572. *Thiadiazoles. Part VIII.* 3-Alkyl(or aryl)-5-alkyl(or aryl)-amino-1,2,4-thiadiazoles.*

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N'-Substituted *N*-acetimidoyl- and *N*-benzimidoyl-thioureas are cyclised by oxidising agents to 3-alkyl(or aryl)-5-alkyl(or aryl)amino-1,2,4-thiadiazoles, some properties of which are described.

As part of an extension of the general synthesis [1,2] of 1,2,4-thiadiazoles by the cyclisation of compounds incorporating the amidinothiono-function, ·C(:NH)·NH·CS·, the oxidation of *N'*-substituted *N*-acimidoylthioureas has been examined. The reaction provides a useful route to the thiadiazole derivatives named in the title of this paper.

N'-Substituted *N*-benzimidoyl thioureas (I; R' = Ph) were readily synthesised from benzamidine and isothiocyanates in 70—80% yield by Pinner's method.[3] *N*-Acetimidoyl homologues (I; R' = Me) were obtained by the same procedure, though in greatly reduced yields (30—40%): the free bases were highly soluble in the aqueous ethanol used as reaction medium, but they were conveniently isolated as toluene-*p*-sulphonates. Attempts to improve yields by varying the conditions were not successful: in pyridine–triethylamine, acetamidine and phenyl isothiocyanate failed to react, *sym*-diphenylthiourea being the main product. The use of sodium alkoxides in acetone, a procedure that is particularly effective in the preparation of substituted amidinothioureas,[4-7] gave mainly *N*-acetyl-*N'*-phenylthiourea, by the hydrolytic conversion of the acetimidoyl- into the acetyl group, either before or after condensation of the base with the isothiocyanate. The well-known tendency of compounds of type (I) to undergo this change [8] is illustrated by the hydrolysis of *NN'*-bisphenylcarbamoylbenzamidine (Ph·NH·CO·N:CPh·NH·CO·NHPh, the condensation product of benzamidine and excess of phenyl isocyanate) to *N*-benzoyl-*N'*-phenylurea when attempts are made to crystallise it from acetic acid.[3]

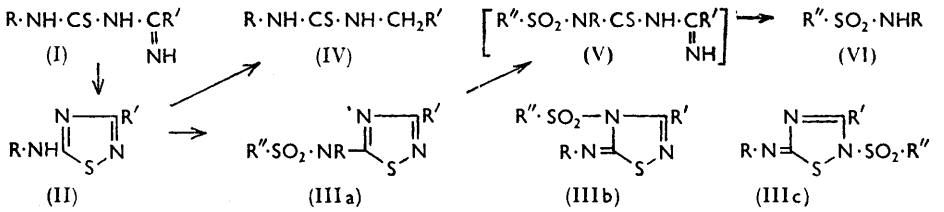
N'-Substituted *N*-acimidoylthioureas (I), or their toluene-*p*-sulphonates, were rapidly cyclised by hydrogen peroxide or bromine under the usual conditions,[2,6,9] affording the corresponding 1,2,4-thiadiazoles (II) in excellent yields. The products were isolated directly, or, when their solubility made it desirable, as the toluene-*p*-sulphonates, from which the base was subsequently liberated. The highly soluble low-melting 5-*n*-butylamino-3-methyl homologue (II; R = Bu^n, R' = Me) was obtained as the picrate and picrolonate only.

Two representatives of the series of thiadiazoles (II) now described have previously

* Part VII, Kurzer and Taylor, *J.*, 1959, 1064.

[1] Ishikawa, *Sci. Papers Inst. Phys. Chem. Res., Tokyo*, 1928, **7**, 237.
[2] Kurzer, *J.*, 1955, 1, and subsequent papers.
[3] Pinner, *Ber.*, 1889, **22**, 1600, 1609.
[4] Slotta, Tschesche, and Drechsler, *Ber.*, 1930, **63**, 208.
[5] Kurzer, *J.*, 1955, 2288.
[6] Kurzer, *J.*, 1956, 2345.
[7] Kurzer, *J.*, 1957, 2999.
[8] Cf. also Pinner and Klein, *Ber.*, 1878, **11**, 6; Pinner, "Die Imidoäther und Ihre Derivate," Oppenheim, Berlin, 1892, p. 155.
[9] Kurzer and Taylor, *J.*, 1958, 379; *J.*, 1959, 1064.

been prepared by other methods and are identical with specimens obtained by the present synthesis. 5-Anilino-3-phenyl-1,2,4-thiadiazole has been obtained by the condensation of benzamidoformaldoxime and phenyl isothiocyanate in chloroform [10] or ethanol,[11] by the interaction of *N*-benzenesulphenylbenzamidine and phenyl isothiocyanate,[12] and,



from the pre-formed heterocyclic system, by the action of aniline on 5-mercapto-3-phenyl-1,2,4-thiadiazole.[13,14] 5-Methylamino-3-phenyl-1,2,4-thiadiazole results from the action of methylamine on the 5-chloro-analogue,[15] which is in turn accessible from benzamidine and trichloromethanesulphenyl chloride ($Cl_3C{\cdot}SCl$).[16] The synthesis of 3-substituted-5-alkyl(or aryl)amino-1,2,4-thiadiazoles (II) now reported provides compounds of unequivocal structure and appears to possess advantages over previous methods because of its wide applicability, the ready availability of the starting materials, and the consistently good yields.

Like most substituted 3,5-diamino-[5,6] and 5-amino-3-hydroxy(or mercapto)-1,2,4-thiadiazoles,[9] 5-phenyl homologues were unaffected by boiling aqueous alkali in the presence of sodium plumbite, but members of the 3-methyl series were gradually desulphurised by this reagent. Acimidoylthioureas (I) were, of course, decomposed almost instantly under these conditions, with deposition of lead sulphide.

5-Anilino-3-phenyl-1,2,4-thiadiazole gave a monoacetyl [10] and a monobenzoyl derivative but failed to react with toluene-*p*-sulphonyl chloride. A monotoluene-*p*-sulphonyl derivative was, however, obtained from 5-anilino-3-methyl-1,2,4-thiadiazole, and gave substantially toluene-*p*-sulphonanilide on reductive hydrolysis, thus establishing structure (IIIa; R = Ph, R′ = Me, R″ = *p*-Me·C_6H_4) for the sulphonyl derivative. The observation that a sulphonyl halide reacts preferentially at the 5-anilino-group in a thiadiazole of type (II) provides the basis for assigning structures (IIIa; R = Me or Ph, R′ = *p*-Me·C_6H_4·SO_2·NH, R″ = *p*-Me·C_6H_4) to the ditosyl derivatives (m. p. 171—173° and 204—205° respectively) of 3-amino-5-methylamino [5] (or anilino [6])-1,2,4-thiadiazole which had previously remained undecided. Further, in the light of this evidence, the disulphonyl derivative [6,7] (m. p. 240—242°) of 3,5-dianilino-1,2,4-thiadiazole may have the 3,5-di-(*N*-toluene-*p*-sulphonanilido)- rather than the structure first [6] suggested, and the site of the substituents in the corresponding trisulphonyl derivatives [5,6] may require reconsideration.

The failure of certain 1,2,4-thiadiazoles (*e.g.*, II; R = Ph, R′ = MeO,[9] MeS,[9] or Ph) to react with sulphonyl chlorides under the usual conditions is not due to steric effects, because of the existence of sulphonyl derivatives of 5-anilino-3-methyl- and 3,5-dianilino-1,2,4-thiadiazole. Since they all yield acetyl and benzoyl derivatives, a consistently parallel behaviour of 1,2,4-thiadiazoles towards acylating agents and sulphonyl halides cannot be assumed, and it is therefore inadmissible to assign structures to acyl derivatives from a knowledge of those of sulphonyl compounds alone. A choice between possible formulations of monoacyl derivatives (analogues of IIIa–c) of thiadiazoles (II) is therefore deferred, as is that of several similar derivatives previously described.[5,6,9]

[10] Koch, *Ber.*, 1891, **24**, 394.
[11] Gheorghiu and Barbos, *Ann. Sci. Univ. Jassy*, 1940, **26**, I, 271.
[12] Goerdeler, Krause-Loevenich, and Wedekind, *Chem. Ber.*, 1957, **90**, 1638.
[13] Crayen, *Ber.*, 1891, **24**, 385.
[14] Barbos, *Ann. Sci. Univ. Jassy*, 1940, **26**, I, 526.
[15] Goerdeler, Huppertz, and Wember, *Chem. Ber.*, 1954, **87**, 68.
[16] Goerdeler, Groschopp, and Sommerlad, *Chem. Ber.*, 1957, **90**, 182.

On treatment with zinc and hydrochloric acid, 5-anilino-3-phenyl-1,2,4-thiadiazole (II; R = R′ = Ph) was slowly converted into *N*-benzyl-*N*′-phenylthiourea (IV; R = R′ = Ph), probably by the usual ring opening at the N–S bond,[2,5,6,7,9] followed by further reductive hydrolysis of the intermediate (I; R = R′ = Ph) to (IV). This interpretation agrees with the observation that *N*-benzimidoyl-*N*′-phenylthiourea also afforded *N*-benzyl-*N*′-phenylthiourea under identical conditions. However, the reduction was much slower and less complete than the smooth and rapid comparable conversion of substituted 3,5-diamino-1,2,4-thiadiazoles into amidinothioureas,[2,6] or of 5-anilino-3-hydroxy-1,2,4-thiadiazole into 1-phenyl-2-thiobiuret,[9] suggesting an enhanced stability of (II; R = R′ = Ph). It also differed from the comparable reduction of 3,5-diphenyl-1,2,4-thiadiazole to *N*-benzylbenzamidine [17,18] in that the amidinothiono-group of the intermediate was reduced at the imino- and not the thiocarbonyl centre, a fact that may be due to its different structural environment in the two compounds. The analogous reduction of the imino-function of a substituted amidine has been observed in the slow and incomplete conversion of *NN*-diethylbenzamidine into benzylamine [19] by lithium aluminium hydride.

Experimental

The pyridine used was the commercially available anhydrous grade. Light petroleum was of boiling range 60—80°. Cellosolve was 2-ethoxyethanol (technical). The solvent used for preparing M-bromine was chloroform. Amalgamated zinc was prepared by heating zinc shavings with 3N-sodium hydroxide until hydrogen was freely evolved, washing the metal with distilled water, treating it with 1% aqueous mercuric chloride at 40°, and rinsing it successively with distilled water and ethanol.

N-*Benzimidoyl*-N′-*phenylthiourea*.—This was prepared by the method outlined by Pinner [3] as follows: To a solution of benzamidine hydrochloride [20] (15·65 g., 0·1 mole) in warm water (20 ml.), cooled to room temperature, phenyl isothiocyanate (13·5 g., 0·1 mole) was added, followed by ethanol (120 ml.), until a one-phase system was obtained. Addition of 3N-sodium hydroxide (33·3 ml., 0·1 mole) gave a clear yellow liquid, the temperature of which rose slightly temporarily. Lustrous yellow prisms separated rapidly, were collected after 12 hours' storage at 0°, and washed with a little cold ethanol [m. p. 122—124° (decomp.); 19·1—20·9 g., 75—82%]. Evaporation of the filtrates in a vacuum to small bulk afforded further small quantities (up to 5%) of the product, but unidentified high-melting (~240—250°) by-products were isolated in some experiments. Two crystallisations from ethanol (8 ml. per g.) gave lustrous pale-yellow prisms of the thiourea, m. p. 124—125° (decomp.) (Found: C, 65·4; H, 4·9. Calc. for $C_{14}H_{13}N_3S$: C, 65·9; H, 5·1%).

N-*Benzimidoyl*-N′-p-*tolylthiourea*.—This was obtained by the same procedure from benzamidine hydrochloride (0·05 mole), water (10 ml.), *p*-tolyl isothiocyanate (7·45 g., 0·05 mole), ethanol (90 ml.), and 3N-sodium hydroxide (0·05 mole) as massive yellow prisms (10·75 g., 80%). Two crystallisations from ethanol (8 ml. per g.) gave pale-yellow prisms of the *thiourea*, m. p. 112—113° (decomp.) (Found: C, 66·1; H, 5·8. $C_{15}H_{15}N_3S$ requires C, 66·9; H, 5·6%).

N-*Benzimidoyl*-N′-*methylthiourea* was similarly obtained from benzamidine hydrochloride (0·05 mole), water (10 ml.), methyl isothiocyanate (3·65 g., 0·05 mole), ethanol (35 ml.), and 3N-sodium hydroxide (0·05 mole), and formed colourless prisms (6·75 g., 70%). Crystallisation from ethanol–light petroleum (6 and 4 ml. respectively per g.) gave lustrous prisms, m. p. 97—99° (decomp.) (Found: C, 56·0; H, 5·5; N, 22·2. $C_9H_{11}N_3S$ requires C, 56·0; H, 5·7; N, 21·8%).

N-*Acetimidoyl*-N′-*phenylthiourea*.—Acetamidine hydrochloride [20] (14·1 g., 0·15 mole) was dissolved in ethanol (100 ml.) with warming; the solution was treated, at room temperature, successively with phenyl isothiocyanate (20·25 g., 0·15 mole), 3N-sodium hydroxide (50 ml., (0·15 mole), and more ethanol (20 ml.) to produce a homogeneous liquid, which was set aside at room temperature during 12 hr. A small quantity of a white infusible product (1—2 g.)

[17] Hofmann and Gabriel, *Ber.*, 1892, **25**, 1578.
[18] Ishikawa, *Sci. Papers Inst. Phys. Chem. Res., Tokyo*, 1925, **3**, 147.
[19] Gilsdorf and Nord, *J. Amer. Chem. Soc.*, 1952, **74**, 1855.
[20] Dox, *Org. Synth.*, Coll. Vol. I, 1941, p. 5, 6.

which separated was removed, and the yellowish-green filtrate treated with toluene-*p*-sulphonic acid (monohydrate; 34·2 g., 0·18 mole; dissolved in 30 ml. of water). After a transient colour-change to deep-brown, the pale-yellow liquid deposited prisms (25 g.), which were collected at 0° and rinsed with a little ethanol (filtrate A). Crystallisation from 90% ethanol (6—8 ml. per g.) gave prisms (16·4—19·2 g., 30—35%) of N-*acetimidoyl*-N′-*phenylthiourea toluene*-p-*sulphonate*, m. p. 170—172° (decomp., somewhat subject to the rate of heating). Evaporation of the filtrates in a vacuum at <40° increased the yield of the salt by 3—6% (Found: C, 52·9; H, 5·0; N, 11·5; S, 17·7. $C_9H_{11}N_3S,C_7H_8O_3S$ requires C, 52·6; H, 5·2; N, 11·5; S, 17·5%). Filtrate A did not afford more crude material on either vacuum-evaporation or dilution with water.

The toluene-*p*-sulphonate (1·83 g., 0·005 mole), suspended in hot water (10 ml.) and treated with 3N-sodium hydroxide (2 ml., 0·006 mole) or 3N-ammonia (5 ml., 0·015 mole), gave a clear solution which deposited an oil on rapid cooling. The solidified oil gave, on crystallisation from ethanol (8 ml. per g.), platelets of N-*acetimidoyl*-N′-*phenylthiourea*, m. p. 153—154° (0·43—0·53 g., 45—55%) [Found: C, 55·4; H, 5·6; N, 21·3%; *M* (cryoscopically in thymol), 180. $C_9H_{11}N_3S$ requires C, 56·0; H, 5·7; N, 21·8%; *M*, 193].

Interaction of acetamidine hydrochloride (0·01 mole) and phenyl isothiocyanate (0·01 mole) in pyridine (20 ml.)–triethylamine (5 ml.) at 100° during 3 hr., followed by addition of the reaction mixture to ice–hydrochloric acid, gave mainly *sym*-diphenylthiourea, m. p. and mixed m. p. 153° (43%).

N-*Acetyl*-N′-*phenylthiourea*.—To the suspension obtained on introducing sodium (0·345 g., 0·015 g.-atom) into anhydrous acetone (50 ml.), a solution of acetamidine hydrochloride (1·42 g., 0·015 mole) in hot Cellosolve (6 ml.) was added, followed by phenyl isothiocyanate (2·03 g., 0·015 mole). The suspension was refluxed during 5 min., distilled in a vacuum to small volume during 5 min., stirred into water (150 ml.), and acidified (to Congo Red) with concentrated hydrochloric acid. The crystalline precipitate (m. p. 165—167°; 1·96 g., 67%) gave, on purification from ethanol, plates of *N*-acetyl-*N*′-phenylthiourea, m. p. and mixed m. p. with authentic material [21] 170—171° (Found: C, 55·8; H, 5·1; N, 13·9; S, 16·1. Calc. for $C_9H_{10}ON_2S$: C, 55·7; H, 5·15; N, 14·4; S, 16·5%).

N-*Acetimidoyl*-N′-p-*tolylthiourea*.—The procedure described for the phenyl homologue gave a crude product (m. p. 158—160°; 40%) which consisted, after crystallisation from ethanol (10 ml. per g., 75% recovery), of platelets of N-*acetimidoyl*-N′-p-*tolylthiourea toluene*-p-*sulphonate*, m. p. 165—167° (Found: C, 53·4; H, 5·65. $C_{10}H_{13}N_3S,C_7H_8O_3S$ requires C, 53·8; H, 5·5%).

N-Acetimidoyl-*N*′-butylthiourea was prepared (from 0·05 mole of each of the appropriate reagents, all in 50 ml. of ethanol) by the same procedure. After storage during 24 hr., the white powdery by-product was filtered off, and the colourless filtrate treated with toluene-*p*-sulphonic acid monohydrate (0·06 mole). Slow separation of silky needles was completed by storage at −8°, and the collected product (6·55 g., 38%) (filtrate F) crystallised from ethanol (8 ml. per g.) to yield needles (26%) of N-*acetimidoyl*-N′-*butylthiourea toluene*-p-*sulphonate*, m. p. 173—174° (Found: C, 49·2; H, 7·1; N, 12·0; S, 18·1. $C_7H_{15}N_3S,C_7H_8O_3S$ requires C, 48·7; H, 6·7; N, 12·2; S, 18·55%). Spontaneous evaporation of filtrates F gave large prismatic needles (1·80 g.) of non-homogeneous material from which no more of the desired thiourea could be isolated.

5-*Anilino*-3-*phenyl*-1,2,4-*thiadiazole*.—(a) *Oxidation by hydrogen peroxide*. A boiling solution of *N*-benzimidoyl-*N*′-phenylthiourea (12·75 g., 0·05 mole) in ethanol (180 ml.) was treated with a mixture of 6% hydrogen peroxide (71 ml., 0·125 mole) and concentrated hydrochloric acid (5 ml., 0·05 mole) during 8—10 min. Towards the end of the addition the yellow colour of the solution was discharged, and crystals appeared, the separation of which was completed by storage at 0° during 4 hr. The collected washed (ethanol) product (m. p. 170—172°; 9·5—10·4 g., 75—82%) was crystallised from ethanol (15 ml. per g.), and consisted of platelets of 5-anilino-3-phenyl-1,2,4-thiadiazole, m. p. 173—174° [Found: C, 66·2; H, 4·2; N, 16·4; S, 12·4%; *M* (cryoscopically, in thymol), 245. Calc. for $C_{14}H_{11}N_3S$: C, 66·4; H, 4·35; N, 16·6; S, 12·65%; *M*, 253]. (b) *Oxidation by bromine*. A solution of *N*-benzimidoyl-*N*′-phenylthiourea (2·55 g., 0·01 mole) in cold chloroform (12 ml.) decolorised M-bromine (10 ml., 0·01 mole) as fast as it was added. The liquid was evaporated in a vacuum at low temperatures to small bulk, and the residual suspension shaken with water (50 ml.). The chloroform and the aqueous layer were separated, and later recombined when all the chloroform had evaporated spontaneously. The

[21] Dixon and Hawthorne, *J.*, 1907, **91**, 128, 130.

collected white solid, on crystallisation from ethanol as above, gave platelets of the 1,2,4-thiadiazole (total, 2·28 g., 90%), m. p. and mixed m. p. with material obtained by method (a) 173—174°. The m. p. of 5-anilino-3-phenyl-1,2,4-thiadiazole given in the literature [10,11,14,12] is 174—176°.

Reduction. To a boiling solution of the reactant (3·80 g., 0·015 mole) in ethanol (75 ml.) containing zinc shavings (8 g.), concentrated hydrochloric acid (8 ml.) was added dropwise during 1 hr., and refluxing continued during a total of 2·5 hr. (another 2 ml. of acid being added after 2 hours' boiling). The decanted liquid (together with 20 ml. of boiling ethanol, used to re-extract the residual zinc) was evaporated in a vacuum (to 15 ml.), set aside at 0° during 2 hr. (Note N), then stirred into water, and the white soft product (2·5 g.) was dissolved in benzene (20 ml.)–acetone (5 ml.). The filtered liquid was set aside for spontaneous evaporation, the solvent being gradually replaced by ethanol. The separated product (m. p. ~140°; 1·5—2·0 g.) crystallised from ethanol (12 ml. per g.) as prisms (1·27—1·65 g., 35—45%) of *N*-benzyl-*N'*-phenylthiourea, m. p. and mixed m. p. 151—152° (Found: C, 69·8; H, 6·0; N, 11·0; S, 12·8. Calc. for $C_{14}H_{14}N_2S$: C, 69·4; H, 5·8; N, 11·6; S, 13·2%). Use of amalgamated zinc did not improve yields.

Note N: In experiments involving a shorter time of refluxing starting material separated from this solution and was removed by filtration at this stage: yields of the thiourea were lowered correspondingly.

Reduction of N-*Benzimidoyl*-N'-*phenylthiourea.*—This compound (3·80 g., 0·015 mole) was reduced as described immediately above. The crude resinous product was dissolved in benzene (20 ml.), the liquid allowed to evaporate to dryness, and the filtered solution of the remaining gum in ethanol (10 ml.) stirred into ice. The soft dry product was redissolved in ethanol (10 ml.); the sticky viscous liquid slowly deposited a white powder (0·85—1 g.) which gave *N*-benzyl-*N'*-phenylthiourea, m. p. and mixed m. p. 151—152° (from ethanol) (0·63 g., 17%).

N-*Benzyl*-N'-*phenylthiourea.*—Benzylamine (3·2 g., 0·03 mole) in pyridine (15 ml.) was treated with phenyl isothiocyanate (3·4 g., 0·025 mole), and the liquid was kept at 100° during 30 min., then poured into ice and hydrochloric acid. The precipitate, crystallised from ethanol (10 ml. per g.), consisted of prisms of the thiourea, m. p. 152—153° (5·55 g., 92%). The m. p. of *N*-benzyl-*N'*-phenylthiourea is given in the literature [19,22] variously between 153° and 158°.

Derivatives.—5-Anilino-3-phenyl-1,2,4-thiadiazole (1·27 g., 0·005 mole), dissolved in pyridine (10 ml.), was treated with acetic anhydride (3·05 g., 0·03 mole), and the solution kept at 100° for 0·5 hr. and stirred into ice (100 g.) and concentrated hydrochloric acid (12 ml.). The washed dried precipitate was crystallised from acetone–ethanol, and gave prisms of the monoacetyl derivative, m. p. 202—204° (0·98 g., 67%) (Found: C, 64·8; H, 4·5; N, 14·35; S, 10·9. Calc. for $C_{16}H_{13}ON_3S$: C, 65·1; H, 4·4; N, 14·2; S, 10·85%). Koch [10] gives m. p. 196°. Interaction of the thiadiazole (0·005 mole) with benzoyl chloride (2·10 g., 0·015 mole) under the same conditions, and crystallisation of the crude product from acetone–ethanol, gave needles of the *monobenzoyl derivative*, m. p. 177—178° (decomp.) (1·45 g., 81%) (Found: C, 70·6; H, 4·05; N, 11·2. $C_{21}H_{15}ON_3S$ requires C, 70·6; H, 4·2; N, 11·8%). 5-Anilino-3-phenyl-1,2,4-thiadiazole (0·005 mole) was recovered unchanged (85 and 65% respectively) after being heated at 100° with toluene-*p*-sulphonyl chloride (0·015 mole during 0·5 hr., or 0·03 mole during 3 hr.) in pyridine (15 ml.).

3-*Phenyl*-5-p-*tolylamino*-1,2,4-*thiadiazole.*—Oxidation of *N*-benzimidoyl-*N'*-*p*-tolylthiourea (2·69 g., 0·01 mole) in boiling ethanol (45 ml.) by method (a), and crystallisation of the separated white product (m. p. 152—154°; 2·06 g., 77%) from ethanol (20 ml. per g.), afforded the 1,2,4-*thiadiazole* as platelets (65%), m. p. 156—157° (Found: C, 67·2; H, 4·7; N, 15·3. $C_{15}H_{13}N_3S$ requires C, 67·4; H, 4·9; N, 15·7%).

5-*Methylamino*-3-*phenyl*-1,2,4-*thiadiazole.*—*N*-Benzimidoyl-*N'*-methylthiourea (1·93 g., 0·01 mole) in boiling ethanol (15 ml.), on oxidation by method (a), gave crystals (m. p. 154—156°; 1·6 g., 84%) which afforded, after crystallisation from ethanol (15 ml. per g.), prisms of the 1,2,4-thiadiazole, m. p. 155—157° (Found: C, 56·2; H, 4·6; N, 21·6. Calc. for $C_9H_9N_3S$: C, 56·5; H, 4·7; N, 22·0%). Goerdeler *et al.*[15] give m. p. 157°.

5-*Anilino*-3-*methyl*-1,2,4-*thiadiazole.*—(a) *Oxidation by hydrogen peroxide.* A boiling solution of *N*-acetimidoyl-*N'*-phenylthiourea toluene-*p*-sulphonate (7·3 g., 0·02 mole) in 90% ethanol

[22] Dixon, *J.*, 1889, **55**, 301; Beckmann, *J. prakt. Chem.*, 1897, **56**, 88; Campbell, Campbell, and Patelski, *Proc. Indiana Acad. Sci.*, 1943, **53**, 119; Weller, Ball, and Sell, *J. Amer. Chem. Soc.*, 1952, **74**, 1104; Horner and Gross, *Annalen*, 1955, **591**, 117.

(50 ml.) was treated, during 3—4 min., with a mixture of 6% hydrogen peroxide (28·5 ml., 0·05 mole) and concentrated hydrochloric acid (2 ml., 0·02 mole), and continued to be boiled during another 2 min. The faintly purple turbid liquid was added to ice-water (200 ml.) and basified with 3N-ammonia (40 ml.). The precipitated solid (which tended to become dark grey on prolonged storage) was collected after 12 hours' storage at 0° [m. p. 109—111° (decomp.); 2·1—2·5 g., 55—65%] (Filtrate: M). The material was crystallised by diluting its filtered ethanolic solution (5 ml. per g.), previously treated at its b. p. with carbon during 5 min., with an equal volume of hot water and formed prismatic needles of *5-anilino-3-methyl-1,2,4-thiadiazole*, m. p. 113—114°, appreciably soluble in boiling water [Found: C, 56·3; H, 4·65; N, 22·2%; *M* (cryoscopically, in thymol), 197. $C_9H_9N_3S$ requires C, 56·5; H, 4·7; N, 22·0%; *M*, 191]. Partial evaporation of filtrate M did not afford more of the required thiadiazole. The dark residue, on crystallisation from ethanol (carbon) gave small quantities of unidentified material (m. p. 195—196°; 0·3—0·4 g.). The use of a larger excess of hydrogen peroxide (3 mols), slightly increased times of reaction (10—12 min.), or prolonged storage of the final reaction mixture, gave lower yields of dark brown to grey crude products, which were purified with greater difficulty by the use of muchcarbon.

(b) *Oxidation by bromine.* The reactant (3·65 g., 0·01 mole) was dissolved in 90% ethanol (50 ml.) with warming, the cooled (approx. 30—35°) solution treated with M-bromine (10 ml., 0·01 mole) (small quantities of crystals which may have separated, redissolved during this addition) and rapidly concentrated to small volume (12—15 ml.) by vacuum-distillation. To the residual colourless liquid, diluted with water (8 ml.), toluene-*p*-sulphonic acid monohydrate (3·80 g., 0·02 mole) was added and dissolved rapidly. The crystals which separated on storage at −8° were collected (1·55—1·7 g.) (filtrate: N) and crystallised from absolute ethanol, forming needles (1·16 g., 32%) of *5-anilino-3-methyl-1,2,4-thiadiazole toluene-p-sulphonate*, m. p. 154—156° (decomp.) (Found: C, 53·2; H, 4·9; N, 11·2. $C_{16}H_{17}O_3N_3S_2$ requires C, 52·9; H, 4·7; N, 11·6%). Spontaneous evaporation of filtrates N to small volume gave syrups that deposited only small quantities (0·2—0·4 g.) of non-homogeneous crystals.

A suspension of the toluene-*p*-sulphonate (0·91 g., 0·0025 mole) in 3N-ammonia (10 ml.) was heated to boiling with good shaking. The resulting suspended oil set to a white granular solid on cooling, and more crystalline product was deposited at 0°. The collected crude base (m. p. 111—114°; 0·41 g., 86%) crystallised as before and formed needles of 5-anilino-3-methyl-1,2,4-thiadiazole, m. p. and mixed m. p. 113—114°.

*3-Methyl-5-toluene-*p*-sulphonanilido-1,2,4-thiadiazole.*—A solution of 5-anilino-3-methyl-1,2,4-thiadiazole (1·91 g., 0·01 mole) in pyridine (25 ml.), treated with toluene-*p*-sulphonyl chloride (7·6 g., 0·04 mole), was kept on the steam-bath during 1½ hr. The dark viscous liquid was stirred into ice (100 g.) and concentrated hydrochloric acid (25 ml.), and the solidified dark-brown precipitate was extracted with 1·5N-sodium hydroxide at 50° during 15 min. (removal of excess of sulphonyl chloride), collected, washed with water, and crystallised from boiling ethanol (10 ml. per g., with addition of carbon–kieselguhr). The light brown filtrate deposited nearly colourless needles of the *toluene-p-sulphonyl derivative*, m. p. 160—161° (after a further crystallisation) (total, including material from mother-liquors, 2·25 g., 65%) (Found: C, 55·7; H, 4·5; N, 12·4; S, 18·8. $C_{16}H_{15}O_2N_3S_2$ requires C, 55·65; H, 4·35; N, 12·2; S, 18·55%).

Reduction.—A solution of the preceding compound (0·69 g., 0·002 mole) in ethanol (25 ml.) containing amalgamated zinc (2 g.) was refluxed during 2 hr. and treated dropwise with concentrated hydrochloric acid (2 × 3 ml.) during the first and third half-hour. The decanted liquid, together with washing alcohol (8 ml.) used in extracting the zinc a second time, was distilled in a vacuum to small volume (5 ml.), and the residue stirred into water. The solidified precipitate (m. p. 98—99°; 0·305 g., 62%) smelled strongly of thiocresol, but was almost pure toluene-*p*-sulphonanilide, m. p. and mixed m. p. 99—100° (prisms, from benzene–light petroleum). The reactant was recovered (75%) after 15 minutes' treatment with zinc (non-amalgamated) and hydrochloric acid under the above conditions.

*3-Methyl-5-*p*-tolylamino-1,2,4-thiadiazole.*—This *base* was prepared from *N*-acetimidoyl-*N'*-*p*-tolylthiourea toluene-*p*-sulphonate (3·8 g., 0·01 mole) (as described for the 5-anilino-homologue, method *a*). The crude product (m. p. 134—136°; 1·75 g., 85%) afforded, on crystallisation from ethanol (10 ml. per g.), elongated prisms, m. p. 136—137° (Found: C, 58·4; H, 5·1. $C_{10}H_{11}N_3S$ requires C, 58·5; H, 5·4%).

*5-*n*-Butylamino-3-methyl-1,2,4-thiadiazole.*—*N*-Acetimidoyl-*N'*-butylthiourea toluene-*p*-sulphonate (0·01 mole) in ethanol (12 ml.) was oxidised (as described for the 5-anilino-analogue,

method *a*), the resulting turbid liquid filtered under reduced pressure (double filter-paper), and the filtrate divided into two equal portions. One half, treated with a solution of picric acid (1·145 g., 0·005 mole) in ethanol (10 ml.) and set aside at 0°, gave the *picrate* (1·78 g., 45%; cf. Table). The other half, treated with picrolonic acid (1·32 g., 0·005 mole) in ethanol (25 ml.), gradually diluted with water (20 ml.), and set aside at 0°, deposited yellow crystals, m. p. 134—136° (decomp.) (1·25 g., 29%) (filtrate F), which on crystallisation from ethanol gave yellow needles of the *picrolonate*, m. p. 133—135° (Found: C, 47·35; H, 4·9. $C_7H_{13}N_3S,C_{10}H_8O_5N_4$ requires C, 46·9; H, 4·8%). Spontaneous evaporation of filtrate F gave more yellow solid (m. p. 110°), which afforded additional picrolonate (8%) on crystallisation (combined yield of thiadiazole, 82%). The base was low-melting and water-soluble: it was extractable by ether, but was not isolated pure.

Picrates of N′-*substituted* N-*acimidoylthioureas*, R·NH·CS·NH·CR′(:NH),$C_6H_3O_7N_3$.

				Found (%)		Required (%)	
R′	R	M. p.*	Formula	C	H	C	H
Ph	Me	175—176°	$C_{15}H_{14}O_7N_6S$	42·7	3·4	42·65	3·3
Ph	Ph	209—210	$C_{20}H_{16}O_7N_6S$	49·95	4·3	49·6	3·3
Ph	*p*-Tolyl	210—211	$C_{21}H_{18}O_7N_6S$	50·9	3·5	50·6	3·6
Me	Ph	211—212	$C_{15}H_{14}O_7N_6S$	42·9	3·1	42·65	3·3
Me	*p*-Tolyl	150—152	$C_{16}H_{16}O_7N_6S$	44·4	3·75	44·0	3·7

Picrates of 3-*alkyl*(*aryl*)-5-*alkyl*(*aryl*)*amino*-1,2,4-*thiadiazoles*, 3-R′-5-R·NH·C_2N_2S,$C_6H_3O_7N_3$

Ph	Me	143—144	$C_{15}H_{12}O_7N_6S$	42·9	2·6	42·9	2·9
Me	Bu^n	138—139	$C_{13}H_{16}O_7N_6S$	39·4	3·7	39·0	4·0
Me	Ph	163—164	$C_{15}H_{12}O_7N_6S$	43·1	3·0	42·9	2·9
Me	*p*-Tolyl	184—185	$C_{16}H_{14}O_7N_6S$	44·5	3·0	44·2	3·2

* Decomp. on melting.

Picrates of *N*′-substituted *N*-benzimidoylthioureas and 3-alkyl(or aryl)-5-alkyl(or aryl)-amino-1,2,4-thiadiazoles were obtained, in 70—90% yield, as deep yellow to orange prisms, from equimolar proportions of the components (0·002 mole) in hot ethanol (12—20 ml.). *N*′-Substituted *N*-acetimidoylthiourea picrates resulted in somewhat lower yields (55—65%) from solutions of the toluene-*p*-sulphonates in 90% ethanol and ethanolic picric acid.

N-Acetimidoyl-*N*′-*n*-butylthiourea, 5-anilino-3-phenyl-1,2,4-thiadiazole, and 3-phenyl-5-*p*-tolylamino-1,2,4-thiadiazole failed to yield picrates, the starting material being recovered.

Sodium Plumbite Tests.—Solutions or suspensions of the compound (approx. 0·1 g.) under examination in 3N-sodium hydroxide (3 ml.) were treated with 3 drops of 10% lead acetate and boiled. All substituted thioureas (I) gave immediate copious precipitates of lead sulphide as soon as the liquid began to boil. 3-Methyl-1,2,4-thiadiazoles (II; R = Bu^n, Ph, or *p*-Me·C_6H_4, R′ = Me) slowly deposited sulphide after 2—3 min.; 3-phenyl homologues (II; R = Me, Ph, or *p*-Me·C_6H_4, R′ = Ph) failed to do so on prolonged boiling.

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