72. *Thioformylation of Amines.*

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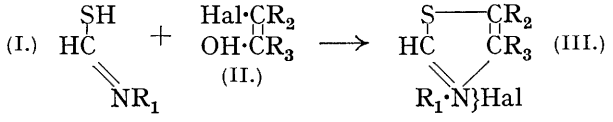
In the course of synthetic investigations in the aneurin series it was found that thiazolium salts of type (III), to which aneurin itself belongs, could be synthesised by condensation of thioformamido-compounds (I) with α-halogenated ketones (II) (Todd, Bergel, and Karimullah, *Ber.*, 1936, **69**, 217; J., 1936, 1557; Clarke and Gurin, *J. Amer. Chem. Soc.*, 1935, **57**, 1876).



Thioformamido-compounds have hitherto been prepared either by treatment of the corresponding formamido-compounds with phosphorus pentasulphide or by the addition of hydrogen sulphide to *iso*nitriles. The first of these methods is not capable of general application, and is in any case useless save with very stable compounds; the scope of the second is limited by the difficulty of obtaining appropriate *iso*nitriles.

The reaction between *iso*cyanates or *iso*thiocyanates and carboxylic acids, originally described by Wurtz (*Jahresber.*, 1851, 501; 1854, 566) and recently investigated by Nägeli

and Tyabji (*Helv. Chim. Acta*, 1934, **17**, 947; 1935, **18**, 142), leads to formation of acylamides according to the scheme :

$$NR_1{:}C{:}O + R_2{\cdot}CO_2H \longrightarrow NHR_1{\cdot}CO{\cdot}O{\cdot}CO{\cdot}R_2 \xrightarrow{\text{heat}} NHR_1{\cdot}CO{\cdot}R_2 + CO_2$$

By replacing the carboxylic acid in the above reaction by a thiolthionic acid (R·CS·SH), thioacylamides can be obtained with elimination of carbonyl sulphide (or, if a thiocyanate is employed, carbon disulphide). By using dithioformic acid, thioformamido-compounds can be prepared in good yield, but here again the value of the method is governed by the accessibility of the *iso*cyanates.

Thioformylation of 5-aminopyrimidines can be effected by mixing aqueous solutions of the amine and potassium dithioformate or dithioformic acid at room temperature (Todd, Bergel, and Karimullah, J., 1936, 1557). The ease with which this reaction occurs led us to test its application to a variety of compounds containing amino- or imino-groups, partly to have available intermediates for thiazolium salt syntheses, and partly in the hope that the thioformyl derivatives might be of value in the separation and identification of amines generally. Thioformylation with potassium dithioformate has been found to be of general application, and methods are now described for carrying out the reaction with amines of widely varying types.

The aliphatic thioformamido-compounds prepared, except that from ethylenediamine, are liquids which, as such, are unsuitable for identification purposes, although they condense readily with amines to give substituted formamidines and with α-halogenated ketones to give thiazolium salts. Thioformylation of aromatic and heterocyclic amines yields crystalline derivatives, usually with sharp melting points, which are useful for identification. No thioformylation occurs with indole, diphenylamine, or methylaniline. From *o*-phenylenediamine an unstable thioformyl derivative can be obtained which passes slowly into benziminazole. With *o*-aminobenzylamine, potassium dithioformate even at room temperature causes immediate production of dihydroquinazoline; no thioformyl derivative could be obtained. The ease with which ring closure occurs in these cases suggests that thioacylamido-derivatives might advantageously be employed in such reactions where acylamido-derivatives are commonly used.

The interaction of dithioformic acid and ammonia may be used for the preparation of thioformamide, the yield being rather better than that obtained in the normal preparation from formamide and phosphorus pentasulphide (Willstätter and Wirth, *Ber.*, 1909, **42**, 1911).

Experimental.

Potassium Dithioformate.—The preparation from chloroform and potassium sulphide (Levi, *Atti R. Accad. Lincei*, 1923, **32**, I, 569) is satisfactory, the yield of recrystallised salt being about 45% of the theoretical.

Dithioformic Acid.—Prepared from the potassium salt according to Levi (*loc. cit.*), the acid is obtained as a cream-coloured, amorphous powder, the reactivity of which diminishes rapidly on keeping. Levi considered the free acid to be termolecular, but it is clear from molecular-weight determinations that it undergoes progressive polymerisation on keeping, which accounts for the diminishing activity (Found, by cryoscopic method in dioxan : after 2 hours, *M*, 154; after 24 hours, *M*, 555; after 72 hours, *M*, 666. Calc. for CH_2S_2 : *M*, 78). Dithioformic acid is best kept in the form of its stable potassium salt, from which it can readily be prepared as required.

Action of Thiolthionic Acids on iso*Cyanates and* iso*Thiocyanates.*—(a) *Phenyl* iso*cyanate.* To a solution of phenyl *iso*cyanate (2 g.) in toluene (*ca.* 10 c.c.), dry, freshly precipitated dithioformic acid (2 g.) was added in portions. When the vigorous reaction had subsided, the semi-solid mass was left over-night, then heated on the water-bath until evolution of carbonyl sulphide ceased and practically everything was in solution (about 2 hours). On removal of the toluene and crystallisation of the residue from water, thioformanilide (2 g.), m. p. 138°, was obtained. When the dithioformic acid in the above preparation was replaced by dithioacetic acid, thioacetanilide, m. p. 75°, was obtained.

(b) *Phenyl* iso*thiocyanate.* A solution of phenyl *iso*thiocyanate (3 g.) in toluene (10 c.c.), treated with dithioformic acid (2 g.) in the manner above described, gave thioformanilide with

evolution of carbon disulphide. Yield, 2 g.; m. p. 138°. A similar experiment with dithioacetic acid gave thioacetanilide, m. p. 75°, in good yield.

General Methods for Thioformylation of Amines.—I. *For amines insoluble or sparingly soluble in water.* The amine, dissolved in ether or chloroform, is shaken with a slight excess of potassium dithioformate. On evaporation of the organic solvent the thioformyl product separates. Alternatively, the whole operation may be carried out in aqueous-alcoholic solution, and the product precipitated by addition of water.

II. *For amines soluble in water.* An aqueous solution of amine or one of its salts is mixed with excess of potassium dithioformate solution; the derivative separates on standing.

III. *For amines giving water-soluble thioformyl derivatives.* In this case, it is generally more convenient to shake together the amine and dithioformic acid in ether or dioxan solution till evolution of hydrogen sulphide ceases, and then remove the solvent by distillation. Alternatively, the amine hydrochloride and potassium dithioformate are shaken together in absolute alcohol.

Examples of Method I.—Aniline. The base (9·3 g.), dissolved in alcohol (20 c.c.), was added to a solution of potassium dithioformate (12 g.) in water (20 c.c.). Separation of thioformanilide soon began, and was complete in 2 hours. Water was added, and the crystalline product collected and recrystallised from hot water. Yield, quantitative.

By the same method, thioform-*o*-toluidide, m. p. 97°, was obtained from *o*-toluidine.

6-*Aminoquinoline.* To a solution of potassium dithioformate (1·5 g.) in water (25 c.c.) was added 6-aminoquinoline (1 g.) dissolved in chloroform, and the mixture was shaken for a few minutes. By bubbling nitrogen through the mixture, the chloroform was gradually evaporated, leaving the *thioformyl* derivative suspended in the aqueous solution; it crystallised from acetone–light petroleum in faintly yellow needles, m. p. 236° (Found: S, 16·6. $C_{10}H_8N_2S$ requires S, 17·0%); yield, quantitative.

Examples of Method II.—5-Aminopyrimidines. See Todd, Bergel, and Karimullah (*loc. cit.*).

Tryptamine. To tryptamine hydrochloride (500 mg.), dissolved in water (80 c.c.), was added potassium dithioformate (400 mg.). After 15 minutes the solution became turbid and an oil separated which slowly crystallised. Recrystallised from chloroform–light petroleum (b. p. 60—80°), the *product* formed large plates, m. p. 82° (Found: S, 15·1; N, 13·7. $C_{11}H_{12}N_2S$ requires S, 15·7; N, 13·7%).

Mezcaline. Mezcaline sulphate (200 mg.) and potassium dithioformate (150 mg.) in water (20 c.c.) deposited after 20 minutes an oil which slowly crystallised; it separated from acetone–light petroleum in colourless prisms, m. p. 92° (Found: N, 5·7; S, 12·2. $C_{12}H_{17}O_3NS$ requires N, 5·5; S, 12·5%). Yield, quantitative.

o-*Phenylenediamine.* An aqueous solution of the amine gave with potassium dithioformate at 0° an unstable thioformyl derivative, m. p. 77°, which even at room temperature changed rapidly into benziminazole, m. p. 170°. At temperatures above 0° the sole product was benziminazole.

Monoacetyl-o-*phenylenediamine.* The *thioformyl* derivative crystallised from acetone–light petroleum in colourless needles, m. p. 173° (Found: C, 55·7; H, 5·3; S, 16·3. $C_9H_{10}ON_2S$ requires C, 55·7; H, 5·1; S, 16·4%). Yield, quantitative.

Benzylamine and o-*nitrobenzylamine.* The *thioformyl* derivatives have m. p. 64° (Found: S, 20·7. C_8H_9NS requires S, 21·2%) and m. p. 94° (Found: S, 15·9. $C_8H_8O_2N_2S$ requires S, 16·3%), respectively.

o-*Aminobenzylamine.* The amine reacted readily with potassium dithioformate in aqueous solution even at room temperature, to give dihydroquinazoline, m. p. 128—129°, in quantitative yield.

Ethylenediamine. With potassium dithioformate *ethylenebisthioformamide*, m. p. 146—147°, is formed (Found: N, 18·8. $C_4H_8N_2S_2$ requires N, 18·9%).

Examples of Method III.—From dimethylamine, diethylamine, and piperidine or their hydrochlorides, thioformyl derivatives were obtained as yellow liquids with the properties recorded by Willstätter and Wirth (*Ber.*, 1909, **42**, 1920), and ethylamine gave the product described by Nef (*Annalen*, 1894, **280**, 297).

*N-iso*Amylthioformamide, prepared from *iso*amylamine and dithioformic acid in ethereal solution, had b. p. 143—146°/10 mm.; condensation with ω-bromoacetophenone and subsequent treatment with picric acid gave 4-*phenyl*-3-iso*amylthiazolium picrate*, m. p. 101° (Found: N, 11·8. $C_{20}H_{20}O_7N_4S$ requires N, 12·1%).

Thioformamide. Aqueous ammonia (12 g.; *d* 0·880) is added with stirring to a suspension of dithioformic acid (7·8 g.) in ether (50 c.c.). After standing for 2 days at room temperature

the ethereal layer is separated, and the aqueous layer extracted several times with small quantities of ether. The combined ethereal solution and extracts are dried over phosphoric oxide, and the ether evaporated. The resulting syrup may be used directly as thioformamide for all ordinary purposes. To obtain solid thioformamide, the dried ethereal solution is concentrated to small bulk (20 c.c.), cooled to − 15°, and precipitated with light petroleum; yield, *ca.* 30%.

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