Synthesis and Reactions of Azido-benzothiazoles and -benzo[*b*]thiophens; Novel Thiazolo[4,5-*g*]benzoxazoles and Dihydrothieno[3,2-*g*]-benzoxazoles

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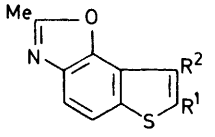
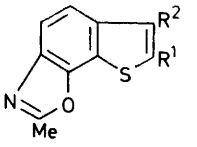
6-Azidobenzothiazole and its 2-methyl and 2-methylthio-derivatives were prepared from the corresponding amine and gave the thiazolo[4,5-*g*]benzoxazoles, (8)—(10), on thermolysis in a polyphosphoric–acetic acid mixture. 6,7-Dihydro-2-methylthieno[3,2-*g*]benzoxazole 8,8-dioxide (12) was prepared similarly. An improved method of synthesis of 2-fluoro-6-nitrobenzothiazole is reported.

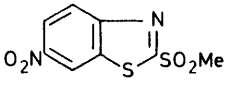
We have prepared several thieno[2,3-*g*]benzoxazoles, (1)—(4),[1] and thieno[3,2-*g*]benzoxazoles, (5) and (6),[2] previously by thermolysis of a 5- or 6-azidobenzo-[*b*]thiophen in a polyphosphoric–acetic acid mixture. A series of 6-azidobenzothiazoles was required in connection with the work described in the following paper. Some of these have been converted into derivatives, (8)—(10), of the hitherto unknown thiazolo[4,5-*g*]-benzoxazole ring system.



(1) $R^1 = R^2 = H$
(2) $R^1 = CO_2Et$, $R^2 = H$
(3) $R^1 = CO_2Me$, $R^2 = H$
(4) $R^1 = H$, $R^2 = Me$



(5) $R^1 = CO_2Me$, $R^2 = H$
(6) $R^1 = R^2 = Br$



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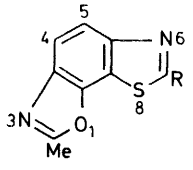
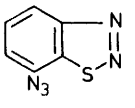


(8) R = H
(9) R = Me
(10) R = SMe



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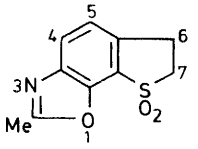
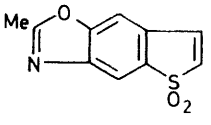


(12)

At the start of our work 6-azido-2-methylbenzothiazole [3] was the only known 6-azidobenzothiazole. This was prepared by the literature method, which involves nitration of 2-methylbenzothiazole,[4] reduction of the resulting 6-nitro-derivative,[4] diazotization of the amine produced, and reaction of the diazonium compound with sodium azide.[3] The other azides required for this work were prepared similarly. Iron and acetic acid [5] was found to be a more convenient reagent system for the reduction of 6-nitrobenzothiazole than those reported in the literature.[6] This reagent system was used also to reduce other nitrobenzothiazoles (see also following paper). Nitration of 2-methylthiobenzothiazole gave the 6-nitro-derivative,[7] which was shown by ^{1}H n.m.r. spectroscopy to be contaminated with small amounts of 2-methylsulphonyl-6-nitrobenzothiazole (7). Reduction of this mixture with tin(II) chloride, however, gave an uncontaminated (^{1}H n.m.r.) sample of 6-amino-2-methylthiobenzothiazole. This could be because nucleophiles readily displace an electron-withdrawing substituent, *e.g.* methylsulphonyl,[8] in the 2-position of benzothiazole, particularly in the presence of a 6-nitro-group.[9,10] Under the conditions used to prepare 6-amino-2-methylthiobenzothiazole (see Experimental section) it is possible than the 2-methylsulphonyl-6-nitrobenzothiazole (7) present in the contaminated starting material was converted into 6-nitrobenzothiazol-2(3*H*)-one, then into 6-aminobenzothiazol-2(3*H*)-one, which would be removed on work-up (alkaline conditions). Alternatively, the methylsulphonyl group may have suffered cleavage to an alkaline-soluble sulphonic acid group. In support of this conjecture it is noteworthy that, in the presence of aqueous sodium hydroxide, 2-benzylsulphonyl-6-nitrobenzothiazole yields 6-nitrobenzothiazol-2(3*H*)-one (as its sodium salt), toluene, and hydrogen sulphide.[10]

6-Azidobenzothiazole and its 2-methyl and 2-methylthio-derivatives were converted into the corresponding thiazolo[4,5-*g*]benzoxazole, (8)—(10), respectively, in a hot polyphosphoric–acetic acid mixture. The formation of these angular products was confirmed by an examination of their ^{1}H n.m.r. spectra and can be rationalised along the lines reported previously.[1,2]

Attempts to convert 7-aminobenzothiazole into 7-azidobenzothiazole *via* diazotization and reaction of the diazonium compound with sodium azide gave a mixture from which an azide ($\nu_{max.}$ 2 120 cm^{-1}) was isolated, which was clearly not the desired product, since its ^1H n.m.r. spectrum lacked a signal at τ 1—2, typical of a benzothiazole 2-proton. This information, together with the mass spectroscopic data (double loss of nitrogen from the parent ion peak at *m/e* 177), microanalytical data, and knowledge of the known [11] conversion of 7-aminobenzothiazole into 7-amino-1,2,3-benzothiadiazole under similar conditions, led us to conclude that our product was 7-azido-1,2,3-benzothiadiazole (11).



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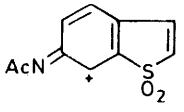

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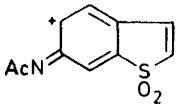

(15)

An attempt to convert 2-chloro-6-nitrobenzothiazole into 2-fluoro-6-nitrobenzothiazole with potassium fluoride in dimethylformamide [12] gave, in our hands, a moderate yield (41%) of 2-dimethylamino-6-nitrobenzothiazole (*cf.* ref. 13) and none of the required product. 2-Fluoro-6-nitrobenzothiazole was prepared, however, in almost quantitative yield by reaction of the 2-chloro-compound with anhydrous potassium fluoride in acetonitrile in the presence of 18-crown-6. Attempts to reduce 2-fluoro-6-nitrobenzothiazole failed owing to the high reactivity of the fluorine atom. With tin and hydrochloric acid, the product was 6-nitrobenzothiazole, whilst iron and acetic acid [5] gave only 6-nitrobenzothiazol-2(3*H*)-one.

6-Azido-2,3-dihydrobenzo[*b*]thiophen 1,1-dioxide gave 6,7-dihydro-2-methylthieno[3,2-*g*]benzoxazole 8,8-dioxide (12) in a hot polyphosphoric–acetic acid mixture. At first sight this result appears surprising in view of the fact, that, under these conditions, 6-azidobenzo[*b*]thiophen gives the linear product (13).[2] In the latter case we rationalised the result by suggesting that intermediate (15) was attacked by acetic acid in preference to the alternative (14), in which there is steric hindrance to approach in the 7-position. Presumably reduction of the 2,3-double bond in (14) gives the ring increased conformational mobility, thereby allowing attack to occur in the 7-position with considerably less steric hindrance.

EXPERIMENTAL

^1H N.m.r. spectra were recorded with a Varian EM360 (60 MHz) or Perkin Elmer R32 (90 MHz) instrument ($SiMe_4$ as internal standard), i.r. spectra (solids as Nujol mulls, liquid as films) with a Perkin Elmer 257 or 297 spectrometer, and mass spectra with an AEI MS12 or MS902S instrument. Masses are given for the ^{35}Cl isotope.

In all solvent extractions the extracts were combined, dried ($MgSO_4$), and the solvent distilled on a rotary evaporator. Light petroleum had b.p. 60—80 °C, unless stated otherwise.

Benzothiazole (freshly distilled before use), benzothiazole-2-thiol, 2-methylbenzothiazole, and 2-aminobenzenethiol were available commercially (Aldrich Chemical Company).

The following compounds were prepared by literature procedures: 2-methyl-6-nitrobenzothiazole (54%), m.p. 168—169 °C (from ethanol) (lit.,[4] 83% and m.p. 165—166 °C); 6-amino-2-methylbenzothiazole (88.5%), m.p. 125—127 °C (from ethanol) (lit.,[4] 122 °C); 2-methylthiobenzothiazole (67%), m.p. 53—54 °C (from aqueous ethanol) (lit.,[7] 52 °C); 2-methylthio-6-nitrobenzothiazole (99%), m.p. 125—127 °C (from acetic acid) (lit.,[7] 132—134 °C) (see Discussion); 2-chlorobenzothiazole (46.5%), b.p. 169—171 °C at 62 mmHg (lit.,[14] 158—162 °C at 50 mmHg); 2-chloro-6-nitrobenzothiazole (59%), m.p. 191—193 °C (from ethanol) (lit.,[15] 190—191 °C); benzo[*b*]thiophen 1,1-dioxide (68%), m.p. 141—142 °C (from water) (lit.,[16] 142—143 °C); 6-nitrobenzo[*b*]thiophen 1,1-dioxide (79%), m.p. 186 °C (from acetone–toluene) (lit.,[17] 188 °C); and 6-amino-2,3-dihydrobenzo[*b*]thiophen 1,1-dioxide (58%), m.p. 202—204 °C (from benzene) (lit.,[18] 198—198.5 °C).

Nitration of benzothiazole was carried out as described in the literature.[19] Two recrystallisations of the product from ethanol gave 6-nitrobenzothiazole (31.5%), m.p. 176 °C (lit., [19]177 °C) and distillation of the solvent from the mother-liquors gave a residue which was chromatographed on alumina. Chloroform eluted 7-nitrobenzothiazole (6%), m.p. 153—154 °C (lit.,[19] 154—155 °C). The 4- and 5-nitro-isomers [19] were not collected.

6-*Aminobenzothiazole*.[5]—A stirred mixture of 6-nitrobenzothiazole (2.2 g, 12.2 mmol), iron powder (80%, 3 g, 43 mg-atom), acetic acid (5.2 ml), and ethanol (35 ml) was heated under reflux for 3 h, and then poured into water (120 ml). Extraction with ether (2 × 100 ml) followed by chloroform (3 × 100 ml) gave 6-aminobenzothiazole (1.22 g, 67%), m.p. 82—84 °C (from n-hexane–chloroform) (lit.,[6] 84—85 °C).

7-Aminobenzothiazole (74%), m.p. 124—125 °C (from n-hexane–chloroform) (lit.,[20] 115—116, °C), was prepared similarly.

6-*Amino-2-methylthiobenzothiazole*.—A mixture of 2-methylthio-6-nitrobenzothiazole (3.0 g, 13.3 mmol), tin(II) chloride dihydrate (12.0 g, 53.3 mmol), methanol (30 ml), and concentrated hydrochloric acid (30 ml) was heated under reflux for 3 h. The mixture was cooled, 30% aqueous sodium hydroxide (100 ml) was added, and extraction with ether (3 × 250 ml) gave the product (1.7 g, 65%), m.p. 108—110 °C (from hexane–chloroform) (lit.,[21] 109—110 °C).

6-*Azido-2-methylbenzothiazole*.—A solution of sodium nitrite (0.428 g, 6.2 mmol) in water (3 ml) was added to a stirred, cold (0 °C) solution of 6-amino-2-methylbenzothiazole (1.0 g, 6.1 mmol) in a mixture of concentrated hydrochloric acid (3 ml) and water (9 ml) and the mixture was stirred for a further 10 min at 0 °C. Then a solution of sodium azide (0.39 g, 6.1 mmol) in water (4 ml) saturated with sodium acetate was added dropwise at 0 °C, and the mixture was stirred at this temperature for a further 20 min. The precipitate was filtered off to give the azide

(0.82 g, 71%), m.p. 68—69 °C (from n-pentane) (lit.,[3] 68 °C), $\nu_{max.}$ 2 110 cm^{-1} (N_3), light sensitive.

The following azides * were prepared similarly: 6-*azidobenzothiazole* (65%) (product extracted with ether), m.p. 60—61 °C (from n-pentane), $\nu_{max.}$ 2 105 cm^{-1} (N_3); $\tau(CDCl_3)$ 1.10 (s, 1 H, 2-H), 1.98 (d, 1 H, $J_{4.5}$ 7.0 Hz, 4-H), 2.46 (d, 1 H, $J_{5.7}$ 2.0 Hz, 7-H), and 2.82 (dd, 1 H, $J_{4.5}$ 7.0 Hz, $J_{5.7}$ 2.0 Hz, 5-H) (Found: C, 47.3; H, 2.5%; M^+, 176.015 2. $C_7H_4N_4S$ requires C, 47.7; H, 2.3%; *M*, 176.015 8): 6-*azido*-2-*methylthiobenzothiazole* (89%) (product extracted with ether), m.p. 88—89 °C (from n-hexane), $\nu_{max.}$ 2 100 cm^{-1} (N_3); $\tau(CDCl_3)$ 2.2 (d, 1 H, $J_{4.5}$ 9.0 Hz, 4-H), 2.65 (d, 1 H, $J_{5.7}$ 2.0 Hz, 7-H), 2.90 (dd, 1 H, $J_{4.5}$ 9.0 Hz, $J_{5.7}$ 2.0 Hz, 5-H), and 7.25 (s, 3 H, Me) (Found: C, 43.2; H, 2.8; N, 25.2; S, 28.9%; M^+, 222. $C_8H_6N_4S_2$ requires C, 43.2; H, 2.7; N, 25.2; S, 28.7%; *M*, 222): and 6-*azido*-2,3-*dihydrobenzo*[b]*thiophen* 1,1-*dioxide* (79%), m.p. 137—139 °C (from ethanol), $\nu_{max.}$ 2 150 cm^{-1} (N_3) (Found: C, 45.9; H, 3.3; N, 20.5%; M^+, 209. $C_8H_7N_3O_2S$ requires C, 45.9; H, 3.4; N, 20.1%; *M*, 209).

* These azides are light sensitive and it is recommended that they are stored in the dark.

1 H, $J_{4.5}$ 8.0 Hz, 4-H), 2.75 (d, 1 H, $J_{4.5}$ 8.0 Hz, 5-H), 6.4 (m, 4 H, 2 × CH_2), and 7.3 (s, 3 H, Me) (Found: C, 53.7; H, 4.1; N, 6.3%; M^+, 223. $C_{10}H_9NO_3S$ requires C, 53.8; H, 4.1; N, 6.3%; *M*, 223).

Reaction of 2-*Chloro*-6-*nitrobenzothiazole with Fluoride Ion.*—(a) *In aqueous dimethylformamide.* Potassium fluoride (13.8 g, 237.9 mmol) was added to a vigorously stirred mixture of 2-chloro-6-nitrobenzothiazole (17.0 g, 79.25 mmol) and dimethylformamide (100 ml) at ambient temperature, and the resulting mixture was heated under reflux for 3 h. Water (1 ml) was added and the mixture heated under reflux for a further 13 h before being poured into water. Attempted steam distillation of the precipitate failed and it was chromatographed on silica gel instead. Ether–ethyl acetate (8 : 2) eluted 2-dimethylamino-6-nitrobenzothiazole (8.0 g, 45%), m.p. 203—204 °C (from ether–ethyl acetate) (lit.,[14] 197.5—199 °C).

(b) *In acetonitrile.* Anhydrous potassium fluoride (2.7 g, 46.6 mmol) and 18-crown-6–acetonitrile complex (0.5 g) were added successively to a stirred solution of 2-chloro-6-nitrobenzothiazole (5.0 g, 23.3 mmol) in anhydrous acetonitrile (50 ml) at ambient temperature and the resulting mixture was heated under reflux for 4 h. The mixture was filtered and distillation of the solvent under reduced pressure gave 2-fluoro-6-nitrobenzothiazole (4.56 g, 99%), m.p. 142—143 °C (from n-hexane–chloroform) (lit., 144—145 °C [22] and 150—151 °C [13]).

Thiazolo[4,5-*g*]benzoxazoles

Compound number	Yield (%)	M.p.[a] (°C)	Work-up[b] procedure	^{1}H N.m.r. chemical shifts[c] 2-Me	4-H	5-H	7-Substituent	$J_{4.5}$ (Hz)	Found (%) C	H	N	Formula	Required (%) C	H	N
(8)	50	162—163	A	7.3s	1.80d	2.16d	0.95 (H)	9.0	56.6	3.3	14.8	$C_9H_6N_2OS$	56.8	3.2	14.7
(9)	42	108—109	B	7.2s	2.13d	2.53d	7.4 (Me)	10.0	49.9	4.6	11.7	$C_{10}H_8N_2OS{\cdot}2H_2O$	49.9	5.0	11.7
(10)	20	138—139	C	7.3s	2.15d	2.40d	7.2 (SMe)	9.0	50.7	3.6	11.6	$C_{10}H_8N_2OS_2$	50.8	3.4	11.85

[a] From hexane. [b] A; crude product recrystallised: B; crude product chromatographed on silica gel; light petroleum–chloroform (8 : 2) eluted the azide: C; crude product chromatographed on alumina; light petroleum–ether (9 : 1) eluted the azide. [c] In $CDCl_3$.

Attempt to Synthesise 7-*Azidobenzothiazole.*—When 7-aminobenzothiazole was diazotized and the resulting diazonium compound treated with sodium azide in the manner described in the preceding section, extraction of the product with ether gave a gum which was chromatographed on alumina. Hexane–chloroform (85 : 15) eluted 7-*azido*-1,2,3-*benzothiadiazole* (11) (14%), m.p. 111—113 °C (from n-pentane–chloroform), $\nu_{max.}$ 2 120 cm^{-1} (N_3); $\tau(CDCl_3)$ 1.6br (d, 1 H, $J_{4.5}$ 8.0 Hz, 4-H), 2.4 (t, 1 H, $J_{4.5} = J_{5.6} = 8.0$ Hz, 5-H), and 2.7br (d, 1 H, *J* 8.0 Hz, 6-H) (Found: C, 40.3; H, 1.8; N, 39.5%; M^+, 177. $C_6H_3N_5S$ requires C, 40.7; H, 1.7; N, 39.5%; *M*, 177).

Thiazolo[4,5-g]*benzoxazoles* (8)—(10). *General Method.*—The azidobenzothiazole (1 g) was added in portions during 10 min to a stirred mixture of polyphosphoric acid (10 g) and acetic acid (10 ml) at 80 °C; the mixture was then heated at 120 °C for a further 1.5 h, cooled, and poured onto ice. Extraction with ether (4 × 125 ml) [the combined extracts were washed successively with sodium hydrogen carbonate (2 × 100 ml) and water (2 × 100 ml), and dried ($MgSO_4$)] gave the crude product. Further details are given in the Table. The mass spectra of these three compounds are consistent with the structures proposed.

6,7-*Dihydro*-2-*methylthieno*[3,2-g]*benzoxazole* 8,8-*Dioxide* (12).—When 6-azido-2,3-dihydrobenzo[*b*]thiophen 1,1-dioxide was treated with a polyphosphoric–acetic acid mixture as described in the preceding experiment (product extracted with chloroform instead of ether) it gave a yellow–orange solid, which was chromatographed on silica gel. Ether–chloroform (94 : 6) eluted 2-*methyl*-6,7-*dihydrothieno*-[3,2-g]*benzoxazole* 8,8-*dioxide* (12) (11%), m.p. 254—255 °C (from ethanol), $\nu_{max.}$ 1 610 cm^{-1} (C=N); $\tau(CDCl_3)$ 2.18 (d,

Reduction of 2-*Fluoro*-6-*nitrobenzothiazole.*—(a) *With iron and acetic acid.*[5] Iron powder (80%, 3.7 g, 53 mg-atom) was added to a stirred mixture of 2-fluoro-6-nitrobenzothiazole (3.0 g, 15.15 mmol), acetic acid (6 ml), and ethanol (50 ml), and the mixture was heated under reflux for 3 h, then poured into water. Extraction with ether [the combined extracts were washed successively with 10% aqueous sodium hydrogen carbonate (2 × 150 ml) and water] gave 6-nitrobenzothiazol-2(3*H*)-one (0.92 g, 31%), m.p. 219—221 °C (from chloroform) (lit.,[23] 226 °C).

(b) *With tin and acid.* A mixture of 2-fluoro-6-nitrobenzothiazole (1.5 g, 7.58 mmol), tin (3.18 g, 26.8 mg-atom), concentrated hydrochloric acid (20 ml), and ethanol (12 ml) was heated under reflux for 1 h. Distillation of the ethanol and addition of aqueous sodium hydroxide to the residue gave a precipitate of 6-aminobenzothiazole (0.070 g, 6%), identical (m.p., and i.r. and ^{1}H n.m.r. spectra) with an authentic sample (see before).

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