50. *Studies in the Azole Series. Part III. The Interaction of Aminoacetonitrile and Carbon Disulphide.*

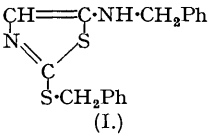
By A. H. Cook, Sir Ian Heilbron, and A. L. Levy.

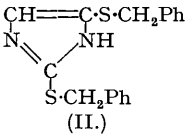
Pure aminoacetonitrile and carbon disulphide under selected neutral conditions give 5-*amino*-2-*mercaptothiazole* (XI), whereas in presence of acetone the corresponding Schiff's *base* (XIII) is obtained. The compound (XI) is converted with remarkable ease into 2 : 4-*dithiohydantoin* (XIV), some derivatives of which can also be prepared by a more direct route, or into 2-*mercaptothiazol*-5-*one* (VI). Aminoacetonitrile and acetone condense to give 5-*imino*-2 : 2-*dimethyloxazolidine* (X) which readily suffers ring fission so that with carbon disulphide it afforded the *dithiocarbamic acid* derivative (IV); the latter was also formed by interaction of crude aminoacetonitrile and carbon disulphide under other conditions. The compound (IV) could also be converted into the mercaptothiazolone (VI) by the action of mineral acid.

In Part II of this series (*J.*, 1947, 1598) the reaction between α-aminonitriles and carbon disulphide was shown to lead generally and smoothly to 5-amino-2-mercaptothiazoles or to dithiohydantoins according to conditions. It was stated, however, that the behaviour of aminoacetonitrile in this connection was more complex, and the present paper is concerned more particularly with the intricacies of this reaction.

It is recorded (U.S.P. 2,143,816) that aminoacetonitrile and carbon disulphide afford dithiohydantoin, but reproduction of the conditions described gave, in our hands, a product which consisted chiefly of a brown resinous material with a crystalline substance as a minor constituent. Subsequently, the latter was recognised as 5-amino-2-mercaptothiazole (XI), a compound which was more conveniently prepared in other ways. It is noteworthy that the experiment in the above patent specifies the use of 2 molecular proportions of aminoacetonitrile, these proportions being employed in the case of other nitriles also. It seems likely that the inconclusiveness of the experiment in our hands, and incidentally the apparent divergence between the results described in the patent and those in this series of papers, are associated with the use of an excess of base, for what are indubitably the primary products, *i.e.*, 5-amino-2-mercaptothiazoles, have in several instances been shown to be susceptible of change under basic conditions. For this reason most of the following experiments employed at least 1 molecular proportion of carbon disulphide.

In preliminary experiments, aminoacetonitrile and carbon disulphide gave an exceedingly unstable compound which darkened eventually to a black powder on being worked up, though by simultaneous benzylation a small yield of a crystalline base, $C_{17}H_{16}N_2S_2$, was obtained. The latter liberated benzylthiol on treatment with alkali (*i.e.*, it contained at least one *S*-benzyl grouping) and two structures, (I) and (II), came into consideration. Later in this work


(I.)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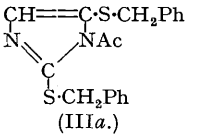
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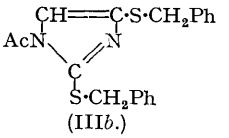
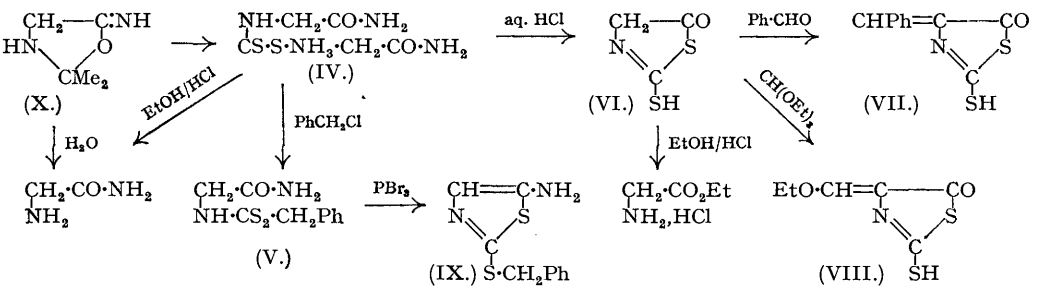

(IIIb.)

dithiohydantoin itself was obtained, and on benzylation afforded the above base, which must therefore be 2 : 4(5)-*dibenzylthioglyoxaline* (II). The exclusion of structure (I) was confirmed by the absorption spectrum of the base which differed markedly from all other 5-aminothiazoles studied (Parts I and II). The base gave a *monoacetyl* derivative which on being kept at just above its m. p. was converted into an *isomeride*, both compounds being hydrolysed under mild conditions to the original base; they are therefore formulated as (III*a*, *b*).

In view of these results attempts were made to carry out the reaction with free, or virtually free, nitrile in organic solvents. To this end aminoacetonitrile sulphate was titrated in ethanol suspension with sodium ethoxide. When the solution was treated with carbon disulphide, the product was pigmented and of indefinite properties. However, similar experiments in acetone suspension gave a compound, $C_5H_{12}O_2N_4S_2$, which for the following reasons was formulated as the *carbamylmethylammonium carbamylmethyldithiocarbamate* (IV). Aminoacetamide hydrochloride was produced by the action of ethanolic hydrogen chloride on it, and benzylation of the supposed dithiocarbamate gave *benzyl carbamylmethyldithiocarbamate* (V), which was also obtained directly from aminoacetamide. The compound (IV) possessed the notable property of being smoothly converted by cold dilute aqueous mineral acid into a compound, $C_3H_3ONS_2$, which was also obtained by acidifying an aqueous solution of the sodium

dithiocarbamate derived from aminoacetamide. The new compound afforded glycine ester hydrochloride on treatment with ethanolic hydrogen chloride and is formulated as 2-*mercapto-*



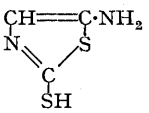
thiazol-5-one (VI), *S*-alkyl derivatives of which have previously been obtained in these laboratories in connection with work on penicillin by dehydrating dithiocarbamic esters of glycine. Formulation (VI) was confirmed by the ready condensation of the compound with benzaldehyde to give 2-*mercapto*-4-*benzylidenethiazol*-5-*one* (VII) and with ethyl orthoformate to yield 2-*mercapto*-4-*ethoxymethylenethiazol*-5-*one* (VIII). On acetylation the parent compound (VI) gave a *monoacetyl* derivative. Other potentialities of 2-mercaptothiazol-5-one, which is more conveniently prepared by another procedure described below, are being examined and will be reported separately. By contrast with the behaviour of the salt (IV), when the ester (V) was treated with phosphorus tribromide it lost the elements of water to give a *hydrobromide* of a base which was evidently 5-*amino*-2-*benzylthiothiazole* (IX). This reaction, which appears to be the first example of the formation of a 5-aminothiazole from an α-aminoamide, proceeded rapidly and quantitatively at room temperature.

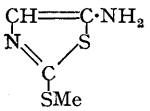
The mechanism of the formation of compound (IV) was revealed on keeping pure aminoacetonitrile in cold acetone with a trace of sodium ethoxide, whereupon a crystalline compound, $C_5H_{10}ON_2$ (*i.e.*, $NH_2{\cdot}CH_2{\cdot}CN + COMe_2$), separated. The latter, presumably 5-*imino*-2:2-*dimethyloxazolidine* (X) was evidently the intermediate by which the remarkably facile hydrolysis of the nitrile leading to (IV) was accomplished. Thus, when (X) was treated with cold water it gave aminoacetamide and acetone, when exposed to moist air it gave aminoacetamide carbonate (?) identical with the product obtained from aminoacetamide itself in air, and with ethanolic carbon disulphide it afforded the salt (IV) in excellent yield. The ease of formation of (X) is notable, and the generality of this kind of reaction is being studied. It is noteworthy that both compound (X) and aminoacetamide are formed in substantially quantitative yield, the latter being indeed most easily made by this means.

When aminoacetonitrile sulphate, suspended in acetone, was treated with sodium methoxide followed by carbon disulphide, it appeared that neutralisation was more prompt than with sodium ethoxide and that formation of (X) and hence of (IV) was practically eliminated. Under these conditions the product consisted of a compound (A) $C_6H_8N_2S_2$, whereas with slight modifications (see Experimental) another compound (B), also $C_6H_8N_2S_2$, was obtained together with a third product the nature of which was not elucidated. The compound (A) was also easily obtained from pure aminoacetonitrile, acetone, and carbon disulphide. On the other hand, when pure aminoacetonitrile was treated with carbon disulphide in ethyl acetate or other solvents so that any local excess of base was avoided, an excellent yield of a compound (C), $C_3H_4N_2S_2$, resulted. The last apparently contained both basic and pseudo-acidic groups, and behaved generally in the manner of 5-aminothiazoles. It was identical with the minor component of the mixture obtained according to U.S.P. 2,143,816 mentioned above, and is regarded as 5-*amino*-2-*mercaptothiazole* (XI). It afforded 5-*acetamido*-2-*mercaptothiazole*, which still dissolved in sodium hydroxide, and coupled, presumably in the 4-position, with diazonium salts. When the above condensation between aminoacetonitrile and carbon disulphide was effected in presence of methyl iodide a homologue of (XI), $C_4H_6N_2S_2$, was obtained. As this was basic but did not exhibit the pseudo-acidic properties of the thiazole (XI), it is best formulated as 5-*amino*-2-*methylthiothiazole* (XII). The thiazole (XI) condensed with acetone to give compound (A) (above), which must then be formulated as the acetone Schiff's *base* (XIII), these structures being compatible with the U.V. absorption of the compounds.

The thiazole (XI) exhibited notable reactivity in two other directions. On treatment with moderately concentrated mineral acid, it first passed into solution, to be replaced later by a precipitate of 2-mercaptothiazol-5-one (VI), this being the more direct route to that compound.

On the other hand, in cold aqueous alkali carbonate the product was a sensitive compound which was undoubtedly *dithiohydantoin* (XIV). It was characterised as its *diacetyl* derivative which


(XI.)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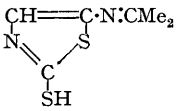
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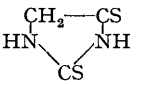
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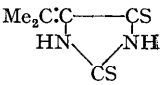
(XV).

readily lost its acetyl groups in sodium hydroxide but not in carbonate solution. Thus, when treated simultaneously with sodium hydroxide and benzyl chloride the acetyl derivative passed into the di-*S*-benzyl compound (II), which had been isolated in early exploratory experiments; this preparation was more satisfactory than direct benzylation of the dithiohydantoin (XIV) owing to the formation of intensely coloured products by that compound in alkaline solution. Incidentally, behaviour of this kind is exhibited by 4- but not by 2-thiohydantoin (Johnson and Chernoff, *J. Amer. Chem. Soc.*, 1912, **34**, 1208). The nature of the dithiohydantoin was conclusively demonstrated by its desulphurisation by means of Raney nickel to give glyoxaline, identified with an authentic specimen. Dithiohydantoin was a remarkably strong acid, liberating carbon dioxide from sodium hydrogen carbonate and even dissolving in aqueous sodium acetate though it was insoluble in water. Dithiohydantoin was also formed from compound (XI) by means of cold alcoholic potassium hydroxide or, in poorer yield, of cold aqueous alkali, being isolated in the former instance *via* a potassium salt. Treatment of the latter with methyl iodide led to methylation and quaternisation with the formation of the *methiodide* of 2-*methylthio*-4-*mercaptoglyoxaline*. The action of alcoholic sodium methoxide or pyridine on the thiazole (XI) gave changed products which, however, were not dithiohydantoin (as they did not give the characteristic acetyl derivative), nor was this compound obtained by the direct interaction of aminoacetonitrile and carbon disulphide in presence of pyridine, ammonia, or aqueous sodium carbonate. On the other hand, when the thiazole (XI) was warmed in pyridine in presence of acetone the sole product was compound (B) (above) which, having regard to its properties and the known rearrangement of 5-amino-2-mercaptothiazoles under similar conditions was formulated as 5-iso*propylidenedithiohydantoin* (XV).

The compound (XI) completely inhibited the growth of *Staphyllococcus aureus* at a dilution of 1 : 50,000, an activity comparable with that of the 4-methyl homologue (Part II, *loc. cit.*) and with that of other mercaptothiazoles (Gibbs and Robinson, *J.*, 1945, 925). In contrast, dithiohydantoin had no appreciable activity of this kind.

Experimental.

Reactions with Aminoacetonitrile Salts.—Aminoacetonitrile sulphate (30·8 g.) in water (50 c.c.) was treated with 20% potassium hydroxide until the solution was alkaline to brilliant-yellow, followed at 0° by potassium hydroxide (11 g.) in water (50 c.c.), carbon disulphide (15 g.), and benzyl chloride (25 g.), and the mixture shaken overnight. The deep brown liquid was extracted with ether, and the extract chromatographed in acetone–benzene (1 : 10) on alumina. The apparently homogeneous material from the eluate consisted of 2 : 4(5)-*dibenzylthioglyoxaline* and crystallised from aqueous methanol in colourless needles, m. p. 95° (Found : C, 65·5; H, 5·1; N, 8·9. $C_{17}H_{16}N_2S_2$ requires C, 65·4; H, 5·1; N, 9·0%). Light absorption (ethanol) : $\lambda_{max.}$ = 2570, 2640 A.; $E^{1\%}_{1\,cm.}$ = 275, 275. Acidification of the aqueous layer (above) gave benzyl *N*-carboxymethyldithiocarbamate, m. p. 163—165°. 2 : 4(5)-Dibenzylthioglyoxaline (3·2 g.), acetic anhydride (5 c.c.), and a few drops of sulphuric acid were warmed on the steam-bath for 5 mins. Evaporation and crystallisation from ethanol or benzene–light petroleum gave 1- or 3-*acetyl*-2 : 4-*dibenzylthioglyoxaline* as needles, m. p. 89—90° (Found : C, 64·3; H, 5·1; N, 8·4%). $C_{19}H_{18}ON_2S_2$ requires C, 64·4; H, 5·1; N, 7·9%). Light absorption (chloroform) : $\lambda_{max.}$ = 2600 A., $E^{1\%}_{1\,cm.}$ = 300; $\lambda_{inflex.}$ = 2800, $E^{1\%}_{1\,cm.}$ = 200. When the preceding compound was maintained at just above its m. p. for 30 mins. it resolidified. The *isomeride* crystallised from ethanol in well-formed plates, m. p. 99—100° (Found : C, 64·3; H, 5·1; N, 8·2%). Light absorption (chloroform) : $\lambda_{max.}$ = 2550, 3080A., $E^{1\%}_{1\,cm.}$ = 270, 135. When either of the above acetyl compounds was kept with ethanolic hydrogen chloride for several days it passed into solution and on evaporation a hydrochloride was obtained. Liberation of the free base in each case gave 2 : 4(5)-dibenzylthioglyoxaline, m. p. 95° undepressed by the original material.

A solution of sodium (4·9 g.) in ethanol (120 c.c.) was added during 2 hrs. to a fine, stirred suspension of aminoacetonitrile sulphate (26 g.) in acetone (150 c.c.) until neutral to phenolphthalein. Sodium sulphate was filtered off, and carbon disulphide (15 c.c.) added to the filtrate. The crystalline precipitate (6 g.) was removed, and a further crop (3·5 g.) obtained by diluting the mother-liquor with ether and keeping it overnight at 0°. Crystallisation of the combined deposit by adding ethanol or acetone to a solution in the minimum of water gave *carbamylmethylammonium carbamylmethyldithiocarbamate* (IV) (6·8 g.) as rectangular plates or needles, m. p. 139° (decomp.) (Found : C, 27·0; H, 5·6; N, 24·7; S, 28·6. $C_5H_{12}O_2N_4S_2$ requires C, 26·8; H, 5·4; N, 25·0; S, 28·6%). The compound (1·2 g.)

was obtained directly by adding carbon disulphide (1 c.c.) to a solution of aminoacetamide (1 g.) in acetone (30 c.c.). In one experiment with the nitrile sulphate, the acetone filtrates were evaporated and treated with ethanol–ether to give an unidentified *product* which crystallised from water in prismatic needles, m. p. 230—231° (decomp.) (Found: C, 38·9; H, 5·8; S, 26·2. $C_8H_{14}ON_4S_2$, *i.e.*, $2NH_2{\cdot}CH_2{\cdot}CN + CS_2 + COMe_2$, requires C, 39·0; H, 5·7; S, 26·0%).

The salt (IV) (2·0 g.) in water (10 c.c.) was shaken overnight with benzyl chloride (2 c.c.) in ether (10 c.c.). The product (1·4 g.; 65%) was *benzyl carbamylmethyldithiocarbamate* (V), which crystallised from toluene in feathery clusters of laths or from water in large plates, m. p. 119° (Found: C, 49·7; H, 5·4; N, 11·7; S, 26·9. $C_{10}H_{12}ON_2S_2$ requires C, 50·0; H, 5·0; N, 11·7; S, 26·7%). It was soluble in acetone or methanol, moderately soluble in ethyl acetate, and insoluble in ether; it was soluble without change in cold 2N-sodium hydroxide. This substance was obtained in poor yield by shaking aminoacetamide with carbon disulphide in 2N-sodium hydroxide and benzyl chloride in ether; the main product was benzyl *N*-carboxymethyldithiocarbamate, m. p. 164°, which was recovered on acidifying the aqueous layer. The original dithiocarbamic acid salt (1 g.) was refluxed for 5 mins. with acetic anhydride (5 c.c.), and the reagent then removed in a vacuum. The *product* (0·3 g.) crystallised in contact with water and recrystallised from ethanol in needles or small prisms, m. p. 176° (Found: C, 38·3; H, 3·8; S, 22·8. $C_9H_{10}O_3N_4S_2$ requires C, 37·8; H, 3·5; S, 22·4%). The salt (IV) (0·7 g.) was shaken with ethanolic hydrogen chloride (10 c.c.) for 20 mins. The crystalline form had changed, and the solid (0·65 g., 95%) consisted of aminoacetamide hydrochloride, which recrystallised from acetic acid in blades, m. p. 203—204° (decomp.) (Found: C, 22·1; H, 6·2. Calc. for $C_2H_7ON_2Cl$: C, 21·7; H, 6·3%); this compound was also prepared with the same m. p. by adding ethanolic hydrogen chloride to aminoacetamide in acetic acid, though Bergell and Wulfing (*Z. physiol. Chem.*, 1910, **64**, 353) quote the m. p. as 186—189°. The original salt (IV) (2·0 g.) in concentrated hydrochloric acid (5 c.c.) was cooled to 0° and diluted with water (10 c.c.), whereupon plates or clusters of small needles separated. *2-Mercaptothiazol-5-one* (VI) (1 g., 85%) recrystallised from benzene in bold needles which charred indefinitely above 300° (Found: C, 27·1; H, 2·3; N, 10·6. $C_3H_3ONS_2$ requires C, 27·1; H, 2·3; N, 10·5%). Light absorption (chloroform): $\lambda_{max.} = 2390, 2800$ A.; $E^{1\%}_{1cm.}$ 550, 1200. The compound dissolved in cold ethanol, methanol, acetone, ethyl acetate, or acetic acid, and in a large volume of hot benzene, chloroform, or ether. It gave an intense red-violet colour when treated with mild oxidising agents (*e.g.*, air, iodine, or ferric chloride) in presence of sodium acetate or bicarbonate but not in caustic alkali or dilute acid; the compound also discoloured easily on keeping. 2-Mercaptothiazol-5-one was also prepared by shaking together aminoacetamide (0·7 g.), potassium carbonate (1·4 g.), carbon disulphide (0·8 g.), and water (5 c.c.) for 5 hrs. at room temperature. The resulting solution was cooled and strongly acidified, the mercaptothiazolone (0·6 g.) being precipitated. A further preparation is described below.

When 2-mercaptothiazol-5-one (0·5 g.) was kept overnight with saturated ethanolic hydrogen chloride (10 c.c.), it slowly passed into solution, and needles (0·33 g.) of glycine ester hydrochloride, m. p. 148°, separated; addition of ether to the filtrate precipitated a further crop (total yield, 80%). The dithiocarbamate (IV) (1 g.) in water (6 c.c.) was treated with benzaldehyde (0·5 g.) and ethanol (3 c.c.) to give a homogeneous solution. Addition of concentrated hydrochloric acid (30 drops) gave a yellow crystalline precipitate of *2-mercapto-4-benzylidenethiazol-5-one* (0·2 g.), which recrystallised from ethanol in yellow needles, m. p. 211° (Found: C, 54·5; H, 3·3; N, 6·3. $C_{10}H_7ONS_2$ requires C, 54·3; H, 3·2; N, 6·3%). 2-Mercaptothiazol-5-one (0·75 g.), ethyl orthoformate (3 c.c.), and acetic anhydride (4 c.c.) were heated together on the steam-bath for 2 hrs.; the crystals (0·5 g.) were removed and washed with benzene. *2-Mercapto-4-ethoxymethylenethiazol-5-one* recrystallised from acetic acid in buff diamond-shaped needles, m. p. 209° (decomp.) (Found: C, 38·2; H, 4·0; N, 7·5; S, 33·55. $C_6H_7O_2NS_2$ requires C, 38·1; H, 3·7; N, 7·4; S, 33·9%). Light absorption (ethanol): $\lambda_{max.} = 2280, 2790, 3450$ A.; $E^{1\%}_{1cm.} = 260, 600, \sim 1400$.

It gave very intense colours with quinaldine methiodide, 2-methylbenzthiazole methiodide, 2-phenyloxazolone, etc., in ethanolic triethylamine. 2-Mercaptothiazol-5-one (1·3 g.), acetic anhydride (5 c.c.), and acetone (1 c.c.) were refluxed together for 45 mins. and excess of reagents removed in a vacuum. Rubbing the residue with water caused it to crystallise (yield, 1·3 g.), and the product was then distilled at 50° in high vacuum and finally crystallised from ether–light petroleum. The *monoacetyl* derivative of 2-mercaptothiazol-5-one formed pale yellow blades, m. p. 50° (Found: C, 34·4; H, 3·0; N, 7·9; S, 35·8. $C_5H_5O_2NS_2$ requires C, 34·3; H, 2·9; N, 8·0; S, 36·6%).

A suspension of aminoacetonitrile sulphate (13 g.) in acetone (60 c.c.) containing a little phenolphthalein was titrated with a solution of sodium (2·3 g.) in methanol (60 c.c.). Neutralisation was rapid (5 mins.) (cf. experiments in ethanol above), and after sodium sulphate had been filtered off, carbon disulphide (10 g.) was added to the filtrate. A red colour developed, and after 30 mins. yellow crystals (3·5 g.) of the acetone Schiff's *base* of 5-amino-2-mercaptothiazole were collected; the compound was best crystallised by chilling a solution in acetone under nitrogen, then separating as very pale cream laths, m. p. 167° (decomp.) (Found: C, 42·5; H, 4·9; N, 16·0; S, 37·4. $C_6H_8N_2S_2$ requires C, 41·9; H, 4·7; N, 16·3; S, 37·2%). The compound dissolved in aqueous sodium hydroxide and, in an inert atmosphere, the solution yielded a yellow powder, m. p. > 400°, on acidification. It was also changed on standing with dilute hydrochloric acid, yellow crystals of high m. p. being deposited.

Aminoacetonitrile sulphate (90 g.) was covered with methanol (400 c.c.) containing a trace of phenolphthalein, and a solution of sodium (16 g.) in methanol (400 c.c.) added during 40 mins. so that the mixture was permanently colourless. Sodium sulphate was filtered off, and the filtrate evaporated in a vacuum. The residual oily nitrile was dissolved in acetone (50 c.c.) and ether (50 c.c.) and treated with carbon disulphide (17 g.) under reflux. *5-iso*Propylidene-2 : 4-dithiohydantoin (see below), m. p. 235° (decomp.), separated in small bright orange needles (6 g.). The filtrate was treated with a further quantity (10 c.c.) of carbon disulphide, and after 2½ hrs. the acetone Schiff's base of 5-amino-2-mercaptothiazole (9 g.), m. p. 161° (decomp.), was removed. Dilution of the filtrate with water gave a product which recrystallised from water in colourless needles, m. p. 205° (decomp.) (Found: C, 42·6; H, 5·3; N, 20·5; S, 31·5%). The above substance (1 g.) was refluxed with 15% hydrochloric acid (10 c.c.)

for 1·5 hrs. Hydrogen sulphide was evolved, and on cooling a halogen-free solid separated; the compound crystallised from water in colourless rectangular prisms, m. p. 243° (decomp.) (Found : C, 41·05; H, 5·35; N, 11·6; S, 13·5%).

Reactions with Aminoacetonitrile.—Preparation. The following appears to be an improvement for large-scale work on that described in *Org. Synth.*, Coll. Vol. I, 298. Concentrated sulphuric acid (500 c.c.) was added during 30 mins. to ethanol (2·5 l.) stirred in a 5-l. flask with moderate cooling. Methyleneaminoacetonitrile (700 g.) (*Org. Synth.*, Coll. Vol. I, 355) was rapidly added to the solution at 45°. After 5—10 mins. crystals separated and were filtered off after a further hour's stirring, and washed with ethanol (1 l.). The product was dissolved in water (1 l.), and the solution run into stirred spirit (3 l.), the neutral sulphate (Found : equiv., 104. Calc. : 105), m. p. 177° (decomp.), being precipitated (655 g.). The filtrate deposited a further crop (70 g.) overnight (total yield 67%). The sulphate (180 g.) was finely powdered, covered with methanol (150 c.c.) containing a trace of phenolphthalein, and neutralised by adding a solution of sodium (32 g.) in methanol (800 c.c.) to the stirred mixture during 1 hour under nitrogen, so that the indicator remained permanently colourless. Sodium sulphate was filtered off and the filtrate evaporated at room temperature in a vacuum. Aminoacetonitrile (64 g. or 82% based on sodium used) distilled without decomposition at 65°/8 mm. and could be stored for several weeks at 0° under nitrogen without change.

Aminoacetonitrile (5 g.) in dry acetone (25 c.c.) was treated with 0·5 c.c. of a solution of sodium (0·1 g.) in ethanol (3·5 c.c.) at 0°. After 15 mins. the solid (9 g.; 90%) was collected; *5-imino-2 : 2-dimethyloxazolidine* crystallised best from dry acetone in bold prismatic needles, m. p. 101—102° (Found : C, 52·2; H, 8·6; N, 24·6. $C_5H_{10}ON_2$ requires C, 52·6; H, 8·8; N, 24·6%). The compound quickly deliquesced and after several days the syrup resolidified to a colourless substance, m. p. 126° (decomp.), which evolved carbon dioxide when treated with dilute mineral acid. The same substance was produced when aminoacetamide was exposed to moist air; Heintz (*Annalen*, 1868, **148**, 195) and Koenigs and Mylo (*Ber.*, 1908, **41**, 4429) noted this property of aminoacetamide but did not record the m. p. of the product. The oxazolidine (3 g.) was dissolved in water (5. c.c.) and the solution evaporated in a vacuum. The residue was dissolved in ethanol (50 c.c.), and carbon disulphide (1 c.c.) added. After standing overnight the salt (IV) (see above), m. p. 133—134° (decomp.) (2·8 g., 95%), was collected.

A solution of carbon disulphide (15 g.) in ethyl acetate (25 c.c.) was treated, with stirring, moderate cooling and in an atmosphere of nitrogen, with a solution of aminoacetonitrile (11 g.) in ethyl acetate (50 c.c.) added during 40 mins., and stirring continued for a further 30 mins. Dense granular yellow crystals of *5-amino-2-mercaptothiazole* (21·5 g., 82%) were collected and washed with ether. The compound darkened at 110° and melted only gradually up to about 230° (Found : N, 21·0. $C_3H_4N_2S_2$ requires N, 21·2%). Light absorption (methanol) : $\lambda_{max.} = 2280, 3380$ A.; $E^{1\%}_{1\,cm.} = 340, 810$. It was difficult to recrystallise, was soluble in methanol, dilute alkali or acid, and moderately so in water, solutions discolouring easily on exposure to air. It gave the following colour reactions : (*a*) a chocolate-coloured precipitate with nitrous acid, (*b*) a black precipitate with bromine-water in neutral or acid solution, (*c*) a deep red colour with methanolic cinnamaldehyde in presence of hydrogen chloride, and (*d*) a deep purple colour with methanolic glyoxal in presence of triethylamine. In an experiment carried out according to U.S.P. 2,143,816 a small quantity of the above aminomercaptothiazole was obtained but none of the dithiohydantoin claimed; moreover, it seemed that the latter product was not present even in crude form in any substantial quantity, for various fractions of the product failed to give the acetyl derivative of the dithiohydantoin described below.

5-Amino-2-mercaptothiazole (1·3 g.), suspended in methanol (15 c.c.), was treated with acetic anhydride (2 c.c.). After a few moments the base passed into solution and its *acetyl* derivative (1·25 g.) separated. This recrystallised from water as colourless laths, m. p. 247° (decomp.) (Found : C, 34·8; H, 3·6; S, 36·8. $C_5H_6ON_2S_2$ requires C, 34·5; H, 3·5; S, 36·8%), which were sparingly soluble in organic solvents except pyridine, but dissolved in 2N-sodium hydroxide to give a solution which coupled smoothly with benzenediazonium chloride giving a crystalline purple dye. 5-Amino-2-mercaptothiazole (0·7 g.) was refluxed with acetone (40 c.c.) for 15 mins. under nitrogen; on standing, the filtered solution deposited the acetone Schiff's base, m. p. 166° (decomp.), described above, which was also prepared more conveniently as follows : Aminoacetonitrile (5 g.) was added to an ice-cold solution of carbon disulphide (7 c.c.) in acetone (25 c.c.). Heat was evolved and almost immediately the Schiff's base began to separate; after standing, it was collected (10·5 g., 70%) and the filtrate treated with acetone–ether (1 : 1) to give the unidentified material, m. p. 205° (decomp.), obtained from aminoacetonitrile sulphate above. 5-Amino-2-mercaptothiazole (1 g.) was kept for 1 hr. at room temperature in 2N-hydrochloric acid (25 c.c.). 2-Mercaptothiazolone (0·45 g., 45%), identical with that described above, was precipitated. Aminoacetonitrile sulphate (10·5 g.) was neutralised with sodium (2·1 g.) in methanol (55 c.c.) as in previous experiments, and the resulting solution of the base was kept at 0° overnight under nitrogen with carbon disulphide (80 g.) and methyl iodide (15 g.). The solution was evaporated to dryness in a vacuum, and the residue treated with ether (100 c.c.) and 2N-sodium hydroxide (25 c.c.). When the ethereal solution was dried, it slowly deposited crystals (ca. 2 g.). The *substance*, possibly 5-amino-2-methylthiothiazole, crystallised from ethanol in blunt, colourless rods, m. p. 152—153° (decomp.) (Found : C, 33·1; H, 4·2. $C_4H_6N_2S_2$ requires C, 32·9; H, 4·1%); it was soluble in dilute acid but insoluble in sodium hydroxide. Light absorption (N-hydrochloric acid) : $\lambda_{inflex.} = 2510$ A., $E^{1\%}_{1\,cm.} = 750$; $\lambda_{max.} = 2800$ A., $E^{1\%}_{1\,cm.} = 1250$.

The benzyl ester (V) (1·7 g.) in dry ethyl acetate (25 c.c.) was treated with phosphorus tribromide (1 g.). *5-Amino-2-benzylthiothiazole hydrobromide* (2·5 g.) was immediately precipitated, and recrystallised from methanol–ether in prisms, m. p. 187° (decomp.) (Found : C, 39·6; H, 3·6; N, 9·2; S, 21·1. $C_{10}H_{11}N_2S_2Br$ requires C, 39·6; H, 3·6; N, 9·2; S, 21·1%). In methanol it gave the following reactions : (*a*) a chocolate-coloured precipitate with aqueous sodium nitrite, (*b*) yellow crystals on adding benzaldehyde, and (*c*) red-purple crystals on adding *p*-nitrosodimethylaniline; it gave no characteristic colour with glyoxal. The above hydrobromide was treated with aqueous sodium hydrogen carbonate, and the crude free base extracted with ether to give *5-amino-2-benzylthiothiazole*, crystallising from

*cyclo*hexane in colourless needles, m. p. 80° (Found : C, 54·2; H, 4·9; N, 12·4; S, 28·3. $C_{10}H_{10}N_2S_2$ requires C, 54·1; H, 4·5; N, 12·8; S, 28·8%). The ether–insoluble material melted at 180—181° (decomp.) after crystallisation from methanol and ether, but was not identified (Found : C, 45·4; H, 4·3; S, 18·3%).

5-Amino-2-mercaptothiazole (2·6 g.) and potassium hydroxide (1·2 g.) were kept in methanol (20 c.c.) under nitrogen for 2·5 hrs. Evaporation of the solvent left a clean crystalline residue of a potassium salt, which was dissolved in water (10 c.c.) and acidified with 2N-hydrochloric acid (15 c.c.) to give a yellow precipitate of 2 : 4-*dithiohydantoin* (1·8 g.), which was purified by precipitation with acid from its solution in sodium acetate (Found : C, 27·6; H, 3·5; S, 48·6. $C_3H_4N_2S_2$ requires C, 27·3; H, 3·0; S, 48·5%); it did not melt below 300°. Dithiohydantoin was a strong acid, being readily soluble in aqueous sodium acetate though almost insoluble in cold water. It readily discoloured, and alkaline solutions were prone to aerial oxidation. It was soluble in cold methanol, ethanol, acetone, or acetic acid, and in hot ethyl acetate or warm ether. Dithiohydantoin was also conveniently obtained by the following procedure : 5-amino-2-mercaptothiazole (19 g.) and potassium carbonate (23 g.) were kept in water (100 c.c.) under nitrogen for 9 hrs., and the solution acidified with 10% hydrochloric acid to precipitate the dithiohydantoin as a creamy yellow solid (15·5 g.).

Dithiohydantoin (1·2 g.) was refluxed in ethanol with Raney nickel (6·0 g.) for 15 mins. Removal of nickel sulphide and evaporation of the filtrate gave glyoxaline (0·2 g.), m. p. 90—91°, undepressed on admixture with an authentic specimen. Dithiohydantoin (8 g.) was refluxed with acetic anhydride (20 c.c.) for 10 mins. On cooling, the mass was washed out with water (100 c.c.) and recrystallised from toluene or benzene to give 1 : 3-*diacetyldithiohydantoin* (7·5 g.) as colourless needles, m. p. 161° (Found : C, 39·3; H, 3·8; N, 12·9; S, 29·7. $C_7H_8O_2N_2S_2$ requires C, 38·9; H, 3·7; N, 13·0; S, 29·6%). Light absorption (chloroform) : $\lambda_{max.} = 2670, 3210$ A.; $E^{1\%}_{1\,cm.} = 435, 465$.

It was soluble in most organic solvents except ether or hydrocarbons, and dissolved in sodium hydroxide undergoing deacetylation to regenerate dithiohydantoin. The acetyl derivative (0·9 g.) in 2N-sodium hydroxide (15 c.c.) was shaken overnight in an atmosphere of nitrogen with benzyl chloride (1·5 g.) in ether (10 c.c.). Evaporation of the ether left a crystalline residue of 2 : 4(5)-dibenzylthioglyoxaline (0·75 g.), identical with that obtained in earlier experiments.

The potassium salt of dithiohydantoin (obtained above) was treated with an excess of methyl iodide in methanol; a vigorous reaction occurred and potassium iodide separated. Evaporation of the solution left the *methiodide* of 4-*mercapto*-2-*methylthioglyoxaline*, which crystallised from acetone–ether in colourless spears, m. p. 136—138° (Found : C, 20·5; H, 3·0; N, 9·3. $C_5H_9N_2S_2I$ requires C, 20·8; H, 3·1; N, 9·7%). When 1 equiv. of methyl iodide was used, the crude monomethyldithiohydantoin was characterised as its *acetyl* derivative by warming with acetic anhydride. It crystallised from ethanol in colourless needles, m. p. 165° (Found : C, 38·7; H, 4·5; N, 14·7. $C_6H_8ON_2S_2$ requires C, 38·3; H, 4·3; N, 14·9%), and was readily hydrolysed to methylthiol. Light absorption (chloroform) : $\lambda_{max.} = 2420, 2580, 3230$ A.; $E^{1\%}_{1\,cm.} = 500, 500, 550$.

5-Amino-2-mercaptothiazole (1 g.) was covered with pyridine (5 c.c.) and acetone (2 c.c.), and the mixture boiled. Cooling to room temperature and dilution with water (10 c.c.) gave 5-iso*propylidene*-2 : 4-*dithiohydantoin* (0·5 g., 38%), which crystallised from pyridine–85% methanol in orange needles, m. p. 235° (decomp.) (Found : C, 42·2; H, 4·8; N, 15·9; S, 37·7. $C_6H_8N_2S_2$ requires C, 41·9; H, 4·7; N, 16·3; S, 37·2%). The same compound was obtained more conveniently as follows : Aminoacetonitrile (1·5 g.), pyridine (10 c.c.), and acetone (3 c.c.) were warmed together (steam-bath) while carbon disulphide (2 c.c.) was added. Cooling and addition of water gave the *iso*propylidene compound (1·25 g.).

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