*A Novel Reaction of Thiourea, the Structure of Jaffé's Base, and Related Studies.**

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Condensation of α-bromo-*p*-chlorophenylacetonitrile with thiourea in acetone solution gave, besides the expected 2 : 4-diamino-5-*p*-chlorophenylthiazole (I; R = Cl), the dihydrobromide of a base $C_5H_{10}N_4S$, shown to be 2 : 6-diamino-4 : 4-dimethyl-1 : 3 : 5-thiadiazine (II) by synthesis of the dihydrobromide from thiodiformamidine dihydrobromide (III) and acetone. This recalled the formation of Jaffé's base, $C_6H_{10}N_4S$, hitherto formulated as a substituted thiodiformamidine (V), on treating ethylenethiourea (IV) with 5 : 5-dibromohydroxyhydrouracil. Jaffé's base, however, is monoacidic, and cannot have the dihydroglyoxalinyl sulphide structure (V); it appears to be 4 : 5-dihydro-1-(4 : 5-dihydroglyoxalin-2-yl)-2-mercaptoglyoxaline (as X), a conclusion supported by a comparison of its ultraviolet absorption spectrum with that of amidinothiourea (XI).

Various heterocyclic compounds derived from acetone by reaction with thiourea–hydrobromic acid, amidinothiourea, and *S*-methyl*iso*thiourea are mentioned, and a refinement of the Grote colour test for certain types of sulphur compounds is described.

IN continuation of our study of aryl-substituted heterocyclic diamines as potential chemotherapeutic agents (Chase, Thurston, and Walker, *J.*, 1951, 3439; Thurston and Walker, *J.*, 1952, 4542; Chase and Walker, *J.*, 1953, 3518, 3548; B.P. 717,250), we have had occasion to prepare 2 : 4-diamino-5-phenyl- (I; R = H) and -5-*p*-chlorophenyl-thiazole (I; R = Cl). Condensation between α-chloro-α-phenylacetonitrile and thiourea in acetone

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solution * at room temperature gave the hydrochloride of 2 : 4-diamino-5-phenylthiazole (I; R = H) in good yield although similar condensation using α-bromo-α-phenylacetonitrile was less satisfactory. When the condensation of α-bromo-*p*-chlorophenylacetonitrile with thiourea was carried out in acetone solution in the cold there was formed, however, in moderate yield, in addition to the expected hydrobromide of 2 : 4-diamino-5-*p*-chlorophenylthiazole (I; R = Cl), the dihydrobromide of a base $C_5H_{10}N_4S$, ostensibly derived from one molecular proportion of acetone and two of thiourea. As the base $C_5H_{10}N_4S$ gave a dihydrobromide it obviously contained two isolated basic centres and the only likely structure was that of 2 : 6-diamino-4 : 4-dimethyl-1 : 3 : 5-thiadiazine (II); confirmation of this structure came when the dihydrobromide was subsequently obtained synthetically by condensation of thiodiformamidine dihydrobromide (III) with acetone.

$$Br\{NH_2{:}C(\cdot NH_2)\cdot S\cdot C(\cdot NH_2){:}NH_2\}Br \quad (III)$$

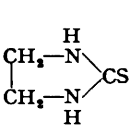
The formation of the thiadiazine dihydrobromide, from acetone and thiourea in the presence of α-bromo-*p*-chlorophenylacetonitrile, recalled the production of a base, $C_6H_{10}N_4S$, by the oxidation of ethylenethiourea (IV) with 5 : 5-dibromohydroxyhydrouracil (in effect, hypobromous acid) (Johnson and Edens, *J. Amer. Chem. Soc.*, 1941, **63**, 1058), which proved to be identical with Jaffé's base, obtained originally by the action of thiocarbonyl chloride on ethylenediamine (Jaffé and Kühn, *Ber.*, 1894, **27**, 1664). In view of its formation by direct oxidation of ethylenethiourea (IV), Johnson and Edens (*loc. cit.*) preferred the dihydroglyoxalinyl sulphide structure (V) for Jaffé's base, a formulation which Jaffé had considered but had discarded in favour of (VI) (Jaffé and Kühn, *loc. cit.*). Johnson and Edens (*J. Amer. Chem. Soc.*, 1942, **64**, 2706) later obtained Jaffé's base by oxidising ethylenethiourea (IV) with iodine to the disulphide (VII), and allowing the hydroperiodide † of the latter to decompose in boiling aqueous solution. Moreover, the hydrochloride (m. p. 270°; Jaffé and Kühn, *loc. cit.*) of Jaffé's base was almost certainly the unidentified substance, "$C_6H_{11}N_4ClS$," m. p. 270°, isolated by Rây and Das (*J.*, 1922, **121**, 323) from the reaction of ethylenethiourea with chloropicrin. Jaffé's base, however, is monoacidic, and, as one would expect the substituted thiodiformamidine structure (V), like thiodiformamidine itself and 2 : 6-diamino-4 : 4-dimethyl-1 : 3 : 5-thiadiazine (II), to be diacidic, we were led to doubt the structure assigned to Jaffé's base by Jaffé and Kühn and by Johnson and Edens (*locc. cit.*). Recently, however, Lecher and Gubernator (*J. Amer. Chem. Soc.*, 1953, **75**, 1087) have shown that the disulphide (VIII) obtained from *NNN'*-trimethylthiourea is unstable in acid aqueous media and decomposes on boiling under these conditions to give sulphur and *N*-(trimethylamidino)-*NN'N'*-trimethylthiourea (IX), as a monoacidic base, together with other decomposition products; they were led by this observation, and its similarity to Johnson and Edens's later method for its preparation from the disulphide (VII), to suggest that Jaffé's base has the structure (X), rather than that (V) advocated by Johnson and Edens (*loc. cit.*), and our observations, recorded below, support thi sview. The substance "$C_4H_{11}N_4ClS$" ($C_4H_{10}N_4S$,HCl) obtained from methylthiourea and chloropicrin (Rây and Das, *loc. cit.*) is presumably also to be formulated as a derivative of amidinothiourea.

Reverting to 2 : 6-diamino-4 : 4-dimethyl-1 : 3 : 5-thiadiazine dihydrobromide (cf. II), one may ascribe its formation from thiourea in acetone solution in the presence of α-bromo-*p*-chlorophenylacetonitrile to decomposition of the intermediate *S*-(*p*-chloro-α-cyanobenzyl)*iso*thiourea, $CH(C_6H_4Cl)(CN)\cdot S\cdot C(:NH)\cdot NH_2$, to give cyanamide, which reacts with unchanged thiourea in the presence of hydrogen bromide (from hydrolysis of the thiuronium

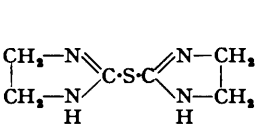
* It may be noted that Miller, Sprague, Kissinger, and McBurney (*J. Amer. Chem. Soc.*, 1940, **62**, 2099) found that the reaction between chloroacetonitrile and thiourea in acetone solution in the cold only proceeded as far as *S*-(cyanomethyl)thiuronium chloride, $CH_2(CN)\cdot S\cdot C(\cdot NH_2){:}NH_2Cl$, which underwent ring-closure to 2 : 4-diaminothiazole hydrochloride in warm alcohol (Land, Ziegler, and Sprague, *J. Org. Chem.*, 1946, **11**, 622), the latter product being obtained directly when the reaction is carried out in cold methanol (Davies, Maclaren, and Wilkinson, *J.*, 1950, 3491) or hot ethanol (Davies *et al.*, *loc. cit.*; Zerweck and Schubert, G.P. 729,853).

† Johnson and Edens (*loc. cit.*) formulated this hydroperiodide as $C_6H_{10}N_4S_2,HI,2I_2$, implying that the disulphide (VII) is monoacidic; the hydroperiodide, however, is more probably $C_6H_{10}N_4S_2,2HI,I_2$, and the analysis of the dihydrochloride of (VII) (Freedman and Corwin, *J. Biol. Chem.*, 1949, **181**, 617) definitely shows that (VII) is, as one would expect, a diacidic base.

bromide) to give thiodiformamidine dihydrobromide (III), and the latter on condensation with acetone gives 2 : 6-diamino-4 : 4-dimethyl-1 : 3 : 5-thiadiazine dihydrobromide. Indeed, reaction between cyanamide and thiourea in the presence of alcoholic hydrogen chloride, or bromide, was found to take place exothermally with great ease (cf. Chabrier, Renard, and Renier, *Compt. rend.*, 1952, **235**, 64) to give thiodiformamidine dihydrochloride, or dihydrobromide (III), and subsequent reaction of (III) with acetone afforded the dihydrobromide of 2 : 6-diamino-4 : 4-dimethyl-1 : 3 : 5-thiadiazine (II) in moderate



(IV)



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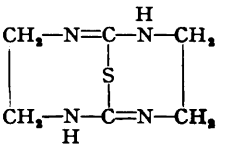

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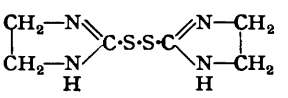
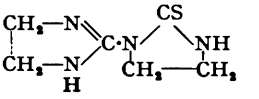
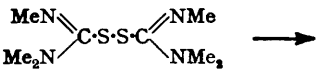
(VII)

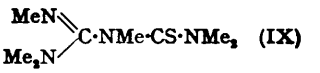




(X)

(VIII)





(IX)

yield. Alternatively,* the " positive " bromine in α-bromo-*p*-chlorophenylacetonitrile might have caused intermediate formation of dithiodiformamidine dihydrobromide, $Br\{NH_2{:}C(\cdot NH_2)\cdot S\cdot S\cdot C(\cdot NH_2){:}NH_2\}Br$, which could decompose to give cyanamide, sulphur, thiourea, and hydrogen bromide (cf. Claus, *Annalen*, 1875, **179**, 142; McGowan, *J.*, 1886, **49**, 192), leading, by the reaction just discussed, to thiodiformamidine dihydrobromide (III), and thence to the dihydrobromide of 2 : 6-diamino-4 : 4-dimethyl-1 : 3 : 5-thiadiazine (II); on the other hand, if dithiodiformamidine were to decompose in accordance with the analogy of Lecher and Gubernator's disulphide (VIII), the product would be amidinothiourea (XI), and this was shown to react with acetone (in the presence of piper-

$$NH_2\cdot C(:NH)\cdot NH\cdot CS\cdot NH_2 \quad (XI)$$

idine) to give 4-amino-1 : 2-dihydro-6-mercapto-2 : 2-dimethyl-1 : 3 : 5-triazine (as XII), since the latter (XII) was also obtained by demethylation of 4-amino-1 : 2-dihydro-2 : 2-dimethyl-6-methylthio-1 : 3 : 5-triazine (XIII) by the method of Fairfull, Lowe, and Peak (*J.*, 1952, 743). The conditions for the condensation of thiodiformamidine with acetone were not studied in detail, but considerations relating to the condensation of *p*-chlorophenyldiguanide with acetone (Carrington, Crowther, and Stacey, *J.*, 1954, 1017) are doubtless applicable; as in the case of the latter reaction, no condensation occurred between free thiodiformamidine base and acetone.

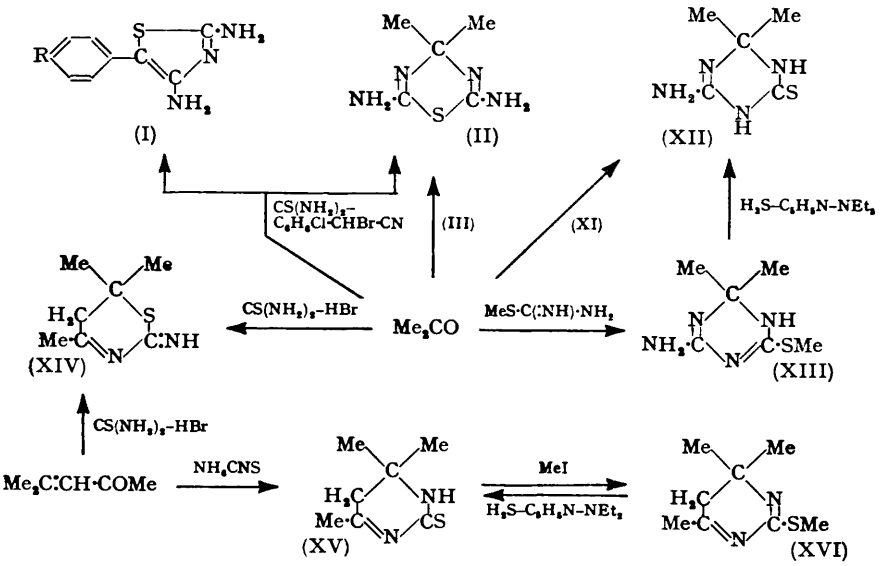
Direct reaction between thiourea and acetone in the presence of hydrobromic acid gave, in small yield, a base $C_7H_{12}N_2S$, characterised as the picrate, and the same substance was obtained more readily from mesityl oxide, thiourea, and concentrated aqueous hydrobromic acid. The substance, forming a picrate, was obviously 2-amino-4 : 6 : 6-trimethyl-1 : 3-thiazine, or a tautomeric form † (XIV), and the picrate was probably identical with the " thiocarbamide-acetone picrate, $C_{10}H_{13}O_8N_5S$ " isolated by Taylor (*J.*, 1922, **121**, 2271) after allowing acetone and thiourea to react in the presence of hydrogen chloride, phosphoryl

* Johnson has reported (*J. Amer. Chem. Soc.*, 1940, **62**, 2269) that 5 : 5-dibromohydroxyhydrouracil and thiourea react in water or alcohol to give 5-bromouracil (quantitatively), free sulphur, cyanamide, and hydrobromic acid.

† A number of substances described in this communication are capable of existing in tautomeric modifications. As the nature of this possible tautomerism is obvious, and not particularly relevant to the main theme, no special mention is made of it. For the sake of convenience, however, (XII) and (XV) are named as dihydromercapto-compounds, rather than tetrahydrothioxo-compounds, although ultraviolet absorption characteristics and colour reactions indicate that the substances contain >C:S rather than >C·SH groups.

chloride, or phosphorus trichloride. The base (XIV) is isomeric with the non-basic 4 : 5-dihydro-2-mercapto-4 : 4 : 6-trimethylpyrimidine (XV), obtained from mesityl oxide and ammonium thiocyanate in boiling toluene; the substance (XV) must have the sulphur atom in the extracyclic position to account for its lack of conventional basicity, and also since it could be methylated to the methylthio-derivative, 4 : 5-dihydro-4 : 4 : 6-trimethyl-2-methylthiopyrimidine (XVI), and regenerated from the latter on demethylation by the method of Fairfull, Lowe, and Peak (*loc. cit.*).

Further evidence concerning the structures of the above substances came from a study of their ultraviolet absorption spectra. Thus, 2 : 6-diamino-4 : 4-dimethyl-1 : 3 : 5-thiadiazine dihydrobromide (cf. II) showed only end-absorption in N-hydrochloric acid,



as did thiodiformamidine dihydrobromide (III) (Fig. 1). In methanol, however, the former salt showed a distinct shoulder at ~240 mμ, while the latter, being more extensively hydrolysed, showed an intense band at 242 mμ. The ultraviolet absorption spectrum of Jaffé's base in methanol (Fig. 2) showed two intense bands, thus excluding the substituted

thiodiformamidine (dihydroglyoxalinyl sulphide) structure (V) or, indeed, a symmetrical structure for this substance, and, in terms of structure (X) for Jaffé's base, the two distinct polar excited states giving rise to the two bands may be written as (XVII) and (XVIII). The correctness of structure (X) for Jaffé's base is strongly supported by the similarity between the ultraviolet absorption spectrum in methanol of that substance and that of amidinothiourea (XI), in which the two bands are displaced to slightly lower frequencies. The ultraviolet absorption spectrum of Jaffé's base (X) was scarcely altered in N-hydrochloric acid but the absorption band at higher frequency in that of amidinothiourea (XI) was suppressed under these conditions, although it was present at reduced intensity in the spectrum of amidinothiourea hydrochloride in methanol (Fig. 2). The two remaining unsymmetrical structures containing the >C:S group, 4-amino-1 : 2-dihydro-6-mercapto-2 : 2-dimethyl-1 : 3 : 5-triazine (XII) and 4 : 5-dihydro-2-mercapto-4 : 4 : 6-trimethylpyrimidine (XV), had ultraviolet absorption spectra suggesting fusion of two bands of equal intensity into one broad band in the case of the latter and fusion of two bands of nearly equal intensity into one band with a shoulder in the case of the former.

The colour reactions given by the above substances with Grote's reagent (*J. Biol. Chem.*, 1931, **93**, 25) also classified Jaffé's base as a substance containing a $>C:S$ grouping. Thus, thiourea, ethylenethiourea (IV), Jaffé's base (X), amidinothiourea (XI), 4-amino-1 : 2-dihydro-6-mercapto-2 : 2-dimethyl-1 : 3 : 5-triazine (XII), and 4 : 5-dihydro-2-mercapto-4 : 4 : 6-trimethylpyrimidine (XV) gave green, blue-green, or blue colours with Grote's reagent, as did the following substances examined in studying the scope of the reaction : monomethylthiourea, *NN'*-dimethylthiourea, *p*-chlorophenylamidino)thiourea, 6-methyl-2-thiouracil, 1 : 4 : 6-trimethyl-2-thiopyrimidone, and 6-methyl-4-thiopyrimidone (cf.

FIG. 1. FIG. 2.

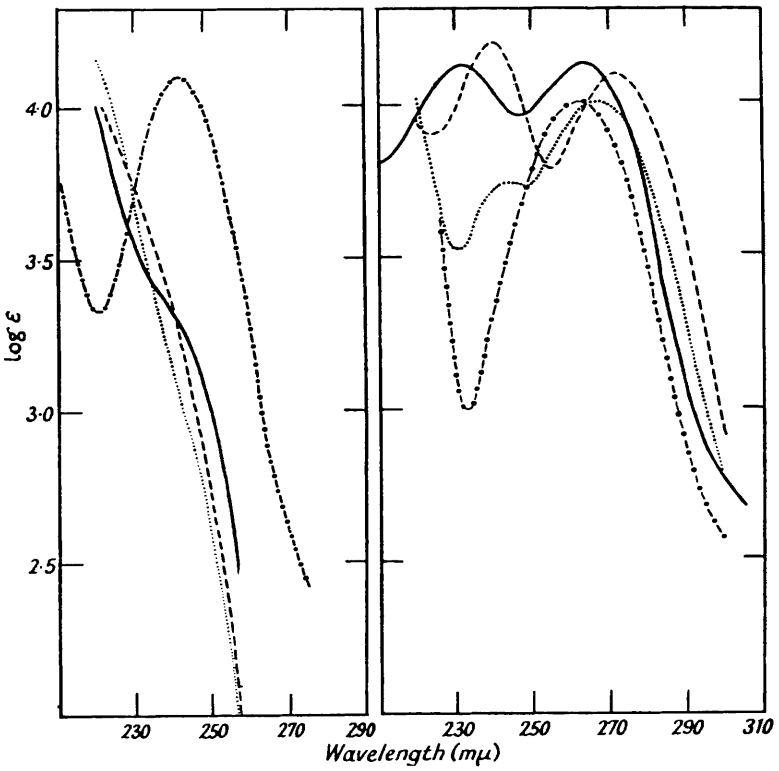


FIG. 1. 2 : 6-*Diamino*-4 : 4-*dimethyl*-1 : 3 : 5-*thiadiazine* (II) *dihydrobromide, in* N-*hydrochloric acid* (— — — —) *and in methanol* (————). *Thiodiformamidine dihydrobromide* (III), *in* N-*hydrochloric acid* (. . . . .) *and in methanol* (— · — · —).

FIG. 2. *Jaffé's base* (X), *in methanol* (————). *Amidinothiourea* (XI), *in methanol* (— — — —) *and in* N-*hydrochloric acid* (— · — · —). *Amidinothiourea hydrochloride, in methanol* (. . . . .).

Marshall and Walker, *J.*, 1951, 1004). Further, the conditions described by Grote, *i.e.*, saturated sodium hydrogen carbonate solution, appeared to be optimal for the development of colour by these substances. On the other hand, the dihydrobromides of 2 : 6-diamino-4 : 4-dimethyl-1 : 3 : 5-thiadiazine (II) and thiodiformamidine gave bluish-purple colours when examined under Grote's standard conditions but the colours were rather fugitive. In the presence of saturated borax, however, the Grote reagent gave intense purple-red colours with the dihydrobromides of the thiadiazine (II) and thiodiformamidine, which faded only very slowly in the course of several days. Buffering by borax also appeared to be more satisfactory for the development of the more transient deep rose-pink colour given by cyanide-reduced cystine with the Grote reagent. On the contrary, the former group of substances, giving green, blue-green, or blue colours with the Grote reagent in saturated sodium hydrogen carbonate, did not develop as intense colours in presence of

borax, and the colours were more fugitive under these conditions. Obviously the components of the Grote reagent, acting differentially with sulphur compounds of distinct types, have different pH optima for colour development, and the test should be applied both with sodium hydrogen carbonate, as Grote described, and with borax. Tschugaeff's reagent (diphenylmethylene chloride) (*Ber.*, 1902, **35**, 2482) was found to be of very restricted application as it failed to give the characteristic blue colour of thiobenzophenone with any of the above cyclic compounds within 5 minutes at 150° (bath-temperature), with the exception of ethylenethiourea, which gave a blue colour within 10 seconds at 150°. The open-chain compounds, thiourea, mono- and di-methylthiourea, amidinothiourea and (*p*-chlorophenylamidino)thiourea all gave blue colours within 5 seconds at 150°.

Experimental

2 : 4-*Diamino-5-phenylthiazole* (I; R = H) *Hydrohalides.*—(*a*) A mixture of α-chloro-α-phenylacetonitrile (Ingham, *J.*, 1927, 695) (6·55 g.), thiourea (3·36 g.), and acetone (10 c.c.) was kept at room temperature for 3 days. The mixture was then partitioned between ether and water. Evaporation to dryness of the aqueous phase and crystallisation of the residue from methanol–ethyl acetate afforded 2 : 4-*diamino-5-phenylthiazole hydrochloride* (7·1 g., 72%), elongated hexagonal plates, m. p. 273—274° (decomp. from 235°) (Found: C, 47·6; H, 4·5; N, 18·2. $C_9H_9N_3S$,HCl requires C, 47·5; H, 4·4; N, 18·5%).

The same compound was also obtained by liberating the free base from the benzenesulphonate (Dodson and Turner, *J. Amer. Chem. Soc.*, 1951, **73**, 4517) and neutralizing this with hydrochloric acid.

(*b*) Nitrogen was passed with stirring over the product of the bromination (as in *Org. Synth.*, **28**, 55) of phenylacetonitrile (29·3 g.) to remove hydrogen bromide and excess of bromine, and the residue was treated with thiourea (19 g.) followed by acetone (300 c.c.). The mixture, which warmed spontaneously to about 40°, was kept at room temperature for 4 days. Solvent was then removed on the steam-bath with stirring and the residue was partitioned between water and chloroform. Evaporation to dryness of the aqueous layer under reduced pressure and crystallisation of the residue from methanol–ethyl acetate gave as first crop a small quantity (3·83 g.) of a colourless substance showing no m. p. below 360°; it was not further examined. The mother-liquors yielded 2 : 4-diamino-5-phenylthiazole hydrobromide in the form of colourless prisms (26 g., 38%), m. p. 260° (decomp.). Davies, Maclaren, and Wilkinson (*J.*, 1950, 3491) obtained an 83% yield when this reaction was carried out in hot, or cold, alcoholic solution and record m. p. >250° (decomp.).

2 : 6-*Diamino*-4 : 4-*dimethyl*-1 : 3 : 5-*thiadiazine* (II) *Dihydrobromide and* 2 : 4-*Diamino*-5-p-*chlorophenylthiazole* (I; R = Cl) *Hydrobromide.*—Bromine (11·1 g.) was added dropwise during 15 min. to *p*-chlorophenylacetonitrile (10 g.) at 110—115° (bath-temp.). The mixture was heated for a further 15 min. at the same temperature, then cooled, and nitrogen was passed over the surface to remove hydrogen bromide and excess of bromine (cf. *Org. Synth.*, **28**, 55). Thiourea (5·5 g.) was then added, followed by acetone (50 c.c.). The mixture, which warmed spontaneously to about 50°, was kept at room temperature for 4 days. After dilution with water and several extractions with ether the aqueous phase was evaporated to dryness under reduced pressure. Crystallisation of the residue from methanol–ethyl acetate afforded, as first crop, colourless plates (3·34 g., 29% based on thiourea) of 2 : 6-*diamino*-4 : 4-*dimethyl*-1 : 3 : 5-*thiadiazine* (II) *dihydrobromide*, m. p. 221—222°; the ultraviolet absorption spectrum showed a shoulder at ~240 mμ (log ε ~3·3) in MeOH, and only end-absorption in N-hydrochloric acid (Found: C, 18·7; H, 3·8; N, 17·4; Br, 49·0. $C_5H_{10}N_4S$,2HBr requires C, 18·8; H, 3·8; N, 17·5; Br, 49·9%).

Fractional crystallisation of the material remaining in the mother-liquors from methanol–ethyl acetate gave colourless needles (5·9 g.; 23%) of 2 : 4-*diamino*-5-p-*chlorophenylthiazole* (I; R = Cl) *hydrobromide*, m. p. 260° (decomp.) (Found: C, 35·2; H, 2·9; N, 13·4. $C_9H_8N_3ClS$,HBr requires C, 35·2; H, 3·0; N, 13·7%).

Thiodiformamidine Dihydrochloride.—A solution of thiourea (14·5 g., 1 mol.) in absolute alcohol (250 c.c.) containing dissolved hydrogen chloride (5·5% w/v; 2 mols.) was added to a solution of cyanamide (8 g.) in a small volume of absolute alcohol. Heat was evolved and a white crystalline solid rapidly separated. After an hour the mixture was cooled, and the product (30·2 g., 84%), m. p. (crude) 181—182° (effervescence) was collected and dried. Recrystallisation from methanol–ethyl acetate (1 : 1) gave plates of thiodiformamidine dihydrochloride,

m. p. 182° (effervescence) (Found: C, 12·9; H, 4·2; N, 29·6. Calc. for $C_2H_6N_4S,2HCl$: C, 12·6; H, 4·2; N, 29·3%). Chabrier, Renard, and Renier (*loc. cit.*) record m. p. 178°.

Thiodiformamidine Dihydrobromide (III).—In a similar manner, cyanamide (3 g.), alcoholic hydrogen bromide (140 c.c. of 8·2% w/v), and thiourea (5·4 g.) afforded *thiodiformamidine dihydrobromide* (14·4 g., 72%), which separated from 90% aqueous acetic acid in colourless flattened needles, m. p. 205—206° (effervescence); ultraviolet light absorption, $\lambda_{max.}$ 242 mμ (log ε 4·10) in MeOH, only end-absorption in N-hydrochloric acid (Found: C, 8·7; H, 3·0; N, 19·9; Br, 56·8. $C_2H_6N_4S,2HBr$ requires C, 8·6; H, 2·9; N, 20·0; Br, 57·1%). A 1% aqueous solution had pH 2·03.

When the hydrogen bromide was supplied in the form of concentrated aqueous solution diluted with about 6 volumes of ethanol the yield dropped to about 50%.

2 : 6-*Diamino*-4 : 4-*dimethyl*-1 : 3 : 5-*thiadiazine* (II) *Dihydrobromide*.—A solution of thiodiformamidine dihydrobromide (5 g.) in methanol (60 c.c.) and acetone (50 c.c.) was kept at room temperature for 4—10 days. The use of methanol as solvent was necessary on account of the insolubility of powdered thiodiformamidine dihydrobromide in bulk in acetone. The solvent was removed as thoroughly as possible at room temperature in a vacuum, finally with two additions of absolute alcohol, giving crystalline material contaminated by gum. The gum was dissolved out in absolute alcohol (10 c.c.), and the crystalline material (1·96 g.) was collected. Recrystallisation from methanol–ethyl acetate (1 : 2) gave colourless plates (1·64 g., 29%) of 2 : 6-diamino-4 : 4-dimethyl-1 : 3 : 5-thiadiazine (II) dihydrobromide, m. p. 221—222° (effervescence) with prior discoloration, having an infrared absorption spectrum identical with that of the specimen obtained as above (Found: C, 18·7; H, 3·8; N, 17·4%). A 1% aqueous solution had pH 2·20.

No condensation took place with free thiodiformamidine base. Thiodiformamidine dihydrochloride (1·91 g.) was added to ethanol (20 c.c.) containing sodium ethoxide (from 0·46 g. of sodium), sodium chloride separating. After *ca.* 10 min. acetone (10 c.c.) was added and the mixture was kept at room temperature for 3 days. The sodium chloride was separated and the calculated volume of N-hydrobromic acid (20 c.c.) was added. The mixture was then taken to dryness below 40° in a vacuum (Craig, *Analyt. Chem.*, 1950, **22**, 1462), finally with two additions of ethanol. The crude product (2·9 g.) had m. p. 175—183° (effervescence) raised to 192—193° (effervescence) on crystallisation from methanol–ethyl acetate. The infrared absorption spectrum of this material showed excellent agreement with that of thiodiformamidine dihydrobromide.

Amidinothiourea (XI) *Hydrochloride*.—4 : 6-Diamino-2-mercapto-1 : 3 : 5-thiadiazine (16 g.), obtained from dicyandiamide and carbon disulphide (U.S.P. 2,364,594; Birtwell, Curd, Hendry, and Rose, *J.*, 1948, 1649), was hydrolysed with concentrated hydrochloric acid as described in the same patent. The solution was then concentrated under reduced pressure to small bulk and propan-1-ol was added. The mixture was warmed and a small quantity of solid was rejected. The solution was taken to dryness several times with ethanol, and the residue was taken up in hot ethanol (*ca.* 50 c.c.) (charcoal) and freed from a small insoluble residue. On cooling and scratching, small stout colourless prisms (5·2 g.) with pointed ends separated, m. p. 172—173° (effervescence); recrystallisation from ~6 parts of ethanol raised the m. p. to 177—178° (effervescence); ultraviolet light absorption, $\lambda_{max.}$ 244, 267 mμ (log ε 3·74, 4·01) in MeOH, 262—263 mμ (log ε 4·01) in N-HCl (Found: C, 15·7; H, 4·4; N, 36·1. Calc. for $C_2H_6N_4S,HCl$: C, 15·5; H, 4·5; N, 36·2%). Rathke (*Ber.*, 1878, **11**, 962) records an analysis but no m. p., while U.S.P. 2,364,954 records neither. The m. p. is almost the same as that, 175—176°, recorded for the free base (cf. Birtwell *et al.*, *loc. cit.*). A 1% aqueous solution had pH 3·70.

Free amidinothiourea was obtained by the method of Birtwell *et al.* (*loc. cit.*); ultraviolet light absorption, $\lambda_{max.}$ 240, 272 mμ (log ε 4·20, 4.10) in MeOH.

4-*Amino*-1 : 2-*dihydro*-6-*mercapto*-2 : 2-*dimethyl*-1 : 3 : 5-*triazine* (XII).—(*a*) A mixture of amidinothiourea (2·36 g.) and acetone (75 c.c.) containing piperidine (0·5 c.c.) was kept at 37° for 18 hr. The crystalline solid, m. p. 178—180°, was collected and a second similar crop was obtained by concentrating the mother-liquors (total yield, 1·75 g., 55%). Recrystallisation from water afforded 4-*amino*-1 : 2-*dihydro*-6-*mercapto*-2 : 2-*dimethyl*-1 : 3 : 5-*triazine* (XII) in the form of colourless flattened needles, m. p. 192—193°; ultraviolet light absorption, $\lambda_{max.}$ 277 mμ (log ε 4·16), shoulder at ~260 mμ (log ε ~4·05) in MeOH (Found: C, 37·4; H, 6·5; N, 35·3. $C_5H_{10}N_4S$ requires C, 38·0; H, 6·4; N, 35·4%). The *picrate* separated from ethanol in yellow rhombs, m. p. 216—217° (Found: C, 34·3; H, 3·6; N, 25·0. $C_5H_{10}N_4S,C_6H_3O_7N_3$ requires C, 34·1; H, 3·4; N, 25·3%).

(*b*) 4-Amino-1 : 2-dihydro-2 : 2-dimethyl-6-methylthio-1 : 3 : 5-triazine (XIII) (obtained in 39% yield from *S*-methyl*iso*thiourea and acetone by the method of Birtwell *et al.*, *loc. cit.*) (0·50 g.) was treated in pyridine (3 c.c.) containing triethylamine (0·4 g.) with a stream of hydrogen sulphide for 4 hr. The solvents were then removed under reduced pressure and the residue was shaken with water (3 c.c.). The solid was collected and recrystallisation from water gave the mercapto-compound (0·3 g., 65%), identical with that prepared as in (*a*) (above), m. p. and mixed m. p. 192—193°.

Condensation of Acetone and of Mesityl Oxide with Thiourea in Presence of Hydrobromic Acid. 2-Amino-4 : 6 : 6-trimethyl-1 : 3-thiazine (XIV) *Picrate.*—(*a*) A mixture of thiourea (7·6 g.), concentrated (48%) aqueous hydrobromic acid (20 c.c.), and acetone (100 c.c.) was kept at room temperature for 6 days. The solvent was removed under reduced pressure and the semi-solid residue was treated with aqueous sodium picrate solution. Recrystallisation from alcohol then afforded yellow needles (4·32 g., 11%) of *2-amino-4 : 6 : 6-trimethyl-1 : 3-thiazine* (XIV) *picrate*, m. p. 196—198° (Found : C, 40·3; H, 3·9; N, 18·2. $C_7H_{12}N_2S,C_6H_3O_7N_3$ requires C, 40·5; H, 3·9; N, 18·2%).

(*b*) A mixture of mesityl oxide (50 c.c.), thiourea (7·6 g.), and concentrated (48%) aqueous hydrobromic acid (20 c.c.) was kept at room temperature for 8 days. The solvent and excess of hydrobromic acid were removed under reduced pressure and the dark residue was treated with aqueous sodium picrate, affording a picrate (29·8 g., 78%), identical with that obtained as in (*a*) (above), m. p. and mixed m. p. 196—198°.

This picrate is probably the same as that of Taylor (*loc. cit.*) who records m. p. 193—194° for " thiocarbamide-acetone picrate."

4 : 5-Dihydro-2-mercapto-4 : 4 : 6-trimethylpyrimidine (XV) (cf. Robbins, U.S.P. 2,539,480; Hill, B.P. 633,353).—A mixture of ammonium thiocyanate (38 g.), mesityl oxide (50 g.), and toluene (50 g.) was boiled under reflux for 8 hr. with the conventional Dean and Stark apparatus, until no further separation of water (8·7 c.c.; calc., 9·0 c.c.) took place. The light brown residue (64 g., 82%) was washed with water and with benzene, and dried at 100°. Recrystallisation from glacial acetic acid yielded colourless needles of 4 : 5-dihydro-2-mercapto-4 : 4 : 6-trimethylpyrimidine, m. p. 253° (decomp.); ultraviolet light absorption, $\lambda_{max.}$ 261—263 mμ (log ε 4·06) (Found : C, 53·5; H, 7·5; N, 17·6. Calc. for $C_7H_{12}N_2S$: C, 53·8; H, 7·7; N, 17·9%). Traube (*Ber.*, 1894, **27**, 277) records m. p. 249° for this substance, prepared from diacetonamine oxalate and potassium thiocyanate, while Mathes, Stewart, and Swedish (*J. Amer. Chem. Soc.*, 1948, **70**, 1452) record m. p. 254—255° for the product from 4-methyl-4-*iso*thiocyanatopentan-2-one (Mathes, *ibid.*, 1953, **75**, 1747) and ammonia. The substance was insoluble in both acid and alkali, and did not form a picrate.

A portion (5·0 g.) was refluxed in ethanol with methyl iodide (4 c.c., 2 mol.) for 3 hr. Removal of solvent under reduced pressure and recrystallisation of the residue from methanol–ethyl acetate afforded colourless needles (8·3 g., 87%) of *4 : 5-dihydro-4 : 4 : 6-trimethyl-2-methylthiopyrimidine hydriodide*, m. p. 162—163° (Found : C, 32·7; H, 5·5; N, 9·2. $C_8H_{14}N_2S,HI$ requires C, 32·2; H, 5·0; N, 9·4%).

This hydriodide (2·98 g.), in a mixture of triethylamine (2·2 g.) and pyridine (10 c.c.), was treated with a stream of hydrogen sulphide for 3 hr. Pouring the mixture into ice-water gave 4 : 5-dihydro-2-mercapto-4 : 4 : 6-trimethylpyrimidine (1·40 g., 90%), m. p. and mixed m. p. 251°.

Jaffé's Base [*4 : 5-Dihydro-1-(4 : 5-dihydroglyoxalin-2-yl)-2-mercaptoglyoxaline* (X)].—This substance was prepared from ethylenethiourea (IV) *via* the disulphide (VII) hydroperiodide as described by Johnson and Edens (*ibid.*, 1942, **64**, 2706); ultraviolet light absorption, $\lambda_{max.}$ 231—232, 263—264 mμ (log ε 4·13, 4·13) in MeOH.

A 1% aqueous solution of the hydrochloride (Johnson and Edens, *ibid.*, 1941, **63**, 1058) had a pH of 4·74. The hydrochloride showed the following ultraviolet light absorption : $\lambda_{max.}$ 231, 265 mμ (log ε 4·09, 4·00) in MeOH; 233—234, 261—262 mμ (log ε 4·18, 4·10) in N-HCl.

Physical Measurements.—Ultraviolet absorption measurements were made with a Unicam SP. 500 quartz spectrophotometer; pH measurements were made with a Doran " alkacid " glass electrode; infrared absorption spectra were observed in pressed potassium bromide discs.

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