylcyclohexanol (VI) (5). Both epoxides gave with potassium hydroxide in 85% DMSO-water the same diaxial glycol VII, m.p. 139-140.5°, as the only product. However, V reacted at a much slower rate than IV.

As previous work (2a) had shown that the stereochemistry of the ring-opening of phenyl-substituted epoxides under acidic conditions can change considerably with the type of solvent, it appeared interesting to investigate the use of DMSO also for such reactions.

Hydrolysis of cis- and trans-silbene oxides with 0.2N sulphuric acid in 75% DMSO-water took place in an entirely trans stereospecific way, to yield respectively (±) and meso-hydrobenzoin.

TABLE I

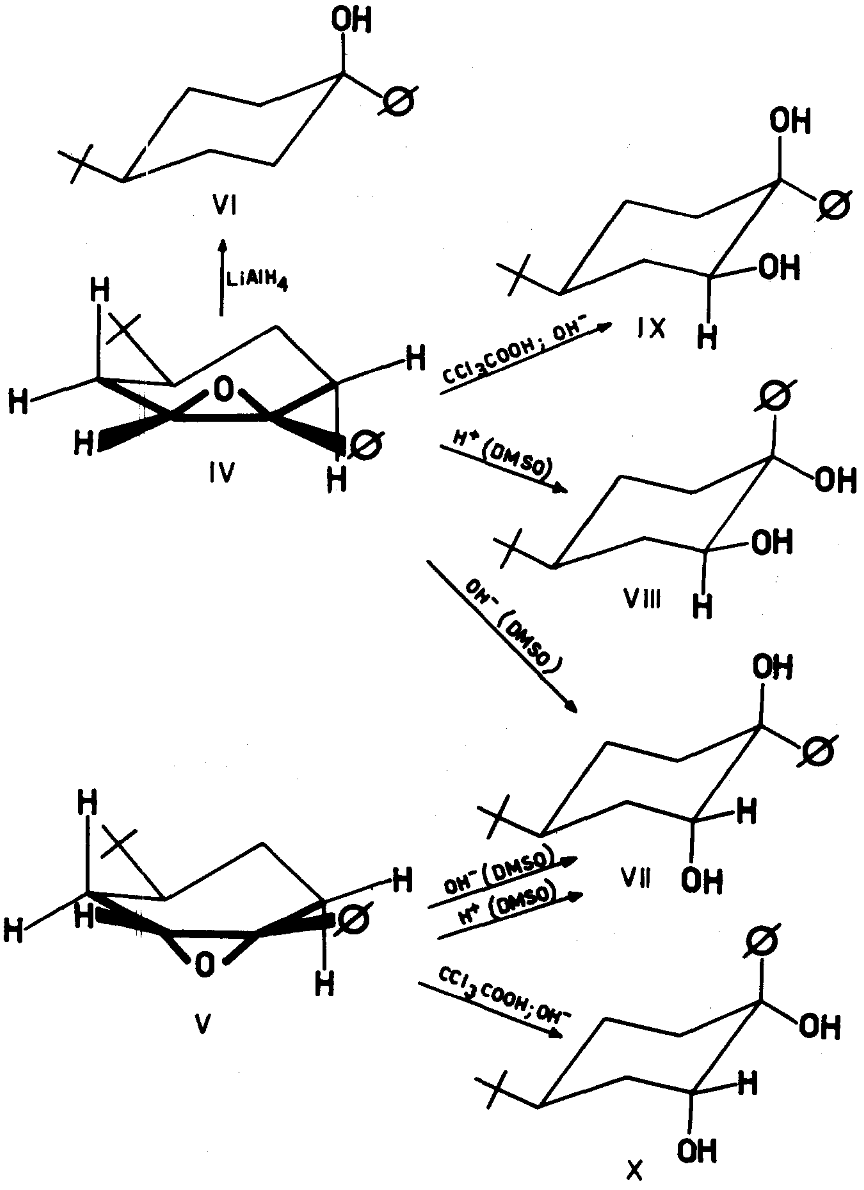
Compositions of Glycol Mixtures Obtained from 1-Phenylcyclohexene oxide

Solvent	Catalyst[a]	%II	%III
85% DMSO-H_2O	KOH	100	0
98% " "	$HClO_4$	40	60
90% " "	"	52	48
60% " "	"	58	42
30% " "	"	45	55
90% " "	H_2SO_4	56	44
75% " "	"	60	40
60% " "	"	60	40
75% HMPA-H_2O	"	64	36
60% Dioxane-H_2O	"	40	60
H_2O	"	30	70
HCOOH[b]	HCOOH	10	90
Benzene[b]	CCl_3COOH	0	100

DMSO = Dimethyl sulphoxide; HMPA = Hexamethylphosphoramide.

[a] All reactions were run on 1% solutions of the epoxide; concentrations of the catalyst were the following: KOH, 0.3N; $HClO_4$ 0.12N; H_2SO_4, 0.2N. [b] See ref. 2b.

Table I summarizes the results of acid-catalyzed ring-openings of I in different DMSO-water mixtures and in some other systems. A preliminary test was also made with hexamethylphosphoramide (HMPA), a new dipolar aprotic solvent which has been recently attracting much attention, because of its unusual properties (6). It can be seen from Table I that, under acidic conditions, it is possible to get anything from 100% retention


OH
Ø
VI
LiAlH₄
H
O
H
H
H
Ø
H
IV
CCl₃COOH; OH⁻
IX
OH
Ø
OH
H
H⁺ (DMSO)
Ø
OH
OH
VIII
H
OH⁻ (DMSO)
OH
Ø
H
VII
OH
H
H
H
O
H
Ø
H
V
OH⁻ (DMSO)
H⁺ (DMSO)
CCl₃COOH; OH⁻
Ø
OH
H
OH
X

(with trichloroacetic acid in benzene) to about 64% inversion (in HMPA-water).

The epoxides IV and V reacted with sulphuric acid in 75% DMSO-water in a more stereospecific way to give exclusively trans glycols, but while V produced only the diaxial glycol VII, IV yielded only the diequatorial isomer VIII, m.p. 110-111°. The remaining two diastereoisomers were obtained in a stereospecific way by cis addition of trichloroacetic acid to IV and V in benzene, followed by hydrolysis of the esters. Their formation from 4-tert-butyl-1-phenylcyclohexene with osmium tetroxide confirmed the cis relation of the hydroxyl groups. It can be safely assumed that the glycol, m.p. 150-150.5°, obtained from IV, has configuration IX, and the glycol, m.p. 101-102.5°, obtained from V, configuration X, as all previous results had shown that trichloroacetic acid adds cis to phenyloxiranes, with opening of the benzylic C-O bond (2b,7). The configurational assignements were confirmed by a study of the OH stretching bands of the four glycols, which will be reported elsewhere, and by the order of elution from a column of alumina, which was VII, IX, X, VIII, in accordance with the order of decreasing hindrance around the hydroxyl groups (5).

Addition of formic acid to IV and V was less stereospecific and gave mixtures of the formic esters of VIII and IX from IV, and of VII and X from V.

Although the results given in this preliminary report will be completed with more data and discussed at length in a forthcoming paper, we wish to stress some points.

1) DMSO appears to be a good solvent for the alkaline hydrolysis of hindered epoxides. In rigid systems, such as IV and V, the rule of diaxial opening (8) is obeyed: in the case of IV this involves the breaking of the non-benzylic C-O bond,

which is less hindered by the phenyl group; furthermore, if one assumes for IV a "half-chair" conformation (9), held rigid by the tert-butyl group, attack should be easier on C_2 than on C_1, as the adjacent hydrogen on the trans side of the oxirane oxygen is pseudo-equatorial on C_3, but pseudo-axial on C_6. On the other hand, diaxial opening of V takes place with breaking of the benzylic C-O bond; in this case, again, the nucleophilic attack occurs on the carbon atom which is nearer to the pseudo-equatorial hydrogen atom trans to the oxygen atom. The rate of reaction is considerably slower than with IV, because of the unfavourable steric effect of the phenyl group; evidently, the weakening effect of the aromatic group on the benzylic bond plays a minor role in such S_N2-type reactions.

2) Under acidic conditions DMSO, and even more HMPA favor trans addition. The rule of diaxial opening is not necessarily followed. Bond-breaking is known to be very important when protonated epoxides are involved (10), therefore the benzylic bond is opened preferentially. The order of solvents giving increasing trans addition appears to be : benzene $<$ formic acid $<$ water $<$ dioxane-water $<$ DMSO-water $<$ HMPA-water. A solvent mixture of high dielectric constant, containing a dipolar aprotic solvent and water, therefore seems to afford the best conditions for trans opening of epoxides in acidic media.

Adequate analytical data were obtained for all new compounds.

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