The Synthesis and Reactions of 4*H*-Tetrazolo[5,1-*c*][1,4]benzothiazines

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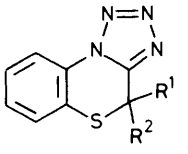
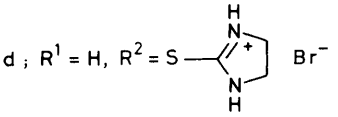
The synthesis of 4*H*-tetrazolo[5,1-*c*][1,4]benzothiazines *via* an intramolecular dipolar addition reaction of 2-(2-azidophenylthio)acetonitrile is described. The methylene protons of the thiazine ring were found to be sufficiently acidic to be readily functionalised by base-catalysed deprotonation followed by reaction with electrophiles (*e.g.* alkyl halides). *N*-Bromosuccinimide also reacted at this position to give 4-bromo-4*H*-tetrazolo[5,1-*c*][1,4]-benzothiazine whilst bromination of 4-methyl-4*H*-tetrazolo[5,1-*c*][1,4]benzothiazine gave 4-bromomethylene-4*H*-tetrazolo[5,1-*c*][1,4]benzothiazine. This material reacted with alkoxides to give unusually acid-stable acetals.

OUR interest in the chemistry and biological activity of condensed heterocyclic systems,[1] allied to the known pharmacological properties of a range of tetrazoles,[2] led us to investigate the synthesis and chemical properties of the previously unreported 4*H*-tetrazolo[5,1-c][1,4]-benzothiazine (1) ring system.



(1) a; $R^1 = R^2 = H$
b; $R^1 = H$, $R^2 = Me$
c; $R^1 = R^2 = Me$
(6) a; $R^1 = H$, $R^2 = Br$
b; $R^1 = H$, $R^2 = OH$
c; $R^1 = H$, $R^2 = OCO \cdot C_6H_4Cl\text{-}m$
(8) a; $R^1 = H$, $R^2 = CH(OMe)_2$
b; $R^1 = H$, $R^2 = CH \cdot O \cdot CH_2 \cdot CH_2 \cdot O$
(9) a; $R^1 = H$, $R^2 = OR$
b; $R^1 = H$, $R^2 = N(R)_2$
c; $R^1 = H$, $R^2 = S{-}C(NH_2){:}NH_2^+ Br^-$

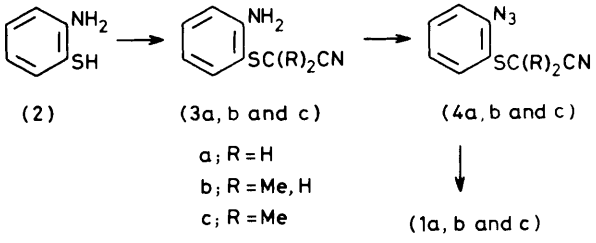


RESULTS AND DISCUSSION

The most appealing route to the benzothiazine (1) is shown in Scheme 1 and envisages the intramolecular, dipolar addition reaction [3] between the nitrile and azide groups in compound (4). Consequently 2-amino(thiophenol) (2) was condensed with chloroacetonitrile to give the known [4] 2-(2-aminophenylthio)acetonitrile (3a) by a modification of the published process.

Diazotisation of the aniline (3a) and reaction with azide anion gave the azide (4a) which was refluxed in xylene to give the benzothiazine (1a) in a satisfactory yield. The reaction sequence could be extended to the preparation of the 4-methyl- and 4,4-dimethyl-tetrazolo[5,1-*c*][1,4]benzothiazines (1b and c), respectively, by using the appropriately substituted α-chloroacetonitriles to give the intermediates (3b and c) and (4b and c).

The methylene group in compound (1a) is sufficiently activated by the tetrazole ring for the protons to be readily removed by strong base, *e.g.* n-butyl-lithium. Thus reaction in tetrahydrofuran (THF) at −78 °C, followed by addition of methyl iodide, gave the methyl-derivative (1b). The remaining proton in compound (1b) is also acidic and repeating the sequence gives the dimethyl analogue (1c), a product which can also be obtained by dialkylation in one step, although in this case the yields are much lower.

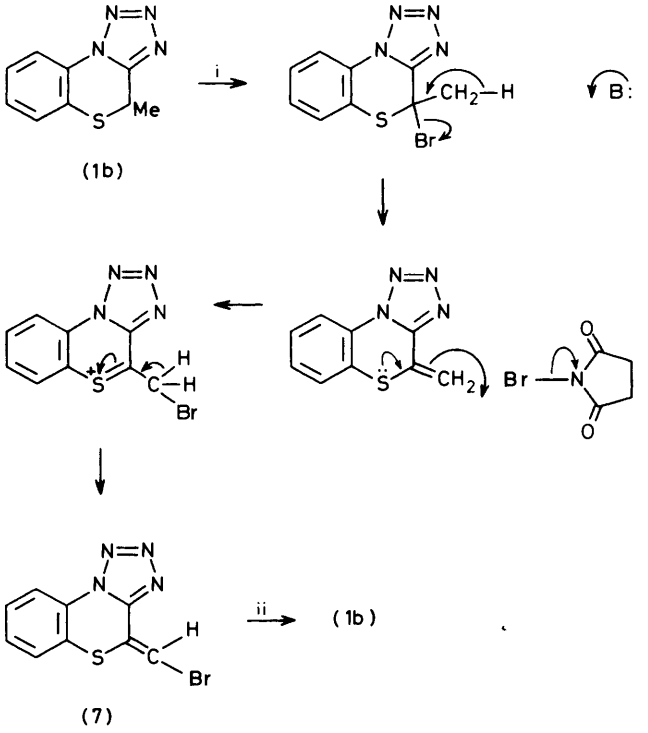


SCHEME 1

Other reactions at the methylene group possibly arise following initial reaction at the sulphur atom. Thus *N*-bromosuccinimide and *m*-chloroperbenzoic acid, both agents which might be expected to yield the sulphoxide (5),[5] gave, respectively, the 4-bromo-derivative (6a) and a mixture of 4-hydroxy- (6b) and 4-(*m*-chlorobenzoyloxy)- (6c) compounds. When the reaction with *N*-bromosuccinimide was extended to the methyl derivative (1b), the product was shown by elemental analysis and ^1H n.m.r. spectroscopy to be 4-bromomethylene-4*H*-tetrazolo[5,1-*c*][1,4]benzothiazine (7). A possible mechanism for this transformation is shown in Scheme 2, but we have no information as to whether the process is ionic or radical. Further support for the proposed structure was provided by catalytic reductive-dehalogenation of the methylene derivative (7) to give compound (1b).

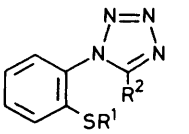
The benzothiazine (7) was found to react with sodium methoxide and disodium ethyleneglycolate to give the acetals (8a and b). The structure of these products was fully supported by elemental analysis, ^1H n.m.r., and, in the case of compound (8a), ^{13}C n.m.r. spectroscopy, but they were both surprisingly resistant to acidic hydrolysis

to the corresponding aldehyde. It is possible that preferential protonation of the tetrazole ring prevents the hydrolytic process.



SCHEME 2 *Reagents:* i, *N*-Bromosuccininide; ii, H_2/Pt

The bromine atom in compound (6a) could be readily displaced by a variety of nucleophiles; reaction with hydroxide, alkoxides, amines, thiourea, and imidazolidine-2-thione in particular gave the corresponding products (9a—d) (Tables 1 and 2). Since the hydroxy-compound (6b) is, of course, a monothioacetal, it can exist, at least theoretically, in equilibrium with its thiol aldehyde isomer (10). An indication that this may be the case in alkaline media is given by the reaction of compound (6b) with dimethyl sulphate in sodium hydroxide solution which yields the sulphide (11) with concomitant loss of the aldehyde group. The analogous



(10) R^1 = H, R^2 = CHO
(11) R^1 = Me, R^2 = H

deacylation of methyl 1-phenyl-1*H*-tetrazol-5-yl ketone has been reported.[6]

The sulphur atom in compound (1a) proved to be resistant to oxidation by sodium metaperiodate, whilst other oxidants, as described previously, gave α-substituted products. The 4-methyl derivative (1b) gave only

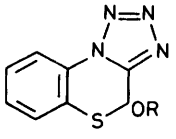
(5) R = H
(12) R = Me

complex, inseparable mixtures with the periodate, whilst the 4,4-dimethyl derivative (1c) was surprisingly readily oxidised to the sulphoxide (12). Presumably the lack of α-protons reduces competing reactions, and the electron-donating effect of the two methyl groups is sufficient to overcome any steric effects, thus increasing the ease of oxidation of the sulphur atom. Compound (12) could be further converted, into the sulphoximide (13a), by reaction with sodium azide in polyphosphoric acid, and this product was found to readily undergo the reactions common to this class of compound [7] [*e.g.* the analogue (13b)].

An alternative approach to the preparation of the sulphoxide (12) attempted to use the dipolar addition-reaction starting from the sulphinylacetonitrile (14). However, diazotisation of compound (14) and reaction with azide ion gave, as the only isolated product, the 1,3,-4-benzothiadiazine (15). Presumably, in this case, the methylene protons in the diazonium ion (16) are so acidic

TABLE 1

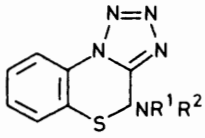
Products from the reaction of compound (6a) with various nucleophiles



R	M.p. (°C)	Yield (%)	Analysis (%) Found C	H	N	S	Required C	H	N	S
H	185—189	52	46.7	3.0	27.3	15.6	46.6	2.9	27.2	15.55
Me	102—103	61	49.0	3.7	25.5	14.5	49.1	3.7	25.4	14.6
Et	112—114	92	51.1	4.3	24.0	13.7	51.3	4.3	23.9	13.7
$CH_2CH{=}CH_2$	87—89	87	53.6	4.1	22.9	12.9	53.6	4.1	22.7	13.0

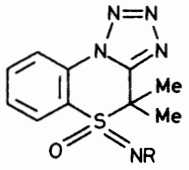
TABLE 2

Products from the reaction of compound (6a) with various nucleophiles



R^1	R^2	M.p. (°C)	Yield (%)	Analysis (%) Found C	H	N	S	Required C	H	N	S
H	H	145—147	56	46.7	3.6	33.7	15.5	46.8	3.4	34.1	15.6
Et	Et	136—137	61	55.2	5.7	27.1	12.2	55.5	5.8	26.8	12.3
Pr^i	Pr^i	138—140	61	58.1	6.5	24.1	11.0	58.1	6.6	24.2	11.1
		235—237	75	52.2	4.7	25.4	11.8	52.35	4.8	25.4	11.6
		177.5—178.5	65	57.2	5.5	25.7	11.7	57.1	5.5	25.6	11.7
		107—109	50	53.8	5.5	22.4	10.3	53.8	5.8	22.4	10.3
		168—170	92	55.5	5.1	27.0	12.4	55.6	5.05	27.0	12.4
		152—154	65	54.1	5.7	28.8	11.3	54.15	5.6	29.1	11.1
		176—177	45	61.5	5.15	24.0	9.2	61.7	5.2	24.0	9.15
		186—187	55	51.95	5.2	24.4	9.2	52.0	5.2	24.3	9.25

that the azide ion causes deprotonation and the resulting nucleophilic centre attacks the diazonium group to yield the observed product (15). It should be noted that this is a different process to that recently described by Garanti [8] for the synthesis of some related compounds.



(13)

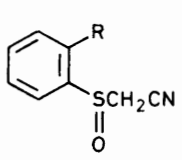
a; R = H

b; R = $COCH_2Cl$

EXPERIMENTAL

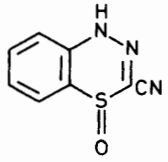
M.p.s were determined on a Köfler hot-stage apparatus. I.r. spectra were recorded with a Pye Unicam SP 1000 spectrophotometer. ^1H N.m.r. spectra were determined with a Perkin-Elmer R 12A spectrometer at 60 MHz, with tetramethylsilane as internal standard. Elemental analyses were carried out by C.H.N. Analysis Ltd., Leicester.

2-(2-Aminophenylthio)acetonitrile (3a).—A solution of 2-amino(thiophenol) (12.5 g), sodium dithionite (20 g), and potassium carbonate (13.8 g) in ethanol–water (1 : 1; 400 ml) was refluxed for 2 h and chloroacetonitrile (8.0 g) was then added. Refluxing was continued under nitrogen for 4 h, the solution was left at room temperature overnight, poured into ice–water, and extracted with diethyl ether. The organic layer was separated, washed (aqueous NaCl), dried ($MgSO_4$), and evaporated to give an oil which slowly crystallised to give 2-(2-aminophenylthio)acetonitrile (13.0 g, 79%); it was purified as a hydrochloride salt, m.p. 147—150 °C (lit.,[4b] 152 °C).



(14) R = NH_2

(16) R = N_2^+



(15)

The following compounds were similarly prepared.

2-(2-Aminophenylthio)propiononitrile (3b). This compound was obtained in 91% yield, m.p. 140 °C (decomp.) (HCl salt) (Found: C, 50.3; H, 5.1; Cl, 16.45; N, 13.05; S, 15.0. $C_9H_{10}N_2S$·HCl requires C, 50.35; H, 5.2; Cl, 16.5; N, 13.05; S, 14.9%).

2-(2-Aminophenylthio)-2-methylpropriononitrile (3c). This compound was obtained in 66% yield, m.p. 140 °C (decomp.) (HCl salt) (Found: C, 52.5; H, 5.6; Cl, 15.55;

N, 12.2; S, 14.2. $C_{10}H_{12}N_2S$·HCl requires C, 52.5; H, 5.7; Cl, 15.5; N, 12.25; S, 14.0%).

2-(2-*Azidophenylthio*)*acetonitrile* (4a).—2-(2-Aminophenylthio)acetonitrile (13 g) was dissolved in 4N-hydrochloric acid (90 ml), cooled to between −2 and −5 °C, and a solution of sodium nitrite (5.6 g) in water (17 ml) was added slowly. After 15 min, sodium hydrogencarbonate (15 g) was added, followed by a solution of sodium azide (5.1 g) in water (25 ml). The solution was kept between −2 and −5 °C for 1 h and then diluted with ice–water and filtered. The solid was dissolved in chloroform, treated with charcoal, filtered, concentrated, and the residue chromatographed on silica gel with chloroform to give 2-(2-*azidophenylthio*)*acetonitrile* (8.5 g, 56%), m.p. 64—65 °C (Found: C, 50.7; H, 3.3; N, 29.5; S, 16.9. $C_8H_6N_4S$ requires C, 50.5; H, 3.2; N, 29.45; S, 16.85%); $\nu_{max.}$ 2 125 (CN) and 2 085 cm^{-1} (N_3); τ($CDCl_3$) 6.40 (2 H, s, CH_2) and 2.3—3.1 (4 H, m, aromatics).

The following compounds were similarly prepared.

2-(2-*Azidophenylthio*)*propiononitrile* (4b). This compound was obtained in 78% yield, m.p. 27—29 °C (Found: C, 52.8; H, 4.0; N, 27.2; S, 15.6. $C_9H_8N_4S$ requires C, 52.9; H, 3.95; N, 27.4; S, 15.7%).

2-(2-*Azidophenylthio*)-2-*methylpropiononitrile* (4c). This compound was obtained in 93% yield, m.p. 25—28 °C (Found: C, 54.95; H, 4.7; N, 25.6; S, 14.8. $C_{10}H_{10}N_4S$ requires C, 55.0; H, 4.6; N, 25.7; S, 14.7%).

4H-*Tetrazolo*[5,1-c][1,4]*benzothiazine* (1a).—A solution of 2-(2-azidophenylthio)acetonitrile (5.5 g) in xylene (200 ml) was refluxed under nitrogen for 4 h and then cooled to 80 °C. After treatment with charcoal the mixture was stirred for 5 min and then filtered, evaporated to 30 ml under reduced pressure and left overnight to crystallise. Filtration gave 4H-*tetrazolo*[5,1-c][1,4]*benzothiazine* (4.0 g, 73%), m.p. 133—135 °C (Found: C, 50.6; H, 3.3; N, 29.5; S, 16.6. $C_8H_6N_4S$ requires C, 50.5; H, 3.2; N, 29.45; S, 16.85%); τ($CDCl_3$) 5.68 (2 H, s, CH_2S), 2.4—2.8 (3 H, m, 6-, 7-, and 8-H), and 1.80—2.10 (1 H, m, 9-H).

The following compounds were similarly prepared.

4-*Methyl*-4H-*tetrazolo*[5,1-c][1,4]*benzothiazine* (1b). This compound was obtained in 86% yield, m.p. 113—115 °C (analysis and spectra given below).

4,4-*Dimethyl*-4H-*tetrazolo*[5,1-c][1,4]*benzothiazine* (1c). This compound was obtained in 84% yield, m.p. 115—117 °C (analysis and spectra given below).

Alkylation of the Thiazine (1a).—(*a*) *Monomethylation*. A solution of compound (1a) (5.7 g) in dry tetrahydrofuran (THF) (150 ml) under a nitrogen atmosphere was cooled to −78 °C, and n-butyl-lithium (20 ml of 1.5 M-THF) added dropwise. The solution was then stirred at −78 °C for a further 30 min, after which time methyl iodide (4.5 g) was added. Stirring was continued for a further 2 h and the solution was then allowed to warm to room temperature before water (5 ml) and 1N-hydrochloric acid (5 ml) were added cautiously. An excess of water was added and the solution extracted with chloroform. The organic layer was separated, washed with sodium metabisulphite solution and water, dried ($MgSO_4$) and evaporated to give a residue which, on trituration with diethyl ether, gave yellow crystals of 4-*methyl*-4H-*tetrazolo*[5,1-c][1,4]*benzothiazine* (1b) (4.9 g, 80%), m.p. 113—115 °C (Found: C, 52.65; H, 3.9; N, 27.3; S, 15.6. $C_9H_8N_4S$ requires C, 52.9; H, 3.95; N, 27.4; S, 15.7%); τ($CDCl_3$) 8.15 (3 H, d, *J* 7 Hz, 4-Me_3), 5.27 (1 H, q, *J* 7 Hz, 4-H), 2.3—2.8 (3 H, m, 6-, 7-, and 8-H), and 1.75—2.1 (1 H, m, 9-H).

(*b*) *Dimethylation*. Repeating the above reaction with a greater than two-fold excess of methyl iodide invariably gave mixtures of products which were identified by t.l.c. analysis as being monomethylated (1b) and dimethylated (1c) benzothiazines. This reaction was therefore abandoned.

4,4-*Dimethyl*-4H-*tetrazolo*[5,1-c][1,4]*benzothiazine* (1c).—To a stirred solution of 4-methyl-4H-tetrazolo[5,1-*c*][1,4]-benzothiazine (1b) (2 g) in dry THF (70 ml) under nitrogen at −78 °C was added dropwise a solution of n-butyl-lithium in THF (6 ml of 1.6M). After 20 min, methyl iodide (2.0 g) was added and the solution allowed to warm to room temperature during 2 h. Water (50 ml) and 1N-hydrochloric acid (50 ml) were added and the mixture extracted with chloroform. The organic layer was washed (H_2O), dried ($MgSO_4$), evaporated and the residue chromatographed on silica gel (chloroform as eluant) to give 4,4-*dimethyl*-4H-*tetrazolo*[5,1-c][1,4]*benzothiazine* (1c) (1.55 g, 66%), m.p. 106—109 °C (Found: C, 54.9; H, 4.65; N, 25.9; S, 14.7. $C_{10}H_{10}N_4S$ requires C, 55.0; H, 4.6; N, 25.7; S, 14.7%); τ($CDCl_3$) 8.19 (6 H, s, 2 × Me), 2.35—2.65 (3 H, m, 6-, 7-, and 8-H), and 1.75—2.02 (1 H, m, 9-H).

4-*Bromo*-4H-*tetrazolo*[5,1-c][1,4]*benzothiazine* (6a).—A suspension of the thiazine (1a) (1.9 g), *N*-bromosuccinimide (1.8 g), and dibenzoyl peroxide (10 mg) in dry carbon tetrachloride (200 ml) was stirred at 50 °C for 4 h, cooled, filtered and evaporated to 10 ml. The cooled solution was filtered to give 4-*bromo*-4H-*tetrazolo*[5,1,c][1,4]*benzothiazine* (6a) (2.5 g, 79%), m.p. 139—141 °C (Found: C, 36.0; H, 1.9; N, 21.0; S, 12.1. $C_8H_5BrN_4S$ requires C, 35.7; H, 1.9; N, 20.8; S, 11.9%); τ($CDCl_3$) 3.02 (1 H, s, 4-H), 2.20—2.70 (3 H, m, 6-, 7-, and 8-H), and 1.55—1.85 (1 H, m, 9-H).

Reaction of Compound (1a) *with* m-*Chloroperbenzoic Acid*.—A solution of the thiazine (1a) (0.2 g) in dichloromethane (20 ml) was refluxed with *m*-chloroperbenzoic acid (0.20 g) for 6 h. During the next 12 h further portions of *m*-chloroperbenzoic acid (0.2 g in total) were added. The solution was then cooled to room temperature, washed with aqueous sodium carbonate and extracted into ethyl acetate. The organic layer was washed with water, dried ($MgSO_4$), evaporated, and the residue chromatographed on silica gel with chloroform to give 4H-*tetrazclo*[5,1-c][1,4]*benzothiazin*-4-*yl m-chlorobenzoate* (6c) (0.05 g, 14%), m.p. 165—167 °C (Found: C, 52.3; H, 2.75; Cl, 10.2; N, 16.25; S, 9.1. $C_{15}H_9ClN_4O_2S$ requires C, 52.25; H, 2.6; Cl, 10.3; N, 16.25; S, 9.3%); $\nu_{max.}$ 1 740 cm^{-1} (CO); τ($CDCl_3$) 2.85 (1 H, s, 4-H), 2.8—2.5 (8 H, m, aromatic), and 1.85—1.5 (1 H, m, 9-H).

Further fractions gave starting material (1a) (0.05 g) and 4-*hydroxy*-4H-*tetrazolo*[5,1-c][1,4]*benzothiazine* (6b) (0.05 g, 23%), m.p. 185—189 °C (Found: C, 46.7; H, 3.0; N, 27.3; S, 15.6. $C_8H_5N_4OS$ requires C, 46.6; H, 2.9; N, 27.2; S, 15.55%); $\nu_{max.}$ 3 200br cm^{-1} (OH); τ($CDCl_3$–CD_3OD) 3.5 (1 H, s, 4-H), 2.2—2.8 (3 H, m, 6-, 7-, and 8-H), and 1.6—2.0 (1 H, m, 9-H).

4-*Bromomethylene*-4H-*tetrazolo*[5,1-c][1,4]*benzothiazine* (7).—A suspension of 4-methyl-4*H*-tetrazolo[5,1-c][1,4]benzothiazine (1b) (12.5 g), *N*-bromosuccinimide (22.5 g), and dibenzoyl peroxide (10 mg) in carbon tetrachloride (1.5 l) was refluxed for 4 h, filtered, concentrated, and diluted with diethyl ether to give 4-*bromomethylene*-4H-*tetrazolo*[5,1-c]-[1,4]*benzothiazine* (12.5 g, 73%), m.p. 186—187 °C (Found: C, 38.6; H, 1.9; Br, 28.2; N, 19.8; S, 11.4. $C_9H_5BrN_4S$ requires C, 38.45; H, 1.8; Br, 28.4; N, 19.9; S, 11.4%); $\nu_{max.}$ 1 594 cm^{-1} (C=C); τ($CDCl_3$) 2.2—2.8 (3 H, m, 6-, 7-, and 8-H), 2.20 (1 H, s, CHBr), and 1.9—2.15 (1 H, m, 9-H).

4-(*Dimethoxymethyl*)-4H-*tetrazolo*[5,1-c][1,4]*benzothiazine* (8a).—Sodium (2.0 g) was dissolved in methanol (120 ml)

under nitrogen and the bromomethylene derivative (7) (2.0 g) added. The solution was refluxed for 3 h, cooled, neutralised with hydrochloric acid, diluted with water (500 ml), and extracted with chloroform. The organic layer was washed (H_2O), dried ($MgSO_4$) and evaporated to give 4-(*dimethyoxymethyl*)-4H-*tetrazolo*[5,1-c][1,4]*benzothiazine* (8a) (1.0 g, 53%), m.p. 109—111 °C (Found: C, 50.05; H, 4.5; N, 21.4; S, 12.2. $C_{11}H_{12}N_4O_2S$ requires C, 50.0; H, 4.6; N, 21.2; S, 12.1%; τ($CDCl_3$) 6.63 (6 H, s, 2 × Me), 5.23 and 5.37 (2 H, q, *J* 5 Hz, CHCH), 2.30—2.80 (3 H, m, 6-, 7-, and 8-H), 1.80—2.1 (1 H, m, 9-H); τ (^{13}C) ($CDCl_3$) 39.5 (d, C-4), 56.0 and 56.3 (2 × q, 2 × OMe), 105.4 [d, *C*H(OMe)$_2$] 119.9, 124.0, 128.4, 128.6, 129.8, 130.9, and 147.6 p.p.m. (aromatic).

Similarly prepared was 4-(*ethylenedioxymethyl*)-4H-*tetrazolo*[5,1-c][1,4]*benzothiazine* (8b) (27%), m.p. 150—153 °C (Found: C, 50.3; H, 3.8; N, 21.3; S, 12.4. $C_{11}H_{10}N_4O_2S$ requires C, 50.4; H, 3.8; N, 21.4; S, 12.2%).

4-*Methoxy*-4H-*tetrazolo*[5,1-c][1,4]*benzothiazine* (9a; R = Me).—A solution of the bromo-compound (6a) (1.0 g) in methanol (50 ml) was warmed on a steam-bath for 5 min, evaporated to dryness and the residue recrystallised from chloroform–diethyl ether to give 4-*methoxy*-4H-*tetrazolo*-[5,1-c][1,4]*benzothiazine* (0.5 g, 61%); τ(CD_3OD) 6.4 (3 H, s, OMe), 3.62 (1 H, s, 4-H), 2.1—2.7 (3 H, m, 6-, 7-, and 8-H), and 1.6—2.0 (1 H, m, 9-H).

In a similar manner the other compounds of Table 1 were prepared.

4-*Morpholino*-4H-*tetrazolo*[5,1-c][1,4]*benzothiazine* (9b; $N(R)_2$ = morpholino).—A solution of the bromo-derivative (6a) (1.25 g), triethylamine (1.1 g), and morpholine (0.90 g) in dichloromethane (25 ml) was stirred for 3 h at room temperature, poured into water and the organic layer separated. The aqueous layer was extracted with chloroform and the combined organic layers washed (H_2O), dried ($MgSO_4$), and evaporated to give 4-*morpholino*-4H-*tetrazolo*[5,1-c][1,4]*benzothiazine* (950 mg, 74%); τ($CDCl_3$) 7.4—7.8 [4 H, m, $(CH_2)_2N$], 6.2—6.6 (4 H, m, $(CH_2)_2O$), 4.13 (1 H, s, 4-H), 2.2—2.8 (3 H, m, 6-, 7-, and 8-H), and 1.6—2.1 (1 H, m, 9-H).

In a similar manner the compounds of Table 2 were prepared.

(4H-*Tetrazolo*[5,1-c][1,4]*benzothiazin*-4-*yl*)*thiouronium Bromide* (9c).—A solution of thiourea (0.4 g) in acetonitrile (60 ml) was azeotroped to 50 ml to remove traces of water. It was then cooled to below reflux point and 4-bromo-4*H*-tetrazolo[5,1-*c*][1,4]benzothiazine (1.35 g) was added giving an immediate precipitate. The mixture was cooled to room temperature and filtered to give (4H-*tetrazolo*[5,1-c]-[1,4]*benzothiazin*-4-*yl*)*thiouronium bromide* (1.25 g, 72%), m.p. 195—198 °C (Found: C, 31.3; H, 2.6; Br, 23.2; N, 24.1; S, 18.6. $C_9H_9BrN_6S_2$ requires C, 31.3; H, 2.6; Br, 23.15; N, 24.3; S, 18.6%); $\nu_{max.}$ 3 300—2 500 (NH) and 1 660 cm^{-1} (CN); τ(CD_3OD) 2.85 (1 H, s, 4-H), 2.0—2.4 (3 H, m, 6-, 7-, and 8-H), and 1.6—1.9 (1 H, m, 9-H).

Similarly 2-(4H-*tetrazolo*[5,1-c][1,4]*benzothiazin*-4-*ylthio*)-*imidazoliumyl bromide* (9d) was prepared, yield 89%, m.p. 180—185 °C (Found: C, 35.6; H, 3.0; Br, 21.55; N, 22.7; S, 17.0. $C_{11}H_{11}BrN_6S_2$ requires C, 35.6; H, 3.0; Br, 21.5; N, 22.6; S, 17.3%); $\nu_{max.}$ 3 080 (NH) and 1 572 cm^{-1} (C=N); τ(CD_3OD) 6.05 (4 H, s, CH_2CH_2), 2.86 (1 H, s, 4-H), 2.2—2.6 (3 H, m, 6-, 7-, and 8-H), and 1.65—2.0 (1 H, m, 9-H).

Methylation of 4-*Hydroxy*-4H-*tetrazolo*[5,1-c][1,4]*benzothiazine* (6b).—A solution of 4-hydroxy-4*H*-tetrazolo[5,1-c]-[1,4]benzothiazine (400 mg) in methanol (10 ml) was treated with 1N-sodium hydroxide (4 ml) at 50 °C for 1 h after which dimethyl sulphate (200 mg) was added. After 2 h at 50 °C further 1N-sodium hydroxide (2 ml) and dimethyl sulphate (200 mg) were added. Heating was continued for a further 1 h and the solution left at room temperature for 48 h and then poured into water and extracted with dichloromethane. The organic layer was separated, washed (H_2O), dried ($MgSO_4$), and evaporated and the residual oil (0.34 g) chromatographed (silica gel; MeOH–CH_2Cl_2, 2% as eluant) to give first 4-methoxy-4*H*-tetrazolo[5,1-*c*][1,4]benzothiazine (100 mg, 23%) and then 1-(2-*methylthiophenyl*)*tetrazole* (11) (100 mg, 27%), m.p. 67—69 °C (Found: C, 49.7; H, 4.2; N, 29.1; S, 16.6. $C_8H_8N_4S$ requires C, 50.0; H, 4.2; N, 29.15; S, 16.7%). $\nu_{max.}$ 3 120 cm^{-1} (CH); τ($CDCl_3$) 7.60 (3 H, s, SMe), 2.35—2.85 (4 H, m, aromatic), and 1.06 (1 H, s, tetrazolyl CH).

4,4-*Dimethyl*-4H-*tetrazolo*[5,1-c][1,4]*benzothiazine* 5-*Oxide* (12).—To a stirred solution of 4,4-dimethyl-4*H*-tetrazolo-[5,1-c][1,4]benzothiazine (2.0 g) in ethanol (100 ml), kept at 70 °C, was added a solution of sodium metaperiodate (2.0 g) in water (100 ml). The mixture was heated for 48 h, evaporated to *ca.* 100 ml and extracted with dichloromethane. The organic layer was washed (H_2O), dried ($MgSO_4$), and evaporated to give, after trituration with diethyl ether, 4,4-*dimethyl*-4H-*tetrazolo*[5,1-c][1,4]*benzothiazine* 5-*oxide* (1.62 g, 75%), m.p. 127—129 °C (Found: C, 51.35; H, 4.2; N, 23.8; S, 14.0. $C_{10}H_{10}N_4OS$ requires C, 51.3; H, 4.3; N, 23.9; S, 13.7%); $\nu_{max.}$ 1 055 cm^{-1} (SO); τ($CDCl_3$) 8.39 (3 H, s, Me), 8.05 (3 H, s, Me), and 1.8—2.8 (4 H, m, aromatic).

5-*Imino*-4,4-*dimethyl*-4H-*tetrazolo*[5,1-c][1,4]*benzothiazine* 5-*Oxide* (13a).—4,4-Dimethyl-4*H*-tetrazolo[5,1-*c*][1,4]-benzothiazine 5-oxide (4.3 g; finely powdered) was suspended in polyphosphoric acid (150 g), stirred at 70 °C, in the presence of ethylene dichloride (10 ml) to improve mobility. Sodium azide (5.0 g) was added during 7 h, after which the mixture was cooled to room temperature, poured onto ice–water and neutralised with ammonia (*d* 0.880). Filtration gave 5-*imino*-4,4-*dimethyl*-4H-*tetrazolo*[5,1-c]-[1,4]*benzothiazine* 5-*oxide* (2.2 g, 44%), m.p. 196—197 °C (Found: C, 48.3; H, 4.4; N, 28.1; S, 12.8. $C_{10}H_{11}N_5OS$ requires C, 48.2; H, 4.45; N, 28.1; S, 12.9%); $\nu_{max.}$ 3 200 cm^{-1} (NH); τ($CDCl_3$) 8.20 (3 H, s, Me), 8.10 (3 H, s, Me), and 1.7—2.5 (4 H, m, aromatic).

5-*Chloroacetylimino*-4,4-*dimethyl*-4H-*tetrazolo*[5,1-c][1,4]-*benzothiazine* 5-*Oxide* (13b).—A solution of 5-imino-4,4-dimethyl-4*H*-tetrazolo[5,1-*c*][1,4]benzothiazine 5-oxide (800 mg) and chloroacetyl chloride (1.0 g) in *N*,*N*-dimethylformamide (DMF) (10 ml) was stirred at 60 °C for 6 h, poured into water and extracted with ethyl acetate. The organic layer was washed (H_2O), dried ($MgSO_4$) and evaporated to give 5-*chloroacetylimino*-4,4-*dimethyl*-4H-*tetrazolo*-[5,1-c][1,4]*benzothiazine* 5-*oxide* (680 mg, 65%), m.p. 156—158 °C (Found: C, 44.2; H, 3.7; Cl, 10.9; N, 21.5; S, 9.7. $C_{12}H_{12}ClN_5O_2S$ requires C, 44.2; H, 3.7; Cl, 10.9; N, 21.5; S, 9.8%); $\nu_{max.}$ 1 690 cm^{-1} (CO); τ($CDCl_3$) 8.32 (3 H, s, Me), 7.77 (3 H, s, Me), 6.15 (2 H, s, CH_2Cl), and 1.4—2.4 (4 H, m, aromatic).

2-*Cyano*-1,3,4-*benzothiadiazine* 1-*Oxide* (15).—(*a*) 2-(2-*Chloroacetamidophenylthio*)*acetonitrile*. A solution of 2-(2-aminophenylthio)acetonitrile (3a) (6.9 g) in DMF (40 ml) was cooled to 0 °C and chloroacetyl chloride (4.8 g) added during 30 min. The mixture was stirred overnight at room temperature, poured into ice–water, extracted with ethyl acetate, the organic extracts washed (H_2O), dried ($MgSO_4$), and evaporated to give, after trituration with diethyl ether,

2-(2-*chloroacetamidophenylthio)acetonitrile* (7.6 g, 81%), m.p. 78—79 °C (Found: C, 50.1; H, 3.8; N, 11.8; S, 13.5. $C_{10}H_9ClN_2OS$ requires C, 49.9; H, 3.87; N, 11.65; S, 13.3%); $\nu_{max.}$ 3 304 (NH), 2 223 (CN), and 1 690 cm^{-1} (CO); τ($CDCl_3$) 6.56 (2 H, s, SCH_2), 5.80 (2 H, s, $COCH_2$), 2.99—2.15 (3 H, m, 4-, 5-, and 6-H), 1.58 (1 H ,d, J 8 Hz, J' 2 Hz, 3-H), 0.40 (1 H, s br, lost with D_2O, NH).

(*b*) 2-(2-*Chloroacetamidophenylsulphinyl)acetonitrile*. A solution of 2-(2-chloroacetamidophenylthio)acetonitrile (7.0 g), as above, and sodium metaperiodate (8.0 g) in ethanol–water (600 ml; 5 : 1) was refluxed for 24 h, evaporated to 100 ml and extracted with chloroform. The organic layer was separated, washed (H_2O), dried ($MgSO_4$), evaporated and the residue chromatographed on silica gel ($CHCl_3$ as eluant) to give 2-(2-*chloroacetamidophenylsulphinyl)acetonitrile* (5.3 g, 71%) as a dark oil (Found: C, 46.4; H, 3.6; N, 10.85. $C_{10}H_9ClN_2O_2S$ requires C, 46.8; H, 3.5; N, 10.9%); $\nu_{max.}$ 3 260 (NH), 2 223 (CN), 1 697 (CO), and 1 073 and 1 050 cm^{-1} (SO); τ($CDCl_3$) 6.10, 5.93 (2 H, AB quartet, J_{AB} 16 Hz, $SOCH_2$), 5.84 (2 H, s, $COCH_2$), 2.80—2.15 (3 H, m, 4-, 5-, and 6-H), and 1.73 (1 H, d, J 8 Hz J' 2 Hz, 3-H).

(*c*) 2-(2-*Aminophenylsulphinyl)acetonitrile*. A solution of the amide from above (5.1 g) and thiourea (1.6 g) in ethanol (120 ml) was heated at 60 °C for 24 h. Further amounts of thiourea (1.3 g) were added and the heating continued for a further 24 h. The solution was evaporated to dryness, water (60 ml) added, the mixture refluxed for 2 h, decanted, basified with sodium hydrogencarbonate and extracted with chloroform. The organic layer was washed (H_2O), dried ($MgSO_4$) and evaporated to give, after chromatography of the residue (silica gel; $CHCl_3$ as eluant), 2-(2-*aminophenylsulphinyl)acetonitrile* (1.6 g, 42%), as a pale yellow oil; $\nu_{max.}$ 3 450 and 3 360 (NH_2), 2239 (CN), and 1 060 and 1 040 cm^{-1} (SO); τ($CDCl_3$) 6.01, 5.79 (2 H, AB quartet J_{AB} 16 Hz, $SOCH_2$), 5.25 (2 H, s br, NH_2), and 3.50—2.40 (4 H, m, aromatic).

(*d*) 2-*Cyano*-1,3,4-*benzothiadiazine* 1-*oxide* (15). A solution of the hydrochloride of the amine from (*c*) (430 mg) in water (3 ml) and concentrated hydrochloric acid (1 ml) was stirred at 0 to −5 °C. Sodium nitrite (140 mg) in water (0.7 ml) was added, followed by sodium azide (130 mg), also in water (1.0 ml). The solution was stirred for 30 min at 0 °C, diluted and filtered to give 2-*cyano*-1,3,4-*benzothiadiazine* 1-*oxide* (240 mg, 63%), m.p. 220—222 °C. (Found: C, 50.0; H, 2.7; N, 22.0. $C_8H_5N_3OS$ requires C, 50.25; H, 2.6; N, 22.0%); $\nu_{max.}$ 2 200 (CN) and 1 010 cm^{-1} (SO); τ($CDCl_3$) 6.62 (1 H, s br, lost with D_2O, NH) and 1.70—2.60 (4 H, m, aromatic); *m/e* 191 (M^+).

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