183. 1,2,3-*Benzothiadiazole. Part III.*[1] *Electrophilic Substitution in 5- and 7-Amino-1,2,3-benzothiadiazoles and the Preparation of Some Substituted 1,2,3-Benzothiadiazoles.*

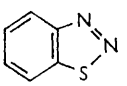
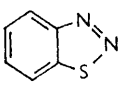
By E. R. Ward and D. D. Heard.

Bromination, iodination, nitration, and diazo-coupling of 5- and 7-amino-1,2,3-benzothiadiazoles, and some *N*-acyl derivatives, have been studied. The results largely confirm the interpretation of electrophilic substitution in the 1,2,3-benzothiadiazole system previously advanced.[1] Some bromination reactions probably proceed by mechanisms other than simple electrophilic substitution.

Spectroscopic analysis of the mixture of 5- and 7-nitro-1,2,3-benzothiadiazoles, obtained by nitration of the parent compound, shows that the 7-nitro-isomer predominates.

Preparation of nitro-, amino-, and hydroxy-1,2,3-benzothiadiazoles has been further investigated, particular attention being given to methods involving ring opening of appropriate benzothiazoles. The synthesis of 4-hydroxy-1,2,3-benzothiadiazole, an analogue of 8-hydroxyquinoline, is described.

In Part II [1] we reported on some electrophilic substitution reactions of 4- and 6-amino-1,2,3-benzothiadiazoles. These data, together with the few available results on substitution in the parent compound and its derivatives, were used to interpret electrophilic substitution in this heterocyclic system. It was suggested that the low reactivity of 1,2,3-benzothiadiazole to electrophiles was largely due to the powerful deactivating effect of the heterocyclic system which operated strongly at the 4- and 6-positions, with the 6-position more deactivated. Furthermore, there was considerable bond fixation in the benzene ring with structure (I) being favoured more than (II).

(I)   (II)

Electrophilic substitution in 4-amino-1,2,3-benzothiadiazole and its *N*-acyl derivatives occurs at the 5- and the 7-positions, with the latter most favoured, and in 6-amino-1,2,3-benzothiadiazole (and *N*-acyl derivatives) at the 7-position. Some brominations proceed abnormally. These results, together with new ones on the corresponding substitution reactions of 5- and 7-amino-1,2,3-benzothiadiazole (summarised in Table 1), are largely in agreement with the general ideas on electrophilic substitution in the 1,2,3-benzothiadiazole system set out above.

In 5- and 7-amino-1,2,3-benzothiadiazole one would expect substitution to be controlled by the strongly activating amino-group. This is the usual situation for electrophilic substitution in a benzene ring where both activating and deactivating groups are present. Thus, in the 5-isomer there is no "*para*" position available and by reason of bond fixation effectively only one available "*ortho*" position at 4 (cf. 2-naphthylamine where 3-substitution is extremely rare). Any likelihood of substitution at the 6-position is further decreased

[1] Part II, Ward and Heard, *J.*, 1963, 4794.

TABLE 1.

Electrophilic substitution in 5- and 7-amino-1,2,3-benzothiadiazoles.

Subst.	Reaction conditions, method of isolation †	Substn. (%) at position * 4	6	4, 6
5-NH_2	Br_2, 1 mol., $CHCl_3$, 20°; C++	97	—	—
5-NHTos	Br_2, 6 mol., pyridine, reflux 4 hr.; HC	57	—	—
5-NH_2	I_2, 1·1 mol., 50% v/v aq. Et_2O, reflux 8 hr.; C	92	—	—
5-NH_2	*p*-$NO_2{\cdot}C_6H_4{\cdot}N_2^+{\cdot}HSO_4^-$, 1·1 mol., 50% v/v aq. AcOH, 5°; C	87·5	—	—
5-NHTos	HNO_3 (*d* 1·5), 1·2 mol., AcOH, 90°	87	—	—
7-NH_2	Br_2, 2 mol., $CHCl_3$, 20°; C	22·5	—	64
7-NHAc	Br_2, 1 mol., 85% v/v aq. AcOH, reflux 1 hr.; HC	68·5	—	—
7-NH_2	I_2, 1·1 mol., 50% v/v aq. Et_2O, reflux 8 hr.; C	72	—	—
7-NH_2	*p*-$NO_2{\cdot}C_6H_4{\cdot}N_2^+{\cdot}HSO_4^-$, 1·1 mol., 50% v/v aq. AcOH, 5°; C	92	—	—
7-NHTos	HNO_3 (*d* 1·5), 1·05 mol., 65% AcOH, 1 hr.; HC[4]	43	27	—

* Yield of pure product after allowance for recovered starting material. † C = Chromatography, HC = hydrolysis and chromatography. ++ 10 mol. Br_2 gave a similar result. Tos = *p*-$Me{\cdot}C_6H_4SO_2$.

by the strong deactivating effect operating there. Hence substitution is exclusively at the 4-position. In particular, 5-toluene-*p*-sulphonamido-1,2,3-benzothiadiazole is not dibrominated in the 4- and 6-positions even under strong forcing conditions. Fries *et al.*[2] similarly found that 5-hydroxy-1,2,3-benzothiadiazole was only brominated at position 4. In contrast to these results the corresponding 6-isomers are both dibrominated in the 5- and the 7-positions;[1,2] substitution at position 5 is probably due to the absence of a strong deactivating effect there.

7-Amino-1,2,3-benzothiadiazole potentially has one "*ortho*" (at 6) and one "*para*" position (at 4) available. Both of these are deactivated by the heterocyclic system, the greater effect being at the 6-position. Hence one would expect substitution to occur predominantly at position 4 with 6 possibly available to the more powerful electrophiles. This is found: exceptionally, appreciable 6-substitution in the nitration of the toluene-*p*-sulphonyl derivative appears to indicate a specific *ortho* enhancing effect from the toluene-*p*-sulphonamido group.[3] The fact that this derivative cannot be dinitrated whilst the amine can be dibrominated by a weaker electrophile suggests that the dibromination is abnormal. It is not entirely analogous to the behaviour of 4-amino-1,2,3-benzothiadiazole for this amine, like 1-naphthylamine and many nitro-1-naphthylamines[4] gives a dibromo-amine but no monobromo-amine. Similarly, bromination of the 7-acetylamine derivative does not entirely parallel that of the 4-isomer. The latter was suggested as proceeding abnormally through an intermediate involving a positive charge in the heterocyclic system: it is not possible to formulate an exactly analogous structure for the 7-isomer.

The monohalogeno-amines were orientated by deamination to known halogeno-1,2,3-benzothiadiazoles using the methods of Hodgson and Turner,[5,6] the mononitro-amines by reduction to the known diamines[1] and 7-amino-4,6-dibromo-1,2,3-benzothiadiazole by its preparation through further bromination of the 4-bromo-amine. Fries *et al.*[2] have shown that diazo-coupling with 5-amino-1,2,3-benzothiadiazole occurs at the 4-position and this is now confirmed by the ultraviolet spectra of our azo-derivatives[1] in which[7] we find the characteristics expected of the presence, or absence, of the *o*-amino-azo grouping.

We have previously shown that nitration of 1,2,3-benzothiadiazole only occurs under severe conditions and gives a mixture of 5- and 7-nitro derivatives in low yield (*ca.* 20—

[2] Fries, Vorbrodt, and Siebert, *Annalen*, 1927, **454**, 172.
[3] Ward and Marriott, *Chem. and Ind.*, 1962, 1760.
[4] Ward and Wells, *J.*, 1961, 4866.
[5] Hodgson and Turner, *J.*, 1942, 748.
[6] Hodgson and Turner, *J.*, 1943, 86.
[7] Ward, Pearson, and Wells, *J. Soc. Dyers and Colourists*, 1959, **75**, 484.

25%).[8] Column chromatography appeared to show that the 5-isomer was predominant. We have now excluded the possibility that under the severe nitration conditions 4- or 6-nitro-1,2,3-benzothiadiazoles might have been preferentially destroyed; in fact, none of the mononitro derivatives is attacked under these conditions. Analysis of the nitration product by ultraviolet spectroscopy shows that it consists of 60(±3)% of 7- and 40(±3)% of 5-isomer. We have been unable to improve the nitration procedure but this route can be used to prepare 7-amino-1,2,3-benzothiadiazole. Reduction of the mixed nitro compounds by stannous chloride–hydrochloric acid[8] yields a mixture of amines from which pure 7-amino-1,2,3-benzothiadiazole, corresponding to about 75% of the 7-nitro-1,2,3-benzothiadiazole in the mixture, can readily be isolated. The compound that Fries and Reitz[9] obtained by reduction of a nitration product of 1,2,3-benzothiadiazole and which they thought was 4-amino-1,2,3-benzothiadiazole is now seen to be the 7-isomer. Similar orientations must be allocated to their supposed 4-acetylamino-4-hydroxy-, 4-acetoxy-, 4-hydroxy-5, 7-dibromo-, and 4-amino-7-phenylazo-1,2,3-benzothiadiazoles.

There are several routes to 7-nitro- and 7-amino-1,2,3-benzothiadiazole. A direct synthesis is by diazotisation of 2-amino-6-nitrothiophenol which can be obtained either by thiolation of 2-amino-1-chloro-6-nitrobenzene or, possibly, by ring opening of 7-nitrobenzothiazole. The former method[10] has some advantages since the starting material, 1-chloro-2,6-dinitrobenzene, is now commercially available and selective reduction of this can be improved by using the method of Gunstone and Tucker.[11] Even so, the route is somewhat tedious. 7-Nitrobenzothiazole is formed in appreciable yield by nitration of benzothiazole[12] but is not easily separated from the mixed nitration products. We have synthesised it directly by treatment of 2-chloro-*N*-formyl-3-nitroaniline with sodium hydrogen sulphide but possibly the most convenient method is by deamination of 6-amino-7-nitrobenzothiazole.[13] Previously, we were unable to obtain the desired thiophenol by ring opening the nitrobenzothiazole with boiling ethanolic hydrazine hydrate.[14] We now find that the nitrobenzothiazole is probably first reduced to 7-aminobenzothiazole and then opened to 2,6-diaminothiophenol. Isolation of the diaminothiophenol from this reaction proved difficult but dizotisation of the crude product followed by addition to aqueous potassium iodide gave a small yield of 7-iodo-1,2,3-benzothiadiazole. Similarly, ring opening of 7-aminobenzothiazole, followed by oxidation of the intermediate thiol, gave di-(2,6-diaminodiphenyl) disulphide in reasonable yield and diazotisation of this eventually gave a 22% yield of 7-iodo-1,2,3-benzothiadiazole. The formation of the iodo compound probably proceeds by diazotisation of the tetra-aminodisulphide followed by fission of the disulphide link in the manner described[15] for the corresponding diaminodiphenyldisulphide.

Ring opening of *N*-acyl-7-aminobenzothiazoles could be used to synthesise 7-*N*-acylamino-1,2,3-benzothiadiazoles directly, but we were unable to devise methods for ring opening and diazotisation that did not remove the protecting acyl group. However, none of the above methods is as convenient as the synthesis of 7-nitro-1,2,3-benzothiadiazole by deamination of 6-amino-7-nitro-1,2,3-benzothiadiazole, a route ultimately based on the ready availability of 6-nitrobenzothiazole.[12]

Reinvestigation of the ring opening of 5-nitrobenzothiazole with boiling ethanolic hydrazine hydrate also showed that, contrary to our previous findings,[8] 2-amino-4-nitrothiophenol could be obtained in moderate yield (45%). This thiol can be more readily prepared by thiolation of 2-amino-1-chloro-4-nitrobenzene but the subsequent conversion

[8] Ward, Poesche, Higgins, and Heard, *J.*, 1962, 2374.
[9] Fries and Reitz, *Annalen*, 1936, **527**, 38.
[10] Hodgson and Dodgson, *J.*, 1948, 1006.
[11] Gunstone and Tucker, *J. Appl. Chem.*, 1952, **2**, 204.
[12] Ward and Poesche, *J.*, 1961. 2825.
[13] Ward and Williams, unpublished work.
[14] Boggust and Cocker, *J.*, 1949, 355.
[15] Burawoy and Turner, *J.*, 1950, 469.

to 5-nitro-1,2,3-benzothiadiazole can be improved by isolating the thiol before diazotisation and by isolating the final product by column chromatography.[16]

Whilst 2-methyl-6-nitrobenzothiazole gave a moderate yield (25%) of the relevant disulphide, 2-methyl-, 2-amino-6-nitro-, 2-mercapto-6-nitro-, and 2-amino-6-methoxybenzothiazole appeared to be largely unattacked by ethanolic hydrazine hydrate. Boiling dilute sodium hydroxide is also an efficient reagent for ring opening of benzothiazoles.[17] This method worked well with 6-nitro- or 7-aminobenzothiazoles but 7-nitro- and 2-amino-6-nitrobenzothiazole were largely unaffected.

These results imply that the type of compound that is ring opened by ethanolic hydrazine hydrate is also attacked by sodium hydroxide, and *vice versa*. This suggests a mechanism involving nucleophilic attack, rather than reduction to a benzothiazoline followed by cleavage, as suggested by Boggust and Cocker.[14] Initial nucleophilic attack at the 2-position is excluded for 2-hydrazinobenzothiazole is not opened by ethanolic hydrazine hydrate.

More drastic methods have been used for this ring-opening; Fridman and Golub[18] used 50% aqueous potassium hydroxide to open 2-amino-6-methoxybenzothiazole and we used this method to synthesise 6-methoxy- and 6-ethoxy-1,2,3-benzothiadiazoles from the corresponding benzothiazoles. 2-Amino-4-methoxybenzothiazole[19] was not affected by this reagent but opening was achieved on addition to a melt of sodium hydroxide, potassium hydroxide, and sodium sulphide at *ca.* 240°.[20] Subsequent diazotisation, however, gave, in place of 4-methoxy-1,2,3-benzothiadiazole, the 4-hydroxy derivative in low yield. This analogue of 8-hydroxyquinoline may have similar useful properties. Attempts to make it by the direct hydrolysis of 4-amino-1,2,3-benzothiadiazole with dilute sulphuric acid in a sealed tube at 200°, by a Bucherer reaction on 4-aminobenzothiazole, followed by ring opening, or by decomposition of diazotised 4-amino-1,2,3-benzothiadiazole[8] all failed. Another possible route was *via* 2-amino-4-methoxybenzothiazole, but this failed to deaminate with cuprous oxide–methanol[6] or hypophosphorous acid following diazotisation by the Hodgson-Turner method.[5]

Whilst 6-hydroxy-1,2,3-benzothiadiazole could not be prepared by refluxing 6-acetamido-1,2,3-benzothiadiazole with 20% sodium hydroxide,[21] or by heating the 6-amino compound with hydrochloric acid, or sodium hydroxide, in a sealed tube, a yield of *ca.* 40% is obtained by heating the latter compound with 10% sulphuric acid in a sealed tube at 200°. The addition of chlorobenzene to the reaction mixture reduces charring.[22] 5-Hydroxy-4-nitro- and 6-hydroxy-7-nitro-1,2,3-benzothiadiazoles were obtained in excellent yield by refluxing the corresponding nitro-amines with 2N-sodium hydroxide. Both have previously been prepared by nitration of the relevant hydroxy-compounds.[2] 7-Hydroxy-1,2,3-benzothiadiazole was prepared in low yield by decomposition of the diazotised 7-amine and appears to be identical with the product[9] obtained through diazotisation of the supposed "4-amino-" compound.

Experimental

Nitration of 1,2,3-*Benzothiadiazole.*—1,2,3-Benzothiadiazole (13·6 g.) was nitrated[8] and the mixture obtained by pouring on to ice was steam distilled. The first runnings (700 ml.) contained starting material (3·74 g.): thereafter the distillate contained mixed 5- (40%) and 7-nitro-1,2,3-benzothiadiazoles (60%) (2·51 g.; m. p. 85·5—88·5°; 19% on converted starting material), analysed by ultraviolet spectroscopy, using peaks at 246 and 330 mμ. Synthetic mixtures of the pure compounds in the range 33—67% of 5- and 67—33% of 7-isomer gave results accurate to not less than ±3%. Reduction of the mixed nitro-compounds (10 g.) by

[16] Hodgson and Dodgson, *J.*, 1948, 870.
[17] B.P. 558,887.
[18] Fridman and Golub, *J. Gen. Chem.* (*U.S.S.R.*), 1961, **31**, 3394.
[19] Feng and Fernando, *J. Amer. Chem. Soc.*, 1960, **82**, 2115.
[20] U.S.P. 3,102,142.
[21] Hodgson and Kilner, *J.*, 1924, 807.
[22] Davies, *J.*, 1955, 2414.

stannous chloride–hydrochloric acid,[8] followed by extraction of the crude product with boiling benzene (120 ml.) gave, on cooling, almost pure 7-amino-1,2,3-benzothiadiazole, m. p. 136°, (3·8 g., 45%). Evaporation of the benzene gave a mixture (2·7 g.; m. p. 60—70°) of this with the 5-isomer; attempted separation by chromatography on alumina failed.

Electrophilic Substitution in 5- and 7-Amino-1,2,3-benzothiadiazoles.—The methods used for the substitution reactions, isolation and separation of mixed products (where required) were usually those employed in the corresponding reactions with the 4- and the 6-isomers.[1] Reaction products are described below. 5-*Amino*-4-p-*nitrophenylazo*-1,2,3-*benzothiadiazole*, yellow needles

Substs.	M. p.	Crystn. solvent	Found (%) C	H	N	Formula	Required (%) C	H	N
5-NH_2-4-Br	183°	Benzene	31·6	1·9	18·5	$C_6H_4BrN_3S$	31·3	1·8	18·3
7-NH_2-4-Br	169	Aq. EtOH	31·4	1·6	18·2				
5-NH_2-4-I	168 *	Aq. EtOH	26·1	1·4	15·1	$C_6H_4IN_3S$	26·0	1·5	15·2
7-NH_2-4-I	167	Aq. EtOH	26·4	1·5	14·7				
5-NH_2-4-NO_2 ...	282 *	AcOH	36·5	1·55	28·5	$C_6H_4N_4O_2S$	36·7	2·0	28·6
7-NH_2-4-NO_2 ...	290 *	Aq. H·CONMe$_2$	36·8	2·4	27·6				
7-NH_2-6-NO_2 ...	240—241 *	Aq. H·CONMe$_2$	36·4	1·9	28·4				
5-NHTos-4-NO_2	175	Aq. AcOH	44·9	3·1	16·0	$C_{13}H_{10}N_4O_4S_2$	44·5	3·1	16·0
7-NH_2-4,6-Br ...	177 *	Aq. EtOH	23·7	1·0	13·8	$C_6H_3Br_2N_3S$	23·3	1·0	13·6

* With decomp.

(from chlorobenzene), m. p. 235° (decomp.) (Found: C, 48·2; H, 2·4; N, 27·9. $C_{12}H_8N_6O_2S$ requires C, 48·0; H, 2·7; N, 27·0%); $\lambda_{max.}$ 233, 390, and 470 mμ (Log ε 4·246, 4·468, and 3·679). 7-*Amino*-4-p-*nitrophenylazo*-1,2,3-*benzothiadiazole*, red powder (from chlorobenzene), m. p. 240° (decomp.) (Found: C, 48·4; H, 2·9; N, 27·7%), $\lambda_{max.}$ 237sh, 290, 310sh, 400, 415sh, 470, and 490sh mμ (log ε 4·24, 3·955, 3·852, 4·402, 4·370, 4·128, and 4·111). The ultraviolet spectra were recorded in 95% v/v aqueous ethanol.

Ring Opening of Benzothiazoles.—The benzothiazole (10 g.) was refluxed with ethanol (200 ml.) and hydrazine hydrate (100%, 20 ml.) for 2 hr. Cooling the reaction mixture often precipitated much starting material. After filtration, the thiol could be obtained by acidification or was oxidised to the disulphide by hydrogen peroxide (20 vol.). Alternatively, the thiol was refluxed with aqueous sodium hydroxide (9% w/v; 100 ml.). By either method 7-aminobenzothiazole gave *di*-(2,6-*diaminophenyl*) *disulphide* (60%), yellow needles (from xylene), m. p. 181° (Found: C, 52·3; H, 5·1. $C_{12}H_{14}N_4S_2$ requires C, 51·8; H, 5·0%). Diazotisation of this by the method used for di-(2-amino-5-nitrophenyl)disulphide,[8] followed by addition to aqueous potassium iodide and steam-distillation gave 7-iodo-1,2,3-benzothiadiazole (22%).

Hydroxy- and Alkoxy-1,2,3-benzothiadiazoles.—2-Amino-6-ethoxybenzothiazole (6·2 g.) was heated with potassium hydroxide (20 g.) and water (20 ml.) under reflux at 160°. After 6 hr. the mixture was cooled, water was added (50 ml.), and the solids were filtered off. The filtrate was neutralised to Congo Red with hydrochloric acid (*d* 1·2), the thiol collected, washed well with water and dried at 50° *in vacuo*. The 2-amino-5-ethoxythiophenol (1·7 g.) was dissolved in sulphuric acid (*d* 1·84; 5 ml.) and 2M-nitrosylsulphuric acid in sulphuric acid (*d* 1·84; 5 ml.) added below 5° with stirring. After 30 min. the mixture was poured on to ice (150 g.) and then steam-distilled. The distillate 700 ml. was kept at 0° for 1 hr., the solids collected (0·21 g.), and further material (0·04 g.) obtained by extracting the filtrate with ether (3 × 100 ml.). 6-*Ethoxy*-1,2,3-*benzothiadiazole* was obtained as needles (from water), m. p. 101° (Found: C, 52·9; H, 4·8. $C_8H_8N_2OS$ requires C, 53·3; H, 4·5%). 6-Methoxy-1,2,3-benzothiadiazole was similarly obtained from 2-amino-6-methoxybenzothiazole, m. p. 77° (Fries and Engelbertz [23] give 72°), and also by refluxing 6-hydroxy-1,2,3-benzothiadiazole with dimethylsulphate and sodium hydroxide (25% yield).

4-*Hydroxy*-1,2,3-*benzothiadiazole*.—2-Amino-4-methoxybenzothiazole (2 g.) was added to a melt of potassium hydroxide (5 g.), sodium hydroxide (5 g.), and anhydrous sodium sulphide (0·5 g.) at 240°. After stirring for 10 min. at 240°, the melt was cooled and added to water (150 ml.), acidified with sulphuric acid (*d* 1·84) and treated below 5° with sodium nitrite (1 g.) in water (4 ml.). After 30 min. the solids were collected, washed with a little water and dried *in vacuo* at 60°. Extraction with boiling light petroleum (b. p. 80—100°; charcoal) followed by concentration to 20 ml. gave crude 4-*hydroxy*-1,2,3-*benzothiadiazole* (100 mg., 5%). Two crystallisations from the same solvent gave needles, m. p. 146° (Found: C, 47·6; H, 2·7; N,

[23] Fries and Engelbertz, *Annalen*, 1915, **407**, 208.

18·4. $C_6H_4N_2OS$ requires C, 47·4; H, 2·7; N, 18·4%). 2-Amino-6-nitro- and 2-amino-4,6-dinitro-benzothiazole both ignited on addition to similar melts.

6-*Hydroxy*-1,2,3-*benzothiadiazole*.—6-Amino-1,2,3-benzothiadiazole (1 g.) was dissolved in a warm mixture of sulphuric acid (*d* 1·84; 2 ml.) and water (18 ml.), chlorobenzene (20 ml.) was added and the mixture heated gradually (1 hr. in a sealed tube) to 200°. After 20 hr. at this temp. the cooled tube was washed out with the minimum amount of water and the solids collected, washed with a little water and dried at 60° *in vacuo*. Basification of the filtrate gave starting material (0·5 g.). The hydroxy-compound crystallised from chlorobenzene (0·2 g., 40% on amine converted). This method failed with 4-amino-1,2,3-benzothiadiazole.

5-*Hydroxy*-4-*nitro*- *and* 6-*Hydroxy*-7-*nitro*-1,2,3-*benzothiadiazoles*.—5-Amino-4-nitro-1,2,3-benzothiadiazole (0·9 g.) was refluxed with 2N-sodium hydroxide (100 ml.) until solution was complete (2 hr.). Acidification precipitated 5-hydroxy-4-nitro-1,2,3-benzothiadiazole (1·4 g.), yellow needles (from ethanol), m. p. 201—203° (decomp.) [Fries *et al.*[2] give 206° (decomp.)]. 6-Hydroxy-7-nitro-1,2,3-benzothiadiazole was similarly obtained in *ca.* 100% yield, m. p. 183° (Fries *et al.*[2] give 180°) from 6-amino-7-nitro-1,2,3-benzothiadiazole.

Miscellaneous Preparations.—7-Nitrobenzothiazole was prepared by treating *N*-formyl-2-chloro-3-nitroaniline (1 g.) in warm ethanol (6 ml.) with sodium sulphide (1·8 g.) and sodium hydrogen carbonate (0·65 g.) in water (5 ml.). After refluxing for 1 hr., the solution was poured on to ice (50 g.) and 2N-sodium hydroxide (2·5 ml.), the mixture filtered, and the filtrate acidified with hydrochloric acid. The solids were collected, washed with water, dried, and dissolved in xylene. Filtration through alumina and concentration gave needles, m. p. 155° (lit.,[12] 155°). 7-Nitro-1,2,3-benzothiadiazole was obtained by dissolving 7-nitro-6-toluene-*p*-sulphonamido-1,2,3-benzothiadiazole (3·5 g.) in 2M-nitrosylsulphuric acid in sulphuric acid (*d* 1·84; 5 ml.), warming to 40°, adding this solution to acetic acid (10 ml.) below 30°, and then achieving deamination by addition to ethanol–cuprous oxide [6] or by adding 50% hypophosphorous acid to the diazo-solution (yields 55—60%). 5-*Toluene*-p-*sulphonamide*-1,2,3-*benzothiadiazole*. was prepared as the 6-isomer,[8] m. p. 198° (decomp.) (from acetic acid) (Found: N, 14·0. $C_{13}H_{11}N_3O_2S_2$ requires N, 13·8%).

The authors thank the Pharmaceutical Society for an Educational Grant (to D. D. H.), and Pfizer Ltd. (Sandwich) for raw materials, analyses, and financial support.

LEICESTER COLLEGE OF TECHNOLOGY, LEICESTER. [*Received, April 9th*, 1964.]