

*iso*Thiocyanates XXVI*. Straight-Chain ω -Methylthioalkyl *iso*Thiocyanates and some Derivatives

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The occurrence in plants of straight-chain compounds, containing a methylthio-grouping in terminal position, is briefly surveyed. Special attention is given to a number of *isothiocyanates* of this general type encountered in Nature.

The preparation as well as properties of the homologous series, $\text{CH}_2\text{S}(\text{CH}_2)_n\text{NCS}$, with values of n ranging from two to nine, are reported, together with the corresponding thiourea-derivatives resulting from interaction of the *isothiocyanates* with ammonia and benzylamine (Tables 1, 2 and 3).

The ω -methylthioalkylamines, (XXI), serving as intermediates in the syntheses of the mustard oils, are produced by varying methods and characterized as crystalline thiourea-derivatives formed upon reaction with phenyl *isothiocyanate* (Table 4).

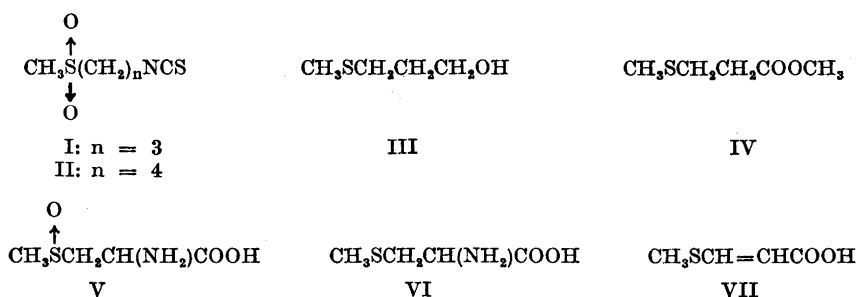
Comparison of a synthetic specimen of 1-benzyl-3-(9-methylthiononyl)-urea, (XXIII), with a product directly derivable from the *Arabis* mustard oil, on which we recently reported^{1*}, establishes beyond doubt the proposed structure of the latter as (-)-9-methylsulphinylnonyl *isothiocyanate* (XI).

The biosynthetic origin of the methylthio-grouping in natural products is briefly discussed.

About fifty years ago, Schneider isolated the *isothiocyanates* cheirolin¹ (I) and erysolin² (II) from seeds of the crucifers *Cheiranthus cheiri* L. and *Erysimum Perofskianum* Fisch. et M.**, respectively. The structural analogy of cheirolin and methionine was commented upon by Barger and Coyne³ in 1928 when these authors first announced the structure and synthesis of the new amino acid. Since then, an additional number of straight-chain compounds, having a terminally located methylthio-grouping in common, has been recognized in Nature. Thus, 3-methylthiopropanol (III), a constituent of soya-sauce⁴, methyl 3-methylthiopropionate (IV), present in the essential oil of pineapple⁵, and the adenythiomethylpentose recognized in yeast many years ago (cf. Ref.⁶), all belong to this structural type.

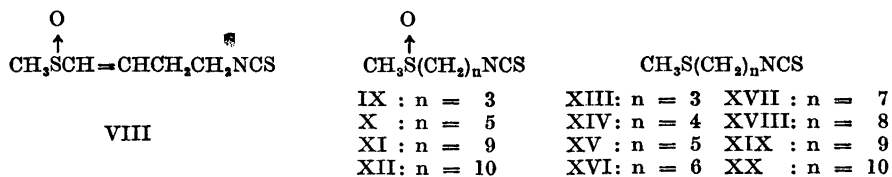
* Part XXV of this series: *Acta Chem.Scand.* 11 (1957) 577.

** Thus far, it has not been possible in this laboratory to confirm the occurrence of an erysoline glucoside in this or other botanical species.



Other examples can be adduced from more recent work. Independently, Syngé and Wood ⁷ and Morris and Thompson ⁸ announced the discovery of (+)-S-methyl-L-cysteine sulphoxide (V) in various crucifers, a finding recently supplemented by the discovery also of the corresponding S-methyl-L-cysteine (VI) as a constituent of higher plants ⁹. The stereoisomeric 3-methylthioacrylic acids (VII), demonstrated by Stoll *et al.* ^{9a} to occur as the acid moieties of two esters present in rhizomes of *Petasites officinalis* Moench, also deserve attention in this connexion.

Besides (I) and (II), a number of straight-chain isothiocyanates, carrying a terminal methylthio grouping as such or oxidized to the sulphoxide stage, has been encountered in various members of the family *Cruciferae*. Thus, Schmid and Karrer ¹⁰ established the structure (VIII) for sulphoraphene, derivable from a glucoside in radish seeds, whereas Schultz and Gmelin ¹¹ assigned the formula (IX) to a mustard oil enzymically liberated from an analogous glucoside in seeds of *Iberis amara* L. In this laboratory, 3-methylthiopropyl ¹² (XIII), 4-methylthiobutyl ¹³ (XIV) and 5-methylthiopentyl ¹⁴ (XV) isothiocyanates have been established as products of enzymic hydrolysis of glucosides present, *inter alia*, in seeds of *Iberis sempervirens* L., *Eruca sativa* Mill. and *Berteroa incana* (L.) DC., respectively. More recently, we have proved also the existence in Nature of glucosides corresponding to the levorotatory sulphoxide isothiocyanates, (X)–(XII), *viz.* in seeds of *Alyssum argenteum* Vitm. ¹⁵, *Arabis alpina* L. ¹⁶ and *Camelina sativa* (L.) Crantz ¹⁷, respectively. It appears likely that these sulphoxides should be regarded as secondary products, biogenetically deriving from the corresponding 5-methylthiopentyl (XV), 9-methylthiononyl (XIX) and 10-methylthio-decyl (XX) isothiocyanates.



On this background, and for various other reasons, it became desirable to have at disposal the individual mustard oils of the general series $\text{CH}_3\text{S}(\text{CH}_2)_n\text{NCS}$, with values of n ranging from two to nine. The present paper records the

Table 1. ω -Methylthioalkyl isothiocyanates, $\text{CH}_3\text{S}(\text{CH}_2)_n\text{NCS}$.

n	Formula	B.p.	mm Hg	n_D^{25}	Analyses					
					Carbon		Hydrogen		Nitrogen	
					Found	Calc.	Found	Calc.	Found	Calc.
2 ^a	$\text{C}_2\text{H}_7\text{NS}_2$	85	2	1.5767	36.00	36.07	5.18	5.30	10.66	10.52
3 ^b	$\text{C}_3\text{H}_9\text{NS}_2$	121	12	1.5610	40.35	40.77	5.98	6.16	9.64	9.51
4 ^c	$\text{C}_4\text{H}_{11}\text{NS}_2$	136 ^d	12	1.5518	44.59	44.68	6.75	6.87	8.51	8.69
5 ^c	$\text{C}_5\text{H}_{13}\text{NS}_2$	155	10	1.5422	48.25	47.97	7.51	7.48	8.09	7.99
6	$\text{C}_6\text{H}_{15}\text{NS}_2$	119	0.5	1.5336	50.75	50.77	7.76	7.94	7.43	7.40
7	$\text{C}_7\text{H}_{17}\text{NS}_2$	117	0.3	1.5274	53.50	53.16	8.41	8.43	6.82	6.89
8	$\text{C}_{10}\text{H}_{19}\text{NS}_2$	122	0.3	1.5242	55.25	55.25	8.46	8.81	6.50	6.45
9	$\text{C}_{11}\text{H}_{21}\text{NS}_2$	130	0.2	1.5189	56.95	57.10	9.09	9.15	6.05	6.05

^a Apparently, Weller *et al.*¹⁷ synthesized this compound, yet without presenting any physical or analytical data for the mustard oil. ^b *cf.* Ref.¹². ^c *cf.* Ref.¹³. ^d Reported b.p. 130–140°/9 mm²⁸. ^e *cf.* Ref.¹⁴.

preparation and properties of these isothiocyanates, together with data for the thiourea-derivatives formed upon their reactions with ammonia and benzylamine. For particular reasons, the symmetric *bis*-(ω -methylthioalkyl)-thioureas, wherein the alkyl represents hexyl, heptyl, octyl, and nonyl, have also been synthesized. In general, the isothiocyanates, (XIII)–(XIX), were produced from the corresponding amines by reaction with thiocarbonyl chloride in a slightly modified version of the traditional reaction. They all distilled as colourless, pungent oils possessing a characteristic taste and odour, reminiscent

Table 2. N-(ω -Methylthioalkyl)-thioureas, $\text{CH}_3\text{S}(\text{CH}_2)_n\text{NHCSNH}_2$.

n	Formula	M.p.°	Analyses					
			Carbon		Hydrogen		Nitrogen	
			Found	Calc.	Found	Calc.	Found	Calc.
2	$\text{C}_4\text{H}_{10}\text{N}_2\text{S}_2$	68	32.15	31.96	6.72	6.71	18.70	18.64
3 ^a	$\text{C}_5\text{H}_{12}\text{N}_2\text{S}_2$	66–67 ^b	36.60	36.55	7.30	7.36	16.98	17.06
4 ^c	$\text{C}_6\text{H}_{14}\text{N}_2\text{S}_2$	53 ^{d,e}	40.38	40.41	7.90	7.91	15.80	15.72
5 ^f	$\text{C}_7\text{H}_{16}\text{N}_2\text{S}_2$	67.5 ^e	43.70	43.71	8.22	8.39	14.35	14.57
6	$\text{C}_8\text{H}_{18}\text{N}_2\text{S}_2$	73	46.55	46.56	8.93	8.79	13.35	13.58
7	$\text{C}_9\text{H}_{20}\text{N}_2\text{S}_2$	79	49.20	49.05	9.09	9.15	12.55	12.71
8	$\text{C}_{10}\text{H}_{22}\text{N}_2\text{S}_2$	76	51.30	51.24	9.34	9.46	11.86	11.95
9	$\text{C}_{11}\text{H}_{24}\text{N}_2\text{S}_2$	88	53.07	53.10	9.74	9.81	11.28	11.08

^a *cf.* Ref.¹². ^b Recrystallized from a mixture of ethyl acetate and pentane. ^c *cf.* Ref.¹³. ^d Reported ²⁸ m.p. 55–56°. ^e Recrystallized from a mixture of chloroform and pentane. ^f *cf.* Ref.¹⁴.

Table 3. 1-Benzyl-3-(ω -methylthioalkyl)-2-thioureas, $C_6H_5CH_2NHCSNH(CH_2)_nSCH_3$.

n	Formula	M.p. ^o	Analyses					
			Carbon		Hydrogen		Nitrogen	
			Found	Calc.	Found	Calc.	Found	Calc.
2	$C_{11}H_{16}N_2S_2$	59 ^a	55.05	54.96	6.56	6.71	11.53	11.65
3	$C_{12}H_{18}N_2S_2$	57	56.77	56.65	6.93	7.13	11.07	11.02
4 ^b	$C_{13}H_{20}N_2S_2$	77–78 ^c	58.25	58.15	7.55	7.51	10.45	10.44
5 ^d	$C_{14}H_{22}N_2S_2$	56–57	59.45	59.54	8.06	7.85	9.97	9.92
6	$C_{15}H_{24}N_2S_2$	45	60.80	60.79	7.96	8.16	9.40	9.45
7	$C_{16}H_{26}N_2S_2$	64	61.85	61.90	8.34	8.44	8.95	9.02
8	$C_{17}H_{28}N_2S_2$	59	63.00	62.92	8.50	8.70	8.49	8.63
9	$C_{18}H_{30}N_2S_2$	73	63.86	63.87	9.01	8.93	8.18	8.28
10 ^e	$C_{19}H_{32}N_2S_2$	73	65.10	64.73	9.06	9.15	8.00	7.95

^a Crystallization of this previously described derivative²⁷ could be induced only after seeding with crystalline material (m.p. 58^o), kindly placed at our disposal by Dr. H. M. Sell. ^b *cf.* Ref.¹³. ^c Recrystallized from a mixture of ethyl acetate and pentane. ^d *cf.* Ref.¹⁵. ^e *cf.* Ref.¹⁷.

of those of fresh radish root. Physical and analytical data for the mustard oils are presented in Table 1, whereas the two series of thioureas are summarized in Tables 2 and 3. For the sake of completeness a few compounds, recorded in previous papers in this series, are included.

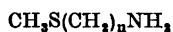
The requisite ω -methylthioalkylamines (XXI), whence the mustard oils derive, were synthesized by a number of different routes as briefly outlined in the sequel. 2-Methylthioethylamine (XXI, $n = 2$), the lowest member of the series, was obtained from ethyleneimine and methanethiol according to Wie-

Table 4. 1-Phenyl-3-(ω -methylthioalkyl)-2-thioureas, $C_6H_5NHCSNH(CH_2)_nSCH_3$.

n	Formula	M.p. ^o	Analyses					
			Carbon		Hydrogen		Nitrogen	
			Found	Calc.	Found	Calc.	Found	Calc.
2	$C_{10}H_{14}N_2S_2$	94	53.15	53.05	6.46	6.23	12.30	12.38
3	$C_{11}H_{16}N_2S_2$	87–88	54.90	54.96	6.60	6.71	11.87	11.65
4	$C_{12}H_{18}N_2S_2$	48–49 ^a	56.84	56.65	7.03	7.13	11.04	11.02
5	$C_{13}H_{20}N_2S_2$	67	58.31	58.15	7.45	7.51	10.68	10.44
6	$C_{14}H_{22}N_2S_2$	55	59.46	59.54	7.82	7.85	9.83	9.92
7	$C_{15}H_{24}N_2S_2$	55.5	60.76	60.79	8.25	8.16	9.50	9.45
8	$C_{16}H_{26}N_2S_2$	57–58	61.73	61.90	8.37	8.44	9.26	9.02
9	$C_{17}H_{28}N_2S_2$	44	62.90	62.92	8.59	8.70	8.78	8.63

^a Reported as an oil by Schmid and Karrer²⁸.

land *et al.*¹⁸ The synthesis of the following two homologues, (XXI, $n = 3$ and 4) was accomplished by lithium aluminium hydride reduction of the corresponding nitriles, as described in earlier papers from this laboratory^{19, 20}. Again, details on the preparation of 5-methylthiopentylamine (XXI, $n = 5$) were presented in a previous memoir¹⁴ of this series*. 6-Chlorohexanol was readily transformed into 6-methylthiohexanol, and the latter, in turn, into 6-chlorohexyl methyl sulphide which served as a common intermediate for the syntheses of 6-methylthiohexylamine (XXI, $n = 6$), *via* N-(6-methylthiohexyl)-phthalimide, and 7-methylthioheptylamine (XXI, $n = 7$), the latter resulting from lithium aluminium hydride reduction of 7-methylthioheptanenitrile. This, in turn, was accessible from the above chlorosulphide by employing the general conditions developed by Brändström²² for the synthesis of organic cyanides. 1,8-Octanediol was converted into its chlorohydrin as described elsewhere^{23, 24}. Again, the further transformations into 8-methylthiooctanol and 8-chloro-octyl methyl sulphide were accomplished according to established methods²⁵. The latter intermediate was processed to N-(8-methylthiooctyl)-phthalimide and 8-methylthiooctylamine (XXI, $n = 8$) in straight-forward reactions. Essentially the same procedure was employed in the preparation of 9-methylthiononylamine (XXI, $n = 9$), characterized as its N-benzoyl derivative, from N-(9-methylthiononyl)-phthalimide and the previously known 9-chlorononyl methyl sulphide²⁵. For the purpose of characterization, the whole series of amines was converted into crystalline phenylthioureas upon reaction with phenyl isothiocyanate. The properties of these derivatives are recorded in Table 4.



XXI



XXII: X = S
XXIII: X = O

The preparation of the thioureas, summarized in Tables 2 and 3, calls for no comments. It is of interest, however, that the synthetic preparation of 1-benzyl-3-(9-methylthiononyl)-thiourea, (XXII), permitted the unequivocal structure determination of the *levorotatory* mustard oil which we recently demonstrated to be liberated on enzymic hydrolysis of a glucoside in seeds of *Arabis alpina* L., and to which we assigned the structure (XI) on strong, though admittedly inconclusive, evidence¹⁶. On treatment of (XXII) with a solution of silver nitrate in dilute ethanol 1-benzyl-3-(9-methylthiononyl)-urea (XXIII) resulted. Its identity with the product of m.p. 99.5°, formerly attained by stepwise degradation of the natural mustard oil¹⁶, was established by mixed melting point determination and coinciding infra-red spectra. Hence, there remains no uncertainty as to the mustard oil, derivable from glucoarabin, being (–)-9-methylsulphinylonyl isothiocyanate (XI).

The numerous and diverse plant constituents, containing a terminal methylthio-grouping, raise the question as to a possible common biogenetic origin of

* Professor P. Karrer kindly informed us that analyses and physical constants for this amine have been recorded in 1950 from his laboratory in a thesis²¹ the existence of which we regret not to have known at the time our manuscript was submitted for publication.

the latter. Positive evidence in favour of any general pathway is lacking. It rather appears that more than one route is needed in order to account for the biosynthesis of these compounds. Thus, very little is known about methionine formation in higher plants, but in *E. coli* and *Neurospora* strains it proceeds, according to general belief, from cysteine and homoserine, *via* cystathionine, to homocysteine, followed by S-methylation of the latter (*cf.* Ref.²⁸). The recent observation by Wolff *et al.*²⁹, that an extract of yeast can accomplish an enzymic synthesis of S-methyl-L-cysteine from L-serine and methanethiol, indicates an alternative mode of introduction of the CH₃S-moiety, involving again, however, the exchange of a terminal hydroxy-grouping with a sulphur-containing fragment. In principle, the newly reported cysteine synthesis in yeast from serine and hydrogen sulphide³⁰ also fits this general scheme. Hence, the function of ω -hydroxyalkyl chains as intermediate stages in the biosynthesis of the various natural ω -methylthioalkyl isothiocyanates, or rather their glucosides, is an attractive possibility. The hypothesis further accommodates the appearance in Nature of several terminally unsaturated isothiocyanates, as well as of masked hydroxyalkyl species such as the 3-benzoyloxypropyl mustard oil lately recognized in this laboratory as a constituent arising from a glucoside in seeds of *Malcolmia maritima* (L.) R. Br.³¹ The investigations on the occurrence and biogenesis of isothiocyanates in higher plants are being continued in this laboratory.

EXPERIMENTAL

All melting points are uncorrected and determined in capillary tubes (soft glass) in a slowly heated bath.

Hexamethylene series

6-Methylthiohexanol. Methanethiol (27 g) was introduced into a solution of sodium (13 g) in methanol (350 ml). 6-Chlorohexanol³² (75 g) was slowly added to this solution, and the stirred reaction mixture was refluxed for 3 h. The salt was then filtered off, the methanol removed by distillation, and water was added to the residue to cause the alcohol to separate. After extraction with ether, it distilled as a colourless, hygroscopic oil, b.p. 125°/9 mm, n_D^{25} 1.4821 (Found: C 56.15; H 10.98; S 21.70. Calc. for C₇H₁₆OS: C 56.71; H 10.88; S 21.63). Yield: 71 g.

6-Chlorohexyl methyl sulphide. In a three-necked flask, provided with a sealed stirrer, reflux condenser and dropping funnel, was placed a solution of 6-methylthiohexanol (69 g) in dry chloroform (40 ml). Purified thionyl chloride (58 g) was added at such a rate as to maintain a steady reflux (about 2 h). Towards the end of the reaction occasional heating was needed to keep the desired refluxing rate. After removal of the solvent, the chlorosulphide was distilled *in vacuo*, b.p. 72–74°/0.3 mm (63 g, 81 %). Redistillation furnished a colourless specimen for analysis, b.p. 103–104°/9 mm, n_D^{25} 1.4818 (Found: C 50.60; H 9.08; S 19.39. Calc. for C₇H₁₆SCl: C 50.42; H 9.07; S 19.23).

N-(6-Methylthiohexyl)-phthalimide. A solution of 6-chlorohexyl methyl sulphide (30 g) and potassium phthalimide (36.5 g) in dimethylformamide (310 ml) was heated and stirred at 100° for 5 h. After cooling, ice water (300 ml) was added and the solution extracted thrice with 250 ml portions of ether. The combined ether extracts were washed with 0.5 N NaOH (300 ml), 0.5 N HCl (300 ml) and water (300 ml). On removal of the solvent from the dried extract a crystalline mass remained. Recrystallization from aqueous ethanol furnished essentially pure material (42 g, 84 %). An analytical specimen separated from pentane as colourless plates, m.p. 51° (Found: C 64.85; H 6.83; N 5.06. Calc. for C₁₆H₁₉NO₂S: C 64.95; H 6.90; N 5.05).

6-Methylthiohexylamine (XXI, $n = 6$). A solution of the phthalimide (39 g) in 96 % ethanol (250 ml) was refluxed for 1 h with 90 % hydrazine hydrate (7.8 g). After being digested with 7 N HCl (400 ml) for another hour the separated phthalhydrazide was removed by filtration. The filtrate was made alkaline with strong NaOH and the amine was extracted with ether (3 × 200 ml). The combined extracts were dried over solid KOH, the ether removed over a small column, and the 6-methylthiohexylamine distilled *in vacuo* care being taken to minimize its exposure to the atmosphere. The colourless amine was obtained in analytically pure form after one redistillation, b.p. 104–105°/10 mm, n_D^{25} 1.4814 (Found: C 56.85; H 11.58; N 9.40. Calc. for $C_7H_{17}NS$: C 57.08; H 11.64; N 9.51).

1,3-bis-(6-Methylthiohexyl)-thiourea. A solution of 6-methylthiohexyl isothiocyanate, prepared according to the general directions given below, and 6-methylthiohexylamine (1.5 mole) in ether, deposited on standing the symmetric thiourea as crystalline material, which was recrystallized thrice from aqueous ethanol before analysis, m.p. 41° (Found: C 53.60; H 9.51; N 8.31. Calc. for $C_{15}H_{33}N_2S_2$: C 53.55; H 9.59; N 8.33).

Heptamethylene series

7-Methylthioheptanenitrile. The reaction between 6-chlorohexyl methyl sulphide (16 g) and NaCN (7 g) was performed in polyethylene glycol (35 ml), essentially following the directions given by Brändström for analogous reactions²². The reflux temperature gradually rose from 180° to about 210° within half an hour, when it remained constant, indicating that the reaction had gone to an end. The organic cyanide was removed in a vacuum and redistilled to furnish 9.5 g (68 %) of a product, b.p. 135–137°/10 mm, n_D^{25} 1.4755, which, according to analyses, may have contained traces of the solvent (Found: C 60.30; H 9.68; N 8.00. Calc. for $C_8H_{17}NS$: C 61.09; H 9.61; N 8.91).

7-Methylthioheptylamine (XXI, $n = 7$). In a three-necked flask, equipped with a Hershberg-stirrer, reflux condenser, dropping funnel and nitrogen inlet, was placed a solution of $LiAlH_4$ (5.0 g) in anhydrous ether (100 ml). In nitrogen atmosphere, a solution of 7-methylthioheptanenitrile (9.8 g) in an equal volume of ether, was added at such a rate as to maintain a steady reflux. The reaction was completed by heating for an hour on the water bath. After cooling, water (6 ml) and 15 % NaOH (6 ml) were carefully added, the precipitate filtered off and thoroughly washed with liberal amounts of ether. The combined filtrates were dried over KOH pellets, the solvent removed over a small column, and the amine distilled. The colourless oil had b.p. 118°/10 mm, n_D^{25} 1.4799, (7.5 g, 75 %) (Found: C 59.30; H 12.12; N 8.68. Calc. for $C_8H_{17}NS$: C 59.59; H 11.88; N 8.69).

1,3-bis-(7-Methylthioheptyl)-thiourea. A pure specimen of this derivative, prepared exactly as described above for the lower homologue, was secured by repeated crystallizations from aqueous ethanol, m.p. 45° (Found: C 56.25; H 9.89; N 7.70. Calc. for $C_{17}H_{35}N_2S_2$: C 56.00; H 9.95; N 7.69).

Octamethylene series

8-Methylthiooctanol. This was prepared, essentially as described above for 6-methylthiohexanol, in 80 % yield from 8-chlorooctanol^{23, 24} and sodium methyl mercaptide. The alcohol distilled as a colourless oil, b.p. 143–145°/10 mm, n_D^{25} 1.4788 (Found: C 61.30; H 11.26; S 17.85. Calc. for $C_9H_{20}OS$: C 61.33; H 11.44; S 18.19). Previously recorded²⁵: b.p. 135–138°/10 mm.

8-Chlorooctyl methyl sulphide. 8-Methylthiooctanol was converted in 73 % yield into the chlorosulphide following the directions given above for the production of 6-chlorohexyl methyl sulphide. The colourless chloride distilled at 86°/0.2 mm, n_D^{25} 1.4783 (Found: C 55.50; H 9.83. Calc. for $C_9H_{19}ClS$: C 55.50; H 9.83). Ref.²⁵ reports: b.p. 113–116°/3 mm, n_D^{25} 1.4821.

N-(8-Methylthiooctyl)-phthalimide. This intermediate was prepared in 90 % yield from the chlorosulphide as described above for the analogous 6-methylthiohexyl-derivative. It separated from hexane in nacreous plates, m.p. 46° (Found: C 66.95; H 7.44; N 4.62. Calc. for $C_{17}H_{25}NO_2S$: C 66.86; H 7.59; N 4.59).

8-Methylthiooctylamine (XXI, $n = 8$). The amine resulted from hydrazinolysis of the phthalimide-derivative performed exactly as reported above for the hexamethylene compound. It distilled as a colourless oil, b.p. $133^\circ/10$ mm, n_D^{25} 1.4780 (Found: C 61.30; H 12.06; N 8.24. Calc. for $C_8H_{17}NS$: C 61.66; H 12.07; N 7.99).

1,3-bis-(8-Methylthiooctyl)-thiourea. This was prepared in the usual way and separated from aqueous ethanol in colourless needles, m.p. 52° (Found: C 58.30; H 10.21; N 7.06. Calc. for $C_{16}H_{34}N_2S_2$: C 58.10; H 10.27; N 7.14).

Nonamethylene series

9-Methylthiononanol. The preparation of a correctly analyzing specimen of this compound was performed from 9-chlorononanol²⁴ and methanethiol according to the established procedure²⁵, b.p. $161^\circ/12$ mm, m.p. 17° , n_D^{25} 1.4783. Yield: 82 %. Ref.²⁵ reports: b.p. $138-142^\circ/9$ mm, m.p. 22° .

9-Chlorononyl methyl sulphide. Upon reaction with thionyl chloride in the usual way, the foregoing alcohol furnished the chlorosulphide in satisfactory yield as a colourless liquid, b.p. $96^\circ/0.1$ mm, n_D^{25} 1.4775. Previously reported²⁵: b.p. $118-124^\circ/2$ mm, n_D^{25} 1.4811.

N-(9-Methylthiononyl)-phthalimide. This resulted in almost quantitative yield from the usual reaction of the chlorosulphide with potassium phthalimide. An analytical specimen separated from dilute ethanol in colourless plates, m.p. 69° (Found: C 67.60; H 7.61; N 4.29. Calc. for $C_{18}H_{25}NO_2S$: C 67.69; H 7.89; N 4.39).

9-Methylthiononylamine (XXI, $n = 9$). Hydrazinolysis in the usual way afforded an 80 % yield of 9-methylthiononylamine from the phthalimide-derivative, b.p. $145^\circ/11$ mm. Because of the extreme readiness of the amine to take up carbon dioxide from the atmosphere, it was preferred to perform the analyses on the crystalline *N-(9-methylthiononyl)-benzamide*, produced under ordinary Schotten-Baumann conditions. It separated from dilute ethanol as colourless needles, m.p. 50° (Found: C 69.20; H 9.12; N 4.70. Calc. for $C_{17}H_{27}NOS$: C 69.59; H 9.28; N 4.77).

1,3-bis-(9-Methylthiononyl)-thiourea. This derivative crystallized in colourless needles from dilute ethanol, m.p. 60° (Found: C 60.20; H 10.60; N 6.42. Calc. for $C_{21}H_{31}N_2S_2$: C 59.94; H 10.54; N 6.66).

1-Benzyl-3-(9-methylthiononyl)-urea (XXIII). An ethanolic solution of 1-benzyl-3-(9-methylthiononyl)-thiourea (cf. Table 3) (581 mg) was treated on the steam bath with another solution, containing silver nitrate (585 mg) in 50 % ethanol. Gradually, enough 1 N NaOH was added to keep the mixture at pH 7. After filtering off precipitated silver sulphide, water was added to the filtrate resulting in precipitation of the urea, which was collected and recrystallized twice from ethyl acetate (Found: C 66.95; H 9.47; N 8.53. Calc. for $C_{18}H_{30}N_2OS$: C 67.02; H 9.38; N 8.68). The colourless product had the m.p. 99.5° , alone or in admixture with a specimen obtained by step-wise degradation of the *Arabis* mustard oil derivative¹⁸. Coinciding infra-red spectra further served to establish the identity of the two specimens.

General synthetic methods

isothiocyantes $CH_3S(CH_2)_nNCS$ ($n = 2-9$). The following procedure was adopted as a standard method of converting the ω -methylthioalkyl amines into the corresponding mustard oils.

To a solution of thiocarbonyl chloride (0.02 mole) in chloroform (20 ml) was added the appropriate amine (0.02 mole) and 12 ml of a 5 % solution of sodium bicarbonate. An exothermic reaction set in upon mixing the components and the flask was thoroughly shaken until all thiophosgene had disappeared (about 10 min). The yellow chloroform layer was separated and the aqueous phase extracted with two additional portions of chloroform. After removal of the solvent, distillation *in vacuo* furnished the mustard oil as a colourless or slightly yellow liquid. In all preparations, considerable quantities of dark-brown by-products were formed, accounting for the fact that yields never exceeded 50 %. Most likely, however, runs on a larger scale would proceed in more satisfactory yields. The physical and analytical data of the individual *isothiocyantes* are summarized in Table 1.

Thioureas. All mono-substituted thioureas (Table 2) were obtained in practically quantitative yields by keeping the *isothiocyanates* overnight at room temperature in methanol, saturated with ammonia. The mostly oily products, remaining upon removal of the solvent, crystallized on chilling and scratching. The thioureas were recrystallized to constant melting points from aqueous ethanol, when not otherwise indicated. Their properties are presented in Table 2.

Similarly, reaction of the *isothiocyanates* in anhydrous ether with 1.5 molecular proportion of benzylamine at room temperature furnished the benzylthioureas in high yields. Analytical specimens, produced by repeated recrystallizations from aqueous ethanol, possessed the properties recorded in Table 3.

The phenylthioureas, summarized in Table 4, were obtained by reaction of the ω -methylthioalkylamines (XXI) with slightly less than one equivalent of phenyl *isothiocyanate* in ether solution at reflux temperature for 2 h. The mostly oily, crude products crystallized usually in contact with a few drops of dilute HCl. Some of the products, however, needed cooling to -80° for crystallization to commence. Again, aqueous ethanol was the preferred solvent for recrystallization of the derivatives to constant melting points.

Paper chromatography. The mono-substituted thioureas (Table 2) could be chromatographed on paper according to our previously published method²³, yet modified to the descending technique. Using Whatman paper No. 1, and water-saturated chloroform as the mobile phase, the thioureas, containing 2, 3, 4, 5 and 6 methylene-groupings, could be clearly distinguished, possessing the R_{Ph} -values²³: 0.58, 0.83, 0.99, 1.12 and 1.15, respectively. The higher members of the series travelled too near the solvent front to make a clean separation possible in this solvent system. It was found, however, that on paper chromatography with formamide as the stationary and chloroform as the mobile phase, a complete and satisfactory separation of even the long-chain thioureas was easily achieved.

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