1,2,3-Benzothiadiazole. Part VI.[1] Investigations on the Quaternisation of 1,2,3-Benzothiadiazole and 1,2,3-Benzoselenadiazole

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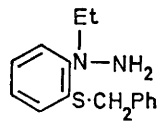
3-Ethyl-1,2,3-benzothiadiazolium bromide, prepared by direct synthesis from 2-aminophenyl benzyl sulphide, proved to be identical with the compound previously obtained by quaternisation. The higher alkyl quaternary salts have been prepared by use of the alkyl esters of 2,4-dinitrobenzenesulphonic acid. Methyl and ethyl quaternary salts of the unstable base 1,2,3-benzoselenadiazole are reported.

WHEN 1,2,3-benzothiadiazole was quaternised with various alkylating agents,[2] there remained some doubt as to whether quaternisation had occurred on N-3 or N-2. It is now established by direct synthesis that N-3 is involved.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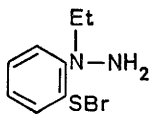
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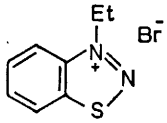
(III)

2-Aminophenyl benzyl sulphide, prepared in high yield by the benzylation of the sodium salt of 2-aminobenzenethiol, was converted into the hydrazine (I) by acetylation, reduction, nitrosation, and finally reduction with lithium aluminium hydride. Attempted aminations of 2-ethylaminophenyl benzyl sulphide with chloramine and with hydroxylamine-*O*-sulphonic acid were unsuccessful.

2-(1-Ethylhydrazino)phenyl benzyl sulphide (I), heated in acetic acid with hydrogen bromide and bromine, cyclised to give 3-ethyl-1,2,3-benzothiadiazolium bromide (III) identical with the compound obtained by quaternisation. Evidently the reaction proceeded by debenzylation, followed by ring closure of the sulphenyl bromide (II) accompanied by oxidation.

The n-butyl, isobutyl, n-pentyl, and isopentyl quaternary salts of 1,2,3-benzothiadiazole were obtained by fusing the appropriate 2,4-dinitrobenzenesulphonate esters with the parent base; the method is essentially identical with that used for 2,1,3-benzothiadiazole and 2,1,3-benzoselenadiazole.[3,4] The products were difficult to crystallise (the m.p. decreased as the molecular weight increased); in fact isobutyl-1,2,3-benzothiadiazolium 2,4-dinitrobenzenesulphonate was isolated only as an oil, but was converted into the crystalline iodide by ion exchange. Preparation of methyl, ethyl, and propyl quaternary salts under the same conditions as for their higher homologues showed that the reactivity of the n-alkyl 2,4-dinitrobenzenesulphonates decreased as the series was ascended.

In view of the thermal instability of 1,2,3-benzoselenadiazole, direct fusion with alkyl 2,4-dinitrobenzenesulphonates at 100° was unsuitable for the preparation of its quaternary salts. However, since selenanthrene formation is slower at 50°, 1,2,3-benzoselenadiazole can be quaternised in nitrobenzene at this

[1] Part V, D. J. Chadbourne and A. J. Nunn, *J. Chem. Soc.*, 1965, 4464.
[2] A. J. Nunn, D. J. Chadbourne, and J. T. Ralph, *J. Chem. Soc.*, 1964, 6061.
[3] A. J. Nunn and J. T. Ralph, *J. Chem. Soc.*, 1965, 6769.
[4] A. J. Nunn and J. T. Ralph, *J. Chem. Soc.* (*C*), 1966, 1568.

temperature, but higher yields were obtained when the mixture was allowed to stand for 1 week at room temperature. Methyl- and ethyl-1,2,3-benzoselenadiazolium 2,4-dinitrobenzenesulphonate were converted into their iodides by double decomposition. Despite the tendency of 1,2,3-benzoselenadiazole to decompose, its quaternary salts were stable both at room temperature and at their m.p.s.

Their properties were very similar to those of 1,2,3-benzothiadiazole; in particular, the parent base was liberated on treatment with alkali.

It is now apparent from this work and that previously reported [3,4] that for a particular alkyl 2,4-dinitrobenzenesulphonate, the order of reactivity of the weak parent bases decreases in the order 1,2,3-benzoselenadiazole > 2,1,3-benzoselenadiazole > 1,2,3-benzothiadiazole > 2,1,3-benzothiadiazole, and this follows closely the magnitude of their pK_a values for the first ionisation constant ($-2{\cdot}25 > -2{\cdot}7 > -3{\cdot}1$ † $> -4{\cdot}5$). The first three of these were determined spectrophotometrically, but the last had to be estimated.[5]

EXPERIMENTAL

I.r. measurements were made on a Perkin-Elmer 257 spectrophotometer.

2-Aminophenyl Benzyl Sulphide.—2-Aminobenzenethiol (40 g.) was added to sodium (7·5 g.) suspended in dry dioxan (300 ml.) and the mixture was refluxed with stirring for 6 hr. The slow addition of benzyl chloride (40 g.) resulted in an immediate exothermic reaction. When the addition was complete, the mixture was stirred for 4 hr. at room temperature. After filtration, dioxan was removed under reduced pressure and the residual oil was poured into ice–water. The solid gave crystalline 2-aminophenyl benzyl sulphide (38 g., 95%), m.p. 44—45° [from light petroleum (charcoal)] (lit.,[6] 43—45°).

Benzyl 2-Ethylaminophenyl Sulphide.—2-Acetamidophenyl benzyl sulphide,[6] m.p. 59—60° (1·19 g.), obtained by acetylation of 2-aminophenyl benzyl sulphide with acetic anhydride in ether, was added slowly in ethereal solution to lithium aluminium hydride (0·3 g.) suspended in ether. The mixture was stirred at room temperature for 6 hr. The complex was decomposed with water and the product was extracted with ether and worked up to give a yellow oil (1·08 g., 90%), $\nu_{max.}$ (film) 3375m (NH), 3060m, 3030m (C=C), 2970m, 2930m (CH_2 and CH_3), and 1600s (aromatic) cm.$^{-1}$.

Benzyl N-Nitroso-2-ethylaminophenyl Sulphide.—Benzyl 2-ethylaminophenyl sulphide (14·5 g.) mixed with concentrated hydrochloric acid (2 ml.) was diluted with water (15 ml.) and to this suspension aqueous sodium nitrite (3·5 g.) was added. The mixture was stirred at 50° for 3 hr., then diluted with water and extracted with ether. The *nitroso-derivative* (9 g., 56%), m.p. 35—37°, gave crystals from light petroleum (Found: C, 66·05; H, 5·85; N, 10·3; S, 11·8. $C_{15}H_{16}N_2OS$ requires C, 66·2; H, 5·95; N, 10·3; S, 11·8%), $\nu_{max.}$ (KBr) 3060m, 3030m (C=C), 2980m, 2940m (CH_2 and CH_3), 1585s (aromatic), 1445vs, and 1428vs (NO) cm.$^{-1}$.

Reduction and Ring Closure to give 3-Ethyl-1,2,3-benzothiadiazolium Bromide.—The nitroso-compound (3·1 g.) in ether was reduced with lithium aluminium hydride under similar conditions to those described previously to give benzyl 2-(1-ethylhydrazino)phenyl sulphide as a brown oil (3 g.), $\nu_{max.}$ (film) 3400—3320w (NH), 3060m, 3020m (C=C), 2970m, 2930m (CH_2 and CH_3), and 1585s (aromatic) cm.$^{-1}$.

The hydrazine compound (1 g.) was dissolved in acetic acid (12 ml.) together with hydrobromic acid (48%; 5 ml.) and bromine (1 ml.) and the mixture was heated under reflux for 1·5 hr., then diluted with water. An insoluble layer of benzyl bromide was separated, and the aqueous layer was decolourised (charcoal) and evaporated on a water-bath. The residue gave pale yellow needles (0·9 g., 90%), m.p. 187—188° (from ethanol); mixed m.p. with authentic 3-ethyl-1,2,3-benzothiadiazolium bromide showed no depression and also the i.r. spectra of samples were identical.

Action of Alkyl 2,4-Dinitrobenzenesulphonates on 1,2,3-Benzothiadiazole (*Table* 1).—1,2,3-Benzothiadiazole is best prepared by the method of Burawoy and Turner.[7]

The alkyl 2,4-dinitrobenzenesulphonates were prepared according to methods previously described.[8] As these esters are unstable they were freshly prepared and carefully purified before use.

General method (0·01 *mole scale*). A mixture of 1,2,3-benzothiadiazole (1·36 g.) and the alkyl 2,4-dinitrobenzenesulphonate was heated in a constant temperature bath at 100° for 30 min. Longer reaction times gave some increase in yield. In the case of methyl- and ethyl-1,2,3-benzothiadiazolium 2,4-dinitrobenzenesulphonates (only slightly soluble in ethanol) the product (solid) was lixiviated with ether and collected. With higher esters the product (oil) was dissolved in ethanol and reprecipitated with ether; usually two such treatments were necessary. Further purification was effected by recrystallisation from ethanol; the alkyl-1,2,3-benzothiadiazolium 2,4-dinitrobenzenesulphonates become increasingly soluble as the series is ascended.

Conversion of Alkyl-1,2,3-benzothiadiazolium 2,4-Dinitrobenzenesulphonates into the Bromides and Iodides (*Table* 2).—*General method.* An aqueous solution of the alkyl-1,2,3-benzothiadiazolium 2,4-dinitrobenzenesulphonate (1·0 g. dissolved in smaller volumes of water as the series was ascended) was treated with Deacidite FF (SRA 65; 7·5 g.) in the bromide or iodide form. Evaporation of the aqueous solution obtained gave an almost quantitative yield of the quaternary bromide or iodide. Recrystallisation from ethanol or ethanol–ether gave pure material.

1,2,3-Benzoselenadiazole.— Bis-(2-aminophenyl) diselenide [9] (10·25 g.) was dissolved in conc. sulphuric acid (50 ml.) and the cooled solution was mixed with 2M-nitrosylsulphuric acid (30 ml.) at 0°. After 30 min. the mixture was poured on crushed ice (1 kg.); 1,2,3-benzoselenadiazole separated immediately and was collected, washed with water, and dried. Dissolution in ethanol, filtration, and reprecipitation with water gave a pale brown solid (6·55 g., 60%), m.p. 32—33°, suitable for quaternisation reactions. Further purification was effected by chromatography in

† W. H. Poesche [*J. Chem. Soc.* (*B*), 1966, 469] reports $-2{\cdot}84 \pm 0{\cdot}04$ at 25°.

[5] J. T. Ralph, Ph.D. Thesis, University of Leicester, October 1966.

[6] A. Sieglitz and H. Koch, *Ber.* 1925, **58**, 78.

[7] A. Burawoy and C. Turner, *J. Chem. Soc.*, 1950, 469.

[8] A. J. Nunn and J. T. Ralph, *Tetrahedron*, 1966, **22**, 1549.

[9] H. Bauer, *Ber.*, 1913, **46**, 92.

ethanol on a short alumina–charcoal column and re-precipitation with water; recrystallisation from methanol (cooling below room temperature) then afforded light yellow needles, m.p. 33—34° (lit.,[10] 34°). The material was stored in the dark.

Methyl-1,2,3-benzoselenadiazolium 2,4-Dinitrobenzenesulphonate.—A mixture of 1,2,3-benzoselenadiazole (1·83 g.) and methyl 2,4-dinitrobenzenesulphonate (2·62 g.) dissolved in dry nitrobenzene (10 ml.) was left in the dark at room temperature for 1 week. Excess of ether was then added, and the product (3·95 g., 89%) was collected, washed with ether, and dried. Recrystallisation from ethanol gave pale yellow *needles* (Found: C, 35·1; H, 2·2; N, 12·5; S, 7·5. $C_{13}H_{10}N_4O_7SSe$ requires C, 35·05; H, 2·3; N, 12·6; S, 7·2%).

In a similar manner pale yellow needles of *ethyl-1,2,3-benzoselenadiazolium 2,4-dinitrobenzenesulphonate* (Found: C, 36·6; H, 2·6; N, 12·3; S, 7·0. $C_{14}H_{12}N_4O_7SSe$ requires C, 36·6; H, 2·6; N, 12·2; S, 7·0%) were obtained.

When the reaction mixtures were heated at 50° for 3 hr. lower yields of product (69 and 28% respectively) resulted.

1,2,3-Benzothiadiazole and methyl 2,4-dinitrobenzenesulphonate heated under the same conditions gave a 60% yield of quaternary salt.

Conversion into the Quaternary Iodides.—Warm aqueous solutions of methyl- or ethyl-1,2,3-benzoselenadiazolium 2,4-dinitrobenzenesulphonate (0·5 g. in 10 ml.) and potassium iodide (0·5 g. in 2·5 ml.) were mixed, stirred, and cooled. The orange solid deposited was collected, washed with ether, and dried (0·4 g.). Recrystallisation from ethanol gave *methyl-1,2,3-benzoselenadiazolium iodide* as orange needles, m.p. 184—185° (Found: C, 25·85; H, 2·1; I, 39·2; N, 8·6. $C_7H_7IN_2Se$ requires C, 25·9; H, 2·2; I, 39·05; N, 8·6%), and *ethyl-1,2,3-benzoselenadiazolium iodide* as orange needles, m.p. 148—149° (Found: C, 28·1; H, 2·55; I, 36·9; N, 8·5. $C_8H_9IN_2Se$ requires C, 28·3; H, 2·7; I, 37·4; N, 8·3%).

TABLE 1

Action of alkyl 2,4-dinitrobenzenesulphonates on 1,2,3-benzothiadiazole

Alkyl ester	Max. temp. attained *	Reaction time (hr.)	Yield of crude product (g.)	(%)	Cryst. form	M.p. (pure compound)
Methyl (2·62 g.)	*ca.* 130°	0·5	3·90	98	Cream needles	196—197° [a]
Ethyl (2·76 g.)	*ca.* 120	0·5	3·70	90	White needles	150—151 [a]
n-Propyl (2·90 g.)	*ca.* 115	0·5	3·30	77	White needles	117—118 [b]
		1	3·60	85		
n-Butyl (3·04 g.)	*ca.* 108	0·5	3·05	70	Off-white crystals	103—104
		1	3·60	82		
n-Pentyl (3·18 g.)	*ca.* 105	0·5	3·15	70	Off-white crystals	96—98 [d]
		1	3·60	79		
Isobutyl (3·04 g.)	[*ca.* 110]†	0·5	Small amount of light brown oil			
Isopentyl (3·18 g.)	*ca.* 105	0·5	2·70	60	White needles	107—108 [e]

* These figures give some indication of the reactivities of the alkyl 2,4-dinitrobenzenesulphonates. † Decomposition of ester in preference to formation of quaternary salt; see ref. 8.

[a] Refs. 2 and 3; [b] ref. 1; [c] Found: C, 43·5; H, 3·65; N, 12·7; S, 14·4. $C_{16}H_{16}N_4O_7S_2$ requires C, 43·6; H, 3·7; N, 12·7; S, 14·55%; [d] Found: C, 45·1; H, 40; N, 12·2; S, 14·0. $C_{17}H_{18}N_4O_7S_2$ requires C, 44·9; H, 4·0; N, 12·3; S, 14·1%; [e] Found: C, 45·2; H, 3·95; N, 12·5; S, 13·65. $C_{17}H_{18}N_4O_7S_2$ requires C, 44·9; H, 4·0; N, 12·3; S, 14·1%.

TABLE 2

Conversion of alkyl-1,2,3-benzothiadiazolium 2,4-dinitrobenzenesulphonates into the bromides and iodides

Alkyl	Anion	Wt. of crude product (g.)	Cryst. form	M.p. of pure compound	Formula	Found (%) C	H	Br	I	N	S	Required (%) C	H	Br	I	N	S
n-Propyl (1·0 g.)	Br^-	0·60	Pale yellow solid [a]	185—186°	$C_9H_{11}BrN_2S$	41·6	4·3	30·9		10·9	12·4	41·7	4·3	30·8		10·8	12·4
	I^-	0·70	Orange-yellow needles [b]	167—168	$C_9H_{11}IN_2S$	34·9	3·6		41·35	9·2	11·0	35·3	3·6		41·45	9·15	10·5
n-Butyl (1·0 g.)	Br^-	0·60	Pale yellow solid [a]	83—85	$C_{10}H_{13}BrN_2S$	43·8	5·0	28·25		10·0	11·2	44·0	4·8	29·25		10·2	11·7
n-Pentyl (1·0 g.)	Br^-	0·60	Pale yellow solid [a]	142—143	$C_{11}H_{15}BrN_2S$	45·7	5·25	27·9		9·8	11·7	46·0	5·3	27·8		9·75	11·2
	I^-	0·70	Orange crystals [b]	101—102	$C_{11}H_{15}IN_2S$	39·6	4·4		37·0	8·5	10·6	39·5	4·5		38·0	8·4	9·6
Isobutyl	I^-	0·10 *	Orange-yellow [a]	149—150	$C_{10}H_{13}IN_2S$	37·6	4·0		39·6	8·6	10·3	37·5	4·1		39·6	8·75	10·0
Isopentyl (1·0 g.)	I^-	0·65	Bright yellow needles [a]	150—151	$C_{11}H_{15}IN_2S$	39·6	4·4		39·6	8·45	10·3	39·5	4·5		38·0	8·4	9·65

* Product from a 0·005 mole scale mixture of 1,2,3-benzothiadiazole and isobutyl 2,4-dinitrobenzenesulphonate converted directly into the iodide.

[a] From ethanol–ether; [b] from ethanol.

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[10] S. Keimatsu and I. Satoda, *J. Pharm. Soc. Japan,* 1935, **55**, 233.