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SOME ASPECTS OF 1,4-DIAZAPHENOTHIAZINE CHEMISTRY

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Abstract—Quinoxalino[2,3-*b*][1,4]benzothiazine 1 and its pyrazino-analogue 6 both give pairs of isomeric *N*-methyl derivatives. The *N*-methyl compounds 2 and 7 on oxidation with iodobenzene dichloride and other reagents give sulphoxides and sulphones (accompanied by some ring substitution) but treatment of 6 with iodobenzene dichloride gives benzothiazole 2-carboxamide 17. The action of sodium nitrite in acetic acid upon the thiazine 6 gives the 3-nitro derivative 25, substitution having occurred in the pyrazine ring; other nitrations are described.

Quinoxalino[2,3-*b*][1,4]benzothiazine 1 has been alkylated[1] but the position of substitution has not been established. Treatment of the performed anion of this compound with methyl iodide gave two isomeric *N*-methyl derivatives in a 2:1 ratio. The major product was identical with an unambiguously synthesized (from 2,3-dichloroquinoxaline and *N*-methyl-*o*-aminobenzenethiol) sample of the 12-methyl compound 2; the minor product, therefore, is the 11-methyl derivative 12.

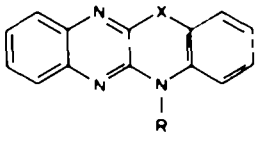
Methylation of pyrazino[2,3-*b*][1,4]benzothiazine 6 likewise gave two products; the major isomer was shown to be the 10-methyl derivative 7 by comparison with an authentic specimen (from 2,3-dichloropyrazine and *N*-methyl-*o*-aminobenzenethiol). The minor, more highly coloured, isomer was isolated by preparative TLC (column chromatography on silica or alumina resulted in extensive decomposition) and its spectral data are consonant with the 1-methyl formulation 14.

The quinoxalino[2,3-*b*][1,4]benzothiazine ring system has been known for many years[2] and in the literature has been arbitrarily assigned the 12H 1 or 11H 11 structure. Comparisons of spectra (PMR, IR, UV) of the parent compound with those of its two *N*-methyl derivatives 2 and 12 show that it exists in the 12H form 1, particularly telling are the ultraviolet spectra (Table 1). The spectra of the parent base and its 12-methyl derivative 2 are very similar, the major difference being a hypsochromic shift of the long wavelength absorption, the magnitude of which is comparable with that observed upon *N*-methylation of phenothiazine.[3] Other spectral data (see experimental) also support the 12H structure.

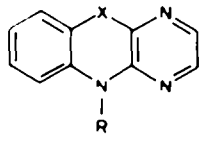
Similarly (Table 1) the UV spectra of the pyrazinobenzothiazine 6 and its 10-methyl derivative 7 are alike, thus showing, not unexpectedly, that the parent thiazine exists in the 10H form 6. That azaphenothiazines may exist with the proton on the azine ring has been demonstrated in the case of the cinnolino compound 15 which, in ethanol, is a mixture of the 7H and 12H tautomers.[4]

Acetylation of the quinoxalino thiazine 1 gave a chromatographically homogeneous material in excellent yield. Clearly, as with methylation, acetylation could have occurred both at position 11 and 12 and the IR spectrum of the product has a double carbonyl absorption. The absence of any long wavelength absorption in the UV spectrum, however, makes it unlikely that any of the 11-acetyl derivative 13 has been formed and the doublet carbonyl is probably due to two different rotameric forms with the carbonyl oxygen in cisoid and transoid relationships with the lone pair at position 11. Similar doublet carbonyls have been reported, *inter alia*, for the methyl and ethyl esters of 5-quinoxaline carboxylic acid.[5] The alternative possibility of the existence of the acetyl group in "extra" and "intra" positions (phenothiazine is not planar)[6] is less likely; various acylphenothiazines have been reported as exhibiting a single absorption in the carbonyl region.

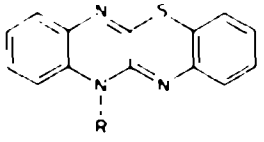
Treatment of the *N*-methyl pyrazinothiazine 7 with potassium permanganate[7] gave a good yield of the sulphone 10; similar treatment of the quinoxalino compound 2 gave a mixture of the sulphoxide 3 and the sulphone 4. Whereas the sulphoxide 3 was formed cleanly by the action of iodobenzene dichloride[8] upon the sulphide 2, similar treatment of the pyrazino compound 7 was accompanied by a small amount of chlorination in the



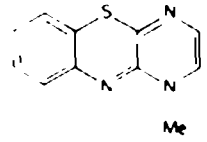
1: X = S, R = H
2: X = S, R = Me
3: X = SO, R = Me
4: X = SO_2, R = Me
5: X = S, R = Ac



6: X = S, R = H
7: X = S, R = Me
8: X = SO, R = H
9: X = SO, R = Me
10: X = SO_2, R = Me



11: R = H
12: R = Me
13: R = Ac



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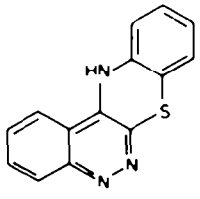

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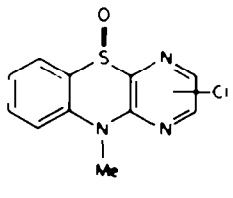

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Table 1. UV data (spectra taken in 96% ethanol)

Compound	λ_{max} nm (ϵ)
1	252 (73,000), 275–287 (8400), 425 (11,100)
2	250 (53,500), 285 (7300), 410 (10,900)
12	255 sh (75,000), 260 (101,000), 430 sh (18,000), 446 (19,500), 470 sh (12,100)
6	244.5 (25,300), 319 (3500), 386 (4200)
7	243 (25,400), 313 (3100), 377 (4900)

pyrazine ring giving **16** in addition to the desired sulphoxide **9**. PMR spectra are a useful diagnostic aid to the oxidation state of the sulphur bridge in the *N*-methyl compounds; the methyl protons undergo a downfield shift of *ca* 0.5 ppm upon oxidation at sulphur (little change is observed in going from sulphoxide to sulphone) and, with the pyrazines, the proton ortho to the sulphur bridge resonates at lower field (*ca* 0.3 ppm) in the sulphone **10** than in the sulphoxides **9** and **16**.

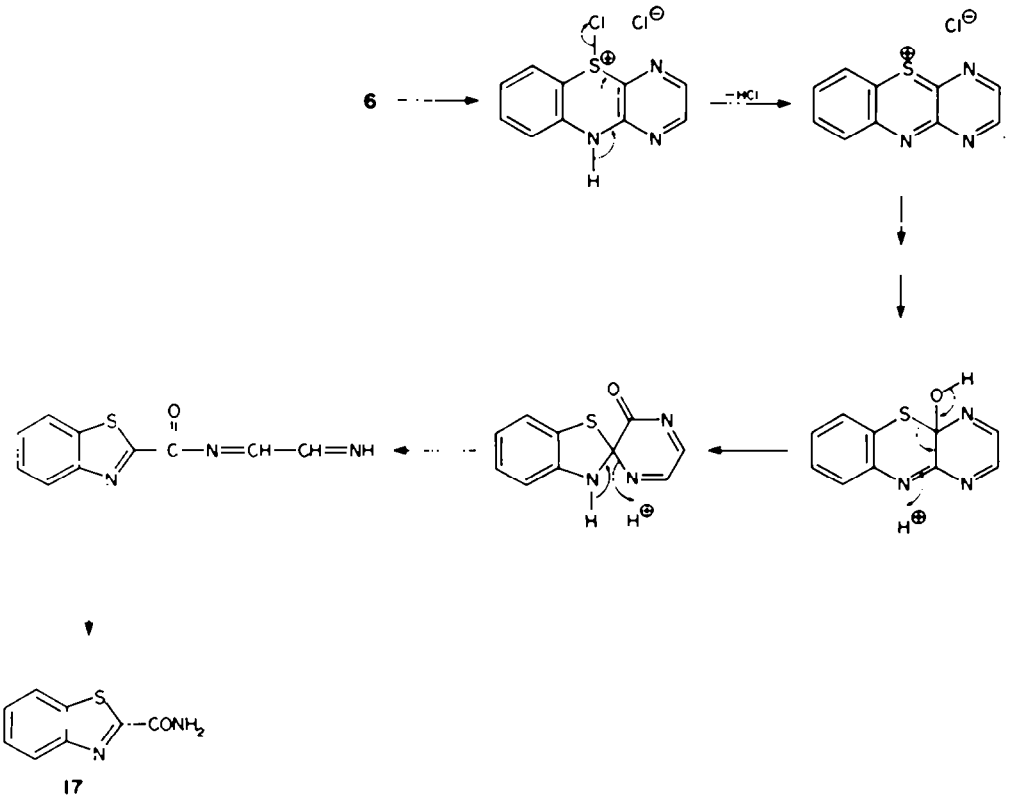
An attempt to form the sulphoxide **9** using ammonium hexanitratocerate(IV)[10] was similarly complicated by the formation of by-products; in this case a mixture of di-nitrated compounds (inseparable by chromatography), unoxidised at sulphur, was obtained in addition to the sulphoxide **9**. The use of ammonium hexanitratocerate(IV) as an oxidising agent is not normally complicated by concurrent nitration,[10,11] although nitrations of acridine and acridone by this reagent have recently been reported.[12] It is likely that the formation of nitro derivatives entails successive electrophilic attack by a nitratocerate anion upon the dication **30** (see Schemes 2 and 3); a mixture of products would be expected were this the case.

Upon treatment with iodobenzene dichloride in aqueous acetonitrile, the pyrazinothiazine **6** did not give the expected sulphoxide (**8**).† The product of reaction was found to be benzothiazole 2-carboxamide **17** and this may well arise from the reaction sequence shown in Scheme 1. A number of benzo[1,4]thiazines[13] are known to undergo ring contraction, of particular relevance is the ready conversion of the indolobenzothiazine **18** to the spiroindole **19**.[14] Also of interest is the formation of a Pummerer product from the pyrimidobenzothiazine **20** which gives a chlorinated material **21** upon treatment with thionyl chloride.

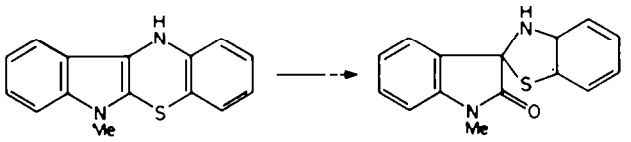
The action of sodium nitrite in acetic acid upon phenothiazine gives the dinitro derivative **22**; in marked contrast *N*-alkylphenothiazines yield sulphoxides.[6] Treatment of the quinoxalino- and pyrazino-*N*-H compounds **1** and **6** with sodium nitrite in acetic acid gave, in each case, a mononitro derivative. These nitrated materials were identified, by spectroscopic means, as the 3-nitro derivatives **23** and **25**. In both cases PMR spectroscopy demonstrated that substitution had either occurred at position 2 or position 3 and the pronounced bathochromic and hyperchromic shifts attendant upon anion formation showed the presence of para nitroaniline type chromophores[16] thus excluding nitration at position 2. Of some interest is the nitration of the pyrazine ring, normally a most difficult accomplishment.

Treatment of the two *N*-methyl compounds **2** and **7** under similar conditions also gave nitrated derivatives but

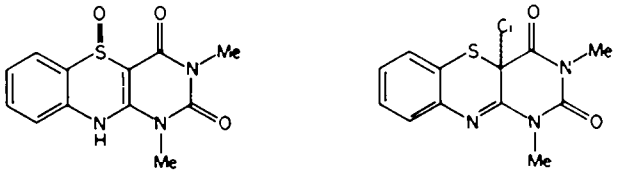
†Since the completion of this work we have succeeded in preparing the S-oxide **8**. The S-oxide is stable in both aqueous acid and base and is not considered to be an intermediate in the ring-contraction sequence.



Scheme



18 19



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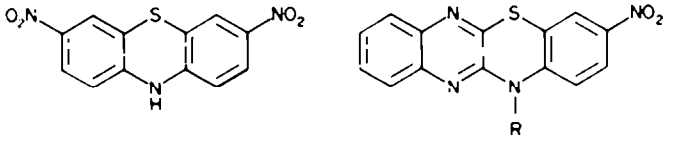
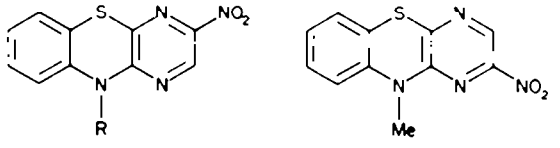
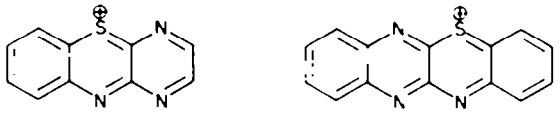


22 23: R = H
24: R = Me



25: R = H
26: R = Me 27



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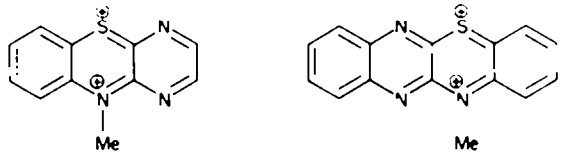

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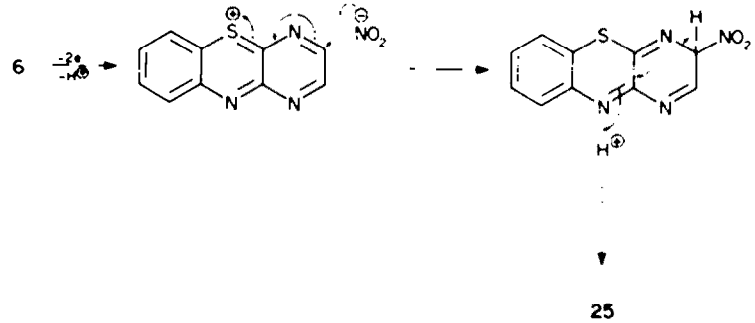

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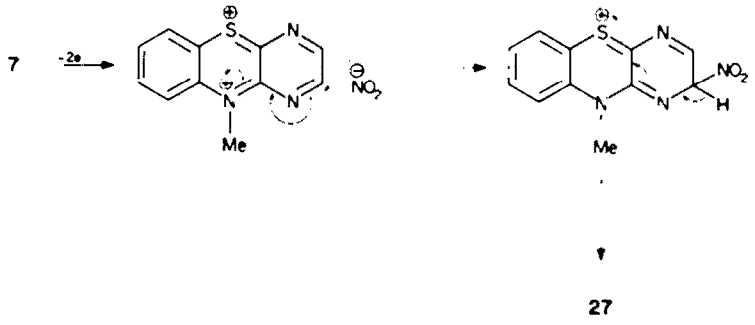
Scheme 2



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Scheme 3

procedure gives 3-substituted derivatives.[17] Consideration of the probable relative oxidation potentials of these various azaphenothiazines (a large number of oxidation potentials are known for phenothiazines)[6] makes it seem likely that all observed features of these reactions with nitrous acid are explicable on the basis of the proposed mechanism, as indeed is the formation of dinitro compounds from the strong oxidizing agent ammonium hexanitratocerate(IV), and further work is in hand upon this topic.

EXPERIMENTAL

M.ps are uncorrected and were determined using a Gallenkamp apparatus or (where stated) a Kofler hotstage. IR spectra were taken on a Unicam SP-200 spectrometer in Nujol or HCBD mulls. UV spectra were taken on a Unicam SP-800A machine in 96% ethanol. NMR spectra were taken using a Perkin-Elmer R12B spectrometer using TMS as an internal standard. Mass spectra were obtained using an AEI MS9 or MS 30 spectrometer at 70 eV and peak abundances are quoted as a percentage of the base peak. Column chromatography was carried out using Merck 7734 silica or Laporte alumina type H.

12H-*Quinoxalino*[2,3-b][1,4]*benzothiazine* 1.[1] 2,3-Dichloroquinoxaline (13.2 g, 66 mmol), *o*-aminobenzenethiol (8.5 g, 66 mmol), and sodium carbonate (20 g, 189 mmol) were heated in refluxing[18] *o*-dichlorobenzene (120 ml) for 30 min. After cooling, the semi-solid reaction mixture was shaken with water (20 ml) and filtered. The resultant bright yellow solid was washed with water and dried giving the product (15.9 g, 91%); m.p. 282–283° (1,4-dioxan), lit.[19] 284–285°; ν_{max} (Nujol and HCBD) 3260 (NH), 1550, 1485, 1415 and 1370 cm^{-1}; δ (DMSO d_6) 6.9–7.3 (4H, m, 1,2,3,4-H) and 7.45–7.8 (4H, m, 7,8,9,10-H); *m/e* 252 (21%), 251 (100%, M), 250 (18%), 219 (19%, M–S), and 125.5 (13%, M^{2+}); m* 191 (251→219). (Found: C, 67.4; H, 3.9; N, 16.3. Calc. for $C_{14}H_8N_2S$: C, 67.0; H, 3.6; N, 16.7%).

10H-*Pyrazino*[2,3-b][1,4]*benzothiazine* 6. 2,3-Dichloropyrazine (6 g, 40 mmol), *o*-aminobenzenethiol (5.2 g, 41 mmol), and sodium carbonate (8.5 g, 80 mmol) were heated in refluxing[18] *o*-dichlorobenzene (35 ml) for 30 min. Work up as above followed by vacuum sublimation (160°; 0.1 mm) gave the bright yellow product (5 g, 62%); m.p. 190–192° (toluene-petrol 100–120°); ν_{max} (Nujol) 3220 cm^{-1} (NH); δ (DMSO d_6) 6.7–7.2 (4H, m, 5,6,7,8-H), 7.75 (2H, s, 2,3-H), and 9.6 br (1H, NH); *m/e* 202 (6%), 201 (100%, M), 200 (4%), 174 (2%, M–HCN), 169 (14%, M–S), 157 (6%, M–CS), and 100.5 (4%, M^{2+}); m* 151 (201→174), 142 (201→169), and 123 (201→157). (Found: C, 60.2; H, 3.8; N, 21.0. $C_{10}H_7N_3S$ requires: C, 59.8; H, 3.5; N, 20.9%).

12-*Methylquinoxalino*[2,3-b][1,4]*benzothiazine* 2. 2,3-Dichloroquinoxaline (2.74 g, 13.8 mmol), *N*-methyl-*o*-aminobenzenethiol[20] (1.9 g, 13.8 mmol) and sodium carbonate (4 g, 38 mmol) were heated[18] at 160° in *o*-dichlorobenzene (15 ml) for 30 min. Work-up as above gave the crude product, m.p. 170–180° (1.4 g, 45%); a further 1.8 g of crude material was obtained by separating the organic layer of the filtrate and reducing it to dryness. Recrystallisation of the crude material from petrol 80–100° gave fine yellow needles; m.p. 182–184°; ν_{max} (Nujol, HCBD and CCl_4) 1530, 1475, 1435, 1405 and 1370 cm^{-1}; δ ($CDCl_3$) 3.55 (3H, s, Me) and 6.9–8.0 (8H, m, ArH); *m/e* 266 (18%), 265 (100%, M), 264 (31%), 250 (24%, M–Me), 233 (7%, M–S), 232 (12%), 151 (9%) and 132.5 (8%, M^{2+}); m* 231 (233→232) and 205 (265→233). (Found: C, 67.6; H, 4.4; N, 15.9. $C_{15}H_{11}N_3S$ requires: C, 67.9; H, 4.2; N, 15.8%).

10-*Methylpyrazino*[2,3-b][1,4]*benzothiazine* 7. 2,3-Dichloropyrazine (7.1 g, 48 mmol), *N*-methyl-*o*-aminobenzenethiol[20] (6.6 g, 48 mmol), and sodium carbonate (6 g, 57 mmol) were heated in refluxing[18] *o*-dichlorobenzene (35 ml) for 1 h. After cooling, the reaction mixture was partitioned between water and chloroform and the organic phase evaporated to dryness, giving a dark brown solid. Recrystallisation from petrol 60–80° gave the pure product as dull yellow crystals (6.6 g, 63%); m.p. 102–103°; δ (CCl_4) 3.34 (3H, s, Me), 6.75–7.45 (4H, m, 6,7,8,9-H) and 7.89 (2H, s, 2,3-H); *m/e* 216 (11%), 215 (100%, M), 214 (8%), 200 (38%, M–Me), 182 (7%, M–SH), 146 (5%) and 107.5 (3%, M^{2+}); m* 186 (215→200). (Found: C, 61.2; H, 4.3; N, 19.7. $C_{11}H_9N_3S$ requires: C, 61.4; H, 4.2; N, 19.5%).

Methylation of 12H-*quinoxalino*[2,3-b][1,4]*benzothiazine* 1. The sodium salt of 1 was prepared by adding the thiazine (200 mg, 0.8 mmol) to sodium hydride (1 mmol) in dry DMF (100 ml) and stirring for 1 h at *ca.* 100° under dry nitrogen. The bright red solution thus obtained was cooled and methyl iodide (200 mg, 1.4 mmol) in dry DMF (50 ml) added dropwise, the colour gradually going yellow. Examination of the product (TLC) revealed the presence of two products of similar mobility as well as traces of

the less mobile starting material. These were separated by column chromatography on alumina (ethyl acetate–petrol 60–80°, 1:9, as eluent) giving the 12-methyl derivative **2**, m.p. 177–178°, (84 mg, 42%) first and subsequently 11-methylquinoxalino[2,3-*b*][1,4]benzothiazine **12** (49 mg, 25%). The identity of the 12-methyl compound was established by comparison with an authentic specimen (spectra and mixed m.p. 176–178°). Recrystallisation of the 11-methyl isomer **12** from petrol 80–100° gave orange rosettes; m.p. 199–200° (Kofler); $\nu_{max.}$ (CCl$_4$) 1545, 1475 and 1365 cm^{-1}; δ (CDCl$_3$) 3.5 (3H, s, Me) and 6.85–7.5 (8H, m, ArH); *m/e* 267 (16%), 266 (50%), 265 (100%, M), 264 (21%), 251 (19%), 250 (30%, M–Me), 233 (11%, M–S), 232 (11%) and 132.5 (37%, M^{2+}); m* 263 (265→264), 236 (265→250) and 205 (265→233). (Found: C, 67.7; H, 4.5; N, 15.8. $C_{14}H_{11}N_3S$ requires: C, 67.7; H, 4.2; N, 15.8%).

Methylation of 10H-*pyrazino*[2,3-b][1,4]*benzothiazine* **6** (with G. Rishman). Treatment of **6** (450 mg, 2.24 mmol) with sodium hydride (3.75 mmol) and methyl iodide (3.5 mmol) as described in the preceding experiment afforded two products. Column chromatography on alumina (chloroform–petrol 40–60°, 1:1 as eluent) gave 10-*methylpyrazino*[2,3-b][1,4]*benzothiazine* **7**, m.p. 100–101° (346 mg, 75%), identified by comparison with an authentic specimen (spectra and mixed m.p. 102–103°). The less mobile, red, product was not isolated as it decomposed in the column. A small (1.2%) amount has been obtained by the use of preparative TLC and has been identified as 1-*methylpyrazino*[2,3-b][1,4]benzothiazine **14** from the following data: δ (CDCl$_3$) 3.1 (3H, s, Me), 6.3 (2H AB, q, $J_{1,2}$ 5 Hz, 2-H and 3-H) and 6.7–7.0 (4H, m, 6,7,8, and 9-H); *m/e* 216 (16%), 215 (100%, M), 200 (36%, M–Me) and 107.5 (23%, M^{2+}). (Found: M$^+$ 215.0517. $C_{11}H_9N_3S$ requires: 215.0515).

Acetylation of 12H-*quinoxalino*[2,3-b][1,4]*benzothiazine* **1**. The thiazine **1** (2.5 g, 10 mmol) and sodium acetate (14 g, 200 mmol) were heated in refluxing acetic anhydride (150 ml) for 5 h and, whilst hot, poured onto crushed ice (300 g) with stirring. The resultant yellow solid was filtered off, washed with water, and dried giving a product (2.8 g, 96%) of m.p. 195–200° with a doublet in the carbonyl region of the IR spectrum. Recrystallisation from THF–EtOH raised the m.p. to 199–201°; further purification [vacuum sublimation (170°; 0.1 mm) and recrystallisation (THF–petrol < 40°)] gave a material of m.p. 219–221°. The finally-obtained material showed no significant differences in its IR to the material of m.p. 199–201°; $\lambda_{max.}$ 228 (ϵ 33,300), 248 (ϵ 33,600) and 368 nm (ϵ 9000); $\nu_{max.}$ (Nujol) 1700 and 1690 cm^{-1} (C=O); δ (CDCl$_3$) 2.37 (3H, s, Me) and 7.3–8.8 (8H, m, ArH); *m/e* 293 (1%, M), 252 (26%), 251 (100%, M–CH$_2$CO), 250 (10%), 219 (13%, M–CH$_2$CO–S) and 207 (3%, M–CH$_2$CO–CS); m* 219–215 br (293→251), 191 (251→219) and 171 (251→207). (Found: C, 65.3; H, 4.2; N, 14.7. $C_{14}H_{11}N_3OS$ requires: C, 65.5; H, 3.8; N, 14.3%).

Identical material was also obtained by the action of acetyl chloride upon the thiazine **1** in pyridine; the yield in this case being poorer and the reaction proceeding less cleanly.

Oxidation of 12-*methylquinoxalino*[2,3-b][1,4]*benzothiazine* **2** *with potassium permanganate*. A solution of KMnO$_4$ (1.2 g, 7.6 mmol) in water (25 ml) was added, over 100 min, to a stirred suspension of **2** (1 g, 3.8 mmol) in acetic acid (50 ml). The resultant dark brown suspension, after decolourising with sodium pyrosulphite, was diluted with water (25 ml) and the bright yellow product filtered off, washed with water, and dried. TLC showed the presence of two products; column chromatography on silica (CH$_2$Cl$_2$ as eluent) gave 12-methylquinoxalino[2,3-*b*][1,4]benzothiazine-S,S-dioxide **4** (493 mg, 44%); m.p. 292–293° (benzene); $\lambda_{max.}$ 255 sh (ϵ 24,000), 273.5 (ϵ 47,500) and 407 nm (ϵ 7100); $\nu_{max.}$ 1300 and 1154 cm^{-1} (–SO$_2$–); δ (CDCl$_3$) 4.0 (3H, s, Me) and 7.4–8.6 (8H, m, ArH); *m/e* 298 (10%), 297 (65%, M), 233, (57%, M–SO$_2$), 232 (100%, M–SO$_2$H), 205 (12%), 136 (21%), 129 (16%) and 100 (27%); m* 231 (233→232) and 182 br (297→232). (Found: C, 60.3; H, 3.9; N, 13.9; M 297.0587. $C_{14}H_{11}N_3O_2S$ requires: C, 60.6; H, 3.7; N, 14.1%; M 297.0572). The less mobile product (240 mg, 23%) was identified as the sulphoxide **3** by comparison with a specimen prepared as described later.

Oxidation of 10-*methylpyrazino*[2,3-b][1,4]*benzothiazine* **2** *with potassium permanganate*. A solution of KMnO$_4$ (1.7 g, 10.8 mmol) in water (25 ml) was added, over 40 min, to a solution of **7** (1.1 g, 5.1 mmol) in acetic acid (12.5 ml). After stirring for a further 15 min the dark brown suspension was decolourised with excess sodium pyrosulphite and the pale yellow product filtered off, washed with water, and dried giving the sulphone **10** in a high degree of purity (1.25 g, 99%). Recrystallisation from ethanol–acetone gave pale yellow crystals (0.9 g, 71%); m.p. 202–204°; $\lambda_{max.}$ 252 (ϵ 19,500), 279 (ϵ 15,700) and 358 nm (ϵ 4900); $\nu_{max.}$ 1293 and 1140 cm^{-1} (–SO$_2$–); δ (CDCl$_3$) 3.9 (3H, s, Me), 7.35–7.9 (3H, m, 7,8,9-H), 8.37 (1H, brd, $J_{6,7}$ 9 Hz, 6H), and 8.6 and 8.78 (each 1H, d, $J_{2,3}$ 2 Hz, 2 and 3H); *m/e* 248 (11%), 247 (100%, M), 215 (11%), 200 (8%), 183 (16%, M–SO$_2$), 182 (42%), 165 (11%), 136 (12%), 129 (11%) and 128 (11%); m* 181 (183→182) and 135 br (247→183). (Found: C, 53.7; H, 3.9; N, 16.5. $C_{11}H_8N_2O_2S$ requires: C, 53.4; H, 3.8; N, 17.0%).

Reactions of iodobenzene dichloride. (a) *With* 12-*methylquinoxalino*[2,3-b][1,4]*benzothiazine* **2**. A solution of iodobenzene dichloride (1.1 g, 4 mmol) in pyridine (10 ml) was added, over 5 min, to a stirred solution of **2** (1 g, 3.8 mmol) in pyridine (60 ml) and water (10 ml). Stirring was continued, with the addition of small amounts of iodobenzene dichloride until no starting material was left (TLC: 2 h). The red reaction mixture was neutralised with sodium carbonate solution and, after evaporation to dryness, partitioned between water and dichloromethane. The extracts were dried (MgSO$_4$) in the presence of charcoal and the solid obtained after evaporation was recrystallised from benzene–petrol 60–80° giving 12-methylquinoxalino[2,3-b][1,4]benzothiazine-S-oxide **3** as a dull yellow solid; m.p. 207–210°; $\lambda_{max.}$ 276.5 (ϵ 5400) and 418 nm (ϵ 8400); $\nu_{max.}$ 1039 and/or 1036 cm^{-1} (–SO–); δ (CDCl$_3$) 4.0 (3H, s, Me) and 7.3–8.5 (8H, m, ArH); *m/e* 281 (4%, M), 266 (11%), 265 (100%, M–O), 264 (16%), 251 (5%), 250 (19%, M–O–Me), 233 (16%, M–SO) and 232 (16%), m* 250 (281→265), 236 (265→250), 231 (233→232) and 203–205 br (265→233). (Found: C, 64.0; H, 4.0; N, 14.7. $C_{14}H_{11}N_3OS$ requires: C, 64.0; H, 3.9; N, 14.9%).

(b) *With* 10-*methylpyrazino*[2,3-b][1,4]*benzothiazine* **7**. Iodobenzene dichloride (2 g, 7.3 mmol) was added to a solution of **7** (1.3 g, 6.1 mmol) in acetonitrile (300 ml) and water (100 ml) and stirred for 1 h. Work up as in (a) gave a mixture (TLC) of two products; dry column chromatography[21] on silica (ethyl acetate as eluent) gave 2 (or 3)-chloro-10-methylpyrazino[2,3-b][1,4]benzothiazine-S-oxide **16** (24 mg, 1.5%) as a pale yellow solid and 10-methylpyrazino[2,3-*b*][1,4]benzothiazine-S-oxide **9** (797 mg, 57%); m.p. (benzene) 186–187°; $\lambda_{max.}$ 258 (ϵ 22,800), 282 (ϵ 13,500) and 364 nm (ϵ 4900); $\nu_{max.}$ 1042 and/or 1030 cm^{-1} (–SO–); δ (CDCl$_3$) 3.95 (3H, s, Me), 7.25–7.7 (2H, m, 7,9-H), 7.8 (1H, m, 8-H), 8.05 (1H, dd, $J_{6,7}$ 8 Hz, $J_{6,8}$ 2 Hz, 6-H), and 8.5 and 8.45 (each 1H, d, $J_{2,3}$ 2 Hz, 2 and 3H); *m/e* 232 (6%), 231 (45%, M), 216 (13%), 215 (100%, M–O), 214 (15%), 200 (40%, M–O–Me), 183 (42%, M–O–S), 182 (60%), 149 (40%), 85 (23%) and 83 (35%); m* 200 (231→215), 186.5 (215→200), 181 (183→182) and 155 (215→193). (Found: C, 56.9; H, 4.1; N, 17.8. $C_{11}H_8N_2OS$ requires: C, 57.1; H, 3.9; N, 18.2%). Structure assignment of the chlorinated material **16** was made on the basis of the following spectral data: $\lambda_{max.}$ 270 and 375 nm; δ (CDCl$_3$) 3.95 (3H, s, Me), 7.2–7.9 (3H, m, 7,8,9-H), 8.1 (1H, brd, $J_{6,7}$ 6 Hz, 6H) and 8.61 (1H, s, 2 or 3H); *m/e* 267 (M, Cl^{37}), 265 (M, Cl^{35}), 251 (M–O, Cl^{37}) and 249 (M–O, Cl^{35}).

(c) *With* 10H-*pyrazino*[2,3-b][1,4]*benzothiazine* **6**. Iodobenzene dichloride (1.2 g, 4.4 mmol) was added to a stirred solution of **6** (750 mg, 3.7 mmol) in acetonitrile (200 ml) and water (30 ml) over 50 min. After stirring for a further 15 min the reaction was worked up as in (a) giving fairly pure (PMR) benzothiazole-2-carboxamide **17**. Recrystallisation from benzene gave 232 mg (35%) of analytical material, identified by comparison with an authentic specimen.

Benzothiazole-2-carboxamide **17**

A solution of 2-ethoxycarbonylbenzothiazole[22] (460 mg) in ether (15 ml) was stirred with aqueous ammonia (0.880; 50 ml) at room temp. The amide started to precipitate out almost immediately, the reaction being complete (TLC) after 3 h. The product was filtered off, washed with water and ether, and dried, giving the pure amide **18** (310 mg, 77%); m.p. 229–231° (lit[23] 228–229°).

Reaction of 10-*methylpyrazino*[2,3-b][1,4]*benzothiazine* **7** *with ammonium hexanitratocerate(IV)*. The cerium salt (5 g, 9.1 mmol)

was added to a stirred solution of **7** (500 mg, 2.3 mmol) in aqueous acetonitrile (75%; 60 ml). An immediate black red colour resulted, passing to a lighter red in *ca.* 0.5 min. After stirring for 15 min, water (25 ml) was added, the products were extracted into ether, dried (Na_2SO_4), and the extracts were evaporated to dryness. The crude product was largely the desired sulphoxide **9** but TLC indicated the presence of a more mobile red compound. Isolation of this latter material by column chromatography on silica (ether–acetone, 4:1 as eluent) gave a red solid (91.4 mg, 13%), spectral data on which corresponded to a mixture of dinitro derivatives (unoxidised at sulphur); m.p. 246° (Kofler; from toluene–petrol 100–120°); λ_{max} ($CHCl_3$) 288, 318, 362 and 442 nm; ν_{max} 1510 and 1325 cm^{-1} ($-NO_2$); *m/e* 305 (100%, M), 259 (8%, M–NO_2); 232 (20%, M–NO_2–HCN), 213 (4%, M–$2NO_2$), 186 (8%, M–$2NO_2$, –HCN), 159 (8%) and 135 (8%); m* 220 (305→259), 208 (259→232), 184 (305→247), 176 (259→213) and 149 (232→186). (Found: C, 43.8; H, 2.7; N, 23.0; M, 305.0221. $C_{11}H_5N_5O_4S$ requires: C, 43.3; H, 2.3; N, 22.9%; M, 305.0219). That this material was a mixture was evident from its PMR spectrum which also confirmed the lack of oxidation at sulphur (see Discussion).

Nitration of 12H-*quinoxalino*[2,3-b][1,4]*benzothiazine* **1**. Sodium nitrite (200 mg, excess) was added to a suspension of **1** (500 mg) in acetic acid (120 ml) and stirred for 50 min, the suspension gradually becoming heavier. A further 200 mg of sodium nitrite was added and, after stirring for 30 min, the whole made neutral with 0.880 ammonia. The orange solid was filtered off, washed with water, and dried giving the crude product (570 mg, 96%); m.p. 325–330° (dec). Recrystallisation from ethyl acetate gave 3-nitro-12H-quinoxalino[2,3-*b*][1,4]benzothiazine **23** as fine golden needles (350 mg, 60%); m.p. 326–328° (Kofler), λ_{max} (EtOH) 238 (ε 41,000), 276 (ε 19,800), 289 (ε 19,000), 305 (ε 19,500) and 424 nm (ε 23,300); λ_{max} (0.05 M KOH in EtOH) 247 (ε 49,000), 292 (ε 14,700) and 546 nm (ε 37,000); ν_{max} 1523 and 1337 cm^{-1} (NO_2); δ (TFA) 7.4 (1H, d, $J_{1,2}$ 9 Hz, 1-H), 7.7–8.0 (4H, m, 7,8,9,10-H), 8.23 (1H, 4-H) and 8.3 (1H, dd, $J_{1,2}$ 9 Hz, $J_{2,4}$ 2 Hz, 2-H); *m/e* 297 (15%), 296 (100%, M), 280 (4%), 266 (24%), 251 (11%), 250 (47%, M–NO_2), 238 (5%), 223 (8%), 206 (12%), 178 (8%), 160 (12%) and 135 (15%), m* 211 (296→250). (Found: C, 56.9; H, 2.9; N, 18.8. $C_{14}H_8N_4O_2S$ requires: C, 56.8; H, 2.7; N, 18.9%).

Nitration of 10H-*pyrazino*[2,3-b][1,4]*benzothiazine* **6**. Sodium nitrite (500 mg, excess) was added to a solution of **6** (500 mg) in chloroform (35 ml) and acetic acid (1 ml) and stirred for 30 min. A further portion of acetic acid (0.5 ml) was then added and the reaction mixture stirred for another 30 min; this procedure was repeated once more, and the precipitated solid was filtered off, washed with acetic acid, ethanol and water, and dried. The dull red product (250 mg, 41%) was recrystallized from ethyl acetate giving black-red needles of 3-nitro-10H-pyrazino[2,3-b][1,4]benzothiazine **25**; m.p. 274°; λ_{max} (EtOH) 259 (ε 21,200) and 445 (br) nm (ε 10,400); λ_{max} (0.05 M KOH in EtOH) 238 (ε 19,300), 302 (ε 15,900) and 544 (br) nm (ε 24,400); ν_{max} 3230 (NH), 1510 and 1320 cm^{-1} (NO_2); δ (DMSO d_6) 6.9–7.25 (4H, m, 6,7,8,9-H) and 8.78 (1H, s, 2H); *m/e* 247 (7%), 246 (84%, M), 200 (5%, M–NO_2), 174 (7%), 173 (100%, M–NO_2–HCN), 160 (6%) and 146 (24%, M–NO_2–2HCN); m* 163 (246→200), 149.7 (200→173) and 123.2 (173→146). (Found: C, 49.1; H, 2.7; N, 22.7. $C_{10}H_6N_4O_2S$ requires: C, 48.9; H, 2.5; N, 22.8%). The same material was also obtained by performing the reaction in acetic acid (as for **1**).

Nitration of 12-*methylquinoxalino*[2,3-b][1,4]*benzothiazine* **2**. A suspension of **2** (900 mg) in acetic acid (100 ml) was stirred with the periodic addition of sodium nitrite (excess) until TLC indicated the absence of starting material (64 h). The suspension was evaporated to dryness and the orange residue triturated with aqueous sodium carbonate; filtration and drying gave the crude product (1050 mg). Recrystallisation from toluene–petrol 100–120° gave 3-nitro-12-methylquinoxalino[2,3-*b*][1,4]benzothiazine **24** (410 mg, 39%); m.p. 234–237°; λ_{max} 226 (ε 34,800), 234 sh (ε 33,400), 275 (ε 20,200), 286 sh (ε 17,900), 298 sh (ε 16,800) and 406 nm (ε 18,300); ν_{max} 1520 (d) and 1340 (d) cm^{-1} (NO_2); δ (TFA) 3.93 (3H, s, Me), 7.58 (1H, d, $J_{1,2}$ 9 Hz, 1-H), 7.83–8.23 (4H, m, 7,8,9,10-H), 8.43 (1H, d, $J_{2,4}$ 2 Hz, 4-H) and 8.53 (1H, dd, $J_{1,2}$ 9 Hz, $J_{2,4}$ 2 Hz, 2-H); *m/e* 311 (16%), 310 (100%, M), 280 (9%), 265 (19%), 264 (69%, M–NO_2), 252 (13%), 249 (9%, M–NO_2–Me), 237 (10%), 232 (10%) and 220 (17%, M–NO_2–CS); m* 235 (264→249), 225 (310→264), 205 (310→252) and 183.5 (264→220). (Found: C, 57.9; H, 3.5; N, 17.9; M, 310.0534. $C_{15}H_{10}N_4O_2S$ requires: C, 58.1; H, 3.3; N, 18.1%; M, 310.0525).

Nitration of 10-*methylpyrazino*[2,3-b][1,4]*benzothiazine* **7**. A solution of **7** (750 mg) in acetic acid (20 ml) was treated with sodium nitrite (excess) as described for **2**. When the reaction was complete (68 h) the mixture was poured into water and basified with aqueous ammonia; the crude product was filtered off and, after drying, recrystallised from ethyl acetate. The recrystallised material (240 mg, 26%) was in two forms, largely fine dark red needles with a smaller quantity of lighter red ferns; ν_{max} 1505 and 1320 (d) cm^{-1} (NO_2); δ (DMSO d_6) 3.46 (3H, s, Me), 7.25–7.55 (4H, m, 6,7,8,9-H) and 9.0 br (1H, s, pyrazinyl-H). (Found: C, 51.0; H, 3.3; N, 21.3. $C_{11}H_6N_4O_2S$ requires: C, 50.8; H, 3.1; N, 21.5%). Manual separation of the two types of crystal gave an impure sample of 3-nitro-10-methylpyrazino[2,3-*b*][1,4]benzothiazine **26**; m.p. (Kofler) 213–224°; λ_{max} 258 and 432 nm; *m/e* 260 (100%, M), 214 (6%, M–NO_2), 187 (80%, M–NO_2–HCN), 160 (7%, M–NO_2–2HCN) and 116 (50%); m* 176 (260→214), 163.5 (214→187) and 137 (187→160); and an impure sample of 2-nitro-10-methylpyrazino[2,3-*b*][1,4]benzothiazine **27**; m.p. (Kofler) 238–244°; λ_{max} 271, 360 and 380 (sh) nm; *m/e* 260 (100%, M), 214 (40%) and 187 (5%). No trace of sulphoxide (**9**) was observed in this reaction (TLC).

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