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Original Scientific Paper**Asymmetric Synthesis of Sulfoxides from Alkenyl Sulphides, Disulphides and Related Compounds, with (1S)-(+)-Percamphoric Acid. Gem-Disulphides and Related Compounds, Part XXIII.¹**

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Partial asymmetric oxidation of sulphides **1**, **2**, **5** and **6** with percamphoric acid is described. The results are summarized on Tables 1—3 and interpreted in terms of the earlier proposed transition state with diamond-lattice structure for the oxidation of sulphides and sulfoxides with percamphoric acid (Schemes 1 and 3). Subclasses of sulphides **1** and **2** gave sulfoxides with the same sign of optical rotation. Sulfoxides from subclasses **5** and **6** have opposite rotations. These facts, as well as the fact that sulfoxides **4a** and **4b** (Table 1) on the one side, and the sulfoxides **7a** and **7b** (Table 2) on the other, have opposite signs of rotation, are strongly in favour of the proposed transition state illustrated on Scheme 1.

Several asymmetric sulfoxide syntheses have been accomplished, although in low optical yields, by oxidizing the appropriate sulphides with such optically active peracids as percamphoric acid, perhydratropic acid, and α -substituted perglutaric acid.^{2,2a,3}

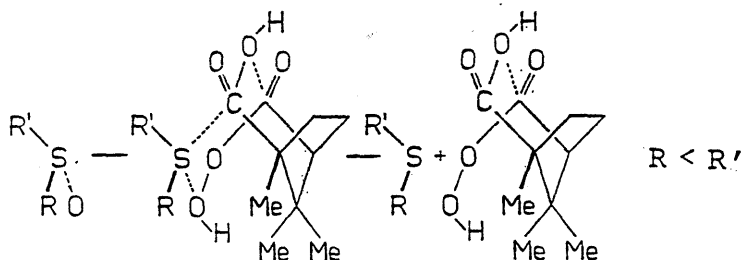
Regarding in retrospect the work on the asymmetric synthesis of sulfoxides in our Laboratory, we attempted to gain information about the absolute configuration of sulfoxides by means of active peracids.³ However, it soon became evident that other laboratories were simultaneously and independently working on the same problem.^{2, 2a}

We later found that during the reaction of butyl methyl sulfoxide⁴ with L-cysteine or (+)-2-mercaptopropionic acid, the (—)-(*R*)-sulfoxide accumulated, indicating that the (*S*)-enantiomer was reduced faster by the thiol⁵ (Scheme 2a).

It is true that our experiments with the optically active reagents we have used gave comparatively low optical yields, but the configuration assigned

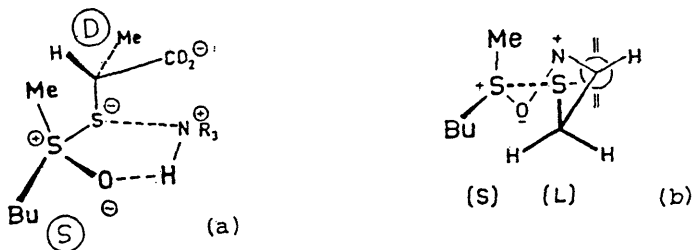
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to the few sulfoxides obtained were proven in later investigations to be correct. We also proposed a hypothetical transition state for these oxidations with diamond-lattice structure (Scheme 1).



Scheme 1

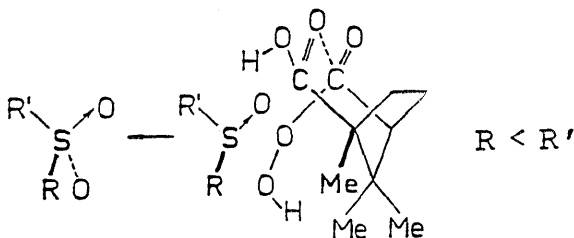
Our hypothetical transition states for the reductions with thiols are presented in Scheme 2a, b.



Scheme 2a, b

It is evident today that no simple rationalization of the optical induction in terms of the eclipsic effect of small, medium and large groups in the respective transition states is possible, because electronic and other effects are important in the formation of transition states. Therefore, at best one might derive particular heuristic rules for predicting absolute configurations for different substrate series. These hypothetical transition states, proposed more than twenty years ago³, were severely criticized at that time as superfluous, since the geometry of the relevant transition states of oxidation remains unknown.⁶ Today the real transition state for the oxidation of sulfoxides still does not exist, and the criticized transition states remain useful in certain cases: for instance, the interesting fact that opposite stereospecificity is found in asymmetric oxidations of sulfoxides and of sulphides with the same peroxy-acid; *i.e.*, the enantiomeric sulfoxides which are preferentially formed,

from the sulphides are found to be those which are oxidized more slowly to sulphones.^{7, 8} Both asymmetric inductions can be interpreted with the same model of transition states proposed earlier.² Our model of the transition state with diamond-lattice structure³ for the oxidation of asymmetric sulphoxides with (1S)-(+)-percamphoric acid has enabled us to interpret both asymmetric inductions^{9, 14} (Scheme 3).



Scheme 3

Therefore, in the present modest experimental contribution we have given new examples of the asymmetric oxidations of several classes of new asymmetric sulphides (**1**, a: R, *t*-butyl, R', allyl; b: R, *n*-amyl, R', allyl) and disulphides (**2**, a: R, *t*-butyl, *n* = 1; b: R, *t*-butyl, *n* = 2)



The resulting sulfoxides were the following: *t*-butylallyl sulfoxide (**3a**); *n*-amylallyl sulfoxide (**3b**); *t*-butylsulphinyl-*t*-butylthio methane (**4a**); 1-*t*-butylsulphinyl-2-*t*-butylthio ethane (**4b**). The results are summarized on Table 1.

TABLE 1

Sulfoxides obtained by oxidation with (1S)-(+)-percamphoric acid in Et₂O solution at -5°

Compound	B.p./mm; m.p.	$[\alpha]_D^{25}$	Solvent
3a	b.p. 55–60°/0.1	+1,62°	MeOH
3b	b.p. 65–70°/0.1	0,0°	"
4a	m.p. 73–74°	+3,5°	"
4b	b.p. 85–89°/0.07	+1,56°	dioxane

We also oxidized the following mercaptals (**5**) and *trans*-1-methylthio-1-alkenes (**6**) with (1S)-(+)-percamphoric acid: 1,1-bismethylthio-3-phthalimido propane (**5a**); 1,1-bismethylthio-4-phthalimido butane (**5b**); *trans*-1-methylthio-1-heptene (**6a**); *trans*-1-methylthio-4-phthalimido-1-butene.

Table 2 summarizes the properties of the resulting sulfoxides: 1-methylsulphanyl-1-methylthio-3-phthalimidopropane (**7a**); 1-methylsulphanyl-1-methylthio-4-phthalimidobutane (**7b**); *trans*-1-methylsulphanyl-1-heptene (**8a**); *trans*-1-methylsulphanyl-4-phthalimido-1-butene (**8b**).

TABLE 2

Sulfoxides obtained from 1-methylthio derivatives 5 and 6 by oxidation with (1S)-(+)-percamphoric acid in Et₂O at 0°C

Compound	m.p.	$[\alpha]_D^{25}$	Solvent
7a *	135—137°	—0.8°	CHCl ₃
7b	101—114°	—5.4°	MeOH
8a	b.p. 62—67°/0.02	—0.6°	MeOH
8b	151—153°	—1.4°	CHCl ₃

* See ref. 9a

Our experiments on the partial asymmetric oxidations of sulphides **1**, **2**, **5**, and **6** with (1S)-(+)-percamphoric acid are summarized on Table 3 in which the sign of optical rotation is correlated with the structure of substituents R and R' as proposed in the hypothetical transition state with diamond-lattice structure illustrated in Scheme 1. It is evident that some subclasses of our sulphides (**1** and **2**) gave the same sign of optical rotation. Other subclasses of sulphides (**5** and **6**) gave opposite signs of rotation. In terms of the large, medium, and small sizes of substituents R and R' as proposed for our transition state, the fact that sulfoxides **4a** and **4b** on the one side and sulfoxides **7a** and **7b** on the other side have opposite signs of optical rotation, is strongly in favour of our proposition for the transition state illustrated on Scheme 1.

TABLE 3

Sulfoxides of the structures 3, 4, 7, 8 (RSOR', R < R') obtained by oxidation from the corresponding sulphides with (1S) — (+) — percamphoric acid: sign of optical rotation correlated with the nature of substituents R and R'.

Compound	R	<	R'	sign of $[\alpha]_D$
3a	allyl	<i>t</i> -butyl		+
3b	allyl	<i>n</i> -amyl		0
4a	<i>t</i> -BuSCH ₂ —	<i>t</i> -butyl		+
4b	<i>t</i> -BuS(CH ₂) ₁ —	<i>t</i> -butyl		+
7a	CH ₃	CH(SCH ₃) (CH ₂) ₂ R''		—
7b	CH ₃	CH(SCH ₃) (CH ₂) ₃ R''		—
8a	CH ₃	<i>trans</i> -CH=CH(CH ₂) ₄ CH ₃		—
8b	CH ₃	<i>trans</i> -CH=CH(CH ₂) ₃ R''		—

R'' = phthalimido

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M. ps. are uncorrected. Tlc was performed on Silica Gel HF₂₅₄ (E. Merck) and spots developed with 1% KMnO₄ solution. Organic sulphides and sulfoxides were detectable with this reagent as intense yellow spots on a pink background. Light petroleum refers to the fraction with the b.p. 40–60°C. IR spectra were taken on a Perkin-Elmer Infracord 137. Optical rotations were measured on a Bendix NPL Automatic Polarimeter 143D. Sulphides **1** and **2** were prepared in liquid ammonia according to the procedure described earlier for the preparation of S-alkyl-cysteines from cystine¹⁰, from di-*t*-butyl disulphide resp. di-*n*-amyl disulphide and the appropriate alkyl halogenide. 1,1-bismethylthio-3-phthalimido propane (**5a**), 1,1-bis methylthio-4-phthalimido butane (**5b**), *trans*-1-methylthio-1-heptene (**6a**) and *trans*-1-methylthio-4-phthalimido-1-butene (**6b**) were prepared following the procedure described earlier.¹¹

Oxidations of 1, 2 5 and 6 with (1S)-(+)-monopercamphoric acid. 1S-(+)-monopercamphoric acid was prepared by oxidation of (+)-camphoric anhydride with sodium peroxide, acidification, and extraction with CHCl₃.¹² Oxidations in Et₂O were performed as described earlier.¹¹ Oxidations in CHCl₃ solution: The titrated CHCl₃ solution of peroxy-acid was added dropwise to a stirred CHCl₃ solution of appropriate sulphide with the temperature maintained at -5°C until the oxidant had disappeared (iodimetric test). At the end of the reaction (after 6–7 hrs.), the CHCl₃ solution was repeatedly extracted with saturated aqueous NaHCO₃, washed with water and dried (MgSO₄). Removal of the solvent and crystallization from CH₂Cl₂-light petroleum gave the corresponding sulfoxides.

TABLE 4

Sulfoxides obtained by oxidation with (1S)-(+)-percamphoric acid

Compound	B.p./mm or m.p.°	Formula	Found (%)		Required (%)	
			C	H	C	H
3a	55–60/0.1	C ₇ H ₁₆ OS	57.30	9.91	57.49	9.65
3b	65–70/0.1	C ₈ H ₁₈ OS	60.10	9.98	59.95	10.06
4a	73–74°	C ₉ H ₂₀ OS ₂	52.45	9.67	51.87	9.68
4b	85–89/0.07	C ₁₀ H ₂₂ OS ₂	55.46	10.48	54.00	9.97
7b	101–114°	C ₁₄ H ₁₇ O ₃ NS ₂	54.01	5.81	53.99	5.50
8a	62–67/0.02	C ₈ H ₁₆ OS	59.49	10.22	59.95	10.06
8b	151–153	C ₁₃ H ₁₉ O ₃ NS	59.44	5.12	59.30	4.98

Each of these compounds has a strong bifurcated absorption band in the IR spectrum characteristic for sulfoxides, $\nu_{\max}$ (KBr) at 1040–1050 cm⁻¹.

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- 9a. O. Nota, M. A. Thesis, University of Zagreb, 1977. In our Laboratory O. Nota obtained **7a** by oxidation of **6a** in the presence of *Aspergillus niger* NRRL 337 Culture showing $[\alpha]_D^{25} + 24.9^\circ$ (CHCl₃), 1.13. Compound **7a** was oxidized with (1S)-(+)-percamphoric acid in CHCl₃ solution at -20°C . At temperatures above -20°C optically inactive products were obtained.
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14. Note added during proof-reading (Dec 5, 1990): Vladimir Prelog and coworkers¹⁵ pointed out that as early as 1941, before the introduction of conformational analysis Speakman used diamond-lattice sectors in a discussion of the probable conformers of perhydrodiphenic acids and the influence of conformation on their dissociation constants, and expressly referred to this possibility.¹⁶ In our laboratory we have used the diamond lattice to interpret the transannular reaction course in cyclodecane derivatives¹⁷ and to characterize the stereoselectivity of oxido-reductases.¹⁸⁻²¹ A well-known chemist close to us (A. E.) has described the diamond lattice as the 'poor man's computer'.²²
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SAZETAK

Asimetrijska sinteza sulfoksida oksidacijom alkenil sulfida, disulfida i srodnih spojeva sa (1S)-(+)-perkamfornom kiselinom. Gem-disulfidi i srodni spojevi, XXIII dio

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Opisana je parcijalna asimetrijska oksidacija sulfida **1**, **2**, **5** i **6** s perkamfornom kiselinom. Rezultati su prikazani u tablicama 1–3, a protumačeni su ranije pretpo-

stavljenom međufazom u ovoj oksidaciji (sheme 1 i 3). Iz sulfida podvrsti **1** i **2** nastaju sulfoksidi s istim predznakom optičke rotacije, dok sulfoksidi nastali iz podvrsti **5** i **6** pokazuju suprotan predznak. Ta činjenica, kao i podatak da sulfoksidi **4a** i **4b** (Tablica 1) imaju suprotan predznak rotacije od sulfoksida **7a** i **7b** (Tablica 2), podupire našu pretpostavku o strukturi međufaze ove oksidacije analogne kristalnoj mrežici diamanta kako je prikazano na shemama 1 i 3.

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Original Scientific Paper**Stereoisomers of 1,1-bis(Methylsulphonyl)-3-phthalimidopropane; Intermediates for the Synthesis of *nor-trans*-Sulphoraphene. Gem-Disulphides and Related Compounds, Part XXIV^{1,2}**Ante Deljac,* Damir Huljev,^{2a} Mira Novak, and Krešimir BalenovićCentre for the Chemistry of Organic Natural Compounds of the Yugoslav
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Preparation of stereoisomers **1**–**3** of the title compound is described. Stereochemical assignment for **1**, **2**, and **3** is reported, using microbial as well as ¹H and ¹³C NMR methods.

It was found earlier⁴ in this Laboratory that geminal disulphoxides (Fig. 1a) are excellent starting materials for the synthesis of (±)-*trans*-sulphoraphene (Fig. 1b, R = CH₂CH₂NCS) and related compounds:⁵

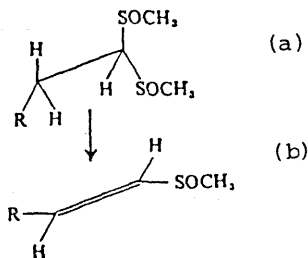
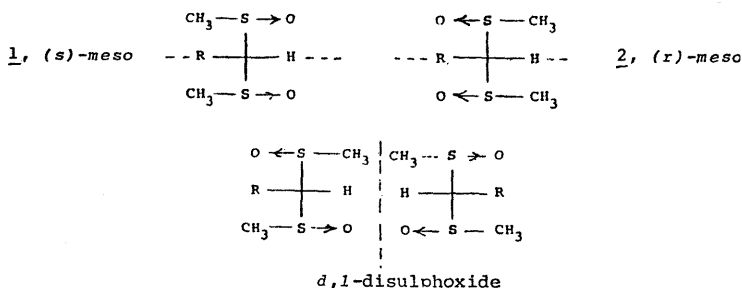


Fig. 1

A description is now given of stereoisomeric disulphoxides as intermediates for the synthesis of *nor-trans*-sulphoraphene (Fig. 1b, R = CH₂NCS) from 1,1-bis(methylsulphonyl)-3-phthalimidopropane (Fig. 1a, R = C₆H₄(CO)₂NCH₂). These compounds have one pseudoasymmetric C-atom and we expect, therefore, two *meso*-disulphoxides (**1**, **2**)⁶ and the *d,l*-disulphoxide (**3**) (**1**–**3**, R = C₆H₄(CO)₂NCH₂CH₂):

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We prepared the stereoisomeric disulphoxides (1–3) by treatment of 1,1-bis(methylthio)-3-phthalimidopropane (4)⁵ with two equivalents of sodium metaperiodate⁷ followed by fractional crystallization. Some constants of the stereoisomers 1–3 are summarized on Table 1.

TABLE 1.

1,1-bis(Methylsulphinyl)-3-phthalimidopropanes 1–3

Stereoisomer	cryst. (EtOH)	M.p.	R_f^*	$\delta^1 \text{H (SOCH}_3\text{)}$
$ \begin{array}{c} \text{O} \leftarrow \text{S} - \text{CH}_3 \\ \\ \text{R ---} \text{--- H} \\ \\ \text{O} \leftarrow \text{S} - \text{CH}_3 \end{array} $ $ \begin{array}{c} \text{H} \text{R} \\ \quad \\ \text{H}_3\text{C} - \text{S} - \text{C} - \text{C} - \text{S} - \text{CH}_3 \\ \quad \\ \text{O} \quad \text{O} \end{array} $ $\underline{2} \text{ (r)-meso}$	plates	153–154°	0.47	2.83 s (6H)
$ \begin{array}{c} \text{CH}_3 - \text{S} \rightarrow \text{O} \\ \\ \text{R ---} \text{--- H} \\ \\ \text{CH}_3 - \text{S} \rightarrow \text{O} \end{array} $ $ \begin{array}{c} \text{H} \text{R} \\ \quad \\ \text{H}_3\text{C} - \text{S} - \text{C} - \text{C} - \text{S} - \text{CH}_3 \\ \quad \\ \text{O} \quad \text{O} \end{array} $ $\underline{1} \text{ (s)-meso}$	prisms	163–164°	0.53	2.88 s (6H)
$ \begin{array}{c} \text{CH}_3 - \text{S} \rightarrow \text{O} \\ \\ \text{H ---} \text{--- R} \\ \\ \text{O} \leftarrow \text{S} - \text{CH}_3 \end{array} $ $ \begin{array}{c} \text{H} \text{R} \\ \quad \\ \text{H}_3\text{C} - \text{S} - \text{C} - \text{C} - \text{S} - \text{CH}_3 \\ \quad \\ \text{O} \quad \text{O} \end{array} $ $\underline{3} \text{ d, l}$	needles	173–175°	0.37	2.70 s (3H) 2.90 s (3H)

* cf. Experimental part

In this Laboratory we also used a strain of *Aspergillus niger* NRRL 337 subcultured in Zagreb over 15 years⁸ to prepare optically active *gem*-disulphide S-oxides **5** and **6** and the (*s*)-*meso*-disulphoxide **1**. The structural assignment was made by intercorrelating the senses of NMR non-equivalence in pseudo-asymmetric disulphoxides **1** and **2** of established configurations with the configurationally related monosulphoxides **5** and **6**.^{9,10} These interrelationships are summarized on Fig. 2.

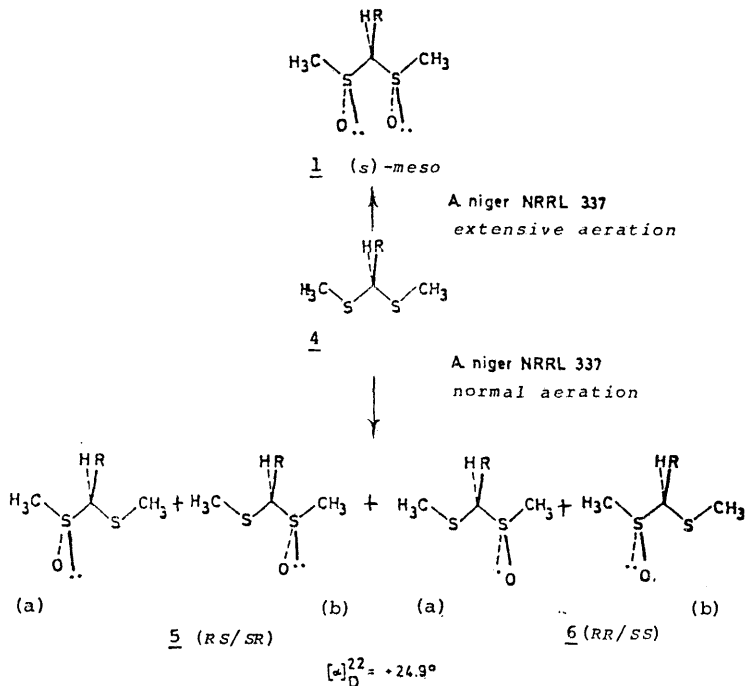


Fig. 2

The diastereomeric ratio **5/6** of about 60:40 was determined by integration of methylsulphonyl NMR signals at δ 2.70 and 2.53, respectively. The use of (*R*)-(-)-1-phenyl-2,2,2-trifluoroethanol (**7**) as chiral solvent allowed the direct determination of enantiomeric composition and empirical assignment of both absolute configurations according to Pirkle *et al.*¹¹ As estimated by NMR (**7**, CCl_4), the ratio of signals (SOCH_3) at δ 2.66 (**5a**)/2.64 (**5b**) was 44:16 and the ratio at δ 2.49 (**6a**)/2.47 (**6b**) was 29:11.¹⁰

These results, combined with ^1H and ^{13}C chemical shifts for stereoisomers **1**–**3** (Table 2) allow complete stereochemical assignments. Compound **3**, *m.p.* 173–175 °C (Table 1) has two ^1H (SOCH_3) signals, δ 2.70 *s* (3H) and 2.90 (3H),

TABLE 2.

^1H and ^{13}C Chemical Shifts of 1,1-bis(Methylsulphinyl)-3-phthalimidopropanes (**1**–**3**)

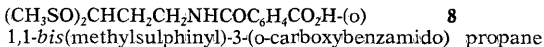
Stereoisomer		SOCH_3	CH (1)	CH_2 (2)	CH_2 (3)
1	δ ^1H	2.88 <i>s</i>	3.83 <i>t</i>	2.55 <i>q</i>	4.03 <i>t</i>
	δ ^{13}C	36.8 <i>q</i>	71.6 <i>d</i>	20.8 <i>t</i>	35.4 <i>t</i>
2	δ ^1H	2.83 <i>s</i>	4.05 <i>t</i>	2.24 <i>q</i>	3.98 <i>t</i>
	δ ^{13}C	37.4 <i>q</i>	74.3 <i>d</i>	21.9 <i>t</i>	36.5 <i>t</i>
3	δ ^1H	2.70 <i>s</i> 2.90 <i>s</i>	3.88 <i>t</i>	2.45 <i>q</i>	4.00 <i>t</i>
	δ ^{13}C	36.0 <i>q</i> 39.5 <i>q</i>	76.1 <i>d</i>	20.3 <i>t</i>	36.6 <i>t</i>

The shift differences for the phthalimido groups were not significant and consequently not incorporated in this table.

respectively, indicating diastereotopic¹² *Re*(*S*) or *Si*(*R*) sulphoxide methyls. Compound **3** is therefore the *d,l*-stereoisomer.

Inspection of possible conformations of both *meso*-isomers, **1** and **2**, on *Dreiding* models suggests that the (*s*)-*meso* form exerts more *gauche*¹³ interactions than the (*r*)-*meso* isomer. This is consistent with higher shielding observed for all C-atoms in the compound **1** (Table 2, ^{13}C NMR shifts). Compound **1**, *m.p.* 163–165 °C, is therefore the (*s*)-*meso* isomer, and compound **2**, *m.p.* 153–154 °C, the (*r*)-*meso* isomer.

In analogy to the resolution of alcohols through hydrogen phthalates¹⁴ in a preliminary experiment we prepared the α -phenylethylammonium salt of phthalamic acid **8** from *d,l*-disulphoxide **3**.



EXPERIMENTAL

M.p.s. are uncorrected, NMR spectra were recorded in CDCl_3 on Varian A-60, T-60 and XL-100 instruments. The chemical shifts are given in ppm from tetramethylsilane as an internal standard. Coupling constants are expressed in Hz (*s*, singlet; *d*, doublet; *t*, triplet; *q*, quartet). Off-resonance decoupling was used to distinguish between the primary, secondary, tertiary and quaternary C-atoms. Optical rotations were measured on a Bendix NPL Automatic Polarimeter 143 D. TLC was performed on Silica Gel 60 F_{254} (E. Merck, Darmstadt, Germany) in the solvent system CHCl_3 -MeOH (9:1), and the spots developed with 1% KMnO_4 -aq. solution. Organic sulphides and sulphoxides were detectable with this reagent as yellow spots on a pink background. In preparative TLC, Silica Gel PF_{254} Plates (20×20 cm, layer 1.00 mm, E. Merck) in the same solvent system were used.

1,1-Bis(methylthio)-3-phthalimidopropane (**4**) was prepared according to the earlier described procedure.³

Stereoisomers 1-3 of 1,1-bis(methylsulphinyl)-3-phthalimidopropane.

Method A: To a solution of sodium periodate (18 g, 0.084 mole) in distilled water (160 ml) and methanol (160 ml) cooled to -5°C , 1,1-bis(methylthio)-3-phthali-

midopropane (11.25 g, 0.04 mole) was added over 10 minutes while stirring. The solution was stirred at 0°C and the progress to the oxidation controlled by TLC. The separation of sodium iodate began immediately. After approximately 10 hours of stirring, some iodine started to separate, colouring the reaction mixture and indicating the end of the oxidation. The sodium iodate was filtered off and the filtrate extracted with CHCl_3 . The combined CHCl_3 extracts were extracted with 1% aq. sodium thiosulphate, washed with H_2O , dried (MgSO_4), and evaporated *in vacuo*. From the remaining pale yellow oil dissolved in boiling EtOH, the crystalline, *d,l*-isomer **3** separated immediately after cooling at room temperature. Crystallization from EtOH gave chromatographically pure colourless needles, m.p. 173–175°C, R_f 0.37, 39%.

Anal. $\text{C}_{15}\text{H}_{15}\text{O}_3\text{NS}_2$
 calc'd: C, 49.82; H, 4.82%
 found: C, 50.19; H, 4.85%

From the filtrate left over from the isolation of the crystalline *d,l*-isomer **3**, after several hours (depending on the concentration) prisms of the m.p. 155–159°C began to separate. Recrystallization from EtOH gave the pure (*s*)-*meso*-isomer **1**, m.p. 163–164°C, R_f 0.53, 20%.

Anal. $\text{C}_{15}\text{H}_{15}\text{O}_3\text{NS}_2$
 calc'd: C, 49.82; H, 4.82%
 found: C, 50.11; H, 5.01%

From the original ethanolic filtrate, a mixture of **1** and the (*r*)-*meso* isomer **2** subsequently began to crystallize as colourless plates, m.p. 150–153°C, which, after recrystallization from EtOH, gave the chromatographically pure **2**, m.p. 153–154°C, R_f 0.47, 24%.

Anal. $\text{C}_{15}\text{H}_{15}\text{O}_3\text{NS}_2$
 calc'd: C, 49.82; H, 4.82%
 found: C, 50.31; H, 4.93%

The combined ethanolic mother liquors were evaporated to dryness *in vacuo* and the remaining mixture of diastereomeric disulphoxides **1–3** was separated by TLC in CHCl_3 -MeOH (9:1).

Method B: 1(*S*)-(+)-monopercamphoric acid was prepared by oxidation of (+)-camphoric acid with sodium peroxide, acidification, and extraction with CHCl_3 ¹⁵. The titrated CHCl_3 solution of peroxy acid (2 moles) was added dropwise to a stirred CHCl_3 solution of 1,1-bis(methylthio)-3-phthalimido propane (**4**, 1 mole) with the temperature maintained at –10°C until the oxidant had disappeared (iodimetric test). At the end of the reaction (after 8–9 hrs.) the separated camphoric acid was filtered off, the CHCl_3 solution repeatedly extracted with saturated aqueous NaHCO_3 , washed with water, and dried (MgSO_4). Removal of the solvent gave a mixture of disulphoxides **1–3** (85–90%) with traces of 1-methylsulphenyl-1-methylthio-3-phthalimido propane.

Preliminary experiments for the preparation of the (–)- α -phenylethylammonium salt of phthalamic acid 8 from d,l-disulphoxide 3.

A mixture of disulphoxide **3** (m.p. 174–175°C, 160 mg, 5 mmoles), EtOH (1.5 ml), (–)- α -phenylethylamine (0.1 ml), and water (0.1 ml) was left at 60°C for 0.5 hr, evaporated *in vacuo*, and dried (room temp., 0.1 torr, overnight). The remaining oily residue of (–)- α -phenylethyl ammonium salt of the phthalamic acid **8**, dissolved in acetone and evaporated to dryness (220 mg) crystallized in rosettes. TLC: one spot, R_f 0.15.

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SAŽETAK

Stereoizomeri 1,1-bis(metilsulfinil)-3-ftalimido propana, posrednici u sintezi nor-trans-sulforafena. Gem-disulfidi i srodni spojevi, XXIV dio

Ante Deljac, Damir Huljev, Mira Novak i Krešimir Balenović

Opisana je priprava i izolacija stereoizomera **1–3**: 1,1-bis(metilsulfinil)-3-ftalimido propana. Konfiguracija spojeva **1**, **2** i **3** određena je ^1H i ^{13}C NMR spektroskopijom i mikrobiološkim oksidacijama dimetil merkaptala **4** s jednim sojem *Aspergillus niger*.

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Original Scientific Paper**Formation of γ -Methylthio- γ -butyrolactones from γ -Methylsulphanyl- γ -methylthiobutyric Acids. Gem-Disulphides and Related Compounds, Part XXV.¹**

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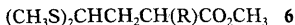
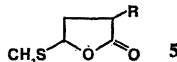
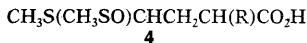
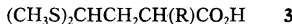
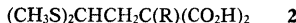
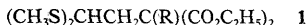
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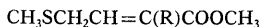
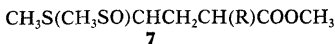
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Pyrolysis of butyric acids **4** [a: R, H; b: R, NHCOCH₃; c: R, o-C₆H₄(CO)₂N] gave the corresponding butyrolactones **5** in good yields. Structures of compounds **5** were determined by chemical and spectral methods. On the other hand, pyrolysed methyl esters of **4** afforded (*E*) and (*Z*) mixtures of the corresponding 4-methylthio-3-butenates **8**.

Earlier investigations in this Laboratory have shown that pyrolysis of 1-alkylsulphanyl-1-alkylthio derivatives afforded the corresponding *trans*-1-alkylthio-1-alkenes.² In our earlier attempts to synthesize (*E*)-2(*S*)-2-amino-4-methylthio-3-butenic acid (»Dehydromethionine«)³ we found that pyrolysis of α -acetamido- γ -methylsulphanyl- γ -methylthiobutyric acid (**4b**) unexpectedly gave α -acetamido- γ -methylthio- γ -butyrolactone (**5b**).⁴



+



a, R: H

b, R: NHCOCH₃c, R: o-C₆H₄(CO)₂Nd, R: NH₂

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Pyrolysis of carboxylic acids **4a** and **4c** gave γ -lactones **5a** and **5c** as well. Compounds **5a-c** have the molecular formulas expected for *trans*-1-alkylthio-1-alkenes but, according to their spectral properties, have γ -lactone structures: Lack of absorption bands in the region 1800–3000 cm^{-1} of the IR spectra, characteristics of carboxylic acids, as well as remarkably higher shifted carbonyl frequencies are in favour of the proposed γ -lactone structure. The NMR spectra are also consistent with this proposition. On the other hand, the pyrolysis of methyl esters **7** leads to the formation of (*E*), (*Z*)-mixtures of 1-alkylthio-1-alkenes **8** and of 1-alkylthio-2-alkenes.

The shift of the sulphinyl absorption from 1050–1020 cm^{-1} to 1000–945 cm^{-1} in γ -sulphinylbutyric acid derivatives **4a-c** indicates the presence of hydrogen bonding⁶ which may be important for the understanding of the pyrolytic reactions of these compounds. Spectral data are presented in Table 1.

Raney-nickel desulphurization gave the definite proof for the γ -lactone structure of compounds **5a** and **5b**: butyrolactone and DL-N-acetylhomoserine lactone, respectively, were obtained. Moreover, the synthesis of γ -methylthio-butylolactone (**5a**) with identical physical constants by spontaneous cyclization of γ -methylmercaptovinylacetic acid has been earlier described.⁷

Compounds **5b-c** can be considered as γ -lactones of hypothetical γ -hydroxymethionine or γ -methylthio-homoserine,⁸ respectively. Subsequent work in this laboratory has recently shown⁹ that the first step in the conversion of compounds **4** to γ -lactones **5** is the earlier described elimination of the methylsulphinyl group,^{2, 3} followed by the well-known intramolecular cyclization¹⁰ of the resulting unsaturated acid to **5**.

The series of *gem*-sulphides and sulphinyl derivatives of γ -substituted butyric acids **2a-4a** was completed with the preparation of 4,4-bis(methylsulphinyl)butyric acid **9** obtained through the one-step oxidation of **2a** with percamphoric acid.

Described conversion of **4** to **5** is an addition to the numerous and efficient syntheses of γ -lactones based on use of organosulphur compounds^{11, 12}.

EXPERIMENTAL

NMR and IR spectra were taken on Varian A-60 and Perkin-Elmer 137 instruments, respectively. Other analytical techniques were applied as described earlier.¹

Ethyl 2-ethoxycarbonyl-4,4-bis(methylthio) butyrate (**1a**).

β,β -Di(ethoxycarbonyl)propionaldehyde¹³ (4.6 g, 22.8 mmol), anhydrous zinc chloride (0.12 g), and methanthiol (2.2 g, 45.6 mmol) were heated in a sealed glass tube at 90°C for 4 hrs. After cooling, the reaction mixture was diluted with ether (20 ml) and washed with water (2 $\times$ 5 ml). After evaporating the dried (Na_2SO_4) ethereal solution under reduced pressure, the oily **1a**, (4.3 g, 67.2%, b.p. 115–125°C/0.1 torr) was obtained. Preparative TLC (silica gel, CHCl_3) afforded the analytical sample as a colourless oil (b.p. 80–85°C/0.03 torr).

Anal. $\text{C}_{11}\text{H}_{20}\text{O}_4\text{S}_2$ (280.40) calc'd: C 47.11; H 7.19%
found: C 47.39; H 7.38%

2-Carboxy-4,4-bis(methylthio) butyric acid (**2a**).

To a solution of ethyl 2-ethoxycarbonyl-4,4-bis(methylthio)-butyrate (**1a**, 5.6 g, 20 mmol) in ethanol (99%, 20 ml), a solution of Na_2CO_3 (7.48 g, 70 mmol) in water (60 ml) was added and the reaction mixture refluxed for 20 hrs (bath temp. 110°C). The volume of the reaction mixture was reduced by distillation to 1/3. Addition of hydrochloric acid (20%) to pH 5, extraction with diethyl ether (2 $\times$ 20 ml),

drying of combined ethereal extracts (Na_2SO_4), and removing of the solvent gave a viscous oil which crystallized on standing. Recrystallization from dichloromethane-petroleum ether gave **2a** (3.42 g, 95%, m.p. 95–102 °C). The analytical sample was obtained by recrystallization from the same solvent system, colourless crystals, m.p. 113–114 °C.

Anal. $\text{C}_7\text{H}_{12}\text{O}_4\text{S}_2$ (224.298) calc'd: C 37.42; H 5.39; S 28.59%
found: C 37.50; H 5.34; S 28.38%

4,4-Bis(methylthio)butyric acid (3a).

A solution of 2-carboxy-4,4-bis(methylthio)butyric acid (**2a**, 0.7 g, 31.12 mmol) in quinoline (10 ml) was heated under reflux at 110–130 °C (bath temp.) until development of CO_2 ceased. To the cooled reaction mixture, 5% aqueous NaOH was added to pH 10 and the quinoline removed with Et_2O (3×10 ml). The aqueous solution was acidified with 5% HCl aq. to pH 5 and extracted with Et_2O (3×10 ml). Drying of combined ethereal extracts (Na_2SO_4) removing of the solvent, and recrystallization afforded **3a** (0.5 g, 90%, m.p. 54–56 °C). The analytical sample was obtained from the same solvent system, colourless prisms, m.p. 54–56 °C.

Anal. $\text{C}_8\text{H}_{12}\text{O}_4\text{S}_2$ (180.288) calc'd: C 39.97; H 6.71%
found: C 40.27; H 6.77%

4-Methylsulphinyl-4-methylthiobutyric acid (4a).

To a solution of 4,4-bis(methylthio)butyric acid (**3a**, 1.8 g, 10 mmol) in Et_2O (30 ml), a solution of perbenzoic acid (10 mmol) in Et_2O (30 ml) was added dropwise under stirring. The temperature was kept at 0 °C. After standing at room temperature, the reaction mixture was left at 0 °C in an ice-box until crystallization of crude 4-methylsulphinyl-4-methylthiobutyric acid (**4a**, 1.5 g, 81%, m.p. 100–108 °C). The mixture of diastereoisomers was crystallized from dichloromethane-petroleum ether, colourless crystals, m.p. 110–111 °C.

Anal. $\text{C}_8\text{H}_{12}\text{O}_4\text{S}_2$ (196.288) calc'd: C 36.71; H 6.16%
found: C 36.73; H 6.11%

γ-Methylthio-γ-butyrolactone (5a).

4-Methylsulphinyl-4-methylthiobutyric acid (**4a**, 1.8 g, 10 mmol) on glass wool (Corning No. 800) was heated under reduced pressure (14 mm) in a micro-distillation flask at 160 °C. Pyrolysis was complete after 2 hrs. The yellow oily distillate (1.75 g) was purified by preparative TLC with CHCl_3 as solvent. γ -Methylthio- γ -butyrolactone (**5a**, 0.825 g, 62.5%, b.p. 115–120 °C (14 torr) was obtained.

Raney nickel desulphurisation of 5a.

γ -Methylthiobutyrolactone (**5a**, 0.3 g) in dry EtOH (15 ml) was refluxed with Raney nickel W-2[®] (3 g) for 3 hrs. The nickel was removed by filtration, washed with absolute EtOH (15 ml), and the combined filtrate and washings evaporated to dryness. After distillation, the oily residue afforded γ -butyrolactone (0.1 g) which was identical with the authentic specimen in every respect.

2-Acetamido-4-methylsulphinyl-4-methylthio butyric acid (4b).

To a solution of 2-acetamido-4,4-bis(methylthio)butyric acid¹ (1.18 g, 5 mmol) in methanol (5 ml) an ethereal solution of 1(S)-(+)-percamphoric acid (5 mmol) was added dropwise with stirring at –8 °C. The crystalline 2-acetamido-4-methylsulphinyl-4-methylthio butyric acid was filtered off and washed with Et_2O (0.8 g, 62%, m.p. 123–125 °C).

Anal. $\text{C}_8\text{H}_{15}\text{NO}_4\text{S}_2$ (253.33) calc'd: C 37.93; H 5.97%
found: C 38.08; H 6.25%

α-Acetamido-γ-methylthio-γ-butyrolactone (5b).

2-Acetamido-4-methylsulphinyl-4-methylthio butyric acid (**4b**, 0.2 g) was heated and distilled at 165–170 °C and 0.1 torr. The crude distillate (0.11 g, 75%) con-

sisting of α -acetamido- γ -methylthio- γ -butyrolactone (**5b**) was crystallized from dichloromethane-petroleum ether and the analytical sample (m. p. 121–122°C) was obtained.^{16,17}

Anal. $C_7H_{11}NO_3S$ (189.24): calc'd: C 44.43; H 5.86%
found: C 44.18; H 6.05%

2-Amino-4, 4-bis (methylthio) butyric acid (3d).

A solution of 2-acetamido-4,4-bis (methylthio) butyric acid¹ (1.18 g, 5 mmol) in 10% aqueous NaOH (11.8 ml) was heated under reflux for 18 hrs in a water bath. The cooled reaction mixture was filtered through Dowex-50 ion exchange resin and eluted with 2% aqueous pyridine. Evaporation of the eluate under reduced pressure gave 2-amino-4,4-bis (methylthio) butyric acid (**3d**, 0.85 g, m.p. 209–215°C). Recrystallization from water gave the analytical sample, colourless needles, m.p. 233–235°C (decomp.).

Anal. $C_8H_{13}NO_2S_2$ (195.29) calc'd: C 36.90; H 6.71%
found: C 37.30; H 6.70%

2-Phthalimido-4,4-bis (methylthio) butyric acid (3c).

A finely powdered mixture of 2-amino-4,4-bis (methylthio) butyric acid (**3d**, 1 g, 5.2 mmol) and phthalic anhydride (0.8 g, 5.4 mmol) was heated under stirring for 1 hr at 125°C. Recrystallization from EtOH — H₂O gave 2-phthalimido-4,4-bis (methylthio) butyric acid (**3c**, 1.24 g, 74.7%) with the m.p. 128–133°C. The analytical sample was recrystallized from EtOH — H₂O, m.p. 136–137°C.

Anal. $C_{14}H_{13}NO_5S_2$ (325.41): calc'd C 51.67; H 4.65%
found C 52.00; H 4.61%

2-Phthalimido-4-methylsulphinyl-4-methylthio butyric acid (4c).

An ethereal solution of 2-phthalimido-4,4-bis (methylthio) butyric acid (**3c**, 1.7 g, 5 mmol) was oxidized with 1 (S)-(+)-percamphoric acid (5 mmol) in diethyl ether at –5°C. The precipitate was recrystallized from methanol — diethyl ether, m.p. 163°C.

Anal. $C_{15}H_{15}NO_5S_2$ (341.41): calc'd C 49.25; H 4.42%
found C 49.02; H 4.31%

Preparation of a mixture of diastereomeric α -phthalimido- γ -methylthio- γ -butyrolactones (5c).

Pyrolysis of 2-phthalimido-4-methylsulphinyl-4-methylthio butyric acid (**4c**, 0.3 g, 1 mmol) was heated for 10 minutes at 165–170°C and 0.1 torr. The pyrolysate was recrystallized from EtOH and gave a mixture of diastereomeric α -phthalimido- γ -methylthio γ -butyrolactones (**5c**, 0.21 g, 88%) with the m.p. 135–140°C.¹⁷

Anal. $C_{15}H_{14}NO_5S$ (277.30): calc'd C 56.31; H 3.99; N 5.05; S 11.65%
found C 56.38; H 4.07; N 5.02; S 11.60%

4,4-Bis(methylsulphinyl)butyric acid (9)

To a solution of 4,4-bis(methylthio)butyric acid (**3a**, 0.9 g, 5 mmol) in methanol (40 ml) an ethereal 0.1 molar solution of 1(S)-(+)-percamphoric acid (100 ml) was added dropwise under stirring at 0°C. After removing the solvent under reduced pressure, the oily residue was washed with Et₂O, crystallization from absolute ethanol yielded 4,4-bis(methylthio)sulphinyl-butyric acid (0.8 g, 80%, m.p. 135–141°C). The analytical sample was obtained by recrystallization from the same solvent, colourless needles, m.p. 143–144°C.

Anal. $C_8H_{12}O_4S_2$ (212.29): calc'd: C 33.94; H 5.70%
found: C 33.90; H 5.94%

Methyl 4-methylsulphinyl-4-methylthiobutyrate (7a)

To a solution of 4,4-bis(methylthio)butyric acid (**3a**, 5.48 g, 30 mmol) in diethyl ether (10 ml) an ethereal solution of diazomethane was added at 0°C.

After the reaction had ended, the solvent was removed under reduced pressure and the reaction product distilled at 0.05 torr. The oily 4,4-bis(methylthio)-butyrate (4.83 g, 84%) was obtained, b.p. 60°/0.05 torr. For the oxidation of this compound two methods were used.

Method A: To a solution of methyl 4,4-bis(methylthio)butyrate (4.2 g, 21.7 mmol) in diethyl ether (30 ml) an ethereal solution of 1(S)-(+)-percamphoric acid (166.5 ml, 21.7 mmol) was added dropwise under stirring at 0°C. After standing at room temperature for 1 hr the diethyl ether was removed and CHCl_3 was added to the residue. The insoluble camphoric acid was filtered off and the filtrate evaporated under reduced pressure. The remaining viscous oil was subjected to preparative TLC (CHCl_3 — MeOH , 9 : 1). Pure methyl 4-methylsulphinyl-4-methylthiobutyrate (**7a**, 3.82 g, 98%) was obtained as a colourless viscous oil.

Anal. $\text{C}_8\text{H}_{14}\text{O}_3\text{S}_2$ (210.31): calc'd: C 39.97; H 6.71%
found: C 39.82; H 6.81%

Method B: To a solution of methyl 4,4-bis(methylthio)-butyrate (**3a**, 2.6 g, 13.4 mmol) in methanol (54 ml) cooled to 0°C, an aqueous solution of sodium periodate (54 ml, 2.87 g, 13.4 mmol) was added dropwise during 1 hr with stirring, the temperature being kept at 0°C. After two more hrs of standing at 0°C, the separated sodium iodate was filtered off. The filtrate was concentrated under reduced pressure to 50 ml and extracted with CHCl_3 (3×50 ml). The combined extracts were dried (Na_2SO_4) and evaporated to dryness. The remaining viscous oil was purified by precipitation from CH_2Cl_2 -petroleum ether. Pure methyl 4-methylsulphinyl-4-methylthiobutyrate (**7a**, 2.28 g, 81%) was obtained, which was identical with the product obtained by Method A.

Preparation of a mixture of (E) and (Z) methyl 4-methylthio-3-butenates (8a).

Methyl 4-methylsulphinyl-4-methylthiobutyrate (2.42 g, 1.5 mmol) on glass wool (Corning No. 800) was heated under reduced pressure (14 torr) in a micro-distillation flask at 140°C. The yellow oily distillate (1.64 g) dissolved in CHCl_3 was purified by filtration through a column of silica gel. A mixture of the (E) and (Z) methylthio-3-butenates (**8a**, 1.15 g, 70%) was obtained. The sample for analysis was distilled at 100°C and 14 torr.

Anal. $\text{C}_5\text{H}_{10}\text{O}_2\text{S}$ (146.21): calc'd: C 49.29; H 6.89%
found: C 48.70; H 6.78%

Hydrolysis of 8a: To a solution of **8a** (1.1 g, 8.3 mmol) in EtOH (40 ml), 0.1 N aqueous NaOH was added dropwise under stirring till the permanent pH 8. The reaction mixture was extracted with diethyl ether (3×50 ml) and the aqueous layer filtered through the ion exchanger Dowex-50. The eluate was extracted with diethyl ether (3×50 ml). The combined ethereal extracts were dried (Na_2SO_4) and evaporated. The residue (0.3 g) was precipitated from dichloromethane — petroleum ether and 0.6 g (60%) of a mixture of isomers of (E) and (Z) 4-methylthio-3-butenic acids and (E) and (Z) methyl 4-methylthio-2-butenic acids was obtained. The analytical sample was distilled at 80–90°C at 0.005 torr.

$\text{C}_5\text{H}_8\text{O}_2\text{S}$ (132.18): calc'd: C 45.43; H 6.10; S 24.26%
found: C 44.99; H 6.16; S 34.03%

Methyl 2-phthalimido-4,4-bis(methylthio) butyrate (6c).

Finely powdered 2-phthalimido-4,4-bis(methylthio) butyric acid (**3c**, 3.25 g, 1 mmol) was gradually added to an ethereal solution of diazomethane (prepared from 8 g of nitrosomethylurea) at 0°C. After standing for 1 hr at 0°C, the ethereal solution was evaporated to dryness under reduced pressure giving 3.2 g (95%) of methyl 2-phthalimido-4,4-bis(methylthio) butyrate (**6c**). The analytical sample, m. p. 93–94°C, was crystallized from ether — light petroleum.

Anal: $\text{C}_{15}\text{H}_{17}\text{NO}_5\text{S}_2$ (339.29) calc'd: C 53.07; H 5.05%
found: C 53.42; H 4.91%

Methyl-2-phthalimido-4-methylsulphinyl-4-methylthiobutyrate (7c).

To a solution of methyl-2-phthalimido-4,4-bis(methylthio) butyrate (**6c**, 1.69 g, 5 mmol) in diethyl ether (30 ml) a solution of perbenzoic acid (0.69 g, 5 mmol) in diethyl ether (30 ml) was added dropwise under stirring. The temperature of the reaction mixture was kept at -2°C . After standing at room temperature for 1 hr the ethereal solution was evaporated to dryness under reduced pressure. Crystallization from dichloromethane—ether afforded the pure methyl-2-phthalimido-4-methylsulphinyl-4-methylthio butyrate (**7c**), m.p. $151-152^{\circ}\text{C}$.

Anal: $\text{C}_{15}\text{H}_{17}\text{NO}_5\text{S}_2$ (355.29) calc'd: C 50.68; H 4.82%
found: C 50.47; H 4.69%

Preparation of a mixture of (E) and (Z) methyl 4-methylthio-2-phthalimido-3-butenates (8c)

Methyl 4-methylsulphinyl-4-methylthio-2-phthalimidobutyrate (**7c**, 0.35 g, 1 mmol) on glass wool (Corning No. 800) was heated under reduced pressure (0.05 torr) in a microdistillation flask at 160°C for half an hour. The oily reaction product was purified by preparative TLC (silica-gel — CHCl_3). Pure oily methyl 4-methylthio-2-phthalimido-3-butenate (**8c**, 0.21 g) was precipitated from diethyl ether — petroleum ether for analysis.

Anal: $\text{C}_{14}\text{H}_{13}\text{NO}_3\text{S}$ (291.33); calc'd: C 57.72; H 5.97%
found: C 57.38; H 6.25%

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Spectroscopic data of compounds 1a-c — 8a-c

TABLE 1.

Structure	^1H , NMR spectra (a)	I.R. (b)
$(\text{CH}_3\text{S})_2\text{CHCH}_2\text{CH}(\text{CO}_2\text{H})_2$, <u>1a</u>	1.26 (t, J=7.0 Hz, 6H, 2 CH_3); 2.08 (s, 6H, 2 SCH_3); 2.03-2.43 (m, 2H, CH_2); 3.56-3.90 (m, 2H, CH); 4.20 (q, J=7 Hz, 4H, 2 CH_2)	1740, 1450, 1375
$(\text{CH}_3\text{S})_2\text{CHCH}_2\text{CH}(\text{CO}_2\text{H})_2$, <u>2a</u>	2.11 (s, 6H, 2 CH_3); 1.90-2.50 (m, 2H, CH_2); 3.75 (t, J=7.65 Hz, 1H, CH); 3.96 (t, J=6.30 Hz, 1H, CH); 9.36 (s, 2H, 2 CO_2H)	3300-2400 1700, 1410
$(\text{CH}_3\text{S})_2\text{CHCH}_2\text{CH}_2\text{CO}_2\text{H}$, <u>3a</u>	2.13 (s, 6H, 2 CH_3); 1.90-2.26 (m, 2H, CH_2); 2.55-2.80 (m, 2H, CH_2); 3.71 (t, J=6.40 Hz, 1H, CH); 10.08 (s, 1H, CO_2H)	3300-2400, 1700, 1410
$(\text{CH}_3\text{S})_2\text{CHCH}_2\text{CH}(\text{R})\text{CO}_2\text{H}$ R=acetamido; <u>3b</u>	1.86 (s, 3H, COCH_3); 2.06 (s, 3H, SCH_3); 2.10 (s, 3H, SCH_3); 3.83 (t, J=7.9 Hz, 1H, CH(SCH_3)); 4.30 (m, 1H, CH-NH); 8.16 (d, J=8.1 Hz, 1H, NH)	3348, 2900-2500, 1705, 1630 (amide I) 1550 (amide II)
$(\text{CH}_3\text{S})_2\text{CHCH}_2\text{CH}(\text{R})\text{CO}_2\text{H}$ R=phthalimido; <u>3c</u>	2.04 (s, 3H, CH_3); 2.08 (s, 3H, CH_3); 2.63 (dd, J=7.6 Hz, J=7.0 Hz, 2H, CH_2); 5.28 (dd, J=7.0 Hz, J=7.3 Hz, 1H, CH); 7.85 (m, 4H, arom.H)	3300, 2900-2500 (CO_2H) 1615, 1540
$(\text{CH}_3\text{S})_2\text{CHCH}_2\text{CH}(\text{R})\text{CO}_2\text{H}$ R= NH_2 ; <u>3d</u>	1.21 (s, 6H, 2 SCH_3); 1.37-1.57 (m, 2H, CH_2); 3.12 (t, J=7.6 Hz, 1H, CHNH $_2$); 3.46 (t, J=6.5 Hz, 1H, CHSCH $_3$)	
$\text{CH}_3\text{S}(\text{CH}_3\text{SO})\text{CHCH}_2\text{CH}_2\text{CO}_2\text{H}$, <u>4a</u>	2.16 (s, 3H, SCH_3); 2.83 (s, 3H, SOCH_3); 1.76-2.73 (m, 4H, CH, CH_2); 3-7.3-4.03 (m, 1H, CH); 10.05 (s, 1H, CO_2H)	3300-2400, 1715, 1420
$\text{CH}_3\text{S}(\text{CH}_3\text{SO})\text{CHCH}_2\text{CH}(\text{R})\text{CO}_2\text{H}$ R=acetamido; <u>4b</u>	1.87 (s, 3H, COCH_3); 2.14 (s, 3H, SCH_3); 2.63 (s, 3H, SOCH_3); 2.07-2.39 (m, 2H, CH_2); 3.40 (dd, J $_1$ =J $_2$ =6 Hz, 1H); 4.63 (m, 1H, CH); 8.25 (d, J=8.5 Hz, 1H, NH)	3300 (NH), 2900-2500, 1725, 1670, 1535, 990, 940
$\text{CH}_3\text{S}(\text{CH}_3\text{SO})\text{CHCH}_2\text{CH}(\text{R})\text{CO}_2\text{H}$ R=phthalimido; <u>4c</u>	2.15 (s, 3H, SCH_3); 2.57 (1.3H, SOCH_3); 2.79-2.99 (m, 2H, CH_2); 3.87 (dd, J=3.2 Hz, 1H, CH); 5.20 (dd, J=2.7 Hz, J=3.0 Hz; 7.91 (m, 4H, arom.H)	2900-2500, 1730, 1390, 950

Table 1. (continued)

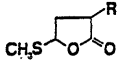
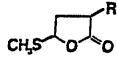
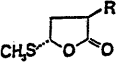
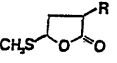
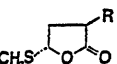
Structure	¹ H, NMR spectra (a)	I.R. (b)
 R=H; <u>5a</u>	1.86-2.58 (m, 4H, CH ₂ CH ₂); 2.11 (s, 3H, SCH ₃); 5.26 (t, J=6.0Hz, 1H, H-4)	1780 (C=O, lactone); 138, 1280
 R=acetamido; <u>5b</u> (±)-cis-	1.85 (m, 1H, CH ₂); 2.056 (s, 3H, COCH ₃); 2.31 (s, 3H, SCH ₃); 3.09 (m, 1H, CH ₂); 4.72 (ddd, J=11.20Hz, J=8.72Hz, 1H, CHNH, J=6.15Hz, H, CHNH); 5.49 (dd, J=5.66Hz, J=10.40Hz, 1H, H-4)	3320 (NH), 1780 (C=O, lactone)
 R=acetamido; <u>5b</u> (±)-trans	2.05 (s, 3H, COCH ₃); 2.28 (s, 3H, SCH ₃); 2.52-2.70 (m, 2H, CH ₂); 4.615 (ddd, J ₁ =J ₂ =9.74Hz, 1H, CHNH, J=6.64Hz, 1H, CHNH); 5.75 (dd, J ₁ =J ₂ =5.13Hz, 1H, H-4)	3320 (NH), 1780 (C=O, lactone)
 R=phthalimido; <u>5c</u> (±)-cis	2.37 (s, 3H, SCH ₃); 2.76-2.90 (m, 2H, CH ₂); 5.20 (dd, J=9.67Hz, J=11.44Hz, 1H, CH); 5.61 (dd, J=6.89Hz, J=9.81Hz, 1H, CH); 7.82 (m, 4H, arom.)	1780 (C=O, lactone) 1725, 1380
 R=phthalimido; <u>5c</u> (±)-trans	2.34 (s, 3H, SCH ₃); 2.36-3.26 (m, 2H, CH ₂); 5.26 (dd, J=10.25Hz, J=9.67Hz, 1H, CH); 5.89 (dd, J=8.20Hz, J=2.34Hz, 1H, CH); 7.82 (m, 4H, arom.)	1780 (C=O, lactone) 1725-1380
$(CH_3)_2CHCH_2CH_2CO_2CH_3$ <u>6a</u>	2.10 (s, 6H, 2SCH ₃); 1.95-2.66 (m, 2H, CH ₂); 2.57 (t, J=7.0Hz, 2H, CH ₂); 3.70 (t, J=7.8Hz, 1H, CH)	1740, 1450, 1375
$(CH_3)_2CHCH_2CH(R)CO_2CH_3$ R=phthalimido; <u>6c</u>	2.07 (s, 3H, SCH ₃); 2.11 (s, 3H, SCH ₃); 2.57-2.85 (m, 2H, CH ₂); 3.60-3.90 (m, 1H); 3.74 (s, 3H, OCH ₃); 5.36 (dd, J=J=6.04Hz, 1H, N-CH); 7.82 (m, 4H, arom.)	1740, 1725, 1380

Table 1. (continued)

Structure	^1H , NMR spectra (a)	I.R. (b)
$\text{CH}_3\text{S}(\text{CH}_3\text{SO})\text{CHCH}_2\text{CH}_2\text{CO}_2\text{CH}_3$ <u>7a</u>	2.18(s, 3H, SCH_3); 2.75(s, 3H, SOCH_3); 3.69 (s, 3H, OCH_3); 1.80-2.10(m, 2H, CH_2); 2.31-2.60(m, 2H, CH_2); 3.65-3.72(m, 1H, CH)	1740, 1440, 1210, 1180, 1035
$\text{CH}_3\text{S}(\text{CH}_3\text{SO})\text{CHCH}_2\text{CH}(\text{R})\text{CO}_2\text{CH}_3$ R=phthalimido; <u>7c</u>	2.27(s, 3H, SCH_3); 2.64(s, 3H, SOCH_3); 2.36-3.17(m, 2H, CH_2); 3.39(dd, $J=J=3.0\text{Hz}$, 1H, CH); 5.39(dd, $J=J=3.2\text{Hz}$, 1H, CH); 7.83(m, 4H, arom.)	
$\text{CH}_3\text{SCH}=\text{CHCH}(\text{R})\text{CO}_2\text{CH}_3$ R=H; <u>8a</u> cis/trans: 25/75	2.10(s, 3H, cis- SCH_3); 2.13(s, 3H, trans- SCH_3); 2.10/2.13 (by integration): 25/75; 2.84-3.30(m, 2H, CH_2); 3.42(s, 3H, OCH_3); 4.83-5.96(m, 2H, $\text{CH}=\text{CH}$)	1720, 1620, 1450, 1310, 1150, 930
$\text{CH}_3\text{SCH}=\text{CHCH}(\text{R})\text{CO}_2\text{CH}_3$ R=phthalimido; <u>8c</u> cis/trans: 31/69	2.27(s, 3H, trans- CH_3); 2.29(s, 3H, cis- SCH_3); 2.29/2.27 (by integration): 31/69; 3.76(s, 3H, OCH_3); 5.40-6.57(m, 3H, $\text{CH}=\text{CH}-\text{CH}$); 7.78(m, 4H, arom.)	1725, 1475, 1400, 730
$(\text{CH}_3\text{SO})_2\text{CHCH}_2\text{CH}_2\text{CO}_2\text{H}$ <u>9</u> mixture of <i>meso</i> , <i>meso</i> and <i>R, S</i> stereoisomers, cf. ref. 1		2900-2400, 1720, 1410, 1210, 1035

(a) All spectra were obtained in CDCl_3 except 3b and 4c ($\text{DMSO}-d_6$) and 3d ($\text{D}_2\text{O}-\text{HCl}$) with tetramethylsilane as an internal standard.

(b) Infrared spectra were recorded as film (liquids) or plates (solids).

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SAŽETAK

Nastajanje γ -metiltio- γ -butirolaktona iz γ -metilsulfinil- γ -metiltiomaslačnih kiselina. Gem-disulfidi i srodni spojevi, XXV dio

A. Deljac, V. Deljac, V. Vela i K. Balenović

Pirolizom maslačnih kiselina **4a-c** nastaju u dobrom iskorištenju odgovarajući butirolaktoni **5a-c**. Strukture tih spojeva određene su kemijskim i spektralnim metodama. Naprotiv, pirolizom metilnih estera istih maslačnih kiselina nastaju smjese (*E*) i (*Z*) isomera odgovarajućih 4-metiltio-3-butenoa **8**.

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