962. *Congeners of Pyridine-4-carboxyhydrazide. Part II.*[1] *Derivatives of* 1,2,3-*Thiadiazole*

By D. L. Pain and R. Slack

The synthesis and biological activity of carboxyhydrazides and sulphonamides of the 1,2,3-thiadiazole series are described. The general chemistry of this ring system was also investigated. Unsuccessful attempts were also made to prepare the sulphonamides without recourse to explosive intermediates.

The work described in this Paper was carried out during the period 1953—1957, simultaneously with our development of the mononuclear isothiazoles,[2] with the initial object of comparing the antituberculosis activity of the hydrazides of these two systems with that of isoniazid. Unlike those for the isothiazoles, methods for the preparation of mononuclear 1,2,3-thiadiazoles have been reasonably well-established since 1896.[3] A review of early work has been published,[4] and further work on the ring system has since been reported.[5-9] Hurd and Mori's method [8] was the most convenient for the preparation of 1,2,3-thiadiazole-4-carboxylic acid, but in our hands this method failed when applied to the synthesis of 5-methyl-1,2,3-thiadiazole-4-carboxylic acid from hydrazones of α-oxobutyric acid.[10] For compounds in the 5-methyl series a modification of Wolff's method [11] was therefore used in which ethyl acetoacetate was converted, without isolation of intermediates, into ethyl diazoacetoacetate, which, on treatment with hydrogen sulphide, gave ethyl 5-methyl-1,2,3-thiadiazole-4-carboxylate.[11] 5-Methyl-1,2,3-thiadiazole [5d,11] and potassium permanganate gave the previously unknown 1,2,3-thiadiazole-5-carboxylic acid, which was

[1] Part I, D. D. Libman and R. Slack, *J.*, 1956, 2253.
[2] (*a*) A. Adams and R. Slack, *Chem. and Ind.*, 1956, 1232; (*b*) A. Adams and R. Slack, *J.*, 1959, 3061; (*c*) D. Buttimore, D. H. Jones, R. Slack, and K. R. H. Wooldridge, *J.*, 1963, 2032; (*d*) A. Adams and R. Slack, B.P. 835,753—4.
[3] H. von Pechmann and A. Nold, *Ber.*, 1896, **29**, 2588.
[4] L. L. Bambas, "The Chemistry of Heterocyclic Compounds," Interscience Publishers Inc., New York, 1952, vol. IV, p. 3.
[5] (*a*) J. C. Sheehan and P. T. Izzo, *J. Amer. Chem. Soc.*, 1949, **71**, 4059; (*b*) M. Tišler, M. Hrovat, and N. Machiedo, *Croat. Chem. Acta*, 1962, **34**, 183; (*c*) E. Lieber, N. Calvanico, and C. N. R. Rao, *J. Org. Chem.*, 1963, **28**, 257; (*d*) U. Schmidt, E. Heymann, and K. Kabitzke, *Chem. Ber.*, 1963, **96**, 1478; (*e*) D. Martin and W. Mucke, *Z. Chem.*, 1963, **3**, 347; (*f*) W. Ried and B. M. Beck, *Annalen*, 1964, **673**, 124, 128; (*g*) J. Goerdeler and G. Gnad, *Tetrahedron Letters*, 1964, 795; (*h*) D. Martin and W. Mucke, *Annalen*, 1965, **682**, 90.
[6] T. Kindt-Larsen and C. Pedersen, *Acta Chem. Scand.*, 1962, **16**, 1800.
[7] E. C. Taylor and E. E. Garcia, *J. Org. Chem.*, 1964, **29**, 2121.
[8] C. D. Hurd and R. I. Mori, *J. Amer. Chem. Soc.*, 1955, **77**, 5359.
[9] F. Eloy and C. Moussebois, *Bull. Soc. chim. belges*, 1959, **68**, 423.
[10] M. Barré, *Compt. rend.*, 1927, **184**, 825.
[11] L. Wolff, *Annalen*, 1904, **333**, 1.

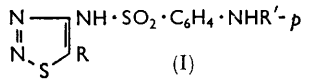
converted into the ethyl ester and hydrazide. Wolff [11] reported that decarboxylation of 1,2,3-thiadiazole-4,5-dicarboxylic acid led to 1,2,3-thiadiazole-4-carboxylic acid, but gave no proof of the orientation. His assumption was, in fact, correct. This corresponds to the decarboxylation of isothiazole-4,5-dicarboxylic acid, which gave isothiazole-4-carboxylic acid.[2b] 1,2,3-Thiadiazole-4-carboxylic acid, prepared according to Hurd and Mori [8] or by oxidation of 4-aminobenzo-1,2,3-thiadiazole [12] followed by decarboxylation, was converted by way of its methyl or ethyl ester into the hydrazide. Ethyl 5-methyl-1,2,3-thiadiazole-4-carboxylate [11] was also converted into the corresponding hydrazide and amide. The various hydrazides had no interesting biological properties.

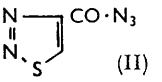
Attention was then turned towards the preparation of sulphonamides from the hitherto-unknown simple amino-1,2,3-thiadiazoles. Attempted conversion of 5-methyl-1,2,3-thiadiazole-4-carbonamide into the corresponding amine by the Hofmann method failed, but the amine was obtained by the Curtius reaction. The carboxyazide was prepared in solution and was converted without isolation into the ethylurethane, benzylurethane, and isocyanate. The ethylurethane could only be hydrolysed with difficulty, but the benzylurethane and isocyanate were both readily hydrolysed by acid to the amine, although the isocyanate route gave the better overall yield. The amine was converted into the N^4-acetylsulphonamide and thence into 4-*p*-aminobenzenesulphonamido-5-methyl-1,2,3-thiadiazole [13] (I; R = Me, R′ = H). The corresponding desmethylsulphonamide [13] (I; R = R′ = H) could be prepared without the use of intermediate diazo-esters. 1,2,3-Thiadiazole-4-carboxylic acid [8] was converted into the acid chloride and thence into the carboxyazide (II), either direct (70% yield) or *via* the hydrazide (56% yield overall). The only satisfactory route from the carboxyazide to the corresponding amine was by way of the isocyanate. Heating the carboxyazide in ethanol gave the ethylurethane, which could not be hydrolysed to the amine (cf. the 5-methyl analogue). The action [14] of hydrogen bromide–acetic acid on the benzylurethane gave a mixture of the amine and 4-acetamido-1,2,3-thiadiazole. The intermediate carboxyazide (II) is highly explosive in the dry state and is *dangerous to handle*.[15] It decomposed smoothly on heating in toluene, but great caution is advised. For satisfactory results the carboxyazide must be perfectly dry, since reaction with water gave the symmetrical urea. 4-Amino-1,2,3-thiadiazole was converted into the N^4-acetylsulphonamide (I; R = H, R′ = Ac). Alkaline hydrolysis of this compound was unsatisfactory, but boiling with N-hydrochloric acid gave a moderate yield of the sulphonamide (I; R = R′ = H). Unstable salts [13] of this sulphonamide could be prepared by the action of methanolic potassium hydroxide or triethylamine. It was converted into the succinoyl (I; R = H, R′ = CO·$[CH_2]_2$·CO_2H) and phthaloyl derivatives (I; R = H, R′ = CO·C_6H_4·CO_2H-*o* by the action of the appropriate anhydride.[16] Many attempts to prepare sulphonamides without recourse to the explosive azides failed. Thus, treatment of 1-acetyl-2-toluene-*p*-sulphonylhydrazine [17] with thionyl chloride gave the chloro-compound (III) and not 4-chloro-1,2,3-thiadiazole. On treatment of the chloro-compound (III) with potassium phthalimide, hydrogen chloride was eliminated to give 1,4-dihydro-3,6-dimethyl-1,4-di(toluene-*p*-sulphonyl)-1,2,4,5-tetrazine.[18] Again, attempts were made to build up the thiadiazole ring from sulphanilyl- and phthaloyl-amidrazone, but these compounds [(IV) and (V)] could not be cyclised.

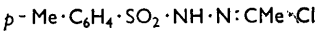
Hurd and Mori's method [8] has been modified to yield 5-amino-1,2,3-thiadiazole.[5g] Phthalimidoacetaldehyde [19] was converted into its ethoxycarbonylhydrazone and this in the presence of thionyl chloride gave 5-phthalimido-1,2,3-thiadiazole, which on treatment

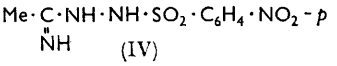
[12] K. Fries and H. Reitz, *Annalen*, 1936, **527**, 38.
[13] R. Slack, D. L. Pain, and H. J. Barber (May and Baker Ltd.), B.P. 806,812.
[14] D. Ben-Ishai and A. Berger, *J. Org. Chem.*, 1952, **17**, 1564.
[15] A.R.D.E. (Woolwich), personal communication.
[16] M. L. Moore and C. S. Miller, *J. Amer. Chem. Soc.*, 1942, **64**, 1572.
[17] K. Freudenberg and F. Blümmel, *Annalen*, 1924, **440**, 45.
[18] R. Huisgen, H. J. Sturm, and M. Seidel, *Chem. Ber.*, 1961, **94**, 1555.
[19] E. Radde, *Ber.*, 1922, **55**, 3174.

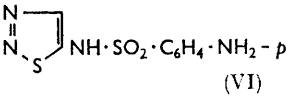
with hydrazine hydrate gave the amine. This was converted into the sulphonamide (VI). Various other *N*-substituents were introduced into 5-amino-1,2,3-thiadiazole in attempts to obtain biologically active analogues of known therapeutic agents. The acetamido-,[5g] chloroacetamido-, and dichloroacetamido-compounds were prepared in the usual way and

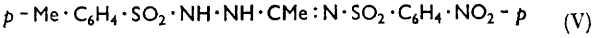

(I)


(II)


(III)


(IV)


(VI)

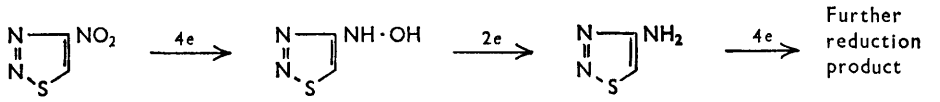

(V)

the second of these was treated with diethylamine to give 5-diethylaminoacetamido-1,2,3-thiadiazole, which is an analogue of the local anæsthetic, Xylocaine.[20] Reaction[21] of 5-amino-1,2,3-thiadiazole with carbonyl chloride gave the symmetrical urea, with ethyl chloroformate a mixture of mono-[5h] and bis-ethoxycarbonyl compounds, and normal azomethines with anisaldehyde and vanillin. Attempts to methylate[22] the amine and to condense it with 2,2-dichloroethyl chloroformate[23] failed.

Only a limited number of compounds can be prepared by the methods described above and direct substitution of the ring was therefore investigated. It has been predicted[24] by molecular-orbital calculations that the 5-position should be the position of maximum reactivity for electrophilic substitution. However, nitration and bromination of 1,2,3-thiadiazole[11] under mild conditions failed and more vigorous conditions ruptured the nucleus. Isothiazole compounds are readily nitrated and brominated in the 4-position. The Friedel–Crafts reaction with acetyl chloride did not take place, nor did the Chichibabin reaction with sodamide. Equally, 1,2,3-thiadiazole-4-carboxylic acid could be neither nitrated nor brominated. 4- and 5-Amino-1,2,3-thiadiazole were both readily nitrated, but in each case the highly explosive *N*-nitro-amine was formed. The structures of these were proved by infrared spectroscopy. Attempted rearrangement[25] of the *N*-nitro-amines in concentrated sulphuric acid merely caused decomposition. Attempted reductions to the hydrazines were also unsuccessful. When the amino-group was blocked, nitration did not occur, but in the nitration of acetamido-compounds under vigorous conditions, the protecting group was removed and then the *N*-nitro-amine was formed. With 5-phthalimido-1,2,3-thiadiazole, only the benzene ring was nitrated. The product was 5-(4-nitrophthalimido)-1,2,3-thiadiazole, reaction with hydrazine hydrate followed by hydrolysis giving 4-nitrophthalic acid. 4-Amino-1,2,3-thiadiazole reacted normally with acetic anhydride. It could be diazotised with difficulty and the diazonium solution coupled with β-naphthol to give a poor yield of a red azo-dye. 5-Amino-1,2,3-thiadiazole did not form azo-dyes,[5g] but a poor yield of 5-chloro-1,2,3-thiadiazole was obtained by the action of nitrous acid and hydrochloric acid in the presence of copper. In the isothiazole series, both 4- and 5-amino-compounds appear to be diazotised normally. Treatment of a mixture of 5-amino-1,2,3-thiadiazole, bromine, and hydrobromic acid with sodium nitrite gave 4,5-dibromo-1,2,3-thiadiazole. A poor yield of 4-nitro-1,2,3-thiadiazole was obtained by the reaction between the corresponding amine and nitrous acid in the presence of sodium

[20] N. M. Löfgren and B. J. Lundqvist, (*a*) *Svensk kem. Tidskr.*, 1946, **58**, 206; (*b*) B.P. 634,072; (*c*) U.S.P. 2,441,498.
[21] D. F. Kutepov and N. S. Rozanova, *Zhur. obshchei Khim.*, 1956, **26**, 1737.
[22] H. T. Clarke, H. B. Gillespie, and S. Z. Weisshaus, *J. Amer. Chem. Soc.*, 1933, **55**, 4571.
[23] J. I. Jones, *J.*, 1957, 2735.
[24] R. Zahradník and J. Koutecký, *Coll. Czech. Chem. Comm.*, 1961, **26**, 156.
[25] J. B. Dickey, E. B. Towne, and G. F. Wright, *J. Org. Chem.*, 1955, **20**, 499; S. Kasman and A. Taurins, *Canad. J. Chem.*, 1956, **34**, 1261.

cobaltinitrite and cuprous cuprisulphite.[26] Polarographic reduction of the nitro-compound indicated, by comparison with nitrobenzene, that reduction took place in three stages;



Attempted reduction of methyl 1,2,3-thiadiazole-4-carboxylate with sodium borohydride failed, since ring cleavage occurred. Distillation of 1,2,3-thiadiazole-4-carboxyamide with phosphoric oxide gave the 4-cyano-compound, which has been reported but not described.[72] With hydrogen sulphide in pyridine the nitrile gave the thioamide. 1-Benzenesulphonyl-2-(1,2,3-thiadiazole-4-carbonyl)hydrazine was prepared from 1,2,3-thiadiazole-4-carbonyl chloride, but it could not be converted into the aldehyde. 1-(1,2,3-Thiadiazole-4-carbonyl)-thiosemicarbazide was obtained from the acid chloride, but attempted cyclisation to the corresponding mercapto-1,2,4-triazole under alkaline conditions failed because of ring cleavage. Diethylamine and 1,2,3-thiadiazole-4-carbonyl chloride under anhydrous conditions gave the diethylcarboxyamide.

Many compounds of the 1,2,3-thiadiazole series are unstable to the action of light. Photolysis is known [28] to produce 1,4-dithiafulvenes. 4-Amino-1,2,3-thiadiazole was the least stable compound encountered; it rapidly became brown. Slow reactions involving the amine were therefore preferably performed in the dark. 1,2,3-Thiadiazole-4-carboxylic acid was difficult to obtain colourless; after it had rapidly turned pale yellow or pink, however, no further decomposition occurred. 4-Cyano-1,2,3-thiadiazole quickly became pink, but other compounds darkened only after long periods of exposure to light. Most of the compounds mentioned above seem stable to moderate heat but all should be treated with care. The explosive nature of the carboxyazides and *N*-nitro-amines has already been mentioned and on one occasion an ethereal extract of 4-amino-1,2,3-thiadiazole, obtained after continuous extraction, exploded as the last traces of solvent were removed. This may have been caused by the presence of unchanged carboxyazide. 1,2,3-Thiadiazole itself can usually be distilled at atmospheric pressure, but once it decomposed explosively. In the preparation of 4-cyano-1,2,3-thiadiazole, however, the corresponding amide was dry-distilled with phosphoric oxide, when a temperature exceeding 250° was probably reached. The 1,2,3-thiadiazole system is very unstable to the action of alkali, especially at temperatures above 60°. For this reason Hofmann degradation of the amides and similar alkaline reactions were impossible, and nearly all hydrolyses had to be carried out with dilute acid. Even here, and particularly in the 5-series, some instability was noted.

1,2,3-Thiadiazole derivatives of benzimidazole, benzoxazole, and benzothiazole are known to have anthelmintic activity.[29] Some phosphorous insecticides incorporating the 1,2,3-thiadiazole ring have also been prepared.[30] The sulphonamides (I; R = R′ = H) and (I; R = Me, R′ = H) showed good antibacterial properties, but the explosive nature of the necessary intermediates made them commercially unacceptable. The sulphonamide (VI) was inactive. The Xylocaine analogue, 5-diethylaminoacetamido-1,2,3-thiadiazole, and 1,2,3-thiadiazole-4-*NN*-diethylcarboxyamide showed no pharmacological activity.

Experimental

Methyl 1,2,3-Thiadiazole-4-carboxylate.—A solution of 1,2,3-thiadiazole-4-carboxylic acid [8] (12·4 g.) in dry methanol (200 ml.) was boiled under reflux for 2 hr., with dry hydrogen chloride

[26] B. Prijs, J. Ostertag, and H. Erlenmeyer, *Helv. Chim. Acta*, 1947, **30**, 1200.
[27] P. Davis *et al.* (Merck and Co. Inc.), F.P. 1,334,102; S. African P. 62/2,838.
[28] W. Kirmse and L. Horner, *Annalen*, 1958, **614**, 4.
[29] L. H. Sarett and H. D. Brown, Belg. P. 599,143 and 614,236; U.S.P. 3,017,415 and 3,055,907.
[30] R. L. McConnell and H. W. Coover (Eastman Kodak Co.), U.S.P. 3,072,669.

being passed in continuously. The solution was evaporated *in vacuo* and the residue recrystallised from light petroleum (b. p. 60—80°) to give the *ester* (7·6 g., 55%) as colourless needles, m. p. 89—90° (Found: N, 19·7; S, 22·4. $C_4H_4N_2O_2S$ requires N, 19·45; S, 22·25%).

Ethyl 1,2,3-thiadiazole-4-carboxylate was prepared similarly. It was recrystallised from light petroleum (b. p. 60—80°) to give colourless needles (48%), m. p. 87—88° (lit.,[8] m. p. 86—86·5°).

1,2,3-*Thiadiazole-5-carboxylic Acid.*—A hot solution of potassium permanganate (31 g.) in water (300 ml.) was added in 4 portions to a boiling mixture of 5-methyl-1,2,3-thiadiazole [11] (9·8 g.), potassium carbonate (30 g.), and water (200 ml.). The first three portions were decolourised within 45 min., but the last portion needed a further 2 hr. reflux. The last traces of permanganate were destroyed with a little ethanol, and the manganese dioxide was removed and extracted with boiling water. The combined aqueous solutions were acidified and concentrated *in vacuo* to small bulk. The concentrate was continuously extracted with ether for 32 hr. and the extract evaporated. The residue was recrystallised from benzene to give the *acid* (6·5 g., 51%) as colourless needles, m. p. 104—106° (Found: N, 21·75; S, 24·9. $C_3H_2N_2O_2S$ requires N, 21·55; S, 24·65%).

Ethyl 1,2,3-*thiadiazole-5-carboxylate* was prepared from the acid by the Fischer–Speier method. The *ester* was obtained as a colourless liquid (60%), b. p. 103—105°/14 mm. (Found: C, 38·4; H, 4·1; S, 20·3. $C_5H_6N_2O_2S$ requires C, 38·0; H, 3·8; S, 20·3%).

Dimethyl 1,2,3-*Thiadiazole-4,5-dicarboxylate.*—A solution of 1,2,3-thiadiazole-4,5-dicarboxylic acid [11] (3·84 g., 0·02 mole) in ether (50 ml.) was added slowly with shaking to an ice-cooled solution of diazomethane in ether (150 ml.; from 15 g. *N*-methyl-*N*-nitrosourea; *ca.* 0·1 mole) keeping the temperature below 10°. After 48 hr. at room temperature, the solution was evaporated *in vacuo* below 30° and the residue was distilled. The first fraction (0·2 g.) was dimethyl oxalate, m. p. 49—51°, b. p. 80—90° (bath)/10 mm. The second fraction was the desired ester (2 g., 50%), a yellow oil, b. p. 160° (bath)/10 mm.

The latter with methanolic hydrazine hydrate gave 1,2,3-*thiadiazole-4,5-di*(*carboxyhydrazide*) as yellow needles, m. p. 161—162° (decomp.) after recrystallisation from water (Found: N, 40·9; S, 15·9. $C_4H_6N_6O_2S$ requires N, 41·55; S, 15·85%).

1,2,3-*Thiadiazole-4-carbonyl Chloride.*[13]—1,2,3-Thiadiazole-4-carboxylic acid (69 g.) in thionyl chloride (300 ml.) was boiled under reflux for 4·5 hr. The excess of thionyl chloride was removed *in vacuo* and the residue recrystallised from a large volume of light petroleum (b. p. 40—60°) to give the acid chloride (75 g., 95%) as colourless plates, m. p. 34—35°, b. p. 52—54°/1 mm. (considerable decomp.) (Found: Cl, 23·95; S, 22·0. Calc. for C_3HClN_2OS: Cl, 23·85; S, 21·6%).

1,2,3-*Thiadiazole-4-carboxyhydrazide.*[13]—(*a*) A methanolic solution of methyl 1,2,3-thiadiazole-4-carboxylate (7·6 g.) was treated at room temperature with hydrazine hydrate (80%). After 2 hr. the solid was collected and recrystallised from water to give the hydrazide (5·1 g., 74%) as blades, m. p. 214° (decomp.) (Found: C, 25·1; H, 2·8; N, 38·7; S, 22·45. Calc. for $C_3H_4N_4OS$: C, 25·0; H, 2·8; N, 38·85; S, 22·25%). The hydrazide may also be prepared (52%) from the ethyl ester, but the reaction mixture must be heated at 50°.

(*b*) 1,2,3-Thiadiazole-4-carbonyl chloride (45 g.) in dry ether (500 ml.) was added slowly to a stirred, ice-cooled solution of hydrazine hydrate (36 ml., 100%) in dry ether (250 ml.), keeping the temperature below 20°. After stirring for a further 0·5 hr., the solid was collected and recrystallised from water to give the hydrazide (32 g., 73%).

1,2,3-*Thiadiazole-5-carboxyhydrazide* was prepared from ethyl 1,2,3-thiadiazole-5-carboxylate by the method (*a*) above. It formed colourless blades (55%), m. p. 151—152°, after two recrystallisations from methanol or ethyl acetate (Found: N, 39·1; S, 22·4%).

5-Methyl-1,2,3-thiadiazole-4-carboxyhydrazide [13] was prepared similarly (79%). It was recrystallised from ethanol to give colourless plates, m. p. 152—153° (Found: N, 35·6; S, 20·4. Calc. for $C_4H_6N_4OS$: N, 35·4; S, 20·25%).

1,2,3-*Thiadiazole-4-carboxyamide.*—1,2,3-Thiadiazole-4-carbonyl chloride (67 g.) in dry acetone (100 ml.) was added dropwise with stirring to an ice-cooled solution of ammonia (100 ml., *d* 0·88) in water (200 ml.). Stirring was continued for a further 10 min. and water was added. The solid was collected, washed with water, and recrystallised from water to give the *amide* (41·4 g., 71%) as colourless needles, m. p. 220—222° (decomp., subl.) (Found: C, 28·1; H, 2·5; N, 32·85; S, 24·95. $C_3H_3N_3OS$ requires C, 27·9; H, 2·35; N, 32·55; S, 24·8%).

5-*Methyl*-1,2,3-*thiadiazole*-4-*carboxyamide.*—Ethyl 5-methyl-1,2,3-thiadiazole-4-carboxylate

(15 g.) and liquid ammonia (20 ml.) were kept at room temperature in a sealed tube for 24 hr. The excess of ammonia was removed and the residue recrystallised from ethanol to give the *amide* (10·9 g., 87%) as colourless needles, m. p. 118—121° (Found: N, 29·15; S, 22·8. $C_4H_5N_3OS$ requires N, 29·35; S, 22·4%).

1,2,3-*Thiadiazole*-4-NN-*diethylcarboxyamide*.—A solution of anhydrous diethylamine (21 g., 30·3 ml.) in dry benzene (50 ml.) was added slowly with stirring to an ice-cooled solution of 1,2,3-thiadiazole-4-carbonyl chloride (17·5 g.) in dry benzene (100 ml.). The mixture was stirred for a further 1 hr. and allowed to stand for 2 hr. After filtration, the solution was saturated with hydrogen chloride and evaporated. The residue was extracted with dry ether and the extract evaporated. The residual oil was distilled to give the *amide* (17·8 g., 68%) as a pale yellow liquid, b. p. 85—89°/0·15 mm. (Found: N, 22·3; S, 17·1. $C_7H_{11}N_3OS$ requires N, 22·7; S, 17·3%).

1,2,3-*Thiadiazole*-4-*carboxyanilide* (71%), m. p. 162—163·5° was prepared similarly (by Dr. E. W. Parnell) (Found: N, 20·4; S, 15·1. $C_9H_7N_3OS$ requires N, 20·4; S, 15·55%).

1-*Benzenesulphonyl*-2-(1,2,3-*thiadiazole*-4-*carbonyl*)*hydrazine* (Prepared by Dr. D. H. Jones).—1,2,3-Thiadiazole-4-carbonyl chloride (15 g.) in chloroform (50 ml.) was added during 15 min. with stirring to a suspension of benzenesulphonylhydrazine (17·2 g.) in chloroform (200 ml.). The temperature rose to 30° and stirring was continued for a further 15 min. The solid was collected, stirred with 2N-sodium carbonate (150 ml.) and charcoal, and filtered. The filtrate was washed with ether and adjusted to pH 7 with glacial acetic acid. The precipitated solid was collected, washed with water and with ethanol, and recrystallised from aqueous dimethylformamide to give the *hydrazine*, m. p. 219—222° (decomp.) (Found: C, 38·1; H, 2·9; N, 20·2; S, 22·2. $C_9H_8N_4O_3S_2$ requires C, 38·0; H, 2·85; N, 19·7; S, 22·25%).

1-(1,2,3-*Thiadiazole*-4-*carbonyl*)*thiosemicarbazide* (Prepared by Dr. D. H. Jones).—1,2,3-Thiadiazole-4-carboxyhydrazide (86 g.) and potassium thiocyanate (116·5 g.) in 3·3N-hydrochloric acid (450 ml.) were heated at 100° for 6 hr. A small amount of unchanged starting material was removed and the filtrate kept at 0°. The *thiosemicarbazide* crystallised as a yellow solid, m. p. 185—188° (Found: C, 23·5; H, 2·2; N, 33·9. $C_4H_5N_5OS_2$ requires C, 23·65; H, 2·5; N, 34·45%).

4-*Cyano*-1,2,3-*thiadiazole*.[27]—A mixture of 1,2,3-thiadiazole-4-carboxyamide (50 g.) and phosphoric oxide (40 g.) was dry-distilled at 10 mm. The solid distillate was extracted with ether, the extract evaporated, and the residue recrystallised from benzene–light petroleum to give the *nitrile* (36 g., 84%) as colourless needles, m. p. 62—63° (Found: C, 32·2; H, 1·0; N, 37·65; S, 29·0. C_3HN_3S requires C, 32·45; H, 0·9; N, 37·8; S, 28·85%).

4-*Thiocarbamoyl*-1,2,3-*thiadiazole*.—Hydrogen sulphide was passed into a solution of 4-cyano-1,2,3-thiadiazole (36 g.) in dry pyridine (250 ml.) for 6 hr. The solution was evaporated *in vacuo* and the residue extracted with cold 2N-sodium hydroxide. Reprecipitation with 2N-hydrochloric acid and recrystallisation from ethanol, with the addition of charcoal, gave the *thioamide* (31 g., 66%) as golden needles, m. p. 176—178° (decomp.) (Found: C, 24·6; H, 2·05; N, 29·0; S, 44·0. $C_3H_3N_3S_2$ requires C, 24·8; H, 2·1; N, 28·95; S, 44·15%).

1,2,3-*Thiadiazole*-4-*carboxyazide* [13] (II).—(*a*) A solution of sodium nitrite (28·6 g.) in water (100 ml.) was added slowly with stirring to an ice-cooled solution of 1,2,3-thiadiazole-4-carboxyhydrazide (51 g.) in water (700 ml.) containing concentrated hydrochloric acid (38 ml.), the temperature of the mixture being kept below 10°. Stirring was continued for a further 0·5 hr., after which the solid (42·5 g., 77%) was collected and dried in a vacuum desiccator. A sample was purified by dissolution in toluene at 30° and cooling to 0°, when the azide was obtained as colourless needles, m. p. 112° (decomp.) (Found: N, 44·7; S, 20·75. Calc. for C_3HN_5OS: N, 45·15; S, 20·65%).

(*b*) 1,2,3-Thiadiazole-4-carbonyl chloride (15 g.) in dry acetone (100 ml.) was added dropwise with stirring to a solution of sodium azide (7 g.) in water (500 ml.), the temperature of the mixture being kept below 5°. After a further stirring lasting for 15 min., the azide (11 g., 70%) was collected, washed with water, and dried in a vacuum desiccator. This compound is extremely explosive in the dry state [15] and is sternutatory.

4-*Amino*-1,2,3-*thiadiazole*.[13]—A suspension of 1,2,3-thiadiazole-4-carboxyazide (42 g.) in dry toluene (1 l.) was heated at 90° until evolution of nitrogen was complete and then for a further 1 hr. The solution was filtered, poured rapidly into concentrated hydrochloric acid (500 ml.), shaken vigorously, and set aside overnight. The aqueous layer was evaporated *in vacuo* and the residue treated with saturated sodium hydrogen carbonate solution (200 ml.) and neutralised

by the addition of solid sodium hydrogen carbonate. The precipitated sodium chloride was removed and the solution extracted with ether (10 × 200 ml.). [Continuous extraction is unsuitable, because of the thermal instability of the product.] The extract was dried (Na_2SO_4) and evaporated *in vacuo* below 30°. The residue (19·2 g., 70%) crystallised on trituration. Two recrystallisations from benzene–light petroleum gave the amine as very pale yellow needles, m. p. 44—46°, which were extremely unstable to light (Found: C, 24·0; H, 3·15; N, 42·4; S, 32·05. Calc. for $C_2H_3N_3S$: C, 23·75; H, 3·0; N, 41·55; S, 31·7%).

4-*Benzyloxycarbonylamino*-1,2,3-*thiadiazole*.—A solution of 1,2,3-thiadiazole-4-carboxyazide (10 g.) in benzyl alcohol (100 ml.) was heated at 80—90° until evolution of nitrogen was complete. The excess of benzyl alcohol was removed at 0·1 mm. below 100°. The residue was recrystallised from light petroleum (b. p. 80—100°) to give the *benzylurethane* (12 g., 76%) as colourless needles, m. p. 93—95° (Found: N, 17·9; S, 13·2. $C_{10}H_9N_3O_2S$ requires N, 17·85; S, 13·65%).

4-*Ethoxycarbonylamino*-1,2,3-*thiadiazole* was prepared similarly. It was recrystallised from light petroleum (b. p. 80—100°) to give the ethylurethane (80%), m. p. 105—107° (Found: C, 34·8; H, 4·2; N, 24·4; S, 18·5. $C_5H_7N_3O_2S$ requires C, 34·65; H, 4·1; N, 24·25; S, 18·5%).

4-*Ethoxycarbonylamino*-5-*methyl*-1,2,3-*thiadiazole*.—5-Methyl-1,2,3-thiadiazole-4-carboxyhydrazide (3·16 g.) was dissolved in N-hydrochloric acid (30 ml.), layered with ether (30 ml.), and cooled to 0°. A concentrated aqueous solution of sodium nitrite (1·5 g.) was added slowly with vigorous stirring, the temperature of the mixture being kept below 10°. After stirring for a further 10 min., the layers were separated and the aqueous solution extracted with ether (2 × 15 ml.). The combined ether solutions (of the azide) were washed with saturated sodium hydrogen carbonate solution, dried ($CaCl_2$) for 5 min., and poured into dry ethanol (40 ml.). The ether was removed through a short column and the ethanol solution boiled under reflux until evolution of nitrogen ceased (1·5 hr.). Evaporation *in vacuo* and recrystallisation from a large volume of light petroleum (b. p. 80—100°) with the addition of charcoal gave the *ethylurethane* (1·7 g., 45%) as colourless needles, m. p. 53—54° (Found: N, 22·2; S, 17·25. $C_6H_9N_3O_2S$ requires N, 22·45; S, 17·15%).

4-*Benzyloxycarbonylamino*-5-*methyl*-1,2,3-*thiadiazole* was prepared similarly. The crude product was recrystallised three times from light petroleum (b. p. 60—80°) to give colourless needles (43%), m. p. 76—78° (Found: N, 16·9; S, 13·3. $C_{11}H_{11}N_3O_2S$ requires N, 16·85; S, 12·85%).

4-*Amino*-5-*methyl*-1,2,3-*thiadiazole*.[13]—(*a*) Prepared as previously described, this formed colourless prisms (41%), m. p. 128° (decomp.) (Found: C, 31·4; H, 4·2; N, 36·8; S, 28·7. Calc. for $C_3H_5N_3S$: C, 31·3; H, 4·35; N, 36·5; S, 27·85%).

(*b*) 4-Benzyloxycarbonylamino-5-methyl-1,2,3-thiadiazole (5·3 g.) was treated with a solution of hydrogen bromide in glacial acetic acid (21 g., 36%) and the mixture set aside overnight. Dry ether was added and the solid collected, washed with dry ether, and dissolved in water. After being washed with ether, the aqueous solution was made alkaline with sodium hydrogen carbonate and extracted with ether. The extract was evaporated and the residue recrystallised from benzene to give the amine (1·4 g., 57%, overall yield from hydrazide 25%).

4-*Acetamido*-5-*methyl*-1,2,3-*thiadiazole* was obtained from the amine by the action of acetic anhydride at 100° for 0·5 hr. It crystallised from benzene–light petroleum (b. p. 80—100°) as colourless needles, m. p. 118—119° (Found: N, 26·6; S, 20·3. $C_5H_7N_3OS$ requires N, 26·75; S, 20·4%).

4-p-*Acetamidobenzenesulphonamido*-1,2,3-*thiadiazole* [13] (I; R = H, R′ = Ac).—A solution of *p*-acetamidobenzenesulphonyl chloride (150 g.) in dry pyridine (750 ml.) was added slowly with stirring to an ice-cooled solution of 4-amino-1,2,3-thiadiazole (60 g.) in dry pyridine (750 ml.). The solution was set aside in the dark for 72 hr., after which it was poured into 2N-sulphuric acid (7·5 l.) containing sufficient ice to keep the final temperature below 10°. The precipitated solid was collected, washed with water, and dissolved in 2N-ammonia. After stirring with charcoal (21 g.) for 0·5 hr. and filtering, the solution was brought to pH 8 and again filtered. 0·1N-Sulphuric acid was added until, at pH *ca.* 7·6, the pure sulphonamide began to crystallise. After being left some time, the almost colourless plates (131 g., 77%), m. p. 185—186° (decomp.) were collected (Found: N, 18·95; S, 21·95. Calc. for $C_{10}H_{10}N_4O_3S_2$: N, 18·75; S, 21·5%).

4-*p*-Acetamidobenzenesulphonamido-5-methyl-1,2,3-thiadiazole [13] (I; R = Me, R′ = Ac) was prepared and purified similarly. It had m. p. 202° (decomp.) (Found: N, 17·7; S, 20·65. Calc. for $C_{11}H_{12}N_4O_3S_2$: N, 17·95; S, 20·55%).

4-p-*Aminobenzenesulphonamido*-1,2,3-*thiadiazole* [13] (I; R = R′ = H).—4-*p*-Acetamidobenzenesulphonamido-1,2,3-thiadiazole (131 g.) in N-hydrochloric acid (4 l.) was boiled under reflux until a clear solution was obtained (0·5 hr.). Charcoal (13 g.) was added and the mixture boiled for a further 5 min. After filtration, the solution was cooled and 2N-ammonia added until the solid just dissolved (pH *ca.* 3·6). The solution was seeded and allowed to crystallise. The sulphonamide (72 g., 60%) was obtained as pale golden plates, m. p. 164—165° (decomp.) (Found: C, 37·5; H, 3·25; N, 21·85; S, 24·85. Calc. for $C_8H_8N_4O_2S_2$: C, 37·5; H, 3·15; N, 21·85; S, 25·0%); pK_a = 7·18 (50% ethanol).

4-*p*-Aminobenzenesulphonamido-5-methyl-1,2,3-thiadiazole [13] (I; R = Me, R′ = H) was prepared similarly. It was recrystallised from ethanol to give pale yellow blades (90%), m. p. 170° (decomp.) (Found: N, 20·6; S, 23·55. Calc. for $C_9H_{10}N_4O_2S_2$: N, 20·75; S, 23·7%); pK_a = 7·76 (50% methanol).

Triethylamine Salt of 4-p-*Aminobenzenesulphonamido*-1,2,3-*thiadiazole*.[13]—Prepared as previously described, this had m. p. 80—81° (decomp.) (Found: N, 19·35; S, 17·7. Calc. for $C_{12}H_{23}N_5O_2S_2$: N, 19·65; S, 18·0%). It became yellow on standing *in vacuo* at room temperature.

4-p-β-*Carboxypropionamidobenzenesulphonamido*-1,2,3-*thiadiazole* [13] (I; R = H, R′ = CO·$[CH_2]_2$·CO_2H).—Prepared as previously described. The monohydrate was obtained as a colourless solid, m. p. 170° (decomp.) (Found: C, 39·2; H, 3·8; N, 15·05; S, 17·4; H_2O, 4·35. Calc. for $C_{12}H_{12}N_4O_5S_2,H_2O$: C, 38·5; H, 3·75; N, 14·95; S, 17·15; H_2O, 4·8%).

4-*p*-2-Carboxybenzamidobenzenesulphonamido-1,2,3-thiadiazole [13] (I; R = H, R′ = CO·C_6H_4·CO_2H-*o*) was prepared as previously described, colourless needles, m. p. 192° (decomp.) (Found: C, 47·6; H, 3·05; N, 13·2; S, 15·8. Calc. for $C_{16}H_{12}N_4O_5S_2$: C, 47·5; H, 3·0; N, 13·85; S, 15·85%).

Phthalimidoacetaldehyde Ethoxycarbonylhydrazone.—A solution of ethoxycarbonylhydrazine (60 g.) in warm toluene (500 ml.) was added slowly to a solution of phthalimidoacetaldehyde (100 g.) in warm toluene (1 l.). After 3 hr. the solid was collected, washed with light petroleum (b. p. 40—60°), and dried. The *hydrazone* (135 g., 93%) was obtained as colourless plates, m. p. 165—167°. A sample recrystallised from ethanol had m. p. 168—169° (Found: C, 57·0; H, 4·75; N, 15·1. $C_{13}H_{13}N_3O_4$ requires C, 56·7; H, 4·75; N, 15·25%).

5-*Phthalimido*-1,2,3-*thiadiazole*.—Phthalimidoacetaldehyde ethoxycarbonylhydrazone (27·5 g.) was added cautiously to thionyl chloride (30 ml.). After a few minutes there was a vigorous evolution of gas and the temperature rose to 40°. After standing overnight, the solid was collected, washed with ethyl acetate, and recrystallised from ethyl acetate or ethanol to give 5-*phthalimido*-1,2,3-*thiadiazole* (20·5 g., 89%) as colourless plates, m. p. 225—226° (Found: N, 17·9; S, 14·5. $C_{10}H_5N_3O_2S$ requires N, 18·2; S, 13·85%).

5-*Amino*-1,2,3-*thiadiazole*.[5g]—A solution of hydrazine hydrate (163 g., 100%) in ethanol (2 l.) was added slowly with stirring to 5-phthalimido-1,2,3-thiadiazole (360 g.) in boiling ethanol (5 l.). After cooling, the hydrazine phthalhydrazide was removed and the solution concentrated to 1 l. Ether (2·5 l.) was added and a further quantity of solid was removed. The filtrate was evaporated and the residue recrystallised from ethanol to give yellowish plates (121 g., 77%). A sample was recrystallised from benzene to give the amine as long colourless needles, m. p. 145—147° (decomp.) lit.,[5g] 152° (decomp.), (Found: N, 41·75; S, 31·4. Calc. for $C_2H_3N_3S$: N, 41·55; S, 31·7%).

5-p-*Acetamidobenzenesulphonamido*-1,2,3-*thiadiazole*.—A solution of 5-amino-1,2,3-thiadiazole (2·02 g.) and *p*-acetamidobenzenesulphonyl chloride (4·67 g.) in dry pyridine (40 ml.) was set aside at room temperature for 90 hr., and then poured into an excess of 2N-sulphuric acid. The solid was collected, washed with water, and recrystallised from ethanol with the addition of charcoal to give the *sulphonamide* (3·7 g., 62%) as pale orange needles, m. p. 188° (decomp.) (Found: N, 18·6; S, 21·7. $C_{10}H_{10}N_4O_3S_2$ requires N, 18·75; S, 21·5%).

5-p-*Aminobenzenesulphonamido*-1,2,3-*thiadiazole* (VI).—A solution of 5-*p*-acetamidobenzenesulphonamido-1,2,3-thiadiazole (13·3 g.) in N-sodium hydroxide (300 ml.) was heated on a steam-bath for 1 hr. After cooling, the solution was brought to pH 4 with 2N-hydrochloric acid. The solid which separated was recrystallised from ethanol, with the addition of charcoal, to give the *sulphonamide* (9 g., 79%) as a pale yellow solid, m. p. 172° (decomp.) (Found: C, 37·7; H, 3·4; N, 21·15; S, 24·9. $C_8H_8N_4O_2S_2$ requires C, 37·5; H, 3·15; N, 21·85; S, 25·0%); pK_a = 4·45 (50% ethanol).

5-*Acetamido*-1,2,3-*thiadiazole*.[5g]—5-Amino-1,2,3-thiadiazole (5 g.) and acetic anhydride (50 ml.) were heated together at 100° for 3 hr. The solid was collected, and evaporation of the

filtrate gave a further quantity of solid. The combined solids were recrystallised three times from water to give the amide (4·4 g., 62%) as colourless needles, m. p. 207—208° (decomp.) lit.,[5g] 212° (decomp.) (Found: N, 29·7; S, 22·8. Calc. for $C_4H_5N_3OS$: N, 29·35; S, 22·4%).

Similarly were prepared (by Mr. D. R. Broad): 5-*Propionamido*-1,2,3-*thiadiazole* (67%), m. p. 120—122° (Found: N, 27·2; S, 20·0. $C_5H_7N_3OS$ requires N, 26·75; S, 20·4%); 5-*isobutyramido*-1,2,3-*thiadiazole* (63%), m. p. 145—147° (Found: N, 24·4. $C_6H_9N_3OS$ requires N, 24·55%).

5-*Chloroacetamido*-1,2,3-*thiadiazole*.—A solution of chloroacetyl chloride (5·6 g.) in dry ether (20 ml.) was added dropwise with stirring to a suspension of 5-amino-1,2,3-thiadiazole (5 g.) in dry ether (150 ml.), the temperature being kept at 15° by occasional cooling. After further stirring lasting 0·5 hr., the solid (9 g., 100%) was collected. A sample was recrystallised twice from ethyl acetate (prolonged heating causes decomposition) to give the *amide* as colourless needles, m. p. 161—162° (Found: Cl, 19·65; S, 18·05. $C_4H_4ClN_3OS$ requires Cl, 19·95; S, 18·05%).

5-*Dichloroacetamido*-1,2,3-*thiadiazole* was prepared similarly (45%). It was recrystallised from ethyl acetate–light petroleum to give a buff solid, m. p. 170° (decomp.) (Found: Cl, 33·1; N, 19·75; S, 15·6. $C_4H_3Cl_2N_3OS$ requires Cl, 33·45; N, 19·8; S, 15·1%).

5-*Diethylaminoacetamido*-1,2,3-*thiadiazole*.—A solution of 5-chloroacetamido-1,2,3-thiadiazole (0·7 g.) and diethylamine (0·74 g., 1·04 ml.) in dry benzene (3 ml.) was boiled under reflux for 5 hr. After being washed with water, the solution was dried (Na_2SO_4) and evaporated *in vacuo*. The residue was recrystallised from light petroleum (b. p. 60—80°) to give the *amide monohydrate* as colourless needles, m. p. 79—80° (Found: N, 24·2; S, 14·05. $C_8H_{14}N_4OS,H_2O$ requires N, 24·1; S, 13·85%).

Action of Carbonyl Chloride on 5-*Amino*-1,2,3-*thiadiazole*.—A solution of 5-amino-1,2,3-thiadiazole (7·7 g.) in dry ethyl acetate (150 ml.) was added slowly with stirring to a solution of carbonyl chloride (35 g.) in dry ethyl acetate (42 ml.), the temperature being kept at 0—5°, and carbonyl chloride gas being passed in continuously. With carbonyl chloride gas still passing, the mixture was stirred at 0° for a further 20 min. and then at room temerature for 0·5 hr. The solid was collected and boiled under reflux with dry 1,2-dichloroethane (100 ml.) for 2·5 hr. The solid was collected and recrystallised from aqueous dimethylformamide to give NN′-*bis*-1,2,3-*thiadiazol*-5-*ylurea* as a buff powder, decomp. 270° (Found: C, 27·6; H, 2·05; N, 36·5; S, 26·2. $C_5H_4N_6OS_2$ requires C, 26·3; H, 1·75; N, 36·8; S, 28·1%).

Action of Ethyl Chloroformate on 5-*Amino*-1,2,3-*thiadiazole*.—A solution of ethyl chloroformate (5·4 g.) in dry ether (5 ml.) was added dropwise with stirring to an ice-cooled suspension of 5-amino-1,2,3-thiadiazole (5·4 g.) in dry ether (25 ml.) containing triethylamine (5·2 g., 7·2 ml.), the temperature being kept at 0—5°. After further stirring lasting 0·5 hr., the solid was collected. More solid was obtained from the filtrate by evaporation. The combined solids were extracted with boiling light petroleum (b. p. 60—80°) containing 5% benzene. The extract gave 5-*di*-(*ethoxycarbonyl*)*amino*-1,2,3-*thiadiazole* as clusters of yellow needles, m. p. 89—90° (Found: C, 41·05; H, 5·0; N, 17·3; S, 13·1. $C_8H_{11}N_3O_4S$ requires C, 39·2; H, 4·5; N, 17·15; S, 13·1%). The insoluble solid was recrystallised from ethyl acetate, with the addition of charcoal, to give 5-ethoxycarbonylamino-1,2,3-thiadiazole, m. p. 203—204° (decomp.) [lit.,[5h] 217° (decomp.)] (Found: C, 35·0; H, 4·25; N, 24·05; S, 17·8. Calc. for $C_5H_7N_3O_2S$: C, 34·65; H, 4·1; N, 24·25; S, 18·5%).

5-p-*Methoxybenzylideneamino*-1,2,3-*thiadiazole*.—5-Amino-1,2,3-thiadiazole (1·01 g.) and anisaldehyde (1·36 g.) in ethanol (10 ml.) were heated under reflux for 0·5 hr. Some solid separated and the liquors were evaporated *in vacuo* to give a further quantity. The combined solids were recrystallised from benzene to give the *Schiff's base* (1·55 g., 71%) as yellow crystals, m. p. 127·5—128·5° (Found: N, 19·4; S, 14·5. $C_{10}H_9N_3OS$ requires N, 19·2; S, 14·65%).

5-(4-*Hydroxy*-3-*methoxybenzylideneamino*)-1,2,3-*thiadiazole* was prepared similarly. It was recrystallised from a large volume of benzene to give bright yellow needles (22%), m. p. 170—171° (decomp.) (Found: N, 17·8; S, 13·8. $C_{10}H_9N_3O_2S$ requires N, 17·85; S, 13·65).

5-*Nitramino*-1,2,3-*thiadiazole*.—5-Amino-1,2,3-thiadiazole (2 g.) was dissolved in concentrated sulphuric acid (10 ml.) with cooling. Nitric acid (1·5 ml.; *d* 1·4) was added dropwise with stirring and ice-cooling. The solution was stirred at 0° for a further 5 min. and then allowed to warm up to room temperature with stirring. The mixture was poured on to ice and the solid collected, washed with water, and recrystallised from ethyl acetate–light petroleum, with the addition of charcoal, to give the *nitramine* as pale yellow plates, which exploded violently at

156°. The compound also exploded on being struck (Found: N, 37·6; S, 22·05. $C_2H_2N_4O_2S$ requires N, 38·35; S, 21·95%). The infrared spectrum showed bands at 1535 and 1342 cm.$^{-1}$, which are characteristic of either C–NO_2 or N–NO_2 bonds. There were no bands at 848 cm.$^{-1}$, which would be shown by C–NO_2 and no band at 1625 cm.$^{-1}$, which would be shown by C–NH_2 bonds.

4-*Nitramino*-1,2,3-*thiadiazole* was prepared similarly. It was recrystallised from ethyl acetate–light petroleum, with the addition of charcoal. It exploded violently at 124° (Found: N, 37·65; S, 22·3. $C_2H_2N_4O_2S$ requires N, 38·35; S, 21·95%).

5-4′-*Nitrophthalimido*-1,2,3-*thiadiazole*.—Nitric acid (2·1 ml., *d* 1·4) was added slowly with stirring to a solution of 5-phthalimido-1,2,3-thiadiazole (2·31 g.) in concentrated sulphuric acid (20 ml.) keeping the temperature at 30°. The solution was heated at 100° for 1 hr. and poured on to ice. The solid was collected and recrystallised from ethanol. It was proved to be 5-4′-nitrophthalimido-1,2,3-thiadiazole as follows:

Treatment with hydrazine hydrate gave 5-amino-1,2,3-thiadiazole and 4-nitrophthalhydrazide. The latter was hydrolysed to give 4-nitrophthalic acid, m. p. 160—161°.

4-(2-*Hydroxy*-1-*naphthylazo*)-1,2,3-*thiadiazole*.—4-Amino-1,2,3-thiadiazole (1 g.) in 4N-hydrochloric acid (10 ml.) was diazotised by treatment with an aqueous solution of sodium nitrite (0·7 g.). The solution was stirred for a further 15 min. and poured into a solution of β-naphthol (1·5 g.) in 2N-sodium hydroxide. The dark red coupling product which separated decomposed on attempted recrystallisation.

4-*Nitro*-1,2,3-*thiadiazole*.—A solution of 4-amino-1,2,3-thiadiazole hydrochloride (6·8 g.) in water (50 ml.) was added dropwise with vigorous stirring to a suspension of sodium nitrite (10 g.), sodium cobaltinitrite (5 g.), and cuprous cuprisulphite (2·5 g.) in water (75 ml.). The mixture was stirred for a further 0·5 hr. and filtered. The filtrate was extracted with ether (2 × 100 ml.) and the extract dried (Na_2SO_4) and evaporated. The residue was extracted with benzene, the extract boiled with charcoal, and the product recovered by precipitation with light petroleum (b. p. 60—80°). The solid was collected and recrystallised from cyclohexane (250 ml.) to give the *nitro-compound* (0·4 g., 7%) as deep yellow needles, m. p. 85—86·5° (Found: C, 18·3; H, 1·0; N, 32·45; S, 24·4. $C_2HN_3O_2S$ requires C, 18·3; H, 0·75; N, 32·05; S, 24·5%).

Polarographic Reduction of 4-*Nitro*-1,2,3-*thiadiazole*.—4-Nitro-1,2,3-thiadiazole (0·044 g.) was reduced polarographically in N-hydrochloric acid containing 5% of methanol, using a mercury anode. The half-wave potentials were found to be 74·3, 106, and 174. The first two correspond to those given by nitrobenzene (67 and 96). The third indicates a further 4*e* reduction of the 4-amino-1,2,3-thiadiazole.

5-*Chloro*-1,2,3-*thiadiazole* (Prepared by Mr. D. R. Broad).—Sodium nitrite (3·5 g.) in water (20 ml.) was added slowly with stirring at −25° to −18° to 5-amino-1,2,3-thiadiazole (5·05 g.) in 5N-hydrochloric acid (50 ml.) containing a trace of copper powder. The mixture was stirred at −10° for a further 1 hr., allowed to attain room temperature, cautiously neutralised with 50% sodium hydroxide solution, and extracted with ether. The extract was dried and evaporated, and the residue distilled to give 5-chloro-1,2,3-thiadiazole (0·82 g., 9%), b. p. 72—74°/27 mm.; $\nu_{max.}$ 3090w, 1435s, 1275w, 1255w, 1217s, 1094m, 1057s, 858s, 726m cm.$^{-1}$. Attempts to perform elemental analyses caused shattering of the apparatus.

4,5-*Dibromo*-1,2,3-*thiadiazole* (Prepared by Mr. D. R. Broad).—Bromine (4·8 ml.) was added to 5-amino-1,2,3-thiadiazole (3·04 g.) in concentrated hydrobromic acid (15·8 ml.; 48%) with ice–salt cooling. Sodium nitrite (5·65 g.) in water (20 ml.) was added dropwise, the temperature being kept below 10°. Copious brown fumes were evolved. After the mixture had attained room temperature, it was extracted with ether (3 × 100 ml.), and the extract was dried and evaporated, and the residue was distilled. Resublimation at 65—70°/21 mm. gave 4,5-*dibromo*-1,2,3-*thiadiazole* (2·1 g., 27%), m. p. 79—80°, b. p. 110—111°/23 mm. (Found: C, 9·85; Br, 66·2; N, 11·5; S, 13·1. $C_2Br_2N_2S$ requires C, 9·85; Br, 65·5; N, 11·5; S, 13·15%).

1-α-*Chloroethylidene*-2-*toluene*-p-*sulphonylhydrazine* (III).—1-Acetyl-2-toluene-*p*-sulphonylhydrazine (2 g.) was added to thionyl chloride and on warming there was a vigorous evolution of hydrogen chloride. The solution was boiled under reflux for a further 2 hr. and the excess of thionyl chloride was removed. The residue solidified on standing and was recrystallised from benzene–light petroleum to give the *chloro-compound* (1·25 g., 58%), m. p. 129—131° (Found: Cl, 14·0; N, 11·5; S, 12·95. $C_9H_{11}ClN_2O_2S$ requires Cl, 14·35; N, 11·35; S, 13·0%).

Attempted Preparation of 1-α-*Phthalimidoethylidene*-2-*toluene*-p-*sulphonylhydrazine*.—A mixture of 1-α-chloroethylidene-2-toluene-*p*-sulphonylhydrazine (2·5 g.), potassium phthalimide

(1·9 g.), and dry xylene (20 ml.) was boiled under reflux for 1 hr. After cooling, the solid was collected, extracted with boiling water, and the residue recrystallised from ethanol to give 1,4-dihydro-3,6-dimethyl-1,4-di(toluene-*p*-sulphonyl)-1,2,4,5-tetrazine, m. p. 182—183° (decomp. to give a pink liquid, which presumably was 3,6-dimethyl-1,2,4,5-tetrazine) [lit.,[18] m. p. 182—184° (decomp. to give red colour)] (Found: C, 51·8; H, 4·7; N, 13·1; S, 15·2%; *M*, 380. Calc. for $C_{18}H_{20}N_4O_4S_2$: C, 51·4; H, 4·8; N, 13·35; S, 15·25%; *M*, 420·4). The m. p. of this compound was depressed on admixture with diacetyl bis(toluene-*p*-sulphonylhydrazone).

1-*Acetimidoyl*-2-p-*nitrobenzenesulphonylhydrazine* (IV).—Ethyl acetimidate (1·74 g., 2·0 ml.) was added to *p*-nitrobenzenesulphonylhydrazine (2·17 g.) and ethanol (10 ml.), and the mixture set aside at room temperature for 15 min. The solid slowly dissolved to give a bright yellow solution, from which a very pale yellow solid separated. The solid was collected and recrystallised from water to give the *amidrazone* (0·4 g., 17%), m. p. 180—181° (decomp.) (Found: N, 21·0; S, 11·2. $C_8H_{10}N_4O_4S$ requires N, 21·7; S, 12·4%).

1-*Acetimidoyl*-2-*toluene*-p-*sulphonyhydrazine* was prepared similarly. It was recrystallised from nitromethane as the *hemihydrate* (1·7 g., 75%), colourless crystals, m. p. 158—159° (decomp.) (Found: N, 17·4; S, 13·7; H_2O, 4·1. $C_9H_{13}N_3O_2S,0{\cdot}5H_2O$ requires N, 17·8; S, 13·6; H_2O, 3·8%). Drying at 78°/10 mm. for 3 hr. gave the anhydrous compound, m. p. 108—110° (decomp.) which on standing over water reverted to the hemihydrate.

1-(N-p-*Nitrobenzenesulphonacetimidoyl*)-2-*toluene*-p-*sulphonylhydrazine* (V).—*p*-Nitrobenzenesulphonyl chloride (2·22 g.) and 1-acetimidoyl-2-toluene-*p*-sulphonylhydrazine (2·27 g.) in dry acetone (50 ml.), containing anhydrous potassium carbonate (2·8 g.) were boiled under reflux for 1 hr. After cooling, the solid was removed and the filtrate was evaporated *in vacuo*. The residue was dissolved in acetone and the addition of light petroleum gave the *product* (3·1 g., 75%) as a colourless solid, m. p. 143° (decomp.) (Found: C, 43·6; H, 4·1; N, 12·3; S, 15·7. $C_{15}H_{16}N_4O_6S_2$ requires C, 43·7; H, 3·9; N, 13·6; S, 15·55%).

1-*Chloro*-4-*methylpentan*-2-*one*.[31]—Isovaleroyl chloride (21·7 g.) was added with stirring, during 0·5 hr., to a solution of diazomethane in ether (750 ml., from 75 g. *N*-methyl-*N*-nitrosourea), the temperature being kept at 0°. After further stirring for 2 hr. the mixture was left overnight at room temperature; hydrogen chloride was then passed into the solution until it was colourless. The solution was washed with aqueous sodium hydrogen carbonate and then with water, dried (Na_2SO_4), and evaporated. The residue was distilled to give the chloroketone (13 g., 54%) as a colourless liquid, b. p. 60—63°/16 mm. (Found: C, 48·6; H, 7·7; Cl, 24·6. Calc. for $C_6H_{11}ClO$: C, 53·55; H, 8·25; Cl, 26·35%).

4-*Methyl*-1-*phthalimidopentan*-2-*one*.—Potassium phthalimide (4·65 g.) and 1-chloro-4-methylpentan-2-one (3·7 g.) in dry xylene (10 ml.) were boiled under reflux for 2 hr. The solvent was removed by steam-distillation and the residual solid collected and recrystallised from light petroleum (b. p. 80—100°, 250 ml.), with the addition of charcoal, to give the *phthalimidoketone* (2·5 g., 41%) as colourless needles, m. p. 113—115° (Found: C, 68·5; H, 6·4; N, 5·9. $C_{14}H_{15}NO_3$ requires C, 68·55; H, 6·15; N, 5·7%).

α-*Oxobutyric Acid Ethoxycarbonylhydrazone*.—A warm solution of ethoxycarbonylhydrazine (2·3 g.) in toluene (5·7 ml.) was added slowly to a warm solution of α-oxobutyric acid (2 g.) in toluene (10 ml.). The reaction was exothermic and an oil separated, which crystallised on standing. Recrystallisation from benzene–light petroleum (b. p. 60—80°) gave the *hydrazone* (100%) as colourless crystals, m. p. 127—129° (Found: C, 45·5; H, 6·3; N, 15·2. $C_7H_{12}N_2O_4$ requires C, 44·65; H, 6·4; N, 14·9%). α-Oxobutyric acid toluene-*p*-sulphonylhydrazone, m. p. 86—89°, was prepared (65%) similarly.

The authors thank Messrs. J. Stevens, B.Sc., and C. D. Bett for technical assistance, Mr. S. Bance, B.Sc., F.R.I.C., for semi-micro analyses, and Dr. H. J. Campbell for physical measurements.

Research Laboratories, May and Baker Ltd.,
Dagenham, Essex.
[*Received, February 22nd,* 1965.]

[31] L. J. Meuli (Dow Chem. Co.), U.S.P. 2,802,768.