158. *A New Reaction of Thiocyanic Esters.*

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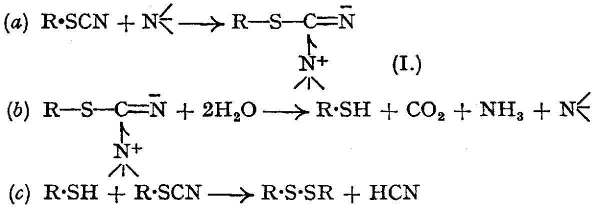
Thiocyanic esters are converted almost quantitatively into disulphides by heating with tertiary amines in acetic acid or with pyridine acetate in alcohol. This reaction also takes place with secondary and primary amines but is then complicated to some extent by side reactions. A mechanism is suggested.

Reactions of thiocyanic esters may be divided broadly into three classes, those in which the thiocyanate radical is severed from the rest of the molecule as in the rearrangement to *iso*thiocyanates, those in which the molecule is broken between the carbon and the sulphur atom as in reduction to thiols, and those in which there is addition to the cyanide part of the radical as, *e.g.*, in the cyclisation of *o*-aminophenyl thiocyanates to aminobenzthiazoles. A new reaction has been observed in which the initial step is thought to be of the third type, though followed by a scission of the adduct with elimination of the carbon and nitrogen atoms. When two molar proportions of a thiocyanic ester are heated with an acetic acid solution of one molar proportion of a tertiary amine, an almost quantitative conversion into disulphide takes place. The reaction has been carried out with *p*-nitrophenyl, *p*-chlorophenyl, *p*-tolyl, and benzyl thiocyanates using pyridine, dimethylaniline, and triethylamine as the amines, and it constitutes an attractive method for the preparation of pure disulphides. The reaction also takes place with secondary amines, *e.g.*, methylaniline, piperidine, and dibutylamine, and with primary amines such as anilines and *n*-butylamine, though the reaction is complicated by side reactions when some of these are used (see p. 817). The speed of the reaction is not influenced to any great extent by the amine used, but the thiocyanates vary in reactivity. Reaction is more rapid with *p*-nitrophenyl than with *p*-tolyl or *p*-chlorophenyl thiocyanates and a higher temperature must also be used in the latter cases. The reaction is slow also with benzyl thiocyanate and very slow with dodecyl thiocyanate. Challenger and Collins (*J.*, 1924, **125**, 1377) found that when *o*-nitrophenyl thiocyanate was boiled with aniline, a mixture of 2 : 2′-dinitrodiphenyl sulphide and the corresponding disulphide was formed. With the 2 : 4-dinitro-thiocyanate the main product was 2 : 4-dinitrodiphenylamine; some phenylthiourea and some 2 : 4 : 2′ : 4′-tetranitrodiphenyl sulphide were isolated and there was some evidence of a small amount of the corresponding disulphide. Although in these cases reaction conditions are very different from ours, disulphide formation may be the result of a reaction similar to that under consideration here.

The case of *p*-nitrophenyl thiocyanate and tertiary amines has been studied in detail and it has been found that the reaction takes place in a current of nitrogen. Since the disulphide crystallises out as the reaction proceeds, its formation cannot be due to aerial oxidation of the thiol. This distinguishes the reaction under discussion from the well-known conversion of thiocyanic esters into disulphides by hydrolysis with acids or alkalis, in which case access of air is necessary to oxidise thiol to disulphide (see, *e.g.*, Rabat, *Bull. Soc. chim.*, 1902, **27**, 690). During the reaction about one molecular proportion of both hydrogen cyanide and carbon dioxide are liberated and may be removed from the carrier gas by acid silver nitrate followed by baryta. No cyanogen was detected by the procedure of Wallis (*Annalen.*, 1906, **345**, 361). After dilution of the reaction mixture with water and separation of the disulphide, the aqueous liquor has been shown to contain about one molecular proportion of ammonia, and the tertiary base may be recovered unchanged. The reaction will not proceed at an appreciable speed with only a trace of tertiary base, and no reaction takes place even with the necessary proportion of base in a non-ionising solvent such as toluene. The reaction is normally carried out with free access of atmospheric moisture and without taking precautions to dry the acetic acid. When care is taken to exclude water, however, no reaction takes place. Similarly, the reaction proceeds smoothly with pyridine acetate in ordinary methyl alcohol, but not if all materials are carefully dried.

To explain the foregoing observations the following mechanism is suggested : (*a*) A primary addition of tertiary base to the carbon atom of the thiocyanate group ; this would be expected to be facilitated by electron-attracting groups in the radical R and explains the much more rapid reaction with *p*-nitrophenyl than with the other thiocyanates used. (*b*) Decomposition of the product (I) of stage (*a*) by water to give a thiol, carbon dioxide, and ammonia, with regeneration of the tertiary base ; this may proceed through cyanic acid as an intermediate step (compare the formation of cyanate by alkaline treatment of 1-thiocyanobenzthiazole ; Davies and Sexton, *J.*, 1944, 11). (*c*) Reaction of the thiol with the remaing thiocyanate to give disulphide and hydrogen cyanide. The final stage has been shown to proceed very readily when an acetic acid solution of equimolecular quantities of a thiocyanate and a thiol is heated.



$$(a)\quad \mathrm{R{\cdot}SCN} + \mathrm{N}\!< \;\longrightarrow\; \mathrm{R{-}S{-}}\underset{\overset{\uparrow}{\mathrm{N^{+}}}}{\mathrm{C}}{=}\bar{\mathrm{N}} \qquad \text{(I.)}$$

$$(b)\quad \mathrm{R{-}S{-}}\underset{\overset{\uparrow}{\mathrm{N^{+}}}}{\mathrm{C}}{=}\bar{\mathrm{N}} + 2\mathrm{H_2O} \longrightarrow \mathrm{R{\cdot}SH} + \mathrm{CO_2} + \mathrm{NH_3} + \mathrm{N}\!<$$

$$(c)\quad \mathrm{R{\cdot}SH} + \mathrm{R{\cdot}SCN} \longrightarrow \mathrm{R{\cdot}S{\cdot}SR} + \mathrm{HCN}$$

With secondary amines such as methylaniline the base is recovered after reaction as the acetyl derivative. A small amount of an unidentified by-product has been isolated also, after alkaline hydrolysis of the separated acetamido-compound. Using aniline, much *s*-diphenylguanidine is formed as well as acetanilide, and this may be ascribed to attack of the postulated intermediate compound (I) by a second molecule of aniline. These side reactions are reflected in the smaller amounts of ammonia and carbon dioxide which are obtained in the reactions with methylaniline and especially aniline. The reaction will also take place (though very much more slowly) with ammonia in the case of *p*-nitrophenyl thiocyanate. It is possible that a certain amount of disulphide is produced in the reactions with amines by the ammonia liberated in stage (*b*) of the postulated mechanism, though in view of the very slow speed of the reaction with ammonia alone, this is not likely to account for any considerable proportion of the product.

The nature of the reagent used to bring about fission of the thiocyanate in this way is such as to suggest that the reaction might proceed under physiological conditions. If this is so, then the reaction described may be associated with the biological activity of the thiocyanates, which covers toxicity to fungi, insects, and higher animals depending on the group attached to SCN.

EXPERIMENTAL.

Reaction of p-*Nitrophenyl Thiocyanate with Various Amines.*—*p*-Nitrophenyl thiocyanate (18 g.), acetic acid (25 c.c.), and an amine (0·05 g.-mol.) were heated for 18 hrs. at 100° (bath temp.). Large yellow prisms, m. p. 180—182°, gradually formed and after a further 6 hrs.' standing, were collected and washed with a little acetic acid. The m. p. was not raised appreciably by crystallisation from 2-ethoxyethanol but this was desirable in some cases (especially with dimethylaniline) to remove a trace of coloured impurity. The following amines were used, with the yields given : pyridine 14·7 g., dimethylaniline 14·4 g., triethylamine 14·2 g., methylaniline 14·5 g., dibutylamine 14·0 g., piperidine 14·2 g., aniline 14·8 g., *p*-toluidine 14·4 g., *n*-butylamine 14·8 g.

Reaction of Various Thiocyanates with Pyridine.—The thiocyanate (0·0333 g.-mol.) in acetic acid (7·5 c.c.) and pyridine (1·3 g.) was heated for 50 hrs. at 130—135° (bath temp.). Water and ice (about 100 c.c.) were added, and the oil allowed to solidify, collected, washed with water, and dried in a vacuum. The following disulphides were prepared and identified by mixed m. p. determinations with authentic samples : 4 : 4′-dichlorodiphenyl (4·5 g.), m. p. 72—74° ; 4 : 4′-ditolyl (3·8 g.), m. p. 45—46° ; dibenzyl (3·4 g.), m. p. 71°. With dodecyl thiocyanate (7·6 g.), only partial conversion was obtained. By distillation of the product, unchanged thiocyanate (3·5 g.), b. p. 148—150°/1·0 mm., and didodecyl disulphide (3·2 g.), b. p. 228—230°/1·0 mm., m. p. 33°, were obtained.

Reaction of p-*Nitrophenyl Thiocyanate with Pyridine.*—A mixture of the thiocyanate (6·0 g., 0·0333 g.-mol.), pyridine (1·3 g., 0·0167 g.-mol.), and acetic acid (7·5 c.c.) was heated at 90—95° (bath temp.) in a slow stream of nitrogen (freed from traces of carbon dioxide by passage through dilute sodium hydroxide solution). The effluent gases were washed in three bubblers containing silver nitrate (10 g.) and concentrated nitric acid (15 c.c.) in distilled water (60 c.c.), and then in three more bubblers containing saturated baryta solution. (The last bubbler of each set remained clear, showing that absorption was complete.) Evolution of hydrogen cyanide and carbon dioxide began as soon as the internal temperature reached 80—85°, and was rapid for 4—5 hrs. By a suitable arrangement of taps, the gas stream was diverted through fresh solutions of silver nitrate and baryta from time to time, and it was found that liberation of these gases ceased after 7—8 hrs. After 12 hrs.' heating in all, the reaction liquid was allowed to cool, and the 4 : 4′-dinitrodiphenyl disulphide (4·7 g., 0·0152 g.-mol. ; m. p. 182—183°) was collected, washed with a little acetic acid, and dried. The filtrate was placed in a Kjeldahl apparatus, treated with saturated potassium hydroxide solution (50 c.c.), and steam-distilled into N-hydrochloric acid (50 c.c.). The back titration (34·5 c.c.) corresponded to 0·0155 g.-mol. of ammonia. The titration liquor was made strongly acid (hydrochloric acid), evaporated under reduced pressure, and the residue treated with saturated potassium hydroxide solution (20 c.c.) (ammonia was plainly recognised by smell). The liberated oil was extracted with ether, dried over sodium hydroxide, and distilled, giving a colourless oil (0·75 g.), b. p. 105—115°. [A better recovery of pyridine was obtained in a second experiment by evaporating the dried ethereal extracts to 10 c.c. and pouring them into a solution of picric acid in alcohol. The picrate was crystallised from aqueous 2-ethoxyethanol, giving yellow needles (3·9 g. = 1·0 g. of base), m. p. 167°.] The silver cyanide (1·85 g., 0·0137 g.-mol.) and barium carbonate (2·8 g., 0·0142 g.-mol.) were washed with hot distilled water and dried to constant weight at 110°. The silver cyanide was identified by evolution of cyanogen on heating (Found : Ag, 80·7. Calc. for AgCN : Ag, 80·6%). In the second experiment referred to above, the effluent gases were absorbed in ammonia solution which was then slowly evaporated in an open dish. The very small residue (ammonium acetate ?) was free from urea, for, when dissolved in a little 50% acetic acid, it gave no precipitate with a solution of xanthhydrol in alcohol. According to Wallis (*loc. cit.*) this proves the absence of cyanogen in the washed gases.

Attempted Conversion of p-*Nitrophenyl Thiocyanate into Disulphide in Presence of a Trace* (*only*) *of Pyridine*.—*p*-Nitrophenyl thiocyanate (6·0 g.), acetic acid (7·5 c.c.), and pyridine (0·1 g.) were heated on the steam-bath for 36 hrs. There was no crystallisation of disulphide during this time. Water (100 c.c.) was added, and the solid collected, and crystallised from 2-ethoxyethanol, giving *p*-nitrophenyl thiocyanate (5·1 g.), m. p. 128—129°. The result was exactly similar when dimethylaniline (0·1 g.) was used in place of the pyridine.

Attempted Conversion of p-*Nitrophenyl Thiocyanate into Disulphide in Toluene*.—The thiocyanate (6·0 g.), pyridine (1·4 g.), and toluene (35 c.c.) were refluxed for 24 hrs. The solvent was evaporated to 10 c.c., light petroleum (50 c.c.) added, and the solid collected and crystallised from 2-ethoxyethanol, giving *p*-nitrophenyl thiocyanate (4·7 g.), m. p. 130°.

Attempted Conversion of p-*Nitrophenyl Thiocyanate into Disulphide with Exclusion of Water*.—A mixture of acetic acid (15 c.c.), acetic anhydride (5 c.c.), and pyridine (1·4 g.) was refluxed under a calcium chloride tube for 5 hrs., *p*-nitrophenyl thiocyanate (6·0 g.) was added, and heating at 95—100° continued for 36 hrs. No disulphide separated, and the reaction liquid was poured into ice and water (200 c.c.), and the solid collected and crystallised from 2-ethoxyethanol, giving *p*-nitrophenyl thiocyanate (2·5 g.), m. p. 128—130°. The result was similar when dry dimethylaniline (2·0 g.) was added along with the thiocyanate to the dried acetic acid.

Reaction of p-*Nitrophenyl Thiocyanate with Pyridine Acetate in Methyl Alcohol*.—A mixture of the thiocyanate (6·0 g.), acetic acid (1 g.), pyridine (1·4 g.), and methyl alcohol (50 c.c.) was heated on the steam-bath under reflux for 18 hrs. After cooling, the solid was collected (4·1 g.), m. p. 182° not depressed by 4 : 4′-dinitrodiphenyl disulphide. The experiment was repeated, but each compound was dried carefully beforehand, and the mixture protected from atmospheric moisture. After cooling, the solid was collected and crystallised from 2-ethoxyethanol, giving *p*-nitrophenyl thiocyanate (5·2 g.), m. p. 131°.

Reaction of p-*Chlorophenyl Thiocyanate with Dimethylaniline*.—The thiocyanate (5·7 g., 0·0333 g.-mol.), acetic acid (7·5 c.c.), and dimethylaniline (2·0 g., 0·0167 g.-mol.) were heated at 130—135° in the apparatus described on p. 816. Evolution of gases took place during 18 hrs., and heating was continued for 20 hrs. in all. Water (50 c.c.) was added to the reaction liquid, and the disulphide (4·5 g., m. p. 73—74°) collected and dried in a vacuum. The filtrate was distilled with alkali into N-hydrochloric acid and found to contain 0·0132 g.-mol. of ammonia. The titration liquid was extracted with ether, and the dimethylaniline dried over sodium sulphide and distilled, giving a colourless oil (1·1 g.), b. p. 190—194°/760 mm. Silver cyanide (2·0 g., 0·0149 g.-mol.) (Found : Ag, 80·9%) and barium carbonate (2·95 g., 0·0150 g.-mol.) were obtained as previously.

Reaction between p-*Chlorophenyl Thiocyanate and* p-*Chlorothiophenol*.—A mixture of *p*-chlorothiophenol (2·4 g.) and *p*-chlorophenyl thiocyanate (2·8 g.) was heated in acetic acid at 100° in a slow stream of nitrogen, until evolution of hydrogen cyanide ceased (8 hrs.). During this time silver cyanide (2·6 g.) collected, and on dilution of the reaction liquid with ice and water, 4 : 4′-dichlorodiphenyl disulphide (4·3 g.), m. p. 73—74°, was obtained.

Reaction of p-*Nitrophenyl Thiocyanate with Methylaniline*.—A mixture of the thiocyanate (6·0 g.), acetic acid (7·5 c.c.), and methylaniline (3·6 g.) was heated for 12 hrs. at 95—100° and gave 4 : 4′-dinitrodiphenyl disulphide (4·8 g.), m. p. 182—183°, and ammonia corresponding to only 0·0101 g.-mol. The amount of barium carbonate (1·95 g., 0·0099 g.-mol.) was also less than in the preceding experiments although the amount of silver cyanide (1·8 g., 0·0134 g.-mol.) was normal. The oil extracted by ether from the titration liquid was distilled, giving methylaniline (1·8 g.), b. p. 194—198°/760 mm., and a higher fraction, b. p. 200—235°/760 mm. (1·0 g.), setting to a crystalline solid. From light petroleum (b. p. 60—80°) the latter crystallised in colourless plates (0·55 g.), m. p. 101°, not depressed by acetmethylanilide. Apparently the base is acetylated in the reaction and only partly hydrolysed in the Kjeldahl apparatus. In a repeat experiment on three times the above scale, the oil extracted from the steam-distillate was hydrolysed by refluxing for 12 hrs. with sodium hydroxide solution, and on distillation gave methylaniline (6·8 g.) and a very small high fraction, b. p. 220—230° (0·8 g.). The latter compound (m. p. 50—52°, depressed by acetmethylanilide) has not been further investigated.

Reaction of p-*Nitrophenyl Thiocyanate with Aniline*.—A mixture of the thiocyanate (6·0 g.), acetic acid (7·5 c.c.), and aniline (3·1 g.) after being heated for 12 hrs. at 95—100° gave the disulphide (5·0 g., m. p. 180°) and ammonia corresponding to only 0·0062 g.-mol. The amount of barium carbonate (1·1 g., 0·0056 g.-mol.) was also much less than usual though the weight of silver cyanide was normal (2·05 g., 0·0153 g.-mol.). The residual liquor in the Kjeldahl apparatus was cooled, and the solid collected and crystallised from benzene–light petroleum, giving *s*-diphenylguanidine (0·9 g.), m. p. 150° (no depression with authentic material). In a repeat experiment on six times the above scale, the acetic acid filtrate after separation of the disulphide was evaporated to dryness, the residue warmed with concentrated hydrochloric acid (50 c.c.) and water (250 c.c.), filtered (charcoal), and allowed to crystallise; colourless leaflets of acetanilide (12·0 g.), m. p. 100—104°, separated. The filtrate was made strongly alkaline with sodium hydroxide solution, and the precipitated solid crystallised from benzene–light petroleum (b. p. 60—80°), giving colouless plates (5·6 g.), m. p. 148°, not depressed by *s*-diphenylguanidine (Found : C, 74·0; H, 6·5; N, 19·6. Calc. for $C_{13}H_{13}N_3$: C, 73·9; H, 6·2; N, 19·9%).

Reaction of p-*Nitrophenyl Thiocyanate with Ammonia.*—The thiocyanate (6·0 g.), ammonium acetate (2·6 g., 0·0333 g.-mol.), and acetic acid (7·5 c.c.) were heated for 50 hrs. at 100—105°. Crystals slowly formed, and after standing for 6 hrs. they were collected and washed with a little acetic acid, giving the disulphide (4·9 g.), m. p. 182—183°. The filtrate contained 0·0421 g.-mol. of ammonia.

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