Cyclization of (+)- and (−)-*S*-(2-Methylprop-1-enyl)-L-cysteine *S*-Oxides

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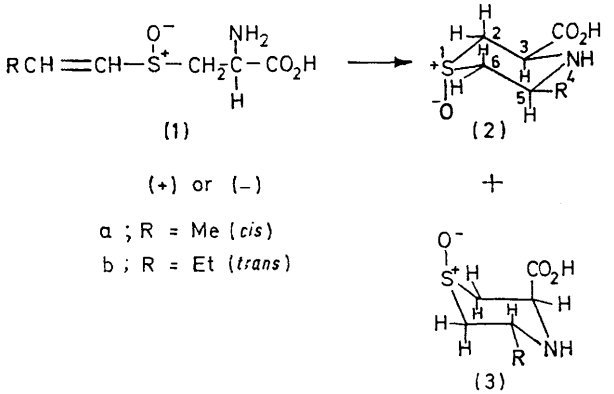
S-(2-Methylprop-1-enyl)-L-cysteine (5) has been oxidized to two sulphoxides (7a), $[\alpha]_D^{25}$ +128°, and (7b), $[\alpha]_D^{25}$ −84.3° (in H_2O). Cyclization in base was stereospecific. The (+)-sulphoxide (7a) yielded the axial sulphoxide, (1*S*.3*R*)-5,5-dimethyltetrahydro-1,4-thiazine-3-carboxylic acid *S*-oxide (9), and the (−)-sulphoxide (7b) yielded the corresponding equatorial (1*R*) sulphoxide (10). This establishes the absolute configurations of the acyclic sulphoxides (7a and b) as *R* and *S*, respectively, at sulphur. Reduction of the cyclic sulphoxides to the corresponding cyclic sulphide, and reoxidation of this compound gave exclusively the equatorial sulphoxide (10), suggesting a large steric effect of the axial methyl group. Assignments of ring conformations and sulphoxide configurations are based on spectroscopic evidence.

In continuation of studies on the base-induced cyclization of (β-substituted vinyl)cysteine *S*-oxides, we have investigated the cyclization of *S*-(2-methylprop-1-enyl)-cysteine *SS*-dioxide (6) and of the corresponding diastereoisomeric *S*-oxides (7a and b) to the cyclic sulphone (8) and cyclic sulphoxides (9) and (10). The products (9) and (10) were reduced to the cyclic sulphide (11) and this was re-oxidized to sulphoxide.

The stereospecificity of these cyclizations and of the oxidation of the cyclic sulphide to sulphoxide was in



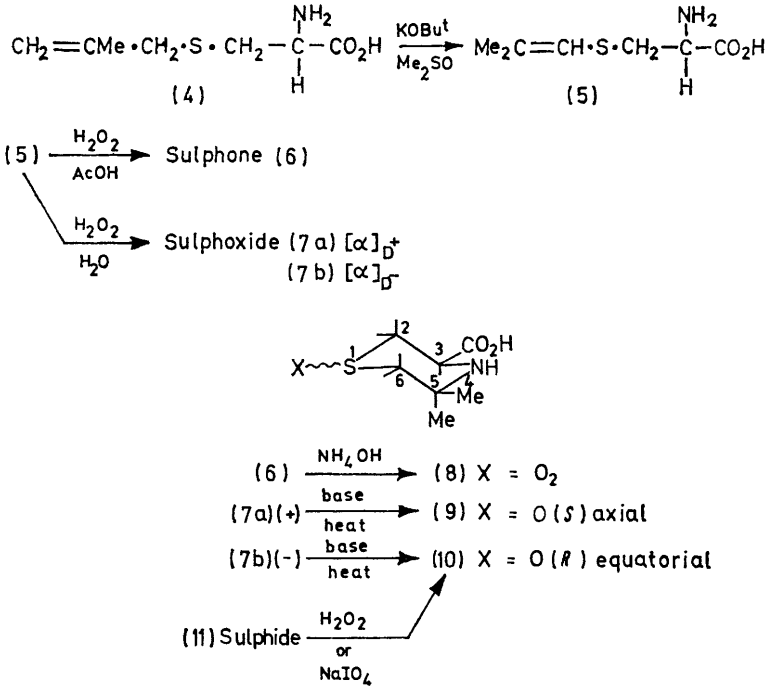
contrast to our previous results with *S*-(prop-1-enyl)- and *S*-(but-1-enyl)-L-cysteine *S*-oxides (1a and b).[1] Thus reaction of the sulphoxides (1) with base in each case yielded both cyclic sulphoxides [(2) and (3)], and was completely non-stereospecific [the proportions of (2) and (3) obtained were independent of the configuration of the original sulphoxide]. This may be a consequence of a sulphoxide–sulphenate rearrangement.[2] Reduction of the product (2) to sulphide and re-oxidation yielded compound (2) quantitatively. However, the sulphide corresponding to (3) on oxidation yielded a 1 : 1 mixture of (3) and the corresponding equatorial sulphoxide.

S-(β-Methylallyl)-L-cysteine (4) was prepared from L-cysteine and 3-chloro-2-methylpropene and then isomerized to *S*-(2-methylprop-1-enyl)-L-cysteine (5). Oxidation of compound (5) with a large excess of hydrogen peroxide in acetic acid produced the sulphone (6), and oxidation with hydrogen peroxide in water yielded a mixture of diastereoisomeric sulphoxides which was separated by fractional crystallization into (7a), $[\alpha]_D^{25}$ +128°, and (7b), $[\alpha]_D^{25}$ −84.3° (in H_2O).

Treatment of the sulphone (6) with ammonium hydroxide yielded the expected cyclic sulphone (8). The isomeric product with an inverted chair conformation was not formed. This would have involved unfavourable Me,CO_2H 1,3-interactions. Cyclization of the sulphoxides (7a and b) could not be achieved in ammonium hydroxide at room temperature (conditions effective in

[1] J. F. Carson and L. M. Boggs, *J. Org. Chem.*, 1966, **31**, 2862; J. F. Carson, R. E. Lndin, and L. M. Boggs, *ibid.*, 1969, **34**, 1966.
[2] R. Tang and K. Mislow, *J. Amer. Chem. Soc.*, 1970, **92**, 2100.

previous reactions), but reaction was effected by heating in sodium carbonate solution. The (+)-isomer (7a) yielded the axial sulphoxide (9), $[\alpha]_D^{25}$ +3°, and the (−)-sulphoxide (7b) the equatorial isomer (10), $[\alpha]_D^{25}$ −19.5° (H_2O). The optical purity of these isomers was greater than 95%, as determined by integration of the methyl proton resonances in the n.m.r. spectra. The cyclization which was determined by n.m.r. Oxidation of (11) with either hydrogen peroxide or sodium periodate yielded the equatorial sulphoxide (10) as the sole product. The preference for equatorial over axial sulphoxide in this case is also shown by the relative difficulty of cyclization of the isomeric acyclic sulphoxides. The (+)-isomer required more drastic conditions for cyclization than the



is therefore stereospecific. Apparently no sulphoxide–sulphenate rearrangement occurs and the formation of an inverted chair conformer would be sterically disfavoured.

Since the absolute configurations of the sulphoxide groups in the cyclic compounds are known (see later), the absolute configurations of the original amino-acid *S*-oxides are also known, if we assume that complete inversion in each case does not occur. The (−)-*S*-oxide (7b) is therefore *S* at sulphur and the (+)-isomer (7a) is *R*. By analogy, (+)-*trans*-*S*-(prop-1-enyl)-L-cysteine *S*-oxide, which occurs naturally in the onion [3] (*Allium cepa*) and undergoes quantitative cyclization to cycloalliin (2; R = Me) has the same configuration at sulphur (*R*) as (7a). These two (+)-substituted cysteine *S*-oxides have the same configuration as (+)-*S*-methyl-L-cysteine *S*-oxide, the exact structure of which is known by *X*-ray analysis.[4]

Reduction of the sulphoxide (9) or (10) with hydriodic acid yielded the cyclic sulphide (11), the conformation of (−)-compound, and although the axial isomer was configurationally pure, the yield was substantially less than that of equatorial isomer obtained from the (−)-sulphoxide.

An indication of steric hindrance in the axial sulphoxide (9) may be obtained from calculations of the distances between methyl hydrogen atoms and oxygen. In cycloalliin (2; R = Me), the distance from sulphoxide oxygen to the 5-axial hydrogen atom is 2.668 Å (from *X*-ray analysis [5]). In the sulphoxide (9), the closest approach of axial methyl hydrogen atom to axial sulphoxide oxygen is calculated to be 1.23 Å (H and O eclipsed) and the maximum distance is 1.64 Å (two H atoms *gauche* to O).*

The preference for axial sulphoxide in thian *S*-oxides has been related to a van der Waals attraction between axial hydrogen in the 3- or 5-position and axial oxygen.[6] Allinger *et al.*[7] have calculated that an axial sulphoxide is more stable than its equatorial isomer in thian *S*-oxides by 0.37 kcal mol^{-1}. Recently Zefirov [8] and Frieze and Evans [9] have suggested that this preference,

* We are indebted to K. J. Palmer for these calculations. They are based on cycloalliin (2) as a model and assume no change in bond angles and distances.

[3] A. I. Virtanen and C. G. Spåre, *Suomen Kem.* (*B*), 1961, **34**, 72; 1962, **35**, 28.

[4] R. Hine and D. Rogers, *Chem. and Ind.*, 1956, 1428; R. Hine, *Acta Cryst.*, 1962, **15**, 635.

[5] K. J. Palmer and K. S. Lee, *Acta Cryst.*, 1966, **20**, 790.

[6] C. R. Johnson and D. McCants, jun., *J. Amer. Chem. Soc.*, 1965, **87**, 1109; J. C. Martin and J. J. Uebel, *ibid.*, 1964, **86**, 2936.

[7] N. L. Allinger, J. A. Hirsh, M. A. Miller, and I. J. Tymanski, *J. Amer. Chem. Soc.*, 1969, **91**, 337.

[8] N. S. Zefirov, *Tetrahedron Letters*, 1975, 1087.

[9] D. M. Frieze and S. A. Evans, *J. Org. Chem.*, 1975, **40**, 2960.

particularly in 1,4-oxathian *S*-oxides, may be due in part to electrostatic interactions. The reversal of axial to equatorial sulphoxide preference for *S*-oxides of thians or 1,4-oxathians with axial substituents other than hydrogen in the 3-position has been demonstrated.†

Ring conformations and sulphoxide configurations were established by i.r. and n.m.r. The cyclic sulphone (8) showed $J_{2,3}$ 12.5 and 2.6 Hz, establishing a *trans*-diaxial relation between protons on C-2 and -3. Sulphoxide configurations in (9) and (10) were established as follows. I.r. stretching frequencies of equatorial sulphoxides are generally higher than those of axial isomers.[10] The isomers (10) and (9) have sulphoxide bands at 1 040—1 050 and 1 025—1 030 cm^{-1}, respectively. According to the '*syn*-axial' rule, a proton 1,3-disposed and *syn*-axial with respect to an axial sulphoxide is more deshielded than a proton in the same position with respect to an equatorial sulphoxide.[11] The sulphoxide (10) has its H-3 n.m.r. signal at δ 3.89 and (9) has the corresponding signal at δ 4.50 (both in D_2O). The (+)-isomer (9) is therefore axial by this rule. Lambert and Keske[12] have established a correlation between the magnitude of *gem*-coupling constants for protons vicinal to a sulphoxide and the configuration of the latter. Values are 1.5—2.0 Hz larger in absolute value for an axial sulphoxide than for the equatorial isomer. This rule and the *syn*-axial rule have been shown to be valid in the cycloalliin series.[1] The (+)-sulphoxide (9) has $|J_{2,2}|$ 14 and $|J_{6,6}|$ 15 Hz (in D_2O–NaOD). The (−)-isomer (10) has $|J_{2,2}|$ 11.5 and $|J_{6,6}|$ 11.8 Hz under the same conditions. This also confirms that the (+)-sulphoxide is axial although the difference (2.5—3.2 Hz) is larger than usually observed.

The cyclic sulphoxides showed substantial long-range couplings between H-2(e) and H-6(e). The isomer (10) also exhibited long-range coupling of 0.75 Hz between the axial methyl protons and H-6(a). The greater breadth of the upfield methyl proton resonances and additional splittings in the lines for H-6(a) suggested such a coupling and this was confirmed by irradiation at both sites.

EXPERIMENTAL

I.r. spectra were obtained for KBr pellets with a Perkin-Elmer 237 spectrophotometer. ^1H N.m.r. spectra were obtained at 100 MHz with a Varian HR-100 spectrometer, equipped with an internal field-frequency lock. For reference compounds, TMS (tetramethylsilane), TSP (sodium β-trimethylsilyl[$^2H_4$]propionate), DSS (sodium 3-trimethylsilylpropane-1-sulphonate), and Bu^{t}OD (δ 1.23) were used. Specific rotations were measured with a Bendix automatic polarimeter (series 1100) with a cell of 2 cm path-length. Paper chromatography was performed with Whatman No. 1 paper; the solvent system BuOH–AcOH–H_2O refers to the mixture with 63 : 10 : 27 proportions, respectively, and coll–lut–H_2O refers to collidine–lutidine (3 : 1) saturated with water.

S-(β-*Methylallyl*)-L-*cysteine* (4).—L-Cysteine hydrochloride hydrate (30 g, 0.171 mol) was suspended in ethanol (1 200 ml) and stirred under nitrogen in an ice-bath. Sodium (14 g, 0.609 equiv.) was added in small pieces and when the reaction was complete 3-chloro-2-methylpropene (31 g, 0.34 mol) was added dropwise with stirring over 3 h. The mixture was stirred overnight at room temperature and then concentrated *in vacuo* to a pasty solid. This was dissolved in water (200 ml) and passed through a column of (1 000 cm^3) of Dowex 50 resin (H^+). The resin was washed with water (5 l) and developed with 2.5N-ammonium hydroxide (3.6 l). Concentration of the eluate *in vacuo* and crystallization from water yielded crude amino-acid (26.1 g, 87%). Recrystallization from water gave platy or micaceous crystals of S-(β-*methylallyl*)-L-*cysteine* (4), $[\alpha]_D^{25}$ −10.8° (*c* 2 in H_2O) and +5.2° (*c* 2.5 in 2.5N-HCl), m.p. 189—194° (decomp.) R_F (w.r.t. alanine) 5.26 (BuOH–AcOH–H_2O) and 2.12 (coll–lut–H_2O); $\nu_{max.}$ 1 575 s (CO_2^-), 1 480s, 1 410s, 1 335m, 1 300m, 1 200w, 1 125w, and 1 035w cm^{-1}; δ(NaOD in D_2O; ref. TMS) 1.82 (3 H, t, CH_3), 2.55—2.92 (2H, dq, β-H_2), 3.35—3.47 (1H, dd, α-H), 3.21 (2 H, s, γ-H_2), and 4.94 (2 H, s, vinylic) (Found: C, 47.85; H, 7.4; N, 8.05. $C_7H_{13}NO_2S$ requires C, 47.95; H, 7.5; N, 8.0%).

S-(2-*Methylprop*-1-*enyl*)-L-*cysteine* (5).—A solution of *S*-(β-methylallyl)cysteine (23 g, 0.131 mol) in dimethyl sulphoxide (1 200 ml) containing potassium t-butoxide (23 g, 0.205 mol) under argon was stirred for 8 h at 10 °C and overnight at room temperature. The solution was poured into ice–water (3 l) and the resulting turbid solution was passed through a column (600 cm^3) of Dowex 50 resin (H^+). The column was washed with water (4 l) and the amino-acid eluted with 2.5N-ammonium hydroxide (3 l). Evaporation *in vacuo* and crystallization of the residue from water (250 ml) yielded the crude product (11.5 g). The mother liquor was concentrated to 30 ml; addition of ethanol (60 ml) then yielded an additional 4.7 g (total yield 70%). Recrystallization from water yielded pure S-(2-*methylprop*-1-*enyl*)-L-*cysteine* (5), $[\alpha]_D^{25}$ +26.5° (*c* 1.5 in H_2O), m.p. 179—180° (decomp.), R_F (w.r.t. alanine) 5.45 (BuOH–AcOH–H_2O); $\nu_{max.}$ 1 575—1 625s (CO_2^-), 1 500s, 1 425s, 1 390s, 1 345s, 1 290m, 1 265w, 1 190w, 1 170w, 1 129w, and 1 050w cm^{-1}; δ(D_2O–NaOD; ref. TSP) 1.77 (6 H, d, 2 CH_3), 2.63—3.17 (2 H, dq, β-H_2), 3.33—3.46 (1 H, dd, α-H), and 5.71 (1 H, s, γ-H) (Found: C, 47.9; H, 7.55; N, 8.05. $C_7H_{13}NO_2S$ requires C, 47.95; H, 7.5; N, 8.0%).

S-(2-*Methylprop*-1-*enyl*)-L-*cysteine* SS-*Dioxide* (6).—*S*-(2-Methylprop-1-enyl)cysteine (6.00 g, 0.0342 mol) in acetic acid (300 ml) was stirred at 45 ± 3 °C for 6 h while 30% hydrogen peroxide (25 ml) was added at 5 ml h^{-1}. The

† An axial methoxy-group 1,3 with respect to sulphur in a 1,4-oxathian directed oxidation to the equatorial sulphoxide; with an equatorial methoxy-group the axial *S*-oxide was formed (see K. W. Buck, A. B. Foster, A. R. Perry, and J. M. Webber, *Chem. Comm.*, 1965, 433; A. B. Foster, Q. H. Hasan, D. R. Hawkins, and J. M. Webber, *ibid.*, 1968, 1084). Perbenzoic acid oxidises 2-thia-5α-androstan-17β-ol oxide (with a β angular methyl group axial and 1,3 to sulphur) to give an 88% yield of equatorial sulphoxide (see B. P. Sollman, R. Nagarajan, and R. M. Dodson, *ibid.*, 1967, 552). *gem*-Dimethyl groups in the 3-position of thian direct oxidation to the equatorial position as established by low-temperature n.m.r. analysis (J. B. Lambert, D. S. Bailey, and C. E. Mixan, *J. Org. Chem.*, 1972, **37**, 377).

[10] P. B. D. de la Mare, D. J. Millen, J. G. Tillet, and D. Watson, *J. Chem. Soc.*, 1963, 1619; R. Nagarajan, B. H. Chollar, and R. M. Dodson, *Chem. Comm.*, 1967, 550.

[11] K. W. Buck, A. B. Foster, W. D. Pardoe, M. H. Quader, and J. M. Webber, *Chem. Comm.*, 1966, 759; A. B. Foster, J. M. Duxbury, T. D. Inch, and J. M. Webber, *ibid.*, 1967, 881.

[12] J. B. Lambert and R. G. Keske, *J. Org. Chem.*, 1966, **31**, 3429.

solution was set aside overnight at room temperature and concentrated *in vacuo* to an oil. Water (100 ml) was added and the solution was concentrated *in vacuo*. The residue crystallized from water–ethanol (1 : 3) (80 ml) to give the product (3.35 g). From the mother liquor an additional 1.81 g was obtained (combined yield 72%). Recrystallization from water–ethanol (1 : 4) yielded pure *sulphone* (6), $[\alpha]_D^{25}$ −0.2° (*c* 2.5 in H_2O), decomp. sharply at 156—157°; $\nu_{max.}$ 1 650s (CO_2^-), 1 525m, 1 400s, 1 375s, 1 325s, 1 300s, 1 230m, and 1 115s cm^{-1} (sym. SO_2); δ(D_2O; ref. TSP) 2.04 (3 H, d, CH_3), 2.18 (3 H, d, CH_3), 3.55—4.01 (2 H, dq, β-H_2), 4.15—4.27 (1 H, q, α-H), and 6.31 (1 H, sept, γ-H) (Found: C, 40.6; H, 6.45; N, 6.75. $C_7H_{13}NSO_4$ requires C, 40.55; H, 6.3; N, 6.75%).

(+)- *and* (−)-S-(2-*Methylprop*-1-*enyl*)-L-*cysteine* S-*Oxides* (7a *and* b).—A solution of *S*-(2-methylprop-1-enyl)cysteine (5) (10.0 g, 0.0571 mol) in oxygen-free water (1 l) was covered with argon and stirred at 10—15 °C while 30% hydrogen peroxide (10 ml) was added at 1.5 ml h^{-1}. The slightly turbid solution was then stirred overnight at room temperature and concentrated *in vacuo* to an amorphous solid (10.3 g). Crystallization from water (30 ml)–acetone (56 ml) at 0 °C for 2 days yielded a product (3.09 g), $[\alpha]_D^{25}$ +99.3° (in H_2O). The residue from the mother liquor [from water (15 ml)–acetone (80 ml)] yielded a second fraction (4.78 g), $[\alpha]_D^{25}$ −36.4°. With increasing proportions of acetone, a third fraction (1.13 g), $[\alpha]_D^{25}$ −62.9°, and a fourth fraction (1.46 g), $[\alpha]_D^{25}$ −20.8°, were obtained (total yield 96%). The first fraction was recrystallized four times from water–acetone (1 : 2) to yield needles (0.986 g) of the S-*oxide* (7a), $[\alpha]_D^{25}$ +128° (*c* 2 in H_2O), unchanged on recrystallization, decomp. 102—103.5°, R_F (w.r.t. alanine) 1.81 (BuOH–AcOH–H_2O); $\nu_{max.}$ 1 650s (CO_2^-) 1 550—1 575s, 1 395s, 1 337s, 1 290m, 1 140w, 1 100w, 1 060w, and 975—1 000s cm^{-1} (*S*-oxide); δ (D_2O–$CF_3{\cdot}CO_3D$, pH 2; ref. Bu^{t}OD) 1.99 (3 H, d, CH_3), 2.06 (3 H, d, CH_3), 3.40—3.47 (2 H, 3 lines, B_2 of AB_2, β-H_2), 4.36—4.49 (1 H, dd, A of AB_2, α-H), and 6.25 (1 H, sept, γ-H) (Found: C, 44.0; H, 7.05; N, 7.25. $C_7H_{13}NO_3S$ requires C, 43.95; H, 6.85; N, 7.3%).

The second and third (laevorotatory) fractions were recrystallized four times from water–acetone (1 : 6) to give needles (0.933 g) of the S-*oxide* (7b), $[\alpha]_D^{25}$ −84.3° (*c* 2.0 in H_2O), decomp. 131—132°, R_F (w.r.t. alanine) 1.77 (BuOH–AcOH—H_2O), $\nu_{max.}$ 1 625s (CO_2^-), 1 550—1 575s, 1 425m, 1 375s, 1 265m, 1 210w, 1 175w, and 1 000s cm^{-1} (*S*-oxide); δ(D_2O; ref. Bu^{t}OD) 2.00 (3 H, d, CH_3), 2.06 (3 H, d, CH_3), 3.24—3.66 (2 H, 7 lines, AB of ABX, β-H_2), 4.33—4.45 (1 H, dd, X of ABX, α-H), and 6.28 (1 H, sept, γ-H) (Found: C, 44.1; H, 6.95; N, 7.35%).

Cyclization of the Sulphone (6).—A solution of the sulphone (6) (1.56 g) in 2N-ammonium hydroxide (200 ml) was kept at room temperature for 4 days, then concentrated *in vacuo*. The solid was crystallized from water–ethanol (1 : 2) to give coarse prisms (1.23 g, 79%) of (3R)-5,5-*dimethyltetrahydro*-1,4-*thiazine*-3-*carboxylic acid* SS-*dioxide* (8), $\nu_{max.}$ 1 620s (CO_2^-), 1 575s, 1 450w, 1 385s, 1 325m, 1 290s, 1 220w, 1 150s, 1 130s, 1 115s (SO_2), 1 075m, and 1 030w cm^{-1}; δ (D_2O; ref. TSP) 3.08 [dd, H-2(a)], 3.56 [dt, H-2(e)], 4.01 [dd, H-3(a)] [by ABX approximation $J_{2.2}$ 14.1, $J_{2.3}$ (aa) 12.5, $J_{2.3}$ (ae) 2.6, and $J_{2.6}$, 2.6 Hz], 3.12 [d, H-6(a)], 3.29 [dd, H-6(e)], 1.39 (s, CH_3), and 1.43 (s, CH_3). By 'AB' analysis $J_{6.6}$ 14.7, $J_{2.3}$ 12.5 and 2.6 Hz, establishing the chair conformation as shown (Found: C, 40.8; H, 6.3; N, 6.8. $C_7H_{13}NSO_4$ requires C, 40.55; H, 6.3; N, 6.75%).

Cyclization of the (−)-S-*Oxide* (7b).—A solution of the *S*-oxide (3.0 g, 0.0157 mol) in water (500 ml) containing N-sodium hydroxide (10 ml) and sodium carbonate (1.2 g) was heated at 90 °C for 8 h. The turbid solution was passed through a column (175 cm^3) of Dowex 50 resin (H^+). The resin was washed with water (1 l) and developed with 2N-ammonium hydroxide (1 l). Concentration of the eluate to dryness and crystallization from ethanol yielded the product (1.90 g, 63%). Recrystallization from water–acetone (1 : 4) yielded needles of (1R,3R)-5,5-*dimethyltetrahydro*-1,4-*thiazine*-3-*carboxylic acid* S-*oxide* (10), $[\alpha]_D^{25}$ −19.5° (*c* 3.3 in H_2O), decomp. 247—252°, R_F (w.r.t. alanine) 1.02 (BuOH–AcOH–H_2O); $\nu_{max.}$ 1 620s (CO_2^-), 1 460m, 1 380s, 1 325w, 1 260w, 1 230w, 1 215w, 1 145w, and 1 040—1 050s cm^{-1} (S–O); δ (D_2O; ref. TSP) 1.37 (3 H, s, CH_3), 1.48 (3 H, s, CH_3), 2.71 [1 H, t, H-2(a)], 2.71 [1 H, d, H-6(a)], 3.67 [1 H, dd, H-6(e)], 3.89 [1 H, dd, H-3(a)], and 4.00 [1 H, dt, H-2(e)]; δ (D_2O–NaOD; ref. TSP) 1.21 (3 H, s, CH_3), 1.33 (3 H, s, CH_3), 2.44 [1 H, t, H-2(a)], 2.44 [1 H, d, H-6(a)], 3.53 [1 H, dd, H-6(e)], 3.59 [1 H, dd, H-3(a)], and 3.84 [1 H, dt, H-2(e)] ($J_{2.2}$ 11.5 $J_{2(a).3(a)}$ 12.2, $J_{2(e).3(a)}$ 2.1, $J_{6.6}$ 11.75, $J_{2(e).6(e)}$ 2.8, $J_{6(a),\ CH_3}$ 0.75 Hz). In base, the resonance of H-3 is selectively shifted upfield by the presence of the adjacent carboxylate group so that it no longer overlaps the resonance of H-2(e). First-order methods could, therefore, be used to obtain the coupling constants. Coupling between the axial methyl and 6-axial protons was established by irradiation at 121 Hz (CH_3) which eliminated the splitting of the H-6(a) lines and irradiation at 244 Hz [H-6(a) lines] which equalized the intensities of the two methyl signals (Found: C, 43.8; H, 6.83; N, 7.45. $C_7H_{13}NO_3S$ requires C, 43.95; H, 6.85; N, 7.3%.)

Cyclization of the S-*Oxide* (7a).—A solution of the *S*-oxide (7a) (3.753 g, 0.0196 mol) {$[\alpha]_D^{24}$ indicates >88% (+)-isomer} containing N-sodium hydroxide (12 ml) and sodium carbonate (1.6 g) in water (500 ml) was heated and the product was isolated with Dowex 50 resin (H^+) as in the reaction with the (−)-isomer. Paper chromatography and ^1H n.m.r. indicated that the isolated product still contained a large amount of starting material. Accordingly, the reaction with base was repeated and unchanged material was removed by addition of sodium 2,4,6-trinitrobenzenesulphonate (2.5 g, 0.0079 mol) to the cooled solution. The resulting red solution was stirred overnight at room temperature, acidified with hydrochloric acid, and filtered. The orange filtrate (*ca.* 500 ml) was extracted with ethyl acetate (4 × 120 ml). The aqueous phase was concentrated *in vacuo* to dryness, and the residue was dissolved in water and purified with Dowex 50 resin (H^+) as described before. The ammoniacal eluate was taken to dryness and the residue crystallized from water–acetone (1 : 4; 25 ml) to give prisms (0.988 g), $[\alpha]_D^{25}$ +3.1° (*c* 3.5 in H_2O). An additional 0.565 g was obtained from the mother liquor (yield 41%). Recrystallization from aqueous acetone gave (+)-(1S,3R)-5,5-*dimethyltetrahydro*-1,4-*thiazine*-3-*carboxylic acid* S-*oxide* (9), $[\alpha]_D^{25}$ +3.0° (*c* 3.7 in H_2O), decomp. 240—241°, R_F (w.r.t. alanine) 1.16 (BuOH–AcOH–H_2O) [^1H n.m.r. analysis indicated that the solid material isolated was free of the (−)-isomer]; $\nu_{max.}$ 1 635s (CO_2^-), 1 460m, 1 365s, 1 325m, 1 235w, 1 210w, 1 135w, 1 080w, and 1 025—1 030s cm^{-1} (*S*-oxide); δ (D_2O; ref. TSP) 1.54 (3 H, s, CH_3), 1.73 (3 H, s, CH_3), 3.10 [1 H, dd, H-2(a)], 3.68 [1 H, dt, H-2(e)], 4.51 [1 H, dd, H-3(a)] [$J_{2.2}$ 15.3, $J_{2.3}$ (aa) 12.9, $J_{2.3}$ (ea) 2.4, $J_{2(e).6(e)}$ 2.4 Hz by ABX analysis], 2.75 [1 H, d, H-6(a)], and 3.40 [1 H, dd, H-6(e)] ($J_{6.6}$ 15.7 Hz) (the values of $J_{2.3}$

established the chair conformation as shown); δ (D_2O–NaOD; ref. TSP) 1.23 (3 H, s, CH_3), 1.45 (3 H, s, CH_3), 2.42 [1 H, d, H-6(a)], 2.66 [1 H, dd, H-2(a)], 3.02 [1 H, dd, H-6(e)], 3.26 [1 H, dt, H-2(e)], and 4.07 [1 H, dd, H-3(a)] [$J_{2.2}$ 14.0, $J_{6.6}$ 15.0 Hz; no long-range coupling between the axial methyl protons and H-6(a) could be resolved; however, the excessive width of the H-6(a) peaks (2.5 Hz) suggests a small coupling of this type] (Found: C, 44.1, H, 6.9; N, 7.4. $C_7H_{13}NO_3S$ requires C, 43.95; H, 6.85; N, 7.3%).

Reduction of the Cyclic S-*Oxide* (10) *to the Cyclic Sulphide* (11).—A solution of the *S*-oxide (1.475 g, 0.007 72 mol) (10) in 48% hydriodic acid (25 ml) was kept in the dark for 3 days and then concentrated *in vacuo* to a dark solid. Iodine was removed by extraction with ether (5 × 50 ml). The resulting pale yellow solid was dissolved in water (50 ml) and passed through a column (50 cm^3) of Dowex-1 resin (acetate). The resin was washed with water (250 ml) and the eluate concentrated *in vacuo* to a solid, which was crystallized from water (10 ml)–acetone (40 ml) to yield (3R)-5,5-*dimethyltetrahydro*-1,4-*thiazine*-3-*carboxylic acid* (11) (0.955 g, 70%), $[\alpha]_D^{25}$ −65.7° (*c* 1.7 in H_2O), sinters at 280—285°; $\nu_{max.}$ 1 600s (CO_2^-) 1 460m, 1 390s, 1 330w, 1 270w, 1 235w, 1 165w, 1 130w, and 1 060w cm^{-1} (no *S*-oxide absorption); δ (D_2O; ref. TSP) 1.53 (3 H, s, CH_3), 1.56 (3 H, s, CH_3), 2.71—2.97 [dd, H-2(a)], 2.98—3.18 [ddd, H-2(e)], 3.87—4.02 [dd, H-3(a)] [$J_{2.3}$ (aa) 12.3, $J_{2.3}$ (ae) 2.8, $J_{2.2}$ 14.5, $J_{2.6}$ 1.6 Hz (ABX analysis)], 2.48—2.64 [dd, H-6(e)], and 2.94—3.10 [dd, H-6(a)] ($J_{6.6}$ 14.8, $J_{2.6}$ 1.6 Hz by AB analysis) (Found: C, 47.8; H, 7.45; N, 8.05. $C_7H_{13}NO_2S$ requires C, 47.95; H, 7.5; N, 8.0%).

Oxidation of the Sulphide (11) *to the S-Oxide* (10).—The sulphide (11) (0.435 g, 0.002 48 mol) in water (35 ml) containing 30% hydrogen peroxide (0.5 ml) was kept for 20 h at room temperature and then concentrated to a solid. Crystallization from water (1.5 ml)–acetone (25 ml) yielded needles (0.411 g, 87%), $[\alpha]_D^{25}$ −18.8° (*c* 3.5 in H_2O), of the *S*-oxide (10), identified by i.r. and ^1H n.m.r. data. Integration of methyl resonances established that the crude product contained over 90% of the (−)-isomer. Oxidation of the sulphide with sodium periodate at 0 °C gave the same results.

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