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Purine Analogues as Amplifiers of Phleomycin. IX* Some 2- and 6-Substituted Thiazolo[4,5-*b*]pyrazines, 2-Substituted Thiazolo[4,5-*c*]- and Thiazolo[5,4-*b*]-pyridines and Related Compounds

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Abstract

Derivatives of the thiazolo[4,5-*b*]pyrazine system are reported including those with 2-phenyl substituents or fused benzene rings (as in thiazolo[4,5-*b*]quinoxalines) together with strongly basic *N,N*-dimethylaminoethylthio or *N,N*-dimethylaminopropylthio side chains. Series of thiazolo[4,5-*c*]-pyridines, thiazolo[5,4-*b*]pyridines and quinoxalines are also described.

A new process for the preparation of 3-*N,N*-dimethylaminopropylthio derivatives of heterocycles by reaction of the mercapto compound with 3-chloro-*N,N*-dimethylpropylamine in ethanolic ammonia has been shown to give more reliable and improved results.

Of the compounds examined for amplification of the activity of phleomycin, *N,N*-dimethyl-3-(2-methylthiazolo[4,5-pyrazin-6-ylthio)propylamine and 3-[3-(3-*N,N*-dimethylaminopropylthio)-quinoxalin-2-ylthio]-*N,N*-dimethylpropylamine were the best, and showed four star activity at 1 mM and 0·5 mM respectively. A 2-phenyl substituent in, or a benzene ring fused to, thiazolo[4,5-*b*]-pyrazines did not increase amplification.

The 2-substituted thiazolo[4,5-*c*]pyridines showed activity comparable to that of the 2-substituted thiazolo[4,5-*b*]pyrazines whereas that of the thiazolo[5,4-*b*]pyrazines was lower.

Introduction

In an earlier paper,[1] the amplification of phleomycin by a series of thiazolo[4,5-*b*]-pyrazines (1) with strongly basic side chains was reported. In this paper additional derivatives of the thiazolo[4,5-*b*]pyrazine system are described including those with nuclear phenyl substituents and fused benzene rings [as in thiazolo[4,5-*b*]quinoxalines (2)], together with the strongly basic dimethylaminoethylthio and dimethylamino-propylthio side chains. Also reported are series of thiazolo[4,5-*c*]pyridines (3), thiazolo[5,4-*b*]pyridines (4) and quinoxalines. Brown *et al.*[2,3] have reported relatively

* Part VIII, *Aust. J. Chem.*, 1983, **36**, 983.

[1] Barlin, G. B., *Aust. J. Chem.*, 1983, **36**, 983.

[2] Brown, D. J., Buttler, B. B., Cowden, W. B., Grigg, G. W., Kavulak, D., and Podger, D. M., *Aust. J. Chem.*, 1981, **34**, 2423.

[3] Brown, D. J., Cowden, W. B., Lan, S.-B., and Mori, K., *Aust. J. Chem.*, 1984, **37**, 155.

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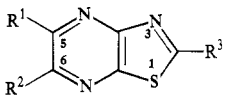
high activity in the unfused bicyclic *N,N*-dimethyl(and *N,N*-diethyl)-2-[4-(pyridin-4-yl)thiazol-2-ylthio]ethylamine,[2] and also in 2(or 4)-(2-dimethylaminoethylthio)-4(or 2)-phenylpyrimidines,[3] and one of us[4] has observed moderate activity in *N,N*-dimethyl-2-[4-(3-phenylpyrazin-2-yl)thiazol-2-yl)thioethylamine dihydrobromide. Accordingly, we have examined the effect of a 2-phenyl substituent in thiazolo[4,5-*b*]-pyrazines, the effect of fusion of a benzene ring, and the effect of variation of aza substitution in the six-membered ring.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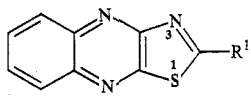
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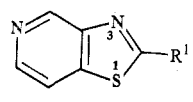
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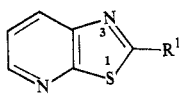
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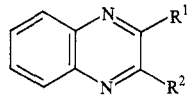
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Syntheses

The 6-substituted 2-phenylthiazolo[4,5-*b*]pyrazines (1; R^3 = Ph) were prepared from 3-amino-6-bromopyrazine-2-thiol by benzoylation, followed by thermal ring closure to 6-bromo-2-phenylthiazolo[4,5-*b*]pyrazine. This compound with potassium hydrogen sulfide gave the mercapto analogue which was alkylated with methyl iodide and 2-chloro-*N,N*-dimethylethylamine in aqueous sodium hydroxide in good yield to 6-methylthio-2-phenylthiazolo[4,5-*b*]pyrazine (1; R^1 = H, R^2 = SMe, R^3 = Ph) and *N,N*-dimethyl-2-(2-phenylthiazolo[4,5-*b*]pyrazin-6-ylthio)ethylamine respectively.

Considerable difficulty has been experienced in the past in the alkylation of mercapto compounds[1,5] in satisfactory yield with 3-chloro-*N,N*-dimethylpropylamine in aqueous sodium hydroxide; accordingly we have re-examined the alkylation of benzthiazole-2(3*H*)-thione[5] with 3-chloro-*N,N*-dimethylpropylamine. It was found that alkylation in saturated ethanolic ammonia gave reliable and good yields, whereas attempted alkylation in the presence of aqueous sodium hydroxide at pH 13, or controlled at pH 10–11, or reaction in the presence of ethanolic triethylamine gave variable or poor results.

Crude 2-phenylthiazolo[4,5-*b*]pyrazine-6-thiol with 3-chloro-*N,N*-dimethylpropylamine similarly in saturated ethanolic ammonia gave *N,N*-dimethyl-3-(2-phenylthiazolo[4,5-*b*]pyrazin-6-ylthio)propylamine in good yield; and *N,N*-dimethyl-3-(2-methylthiazolo[4,5-*b*]pyrazin-6-ylthio)propylamine was obtained in like manner.

N,N-Dimethyl-2-(2-methylthiazolo[4,5-*b*]pyrazin-6-ylthio)ethylamine, prepared previously[1] by alkylation of the mercapto compound, was also prepared by reaction of 6-bromo-2-methylthiazolo[4,5-*b*]pyrazine with sodium 2-dimethylaminoethylmercaptide. *N,N*-Dimethyl-3-(5,6-dimethylthiazolo[4,5-*b*]pyrazin-2-ylthio)propylamine was prepared (in poor yield), prior to the alkylation studies in ethanolic ammonia, from 5,6-dimethylthiazolo[4,5-*b*]pyrazine-2-thiol[1] with 3-chloro-*N,N*-dimethylpropylamine in aqueous sodium hydroxide.

[4] Barlin, G. B., *Aust. J. Chem.*, 1984, **37**, 1049.
[5] Barlin, G. B., *Aust. J. Chem.*, 1982, **35**, 2299.

Alkylation of thiazolo[4,5-*c*]pyridin-2-thiol[6] (3; R^1 = SH) with 2-chloro-*N*,*N*-dimethylethylamine in aqueous sodium hydroxide gave *N*,*N*-dimethyl-2-(thiazolo-[4,5-*c*]pyridin-2-ylthio)ethylamine; but with 3-chloro-*N*,*N*-dimethylpropylamine in ethanolic ammonia (followed by adjustment of the solution with sodium ethoxide solution) it gave not only *N*,*N*-dimethyl-3-(thiazolo[4,5-*c*]pyridin-2-ylthio)propylamine in good yield but also a quantity of 2-ethoxythiazolo[4,5-*c*]pyridine. The latter was formed presumably by replacement of the substituent at the 2-position by ethoxide ions. Its structure was established by analysis and by ^{1}H and ^{13}C n.m.r.

Thiazolo[5,4-*b*]pyridin-2-thiol (4; R^1 = SH) was prepared from 3-aminopyridine-2-thiol[7] by reaction with carbon disulfide in dimethylformamide,[8] and also by reaction with potassium ethyl xanthate in refluxing pyridine, as shown by its methylation to the known 2-methylthiothiazolo[5,4-*b*]pyridine.[9] *N*,*N*-Dimethyl-3-(thiazolo[5,4-*b*]-pyridin-2-ylthio)propylamine and *N*,*N*-dimethyl-2-(thiazolo[5,4-*b*]pyridin-2-ylthio)-ethylamine were prepared from the mercapto compound by alkylation procedures similar to those outlined above.

Thiazolo[4,5-*b*]quinoxaline-2(3*H*)-thione[10] (2; R^1 = SH) has been reported as the product from refluxing 2,3-dichloroquinoxaline (5; $R^1 = R^2$ = Cl) with ammonium dithiocarbamate and anhydrous sodium acetate in ethanol;[10] however, in our hands, this gave quinoxaline-2,3(1*H*,4*H*)-dithione because methylation of the product(s) of the reaction with methyl iodide gave 2,3-bismethylthioquinoxaline (5; $R^1 = R^2$ = SMe) as the only significant methylthio compound. The quinoxaline-2,3-(1*H*,4*H*)-dithioen with 2-chloro-*N*,*N*-dimethylethylamine in aqueous sodium hydroxide or with 3-chloro-*N*,*N*-dimethylpropylamine in ethanolic ammonia gave 2-[3-(2-dimethylaminoethylthio)quinoxalin-2-ylthio]-*N*,*N*-dimethylethylamine and 3-[3-(3-dimethylaminopropylthio),quinoxalin-2-ylthio]-*N*,*N*-dimethylpropylamine respectively.

Thiazolo[4,5-*b*]quinoxaline-2(3*H*)-thione was, however, prepared from 3-amino-quinoxaline-2-thiol[11] with potassium ethyl xanthate in pyridine. The product in aqueous alkali with methyl iodide or 2-chloro-*N*,*N*-dimethylethylamine gave 2-methylthiothiazolo[4,5-*b*]quinoxaline or *N*,*N*-dimethyl-2-(thiazolo[4,5-*b*]quinoxalin-2-ylthio)-ethylamine.

Biological Activities

The compounds tested were examined as outlined previously[2] (Table 1).

The results clearly show that a 2-phenyl substituent in thiazolo[4,5-*b*]pyrazines gives an amplification slightly lower than in the 2-methyl analogue. Thus *N*,*N*-dimethyl-2-(2-phenylthiazolo[4,5-*b*]pyrazin-6-ylthio)ethylamine (1; R^1 = H, R^2 = $SCH_2CH_2NMe_2$, R^3 = Ph) showed two star activity whereas the 2-methyl analogue showed three star activity. This contrasts with observations in the pyrimidine series.[3]

Fusion of a benzene ring as in *N*,*N*-dimethyl-2-(thiazolo[4,5-*b*]quinoxalin-2-ylthio)-ethylamine (2; R^1 = $SCH_2CH_2NMe_2$) also gave lower amplification, by one and

[6] Petrič, A., Stanovnik, B., and Tišler, M., *J. Heterocycl. Chem.*, 1977, **14**, 1045.
[7] Barlin, G. B., *J. Chem. Soc., Perkin Trans. 2*, 1972, 1459.
[8] Foye, W. O., Kauffman, J. M., Lanzillo, J. J., and LaSala, E. F., *J. Pharm. Sci.*, 1975, **64**, 1371.
[9] Bednyagina, N. P., Gulemina, N. N., Lipunova, G. N., and Saloutina, L. V., *Chem. Heterocycl. Compd. (USSR)*, 1975, **11**, 811.
[10] Chadha, V. K., and Saxena, V. K., *J. Indian Chem. Soc.*, 1980, **57**, 946.
[11] Saikachi, H., and Tagami, S., *Pharm Bull.*, 1961, **9**, 941.

two stars, than its non-benzoanalogue *N,N*-dimethyl-2-(thiazolo[4,5-*b*]pyrazin-2-ylthio)ethylamine[1] (1; $R^1 = R^2 = H$, $R^3 = SCH_2CH_2NMe_2$) or its 5,6-dimethyl derivative.[1]

In variations to aza substitution, the 2-substituted thiazolo[4,5-*c*]pyridines (3) showed amplification activity comparable to that of the 2-substituted thiazolo[4,5-*b*]-pyrazines (1), but in the thiazolo[5,4-*b*]pyridines (4) the observed activity was lower by one star.

Table 1. Activities as amplifiers of phleomycin

Measured at 3·3 mM, solubility permitting; for details of method and activity see ref. 2

Compound	Activity
(1; $R^1 = H$, $R^2 = SCH_2CH_2NMe_2$, $R^3 = Me$)	*** [A]
(1; $R^1 = H$, $R^2 = SCH_2CH_2CH_2NMe_2$, $R^3 = Me$)	*** [B]
(1; $R^1 = R^2 = Me$, $R^3 = SCH_2CH_2NMe_2$)	*** [A]
(1; $R^1 = R^2 = Me$, $R^3 = SCH_2CH_2CH_2NMe_2$)	**
(1; $R^1 = H$, $R^2 = SCH_2CH_2NMe_2$, $R^3 = Ph$)	**
(1; $R^1 = H$, $R^2 = SCH_2CH_2CH_2NMe_2$, $R^3 = Ph$)	***
(3; $R^1 = SCH_2CH_2NMe_2$)	**
(3; $R^1 = SCH_2CH_2CH_2NMe_2$)	***
(4; $R^1 = SCH_2CH_2NMe_2$)	*
(4; $R^1 = SCH_2CH_2CH_2NMe_2$)	**
(5; $R^1 = R^2 = SCH_2CH_2NMe_2$)	toxic
(5; $R^1 = R^2 = SCH_2CH_2CH_2NMe_2$)	**** [C]
(2; $R^1 = SCH_2CH_2NMe_2$)	* [D]

[A] Ref. 1. [B] At 2 mM; **** at 1 mM. [C] At 0·5 mM; toxic at higher concentrations. [D] At 1 mM.

Of the six *N,N*-dimethylaminopropylthio compounds reported here, most were observed to have a higher activity (by one star) than their *N,N*-dimethylaminoethylthio analogues (compare with data in ref.[1]) except that *N,N*-dimethyl-3-(5,6-dimethylthiazolo[4,5-*b*]pyrazin-2-ylthio)propylamine was lower. Whereas 2-[3-(2-dimethylaminoethylthio)quinoxalin-2-ylthio]-*N,N*-dimethylethylamine was toxic its propyl analogue, 3-[3-(3-dimethylaminopropylthio)quinoxalin-2-ylthio]-*N,N*-dimethylpropylamine, gave a four star activity.

Experimental

Solids for analysis were dried at 100° (unless otherwise specified) and melting points were taken in Pyrex capillaries. Analyses were performed by The Australian National University Analytical Services Unit. ^1H n.m.r. spectra were recorded at 60 MHz and 35° with a Varian T-60A, or at 90 MHz and 30° with a JEOL FX90Q Fourier transform spectrometer with tetramethylsilane (in $CDCl_3$) and sodium 3-trimethylsilylpropanesulfonate (in D_2O) as internal standards. The ^{13}C n.m.r. was recorded with the last-named instrument.

*6-Bromo-2-phenylthiazolo[4,5-*b*]pyrazine*

3-Amino-6-bromopyrazine-2-thiol[12] (0·5 g) was dissolved in 1 M sodium hydroxide (10·0 ml) and shaken with benzoyl chloride (0·5 ml) for 1 h. The solid was filtered from the alkaline solution which was shaken further with benzoyl chloride (0·2+0·2+0·2 ml) for 1 h, readjusted to pH > 7, and the precipitate filtered off.

[12] Palamidessi, G., and Bernardi, L., *Gazz. Chim. Ital.*, 1961, **91**, 1438.

The combined solids, after drying, were heated in a test tube in an oil bath to *c.* 146° and maintained at this temperature for 45 min.

The product was dissolved in chloroform and chromatographed over silica (26 cm by 2·5 cm diameter), and the product eluted in the early fractions was recrystallized from cyclohexane to give *6-bromo-2-phenylthiazolo[4,5-*b*]pyrazine* (0·307 g), m.p. 194–195° (Found: C, 45·3; H, 2·0; N, 14·1. $C_{11}H_6BrN_3S$ requires C, 45·2; H, 2·1; N, 14·4%). ^{1}H n.m.r. ($CDCl_3$): δ 7·58, complex, 8·20, complex, Ph; 8·74, s, H 5.

*6-Methylthio-2-phenylthiazolo[4,5-*b*]pyrazine*

A mixture of 6-bromo-2-phenylthiazolo[4,5-*b*]pyrazine (0·066 g) and methanolic potassium hydrogen sulfide (9·0 ml; prepared from 5·3 g potassium hydroxide in 40 ml methanol saturated with hydrogen sulfide) was heated in a sealed tube at 100° for 5 h. The reaction mixture was diluted with water and adjusted to pH *c.* 2·5 with 10 M hydrochloric acid, and evaporated under reduced pressure. The residue was dissolved in aqueous sodium hydroxide and shaken with methyl iodide (0·5 ml) for 15 min. The product (0·050 g) was extracted into chloroform, and subjected to t.l.c. (alumina; chloroform) and recrystallized from cyclohexane to give *6-methylthio-2-phenylthiazolo-[4,5-*b*]pyrazine*, m.p. 132–133·5° (Found: C, 55·5; H, 3·5; N, 16·1. $C_{12}H_9N_3S_2$ requires C, 55·6; H, 3·5; N, 16·2%). ^{1}H n.m.r. ($CDCl_3$): δ 2·65, s, MeS; 7·50, complex, 8·10, complex, Ph; 8·48, s, H 5.

N,N-*Dimethyl-2-(2-phenylthiazolo[4,5-*b*]pyrazin-6-ylthio)ethylamine*

A mixture of 6-bromo-2-phenylthiazolo[4,5-*b*]pyrazine (0·300 g) and potassium hydrogen sulfide (40 ml; prepared from 10·6 g potassium hydroxide in 80 ml methanol saturated with hydrogen sulfide) in a sealed tube was heated at 100° for 5 h. The reaction mixture was adjusted to pH *c.* 1·5 with 10 M hydrochloric acid and evaporated under reduced pressure to remove most of the hydrogen sulfide and methanol. The residue was dissolved in aqueous sodium hydroxide and shaken with 2-chloro-*N,N*-dimethylethylamine hydrochloride (1·0 g+0·8 g) for *c.* 1 h. This mixture was extracted with chloroform and the product chromatographed in chloroform over alumina (20 cm by 2·5 cm diameter) and recrystallized from cyclohexane to give light yellow N,N-*dimethyl-2-(2-phenylthiazolo-[4,5-*b*]pyrazin-6-ylthioethylamine* (0·269 g), m.p. 162·5–163·5° (Found: C, 57·2; H, 5·1; N, 17·8. $C_{15}H_{16}N_4S_2$ requires C, 56·9; H, 5·1; N, 17·7%). ^{1}H n.m.r. ($CDCl_3$): δ 2·33, s, MeS; 2·67, t, *J* 7 Hz, CH_2N; 3·42, t, *J* 7 Hz, CH_2S; 7·57, complex, 8·14, complex, Ph; 8·51, s, H 5.

N,N-*Dimethyl-3-(2-phenylthiazolo[4,5-*b*]pyrazin-6-ylthio)propylamine*

A mixture of 6-bromo-2-phenylthiazolo[4,5-*b*]pyrazine (0·212 g) and methanolic potassium hydrogen sulfide (from 6·6g potassium hydroxide in 50 ml methanol saturated with hydrogen sulfide) was heated in a sealed tube at 100° for 5·5 h. The reaction mixture was acidified to pH 1·5–2·0 with 10 M hydrochloric acid, and evaporated to dryness under reduced pressure. This residue was shaken with ethanolic ammonia (100 ml; saturated at 20°) and 3-chloro-*N,N*-dimethylpropylamine hydrochloride (1·0 g+0·5 g) for *c.* 5 min, allowed to stand at 20° for 1 h, and refluxed for 40 min. After cooling, the mixture was treated with methanolic sodium methoxide until a test sample with water had pH *c.* 12·5. The mixture was then diluted with water (40 ml), and the ethanol removed on a rotary evaporator. The aqueous solution was extracted with chloroform, the extract dried (Na_2SO_4) and the solvent evaporated to give a yellow oil which was subjected to t.l.c. (alumina; chloroform) and the product recrystallized from light petroleum (b.p. 40–60°) to give N,N-*dimethyl-3-(2-phenylthiazolo[4,5-*b*]pyrazin-6-ylthio)propylamine* (0·182 g), m.p. 93° (Found: for sample dried at 20° and 20 mmHg for 2·5 h: C, 58·2; H, 5·6; N, 17·0. $C_{16}H_{18}N_4S_2$ requires C, 58·2; H, 5·5; N, 17·0%). ^{1}H n.m.r. ($CDCl_3$): δ 1·88, complex, $CH_2CH_2CH_2$; 2·22, s, Me_2N; 2·40, t, *J* 7 Hz, CH_2N; 3·25, t, *J* 7 Hz, CH_2S; 7·46, complex, 8·03, complex, Ph; 8·41, s, H 5.

*3-(Benzothiazol-2-ylthio)-*N,N*-dimethylpropylamine Dihydrobromide*

Benzothiazole-2(3*H*)-thione (0·5 g), ethanolic ammonia (50 ml; saturated at 0°) and 3-chloro-*N,N*-dimethylpropylamine hydrochloride (0·73 g) were shaken at 20° for 45 min, then refluxed for 30 min. After cooling, the mixture was adjusted with sodium ethoxide solution until a test sample with water had pH 12·5. It was then diluted with water, the ethanol evaporated under reduced

pressure, and the mixture extracted with chloroform, and the product chromatographed in chloroform over alumina (25 cm by 2·5 cm diameter) to give an oil (0·6 g). This oil was treated with 10% ethanolic hydrogen bromide and precipitated with ether to give *3-(benzothiazol-2-ylthio)*-N,N-*dimethylpropylamine dihydrobromide* (0·77 g), m.p. 175–178° (from ethanol/ether) (Found: C, 34·2; H, 4·2; N, 6·5. $C_{12}H_{18}Br_2N_2S_2$ requires C, 34·8; H, 4·4; N, 6·8%). ^{1}H n.m.r. (free base in $CDCl_3$): δ 1·93, complex, $CH_2CH_2CH_2$; 2·17, s, Me_2N; 2·37, t, *J* 7 Hz, CH_2N; 3·35, t, *J* 7 Hz, CH_2S; 7·50, complex, H 4,5,6,7; the dihydrobromide (in D_2O): 2·26, complex, $CH_2CH_2CH_2$; 2·90, s, Me_2N; 3·43, complex, $SCH_2CH_2CH_2N$; 7·60, complex, H 4,5,6,7.

N,N-*Dimethyl-2-(2-methylthiazolo[4,5-*b*]pyrazin-6-ylthio)ethylamine Hydrobromide*

A mixture of 6-bromo-2-methylthiazolo[4,5-*b*]pyrazine (0·5 g), 2-dimethylaminoethylmercaptan hydrochloride (0·68 g) and ethanolic sodium ethoxide (from 0·2 g sodium and 30 ml ethanol) was heated in a sealed tube at 100° for 4·5 h. The solvent was evaporated and the residue diluted with water and extracted with chloroform to give a thick oil which was subjected to t.l.c. (alumina; chloroform). The product was treated with 10% ethanolic hydrogen bromide and the precipitate with ether was recrystallized from isopropyl alcohol to give a yellow crystalline solid (0·170 g) with ^{1}H n.m.r. (D_2O) identical with that reported previously[1] from alkylation of the corresponding mercapto compound.

N,N-*Dimethyl-3-(2-methylthiazolo[4,5-*b*]pyrazin-6-ylthio)propylamine*

2-Methylthiazolo[4,5-*b*]pyrazine-6-thiol[1] (0·525 g), ethanolic ammonia (90 ml; saturated at 20°) and 3-chloro-*N,N*-dimethylpropylamine hydrochloride (1·5 g) were shaken for a few minutes, allowed to stand at 20° for 45 min, and refluxed for 30 min. After cooling, the mixture was treated with sodium methoxide solution until a test sample with water had pH 12·3–12·5. Water (30 ml) was then added and the ethanol evaporated under reduced pressure. The aqueous residue was extracted with chloroform, extract dried (Na_2SO_4) and solvent evaporated to give an oil (0·6 g). This product was subjected to t.l.c. (alumina; chloroform and alumina; ethyl acetate), extracted with chloroform and freed from solvent at 50° and 20 mmHg for 30 min to give N,N-*dimethyl-3-(2-methylthiazolo[4,5-*b*]pyrazin-6-ylthiopropylamine* (0·35 g) (Found: C, 49·4; H, 6·4; N, 20·4. $C_{11}H_{16}N_4S_2$ requires C, 49·2; H, 6·0; N, 20·9%). ^{1}H n.m.r. ($CDCl_3$): δ 1·85, complex, $CH_2CH_2CH_2$; 2·18, s, Me_2N; 2·27, t, CH_2N; 2·85, s, MeC; 3·22, t, CH_2S; 8·37, s, H 5.

N,N-*Dimethyl-3-(5,6-dimethylthiazolo[4,5-*b*]pyrazin-2-ylthio)propylamine 1·6 Hydrobromide*

5,6-Dimethylthiazolo[4,5-*b*]pyrazine-2-thiol was prepared from 3-amino-5,6-dimethylpyrazine-2-thiol (1·25 g), as reported previously.[1] The product was suspended in water, dissolved by addition of aqueous sodium hydroxide to pH 11 and shaken with 3-chloro-*N,N*-dimethylpropylamine hydrochloride (6·0 g + 2·5 g after 15 min) over *c.* 30 min, while the pH was adjusted periodically to pH 11. The mixture was extracted with chloroform, extract dried (Na_2SO_4) and solvent evaporated to give a thick oil which was chromatographed in chloroform over alumina (20 cm by 4 cm diameter). The product was treated with 10% ethanolic hydrogen bromide and the yellow crystalline solid (0·235 g) recrystallized from ethanol/ether to give N,N-*dimethyl-3-(5,6-dimethylthiazolo[4,5-*b*]pyrazin-2-ylthio)-propylamine 1·6 hydrobromide*, m.p. *c.* 178° (Found: C, 35·2; H, 4·8; N, 13·3. $C_{12}H_{18}N_4S_2.1·6HBr$ requires C, 35·0; H, 4·8; N, 13·6%). ^{1}H n.m.r. (free base in $CDCl_3$): δ 1·99, complex, CH_2CH_2-CH_2; 2·23, s, Me_2N; 2·36, t, *J* 6 Hz, CH_2N; 2·59, s, 2·62, s, 5,6-Me_2; 3·49, t, *J* 6 Hz, CH_2S; the hydrobromide (in D_2O): δ 2·35, complex, $CH_2CH_2CH_2$; 2·61, s, Me_2N; 2·91, s, 5,6-Me_2; 3·36, t, *J* 7 Hz; CH_2N; 3·50, t, *J* 7 Hz, CH_2S.

N,N-*Dimethyl-2-(thiazolo[4,5-*c*]pyridin-2-ylthio)ethylamine Dihydrobromide*

Thiazolo[4,5-*c*]pyridin-2-thiol[6] (0·5 g) was dissolved in 1 M sodium hydroxide (15 ml) and shaken with 2-chloro-*N,N*-dimethylethylamine hydrochloride (0·75 g + 0·5 g after 5 min) for 15 min. The alkaline solution was extracted with chloroform and the product subjected to t.l.c. (alumina; chloroform). The main band gave a clear oil which was treated with freshly prepared 10% ethanolic hydrogen bromide to yield N,N-*dimethyl-2-(thiazolo[4,5-*c*]pyridin-2-ylthio)ethylamine dihydrobromide* (0·342 g), m.p. 226–228° (from ethanol) (Found, for sample dried at 20° in a vacuum: C, 29·8; H, 3·8; N, 10·4. $C_{10}H_{15}Br_2N_3S_2$ requires C, 29·9; H, 3·8; N, 10·5%). ^{1}H n.m.r.

(free base in $CDCl_3$): δ 2·27, s, Me_2N; 2·68, t, J 7 Hz, CH_2N; 3·48, t, J 7 Hz, CH_2S; 7·58, d, J 6 Hz, H6; 8·30, d, J 6 Hz, H7; 8·53, s, H4; the dihydrobromide (in D_2O): δ 3·03, s, Me_2N; 3·82, complex, CH_2CH_2; 8·56, s, H6,7; 9·28, s, H4.

N,N-*Dimethyl-3-(thiazolo[4,5-*c*]pyridin-2-ylthio)propylamine Dihydrobromide and 2-Ethoxythiazolo-[4,5-*c*]pyridine*

Thiazolo[4,5-*c*]pyridin-2-thiol[6] (0·5 g) was dissolved in ethanolic ammonia (60 ml; saturated at 0°) and shaken with 3-chloro-*N,N*-dimethylpropylamine hydrochloride (0·9 g+0·6 g+1·5 g at 15-min intervals) and the mixture shaken at 20° for a total of 30 min, then refluxed for 40 min.

The cooled reaction mixture was treated with sodium ethoxide solution (from 3·0 g sodium and 80 ml ethanol) until a test sample with water had pH 12·5.

The mixture was diluted with water, the ethanol evaporated on the rotary evaporator, and the aqueous solution extracted with chloroform, extract dried (Na_2SO_4) and solvent evaporated to give an oil which was subjected to chromatography in chloroform over alumina (25 cm by 2·5 cm diameter). The first fractions gave a white crystalline solid and the later fractions gave an oil.

The white solid recrystallized from light petroleum (b.p. 40–60°) to give *2-ethoxythiazolo[4,5-*c*]-pyridine* (0·084 g), m.p. 75–78° (Found, for a sample dried at 20° in a vacuum: C, 53·7; H, 4·5; N, 15·6. $C_8H_8N_2OS$ requires C, 53·3; H, 4·5; N, 15·6%). ^{1}H n.m.r. ($CDCl_3$): δ 1·50, t, J 8 Hz, CH_3; 4·66, q, J 8 Hz, CH_2; 7·58, q, $J_{6,7}$ 5·4 Hz, $J_{4,6}$ 0·8 Hz, H6; 8·38, d, $J_{6,7}$ 5·4 Hz, H7; 8·94, d, $J_{4,6}$ 0·8 Hz, H4. ^{13}C n.m.r. ($CDCl_3$): δ 14·20, CH_3; 68·53, CH_2; 115·96, C7; 140·31, C7a; 141·88, C6; 142·69, C4; 146·27, C4a; 172·87, C2.

The oil in the latter fractions was subjected to further chromatography in benzene over alumina (25 cm by 2·5 cm diameter) and the oil obtained was treated with freshly prepared 10% ethanolic hydrogen bromide to give a white solid (0·62 g) which was reprecipitated from ethanol by addition of ether to give N,N-*dimethyl-3-(thiazolo[4,5-*c*]pyridin-2-ylthio)propylamine dihydrobromide*, m.p. 202–204° (Found, for sample dried at 20° in a vacuum: C, 31·6; H, 4·2; N, 9·9. $C_{11}H_{17}Br_2N_3S_2$ requires C, 31·8; H, 4·1; N, 10·1%). ^{1}H n.m.r. (the dihydrobromide in D_2O): δ 2·36, complex, $CH_2CH_2CH_2$; 2·94, s, Me_2N; 3·30, t, J 7 Hz, CH_2N; 3·60, t, J 7 Hz, CH_2S; 8·58, s, H6,7; 9·26, s, H4.

*2-Methylthiothiazolo[5,4-*b*]pyridine*

Crude 3-aminopyridine-2-thiol[7] (0·33 g), potassium ethyl xanthate (2·0 g) and pyridine (14·0 ml) were refluxed for 24 h, then evaporated to near dryness under reduced pressure. The residue was diluted with water, acidified with 10 M hydrochloric acid to pH 1, and warmed on a steam bath for 5 min. The mixture was then made alkaline with 10 M sodium hydroxide and shaken with methyl iodide (0·6 ml) for *c.* 20 min, and extracted with chloroform. The product was chromatographed in toluene over alumina (25 cm) and the major fraction recrystallized from light petroleum (b.p. 40–60°) to give 2-methylthiothiazolo[5,4-*b*]pyridine (0·20 g), m.p. 82–84·5° (lit. 88·5°,[13] 95°[9]) (Found, for sample dried at 20° in a vacuum: C, 45·8; H, 3·3; N, 15·0. Calc. for $C_7H_6N_2S_2$: C, 46·1; H, 3·3; N, 15·4%). ^{1}H n.m.r. ($CDCl_3$): δ 2·80, s, MeS; 7·34, q, $J_{4,5}$ 8·2 Hz, $J_{5,6}$ 4·7 Hz, H5; 8·07, q, $J_{4,5}$ 8·2 Hz, $J_{4,6}$ 2·0 Hz, H4; 8·43, q, $J_{5,6}$ 4·7 Hz, $J_{4,6}$ 2·0 Hz, H6.

This product was identical (^{1}H n.m.r.) with that obtained by methylation of thiazolo[5,4-*b*]-pyridine-2-thiol[8] as described by Bednyagina *et al.*[9]

N,N-*Dimethyl-2-(thiazolo[5,4-*b*]pyridin-2-ylthio)ethylamine 1·9 Hydrobromide*

Thiazolo[5,4-*b*]pyridin-2-thiol[8] (0·2 g) was dissolved in 1 M sodium hydroxide (6·0 ml) and shaken with 2-chloro-*N,N*-dimethylethylamine hydrochloride (0·3 g+0·2 g after 5 min) for 15 min. The reaction mixture was extracted with chloroform and the product subjected to t.l.c. (alumina; chloroform), and the oil obtained treated with freshly prepared 10% ethanolic hydrogen bromide to give N,N-*dimethyl-2-(thiazolo[5,4-*b*]pyridin-2-ylthio)ethylamine 1·9 hydrobromide* (0·326 g), m.p. 175–177° (from ethanol/ether) (Found, for sample dried at 20° in a vacuum: C, 30·5; H, 4·2; N, 10·4. $C_{10}H_{13}N_3S_2.1{\cdot}9HBr$ requires C, 30·5; H, 3·8; N, 10·7%). ^{1}H n.m.r. (free base in $CDCl_3$):

[13] Gayral, P., Bourdais, J., Lorre, A., Abenhaim, D., Dusset, F., Pommiès, M., and Fouret, G., *Eur. J. Med. Chem.—Chim. Ther.*, 1978, **13**, 171.

δ 2·27, s, Me_2N; 2·67, t, *J* 7 Hz, CH_2N; 3·47, t, *J* 7 Hz, CH_2S; 7·18, q, $J_{4,5}$ 8·7 Hz, $J_{5,6}$ 5·0 Hz, H 5; 7·87, q, $J_{4,5}$ 8·7 Hz, $J_{4,6}$ 1·5 Hz, H 4; 8·23, q, $J_{5,6}$ 5·0 Hz, $J_{4,6}$ 1·5 Hz, H 6; the dihydrobromide (in D_2O): δ 3·02, s, Me_2N; 3·72, complex, SCH_2CH_2N; 7·65, q, $J_{4,5}$ 8·7 Hz, $J_{5,6}$ 5·0 Hz, H 5; 8·33, q, $J_{4,5}$ 8·7 Hz, $J_{4,6}$ 1·5 Hz, H 4; 8·53, q, $J_{5,6}$ 5·0 Hz, $J_{4,6}$ 1·5 Hz, H 6.

N,N-*Dimethyl-3-(thiazolo[5,4-*b*]pyridin-2-ylthio)propylamine Dihydrobromide*

Thiazolo[5,4-*b*]pyridin-2-thiol[8] (0·6 g) was dissolved in ethanolic ammonia (60 ml; saturated at 0°) and shaken with 3-chloro-*N,N*-dimethylpropylamine hydrochloride (0·9 g+0·6 g+1·5 g at 15-min intervals) for 30 min, then refluxed for 45 min.

The reaction mixture was worked up as for the isomer above and the product subjected to chromatography in chloroform over alumina (25 cm by 2·5 cm diameter) and then treated with freshly prepared ethanolic hydrogen bromide to give N,N-*dimethyl-3-(thiazolo[5,4-*b*]pyridin-2-ylthio)propylamine dihydrobromide* (0·725 g), m.p. 189–193° (from ethanol/ether) (Found: C, 31·9; H, 4·2; N, 9·8. $C_{11}H_{17}Br_2N_3S_2$ requires C, 31·8; H, 4·1; N, 10·1%). ^{1}H n.m.r. (free base in $CDCl_3$): δ 1·98, complex, $CH_2CH_2CH_2$; 2·23, s, Me_2N; 2·43, t, *J* 7 Hz, CH_2N; 3·41, t, *J* 7 Hz, CH_2S; 7·30, q, $J_{4,5}$ 8·2 Hz, $J_{5,6}$ 4·7 Hz, H 5; 8·02, q, $J_{4,5}$ 8·2 Hz, $J_{4,6}$ 1·6 Hz, H 4; 8·41, q, $J_{5,6}$ 4·7 Hz, $J_{4,6}$ 1·6 Hz, H 6; the dihydrobromide (in D_2O): 2·29, complex, $CH_2CH_2CH_2$; 2·91, s, Me_2N; 3·40, complex, $SCH_2CH_2CH_2N$; 7·61, q, $J_{4,5}$ 8·2 Hz, $J_{5,6}$ 4·7 Hz, H 5; 8·26, q, $J_{4,6}$ 1·6 Hz, $J_{4,5}$ 8·2 Hz, H 4; 8·51, q, $J_{5,6}$ 4·7 Hz, $J_{4,6}$ 1·6 Hz, H 6.

2,3-Bismethylthioquinoxaline

A mixture of 2,3-dichloroquinoxaline[14] (0·5 g), ammonium dithiocarbamate[15] (0·28 g) and anhydrous sodium acetate (0·4 g) in ethanol (15 ml) were refluxed on a steam bath for 3 h. After cooling, the yellow mercapto compound (0·4 g) was filtered off and dried at 100°.

This solid was mostly dissolved in 1 M sodium hydroxide (5·0 ml) and shaken with methyl iodide (0·5 ml) for 20 min, and the mixture extracted with chloroform. The product obtained was extracted with benzene to remove a little yellow insoluble solid and the soluble product chromatographed in chloroform over silica (20 cm by 2·5 cm diameter), and recrystallized from light petroleum (b.p. 60–80°) to give 2,3-bismethylthioquinoxaline (0·179 g), m.p. 128–128·5° (lit.[16] 134–135°) (Found: C, 54·2; H, 4·5; N, 12·4. Calc. for $C_{10}H_{10}N_2S_2$: C, 54·0; H, 4·5; N, 12·6%). ^{1}H n.m.r. ($CDCl_3$): δ 2·69, s, MeS; 7·51, complex quartet, 7·86, complex quartet, H 5,6,7,8.

2-[3-(2-Dimethylaminoethylthio)quinoxalin-2-ylthio]-N,N-*dimethylethylamine Dihydrobromide*

A mixture of 2,3-dichloroquinoxaline[14] (0·625 g), ammonium dithiocarbamate[15] (0·35 g) and anhydrous sodium acetate (0·5 g) in ethanol (20 ml) were refluxed for 3 h, and, after cooling, the solid mercapto compound was filtered off. This solid was mostly dissolved in 1 M sodium hydroxide (15 ml) and shaken with 2-chloro-*N,N*-dimethylethylamine hydrochloride (1·2 g) for 1·5 h. The product extracted into chloroform was chromatographed in chloroform over alumina (25 cm by 2·5 cm diameter), and the main product treated with freshly prepared 10% ethanolic hydrogen bromide to give *2-[3-(2-dimethylaminoethylthio)quinoxalin-2-yl]*-N,N-*dimethylethylamine dihydrobromide* (0·287 g), m.p. 306–307° (from methanol/ethanol) (Found, for sample dried at 20° in a vacuum: C, 38·7; H, 5·3; N, 11·2. $C_{16}H_{26}Br_2N_4S_2$ requires C, 38·6; H, 5·3; N, 11·2%). ^{1}H n.m.r. (free base in $CDCl_3$): δ 2·35, s, Me_2N; 2·68, t, *J* 7 Hz, CH_2N; 3·49, t, *J* 7 Hz, CH_2S; 7·53, complex quartet, 7·84, complex quartet, H 5,6,7,8; the dihydrobromide (in D_2O): δ 3·05, s, Me_2N; 3·68, complex, SCH_2CH_2N; 7·82, complex quartet, 7·95, complex quartet, H 5,6,7,8.

3-[3-(3-Dimethylaminopropylthio)quinoxalin-2-ylthio]-N,N-*dimethylpropylamine Dihydrobromide*

The crude mercapto compound (0·5 g) [prepared as described above from 2,3-dichloroquinoxaline (0·625 g)] was mixed with ethanolic ammonia (60 ml; saturated at 0°) and shaken with 3-chloro-*N,N*-dimethylpropylamine hydrochloride (0·9 g+0·6 g after 15 min+1·5 g at start of reflux) at

[14] Komin, A. P., and Carmack, M., *J. Heterocycl. Chem.*, 1976, **13**, 13.
[15] Redemann, C. E., Icke, R. N., and Alles, G. A., *Org. Synth.*, 1947, **27**, 73.
[16] Daiichi Industrial Drug Manufacturing Co. (by Kazuo Asano and Satoo Asai) Jpn Pat. 3375 (*Chem. Abstr.*, 1960, **54**, 14278b).

room temperature for 30 min, then refluxed for 40 min. The mixture was then adjusted with sodium ethoxide solution until a test sample with water had pH 12·5, then diluted with water, and the ethanol evaporated under reduced pressure. The mixture was then extracted with chloroform and the product subjected to t.l.c. (alumina; chloroform) and the main product treated with freshly prepared 10% ethanolic hydrogen bromide to give *3-[3-(3-dimethylaminopropylthio)quinoxalin-2-ylthio]*-N,N-*dimethylpropylamine dihydrobromide* (0·243 g), m.p. 245° (from ethanol) (Found: C, 41·3; H, 5·8; N, 10·7. $C_{18}H_{30}Br_2N_4S_2$ requires C, 41·1; H, 5·7; N, 10·6%). ^{1}H n.m.r. (free base in $CDCl_3$): δ 1·92, complex, $CH_2CH_2CH_2$; 2·17, s, Me_2N; 2·40, t, *J* 7 Hz, CH_2N; 3·32, t, *J* 7 Hz, CH_2S; 7·48, complex, H 5,6,7,8; the hydrobromide (in D_2O): δ 2·26, complex, $CH_2CH_2CH_2$; 2·93, s, Me_2N; 3·37, complex, $SCH_2CH_2CH_2N$; 7·85, complex, H 5,6,7,8.

*2-Methylthiothiazolo[4,5-*b*]quinoxaline*

3-Aminoquinoxaline-2-thiol[11] (0·4 g) and potassium ethyl xanthate (1·25 g) in pyridine (4·5 ml) were refluxed for 24 h, then evaporated under reduced pressure, diluted with water and evaporated three times to remove pyridine, diluted with water, acidified to pH 1 with 10 M hydrochloric acid, and heated on a steam bath for 5 min. The mixture was then made alkaline and shaken with methyl iodide (0·6 ml) for 20 min, extracted with chloroform, and the product recrystallized from cyclohexane to give *2-methylthiothiazolo[4,5-*b*]quinoxaline* (0·084 g), m.p. 141–143° (Found: C, 51·3; H, 3·1; N, 17·7. $C_{10}H_7N_3S_2$ requires C, 51·5; H, 3·0; N, 18·0%). ^{1}H n.m.r. ($CDCl_3$): δ 2·94, s, MeS; 7·75, complex, 8·13, complex, H 5,6,7,8.

2-Methylthioquinoxalin-2-amine

3-Aminoquinoxaline-2-thiol[11] was methylated in aqueous sodium hydroxide with methyl iodide and the product extracted into chlorform and recrystallized from cyclohexane to give 2-methylthioquinoxalin-2-amine, m.p. 170–171·5° (lit.[11] 170°). ^{1}H n.m.r. ($CDCl_3$): 2·76, s, MeS; 4·94, bs, H_2N; 7·58, complex, H 5,6,7,8.

N,N-*Dimethyl-2-(thiazolo[4,5-*b*]quinoxalin-2-ylthio)ethylamine Hydrobromide*

Thiazolo[4,5-*b*]quinoxaline-2-thiol was prepared from 3-aminoquinoxaline-2-thiol[11] (0·4 g) and potassium ethyl xanthate (1·25 g), as described above. A solution of the mercapto compound in aqueous sodium hydroxide was shaken with 2-chloro-*N,N*-dimethylethylamine hydrochloride (1·5 g) for 30 min. The product was extracted into chloroform and purified by t.l.c. (alumina; chloroform), and with freshly prepared 10% ethanolic hydrogen bromide gave N,N-*dimethyl-2-(thiazolo[4,5-*b*]quinoxalin-2-ylthio)ethylamine hydrobromide* (0·22 g), m.p. 239·241° (from methanol) (Found: for sample dried at 20° in a vacuum: C, 41·7; H, 4·0; N, 14·7. $C_{13}H_{15}BrN_4S_2$ requires C, 42·1; H, 4·1; N, 15·1%). ^{1}H n.m.r. (free base in $CDCl_3$): δ 2·34, s, Me_2N; 2·80, t, *J* 7 Hz, CH_2N; 3·73, t, *J* 7 Hz, CH_2S; 7·75, complex, 8·05, complex, H 5,6,7,8; the hydrobromide (in D_2O): 3·08, s, Me_2N; 3·76, complex, SCH_2CH_2N; 7·82, bs, H 5,6,7,8.

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