925. *Aspects of Stereochemistry. Part VIII.* The Reaction of* cyclo-*Hex-3-enol with Perbenzoic Acid. An Improved Method for the Isolation of Water-soluble Epoxides.*

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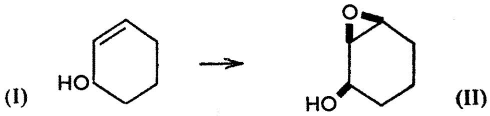
In the reaction of *cyclo*hex-3-enol with perbenzoic acid the hydroxyl group exerts no detectable directing effect, approximately equal parts of the two epoxides being formed. Much improved yields of epoxy-alcohols may be obtained from the action of peroxyacids on unsaturated alcohols if organic acids are removed from the final reaction solution with calcium hydroxide. The reduction of cyclic *trans*-hydroxy-epoxides by lithium aluminium hydride can apparently take place by an intramolecular mechanism.

IN Part I of this series,[1] it was shown by structural determinations and by kinetic measurements that the allylic hydroxyl group in *cyclo*hex-2-enol (I) directs *cis*-approach of peracids to the olefinic bond. The stereospecificity of this reaction has been confirmed by the isolation of the *cis*-hydroxy-epoxide (II) in an improved yield (90%) by a modified technique (see below).



The rate of epoxidation of the corresponding $\beta\gamma$-unsaturated alcohol (III) is appreciably slower than that of the allylic alcohol (I) despite the fact that in the former compound the electron-attracting hydroxyl group is farther from the olefinic bond. Thus it seemed unlikely that the hydroxyl group in (III) could be exerting any considerable assisting or directing effect in the reaction with peracid: this supposition has now been confirmed by the isolation of a mixture of epoxides.

The reaction of the olefin (III) with perbenzoic acid has been reported previously,[2] a

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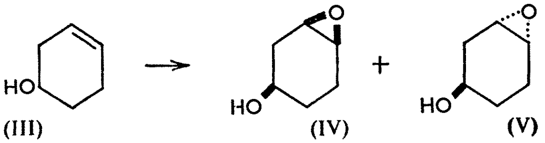
* Part VII, preceding paper.

[1] Henbest and Wilson, *J.*, 1957, 1958.

[2] Zelinski and Titova, *Ber.*, 1931, **64**, 1399.

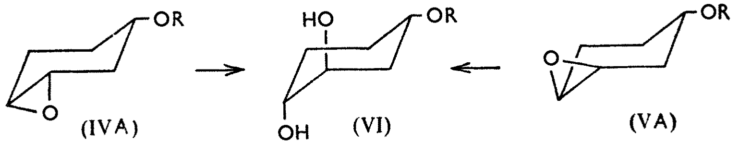
triol of m. p. 122° being isolated by an unspecified method. Repetition, with ether as solvent followed by the usual procedure of removing benzoic acid with aqueous potassium hydrogen carbonate, afforded hydroxy-epoxide (11%). The remainder of the material was recovered from the aqueous phase as a triol * (77%), m. p. 122—125°, apparently the same as that described earlier. The isolation of the triol, and not its monobenzoate, indicated that hydrolysis was occurring during isolation, assisted probably by the solubility of the hydroxy-epoxide in the aqueous phase used to wash out organic acids. In agreement, neutralisation of the reaction solution by shaking with solid calcium hydroxide gave the epoxide in much higher yield. Three water-soluble epoxy-alcohols † have been prepared in good yields with the help of this method (see Table). Also the epoxide from the acetate of (III), which is only slightly soluble in water, has been obtained in yields of 89% (old method) and 95% (new method).



	Epoxide yields (%)	
	Old method	New method
*cyclo*Hex-2-enol (I)	12	90
*cyclo*Hex-3-enol (III)	11	88
But-3-enol	—	76

The epoxide mixture produced from the olefinic alcohol (III) was separated by chromatography of the α-naphthylurethanes, the crystalline *cis*- and *trans*-derivatives being obtained in 52 and 40% yield respectively. The relative configurations of these urethanes was established by reduction of the lower-melting isomer to *cyclo*hexane-*trans*-1 : 4-diol by means of lithium aluminium hydride (conformational aspects of this reaction are discussed below).

By prolongation of the contact time with chromatographic alumina, each epoxynaphthylurethane was hydrated to a higher-melting dihydroxy-compound. The formation of this product (VI; $R = CO{\cdot}NH{\cdot}C_{10}H_7$) is envisaged as proceeding by diaxial opening of either epoxide ring in the conformations shown (IVA), (VA) with the large urethane groupings placed equatorially. The production of a single triol from the overall hydroxylation of the unsaturated alcohol (III) may be explained similarly, and this compound is therefore formulated as (VI; R = H). The formation of this triol by hydroxylation of the benzyl ether of the alcohol (III) with performic acid, followed by removal of the benzyl group (lithium in ethylamine technique [5]) strengthens the argument that, in all of these reactions, opening of the epoxide ring takes place from the conformation with the original hydroxyl group or its derived ether or urethane in an equatorial position.



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* The triol (87%) was also obtained by oxidation of the olefin (III) with performic acid followed by hydrolysis of the monoformate with steam.[3]

† Some aspects of the infra-red absorption of these vicinal epoxides, and of the *cyclo*hexenols (I) and (III), have been discussed recently.[4]

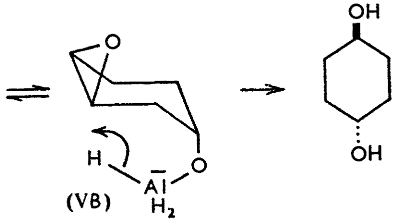
[3] Cf. Brown, Henbest, and Jones, *J.*, 1950, 3634.

[4] Henbest, Meakins, Nicholls, and Taylor, *J.*, 1957, 1459; Henbest, Meakins, Nicholls, and Wilson, *J.*, 1957, 997.

[5] Benkeser, Robinson, Sauve, and Thomas, *J. Amer. Chem. Soc.*, 1955, **77**, 3230.

Reduction of the epoxide mixture (IV) and (V) with lithium aluminium hydride gave *cyclo*hexane-*cis*- and -*trans*-1 : 4-diol, separated and identified as dibenzoates. The formation of the *cis*-1 : 4-diol is explicable as before, the bulky aluminium hydride complex being equatorial in the intermediate complex (IVA; R = AlH_3^-). Instead of giving *cyclo*hexane-*trans*-1 : 3-diol from the similar conformation (VA; R = AlH_3^-), the

(VA ; R = AlH_3^-)



(VB)

(VII)

trans-hydroxy-epoxide (and its urethane, above) yielded the *trans*-1 : 4-diol (VII). This result is best explained in terms of an intramolecular process brought about by the O·AlH_3^- group in the alternative conformation (VB). The greater ease of the intramolecular reaction * apparently more than offsets the fact that the molecule has to adopt a somewhat less favourable conformation. To a much smaller extent, hydride reduction of the isomeric 2 : 3-epoxy-*trans*-*cyclo*hexanol also takes place by a similar intramolecular mechanism.[1]

The reaction of the acetate of *cyclo*hex-3-enol (III) with perbenzoic acid was also non-stereospecific, the epoxy-acetate mixture furnishing the *cis*- and the *trans*-1 : 4-diol (29 and 53% respectively as dibenzoates) upon reduction with lithium aluminium hydride.

EXPERIMENTAL

Oxidations were carried out with perbenzoic acid prepared from benzoyl peroxide and sodium methoxide. Care is necessary to ensure that as little methyl benzoate as possible is present in the peracid solution as the b. p. of this ester (~90°/10 mm.) is close to those of some of the epoxides.

Epoxidation of cyclo*Hex-3-enol*.—The alcohol (9·3 g.) and perbenzoic acid (0·43 mol.) in ether (300 c.c.) were kept at 0° until reaction was complete (14 days). Calcium hydroxide (40 g.) was added and the mixture was shaken until neutral. After simple distillation from a Claisen flask, the product was distilled fractionally, to give the epoxy-alcohol mixture (9·47 g.), b. p. 99·5—104°/10 mm., n_D^{24} 1·4840—1·4843 (Found: C, 62·8; H, 8·6. Calc. for $C_6H_{10}O_2$: C, 63·15; H, 8·85%). The heterogeneity of the product was shown by conversion of samples of each fraction into a wide-melting α-naphthylurethane (see below).

A much lower yield of epoxide was obtained by washing the reaction solution [from alcohol (4·92 g.) and perbenzoic acid (0·65 mol.) in ether (125 c.c.)] with saturated aqueous potassium hydrogen carbonate solution. The ethereal solution was dried ($MgSO_4$) and evaporated: distillation then gave the epoxy-alcohol mixture (0·61 g.), n_D^{19} 1·4810—1·4842. The aqueous washings were evaporated *in vacuo* and the residue repeatedly extracted with hot ethyl acetate–acetone (3 : 1). Removal of the solvent gave a residue that partially crystallised, and this solid was recrystallised from chloroform–acetone to give the triol (VI; R = H) (2·41 g.), m. p. 123—125°. The remainder of the triol in the mother-liquors was isolated as its *tribenzoate* (8·78 g.), m. p. 155·5—157° (from methanol) (Found: C, 73·0; H, 5·6. $C_{27}H_{24}O_6$ requires C, 72·95; H, 5·45%). The same benzoate was obtained from benzoylation of the pure crystalline triol.

Hydroxylation of cyclo*Hex-3-enol and its Benzyl Ether*.—Hydrogen peroxide (7 c.c.; 100-vol.) was added dropwise to a stirred solution of the alcohol (5·15 g.) in 98% formic acid (18·5 g.) at 45—50°. After being stirred for an hour at this temperature the mixture (then homogeneous) was steam-distilled until the distillate was neutral to litmus. The solution was evaporated to

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* Cyclic transition states have been proposed for the reduction of certain open-chain halogeno-acids by lithium aluminium hydride.[6]

[6] Eliel and Traxler, *J. Amer. Chem. Soc.*, 1956, **78**, 4049.

dryness and the residue extracted with hot acetone. Concentration and cooling of the acetone extract gave (±)-*cyclo*hexane-1β : 2α : 4β-triol (VI; R = H) (5·86 g.), m. p. 122—125°. Benzoylation afforded the same tribenzoate (m. p. 154—155°) as before.

Similar hydroxylation of 1-benzyloxy*cyclo*hex-3-ene (1·38 g.) in 98% formic acid (3·1 g.) with hydrogen peroxide (1·4 c.c.; 100-vol.) yielded the monobenzyl ether of the triol as a viscous gum. This was dissolved in ethylamine (30 c.c.), finely cut lithium (0·6 g.) was added, and the mixture shaken until the blue colour disappeared (2 hr.). The product isolated by extraction with acetone was benzoylated to give the above tribenzoate (2·67 g.), m. p. 153—155°.

1-*Benzyloxy*cyclo*hex*-3-*ene*.—A mixture of *cyclo*hex-3-enol (10·1 g.), benzyl chloride (50 c.c.), powdered potassium hydroxide (120 g.), and pure dioxan (250 c.c.) was stirred at 50° for 1 hr. After cooling, the solution was treated with water (500 c.c.), and the product isolated with ether. Distillation afforded the *benzyl ether* (18·4 g., 97%), b. p. 78·5—80°/0·5 mm., n_D^{19} 1·5330 (Found: C, 82·8; H, 8·4. $C_{13}H_{16}O$ requires C, 82·95; H, 8·55%).

Lithium Aluminium Hydride Reduction of 3 : 4-*Epoxy*cyclo*hexanol*.—Solutions of the epoxy-alcohol (3·23 g. of combined distillate) in ether (20 c.c.) and lithium aluminium hydride in ether (75 c.c. of 0·4M-solution) were mixed and heated under reflux for 2 hr. Ethyl acetate (50 c.c.) and 2N-sulphuric acid (50 c.c.) were added to the cooled mixture, and the aqueous solution was extracted continuously with ethyl acetate. The crude diol obtained was benzoylated with benzoyl chloride in pyridine at 20°. A cooled solution of the diester in methanol gave *cyclo*hexane-*trans*-1 : 4-diol dibenzoate (4·54 g., 47%), m. p. 140—148° (m. p. 149·6—151° on recrystallisation). The diester from the mother-liquor was distilled in a short-path still at 10^{-5} mm., to give a product that solidified (m. p. 108—115°) at 0°. Recrystallisation from light petroleum (b. p. 80—100°) furnished *cyclo*hexane-*cis*-1 : 4-diol dibenzoate (3·12 g., 34%), m. p. 112·5—114°. Some of the *cis*-dibenzoate was probably lost during the distillation, owing to partial elimination of benzoic acid (which collected as a sublimate).

Formation, Separation, and Reactions of the α-Naphthylurethanes of the Epoxy-alcohols (IV) *and* (V).—The epoxy-alcohol mixture (224 mg.) and α-naphthyl *iso*cyanate (340 mg.) were heated under reflux in light petroleum (b. p. 100—120°) for 20 min. The mixture of derivatives (551 mg.) separated on cooling. This, in light petroleum–benzene (9 : 1), was adsorbed on deactivated alumina (60 g.). Elution with light petroleum–benzene (4 : 1) afforded the *α-naphthylurethane* (286 mg.), m. p. 165—166°, of the *cis*-hydroxy-epoxide (Found: C, 71·9; H, 5·95. $C_{17}H_{17}O_3N$ requires C, 72·05; H, 6·05%). Elution with light petroleum–benzene (7 : 3) afforded the *α-naphthylurethane* (220 mg.), m. p. 146·5—148° (from light petroleum, b. p. 100—120°), of the *trans*-hydroxy-epoxide (Found: C, 72·0; H, 6·05%). Finally elution with ether–methanol (4 : 1) gave the 4-*mono-α-naphthylurethane* (39 mg.), m. p. 199·5—200·5° (from acetone–*iso*propyl ether), of the triol (VI) (Found: C, 67·8; H, 6·2. $C_{17}H_{19}O_4N$ requires C, 67·75; H, 6·35%).

The *cis*-α-naphthylurethane (215 mg.) was adsorbed on deactivated alumina (20 g.) as above. After 18 hr. the column was eluted with ether–methanol (4 : 1) to give the triol mono-α-naphthylurethane (178 mg.), m. p. 188—195°. Recrystallisation gave needles, m. p. 199—200°. Similar treatment of the *trans*-α-naphthylurethane (183 mg.) again yielded the triol mono-α-naphthylurethane (41 mg.), m. p. 198·5—200°.

A solution of the *trans*-α-naphthylurethane (507 mg.) and lithium aluminium hydride (1 g.) in tetrahydrofuran (50 c.c.) was heated under reflux for 3 hr. Ethyl acetate and dilute sulphuric acid were added and the diol was isolated by continuous extraction with ethyl acetate. The diol was benzoylated with benzoyl chloride in pyridine; crystallisation of the product from methanol furnished the dibenzoate, m. p. and mixed m. p. 149—151°, of *cyclo*hexane-*trans*-1 : 4-diol (342 mg., 59%).

Epoxidation of 1-*Acetoxy*cyclo*hex*-3-*ene*.—The ester (10·03 g.) and perbenzoic acid in ether (143 c.c.; 0·59M) were mixed and kept at 0° until one mol. of peracid had been consumed. After working up by the calcium hydroxide method, distillation afforded the epoxy-acetate mixture (10·43 g., 95%), b. p. 94—97·5°/10 mm. n_D^{21}, 1·4666—1·4618 (Found: C, 61·3; H, 7·9. Calc. for $C_8H_{12}O_3$: C, 61·5; H, 7·8%).

Part of the epoxy-acetate mixture (3·02 g.) was reduced with lithium aluminium hydride (2 g.) in ether (150 c.c.) as described above for the epoxy-alcohol mixture. Benzoylation of the diol afforded the *trans*-1 : 4-dibenzoate (3·33 g., 53%), m. p. 140—148° (149·5—151° on recrystallisation), and the *cis*-1 : 4-dibenzoate (1·82 g., 29%), m. p. 113—114°.

The 1-*acetoxy*cyclo*hex*-3-*ene* was prepared in 95% yield from the alcohol (III) (15 g.), acetic anhydride (40 g.), and pyridine (40 g.). It had b. p. 71—72°/20 mm., n_D^{17} 1·4600 (Found: C, 68·2; H, 8·5. $C_8H_{12}O_2$ requires C, 68·55; H, 8·65%).

Epoxidation of cyclo*Hex-2-enol.*—The alcohol (4·2 g.) was oxidised with perbenzoic acid (0·45 mol.) in ether (190 c.c.) as described for the βγ-unsaturated alcohol above, calcium hydroxide being used finally to remove acids. The *cis*-hydroxy-epoxide (4·4 g.), b. p. 102—103°/18 mm., n_D^{21} 1·4815, was isolated. The α-*naphthylurethane*, m. p. 173·5—175° [from light petroleum (b. p. 100—120°)], was obtained pure in 91% yield (Found: C, 71·9; H, 5·95. $C_{17}H_{17}O_3N$ requires C, 72·05; H, 6·05%).

Epoxidation of But-3-enol.—The alcohol (7·52 g.) was treated with perbenzoic acid as before and the product was isolated by the calcium hydroxide technique. Distillation gave the *epoxide* (6·96 g.), b. p. 80—82°/16 mm., n_D^{22} 1·4397 (Found: C, 54·3; H, 9·2. $C_4H_8O_2$ requires C, 54·55; H, 9·15%).

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