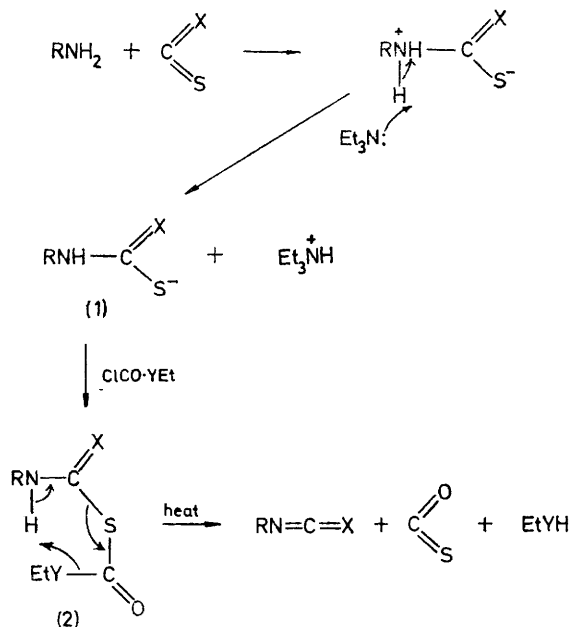


A New Synthesis of Isocyanates

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The isocyanates (3)—(7) were prepared from the corresponding amine, carbonyl sulphide, and *S*-ethyl chlorothioformate by a procedure analogous to the Andreasch–Kaluza synthesis of isothiocyanates.

For work which we shall describe elsewhere we required various arylalkyl isothiocyanates together with the corresponding isocyanates. The former compounds were

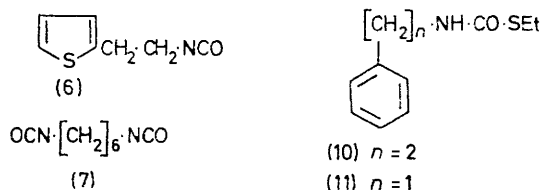
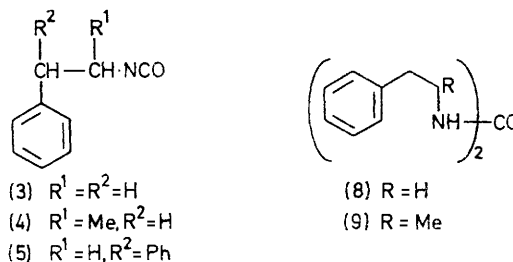


prepared by the Hodgkins–Ettlinger^{1,2} modification of the Andreasch–Kaluza procedure (Scheme; X = S, Y = O). However, an analogous synthesis of isocyanates appears not to have been reported previously. We have devised a procedure (Scheme; X = O, Y = S) which involves the reaction of a primary amine with carbonyl sulphide in the presence of triethylamine (chloroform is a suitable solvent), condensation of the resultant monothiocarbamate salt (1) with *S*-ethyl chlorothioformate, and isolation and thermal decomposition of the product (2). *S*-Ethyl chlorothioformate was chosen rather than ethyl chloroformate because the

¹ J. E. Hodgkins and M. G. Ettlinger, *J. Org. Chem.*, 1956, **21**, 404.

latter would yield ethanol: unlike ethanol, ethanethiol does not react with isocyanates. Thermal decomposition of the intermediates (2) is best carried out by distillation from glass powder. Anhydrous conditions are preferred throughout because of the susceptibility of isocyanates to hydrolysis. In this way we prepared the isocyanates (3)—(6).

The intermediates (2; X = O, Y = S) appear to be more stable under the reaction conditions than the corresponding intermediates (2; X = S, Y = O) (Scheme). This is probably due to the differing acidities of the NH protons and allows the preparation of the former intermediates in aqueous solution prior to their isolation and decomposition. Thus, when our procedure was followed starting with phenethylamine in water containing sodium hydroxide as the base, phenethyl isocyanate (3) was obtained in yields varying from 37 to



59% (after distillation of the intermediate), together with the urea (8). In the same way hexamethylenediamine yielded hexamethylene di-isocyanate (7).

The reactions of carbonyl sulphide with amines have
² E. E. Reid, 'Organic Chemistry of Bivalent Sulfur,' vol. VI, Chemical Publishing Co., New York, 1966, p. 64.

been reviewed.³ With a strongly basic amine it reacts in the cold, usually to form an isolable amine thiocarbamate salt which, on heating, gives a 1,3-disubstituted symmetrical urea. In some cases the ureas are formed directly. Under the conditions used previously, hexamethylenediamine is reported to yield only a linear polymer [*cf.* the present synthesis of hexamethylene diisocyanate (7)]. We can find only one reference to the synthesis and isolation of an isocyanate (benzyl isocyanate) from an amine and carbonyl sulphide.⁴

An attempt to generate phenethyl isocyanate by successive treatment of phenethylamine with carbon dioxide (see ref. 2) and S-ethyl chlorothioformate (Scheme; COS replaced by CO₂) in water containing sodium hydroxide gave only the monothiocarbamate (10), presumably because the amine carbonate [(RN⁺H₃)₂⁺(CO₃²⁻)] was formed instead of the carbamate corresponding to intermediate (1) in the Scheme.

The scope of this novel synthesis of isocyanates has not been investigated thoroughly. Under the same conditions, however, benzylamine gave a small amount of isocyanate but the major product was the monothiocarbamate (11). n-Butylamine gave only the corresponding monothiocarbamate.⁵ Presumably, these amines react either slowly or reversibly with carbonyl sulphide.

EXPERIMENTAL

¹H N.m.r. spectra were recorded with a Varian A60 spectrometer (Me₄Si as internal standard), i.r. spectra with a Perkin-Elmer 257 instrument, and mass spectra with an A.E.I. MS12 instrument. Mass spectra of all the compounds reported were consistent with the assigned structures.

No attempts were made to optimise yields.

Syntheses of Isocyanates.—General procedure. Carbonyl sulphide (1.02 mol) is bubbled through a stirred solution of the amine (1.0 mol) and triethylamine (1.0 mol) in chloroform (100 ml) at ambient temperature. The resulting mixture is cooled to -5 °C and S-ethyl chlorothioformate (1.0 mol) is added dropwise. Then the mixture is allowed to warm to ambient temperature and more triethylamine (125 ml) is added. The mixture is stirred for 30 min at this temperature, then poured into dry ether, and the triethylamine hydrochloride is filtered off. Distillation under reduced pressure leaves the intermediate (2) [in the synthesis of phenethyl isocyanate the yield of this was 89% and it had ν_{\max} (film) 1 650 (C=O) and 3 300 cm⁻¹ (NH)], which is distilled with decomposition from glass powder.

Phenethyl isocyanate (3) (81%) had b.p. 105–120° at 12.0 mmHg (lit.,⁶ 98–100° at 10.0 mmHg), ν_{\max} (film) 2 270 cm⁻¹ (NCO), τ (CDCl₃) 2.50–2.90 (5 H, m, aromatic), 6.55 (2 H, t, *J* 6.5 Hz, α -CH₂), and 7.15 (2 H, t, *J* 6.5 Hz, β -CH₂) (fine splitting was observed for the CH₂ triplets).

The following isocyanates were prepared similarly: (+)-1-methyl-2-phenylethyl isocyanate (4) (dexamphet-

³ E. E. Reid, 'Organic Chemistry of Bivalent Sulfur,' vol. IV, Chemical Publishing Co., New York, 1962, ch. 4, p. 397, and references cited therein.

⁴ G. Haggeloch, *Chem. Ber.*, 1950, **83**, 258.

⁵ Ref. 3, ch. 3, p. 266.

⁶ I. G. Farbenindustrie A. G., Fr. P. 809,233/1937 (*Chem. Abs.*, 1937, **31**, 6676).

⁷ L. W. Jones and E. S. Wallis, *J. Amer. Chem. Soc.*, 1926, **48**, 169.

amine isocyanate) (67%), b.p. 105° at 14.0 mmHg (lit.,⁷ 82° at 5.0 mmHg), ν_{\max} (film) 2 260 cm⁻¹ (NCO), τ (CDCl₃) 2.60–3.00 (5 H, m, aromatic), 6.30 (1 H, sextet, CH), 7.40 (2 H, d, *J* 5.0 Hz, CH₂), and 8.89 (3 H, d, *J* 5.0 Hz, Me), *m/e* 161 (*M*⁺); 2,2-diphenylethyl isocyanate (5) (58%), b.p. 218° at 14.0 mmHg, ν_{\max} (film) 2 265 cm⁻¹ (NCO), τ (CDCl₃) 2.50–2.90 (10 H, m, aromatic), 5.70–6.00 (1 H, m, CH), and 6.20–6.40 (2 H, m, CH₂) [the derivative *NN'*-bis-(2,2-diphenylethyl)urea had m.p. 205° (from aqueous ethanol) (lit.,⁸ 198°), ν_{\max} (Nujol) 1 610 (C=O) and 3 310 cm⁻¹ (NH), τ (CDCl₃) 2.70 (20 H, s, aromatic), 4.25br (2 H, t, exchangeable, 2 × NH), 5.65–6.00 (2 H, m, 2 × CH), and 6.15–6.45 (4 H, m, 2 × CH₂) (Found: C, 83.0; H, 6.85; N, 6.6%; *M*⁺, 420. Calc. for C₂₉H₂₈N₂O: C, 82.8; H, 6.7; N, 6.7%; *M*, 420)]; 2-(2-thienylethyl)ethyl isocyanate (6) (96%), b.p. 127–135° at 15 mmHg, ν_{\max} (film) 2 260 cm⁻¹ (NCO), τ (neat liquid) 2.98 (1 H, m, 5-H), 3.10–3.30 (2 H, m, 3- and 4-H), 6.65 (2 H, t, *J* 7.0 Hz, α -CH₂), and 7.18 (2 H, t, *J* 7.0 Hz, β -CH₂) (fine splitting was observed for the CH₂ triplets) [the derivative *N-phenyl-N'*-2-(2-thienylethyl)urea had m.p. 172–173° (from ethanol) (Found: C, 63.3; H, 5.7; N, 11.45. C₁₃H₁₄N₂OS requires C, 63.4; H, 5.7; N, 11.4%); and hexamethylene diisocyanate (52%), b.p. 130–140° at 14 mmHg (lit.,⁹ b.p. 150–152° at 30 mmHg), ν_{\max} (film) 2 270 cm⁻¹ (NCO) (in this case an aqueous solution containing sodium hydroxide and cooled to 0 °C was used and the intermediate which separated was extracted with ether prior to thermal decomposition). In the preparation of dexamphetamine isocyanate (4), dissolution of the distillation residue in acetone and dropwise addition of water to the stirred solution gave a precipitate, which was filtered off and washed with aqueous acetone, to yield *NN'*-bis-[(+)-1-methyl-2-phenylethyl]urea (9) (27%), m.p. 150° (lit.,¹⁰ 149–151°), ν_{\max} (Nujol) 1 620 (C=O) and 3 320 cm⁻¹ (NH), τ (CDCl₃) 2.70 (10 H, s, aromatic), 5.20br (2 H, s, exchangeable, 2 × NH), 5.73–6.25 (2 H, m, 2 × CH), 6.94–7.61 (4 H, m, 2 × CH₂), and 8.88 (6 H, d, *J* 6.5 Hz, 2 × Me), *m/e* 296 (*M*⁺).

When benzylamine (5.15 g, 0.05 mol) was treated similarly and the product corresponding to (2) in the Scheme (X = O, Y = S), ν_{\max} (Nujol) 1 645 (C=O) and 3 320 cm⁻¹ (NH), was distilled from glass powder at 12.00 mmHg, two fractions were obtained: (i) a mixture (2.8 g), b.p. 180–190°, which i.r. and n.m.r. analysis showed to be a mixture of an isocyanate, ν_{\max} (film) 2 265 cm⁻¹ (NCO), and a monothiocarbamate, ν_{\max} 1 645 (C=O) and 3 320 cm⁻¹ (NH) (ratio 30 : 70); and (ii) ethyl *N*-benzylmonothiocarbamate (11) (4.1 g), b.p. 190–200°, m.p. 63–64° [from light petroleum (b.p. 60–80°)] (lit.,¹¹ 66°), ν_{\max} (film) 1 645 (C=O) and 3 320 cm⁻¹ (NH), τ (CDCl₃) 2.75 (5 H, s, aromatic), 3.95br (1 H, s, exchangeable, NH), 5.61 (2 H, d, *J* 6.0 Hz, CH₂), 7.13 (2 H, q, *J* 8.5 Hz, CH₂), and 8.75 (3 H, t, *J* 8.5 Hz, Me) (Found: C, 61.5; H, 6.7; N, 7.2%; *M*⁺, 195. Calc. for C₁₀H₁₃NOS: C, 61.5; H, 6.7; N, 7.2%; *M*, 195).

Reaction of Phenethylamine with Carbonyl Sulphide and S-Ethyl Chlorothioformate in Water.—Carbonyl sulphide was bubbled through a stirred mixture of phenethylamine (60.5 g, 0.5 mol), sodium hydroxide (20.0 g, 0.5 mol), water (100 ml), and ethanol (50 ml) at ambient temperature until

⁸ A. Sieglitz, *Ber.*, 1922, **55B**, 2040.

⁹ M. W. Farlow, U.S.P. 2,374,340/1945 (*Chem. Abs.*, 1945, **39**, 3555).

¹⁰ S. L. Shapiro, I. M. Rose, and L. Freedman, *J. Amer. Chem. Soc.*, 1958, **80**, 6065.

¹¹ W. Schneider, D. Clibbens, G. Hüllweck, and W. Steibelt, *Ber.*, 1914, **47**, 1248.

an equivalent amount (30 g) of the gas had been taken up. The mixture was cooled to -5° , *S*-ethyl chlorothioformate (62.3 g, 0.5 mol) was added dropwise, and the resulting mixture was stirred for 30 min at this temperature, then allowed to warm to ambient temperature. Water was added; extraction with chloroform and distillation at 13.0 mmHg then gave, besides solvent: (i) a mixture (7.8 g) (t.l.c.), b.p. $30-45^{\circ}$, which contained *S*-ethyl chlorothioformate (i.r.); (ii) phenethyl isocyanate (3) (27.0 g, 37%), b.p. $120-140^{\circ}$, identical (i.r. and n.m.r. spectra) with an authentic sample; and (iii) a residue which was dissolved in acetone (100 ml); the solution was treated dropwise with water (100 ml) to give a precipitate of *NN'*-bis(phenethyl)urea (8) (21.0 g, 31%), m.p. 139° (from ethanol) (lit.,¹² $137-138^{\circ}$), ν_{\max} (Nujol) 1 625 (C=O) and 3 340 cm^{-1} (NH), τ (CDCl_3) 2.80 (10 H, s, aromatic), 5.00br (2 H, t, exchangeable, $2 \times \text{NH}$), 6.67 (4 H, q which collapsed to t on deuteration, $2 \times \alpha\text{-CH}_2$), and 7.29 (4 H, t, J 5.0 Hz, $2 \times \beta\text{-CH}_2$) (Found: C, 76.2; H, 7.6; N, 10.4%; M^+ , 268. $\text{C}_{17}\text{H}_{20}\text{N}_2\text{O}$ requires C, 76.1; H, 7.5; N, 10.4%; M , 268). When this reaction was repeated but with carbonyl sulphide saturation and *S*-ethyl chlorothioformate addition carried out at 0°C , the isocyanate was obtained in 59% yield (70% yield before redistillation).

Ethyl N-Phenethylmonothiocarbamate (10).—Powdered solid carbon dioxide (17.0 g, 0.39 mol) was added to a stirred mixture of phenethylamine (46.0 g, 0.38 mol), sodium hydroxide (15.2 g, 0.38 mol), water (80 ml), and ethanol (50 ml). The mixture was cooled to -5°C , *S*-ethyl chlorothioformate (47.5 g, 0.38 mol) was added, and the reaction was worked up as described before, to give *ethyl N-phenethylmonothiocarbamate* (10) (72.0 g, 91%), m.p. 45° , ν_{\max} (Nujol) 1 655 (C=O) and 3 250 cm^{-1} (NH), τ (CDCl_3) 2.75 (5 H, s, aromatic), 4.45br (1 H, t, exchangeable, NH), 6.49 (2 H, q which collapsed to t on deuteration, $\alpha\text{-CH}_2$), 7.11 (2 H, q, J 7.0 Hz, CH_2), 7.20 (2 H, t, J 6.5 Hz, $\beta\text{-CH}_2$), and 8.72 (3 H, t, J 7.0 Hz, Me), m/e 209 (M^+) (Found: C, 62.6; H, 7.2; N, 7.1. $\text{C}_{11}\text{H}_{15}\text{NOS}$ requires C, 63.1; H, 7.2; N, 6.7%).

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¹² T. Hayashi and M. Kuyama, *Nat. Sci. Reports Ochanomizu Univ.*, 1951, **2**, 79 (*Chem. Abs.*, 1954, **48**, 1274).