61. *Studies in the Thiazole Series. Part I. The Reaction between Thiourea and* s-*Dichloroacetone.*

By JOHN HARLEY-MASON.

The reaction between two molecules of thiourea and one molecule of *s*-dichloroacetone gives rise to two products according to the temperature of reaction. In boiling methyl alcoholic solution, 2-*amino*-4-*thiazolylmethyl*iso*thiourea dihydrochloride* (I) is formed, whereas by reaction without a solvent at *ca.* 220° the product is 2 : 2′-*diamino*-4 : 4′-spiro*thiazoline dihydrochloride* (II). At intermediate temperatures, mixtures of these products are obtained. Treatment of (I) with alkali leads to the normal *iso*thiourea dismutation, giving 2-*amino*-4-*mercaptomethylthiazole* (III).

THE reaction between thiourea and aldehydes and ketones halogenated in the α-position is well known, 2-aminothiazoles being obtained. There appears to be no record, however, of the condensation of thiourea with an αγ-dihalogenated ketone,* and accordingly the reaction between thiourea and *s*-dichloroacetone was studied.

The reaction was first examined in ethyl alcoholic solution. When an ethyl alcoholic solution of two molecular proportions of thiourea and one of dichloroacetone was heated gently, an exothermic reaction began when the temperature reached 50°. The mixture boiled spontaneously, the reaction being apparently complete in a few mixtures. On cooling, a large amount of white crystalline material separated. This material (*A*) decomposed without melting above 250°, was readily soluble in water, and analysis of a recrystallised sample indicated the empirical formula $C_5H_{10}N_4Cl_2S_2$, showing that it was formed from two molecules of thiourea and one molecule of dichloroacetone with the elimination of one molecule of water. On treatment with aqueous alkali and warming, decomposition occurred, giving an oil which contained a free thiol group, and dicyanodiamide. Evidently, therefore, this decomposition represented the normal dismutation of an *iso*thiourea (cf. *e.g.*, Arndt, *Ber.*, 1921, **54**, 2236). The substance (*A*) was therefore regarded as 2-*amino*-4-*thiazolylmethyl*iso*thiourea dihydrochloride* (I) and the thiol as 2-*amino*-4-*mercaptomethylthiazole* (III). The compound (III), which could be purified by high-vacuum distillation, formed a thick oil which failed to crystallise. It was characterised by oxidation to the corresponding *disulphide* (IV), which was a solid, and by the formation of a *diacetyl* and a *dibenzoyl* derivative.

It was observed that the comparatively violent reaction which took place between thiourea and dichloroacetone in very concentrated alcoholic solution gave a by-product on performing the alkaline dismutation of the product. This separated from the aqueous solution in small plates, m. p. 192—194° (decomp.) (*B*), was a diacid base, and formed a dihydrochloride (decomp. without melting above 250°) analysis of which indicated the same formula as (I). It was, however, not identical with (I), since on treatment with alkali it merely regenerated the base (*B*), which was stable to alkali. It appeared, therefore, that the dihydrochloride of (*B*) was formed as a by-product when the reaction was allowed to become violent so that local over-heating occurred. Accordingly, the reaction at temperatures higher than that of boiling ethyl alcohol was investigated.

When an intimate mixture of the two components was heated gently, reaction set in at about 60° and became very violent, the temperature rising to about 220°, with formation of a hard mass. On dissolving this in water, boiling with charcoal to remove dark impurities, and basifying the filtrate, an excellent yield of the base (*B*) was obtained. There was no indication of the formation of (I). The base was very sparingly soluble in most organic solvents, but could be recrystallised from water. It was a rather stable substance, being unchanged by boiling acid and by short boiling with 10% sodium hydroxide solution. Longer boiling with the latter reagent caused slow decomposition with darkening and evolution of ammonia, but no definite product could be identified. A *dihydrochloride* (II) and a *dipicrate* were readily obtained. It was regarded as 2 : 2′-*diamino*-4 : 4′-spiro*thiazoline* (V), isomeric with the free base corresponding to (I).

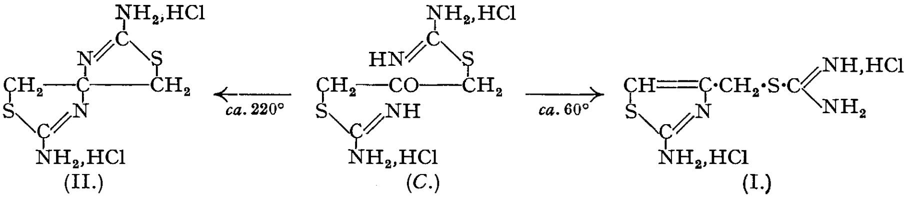
Evidently the reaction could proceed in either of two directions according to the temperature, and it was found that, by working in methyl alcoholic solution, (I) could be obtained free from

---

* *Note added in Proof.*—Since this paper was submitted for publication, work on the reaction between thiourea and *s*-dichloroacetone has been described by Sprague, Land, and Ziegler (*J. Amer. Chem. Soc.*, 1946, **68**, 2155). These authors prepared the compound (I) by reaction of the two components in ethyl alcoholic solution, and from it the disulphide (IV) by a method similar to that described above. They did not, however, examine the reaction at higher temperatures and consequently did not obtain the spirocyclic compound (V).

(II), while on the other hand, by working without a solvent at a much higher temperature, (II) could be obtained free from (I). At intermediate temperatures, mixtures were obtained, *e.g.*, in 2-ethoxyethyl alcohol (b. p. 135°) a mixture containing approximately 60% of (I) and 40% of (II) was obtained. In ethyl alcohol, (I) alone was formed if the solution was relatively dilute, but in concentrated solution, when local overheating may have occurred due to the violence of the reaction, a small amount of (II) was formed.

The reaction may be represented as under, elimination of water from the hypothetical intermediate (*C*) occurring in either of two directions.



It was of interest to know whether the reaction paths were independent, or whether (I) was always first formed, and converted into (II) at higher temperatures, Both (I) and (II) decomposed completely without melting above 250°, without showing any signs of previous interconversion. (I) was recovered completely unchanged after 12 hours' boiling in 2-ethoxyethyl alcohol containing a little water. The free base (V) decomposed completely at its melting point, while the free base from (I), prepared by basifying an ice-cold concentrated solution with the calculated amount of alkali, decomposed very readily even at room temperature to give (III), and no sign of isomerisation could be detected. It seems therefore that the two reaction paths are quite independent.

An attempt was made to prepare a bissulphanilyl derivative of the disulphide (IV), by treatment with *p*-acetamidobenzenesulphonyl chloride in pyridine. No crystalline product could, however, be isolated and it appeared that the sulphonyl chloride had attacked the disulphide linkage. Attempts to cause the spirocyclic base to react with the same reagent were also unsuccessful. The disulphide was, however, readily converted into a *diacetyl* derivative by acetic anhydride.

Resolution of the racemic *spiro*-compound (II) was not attempted.

EXPERIMENTAL.

2-*Amino*-4-*thiazolylmethyl*iso*thiourea Dihydrochloride* (I).—Finely powdered thiourea (31 g.) and *s*-dichloroacetone (25 g.) were added to methyl alcohol (200 c.c.). The mixture was heated under reflux on the water-bath. A vigorous reaction set in, and subsided in about 5 minutes. Heating was continued for a further 10 minutes. On cooling, the *product* (47 g., 90%) separated as a white crystalline mass. A small portion was recrystallised from alcohol containing a little water and formed prisms, which decomposed without melting above 250° (Found : C, 22·5; H, 4·0; N, 21·2. $C_5H_8N_4S_2,2HCl$ requires C, 22·9; H, 3·8; N, 21·5%).

The dihydrochloride (2·6 g.) was dissolved in water (6 c.c.) and 10% sodium hydroxide solution (8 c.c.) added with ice-cooling and stirring. The *base* which separated in small white plates was rapidly filtered off, washed with a little water, and dried in a vacuum desiccator; m. p. 106° (decomp.) (on rapid heating) (Found : N, 29·6. $C_5H_8N_4S_2$ requires N, 29·8%). The compound was unstable and soon decomposed on standing even at room temperature, acquiring a " mercaptan " odour.

2-*Amino*-4-*mercaptomethylthiazole* (III).—2-Amino-4-thiazolylmethyl*iso*thiourea dihydrochloride (52 g.) was dissolved in water (150 c.c.), and a solution of sodium hydroxide (16 g.) in water (80 c.c.) was added. The mixture was rapidly heated to 100°, kept at this temperature for 2 minutes, and rapidly cooled; some of the product then separated as an oil. Sodium hydrosulphite (3 g.) was added to prevent oxidation of the thiol, and the mixture was extracted with ether (3 × 100 c.c.). The ethereal solution was dried (Na_2SO_4), the ether removed, and the residual pale yellow oil distilled in a vacuum in a current of hydrogen. The *product* formed a very viscous oil, b. p. 135—140°/2 mm., which failed to crystallise. Yield, 15 g. (51%) (Found : C, 32·4; H, 4·0; N, 19·1. $C_4H_6N_2S_2$ requires C, 32·8; H, 4·1; N, 19·2%). Concentration of the aqueous solution yielded dicyanodiamide (m. p. and mixed m. p. 205°). A portion of the thiol was shaken with benzoyl chloride and aqueous sodium hydroxide, yielding the *dibenzoyl* derivative, needles (from alcohol), m. p. 147—148° (Found : N, 7·8. $C_{18}H_{14}O_2N_2S_2$ requires N, 7·9%). Another portion was boiled with acetic anhydride and acetic acid, and poured into water to precipitate the *diacetyl* derivative; white felted needles (from dilute alcohol), m. p. 145—147° (Found : N, 12·4. $C_8H_{10}O_2N_2S_2$ requires N, 12·2%).

Bis-(2-*amino*-4-*thiazolylmethyl*) *Disulphide* (IV).—2-Amino-4-mercaptomethylthiazole (3 g.) was dissolved in 2N-hydrochloric acid (10 c.c.) and 3% hydrogen peroxide (12 c.c.) was added. After 1 hour at room temperature, the *disulphide* was precipitated by the addition of ammonia and recrystallised from alcohol (sparingly soluble); it formed prisms, m. p. 168° (Found : N, 19·5. $C_8H_{10}N_4S_4$ requires N, 19·3%). A portion was acetylated by boiling with acetic anhydride and acetic acid, and poured into water; the *diacetyl* derivative separated and was recrystallised from 2-ethoxyethyl alcohol, from which it separated in prisms, m. p. 227—228° (Found : N, 14·4. $C_{12}H_{14}O_2N_4S_2$ requires N, 14·8%).

2 : 2′-*Diamino*-4 : 4′-spiro*thiazoline* (V).—An intimate mixture of thiourea (16 g.) and dichloroacetone (12·5 g.) was placed in a 200 c.c. bolt-head flask and heated cautiously on the water-bath. When the temperature of the mixture reached *ca.* 60°, a violent reaction began, and the flask was at once removed from the water-bath. The temperature rose rapidly to *ca.* 220° and the mixture, which had at first liquefied, set to a hard solid mass and some darkening occurred. When cold, the mass was chipped out, ground, and extracted with boiling alcohol (100 c.c.) to remove soluble impurities. The residue was dissolved in water (100 c.c.), boiled with charcoal, and ammonia added to the hot filtrate. The product was precipitated in crystalline form, and after cooling was collected and washed. Recrystallised from water (rather sparingly soluble) it formed prisms, m. p. 192—194° (decomp.) (Found : C, 32·2; H, 4·6; N, 30·1. $C_5H_8N_4S_2$ requires C, 31·9; H, 4·3; N, 29·8%). Yield, 14·5 g. (78%). Treatment with hydrochloric acid gave the *dihydrochloride* (prisms) which was recrystallised by dissolving it in a small amount of hot water and adding concentrated hydrochloric acid until separation began; it decomposed without melting above 250° (Found : Cl, 27·5. $C_5H_8N_4S_2,2HCl$ requires Cl, 27·1%). The *dipicrate* formed yellow prisms from hot water, m. p. 210—212° (decomp.) (Found : N, 15·3. $C_5H_8N_4S_2,2C_6H_3O_7N_3$ requires N, 15·1%).

Reaction in 2-Ethoxyethyl Alcohol.—Finely powdered thiourea (50 g.) and dichloroacetone (40 g.) were added to 2-ethoxyethyl alcohol (200 c.c.), and the mixture was heated over a free flame under reflux until reaction set in; the flame was then at once removed. As the reaction proceeded, the mixture boiled and some of the product began to separate. After cooling, the product was filtered off. Yield, 75 g. of mixed hydrochlorides.

The mixed hydrochlorides (52 g.) were dissolved in water (150 c.c.) and to the boiling solution a concentrated solution of sodium hydroxide (16 g.) was added. Some of the spirocyclic base separated at once and was filtered off hot. The filtrate was cooled, treated with sodium hydrosulphite (3 g.), and extracted with ether (3 × 100 c.c.). Some more of the spirocyclic base separated during the extraction and was filtered off. Total yield, 15·1 g. The ethereal solution was worked up for the thiol as above. Yield, 13·4 g.

The greater part of this work was done in No. 2 Anti-Gas Laboratory R.E. during 1944, and it was completed at the Chemical Defence Experimental Station, Porton, Wilts.

I am indebted to the Director General of Scientific Research (Defence), Ministry of Supply, and to the War Office, for permission to publish these results, and to Mr. J. H. R. Slade for much experimental assistance. Micro-analyses were performed by Mr. G. Ingram.

UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE.

[*Received, June* 29*th*, 1946.]