Dithiols. Part XXIII.[1] Optically Active Forms of 2,3-Dimercaptopropanol and Related Thiols

By **A. K. M. Anisuzzaman** and **L. N. Owen**, Chemistry Department, Imperial College of Science and Technology, London S.W.7

A new synthesis of 2,3-dimercaptopropanol, from 1,2-*O*-isopropylideneglycerol, by way of benzyl 2,3-epoxypropyl ether, is described. Following a similar route, (*R*)-2,3-dimercaptopropanol has been synthesised from (*S*)-1,2-*O*-isopropylideneglycerol through (*S*)-benzyl 2,3-epoxypropyl ether. By other routes, (*S*)-1,2-*O*-isopropylideneglycerol is also converted (*i*) through (*R*)-benzyl 2,3-epoxypropyl ether into (*S*)-2,3-dimercaptopropanol, (ii) through (*R*)-2,3-isopropylidenedioxypropyl thiolacetate into (*R*)-3-mercaptopropane-1,2-diol, and (iii) through (*R*)-benzyl 2,3-epithiopropyl ether into (*S*)-2-mercaptopropanol.

An alternative synthesis of (*R*)-2,3-dimercaptopropanol failed to give an optically active product because of complete racemisation during the reduction, by lithium aluminium hydride, of (*R*)-2,3-carbonyldithiopropionaldehyde. This unusual behaviour of the reagent is attributed to stabilisation of the enolate anion of the aldehyde by resonance involving the sulphur atom at C-2.

ALTHOUGH many optically active sulphur-containing compounds are known, in relatively few of them is the activity due solely to the chirality of the centre to which the sulphur is attached. Compounds of the latter type include alkanethiols,[2] mercapto-acids,[3] and a mercaptoamine,[4] but the absolute configurations of these are either unknown or are based on the quasi-racemate method [5] of comparison with a sulphur-free analogue of known configuration. Although the value of this physical method is recognised, there is evident scope for the development of chemical methods of correlation in this field. Corey and Mitra [6] provided an excellent example of this approach in their synthesis of L-(+)-butane-2,3-dithiol.

The utility of 2,3-dimercaptopropanol as an antiarsenical agent prompted the work which initiated this Series of Papers.[7] Extensive pharmacological investigations have been made on the applications of this dithiol and its derivatives in the treatment of poisoning by various metals [8a] and as antitubercular drugs,[8b] but all these studies have been conducted on racemic material. It is not known whether there is any difference in biological activity, or in toxicity, between the enantiomeric forms of the dithiol, and we therefore chose these as our first objective. The racemic compound can be made, directly or indirectly, from 2,3-dichloro-[9] or 2,3-dibromo-propanol,[10,11] and by the addition of thiolacetic acid to propargyl alcohol,[12] but these methods are unsuitable for a stereospecific synthesis, and a new route was devised. To establish optimum conditions, the reaction sequences were first carried through on racemic materials derived from glycerol.

Benzyl 2,3-dihydroxypropyl ether (I), prepared [13,14] from DL-1,2-*O*-isopropylideneglycerol, on selective esterification with 1 mol. of toluene-*p*-sulphonyl chloride in pyridine, followed by treatment with sodium methoxide, gave benzyl 2,3-epoxypropyl ether (III),[15] which on reaction with potassium methyl xanthate furnished the trithiocarbonate (IV), and thence, by reduction with lithium aluminium hydride [16] the dithiol (V). Removal of the benzyl group by reaction with sodium in liquid ammonia then gave 2,3-dimercaptopropanol (VI), characterised as the crystalline 2,3-*S*-cyclohexylidene derivative;[10] on reaction with potassium methyl xanthate it gave the trithiocarbonate (VII). In this sequence, the racemic forms of formulæ (I)—(VII) are to be understood.

(*R*)-Benzyl 2,3-dihydroxypropyl ether, of absolute configuration (I), was then prepared [14] from D-mannitol by way of (*S*)-1,2-*O*-isopropylideneglycerol,[17] and converted into the (*S*)-toluene-*p*-sulphonate (II).[18] This gave, successively, (*S*)-benzyl 2,3-epoxypropyl ether (III), (*R*)-benzyl 2,3-thiocarbonyldithiopropyl ether (IV), (*R*)-benzyl 2,3-dimercaptopropyl ether (V), and (*R*)-2,3-dimercaptopropanol (VI). It is evident that the

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[2] P. A. Levene and L. A. Mikeska, *J. Biol. Chem.*, 1924, **59**, 473; 1925, **63**, 85; B. Holmberg, *Arkiv Kemi, Min., Geol.*, 1939, **13***A*, no. 8.

[3] P. A. Levene, *J. Biol. Chem.*, 1924, **60**, 1; P. A. Levene, T. Mori, and L. A. Mikeska, *ibid.*, 1927, **75**, 337; B. Holmberg, *Arkiv Kemi, Min., Geol.*, 1921, **8**, no. 8; M. Matell, *Arkiv Kemi*, 1952, **5**, 17; K. Mislow and W. C. Meluch, *J. Amer. Chem. Soc.*, 1956, **78**, 5920; von M. Gerecke, E. A. H. Friedheim, and A. Brossi, *Helv. Chim. Acta*, 1961, **44**, 955.

[4] J. R. Piper and T. P. Johnston, *J. Org. Chem.*, 1964, **29**, 1657.

[5] A. Fredga, *Tetrahedron*, 1960, **8**, 126. See also J. H. Brewster, *J. Amer. Chem. Soc.*, 1959, **81**, 5475.

[6] E. J. Corey and R. B. Mitra, *J. Amer. Chem. Soc.*, 1962, **84**, 2938.

[7] J. F. Danielli, M. Danielli, J. B. Fraser, P. D. Mitchell, L. N. Owen, and G. Shaw, *Biochem. J.*, 1947, **41**, 325.

[8] (*a*) *Inter al.*, R. V. Randall and A. O. Seeler, *New England J. Med.*, 1948, **239**, 1004, 1040; R. A. Peters, *Brit. Med. Bull.*, 1948, **5**, 313; *J. Roy. Inst. Pub. Health Hyg.*, 1952, **15**, 122; L. A. Stocken and R. H. S. Thompson, *Physiol. Rev.*, 1949, **29**, 168; L. S. Goodman and A. Gilman, "The Pharmacological Basis of Therapeutics," Macmillan, New York, 3rd edn., 1965, p. 930; (*b*) P. Acred and D. M. Brown, *Brit. J. Pharmacol.*, 1960, **15**, 485; P. Acred, D. M. Brown, and D. Wright, *ibid.*, p. 496.

[9] H. R. Ing, *J. Chem. Soc.*, 1948, 1393.

[10] L. A. Stocken, *J. Chem. Soc.*, 1947, 592.

[11] B. Sjöberg, *Ber.*, 1942, **75**, 13.

[12] A. T. Blomquist and J. Wolinsky, *J. Org. Chem.*, 1958, **23**, 551.

[13] R. J. Howe and T. Malkin, *J. Chem. Soc.*, 1951, 2663.

[14] M. Kates, T. H. Chan, and N. Z. Stanacev, *Biochemistry*, 1963, **2**, 394.

[15] M. M. Baizer, J. R. Clark, and J. Swidinsky, *J. Org. Chem.*, 1957, **22**, 1595.

[16] S. M. Iqbal and L. N. Owen, *J. Chem. Soc.*, 1960, 1030.

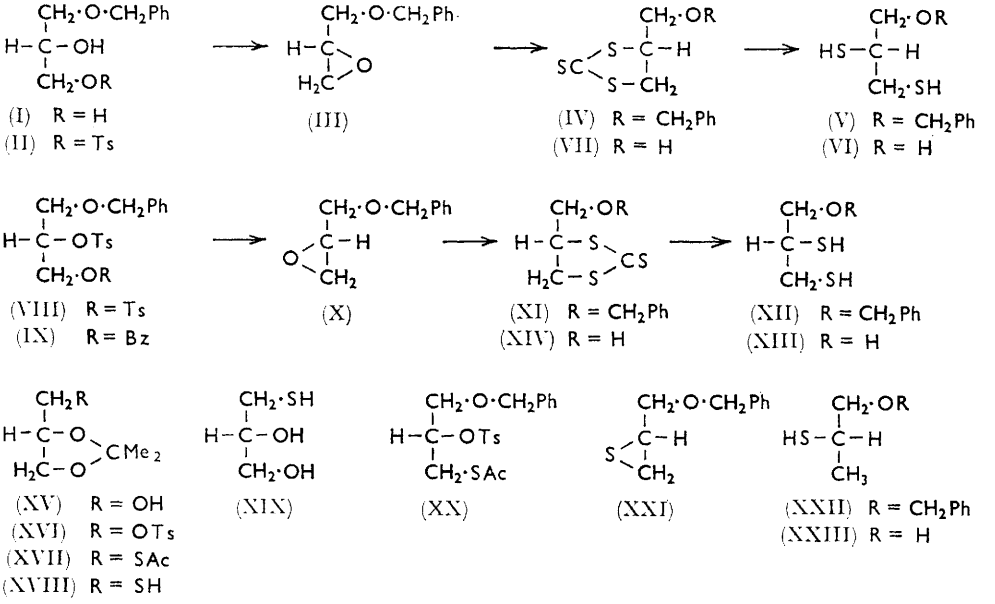
[17] E. Baer and H. O. L. Fischer, *J. Biol. Chem.*, 1939, **128**, 469.

[18] B. Belleau and J. Puranen, *J. Medicin. Chem.*, 1963, **6**, 325.

epoxide (III) must have the same configuration at C-2 as the diol (I), but the reaction of an epoxide with potassium methyl xanthate proceeds through an intermediate sulphide (of opposite configuration) which then reacts further (with retention of configuration) to give the trithiocarbonate;[19] consequently there is an overall inversion at C-2 at this stage. The reductive processes involved in the remaining two stages would not result in any further stereochemical change, and the absolute configuration of the dithiol (VI) must therefore be as shown. The compound showed $[\alpha]_D$ +3·0° in chloroform and −9·6° in methanol. On reaction with potassium methyl xanthate it gave (*R*)-2,3-thiocarbonyldithiopropanol (VII) which showed a large rotation, $[\alpha]_D$ +291°, in chloroform. The retention of configuration at C-2 in the formation of the trithiocarbonate (VII) from the dithiol (VI) is a consequence of the mechanism proposed[1] for this type of reaction, and is confirmed by the close similarity of the optical rotatory dispersion curves shown by this compound and the trithiocarbonate (IV).

The (*R*)-diol (I) was next converted into the (*S*)-ditoluene-*p*-sulphonate (VIII). Selective replacement of the primary sulphonyloxy group by a benzoyloxy group was then effected by treatment with 1 mol. of sodium benzoate in dimethylformamide; the resulting (*S*)-benzyl 3-benzoyloxy-2-toluene-*p*-sulphonyloxypropyl ether (IX), on treatment with sodium methoxide, gave (*R*)-benzyl 2,3-epoxypropyl ether (X), inversion of configuration at C-2 being an obvious consequence of the last reaction. A series of reactions similar to those described above led to the (*S*)-trithiocarbonate (XI), the (*S*)-dithiol (XII), and finally (*S*)-2,3-dimercaptopropanol (XIII). The last product, on treatment with potassium methyl xanthate, gave (*S*)-2,3-thiocarbonyldithiopropanol (XIV). The optical rotations of the compounds (X)—(XIV) were essentially the same as those of the enantiomers, but of opposite sign. The optical rotatory dispersion curves for the two thiols (XII) and (XIII) showed in each case the first extremum of a negative Cotton effect, as a trough at 234—235 mμ.

The availability of certain intermediates in the above reaction schemes facilitated the synthesis of two other optically active mercapto-alcohols. (*S*)-1,2-*O*-Isopropylideneglycerol (XV) was converted into the (*R*)-toluene-*p*-sulphonate (XVI) which, without purification, was treated with potassium thiolacetate in boiling acetone to give the (*R*)-acetylthio-compound (XVII). Deacetylation of this by base-catalysed solvolysis in methanol gave the (*R*)-thiol (XVIII), which on acid hydrolysis



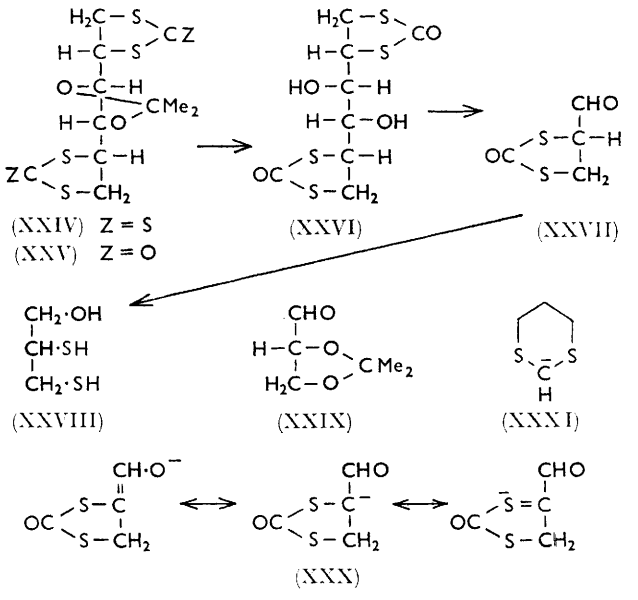
furnished (*R*)-3-mercaptopropane-1,2-diol (XIX), $[\alpha]_D$ −8° in ethanol.

The difference in reactivity between a primary and a secondary sulphonyloxy group towards replacement by thiolacetate[20] provides a useful route to episulphides,[19] and advantage of this fact was taken in the reaction of the ditoluene-*p*-sulphonate (VIII) with 1 mol. of potassium thiolacetate to give a crude monothiolacetate (XX), which, when treated with sodium methoxide, gave (*R*)-benzyl 2,3-epithiopropyl ether (XXI). The configuration of this episulphide, which follows from its method of preparation, was confirmed by reaction of the compound with potassium methyl xanthate (retention of configuration), to give the crystalline trithiocarbonate (IV) previously described. When the episulphide was reduced with lithium aluminium hydride it gave the (*S*)-thiol (XXII) from which (*S*)-2-mercaptopropanol (XXIII), $[\alpha]_D$ +24·5°, was obtained by treatment with sodium and liquid ammonia. The formation of an

[19] A. M. Creighton and L. N. Owen, *J. Chem. Soc.*, 1960, 1024.
[20] J. H. Chapman and L. N. Owen, *J. Chem. Soc.*, 1950, 597.

optically active product provides direct proof that the terminal episulphide is cleaved by lithium aluminium hydride to give the secondary thiol, in agreement with the direction of fission observed [21] with 1,2-epithiopropane and 1,2-epithiohexane.

A route to (*R*)-2,3-dimercaptopropanol, different from that described above, was also examined. 1,2,5,6-Tetradeoxy-3,4-*O*-isopropylidene-1,2:5,6-di(thiocarbonyldithio)-L-iditol (XXIV) was prepared [16] from D-mannitol, and converted, by treatment with mercuric acetate, into the bisdithiocarbonate (XXV), which on mild hydrolysis in aqueous acetic acid afforded 1,2,5,6-tetradeoxy-1,2:5,6-di(carbonyldithio)-L-iditol (XXVI). This change of the trithiocarbonate into the dithiocarbonate system was carried out because it had been established [22] that the latter, unlike the former, is not attacked by lead tetra-acetate. When the diol (XXVI) was treated with this reagemt it gave a crude aldehyde (XXVII) (characterised as the 2,4-dinitrophenylhydrazone) which, on reduction with lithium aluminium hydride, gave 2,3-dimercaptopropanol (XXVIII). Surprisingly, the product was optically inactive, even when examined by the o.r.d. technique. Since the crude aldehyde (XXVII) and the pure 2,4-dinitrophenyl-



hydrazone were both active, it is evident that complete racemisation must have occurred during the final reaction with lithium aluminium hydride. Although there are a few reports to the contrary,[23] it is generally assumed that this method of reduction does not affect the configuration at an adjacent centre, and when, for comparison, (*R*)-2,3-*O*-isopropylideneglyceraldehyde (XXIX) was reduced with lithium aluminium hydride it gave optically pure (*S*)-1,2-*O*-isopropylideneglycerol (XV), identical with that obtained by hydrogenation of the same aldehyde over Raney nickel. This indicates that the racemisation accompanying the reduction of the aldehyde (XXVII) must be due to the presence of the sulphur atom at C-2; the effect of this atom is to stabilise the enolate anion (XXX) by resonance involving a vacant 3*d*-orbital, which is not possible when the substituent at C-2 is oxygen rather than sulphur. Stabilisation of simple carbanions by at least *two* neighbouring bivalent sulphur atoms is well known, for example in the structure (XXXI).[24] In the present instance the stabilisation produced by one sulphur atom is sufficient because the resonance also involves the carbonyl group.[25]

EXPERIMENTAL

Unless otherwise stated, i.r. spectra were measured in chloroform and u.v. spectra in ethanol. The o.r.d. measurements were kindly made available through the courtesy of Professor C. Djerassi (two trithiocarbonates) and of Professor W. Klyne and Dr. P. M. Scopes (two dithiols). Petroleum was the fraction of b. p. 40—60°, unless specified otherwise.

Benzyl 2,3-Isopropylidenedioxypropyl Ether.—This was prepared (85%) from 1,2-*O*-isopropylideneglycerol by the method described [14] for the (+)-isomer, except that an equivalent amount of powdered sodium hydroxide was used instead of potassium hydroxide. The product had b. p. 104—106°/0·4 mm. (lit.,[13] 117—121°/3 mm.), n_D^{22} 1·4930.

Benzyl 2,3-Dihydroxypropyl Ether.—Hydrolysis [13] of the preceding compound with 10% aqueous acetic acid at 100° gave the diol (95%), b. p. 117—118°/10^{-4} mm. (lit.,[13] 140—145°/1 mm.), n_D^{20} 1·5330.

Benzyl 2,3-Epoxypropyl Ether.—A solution of toluene-*p*-sulphonyl chloride (38·7 g.) and pyridine (26 g.) in chloroform (300 c.c.) was added dropwise during 12 hr. to a solution of the above diol (34·5 g.) in chloroform (300 c.c.) at 0°. The mixture was set aside for 24 hr. and then washed with hydrochloric acid, sodium hydrogen carbonate solution, and water, dried, and treated at −5° with methanolic sodium methoxide, prepared by interaction of sodium (4·8 g.) and methanol (160 c.c.). After being stirred for 2 hr., the temperature being allowed to rise slowly to 7°, the mixture was neutralised with carbon dioxide and diluted with water to dissolve the sodium toluene-*p*-sulphonate. The chloroform layer was removed, combined with one further extraction (with chloroform) of the aqueous layer, then dried and distilled, to give an oil, which on redistillation gave the epoxide (18 g.), b. p. 62—63°/10^{-3} mm., n_D^{20} 1·5175 (lit.,[15] b. p. 76—81°/0·3—0·7 mm., n_D^{25} 1·5148—1·5150).

Benzyl 2,3-Thiocarbonyldithiopropyl Ether.—A solution of the epoxide (2·4 g.), potassium hydroxide (5·0 g.), and carbon disulphide (8·0 g.) in methanol (30 c.c.) was boiled under reflux for 2 hr. Water (100 c.c.) was added to the cooled mixture, which was then extracted with chloroform (3 × 30 c.c.), to give a yellow oil; by chromatography on

[21] F. G. Bordwell, H. M. Andersen, and B. M. Pitt, *J. Amer. Chem. Soc.*, 1954, **76**, 1082.
[22] T. J. Adley, A. K. M. Anisuzzaman, and L. N. Owen, *J. Chem. Soc.* (*C*), 1967, 807.
[23] W. Hückel and C. Z. K. Cheema, *Chem. Ber.*, 1958, **91**, 311; G. Ohloff, J. Osiecki, and C. Djerassi, *ibid.*, 1962, **95**, 1400; J. A. Berson and M. A. Greenbaum, *J. Amer. Chem. Soc.*, 1959, **81**, 6456.
[24] E. J. Corey and D. Seebach, *Angew. Chem., Internat. Edn.*, 1965, **4**, 1075, 1077.
[25] Cf. V. Georgian and L. L. Skaletzky, *J. Org. Chem.*, 1964, **29**, 51.

alumina, with benzene as eluent, this furnished the *trithiocarbonate* (2·3 g.), which crystallised from ether–petroleum, m. p. 42—43° (Found: C, 51·3; H, 4·7; S, 37·7. $C_{11}H_{12}OS_3$ requires C, 51·5; H, 4·7; S, 37·5%).

Benzyl 2,3-Dimercaptopropyl Ether.—The trithiocarbonate (11·0 g.) in dry ether (100 c.c.) was slowly added to a stirred suspension of lithium aluminium hydride (4·0 g.) in dry ether (100 c.c.). After 2 hr., the excess of hydride was destroyed with ethyl acetate and the mixture was acidified with hydrochloric acid. The ether layer was removed and the aqueous portion was extracted with fresh ether. Distillation of the washed and dried extracts gave the crude dithiol (8·3 g.), b. p. 102—120°/10^{-4} mm., n_D^{21} 1·5740—1·5760 (Found: S, 28·6. Calc. for $C_{10}H_{14}OS_2$: S, 29·9%).

2,3-Dimercaptopropanol.—The crude benzyl 2,3-dimercaptopropyl ether (5·0 g.) was dissolved in liquid ammonia (50 c.c.), and small pieces of sodium were added until a persistent blue colour was obtained. The colour was then discharged by the addition of ammonium chloride, and the ammonia was allowed to evaporate, the last traces being removed in a stream of nitrogen. The residue was acidified with hydrochloric acid and extracted with chloroform, to give 2,3-dimercaptopropanol (1·6 g.), b. p. 68—69°/10^{-4} mm., n_D^{24} 1·5712 (Found: thiol-S, 50·6. Calc. for $C_3H_8OS_2$: S, 51·6%); the i.r. spectrum was identical with that of an authentic sample (lit.,[10] n_D^{20} 1·5733). The 2,3-*S*-cyclohexylidene derivative, m. p. 63° (from benzene–petroleum), was also identical with the derivative, m. p. 63°, of the authentic dithiol (lit.,[10] m. p. 70°).

2,3-Thiocarbonyldithiopropanol.—A solution of 2,3-dimercaptopropanol (0·62 g.), potassium hydroxide (1·4 g.), and carbon disulphide (2·5 c.c.) in methanol (20 c.c.) was set aside for 7 days and then diluted with water. Extraction with chloroform gave a yellow oil which, after chromatography on silica gel with chloroform as eluent, gave the *trithiocarbonate* (0·35 g.), b. p. 150—160°(bath)/10^{-4} mm., $\lambda_{max.}$ 317 mμ (ε 14,700) (Found: C, 28·9; H, 3·7; S, 57·5. $C_4H_6OS_3$ requires C, 28·9; H, 3·6; S, 57·85%).

(S)-*Benzyl 2,3-Isopropylidenedioxypropyl Ether*.—Prepared from (*S*)-1,2-*O*-isopropylideneglycerol[17] in 96% yield by the modified method indicated above for the racemic compound, this had b. p. 122—126°/1 mm., n_D^{19} 1·4950, $[\alpha]_D^{22}$ +21·3° (*c* 4 in $CHCl_3$) {lit.,[26] b. p. 95—97°/0·3 mm., n_D^{16} 1·4970, $[\alpha]_D$ +16·8° (neat)}.

(S)-*Benzyl 2-Hydroxy-3-toluene*-p-*sulphonyloxypropyl Ether* (II).—Hydrolysis of the preceding isopropylidene compound (83·0 g.) with 10% aqueous acetic acid gave (*R*)-benzyl 2,3-dihydroxypropyl ether (65·6 g.), b. p. 142—146°/0·6 mm., n_D^{19} 1·5325, α_D^{20} +6·5° (1 dm., neat) [lit.,[26] b. p. 138—139°/0·3 mm., n_D^{16} 1·5342, $[\alpha]_D$ +5·3° (neat)]. Treatment of this diol (9·1 g.) in pyridine (18 c.c.) with toluene-*p*-sulphonyl chloride (9·55 g.) in pyridine (18 c.c.) gave a crude product which, after chromatography on silica gel with ether–petroleum (b. p. 60—80°) as eluent, gave the (*S*)-3-toluene-*p*-sulphonate (6·5 g.), m. p. 53—54° (from ether–hexane), $[\alpha]_D^{21}$ +8·5° (*c* 6 in MeOH) (lit.,[18] m. p. 48°, $[\alpha]_D^{23}$ +4·6 (*c* 5 in MeOH).

(S)-*Benzyl 2,3-Epoxypropyl Ether* (III).—The (*S*)-toluene-*p*-sulphonate (5 g.) in chloroform (25 c.c.) was mixed at −5° with a solution prepared from sodium (0·35 g.) and methanol (25 c.c.). After 15 min., the mixture was neutralised with carbon dioxide and diluted with water (20 c.c.). The aqueous layer was removed and extracted with chloroform, and the combined organic layers were washed, dried, and distilled, to give the (S)-*epoxide* (2·0 g.), b. p. 68°/10^{-4} mm., n_D^{15} 1·5187, d^{20} 1·06, $[\alpha]_D^{20}$ −15·3° (neat) (Found: C, 73·2; H, 7·2. $C_{10}H_{12}O_2$ requires C, 73·1; H, 7·4%).

(R)-*Benzyl 2,3-Thiocarbonyldithiopropyl Ether* (IV).—Reaction of the (*S*)-epoxide (0·40 g.) with potassium hydroxide (0·8 g.), carbon disulphide (1·6 c.c.), and methanol (5 c.c.), as described for the racemic compound, gave a solid (no chromatography was necessary) which crystallised from ether–petroleum to form the (R)-*trithiocarbonate*, plates (0·30 g.), m. p. 64°, $[\alpha]_D^{23}$ +175° (*c* 2 in $CHCl_3$); o.r.d. (*c* 0·066 in MeOH) $[\phi]_{480}$ +4600° (peak), $[\phi]_{410}$ −6540° (trough), $[\phi]_{380}$ −5750° (peak), $[\phi]_{330}$ −20,170° (trough), $[\phi]_{296}$ +15,510° (peak), $[\phi]_{240}$ +1550° (trough), $[\phi]_{218}$ +18,620° (peak) (Found: C, 51·8; H, 4·6; S, 37·35. $C_{11}H_{12}OS_3$ requires C, 51·5; H, 4·7; S, 37·5%).

(R)-*Benzyl 2,3-Dimercaptopropyl Ether* (V).—Reduction of the (*R*)-trithiocarbonate (7·0 g.) with lithium aluminium hydride (2·6 g.) as described for the racemic compound gave the (*R*)-*dithiol* (5·0 g.), b. p. 93—95°/5 × 10^{-4} mm., n_D^{19} 1·5732, $[\alpha]_D^{25}$ −7·6° (*c* 15 in $CHCl_3$) (Found: C, 56·2; H, 6·45; S, 30·1; thiol-S, 29·3. $C_{10}H_{14}OS_2$ requires C, 56·0; H, 6·6; S, 29·9%).

(R)-*2,3-Dimercaptopropanol* (VI).—The preceding benzyl ether (4·0 g.) was reduced with sodium in liquid ammonia, as described above, to give the (R)-*dimercapto-alcohol* (1·7 g.), b. p. 65°/10^{-4} mm., n_D^{18} 1·5740, $[\alpha]_D^{21}$ −9·6° (*c* 7 in MeOH), $[\alpha]_D^{25}$ +3·0° (*c* 9 in $CHCl_3$) (Found: C, 29·4; H, 6·4; S, 52·0; thiol-S, 51·4. $C_3H_8OS_2$ requires C, 29·0; H, 6·5; S, 51·6%).

The (R)-2,3-S-*cyclohexylidene derivative* had m. p. 50—51° (from benzene–petroleum) (Found: C, 52·8; H, 7·9. $C_9H_{16}OS_2$ requires C, 52·9; H, 7·9%).

(R)-*2,3-Thiocarbonyldithiopropanol* (VII).— Prepared from (*R*)-2,3-dimercaptopropanol (0·50 g.) by the method used for the racemic compound, the *trithiocarbonate* (0·35 g.) had b. p. 150—160°(bath)/10^{-4} mm., $\nu_{max.}$ (liquid film) 1085, 3425 cm.$^{-1}$, $[\alpha]_D^{26}$ +291° (*c* 3 in $CHCl_3$); o.r.d. (*c* 0·0375 in MeOH) $[\phi]_{589}$ +394°, $[\phi]_{477}$ +4450° (peak), $[\phi]_{412}$ −6400° (trough), $[\phi]_{384}$ −5910° (peak), $[\phi]_{328}$ −18,720° (trough), $[\phi]_{295}$ +18,720° (peak), $[\phi]_{245}$ +7390° (trough), $[\phi]_{222}$ +19,700° (peak) (Found: C, 29·2; H, 3·2; S, 57·65. $C_4H_6OS_3$ requires C, 28·9; H, 3·6; S, 57·85%).

(S)-*Benzyl 2,3-Ditoluene*-p-*sulphonyloxypropyl Ether* (VIII).—A solution of (*R*)-benzyl 2,3-dihydroxypropyl ether (48 g.) and toluene-*p*-sulphonyl chloride (110 g.) in pyridine (250 c.c.) was kept at ambient temperature for 3 days. Dilution with water and extraction with chloroform gave, from the washed and dried extracts, the *ditoluene*-p-*sulphonate* (116 g.), m. p. 60—61° (from methanol), $[\alpha]_D^{23}$ −2·7° (*c* 15 in pyridine) (Found: C, 58·8; H, 5·3; S, 13·4. $C_{24}H_{26}O_7S_2$ requires C, 58·8; H, 5·35; S, 13·1%).

(S)-*Benzyl 3-Benzoyloxy-2-toluene*-p-*sulphonyloxypropyl Ether* (IX).—The ditoluene-*p*-sulphonate (20 g.), sodium benzoate (6 g.), and dimethyl formamide (600 c.c.) were stirred and heated together at 92—95° for 5 hr. The solvent was then removed by distillation, and the residue was extracted with chloroform, to give the *benzoate* (9·7 g.), m. p. 106° (from ether), $\nu_{max.}$ 1375, 1718 cm.$^{-1}$, $[\alpha]_D^{22}$ +26·4° (*c* 8 in $CHCl_3$) (Found: C, 65·7; H, 5·2; S, 7·4. $C_{24}H_{24}O_6S$ requires C, 65·5; H, 5·5; S, 7·3%).

[26] J. C. Sowden and H. O. L. Fischer, *J. Amer. Chem. Soc.*, 1941, **63**, 3244.

(R)-*Benzyl* 2,3-*Epoxypropyl Ether* (X).—When the reaction of sodium (1·1 g.) with methanol (50 c.c.) was complete, the solution was cooled to −5° and added to a solution of the above benzoate (19·5 g.) in chloroform (125 c.c.), also at −5°. The mixture was stirred for 1 hr. at 0—2°, and then worked up, as described for the preparation of the enantiomer, to give the (R)-*epoxide* (5·0 g.), b. p. 63°/10^{-4} mm., n_D^{14} 1·5190, d^{14} 1·07, $[\alpha]_D^{21}$ +15·0° (neat) (Found: C, 73·2; H, 7·3. $C_{10}H_{12}O_2$ requires C, 73·1; H, 7·4%).

(S)-*Benzyl* 2,3-*Thiocarbonyldithiopropyl Ether* (XI).—Prepared from the (*R*)-epoxide (4·6 g.) by the method used for the enantiomer, the *trithiocarbonate* (4·2 g.) had m. p. 64° (from ether–petroleum), $\lambda_{max.}$ 317 mμ (ε 15,500), $[\alpha]_D^{24}$ −176° (*c* 2 in $CHCl_3$) (Found: C, 51·6; H, 4·6; S, 37·8. $C_{11}H_{12}OS_3$ requires C, 51·5; H, 4·7; S, 37·5%). When a 1 : 1 mixture of this trithiocarbonate and its enantiomer was crystallised from ether–petroleum it gave the racemic compound, m. p. 42—43°, identical with that already described.

(S)-*Benzyl* 2,3-*Dimercaptopropyl Ether* (XII).—Reduction of the preceding (*S*)-trithiocarbonate (4 g.) with lithium aluminium hydride (1·5 g.), as described for the racemic compound, gave the (S)-*dithiol* (2·7 g.), b. p. 93—96°/10^{-4} mm., n_D^{26} 1·5725, $[\alpha]_D^{26}$ +7·2° (*c* 10 in $CHCl_3$); o.r.d. (*c* 0·054 in MeOH) $[\phi]_{234}$ −565° (trough), $[\phi]_{227}$ −375° (Found: C, 55·8; H, 6·6; thiol-S, 29·2. $C_{10}H_{14}OS_2$ requires C, 56·0; H, 6·6; S, 29·9%).

(S)-2,3-*Dimercaptopropanol* (XIII).—Treatment of the preceding benzyl ether (2·0 g.) with sodium in liquid ammonia, as described above, gave the (S)-*dimercapto-alcohol* (0·76 g.), b. p. 65°/10^{-4} mm., n_D^{23} 1·5715, $[\alpha]_D^{25}$ +9·6° (*c* 6 in MeOH) (Found: C, 29·0; H, 6·2; S, 51·4. $C_3H_8OS_2$ requires C, 29·0; H, 6·5; S, 51·6%).

(S)-2,3-*Thiocarbonyldithiopropanol* (XIV).—(*S*)-2,3-Dimercaptopropanol (0·30 g.), in a reaction similar to that on the racemic compound, gave the *trithiocarbonate* (0·21 g.), b. p. 150—160°(bath)/10^{-14} mm., $\nu_{max.}$ (liquid film) 1085, 3425 $cm.^{-1}$, $[\alpha]_D^{25}$ −299° (*c* 1·4 in $CHCl_3$); o.r.d. (*c* 0·095 in MeOH) $[\phi]_{235}$ −440° (trough), $[\phi]_{227}$ −260° (Found: S, 58·1. $C_4H_6OS_3$ requires S, 57·85%).

(R)-2,3-*Isopropylidenedioxypropyl Thiolacetate* (XVII).—A solution of toluene-*p*-sulphonyl chloride (11·5 g.) and (*S*)-1,2-*O*-isopropylideneglycerol (7·2 g.) in pyridine (40 c.c.) was kept at −5° for 3 hr. and then set aside for 15 hr. Dilution with water and extraction with chloroform gave an oil (15·0 g.) which was boiled under reflux in acetone (300 c.c.) with potassium thiolacetate (7·5 g.) for 19 hr. The cooled and filtered mixture was concentrated, and the residue treated with water (50 c.c.) and extracted with ether, to give the *thiolacetate* (8·6 g.), b. p. 118°/20 mm., n_D^{18} 1·4750, $\lambda_{max.}$ 231 mμ (ε 4300), $\nu_{max.}$ (liquid film) 1690 $cm.^{-1}$ (SAc), $[\alpha]_D^{19}$ −7·4° (*c* 14 in $CHCl_3$) (Found: C, 50·6; H, 7·9; S, 16·6. $C_8H_{14}O_3S$ requires C, 50·5; H, 7·4; S, 16·85%) (lit.,[27] b. p. 114°/15 mm., n_D^{22} 1·4740, for the racemic compound).

(R)-2,3-*Isopropylidenedioxypropanethiol* (XVIII).—Sodium (15 mg.) was added to a solution of the preceding thiolacetate (1·3 g.) in methanol (25 c.c.). The mixture was kept under nitrogen for 6 days, evaporated to an oil which was taken up in ether, washed with water, and distilled, to give the (R)-*thiol* (0·4 g.), b. p. 82°/25 mm., n_D^{20} 1·4632, $[\alpha]_D^{23}$ +31·4° (*c* 5·5 in $CHCl_3$) (Found: C, 48·4; H, 8·7; thiol-S, 21·6. $C_6H_{12}O_2S$ requires C, 48·6; H, 8·2; S, 21·7%) (lit.,[11] b. p. 46—47°/3 mm., n_D^{20} 1·4651, for the racemic compound). The (*R*)-thiol was characterised as the S-2,4-*dinitrophenyl derivative*, m. p. 115—116° (from ethanol) (Found: C, 45·6; H, 4·4; N, 9·15. $C_{12}H_{14}O_6N_2S$ requires C, 45·85; H, 4·5; N, 8·9%).

(R)-3-*Mercaptopropane*-1,2-*diol* (XIX).—The preceding isopropylidene compound (4·7 g.) was boiled under reflux with methanol (30 c.c.) and concentrated hydrochloric acid (6·5 c.c.) for 40 hr. under nitrogen. The solution was then neutralised with sodium carbonate, filtered, and concentrated. Extraction of the residue with ethyl acetate gave the (R)-*mercapto-diol* (1·5 g.), b. p. 102°/0·9 mm., n_D^{22} 1·5230, $[\alpha]_D^{25}$ −8° (*c* 11 in EtOH) (Found: C, 33·6; H, 7·8; S, 29·4; thiol-S, 29·6. $C_3H_8O_2S$ requires C, 33·3; H, 7·5; S, 29·65%) (lit.,[11] b. p. 97°/0·9 mm., n_D^{20} 1·5268, for the racemic compound).

(R)-*Benzyl* 2,3-*Epithiopropyl Ether* (XXI).—Potassium thiolacetate (5·2 g.), (*S*)-benzyl 2,3-ditoluene-*p*-sulphonyloxypropyl ether (20·0 g.), and acetone (300 c.c.) were stirred and boiled together under reflux for 22 hr. The cooled mixture was then filtered and concentrated, and the residue was extracted with ether. Evaporation of the washed and dried extract gave an oil (15·5 g.), $\nu_{max.}$ (liquid film) 1695 (SAc), 1375 $cm.^{-1}$ ($O{\cdot}SO_2$), which was dissolved in chloroform (150 c.c.) and mixed at −5° with a solution prepared from sodium (1·0 g.) and methanol (60 c.c.). After 15 min., the mixture was worked up as described for the above epoxides, and gave the *episulphide* (5·5 g.), b. p. 79—82°/10^{-4} mm., n_D^{15} 1·5610, $[\alpha]_D^{23}$ +11·8° (*c* 8 in $CHCl_3$) (Found: C, 66·7; H, 6·2; S, 18·2. $C_{10}H_{12}OS$ requires C, 66·6; H, 6·7; S, 17·8%). On treatment with potassium methyl xanthate, the episulphide gave (*R*)-benzyl 2,3-thiocarbonyldithiopropyl ether, m. p. and mixed m. p. 64°.

(S)-*Benzyl* 2-*Mercaptopropyl Ether* (XXII).—A mixture of the preceding episulphide (5·5 g.), lithium aluminium hydride (3 g.), and dry ether (100 c.c.) was boiled under reflux for 5 hr. and then worked up as described above for the reduction of the trithiocarbonates. The *thiol* (4·3 g.) had b. p. 57°/10 mm., n_D^{15} 1·5330, $[\alpha]_D^{24}$ +5° (*c* 10 in $CHCl_3$) (Found: C, 65·9; H, 7·8; S, 17·9; thiol-S, 17·9. $C_{10}H_{14}OS$ requires C, 65·9; H, 7·7; S, 17·6%).

(S)-2-*Mercaptopropanol* (XXIII).—Sodium, in small pieces, was added to a solution of the benzyl ether (XXII) (1·8 g.) in liquid ammonia (50 c.c.) until a persistent blue colour was obtained. The colour was then discharged by the addition of ammonium chloride and the ammonia allowed to evaporate in a stream of nitrogen. The residue was acidified with dilute hydrochloric acid and extracted with chloroform (50 c.c.). This extract was extracted with 2N-sodium hydroxide (2 × 10 c.c.), and this alkaline solution was acidified at 0° with concentrated hydrochloric acid and finally extracted with chloroform, to give (S)-2-*mercaptopropanol* (0·5 g.), b. p. 50—51°/20 mm., n_D^{12} 1·4870, $[\alpha]_D^{22}$ +24·5° (*c* 14 in $CHCl_3$) (Found: C, 38·95; H, 8·8; S, 35·3; thiol-S, 35·2. C_3H_8OS requires C, 39·1; H, 8·7; S, 34·9%) (lit.,[28] b. p. 60—62°/12 mm., n_D^{17} 1·4818, and [29] b. p. 54°/11 mm., n_D^{21} 1·4843, for the racemic compound).

1,2,5,6-*Tetradeoxy*-3,4-O-*isopropylidene*-1,2:5,6-*di*(*carbonyldithio*)-L-*iditol* (XXV).—A mixture of 1,2,5,6-tetradeoxy-3,4-*O*-isopropylidene-1,2:5,6-di(thiocarbonyldithio)-L-iditol[16] (10·5 g.), mercuric acetate (65 g.), and acetic acid (250 c.c.) was stirred at ambient temperature until the

[27] P. S. Fitt and L. N. Owen, *J. Chem. Soc.*, 1957, 2240.
[28] W. Davies and W. E. Savige, *J. Chem. Soc.*, 1950, 317.
[29] H. Böhme, H. Bezzenberger, and H. D. Stachel, *Annalen*, 1957, **602**, 1.

colour disappeared (1 hr.). It was then filtered, and the solid was washed with chloroform. The filtrate and washings were concentrated, diluted with water, and extracted with chloroform. This extract was washed with aqueous sodium hydrogen carbonate and with water, and dried. Evaporation gave a solid residue (9·5 g.) which on crystallisation from methanol gave the *bisdithiocarbonate* (5·5 g.), m. p. 130—131°, $\nu_{max.}$ 1660, 1720 cm.$^{-1}$, $[\alpha]_D^{25}$ +157° (*c* 4 in $CHCl_3$) (Found: C, 39·4; H, 4·2; S, 37·9. $C_{11}H_{14}O_4S_4$ requires C, 39·0; H, 4·2; S, 37·9%).

1,2,5,6-*Tetradeoxy*-1,2:5,6-*di*(*carbonyldithio*)-L-*iditol* (XXVI).—The isopropylidene compound (XXV) (3·5 g.) was boiled under reflux in 40% aqueous acetic acid for 20 hr. The crystals which separated from the cooled solution were recrystallised from chloroform and then from ethanol, to give the *diol* (2·5 g.), m. p. 203°, $[\alpha]_D^{24}$ +175° (*c* 1 in acetone) (Found: C, 32·3; H, 3·15; S, 43·4. $C_8H_{10}O_4S_4$ requires C, 32·2; H, 3·4; S, 43·0%).

(R)-2,3-*Carbonyldithiopropionaldehyde* (XXVII).—The preceding iditol derivative (9·7 g.), lead tetra-acetate (20 g.), acetic acid (200 c.c.), and water (25 c.c.) were stirred together for 2 hr. and concentrated under reduced pressure at 40°. Extraction of the residue with chloroform gave the crude aldehyde (6·0 g.), $[\alpha]_D^{20}$ +20° (*c* 5 in $CHCl_3$). Treatment of a portion with 2,4-dinitrophenylhydrazine in acetic acid furnished the 2,4-*dinitrophenylhydrazone*, m. p. 166—167° (from methanol), $[\alpha]_D^{22}$ +55° (*c* 1 in ethyl acetate) (Found: C, 37·0; H, 2·5; N, 16·9. $C_{10}H_8N_4O_5S_2$ requires C, 36·7; H, 2·5; N, 17·1%).

Reduction of (R)-2,3-*Carbonyldithiopropionaldehyde*.—A solution of the crude aldehyde (3·5 g.) in dry ether (100 c.c.) was added to a stirred slurry of lithium aluminium hydride (4 g.) and dry ether (100 c.c.). The mixture was boiled under reflux for 2 hr., cooled, and cautiously treated with water to destroy the excess of hydride. After acidification with hydrochloric acid, the mixture was saturated with sodium chloride and the ether layer was removed. The aqueous portion was twice extracted with ether, and the combined organic solutions were dried and distilled, to give 2,3-dimercaptopropanol (1·5 g.), b. p. 65—67°/10^{-4} mm., n_D^{26} 1·5680, $[\alpha]_D^{26}$ 0° (*c* 15 in MeOH).

The 2,3-*S*-cyclohexylidene derivative was identical with a sample prepared from authentic racemic 2,3-dimercaptopropanol; it had m. p. and mixed m. p. 62—63° (from benzene–petroleum) (Found: C, 52·9; H, 7·9; S, 31·5. Calc. for $C_9H_{16}OS_2$: C, 52·9; H, 7·9; S, 31·4%).

Reduction of (R)-2,3-O-*Isopropylideneglyceraldehyde*.—(*a*) The crude aldehyde, prepared [17] from 1,2:5,6-di-*O*-isopropylidene-D-mannitol (78·0 g.), was hydrogenated at 100 atm. in ethyl acetate (600 c.c.) in the presence of Raney nickel (100 g.), to give (*S*)-1,2-*O*-isopropylideneglycerol (54·9 g.), b. p. 85°/15 mm., n_D^{18} 1·4350, $[\alpha]_D^{25}$ +11·3° (*c* 10 in MeOH) {lit.,[17] b. p. 80—80·5°/11—12 mm., n_D^{20} 1·4347, $[\alpha]_D^{20}$ +10·7° (*c* 13 in MeOH)}.

(*b*) The crude aldehyde (2·4 g.) was reduced with lithium aluminium hydride (1·0 g.) in dry ether (80 c.c.) under the conditions used for the reduction of (*R*)-2,3-carbonyldithiopropionaldehyde (see above). The product was (*S*)-1,2-*O*-isopropylideneglycerol (1·4 g.), b. p. 56°/1 mm., n_D^{20} 1·4345, $[\alpha]_D^{23}$ +11·1° (*c* 8 in MeOH).

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