70. *Thiadiazoles. Part VI.** 5-*Amino*-3-*hydroxy*-1 : 2 : 4-*thiadiazole Derivatives.*

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1-Aryl(or -alkyl)-2-thio-4-*iso*biurets and the 2-thiobiurets obtained therefrom by dealkylation are smoothly dehydrogenated by bromine or hydrogen peroxide, to 3-alkoxy(or -hydroxy)-5-aryl(or alkyl)amino-1 : 2 : 4-thiadiazoles. *N*-Aryl-*N'*-cyanothioureas, on treatment with alkaline hydrogen peroxide, similarly afford good yields of 5-arylamino-3-hydroxy-1 : 2 : 4-thiadiazoles.

Some properties of the new thiadiazoles are described.

COMPOUNDS incorporating the ·C(:NH)·NH·C(:S)· grouping in their structure, including *N*-arylimidoarylthioamides,[1] amidinothioureas,[2] and thioaroylguanidines[3] are cyclised to substituted 1 : 2 : 4-thiadiazoles by a number of oxidising agents. In conformity with this generalisation, 1-substituted 2-thiobiurets are now shown[4] to be convertible into *O*-substituted 5-aryl(or alkyl)amino-3-hydroxy-1 : 2 : 4-thiadiazoles. Goerdeler and Bechlars[5] recently obtained related 3-aryloxy(or -alkoxy)-5-amino-1 : 2 : 4-thiadiazoles from *N*-halogenated *iso*ureas and thiocyanate ions. This synthesis, and the cyclisation of thiobiurets and cyanothioureas outlined in the present paper, provide independent preparative routes.

Biurets required as starting materials were produced by modification of existing methods.[6] Bruce's synthesis[7] of *O*-methyl-1-phenyl-2-thio*iso*biuret (I; R = Ph, Alk = Me) from phenyl *iso*thiocyanate and the *iso*urea was improved by the use of aqueous acetone as medium, in which the reaction proceeded smoothly, and furnished up to 85% yields of the methyl- or ethyl homologues. Contrary to Bruce's observation, such *iso*biurets did not decompose at their melting points or on storage at 0°. Anhydrous conditions were required for production of the 1-alkyl analogues: to the suspension obtained on addition of sodium to acetone,[8] the *iso*urea hydrochloride and methyl *iso*thiocyanate were added successively; the *O*-alkyl-1-methyl-2-thio*iso*biurets (I; R = Me, Alk = Me or Et) were isolated in good yield as the hydrochlorides. These salts could not be satisfactorily

* Part V, *J.*, 1957, 2999.

[1] Ishikawa, *Sci. Papers Inst. Phys. Chem. Res.* (*Tokyo*), 1928, **7**, 237.
[2] Kurzer, *J.*, (*a*) 1955, 1; (*b*) 1955, 2288; (*c*) 1956, 2345; (*d*) 1956, 4524; (*e*) 1957, 2999.
[3] Goerdeler and Fincke, *Chem. Ber.*, 1956, **89**, 1033.
[4] For a preliminary announcement see *Chem. and Ind.*, 1956, 1482.
[5] Goerdeler and Bechlars, *Chem. Ber.*, 1955, **88**, 843.
[6] Kurzer, *Chem. Rev.*, 1956, **56**, 95.
[7] Bruce, *J. Amer. Chem. Soc.*, 1904, **26**, 449.
[8] Slotta, Tschesche, and Dressler, *Ber.*, 1930, **63**, 208.

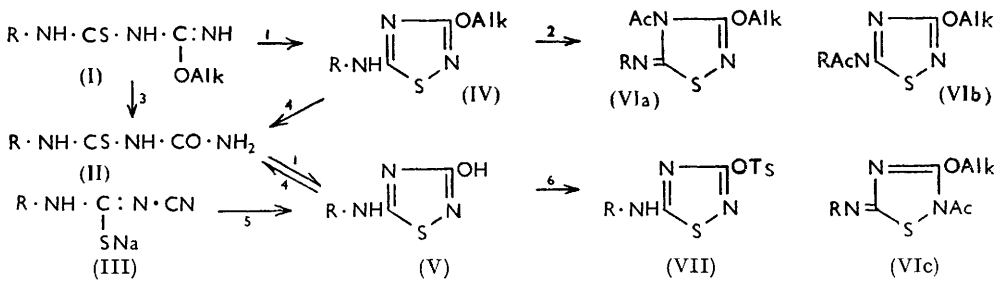
crystallised, since partial dealkylation occurred in boiling solvents under the influence of the mineral acid present. Analytically pure specimens were obtained, however, when the hydrochlorides were slowly reprecipitated from their warm solutions in methanol or chloroform by ether. Purification of the corresponding picrates required similar care. The free base was isolated and purified in the case of the ethyl homologue (I; R = Me; Alk = Et); the low m. p. of the methyl*iso*biuret precluded its isolation in the crystalline state.

It has been stated [7] that hydrogen chloride at 75—90° dealkylates *O*-methyl-1-phenyl-2-thio*iso*biuret to 1-phenyl-2-thiobiuret (II; R = Ph), m. p. 171°. We have been unable to confirm this, but have carried out this reaction in boiling aqueous-ethanolic hydrochloric acid. The m. p. (159—161°) of 1-phenyl-2-thiobiuret thus obtained agrees with that given by Birckenbach and Kraus [9] (161°) for this compound synthesised unequivocally from aniline and carbamoyl *iso*thiocyanate. 1-Methyl-2-thiobiuret was similarly prepared from the *O*-methyl- or *O*-ethyl-*iso*biuret in satisfactory yields.

Oxidation of *O*-alkyl-1-aryl(or alkyl)-2-thio*iso*biurets (I; R = Ph or Me, Alk = Me or Et) gave products which are formulated as 3-alkoxy-5-aryl(or alkyl)amino-1 : 2 : 4-thiadiazoles (IV) on the basis of their mode of formation and their chemical properties (see below). 1-Substituted 2-thiobiurets (II; R = Ph or Me) similarly afforded 5-aryl(or alkyl)amino-3-hydroxy-1 : 2 : 4-thiadiazoles (V). As in the analogous oxidative cyclisation of amidinothioureas,[2] the reaction went to completion almost at once with the calculated quantity of bromine, even at low temperatures. An excess of the oxidising agent had to be avoided, particularly in the aromatic series (I, II; R = Ph), to prevent the formation of non-homogeneous halogenated products. 1-Aryl- and 1-alkyl-substituted thiobiurets (I and II; R = Ph or Me, Alk = H, Me or Et) were cyclised with equal facility: in the latter series, biuret hydrochlorides were employed and were oxidised in aqueous solution.

Alternatively, cyclisations were carried out by means of an excess of hydrogen peroxide, as on previous occasions,[2] in the presence of mineral acid. 1-Phenyl-2-thiobiuret appeared to decompose under these conditions, but was cyclised in alkaline medium. Both methods of oxidation are notable for their speed, the absence of side-reactions, and the high yields of the heterocyclic compounds.

By taking advantage of the well-known conversion of the cyano- into the carbamoyl group under the influence of alkaline hydrogen peroxide,[10] *N*-aryl-*N'*-cyano*iso*thioureas (III; R = Ph or *p*-Me·C_6H_4) in the form of their sodio-derivatives were directly oxidised to 5-arylamino-3-hydroxy-1 : 2 : 4-thiadiazoles (V) in one operation. Although 1-aryl-2-thiobiurets were undoubtedly formed as intermediates, being independently shown to be



Reagents: 1, H_2O or Br_2; 2, Ac_2O or AcCl; 3, HCl; 4, Zn–HCl; 5, H_2O_2–NaOH; 6, *p*-$C_6H_4Me{\cdot}SO_2Cl$–C_5H_5N.

cyclised (to V) under the same conditions, it was not possible to terminate the reaction at this stage (II): the thiadiazole (V; R = Ph) was the only identifiable main product when as little as one molar proportion of hydrogen peroxide was used. Indeed, yields (of V) were not improved by the use of more oxidising agent.

[9] Birckenbach and Kraus, *Ber.*, 1938, **71**, 1492.
[10] Noller, *Org. Synth.*, Coll. Vol. II, p. 586.

The chemical properties of the new thiadiazoles agree with their assigned structures. 5-Anilino-3-hydroxy-1 : 2 : 4-thiadiazole dissolved in dilute alkalis with formation of a sodio-derivative; it was reprecipitated by dilute acids, but was appreciably soluble in more concentrated mineral acids (*e.g.*, 3N-hydrochloric acid), owing to the basic character of the heterocyclic nucleus. The products are phenolic rather than ketonic as they do not give carbonyl derivatives but give purple colours with neutral ferric chloride solution. As with all substituted 3 : 5-diamino-1 : 2 : 4-thiadiazoles so far examined,[2a,b,c,e] reduction by zinc and hydrochloric acid opened the nucleus at the S–N link, reconverting 5-anilino-3-hydroxy-1 : 2 : 4-thiadiazole into 1-phenyl-2-thiobiuret in good yield. The 3-alkoxy-compounds of this series did not give colour reactions with ferric chloride and were insoluble in dilute alkalis and acids. 5-Anilino-3-methoxy-1 : 2 : 4-thiadiazole (but not the 3-ethoxy-homologue) was unexpectedly soluble in hot 3N-sodium hydroxide, from which it was deposited almost quantitatively on cooling; in this respect it resembled 3-amino-5-anilino-1 : 2 : 4-thiadiazole.[2c] Unlike their parent thiobiurets, which were quickly desulphurised by alkaline sodium plumbite, 3-hydroxythiadiazole derivatives resisted the action of this reagent, even in an excess of boiling alkali.

A monoacetyl and a monobenzoyl derivative were obtained from 5-anilino-3-methoxy-1 : 2 : 4-thiadiazole, but no toluene-*p*-sulphonyl derivative could be prepared. Since the site of substitution of acyl groups is most conveniently determined by the reductive hydrolysis of the sulphonyl derivative,[2b,e] the structures of the monoacyl derivatives remain doubtful, formulæ (VIa—c) being possible. 5-Anilino-3-hydroxy-1 : 2 : 4-thiadiazole similarly afforded a diacetyl and dibenzoyl derivative, neither of which gave a colour reaction with ferric chloride: one of the acyl groups has attacked the reactive hydroxyl group, the other occupying one of the possible positions suggested by structures (VIa—c). A monosulphonyl derivative obtained from (V; R = Ph) and an equivalent of toluene-*p*-sulphonyl chloride in pyridine is, for the same reason, formulated as the 3-acyloxy-compound (VII; R = Ph). Goerdeler and Bechlars's 5-amino-3-aralkoxy-1 : 2 : 4-thiadiazoles [5] also yielded monoacetyl derivatives under the same conditions and were designated 5-acetamido-compounds.

Experimental

Light petroleum had b. p. 60—80°.

In the preparation of picrates, aqueous picric acid saturated at 30° (containing 0·06 mole of the reactant per l.) was employed,[11] unless otherwise stated.

O-Ethyl-1-methyl-2-thio*iso*biuret, and 3-methoxy(or ethoxy)-5-methylamino-1 : 2 : 4-thiadiazole, crystallised from benzene, gave high carbon values. One further crystallisation of such specimens from ethanol, though not changing the m. p., gave products of satisfactory composition. Benzene appears to be occluded in crystals of these compounds, but does not form solvates.

All the thiobiurets rapidly gave a precipitate of lead sulphide when heated with sodium plumbite (3N-sodium hydroxide containing a few drops of 10% aqueous lead acetate), but 3-hydroxy-1 : 2 : 4-thiadiazole derivatives resisted this reagent during 2 minutes' boiling.

O-*Methyl*-1-*phenyl*-2-*thio*iso*biuret*.—To a solution of potassium hydroxide (85%) (13·2 g., 0·2 mole) in water (50 ml.) were added successively *O*-methyl*iso*urea hydrochloride [12] (22·1 g., 0·2 mole) and acetone (100 ml.). The resulting suspension was treated with phenyl *iso*thiocyanate (20·25 g., 0·15 mole), and the rapidly stirred liquid refluxed during 30 min. The acetone was then quickly distilled off under reduced pressure, and the residual two-phase system stirred into ice (300 g.). The collected pale-yellow granular solid was once crystallised from benzene–light petroleum (150 and 20 ml.), and then from benzene. The product formed prisms, m. p. 129—131° (22·2—26·6 g., 71—85%).

O-*Ethyl* 1-*phenyl*-2-*thio*iso*biuret*.—Condensation of phenyl *iso*thiocyanate (0·15 mole) and *O*-ethyl*iso*urea hydrochloride (0·225 mole) by the above procedure gave a crystalline *product*,

[11] Dolinski, *Ber.*, 1905, **38**, 1836.
[12] Kurzer and Lawson, *Org. Synth.*, 1954, **34**, 67.

which afforded, after crystallisation from benzene, prisms (23·4—26·7 g.), m. p. 98—99° (Found: C, 53·7; H, 6·1; N, 18·7; S, 14·8. $C_{10}H_{13}ON_3S$ requires C, 53·8; H, 5·8; N, 18·8; S, 14·35%).

1-*Phenyl*-2-*thiobiuret*.—A solution of *O*-methyl-1-phenyl-2-thio*iso*biuret (15·7 g.) in hot ethanol (150 ml.) was treated with concentrated hydrochloric acid (30 ml.) and refluxed until the evolution of methyl chloride was complete (8—12 min.). The solution was stirred into water (1·2 l.), and the separated product collected after storage at 0° for 24 hr. Crystallisation from ethanol–light petroleum (6 and 3 ml. per g.) gave prismatic needles (5·85—6·6 g.) of 1-phenyl-2-thiobiuret, m. p. 159—161° (Found: C, 49·7; H, 4·8. Calc. for $C_8H_9ON_3S$: C, 49·2; H, 4·6%). Partial evaporation of the mother-liquors gave low-melting fractions, from which further small quantities (5—10%) of 1-phenyl-2-thiobiuret were isolated by continued crystallisation.

Use of 2N-ethanolic hydrogen chloride under identical conditions gave similar yields (50—60%), but gave rise to a nauseating and most persistent odour. Hydrolysis of *O*-ethyl-1-phenyl-2-thio*iso*biuret similarly afforded 1-phenyl-2-thiobiuret, m. p. and mixed m. p. 158—160°, albeit in lower yields (28%) (Found: C, 49·5; H, 4·6%).

1-*Phenyl*-2-*thiobiuret picrate* was slowly deposited (65%) when hot saturated ethanolic solutions of equimolecular quantities of the thiobiuret and picric acid were mixed. It formed yellow leaflets, m. p. 129—131° (from ethanol) (Found: C, 39·0; H, 2·6. $C_8H_9ON_3S,C_6H_3O_7N_3$ requires C, 39·6; H, 2·8%).

5-*Anilino*-3-*methoxy*-1 : 2 : 4-*thiadiazole*.—(*a*) A solution of *O*-methyl-1-phenyl-2-thio*iso*biuret (6·30 g., 0·03 mole) in hot ethanol (75 ml.) was allowed to cool to 35—40°, and rapidly treated, with cooling, with ice-cold freshly prepared M-ethanolic bromine (30 ml.). The solution was decolorised instantly, and crystals separated towards the end of the oxidation. Addition of the mixture to ice-water (750 ml.) converted the suspended solid into a granular precipitate, which was collected, washed with water (m. p. 156—158°; 4·65—5·30 g., 75—85%), and crystallised from acetone–ethanol (10 and 3 ml. per g.) as prismatic needles of 5-*anilino*-3-*methoxy*-1 : 2 : 4-*thiadiazole*, m. p. 158—159° [Found: C, 52·35; H, 4·1; N, 20·2; S, 15·2%; *M* (cryoscopically in thymol), 195. $C_9H_9ON_3S$ requires C, 52·2; H, 4·35; N, 20·3; S, 15·5%; *M*, 207]. The product, though very sparingly soluble in boiling water (approx. 1 g. per l.), was appreciably soluble in hot 3N-aqueous sodium hydroxide and was deposited therefrom unchanged almost quantitatively on cooling.

(*b*) A boiling solution of *O*-methyl-1-phenyl-2-thio*iso*biuret (2·10 g., 0·01 mole) in ethanol (25 ml.) was treated with a mixture of concentrated hydrochloric acid (1 ml., 0·01 mole) and 6% hydrogen peroxide (5·7 ml., 0·01 mole), followed, at three-minute intervals, by two further equivalents of the oxidant. The pink turbid liquid was stirred into ice-water (150 ml.), and the precipitated solid collected after 12 hours' storage at 0°, and crystallised as above, affording 5-anilino-3-methoxy-1 : 2 : 4-thiadiazole (1·5 g., 72%), m. p. and mixed m. p. 158—160° (Found: C, 52·6; H, 4·3; N, 20·6; S, 15·8%). In the absence of mineral acid, the same product was obtained in improved yields (85—90%).

A solution of this thiadiazole (1·03 g., 0·005 mole) in acetic anhydride (10 ml.) was refluxed during 0·5 hr., then stirred into ice-water. The white precipitate, crystallised from acetone–ethanol, consisted of platelets (1·0 g., 80%) of the *monoacetyl derivative*, m. p. 209—210° (Found: C, 52·6; H, 4·4; N, 16·3. $C_{11}H_{11}O_2N_3S$ requires C, 53·0; H, 4·4; N, 16·9%). Interaction of the thiadiazole (0·005 mole) with benzoyl chloride (1·40 g., 0·01 mole) in pyridine (10 ml.) at 100° during 20 min., followed by addition to ice–hydrochloric acid, gave a crude product which was extracted with hot water (removal of benzoic acid) and crystallised from acetone–ethanol. The resulting *monobenzoyl derivative* formed needles, m. p. 180—181° (1·27 g., 82%) (Found: C, 61·4; H, 4·2; S, 9·7. $C_{16}H_{13}O_2N_3S$ requires C, 61·7; H, 4·2; S, 10·3%).

The reactant, after treatment with toluene-*p*-sulphonyl chloride (1 or 2 mols.) in pyridine at 95—100° during 5 min., was mostly recovered unchanged. The use of 2 or 4 mols. of sulphonyl chloride during 1 hr. gave intractable oils or granular products, while intermediate conditions gave mixtures of starting material and uncrystallisable oils. Hinsberg and Kessler's [13] procedure also failed to yield a sulphonyl derivative.

5-*Anilino*-3-*ethoxy*-1 : 2 : 4-*thiadiazole*, obtained (*a*) in 75—80% yield by cyclising *O*-ethyl-1-phenyl-2-thio*iso*biuret with bromine, crystallised from ethanol (20 ml. per g.) as needles, m. p. 167—168° [Found: C, 53·9; H, 5·05; N, 18·5; S, 14·2%; *M* (cryoscopically in thymol), 230. $C_{10}H_{11}ON_3S$ requires C, 54·3; H, 5·0; N, 19·0; S, 14·5%; *M*, 221] or (*b*) by oxidation of

[13] Hinsberg and Kessler, *Ber.*, 1905, **38**, 906.

the *O*-ethyl*iso*biuret by hydrogen peroxide in the presence of mineral acid, similarly afforded 80% yields of the same 1 : 2 : 4-thiadiazole, m. p. and mixed m. p. 166—168° (Found: C, 54·8; H, 4·9%). Neither this compound nor the 3-methoxy-analogue (IV; R = Ph, Alk = Me) gave a colour with neutral ferric chloride solution.

5-*Anilino*-3-*hydroxy*-1 : 2 : 4-*thiadiazole.*—*From* 1-*phenyl*-2-*thiobiuret.* (*a*) A stirred solution of 1-phenyl-2-thiobiuret (5·85 g., 0·03 mole) in ethanol (45 ml.) at 35—40° was treated (with external cooling) during 1 min., with 1M-bromine in chloroform (30 ml.), which was decolorised instantly. The liquid was added to water (300 ml.), and the aqueous phase (containing a little suspended solid) decanted from the separated chloroform layer, from which the solvent was then evaporated rapidly at room temperature. The residual white product was recombined with the aqueous suspension, and the solid collected. It crystallised from acetone–ethanol, and then ethanol alone (100 ml. per g.), giving prisms of 5-*anilino*-3-*hydroxy*-1 : 2 : 4-*thiadiazole*, m. p. 210—212° (decomp., somewhat subject to the rate of heating) (yield, including material from the mother-liquors, 3·5—4·35 g., 60—75%) [Found: C, 50·0 49·8; H, 3·5, 3·7; N, 21·9, 21·6; S, 16·7, 16·4%; *M* (cryoscopically in thymol), 200, 180. $C_8H_7ON_3S$ requires C, 49·7; H, 3·6; N, 21·8; S, 16·6%; *M*, 193].

The thiadiazole was sparingly soluble in boiling water, and crystallised in needles therefrom. It dissolved freely in warm N-sodium hydroxide and was reprecipitated by the addition of dilute acid, but was also soluble in more concentrated (*e.g.*, 3N-hydrochloric) acid. Warm solutions of the thiadiazole (0·001 mole) in 3N-sodium hydroxide (5 ml.) deposited, on cooling, almost quantitatively the sodium derivative, as prisms (from a little boiling water), m. p. 208—210° (decomp.).

The product did not yield a 2 : 4-dinitrophenylhydrazone on treatment with Brady's reagent, or an oxime on treatment with hydroxylamine, under the usual conditions. It gave a violet-purple colour with ferric chloride in methanolic, but not in aqueous, solution.

(*b*) A solution of 1-phenyl-2-thiobiuret (1·95 g., 0·01 mole) in water (20 ml.) containing sodium hydroxide (0·80 g., 0·02 mole) was treated with 6% hydrogen peroxide (8·5 ml., 0·015 mole). The liquid, the temperature of which rose spontaneously, was kept at 50° during 5 min., then cooled, and the separated solid collected at 0° (filtrate A). Its solution in hot water (75 ml.) was acidified with dilute acetic or hydrochloric acid, and the precipitated solid (m. p. 207—208°; 1·45 g., 75%) crystallised as above, the thiadiazole, m. p. and mixed m. p. 210—212°, being obtained (Found: C, 50·2; H, 3·3%). Filtrate A gave a further 5—10% of the same product on acidification.

From N-*cyano*-N′-*phenylthiourea.* (i) Sodium *N*-cyano-*N*′-phenyl*iso*thiourea [14] (1·99 g., 0·01 mole), nearly dissolved in a mixture of ethanol (5 ml.) and aqueous sodium hydroxide (3N; 3·3 ml., 0·01 mole), was treated, with stirring, between 45 and 50°, dropwise with 6% hydrogen peroxide (20 ml., 0·035 mole). The resulting suspension was kept at 50° during another 15 min., then diluted with ethanol (5 ml.) and cooled, and the sodium salt was collected at 0° (filtrate A). Treatment as described under (*b*) afforded the thiadiazole (m. p. and mixed m. p. 210—212°; 0·81 g., 42%). Filtrate A did not afford more product on acidification, with or without previous partial evaporation in a vacuum.

In the absence of ethanol, or of the extra equivalent of alkali, or at 30—35°, the yield fell to 20—30%. Above 50°, the temperature was difficult to control and complete decomposition occurred, with formation of intractable gums. The intermediate 1-phenyl-2-thiobiuret could not be isolated by the use of only 1 equivalent of the oxidising agent: the thiadiazole was again obtained (in 38% yield).

(ii) A solution of cyanamide (4·2 g., 0·1 mole) in water (6 ml.) was successively treated with 10N-sodium hydroxide (10 ml., 0·1 mole) and phenyl *iso*thiocyanate (6·75 g., 0·05 mole). Ethanol (10 ml.) was added, until the system consisted of a single phase, which was next heated on the steam-bath during 18 min. The resulting yellow liquid, diluted with water (40 ml.) and cooled, was treated at 30—40° with 6% hydrogen peroxide (0·075 mole) during 5—10 min., and kept at 45° during 15 min. The separated sodium salt, collected at 0°, was converted into 5-anilino-3-hydroxy-1 : 2 : 4-thiadiazole (5·40 g., 56%), m. p. and mixed m. p. 210—212° (decomp.), as described above. The identity of this 1 : 2 : 4-thiadiazole with specimens obtained by methods (*a*) and (*b*) was confirmed by a comparison of their dibenzoyl derivative, m. p. and mixed m. p. 180—184°.

Derivatives. 5-Anilino-3-hydroxy-1 : 2 : 4-thiadiazole (0·965 g., 0·005 mole), heated in pyridine (10 ml.) with toluene-*p*-sulphonyl chloride (1·14 g., 0·006 mole) at 100° during 20 min.

[14] Fromm and Wenzl, *Ber.*, 1922, **55**, 805.

and stirred into ice–hydrochloric acid, gave a flocculent precipitate. After three crystallisations from benzene, it consisted of prisms of 5-*anilino*-3-*toluene*-p-*sulphonyloxy*-1 : 2 : 4-*thiadiazole*, m. p. 160—162° (0·52 g., 30%) (Found: C, 51·6; H, 3·3; N, 12·1; S, 17·9. $C_{15}H_{13}O_3N_3S_2$ requires C, 51·9; H, 3·75; N, 12·1; S, 18·4%). The thiadiazole gave (on treatment as described for the 5-methoxy-analogue, see above) needles (from acetone–ethanol) of a *diacetyl derivative*, m. p. 253—255° (somewhat subject to the rate of heating) (72%) (Found: C, 51·9; H, 3·4; N, 15·5; S, 11·7. $C_{12}H_{11}O_3N_3S$ requires C, 52·0; H, 4·0; N, 15·2; S, 11·55%). Analogously, there was prepared the *dibenzoyl derivative*, forming prisms (from benzene), m. p. 182—184° (somewhat subject to the rate of heating) (50%) (Found: C, 66·1; H, 3·4; N, 10·55; S, 7·95. $C_{22}H_{15}O_3N_3S$ requires C, 65·8; H, 3·7; N, 10·5; S, 8·0%). None of the derivatives gave a colour reaction with neutral ferric chloride solution.

Reduction. (*a*) A refluxing suspension of 5-anilino-3-hydroxy-1 : 2 : 4-thiadiazole (3·86 g., 0·02 mole) and zinc turnings (6 g.) in ethanol (60 ml.) was treated dropwise with concentrated hydrochloric acid (5 ml.) during 8 min., and refluxing continued for another 4 min. The solution was decanted, the residual zinc extracted with more boiling ethanol (4 × 5 ml.), and the whole liquid reduced to a third of its bulk in a vacuum, then stirred into ice–water (100 ml.). The collected solid (filtrate F), on crystallisation from ethanol, consisted of 1-phenyl-2-thiobiuret (2·65 g., 68%), m. p. and mixed m. p. 157—159°. Filtrate F did not contain aniline. (*b*) 5-Anilino-3-methoxy-1 : 2 : 4-thiadiazole (0·02 mole), when similarly reduced, during 6 min., gave a crude product (2·5 g.), which yielded, on fractional crystallisation from ethanol and benzene–acetone, small quantities of 1-phenyl-2-thiobiuret (0·90 g., 23%), m. p. and mixed m. p. 158—159°. The aqueous filtrates (corresponding to F, as immediately above) contained aniline, which was isolated from the basified solution by ether-extraction and identified as the benzoyl derivative (15%).

3-*Hydroxy*-5-p-*tolylamino*-1 : 2 : 4-*thiadiazole*.—An experiment with *p*-tolyl *iso*thiocyanate (7·45 g., 0·05 mole) according to procedure (ii, above) gave the sodium salt, which was collected at 0°. Dissolution in hot water (150 ml.) (addition of a little alkali), filtration, and acidification with concentrated hydrochloric acid (to Congo-red; ice-cooling) gave a precipitate (m. p. 203—208°; 4·95 g., 48%). This afforded, from 1 : 1 acetone–ethanol, prisms of 3-*hydroxy*-5-p-*tolylamino*-1 : 2 : 4-*thiadiazole*, m. p. 212—214° (decomp., somewhat subject to the rate of heating) (Found: C, 52·5; H, 4·1; N, 20·0; S, 15·2. $C_9H_9ON_3S$ requires C, 52·2; H, 4·35; N, 20·3; S, 15·5%).

1 : O-*Dimethyl*-2-*thio*iso*biuret*.—Sodium (3·22 g., 0·14 g.-atom) was added to cooled anhydrous acetone (125 ml.) during 8—12 min. The resulting orange-red suspension was treated, at 35—40°, with powdered methyl*iso*urea hydrochloride (14·4 g., 0·13 mole) followed by methyl *iso*thiocyanate (8·0 g., 0·11 mole, dissolved in 10 ml. of acetone). The stirred suspension was heated to boiling during 5 min., and refluxed until smelling no longer of *iso*thiocyanate (30—45 min.). The bulk of the acetone was removed under reduced pressure, the residual thick suspension diluted with water (75 ml.), and the resulting two-phase system separated. The aqueous layer was extracted with ether (2 × 30 ml.), and the extracts were added to the orange (upper) layer, which was diluted with more ether (100—150 ml.), washed with warm water (3 × 10 ml.), and dried (Na_2SO_4; 24 hr.). To the filtered orange solution, 3·5N-ethanolic hydrochloric acid (28 ml., 0·1 mole) was slowly added, and the precipitate collected after several hours' storage at 0° (on a large Buchner funnel) and washed with ether. The white microcrystalline product, dried in a vacuum, was 1 : O-*dimethyl*-2-*thio*iso*biuret hydrochloride*, m. p. 154—156° (after sintering at 145—150°) (13·1—14·5 g., 65—72%). Reprecipitation of the product by ether from its warm methanolic solution did not improve the m. p., but gave a nearly pure specimen (Found: C, 26·9; H, 5·4; Cl, 19·0. $C_4H_9ON_3S,HCl$ requires C, 26·2; H, 5·45; Cl, 19·3%). The hydrochloride was soluble in boiling methanol and ethanol but, owing to partial dealkylation, did not crystallise satisfactorily therefrom. The product gave a black precipitate with sodium plumbite.

The base, liberated by caustic alkali, was low-melting and was not obtained crystalline.

Treatment of the hydrochloride (0·37 g., 0·002 mole) in water (3 ml.) with picric acid (0·002 mole) precipitated the *picrate* (85%) which consisted, after *rapid* crystallisation from ethanol (15 ml. per g., containing a few drops of water), of yellow needles, m. p. 154—156° (decomp., after sintering at 136°) (Found: C, 32·3; H, 3·1; N, 22·6; S, 8·2. $C_4H_9ON_3S,C_6H_3O_7N_3$ requires C, 31·9; H, 3·2; N, 22·3; S, 8·5%).

O-*Ethyl*-1-*methyl*-2-*thio*iso*biuret*.—Interaction of sodium, ethyl*iso*urea hydrochloride, and

methyl *iso*thiocyanate (as described for the methyl *iso*-homologue, except for the time of refluxing, which was 15 min.) afforded, by the same technique, the crude hydrochloride, m. p. 99—101° (decomp.) (60—70%). Crystallisation, by dissolution in warm chloroform (10 ml. per g.) and dilution with a little ether, gave white *O-ethyl-1-methyl-2-thioisobiuret hydrochloride*, m. p. 105—106° (decomp.) (Found: C, 30·3; H, 6·3; N, 21·5; Cl, 17·9. $C_5H_{11}ON_3S,HCl$ requires C, 30·4; H, 6·1; N, 21·3; Cl, 18·0%).

The hydrochloride was converted almost quantitatively into the *picrate*, which formed yellow prisms, m. p. 125—126° (decomp.) (from ethanol) (Found: C, 33·4; H, 3·4. $C_5H_{11}ON_3S,C_6H_3O_7N_3$ requires C, 33·8; H, 3·6%).

The crude hydrochloride obtained in an experiment starting with 0·11 mole of methyl *iso*thiocyanate was treated in water (30 ml.) with 3N-sodium hydroxide (20 ml.). The precipitated oil solidified presently, was collected, washed with a little water, air-dried, and crystallised successively from benzene (5 ml. per g.) and aqueous ethanol. The resulting *O-ethyl-1-methyl-2-thioisobiuret* formed large prisms (from benzene) or platelets (from aqueous ethanol), m. p. 90—91° (yield, including material from filtrates, 62%) (Found: C, 37·6; H, 6·8; S, 20·2. $C_5H_{11}ON_3S$ requires C, 37·3; H, 6·8; S, 19·9%).

1-Methyl-2-thiobiuret.—1 : *O*-Dimethyl-2-thio*iso*biuret hydrochloride (5·5 g.) rapidly dissolved in methanol (60 ml.) and concentrated hydrochloric acid (12 ml.) on boiling, which was continued until evolution of methyl chloride ceased (12—15 min.). The liquid was evaporated in a vacuum at the lowest possible temperature, in two stages to small bulk (approx. 20 and 5 ml., respectively), and the separated crude product each time collected at 0° (total, 3—3·5 g.). One crystallisation from boiling water (4—6 ml. per g.) gave a white crystalline powder of *1-methyl-2-thiobiuret*, m. p. 172—174° (decomp., after sintering slightly about 160°) (1·8—2·1 g., 45—52%), which consisted, after two further crystallisations from water, of needles, m. p. 174—175° (decomp.) (Found: C, 26·9; H, 5·25; N, 31·1. $C_3H_7ON_3S$ requires C, 27·1; H, 5·3; N, 31·6%). 1-Methyl-2-thiobiuret is highly soluble in methanol and ethanol, and sparingly so in benzene and light petroleum. It gives a white precipitate with silver nitrate in the presence of nitric acid, and an immediate black precipitate of lead sulphide with sodium plumbite and excess of alkali. It crystallises unchanged from boiling 3N-hydrochloric acid.

Hydrolysis of *O*-ethyl-1-methyl-2-thio*iso*biuret (in ethanol, duration 18—20 min.) similarly gave 1-methyl-2-thiobiuret, m. p. 172—174° (decomp., after sintering about 165°), in improved yield (68%).

3-Methoxy-5-methylamino-1 : 2 : 4-thiadiazole.—A solution of 1 : *O*-dimethyl-2-thio*iso*biuret hydrochloride (crude, 3·67 g., 0·02 mole) in warm water (10 ml.) was treated with M-bromine (in chloroform, 20 ml.). The colourless two-phase system was separated, and the aqueous layer made alkaline with 3N-sodium hydroxide. The separated solid was collected at 0° (m. p. 118—121°; 1·6—1·8 g., 55—62%) and crystallised successively from benzene (5 ml. per g.) and methanol, affording needles of *3-methoxy-5-methylamino-1 : 2 : 4-thiadiazole*, m. p. 120—121° (Found: C, 33·55; H, 4·9; N, 29·2, 28·7; S, 22·1. $C_4H_7ON_3S$ requires C, 33·1; H, 4·8; N, 29·0; S, 22·1%). Evaporation of the chloroform layer, followed by reprecipitation of the residue from its solution in dilute hydrochloric acid by alkali gave another 3—6% of the crude thiadiazole.

Addition of picric acid (0·0025 mole) to the thiadiazole (0·36 g., 0·0025 mole) in warm water (15 ml.) gave a precipitate (0·66 g., 71%), which consisted, after crystallisation from aqueous ethanol (75%), of yellow prisms of the *picrate*, m. p. 155—157° (Found: C, 32·2; H, 2·7; N, 22·4; S, 8·1. $C_4H_7ON_3S,C_6H_3O_7N_3$ requires C, 32·1; H, 2·7; N, 22·5; S, 8·6%).

3-Ethoxy-5-methylamino-1 : 2 : 4-thiadiazole.—Oxidation of *O*-ethyl-1-methyl-2-thio*iso*biuret hydrochloride (as described for the methyl homologue) gave a product (m. p. 121—123°; yield 35 and 45%, from the aqueous and the chloroform phase, respectively) which, after successive crystallisation from benzene and ethanol, consisted of needles of the *thiadiazole*, m. p. 122—123° (Found: C, 37·8; H, 5·65; N, 26·5. $C_5H_9ON_3S$ requires C, 37·7; H, 5·7; N, 26·4%).

3-Hydroxy-5-methylamino-1 : 2 : 4-thiadiazole.—1-Methyl-2-thiobiuret (1·0 g., 0·0075 mole) in methanol (20 ml.) was treated with M-bromine in chloroform (7·5 ml.) below 30°, the white crystalline precipitate collected after 3 hours' storage at 0°, and the filtrate evaporated at room-temperature in a vacuum to recover further small quantities of product. The combined solids were dissolved in 3N-sodium hydroxide (4 ml.) and slowly reprecipitated with 3N-hydrochloric acid (until just acid to litmus). The collected *product* (0·37 g., 38%), when crystallised from ethanol, consisted of off-white opaque granules, m. p. (decomp.) dependent on the rate of

heating * (Found: C, 27·7; H, 4·0; N, 32·5; S, 24·9. $C_3H_5ON_3S$ requires C, 27·5; H, 3·8; N, 32·1; S, 24·4%). Solutions of the compound in methanol gave a purple colour with ferric chloride solution. The following derivatives were obtained by the usual methods: the *picrate* (85%) formed yellow clusters of needles, m. p. 168—169° (decomp.), from 1 : 1 aqueous ethanol (Found: C, 30·3; H, 2·3. $C_3H_5ON_3S,C_6H_3O_7N_3$ requires C, 30·0; H, 2·2%). The *dibenzoyl derivative* (54%) consisted of needles (from acetone–ethanol), m. p. 203—204° (decomp.; somewhat subject to the rate of heating) (Found: C, 60·1; H, 3·7. $C_{17}H_{13}O_3N_3S$ requires C, 60·2; H, 3·8%).

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* When heated from room temperature, samples of the thiadiazole began sintering at 180° and continued to decompose slowly though incompletely up to 280°; when inserted into the bath at 240°, specimens decomposed instantly; at 220° and 200° they did so after a time lag.