[Contribution from the Chemistry Department of the Rice Institute]

The Synthesis of Isothiocyanates from Amines

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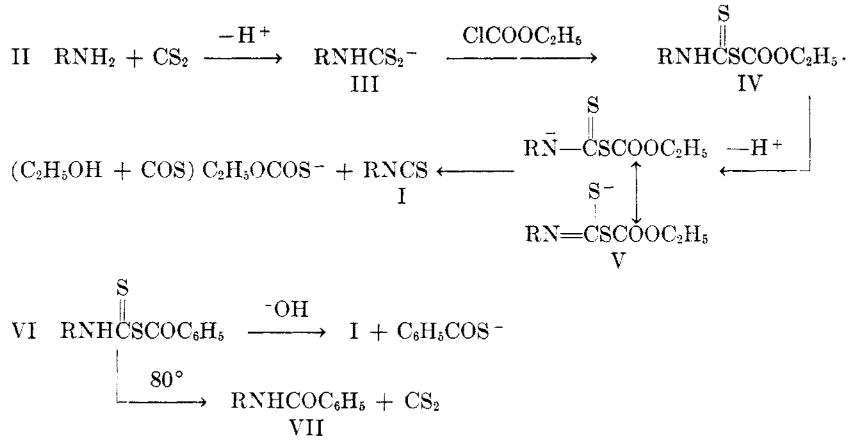
The Kaluza synthesis of isothiocyanates has been improved by base-catalyzed decomposition of the intermediate carboethoxy dithiocarbamate derivatives.

Prior to synthesis of butenyl isothiocyanates,[2] the model preparation of *n*-butyl mustard oil [Ia: I, R = $CH_3(CH_2)_3$] from *n*-butylamine [II, R = $CH_3(CH_2)_3$] was studied intensively. Slotta and Dressler[3] have reviewed practical methods to convert an aliphatic amine to the corresponding isothiocyanate and have given their opinion in favor of the Kaluza[4] procedure on grounds of yield and convenience. If the use of thiophosgene is avoided, all routes begin with reaction of the amine (II), carbon disulfide, and a base to form the dithiocarbamate (III). The dehydrosulfuration of III to the isothiocyanate (I) may be accomplished with a basic lead salt,[5] but neither thus nor by an adaptation of the von Braun method,[6] oxidation of III with iodine and potassium hydroxide in methanol, could we achieve yields of Ia greater than some 65% of the theoretical. Schmidt and co-workers[7] have recently described the oxidation of III [R = $CH_3(CH_2)_3$] to Ia in 80% yield by alkaline hypochlorite, but it appears doubtful whether the procedure would apply to unsaturated amines.



The Andreasch-Kaluza synthesis of isothiocyanates consists in treatment of III with ethyl chlorocarbonate to furnish the carboethoxy dithiocarbamate (IV), which undergoes fission to ethanol, carbon oxysulfide, and I. The esters IV were considered unstable and were allowed to decompose[8] during the exothermic carboethoxylation, and the formation of I could be completed at 100°. However, if the temperature is kept below 0° during carboethoxylation, IVa [IV, R = $CH_3(CH_2)_3$] can be isolated in crude condition and is stable at room temperature. When heated for two to five hours at 95° without solvent or in water, or in boiling benzene or in 2,2,4-trimethylpentane, IVa furnished Ia in 70–90% yields.

The rate of cleavage of IVa in hot aqueous medium proved to be remarkably dependent on alkalinity,[9] for the substance was relatively stable in 0.005 N hydrochloric acid but decomposed almost instantaneously in hot 0.1 N potassium hydroxide. Furthermore, in sufficiently concentrated alkali, 20–50% potassium hydroxide, IVa was rapidly converted to Ia in 80–95% yields at room temperature.

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(2) Ettlinger and Hodgkins, *J. Am. Chem. Soc.*, **77**, 1831 (1955).

(3) Slotta and Dressler, *Ber.*, **63**, 888 (1930).

(4) Kaluza, *Monatsh.*, **33**, 363 (1912); *cf.* Kaluza, *Monatsh.*, **30**, 701 (1909); Stieger, *Monatsh.*, **37**, 635 (1916); Moore and Crossley, *Org. Syntheses*, **21**, 81 (1941).

(5) Delépine, *Bull. soc. chim.*, [4] **3**, 641 (1908).

(6) V. Braun, *Ber.* **35**, 817 (1902); V. Braun and Deutsch, *Ber.*, **45**, 2188 (1912).

(7) Schmidt, Zaller, Moosmueller, and Kammerl, *Ann.*, **585**, 230 (1954); *cf.* Schmidt, *et. al.*, *Ann.*, **594**, 233 (1955).

(8) Sergeev and Ivanova (*J. Gen. Chem.* (U.S.S.R.), **7**, 1495 (1937); [*Chem. Abstr.*, **32**, 2534 (1938)]) isolated crystalline carbomethoxy 2-hydroxyethyldithiocarbamate; *Cf.* also Yakuhovich and Klimova, *J. Gen. Chem.* (*U.S.S.R.*), **9**, 1777 (1939); [*Chem. Zentr.*, **I**, 1973 (1940)].

(9) In the Kaluza procedure, IV decomposed as formed in the presence of III, *i.e.*, in weak base.

Base catalysis of the isothiocyanate formation was demonstrated also in non-aqueous solvents, for the decomposition of IVa was fast at room temperature in a mixture of chloroform and triethylamine. The plausible interpretation is that IV, in common with N-unsubstituted or monosubstituted thioamides, is weakly acidic like phenol and reacts with base to form the anion V, which splits to I and O-ethylthiocarbonate ion, leading in the absence of excess hydroxide ion to ethanol and carbon oxysulfide.

The alkaline cleavage of IV is analogous to that of benzoyl ethyldithiocarbamate and phenyldithiocarbamate[10] (VI, R = C_2H_5 and C_6H_5), giving the isothiocyanates I and thiobenzoate ion. However, VI curiously undergoes fission in boiling alcohol to the benzamide (VII) and carbon disulfide,[11] whereas the apparent thermal decomposition of IV, perhaps catalyzed by adventitious traces of base, usually gives at most a trifle of the urethan.[12]

In a paper received after termination of our work, Schultz and Barthold[13] described crystalline carboethoxy phenyldithiocarbamate (IV, R = C_6H_5) and showed that it was stable to cold acid but decomposed in weak alkali or slowly in bicarbonate to give phenyl isothiocyanate (I, R = C_6H_5) in 95% yield. The phenyl substituent would be expected to increase the acidity of IV. Schultz and Barthold also noted without detail that the benzyldithiocarbamate IV (R = $CH_2C_6H_5$) was cleaved in water to the isothiocyanate only by hydroxide ion, and that IVa was still harder to decompose.

The preparative method developed for Ia, as previously[2] indicated, was to obtain IVa at low temperature and decompose it at 30–50° by addition of enough 50% potassium hydroxide to the mixture to make a 20% aqueous solution of catalyst. The yields of Ia from the amine, 80–90% of theoretical, were similar to those obtained by thermal cleavage of IVa, but the reaction was better controlled and the isothiocyanates appeared free from the troublesome by-products occasionally encountered in the original Kaluza procedure.[2,14] Reaction of IV and triethylamine might be useful if strong aqueous alkali were to be avoided. The Kaluza method is a poor way to obtain aryl isothiocyanates because of the formation of N,N′-diarylureas. However, the base-catalyzed decomposition of IV may be a feasible preparation, to judge by the results of Schultz and Barthold, and more convenient than treatment of III with phosgene in the absence of water.[3] The present method applied to the synthesis of benzyl isothiocyanate also proved to be highly advantageous.[15]

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EXPERIMENTAL

Trials were generally made with 4–5 g. portions of *n*-butylamine, though isopropylamine and isobutylamine were also used. The dithiocarbamate was prepared[2] from the amine and an equivalent of potassium hydroxide with a slight excess of carbon disulfide at 0° or below, and the reaction was completed at 30–100°. Water was a satisfactory solvent, but 50–60% methanol or *tert*-butanol were also employed. Ammonia[7] or triethylamine could be substituted for potassium hydroxide, and with triethylamine, dioxane or benzene could serve as solvents. Carboethoxylation was accomplished[2] by addition of an equivalent of ethyl chlorocarbonate dropwise at −10°. The carboethoxy derivative separated from aqueous media as an oil and could be isolated by extraction with ether and evaporation of solvents *in vacuo.* During an attempt to distill the substance at 0.4 mm., it began to decompose with rising pressure at a bath temperature of 75°.

The fission of carboethoxy *n*-butyldithiocarbamate in 20% or stronger aqueous potassium hydroxide or in 10% potassium hydroxide in 40% methanol proceeded without evolution of gas and could be followed by the separation of the product as upper phase. *n*-Butyl isothiocyanate, isolated by extraction with ether and distillation, boiled at 83.5° at 32 mm. and had n_D^{26} 1.4933 (lit.[7] b.p. 58–59° at 9 mm., n_D^{20} 1.5010). Isobutyl isothiocyanate boiled at 72.5° at 29 mm. In a few experiments, small after-runs were obtained, perhaps of ethyl butylcarbamate. Attempts to prepare *n*-butylthiourea directly from the carboethoxy compound by cleavage in concentrated aqueous ammonia gave a maximum yield of 7%. Cleavage in 40% aqueous triethylamine containing an equivalent of hydrochloride at 30–70° afforded a 65% yield of *n*-butyl isothiocyanate.

The decomposition of the carboethoxy compound by triethylamine proceeded at markedly increasing rate as the solvent was changed from benzene to dioxane to chloroform. The following procedure exemplifies the synthesis of isothiocyanate from amine in anhydrous medium. A mixture of 7 cc. (5.1 g.) of *n*-butylamine, 10 cc. of triethylamine and 10 cc. of dioxane was chilled to −10° and treated with 4.2 cc. of carbon disulfide. The solution was allowed to warm to room temperature, chilled and treated dropwise with 7.5 cc. of ethyl chlorocarbonate. The triethylamine hydrochloride was filtered and the liquid was diluted with 20 cc. of chloroform and 10 cc. of triethylamine. After the precipitate had dissolved and the copious evolution of carbon oxysulfide had ceased in five minutes at room temperature, the solution was distilled *in vacuo* to furnish 6.0 g. (75%) of *n*-butyl isothiocyanate.

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[10] V. Braun, *Ber.*, **36**, 3520 (1903).

[11] The facile reaction of I and thiobenzoic acid to give VII and carbon disulfide may proceed through VI; *cf.* Wheeler and Merriam, *J. Am. Chem. Soc.*, **23**, 283 (1901).

[12] The reaction of dialkylammonium dialkyldithiocarbamates and ethyl chlorocarbonate leads to urethans,[10] but not necessarily through an analog of IV.

[13] Schultz and Barthold, *Arch. Pharm.*, **285**, 267 (1952).

[14] *cf.* Kjaer, Rubinstein and Jensen, *Acta Chem. Scand.*, **7**, 518 (1953).

[15] Ettlinger and Hodgkins, *J. Org. Chem.*, **21**, 204 (1956).