558. *Preparation and Reactions of Thiocarbamoyl- and Thioureido-amidines.*

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Attempts to prepare the substances mentioned in the title are described. Ethoxymethylenearylamines and thiosemicarbazide give *N*-thioureido-*N'*-arylformamidines; various ring-closure reactions of these products are discussed.

This report concerns attempts to synthesise some thiocarbamoyl- and thioureido-formamidines as analogues of the antitubercular thiosemicarbazones, and some of the reactions of the substances obtained.

Existing knowledge of such compounds is scanty, but *C*-thiocarbamoylformamidines were obtained by Sandmeyer in one of his classical syntheses of indigo, by the reactions (I) ⟶ (II).

$$\underset{\text{(I)}}{\text{Ar·NH·CS·NHR}} \xrightarrow[+\text{HCN}]{-H_2S} \text{Ar·N:C(CN)·NHR} \xrightarrow{+H_2S} \underset{\text{(II)}}{\text{Ar·N:C(CS·NH}_2\text{)·NHR}}$$

In Sandmeyer's example, R was also an aryl group and later workers [2] have described similar compounds. The reactions proceed equally well when R is alkyl, but, when it is hydrogen, loss of hydrogen sulphide is the sole result of the first step and the product is an arylcyanamide. *C*-Thioureidoformamidines, *e.g.*, Ar·NH·C(=NH)·NH·CS·NH_2, are also known, being obtained by the action of hydrogen sulphide on substituted dicyandiamides.[3]

The corresponding *N*-substituted derivatives appeared to be unknown and are not readily obtainable. Ethyl *p*-methoxybenzimidate hydrochloride, on reaction with thiosemicarbazide, gave the non-basic thiosemicarbazone of ethyl *p*-anisate, *p*-MeO·C_6H_4·C(OEt):N·NH·CS·NH_2. Attempts to cause the ethoxy-group to react with ammonia did not lead to an amidine. Alcoholic ammonia gave a mixture of 5-mercapto-3-*p*-methoxyphenyl-1 : 2 : 4-triazole and 5-amino-2-*p*-methoxyphenyl-1 : 3 : 4-thiadiazole; ammonium acetate in acetic acid gave the latter compound together with its acetyl derivative.

p-Methoxy-*N*-thiocarbamoylbenzamidine could not be prepared. Whereas arylamine thiocyanates are isomerised by heat to arylthioureas, it seemed unlikely that this approach would succeed with an amidine thiocyanate in view of Partridge and Short's work [4] on the preparation of the latter salts from aryl cyanides at high temperatures. Amidines do, however, resemble amines in their ready reaction with alkyl *iso*thiocyanates to yield substituted thiocarbamoyl derivatives such as Ar·C(=NH)·NH·CS·NHR and if R is a removable group this seems to offer a possible synthesis. However, on attempted reduction of the benzyl derivative with sodium in liquid ammonia, the amidine grouping was split and a high yield of benzylthiourea resulted. If R were benzoyl, alkaline hydrolysis (cf. ref. 5) would probably suffice, but *p*-methoxybenzamidine and benzoyl *iso*thiocyanate in chloroform did not give a pure product, formation of 50% of the amidine thiocyanate showing that metathesis occurred in preference to addition. Finally, *N*-cyano-*p*-methoxybenzamidine, prepared by Goerdeler and Loevenich's method,[6] could not be made to add

[1] See Geigy, G.P. 113,978; Fierz-David, "Fundamental Processes in Dye Chemistry," Churchill, London, 1921, pp. 161 *et seq.*
[2] Ferber and Schmolke, *J. prakt. Chem.*, 1940, **155**, 234; Roe and Teague, *J. Amer. Chem. Soc.*, 1949, **71**, 4019.
[3] Britwell, Curd, Hendry, and Rose, *J.*, 1948, 1653.
[4] Partridge and Short, *J.*, 1947, 390.
[5] Douglas and Dains, *J. Amer. Chem. Soc.*, 1934, **56**, 1408.
[6] Goerdeler and Loevenich, *Chem. Ber.*, 1953, **86**, 890.

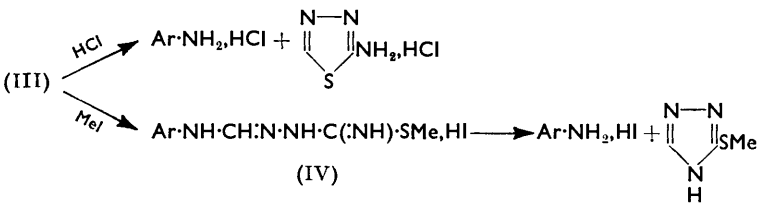
hydrogen sulphide, even by methods [7] known to succeed with cyanamide derivatives. This suggests that the compound does not contain the ·NH·CN grouping, but the alternative =N·CN.

One type of *N*-thioureidoamidine is, however, readily prepared, namely, those of type (III), which are obtained from *N*-aryl-ethoxymethyleneamines (ethyl formimidates) and

$$Ar{\cdot}NH{\cdot}CH{:}N{\cdot}NH{\cdot}CS{\cdot}NH_2 \quad (III)$$

thiosemicarbazide. This reaction appears to be restricted to formimidates, for even acetimidates behave like the previously mentioned benzimidates and give ethyl acetate thiosemicarbazone, $EtO{\cdot}CMe{:}N{\cdot}NH{\cdot}CS{\cdot}NH_2$, also obtained by Ainsworth [8] from thiosemicarbazide and ethyl orthoacetate.

Compounds of structure (III) show interesting ring-closure reactions. When dissolved in aqueous hydrochloric acid, they are quantitively split into arylamine hydrochloride and 2-amino-1 : 3 : 4-thiadiazole hydrochloride. Treated with methyl iodide in hot alcohol, they are first methylated on the sulphur atom, and the hydriodide of this product then undergoes a similar breakdown, to yield arylamine hydriodide and 3-methylthio-1 : 2 : 4-triazole. This type of ring closure with elimination of the arylamine appears



to require the presence of acid because (i) compounds (III) dissolve in aqueous sodium hydroxide without change, and (ii) methylation with methyl sulphate and alkali, whereby the base corresponding to (IV) is first produced, is followed by loss of methanethiol and formation of 3-amino-4-aryl-1 : 2 : 4-triazole. Dains [9] and others [10] have studied the reaction in which diarylformamidines react with compounds containing a reactive methylene group, with elimination of arylamine, and Wagner [11] has studied cases in which reaction takes place with amino-groups, noting acid-catalysis in some cases. It appears that the present observations represent intramolecular examples of the same general reaction.

Experimental

Ethyl p-*Anisate Thiosemicarbazone.—Formation.* Ethyl *p*-methoxybenzimidate hydrochloride (16·2 g.), powdered thiosemicarbazide (6·9 g.), and absolute alcohol (165 ml.) were stirred together at 40—45° for 24 hr. The filtered product was extracted with cold water, to leave 10·05 g. (53%) of the *thiosemicarbazone*, m. p. 157—158° unchanged by crystallisation from alcohol (Found: C, 52·15, 52·15; H, 5·85, 5·85; N, 16·2, 16·25; S, 12·55, 12·4. $C_{11}H_{15}O_2N_3S$ requires C, 52·2; H, 5·9; N, 16·6; S, 12·65%). The imidate base did not react under the same conditions.

Reaction with ammonia. (i) The compound (2 g.) was heated with saturated alcoholic ammonia (25 ml.) at 140—150° for 7½ hr. After evaporation, the residue was shaken with dilute hydrochloric acid, and the non-basic product (0·85 g.) filtered off and crystallised from alcohol, to give 5-mercapto-3-*p*-methoxyphenyl-1 : 2 : 4-triazole, m. p. 259—261° (Found:

[7] Fairfull, Lowe, and Peak, *J.*, 1952, 742.
[8] Ainsworth, *J. Amer. Chem. Soc.*, 1956, **78**, 1973.
[9] For refs. see Shriner and Neumann, *Chem. Rev.*, 1944, **35**, 409, 412.
[10] I.C.I., Ltd., Piggott, and Rodd, B.P. 344,409.
[11] Wagner, *J. Org. Chem.*, 1940, **5**, 133; Hölljes and Wagner, *ibid.*, 1944, **9**, 31.

C, 52·4; H, 4·55; N, 20·35; S, 15·35. Calc. for $C_9H_9ON_3S$: C, 52·2; H, 4·35; N, 20·3; S, 15·45%). Hoggarth [12] gave m. p. 257°. The basic product (0·35 g.) was recovered and crystallised from aqueous alcohol, to give 5-amino-2-*p*-methoxyphenyl-1 : 3 : 4-thiadiazole, m. p. 192—193°, identical with authentic material [13] (Found : C, 52·6; H, 4·35; N, 20·45; S, 15·8. Calc. for $C_9H_9ON_3S$: C, 52·2; H, 4·35; N, 20·3; S, 15·45%).

(ii) The compound (2 g.) was boiled for 1¼ hr. with acetic acid (20 ml.) containing ammonium acetate (7·5 g.). After cooling, the separated crystals (0·6 g. ; m. p. 280—290°) were filtered off and washed. The filtrate was evaporated, diluted, and basified to give the above thiadiazole (1·1 g.), m. p. 192—193° (from aqueous alcohol). The substance of m. p. 280—290° was soluble in dilute sodium hydroxide and, crystallised from acetic acid, had m. p. 289—291° ; it was identified with an authentic specimen, as 5-*acetamido*-2-p-*methoxyphenyl*-1 : 3 : 4-*thiadiazole* (Found : C, 53·15, 52·95; H, 4·5, 4·6; N, 16·75; S, 12·9. $C_{11}H_{11}O_2N_3S$ requires C, 53·0; H, 4·4; N, 16·9; S, 12·85%).

N-(*Benzylthiocarbamoyl*)-p-*methoxybenzamidine*.—*p*-Methoxybenzamidine hydrochloride monohydrate (4·1 g.) was added to a solution of sodium (0·46 g.) in alcohol (30 ml.), followed by benzyl *iso*thiocyanate (3 g.). Next day, the mixture was warmed for 15 min. on the steam-bath, cooled, and diluted with water (30 ml.). The *product* (5·4 g.), crystallised from alcohol, had m. p. 115—116° (Found : C, 64·2; H, 5·75; N, 14·05; S, 10·6. $C_{16}H_{17}ON_3S$ requires C, 64·2; H, 5·7; N, 14·1; S, 10·7%).

The compound (2 g.) was added to a solution of sodium (0·5 g.) in liquid ammonia (50 ml.) and, when the blue colour had changed to pink, ammonium chloride (1·5 g.) was added. The solid left after removal of ammonia and digestion with water crystallised from methanol ; it had m. p. 163—164° and appeared to be benzylthiourea (reported m. p. 164°) (Found : C, 58·15, 58·05; H, 6·0, 6·0; N, 17·05, 17·05; S, 19·1. Calc. for $C_8H_{10}N_2S$: C, 57·9; H, 6·0; N, 16·9; S, 19·3%).

N-*Cyano*-p-*methoxybenzamidine*.—*p*-Methoxybenzamidine hydrochloride hydrate (11·12 g.), in ice-cold water (10 volumes), was treated with a sodium hypobromite solution prepared from bromine (8 g.) and 2N-sodium hydroxide (60 ml.) ; the white crystalline precipitate (11 g.) had m. p. 99—100° (decomp.) (Found : Br, 35·0. $C_8H_9ON_2Br$ requires Br, 34·95%). The *bromo-amidine* (5·7 g.) and silver cyanide (13·4 g.) were boiled in xylene (150 ml.) suspension for 7 min. The decanted solution crystallised on cooling. The silver residues were extracted, first with benzene and then with ether (Soxhlet), to give further crops of the product (total 62·5%). Crystallised from 65% alcohol (charcoal), the *cyano-amidine* had m. p. 200—202° (Found : C, 61·8; H, 5·45; N, 23·6. $C_9H_9ON_3$ requires C, 61·7; H, 5·2; N, 24·0%).

This compound failed to add hydrogen sulphide under any of the following conditions : (i) in pyridine solution, in the presence of triethylamine, at 35° for 2½ hr. ; (ii) with yellow ammonium sulphide and 2-methoxyethanol at 40° for 40 hr. ; and (iii) with sodium methoxide in methanol at 60—70° for 24 hr.

N-p-*Methoxyphenyl*-N′-*thioureidoformamidine* (III ; Ar = *p*-MeO·C_6H_4).—*Formation*. Ethoxymethylene-*p*-anisidine (9 g.), thiosemicarbazide (4·55 g.), and alcohol (25 ml.) were stirred at 50—60° for 3 hr. Filtration when cold gave the *product* (8·8 g.), which formed colourless crystals, m. p. 129—130°, from alcohol (Found : C, 48·2; H, 5·45; N, 25·0; S, 14·45. $C_9H_{12}ON_4S$ requires C, 48·2; H, 5·35; N, 25·0; S, 14·3%), soluble in sodium hydroxide and reprecipitated unchanged by ammonium chloride.

Action of acid. The base (3·36 g.) required 2 mols. (30 ml.) of N-hydrochloric acid for dissolution ; after evaporation in a vacuum, the residue (4·4 g.) was crystallised twice from propan-2-ol–ethyl acetate to give colourless leaflets (3·4 g.), m. p. 124—126° (Found : C, 36·7; 36·9; H, 4·9, 4·55; N, 19·35, 19·15; Cl, 24·0, 23·9. Calc. for $C_9H_{12}ON_4S,2HCl$: C, 36·4; H, 4·7; N, 18·85; Cl, 23·9%), identified as a mixture in two ways : (i) Equimolecular amounts of *p*-anisidine hydrochloride and 2-amino-1 : 3 : 4-thiadiazole hydrochloride were mixed and recrystallised as above, to give leaflets of m. p. 124—126°, undepressed by the above (Found : C, 36·4; H, 4·5; Cl, 24·05%). (ii) The substance (2 g.), in 50% aqueous alcohol, was de-acidified by the use of a resin column (Dowex 2), and the mixed bases (1·35 g.) were recovered ; digestion with benzene (5 ml.) left undissolved 2-amino-1 : 3 : 4-thiadiazole (0·65 g., 95·5%), m. p. and mixed m. p. 188—190°, raised to 191—192° by crystallisation from propan-2-ol (Found : C, 24·25; H, 2·85; N, 40·5; S, 31·5. Calc. for $C_2H_3N_3S$: C, 23·8; H, 3·0; N, 41·6;

[12] Hoggarth, *J.*, 1949, 1160.
[13] Bernstein, Yale, Losee, Holsing, Martins, and Lott, *J. Amer. Chem. Soc.*, 1951, **73**, 906.

S, 31·7%). The benzene extract yielded *p*-anisidine (0·65 g., 78%), identified as its acetyl derivative.

N-*Phenyl*-N′-*thioureidoformamidine* (III; Ar = Ph).—Prepared as above from ethoxymethyleneaniline and thiosemicarbazide, this *amidine* crystallised from alcohol and had m. p. 130—131° (Found: C, 49·25, 49·2; H, 4·85, 4·95; N, 28·8, 28·85; S, 16·45. $C_8H_{10}N_4S$ requires C, 49·5; H, 5·15; N, 28·9; S, 16·5%).

The substance (9·7 g.), methyl iodide (7·8 g.), and alcohol (50 ml.) were gently boiled for 1½ hr., then evaporated in a vacuum. The residue was digested with ethyl acetate, and the insoluble white crystals of aniline hydriodide (8·8 g., 80%) were filtered off and crystallised from alcohol–ethyl acetate (m. p. ≮280°) (Found: C, 32·8, 32·55; H, 3·7, 3·6; N, 6·4, 6·55; I, 57·8. Calc. for C_6H_8NI: C, 32·6; H, 3·6; N, 6·35; I, 57·5%), identified also by conversion into acetanilide. The ethyl acetate filtrate was evaporated, and the residue dissolved in dilute acid and extracted repeatedly with ether. The extracts yielded solids which, after crystallisation from benzene, had m. p. 98—100° and gave no depression with 3-methylthio-1 : 2 : 4-triazole (total yield: 3·5 g., 61%) (Found: C, 31·25, 31·2; H, 4·3, 4·2; N, 35·45, 35·55; S, 27·35. Calc. for $C_3H_3N_3S$: C, 31·3; H, 4·35; N, 36·5; S, 27·8%).

The amidine (9·7 g.) was added to warm 2N-sodium hydroxide (50 ml.), then the solution was cooled to 20° and treated dropwise with methyl sulphate (6·3 g.). After 2 hr. it was boiled to half-bulk [giving a little aniline, identified as acetanilide (1·9 g.)] and then cooled. Crystals of 3-*amino*-4-*phenyl*-1 : 2 : 4-*triazole* (4·7—5·5 g.) (soluble in dilute acid), m. p. 219—221°, separated and after recrystallisation from water had m. p. 221—223° (Found: C, 60·2, 60·25; H, 5·05, 4·9; N, 35·35, 35·35. $C_8H_8N_4$ requires C, 60·0; H, 5·0; N, 35·0%).

Ethyl Acetate Thiosemicarbazone.—(1-Ethoxyethylidene)aniline (25·3 g.), thiosemicarbazide (14·3 g.), and alcohol (85 ml.) were stirred at 50—60° for 1½ hr. and then boiled for 5 hr. The hot solution was filtered and cooled to give crystals (A); the filtrate, on concentration to a small volume, gave product B. Product A was extracted with cold water to leave a substance (8·75 g.) crystallising from alcohol in prisms (7·4 g.), m. p. 146—147° (Found: C, 36·45; H, 6·4%). Because it was suspected that this was still contaminated with thiosemicarbazide, it was shaken with *p*-dimethylaminobenzaldehyde methosulphate (11 g.) in warm water (75 ml.), leaving a substance, m. p. 151° (6·35 g.). Recrystallised from alcohol this gave ethyl acetate thiosemicarbazone, m. p. 151—152° (Ainsworth [8] gave the same m. p.) (Found: C, 37·65; H, 6·95; N, 25·55; S, 19·6. Calc. for $C_5H_{11}ON_3S$: C, 37·3; H, 6·85; N, 26·1; S, 19·9%).

Product B was extracted with cold water, to leave 2·1 g., m. p. 265—270°, crystallising from water in colourless laminæ (1·65 g.), m. p. 274—276°, identified, by comparison with an authentic sample, as 5-mercapto-3-methyl-1 : 2 : 4-triazole (Found: C, 31·55, 31·35; H, 3·7, 3·65; N, 34·2; S, 27·8. Calc. for $C_3H_5N_3S$: C, 31·3; H, 4·35; N, 36·5; S, 27·8%).

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