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SYNTHESIS OF (±) SULPHORAPHENE[1]

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Abstract—The synthesis of (±) sulphoraphene (I, R = CH_2CH_2NCS) has been achieved from γ-phthalimidobutyraldehyde dimethyl mercaptal (III) by conversion to 4,4-di-(methylsulphinyl)butyl isothiocyanate (V, R = CH_2CH_2NCS) and subsequent reaction stages IV and V. Stereospecific elimination of one methylsulphinyl group from V gave *trans*-4-methylsulphinyl-3-butenyl isothiocyanate (I; (±) sulphoraphene). IR and NMR spectra of (±), and (−) sulphoraphene, as well as of their phenylthiourea derivatives are discussed.

THE naturally derived sulphoxide, (−) sulphoraphene, isolated from seeds of the *Raphanus sativus* L. var. *alba*, was assumed to be (−) 4-methylsulphinyl-3-butenyl isothiocyanate (I, R = CH_2CH_2NCS).[3] This compound was the first natural product in which the optical activity is due to an asymmetric sulphur atom. Optically active mustard oils of this type occur abundantly in *Cruciferae*, and as the result of intensive studies by Kjaer *et al.*[4] the discovery of sulphoraphene was followed in the last decade by new isothiocyanates with the skeleton II (n = 3, 4, 5, 6, 8, 9 and 10). Recently, the absolute configuration of sulphoxide mustard oils has been reported.[5,6]

$CH_3SOCH{=}CH{-}R$ (I) $\qquad$ $CH_3SO(CH_2)_nNCS$ (II)

Although the synthesis of saturated sulphoraphane (II, n = 4) and analogous mustard oils (II) has been developed,[7,8] no synthesis of α,β-unsaturated sulphoxides of the sulphoraphene type has been published. A report of the synthesis of (±) sulphoraphene (I) starting from γ-aminobutyric acid is now given.

The first approach to the synthesis of sulphoraphene, by pyrolysis of 1,1-di-(methylthio)-4-phthalimidobutane (III) to the thioenol (VI) according to Arens[9] was unsatisfactory because of the high temperatures required. Instead, the stereospecific low temperature transformation of sulphoxide to olefin was applied.[10,11]

III $RCH_2CH(SCH_3)_2$ $\qquad$ IV $RCH_2CH(SOCH_3)SCH_3$
V $RCH_2CH(SOCH_3)_2$ $\qquad$ VI $RCH{=}CHSCH_3$
III–VI: R = $CH_2CH_2N(CO)_2C_6H_4$

[1] Presented in part at the XIX*th International Congress of Pure and Applied Chemistry*, London July (1963).
[2] Taken in part from I. Monković, Ph.D. Dissertation, University of Zagreb (1962); present address: N.R.C. Post-Doctoral Fellow, McMaster University, Hamilton, Ont., Canada.
[3] H. Schmid and P. Karrer, *Helv. Chim. Acta* **31**, 1017 (1948).
[4] cf.e.g. A. Kjaer, *Fortschr. Chem. Org. Naturstoffe* **18**, 122 (1960).
[5] K. K. Cheung, A. Kjaer and G. A. Sim, *Chem. Comm.* 100 (1965).
[6] K. Mislow, M. M. Green, P. Laur and D. R. Chisholm, *J. Amer. Chem. Soc.* **87**, 665 (1965).
[7] H. Schmid and P. Karrer, *Helv. Chim. Acta* **31**, 1497 (1948).
[8] A. Kjaer, I. Larsen and R. Gmelin, *Acta Chem. Scand.* **9**, 1311 (1955).
[9] H. J. Boonstra, L. Brandsma, A. M. Wiegman and J. F. Arens, *Rec. Trav. chim.* **78**, 252 (1959).
[10] C. A. Kingsbury and D. J. Cram, *J. Amer. Chem. Soc.* **82**, 1810 (1960).
[11] T. Colclough and J. I. Cunneen, *Chem. & Ind.* 626 (1960).

Accordingly, *cis*-elimination of 1-methyl-thio-1-methylsulphinyl or 1,1-di(methylsulphinyl)-derivatives, obtained by oxidation of dimethyl mercaptals with peroxy acids to the monosulphoxide or disulphoxide stage and pyrolysis of these sulphoxides afforded 1-methylthio-1-alkenyl derivatives (VI) and 1-methylsulphinyl-1-alkenyl derivatives (I) in good yields.

It is evident from Fig. 1 that *cis*-elimination[10] of the sulphoxide group connected with the most favourable conformation of other groups (methylthio or methylsulphinyl) in the molecule affords predominantly *trans*-olefin:

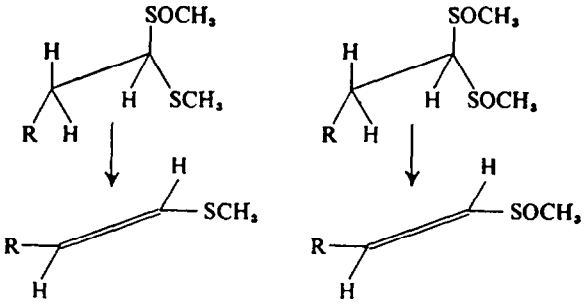


FIG. 1

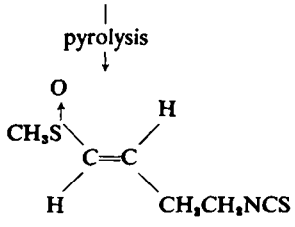
Application of this reaction to mercaptals of several aliphatic, aromatic, and heterocyclic aldehydes resulted in a ratio of, *trans-cis* products ranging between the factors 4 and 10. For instance, phenylacetaldehyde gave 75% *trans*-methyl-ω-styryl sulphide and less than 10% of the *cis*-compound.[12] An earlier preparation of this compound by Truce *et al.*,[13] by nucleophilic addition of methyl mercaptane to phenylacetylene predominantly afforded the *cis*-derivative. These configurational assignments are supported by spectral data: The NMR spectra of the higher melting sulphides, sulphoxides and sulphones[12] reveal the coupling constant values evident from the spin-spin splitting pattern of the two proton nuclei on the double bond in the range of 14 to 16 c/s. The standard interval attributed to protons on *trans* ethylenic double bonds is 11 to 18 c/s.[14]

IR spectra of these compounds have strong absorption bands between 980 and 965 cm^{-1}, assigned to the *trans* hydrogens in 1,2-disubstituted ethylenes.[15] The IR spectrum of (−) sulphoraphene isolated in our laboratory from *Raphanus sativus* L. var. *radicula*[16] also shows this absorption band. Groups of resonance lines in the NMR spectrum belonging to double bond protons show in this case a considerable fine structure because of very similar chemical shift values and spin-spin interactions with protons of a contiguous methylene group. Their structure may be an ABX_2 system[17] with observed values $J_{AB} = 15$ c/s and $\delta_{AB} = 10$ c/s.

[12] A. Deljac, Ph.D. Dissertation, University of Zagreb (1965); Ms in preparation.
[13] W. E. Truce and J. A. Simms, *J. Amer. Chem. Soc.* **78**, 2756 (1956).
[14] L. M. Jackman, *Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry*. Pergamon, New York (1959).
[15] cf. L. J. Bellamy, *The Infra-red Spectra of Complex Molecules* (2nd Edition) p. 45. Methuen, London (1959).
[16] A. Deljac, I. Monković and K. Balenović, *Bull. Sci. Acad. Youg.* Section A, 211 (1965).
[17] M. F. Barnes, W. D. Ollis, I. O. Sutherland, O. R. Gottlieb and M. Taveira Magalhães, *Tetrahedron* **21**, 2707 (1965).

A convenient route for the preparation of (±) sulphoraphene in substantial quantities is as follows: 1-Methylsulphinyl-1-methylthio-4-phthalimidobutane (IV) was oxidized with peroxy acid to 1,1-di(methylsulphinyl)-4-phthalimidobutane (V). Subsequent hydrazinolysis of V afforded 4-amino-1,1-di(methylphinyl) butane (V, R = $CH_2CH_2NH_2$). From this compound 4,4-di-(methylsulphinyl)-butyl isothiocyanate (V, R = CH_2CH_2NCS) was obtained in fairly good yields by a modification of the usual procedure[18] for the conversion of the amino into the isothiocyanato group using trimethylamine as a base:

$$(CH_3SO)_2CHCH_2CH_2CH_2NH_2 + CS_2 + (CH_3)_3N$$
$$\downarrow$$
$$(CH_3SO)_2CHCH_2CH_2CH_2NHCSSH,N(CH_3)_3$$
$$I_2 \downarrow (CH_3)_3N$$
$$(CH_3SO)_2CHCH_2CH_2CH_2NCS + 2(CH_3)_3NHI + S$$



trans (±) sulphoraphene

Pyrolysis of V(R = CH_2CH_2NCS) at 130° in high vacuum (0·05 mm) afforded after purification *trans* (±) sulphoraphene in a 50% yield, showing satisfactory analytical results as well as IR and NMR spectra with characteristic maxima indistinguishable from those of natural (−) sulphoraphene.

For characterization the phenylthiourea derivative[3] was prepared, which showed good analytical results and the same NMR spectrum as the corresponding derivative of the (−) sulphoraphene; IR spectra measured by the KBr method were slightly different whilst a $CHCl_3$ solution furnished completely coincedent spectra.

EXPERIMENTAL

M.ps are uncorrected. The NMR spectrograms were measured with a Varian A-60 instrument for $CDCl_3$ solutions containing tetramethylsilane as internal reference. All chemical shifts are quoted on the τ-scale.

The IR spectra were obtained from KBr discs and in $CHCl_3$ solution with Perkin–Elmer infracord 137. TLC was performed on Silica Gel G (E. Merck, Darmstadt, Germany) and spots developed with 1% $KMnO_4$aq solution.[19] In preparative TLC, plates (40 × 30 × 0·3 cm) of Silica Gel HF_{254} (E. Merck) were used. Light petroleum refers to the fraction bp. 40–60°.

1,1-*Di(methylthio)-4-phthalimidobutane* (III). γ-Phthalimidobutyraldehyde[20] (8·2 g, 0·029 mole) anhydrous $ZnCl_2$ (0·16 g), and methyl mercaptan (3·5 ml, 0·065 mole) were heated in a sealed glass tube at 90° for 3 hr. After cooling, the reaction mixture was diluted with benzene (20 ml) and washed

[18] H. Schmid and P. Karrer, *Helv. Chim. Acta* **31**, 1497 (1948); J. v. Braun, *Ber. Dtsch. Chem. Ges.* **35**, 817 (1902), **45**, 2188 (1912).

[19] Organic sulphides and sulphoxides are detectable with this reagent as intensive yellow spots on pink background.

[20] K. Balenović, I. Jambrešić and I. Furić, *J. Org. Chem.* **17**, 1459 (1952).

in turn with water (5 ml), 5% $NaHCO_3$aq (10 ml) and water (5 ml). After evaporating the benzene *in vacuo* an oil remained, which crystallized on standing. Recrystallization from MeOH afforded III (7·44 g, 87%). The analytical sample distilled at 125–130°/0·01 mm, m.p. 55–57°. (Found: C, 57·31; H, 5·70. $C_{14}H_{17}O_3NS_2$ requires: C, 56·92; H, 5·80%.)

1-*Methylsulphinyl*-1-*methylthio*-4-*phthalimidobutane* (IV). To a solution of III (5·91 g, 0·02 mole) in ether (80 ml) cooled to 0° an ethereal solution of perbenzoic acid[21] (0·25 M, 80 ml, 0·02 mole) was added dropwise during 1 hr under stirring, the temp being kept at 0°. After 15 more min stirring at 0° the separated IV was filtered off and washed with ether (4 × 10 ml), yield 5·5 g (88%) m.p. 96–113°.[22] Crystallization from CH_2Cl_2–light petroleum afforded the analytical sample, m.p. 127–129°. (Found: C, 54·08; H, 5·54. $C_{14}H_{17}O_3NS_2$ requires: C, 53·99; H, 5·50%.)

1,1-*Di*(*methylsulphinyl*)-4-*phthalimidobutane* (V). To a solution of IV (m.p. 96–113°, 4·67 g, 0·015 mole) in $CHCl_3$ (50 ml) cooled to −15°, a solution of perbenzoic acid (0·4 M, 37·5 ml, 0·015 mole) in $CHCl_3$ was added dropwise during 2 hr under stirring, and a temp of −15°. The reaction mixture was evaporated *in vacuo* and the residual oil crystallized on addition of ether (20 ml). The crystals of V were filtered off and washed with ether (3 × 10 ml); yield 4·6 g (93%), m.p. 127–136°. TLC showed a weak spot of starting material and two intensive spots belonging to diastereomers of V. The analytical sample was crystallized from CH_2Cl_2–ether, m.p. 137–141°. (Found: C, 51·16; H, 5·25. $C_{14}H_{17}O_4NS_2$ requires: C, 51·36; H, 5·23%.)

4-*Amino*-1,1-*di*(*methylsulphinyl*) *butane* (V, R = $CH_2CH_2NH_2$). A solution of V (m.p. 134–137°[23], 6·2 g, 0·022 mole) in molar ethanolic hydrazine hydrate (44 ml) was refluxed for ½ hr. After cooling, diluting with water (25 ml), and adjusting the pH 5·5 with dil HCl, the reaction mixture was kept at 50° for 10 min. After standing 5 hr at room temp, the precipitated phthaloyl hydrazide was filtered off, and the filtrate evaporated to dryness *in vacuo*. The residue was mixed with powdered anhydrous Na_2CO_3 (10 g), $CHCl_3$ added (50 ml), and after shaking it was filtered. The remaining crude mixture was washed with $CHCl_3$ (2 × 50 ml), the combined filtrates dried (Na_2CO_3), and evaporated to dryness at room temp. The residual viscous oil was dried *in vacuo* (P_2O_5) and consisted of V (R = $CH_2CH_2NH_2$) (3·55 g, 82%). The analytical sample was purified by precipitation from CH_2Cl_2–ether (Found: C, 36·59; H, 7·67. $C_6H_{15}O_2NS_2$ requires: C, 36·52; H, 7·66%.)

4,4-*Di*(*methylsulphinyl*)-*butyl* iso*thiocyanate* (V, R = CH_2CH_2NCS). A solution of V (R = $CH_2CH_2NH_2$) (3·6 g, 18·2 mmole) in 4·5 molar methanolic Me_3N (20·5 ml, 91·9 mmoles) was cooled to −5° and a molar ethanolic solution of CS_2 (18·2 ml) was added. After standing at 0° for 5 hr the mixture was stirred 1 hr at room temp, and then a 0·5N methanolic I_2 (78 ml, 36·4 mmoles) added dropwise under continuous stirring during 1 hr at room temp. The reaction mixture was cooled to −5°, the precipitate filtered off, and after evaporating the filtrate *in vacuo* the residue was extracted with benzene (3 × 30 ml). The benzene extracts were evaporated to dryness at room temp, and the crude V (R = CH_2CH_2NCS) as a pale yellow oil; (3 g, 68%) was purified by precipitation from CH_2Cl_2–ether. (Found: C, 35·62; H, 5·48. $C_7H_{13}O_2NS_3$ requires: C, 35·12; H, 5·47%.)

(±)*Sulphoraphene* (trans-4-*methylsulphinyl*-3-*butenyl isothiocyanate* I, R = CH_2CH_2NCS). 4,4-Di(methylsulphinyl)-butyl isothiocyanate (0·5 g, 2·09 mmoles) absorbed on glass wool was pyrolysed in a micro-distillation apparatus (bath temp 130–140°, 3 hr, 0·05 mm), yield 0·28 g (83%) of distillate. The distillate (1 g) was dissolved in ether (10 ml) and extracted with water (2 × 10 ml). After evaporating the water extracts *in vacuo* crude I remained (0·78 g, 60%) as a pale yellow oil. TLC in $CHCl_3$–EtOH (9:1) showed intensive spot R_F value 0·57 identical with natural (−)sulphoraphene and 3 weaker spots. Purification was carried out by preparative TLC in the same solvent system. Crude mixture (0·3 g) was applied on one TLC-plate (40 × 30 × 0·3 cm). After the chromatography, the zone with adsorbed (±)sulphoraphene was extracted with $CHCl_3$ and the solvent removed under red. press. From 1 g of crude mixture purified in this way 0·81 g (total yield 49%) of pure (±)sulphoraphene was obtained. Subsequent drying at 40°/0·04 mm yielded the analytical sample. (Found: C, 41·34; H, 5·28. $C_6H_9ONS_2$ requires: C, 41·12; H, 5·18%); ν_{max} (in KBr) 966, 1050, 1347, 2102, 2188 cm^{-1}. NMR spectrum (in $CDCl_3$) [τ 8·58–8·94 weak multiplet (corresp. 0·24H), τ 7·33 singlet (CH_3SO—), τ 7·60–7·00 multiplet (=$CHCH_2CH_2N$=), τ 6·50–6·09 multiplet (=$CHCH_2CH_2N$=) τ 3·83–3·08 multiplet (—CH=CH—CH_2—)]. Spectral data for natural (−)sulphoraphene: ν_{max} (in

[21] *Organic Syntheses*, Coll. Vol. **1**, 431 (1941).

[22] TLC of this product showed also weak spots of disulphoxide(V).

[23] Crude product crystallized once from EtOH showed this m.p.

KBr) 967, 1049, 1348, 2109, 2188 cm^{-1}. NMR spectrum (in $CDCl_3$) [τ 8·73 weak (corresp. 0·31H), τ 7·32 singlet (CH_3SO—), τ 7·08–7·50 multiplet (=$CHCH_2CH_2N$=), τ 6·96 broad (corresp. 0·5H), τ 6·38–6·10 multiplet (—CH_2CH_2N=), τ 3·80–3·11 muliplet (—CH=CH—CH_2—)].

(±)*1-(4-Methylsulphinyl-3-butenyl)-3-phenylthiourea.* Pure (±)sulphoraphene (0·274 g) and aniline (0·175 g) in abs EtOH (0·65 ml) were refluxed for 15 min, cooled and ether added to the first cloudiness. After standing overnight at 0° colourless crystals of 1-(4-methylsulphinyl-3-butenyl)-3-phenylthiourea deposited, yield 0·32 g (76%) m.p. 84–89°. Recrystallization from MeOH–ether gave an analytical sample m.p. 87–89°. The same derivative obtained from (−)sulphoraphene had m.p. 121° (Lit.,[8] m.p. 121°). (Found: C, 53·98; H, 5·84. $C_{12}H_{16}N_2OS_2$ requires: C, 53·70; H, 6·01%); ν_{max} (in KBr) 723, 769, 955, 1005 1035, 1322, 1354, 1498, 1548, 3070, 3310 cm^{-1}; ν_{max} (in $CHCl_3$) 962, 1045, 1210, 1495, 1535, 3000, 3400 cm^{-1}. NMR spectrum (in $CDCl_3$) [τ 7·43 singlet (CH_3SO—), τ 7·68–7·20 multiplet (=$CHCH_2CH_2NH$—), τ 6·50–5·90 multiplet (—CH_2CH_2NH—), τ 3·40–3·75 multiplet (—CH=CH—CH_2—), τ 3·30 broad (—CH_2NHCS—), τ 3·00–2·36 multiplet (—CS—NH—C_6H_5), τ 1·17 broad (—CSNH—C_6H_5)]. Spectral data for phenylthiourea derivative of natural (−)sulphoraphene: ν_{max} (in KBr) 720, 765, 965, 978, 998, 1295, 1310, 1345, 1490, 1520, 3040, 3280 cm^{-1}; ν_{max} (in $CHCl_3$) 961, 1045, 1208, 1492, 1530, 3000, 3400 cm^{-1}. NMR spectrum (in $CDCl_3$) [τ 7·44 singlet (CH_3SO—), τ 7·70–7·22 multiplet (=$CHCH_2CH_2NH$—), τ 6·66–5·95 multiplet (=$CHCH_2CH_2NH$—), τ 3·43–3·75 multiplet (—CH=$CHCH_2$—), τ 3·27 broad (—CH_2CH_2NHCS—), τ 2·97–2·35 multiplet (—$CSNHC_6H_5$), τ 1·18 broad (—$CSNHC_6H_5$)].

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