

Mass Spectra of Isothiocyanates

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The mass spectra of 40 diversely substituted isothiocyanates have been examined and a number of characteristic features noted, which should prove helpful in the micro-identification of naturally derived or synthetic isothiocyanates. Thus all of the alkyl isothiocyanates exhibit a peak at m/e 72 corresponding to the ion CH_2NCS^+ . Lower alkyl isothiocyanates exhibit an m/e 59 ion (NCSH^+), while higher ones (beyond pentyl) show $M-33$ (loss of SH) and m/e 115 fragments. Branching in the α - or β -positions as well as introduction of unsaturation into the alkyl portion are easily detected by mass spectrometry. Introduction of a methylthio substituent — so common among naturally derived isothiocyanates — drastically changes the mass spectral behaviour, which can again be correlated with the size of the alkyl fragment separating the methylthio substituent from the isothiocyanate grouping. The mass spectra of some isothiocyanates containing aromatic substituents are also reported.

Isothiocyanates derived from glucosidic progenitors in higher plants have been studied extensively in recent years (*cf.* Ref.¹) and their fast and reliable identification is a matter of considerable interest. Micro-identification procedures would be highly desirable for this purpose and since mass-spectrometry would satisfy these criteria, the mass spectra of an extensive series of naturally derived as well as synthetic isothiocyanates were measured. Bailey *et al.*² reported previously the mass spectrum of allyl isothiocyanate in connection with a study of flavour constituents in cabbage, and one of the present authors recently utilized mass spectra for the identification of a naturally

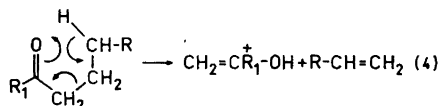
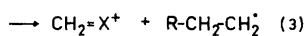
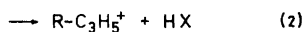
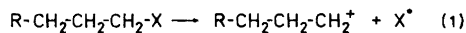
* Part LI of a series of papers on isothiocyanates; for paper I, see P. Friis and A. Kjær: *Acta Chem. Scand.* 17 (1963) 1515.

** Part XXIX of a series of papers on "Mass Spectrometry in Structural and Stereochemical Problems"; for paper XXVIII, see L. Olivier, J. Levy, J. Le Men, M. M. Janot, C. Djerassi, H. Budzikiewicz, J. M. Wilson, and J. L. Durham, *Bull. Soc. Chim. France* 1963 646.

derived keto-isothiocyanate;³ otherwise, mass spectra of mustard oils do not seem to have been recorded. As shown below, several correlations between mass spectral fragmentation behaviour and structure could be made and there is little doubt that this physical tool, possibly combined with vapour phase chromatography, may prove to be uniquely useful for the rapid characterization of naturally occurring isothiocyanates. In a number of instances, hydrogen rearrangements were observed, for which plausible paths are postulated. A detailed examination of such hydrogen transfers is reserved for a subsequent paper, where the synthesis and mass spectra of suitably deuterated isothiocyanates will be considered.

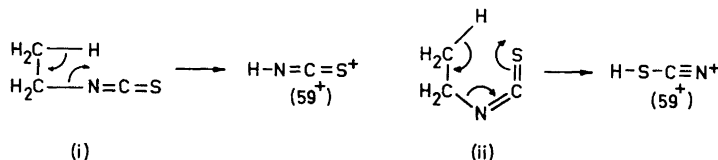
STRAIGHT CHAIN ALKYL ISOTHIOCYANATES

The normal alkyl isothiocyanates comprise the largest single group of the compounds studied, and these shall be considered first. In this consideration it is possible to make comparisons with the published spectra of a large number of monofunctional derivatives of the aliphatic hydrocarbons.⁴ Among those compounds whose spectra are reported the most common processes are fissions of the bonds α or β to the functional group as follows.

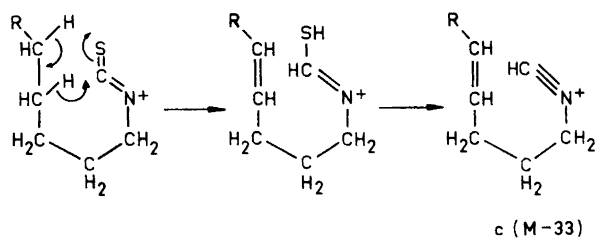


As can be seen in Fig. 1 fission α to the isothiocyanate group is not favoured except in the case of the lower members of the series. Ions of the type $\text{C}_n\text{H}_{2n+1}^+$ ($M-58$) are not found where n is greater than 5. It is noticeable that in the higher members of the series there is no appreciable increase in the hydrocarbon character of the mass spectra as was found in the case of the aliphatic nitriles.⁵ α -Fission with rearrangement and with ionization of either the isothiocyanate-containing fragment, or the moiety nominally corresponding to the olefin ions, is found only with the smaller molecules. This process can be formulated as taking place via a six-membered-ring transition state* similar

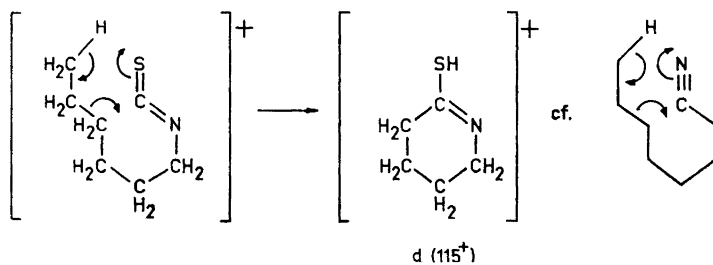
* There exists also the possibility of a four-membered (i) rather than six-membered (ii) intermediate. The two possible products, HNCS^+ and HSCN^+ , have similar ΔH_f values, so a decision between the two could not be made in ethyl isothiocyanate by measuring the appearance potential of the m/e 59 ion (R. C. Shenkel, B. G. Hobrock and R. W. Kiser *J. Phys. Chem.* **66** (1962) 2074).



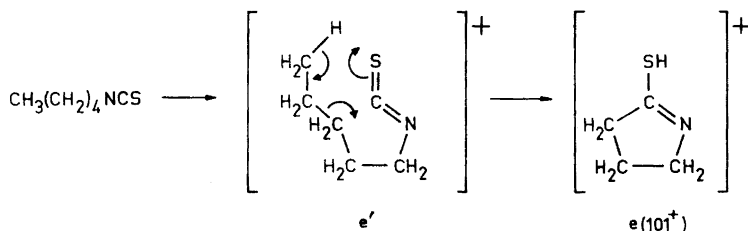
In the mass spectrum (Fig. 1) of pentyl isothiocyanate there is a peak at m/e 96 which cannot be described as being analogous to any peak in the spectra of its lower homologues. In a molecule of this formula this peak can only correspond to the loss of SH from the molecular ion. Analogous M-33 peaks are found in the spectra of the higher compounds; the intensity of these increases with the molecular weight of the parent compound. It is impossible to decide definitely the origin of the hydrogen atom which is lost with the sulfur atom, without examining the spectra of deuterated analogues. However, the fact that this cleavage requires a carbon chain of five atoms suggests that a hydrogen on C-5 is involved. The following scheme appears plausible.



In the spectrum of hexyl isothiocyanate and its higher homologues there is a peak at m/e 115, whose intensity increases with increasing molecular weight. In the case of the hexyl compound this corresponds to the loss of ethylene (the only plausible interpretation of 28 mass units in such a compound). The mechanism shown gives an explanation of striking difference in this mass region between the spectra of pentyl and hexyl isothiocyanates. It is also rather similar to that suggested for the formation of the ion of m/e 97 in nitrile spectra.⁵ In both cases it might be expected that the linear geometry of the functional group might prevent formation of such an intermediate, but linearity may not be retained in the excited molecular ion which is the precursor of this intermediate.



The lower homologue of the m/e 115 fragment ion is found at m/e 101. It is present in the spectrum of pentyl isothiocyanate, where it is impossible to form the m/e 115 ion (*d*), and must be formulated as having a five-membered ring (*e*). The greater deviation from linearity required to form the intermediate (*e'*) is probably responsible for the much lower abundance of *e* as compared to *d*.



One other peak of interest is found at m/e 96 and appears only when the aliphatic chain is eight or more carbon atoms long. Although the elemental constitution of this ion has not been determined, from simple considerations of mass number it seems probable that it does not contain sulphur. We hope to settle the nature of this fragment by the synthesis of suitably deuterated analogues.

BRANCHED ALKYL ISOTHIOCYANATES

In the branched-chain alkyl isothiocyanates there are few exceptions to the patterns of behaviour found among the normal chain compounds. In the spectra (Fig. 2) of the two α -branched compounds, isopropyl and *sec*-butyl

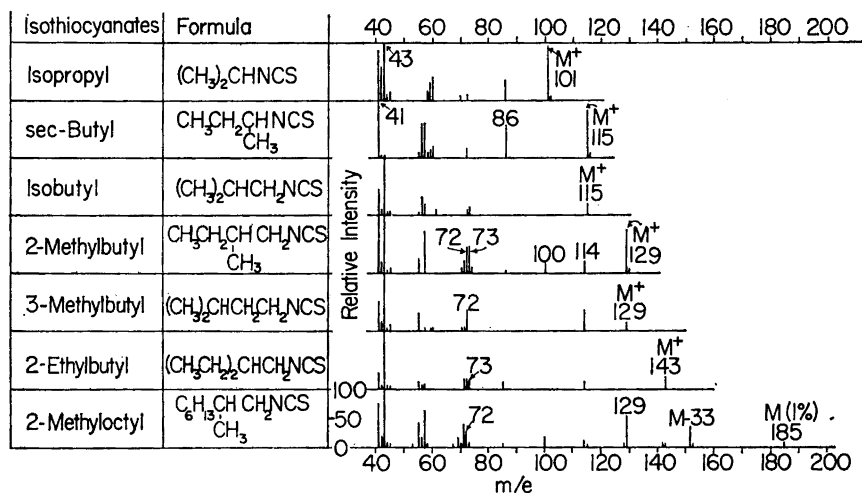
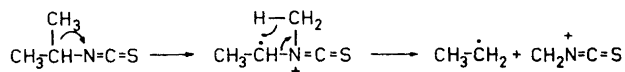


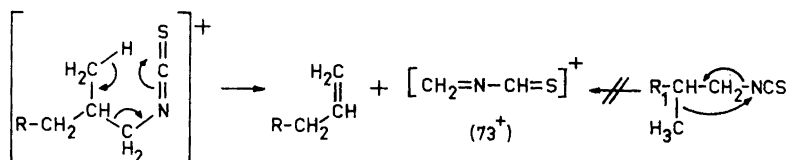
Fig. 2. Mass spectra of branched alkyl isothiocyanates.

isothiocyanates, the ion b now appears at m/e 86 as would be expected for the ion $\text{CH}_3\text{CH}=\text{NCS}^+$ obtained by β -fission. There is, however, a peak at m/e 72 in both cases. This must be due to CH_2NCS^+ which can only be formed by a rather involved rearrangement process. There is an analogy in the formation of the C_2H_5^+ ion in the mass spectrum of isobutane,⁸ which has been studied with the use of labelled compounds.⁹ This involves a rearrangement

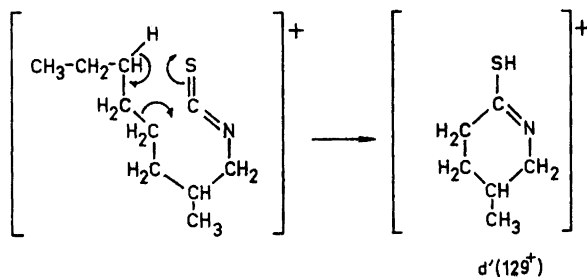
in which all the carbon atoms of isobutane become equivalent, but a more specific process is probable in the case of the isothiocyanates, *e.g.* transfer of an α -methyl group to the nitrogen as shown. This hypothesis could be tested by labelling in the α -position.



In the spectra of the four β -branched compounds, there occurs along with the peak at m/e 72 another one at m/e 73. This must be produced by the other possible six-membered ring transition state of type (4). In these four compounds there are a larger number of hydrogen atoms available for transfer than in the straight-chain analogues. Another possibility involving methyl migration could be excluded, because there exists no peak at m/e 87 (corresponding to $\text{C}_2\text{H}_5\text{NCS}^+$) in the spectrum (Fig. 2) of 2-ethylbutyl isothiocyanate, which was synthesized for this specific purpose.



It is interesting to note that in the spectrum (Fig. 2) of 2-methyloctyl isothiocyanate, there are found strong peaks at m/e 152 (*c*: $\text{M}-33$) and m/e 129 (*d'*). These are consistent with the earlier discussed fragmentation of long-chain alkyl isothiocyanates (Fig. 1), while only a weak m/e 73 peak — associated with β -branching — is noted. Clearly, the former type of fragmentation is preferred when both paths are available.



So far it has not been possible to predict the direction of cleavage at the branched carbon atom. Loss of an alkyl branch is found in all cases except in isobutyl isothiocyanate, where the predominant peak is m/e 43 (C_3H_7^+). The difference is probably determined by the stability of the latter ion with respect to the other products of branch cleavage.

METHYLTHIOALKYL ISOTHIOCYANATES

In Fig. 3 are shown the mass spectra of some straight-chain methylthioalkyl isothiocyanates. In all cases except one (3-methylthiopropyl isothiocyanate)

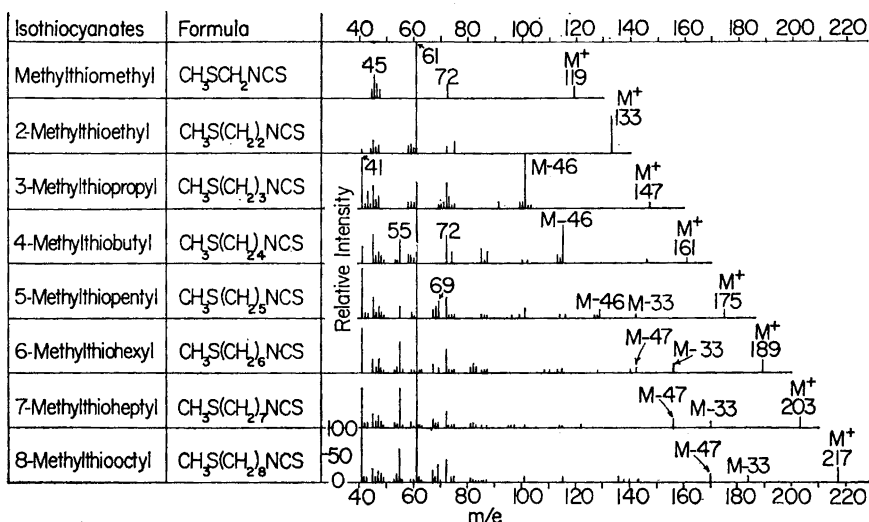
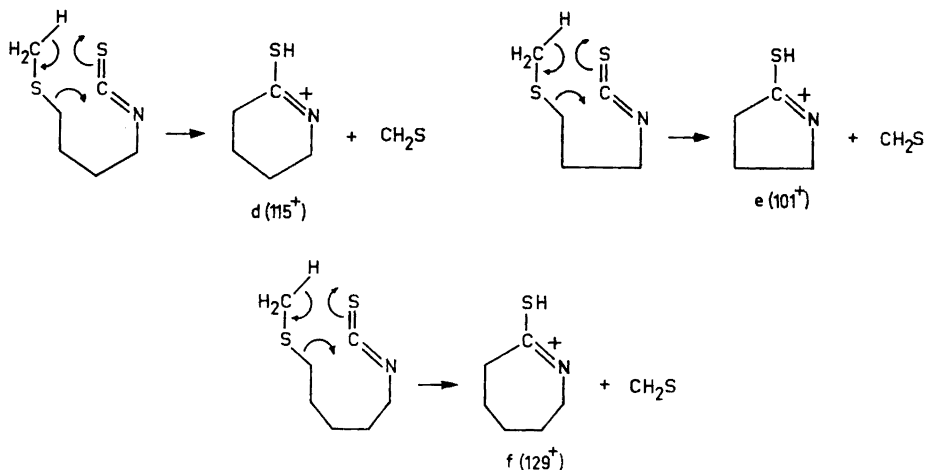


Fig. 3. Mass spectra of ω -methylthioalkyl isothiocyanates.

the base peak occurs at m/e 61 which is also the base peak of all simple alkyl methyl sulphides.¹⁰ This is a typical example of type (3) β -fission with stabilisation of the resultant ion as $\text{CH}_3\text{S}^+=\text{CH}_2$. Many of the peaks at m/e 41, 55 and 69 (C_3H_5^+ , C_4H_7^+ and C_5H_9^+) are present in the thioether spectra but not those (see Fig. 1) at m/e 43 and 57 (C_3H_7^+ and C_4H_9^+). This is to be expected since formation of one of the latter ions from a methylthioalkyl isothiocyanate would involve transfer of a hydrogen from a fragment containing an electronegative atom to one containing only carbon and hydrogen. In all cases the $\text{CH}_2^+=\text{NCS}$ ion is present at m/e 72.

In the spectrum (Fig. 3) of methylthiopropyl isothiocyanate the base peak is at m/e 101 rather than m/e 61. In the next higher (butyl) homologue there is an intense peak at m/e 115. Both peaks represent the loss of 46 mass units (equivalent to thioformaldehyde) from the molecular ion, and they could be produced by a mechanism similar to that invoked for the formation of ions *d* and *e* in the alkyl isothiocyanate series. The next homologous peak occurs at m/e 129 in the spectrum of methylthiopentyl isothiocyanate. Its low intensity is a consequence of the lower probability of formation of the necessary seven-membered ring (*f*).

It is noticeable that when the thioether function becomes further removed from the isothiocyanate group the m/e 101 and 115 peaks reappear as does the M-33 peak. Again the requirements of carbon chain length for forma-



tion of these ions are the same, as are found (Fig. 1) for the higher alkyl isothiocyanates: C_5 for $M-33$ and m/e 101, C_6 for m/e 115. In the spectra of the higher homologues there is a peak at $M-47$ which must be due to the loss of SCH_3 .

UNSATURATED ISOTHIOCYANATES

In the spectra of the unsaturated isothiocyanates (Fig. 4) allylic fission dominates. Where the allylic bond is α to the nitrogen atom (first four examples

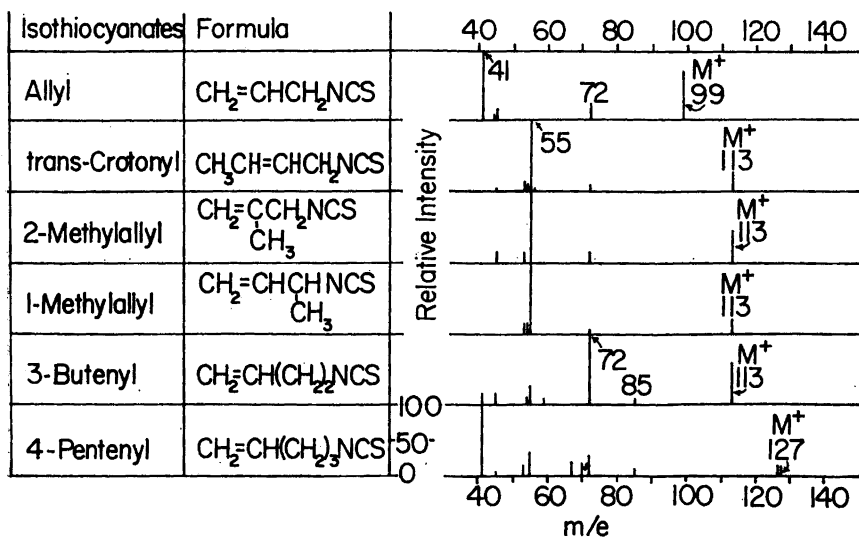
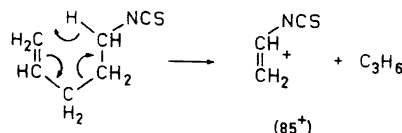


Fig. 4. Mass spectra of alkenyl isothiocyanates.

in Fig. 4), the most abundant ion will be the allyl ion at m/e 41 or 55. When the allylic bond is β to the nitrogen atom, as in the case of 3-butenyl isothiocyanate, the predominant ionized fragment is $\text{CH}_2=\overset{+}{\text{NCS}}$ at m/e 72. Finally, where a γ -relationship exists as in 4-pentenyl isothiocyanate, the most abundant ion is the allyl ion C_3H_5^+ . This behaviour is consistent with our knowledge of the behaviour of the saturated compounds, *i.e.* that CH_2NCS^+ is a much more stable ion than NCS^+ or $\text{CH}_2\text{CH}_2\text{NCS}^+$. In the spectrum of the last-mentioned compound, the peak at m/e 85 can be explained by postulation of a process similar to that invoked for the formation of the ion of m/e 42 in the spectrum of pent-1-ene.



AROMATIC ISOTHIOCYANATES

In the spectra (Fig. 5) of the aromatic isothiocyanates similarities can be found to the behaviour of other aromatic compounds. The most intense peak

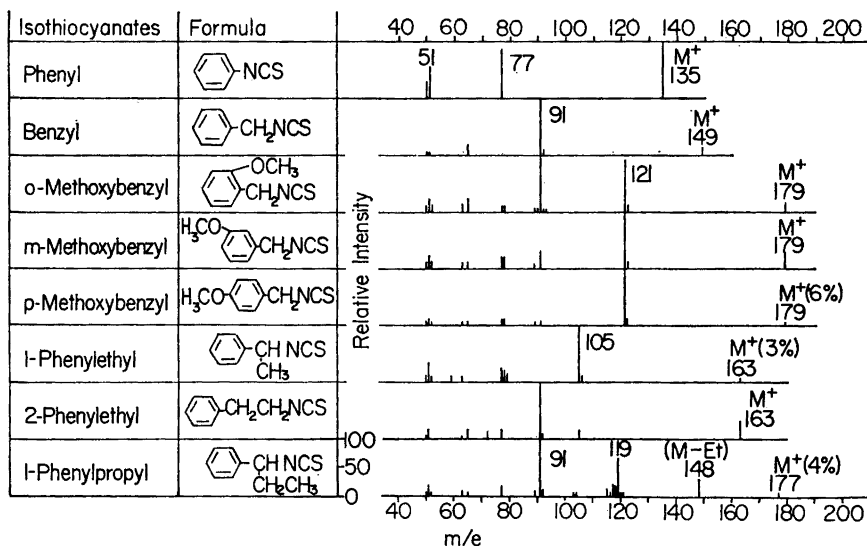


Fig. 5. Mass spectra of aromatic isothiocyanates.

in the spectrum of phenyl isothiocyanate is C_6H_5^+ (m/e 77) which is formed by fission of the only single bond in the molecule. As was found with the allyl isothiocyanates, the fragment NCS^+ does not appear as an ion to any great extent. The behaviour of the benzyl homologue is similar except that the increased lability of a benzylic over a phenylic bond is reflected in the lower

Several of the compounds were specifically synthesized in connection with current studies of naturally derived isothiocyanates, including 2-butyl,¹⁷ 2-methylbutyl,¹⁷ methylthiomethyl,¹⁸ 2-methylthioethyl,¹⁹ 3-methylthiopropyl,²⁰ 4-methylthiobutyl,²¹ 5-methylthiopentyl,²² 6-methylthiohexyl,¹⁹ 7-methylthioheptyl,¹⁹ and 8-methylthiooctyl isothiocyanate.¹⁹ Again, *trans*-crotyl,²³ 1-methylallyl,²³ 2-methylallyl,²³ 3-butenyl,²³ and 4-pentenyl isothiocyanate²⁴ were species prepared for similar purposes. Of the aromatic mustard oils, *o*-methoxybenzyl,²⁵ *m*-methoxybenzyl,²⁶ and *p*-methoxybenzyl isothiocyanate²⁷ were synthesized as reference samples for these studies.

The majority of the products utilized for mass spectrometry were analytical specimens, proved to be homogeneous on vapour phase chromatography.

The following three isothiocyanates were prepared for the first time in connection with the present studies.

(\pm)-1-Phenylpropyl isothiocyanate. (\pm)-1-Phenylpropylamine (5.4 g), prepared from propiophenone by the Leuckart-reaction, was dissolved in chloroform (50 ml) and added, in the course of 2 h, to an ice-cooled solution of thiocarbonyl chloride (6.9 g) in chloroform (200 ml).

Excess chloroform and thiocarbonyl chloride were distilled through a column, and the residue was distributed between ether and dilute HCl. From the aqueous phase, unchanged amine (2.2 g) was recovered. After removal of the solvent, the isothiocyanate was distilled twice to give a pure specimen (58 % yield, based on unrecovered amine), as a colourless oil, b.p. 128–129°/9 mm, n_D^{25} 1.5717 (Found: C 67.86; H 6.31; N 7.92. Calc. for C₁₀H₁₁NS: C 67.75; H 6.26; N 7.90).

On reaction with ammonia, the isothiocyanate was converted into 1-(1-phenylpropyl)-thiourea, m.p.* 135–136° (Found: C 61.71; H 7.40; N 14.29; Calc. for C₁₀H₁₄N₂S: C 61.80; H 7.26; N 14.42). The corresponding phenylthiourea was formed on reaction with aniline, m.p. 128°. (Found: C 71.24; H 6.78; N 10.48. Calc. for C₁₆H₁₈N₂S: C 71.08; H 6.71; N 10.36).

2-Ethylbutyl isothiocyanate. 2-Ethylbutanenitrile, prepared in 70 % yield from 2-ethylbutyric acid *via* the acid chloride and amide, essentially as described elsewhere,²⁸ served as a convenient starting material for the synthesis of 2-ethylbutylamine, required for production of the mustard oil.

The nitrile (13.4 g) was reduced with lithium aluminium hydride (7.8 g) in ether solution (200 ml) in the usual way to give a 74 % yield of distilled 2-ethylbutylamine, b.p. 124°, n_D^{25} 1.4200 (Lit. values: b.p. 121–122°/725 mm,²⁸ 74–75°,³⁰ 125°³¹). The picrate was prepared, m.p. 175–177° (Lit. 168–169°^{30,31}).

The amine (9.1 g), dissolved in chloroform (35 ml), was added, in the course of 15 min, to a cooled and vigorously stirred mixture of thiocarbonyl chloride (20.7 g), dissolved in chloroform (100 ml), and sodium hydroxide (20 g) in water (100 ml). The organic phase was washed with acid and water, and dried. After removal of the solvent over a small column, 2-ethylbutyl isothiocyanate distilled as a colourless oil (7.1 g). The product was redistilled before analysis, b.p. 80.5°/9 mm, n_D^{25} 1.4967 (Found: C 58.61; H 9.13; N 9.64. Calc. for C₇H₁₃NS: C 58.71; H 9.15; N 9.78). The phenylthiourea, formed upon reaction with aniline, separated from ether/pentane in colourless prisms, m.p. 57°. (Found: C 66.00; H 8.58; N 11.72. Calc. for C₁₃H₂₀N₂S: C 66.06; H 8.53; N 11.85).

(\pm)-2-Methyloctyl isothiocyanate. (\pm)-2-Octanol was converted into 2-chlorooctane, uncontaminated with the 3-isomer,³² with thionyl chloride by a procedure based on the extensive studies of this reaction by Gerrard.³³

A solution of 2-octanol (69.1 g) in ether (50 ml) was added dropwise in the course of 1 h to another solution of thionyl chloride (70 g) in ether (100 ml). The yellow solution was kept in the ice-box overnight. Ether and excess thionyl chloride was removed *in vacuo* at room temperature. Pyridine hydrochloride (10 g) was now added to the residue, largely consisting of 2-octyl chlorosulphite, and the mixture was kept at 60° for 1.5 h and then poured into water. The organic phase was separated and dried. After removal of the ether, 2-chlorooctane (48.2 g) distilled at 74°/27 mm, following a forerun (13 g), containing some octene. Redistillation, b.p. 68.5°/24 mm, afforded a pure product, as estimated from gas chromatography.

2-Chlorooctane was converted into 2-methyloctanenitrile by reaction with sodium cyanide, essentially as described by Smiley and Arnold.³⁴ The nitrile was distilled, b.p. 79–81°/10 mm, n_D^{25} 1.4187. (Lit.³⁴: b.p. 88°/12 mm).

* Melting points are uncorrected and determined in capillary tubes.

2-Methyloctanenitrile was then reduced with lithium aluminum hydride in ether solution in the usual way to give 2-methyloctylamine in 74 % yield, b.p. 85–86°/9 mm. (Lit.³⁵; b.p. 185–186°). The hydrochloride was prepared, m.p. 130° (Lit.³⁵; m.p. 130°).

On reaction with thiocarbonyl chloride, as described above, the amine was converted into 2-methyloctyl isothiocyanate in 84 % yield. A yellow contamination was removed from the distillate by treatment with charcoal and redistillation. The colourless mustard oil had b.p. 119–120°/8 mm, n_D^{25} 1.4852 (Found: C 64.65; H 10.35; N 7.42. Calc. for $C_{10}H_{19}NS$: C 64.80; H 10.33; N 7.56) and was homogeneous on gas chromatography.

Upon reaction with aniline the crystalline phenylthiourea was obtained, m.p. 55–58°. (Found: C 69.07; H 9.34; N 10.24. Calc. for $C_{16}H_{26}N_2S$: C 69.00; H 9.41; N 10.07).

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

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