650. *Thiadiazoles. Part IX.* Reactions of Diazonium Salts Derived from 3-Amino-1,2,4-thiadiazoles.*

By Frederick Kurzer and Sheila A. Taylor.

3-Halogeno- and 3-hydroxy-1,2,4-thiadiazoles are synthesised from the corresponding 3-amino-compounds by way of the diazonium salts.

Of the properties of the new 3-halogeno-1,2,4-thiadiazoles, their remarkable stability, and the relative inertness of the 3-halogen substituent are noteworthy.

3-Halogeno-1,2,4-thiadiazoles (IV; X = halogen) have not previously been described. Unlike the 5-halogeno-isomers [1,2] they are not available by ring-closure of suitable precursors. No 1,2,4-thiadiazoles [except the parent compound (IV; R = X = H)] are known in which the free 3-position is available for direct halogenation. Our preliminary work aimed at replacing 3-hydroxy-groups by halogen gave discouraging results; in any case, the scope of this route is at present limited, because only few 3-hydroxy-1,2,4-thiadiazoles are known.[3] On the other hand, a variety of 3-amino-1,2,4-thiadiazoles (II) is readily obtainable,[4-7] and, in the form of the corresponding diazonium salts, these are clearly a potential source of both 3-halogeno- and 3-hydroxy-derivatives. The applicability of the Sandmeyer–Gattermann and related reactions, already established in the synthesis of the 5-halogeno-analogues,[8] has therefore now been examined in some detail. Our experiments using representative 3-amino-5-aryl(or alkylamino or arylamino)-1,2,4-thiadiazoles have met with varying success.

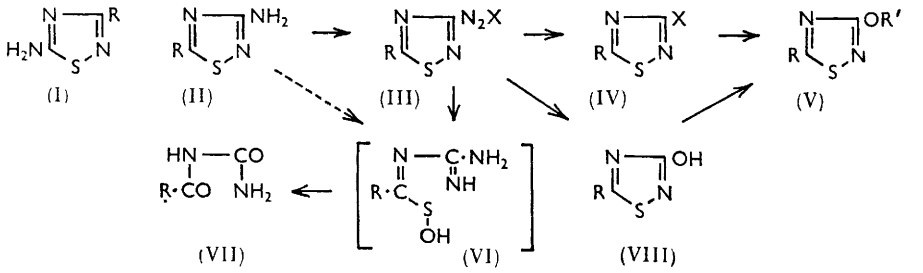
Favourable results were obtained with 3-amino-5-aryl-1,2,4-thiadiazoles (II; R = Ar). In spite of the presence of the guanidino-group, they are very feeble bases (*e.g.*, II, R = Ph, has pK_a 0·1),[6] being markedly weaker than the 5-amino-isomers (*e.g.*, I, R = Ph, pK_a 1·4). In strong acids (*e.g.*, concentrated phosphoric acid) the 3-amino-homologue (II; R = Ph) is convertible into the diazonium salt which undergoes coupling reactions, but with active compounds only,[6] in contrast to the diazonium salt derived from the isomer (I; R = Ph), which couples readily with phenol ethers and aromatic hydrocarbons.[9]

3-Chloro-5-phenyl-1,2,4-thiadiazole (IV; R = Ph, X = Cl) was obtained in fair yield (40—54%) by diazotising the 3-amino-analogue (II; R = Ph) in concentrated hydrochloric acid in the presence of copper. Yields were reduced when copper was absent, or when it was added after the diazotisation was complete, or on employing the " inverse

* Part VIII, *J.*, 1959, 2851

[1] Goerdeler, Groschopp, and Sommerlad, *Chem. Ber.*, 1957, **90**, 182.
[2] Goerdeler and Sperling, *Chem. Ber.*, 1957, **90**, 892.
[3] Kurzer, *Chem. and Ind.*, 1956, 1482; Kurzer and Taylor, *J.*, 1958, 379.
[4] Kurzer, *J.*, 1955, 1, 2288.
[5] Kurzer, *J.*, 1956, 2345.
[6] Goerdeler and Finke, *Chem. Ber.*, 1956, **89**, 1033.
[7] Kurzer, *J.*, 1956, 4524.
[8] Goerdeler, Ohm, and Tegtmeyer, *Chem. Ber.*, 1956, **89**, 1534.
[9] Taube, G.P. 927,944/1955.

procedure" (cf. Experimental).[11] Substantial proportions of by-product, which were invariably formed, consisted of 3-hydroxy-5-phenyl-1,2,4-thiadiazole (VIII; R = Ph) and benzoylurea [10] (VII; R = Ph). The formation of the latter is probably due to the usual ring fission of the heterocyclic nucleus at the sulphur–nitrogen link [4,5] (in either II or III), followed by loss of sulphur, and hydrolysis of the guanidino-residue of the intermediate



(*e.g.*, VI). The 3-hydroxy-analogue (VIII) arises directly from the diazonium salt in a parallel reaction, because it is unobtainable from the 3-chloro-compound (IV; R = Ph, X = Cl) (see below) but becomes the main product of the diazotisation under appropriate conditions. 3-Bromo-5-phenyl-1,2,4-thiadiazole (IV; R = Ph, X = Br) was obtained in low yield by the "inverse procedure;" [11] the Sandmeyer reaction employing cuprous bromide [11] instead of copper powder gave at most only traces of the required compound.

3-Amino-5-methylamino- and -anilino-1,2,4-thiadiazole afforded only minute yields (5 and 8% respectively) of the 3-chloro-derivatives (IV; R = Me·NH or Ph·NH, X = Cl). Since the reaction mixtures were intensely deep green to brown in these, but not other, diazotisations it is probable that the formation of labile nitrosamines, involving the methylamino- or anilino-group, interfered with the course of the reaction.

In contrast with 5-halogenated 1,2,4-thiadiazoles, 3-chloro-5-phenyl-1,2,4-thiadiazole was remarkable for its stability and for the relative inertness of the halogen substituent towards most nucleophilic reagents. It resisted catalytic hydrogenation under conditions that change the 5-bromo-analogue into the parent base [8] and was unaffected by hot concentrated sulphuric acid which converts 5-chloro-1,2,4-thiadiazole [8] and its 3-phenyl analogue [1] into the hydroxy-compounds. It yielded neither 3-alkyl(or aryl)amino-derivatives, nor the toluene-*p*-sulphonylhydrazine; Albert and Royer's [12] indirect route to the hydrocarbon (IV; X = H) by hydrolytic decomposition of the latter derivative was therefore inapplicable. Reductive diazotisation [11] of the 3-amino-compound also failed to yield the hydrocarbon. The halogen in (IV; R = Ph, X = Cl) was not replaceable by cyano- or thiol groups by the action of cuprous cyanide, or by thiourea and potassium hydroxide.[1] The attempted direct introduction of the cyano-group by treatment of the diazonium salt (III) solution with cuprous cyanide [11] was also unsuccessful. In alkaline media, however, the stability of 3-chloro-5-phenyl-1,2,4-thiadiazole was much reduced, the compound being decomposed completely by alcoholic potassium hydroxide. Nucleophilic substitution of halogen by alkoxy-groups occurred under the influence of sodium alkoxide in an excess of the appropriate alcohol: 3-methoxy-, 3-benzyloxy-, and 3-2′-hydroxyethoxy-derivatives (V; R = Ph, R′ = Alk) were thus obtained in good yield.

Although numerous observations are on record concerning the contrasting reactivity towards nucleophilic reagents of halogen substituents in different positions of heterocyclic systems, the behaviour of relatively few strictly comparable sets of isomers appears to have been studied.[13] The inertness of chlorine to nucleophilic reagents in 3-chloro-5-phenyl-1,2,4-thiadiazole, and its known [1,2,14] mobility in the 5-chloro-3-phenyl isomer

[10] Ostrogovich, *Bul. soc. stiinte Cluj*, 1929, **4**, 538.
[11] Saunders, "The Aromatic Diazo Compounds," Arnold, London, 1947.
[12] Albert and Royer, *J.*, 1949, 1148.
[13] See, for example, Chapman and Rees, *J.*, 1954, 1190; Chapman and Russell-Hill, *J.*, 1956, 1563.
[14] Goerdeler and Deselaers, *Chem. Ber.*, 1958, **91**, 1025.

suggests, in general terms, a high electron-density in the region of the 3-position, and an electron-deficiency in that of the 5-position of the 1,2,4-thiadiazole system. Attention is drawn to the formal analogy of the present results with relevant observations in the thiazole series: 2-halogenothiazoles (in which the halogen occupies a position between heterocyclic nitrogen and sulphur, as in 5-chloro-1,2,4-thiadiazoles) are reactive, while the 4- and the 5-halogenated isomers are inert.[15]

3-Hydroxy-5-phenyl-1,2,4-thiadiazole (VIII; R = Ph) was unobtainable from the 3-chloro-compound, but was prepared in satisfactory yields by decomposition of the diazonium salt (III) in warm aqueous sulphuric acid. This observation accounts for the occurrence of the hydroxy-compound as a by-product in other reactions involving diazonium salt solutions. As expected it was a stable compound of phenolic character, which gave, like the 5-anilino-analogue,[3] a red colour with neutral ferric chloride, but failed to afford ketonic derivatives. Its mono-acyl and -sulphonyl derivatives, obtained by the usual methods, are formulated as phenolic esters (V; R′ = Ac, Bz, or *p*-$C_6H_4Me{\cdot}SO_2$).

Diazotisation of 3-amino-5-anilino-1,2,4-thiadiazole with nitrosylsulphuric acid in concentrated sulphuric acid and subsequent decomposition of the diazonium salt with water similarly provided the known [3] 5-anilino-3-hydroxy-1,2,4-thiadiazole, though in low yield. This diazotisation failed in the presence of water, possibly owing to formation of the 5-nitrosamine. This suggestion is supported by the observation [14] that the yield of 3-methyl-5-nitrosamino-1,2,4-thiadiazole from the 5-amine varies inversely with the acidity of the medium.

Experimental

Light petroleum was of boiling range 40—60° unless otherwise stated. Pyridine was the commercially available anhydrous grade.

3-*Chloro-5-phenyl*-1,2,4-*thiadiazole*.—A solution of 3-amino-5-phenyl-1,2,4-thiadiazole [7] (7·08 g., 0·04 mole) in concentrated hydrochloric acid (120 ml., 1·2 moles) was cooled to approximately −10° (ice–calcium chloride hexahydrate). A little copper powder [16] was added and the stirred suspension was treated dropwise with sodium nitrite (5·6 g., 0·08 mole) in water (15 ml.) during 45 min. at −10° to −5° (avoiding the production of nitrous fumes). A little more copper powder was added and the yellow-to-green frothy suspension stirred during 15 min. at −8°, during 1—1·5 hr. at room temperature, and finally during 20 min. at 50—60° to complete the decomposition of the diazonium salt. The resulting suspension of yellow-to-green powder (and occasionally oily droplets) and pale brown liquid was diluted with water (200 ml.) and stored at 0° (the oil solidified). The crude solid was collected, washed with water, air-dried, and exhaustively extracted with boiling light petroleum (residue A). Evaporation of the extracts under reduced pressure gave 3-*chloro-5-phenyl*-1,2,4-*thiadiazole* as yellow granules, m. p. 60—62° (after sintering at 58°) (3·3—4·2 g., 42—54%). Repeated crystallisation from light petroleum gave a pale yellow powder, m. p. 62—63° (after sintering at 61°) (Found: C, 49·2; H, 2·5; N, 13·9; S, 16·3. $C_8H_5N_2SCl$ requires C, 48·9; H, 2·5; N, 14·25; S, 16·3%). The compound was highly soluble in the usual organic solvents except light petroleum, but was also crystallisable from small volumes of aqueous ethanol (1 : 9) or acetone (1 : 4); it was light-sensitive, slowly becoming orange-pink on exposure.

The use of the " inverted procedure " (cf. 3-chloro-5-anilino-1,2,4-thiadiazole, below) gave diminished yields (25%) of 3-chloro-5-phenyl-1,2,4-thiadiazole, as did experiments carried out without the use of copper [17] (10—15%).

Residue A (2·5—5·5 g.) was green or greenish-brown, depending on the amount of copper present. It was partially fractionated into its constituents as follows: (*a*) The residue (2·5 g.) from an experiment was extracted at 50° with N-sodium hydroxide (30 and 15 ml. successively), and the filtered (pump) combined extracts (alkali-insoluble residue: 0·85 g.) were acidified to

[15] Sprague and Land, in Elderfield, " Heterocyclic Compounds," Vol. V, Wiley, New York and London, 1957, pp. 542—547.

[16] Cumming, Hopper, and Wheeler, " Systematic Organic Chemistry," Constable, London, 1937, p. 508.

[17] Kogon, Minin, and Overberger, *Org. Synth.*, 1955, **35**, 34.

Congo Red with 3N-hydrochloric acid. The white precipitate was collected, washed with water (1·3 g.), and gave, on crystallisation from ethanol, 3-hydroxy-5-phenyl-1,2,4-thiadiazole, m. p. and mixed m. p. with authentic material (see below) 202—203° (decomp.) (0·65 g.).

(*b*) The residue (5 g.) was extracted with boiling water (5 × 30 ml.). The filtered aqueous extracts deposited a white solid (1·8 g.) which was extracted with boiling ethanol (20 ml.). The insoluble fraction (1·1 g.) gave, on two crystallisations from acetone–ethanol, needles of benzoylurea (0·85 g.), m. p. and mixed m. p. with authentic material [10] 211—213° (Found: C, 58·4; H, 4·6; N, 17·6. Calc. for $C_8H_8O_2N_2$: C, 58·5; H, 4·9; N, 17·1%). The ethanol extracts gave, on spontaneous evaporation, reprecipitation of the crystalline residue from its alkaline solution by acid, and recrystallisation of the precipitate, 3-hydroxy-5-phenyl-1,2,4-thiadiazole, m. p. and mixed m. p. 201—203° (decomp.) (0·4 g.). The water-insoluble residue (2·8 g.) contained the same compound, m. p. 202—203° (decomp.), which was isolated as described in (*a*) (0·3 g.).

3-Chloro-5-phenyl-1,2,4-thiadiazole resisted hydrogenation at atmospheric pressure in the presence of Raney nickel [8] or Adams platinum catalyst,[18] being recovered almost quantitatively. It was unaffected when heated in concentrated sulphuric acid solution at 100° during 3 hr.,[8] but was completely decomposed when refluxed in M-potassium hydroxide (in 50% aqueous ethanol) during 30 min. The compound was recovered (70%) after treatment with methylamine under conditions which convert 5-bromo- into 5-methylamino-1,2,4-thiadiazole [8] and failed to yield the 3-anilino-analogue with potassium–aniline.[19] It was destroyed by hydrazine,[2] and failed to react with toluene-*p*-sulphonylhydrazine [12] (recovery 80%). It was not convertible into the 3-cyano-derivative by cuprous cyanide, in the absence [20] or presence [21] of pyridine, the reactant being recovered in the former case, and converted into intractable gums in the latter. It did not give the 3-thiol on treatment with thiourea–potassium hydroxide [1] (recovery 90%).

3-*Bromo*-5-*phenyl*-1,2,4-*thiadiazole*.—An intimate mixture of 3-amino-5-phenyl-1,2,4-thiadiazole [7] (1·77 g., 0·01 mole) and sodium nitrite (3·45 g., 0·05 mole) was added in small portions at −6° to −8° during 30 min. to stirred 35% hydrobromic acid (35 ml.) containing a little copper powder.[16] The resulting brown suspension was stirred at −8° during 20 min., during 1·5 hr. while it attained room-temperature, and finally at 50—55° until no more nitrogen was evolved. After being cooled to room temperature, the brown mixture containing oil was added to water (50 ml.), the oily layer B separated from the aqueous phase, and the latter extracted with ether (3 × 25 ml.). The oily layer B was also extracted with ether (5 × 25 ml.), giving an orange ethereal solution and an unidentified olive-brown solid residue (0·8—1 g., which was probably similar in composition to residue A, above). The combined ethereal extracts were evaporated and the remaining yellow oil extracted with light petroleum (3 × 10 ml.), leaving a residue of yellow gum. The extract afforded 3-*bromo*-5-*phenyl*-1,2,4-*thiadiazole*, as minute pale yellow flakes, m. p. 64—66·5° (after sintering at 62°) [from light petroleum (b. p. 60—80°)] (0·52 g., 22%) (Found: C, 39·9; H, 2·1; N, 11·6. $C_8H_5N_2SBr$ requires C, 39·85; H, 2·1; N, 11·6%). This compound was also obtained in 12% yield by the procedure described for the 3-chloro-analogue (but with 60% hydrobromic acid), and formed white granules, m. p. and mixed m. p. 64—66°.

5-*Anilino*-3-*chloro*-1,2,4-*thiadiazole*.—A mixture of 3-amino-5-anilino-1,2,4-thiadiazole [5] (solvate; 2·38 g., 0·01 mole) and sodium nitrite (3·45 g., 0·05 mole) was added during 45 min. to stirred concentrated hydrochloric acid (30 ml.) at −8°, and the intense green mixture treated and worked up as described in the foregoing paragraph. The dark-brown crude product was extracted with boiling methanol (70 ml.), the extracts were evaporated to dryness, and the residue was extracted with boiling chloroform (20 ml.). This extract gave, on spontaneous evaporation, a pale brown powder (m. p. 138—141°; 0·15 g., 7%) which yielded, on crystallisation from 50% aqueous ethanol (4 ml.), pale pink granular 5-*anilino*-3-*chloro*-1,2,4-*thiadiazole*, m. p. 139—141° (Found: C, 45·6; H, 2·9; N, 20·1; S, 14·9. $C_8H_6N_3SCl$ requires C, 45·4; H, 2·8; N, 19·9; S, 15·1%).

3-*Chloro*-5-*methylamino*-1,2,4-*thiadiazole*.—Finely powdered 3-amino-5-methylamino-1,2,4-thiadiazole toluene-*p*-sulphonate [4] (3·02 g., 0·01 mole), suspended in concentrated hydrochloric

[18] Adams, Voorhees, and Shriner, *Org. Synth.*, Coll. Vol. I, p. 463 (1941).
[19] Scardiglia and Roberts, *J. Org. Chem.*, 1958, **23**, 629.
[20] Adams and Slack, *J.*, 1959, 3061.
[21] Ashley and Macdonald, *J.*, 1957, 1668.

acid (30 ml.) containing copper powder,[16] was treated with sodium nitrite (1·4 g., 0·02 mole) in water (5 ml.) at −8° during 15 min., and the mixture was stirred at −8° during 15 min., at room temperature during 30 min. and at 50—60° during 15 min. The green suspension was diluted with water (50 ml.) and extracted exhaustively with ether (4 × 30 ml.), then chloroform (4 × 20 ml.). Removal of the solvents from the combined extracts gave a minute yellow residue, which, crystallised from water (2 ml.), consisted of pale yellow felted needles (0·07—0·1 g., 5—7%) of 3-*chloro*-5-*methylamino*-1,2,4-*thiadiazole*, m. p. 132—134° (Found: C, 24·6; H, 2·8. $C_3H_4N_3SCl$ requires C, 24·1; H, 2·7%). The product was very soluble in water.

A number of attempts to prepare 3-iodo-5-phenyl-1,2,4-thiadiazole by interaction of the appropriate diazonium salt solution with potassium iodide under various conditions were unsuccessful. One example [22] is the following:

The stirred yellow liquid obtained on dissolving 3-amino-5-phenyl-1,2,4-thiadiazole [7] (1·77 g., 0·01 mole) in concentrated sulphuric acid (10 ml.) was treated successively at −8° with sodium nitrite (0·76 g., 0·011 mole) in concentrated sulphuric acid (10 ml.) during 10 min., with 80% phosphoric acid (10 ml.) during 60 min., powdered urea (2 g.) during 5 min., and finally potassium iodide (1·7 g., 0·01 mole) in water (2 ml.)–80% phosphoric acid (1 ml.) during 30 min. The mixture was stirred at room temperature during 3 hr., then added to ice (100 g.), the almost black solid was collected (filtrate F), washed with aqueous sodium hydrogen sulphite, and the brown powdery residue almost completely dissolved in N-sodium hydroxide (2 × 10 ml.). Acidification of the filtered extract gave a white precipitate (m. p. 196—200°; 0·68 g., 38%) of 3-hydroxy-5-phenyl-1,2,4-thiadiazole, m. p. and mixed m. p. 202—204° (from ethanol). Basification of filtrate F (cooling) gave a white precipitate (m. p. 129—134°; 0·40 g., 23%) of the starting material.

3-*Methoxy*-5-*phenyl*-1,2,4-*thiadiazole*.—3-Chloro-5-phenyl-1,2,4-thiadiazole (0·49 g., 0·0025 mole), dissolved in a solution from sodium (0·23 g., 0·01 g.-atom) in methanol (5 ml.), was refluxed during 2 hr. A white precipitate was formed slowly. The mixture was stirred into ice-water, and the white solid collected at 0°. The aqueous filtrate contained chloride ions. The crude product (0·44 g.) gave lustrous white prisms of 3-*methoxy*-5-*phenyl*-1,2,4-*thiadiazole*, m. p. 50—51° (from very little light petroleum) (0·33 g., 68%) (Found: C, 56·8; H, 4·25; N, 14·3; S, 16·15. $C_9H_8ON_2S$ requires C, 56·25; H, 4·2; N, 14·6; S, 16·7%).

3-*Benzyloxy*-5-*phenyl*-1,2,4-*thiadiazole*.—3-Chloro-5-phenyl-1,2,4-thiadiazole (0·0025 mole), when added to a solution from sodium (0·01 g.-atom) in benzyl alcohol (4 ml.) at 80°, gave a brown suspension, which was heated on the steam-bath during 1·5 hr. The mixture was diluted with 0·5N-hydrochloric acid (0·015 mole), the benzyl alcohol removed by steam-distillation, and the residual oil extracted with ether. Removal of the solvent, storage of the residue in a vacuum-desiccator (to remove the last traces of benzyl alcohol), and crystallisation from light petroleum (b. p. 60—80°) gave large prisms (0·36 g., 54%) of 3-*benzyloxy*-5-*phenyl*-1,2,4-*thiadiazole*, m. p. 67—69° (Found: C, 67·2; H, 3·8; N, 10·1; S, 11·4. $C_{15}H_{12}ON_2S$ requires C, 67·2; H, 4·5; N, 10·45; S, 11·9%).

3-2′-*Hydroxyethoxy*-5-*phenyl*-1,2,4-*thiadiazole*.—3-Chloro-5-phenyl-1,2,4-thiadiazole (0·0025 mole), in a solution from sodium (0·012 g.-atom) in ethylene glycol (4 ml.), was heated, with occasional shaking, on the steam-bath during 2 hr. The lower layer gradually dissolved, giving a brown suspension. The mixture was stirred into water (50 ml.), and the solidified oil (m. p. 81—82°; 0·42 g., 75%) crystallised from light petroleum–methanol (30 : 1); the *thiadiazole* formed needles, m. p. 83—84° [Found: C, 54·4; H, 4·8; N, 12·1%; *M* (cryoscopically, in thymol), 200. $C_{10}H_{10}O_2N_2S$ requires C, 54·1; H, 4·5; N, 12·6%; *M*, 222].

3-*Hydroxy*-5-*phenyl*-1,2,4-*thiadiazole*.—Finely powdered 3-amino-5-phenyl-1,2,4-thiadiazole [7] (1·77 g., 0·01 mole) was dissolved in concentrated sulphuric acid (15 ml.) and water (15 ml.). The stirred suspension, kept at approx. −10°, was diazotised by the dropwise addition of a solution of sodium nitrite (1·04 g., 0·015 mole) in water (4 ml.) during 12 min. and then stirred at −10° for a further 15—20 min. The temperature of the resulting yellow frothy mixture was allowed to rise spontaneously to 25° during 30 min., the turbid yellow liquid diluted with water (25 ml.), and the resulting suspension heated to 100° to complete the reaction. After storage at 0°, the coagulated solid was collected, washed with water, and dissolved in N-aqueous sodium hydroxide (20 ml., 0·02 mole). Acidification of the filtered solution with hydrochloric acid gave a pale yellow powder which recrystallised from ethanol (15—20 ml. per g.), affording lustrous flakes of 3-*hydroxy*-5-*phenyl*-1,2,4-*thiadiazole*, m. p. 203—204° (after sintering at 202°)

[22] Sandin and Cavins, *Org. Synth.*, Coll. Vol. II, p. 604 (1943).

(1·04 g., 58%) (Found: C, 54·3; H, 3·7; N, 15·6; S, 18·2. $C_8H_6ON_2S$ requires C, 53·9; H, 3·4; N, 15·7; S, 18·0%). A small second crop (10%) was obtained from the filtrate. A solution of the thiadiazole in methanol gave a deep red colour with aqueous ferric chloride. The compound failed to yield a 2,4-dinitrophenylhydrazone under the usual conditions.

Derivatives. 3-Hydroxy-5-phenyl-1,2,4-thiadiazole (0·45 g., 0·0025 mole) in acetic anhydride (8 ml.) was refluxed during 20 min. and then stirred into ice-water. The pale brown precipitate, crystallised from ethanol, gave pale yellow needles (0·36 g., 65%) of the *monoacetyl derivative*, m. p. 141—142° (after sintering at 138°) (Found: C, 54·8; H, 3·8. $C_{10}H_8O_2N_2S$ requires C, 54·5; H, 3·6%). The thiadiazole (0·0025 mole) in pyridine (5 ml.) was treated with benzoyl chloride (0·7 g., 0·005 mole) at 100° during 15 min. The *monobenzoyl derivative*, isolated in the usual manner, formed yellow prisms, m. p. 73—75° (from ethanol) (total, 0·42 g., 60%) (Found: C, 63·3; H, 3·6. $C_{15}H_{10}O_2N_2S$ requires C, 63·8; H, 3·5%). Interaction of the thiadiazole (0·0025 mole) and toluene-*p*-sulphonyl chloride (0·95 g., 0·0025 mole) in pyridine (4 ml.) at 100° during 30 min., followed by the usual isolation, gave the *monotoluene*-p-*sulphonyl derivative*, forming needles, m. p. 93—94°, after three crystallisations from ethanol (0·67 g., 81%) (Found: C, 54·3; H, 3·5; N, 8·2; S, 19·2. $C_{15}H_{12}O_3N_2S_2$ requires C, 54·2; H, 3·6; N, 8·4; S, 19·3%).

3-Hydroxy-5-p-nitrophenyl-1,2,4-thiadiazole.—3-Amino-5-*p*-nitrophenyl-1,2,4-thiadiazole [7] (0·55 g., 0·0025 mole) in concentrated sulphuric acid (5 ml.)–water (5 ml.) was treated, at −6° to −8°, with sodium nitrite (0·26 g., 0·00375 mole) in water (2 ml.) during 10 min. (transient colour change to green), stirred at −6° to −8° during 15 min., and finally allowed to come to room-temperature (1 hr.). After being diluted with water (10 ml.), the suspension was kept at approx. 100° for a few minutes until effervescence ceased. After storage at 0°, the crude product (0·42 g.) was collected, washed with water, and air-dried. Crystallisation from methanol (45 ml. per g.) yielded *3-hydroxy-5-p-nitrophenyl-1,2,4-thiadiazole* as orange granules, m. p. 251—253° (decomp., subject to the rate of heating) (0·18—0·24 g., 33—43%) (Found: C, 42·8; H, 2·3; N, 19·4. $C_8H_5O_3N_3S$ requires C, 43·05; H, 2·2; N, 18·8%).

5-Anilino-3-hydroxy-1,2,4-thiadiazole.—Powdered sodium nitrite (1·04 g., 0·015 mole) was added to chilled concentrated sulphuric acid (10 ml.), the temperature being allowed to rise sufficiently so that all the solid dissolved. This solution was added during 15 min. to a stirred suspension of finely powdered 3-amino-5-anilino-1,2,4-thiadiazole solvate [5] (2·38 g., 0·01 mole) in concentrated sulphuric acid (10 ml.), kept at −8° to −10°. The mixture was stirred vigorously at <5° while 85% phosphoric acid (15 ml.) was added during 40 min. to complete the diazotisation.[11] After being stirred for a further 45 min. at −5°, the viscous solution was carefully poured into ice-water (frothing). The liquid was warmed to 50° during 10 min., filtered from a little gum, and adjusted to pH 4 with 40% aqueous sodium hydroxide (80 ml.). The resulting precipitate was collected at 0°, washed with water, extracted with cold 3N-sodium hydroxide (2 × 10 ml.; extract C), and finally dissolved in hot 1·5N-sodium hydroxide (2 × 20 ml.). Acidification of the filtered solution with hydrochloric acid gave a precipitate (0·85 g.) which consisted, after crystallisation from acetone–ethanol, of 5-anilino-3-hydroxy-1,2,4-thiadiazole, m. p. and mixed m. p. 207—208° (0·72 g., 37%) (Found: C, 50·2; H, 3·6. Calc. for $C_8H_7ON_3S$: C, 49·7; H, 3·6%). Extract C: Acidification gave a small yield of crude unidentified material, m. p. between 152° and 159°, not identical with the required product.

Attempted Halogenation using Phosphorus Oxychloride.—A solution of 5-anilino-3-hydroxy-1,2,4-thiadiazole [3] (0·5 g.) in phosphorus oxychloride (3 ml.) was refluxed during 30 min.[23] The yellow liquid, stirred into ice, gave an uncrystallisable resinous solid. After treatment at 60—70° during 30 min., the starting material was substantially recovered. Addition to the above mixture of dimethylaniline (1 ml.) (which greatly accelerates the formation of 2,4,6-trichloropyrimidine from barbituric acid [24]) did not give more favourable results.

We thank the Council of the Chemical Society for a grant from the Research Fund.

ROYAL FREE HOSPITAL SCHOOL OF MEDICINE,
(UNIVERSITY OF LONDON), W.C.1.

[*Received, October 5th*, 1959.]

[23] Andersag and Westphal, *Ber.*, 1937, **70**, 2035.
[24] Baddiley and Topham, *J.*, 1944, 678.