899. *Urea and Related Compounds. Part IV.* Some Aromatic and Aliphatic Dithioformamidines.*

By FREDERICK KURZER and PHYLLIS M. SANDERSON.

Di-*ortho*-substituted arylthioureas are readily oxidised by bromine or hydrogen peroxide to diaryldithioformamidines, which are isolated in the form of their salts.

The preparation of dialkyl- and tetra-alkyl-dithioformamidine salts by this general reaction is also described.

IT is well known that thiourea is easily converted into dithioformamidine (I; R = H) by a variety of oxidising agents. This general reaction is applicable to *N*-alkylthioureas, several of which have been successfully oxidised to *N*-alkylated dithioformamides.[1-5] Aromatic thioureas, on the other hand, display a markedly different behaviour, yielding heterocylic products on treatment with the same oxidising agents. In general, benzothiazoles (II) are produced in non-polar media,[6-9] but " Hector's bases " † (III) result in ionising solvents, particularly in the presence of mineral acids.[10]

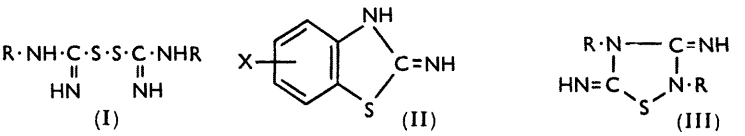
All previous efforts to obtain aromatic dithioformamidines appear to have been unsuccessful or inconclusive. The closest approach is Fichter and Braun's [2] general electrolytic method of oxidising thioureas to dithioformamidines. Their product from phenylthiourea, formulated as *s*-diphenyldithioformamidine hydrochloride, was however instantly decomposed in contact with water and could not be isolated in the pure state. Claims for the production of aromatic dithioformamidines by purely chemical methods have invariably proved erroneous. 2-Iminobenzothiazoline was first [11] formulated as the disulphide (I; R = Ph) and only later [7] correctly identified (as II; X = H). Fromm and Heyder's [12] efforts to synthesise *s*-diphenyldithioformamidine by using toluene-*p*-sulphonyl

* Part III, *J.*, 1953, 3360.

† In common with accepted practice, Hector's bases are represented, in the present paper, as 2 : 4-diaryl-3 : 5-di-imino-1 : 2 : 4-thiadiazolidines (III), although conclusive proof of this formulation has yet to be provided.

[1] Hector, *J. prakt. Chem.*, 1891, **44**, 492.
[2] Fichter and Braun, *Ber.*, 1914, **47**, 1529.
[3] (*a*) Lecher, Graf, Heuck, Köberle, Gnädiger, and Heydweiller, *Annalen*, 1925, **445**, 35; (*b*) Sahasrabudhey, *J. Indian Chem. Soc.*, 1951, **28**, 341.
[4] Klöping and van der Kerk, *Rec. Trav. chim.*, 1951, **70**, 917.
[5] Sahasrabudhey and Singh, *J. Indian Chem. Soc.*, 1952, **29**, 636.
[6] Fischer and Besthorn, *Annalen*, 1882, **212**, 326; Besthorn, *Ber.*, 1910, **43**, 1519; Hunter, *J.*, 1926, 1386.
[7] Hugershoff, *Ber.*, 1903, **36**, 3121, 3134; 1906, **39**, 1014.
[8] Sahasrabudhey and Krall, *J. Indian Chem. Soc.*, 1944, **21**, 17.
[9] Passing, *J. prakt. Chem.*, 1939, **153**, 10.
[10] For references see Kurzer, *J.*, 1955, 1.
[11] Hugershoff, *Ber.*, 1901, **34**, 3130.
[12] Fromm and Heyder, *Ber.*, 1909, **42**, 3804.

chloride as oxidising agent gave 3 : 5-di-imino-2 : 4-diphenyl-1 : 2 : 4-thiadiazolidine. Similarly, the alleged " disulphides " resulting in the sulphur monochloride-[13] or nitrous acid-oxidation[14] of *N*-methyl-*N*-phenylthiourea were recognised, in due course, as 2-imino-2-methylbenzothiazoline,[8] and the appropriate thiadiazolidine,[15] respectively. *N*-Methyl-*N'*-phenylthiourea, on treatment with nitrous acid, failed to yield a dithioformamidine,[16] as did *NN'*-diphenylthiourea which was studied in detail by Fromm.[17] Sahasrabudhey and Krall[15] were in fact thus led to the conclusion " that arylthiocarbamides do not yield disulphides on oxidation." On the other hand, aromatic dithioformamidines have frequently been assumed[1,2,12,18] to be involved as primary intermediates in the oxidation of arylthioureas to Hector's bases; indirect experiments have failed, however, to confirm or definitely refute this hypothesis.[15,17,19] Our first aim, therefore, in the present work was to isolate aromatic dithioformamidines (I; R = Ar) in some suitable form.



The oxidation of aromatic thioureas to 2-iminobenzothiazolines necessitates the elimination of the *o*-hydrogen atom. It seemed probable, therefore, that blocking of both *ortho*-positions with substituents would make the synthesis of the desired disulphides (I) feasible: our experiments confirmed this. 2 : 6-Dimethylphenylthiourea, on treatment with the theoretical quantity of bromine in a neutral solvent, afforded excellent yields of the corresponding dithioformamidine hydrobromide. With proper care, this could be isolated as such, or converted into other salts (including the toluene-*p*-sulphonate and picrate). 2 : 4 : 6-Tribromophenylthiourea gave comparable results.

Under the influence of hydrogen peroxide, the oxidation took one of several paths, which could be selected by a choice of the appropriate conditions. *s*-Di-(2 : 6-dimethylphenyl)dithioformamidine (I; R = 2 : 6-$C_6H_3Me_2$) hydrobromide was readily obtained in 75% yield when the thiourea was treated with the calculated quantity of the reagent at 0°, in the presence of a large excess of hydrobromic acid. In hot alcoholic media containing mineral acid [*i.e.*, under conditions that normally promote the formation of thiadiazolidines (III) in the aromatic series[10]], the peroxide merely desulphurised the starting material to 2 : 6-dimethylphenylurea (60%), while the expected thiadiazolidine (III; R = 2 : 6-$C_6H_3Me_2$) arose in only minute yields (4%). Meanwhile, in another connexion, an improved procedure for oxidising phenylthiourea had been evolved (use of perhydrol in absolute ethanol[20]) which raised the yield of Hector's base (III; R = Ph) from the usual 40—50% to 80—90%. Application of this modified procedure to the present case, though increasing the yields of 3 : 5-di-(2 : 6-dimethylphenyl)-2 : 4-di-imino-1 : 2 : 4-thiadiazolidine (III; R = 2 : 6-$C_6H_3Me_2$) (to 8—15%), resulted also in larger quantities (25—35%) of the by-product *NN'*-di-(2 : 6-dimethylphenyl)guanidine. *NN'*-Diarylguanidines are the chief products of the hydrolytic and reductive degradation[21] of Hector's bases; further, *s*-triphenylguanidine, instead of the expected thiadiazolidine, becomes the main product when *NN'*-diphenylthiourea is more vigorously oxidised.[17] The present observations fall in line with this general experience, although the exceptionally low yields of the thiadiazolidine may partly be due to steric effects.

[13] Dost, *Ber.*, 1906, **39**, 1014.
[14] Lal and Krall, *J. Indian Chem. Soc.*, 1937, **14**, 478.
[15] Sahasrabudhey and Krall, *ibid.*, 1945, **22**, 37.
[16] Lal and Krall, *ibid.*, 1938, **15**, 217.
[17] Fromm, *Annalen*, 1913, **394**, 284.
[18] De and Chakravarty, *J. Indian Chem. Soc.*, 1928, **5**, 661.
[19] Lal and Krall, *ibid.*, 1939, **16**, 31.
[20] Kurzer and Sanderson, unpublished work.
[21] Hector, *Oefvers. Kongl. Vet. Akad.*, 1892, 83 (cf. *Ber.*, 1892, **25**, ref. 799).

Like all other dithioformamidines, the *s*-diaryl-homologues were incapable of existing as the free bases; they decomposed instantly with elimination of sulphur when attempts were made to liberate them from their salts by alkalis or alkali carbonates. The salts themselves, being sensitive to hydrolysis, were also labile: aqueous or ethanolic solutions of the hydrobromide or toluene-*p*-sulphonate of (I; R = 2 : 6-$C_6H_3Me_2$), for example, slowly deposited colloidal sulphur on storage when cold, and more rapidly when heated. The presence of a small excess of mineral acid stabilised such aqueous solutions, which then remained clear even at higher temperatures. Aryldithioformamidine salts were successfully crystallised, though not without difficulty, from suitable mixtures of solvents in the cold; unlike their aliphatic analogues (see below), they invariably formed dihydrates. The correctness of their structure (I), supported by their composition and the bromine uptake during their formation, was also confirmed by reductive hydrolysis; zinc and hydrochloric acid reconverted *s*-di-(2 : 6-dimethylphenyl)dithioformamidine almost quantitatively into the original thiourea.

Both methods of oxidising thioureas were finally extended to the synthesis of a series of new *s*-di- and tetra-alkyldithioformamidines (Alk = Me or Et) hydrobromides and picrates. The use of hydrogen peroxide at low temperatures, in conjunction with an excess of hydrobromic acid, added to suppress hydrolysis of the products, is a convenient general procedure for preparing alkyl homologues in this series. Hector [1] has reported the formation of diallyldithioformamidine by oxidation of the thiourea with acidified hydrogen peroxide at its boiling point. Since sulphur was deposited during the oxidation, and the alleged " free base " was isolated after treatment that is now known to decompose dithioformamidines (see ref. 2), this claim must be set aside. Bromine in chloroform has recently been used in oxidising *NN*-dimethylthiourea, but the product was incorrectly formulated.[5] The present experiments have shown that the halogen uptake is accelerated remarkably in the presence of water, which was therefore preferred as solvent for the thioureas. In their properties, the alkyldithioformamidines resembled the aromatic analogues; their salts were equally or even more labile.

A number of new substituted ureas and thioureas required in this work were prepared by suitable modifications of standard methods. *NN*-Dimethyl- and -diethyl-thiourea, previously synthesised by Wallach [22,23] from the dialkylcyanamide and ammoniacal ethanolic hydrogen sulphide, have now been obtained more conveniently by the use of Fairfull, Lowe, and Peak's excellent general procedure [24] of adding the elements of hydrogen sulphide to the cyano-group. 2 : 6-Dimethylphenyl-urea and -thiourea were produced without difficulty from 2 : 6-dimethylaniline by the action of cyanic and thiocyanic acid, respectively.[25] This urea displayed to a large degree, even below its melting point, the general tendency of arylureas to disproportionate into *s*-diarylureas.[26] Since its physical properties were therefore difficult to determine, it was converted, for identification, into sulphonylcyanamides almost quantitatively by the usual method.[27] 2 : 6-Dimethylphenylthiourea gave an addition compound with zinc chloride which proved useful in the isolation of the thiourea obtained in zinc-reduction experiments. The general method of preparing and isomerising the amine thiocyanate proved inapplicable to the synthesis of 2 : 4 : 6-tribromophenylthiourea, presumably because of the low basicity * of the tribromoaniline. Although the thiourea was obtainable by this reaction by employing Passing's

* Although figures for a direct comparison of the basicity of 2 : 6-dimethyl- and 2 : 4 : 6-tribromoaniline are not available, the lower basic strengths of bromine derivatives are clearly shown by the dissociation constants of the following anilines: *p*-methyl, 20×10^{-10}; *p*-bromo, $0{\cdot}2 \times 10^{-10}$; *o*-methyl, 3×10^{-10}; *o*-bromo, $0{\cdot}01 \times 10^{-10}$.

[21] Wallach, *Ber.*, 1899, **32**, 1874.
[23] Preisler, *J. Amer. Chem. Soc.*, 1949, **71**, 2849.
[24] Fairfull, Low, and Peak, *J.*, 1952, 742.
[25] Kurzer, *Org. Synth.*, 1951, **31**, 8, 21.
[26] Kurzer, *J.*, 1949, 2292.
[27] Kurzer, *J.*, 1949, 1034, 3029.

experimental modification [9] (interaction of suspended amine hydrochloride and ammonium thiocyanate in boiling chlorobenzene) yields were erratic and low. The thiourea was finally synthesised in consistently excellent yield by Frank and Smith's method,[28] involving condensation of 2 : 4 : 6-tribromoaniline with benzoyl *iso*thiocyanate prepared *in situ*, followed by the hydrolytic removal of the benzoyl group from the intermediate *N*-acyl-*N'*-arylthiourea.

Experimental

Bromide in dithioformamidine hydrobromides was estimated volumetrically by Volhard's method on specimens (approx. 0·2 g.) dissolved in cold water, with addition of a few drops of 3N-nitric acid. Since warming such solutions was inadmissible (separation of silver sulphide), the need for coagulating and removing the precipitated silver bromide was avoided by the use of nitrobenzene.

Contact of wet dithioformamidine salts with metal spatulas is to be avoided to prevent local decomposition.

In the preparation of dithioformamidine picrates, aqueous picric acid, saturated at 30° (containing 0·06 mole of the reactant per l.[29]), was employed.

Aromatic Dithioformamidines

2 : 6-*Dimethylphenylurea*.—A solution of 2 : 6-dimethylaniline (36 g., 0·3 mole) in acetic acid (150 ml.), diluted with water (100 ml.), was treated with an aqueous suspension of sodium cyanate (39 g., 0·6 mole, in 100 ml.) with very vigorous stirring at room temperature. The crude urea separated immediately with slight warming and frothing and formed a paste-like suspension, which was set aside for several hours. The product was collected, washed with water, and consisted of white crystalline 2 : 6-*dimethylphenylurea* (42 g., 85%). Recrystallisation from aqueous ethanol (ethanol, 25 ml., and water, 5 ml., per g.) gave felted needles (Found: C, 65·8; H, 7·4. $C_9H_{12}ON_2$ requires C, 65·85; H, 7·3%). The urea changes to the *NN'*-diarylurea below its m. p. and hence does not melt when slowly heated. When determined by the " inverted " procedure,[26] the m. p. was found to be between 242° and 236°.

N-*Benzenesulphonyl*-N-(2 : 6-*dimethylphenyl*)*cyanamide*.—2 : 6-Dimethylphenylurea (8·2 g., 0·05 mole) in pyridine (45 ml.) was treated with benzenesulphonyl chloride (26·4 g., 0·15 mole), and the resulting hot liquid set aside during 15 min. and poured into acidified ice-water (300 ml.). The resulting solidified oil gave, after three crystallisations from acetone–ethanol–water (1, 2, and 0·5 ml. respectively, per g.), prisms of the *cyanamide*, m. p. 106—108° (85%) (Found: C, 62·3; H, 4·6; N, 9·9. $C_{15}H_{14}O_2N_2S$ requires C, 62·9; H, 4·9; N, 9·8%). N-(2 : 6-*Dimethylphenyl*)-N-*toluene*-p-*sulphonylcyanamide*, similarly prepared [27] in 90% yield, consisted of glass-like prisms, m. p. 131—132° (from aqueous ethanol–acetone) (Found: C, 63·7; H, 5·3. $C_{16}H_{16}O_2N_2S$ requires C, 64·0; H, 5·3%). Small quantities of unchanged 2 : 6-dimethylphenylurea were recovered as fractions sparingly soluble in acetone, in both experiments.

2 : 6-*Dimethylphenylthiourea*.—A solution of 2 : 6-dimethylaniline (60·5 g., 0·5 mole) in 1·5N-hydrochloric acid (500 ml., 0·75 mole) was treated with ammonium thiocyanate (76 g., 1 mole), and the liquid was kept at 100° during 1 hr. and then allowed to cool to room temperature. Evaporation on the steam-bath (4 hr.) gave a yellow residue which was kept at 100° for a further 8 hr. The powdered solid was extracted with warm water, and the residual white powder (80 g., 89%) twice crystallised from boiling ethanol (400 ml.), needles of 2 : 6-dimethylphenylthiourea, m. p. 202—204°, being obtained (Found: C, 59·9; H, 6·6. Calc. for $C_9H_{12}N_2S$: C, 60·0; H, 6·7%). The compound has previously been prepared from the *iso*thiocyanate and ammonia, but the m. p. given was 190°.[30]

2 : 4 : 6-*Tribromophenylthiourea*.—(*a*) A solution of 2 : 4 : 6-tribromoaniline (49·5 g., 0·15 mole) in warm anhydrous chlorobenzene (150 ml.) was rapidly treated with hydrogen chloride (approx. 6·5 l., 0·3 mole) until separation of the hydrochloride was complete. To the white paste, finely powdered ammonium thiocyanate (58 g., 0·75 mole, previously dried at 80° during 2 hr.) was added. The stirred mixture was heated to 100° during the first hour, then gently boiled under reflux. Small quantities of a dark orange oil that had first separated redissolved, and the suspended material changed gradually to a pale yellow powder, while some hydrogen

[28] Frank and Smith, *Org. Synth.*, Coll. Vol. III, p. 735 (1955).
[29] Dolinski, *Ber.*, 1905, **38**, 1836.
[30] Dyson, George, and Hunter, *J.*, 1927, 436.

sulphide was evolved. After 4 hours' refluxing, the solid was quickly filtered off with suction (filtrate A) and rinsed with a little chlorobenzene. After being suspended in water to remove ammonium salts, the crude product (dry weight 20—24 g., 34—41%) was crystallised by dissolution in boiling acetone (25—30 ml. per g.), distillation of the filtered liquid to about half-bulk, and dilution with ethanol (10 ml. per g.). Two crystallisations gave prisms of 2 : 4 : 6-*tribromophenylthiourea*, m. p. 240—242° (decomp.) (Found: C, 22·2; H, 1·6; N, 7·05; S, 8·2; Br, 62·0. $C_7H_5N_2Br_3S$ requires C, 21·6; H, 1·3; N, 7·2; S, 8·2; Br, 61·7%).

Most of the unconverted starting material contained in filtrate (A) separated when the liquid was distilled to small bulk. The use of a smaller excess of ammonium thiocyanate (2 mols.) reduced the yield to 7—10%.

(*b*) Benzoyl chloride (14·1 g., 0·1 mole) was run into a stirred solution of ammonium thiocyanate (8·5 g., 0·11 mole) in anhydrous acetone (50 ml.) during 5 min., and the resulting suspension refluxed during a further 5 min. A solution of 2 : 4 : 6-tribromoaniline (33·0 g., 0·1 mole) in nearly boiling acetone (150 ml.) was next added during 10 min., and the stirred yellow suspension refluxed during another 45 min. Its addition to ice-water (750 ml.) produced a yellow precipitate of crude *N*-benzoyl-*N'*-2 : 4 : 6-tribromophenylthiourea, which was collected and immediately boiled with 3N-sodium hydroxide (180 ml.) during 6 min. The resulting liquid was decanted from a small quantity of undissolved residue (3—6 g., consisting of crude 2 : 4 : 6-tribromoaniline, m. p. and mixed m. p. 118—119°, after crystallisation from ethanol), diluted with ice (to a total volume of 300 ml.), stirred with carbon (3 g.), and filtered at the pump. The clear filtrate gave, on acidification with concentrated hydrochloric acid (to Congo-red), a white crystalline precipitate, which was collected at 0°, washed with water (dry wt., 40—45 g.), and crystallised as above, affording colourless prisms of 2 : 4 : 6-tribromophenylthiourea, m. p. 240—242° (decomp.) (yield, including good material from the mother-liquors, 25·3—29·2 g., 65—75%) (Found: C, 22·0; H, 1·4; Br, 61·3%).

s-*Bis*-(2 : 6-*dimethylphenyl*)*dithioformamidine*.—(a) *Bromine oxidation.* Finely divided 2 : 6-dimethylphenylthiourea (3·60 g., 0·02 mole), suspended in chloroform (35 ml.), was treated dropwise, with external ice-cooling, with M-bromine in chloroform (10 ml., 0·01 mole). The resulting clear colourless liquid was rapidly evaporated in a vacuum at room temperature, the residual solid dissolved in water (10, 5, and 5 ml.), and the solution separated from a drop of chloroform (liquid A) if necessary, and filtered (Filtrate F).

Hydrobromide. To the clear filtrate (F), cold saturated, aqueous sodium bromide (0·02 mole) was slowly added with external cooling, until a faint turbidity appeared; the crystalline material which separated on storage at room temperature was collected, quickly washed with the minimum of ice-water, then with ether, and dried in a vacuum. It consisted of white prisms (4·45 g., 80%) of s-*bis*-(2 : 6-*dimethylphenyl*)*dithioformamidine dihydrobromide dihydrate*, m. p.* 127—128° (decomp., after sintering at 125°) (Found: C, 38·2; H, 4·8; N, 10·3; S, 11·8; Br, 29·5, 29·8. $C_{18}H_{22}N_4S_2,2HBr,2H_2O$ requires C, 38·9; H, 5·0; N, 10·1; S, 11·5; Br, 28·75%). The dihydrobromide was crystallised by being dissolved in *cold* ethanol (15 ml.); the solution, acidified with 60% hydrobromic acid (2 drops) and filtered if necessary, was slowly diluted with ether (12 ml.); the crystalline product, m. p. 129—130° (after sintering at 125°), was collected at 0° and rinsed with 1 : 2 ethanol–ether (recovery, approx. 75%). The salt was stable in aqueous solution, even on warming, if acidified with little mineral acid. Its aqueous solution deposited colloidal sulphur instantly on being made alkaline, and more slowly on being heated.

Liquid A consisted of a solution of traces of starting material in chloroform.

Alternatively, filtrate F was slowly treated, with external cooling, with 60% hydrobromic acid (5 ml.), and the separated dihydrobromide (m. p.* 130—132°, after sintering at 128°; 4·15 g., 75%) collected after storage at 0° (Found: C, 38·5; H, 5·0; Br, 29·5%).

Toluene-p-*sulphonate.* Filtrate F was treated with toluene-*p*-sulphonic acid monohydrate (3·80 g., 0·02 mole) dissolved in water (5 ml.). The resulting white precipitate was collected after storage at 0°, washed with little ether, and air-dried at room-temperature [m. p. 112—114° (decomp.); 6·20 g., 84%]. If crystallisation was desired, the *freshly* collected filter-cake was suspended in cold ethanol (25 ml.) and dissolved by prolonged stirring, and the filtered solution (vacuum) slowly diluted with ether (150—180 ml.) and stored at −8°. The collected

* The m. p. of the hydrobromide obtained by the addition of sodium bromide was slightly lower than that of specimens separated by the use of hydrobromic acid, probably because of the difficulty of completely removing the sodium bromide without redissolving the desired product.

prisms (2·65 g., 36%) were s-*bis*-(2 : 6-*dimethylphenyl*)*dithioformamidine ditoluene*-p-*sulphonate dihydrate*, m. p. 116—117° (decomp.) (Found: C, 52·1, 51·8; H, 5·9, 5·5; S, 17·7. $C_{18}H_{22}N_4S_2,2C_7H_8O_3S,2H_2O$ requires C, 52·0; H, 5·7; S, 17·3%). The salt decomposed with deposition of sulphur when its ethanolic solution was boiled, or its aqueous solution was basified or heated (except in the presence of mineral acid).

Addition of *m*-nitrobenzenesulphonic acid (0·02 mole) in water (15 ml.) to filtrate (F) gave an almost colourless oil (4—5 ml.) which was highly soluble in the usual organic solvents and did not crystallise therefrom. Benzenesulphonic acid, analogously, gave a minute quantity of oil. The filtrate F did not deposit salts on being treated with salicylsulphonic, oxalic or succinic acid.

Picrate. Filtrate F was slowly stirred into aqueous picric acid (0·018 mole). The yellow crystalline precipitate, collected at 0° and dried at room temperature in a vacuum over phosphoric oxide (yield, 5·80 g., 68%), was the *dipicrate dihydrate*, m. p. 92—94° (decomp.) (Found: C, 42·6; H, 3·8. $C_{18}H_{22}N_4S_2,2C_6H_3O_7N_3,2H_2O$ requires C, 42·25; H, 3·8%). Dissolution of this product in cold methanol–acetone (1 : 2; 3 ml. per g.), followed by dropwise dilution of the filtered liquid with water (6—8 drops per g.), gave lemon-yellow prisms (recovery, 50%) of the anhydrous *dipicrate*, m. p. 105—107° (decomp., after sintering at 101—103°) (Found: C, 44·6; H, 3·4; N, 16·8. $C_{18}H_{22}N_4S_2,2C_6H_3O_7N_3$ requires C, 44·1; H, 3·4; N, 17·2%).

(b) *Hydrogen peroxide oxidation.* A suspension of 2 : 6-dimethylphenylthiourea (3·6 g.; 0·02 mole) in water (10 ml.) and 60% hydrobromic acid (5 ml.) was shaken, at 0°, with 6% hydrogen peroxide (6·2 ml., 0·011 mole) during 10—15 min. Almost complete dissolution occurred at one stage, and separation of the salt was completed, as far as possible, by addition of ethanol (5 ml.) and storage at 0°. The collected product (4·2 g., 75%) was *s*-bis-(2 : 6-dimethylphenyl)dithioformamidine dihydrobromide dihydrate, m. p. and mixed m. p. 130—132° after sintering at 127°).

(c) *Reductive hydrolysis.* A boiling solution of *s*-bis-(2 : 6-dimethylphenyl)dithioformamidine dihydrobromide dihydrate (2·78 g., 0·005 mole) in ethanol (25 ml.) containing concentrated hydrochloric acid (1 drop) was treated with zinc foil (4 g.), followed by concentrated hydrochloric acid (4 ml., added during 10 min.), and the effervescing suspension refluxed during 0·5 hr. The liquid was decanted, the residual zinc re-extracted with 85% ethanol (2 × 5 ml.), and the combined extracts were filtered hot. They deposited crystals (m. p. 235—236°, 1·9 g.) on cooling, and more of the same product (0·5 g., *i.e.*, total 93%) on partial evaporation. Crystallisation from 85% ethanol gave white prisms of 2 : 6-*dimethylphenylthiourea–zinc chloride hydrate*, m. p. 238—240° (decomp.) (Found: C, 41·6; H, 4·9; S, 12·8; Cl, 14·1. $2C_9H_{12}N_2S,ZnCl_2,H_2O$ requires C, 42·0; N, 5·05; S, 12·4; Cl, 13·8%).

The same product was obtained (92%) when equimolar quantities of 2 : 6-dimethylphenylthiourea (in hot ethanol) and zinc chloride (in water) were mixed.

s-*Bis*-(2 : 4 : 6-*tribromophenyl*)*dithioformamidine*.—A suspension of finely divided 2 : 4 : 6-tribromophenylthiourea (1·95 g., 0·005 mole) in chloroform (50 ml.) containing water (2 ml.) was continuously ground in a mortar, while 0·1M-bromine in chloroform (25 ml., 0·0025 mole) was added dropwise during 10—15 min. The crystalline starting material was thereby converted into a suspended white microgranular solid which was collected at the pump, washed with chloroform, and dried in a vacuum (2·13 g., 88%). It consisted of s-*bis*-(2 : 4 : 6-*tribromophenyl*)*dithioformamidine dihydrobromide dihydrate*, m. p. 160—162° (decomp., after sintering at 156°) (Found: C, 17·5; H, 1·5; N, 5·8; Br, 65·2. $C_{14}H_8N_4S_2Br_6,2HBr,2H_2O$ requires C, 17·3; H, 1·4; N, 5·75; Br, 65·7%). Addition of water appears to prevent the formation of local orange agglomerates of brominated material.

Oxidation of 2 : 6-*Dimethylphenylthiourea by Hydrogen Peroxide*.—(a) *Desulphurisation.* A boiling solution of 2 : 6-dimethylphenylthiourea (1·80 g., 0·01 mole) in ethanol (12 ml.) and water (4 ml.), containing concentrated hydrochloric acid (0·5 ml., 0·005 mole) was treated with 6% hydrogen peroxide (8·5 ml., 0·015 mole) during 2—3 min. The resulting turbid liquid, containing precipitated sulphur, was boiled for a further 6 min., and the nearly clarified solution decanted from the sulphur, stirred into water (50 m.), and made just alkaline with 3N-aqueous ammonia. The crystalline precipitate, collected at 0° (1·37 g.) (filtrate A), gave, after crystallisation from ethanol–water (5 : 1), needles of 2 : 6-dimethylphenylurea [the identity of which was established by its almost quantitative conversion into *N*-(2 : 6-dimethylphenyl)-*N*-toluene-*p*-sulphonylcyanamide, m. p. and mixed m. p. 131—132°]. The alcoholic mother-liquors therefrom were allowed to evaporate to dryness and the residue extracted with cold 3N-hydrochloric

acid (3 × 5 ml.). The small insoluble residue consisted of more 2 : 6-dimethylphenylurea; basification of the acid extracts precipitated a mixture of 3 : 5-di-(2 : 6-dimethylphenyl)-2 : 4-di-imino-1 : 2 : 4-thiadiazolidine (0·06 g., 4%) and *NN'*-di-(2 : 6-dimethylphenyl)guanidine (0·2 g., 12%) which were separated and identified as described in section (b). Evaporation of the aqueous filtrate A gave a further small fraction of 2 : 6-dimethylphenylurea (total, 0·98 g., 60%).

(b) 3 : 5-*Di*-(2 : 6-*dimethylphenyl*)-2 : 4-*di-imino*-1 : 2 : 4-*thiadiazolidine*. A boiling solution of the thiourea (0·02 mole) in ethanol (40 ml.) and concentrated hydrochloric acid (0·5 ml.) was treated with 30% hydrogen peroxide (2·5 ml., 0·022 mole) during 3—5 min. The liquid was boiled during another 5—8 min., decanted from the coagulated sulphur (0·3—0·45 g.), and stirred into water (250 ml.), and the precipitated solid collected at 0°. This was extracted with 3N-hydrochloric acid (3 × 5 ml.), and the undissolved 2 : 6-dimethylphenylurea (0·16—0·34 g., 5—10%) removed by filtration. Basification of the extracts gave a white solid (1·6—2·0 g.), which was dissolved in acetone–methanol (1 : 2). The separated product (filtrate F) [m. p. 229—230° (decomp.); 0·26—0·48 g., 8—15%] was recrystallised from the same solvents, and consisted of prisms of 3 : 5-*di*-(2 : 6-*dimethylphenyl*)-2 : 4-*di-imino*-1 : 2 : 4-*thiadiazolidine*, m. p. 226—228° (decomp.) (Found: C, 66·5; H, 5·8; N, 17·6; S, 10·1. $C_{18}H_{20}N_4S$ requires C, 66·7; H, 6·2; N, 17·3; S, 9·9%).

Gradual dilution of filtrates F with water precipitated a white solid (m. p. 95—98°; 0·83—1·16 g., 25—35%), which was crystallised by dissolution in ethanol and dilution with a little water, affording prisms of *NN'-di*-(2 : 6-*dimethylphenyl*)*guanidine*, m. p. 98—99° (Found: C, 68·6, 68·9; H, 8·2, 8·3; N, 13·2. $C_{17}H_{21}N_3,H_2O,C_2H_5OH$ requires C, 68·9; H, 8·8; N, 12·7%). Its *picrate*, prepared by the interaction of equimolar quantities of guanidine and picric acid in saturated ethanolic solution, and crystallised from ethanol, formed yellow platelets, m. p. 170—172° (Found: C, 47·8; H, 4·1; N, 17·0. $C_{17}H_{21}N_3,2C_6H_3N_3O_7$ requires C, 48·0; H, 3·7; N, 17·4%).

In marked contrast, phenylthiourea was converted, under the conditions of experiments (b), into 2 : 4-di-imino-3 : 5-diphenyl-1 : 2 : 4-thiadiazolidine consistently in 80—90% yield.

Interaction of the above thiadiazolidine (0·001 mole) with toluene-*p*-sulphonyl chloride (0·003 mole) in pyridine (5 ml.) at 100° during 0·5 hr. afforded nearly quantitatively its *monotoluene*-p-*sulphonyl derivative*, m. p. 257—259° (from acetone) (Found: C, 62·4; H, 5·5. $C_{25}H_{26}O_2N_4S_2$ requires C, 62·8; H, 5·4%).

Aliphatic Dithioformamidines

NN-*Dimethylthiourea*.—Dry hydrogen sulphide was slowly passed through a solution of dimethylcyanamide (17·5 g., 0·25 mole) in anhydrous pyridine (35 ml.) and triethylamine (25·25 g., 0·25 mole), the temperature of which rose spontaneously and was kept at 60°. Much crystalline solid had separated after 0·5 hr., but passage of gas was continued during 2 hr. The mixture was diluted with light petroleum (50 ml.), and the prisms were collected at 0° (m. p. 158—160°; 18·7 g., 72%) and rinsed with light petroleum. Crystallisation from water gave prisms of *NN*-dimethylthiourea, m. p. 162—163°. (The m. p. is variously given between 155° and 164° in the literature.[5, 22, 23, 31])

NN-*Diethylthiourea*.—Treatment of diethylcyanamide (0·25 mole) as above during 5 hr. (an additional 0·125 mole of triethylamine being added after 2 hr.) gave a clear green liquid, which was stirred into concentrated hydrochloric acid (50 ml.) and ice (100 g.). The precipitated colourless prisms were collected at 0° (m. p. 100—101°; 18·5 g., 56%). Crystallisation from water gave prismatic *NN*-diethylthiourea, m. p. 101—102° (lit.,[22, 23] 101—102°).

s-*Diethyldithioformamidine*.—(a) *By bromine oxidation*. A suspension of ethylthiourea (2·08 g., 0·02 mole) in chloroform (20 ml.) at 0° slowly absorbed M-bromine (in chloroform) (10 ml., 0·01 mole), added to it in portions, with vigorous shaking, during 10—15 min. After the removal of the solvent at room temperature (vacuum), the white crystalline residue was dissolved in cold water (15 ml.), and the colourless liquid filtered (filtrate F).

Hydrobromide. Addition of 60% hydrobromic acid (5 ml.), followed by storage at 0°, gave a fine white precipitate, which was collected (4·25 cm. Buchner funnel) and washed successively with ethanol, ethanol–ether, and ether. The air-dried product [m. p. 184—187° (decomp.);

[31] Salkowski, *Ber.*, 1893, **26**, 2505; Schenk and von Graevenitz, *Z. physiol. Chem.*, 1924, **141**, 138; Birtwell, Curd, Hendry, and Rose, *J.*, 1948, 1645; Singh and Saikia, *J. Indian Chem. Soc.*, 1953, **30**, 695.

2·75 g., 75%], purified by being redissolved in water (12—15 ml.), and separated by the addition of 60% hydrobromic acid, consisted of prisms (2 g.) of s-*diethyldithioformamidine dihydrobromide*, m. p. 185—187° (decomp., after sintering at 183°) (Found: C, 20·0; H, 4·2; N, 15·8; Br, 43·8. $C_6H_{14}N_4S_2,2HBr$ requires C, 19·6; H, 4·35; N, 15·2; Br, 43·45%). The salt was moderately soluble in hot ethanol (but slowly deposited sulphur on boiling), sparingly soluble in cold ethanol, and almost insoluble in ether.

Picrate. Treatment of filtrate F with aqueous picric acid (0·018 mole) gave a yellow crystalline precipitate, which, collected at 0°, consisted of the *dipicrate* (4·65 g.), m. p. 120—121° (decomp., after sintering at 116°) (Found: C, 32·8; H, 2·9; N, 20·7; S, 9·4. $C_6H_{14}N_4S_2,2C_6H_3O_7N_3$ requires C, 32·5; H, 3·0; N, 21·1; S, 9·6%). The material slowly deposited sulphur on being boiled in ethanol or methanol, but did not crystallise therefrom without partial decomposition.

Filtrate F remained clear after being treated with toluene-*p*-sulphonic acid (0·02 mole).

(b) *By hydrogen peroxide oxidation.* A suspension of ethylthiourea (2·08 g., 0·02 mole) in water (10 ml.) and 60% hydrobromic acid (1 ml.) was treated, during 10 min., with 6% hydrogen peroxide (6·2 ml., 0·011 mole), with shaking and external cooling to maintain the mixture below 30°. The resulting clear liquid, diluted with more 60% hydrobromic acid (5 ml.), deposited white crystalline *s*-diethyldithioformamidine dihydrobromide (1·8 g., 50%), m. p. and mixed m. p. 185—187°, which was collected after 24 hours' storage at 0°. Alternatively, the clear solution obtained by the above oxidation [but in the presence of concentrated hydrochloric acid (1 ml., 0·01 mole)], when treated with aqueous picric acid (0·018 mole), gave a precipitate (2·65 g., 40%) of *s*-diethyldithioformamidine dipicrate, m. p. and mixed m. p. 120—121° (decomp., after sintering at 116°).

s-*Dimethyldithioformamidine.*—*By bromine oxidation.* A solution of methylthiourea (1·80 g., 0·02 mole) in water (10 ml.) rapidly decolorised M-bromine in chloroform (10 ml., 0·01 mole). The resulting crystalline precipitate was redissolved by the addition of more water (10 ml.) and shaking, and the separated filtered aqueous layer (L) treated with 60% hydrobromic acid (5 ml.). The resulting crystals, collected at 0°, were successively washed with cold ethanol and ether, affording (1·50 g., 45%) felted needles of s-*dimethyldithioformamidine dihydrobromide*, m. p. 204—205° (Found: C, 14·3; H, 3·7; N, 16·0; Br, 47·15. $C_4H_{10}N_4S_2,2HBr$ requires C, 14·1; H, 3·5; N, 16·5; Br, 47·0%). Unlike the ethyl homologue, methylthiourea failed to decolorise bromine in chloroform, unless water was present.

Alternatively, solution L, treated with aqueous picric acid (0·018 mole), deposited yellow prisms (2·55 g., 40%) of the *dipicrate*, m. p. 119—120° (decomp.) (Found: C, 29·9; H, 2·3. $C_4H_{10}N_4S_2,2C_6H_3O_7N_3$ requires C, 30·2; H, 2·5%).

Oxidation of methylthiourea by hydrogen peroxide [as described for the ethyl homologue, except that the reactant was initially dissolved in 50% aqueous ethanol (10 ml.)] similarly afforded the above dihydrobromide, m. p. 204—206° (decomp.), and dipicrate, m. p. 119—120° (decomp.), in 60 and 45% yield, respectively.

Bis-(NN-*dimethyl*)*dithioformamidine.*—(i) *By bromine oxidation.* (*a*) A solution of *NN*-dimethylthiourea (2·08 g., 0·02 mole) in water (4 ml.) rapidly decolorised M-chloroformic bromine (0·01 mole), while a white solid appeared. After removal of the chloroform (at room temperature), the residual suspension was diluted with ethanol (5 ml.) and 60% hydrobromic acid (1 ml.), and the separated white crystalline tetramethyl derivative dihydrobromide (2·75 g.), m. p. 209—210° (decomp., after sintering at 205°), was collected at 0° and washed with ether (Found: C, 20·0; H, 4·3; N, 15·1; S, 16·9; Br, 43·9. Calc. for $C_6H_{14}N_4S_2,2HBr$: C, 19·6; H, 4·35; N, 15·2; S, 17·4; Br, 43·45%). The product was exceedingly water-soluble: purification by reprecipitation from saturated aqueous solution by 60% hydrobromic acid, ethanol, and ether was wasteful and did not raise the m. p.

(*b*) Oxidation as above, but followed by dissolution of the distilled residue in water (15 ml.) and treatment with picric acid (0·018 mole), gave the pale yellow *dipicrate*, m. p. 104—105° (decomp.) (4·67 g., 70%) (Found: C, 33·0; H, 3·0; N, 20·8. $C_6H_{14}N_4S_2,2C_6H_3O_7N_3$ requires C, 32·5; H, 3·0; N, 21·1%).

(ii) *By hydrogen peroxide oxidation.* A solution of the reactant (0·02 mole) in ethanol (10 ml.), diluted with 60% hydrobromic acid (1 ml.), was treated, with external cooling and shaking, with 30% hydrogen peroxide (1·25 ml., 0·011 mole), and the resulting dihydrobromide, m. p. and mixed m. p. 208—209°, collected at 0° (56%) (Found: C, 19·85; H, 4·5%). This variation of the usual conditions was necessitated by the high solubility of the salt in water.

Oxidation, by 6% hydrogen peroxide, as described for ethylthiourea, afforded the dipicrate (3·45 g., 52%), m. p. and mixed m. p. 104—105° (Found: C, 32·8; H, 2·95; N, 20·8%).

Bis-(NN-*diethyl*)*dithioformamidine*.—Oxidation of *NN*-diethylthiourea (2·64 g., 0·02 mole) by bromine or hydrogen peroxide (as described for the dimethyl homologue), and addition of picric acid (0·018 mole) gave pale yellow *bis*-(NN-*diethyl*)*dithioformamidine dipicrate*, m. p. 109—110° (decomp.) [Found: (*a*) C, 36·4; H, 3·6. (*b*) C, 36·7; H, 4·1; N, 19·4; S, 8·9. $C_{10}H_{22}N_4S_2,2C_6H_8O_7N_3$ requires C, 36·7; H, 3·9; N, 19·4; S, 8·9%] [yield, (*a*) 72%; (*b*) 56%]. Because of its high solubility, the dihydrobromide could not be isolated.

ROYAL FREE HOSPITAL SCHOOL OF MEDICINE,
(UNIVERSITY OF LONDON), LONDON, W.C.1.

[*Received, June 3rd*, 1957.]