319. *Studies in the Azole Series. Part II. The Interaction of α-Amino-nitriles and Carbon Disulphide.*

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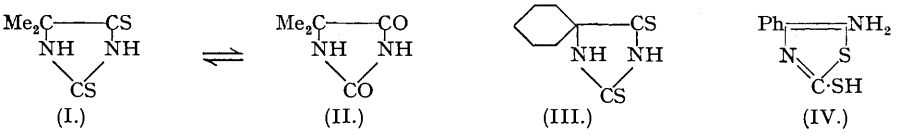
The reaction between α-amino-nitriles and carbon disulphide leads, according to conditions, to 5-amino-2-mercaptothiazoles or derivatives thereof, or to dithiohydantoins. The former may be transformed into dithiohydantoins, or hydrolysed to α-amino-acids. The constitutions of representative compounds were confirmed by desulphurisation to 5-aminothiazoles or iminazoles. The further chemistry of 5-amino-2-mercapto-4-phenylthiazole (IV), in particular including its acetylation, methylation, condensation with aldehydes or ketones, and oxidation, is described, and some implications of these reactions are discussed.

The preceding paper described the preparation and properties of 5-amino-2-benzylthiazole and some near derivatives. The preparative method, *viz.*, interaction of aminoacetonitrile and sodium or methyl dithiophenylacetate, promised to be of extensive application and the present communication deals with a detailed study of the reaction between α-amino-nitriles and carbon disulphide, which may be regarded as the anhydride of dithiocarbonic acid.

This reaction is stated (U.S.P. 2,143,816) to yield dithiohydantoins but the only example

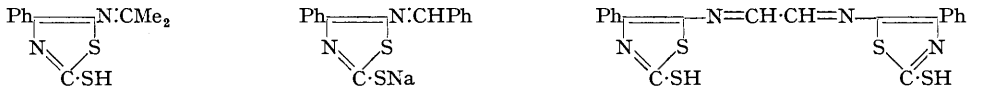
described in detail is that with α-amino*iso*butyronitrile. That the product was (I) was proved by oxidising it to the known 5 : 5-dimethylhydantoin which was reconverted into the dithio-compound by heating with phosphorus pentasulphide (Henze and Smith, *J. Amer. Chem. Soc.*, 1943, **65**, 1090; cf. also Jacobson, *ibid.*, 1945, **67**, 1996). According to B.P. 512,629, *spiro*dithiohydantoins, *e.g.*, (III), are similarly formed from amino-nitriles derived from cyclic ketones. It is interesting in view of these findings to recall that Bücherer and Lieb (*J. pr. Chem.*, 1934, **141**, 5) had, by analogy with the formation of hydantoins from carbon dioxide and moist α-amino-nitriles, unsuccessfully attempted the similar formation of dithiohydantoins.



(I.) (II.) (III.) (IV.)

Because of complications in the reaction between aminoacetonitrile and carbon disulphide, attention was first directed to the reaction between carbon disulphide and α-aminobenzyl cyanide; this base is easily accessible from benzaldehyde, hydrogen cyanide, and ammonia (Dubsky, *Ber.*, 1919, **52**, 232). The reaction was easily effected at room temperature, carbon disulphide being used in aqueous suspension. The product was a high-melting yellow crystalline solid, $C_9H_8N_2S_2$, which was obviously not 5-phenyl-2 : 4-dithiohydantoin. Contrary to this formulation it readily condensed with acetone to give a new compound, $C_{12}H_{12}N_2S_2$, which quickly reverted to the first material in presence of dilute mineral acid. This, together with other facts noted below, indicated that the primary product is more properly formulated as 5-*amino*-2-*mercapto*-4-*phenylthiazole* (IV), and the condensation product as the *Schiff's base* (V). It is interesting to note that the analogous benzaldehyde *Schiff's base* is formed in small yield by the direct interaction at room temperature of benzaldehyde, ammonium cyanide, and carbon disulphide in ethanol. The thiazole (IV) itself condensed equally easily with other aldehydes and ketones such as acetophenone and cinnamaldehyde to give yellow-orange, highly crystalline condensation products. All these bases were sensitive to mineral acid but more stable towards alkali, giving sparingly soluble sodium salts. Thus the benzaldehyde *salt* (VI) was obtained in yellow crystals, almost insoluble in water but soluble in ethanol, ethyl acetate, or acetone like metallic derivatives of dithiocarbamic acids to which they are obviously allied (cf. Delépine, *Bull. Soc. chim.*, 1908, **3**, 643).

The chromophoric properties of the 5-aminothiazole system were particularly well illustrated by reaction of (IV) with glyoxal whereby the deep-red *bisazomethine* (VII) was readily formed; it gave a deep purple disodium salt soluble in acetone with an intense blue colour. Exactly similar red colours were observed on boiling (IV) in pyridine with diacetyl, phenylmethylglyoxal, or benzil, the colours in each case deepening considerably in presence of alkali. Condensation proceeded remarkably easily between the hydrochloride of (IV) and carbonyl compounds in cold methanol; in this way *Schiff's bases* derived from phenanthraquinone and isatin were also obtained.

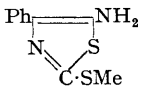


(V.) (VI.) (VII.)

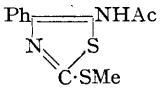
Hydrolysis of (IV) under moderately vigorous acid conditions gave α-aminophenylacetic acid and carbon disulphide. It was weakly basic and pseudoacidic; it formed a *hydrochloride*, and when treated with methyl sulphate in an aqueous alkaline medium was converted into 5-*amino*-2-*methylthio*-4-*phenylthiazole* (VIII). Similar alkylation with benzyl chloride afforded 5-*amino*-2-*benzylthio*-4-*phenylthiazole*. Methylation was effected more easily by refluxing with methyl iodide in ethanol, the *hydriodide* of (VIII) being obtained. When the first method was used, a water-soluble methosulphate formed a by-product. This compound could still be diazotised and coupled with β-naphthol and is formulated as 5-*amino*-2-*methylthio*-4-*phenylthiazole methosulphate*. It condensed remarkably easily with compounds containing reactive methyl or methylene; for instance, on mixing with an aqueous solution of quinaldine methiodide, methylthiol was evolved and a cyanine dyestuff separated in purple crystals. This and similar reactions will be reported in detail in due course.

Diazotisation of (VIII) gave a diazonium salt solution which coupled readily with

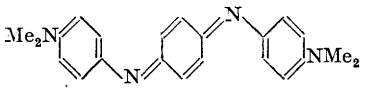
5-amino-2-benzylthiazole to a deep red dye. Similarly, by using β-naphthol, the crystalline *azo-dye* was isolated. Condensation of (VIII) with glyoxal in ethanol gave the SS'-*dimethyl* derivative of (VII) which separated almost immediately as maroon crystals. A better reagent was a cold methanolic solution of the hydrochloride of (VIII), which reacted immediately with numerous carbonyl compounds (see experimental portion), to give the corresponding *Schiff's bases*. It may be mentioned that a colour with glyoxal under these conditions seems diagnostic of the presence of a 5-amino-2-mercaptothiazole. Acetylation of (VIII) gave 5-*acetamido*-2-*methylthio*-4-*phenylthiazole* (IX), also obtained by the action of alcoholic methyl iodide on 5-acetamido-2-mercapto-4-phenylthiazole (see below); (IX) was relatively stable to boiling sodium hydroxide and ethanolic hydrogen chloride.



(VIII.)



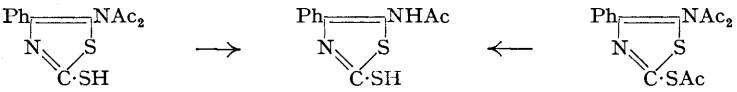
(IX.)



(X.)

Many attempts were made to condense 5-amino-2-mercapto-4-phenylthiazole (IV) with *p*-nitrosodimethylaniline, a variety of products being obtained under different conditions. Insofar as they were examined, however, the reaction seemed one of oxidation–reduction rather than condensation. For instance, in pyridine considerable heat was evolved and a deep red colour developed; analysis of the red-brown crystalline product agreed best, though not completely satisfactorily, with the *quinoneimine* (X). This formed a labile hydrochloride which on more prolonged treatment with ethanolic hydrochloric acid was converted into the bis-hydrochloride of *p*-aminodimethylaniline.

When (IV) was acetylated for a short time under mild conditions, an alkali-soluble monoacetyl derivative formulated as 5-*acetamido*-2-*mercapto*-4-*phenylthiazole* (XII) was obtained, though perhaps as a result of hydrolysis of the diacetyl derivative. More drastic treatment gave an alkali-labile diacetyl derivative regarded as 5-*diacetylamino*-2-*mercapto*-4-*phenylthiazole* (XI), and still more prolonged treatment gave a triacetyl derivative. Both di- and tri-acetyl derivatives reverted to (XII) on mild hydrolysis and the triacetyl compound must, it appears, be formulated as 5-*diacetylamino*-2-*acetylthio*-4-*phenylthiazole* (XIII).



(XI.) (XII.) (XIII.)

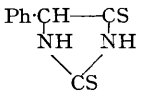
When (IV) was allowed to stand with alkaline hydrogen peroxide it was converted into a red sodium salt, from which the free *compound* was obtained as an orange pigment. Treatment of the sodium salt with methyl sulphate gave a non-acidic orange *dimethyl* derivative. Analyses suggested empirical formulæ of the type $C_{36}H_{22}ON_6S_4$ and $C_{38}H_{26}ON_6S_4$ respectively for these products (*i.e.*, four thiazole nuclei with two methyl groups or methylatable hydrogen atoms) although the molecular weight of the methyl derivative in camphor seemed to be 306; there is as yet insufficient evidence to suggest detailed structures for these compounds. The same acidic product was formed on aerial oxidation of (IV) or with sodium nitroprusside in alkaline solution, and in surprisingly good yield by treating (IV) with alkali and acetylsulphanilyl chloride.

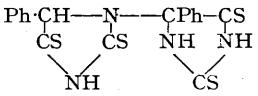
Many other colour reactions of the mercaptothiazole were observed; *e.g.*, intense red colours were developed on warming with benzoyl chloride or 2 : 4-dinitrochlorobenzene but the nature of the products was not investigated.

In view of the antibacterial activity of certain cyclic thiols (Gibbs and Robinson, *J.*, 1945, 925), the effect of (IV) was examined. At a concentration of 1 mg./c.c. in neutral phosphate buffer it showed considerable inhibition of the growth of *Staph. aureus*.

Convincing evidence of the correctness of the thiazole structures was afforded by treating (IV) and its derivatives with alkali and Raney nickel respectively. For example, when (IV) was brought into contact with the latter reagent in hot ethanol, removal of one atom of sulphur proceeded spontaneously to give the known 5-amino-4-phenylthiazole (Part I, preceding paper), which, unlike the parent mercapto-compound, gave no characteristic colours with glyoxal. The base was also obtained by desulphurising the corresponding acetone or benzaldehyde Schiff's bases of (IV), and the acetyl derivative was smoothly prepared by desulphurising 5-acetamido-2-mercapto-4-phenylthiazole.

When (IV) was boiled with aqueous ammonia the solution soon ceased to give the characteristic Schiff's base with glyoxal, and an isomeride of the original base was isolated; from results described below this is formulated as 2 : 4-*dithio*-5-*phenylhydantoin* (XIV). The same dithiohydantoin was obtained by treatment of (IV) with caustic alkali, together with 1′ : 5-*bis*-(2 : 4-*dithio*-5-*phenylhydantoin*) (XV). The latter structure is assigned by analogy with diphenylhydantil, formed by the action of alkali on 5-phenylhydantoin (Pinner, *Ber.*, 1888, **21**, 2320; Gabriel, *Annalen*, 1906, **250**, 118). (XV) was more readily obtained by the action of mild oxidising agents on the dithiohydantoin. Treatment of 5-amino-2-methylthio-4-phenylthiazole (VIII) with alkali led to elimination of methylthiol and formation of 4-thio-5-phenylhydantoin (XVI) with the same properties as that described by Johnson and Chernoff (*J. Amer. Chem. Soc.*, 1912, **34**, 1212). The structure of (XIV) was indicated by its pseudoacidic and non-basic character and especially by its behaviour with Raney nickel. By contrast with the parent thiazole (IV) both sulphur atoms were labile, the product being 5(4)-phenyliminazole (XVII), also obtained from (XV) by similar means. Further examples of this facile synthesis of iminazoles of more general interest will be described in later communications. An attempt was made to synthesise (XIV) by the action of phosphorus pentasulphide on 5-phenylhydantoin, but surprisingly the product proved to be 5(4)-phenyliminazole (XVII). Both (XIV) and (XV) were remarkably stable to acid and alkaline hydrolysis, more so than their oxygen analogues.


(XIV.)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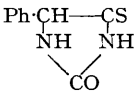
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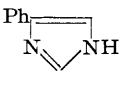
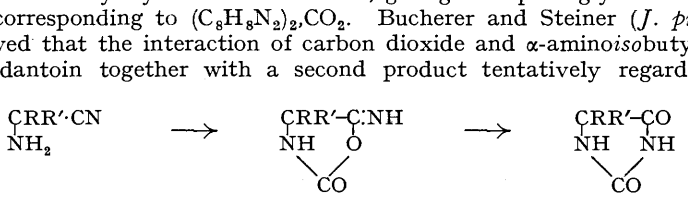

(XVII.)

When α-aminopropionitrile was treated with carbon disulphide under conditions comparable with those in the foregoing experiments, two products were obtained in approximately equal yield. One was a pseudo-acid with no observable basic properties and is probably to be formulated as 2 : 4-dithio-5-methylhydantoin. The second product evolved acetaldehyde on warming with mineral acid and is regarded as the *acetaldehyde Schiff's base* of 5-amino-2-mercapto-4-methylthiazole, treatment with hydrogen chloride giving 5-*amino*-2-*mercapto*-4-*methylthiazole hydrochloride* characterised by the scarlet colour with glyoxal. The formation of the acetaldehyde Schiff's base is clearly similar to that of the corresponding phenyl compound described above. Indeed, when the present reaction was deliberately carried out in presence of acetaldehyde, dithiohydantoin formation was completely inhibited and the aminothiazole derivative was the sole product.

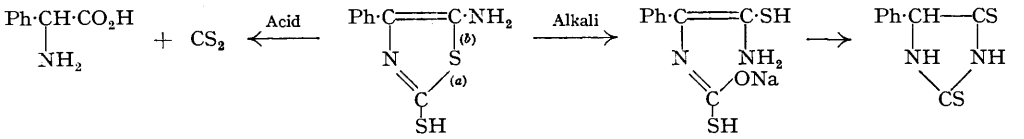
On similar reaction of ethyl aminocyanoacetate (cf. preceding paper) a product was easily isolated which although failing to diazotise under normal conditions did so in concentrated sulphuric acid solution and must be formulated as 5-*amino*-2-*mercapto*-4-*carbethoxythiazole*. This was confirmed by treatment with Raney nickel, whereby it was converted into 5-amino-4-carbethoxythiazole, identified with the material described in the preceding paper. When the condensation with carbon disulphide was carried out in acetone solution an unstable intermediate, probably the acetone Schiff's base, was obtained which passed into the above aminomercaptocarbethoxythiazole on recrystallisation.

The above examples indicate therefore a general reaction leading to aminothiazoles or dithiohydantoins according to conditions. It is possible, moreover, that analogous reactions take place between α-amino-nitriles and carbon dioxide, for a facile combination of carbon dioxide and α-aminobenzyl cyanide was observed, giving a surprisingly stable *product* having a composition corresponding to $(C_8H_8N_2)_2,CO_2$. Bucherer and Steiner (*J. pr. Chem.*, 1934, **140**, 291) observed that the interaction of carbon dioxide and α-amino*iso*butyronitrile led to 5 : 5-dimethylhydantoin together with a second product tentatively regarded as (XVIII; R, R′ = Me).


(XVIII.)

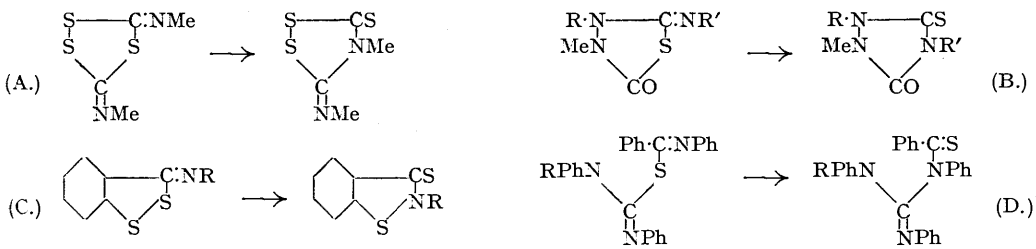
The genesis of both products is readily understood if the formation of an imino-oxazolidone as an intermediate comparable with the above aminothiazoles be assumed. In this case the product from α-aminobenzyl cyanide is best regarded as (XVIII; R = H, R′ = Ph). The rearrangement of the imino-oxazolidone to the hydantoin may be compared with the transformation of *o*-cyanobenzoic acid into phthalimide presumably *via* an imino-compound (Sandmeyer, *Ber.*, 1885, **18**, 1499).

It will be noticed that in the above examples an aminothiazole was obtained in the case of the reactions with α-aminobenzyl cyanide or ethyl aminocyanoacetate and that in the former instance a medium such as alkali or moist pyridine was required to complete the transformation into the dithiohydantoin. This reflects a stabilising influence of the phenyl and the carbethoxyl group on the thiazole ring and, secondly, suggests that the mechanism of the transformation consists first in fission of the bond (*a*) :



The closely analogous cyclisation of α-carbethoxyaminophenylthioacetamide in alkali to 4-thio-5-phenylhydantoin (XVI) has been described by Johnson and Chernoff (*loc. cit.*). When 5-amino-2-mercapto-4-phenylthiazole was boiled, on the other hand, with dilute mineral acid, α-aminophenylacetic acid and carbon disulphide were formed indicating fission at (*b*) which may be preceded by elimination of ammonia. This indirect hydrolysis of an α-amino-nitrile has been applied to the preparation of more complicated α-amino-acids which will be described elsewhere. The process offers advantages in that the aminothiazole derivatives are more readily isolated and crystallise easily compared with α-amino-nitriles.

The above transformation into a dithiohydantoin presents no essential novelty, being paralleled in other heterocyclic series of varying complexity. Thus the transformation (A) was noted by Freund (*Annalen*, 1895, **285**, 154), (B) by Busch and Limpach (*Ber.*, 1911, **44**, 560),



and (C) by McClelland and Salkeld (*J.*, 1936, 1143). The observation of " acyclic " transformations of this kind, of which (D) is a recent example (Rivie and Langer, *Helv. Chim. Acta*, 1943, **26**, 1722), points to a probable oversimplification in the mechanism suggested under (*a*) above.

The absorption spectra of most of the above thiazoles are tabulated below. A practically invariable feature is a band at *ca.* 2900 A. which reflects a strong bathochromic effect of the 5-amino-grouping, as thiazoles and alkylthiazoles exhibit a band at *ca.* 2400 A. (Ruehle, *J. Amer. Chem. Soc.*, 1935, **57**, 1887; Jones, Robinson, and Strachan, *J.*, 1946, 91).

Experimental.

Reactions with α-Aminobenzyl Cyanide.—Redistilled benzaldehyde (367 g.) was mixed with anhydrous hydrogen cyanide (103 g.), and aqueous ammonia (*d* 0·880, 1—2 c.c.) added to initiate the reaction, which was moderated by strong cooling. After the mixture had stood at room temperature for 7 hours, liquid ammonia (65 g.) dissolved in ethanol (150 c.c.) was added and the mixture stood for 1 day at room temperature and 2 days at 0°. The large plates of α-aminobenzyl cyanide (115 g.) which had separated were filtered off and washed with plain spirit (500 c.c.); m. p. 55°. The syrupy filtrate was treated with carbon disulphide (200 c.c.), and large yellow crystals (126 g.) of the thiazole (see below) were soon deposited. This crude product (m. p. 259°, decomp.) contained about 8% of the corresponding benzylidene derivative, which can be removed as its insoluble sodium salt by treatment with aqueous sodium hydroxide.

α-Aminobenzyl cyanide (13·5 g.) was refluxed in ether (250 c.c.) with carbon disulphide (10 g.) for 8 hours. The yield of yellow crystals (12·8 g.) was augmented by standing the filtrate with carbon

disulphide (10 g.) overnight (total yield, 19·6 g., 93%). In another preparation the nitrile (20 g.) in ether (500 c.c.) was kept with carbon disulphide (11 c.c.) for 2½ days, and the crystals (26 g.) collected; on longer standing a further 4 g. separated (total yield, 95%).

α-Aminobenzyl cyanide hydrochloride (1·0 g.) in water (10 c.c.) was neutralised to phenolphthalein with 2N-sodium hydroxide, and carbon disulphide (0·5 c.c.) and a little methanol added. After 17 hrs.' shaking at room temperature, crude 5-*amino*-2-*mercapto*-4-*phenylthiazole* (IV) (0·65 g.) was obtained. This was sparingly soluble in ethanol, from which it separated in bright yellow tablets, and in most common solvents, but crystallised well from pyridine–ethanol in needles, and then had m. p. 261—262° (decomp.) (Found : C, 52·3; H, 3·9. $C_9H_8N_2S_2$ requires C, 51·9; H, 3·9%). It was converted into a very insoluble product in boiling nitrobenzene but dissolved in alkali and was precipitated unchanged by acid; it was soluble in aqueous baryta, a barium salt soon crystallising in plates. The thiazole dissolved in concentrated sulphuric acid to a lemon-yellow solution and deposited a chocolate-brown precipitate on dilution. Treatment with benzoyl chloride or 2 : 4-dinitrochlorobenzene in dioxan gave an intense red colour.

The thiazole (IV) was shaken with ethanolic hydrogen chloride. After about 1 hour the flask was filled with a thick cream of hydrochloride. 5-*Amino*-2-*mercapto*-4-*phenylthiazole hydrochloride* could be recrystallised from ethanol–ethereal hydrogen chloride but crystallised best from methanol on adding concentrated hydrochloric acid; it formed colourless needles, m. p. 189° (decomp.) (Found : C, 44·0; H, 4·0; N, 11·1. $C_9H_9N_2S_2Cl$ requires C, 44·2; H, 3·7; N, 11·4%).

The thiazole (IV) was refluxed with excess of acetone. After 1 hour a clear solution was obtained which was evaporated in a vacuum and the residue taken up in ethanol. On cooling, the *Schiff's base* (V) separated in pale yellow needles, m. p. 187°, in almost theoretical yield (Found : C, 58·2; H, 5·1; N, 10·9. $C_{12}H_{12}N_2S_2$ requires C, 58·1; H, 4·8; N, 11·3%). The same product (1 g.) was obtained when α-aminobenzyl cyanide (1 g.) was refluxed with carbon disulphide (5 c.c.) and acetone (20 c.c.) for 3 hours, and the solution evaporated until it crystallised. 5-Amino-2-mercaptothiazole was refluxed overnight in ethanol with an excess of acetophenone. On filtering and cooling an excellent yield of the acetophenone *Schiff's base* crystallised. It could be recrystallised from ethanol containing dioxan in yellow needles, m. p. 212° (Found : C, 65·5; H, 4·2; N, 8·6. $C_{17}H_{14}N_2S_2$ requires C, 65·8; H, 4·5; N, 9·0%); it was also formed, though in poorer yield, on boiling the components in pyridine. The aminothiazole (IV) (2 g.) was refluxed with ethanol (50 c.c.) and cinnamaldehyde (2 g.) for 5 mins., the contents of the flask then having set almost solid with a mass of orange crystals (2·7 g.). The cinnamaldehyde *Schiff's base* was insoluble in ethanol, moderately soluble in hot toluene, chloroform, acetone, or ethyl acetate, from which it crystallised in needles, or in acetic acid from which it separated in spear-shaped crystals. It was best crystallised from ethanol–dioxan (2 : 1) in orange needles; m. p. 226° (Found : C, 68·6, 66·6; H, 4·5, 4·9; N, 8·9. $C_{18}H_{14}N_2S_2$ requires C, 67·1; H, 4·4; N, 8·7%). It gave a red crystalline sodio-derivative crystallising from aqueous ethanol, and an intense red colour with ethanolic hydrogen chloride or concentrated sulphuric acid, but dilute acid quickly hydrolysed it to its components.

The benzaldehyde *Schiff's base*, which could be prepared in the usual manner, crystallised from ethanol containing a little water in fine yellow needles, m. p. 226—229° (slow heating) after contracting at 205° (Found : C, 65·0; H, 4·1; N, 9·55. $C_{16}H_{12}N_2S_2$ requires C, 64·9; H, 4·1; N, 9·5%). Benzaldehyde (10·5 g.) in ethanol (50 c.c.) was kept over-night with ammonium cyanide (4·5 g.) and carbon disulphide (8 g.). The Schiff's base (4·0 g.) separated and a further 2·5 g. separated after 1 week. The benzaldehyde Schiff's base dissolved in 2N-sodium hydroxide to a lemon-yellow solution which on standing deposited a yellow solid. This *sodium* salt (VI) was soluble in acetone, ethanol, or ethyl acetate and was purified by extraction with acetone and precipitation with light petroleum or by crystallisation from aqueous sodium hydroxide, then separating in jagged yellow laths having a pearly lustre, m. p. 298° (Found : C, 52·0; H, 4·7; N, 7·7. $C_{16}H_{11}N_2S_2Na,3H_2O$ requires C, 51·6; H, 4·6; N, 7·5%); it gave the original mercapto-compound on acidification.

5-Amino-2-mercapto-4-phenylthiazole (IV) (2 g.) in 2N-sodium hydroxide (6 c.c.) diluted to 25 c.c. was treated with 50% glyoxal (1·5 c.c.) in water (5 c.c.). An intense purple colour appeared immediately, heat was evolved, and a sodium salt soon separated. The salt was suspended in hot water (100 c.c.) and acidified to give the free condensation product; more was obtained from the filtrate from the sodium salt (total yield 1·8 g.). The *bisazomethine* compound (VII) was practically insoluble in ethanol, acetic acid, dioxan, toluene, and other solvents but crystallised from pyridine–ethanol in sheaves of purple needles, m. p. 292—293° (decomp.) (Found : C, 55·0; H, 3·4. $C_{20}H_{14}N_4S_4$ requires C, 54·8; H, 3·2%). It was soluble in alcoholic ammonia to a purple solution which became deep blue in acetone, the sodium salt also giving a blue solution with acetone. The colour was observed also in pyridine but not in dioxan, ethanol, ethyl acetate, or diethylamine.

5-Amino-2-mercapto-4-phenylthiazole (IV) (2 g.), acetic anhydride (10 c.c.), and 1 drop of concentrated sulphuric acid were refluxed for 3 minutes and solvent removed in a vacuum. The crystalline residue was dissolved in hot ethanol (15 c.c.). On cooling, the crystals (0·7 g.), m. p. 162—163°, were collected, and a second crop (1·5 g.), m. p. 148—158°, isolated from the mother-liquor (this material consisted mainly of the diacetyl derivative and on crystallisation from aqueous ethanol the m. p. rose considerably). The solid in the minimum of acetone–benzene (1 : 3) was chromatographed on alumina and eluted with 10% and ultimately with 90% acetone in benzene. The material from 10 fractions was substantially homogeneous (m. p. 244—247°). It was insoluble in hydrocarbons, chloroform, ethyl acetate, ether, or water, but soluble in hot ethanol, acetone, or acetic acid. 5-*Acetamido*-2-*mercapto*-4-*phenylthiazole* (XII) separated from ethanol in colourless needles, m. p. 244—245° (Found : C, 53·1; H, 4·0; N, 10·9. $C_{11}H_{10}ON_2S_2$ requires C, 52·8; H, 4·0; N, 11·2%), which dissolved immediately in alkali. In a larger preparation 5-amino-2-mercapto-4-phenylthiazole (30 g.) was heated to boiling with acetic anhydride (100 c.c.), and the clear solution poured into water (1 l.). The precipitated oil rapidly granulated and was dissolved in sufficient warm 2N-sodium hydroxide and precipitated with concentrated hydrochloride acid from a total volume of 2 l. The product (35·5 g.), after being washed and dried at 100°, had m. p. 244° (decomp.). The parent aminothiazole (IV)

(1 g.) was refluxed for 5 mins. with acetic anhydride (5 c.c.). On cooling, the solid was collected and washed with ether, more being obtained from the filtrate on adding light petroleum (total yield, 1·15 g.). 5-*Diacetylamino*-2-*mercapto*-4-*phenylthiazole* (XI) recrystallised best from acetic anhydride in prismatic needles, m. p. 166° (Found: C, 53·2; H, 4·2. $C_{13}H_{12}O_2N_2S_2$ requires C, 53·4; H, 4·1%); it dissolved (0·5 min.) in cold 2N-sodium hydroxide, the preceding monoacetyl derivative being recovered on acidification, and hydrolysis also took place slowly on exposure to air. The parent aminothiazole (IV) (2 g.) was warmed for 45 mins. at 100° with acetic anhydride (10 c.c.) containing a little sulphuric acid, and the solution finally refluxed for 3 mins. and evaporated in a vacuum. The residue crystallised and was recrystallised (yield 0·9 g.) from ethanol to give the *triacetyl* derivative (XIII) as prisms, m. p. 132° (Found: C, 54·0; H, 4·3; N, 8·5. $C_{15}H_{14}O_3N_2S_2$ requires C, 53·9; H, 4·2; N, 8·4%). This compound also reverted to the *N*-monoacetyl compound on mild hydrolysis.

5-Amino-2-mercapto-4-phenylthiazole (IV) (10 g.) in 2N-sodium hydroxide (20 c.c.) was stirred with chloroform (50 c.c.) and methyl sulphate (5 c.c.) dropped in during 5 mins. Acidification of the aqueous layer gave unchanged starting material (1 g.). Evaporation of the chloroform layer and addition of alcoholic hydrogen chloride gave 5-*amino*-2-*methylthio*-4-*phenylthiazole hydrochloride*, which crystallised from ethanol in magnificent, pale yellow needle clusters, m. p. 175° (decomp.) (Found: C, 46·3; H, 4·3; N, 10·6. $C_{10}H_{11}N_2S_2Cl$ requires C, 46·4; H, 4·3; N, 10·8%). The crude free base obtained from the chloroform solution above was mixed with a small excess of acetic anhydride; heat was evolved and the mixture solidified. 5-*Acetamido*-2-*methylthio*-4-*phenylthiazole* (IX) crystallised from ethanol in well-formed needles, m. p. 168° (Found: C, 54·9; H, 4·6; N, 10·4. $C_{12}H_{12}ON_2S_2$ requires C, 54·6; H, 4·6; N, 10·6%). The compound was still a base, affording a crystalline hydrochloride with hydrogen chloride in ethyl acetate.

In a larger methylation experiment (41·6 g. of aminomercapto-compound) the chloroform was evaporated and the semi-crystalline residue treated with ethyl acetate to give 5-*amino*-2-*methylthio*-4-*phenylthiazole methosulphate* (5·0 g.), which crystallised best from *tert.*-butanol in long needles, m. p. 123° (Found: C, 41·0; H, 5·0; N, 8·0. $C_{12}H_{16}O_4N_2S_3$ requires C, 41·4; H, 4·6; N, 8·0%). The compound was water-soluble, and reaction with aqueous quinaldine methiodide containing 1 equiv. of sodium hydroxide gave a deep purple precipitate; no colouration was obtained with glyoxal. The substance was biologically inactive towards *Staph. aureus* in 0·2% phosphate buffer (pH 7). The corresponding *picrate* crystallised from acetic acid in needles, m. p. 202° (Found: C, 44·3; H, 3·4; N, 14·9. $C_{17}H_{15}O_7N_5S_2$ requires C, 43·9; H, 3·2; N, 15·0%). The ethyl acetate filtrate (above) was evaporated, and the residue in ether run on to an alumina column and developed with 20% ether in light petroleum. The eluates yielded 5-*amino*-2-*methylthio*-4-*phenylthiazole* (VIII), which crystallised from light petroleum (b. p. 80—100°) in colourless needles, m. p. 70—71° (Found: C, 54·0; H, 5·0; N, 12·8. $C_{10}H_{10}N_2S_2$ requires C, 54·0; H, 4·5; N, 12·6%).

5-Amino-2-mercapto-4-phenylthiazole (IV) (2 g.) was refluxed with methyl iodide (1·5 g.) in ethanol (10 c.c.) for 0·5 hour. On cooling, a mass of pale needles separated (2·7 g.), which recrystallised from ethanol to give 5-*amino*-2-*methylthio*-4-*phenylthiazole hydriodide*, m. p. 172° (decomp.) (Found: C, 34·5; H, 3·5. $C_{10}H_{11}N_2S_2I$ requires C, 34·3; H, 3·14%).

5-Acetamido-2-mercapto-4-phenylthiazole (XII) (34 g.) was refluxed with methyl iodide (20 g.) in ethanol (200 c.c.) for 10 minutes, the reaction being exothermic. Pyridine (10 c.c.) was added, and the mixture cooled to yield 5-acetamido-2-methylthio-4-phenylthiazole (IX) (37 g.), m. p. 162—210°; dilution of the filtrate with water gave a second crop (8·5 g.), m. p. 167°. The combined crops were recrystallised from ethanol (250 c.c.) to yield the pure thiazole above, m. p. 168°.

α-Aminobenzyl cyanide (2·6 g.), benzyl chloride (2·5 g.), and carbon disulphide (1·5 g.) were kept at room temperature in pyridine (10 c.c.) for 18 hours. The solvent was evaporated in a vacuum, and the syrupy residue treated with water (20 c.c.) and ether (20 c.c.); a small quantity of 5-amino-2-mercapto-4-phenylthiazole separated and was removed by filtration. The ether was washed successively with 2N-sodium hydroxide (20 c.c.), 2N-hydrochloric acid (10 c.c.), and water (20 c.c.) and dried and evaporated to yield 5-*amino*-2-*benzylthio*-4-*phenylthiazole*, m. p. 107° (Found: C, 65·0; H, 5·0; N, 9·2; S, 21·4. $C_{16}H_{14}N_2S_2$ requires C, 64·4; H, 4·7; N, 9·2; S, 21·5%). The compound crystallised best from *cyclo*hexane, and lost benzylthiol on treatment with aqueous alkali. It readily condensed with glyoxal to give a scarlet Schiff's base and could be diazotized in acid solution.

5-Amino-2-methylthio-4-phenylthiazole hydrochloride (2·5 g.), dissolved in acetic acid (25 c.c.) containing concentrated sulphuric acid (2 c.c.), was cooled in a freezing mixture, and treated during 5 minutes with N-sodium nitrite (10 c.c.). After standing in ice for a further 10 minutes, the diazotised base was added to a solution of β-naphthol (1·4 g.) in ethanol (40 c.c.) and water (10 c.c.) containing saturated aqueous sodium acetate (10 c.c.), and the precipitated dye collected. Extraction with hot ethanol followed by solution in warm benzene and precipitation with light petroleum (b. p. 40—60°) gave 2-*methylthio*-4-*phenylthiazole*-5-*azo*-β-*naphthol* (1·5 g.), which crystallised from ethyl acetate in long red needles, m. p. 170—171°, and gave an intense blue solution in concentrated sulphuric acid (Found: C, 63·2; H, 4·2; N, 11·3. $C_{20}H_{15}ON_3S_2$ requires C, 63·6; H, 4·0; N, 11·1%).

5-Amino-2-methylthio-4-phenylthiazole (VIII) (1·7 g.) in cold ethanol (30 c.c.) was treated with 50% glyoxal (3 c.c.) in ethanol (10 c.c.). A scarlet colour and crystalline precipitate appeared within 20 secs. The solution was heated to boiling and filtered hot (yield, 0·7 g.). The *azomethine* compound was insoluble in ethanol, acetic acid, or ethyl acetate, moderately soluble in hot chloroform, benzene, or toluene, and crystallised from benzene containing a little light petroleum in needles, m. p. 242—243° (decomp.). The compound appeared to form a labile brown hydrochloride, dissolved in concentrated sulphuric acid to a purple solution, and was apparently stable to boiling 2N-sodium hydroxide.

In another preparation of this and other methylated *Schiff's bases* equivalent proportions of the carbonyl compound and 5-amino-2-methylthio-4-phenylthiazole hydrochloride were mixed in cold methanol, and the condensation product crystallised in almost quantitative yield. The results are summarised in the following table. This method was also most convenient for preparing the mercapto-Schiff's bases from 5-amino-2-mercapto-4-phenylthiazole hydrochloride, and the last two entries in the table are examples of its use.

Carbonyl component.	M. p. and colour.	Recryst. from : *	Formula.	Analysis. Found, %. C.	H.	N.	Required, %. C.	H.	N.
Benzaldehyde	119°, yellowish-green	A	$C_{17}H_{14}N_2S_2$	65·2	4·4	8·4	65·8	4·5	9·0
Cinnamaldehyde	143°, bronze	B	$C_{19}H_{16}N_2S_2$	68·5 66·8	5·8 4·6	8·1	67·9	4·8	8·3
Glyoxal	241—242°, deep red	C	$C_{22}H_{18}N_4S_4$	57·0	4·2	12·2	56·7	3·9	12·0
Phenanthraquinone	187—188°, brown, green reflex	D	$C_{24}H_{16}ON_2S_2$	69·5	4·0	6·5	69·9	3·9	6·8
Isatin	230°, scarlet-red	C	$C_{18}H_{13}ON_3S_2$	61·9	3·9	11·6	61·5	3·7	12·0
Alloxan	288°, red	E	$C_{14}H_{10}O_3N_4S_2$	49·2 48·0	3·1 2·8	16·4	48·6	2·9	16·2
Phenanthraquinone (SH)	211°, deep purple	—	$C_{23}H_{14}ON_2S_2$	69·0	3·8	6·4	69·3	3·5	7·0
Isatin (SH)	311°, purple, coppery lustre	E	$C_{17}H_{11}ON_3S_2$	60·4	3·7	12·1	60·5	3·3	12·5

* A = ethanol; B = acetic acid; C = benzene; D = ethyl acetate; E = pyridine.

5-Amino-2-mercapto-4-phenylthiazole (IV) (5 g.) and *p*-nitrosodimethylaniline (5 g.) were warmed in pyridine (25 c.c.) to initiate the exothermic reaction. Evaporation and addition of water–ethanol (1 : 4, 40 c.c.) gave red-brown crystals which were recrystallised in similar manner or from light petroleum and then had m. p. 92°; this is probably the *quinoneimine* (X) (Found : C, 77·1; H, 7·4. $C_{22}H_{22}N_4$ requires C, 77·5; H, 6·4%). On rapid treatment with ethanolic hydrogen chloride a labile hydrochloride was obtained, but longer treatment (at room temp. for 10 mins.) followed by addition of ether gave *p*-aminodimethylaniline dihydrochloride, m. p. 208° (decomp.) (lit. m. p. 218°) (Found : C, 46·6; H, 6·9; N, 12·7. Calc. for $C_8H_{14}N_2Cl_2$: C, 46·0; H, 6·7; N, 13·4%). It gave known colour reactions with ferric chloride, sodium nitrite, sodium nitroprusside, hydrogen peroxide, alkaline ferricyanide, and iodine in potassium iodide, and the methylene-blue reaction with hydrogen sulphide followed by ferric chloride.

Oxidation Experiments.—5-Amino-2-mercapto-4-phenylthiazole (IV) was oxidised in aqueous alkali under a variety of conditions, forming an insoluble, red, crystalline, sodium salt, and a number of other more complex green oxidation products which have not been investigated. Hydrogen peroxide, oxygen, potassium ferricyanide, sodium nitroprusside, and benzoquinone all gave red and green products, though the proportion seemed to vary with the oxidising agent employed. None of the simple disulphide was isolated in these experiments, though there is evidence that it was formed in acid solution.

In a typical large-scale experiment, the aminothiazole (15 g.) was dissolved in 2N-sodium hydroxide (40 c.c.), and oxygen passed through the solution for 16 hours. The red needle crystals (1·8 g.) which were precipitated were filtered off, washed with a little water and dried. They decomposed at 277—278° and contained sodium. Solution in ethanol, acetone, ethyl acetate, dioxan, or pyridine was very ready, and the material could be crystallised from these solvents by adding ether or light petroleum. Crystallisation was best effected, however, from warm water, in which the salt was readily soluble. In all but acetone and pyridine the solutions were deep red, but in these two solvents the reagent colour was very similar to the rhodamines, showing also a violet fluorescence (cf. behaviour of sodium salt of glyoxal Schiff's base). Addition of other metallic ions to the aqueous sodium salt solution caused precipitation of crystalline and highly coloured metallic derivatives; *e.g.*, the barium salt melted at 267—270° and crystallised beautifully from hot aqueous ethanol. Acidification of the sodium salt caused precipitation of the free acid (see below) as light orange needles, m. p. 241°. 5-Amino-2-mercapto-4-phenylthiazole (IV) (2 g.) in 2N-sodium hydroxide (12 c.c.) was treated with acetylsulphanilyl chloride (2 g.), producing an intense purple colour which later became green. After being shaken for 1 hour at room temperature, the mixture was filtered, and the insoluble material (0·95 g.) purified by recrystallisation from warm sodium carbonate solution, forming deep red needles, m. p. 268—269°, identical with the above sodium salt.

The sodium salt (1·8 g.) was dissolved in hot water (200 c.c.) and filtered from a little insoluble material. Sodium hydrogen carbonate solution (20 c.c.) was added, followed by chloroform (100 c.c.), and methyl sulphate was dropped into the well-stirred mixture until the intense colour had passed from the aqueous to the organic layer. The mixture was filtered from some orange material (substance A) which had separated during the reaction and the chloroform was separated, washed, dried, and evaporated to yield a mass of dark crystals. These were washed with ether which removed most of the colour, leaving a yellow *substance* which crystallised well from hot ethanol in needles, m. p. 128° [Found : C, 64·5; H, 3·9; N, 11·7; *M* (Rast), 306. $C_{38}H_{26}ON_6S_4$ requires C, 64·2; H, 3·7; N, 11·8%; *M*, 710]. Light absorption (chloroform) : $\lambda_{max.}$ = 265, 282, 327, 450 mμ; $E^{1\%}_{1\,cm.}$ = 525, 525, 320, 820.

Substance A melted at 239—240°, and was identical with the free acid. It was insoluble in both hot and cold water, ether, alcohol, acetic acid, and toluene, sparingly soluble in hot ethyl acetate and chloroform, and readily soluble in acetone, dioxan, and pyridine on gentle warming. However, crystallisation proved difficult; use of mixed solvents in the cold caused either too rapid precipitation or none, and prolonged heating with acetic acid or aqueous dioxan caused decomposition into alkali-insoluble materials, and yellow materials soluble or insoluble in alkali according to conditions. These degradation products were not further investigated. The *compound* crystallised best from a large volume of hot chloroform in small orange needles, m. p. 239—240° (Found : C, 62·9; H, 3·4; N, 12·1. $C_{36}H_{22}ON_6S_4$ requires C, 63·3; H, 3·3; N, 12·3%). Light absorption (dioxan) : $\lambda_{max.}$ = 223, 260, 270, 315, 450 mμ. $E^{1\%}_{1\,cm.}$ = 400, 500, 400, 400.

5-Amino-2-mercapto-4-phenylthiazole (IV) (10 g.) and Raney nickel (24 g.) were suspended in ethanol (120 c.c.) and the mixture heated to boiling, after which the heat of reaction caused spontaneous refluxing. When reaction was complete the mixture was cooled, filtered from nickel sulphide, and evaporated in a vacuum. The brown semicrystalline residue possessed an amine-like odour and gave an intense green fluorescence in ethanol, probably due to small amounts of 2 : 2′-bisthiazoles (Karrer and Sanz, *Helv. Chim. Acta*, 1944, **27**, 619). It was dissolved in benzene and chromatographed on alumina; development and elution with this solvent gave, on evaporation, 5-amino-4-phenylthiazole, m. p. 135—136°. Continued elution with 20% acetone in benzene yielded a further quantity of the aminothiazole, best isolated as the hydrochloride. This substance did not give a red Schiff's base with methanolic glyoxal. 5-Acetamido-2-mercapto-4-phenylthiazole (XII) (0·5 g.) and Raney nickel (1·2 g.) were suspended in ethanol (20 c.c.), and the mixture refluxed for 10 minutes. Nickel sulphide was removed by filtration, and evaporation in a vacuum gave 5-acetamido-4-phenylthiazole, m. p. 147—148°. The reaction was cleaner than with the parent amine. The benzaldehyde Schiff's base of 5-amino-2-mercapto-4-phenylthiazole (1·0 g.) and Raney nickel (3 g.) were refluxed in ethanol (20 c.c.) for 15 minutes. After filtration and evaporation in a vacuum a rather poor yield of 5-amino-4-phenylthiazole hydrochloride, m. p. 216° (decomp.), was obtained by treating the residue with ethereal hydrogen chloride containing a little ethanol. The acetone Schiff's base of 5-amino-2-mercapto-4-phenylthiazole (V) (0·5 g.) and Raney nickel (3 g.) were refluxed in ethanol (15 c.c.) for 15 minutes. Filtration and evporation gave, on rubbing with benzene, 5-amino-4-phenylthiazole m. p. 135—136°.

5-Amino-2-mercapto-4-phenylthiazole (IV) (5 g.) was moistened with ethanol and boiled with 2N-hydrochloric acid (50 c.c.) for 1·5 hours. No hydrogen sulphide was produced, but an oily liquid was formed which was distilled out and collected in methanol containing some α-aminobenzyl cyanide. The solution, on standing for a day, deposited yellow crystals of 5-amino-2-mercapto-4-phenylthiazole (IV), m. p. 261°, together with a small quantity of red, alkali-soluble crystals, m. p. 272—273°. Essentially, therefore, the sulphur is split out as carbon disulphide. The hydrolysate was filtered from some insoluble material (0·7 g.; a mixture of unreacted thiazole and an orange-brown substance) and evaporated to dryness. The residue was treated with acetone to give colourless rods of α-aminophenylacetic acid hydrochloride (2·7 g.). Recrystallised from 18% hydrochloric acid it had m. p. 212° (decomp.); mixed m. p. with authentic material, 209° (decomp.). Treatment with potassium acetate solution gave the free base, subliming at 285—290°; authentic α-aminophenylacetic acid sublimed at 281—283°.

5-Amino-2-mercapto-4-phenylthiazole (IV) (20 g.) was boiled with 2N-sodium hydroxide (100 c.c.) for 1 hour. The solution, which now failed to give a scarlet Schiff's base with glyoxal, was diluted with water (600 c.c.), and the product precipitated by 2N-hydrochloric acid (200 c.c.) was extracted with boiling acetic acid (300 c.c., 300 c.c., 200 c.c.). The orange residue (4 g.) was insoluble in all common solvents except pyridine and was crystallised from alcoholic potash by addition of acetic acid to give 1′ : 5-*bis*-(2 : 4-*dithio*-5-*phenylhydantoin*) (XV), m. p. 270—271° (decomp.) (Found : C, 51·8; H, 3·15; N, 13·6. $C_{18}H_{14}N_4S_4$ requires C, 52·2; H, 3·4; N, 13·5%). The acetic acid filtrates were cooled to 0° and the 2 : 4-*dithio*-5-*phenylhydantoin* (XIV) which separated (10·5 g.) was recrystallised rapidly from acetic acid, forming colourless clusters of stout needles, m. p. 264—265° (decomp.) (Found : C, 51·9, 52·5; H, 4·3, 3·8. $C_9H_8N_2S_2$ requires C, 51·9; H, 3·9%). This substance readily darkened on exposure to air or undue heating in solvents. It was soluble in pyridine and dioxan on gentle warming, moderately soluble in hot acetic acid, sparingly soluble in hot ethanol, and insoluble in other common solvents.

5-Amino-2-mercapto-4-phenylthiazole (IV) (1 g.) was boiled gently in aqueous ammonia (*d* 0·880) for 2 hours, a sufficient concentration of ammonia being maintained to keep the thiazole in solution. The ammonia was then boiled off, and after filtration from unreacted mercaptothiazole, the solution was acidified to yield 2 : 4-dithio-5-phenylhydantoin (XIV), m. p. 264—265° (decomp.). 5-Amino-2-mercapto-4-phenylthiazole (IV) (5 g.) was refluxed in pyridine (20 c.c.) for 15 minutes; some hydrogen sulphide was evolved and the solution became deep red. On cooling, a mass of deep red crystals was produced, which could be recrystallised from pyridine, and melted at about 75°. On exposure to air for 10 minutes, or treatment with ethanol or water, the material fell to an insoluble orange powder, m. p. 270—271°, identical with 1′ : 5-bis-(2 : 4-dithio-5-phenylhydantoin) (XV). The same result was obtained when 2 : 4-dithio-5-phenylhydantoin (XIV) was substituted for the aminothiazole in the above experiment. The deep red crystals were not produced, however, when a saturated pyridine solution of the bisdithiohydantoin (XV) was cooled. 5-Amino-2-methylthio-4-phenylthiazole hydriodide (1 g.) was refluxed with 2N-sodium hydroxide (20 c.c.) for 0·5 hour. The solution was filtered from a little unsaponified material and acidified with concentrated hydrochloric acid. Methylthiol was evolved and yellow granular crystals of 4-thio-5-phenylhydantoin (XVI) were precipitated, m. p. 259—260° (decomp.) (Johnson and Chernoff, *loc. cit.*, give m. p. 259°, decomp.); mixed m. p. with the dithiohydantoin (XIV) 244° (decomp.).

2 : 4-Dithio-5-phenylhydantoin (XIV) (2 g.) and Raney nickel (6 g.) were suspended in ethanol (50 c.c.), and the mixture refluxed for 10 minutes. After filtration from nickel sulphide and evaporation to dryness, the residue was extracted with ether to yield, on removal of solvent, 5(4)-phenyliminazole (XVII) (0·5 g.) (Found : C, 75·0; H, 5·8. Calc. for $C_9H_8N_2$: C, 75·0; H, 5·6%), which crystallised from benzene in plates, m. p. 133—134° (Pinner, *Ber.*, 1902, **35**, 4135, gives m. p. 128—129°). 1′ : 5-Bis-(2 : 4-dithio-5-phenylhydantoin) (XV) (2·5 g.) was refluxed in ethanol (50 c.c.) with Raney nickel (6 g.) for 0·5 hour. Filtration and evaporation yielded 5(4)-phenyliminazole (XVII), m. p. 133—134°, extracted from the residue with ether.

5-Phenylhydantoin (1·2 g.) (Lehmann, *Ber.*, 1901, **34**, 372) was boiled in tetralin (20 c.c.) with phosphorus pentasulphide (3 g.) for 2 hours. The hot solvent was decanted from the lower oily layer which dissolved in warm 2N-sodium hydroxide (50 c.c.), and yielded 5(4)-phenyliminazole (XVII) (0·6 g.), m. p. 132—133° (mixed m. p. with product from Raney nickel desulphurisation of the dithiohydantoin, 133—134°), on cooling.

5-Amino-2-mercapto-4-phenylthiazole (IV) (20 g.) was boiled with 2N-sodium hydroxide (250 c.c.) until the solution no longer gave an intense red colour with aqueous glyoxal (0·5 hr.). Chloroform

(100 c.c.) and benzyl chloride (25 g.) were then added, and the mixture shaken for 4 hours. The plates, m. p. 108°, which had separated (28 g.) were filtered off and washed with chloroform. This substance was a sodium salt, recrystallisation of which from acetic acid yielded 2 : 4-*dithio*-5-*phenyl*-1(or 3)-*benzylhydantoin* in needles, m. p. 194° (Found : C, 64·2; H, 4·6; N, 9·2. $C_{16}H_{14}N_2S_2$ requires C, 64·2; H, 4·7; N, 9·4%). Light absorption (ethanol) : $\lambda_{max.}$ 277 mμ, $E^{1\%}_{1cm.}$ = 750. The above sodium salt (16 g.) was dissolved in warm ethanol (50 c.c.), and benzyl chloride (6·5 g.) added. After standing at room temperature for 1 hour the sodium chloride was filtered off, and evaporation of the filtrate to small bulk in a vacuum gave a mass of colourless needles. 2 : 4-*Dithio*-5-*phenyl*-1 : 3-*dibenzylhydantoin* crystallised from chloroform–light petroleum (b. p. 40—60°) in needles, m. p. 114° (Found : C, 69·6; H, 5·2; N, 7·4; S, 16·7. $C_{23}H_{20}N_2S_3$ requires C, 71·1; H, 5·2; N, 7·2; S, 16·5%). Light absorption (chloroform) : $\lambda_{max.}$ 277 mμ, $E^{1\%}_{1cm.}$ 390. The substance was recovered unchanged after refluxing for 0·5 hour in acetic anhydride. A little of the dibenzyl derivative was dissolved in acetic acid, and the crystalline hydrochloride precipitated by addition of a few drops of ethanolic hydrogen chloride. 2 : 4-*Dithio*-5-*phenyl*-1 : 3-*dibenzylhydantoin hydrochloride* crystallised from acetic acid in colourless needles, m. p. 168—170° (Found : C, 64·6; H, 5·1; N, 6·6; S, 14·7. $C_{23}H_{20}N_2S_2$,HCl requires C, 65·0; H, 5·0; N, 6·6; S, 15·1%). It was soluble in ethanol and insoluble in acetone.

1′ : 5-Bis-(2 : 4-dithio-5-phenylhydantoin) (XV) (0·5 g.) was refluxed with 2N-sodium hydroxide (10 c.c.) for 1 hour. Acidification yielded 2 : 4-dithio-5-phenylhydantoin (XIV) (0·4 g.), m. p. 267—268° (decomp.); (XIV) was stable in alkali. 2 : 4-Dithio-5-phenylhydantoin (2 g.) was boiled with 50% sulphuric acid (25 c.c.) for 24 hours, the material initially turning orange with simultaneous evolution of sulphur dioxide. The mixture was diluted with water, and the insoluble crystals, m. p. 261° (decomp.), collected. After treatment with 2N-sodium hydroxide and removal of a little insoluble material, m. p. 257—261°, acidification gave orange 1′ : 5-bis-(2 : 4-dithio-5-phenylhydantoin) (XV), m. p. 270—271° (decomp.).

A warm saturated solution of the dithiohydantoin (XIV) in ethanol was treated with iodine in ethanol; immediate decolourisation occurred and 1′ : 5-bis-(2 : 4-dithio-5-phenylhydantoin) (XV) was precipitated, m. p. 272° (decomp.). Ferric chloride added to an acetic acid solution gave a similar result. Hydrogen peroxide in ethanol gave an insoluble product, m. p. 271—272° (decomp.), which, however, was not identical with 1′ : 5-bis-(2 : 4-dithio-5-phenylhydantoin). When an ethanolic solution of 2 : 4-dithio-5-phenylhydantoin was refluxed, the bis-compound (XV) was slowly deposited owing to aerial oxidation.

Reactions with α-Aminopropionitrile.—Acetaldehyde-ammonia (73 g.) was added in portions during 2 hours to ice-cold anhydrous hydrogen cyanide (48 c.c.), and the mixture kept for 2 hours at room temperature and distilled at 12—15 mm. (Delépine, *Bull. Soc. chim.*, 1903, **29**, 1184). Two main fractions were obtained, (A) b. p. 65—75°, and (B), b. p. 115—125°, as well as smaller intermediate fractions. Fraction (A), which is essentially α-aminopropionitrile (2·1 g.), was kept with carbon disulphide (2·3 g.) in ethanol (25 c.c.) for 2 days. 2 : 4-Dithio-5-methylhydantoin (3 g.) separated, m. p. 224° (decomp.), and was crystallised by solution in aqueous ammonia (*d* 0·880), dilution with 50% ethanol, and precipitation with 2N-hydrochloric acid. The compound was insoluble in common solvents except pyridine, and readily darkened on exposure to light and air. It was soluble in aqueous alkali and the solution gave a red colour with sodium nitroprusside but not with glyoxal. In the presence of acetaldehyde, formation of dithiohydantoin in the above reaction was completely inhibited and the acetaldehyde Schiff's base of the corresponding thiazole (see below) was obtained, though in poor yield.

Fraction (B), diluted with ethanol, was kept overnight with excess of carbon disulphide, and a mass of colourless needles of the acetaldehyde *Schiff's base* of 5-amino-2-mercapto-4-methylthiazole, m. p. 203° (decomp.), separated (Found : C, 42·1; H, 4·8; N, 16·1; S, 37·2. $C_6H_8N_2S_2$ requires C, 41·9; H, 4·7; N, 16·3; S, 37·2%). The compound was soluble in hot ethanol, ethyl acetate, and acetic acid, and in cold dioxan and pyridine. It readily darkened on exposure to light or on heating in solvents. The Schiff's base was readily soluble in aqueous alkali, and on warming, acetaldehyde was evolved; warm dilute acids also liberated acetaldehyde. When ethanolic hydrogen chloride was added to a solution of the Schiff's base in warm ethyl acetate, 5-*amino*-2-*mercapto*-4-*methylthiazole hydrochloride*, m. p. 197° (decomp.), was rapidly precipitated (Found : C, 26·6; H, 4·1; N, 14·8. $C_4H_7N_2S_2Cl$ requires C, 26·3; H, 3·8; N, 15·3%). The compound was insoluble in acetic acid, acetone, and ethanol, soluble in methanol and water, and was best crystallised from methanol and ether. It darkened on exposure to light, and did not yield a free base on treatment with aqueous sodium hydrogen carbonate; treatment of a methanolic or aqueous solution of the above hydrochloride with aqueous glyoxal gave an immediate scarlet precipitate.

α-Aminopropionitrile hydrochloride (5·3 g.) (Dubsky, *Ber.*, 1916, **49**, 1048) was suspended in ethanol (25 c.c.) containing a little phenolphthalein and titrated to neutrality with N-ethanolic sodium ethoxide. After filtration from sodium chloride, the mixture was set aside over-night at 0° with carbon disulphide (4 c.c.). 2 : 4-Dithio-5-methylhydantoin (1·1 g.), m. p. 223° (decomp.), separated, and addition of ethereal hydrogen chloride to the filtrate gave 5-amino-2-mercapto-4-methylthiazole hydrochloride (1·1 g.), m. p. 197° (decomp.).

Reaction with Ethyl Aminocyanoacetate.—An ethereal solution of the ester (see Part I, *loc. cit.*) was kept overnight at 0° with excess of carbon disulphide. Extraction and crystallisation of the residue from ethanol yielded colourless barrel-shaped tablets of 5-*amino*-2-*mercapto*-4-*carbethoxythiazole*, m. p. 182—183° (decomp.) (Found : C, 35·7; H, 4·0; N, 13·4. $C_6H_8O_2N_2S_2$ requires C, 35·3; H, 3·9; N, 13·7%). The compound contains a diazotisable group but did not give a colour with glyoxal. The above compound (2 g.) was suspended in ethanol (30 c.c.) with Raney nickel (6 g.) and refluxed for 15 minutes. Filtration of the intensely blue fluorescent solution and evaporation yielded 5-amino-4-carbethoxythiazole, m. p. 163° after crystallisation from ethyl acetate, undepressed by the material described in the preceding paper.

5-Amino-2-mercapto-4-carbethoxythiazole (1·0 g.) was refluxed with methyl iodide (1·0 g.) in ethanol (5 c.c.) for 3 minutes, and the plates (1·5 g.) which separated on cooling recrystallised from methanol and

ether to give *5-amino-2-methylthio-4-carbethoxythiazole hydriodide*, m. p. 164—165° (decomp.) (Found : N, 8·1. $C_7H_{11}O_2N_2IS_2$ requires N, 8·1%). Treatment with aqueous sodium hydrogen carbonate readily yielded the corresponding *base*, which crystallised from aqueous ethanol in long needles, m. p. 108° (Found : C, 38·8; H, 5·1; N, 13·1; S, 29·4. $C_7H_{10}O_2N_2S_2$ requires C, 38·5; H, 4·6; N, 12·8; S, 29·4%).

Reaction with Carbon Dioxide.—α-Aminobenzyl cyanide (1 g.) was dissolved in ethanol (30 c.c.), and a slow stream of carbon dioxide passed through the solution overnight. The flocculent precipitate was recrystallised from acetic acid to give *α-cyano-α'-carbamyldibenzylurea* (XVIII; R = H, R' = Ph), m. p. 224° (decomp.) (Found : C, 66·0; H, 5·3. $C_{17}H_{16}O_2N_4$ requires C, 66·2; H, 5·2%). The compound was only slowly attacked by boiling dilute acids and alkalis.

Light absorption of thiazoles, 

Substituents : 2.	4.	5.	Solvent.	$\lambda_{max.}$	$E^{1\%}_{1\,cm.}$	
SH	Ph	NH_2	Dioxan	281		
				290	460	
				300		
				223	680	
			Aq.NaOH	306	660	
				223	980	
SAc	Ph	NAc_2	$CHCl_3$	290 (inflexion)	195	
				242	660	
SH	Ph	NAc_2	$CHCl_3$	235	560	
				282	420	
				291		
				306	360	
SH	Ph	NHAc	Dioxan	228	700	
				281	510	
				290		
				308	410	
				323	310	
SMe	Ph (hydrochloride)	NH_2	MeOH	223	560	
				281	390	
				290		
				308	370	
SH	CO_2Et	NH_2	Dioxan	282	490	
				291	480	
				306	420	
				320	370	inflexions
				336	300	
SMe	Ph (methosulphate)	NH_2	EtOH	228	220	inflexions
				242	165	
				350	280	
SMe	Ph	NHAc	$CHCl_3$	235	600	
				282	460	
				290		
				300	490	
				308		
SNa	Ph	N:CHPh	EtOH	219	600	
				265	650	
				282	600	
				290	500	
				428	625	
SH	Ph	N:CMePh	Dioxan	255	875	
				328	240	
				401	400	
				267	535	
				280	440	after 1 day
				365	240	
SH	Ph	$N{:}CMe_2$	Dioxan	290	500	
				352	230	
				260	650	
				372	300	after 1 day
SMe	Ph	N:CH·CH:N (bis-azomethine)	$CHCl_3$	265	520	
				281	600	
				290		
				498	715	

We thank I.C.I. Ltd. (Dyestuffs Division) for gifts of chemicals, and Dr. E. A. Braude for the absorption spectra.

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[*Received, January 23rd,* 1947.]