777. *Antituberculous Compounds. Part X.* Some Reactions of Quaternary Compounds Derived from* NN*-Disubstituted Thioamides.*

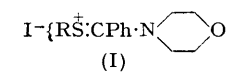
By D. A. Peak and F. Stansfield.

Whereas semicarbazide reacts with the quaternary " methiodide " (II: R = Me) of thiobenzomorpholide to give 1-α-methylthiobenzylidenesemicarbazide (VII; R = Ph, X = O) (Chabrier and Renard, *Compt. rend.*, 1950, **230**, 1673; *Bull. Soc. chim.*, 1951, **18**, 348), thiosemicarbazide yields by cyclisation 2-amino-5-phenyl-1 : 3 : 4-thiadiazole (IX). Under alkaline conditions semicarbazide condenses with (II; R = Me) with the elimination of methanethiol instead of morpholine hydriodide to give 1-α-morpholinobenzylidenesemicarbazide (VIII; R = Ph, X = O). Thiosemicarbazide reacts analogously and the reaction is general for quaternary derivatives of other thioamides, both open-chain and cyclic, and fully substituted thiuronium salts. The compounds so obtained have low antituberculous activity.

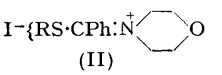
The course of the reaction between (II; R = Me) and ammonia to give benzamidine has been investigated. Aniline reacts with (II; R = Me) to give the *NNN'*-trisubstituted benzamidine salt (XX) whilst morpholine gives the quaternary amidinium salt (XXI; R = Ph).

The quaternised thioacylmorpholides are readily thiohydrolysed by hydrogen sulphide, and the reaction constitutes a convenient source of dithiocarboxylic esters.

Chabrier and Renard (*Compt. rend.*, 1950, **230**, 1673) have described the reaction of methyl and ethyl iodide with thiobenzomorpholide giving quaternary derivatives to which they assigned the structure (I; R = Me or Et). Böttcher and Bauer (*Annalen*, 1950, **568**, 218) obtained similar compounds by the action of methyl iodide on *S*-methyl*iso*-thioamides of type (III) and represented these by the structure (IV; R'' = Me). Analogous cyclic quaternary derivatives, *e.g.*, 2-alkylthiobenzothiazole alkiodides (V), have also



(I)



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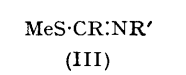
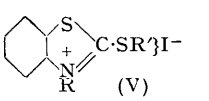
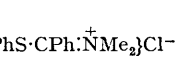


(III)

(IV)



(V)



(VI)

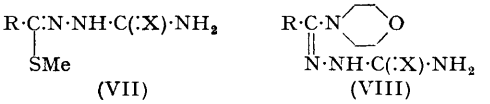
generally been formulated as ammonium rather than sulphonium derivatives. Fry and Kendall (*J.*, 1951, 1716) have recently shown that it is not even necessary to postulate the intermediate existence of the sulphonium form as suggested by Davies and Sexton (*J.*, 1942, 304) and Mann and Watson (*J. Org. Chem.*, 1948, **13**, 502) to explain the formation of mixtures of quaternary salts when R and R' are different alkyl groups.

We are indebted to Dr. J. D. S. Goulden for the examination of the infra-red absorption spectra of the Chabrier–Renard compounds. The main features are the absence of a band in the 1300—1400-cm.$^{-1}$ region, where a thiono-group (C:S) normally absorbs, and a strong band at 1580 cm.$^{-1}$. This is somewhat lower than the frequency usually associated with the C:N$^+$ group (Randall, Fowler, Fuson, and Dangl, " Infrared Determination of Organic Structures," Van Nostrand Co, Inc., New York, 1949, p. 5) probably owing to the effect of the substituent methylthio-group. If a resonance hybrid state exists between these two forms, therefore, the contribution of the sulphonium form must be small and the compounds are more accurately represented by (II) than by (I). The ready hydrolysis

* Part IX, *J.*, 1951, 3292.

of the compounds to alkyl thiolbenzoates is also in conformity with the absence of resonance stabilisation. Raison (*J.*, 1949, 3319) came to similar conclusions regarding the structure of his hypothetical intermediate (VI) from the condensation of benzodimethylamide and thiophenol in the presence of phosphoryl chloride.

Chabrier and Renard (*loc. cit.*) observed that (II; R = Me) condensed with semicarbazide hydrochloride in aqueous ethanol to give the compound (VII; R = Ph, X = O). This reaction appeared of considerable interest since an analogous condensation with thiosemicarbazide might lead to 1-α-alkylthiobenzylidenethiosemicarbazides (VII; R = aryl, X = S) which, because of their close relationship to thiosemicarbazones such as *p*-acetamidobenzaldehyde thiosemicarbazone ("Thiacetazone"), might possess chemotherapeutic activity against *Mycobacterium tuberculosis*. Compound (II; R = Me) was found to condense with thiosemicarbazide under acid or neutral conditions with, presumably, the intermediate formation of (VII; R = Ph, X = S) which, however, was too unstable for isolation since it readily cyclised to 2-amino-5-phenyl-1 : 3 : 4-thiadiazole (IX) with the loss of methanethiol. This spontaneous cyclisation is in contrast to the behaviour of the oxygen analogue (VII; R = Ph, X = O) which does not cyclise. The latter is unaffected by ethanolic alkali but with aqueous ethanolic hydrochloric acid it undergoes rapid fission to methyl thiolbenzoate and semicarbazide. The *p*-ethanesulphonyl derivative (VII; R = *p*-Et·SO_2·C_6H_4, X = O) is similarly cleaved. On pyrolysis at 210° (VII; R = Ph, X = O) cyclises to 3-hydroxy-5-phenyl-1 : 2 : 4-triazole (X; X = O).



(VII) (VIII) (IX) (X)

The compound (VII; R = Ph, X = O) showed appreciable antituberculous activity *in vitro* but an attempt to exploit this by the introduction of *p*-substituents which exert a favourable influence in the thiosemicarbazone type of compound, *e.g.*, methoxy, acetamido, and ethanesulphonyl, afforded compounds devoid of activity.

Under alkaline conditions, *e.g.*, in aqueous potassium hydrogen carbonate or in pyridine, preferably in the presence of a strong base such as di- or tri-ethylamine, the condensation of (II; R = Me) with thiosemicarbazide took a different course, the methylthio-group being eliminated instead of the morpholino-group, with the formation of 1-α-morpholinobenzylidenethiosemicarbazide (VIII; R = Ph, X = S). This compound was soluble in dilute acids but was rapidly cyclised to 2-amino-5-phenyl-1 : 3 : 4-thiadiazole (IX). It was much more stable to alkali but was cyclised by long boiling with alcoholic potassium hydroxide to 3-mercapto-5-phenyl-1 : 2 : 4-triazole (X; X = S). Its behaviour is therefore similar to that of 1-benzoylthiosemicarbazide under acid and alkaline conditions of dehydration (Hoggarth, *J.*, 1949, 1163).

A similar condensation occurred with semicarbazide under the same conditions, to give 1-α-morpholinobenzylidenesemicarbazide (VIII; R = Ph, X = O).

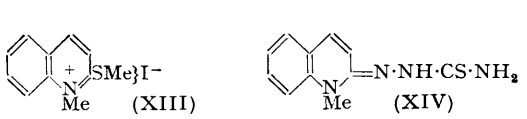
This reaction was found to be quite general. A number of *NN*-disubstituted thioamides (XI) were prepared by standard procedures and converted into the methiodides (IV) in which R was variously aryl, alkyl, or aralkyl and R′ and R″ were either aryl or

(XI) R·CS·NR′R″ R·C(NR′R″):N·NH·CS·NH_2 (XII)

alkyl or jointly the residue of a heterocycle such as morpholine or piperidine. These readily afforded the thiosemicarbazono-derivatives (XII), none of which, however, exhibited appreciable activity *in vitro*. 1-α-Morpholinobenzylidenesemicarbazide (VIII; R = Ph, X = O) showed activity *in vitro* comparable to that of "Thiacetazone" but it had no action on experimental tuberculosis in mice.

The reaction was found to be equally applicable to quaternary derivatives of cyclic thioamides. Thus, 1-methyl-2-methylthioquinolinium iodide (XIII) with thiosemicarbazide readily gave 1 : 2-dihydro-1-methyl-2-thiosemicarbazonoquinoline (XIV) and a "vinylogue," 1 : 4-dihydro-1 : 2-diphenyl-4-thiosemicarbazonoquinoline (XV), was similarly obtained from 4-methylthio-1 : 2-diphenylquinolinium iodide. Analogous thiosemi-

carbazono-derivatives of other heterocycles such as pyridine, *iso*quinoline, benzothiazole, and pyrimidine were obtained from the appropriate quaternised methylthio-heterocyclic compounds. The reaction also proceeded with fully substituted thiuronium salts. Thus *SN*-dimethyl-*NN'*-diphenyl*iso*thiourea was quaternised with methyl iodide and the product condensed with thiosemicarbazide, to give *NN'*-dimethyl-*NN'*-diphenyl-*N''*-thioureidoguanidine (XVII). The intermediate quaternary derivative must therefore

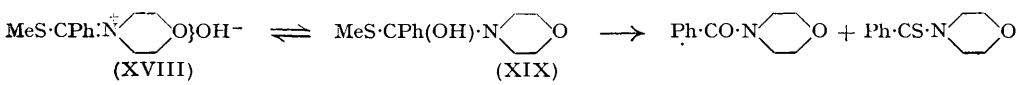


(XIII) (XIV) (XV)

(XVI) $PhMeN{\cdot}C(SMe){:}\overset{+}{N}MePh\}I^-$ $PhMeN{\cdot}C(\cdot NMePh){:}N{\cdot}NH{\cdot}CS{\cdot}NH_2$ (XVII)

have the structure (XVI), in accordance with the general rule that the doubly-linked nitrogen atom of an amidine group is preferentially attacked by a quaternising or alkylating agent (Pyman, *J.*, 1923, **123**, 3362).

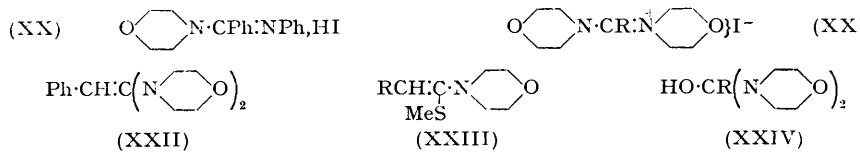
Chabrier and Renard observed that a solution of (II; R = Me) in aqueous ammonia soon deposited an oil which later solidified and finally redissolved, the end products being benzamidine and morpholine hydriodide. Examination of this solid has shown that its properties are consistent with its formulation as a *pseudo*-base (XIX), corresponding to the hypothetical quaternary hydroxide (XVIII). It is too unstable to be satisfactorily purified for analysis. It is an almost neutral substance but is reconverted by hydrogen iodide into the original compound (II; R = Me). When boiled with aqueous ethanol it



(XVIII) (XIX)

gives a mixture of benzo- and thiobenzo-morpholide which could be formed by loss of either methanethiol or methanol from (XIX). It is an intermediate and not a side-product in the formation of benzamidine since it affords benzamidine when dissolved in aqueous ammonia, although some thiobenzomorpholide is simultaneously formed.

Under similar conditions, Chabrier and Renard showed that the primary amine, methylamine, gave *NN'*-dimethylbenzamidine while the secondary amine, diethylamine, gave mainly thiobenzomorpholide with some benzodiethylamide. Under anhydrous conditions the reaction with primary and secondary amines proceeds differently. Thus, (II; R = Me) with aniline afforded the expected *N*-phenylbenzimidoylmorpholide hydriodide (XX). With morpholine, the quaternary amidinium compound (XXI;



(XXII) (XXIII) (XXIV)

R = Ph) was formed. The structure of this compound is unambiguous but it is possible to formulate the analogous phenylacetamidinium derivative, similarly obtained although not in an analytically pure state, either as (XXI; R = $Ph{\cdot}CH_2$) or as the hydriodide of (XXII). A similar doubt applies to the quaternary methiodides of thioaceto- and phenylthioaceto-morpholide, which might exist as the hydriodides of (XXIII; R = H and Ph respectively). This is unlikely because of the great similarity of the infra-red spectra to that of (II). We have, however, confirmed Rogers' observation (*J.*, 1950, 3350) that, in the presence of excess of aqueous morpholine, (XXI; R = $Ph{\cdot}CH_2$) loses the elements of hydrogen iodide and gives a compound which can be formulated only as (XXII). On the other hand, (XXI; R = Ph) is rapidly converted into benzomorpholide and morpholine by one equivalent of alkali, presumably *via* the unstable *pseudo*-base (XXIV; R = Ph) which cannot attain a stable state by the elimination of water as in the case of (XXIV; R = $Ph{\cdot}CH_2$).

The ready hydrolysis of (II; R = Me) to methyl thiolbenzoate suggested that com-

pounds of this type might also react with hydrogen sulphide to give dithiocarboxylic esters. This proved to be the case and (II; R = Me) reacted readily with hydrogen sulphide in pyridine or ethanol to give methyl dithiobenzoate (64%). 4-(1-Methylthio-2-phenylethylidene)morpholinium iodide similarly gave methyl phenyldithioacetate (44%), and 4-1'-methylthioethylidenemorpholinium iodide gave methyl dithioacetate (77%), obtained as a methanol azeotrope and estimated by conversion into thioacetobenzylamide. Because of the ready availability of *NN*-disubstituted thioamides the reaction offers a very convenient route to dithiocarboxylic esters. The intermediate quaternary salts need not be isolated.

During this work discrepancies were noted in the melting-points of some of the compounds compared with those recorded by Chabrier and Renard (*loc. cit.*) and these are noted in the Experimental section.

Experimental

All m. p.s uncorrected.

Preparation of Thioamides and iso*Thioamides.—Method A* (Willgerodt–Kindler reaction). Benzaldehyde (42·5 g.), morpholine (52·0 g., 1·5 mols.), and sulphur (19·2 g., 1·5 atoms) were heated together under reflux on the steam-bath. An exothermic reaction occurred and the mixture boiled. After 3 hours' heating, the resulting dark brown oil (which sometimes solidified) was dissolved in boiling ethanol (800 c.c.), and the hot solution was filtered from a small insoluble residue. The filtrate, on cooling, deposited thiobenzomorpholide as golden-yellow needles (73·5 g., 0·89 mol.), m. p. 135—136°. It still contained a small amount of sulphur, which could be removed, if desired, by shaking it with concentrated sodium sulphide solution. McMillan (*J. Amer. Chem. Soc.*, 1948, **70**, 869) gives m.p. 137—138°.

In the same way, there were obtained from the respective aldehydes p-*methoxythiobenzomorpholide* (83%; m. p. 107°), golden-yellow needles (from ethanol), m. p. 109—110° (Found: C, 61·3; H, 6·4; N, 5·55. $C_{12}H_{15}O_2NS$ requires C, 60·8; H, 6·3; N, 5·9%), p-*acetamidothiobenzomorpholide* (94%; m. p. 211—215°), lemon yellow elongated plates (from ethanol), m. p. 214—216° (Found: N, 10·9. $C_{13}H_{16}O_2N_2S$ requires N, 10·6%), p-*ethanesulphonylthiobenzomorpholide* (88%), slightly yellow plates (from ethanol), m. p. 186° (Found: C, 52·65; H, 5·7. $C_{13}H_{17}O_3NS_2$ requires C, 52·2; H, 5·7%), and thiobenzopiperidide (impure product obtained as an oil) (Russell, *J.*, 1910, **97**, 955, gives m. p. 65—66°).

Method B. Acetomorpholide (60·0 g.) in carbon disulphide (80 c.c.) was shaken with phosphorus pentasulphide (103·3 g., 1 mol.) for 2 hours. Some heat was produced and the mixture was cooled occasionally. Finally the mixture was boiled under reflux on the steam-bath for 2 hours and then cooled. Water was added to decompose the phosphorus compounds and the mixture kept overnight. The product, isolated in chloroform, was obtained as an oil which solidified on cooling. The crude thioacetomorpholide (55·5 g., 82%; m. p. 80°) crystallised from ethanol (charcoal) in colourless rods, m. p. 89° (Levesque, U.S.P. 2,489,094, gives m. p. 89—90°). In some preparations the amount of phosphorus pentasulphide was reduced to as little as 0·3 mol. with only slight diminution in yield.

Similarly, from the respective amides, there were obtained *N*-methylthiobenzanilide (44%; m. p. 101·5°) which crystallised from light petroleum (b. p. 80—100°) in lemon-yellow cubes, m. p. 101·5° (Found: C, 73·6; H, 5·35. Calc. for $C_{14}H_{13}NS$: C, 74·0; H, 5·7%) (May, *J.*, 1913, **103**, 2274, gives m. p. 90—91°), and 1-methyl-2-quinolthione (not purified, crude m. p. 90°) (Gutbier, *Ber.*, 1900, **33**, 3359, gives m. p. 118°).

Method C (cf. Klingsberg and Papa, *J. Amer. Chem. Soc.*, 1951, **73**, 4988). 2-Methyl-1-*iso*quinolone (33·9 g.) was dissolved in dry pyridine (100 c.c.) under a reflux air-condenser, and phosphorus pentasulphide (56·8 g., 1·2 mols.) was added, the heat produced being sufficient to cause ebullition. When the reaction began to subside, boiling was continued over a gauze for 2 hours. The product was then poured slowly, with stirring, into water (350 c.c.) previously heated almost to boiling, to decompose phosphorus compounds. After cooling, the product was extracted with chloroform, and the extract washed with water, dried (Na_2SO_4), and treated with charcoal. Evaporation of the solvent afforded crude 2-*methyl*-1-iso*quinolthione* (23·0 g., 62%), m. p. 90°. It crystallised from light petroleum (b. p. 80—100°) as orange-yellow needles, m. p. 110° (Found: C, 68·6; H, 5·1. $C_{10}H_9NS$ requires C, 68·6; H, 5·15%).

In the same way, but without chloroform-extraction, there were obtained NNN'N'-*tetraethyldithioterephthalamide* (by using 2·4 mols. of phosphorus pentasulphide) (96%), small, deep yellow needles (from ethanol), m. p. 202—203° (Found: N, 9·3. $C_{16}H_{24}N_2S_2$ requires N, 9·1%),

1 : 2-*diphenyl*-4-*quinolthione* (69%), orange-brown needles (from ethyl acetate), m. p. 267° (Found : C, 80·6; H, 4·9. $C_{21}H_{15}NS$ requires C, 80·5; H, 4·8%), and 9-*phenanthridthione* (68%), small, deep yellow needles (from dioxan), m. p. 273—274° (Found : C, 74·15; H, 4·3. $C_{13}H_9NS$ requires C, 73·9; H, 4·2%).

9-*Methylthiophenanthridine*.—9-Phenanthridthione (18·0 g.) was boiled under reflux, moisture being excluded, with methyl iodide (50 c.c.) and dry acetone (200 c.c.) for 4 hours. After cooling, ether (200 c.c.) was added gradually, with stirring, and the solid formed was filtered off, washed with ether, and decomposed with sodium hydroxide solution. The free base was extracted with chloroform, and the solution dried (Na_2SO_4), treated with charcoal, and filtered. The solvent was evaporated, leaving 9-*methylthiophenanthridine* (11·5 g.), m. p. 70°, which after recrystallisation from ethanol, formed orange-yellow hair crystals, m. p. 70—71° (Found : C, 75·2; H, 4·8. $C_{14}H_{11}NS$ requires C, 74·65; H, 4·9%).

1-*Methyl*-2-*pyridthione*.—This was prepared by the method of Michaelis and Hölken (*Annalen*, 1904, **331**, 248).

4 : 6-*Dimethyl*-2-*methylthiopyrimidine*.—This compound was obtained by the method of Wheeler and Jamieson (*Amer. Chem. J.*, 1904, **32**, 356).

Preparation of Quaternary Salts.

The methiodides were prepared from the corresponding *NN*-disubstituted thioamides (or *N*-monosubstituted-*S*-methyl*iso*thioamides) and a large excess of methyl iodide (usually 3 mols. or more) in boiling, dry, methanol-free acetone, under reflux with exclusion of moisture for an appropriate time. If necessary, some of the solvent was then evaporated, care being taken to avoid decomposition of the methiodide by heat, and, after cooling, ether was added with stirring to the cooled concentrate. The compound (often well crystallised) was filtered off, rapidly washed with ether, and dried at once in a vacuum-desiccator. Products so obtained were used directly for further reactions, but purification for analysis was often accomplished by dissolving them in absolute ethanol at room temperature and precipitating them in crystalline form by slow addition of ether with stirring and seeding if necessary.

The quaternary salts are soluble in water, but are slowly decomposed, even by atmospheric moisture, and all melt with decomposition (usually with liberation of methyl iodide and regeneration of the thioamide).

The following compounds were prepared in this way (from the *NN*-disubstituted thioamides except where otherwise stated), reaction times and yields being given parenthetically : 4-1′-*methylthioethylidenemorpholinium iodide* (30 minutes; 99%), colourless plates (from acetone), m. p. 131—132° (decomp.) (Found : C, 29·1; H, 4·7; N, 4·9; S, 10·6. $C_7H_{14}ONIS$ requires C, 29·3; H, 4·9; N, 4·9; S, 11·15%); 4-(1-methylthio-2-phenylethylidene)morpholinium iodide, colourless, flat needles, m. p. 158° (decomp.), from nitromethane by precipitation with benzene (Found : C, 42·6; H, 4·9. Calc. for $C_{13}H_{18}ONIS$: C, 43·0; H, 4·95%) [Rogers, *loc. cit.*, gives m. p. 172° (decomp.)]; 4-α-methylthiobenzylidenemorpholinium iodide (10 minutes; 90%), thin yellow plates, m. p. 158° (decomp.), from ethanol–ether (Found : C, 41·1; H, 4·75. Calc. for $C_{12}H_{16}ONIS$: C, 41·3; H, 4·6%) (Chabrier and Renard, *Compt. rend.*, 1949, **228**, 850, give m. p. 138°; Chabrier, Renard, and Smarzewska, *Bull. Soc. chim.*, 1950, **17**, 1167, give m. p. 170°); 4-(4-*methoxy*-α-*methylthiobenzylidene*)*morpholinium iodide* (10 minutes; 86%), yellow hairs (from ethanol–ether), m. p. 142° (decomp.) (Found : C, 41·2; H, 4·7. $C_{13}H_{18}O_2NIS$ requires C, 41·15; H, 4·75%); 4-(4-acetamido-α-methylthiobenzylidene)morpholinium iodide (not purified; m. p. 136—138°); 4-(4-ethanesulphonyl-α-methylthiobenzylidene)morpholinium iodide (not purified); 1-α-*methylthiobenzylidenepiperidinium iodide* (1 hour; 58%) (overall yield based on benzaldehyde used in the Willgerodt reaction, the crude product from which was used), yellow plates (from ethanol–ether), m. p. 111° (decomp.) (Found : C, 44·7; H, 5·5. $C_{13}H_{18}NIS$ requires C, 44·95; H, 5·2%); *NN*-dimethyl-α-methylthiobenzylideneammonium iodide (Böttcher and Bauer, *loc. cit.*); N-*methyl*-α-*methylthiobenzylideneanilinium iodide* (10 minutes; 97%), elongated yellow plates (from ethanol–ether), m. p. 148—150° (decomp.) (Found: C, 49·0; H, 4·15. $C_{15}H_{16}NIS$ requires C, 48·8; H, 4·3%); αα′-*dimethylthio*-p-*xylylidenebisdiethylammonium di-iodide* (7 hours; 97%), elongaged plates (from acetone), m. p. 193—197° (decomp.) (Found : C, 36·6; H, 5·5. $C_{18}H_{30}N_2I_2S_2$ requires C, 36·5; H, 5·1%); 1-methyl-2-methylthiopyridinium iodide (Michaelis and Hölken, *loc. cit.*); 1-methyl-2-methylthioquinolinium iodide (Fischer, *Ber.*, 1902, **35**, 3677); 2-*methyl*-1-*methylthio*isoquinolinium *iodide* (2 hours; 97%), deep yellow needles (from ethanol–ether), m. p. 134° (decomp.) (Found : C, 41·5; H, 3·9. $C_{11}H_{12}NIS$ requires C, 41·65; H, 3·8%); 4-*methylthio*-1 : 2-*diphenylquinolinium iodide* (2 hours; 93%), golden-yellow plates (from ethanol–ether), m. p. 245° (decomp.) (Found:

C, 57·8; H, 4·0. $C_{22}H_{18}NIS$ requires C, 58·0; H, 3·95%); 1 : 4 : 6-*trimethyl*-2-*methylthiopyrimidinium iodide* (from 4 : 6-dimethyl-2-methylthiopyrimidine) (36 hours; 71%) (experiment by Dr. P. E. MACEY), pale yellow needles (from acetone–benzene), m. p. 185° (decomp.) (Found : N, 9·2. $C_8H_{13}N_2IS$ requires N, 9·45%); and 3-methyl-2-methylthiobenzothiazolium iodide (Fry and Kendall, *loc. cit.*).

In the same way, *SN*-dimethyl-*NN'*-diphenyl*iso*thiourea (Bertram, *Ber.*, 1892, **25**, 57), with methyl iodide in boiling acetone for 24 hours, gave SNN'-*trimethyl*-NN'-*diphenylthiuronium iodide* (95%), colourless elongated plates (from ethanol–ether), m. p. 161—162° (Found : C, 48·2; H, 4·7. $C_{16}H_{19}N_2IS$ requires C, 48·2; H, 4·8%).

Thiobenzomorpholide (2·07 g.) in dry, methanol-free acetone (10 c.c.) with ethyl iodide (1·6 c.c.), under reflux for 2 hours, gave 4-α-ethylthiobenzylidenemorpholinium iodide (2·27 g.), m. p. 136°, which formed yellow plates or needles, m. p. 136—137°, from alcohol–ether (Found : C, 43·0; H, 5·0; I, 35·0. Calc. for $C_{13}H_{18}ONIS$: C, 43·0; H, 4·95; I, 35·0%) (Chabrier, Renard, and Smarzewska, *loc. cit.*, give m. p. 193°). The same compound, m. p. 136°, was obtained when thiobenzomorpholide (2·07 g.) with ethyl iodide (1·6 c.c.) in acetone (34 c.c.) was kept for 10 days at room temperature, and the product gave no depression of m. p. on admixture with the ethiodide prepared in boiling solution.

Thiosemicarbazono-derivatives.

An equimolecular mixture of thiosemicarbazide and the methiodide was dissolved or suspended in an excess of an organic base (or combination of bases) and shaken mechanically at room temperature, usually for 16 hours. Although pyridine was an excellent solvent, the reaction proceeded in some cases only very slowly unless a stronger base such as diethylamine, triethylamine, or piperidine, was present. Finally, the solvent was removed under reduced pressure (bath-temperature 40°), the residue triturated with water, and the product filtered off, washed, and dried at room temperature.

In this way there were prepared (the base or bases used and their respective volume ratio, time of reaction, and yield being indicated parenthetically in that order) : 1-1'-*morpholinoethylidenethiosemicarbazide* (diethylamine; 16 hours; 72%), colourless small cubes (from ethanol), m. p. 133° (decomp.) (Found : C, 42·05; H, 7·4; N, 27·5; S, 15·55. $C_7H_{14}ON_4S$ requires C, 41·6; H, 6·9; N, 27·7; S, 15·85%); 1-α-*morpholinobenzylidenethiosemicarbazide* (pyridine–piperidine, 7 : 1; 24 hours; 57%), colourless rods (from methyl acetate or ethanol), m. p. 141° (Found : C, 54·7; H, 6·0; N, 20·7, 21·1; S, 12·65. $C_{12}H_{16}ON_4S$ requires C, 54·55; H, 6·05; N, 21·2; S, 12·1%), also prepared from the ethiodide (piperidine; 24 hours; 84%), and from the methiodide in aqueous potassium hydrogen carbonate; 1-(4-*methoxy*-α-*morpholinobenzylidene*)*thiosemicarbazide* (diethylamine; 10 minutes; 72%), small colourless cubes (from methyl acetate), m. p. 147° (Found : C, 52·8; H, 6·1. $C_{13}H_{18}O_2N_4S$ requires C, 53·1; H, 6·1%); 1-α-*piperidinobenzylidenethiosemicarbazide* (pyridine–piperidine, 3 : 1; 16 hours; 83%), colourless cubes (from ethyl acetate), m. p. 140° (Found : N, 21·4. $C_{13}H_{18}N_4S$ requires N, 21·4%); 1-α-*dimethylaminobenzylidenethiosemicarbazide* (pyridine–triethylamine, 1 : 1; 16 hours; 71%), large colourless rhombs (from ethyl acetate), m. p. 131° (decomp.) (Found : C, 54·2; H, 6·0; N, 24·7. $C_{10}H_{14}N_4S$ requires C, 54·05; H, 6·3; N, 25·2%); 1-(α-N-*methylanilinobenzylidene*)*thiosemicarbazide* (diethylamine; 16 hours; 93%), faintly yellow flat needles (from ethanol or ethyl acetate), m. p. 152° (Found : C, 63·3; H, 5·6. $C_{15}H_{16}N_4S$ requires C, 63·4; H, 5·6%); 1 : 2-*dihydro*-1-*methyl*-2-*thiosemicarbazonopyridine* (diethylamine–pyridine, 3 : 2; 9 days; 55%), lemon-yellow cubes (from methanol), m. p. 198° (decomp.) with much darkening above 160° (Found : C, 46·1; H, 5·7. $C_7H_{10}N_4S$ requires C, 46·15; H, 5·5%); 1 : 2-*dihydro*-1-*methyl*-2-*thiosemicarbazonoquinoline* (diethylamine; 16 hours; 59%), deep yellow rods with tapering ends (from methanol), m. p. 206° (decomp.) preceded by darkening and shrinking above 180° (Found : C, 57·0; H, 5·05. $C_{11}H_{12}N_4S$ requires C, 56·9; H, 5·2%); 1 : 2-*dihydro*-2-*methyl*-1-*thiosemicarbazono*iso*quinoline* (pyridine–diethylamine, 5 : 1; 16 hours; 98%), greenish-yellow clusters of rods (from ethanol), m. p. 157—158° (decomp.) (Found : C, 56·3; H, 5·2%); 1 : 4-*dihydro*-1 : 2-*diphenyl*-4-*thiosemicarbazonoquinoline* (pyridine–diethylamine, 10 : 1; 4 hours; 88%), deep yellow needles (from ethanol–ethyl lactate), chars above 235° without melting (Found : C, 71·05; H, 4·8. $C_{22}H_{18}N_4S$ requires C, 71·35; H, 4·85%); 1 : 2-*dihydro*-1 : 4 : 6-*trimethyl*-2-*thiosemicarbazonopyrimidine* (pyridine–triethylamine, 10 : 1; 2 days; 82%), small orange-yellow needles (from ethanol), m. p. 202° (decomp.) (Found : C, 45·75; H, 6·3. $C_8H_{13}N_5S$ requires C, 45·5; H, 6·15%); 2 : 3-*dihydro*-3-*methyl*-2-*thiosemicarbazonobenzothiazole* (pyridine–diethylamine, 2 : 1; 54 hours; 67%), colourless rods (from ethanol), m. p. 214° (decomp.) (Found : C, 45·9; H, 4·4. $C_9H_{10}N_4S_2$ requires C, 45·4; H,

4·2%); and *NN'-dimethyl-NN'-diphenyl-N''-thioureidoguanidine* (pyridine–triethylamine. 10 : 1; 66 hours; 92%), colourless plates (from ethanol), m. p. 183° (Found: C, 61·6; H, 5·9; N, 22·6; S, 9·65. $C_{16}H_{19}N_5S$ requires C, 61·35; H, 6·1; N, 22·4; S, 10·2%).

1 : 2-*Dihydro*-1-*methyl*-2-S-*methyl*isothiosemicarbazonopyridine *Hydriodide*.—1 : 2-Dihydro-1-methyl-2-thiosemicarbazonopyridine (1·5 g.), on being heated under reflux with methyl iodide (5 c.c.) and dry acetone (20 c.c.) for 4 hours, cooled, and treated with ether, gave 1 : 2-*dihydro*-1-*methyl*-2-S-*methyl*isothiosemicarbazonopyridine *hydriodide* (2·4 g.), deep yellow clusters of plates (from ethanol), m. p. 167° (decomp.) (Found: C, 29·8; H, 3·9. $C_8H_{13}N_4IS$ requires C, 29·6; H, 4·0%). The location of the methyl group was indicated by the liberation of methanethiol with boiling 5N-sodium hydroxide.

Reaction with Acid.—1-α-Morpholinobenzylidenethiosemicarbazide (2·0 g.) was shaken with N-hydrochloric acid (25 c.c.) at room temperature. The solid quickly dissolved to a clear solution. Scratching yielded at once a white precipitate (hair crystals) which was filtered off, washed, and dried (1·0 g.). This was presumably the hydrochloride of 2-amino-5-phenyl-1 : 3 : 4-thiadiazole since with potassium hydrogen carbonate solution effervescence occurred and the free base was liberated, m. p. 225°, undepressed on admixture with an authentic specimen prepared by Hoggarth's method (*loc. cit.*).

An attempt to decompose 1 : 2-dihydro-1-methyl-2-thiosemicarbazonoquinoline by boiling it with N-hydrochloric acid for 5 minutes, led only to recovery of the starting material.

Reaction with Alkali.—1-α-Morpholinobenzylidenethiosemicarbazide (1·0 g.) was boiled under reflux for 2 hours with a solution of potassium hydroxide (1·0 g.) in alcohol (50 c.c.). After evaporation of solvent, the residue was triturated with water (25 c.c.). The undissolved solid, when filtered off, washed, and dried, proved to be unchanged starting material (0·6 g.), m. p. 141°, undepressed on admixture with the original compound. The combined filtrate and washings were acidified and the precipitated solid was filtered off, washed, and dried. This was 3-mercapto-5-phenyl-1 : 2 : 4-triazole (0·25 g.), m. p. 254°, raised by recrystallisation from aqueous ethanol to 255° and undepressed on admixture with a specimen prepared by the method of Hoggarth (*loc. cit.*).

Effect of Heat.—1-α-Morpholinobenzylidenethiosemicarbazide (4·0 g.) was heated at 180° for 1 hour. Morpholine distilled over and was removed finally *in vacuo*. The solid residue was recrystallised from aqueous ethanol (charcoal), yielding colourless crystals of 3-mercapto-5-phenyl-1 : 2 : 4-triazole (1·7 g.), m. p. and mixed m. p. 252°. It was completely soluble in dilute sodium hydroxide solution.

Semicarbazono-derivatives.

1-α-*Morpholinobenzylidenesemicarbazide*.—Semicarbazide hydrochloride (4·5 g.) was added to pyridine (30 c.c.), followed by 4-α-methylthiobenzylidenemorpholinium iodide (14·1 g., 1 mol.). The mixture was shaken for 16 hours, pyridine removed *in vacuo* (bath temperature <35°), and the residue triturated with water, filtered off, washed, and dried. The crude product (4·6 g.) was recrystallised from ethyl acetate, giving colourless needles of the *semicarbazide*, m. p. 162—163° (Found: C, 57·9; H, 6·0; N, 22·6. $C_{12}H_{16}O_2N_4$ requires C, 58·05; H, 6·45; N, 22·6%).

1-α-*Methylthiobenzylidenesemicarbazide*.—To a solution of semicarbazide hydrochloride (4·5 g.) and hydrated sodium acetate (5·5 g., 1 mol.) in water (80 c.c.) at room temperature was added 4-α-methylthiobenzylidenemorpholinium iodide (11·2 g., 0·8 mol.). After being shaken to dissolve the latter, the mixture was set aside for 16 hours. The white crystalline precipitate of the semicarbazide was filtered off, washed with water, and dried (4·2 g., 0·5 mol.; m. p. 151—153°). On recrystallisation from ethanol, it gave colourless prisms, m. p. 156—157° (Chabrier and Renard, *Bull. Soc. chim.*, 1951, **18**, 348, give m. p. 131°) (Found: C, 52·0; H, 5·25; N, 19·9. Calc. for $C_9H_{11}ON_3S$: C, 51·7; H, 5·25; N, 20·1%).

In this way there were also prepared: 1-(4-*methoxy*-α-*methylthiobenzylidene*)*semicarbazide* (52%), prisms (from ethanol), m. p. 163° (Found: C, 50·05; H, 5·25. $C_{10}H_{13}O_2N_3S$ requires C, 50·2; H, 5·45%); 1-(4-*acetamido*-α-*methylthiobenzylidene*)*semicarbazide* (59%), prisms (from ethanol), m. p. 204° (decomp.) (Found: C, 49·9; H, 5·0. $C_{11}H_{14}O_2N_4S$ requires C, 49·6; H, 5·25%); and 1-(4-*ethanesulphonyl*-α-*methylthiobenzylidene*)*semicarbazide* (20%), plates (from ethanol), m. p. 172° (Found: C, 44·0; H, 4·8. $C_{11}H_{15}O_3N_3S_2$ requires C, 43·85; H, 5·0%).

Decomposition with Acid.—A solution of 1-α-methylthiobenzylidenesemicarbazide (1·0 g.) in a mixture of concentrated hydrochloric acid (10 c.c.) and ethanol (30 c.c.), was boiled under reflux on the steam-bath for 1 hour and then evaporated to dryness at room temperature. The residue was triturated with chloroform (20 c.c.), then filtered, and the solid [0·48 g.; m. p.

160° (decomp.)] recrystallised from aqueous ethanol (charcoal), giving semicarbazide hydrochloride, colourless plates, m. p. 169° (decomp.), further identified by conversion into benzaldehyde semicarbazone, m. p. and mixed m. p. 214°.

The solvent was evaporated from the chloroform-soluble fraction, and the remaining oil distilled (bath-temperature 230—240°) yielding methyl thiolbenzoate as a colourless liquid, identified by alkaline hydrolysis to methanethiol and benzoic acid, m. p. and mixed m. p. 122°.

1-(4-Ethanesulphonyl-α-methylthiobenzylidene)semicarbazide (6·0 g.) was hydrolysed by boiling it under reflux with concentrated hydrochloric acid (60 c.c.) and ethanol (180 c.c.) for 30 minutes, the solution evaporated to dryness at room temperature and the residue triturated with water (40 c.c.). The undissolved solid was filtered off, washed, and dried, yielding *methyl 4-ethanesulphonylthiolbenzoate* (4·6 g.; m. p. 66°) which formed colourless needles, m. p. 87—88°, from light petroleum (b. p. 80—100°) or from *iso*propyl alcohol (Found : C, 48·8; H, 4·9. $C_{10}H_{12}O_3S_2$ requires C, 49·2; H, 4·9%).

The aqueous filtrate, on evaporation to dryness at room temperature, yielded semicarbazide hydrochloride (2·2 g.), m. p. 161—164° (decomp.), raised by recrystallisation from aqueous ethanol to 168° (decomp.) undepressed by an authentic specimen.

Attempted Decomposition with Alkali.—1-α-Methylthiobenzylidenesemicarbazide (1·0 g.) after 12 hours' boiling under reflux with a solution of potassium hydroxide (1·0 g.) in ethanol (30 c.c.), followed by partial evaporation of the solvent and addition of water, yielded only the starting material (0·6 g.; m. p. 154°).

Effect of Heat.—1-α-Methylthiobenzylidenesemicarbazide (0·8 g.) was heated at 210—215° for 1·5 hours. Methanethiol was rapidly evolved and the melt resolidified. The solid (0·5 g.) dissolved almost entirely in 5N-sodium hydroxide. Precipitation by acid and recrystallisation from ethanol gave 3-hydroxy-5-phenyl-1 : 2 : 4-triazole, m. p. 316° (Found : C, 59·65; H, 4·0. Calc. for $C_8H_7ON_3$: C, 59·65; H, 4·35%). Young and Witham (*J.*, 1900, **77**, 228) give m. p. 321—322°.

Reactions of methiodides with ammonia and amines.

Reaction with Aqueous Ammonia.—4-α-Methylthiobenzylidenemorpholinium iodide (10 g.) was shaken at room temperature with ammonia solution (100 c.c.; *d* 0·935). The methiodide immediately dissolved and an oil separated which solidified in a few minutes. There was a strong smell of methanethiol. On mechanical shaking for 16 hours, most of the solid redissolved. The filtered solution gave with aqueous lithium picrate a copious precipitate of benzamidine picrate, m. p. and mixed m. p. 235° after crystallisation from water.

In a duplicate experiment, the reaction was stopped when the oil solidified, and the solid was immediately filtered off, washed with water, and dried in a vacuum-desiccator. It appeared to be decomposed by atmospheric moisture, producing a strong smell of methanethiol. A little was decomposed by boiling 50% aqueous ethanol (2 hours) with the liberation of much methanethiol. On cooling, yellow hair crystals separated. After recrystallisation from ethanol, these were identified as thiobenzomorpholide, m. p. 136°, undepressed by an authentic specimen. The aqueous-alcoholic mother-liquor was evaporated to dryness and the residual oil solidified on being rubbed. Recrystallisation from ethanol gave benzomorpholide, m. p. 72°, undepressed by a specimen m. p. 74°.

Another portion of the solid intermediate compound was shaken mechanically at room temperature for 21 hours with ammonia solution (*d* 0·935). A small insoluble residue was filtered off and, after recrystallisation from ethanol, yielded yellow needles of thiobenzomorpholide, m. p. 137°. The filtrate was evaporated to dryness *in vacuo* and the residue, when dissolved in water, gave with lithium picrate solution a precipitate of benzamidine picrate, m. p. and mixed m. p. 232° after recrystallisation from water.

Some of the solid intermediate product was dissolved in acetone, and a few drops of constant-boiling hydriodic acid were added, excess being avoided. The solution was poured into much ether, and the precipitated yellow oil slowly solidified on being rubbed. It was washed by decantation with ether and purified twice by precipitation from absolute ethanol with ether, giving 4-α-methylthiobenzylidenemorpholinium iodide, m. p. 158° (decomp.), undepressed by the original compound.

The solid intermediate product, when washed with water and re-dissolved in aqueous ethanol, gave a solution of pH 8—9.

Reaction with Aniline.—4-α-Methylthiobenzylidenemorpholinium iodide (24·5 g.) was shaken mechanically at room temperature with absolute ethanol (70 c.c.) and redistilled aniline (7 c.c.). The reaction mixture became warm and a solid soon began to crystallise. After 16 hours, the

product was filtered off, washed with small quantities of ethanol, and dried. The colourless material (24·1 g.) was purified by recrystallisation from ethanol and from water, giving needles or hair crystals of N-*phenylbenzimidoylmorpholide hydriodide*, m. p. 288—289° (decomp.) (Found : C, 51·9; H, 4·75; N, 7·35. $C_{17}H_{19}ON_2I$ requires C, 51·8; H, 4·8; N, 7·1%).

Reaction with Morpholine.—4-α-Methylthiobenzylidenemorpholinium iodide (22·0 g.) and morpholine (15 c.c.) were heated on the steam-bath, moisture being excluded. A vigorous reaction with evolution of methanethiol occurred almost at once and heating was continued for 2 hours. The mixture was cooled and the solid triturated with ether, filtered off, washed with ether, and dried. The product (23·5 g.) was purified by recrystallisation from ethanol, giving pale yellow needles of 4-α-*morpholinobenzylidenemorpholinium iodide*, m. p. 291° (decomp.) (Found : C, 46·75; H, 5·3; N, 7·4. $C_{15}H_{21}O_2N_2I$ requires C, 46·4; H, 5·4%; N, 7·2%). It was soluble in water to the extent of about 1% at room temperature, giving an almost neutral solution.

The *picrate* formed deep yellow leaflets (from ethanol), m. p. 153—154° (Found : C, 51·0; H, 4·7. $C_{21}H_{23}O_9N_5$ requires C, 51·5; H, 4·7%).

The experiment of Rogers (*loc. cit.*), with 4-(1-methylthio-2-phenylethylidene)morpholinium iodide and morpholine, was repeated, and there was obtained ββ-dimorpholinostyrene, m. p. 134—135° (Found: C, 70·5; H, 8·2. Calc. for $C_{16}H_{22}O_2N_2$: C, 70·05; H, 8·0%) (Rogers, *loc. cit.*, gives m. p. 131—132°).

Hydrolysis of 4-α-*Morpholinobenzylidenemorpholinium Iodide.*—The iodide (3·0 g.) was shaken mechanically for 2 days with N-sodium hydroxide (7·7 c.c., 1 mol.), water (2·3 c.c.), and chloroform (20 c.c.). The chloroform layer was separated and dried (Na_2SO_4), and the solvent evaporated. The residual oil solidified yielding benzomorpholide (1·4 g., 95%), m. p. 72°.

Dithioesters.

Methyl Dithioacetate.—4-1-Methylthioethylidenemorpholinium iodide (47 g.) was added to dry methanol (300 c.c.) saturated at 0° with dry hydrogen sulphide. Crystals of morpholine hydriodide were deposited almost immediately. The cooling-bath was removed and passage of hydrogen sulphide continued for 3 hours, whereafter the mixture was set aside for 2 days. Distillation afforded a mixture of methyl dithioacetate and methanol, and a residue of large crystals of morpholine hydriodide which were collected, washed with ether, and dried (34·4 g., 98%; m. p. 206°). Recrystallisation from ethanol raised the m. p. to 209—210°, undepressed by an authentic sample prepared from morpholine and hydriodic acid.

The deep yellow methanolic distillate was added to benzylamine (27 c.c.) with shaking, and the solution, now colourless, was kept for 16 hours and the methanol evaporated. Trituration of the oily residue with cold 2N-hydrochloric acid (75 c.c.) afforded thioacetobenzylamide as colourless crystals (20·8 g., 77%; m. p. 63°). Worrall (*J. Amer. Chem. Soc.*, 1928, **50**, 1459) gives m. p. 62—63°.

Methyl Dithiobenzoate.—Thiobenzomorpholide (50 g.), dry, methanol-free acetone (250 c.c.), and methyl iodide (18 c.c.) were boiled together under reflux for 20 minutes, during which the methiodide separated. The mixture was cooled, diluted with dry pyridine (50 c.c.) saturated with dry hydrogen sulphide for 6 hours, and kept for 14 hours. Most of the acetone was then evaporated under reduced pressure and the residue poured on ice and dilute hydrochloric acid. The methyl dithiobenzoate was extracted with ether and obtained as a bright red oil (26·1 g., 64%), b. p. 118°/3 mm., 105°/1 mm.

The ester was also prepared from the methiodide in absolute ethanol saturated with hydrogen sulphide in 69% yield, b. p. 123°/4 mm.

Methyl Phenyldithioacetate.—Crude phenylthioacetomorpholide (50 g.) (from the Willgerodt reaction with acetophenone) was converted into the methiodide which was filtered off, washed with ether, and dissolved at once in dry pyridine (75 c.c.). The solution was saturated with hydrogen sulphide, kept for 24 hours, and worked up as previously, affording methyl phenyldithioacetate as an orange oil, b. p. 120°/1 mm. (18 g., 44%).

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