## 218. *Thiadiazoles. Part VII.*[1] *5-Amino-3-mercapto-1 : 2 : 4-thiadiazole Derivatives.*

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1-Aryl(or alkyl)-4-alkyl*iso*-2 : 4-dithiobiurets are cyclised almost quantitatively by oxidising agents to 3-alkylthio-5-aryl(or alkyl)amino-1 : 2 : 4-thiadiazoles.

Some properties of this class of thiadiazole are described.

THE preceding Part [1] of this series described the oxidative ring-closure of 1-substituted 2-thiobiurets to 5-amino-3-hydroxy-1 : 2 : 4-thiadiazole derivatives. This general reaction [2] has now been extended to the synthesis of the analogous 3-alkylthio-heterocycles (II) from suitably substituted dithiobiurets (I). As before,[2] the cyclisation involves the dehydrogenation of the amidinothiono-grouping [·C(:NH)·NH·C(:S)·].

Although 1-substituted 2 : 4-dithiobiurets (VII) incorporate this system in their structure, they are, unlike 1-substituted 2-thiobiurets,[1] unsuitable as precursors of 1 : 2 : 4-thiadiazoles, since on oxidation their two potential mercapto-groups are preferentially affected, affording products that have been formulated [3] as 1 : 2 : 4-dithiazolidines (VIII). The reversible oxidation–reduction of the parent compound dithiobiuret (VII; R = H) and its oxidation product (VIII; R = H) has been similarly interpreted.[4] More recently, the possible alternative representation of oxidation products of dithiobiurets (VII; R = H or Ar) as 1 : 2 : 4-thiadiazoles (V) has been discussed by Bambas.[5] In the absence of further experimental results, however, the available evidence [3] appears to favour their cyclic disulphide (VIII) structure.[6] In the present work such structural uncertainties are avoided by the use of dithiobiurets in which one of the reactive sulphur atoms is blocked by an alkyl group. Of the two possible series of homologues, 1-substituted *S*[4]- (I) and *S*[2]-alkyl*iso*-2 : 4-dithiobiurets [R·NH·C(SR'):N·CS·$NH_2$], only the former, containing the amidinothiono-system, are convertible into 1 : 2 : 4-thiadiazoles.

Substituted dithiobiurets (I) required as starting materials were obtained by condensation of *iso*thiocyanates and *S*-alkyl*iso*thioureas by Johnson and Bristol's method.[7-9]

[1] Part VI, Kurzer and Taylor, *J.*, 1958, 379.
[2] Kurzer, *J.*, 1955, 1, and subsequent papers.
[3] Fromm, *Annalen*, 1893, **275**, 20, and subsequent papers; see also ref. 6.
[4] Preisler and Bateman, *J. Amer. Chem. Soc.*, 1947, **69**, 2632; Preisler, *ibid.*, 1949, **71**, 2849.
[5] Bambas, "The Chemistry of Heterocyclic Compounds," Interscience Publ. Inc., New York, 1952, Vol. IV, pp. 44—51.
[6] Kurzer, *Chem. Rev.*, 1956, **56**, 95, 154.
[7] Johnson and Bristol, *Amer. Chem. J.*, 1903, **30**, 172.
[8] Underwood and Dains, *Univ. Kansas Sci. Bull.*, 1936, **24**, 5.
[9] Birtwell, Curd, Hendry, and Rose, *J.*, 1948, 1645, 1654.

As in the corresponding synthesis of 1-substituted 2-thio-4-*iso*biurets,[1] the original procedure [7] was improved by performing the reaction in one phase at higher temperatures. Ethanol [9] was not used, however, because it tends to react with *iso*thiocyanates, particularly aromatic ones.[10] Boiling aqueous acetone, at various concentrations (cf. Experimental section), preferably with the addition of a tertiary base such as triethylamine as a catalyst, proved to be a satisfactory medium in all the cases studied. 1-Aryl-*S*[4]-alkyl(or aryl)*iso*-2 : 4-dithiobiurets (I; R = Ph, R′ = Me, $CH_2Ph$, or Ph) were thus obtained readily in 60—75% yields; 1-alkyl derivatives (I; R = Me, $Pr^n$, R′ = Me, or $CH_2Ph$), isolated as hydrochlorides because of the unfavourable physical properties of the free bases, were accessible in lower yields (25—45%) only. Methyl *iso*thiocyanate and *S*-methyl*iso*thiourea failed to react in the aqueous solvent, but afforded the required dithiobiuret (I; R = R′ = Me) under anhydrous conditions, in the presence of sodium as condensing agent. Unlike hydrochlorides of *O*-alkyl-1-methyl-2-thio*iso*biurets [NHMe·CS·NH·C(OAlk):NH,HCl], which are rapidly dealkylated in boiling solvents, salts of the present series of compounds (I) were purified without difficulty by crystallisation, since the corresponding thiohydrolysis of the S–alkyl link occurs only under special conditions.[8,9,11]

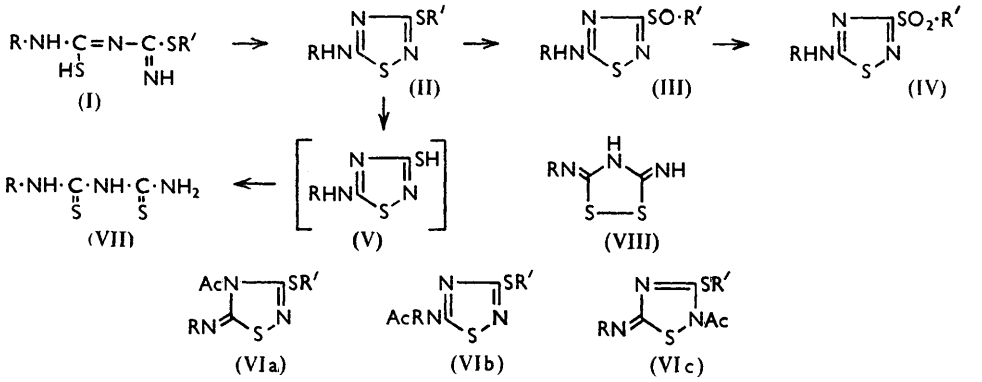
1-Substituted 4-*iso*-2 : 4-dithiobiurets (I) thus obtained were readily cyclodehydrogenated to homologues of 5-amino-3-mercapto-1 : 2 : 4-thiadiazole (II). Excess of hydrogen peroxide in the presence of mineral acid proved to be the superior oxidising agent, producing the heterocycles in 75—95% yield. The use of equimolecular proportions of bromine in organic solvents afforded the same products in somewhat lower yields. The halogen uptake was practically instantaneous, showing that ring closure occurred with almost ionic velocity: dithiobiuret (I) salts, which were insoluble in the usual non-polar solvents, were therefore readily oxidised in methanol, there being no significant halogen consumption in side-reactions with the solvent. Regardless of the nature of the medium used, however, certain dithiobiurets containing aromatic nuclei, particularly benzyl groups, tended to absorb more than the calculated quantity of bromine, probably because of slight losses of the reagent due to nuclear bromination: it is well established that benzene nuclei attached to amino- or substituted amino-groups are rapidly halogenated under the mildest conditions.[12] Certain dithiobiurets (I; R = Me, $Pr^n$, R′ = $CH_2Ph$) changed, in the presence of alkali, into the 1 : 2 : 4-thiadiazoles (II) merely in contact with air, demonstrating the remarkable ease with which this heterocyclic system is formed; similar observations are on record concerning the oxidation of thiobenzoylguanidine.[13]

An alternative synthesis of 5-alkylamino-3-alkylthio-1 : 2 : 4-thiadiazoles, by the action of methyl- or benzyl-amine on 3-alkylthio-5-chloro-1 : 2 : 4-thiadiazoles, has been described by Goerdeler and Sperling.[14] The fact that representative examples of this series of compounds (II; R = Me, R′ = Me or $CH_2Ph$) prepared by both methods were identical further confirms the interpretation of the chemical changes involved in both syntheses.

The heterocyclic thiol derivatives (II) now synthesised showed properties in accord with their structure and, in particular, exhibited certain similarities with the corresponding oxy-compounds (cf. Part VI [1]). They were stable solids, which resisted desulphurisation by alkaline sodium plumbite, the heterocyclic nucleus being obviously stabilised [2] by the presence of the substituents. They were generally insoluble in acids and alkalis: 5-anilino-3-methylthio-1 : 2 : 4-thiadiazole, however, shared with the 3-amino- [2] and the 3-methoxy-analogue [1] the exceptional solubility in hot aqueous sodium hydroxide. 5-Anilino-3-methylthio-1 : 2 : 4-thiadiazole, like the 3-methoxy-analogue, gave a monoacetyl and a monobenzoyl derivative and failed to afford a toluene-*p*-sulphonyl derivative, as expected.

[10] Slotta, Tschesche, and Drechsler, *Ber.*, 1930, **63**, 208.
[11] Fairfull and Peak, *J.*, 1955, 796.
[12] See, for example, Robertson, de la Mare, and Swedlund, *J.*, 1953, 782.
[13] Goerdeler and Fincke, *Chem. Ber.*, 1956, **89**, 1033.
[14] Goerdeler and Sperling, *ibid.*, 1957, **90**, 892.

This provides yet another example of the frequently observed [1,2,15] lower reactivity of aminothiadiazoles towards sulphonyl halides than of acyl halides or anhydrides. For the reasons previously given in the oxy-series,[1] the site of substitution of the acyl group remains, for the time being, undecided, formulæ (VIa—c) being possible. In view of the known [16] greater reactivity of the 4- than of the 2-position in the 1 : 2 : 4-thiadiazole nucleus,



structure (VIc) can probably be ruled out. Alkylthio-groups in thiadiazoles (II) behaved normally in that their sulphur atom was convertible into the sulphoxyl or sulphonyl grouping; 5-anilino-3-methylthio-1 : 2 : 4-thiadiazole, for example, reacted with the appropriate quantities of monoperphthalic acid to give the sulphoxide or sulphone (III or IV; R = Ph, R′ = Me). Similar observations made with 5-amino-3-ethylthio-1 : 2 : 4-thiadiazole have been described by Goerdeler and Linden.[15]

The dealkylation of 3-alkylthio-5-anilino-1 : 2 : 4-thiadiazoles (II ⟶ V; R = Ph) was of special interest, since a comparison of authentic 5-anilino-3-mercapto-1 : 2 : 4-thiadiazole, if accessible by this method, with the oxidation product of 1-phenyldithiobiuret (" thiuret ") [3] would provide the information for a conclusive choice between the two possible structures (V, VIII) of the latter.[3,5] A widely applicable method for dealkylating methylthio-compounds, using hydrogen sulphide in pyridine–triethylamine, has recently been introduced by Fairfull, Lowe, and Peak,[17] and benzylthio-compounds have been converted into their parent thiols by du Vigneaud and his school [18] employing sodium in liquid ammonia. In the present series, however, the methylthio-compound and the benzyl analogue (II; R = Ph, R′ = Me or $CH_2Ph$) were converted directly into 1-phenyldithiobiuret by these methods. It is probable that the thiol (V; R = Ph) was formed in the first place, but was simultaneously ring-opened to the dithiobiuret (VII; R = Ph) under the reductive conditions of both dealkylation procedures. The ready reduction of 5-anilino-3-hydroxy-1 : 2 : 4-thiadiazole to 1-phenyl-2-thiobiuret [1] supports this view.

## Experimental

Pyridine was the commercially available anhydrous grade. Light petroleum was of boiling range 60—80°.

The solvent used for preparing 1M-bromine was chloroform unless otherwise stated. Aqueous picric acid was used as 0·06M-solution (saturated at 30°).[19]

*5-Arylamino-3-mercapto-1 : 2 : 4-thiadiazoles.*—S[4]-*Methyl*-1-*phenyl*iso-2 : 4-*dithiobiuret*, prepared in 60—75% yield by the method of Johnson and Bristol [7] (but in an aqueous acetone as described immediately below), formed needles, m. p. 123—124° (from benzene).

S[4]-*Benzyl*-1-*phenyl*iso-2 : 4-*dithiobiuret.*—Benzyl*iso*thiuronium chloride (20·25 g., 0·1 mole)

[15] Goerdeler and Linden, *Chem. Ber.*, 1956, **89**, 2742.
[16] Goerdeler, Huppertz, and Wember, *ibid.*, 1954, **87**, 68.
[17] Fairfull, Lowe, and Peak, *J.*, 1952, 742.
[18] du Vigneaud *et al.*, *J. Amer. Chem. Soc.*, 1930, **52**, 4500; *J. Biol. Chem.*, 1935, **108**, 753; 1935, **109**, 97; 1935, **111**, 393; 1938, **123**, 327; Carter, Stevens, and Ney, *ibid.*, 1941, **139**, 247.
[19] Dolinski, *Ber.*, 1905, **38**, 1836.

was added to a solution of 5M-potassium hydroxide (20 ml., 0·1 mole), followed by acetone (75 ml.) and phenyl *iso*thiocyanate (10·13 g., 0·075 mole). The stirred suspension (later solution) was refluxed during 20—25 min. and added to ice-water (250 ml.), and the precipitated oil collected (when solidified at 0°) and air-dried. Crystallisation from benzene (150 ml.) gave needles (m. p. 115—117°; 15·6 g., 69%) of the *dithiobiuret*. Two further crystallisations from the same solvent afforded pale ivory needles, m. p. 116—118° (Found: C, 60·0; H, 5·3; N, 13·4; S, 21·8. $C_{15}H_{15}N_3S_2$ requires C, 59·8; H, 5·0; N, 13·95; S, 21·3%).

1-*Phenyl*-S⁴-*phenyl*iso-2 : 4-*dithiobiuret*.—A solution of *S*-phenyl*iso*thiourea [20] (7·6 g., 0·05 mole) in warm acetone (150 ml.) was treated with phenyl *iso*thiocyanate (6·75 g., 0·05 mole) and anhydrous triethylamine (1 ml.). The resulting yellow liquid was refluxed during 10 min., distilled to small volume (50 ml.), cooled, and stirred into ice-water (250 ml.). The solidified oil was broken up, collected, air-dried (11 g.), and successively crystallised from benzene (30 ml. per g.) and from chloroform–benzene (1 : 1), opaque needles of the *dithiobiuret*, m. p. 134—135°, being obtained [total yield, (here, and later, this term includes material from the mother-liquors), 10·05 g., 70%] (Found: C, 58 7; H, 4·7; N, 14·3; S, 21·7. $C_{14}H_{13}N_3S_2$ requires C, 58·5; H, 4·5; N, 14·6; S, 22·3%).

5-*Anilino*-3-*methylthio*-1 : 2 : 4-*thiadiazole*.—(*a*) A stirred solution of *S*⁴-methyl-1-phenyl-*iso*-2 : 4-dithiobiuret (2·25 g., 0 01 mole) in benzene (50 ml.) at 35—40° was treated, with external cooling, with bromine in chloroform (1M; 10 ml., 0·01 mole) which was rapidly decolorised. The separated crystalline precipitate was collected after 12 hours' storage at 0° (filtrate A) and dissolved in ethanol (120 ml.), the solution stirred into ice-water (500 ml.), and the product (m. p. 152—155°; 1·75—1·90 g., 80—85%) collected at 0°. Crystallisation from benzene (15 ml. per g., recovery 90%) gave needles of 5-*anilino*-3-*methylthio*-1 : 2 : 4-*thiadiazole*, m. p. 154—155° (Found: C, 48·9, 48·7; H, 4·1, 3·9; N, 18·9; S, 28·1. $C_9H_9N_3S_2$ requires C, 48·4; H, 4·0; N, 18·8; S, 28·7%). The benzene filtrates (A) gave only minute quantities (1—2%) of the same thiadiazole on evaporation. [Oxidation of the dithiobiuret (0·01 mole) in ethanol (40 ml.) as above resulted in lower yields (40%).]

(*b*) A solution of the reactant (0·03 mole) in ethanol (75 ml.) at 65° was treated dropwise with 6% hydrogen peroxide (51 ml., 0·09 mole) during 15 min. The crystals which separated were collected at 0° and rinsed with ethanol (m. p. 154—156°; 6·35 g., 95%); they consisted of almost pure 1 : 2 : 4-thiadiazole. The product was very sparingly soluble in boiling water, but very soluble in hot 3N-aqueous sodium hydroxide, and was deposited therefrom unchanged on cooling.

*Derivatives*. A solution of 5-anilino-3-methylthio-1 : 2 : 4-thiadiazole (1·12 g., 0·005 mole) in acetic anhydride (10 ml.) was boiled during 30 min., then added to water. The product, after crystallisation from acetone–ethanol, consisted of platelets (1·2 g., 90%) of the *monoacetyl derivative*, m. p. 204—206° (Found: C, 49·7; H, 4·1; N, 15·6. $C_{11}H_{11}ON_3S_2$ requires C, 49·8; H, 4·15; N, 15·85%). Interaction of the thiadiazole (0·005 mole) and benzoyl chloride (1·4 g., 0·01 mole) in pyridine (10 ml.) at 100° during 30 min., addition of the liquid to N-hydrochloric acid (120 ml.) at 0°, and crystallisation of the product from acetone–ethanol gave needles (90%) of the *monobenzoyl derivative*, m. p. 188—190° (Found: C, 59·0; H, 3·8; N, 12·8; S 20·1. $C_{16}H_{13}ON_3S_2$ requires C, 58·7; H, 4·0; N, 12·8; S, 19·6%). The thiadiazole did not yield a toluene-*p*-sulphonyl derivative by the usual procedure.[1]

3-(5-*Anilino*-1 : 2 : 4-*thiadiazolyl*) *Methyl Sulphoxide*.—A solution of 5-anilino-3-methylthio-1 : 2 : 4-thiadiazole (1·12 g., 0·005 mole) in chloroform (100 ml.) was treated at −30° (solid carbon dioxide–ethanol) with 0·2N-ethereal monoperphthalic acid [21] (50 ml., 0·005 mole) previously cooled to the same temperature. The solution, which deposited phthalic acid slowly, was stored at 0° during 24 hr., and at room temperature during 2 days, the oxidising agent then having been consumed (negative potassium iodide–starch test). The decanted colourless solution was evaporated in a vacuum at 35—45°, and the residue basified with 3N-sodium carbonate. The undissolved (solidified) residue (1·25 g.) was crystallised from ethanol (10 ml.), giving prisms (m. p. 146—147°; 0·87 g., 72%) which consisted, after further crystallisation from ethanol, and then from chloroform, of white opaque microcrystalline *sulphoxide*, m. p. 147—148° (Found: C, 45·3; H, 3·95; S, 27·8. $C_9H_9ON_3S_2$ requires C, 45·2; H, 3·8; S, 26·8%).

3-(5-*Anilino*-1 : 2 : 4-*thiadiazolyl*) *Methyl Sulphone*.—A solution of the reactant was similarly

[20] Arndt, *Annalen*, 1911, **384**, 322; 1913, **396**, 1, 6.
[21] Böhme, *Ber.*, 1937, **70**, 379; *Org. Synth.*, Coll. Vol. III, p. 619 (1955).

treated at −30° with an excess of 0·2N-monoperphthalic acid [21] (200 ml., 0·02 mole). The reaction was exothermic. The liquid was kept at 0° during 24 hr., and at room temperature during 6 days, but excess of oxidant was still present. The decanted yellow liquid was treated as above, and the solidified oil crystallised from benzene–acetone. The resulting product (m. p. 138—143°; 0·82 g., 65%) gave, after further crystallisation from benzene and from ethanol–light petroleum, platelets of the *sulphone*, m. p. 140—141° (after sintering at 138°) (Found: C, 42·4; H, 3·65; N, 16·2; S, 26·2. $C_9H_9O_2N_3S_2$ requires C, 42·35; H, 3·5; N, 16·5; S, 25·1%).

1-*Phenyldi.hiobiuret.*—(a) *By demethylation of* 5-*anilino*-3-*methylthio*-1 : 2 : 4-*thiadiazole.* Through a solution of the reactant (2·23 g., 0·01 mole) in anhydrous pyridine (20 ml.)–triethylamine (1·1 g., 0·011 mole), kept at 48—52°, a slow stream of dry hydrogen sulphide (successive passage through calcium chloride and glycerol) was passed during 1·5 hr. More triethylamine (1 g., 0·01 mole) was added half-way through the reaction. The dark brown liquid was stirred into ice (30 g.) and concentrated hydrochloric acid (18 ml.), and the solidified pale yellow precipitate was collected at 0° and washed with water. The air-dried crude product (2·3 g.) was dissolved in 1·5N-sodium hydroxide (12 ml.), a small insoluble residue (mostly sulphur) removed, and the diluted stirred yellow filtrate (approx. 50 ml.) acidified (to pH 7—6) with 1·5N-hydrochloric acid. The white precipitate was collected at 0° (filtrate F), rinsed with water, air-dried [m. p. 164—166° (decomp.) after sintering at 160°; 1·9 g.], and crystallised from boiling methanol (25 ml. per g.) (a little undissolved sulphur being again removed), giving lustrous flakes of 1-phenyldithiobiuret, m. p. and mixed m. p. with authentic product [22–24] 166—168° [decomp., after sintering at 162°, subject to the rate of heating] (1·31 g., 62%). A specimen for analysis was further crystallised from boiling water, with the addition of a trace of sodium dithionite (Found: C 45·8; H, 4·3; N, 20·0; S, 30·8. Calc. for $C_8H_9N_3S_2$: C, 45·5; H, 4·3; N, 19·9; S, 30·3%). Evaporation of the methanolic filtrates in a vacuum under nitrogen gave further small crops of 1-phenyldithiobiuret, m. p. 162—166° (decomp.) (6—8%).

Filtrate F, on being acidified to pH 1, gave a yellow solid (0·4 g.) of indefinite m. p. [125—140° (decomp.)], from which up to one-third of its weight of 1-phenyldithiobiuret was obtainable by crystallisation from methanol.

Reducing the time of reaction to 1 hr. lowered the yield of the dithiobiuret to 40%. At room temperature, hydrogen sulphide in pyridine–triethylamine was without effect, the reactant being substantially recovered (65%) after 15 minutes' treatment.

(b) *By debenzylation of* 5-*anilino*-3-*benzylthio*-1 : 2 : 4-*thiadiazole.* To a solution of the reactant (2·99 g., 0·01 mole) in liquid ammonia (approx. 100 ml.), protected against atmospheric moisture, thin slices of sodium (0·92 g., 0·04 g.-atom) were added during 0·5 hr. with gentle shaking. The residual, nearly white solid (S) obtained on allowing the ammonia to volatilise at room temperature was dissolved in water (25 ml.) (with addition of a few drops of 3N-ammonia if necessary). The filtered liquid (removal of traces of floating oil) was acidified (to Congo Red) with 3N-hydrochloric acid (with addition of ice; slight evolution of hydrogen sulphide), and the precipitated white solid collected. It was fractionally reprecipitated (cf. section a), and the crude 1-phenyldithiobiuret so obtained (50—80%) crystallised from methanol, affording platelets (0·76 g., 36%), m. p. and mixed m. p. 165—166° (decomp.) (Found; C, 45·0; H, 4·5%).

The use of less sodium (0·02—0·03 g.-atom) and lower temperatures (external cooling by solid carbon dioxide–ethanol) gave a crude residue (S), the alkali-insoluble part of which was unchanged reactant [30—40%, m. p. and mixed m. p. 150—151° (from ethanol)], and correspondingly lower yields of the dithiobiuret.

The identity of 1-phenyldithiobiuret thus obtained was confirmed by its conversion, on condensation with benzaldehyde in the presence of hydrogen chloride, into hexahydro-1 : 2-diphenyl-4 : 6-dithiono-1 : 3 : 5-triazine [3,24] (in approx. 50% yield), m. p. and mixed m. p. with material prepared from authentic 1-phenyldithiobiuret [22,23] 217—219° (decomp.) (lit.,[3,24] m. p. 227°).

Widely differing m. p.s of 1-phenyldithiobiuret, ranging between 169° and 184° are given in the literature.[3,11,23,25] Our observations showed that this decomposition temperature was very dependent on the initial bath-temperature and the rate of heating. The m. p. (decomp.)

[22] Wunderlich, *Ber.*, 1886, **19**, 449.
[23] Hecht, *Ber.*, 1892, **25**, 749.
[24] Fairfull and Peak, *J.*, 1955, 803.
[25] Bousquet and Guy, U.S.P. 2,410,862.

here given was obtained by inserting samples into the preheated bath at 150° and raising its temperature at approx. 5° per min.

5-*Anilino*-3-*benzylthio*-1 : 2 : 4-*thiadiazole*.—(a) Oxidation of $S^4$-benzyl-1-phenyl-*iso*-2 : 4-dithiobiuret (3·0 g., 0·01 mole) in benzene (75 ml.) [as described for the 4-methyl homologue] gave a crude product which was stirred with water (300 ml.), collected, and successively crystallised from a little acetone and ethanol, affording needles of the *thiadiazole*, m. p. 150—151° (total yield, 1·35 g., 45%) (Found: C, 60·8; H, 4·2; N, 13·8; S, 21·2. $C_{15}H_{13}N_3S_2$ requires C, 60·2; H, 4·35; N, 14·05; S, 21·4%).

(b) *By hydrogen peroxide oxidation.* $S^4$-Benzyl-1-phenyl*iso*-2 : 4-dithiobiuret (0·025 mole) in ethanol (80 ml.) was treated dropwise, at 65—75° during 10 min., with 6% hydrogen peroxide (42·5 ml., 0·075 mole), and the resulting crystalline suspension boiled during 5 min. The solid (m. p. 149—151°; 6·0—6·35 g., 80—85%), collected at 0° and crystallised as above, formed needles of the thiadiazole, m. p. and mixed m. p. 150—151°.

5-*Anilino*-3-*phenylthio*-1 : 2 : 4-*thiadiazole*. A solution of 1-phenyl-$S^4$-phenyl*iso*-2 : 4-dithiobiuret (2·87 g., 0·01 mole) in chloroform (70 ml.) decolorised bromine (1M; 10 ml., 0·01 mole) as rapidly as it was added. The clear liquid was evaporated in a vacuum, the residual solid (which smelled slightly of phenyl *iso*thiocyanate) treated with water (50 ml.), the suspension made just alkaline with 3N-sodium hydroxide, and the solid collected (2·5 g.). Successive crystallisation from benzene (25 ml. per g.) and ethanol (30 ml. per g.) gave lustrous needles of 5-*anilino*-3-*phenylthio*-1 : 2 : 4-*thiadiazole*, m. p. 173—174° (total yield, 2·22 g., 78%) (Found: C, 58·9; H, 3·9; N, 15·0; S, 22·6. $C_{14}H_{11}N_3S_2$ requires C, 58·95; H, 3·9; N, 14·7; S, 22·45%).

5-*Alkylamino*-3-*mercapto*-1 : 2 : 4-*thiadiazoles*.—1-*Methyl*-$S^4$-*methyl*iso-2 : 4-*dithiobiuret*. Sodium (1·26 g., 0·055 mole) was introduced into acetone (50 ml.), and the resulting suspension treated with finely powdered methyl*iso*thiuronium sulphate (6·95 g., 0·05 mole), followed by methyl *iso*thiocyanate (3·65 g., 0·05 mole). The stirred mixture was refluxed during 30—40 min., the bulk of the acetone removed in a vacuum, and the residual two-phase system extracted with ether. The combined dried ($Na_2SO_4$) extracts were treated with 4N-ethanolic hydrochloric acid (12·5 ml., 0·05 mole). The precipitated solid was collected at 0°, washed with ether and dried in a vacuum [m. p. 189—192° (decomp.); 4·5 g., 45%]. Two crystallisations from methanol (25 ml. per g., followed by dilution with a little ether) gave clusters of needle-shaped 1-*methyl*-$S^4$-*methyl*iso-2 : 4-*dithiobiuret hydrochloride*, m. p. 190—191° (decomp.) (Found: C, 23·9; H, 5·0; Cl, 17·5. $C_4H_9N_3S_2$,HCl requires C, 24·1; H, 5·0; Cl, 17·8%). The base, precipitated by alkali from an aqueous solution of the hydrochloride, formed oily droplets.

The *picrate*, obtained quantitatively, from aqueous solutions formed yellow prisms, m. p. 172—174° (from ethanol) (Found: C, 30·7; H, 2·8. $C_4H_9N_3S_2$,$C_6H_3O_7N_3$ requires C, 30·6; H, 3·1%).

$S^4$-*Benzyl*-1-*methyl*iso-2 : 4-*dithiobiuret*. To potassium hydroxide (85%, 1·65 g., 0·025 mole) in water (4 ml.) were successively added acetone (20 ml.), and a solution of benzyl*iso*thiuronium chloride (5·06 g., 0·025 mole) in warm water (15 ml.). The suspension was stirred until all had dissolved (addition of a little acetone, if necessary), methyl *iso*thiocyanate (1·8 g., 0·025 mole) added, and the stirred liquid refluxed during 1 hr., cooled, and stirred into water (200 ml.). The precipitated oil solidified slowly (72 hr.) on storage at 0°; it was collected, rinsed with water, and crystallised from benzene (15 ml.). The separated granular *dithiobiuret* (m. p. 93—96°; 1·50 g., 25%) consisted, after a further crystallisation from benzene of a white powder, m. p. 96—97° (Found: C, 50·2; H, 5·4; N, 17·8; S, 27·1. $C_{10}H_{13}N_3S_2$ requires C, 50·2; H, 5·4; N, 17·6; S, 26·8%). The benzene filtrate gave, on partial evaporation, small crops (0·27 g., 4·5%) of 3-benzylthio-5-methylamino-1 : 2 : 4-thiadiazole, m. p. and mixed m. p. with authentic material (see below) 139—141° (after further crystallisation from ethanol).

$S^4$-*Methyl*-1-*propyl*iso-2 : 4-*dithiobiuret*. To 5M-aqueous potassium hydroxide (0·05 mole), methyl*iso*thiuronium sulphate (6·95 g., 0·05 mole) dissolved in water (20 ml.) was added, followed by acetone (40 ml.) and propyl *iso*thiocyanate (5·05 g., 0·05 mole). The stirred liquid was refluxed during 40—50 min. and rapidly evaporated to small bulk under reduced pressure, and the crude hydrochloride [m. p. 179—180° (decomp., after sintering at 175°), 3·65 g., 32%] isolated as described for the lower homologue (in the present case the precipitate was exceptionally finely divided and was collected on hard filter-paper). Crystallisation from methanol (15 ml. per g., recovery 70%) gave lustrous flakes of $S^4$-*methyl*-1-*propyl*iso-2 : 4-*dithiobiuret hydrochloride*, m. p. 182—184° (decomp., somewhat subject to the rate of heating; inserted at 170°) (Found: C, 31·9; H, 6·1; N, 18·6; Cl, 15·9. $C_6H_{13}N_3S_2$,HCl requires C, 31·65; H, 6·15; N, 18·5; Cl, 15·6%). The hydrochloride was also recrystallisable from water. The free base,

liberated from the aqueous hydrochloride, was a low-melting oil. Attempts to prepare a picrate (in aqueous or methanolic solution) gave only yellow gums.

The dithiobiuret gave a pale yellow precipitate with hot sodium plumbite (in 3N-sodium hydroxide); no lead sulphide was precipitated even on prolonged boiling.

S[4]-*Benzyl*-1-*propyl*iso-2 : 4-*dithiobiuret* was prepared (by the procedure detailed for the methyl homologue) by using benzyl*iso*thiuronium chloride (10·12 g., 0·05 mole); it was isolated by ether-extraction and precipitated as the hydrochloride [m. p. 171—172° (decomp.); 6·1 g., 40%]. Two crystallisations from methanol (15 ml. per g., recovery 60—70%) gave white flakes of S[4]-*benzyl*-1-*propyl*iso-2 : 4-*dithiobiuret hydrochloride*, m. p. 179—180° (decomp., after sintering at 174—176°; somewhat subject to the rate of heating; inserted at 170°) (Found: C, 47·7; H, 6·1; N, 13·4. $C_{12}H_{17}N_3S_2$,HCl requires C, 47·45; H, 5·9; N, 13·8%). Recovery of hydrochloride by evaporation (spontaneous, or in a vacuum) of the methanolic mother liquors was not practicable, small quantities of the corresponding 1 : 2 : 4-thiadiazole (presumably formed by atmospheric oxidation) being isolated in some of the experiments.

Attempts to prepare a picrate (in ethanolic solution) were unsuccessful, the hydrochloride being substantially recovered.

Treatment of the hydrochloride (0·0033 mole), suspended in water (20 ml.), with 3N-sodium hydroxide (0·0066 mole) and thorough grinding, gave an oil which solidified at 0°. It consisted, after crystallisation from light petroleum, of 3-benzylthio-5-propylamino-1 : 2 : 4-thiadiazole (54%), m. p. and mixed m. p. with authentic material (see below) 90—92°. [During the working-up and crystallisation, the product was exposed to air for prolonged periods.]

5-*Methylamino*-3-*methylthio*-1 : 2 : 4-*thiadiazole*. Addition of M-bromine (5 ml., 0·005 mole) to an externally cooled solution of 1-methyl-S[4]-methyl*iso*-2 : 4-dithiobiuret hydrochloride (1·0 g., 0·005 mole) in methanol (25 ml.), followed by vacuum-distillation of the almost colourless liquid to half volume, addition to water (30 ml.), and basification with aqueous ammonia, gave a pale buff precipitate (m. p. 143—145°; 0·68 g., 85%). Three crystallisations from ethanol afforded colourless prisms of the thiadiazole, m. p. 144—145° (Found: C, 29·7; H, 4·4. Calc. for $C_4H_7N_3S_2$: C, 29·8; H, 4·35%). Goerdeler and Sperling [14] give m. p. 144·5—145° (sintering at 120°).

3-*Benzylthio*-5-*methylamino*-1 : 2 : 4-*thiadiazole*. Addition of M-bromine (0·005 mole) to a stirred solution of S[4]-benzyl-1-methyl*iso*-2 : 4-dithiobiuret (1·2 g., 0·005 mole) in benzene (30 ml.) at 30° gave a creamy soft deposit, which later solidified. Its solution in ethanol (50 ml.) was diluted with water (200 ml.) and the precipitate collected after storage at 0° (m. p. 137—140°, after sintering at 130°; 0·72 g., 60%). Two crystallisations from ethanol gave needles of the thiadiazole, m. p. 139—140° (Found: C, 50·6; H, 4·9. Calc. for $C_{10}H_{11}N_3S_2$: C, 50·6; H, 4·6%). Goerdeler and Sperling give m. p. 139—140° (sintering at 125°).

3-*Methylthio*-5-*propylamino*-1 : 2 : 4-*thiadiazole*. Oxidation of S[4]-methyl-1-propyl*iso*-2 : 4-dithiobiuret hydrochloride (1·14 g., 0·005 mole) in methanol (30 ml.) with M-bromine (0·005 mole), followed by vacuum-evaporation of the clear liquid (to 3 ml.), dilution with water (10 ml.), and basification with 3N-ammonia (10 ml.), gave an oil, which solidified at 0° (m. p. 64—67°; 0·86 g., 90%). Crystallisation from light petroleum (10 ml. per g.) and ethanol–water (1 : 1, 10 ml. per g.) gave needles of the *thiadiazole*, m. p. 68—70° (Found: C, 38·1; H, 5·85; N, 22·2. $C_6H_{11}N_3S_2$ requires C, 38·1; H, 5·8; N, 22·2%). The product is highly soluble in cold methanol, ethanol, and acetone. The *picrate*, prepared from hot saturated ethanolic solutions, formed yellow plates (85%), m. p. 138—139° (Found: C, 35·0; H, 3·3. $C_6H_{11}N_3S_2$,$C_6H_3O_7N_3$ requires C, 34·45; H, 3·35%).

3-*Benzylthio*-5-*propylamino*-1 : 2 : 4-*thiadiazole*. A solution of S[4]-benzyl-1-propyl*iso*-2 : 4-dithiobiuret hydrochloride (1·52 g., 0·005 mole) in methanol (30 ml.) at 60° was treated with 6% hydrogen peroxide (8·5 ml., 0·015 mole) during 5 min., the clear liquid was boiled during 5 min., cooled somewhat, basified with ammonia, and diluted with water (30 ml.), and the needles were collected at 0°. Two crystallisations from light petroleum gave needles of the *thiadiazole*, m. p. 90—91° (total 1·0 g., 75%) (Found: C, 54·2; H, 5·5; N, 15·7; S, 23·9. $C_{12}H_{15}N_3S_2$ requires C, 54·3; H, 5·7; N, 15·85; S, 24·15%). The *picrate*, prepared from hot saturated ethanolic solution, formed yellow needles (75%), m. p. 131—132° (from ethanol) (Found: C, 43·9; H, 3·7. $C_{12}H_{15}N_3S_2$,$C_6H_3O_7N_3$ requires C, 43·7; H, 3·6%).

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