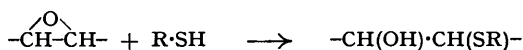


660. Dithiols. Part XI.* The Reactions of Epoxides with Hydroxy- and Poly-thiols.

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The reactions of propylene oxide and *cyclohexene* oxide with 2-mercaptoethanol and with ethane-1 : 2-dithiol, in the presence of sodium ethoxide, have been studied. The oxides attack 2-mercaptoethanol preferentially at the thiol group, and they react with the dithiol to give mono- and di-addition products. 1 : 2-Di-(2-hydroxycyclohexylthio)ethane, the di-addition compound from *cyclohexene* oxide and ethane-1 : 2-dithiol, has been obtained in two stereoisomeric forms, both of which differ from the substance described by Culvenor, Davies, and Heath (*J.*, 1949, 278). *trans*-2-Hydroxycyclohexyl 2 : 3-dimercaptopropyl sulphide (isolated as the triacetyl derivative) has been prepared from *cyclohexene* oxide and propane-1 : 2 : 3-trithiol.

COMPOUNDS containing the ethylene oxide ring system reacts with thiols according to the general scheme :



For example, ethylene oxide with hydrogen sulphide gives 2-mercaptoethanol, whilst with ethanethiol it gives ethyl 2-hydroxyethyl sulphide; similarly, *cyclohexene* oxide and propane-thiol give 2-hydroxycyclohexyl propyl sulphide (Tschitchibabine and Bestougeff, *Compt. rend.*, 1935, 200, 242; Nenitzescu and Scărlătescu, *Ber.*, 1935, 68, 587; Woodward, *J.*, 1948, 1892). Thiolacetic acid (R = Ac) also reacts in the same way, to give the S-acetyl derivative of a hydroxy-thiol (Nylen and Olsen, *Svensk. Kem. Tidsk.*, 1941, 53, 274; Sjöberg, *Ber.*, 1942, 75, 13). If in the reaction of ethylene oxide with hydrogen sulphide the oxide is present in excess, the main product is di-2-hydroxyethyl sulphide (thiodiglycol); this clearly indicates that the primary product, 2-mercaptoethanol, reacts preferentially at its thiol rather than at its hydroxyl group with the second molecule of oxide. The present paper describes some exploratory experiments which have been carried out with the object of extending these reactions to the use of hydroxy- and poly-thiols.

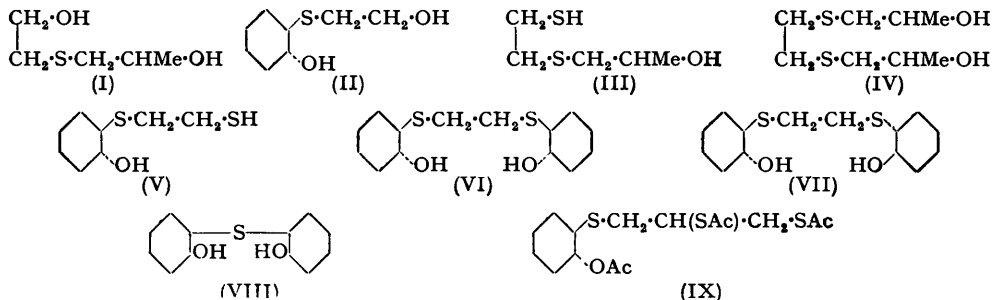
2-Mercaptoethanol reacted readily with 1 mol. of propylene oxide or *cyclohexene* oxide in ethanol, in the presence of a catalytic amount of sodium ethoxide, to give 2-hydroxyethyl 2-hydroxypropyl sulphide (I) and *trans*-2-hydroxyethyl 2-hydroxycyclohexyl sulphide (II) respectively. The structure allocated to (I) is based on analogy with the reaction of propylene oxide with alkoxides, in which the alkoxy-group becomes attached to the primary position (see, *inter al.*, Sadle, *J. Amer. Chem. Soc.*, 1950, 72, 1251; cf. Todsén, Pollard, and Rietz, *ibid.*, p. 4000); the *trans*-structure is assigned to (II) on the assumption that the usual Walden inversion occurs when the oxide ring is opened. The preferential reaction of the oxides with the thiol group is therefore confirmed.

These results show that it would be impracticable to prepare *O*-derivatives of 2 : 3-dimercaptopropanol ("BAL") by reaction of the latter with epoxides, unless the two thiol groups were previously protected (cf. Miles and Owen, *J.*, 1950, 2938). By the use of propane-1 : 2 : 3-trithiol, however, it should be possible, by reaction with 1 mol. of an epoxide, to obtain thio-analogues of such derivatives, *e.g.* :



Preliminary experiments were carried out with ethane-1 : 2-dithiol in order to assess the extent to which the second thiol group becomes involved in the reaction. By using equimolecular proportions of dithiol and epoxide, a mixture of mono- and di-condensation products was formed, separable by fractional distillation. Thus, from propylene oxide, 2-hydroxypropyl 2-mercaptoethyl sulphide (III) and 1 : 2-di-(2-hydroxypropylthio)ethane (IV) were obtained, whilst *cyclohexene* oxide gave *trans*-2-hydroxycyclohexyl 2-mercaptoethyl sulphide (V) and 1 : 2-di-(2-hydroxycyclohexylthio)ethane (the use of an excess of either oxide gave the bis-compounds exclusively). Shortly after the completion of this part of the work, Culvenor, Davies, and Heath (*J.*, 1949, 278) reported the formation of the last compound by a somewhat similar method, but gave m. p. 47–49°, whereas our product had m. p. ca. 74°. This difference could be attributed to stereoisomerism, since if a Walden inversion occurs at each opening of an oxide

ring the product formed when the second mol. of *cyclohexene oxide* reacts with (V) can be either the *meso*- (VI) or the racemic-form (VII). On careful fractional recrystallisation, however, it was possible to isolate from the material of m. p. *ca.* 74° a small amount of an isomer, m. p. 100°; the residual portion, even after repeated recrystallisation from different solvents, had m. p. 72°, and no indication was obtained of the presence of any isomer of m. p. 47—49°.



The preparation was therefore repeated, this time under the exact conditions described by Culvenor, Davies, and Heath, but again no low-melting isomer could be obtained; fractional recrystallisation gave a very small amount of the high-melting compound, the main bulk having m. p. 72°. There can be little doubt that the isomer, m. p. 100°, is stereochemically pure (VI) or (VII); the material of m. p. 72° may be the other stereoisomer (in which case the compound of Culvenor *et al.* is possibly a metastable form) or it may be an inseparable mixture of the two. It is of interest that Mousseron, Bousquet, and Marret (*Bull. Soc. chim.*, 1948, 84) have obtained two stereoisomers of di-(2-hydroxycyclohexyl) sulphide (VIII). The bis-compound (IV) from the reaction with propylene oxide can also exist in *meso*- and racemic forms, but the product in this case was a low-melting solid and no indication was obtained of any separation of isomers.

Since the use of equimolecular quantities of epoxide and dithiol had given mixtures of mono- and di-addition products, an excess of propanetrithiol was used in its reaction with *cyclohexene oxide*. The product, however, was again a mixture, and the boiling point was too high to allow of separation without serious decomposition, but this was possible after acetylation; fractional distillation then gave *trans*-2-acetoxycyclohexyl 2:3-bisacetylthio-propyl sulphide (IX).

The ethanedithiol required for these investigations was prepared in several different ways. Following Stocken's procedure (*J.*, 1947, 592) for the preparation of dithiols, it was obtained in 41% yield by reaction of a large excess of ammonium hydrogen sulphide with ethylene dibromide in methanol at room temperature. By reaction of ethylene dibromide with potassium thiolacetate, the crystalline diacetyl derivative of ethanedithiol was obtained (90%); this was also prepared (59%) from the ditoluene-*p*-sulphonate of ethylene glycol by the method of Chapman and Owen (*J.*, 1950, 579). Hydrolysis of the diacetyl derivative with methanolic barium methoxide gave the dithiol (*via* the barium salt) in 62% yield. The method recently described in *Organic Syntheses* (1950, 30, 35) gives a 55—62% yield *via* ethylene diisothiuronium bromide.

EXPERIMENTAL.

1:2-Bisacetylthioethane.—(i) Ethylene dibromide (30 g.) and potassium thiolacetate (40 g., 10% excess) in ethanol (200 c.c.) containing a few drops of thiolacetic acid were stirred and heated under reflux for 4 hours under nitrogen; potassium bromide separated from the red solution. After the mixture had cooled, ether was added until no more potassium salts were precipitated and the filtered solution was concentrated under reduced pressure. The residue was dissolved in ether, washed with water, dried (Na_2SO_4), and evaporated to a solid residue, which was recrystallised from light petroleum (b. p. 40—60°) giving 1:2-bisacetylthioethane (25.5 g., 90%), m. p. 69°. Mathias (*Chem. Abs.*, 1946, 40, 2792) gives m. p. 68—69°.

(ii) 1:2-Ditoluene-*p*-sulphonyloxyethane (14 g.) in ethanol (150 c.c.) was treated with potassium thiolacetate (17.5 g., 100% excess) in ethanol (150 c.c.) at room temperature and then heated under reflux for 30 minutes. After cooling, the potassium toluene-*p*-sulphonate (13 g., 83%) which had been deposited, was filtered off and the filtrate was concentrated. The crude product was precipitated by addition of water, and recrystallised from light petroleum (b. p. 40—60°). The yield was 4 g. (59%), and the m. p. and mixed m. p. 69°.

Ethane-1:2-dithiol.—A stirred solution of the diacetyl derivative (40 g.) in dry methanol (100 c.c.), cooled to -10° , was slowly treated with 1.1N-methanolic barium methoxide (400 c.c.). The stirring was continued for 30 minutes at -10° , whereafter ice-cold dry ether was added until no more solid was

precipitated. The barium salts were rapidly filtered off under nitrogen and dissolved in 2*N*-aqueous hydrochloric acid; the dithiol liberated was isolated by extraction with ether. The crude material thus obtained was distilled to give ethane-1 : 2-dithiol (13.2 g., 62%), b. p. 51—52°/24 mm., n_D^{20} 1.5595.

Hydrolysis of the diacetyl derivative with methanolic hydrogen chloride or aqueous sodium hydroxide gave poor yields of the dithiol.

Reaction of Propylene Oxide with 2-Mercaptoethanol.—2-Mercaptoethanol (4 g.) and sodium (0.12 g.) were dissolved in dry ethanol (15 c.c.) contained in a pressure bottle. The solution was cooled to 0°, propylene oxide (3 g.) was rapidly added, and the vessel was sealed. Much heat was evolved, and when the initial reaction had subsided the bottle was heated at 100° for 2 hours. After being cooled, the solution was neutralised with carbon dioxide (a few drops of water being added), filtered, and concentrated. Distillation then gave 2-hydroxyethyl 2-hydroxypropyl sulphide (4.05 g., 58%), b. p. 114—115°/2 mm., 102—103°/0.5 mm., n_D^{25} 1.5091 (Found : C, 44.7; H, 8.8; S, 23.4; thiol-S, 0. C₆H₁₂O₂S requires C, 44.1; H, 8.9; S, 23.5%).

Reaction of cycloHexene Oxide with 2-Mercaptoethanol.—2-Mercaptoethanol (2 g.) in dry ethanol (5 c.c.) containing sodium (0.06 g.) was treated with cyclohexene oxide (2.5 g.) and heated in a pressure bottle for 2 hours at 100°. The cooled solution was worked up as described above to give 2-hydroxyethyl 2-hydroxycyclohexyl sulphide, (2.9 g., 63%), b. p. 122—123°/0.1 mm. The product solidified and on recrystallisation from light petroleum (b. p. 40—60°) had m. p. 46° (Found : C, 54.4; H, 9.2; S, 18.45; thiol-S, 0. C₈H₁₆O₂S requires C, 54.5; H, 9.2; S, 18.2%).

Reaction of Propylene Oxide with Ethane-1 : 2-dithiol.—(i) Ethane-1 : 2-dithiol (5 g.), propylene oxide (3.0 g., 1 mol.), and sodium (0.12 g.) in ethanol (15 c.c.) were heated at 100° for 2 hours. Fractional distillation of the product gave 2-hydroxypropyl 2-mercaptoethyl sulphide (1.75 g., 21%), b. p. 95°/0.7 mm., n_D^{19} 1.5570 (Found : thiol-S, 20.9. C₅H₁₂OS₂ requires thiol-S, 21.5%), and 1 : 2-di-(2-hydroxypropylthio)ethane (1.6 g., 20%), b. p. 140°/0.7 mm., n_D^{15} 1.5378 (Found : C, 45.9; H, 8.7; S, 30.3. C₈H₁₈O₂S₂ requires C, 45.7; H, 8.6; S, 30.5%), which solidified and had m. p. 38°; attempts to recrystallise the latter compound were unsuccessful.

(ii) Ethane-1 : 2-dithiol (5 g.), treated with propylene oxide (6 g., 2 mol.) under the above-mentioned conditions, gave only 1 : 2-di-(2-hydroxypropylthio)ethane (8 g., 73%).

Reaction of cycloHexene Oxide with Ethane-1 : 2-dithiol.—(i) Ethane-1 : 2-dithiol (5 g.) and cyclohexene oxide (5 g.) in ethanol (15 c.c.), containing sodium (0.12 g.), were heated at 100° for 2 hours to give 2-hydroxycyclohexyl 2-mercaptoethyl sulphide (2.08 g., 20%), b. p. 95—98°/0.1 mm., n_D^{20} 1.5587 (Found : C, 50.4; H, 8.7; S, 33.2; thiol-S, 16.8. C₈H₁₆OS₂ requires C, 50.0; H, 8.4; S, 33.3; thiol-S, 16.7%).

The residue, which solidified when cold, was distilled at 135° (air-bath)/2 × 10⁻⁴ mm., to give a product (1.52 g., 15%), m. p. 66—69°, which crystallised from light petroleum (b. p. 40—60°) in needles, m. p. 68—69°. Further recrystallisation from the same solvent gave 1 : 2-di-(2-hydroxycyclohexylthio)ethane, m. p. ca. 74° (Found : C, 58.1; H, 9.3; S, 22.1. Calc. for C₁₄H₂₆O₂S₂ : C, 57.9; H, 9.0; S, 22.1%). Three recrystallisations of this material from a mixture of benzene and light petroleum (b. p. 40—60°) gave an isomer, m. p. 100° (Found : C, 58.2; H, 9.2%). The material which remained in the mother-liquors was recovered (m. p. 70—72°), but further recrystallisation from the same solvent, from light petroleum, and from aqueous methanol failed to raise the m. p. above 72°. The m. p.s of the two forms were unchanged after each form had been heated above its m. p. for 10 minutes, and a mixture melted over the range 70—90°.

(ii) Ethane-1 : 2-dithiol (2.3 g.) in ethanol (30 c.c.) containing potassium hydroxide (2.8 g.) was treated with cyclohexene oxide (4.9 g.) according to the method of Culvenor, Davies, and Heath (*loc. cit.*), to give 1 : 2-di-(2-hydroxycyclohexylthio)ethane (6.9 g., 95%), m. p. 69—72° (after distillation), raised after recrystallisation from light petroleum (b. p. 40—60°) to ca. 72°. The material was separated, as described above, into two forms, m. p. 97° (Found : C, 57.8; H, 8.7; S, 21.7%) and m. p. 72° (Found : C, 58.3; H, 9.1; S, 21.7%). There was insufficient of the higher-melting isomer for further recrystallisation. A mixture of the two isomers melted over the range 70—90° and mixed m. p.s with the corresponding compounds obtained as recorded in (i) showed no depression.

Reaction of cycloHexene Oxide with Propane-1 : 2 : 3-trithiol.—cycloHexene oxide (5 g.) was added to propane-1 : 2 : 3-trithiol (8 g.) (Miles and Owen, *J.*, 1950, 2943) in dry ethanol (150 c.c.) containing sodium (0.2 g.), and the homogeneous solution was set aside for 20 hours at ordinary temperature. The product was isolated as previously described; it was an almost colourless, viscous liquid (7.4 g.) (Found : thiol-S, 16.0. Calc. for C₆H₁₀OS₃ : thiol-S, 27.0. Calc. for C₁₅H₂₆O₂S₃ : thiol-S, 9.5%). Attempts to distil the material at 10⁻⁴ mm. were unsuccessful, and the crude mixture (7 g.) in dry pyridine (50 c.c.) was acetylated by treatment with acetic anhydride (10 g.). After 24 hours the solution was diluted with water and extracted with chloroform (100 c.c.). The chloroform solution was washed with dilute sulphuric acid, water, and saturated sodium hydrogen carbonate solution, dried (MgSO₄), and concentrated to a viscous liquid, which on distillation at 180—195° (air-bath)/5 × 10⁻⁵ mm. gave 2-acetoxycyclohexyl 2 : 3-bisacetylthiopropyl sulphide (6.5 g.), n_D^{20} 1.5431 (Found : C, 50.3; H, 6.8; S, 25.2. C₁₅H₂₄O₄S₃ requires C, 49.5; H, 6.6; S, 26.4%). Light absorption : λ_{max} 2300 Å, ϵ 7500.

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