1166. 1,2,3-*Benzothiadiazole. Part IV.*[1] *Preliminary Investigations in the Quaternisation of* 1,2,3-*Benzothiadiazole. Methyl- and Ethyl-*1,2,3-*benzothiadiazolium Salts.*

By A. J. Nunn, D. J. Chadbourne, and J. T. Ralph.

1,2,3-Benzothiadiazole will only combine with one molecular proportion of quaternising agent. The merits of various quaternising agents for the preparation of methyl- and ethyl-1,2,3-benzothiadiazolium salts are discussed, with a view to finding a suitable method of obtaining higher members of the series. In practice only one of the three possible isomers of monoalkyl-1,2,3-benzothiadiazolium salts can be obtained, the problem of the red and yellow crystalline forms of both methyl- and ethyl-1,2,3-benzothiadiazolium iodide being resolved. The position of alkylation is considered most likely to be N-3, in the light of evidence obtained from reductive cleavage, reaction with alkali, and ultraviolet spectroscopy.

The alkyl quaternary salts of the weak base 1,2,3-benzothiadiazole have been little studied. They were at the time considered to be sulphonium salts; we present evidence to suggest that they are in fact quaternary salts. In view of the uncertainty as to the position of quaternisation, and the potential biological activity, it was decided to investigate these compounds further.

Jacobson and Janssen[2] obtained methyl- and ethyl-1,2,3-benzothiadiazolium iodides as red crystals by heating the base with a ten-fold excess of the respective alkyl iodide in a sealed tube at 100° for 1 to 3 days. The chlorides and picrates were prepared from the iodides by double decomposition. These compounds were little characterised, with the exception of ethyl-1,2,3-benzothiadiazolium chloride, reported to have melted at between 70° and 80° in its own water of crystallisation. The methiodides of 6-methyl- and 4,6-dimethylbenzothiadiazole were also prepared.[3] Later Hantzsch[4] prepared methyl-1,2,3-benzothiadiazolium iodide in a similar manner to that adopted by Jacobson and Janssen, obtaining yellow crystals after crystallisation from ethanol, instead of water; but no yield was stated.

We have found that prolonged refluxing of 1,2,3-benzothiadiazole with methyl and ethyl iodides (the latter being less reactive[5]) gave very small yields of product. The sealed-tube experiments have been repeated and the low yields obtained may be usefully compared with those of Jacobson and Janssen (see Table 1).

Table 1.

Quaternisation of 1,2,3-benzothiadiazole by alkyl iodides.

	Jacobson and Janssen's results	Repeat of sealed tube expts.*		Prolonged refluxing		
Product	Crude yield	Yield after crystn.	M. p.	Crude yield	M. p.	Authentic m. p.
Methyl-1,2,3-benzothiadiazolium iodide	45%	15%†	160°	1%	162°	168–169°
Ethyl-1,2,3-benzothiadiazolium iodide	16%	8%†	172°	0·8%	180°	181–182°

* Method reported in Experimental section.
† The crude product was contaminated with large amounts of free iodine.

Certain increases in yield resulted from the use of polar solvents.[6]

[1] Part III, E. R. Ward and D.D. Heard, *J.*, 1965, 1023.
[2] P. Jacobson and H. Janssen, *Annalen*, 1893, **277**, 218.
[3] P. Jacobson and E. Ney, *Annalen*, 1893, **277**, 232.
[4] A. Hantzsch. *Ber.*, 1909, **42**, 81.
[5] N. Menschutkin, *Z. phys. Chem.* (*Leipzig*), 1890, **6**, 41.
[6] (*a*) H. V. Halban, *Z. phys. Chem.* (*Leipzig*), 1913, **84**, 129; (*b*) O. Westphal and D. Jerchel, *Ber.*, 1940, **73**, 1002.

1,2,3-Benzothiadiazole was successfully quaternised with dimethyl and diethyl sulphates at 100°, although the yields never exceeded 55% (see Table 2) and isolation of the quaternary salts was difficult.

TABLE 2.

Quaternisation of 1,2,3-benzothiadiazole with dialkyl sulphates.

(*a*) Dimethyl sulphate Product: methyl-1,2,3-benzothiadiazolium hydrogen sulphate		(*b*) Diethyl sulphate Product: ethyl-1,2,3-benzothiadiazolium hydrogen sulphate	
Time of heating (hours)	Yield (%)	Time of heating (hours)	Yield (%)
3	28	3	21
6	43	6	34
12	52	12	49
24	38	24	55

It is possible that the methyl hydrogen sulphate quaternary salt was obtained as a result of hydrolysis of the methosulphate anion. However, when the reaction was carried out under anhydrous conditions the same product was obtained (cf. ref. 7).

Both methyl- and ethyl-1,2,3-benzothiadiazolium hydrogen sulphate underwent certain ion-exchange reactions, but with the anions of weak acids, like thiocyanate, the exchange was incomplete. Direct fusion of methyl toluene-*p*-sulphonate and 1,2,3-benzothiadiazole at 100° for 4 hours gave a 71% yield of methyl-1,2,3-benzothiadiazolium toluene-*p*-sulphonate, the melting point of which (about 165°) was raised with difficulty by recrystallisation from ethanol. The use of polar solvents and the same reaction conditions gave a much lower yield. Ethyl toluene-*p*-sulphonate was used under the same conditions as methyl toluene-*p*-sulphonate, or for longer reaction times. Even higher temperatures and the use of polar solvents failed to give any product. This is in accordance with the decreased rate of alcoholysis and hydrolysis of ethyl toluene-*p*-sulphonate recorded by Ingold[8] and the decreased rate of acetolysis of higher alkyl toluene-*p*-sulphonates observed by Pritzkow and Schöppler.[9]

Although direct quaternisation of 1,2,3-benzothiadiazole with alkyl toluene-*p*-sulphonates appears very limited, alkyl-1,2,3-benzothiadiazolium toluene-*p*-sulphonates can be obtained by a general method involving double decomposition. Ethyl-1,2,3-benzothiadiazolium toluene-*p*-sulphonate was obtained by treatment of the ethiodide with the silver salt of toluene-*p*-sulphonic acid. The methyl-1,2,3-benzothiadiazolium toluene-*p*-sulphonate prepared in this way was found to have a melting point about 10° higher than that of the compound prepared by direct quaternisation. Moreover, the material appeared to be identical with the product obtained when 1,2,3-benzothiadiazole is treated with methyl toluene-*p*-sulphonate in refluxing toluene. However, when the compound obtained by direct fusion was dissolved in ethanol and reprecipitated with toluene, the resulting material showed a significant rise in melting point. This excluded the important possibility of structural isomers.

The toluene-*p*-sulphonate anion was replaced quantitatively by chloride, bromide, iodide, perchlorate, and thiocyanate using ion-exchange columns.

The greater reactivity of the alkyl esters of nitro-substituted, benzenesulphonic acids compared with the alkyl esters of benzene- and toluene-sulphonic acids is well known.[10–15]

[7] J. M. Z. Gladych and E. P. Taylor, *J.*, 1962, 1481.
[8] C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Bell, London, 1953, p. 341.
[9] W. Pritzkow and K. H. Schöppler, *Chem. Ber.*, 1962, **95**, 834.
[10] L. Demény, *Rec. Trav. chim.*, 1931, **50**, 60.
[11] M. S. Morgan and L. H. Cretcher, *J. Amer. Chem. Soc.*, 1948, **70**, 375.
[12] R. E. Robertson, *Canad. J. Chem.*, 1953, **31**, 589.
[13] A. I. Kiprianov and A. I. Tolmatschev, Proc. XIVth Internat. Congr. Pure Appl. Chem., 1955, p. 320.
[14] A. I. Kiprianov and A. I. Tolmatschev, *J. Gen. Chem.* (*U.S.S.R.*), 1957, **27**, 157.
[15] E. Lunt, *May and Baker Lab. Bull.*, 1958, **3**, 13.

Methyl-1,2,3-benzothiadiazolium 2,4-dinitrobenzenesulphonate has been prepared in a good yield (68%) by fusing the reactants for a short time at 100°. Slightly improved yields (75%) were obtained by the use of a polar solvent (*e.g.*, nitrobenzene or nitromethane), at 50° for 1 day. Kiprianov and Tolmatschev[14] commented upon the small effect that polar solvents had on quaternisations involving methyl 2,4-dinitrobenzenesulphonate. The use of ethyl 2,4-dinitrobenzenesulphonate under the same conditions of fusion gave a high yield (89%). This was surprising in view of the usually greater reactivity of methyl esters and the comparative rates of alkylation of 2-methylbenzothiazole by alkyl 2,4-dinitrobenzenesulphonates given by Kiprianov and Tolmatschev.[14] Conversion of methyl- and ethyl-1,2,3-benzothiadiazolium 2,4-dinitrobenzenesulphonate into the metho- and etho-halides was readily achieved in quantitative yield by using anion-exchange resins.

As has been shown, only methyl-1,2,3-benzothiadiazolium toluene-*p*-sulphonate can be prepared directly from 1,2,3-benzothiadiazole and the alkyl toluene-*p*-sulphonate. Dimethyl and diethyl sulphate give moderate yields of quaternary salts, but the method is limited in its usefulness, on account of the difficulty of obtaining the higher dialkyl sulphates. Thus, it is the alkyl 2,4-dinitrobenzenesulphonates which appear to offer the greatest potential.

Simplest considerations of the 1,2,3-benzothiadiazole system suggest the possibility of three isomers on monoalkylation. It has been observed that certain cinnolines and triazines give mixtures of monoquaternary salts. Thus 4-amino-6-nitrocinnoline methiodide was obtained in the form of red needles and yellow prisms, each having distinctly different properties[16] and the basic centre of the parent cinnoline is still in some doubt.[16,17] Also, 5,6-diphenyl- and 3-methyl-5,6-diphenyl-1,2,4-triazine each gave a mixture of a colourless and a red methiodide.[18] It seemed that a similar situation might apply in the case of 1,2,3-benzothiadiazole, for the methiodide on recrystallisation from ethanol could be made to give a mixture of red and yellow needles, the predominant form being yellow.

The initial crop in such a recrystallisation consists almost entirely of yellow needles. Further material obtained from the mother liquor on standing several days contained a proportion of the red form. This mixture chromatographed on alumina in ethanol–benzene (1:1) gave only yellow needles with a melting point a few degrees above that given by Hantzsch.[4] Jacobson and Janssen[2] recorded no melting point for their red needles recrystallised from water, but quoted satisfactory analysis figures for iodine and sulphur.

In the present work the yellow and the red needles (the latter obtained by careful isolation from the surrounding yellow form) had different melting points but gave identical infrared, ultraviolet, and n.m.r. spectra. It seemed possible that the red needles might be a complex of the yellow crystals with iodine. Red needles, having analyses as for the tri-iodide but which differed slightly in respect of melting point from those mentioned above, were obtained by recrystallising the yellow form from ethanol containing iodine. The most likely explanation of these phenomena is that the red needles obtained from the mother liquors of a normal recrystallisation consist essentially of yellow material contaminated with small amounts of the iodide complex.

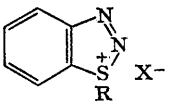
During normal crystallisations of the methiodide, traces of the solid green form mentioned by Hantzsch[4] (which he inferred was a trimer) were noticed, but these quickly reverted to the yellow form when moistened with ethanol. The unstable green form was also readily obtained by dissolution of the methiodide in ethanol and reprecipitation with ether. Ethyl-1,2,3-benzothiadiazolium iodide also gave red needles (both from recrystallisation mother liquors after removal of the yellow form and by complexing with iodine) and occasionally showed existence as an unstable green form. It was confirmed that both methyl- and ethyl-1,2,3-benzothiadiazolium iodides exhibit the phenomenon of thermochromism.

Certain colour changes of the methiodide in various solvents were observed by Hantzsch.[4] It is important that while the metho- and etho-chlorides show little variation of colour in

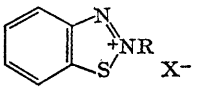
[16] C. M. Atkinson and A. Taylor, *J.*, 1955, 4236.
[17] D. E. Ames and (Miss) H. Z. Kucharska, *J.*, 1964, 283.
[18] C. M. Atkinson and H. D. Cossey, *J.*, 1963, 1628.

different solvents, the bromides are found to be light yellow in ethanol and intense yellow in chloroform solutions, and the iodides are almost colourless in water, light yellow in ethanol, and bright pink in chloroform.

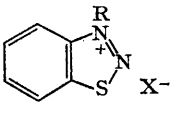
Several authors who have not worked on the quaternary salts of 1,2,3-benzothiadiazole have speculated about the position of alkylation. Jacobson[2] (and Hantzsch[4]) suggested that alkylation occurred on the sulphur atom (I).



(I)



(II)

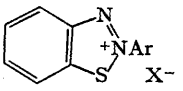


(III)

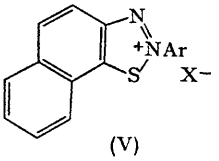
(R = Me, Et)

Bambas in his review article[19] mentions the three possibilities (I), (II), and (III). In review articles by Hodgson and Dodgson[20] and Sherman[21] the colour changes in the salts are attributed to structures which might result from a sulphonium salt, so they have no hesitation in supporting the idea of alkylation on the sulphur atom. We consider that alkylation on the sulphur atom is unlikely, as it is the nitrogen atom which is involved in the comparable system of benzothiazole.[22] The results of Burawoy and his co-workers[23] led us to expect that alkylation on N-2 was the most probable, structure (II), but the evidence we give below favours structure (III).

A few quaternary salts of 1,2,3-benzothiadiazole have been obtained by ring-closure methods. The preparation and properties of various azobenzene-2-sulphenyl and 2-phenylazonaphthalene-1-sulphenyl derivatives [(IV) and (V)] have been recorded by Burawoy and his co-workers.[24–26] Comparison of the properties of such compounds with those of the



(IV)



(V)

Ar = Ph or *o*- or *p*-$C_6H_4 \cdot NO_2$
X = Cl, Br, I, ClO_4, SCN, CN

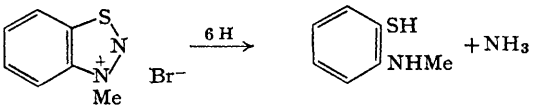
quaternary salts prepared from the parent system may provide information concerning the position of quaternisation.

The colour of the azobenzene-2-sulphenyl compounds (IV; Ar = C_6H_5) obtained by Burawoy in crystalline form varied from greenish-yellow for the perchlorate to light-yellow for the chloride and bromide, orange-yellow for the cyanide, orange for the thiocyanate, and orange-red for the iodide.[27] Methyl- and ethyl-1,2,3-benzothiadiazolium salts show a similar gradation in colour; white for the perchlorates, off-white for the chlorides, pale-

[19] L. L. Bambas, "The Chemistry of Heterocyclic Compounds," ed. A. Weissberger, Interscience New York, 1952, vol. IV, p. 11.
[20] H. H. Hodgson and D. P. Dodgson, *J. Soc. Dyers and Colourists*, 1948, **64**, 65.
[21] W. R. Sherman, "Heterocyclic Compounds," ed. R. C. Elderfield, Wiley, New York, 1961, vol. VII, pp. 556—558.
[22] A. I. Kiprianov and Z. N. Pazenko, *J. Gen. Chem.* (*U.S.S.R.*), 1949, **19**, 1529.
[23] A. Burawoy, "Organic Sulphur Compounds," ed. N. Kharasch, Pergamon London, 1961, vol. I, p. 281.
[24] A. Burawoy and C. E. Vellins, *J.*, 1954, 90.
[25] A. Burawoy, A. Chaudhuri, and W. I. Hyslop, *J.*, 1956, 96.
[26] A. Burawoy, A. Chaudhuri, and C. E. Vellins, *J.*, 1956, 90.
[27] A. Burawoy, F. Liversedge, and C. E. Vellins, *J.*, 1954, 4481.

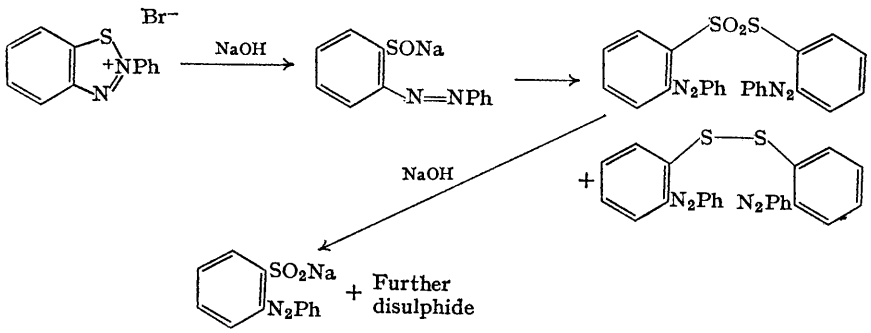
yellow for the bromides, yellow for the thiocyanates, and intense yellow for the iodides. The cyanides are obtained as yellowish-brown oils which will not solidify.

Jacobson and Janssen found that reduction of 1,2,3-benzothiadiazole with tin and concentrated hydrochloric acid yielded *o*-aminothiophenol.[2] We have found that similar reduction of methyl-1,2,3-benzothiadiazolium bromide led to the formation of 2-methylaminothiophenol and ammonia:

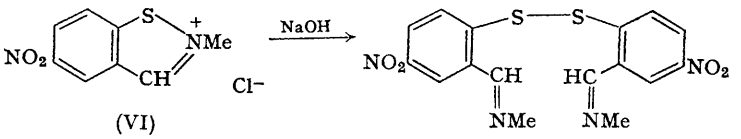


Oxidation of the thiophenol obtained yielded the known di-(2-*N*-methylaminophenyl) disulphide. No other disulphide nor methylamine could be detected, suggesting that quaternisation had occurred on N-3, but it is not conclusive since rearrangement could have taken place.

The reactions of methyl- and ethyl-1,2,3-benzothiadiazolium salts with aqueous alkali were also somewhat inconclusive. Jacobson and Janssen[2] attempted the formation of the quaternary hydroxide using moist silver oxide, but found that both the methiodide and ethiodide rapidly decomposed in solution giving what they assumed was the parent base. If the alkyl group is attached to N-2 then a similar sequence of reactions as reported by Burawoy and Chaudhuri[28] for 2-phenyl-1,2,3-benzothiadiazolium bromide might be



expected. The 2-phenylnaphtho[2,1-*d*][1,2,3]thiadiazolium salts (V) behaved similarly on treatment with alkali.[28] Fries, Eishold, and Vahlberg[29] have shown that 2-methyl-5-nitro-1,2-benzisothiazolium chloride (VI) behaves similarly on treatment with alkali. However, this is not the case with all benzisothiazolium salts, especially if ammonia is used, the parent base being regenerated.[29]



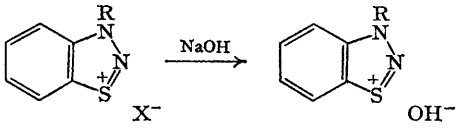
(VI)

The characteristic blue colour of sodium sulphenates was observed only when methyl- and ethyl-1,2,3-benzothiadiazolium hydrogen sulphate and metho- and etho-chloride were treated with aqueous sodium hydroxide; it was more usual to obtain a red coloration. In all

[28] A. Burawoy and A. Chaudhuri, *J.*, 1956, 653.
[29] (*a*) K. Fries, K. Eishold, and B. Vahlberg, *Annalen*, 1927, **454**, 264; (*b*) L. L. Bambas, "The Chemistry of Heterocyclic Compounds," ed. A. Weissberger, Interscience, New York, 1952, Vol. V, p. 250.

cases, however, the colours were transient phenomena and the quaternary salts were ultimately decomposed to the parent base. 1,2,3-Benzothiadiazole was isolated, crystalline, from methyl-1,2,3-benzothiadiazolium toluene-*p*-sulphonate and sodium hydroxide by steam-distillation of the reaction mixture. Treatment of methyl and ethyl quaternary salts with aqueous sodium hydrogen carbonate brought about slow decomposition.

Whilst the transient colorations of the methyl- and ethyl-1,2,3-benzothiadiazolium salts with aqueous sodium hydroxide indicate similarity with 2-phenyl-1,2,3-benzothiadiazolium salts, no ring opening appears to occur. If direct quaternisation of 1,2,3-benzothiadiazole occurs on N-3, the characteristic colour of a sodium sulphenate might arise as a result of structure (VII; R = Me,Et) being a contributing form to the resonance hybrid.



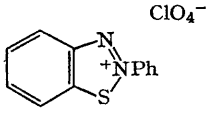
(VII)

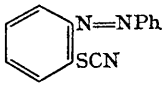
Alternatively, a mechanism involving ring opening and elimination of alcohol, followed by ring closure, might be involved.

Burawoy and Chaudhuri[30] found that 2-phenyl-1,2,3-benzothiadiazolium bromide reacted readily, presumably *via* the sulphenyl bromide, with acetone, malonic acid, and acetophenone to give 2-substituted benzothiazole derivatives and aniline. The lack of sulphenyl halide behaviour in the methyl and ethyl quaternary salts with compounds containing active methylene groups is not necessarily supporting evidence in favour of N-3 as the site for quaternisation, since the 2-phenylnaphtho[2,1-*d*][1,2,3]thiadiazolium salts show no reaction either.[30]

Burawoy and his co-workers[27] found that, whilst the crystalline 2-phenyl-1,2,3-benzothiadiazolium iodide dissolved in water with a pale greenish-yellow colour, solutions in benzene and chloroform were blue and violet-red, respectively. This is similar to the behaviour of other quaternary iodides, *e.g.*, the methiodides of pyridine and quinoline[4] and of cinnoline.[31]

The appearance of these new characteristic absorption bands in the visible spectrum has been attributed to the presence of these iodides in non-ionic forms.[27] Burawoy thought that a covalent structure for azobenzene-2-sulphenyl perchlorate was most unlikely, while the cyanide should be non-ionic (insoluble in water). These were considered to be the extremes of ring-closed and ring-opened structures and the colour of the crystalline thiocyanate and iodide was taken as an indication of the presence of some non-ionic molecules.





To some extent the ideas were supported by spectroscopic measurements in the ultraviolet and visible regions. *R*-Bands (which generally become more intense as the dielectric constant of the solvent is increased) associated with a true azo-group, were absent from the spectrum of the perchlorate for solutions in water, ethanol, chloroform, and benzene. The spectra of the halides in chloroform and benzene showed at longer wavelengths a band of increasing prominence in the order Cl, Br, and I. Burawoy attributed this gradation to displacement of the equilibrium between ionic and non-ionic forms, the concentration of the

[30] A. Burawoy and A. Chaudhuri, *J.*, 1956, 648.
[31] M. Busch and A. Rast, *Ber.*, 1897, **30**, 521.

latter being greatest in the iodide and least in the chloride. This indicated that the tendency of the S–halogen linkages to ionise increased in the order I < Br < Cl, *i.e.*, the reverse of the order known for C–halogen bonds.

The spectrum of methyl-1,2,3-benzothiadiazolium iodide in chloroform differs from that in water by showing extra bands of considerable intensity in the longer-wavelength region. The spectrum of the corresponding bromide showed a slight bathochromic shift in chloroform, compared with water. If Burawoy is correct in his assignments it must mean that the methyl (and ethyl) quaternary salts are capable of existing in ring-open forms, which seems to suggest that quaternisation has occurred on N-2. However, such absorption may well arise from charge-transfer complexes between halide ion and non-polar solvent;[32] these are marked in the case of iodine, weak in the case of bromine, and almost non-existent for chlorine. This explanation gains support from the fact that the spectrum of methyl-2,1,3-benzothiadiazolium iodide in chloroform shows similar characteristics to those found in the spectrum of methyl-1,2,3-benzothiadiazolium iodide,[33] ring-open forms being impossible here.

While similarities between our quaternary salts and Burawoy's compounds are also apparent in the spectrum of the thiocyanate, the cyanide is completely different. Although it may be true that 2-phenyl-1,2,3-benzothiadiazolium cyanide exists entirely as the ring-open form, the spectrum of methyl-1,2,3-benzothiadiazolium cyanide is unique, and a ring-open form for this would be unstable.

Although the $\lambda_{max.}$ value for the iodide charge-transfer complex of methyl-1,2,3-benzothiadiazolium iodide is very similar to the value for iodine in chloroform,[34] it is unlikely that the colour of the quaternary salt is due to the presence of free iodine; the $\lambda_{max.}$ value for methyl-2,1,3-benzothiadiazolium iodide in chloroform is quite different and the spectrum of the methyl-1,2,3-benzothiadiazolium thiocyanate also shows typical charge-transfer phenomena.

Only the ultraviolet spectra of the methyl quaternary salts prepared have been accurately recorded. These were determined in aqueous solution to avoid the difficulties of charge-transfer complexes. Buffer solutions were not used since the pK_a value must be very low, so there is little danger of having more than one ionic species present. Even in concentrated hydrochloric acid the quaternary salts show little tendency to protonate.

The ultraviolet spectra of the methohalides in water show a marked resemblance to that of 1,2,3-benzothiadiazole in concentrated hydrochloric acid, demonstrating that only monoprotonation has occurred.[35] Even in concentrated sulphuric acid no tendency to diprotonate is shown, so it is unlikely that diquaternary salts of 1,2,3-benzothiadiazole can ever be obtained.

The method of Albert and Serjeant[36] enabled an approximate pK_a value for 1,2,3-benzothiadiazole to be determined. The value of -3 confirmed the fact that it is a very weak base.

These quaternary salts have been found to be potent inhibitors of monoamine oxidase *in vitro*, but the activity was greatly diminished *in vivo*.

Experimental

Sealed-tube Experiments.—(*a*) *With methyl iodide.* 1,2,3-Benzothiadiazole (5·0 g.) and methyl iodide (50 ml.), contained in a sealed tube, were heated in a Carius furnace at 100° for 48 hr. All the solid formed was collected and washed with a little ether. As the required methiodide was obviously contaminated with large amounts of free iodine, the dark-red crystalline solid was

[32] (*a*) E. M. Kosower and P. E. Klindinst, *J. Amer. Chem. Soc.*, 1956, **78**, 3493; (*b*) S. F. Mason, *J.*, 1960, 2437.
[33] A. J. Nunn and J. T. Ralph, unpublished work.
[34] J. Kleinberg and A. W. Davidson, *Chem. Rev.*, 1948, **42**, 601.
[35] E. Spinner, *Austral. J. Chem.*, 1963, **16**, 174.
[36] A. Albert and E. P. Serjeant, "Ionisation Constants of Acids and Bases," Methuen, London, 1962, ch. 4.

treated with water. The aqueous extract was evaporated to dryness and the residual red solid recrystallised from ethanol (~ 50 ml.) to give orange-yellow needles (1·5 g.), m. p. ~ 160°. Comparison of the infrared spectrum with that of methyl-1,2,3-benzothiadiazolium iodide confirmed the identity of the compound.

(*b*) *With ethyl iodide.* 1,2,3-Benzothiadiazole (3·0 g.) and ethyl iodide (30 ml.), contained in a sealed tube, were heated in a Carius furnace at 100° for 48 hr. The black shiny product was collected and extracted with water. The aqueous solution was evaporated to dryness and the orange-red residue recrystallised from ethanol (~ 15 ml.) to give orange needles (0·5 g.), m. p. 172—173°. The identity of this compound was confirmed by comparison of its infrared spectrum with that of ethyl-1,2,3-benzothiadiazolium iodide, prepared by ion-exchange methods.

TABLE 3

Experiments under reflux for 9 hr.

(a) *With methyl iodide*

1,2,3-Benzothiadiazole (g.)	Methyl iodide (ml.)	Polar solvent (ml.)	Material deposited (g.)	Colour	M.p.
5·0	50	—	0·1	Orange-yellow	162—163°
5·0	25	$PhCH_3$ (25)	0·1	Yellow-brown	~155
5·0	25	$PhNO_2$ (25)	0·8	Orange-yellow	~162
5·0	25	$EtNO_2$ (25)	0·75	Yellow	~162

(b) *With ethyl iodide*

3·0	30	—	0·09	Orange-yellow	180—181
3·0	15	$PhNO_2$ (15)	0·45	,,	~175
3·0	15	$EtNO_2$ (15)	0·45	,,	~178

Methyl-1,2,3-benzothiadiazolium Hydrogen Sulphate.—(*a*) 1,2,3-Benzothiadiazole (13·6 g., 0·1 mole) and dimethyl sulphate (9·5 ml., 0·1 mole) were heated on a boiling-water bath for 12 hr., after the initial exothermic reaction had subsided. The dark-brown, viscous oil was extracted with water (250 ml.), and the aqueous extract filtered through charcoal and Kieselguhr. The aqueous solution was concentrated to give a viscous brown oil which was dissolved in hot ethanol, from which fawn needles (13·5 g., 52%) were obtained on cooling. Crystallisation from ethanol gave white needles of *methyl-1,2,3-benzothiadiazolium hydrogen sulphate*, m. p. 161—162° (Found: C, 33·8; H, 3·3; N, 11·3; S, 26·1. $C_7H_8N_2O_4S_2$ requires C, 33·9; H, 3·3; N, 11·3; S, 25·8%). With heating periods of 3, 6, and 24 hr. the yields of product were 28, 43, and 38%, respectively.

(*b*) 1,2,3-Benzothiadiazole (1·36 g., 0·01 mole) and dimethyl sulphate (0·95 ml., 0·01 mole) were mixed with dry nitrobenzene (5 ml.) and heated at 50° for 4 weeks. The mixture was allowed to cool, and the solidified mass triturated with ether. The cream solid (1·20 g., 46%) was filtered off and on crystallisation from ethanol gave white needles identical with the compound described above in (*a*).

Ethyl-1,2,3-benzothiadiazolium Hydrogen Sulphate.—1,2,3-Benzothiadiazole (0·1 mole) and diethyl sulphate (0·1 mole) were treated as described above in (*a*). Crystallisation from ethanol gave white needles of *ethyl-1,2,3-benzothiadiazolium hydrogen sulphate*, m. p. 162—163° (Found: C, 36·7; H, 3·9; N, 10·7; S, 24·3. $C_8H_{10}N_2O_4S_2$ requires C, 36·6; H, 3·8; N, 10·7; S, 24·4%). With heating periods of 3, 6, 12, and 24 hr. the yields of quaternary salt were 21, 34, 49, and 55%, respectively.

Methyl-1,2,3-benzothiadiazolium Toluene-p-sulphonate.—(*a*) 1,2,3,-Benzothiadiazole (1·36 g., 0·01 mole), purified methyl toluene-*p*-sulphonate (1·86 g., 0·01 mole), and dry toluene (5 ml.) were refluxed for 6 hr. The dark-brown solid (3·1 g.) was crystallised from ethanol to yield a solid (1·93 g., 60%), m. p. 175—177°. Crystallisation from ethanol yielded white needles of *methyl-1,2,3-benzothiadiazolium toluene-p-sulphonate*, m. p. 178—179° (Found: C, 51·9; H, 4·1; N, 8·8; S, 20·2. $C_{14}H_{14}N_2O_3S_2$ requires C, 52·2; H, 4·4; N, 8·7; S, 19·9%).

(*b*) 1,2,3-Benzothiadiazole (13·6 g.) and purified methyl toluene-*p*-sulphonate (18·6 g.) were heated on a boiling-water bath for 4 hr. The product was dissolved portionwise in hot ethanol (50 ml.) and the solution kept in a refrigerator overnight. The cream solid (22·7 g., 71%), m. p. 164—166°, was filtered off and washed with a very small amount of ethanol. Crystallisation from ethanol gave white needles, m. p. 166—167° (Found: C, 52·3; H, 4·3; N, 8·9%). Further crystallisations from ethanol eventually gave white needles, m. p. 178—179°, identical with the product obtained as described in (*a*) (mixed melting point).

(*c*) Use of the same quantities as in (*a*), but replacing toluene by nitrobenzene and heating at 100° for 4 hr., gave a white solid (27%), m. p. 163—165°.

(*d*) When nitromethane was used instead of nitrobenzene, a product (34%) melting at 162—164° was obtained.

(*e*) Toluene-*p*-sulphonic acid (0·65 g. in 25 ml. water) was treated with silver carbonate (0·5 g.) and the mixture warmed. The solution was decanted from a small amount of insoluble material and added to a warm aqueous solution of methyl-1,2,3-benzothiadiazolium iodide (1·05 g. in 25 ml. of water). The mixture rapidly precipitated silver iodide with fading of the orange colour. After the mixture had cooled, the precipitate was filtered off and the colourless filtrate evaporated to dryness to give a light-yellow solid (1·1 g., 90%). Crystallisation from ethanol (fairly soluble) afforded an off-white solid, m. p. 177—179° and mixed m. p. 177—179° with the product from the preparation described in (*a*).

*Preparation of Ethyl-1,2,3-benzothiadiazolium Toluene-*p*-sulphonate by Double Decomposition.*—An aqueous solution of silver toluene-*p*-sulphonate [prepared as indicated in (*e*) above] was added to a warm aqueous solution of ethyl-1,2,3-benzothiadiazolium iodide (1·0 g. in 25 ml. of water). After the mixture had cooled, the precipitate was filtered off, and the colourless filtrate evaporated to dryness. The residual oil eventually gave an off-white solid. Dissolution in ethanol and reprecipitation with ether gave an off-white powder (1·0 g., 87%), m. p. 125°. Several crystallisations from ethanol (very soluble) gave white crystalline *ethyl-1,2,3-benzothiadiazolium toluene-*p*-sulphonate*, m. p. 131—132° (Found: C, 51·2; H, 4·8; N, 8·5; S, 19·4. $C_{15}H_{16}N_2O_3S_2$ requires C, 53·6; H, 4·8; N, 8·3; S, 19·1%). The methyl and ethyl 2,4-dinitrobenzenesulphonates were prepared by the method of Lunt,[15] or Kiprianov and Tolmatschev.[14]

Methyl-1,2,3-benzothiadiazolium 2,4-Dinitrobenzenesulphonate.—(*a*) 1,2,3-Benzothiadiazole (1·36 g., 0·01 mole) and methyl 2,4-dinitrobenzenesulphonate (2·62 g., 0·01 mole) were heated on a boiling-water bath for 30 min. The mixture was dissolved in hot ethanol, and the solution concentrated and cooled to give fawn needles (2·72 g., 68%), m. p. 183—185°. Crystallisation from ethanol gave *methyl-1,2,3-benzothiadiazolium 2,4-dinitrobenzenesulphonate* as cream needles, m. p. 196—197° (Found: C, 39·1; H, 2·4; N, 14·0; S, 16·0. $C_{13}H_{10}N_4O_7S_2$ requires C, 39·2; H, 2·5, N, 14·1; S, 16·1%).

(*b*) 1,2,3-Benzothiadiazole (0·01 mole) was heated with methyl 2,4-dinitrobenzenesulphonate (0·01 mole), either alone or in solvent (5 ml., dried over anhydrous calcium chloride) at the temperature stated and for the time given in Table 4.

TABLE 4

Reaction of 1,2,3-benzothiadiazole with methyl 2,4-dinitrobenzenesulphonate.

	Reaction temp. 50°				Reaction temp. 100°			
	1 day Yield		3 days Yield		20 min. Yield		60 min. Yield	
Solvent	(g.)	M.p.	(g.)	M.p.	(g.)	M.p.	(g.)	M.p.
None	2·55	182—184°	2·69	183—186°	2·71	183—185°	2·73	182—184°
Acetonitrile	2·82	176—178	2·61	177—179	2·61	185—187	2·37	182—185
Nitromethane	2·97	183—185	2·88	179—181	2·89	185—187	2·77	183—185
Nitroethane	3·01	185—186	2·87	178—180	2·82	182—184	2·66	181—183
Nitrobenzene	3·00	183—184	2·87	183—185	2·77	183—184	2·69	183—185

Ethyl-1,2,3-benzothiadiazolium 2,4-Dinitrobenzenesulphonate.—1,2,3-Benzothiadiazole (1·36 g., 0·01 mole) and ethyl 2,4-dinitrobenzenesulphonate (2·76 g., 0·01 mole) were treated as described above in (*a*). Crystallisation of the crude product (3·68 g., 89%), m. p. 141—145°, from ethanol yielded *ethyl-1,2,3-benzothiadiazolium 2,4-dinitrobenzenesulphonate* as white needles, m. p. 150—151° (Found: C, 41·3; H, 3·0; N, 14·0. $C_{14}H_{12}N_4O_7S_2$ requires C, 40·8; H, 2·9; N, 13·6%).

General Methods of Ion-exchange to Obtain the Quaternary Salts listed in Tables 5 and 6.—An aqueous solution of methyl- or ethyl-1,2,3-benzothiadiazolium hydrogen sulphate, toluene-*p*-sulphonate, or 2,4-dinitrobenzenesulphonate (2 g.) was ion-exchanged on De-Acidite FF (SRA 65; 12 g.) in the appropriate form. Evaporation of the aqueous solution obtained gave a quantitative yield of the appropriate quaternary salt, which was crystallised from ethanol to give the pure compound. The hydrogen sulphate anion gave incomplete exchange with thiocyanate anion, so

that the sulphonates were used to obtain thiocyanates. Ion-exchange columns in the acetate, cyanide, and dihydrogen phosphate forms failed to give the corresponding quaternary salts when treatment with an aqueous solution of methyl-1,2,3-benzothiadiazolium toluene-*p*-sulphonate was tried.

TABLE 5.

Methyl-1,2,3-benzothiadiazolium salts.

No.	Anion	Cryst. form	Crystn. solvent	M. p.	Formula
1.	Cl	Off-white needles	Ethanol–ether	183—184° (d)	$C_7H_7ClN_2S$
2.	Br	Pale-yellow needles	Ethanol	180—181	$C_7H_7BrN_2S$
3.	I	Golden-yellow needles	Ethanol	168—169	$C_7H_7IN_2S$
4.	ClO_4	White needles	Ethanol	121—123	$C_7H_7ClN_2O_4S$
5.	CNS	Lemon-yellow prisms	Ethanol	116—117	$C_8H_7N_3S_2$
6.	Picrate	Yellow leaflets	Ethanol	177—178	$C_{13}H_9N_5O_7S$

	Found (%)							Required (%)				
No.	C	H	Br	Cl	I	N	S	C	H	Hal.	N	S
1.	45·1	3·9		18·4		15·1	17·2	45·0	3·8	19·0	15·0	17·2
2.	36·5	3·1	34·8			12·3		36·4	3·1	34·6	12·3	
3.	30·2	2·7			45·2	10·3		30·2	2·5	45·6	10·3	
4.	33·2	2·9		14·2		11·2		33·5	2·8	14·2	11·2	
5.	46·1	3·8				20·1	29·9	45·9	3·4		20·1	30·6
6.	41·2	2·4				18·7	8·5	41·2	2·4		18·5	8·5

TABLE 6.

Ethyl-1,2,3-benzothiadiazolium salts.

No.	Anion	Cryst. form	Crystn. solvent	M. p.	Formula
1.	Cl	Off-white needles	Ethanol–ether	173—174°	$C_8H_9ClN_2S$
2.	Br	Pale-yellow needles	Ethanol	189—190	$C_8H_9BrN_2S$
3.	I	Orange-yellow needles	Ethanol	181—182	$C_8H_9IN_2S$
4.	ClO_4	White needles	Ethanol	112—113	$C_8H_9ClN_2O_4S$
5.	CNS	Bright-yellow needles	Ethanol	99—100	$C_9H_9N_3S_2$
6.	Picrate	Yellow leaflets	Ethanol	173—174	$C_{14}H_{11}N_5O_7S$

	Found (%)							Required (%)				
No.	C	H	Br	Cl	I	N	S	C	H	Hal.	N	S
1.	48·2	4·6		17·5		14·2	15·8	47·9	4·5	17·7	14·0	16·0
2.	38·3	3·6	32·3			11·7		39·2	3·7	32·6	11·4	
3.	32·8	3·0			42·7	9·5		32·9	3·1	43·4	9·6	
4.	36·6	3·4		13·4		10·7	12·5	36·3	3·4	13·4	10·6	12·1
5.	48·3	4·2				18·7	29·1	48·4	4·1		18·8	28·7
6.	42·8	2·9				17·6	8·1	42·8	2·8		17·8	8·2

Metho- and etho-picrates were obtained in good yield by treating the iodide dissolved in ethanol with an equivalent quantity of an ethanolic solution of picric acid.

Complex of Methyl-1,2,3-benzothiadiazolium Iodide with Iodine.—Crystallisation of methyl-1,2,3-benzothiadiazolium iodide from ethanol containing iodine gave red needles of the *complex*, m. p. 98—99° (Found: C, 15·8; H, 1·4; I, 71·9; N, 5·5; S, 6·3. $C_7H_7I_3N_2S$ requires C, 15·8; H, 1·3; I, 71·6; N, 5·3; S, 6·0%). The infrared spectrum was identical with that of the red needles, which were hand-picked from a mixture of red and yellow needles.

Reduction of Methyl-1,2,3-benzothiadiazolium Bromide.—Methyl-1,2,3-benzothiadiazolium bromide (1 g.), granulated tin (6 g.), and concentrated hydrochloric acid (18 ml.) were heated for 2 hr. on a steam-bath. The homogeneous solution was cooled and saturated with hydrogen chloride, and the yellow precipitate filtered off. The solid was suspended in water and the suspension added slowly with stirring to sodium hydroxide solution (1·73 ml., 40% w/v). Excess of hydrogen peroxide solution (20-vol.) was added and the yellow suspension extracted with chloroform; the extract was dried (Na_2SO_4) and evaporated to dryness to give yellow needles (0·48 g.,

80%), m. p. 66—68°, not depressed by mixing with authentic di-(2-methylaminophenyl) disulphide.[22]

The filtrate from the tin double-salt was made alkaline with sodium hydroxide, and the mixture distilled into concentrated hydrochloric acid. Concentration of the acid solution afforded ammonium chloride. The absence of methylamine hydrochloride was shown by various spot tests.[37,38]

*Action of Aqueous Sodium Hydroxide on Methyl-1,2,3-benzothiadiazolium Toluene-*p*-sulphonate.*—Methyl-1,2,3-benzothiadiazolium toluene-*p*-sulphonate (10 g. in 25 ml. of water) was treated with 20% aqueous sodium hydroxide solution (25 ml.). The initial dark-red colour of the solution changed fairly rapidly to greenish-brown with deposition of a brown oil. Cooling in ice failed to bring about solidification of the oil so the mixture was extracted with ether (2 × 100 ml.), leaving burgundy-red mother liquors. The greenish-yellow ether extract was evaporated to dryness and the residual greenish-brown oil steam-distilled to give a sticky yellowish-brown solid (2·7 g., m. p. ~ 30°). Crystallisation from light petroleum (b. p. 40—60°) (charcoal) gave glittering white crystals, m. p. 37—38°.

Attempts to identify the 1,2,3-benzothiadiazole in the initial brown oil by preparation of the picrate were unsuccessful.

TABLE 7.

Accurate ultraviolet spectra ($\lambda_{max.}$ values; log ε in parentheses) determined on a Unicam S.P. 500 spectrophotometer in 1·0-cm. silica cells at a concentration of 10 mg./l.

1,2,3-Benzothiadiazole: (in H_2O) 213·5 (4·20),* 266·0 (3·72), 312·5 (3·40); (in conc. HCl) 233·0 (4·02), 298·5 (3·75), 329—332 (3·41); (in conc. H_2SO_4) 232·5 (4·03), 298·0 (3·78), 334·0 (3·43).
Methyl-1,2,3-benzothiadiazolium chloride: (in water) 232·5 (4·13), 297·0 (3·76), 330·0 (3·49); (in conc. HCl) 233·5 (4·10), 300·5 (3·76), 333·0 (3·49).
Methyl-1,2,3-benzothiadiazolium bromide: (in water) 232·5 (4·11), 297·5 (3·81), 331 br (3·48).
Methyl-1,2,3-benzothiadiazolium iodide: (in water) 229·5 (4·39), 297·0 (3·79), 330 br (3·52).

Notes. The machine was calibrated before use with a solution of potassium chromate in potassium hydroxide. $\lambda_{max.}$ values are accurate to ±0·5 mμ; log ε values to ±1%.

* These values for 1,2,3-benzothiadiazole were determined in an aqueous buffer, pH 7·0, of sodium dihydrogen phosphate and sodium hydroxide.

TABLE 8.

Approximate ultraviolet spectra of quaternary salts of 1,2,3-benzothiadiazole ($\lambda_{max.}$ values; log ε in parentheses) determined on a Unicam S.P. 700 spectrophotometer in 1·0-cm. silica cells at a concentration of 2 mg./100 ml.

Methiodide: (in water) 296 (3·90), 330 (3·74); (in chloroform) 249·5 (4·03), 293·5 (3·93), 332 (3·77), 495 (3·44).
Methobromide: (in water) 297 (3·85), 330 (3·55); (in chloroform) 247 (3·86), 301 (3·87), 340 (3·73).
Methochloride: No significant variation with change of solvent.
Methothiocyanate: (in water 230 (4·00), 297 (3·85), 328 (3·67); (in chloroform) 245 (3·85), 299 (3·84), 331 (3·72), 437 (3·14).
Methocyanide: (insoluble in water); (in chloroform) 248 (3·88), 267 (3·89), 385 (3·85).
Methyl-2,1,3-benzothiadiazolium iodide: (unstable in water); (in ethanol) 214 (4·16), 316 infl. (4·03), 323·5 (4·05), 357 infl. (3·42); (in chloroform) 246 (3·99), 310·5 (4·05), 369 (3·73), 535 (3·94).

Note. $\lambda_{max.}$ values are accurate to ±1 mμ, log ε values to ±10%.

Though the colorations and speed of reactions were somewhat variable, all the methyl- and ethyl-1,2,3-benzothiadiazolium quaternary salts, when treated with aqueous alkali, ultimately gave a brown oil possessing a smell characteristic of 1,2,3-benzothiadiazole.

1,2,3-Benzothiadiazole Picrate.—1,2,3-Benzothiadiazole formed a *picrate* as yellow needles, m. p. 62—63° (from ethanol) (Found: C, 39·3; H, 2·3; N, 19·0; S, 8·7. $C_{12}H_7N_5O_7S$ requires C, 39·5; H, 1·9; N, 19·2; S, 8·8%).

The authors thank the College authorities for a Bentley Award (to D. J. C.) and Pfizer Ltd. (Sandwich) for raw materials and financial support.

LEICESTER COLLEGE OF TECHNOLOGY, LEICESTER. [*Received, August 27th,* 1964.]

[37] F. J. Smith and E. Jones, "A Scheme of Qualitative Organic Analysis," Blackie, London, 1948, p. 110.
[38] F. Feigl, "Spot Tests, Vol. II: Organic Applications," Elsevier, Amsterdam, 1954, 4th edn. p. 187.