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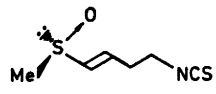
Intramolecular Cyclizations of Thioureas Derived from Sulphoraphene: a Case of Asymmetrically Induced Additions to Vinylic Sulphoxides*

JAN JØRN HANSEN and ANDERS KJÆR**

Department of Organic Chemistry, Technical University of Denmark, DK-2800 Lyngby, Denmark

Sulphoraphene *1*, isolated from radish seeds, yields a thiourea *3a* on controlled reaction with ammonia. Upon more severe treatment, *3a* undergoes intramolecular cyclization to the epimeric $(R)_S$-4-methylsulphinylmethyl-tetrahydropyrimidine-2-thiones, *4a* and *4b*. The absolute configurations of the latter are established by stereospecific synthesis of one of the reduced isomers, *5b*, starting from (*R*)-β-methionine *6*. The degree of asymmetric induction in the cyclization of *3a* is determined and the mechanism discussed. The *N*-phenyl (*3b*) and *N*-methyl thiourea (*3c*) undergo similar cyclizations.



1

Me S(O)CH=CH $[CH_2]_2$ $NHCSNH_2$

2

Scheme 1.

Sulphoraphene ((*R*)-4-methylsulphinyl-3(*E*)-butenyl isothiocyanate) *1*,[1-3] derivable, by enzymic hydrolysis, from a glucosinolate (*cf.* Ref. 4) present in seeds of radish (*Raphanus sativus* L.),[1] possesses the notable property of being the first naturally derived compound that is optically active solely by virtue of an asymmetric sulphur atom. Upon prolonged treatment with alcoholic ammonia at 37°, sulphoraphene was converted by Schmid and Karrer,[1] its discoverers, into a levorotatory, crystalline compound, $C_6H_{12}N_2OS_2$, m.p. 219 – 220°, formulated as "sulphoraphene thiourea" *2*. We have investigated the structure and formation of this product and present the results.

When a chloroform solution of sulphoraphene, produced by enzymic hydrolysis of the glucosinolate fraction from radish seed extracts, was treated with ammonia-saturated methanol for 4 h at room temperature, the thiourea *3a*, m.p. 88 – 89°, was formed in an unexceptional reaction. Its composition and spectroscopical properties, including NMR-signals from its two vinylic protons, were in accord with the linear thiourea-structure *3a*.

Prolonged treatment of *3a*, or sulphoraphene itself, with methanolic ammonia, followed by repeated recrystallization of the product mixture, afforded an apparently homogeneous substance, possessing the properties previously attributed to "sulphoraphene-thiourea"[1] and, in fact, indistinguishable from the latter on comparison.* The composition, chemical properties, and spectroscopic characteristics all support the structure *4a*, or *4b*, for this product. With the multiple purpose of substantiating the proposed

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** To whom correspondence should be addressed.

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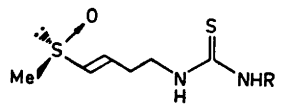
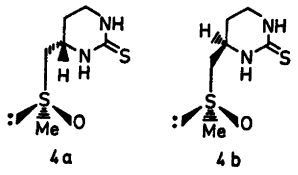
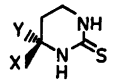


3a: R=H
3b: R=Ph
3c: R=Me



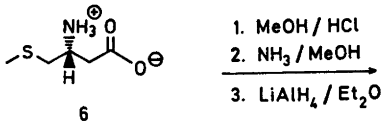
4a 4b



5a: X=H; Y=MeSCH$_2$
5b: X=MeSCH$_2$; Y=H

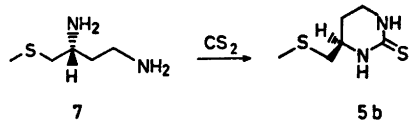
Scheme 2.

structure, establishing its absolute configuration, and assessing the degree of asymmetric induction in the cyclization reaction, the cyclic sulphoxide was reduced to the monochiral sulphide *5a*, the enantiomer of which was synthesized, in a stereospecific fashion, from (*R*)-*β*-methionine *6* through the sequence of reactions shown in Scheme 3.



6

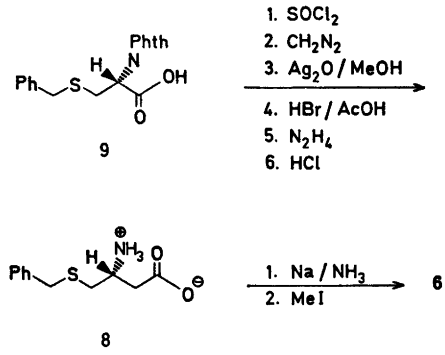
1. MeOH / HCl
2. NH_3 / MeOH
3. $LiAlH_4$ / Et_2O



7 5b

Scheme 3.

(*R*)-*β*-Methionine *6*, in its turn, was synthesized by Arndt-Eistert homologization [5,6] of (*R*)-*N*-phthaloyl-*S*-benzylcysteine [7] *9*, followed by dephthaloylation to (*R*)-*S*-benzyl-*β*-homocysteine [6] *8*, debenzylation, and, finally, S-methylation:



1. $SOCl_2$
2. CH_2N_2
3. Ag_2O / MeOH
4. HBr / AcOH
5. N_2H_4
6. HCl

9

1. Na / NH_3
2. MeI

6

8

Scheme 4.

Production of (*R*)-*N*-phthaloyl-*S*-benzylcysteine *9* by phthaloylation of (*R*)-*S*-benzylcysteine, in acceptable yield and with stereochemical integrity, is not straightforward, however. The proposed application of *o*-carbethoxythiobenzoic acid for this purpose [9] failed in our hands, whereas heating of *S*-benzylcysteine with phthalic anhydride at 110° for 30 min [7,10] led to low yields of slightly racemized product. Adoption of the Nefkens procedure,[11] however, involving *N*-carbethoxyphthalimide, permitted the preparation, in 90 % yield and high optical purity, of amorphous *9*, easily converted into its crystalline methyl ester. The chain-lengthening *9*→*8* proceeded through a sequence of unexceptional steps, essentially according to directions in the literature.[6,12] Further processing of *8* into (*R*)-*β*-methionine *6*,[8] and thence into its methyl ester hydrochloride,[13] went smoothly, as did the ammonolysis of the latter, followed by $LiAlH_4$-reduction to the diamine *7*, characterized as its dipicrate. An attempt to circumvent the described sequence by subjecting the hitherto unknown methyl ester hydrochloride of (*R*)-*S*-benzyl-*β*-homocysteine to treatment with Na/NH_3, followed by MeI, in order to arrive directly at (*R*)-*β*-methionine amide, proved of no avail.

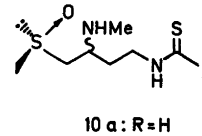
Known methods for converting 1,3-diamines, such as *7*, into tetrahydropyrimidine-2-thiones include thermolysis at 125 – 160° of dithiocarbamates, formed upon reaction with CS_2,[14,15] or,

alternatively, heating of the diamines at high temperature with thiourea [16] or thiocyanic acid.[17] In attempts to achieve ring-formation under milder conditions the reaction of aliphatic 1,3-diamines with thiocarbonyl chloride, a reaction apparently without literature precedent, was studied. Despite extensive variation of reaction conditions, yields never exceeded 27 % of the desired, cyclic products. On this background, it was unexpected to find the dithiocarbamate of (*R*)-1,3-diamino-4-methylthiobutane *7* undergoing quantitative and facile ring-closure in ethanol suspension at 25° to supposedly optically pure (*R*)-4-methylthiomethyl-tetrahydropyrimidine-2-thione *5b*, $[\alpha]_D$ −168°. The enantiomeric relationship of the latter to a repeatedly recrystallized, dextrorotatory, cyclic sulphide-thiourea of natural derivation was established by rotation measurements and mirror-image CD curves. On admixture, equal proportions of the enantiomers formed a lower-melting racemic compound.

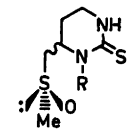
A preparation of the cyclic sulphoxide, with $[\alpha]_D$ −65°, produced from sulphoraphene according to literature directions,[1] afforded on reduction an analytically pure, non-fractionated, cyclic sulphide-thiourea with the rotation value $[\alpha]_D$ +145°, consequently representing an optical purity of 86 %. Assuming optical purity of naturally derived sulphoraphene *1*, and steric stability of the chiral S-atom during treatment with ammonia, the observed rotation signifies the composition 93 % R_SS_C- (*4a*) and 7 % R_SR_C-isomer (*4b*) for the thiourea with $[\alpha]_D$ −65°. The previously reported rotation, $[\alpha]_D$ −72°,[1] hence represents a 88:12 composition of the same two diastereoisomers.

The rotation, $[\alpha]_D$ +24°, of the cyclic sulphide thiourea, obtained upon quantitative reduction of a non-fractionated mixture of cyclic sulphoxides, $[\alpha]_D$ −119°C, reveals an asymmetric induction of 14 % in the cyclization of the linear sulphoxide thiourea *3a*, with the (R_SS_C)-isomer *4a* being the predominant one. The combined experimental data permit calculations of the rotation values: $[\alpha]_D$ −54° and $[\alpha]_D$ −205° for the pure (R_SS_C)- (*4a*) and (R_SR_C)-isomer, *4b*, respectively.

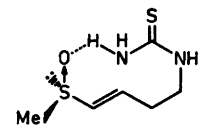
The observed cyclization is hardly trivial. Intramolecular nucleophilic addition of a thiourea grouping across the double bond should expectedly yield 2-amino-1,3-thiazine-derivatives rather than, as observed, pyrimidine-2-thiones. Addition-elimination reactions, involving ammonia, can be ruled out in view of the following observations: (i) identical cyclization takes place thermally, in the presence or absence of ethanol, but considerably faster in soda glass than in Pyrex glass: (ii) cyclization proceeds rapidly in aqueous base; (iii) methylamine, instead of ammonia, causes *competitive* formation of linear adducts, *10a*, and *non-methylated*, cyclic diastereomers *11a*. A controlling experiment revealed no aptitude for the linear sulphoxide thiourea to react with extraneous thiourea.



10 a : R = H
10 b : R = Me



11 a : R = H
11 b : R = Ph
11 c : R = Me



12

Scheme 5.

A base-catalyzed, intramolecular attack of the terminal nitrogen at the vinylic β-carbon atom, accompanied or followed by protonation of the resulting α-sulphinylcarbanion, hence seems to be best in accord with the experimental results. It deserves attention that no cyclization is observed when the linear thiourea is treated with ammonia in chloroform solution. Hydrogen bonding, possibly *via* solvent bridges, between the sulphoxide and the reacting NH_2-grouping, as suggested in *12*, may conceivably be instrumental in facilitating and governing the cyclization reaction.

Noticeable stereoselectivity in kinetically controlled, nucleophilic additions to vinylic sulphoxides is not without precedent. Thus, additions of piperidine,[18] or diethyl malonate and ethyl acetoacetate [19] to vinylic sulphoxides have been shown to proceed with a considerable degree of asymmetric induction. Additional re-

sults from this laboratory [20] confirm and extend these results.

Cyclizations, as described above, also occur with terminally substituted thioureas. Thus, the phenylthiourea *3b*, obtained, as described,[1] from sulphoraphene *1* and aniline, undergoes cyclization on prolonged exposure to aniline in ethanol at 37° to give a mixture of diastereomers *11b*, $[\alpha]_D$ +12°, from which a supposedly homogeneous isomer, $[\alpha]_D$ +22°, was obtained after repeated recrystallizations. A similarly composed mixture was rapidly produced on heating the thiourea *3b* in ethanol at 80° in a soft glass vessel; in Pyrex glass, the reaction proceeded at a greatly diminished rate. With methylamine, under carefully controlled conditions, sulphoraphene affords the expected *N*-methylthiourea *3c*. This, on treatment with aqueous base or ethanolic ammonia, undergoes cyclization to a mixture of diastereomers, *11c*, from which an apparently homogeneous isomer could be obtained after several recrystallizations. Exposed to methylamine for a prolonged period of time, the *N*-methylthiourea affords, as with other bases, a mixture of two cyclized epimers *11c*, but in addition, another product mixture, *10b*, arising from competitive addition of methylamine across the double bond of the linear thiourea.

The observed reactions provide interesting synthetic perspectives which are presently being pursued in this laboratory.

EXPERIMENTAL

Melting points are uncorrected and determined in capillary tubes in a heated bath. Paper chromatography (PC) was conducted by the descending technique on Schleicher and Schüll paper 2043b, with the upper layer of the system BuOH:EtOH:H_2O (4:1:4) as the mobile phase.

Rotations are measured on a Perkin-Elmer 141 polarimeter; CD curves on a Jouan CD-185 Dicrographe. UV-Spectra are recorded on a Perkin-Elmer 402 spectrophotometer, IR spectra (in KBr when not otherwise indicated) on a Perkin-Elmer 421 grating instrument, and mass spectra on the Perkin-Elmer 270 mass spectrometer at 70 eV. ^{1}H NMR-Spectra are determined at 60 MHz or 100 MHz on Varian instruments, with TMS, or, for D_2O-solutions, the Na-salt of DSS as internal standards. ^{13}C NMR-Spectra are measured as proton-noise decoupled spectra on a Bruker WH-90 instrument with Fourier Transform pulse technique, and are reported as δ-values in ppm downfield from TMS.

Microanalyses were performed by Mr. G. Cornali and his staff.

Sulphoraphene 1. Commercial radish seeds (66 g) were finely ground and defatted by extraction with two 2 l portions of hot petroleum ether. The glucoside fraction was removed by boiling the residue with two 2 l portions of 70 % MeOH. MeOH was removed from the filtrate by concentration *in vacuo*, and the aqueous solution was diluted with 1 l of H_2O, filtered through Hyflo-Supercel, and extracted once with ether (200 ml) and once with $CHCl_3$ (200 ml). The organic phases were discarded. Residual organic solvents were removed *in vacuo*, and the aqueous solution was buffered at pH 6.5 by adding a saturated Na_2HPO_4 -solution. Enzymic hydrolysis was accomplished by adding a crude cell-free myrosinase solution (18 ml), produced from yellow mustard, and a few mg's of ascorbic acid. After being kept at 40° for 3.5 h, the solution was extracted with five 150 ml portions of $CHCl_3$. The combined extracts (800 ml), containing sulphoraphene *1*, were dried over Na_2SO_4 and used for production of the various thioureas described in the sequel.

(R)-1-(4-Methylsulphinyl-3(E)-butenyl)-thiourea 3a. An aliquot of the $CHCl_3$-solution of sulphoraphene (300 ml) was treated with MeOH (12 ml), saturated at 0° with NH_3, for 4 h at 25°. The solution was concentrated in vacuum to an oily residue.

Paper chromatography revealed the contents in this solution of one major (R_F 0.56) and two minor (R_F 0.51 and 0.39) thioureas, the latter of which represents the cyclized product(s) described below. The thiourea with R_F 0.51, present only in trace amounts, is believed to represent the saturated counterpart of the thiourea derived from sulphoraphene, *i.e.* (*R*)-1-(4-methylsulphinylbutyl)-thiourea, on the basis of coinciding chromatographic behaviour in three solvent systems with an authentic specimen. Undoubtedly, this thiourea derives from sulphoraphane originating from trace amounts of the saturated glucosinolate, known from other sources,[21] in radish seeds.

The crude thiourea mixture was chromatographed on a silica gel column (60 g), with $CHCl_3$, containing a gradient of EtOH from 0 to 10 %, as the eluent. The thiourea-containing fractions, revealed by the production of a blue colour with Grote's reagent, were combined and evaporated to dryness (118 mg). The crystalline residue was recrystallized twice from MeOH:Et_2O to give an analytical specimen of *3a* as colourless crystals, homogeneous on chromatography, m.p. 88–89°; $[\alpha]_D^{22}$ −70° (*c* 0.7, H_2O) (Found: C 37.28; H 6.34; N 14.27. Calc. for $C_6H_{12}N_2OS_2$: C 37.47; H 6.29; N 14.57). Spectroscopic characteristics: UV: λ_{max} (EtOH) 243 nm (ε 15 000), 205 nm (13 740); IR: 3210 (vs), 3110 (vs), 1645 (vs,) 1540 (vs), 1450 (m), 1410 (m), 1350 (m), 1318 (s), 1295 (s), 1270 (s), 1195 (s), 1130 (s), 1060 (w), 1030 (vs), 963 (m), 950 (s), 818 (m), 765 (s), and 690 cm^{-1} (s). MS: *m/e*

192 (M^+). ^{1}H NMR ,in $(CD_3)_2SO$: δ 2.4 (2 H, m), 2.61 (3 H, s), 3.4 (2 H, m), 6.35 (1 H, dt, J 16 and 7 Hz), 6.75 (1 H, d, J 16 Hz), and 7.1–7.9 ppm (3 H, exchangeable).

In keeping with its structure as a vinylic thioether, *3a* decomposes readily in acid to give MeSH.

C-Epimers of 4-((R)-methylsulphinylmethyl)-tetrahydropyrimidine-2-thione, 4a and 4b. A solution of the linear thiourea *3a* (55 mg) in EtOH (5 ml), to which was added a saturated EtOH-solution of NH_3 (3 ml), was kept for 8 days at 40°, when PC revealed virtually complete transformation of *3a* (R_F 0.56) into a new type of product (R_F 0.39). Trace amounts of starting material and more polar by-products were removed by chromatography on a silica gel column (10 g), with EtOAc:MeOH (1:1) as the eluent. The chromatographically homogeneous epimer mixture (40 mg), $[\alpha]_D^{23}$ −119° (*c* 1.1, H_2O), was subjected to five recrystallizations from MeOH:Et_2O to give what is supposedly the almost homogeneous (R_SS_C)-epimer *4a*, m.p. 223–224°, $[\alpha]_D^{25}$ −61° ±4° (*c* 0.4, H_2O). (Found: C 37.63; H 6.34; N 14.31; S 33.02. Calc. for $C_6H_{12}N_2OS_2$: C 37.47; H 6.29; N 14.57; S 33.34). Spectroscopic characteristics, UV: λ_{max}(EtOH) 247 nm (ε 15 500), 208 nm (11 100); IR: 3300 (s), 3200 (vs), 1550 (vs), 1510 (vs), 1460 (m), 1430 (s), 1355 (s), 1335 (s), 1320 (s), 1260 (m), 1230 (m), 1195 (vs), 1180 (s), 1105 (w), 1065 (m), 1025 (m), 998 (vs), 963 (s), 938 (m), 920 (w), 892 (w), 872 (w), 832 (w), and 705 (br.) cm^{-1} MS: *m/e* 192 (M^+). ^{1}H NMR, in $(CD_3)_2SO$: δ 1.9 (2 H, m) (C-5), 2.61 (3 H, s), 2.95 (2 H, d, J 6.5 Hz) (−S(O)CH_2)−, 3.2 (2 H, m) (C-6), 3.75 (1 H, m) (C-4), and 7.8–8.1 ppm (2 H, exchangeable).

No methanethiol was produced on heating the epimer mixture with acid.

In contrast to the above described behaviour, a *chloroform* solution of the linear thiourea *3a*, saturated with NH_3, underwent no changes within 30 days at 25°, as estimated from PC.

Though unchanged in aqueous solution after 4 weeks, the thiourea *3a* undergoes quantitative cyclization in less than 30 min in 0.5 M NaOH at 25° to a mixture of the epimers, *11a*.

In ethanolic $MeNH_2$, *3a* reacts to a mixture of products within 1 h at 25°. Separation by preparative TLC on silica gel (eluent MeOH) affords a more lipophilic fraction (60 %), m.p. 195–203°, identified as the mixture *11a*, and a more polar, basic component (40 %), yielding a red colouration with ninhydrin. This very hygroscopic material possesses spectroscopical characteristics supporting its identity as a mixture of adducts, *10a*. UV: λ_{max}(EtOH) 245 nm ($\varepsilon \sim 10^4$); ^{1}H NMR (in CD_3OD): δ 1.8–2.0 (2 H, m) (−C−CH_2−C), 2.41 and 2.43 (3H, 2s) (CH_3−NH−C−, in the epimers, *10a*), 2.73 (3 H, s) [MeS(O)], 2.8–3.2 (2 × 2 H, m) [−S(O)-CH_2− and −CH_2−NH−], 3.5–3.7 (1 H, m) [−C*H*(NHMe)−], and 4.73 ppm (*ca.* 3 H, s) (−NH and −NH_2) (the cyclized product *11c*, containing the Me−N−CS-grouping, should exhibit CH_3−N-absorption at δ 3.0–3.5 ppm [22]). The mixture of adducts remained unchanged on standing at 40° in ethanolic methylamine for 8 days, excluding its role as an intermediate in the production of the cyclic products.

Heating *3a* to 90° for 86 h in a capillary, made of soft glass, brings about extensive cyclization to *11a*. In Pyrex glass, very little cyclization is observed. Heating in EtOH at 80°, in soft glass, quantitatively converts *3a* into *11a* in the course of 63 h.

(R)-S-Benzyl-N-phthaloylcysteine methyl ester. *(R)-S*-Benzylcysteine (22.6 g) and Na_2CO_3. $10H_2O$ (32.7 g) were dissolved in hot water (175 ml). After cooling to 25°, *N*-carbethoxyphthalimide [11] (26 g) was added. After 1 h, the solution was acidified with 6 N HCl, when a colourless syrup separated. Next day, $CHCl_3$ (400 ml) was added, and unreacted *S*-benzylcysteine (2 g) was removed by filtration. The filtrate was extracted with three 75 ml portions of water to remove most of the unreacted urethan. After drying and removal of $CHCl_3$, a colourless syrup remained, consisting of *(R)-S*-benzyl-*N*-phthaloylcysteine *9* (34.7 g, 90 % yield, on the basis of non-recovered starting material) with a maximum content of 10 % urethan according to ^{1}H NMR-analysis. This product, $[\alpha]_D^{25}$ −154° (*c* 1, MeOH) [reported:[7] $[\alpha]_D^{25}$ −167° (*c* 0.6, MeOH)], was used for the subsequent synthesis without further purification.

The above acid (66 mg), dissolved in Et_2O (3 ml), was treated with excess CH_2N_2. Next day, the solvent was removed and the crystalline methyl ester was recrystallized thrice from MeOH before analysis, m.p. 66°, $[\alpha]_D^{24}$ −162°. (*c* 0.8, C_6H_6). (Found: C 63.81; H 4.92; N 3.83. Calc. for $C_{19}H_{17}NO_4S$: C 64.21; H 4.82; N 3.94).

(R)-S-Benzyl-β-homocysteine 8. The above cysteine derivative *9* was converted into its acid chloride, $[\alpha]_D^{22}$ −140° (*c* 1.2, C_6H_6) [reported: $[\alpha]_D^{16}$ −136° [7]], and thence into the corresponding diazoketone, $[\alpha]_D^{23}$ −188° (*c* 0.3, C_6H_6) [reported for a benzene solvate: $[\alpha]_D^{16}$ −170° (*c* 0.4, C_6H_6) [7]], essentially as described.[6,7,12] Again, further processing of the latter into *(R)-S*-benzyl-*N*-phthalimido-homocysteine methyl ester, a syrup with $[\alpha]_D^{25}$ −59° (*c* 2, C_6H_6) [reported: m.p. 67°, $[\alpha]_D^{20}$ −80° (*c* 1.12, C_6H_6) [6]], the corresponding free acid, also a syrup, $[\alpha]_D^{22}$ −83° (*c* 2.3, C_6H_6) [reported: $[\alpha]_D^{14}$ −78° (*c* 1.8, C_6H_6) [6]], and *S*-benzyl-*β*-homocysteine *8*, m.p. 182–183° (dec.), $[\alpha]_D^{23}$ −58° (*c* 1.1, 1 N HCl) [reported: m.p. 173° (dec.),[6] $[\alpha]_D^{19}$ −57° (*c* 1.19, 1 N HCl),[6] m.p. 171–174° (dec.),[23] $[\alpha]_D^{23}$ −64° (*c* 1.16, 1 N HCl)[23]], took place with little deviation from the reported procedures.

(R)-S-Benzyl-β-homocysteine methyl ester hydrochloride. The amino acid above was converted into its methyl ester hydrochloride on treatment with anhydrous HCl in MeOH in the usual way. After two recrystallizations from MeOH/Et_2O an analytical sample was obtained,

m.p. 116–117°, $[\alpha]_D^{25}$ −37° (*c* 0.5, MeOH). (Found: C 52.00; H 6.64; N 11.68. Calc. for $C_{12}H_{18}NO_2SCl$: C 52.25; H 6.58; N 11.62).

(R)-β-Methionine amide hydrochloride. (*R*)-*S*-Benzyl-β-homocysteine, described above, was converted into (*R*)-β-methionine as reported,[8] in 79 % yield. Esterification with MeOH and anhydrous HCl yielded the hygroscopic (*R*)-β-methionine methyl ester hydrochloride, m.p. 86–87°, $[\alpha]_D^{25}$ −14.5° (*c* 0.8, H_2O) [reported: m.p. 88–90°, $[\alpha]_D$ −14.3° (*c* 5, H_2O) [13]]. On treatment of the ester hydrochloride (730 mg), dissolved in anhydrous MeOH (40 ml) saturated at 0° with dry NH_3, for 14 days at 5°, a quantitative yield of (*R*)-β-methionine amide hydrochloride was obtained. An analytical specimen was obtained by recrystallization from MeOH/Et_2O, m.p. 161–163°, $[\alpha]_D^{25}$ −2° ± 0.5° (*c* 1.1, MeOH), −17° (*c* 0.5, 2 N NH_3). (Found: C 32.52; H 7.05; N 14.48; S 17.56. Calc. for $C_5H_{13}N_2OSCl$: C 32.52; H 7.10; N 15.17; S 17.36).

(R)-1,3-Diamino-4-methylthio-butane 7. To the above amide hydrochloride (128 mg), suspended in anhydrous Et_2O (50 ml), was added $LiAlH_4$ (390 mg), and the mixture was refluxed for 26 h, when an additional amount of $LiAlH_4$ (100 mg) was added; the refluxing was continued for 45 h. After cooling, water-saturated ether, followed by a saturated solution of KNa-tartrate, were added to the reaction mixture. The combined ether extracts were dried over KOH. On evaporation, the diamine was obtained as a colourless syrup.

For characterization, the amine was converted into its crystalline dipicrate, recrystallized, before analysis, from MeOH/Et_2O, m.p. 185–186° (dec.), $[\alpha]_D^{25}$ +2.9° (*c* 0.6, MeOH), $[\alpha]_{546}^{25}$ +5.6° (*c* 0.6, MeOH). (Found: C 34.42; H 3.45; N 18.83; S 5.80. Calc. for $C_{17}H_{20}N_8O_{14}S$: C 34.46; H 3.40; N 18.91; S 5.41).

(R)-4-Methylthiomethyl-tetrahydropyrimidine-2-thione 5b. The above diamine, resulting from the reduction of β-methionine amide hydrochloride (118 mg), was dissolved in EtOH (5 ml). The solution was slowly added to a mixture of CS_2 (3 ml) and EtOH (5 ml). The suspension of the dithiocarbamate was stirred at 25° for 24 h when no more precipitate was present. Evaporation to dryness gave a crystalline residue, which, after treatment with charcoal in $CHCl_3$, was recrystallized twice from MeCN to give an analytical specimen, m.p. 178–179°, $[\alpha]_D^{25}$ −168° (*c* 0.5, $CHCl_3$). (Found: C 40.97; H 6.72; N 15.99; S 36.26. Calc. for $C_6H_{12}N_2S_2$: C 40.88; H 6.86; N 15.89; S 36.38). Spectroscopic characteristics: λ_{max}(EtOH) 249 nm (ε 14 800), λ_{max} (MeCN) 255 nm (ε 17 300), 222 nm (sh.); ^1H NMR in $CDCl_3$: δ 1.8–2.2 (2 H, m), 2.15 (3 H, s), 2.5–2.7 (2 H, m), 3.3–3.8 (2+1 H, m), and 6.9 (2 H, "s", exchangeable) ppm. ^{13}C NMR, in $CDCl_3$: δ 15.7 (CH_3-S-), 25.5 ($-C-CH_2-C$), 39.2 (or 39.7) ($-S-CH_2-$), 39.7 (or 39.2) ($-NH-CH_2$), 49.2 ($N-C(H)-C$), and 176.8 ($-N-CS-N$) ppm.

Reduction of cyclic sulphoxide(s) 11a. A cyclic sulphoxide fraction (21 mg), $[\alpha]_D^{23}$ −65° (*c* 1.0, H_2O), obtained by ammonia-induced cyclization of *3a* as described above, was dissolved in AcOH (7 ml). Solid $NaHCO_3$ (1 g) was added (to dispel dissolved O_2) and a 0.11 N $TiCl_3$-solution (5 ml) was added. After standing at 80° for 90 min, excess $TiCl_3$ was removed with 0.5 N $Fe^{III}NH_4$-sulphate (5 ml). Water was added to a volume of 30 ml and pH was adjusted to 7 with solid Na_2CO_3. The organic product was removed by extraction with $CHCl_3$ (3 × 30 ml). After drying, the combined extracts were evaporated to give a crystalline product (17 mg, 90 %), $[\alpha]_D^{27}$ +145° (*c* 0.7, $CHCl_3$), which, according to TLC, was homogeneous. After recrystallization from MeOH a product was obtained with m.p. 176–178°, $[\alpha]_D^{27}$ +142 (*c* 1.0, $CHCl_3$). On comparison, its MS-, ^1H NMR- and IR-spectrum (in $CDCl_3$) proved indistinguishable from those of the above described synthetic compound *5b*.

Upon two recrystallizations from MeCN, the reduced product afforded a crystalline fraction, m.p. 178–179°, $[\alpha]_D^{25}$ + 168° (*c* 0.6, $CHCl_3$), supposedly representing the homogeneous (*S*)-enantiomer *5a*.

On measuring the CD-curves in MeCN, the following $\Delta\varepsilon$-values were obtained:

λ nm	(*R*)-isomer *5b*	(*S*)-isomer *5a*
206	−8.3	+8.8
228	+1.1	−1.7
249	−1.2	+0.8
273	+0.33	−0.41

On mixing equal amounts of the enantiomers in $CHCl_3$ and recrystallizing the residue from MeCN, the racemic compound was obtained, m.p. 142–143°, $[\alpha]_D \sim 0°$.

Cyclization of the linear N-phenylthiourea 3b. When the phenylthiourea *3b* (34 mg), obtained from sulphoraphene and aniline,[1] was left in ethanol (5 ml), saturated with NH_3, for 24 h, it was converted into a chromatographically homogeneous, new product, $[\alpha]_D^{25}$ +12° (*c* 0.4, $CHCl_3$), which could be recrystallized from EtOH/Et_2O to constant rotation, m.p. 208–209°, $[\alpha]_D^{25}$ +22° (*c* 0.5, $CHCl_3$). (Found: C 53.66; H 6.24; N 10.19; S 23.74. Calc. for $C_{13}H_{16}N_2OS_2$: C 53.78; H 6.02; N 10.45; S 23.93). Spectroscopic data: λ_{max}(EtOH) 253 nm (ε 7 000), 238 nm (sh); ^1H NMR, in $CDCl_3$: δ 2.1–2.7 (2 H, m), 2.54 (3 H, s), 3.00 (2 H, "d"), 3.3–3.7 (2 H, m), 4.2–4.6 (1 H, m), 7.3–7.5 (5 H, m), and 7.9 (1 H, "s", exchangeable) ppm; MS: 268 (M^+).

The stability to alkali, blue colour with Grote's reagent, and absence of IR-absorption in the 1600–1650 cm^{-1} range,[24] all are in agreement with the structure *11b* for the cyclization product rather than the isomeric 1,3-thiazine isomer.

Heating an EtOH-solution of *3b* in a soda-glass tube at 40° brings about a slow conversion

into cyclic products; after 10 days, non-cyclized thiourea remains. At 80°, however, the cyclization reaction is complete within less than 24 h, whereas, in borosilicate glass, the greater part of the linear thiourea *3b* is unchanged after 5 days under the same conditions.

Cyclization of the linear N-*methylthiourea 3c.* To a $CHCl_3$-solution (45 ml) of sulphoraphene, arising from 32 g of radish seeds, 12 drops of a saturated solution of $MeNH_2$ in EtOH were gradually added, in the course of 3 h. The residue from evaporation of the mixture was chromatographed on a silica gel column, using first EtOAc:MeOH (9:1), later MeOH as the eluent. The Grote-positive fractions were evaporated to dryness to give a colourless syrup, homogeneous on PC (R_F 0.68) and giving the ^1H NMR-spectrum expected for the linear *N*-methylthiourea *3c*: (in $CDCl_3$): δ 2.4 – 2.8 (2 H, m), 2.70 (3 H, s), 3.02 (3 H, d), 3.74 (2 H, "q"), 6.4 – 6.6 (2 × 1 H, m) and 7.1 (2 H, "s", exchangeable) ppm.

The thiourea (57 mg) was kept at 20° for 48 h in EtOH, saturated with NH_3. The solid residue proved homogeneous on PC (R_F 0.48), After three recrystallizations from EtOH, a colourless, crystalline product (16 mg) m.p. 232 – 238°, $[\alpha]_D \sim -87°$ (*c* 0.2, MeCN), was obtained, giving a typical blue Grote-reaction and exhibiting spectroscopic characteristics in accord with the cyclic structure *11c*. UV: λ_{max}(EtOH) 248 nm (ε 10 000); MS: *m/e* 206 (M^+); IR: no absorption within the range 1610 – 1630 cm^{-1}; ^1H NMR: (in CD_3CN + 25 % D_2O): δ 1.9 – 2.3 (2 H, m) 2.71 (3 H, s) 3.0 – 3.5 (2 × 2 H, m), 3.39 (3 H, s), and 3.9 – 4.3 (1 H, m) ppm.

A similar product was obtained when the linear thiourea *3c* was kept at 25° in 0.5 N NaOH for 1 h.

When treated with ethanolic $MeNH_2$ at 25° for 2 h, the methylthiourea *3c* (23 mg) afforded two Grote-positive products, which were separated on a silica gel column, with MeOH as an eluent. The fastest moving component (11 mg) proved identical with the cyclic product(s) *11c* discussed above. The slower-moving product (4 mg) possessing an R_F-value of 0.39 in PC, was identified as the adduct(s) *10b*, mainly on the basis of its UV-spectrum, λ_{max}(EtOH) 243 nm, typical for a non-cyclic thiourea, its MS (*m/e* 223, M^+), and IR-spectrum. On prolonged treatment with $MeNH_2$ in EtOH, the adduct showed no signs of undergoing reaction as estimated from chromatographic analysis.

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