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Heterocyclic Amplifiers of Phleomycin. III* 5-Substituted 1*H*-Imidazo[4,5-*b*]pyrazines and 6-Substituted Pyrazino[2,3-*b*]pyrazines

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Abstract

A series of 1*H*-imidazo[4,5-*b*]pyrazines has been prepared from 5-bromopyrazine-2,3-diamine and 5-bromo-3-methylaminopyrazin-2-amine with diethoxymethyl acetate, acetic anhydride or potassium ethyl xanthate; and 6-substituted pyrazino[2,3-*b*]pyrazines from 5-bromopyrazine-2,3-diamine with α,β-dicarbonyl compounds. Reactions of these compounds have been examined.

Diazomethane methylation of 5-bromo-1*H*-imidazo[4,5-*b*]pyrazine-2(3*H*)-thione gave five dimethyl derivatives which have been identified as the 1,3- and the four *N*,*S*-dimethyl derivatives.

2-Bromo-6,7-dimethylpyrazino[2,3-*b*]pyrazine with 0·4 M and 2·0 M methanolic sodium methanethiolate gave as principal products 2,3-dimethyl-6-methylthio- and 2,3-dimethyl-6,7-bismethylthiopyrazino-[2,3-*b*]pyrazines, respectively.

The 1*H*-imidazo[4,5-*b*]pyrazines showed only slight activity as amplifiers of phleomycin.

Introduction

In an earlier paper[1] the synthesis, and activity as amplifiers of phleomycin, of some derivatives of 2-hydroxy-(and 2-mercapto-)1*H*-imidazo[4,5-*b*]pyrazines was reported. This work has now been extended to a study of some derivatives of 5-bromo-1*H*-imidazo[4,5-*b*]pyrazine (1; $R^1 = R^2 = H$), 1*H*-imidazo[4,5-*b*]pyrazine-5(4*H*)-thione (2) and 6-substituted pyrazino[2,3-*b*]pyrazines, for example (3).

Syntheses

3,5-Dibromopyrazin-2-amine[2] was the starting material for the reactions described in this paper. It reacted with aqueous ammonia at 130°,[3] ethanolic methylamine at 100°, and hydrazine hydrate at 100° to give 5-bromopyrazine-2,3-diamine,[3] 5-bromo-3-methylaminopyrazin-2-amine and 5-bromo-3-hydrazinopyrazin-2-amine, respectively. 5-Bromopyrazine-2,3-diamine with diethoxymethyl acetate[4] at 140° or

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[1] Barlin, G. B., *Aust. J. Chem.*, 1982, **35**, 2299.
[2] Barlin, G. B., *Aust. J. Chem.*, 1983, **36**, 983.
[3] Camerino, B., and Palamidessi, G., *Gazz. Chim. Ital.*, 1960, **90**, 1807.
[4] Montgomery, J. A., and Fitzgibbon, W. E., in 'Nucleic Acid Chemistry' (Eds L. B. Townsend and R. S. Tipson) Part 2, p. 995 (John Wiley: New York 1978).

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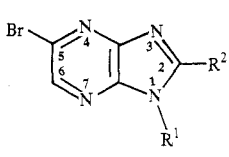
acetic anhydride at reflux gave 5-bromo-1*H*-imidazo[4,5-*b*]pyrazine (1; $R^1 = R^2 = H$) or its 2-methyl derivative (1; $R^1 = H$, $R^2 = Me$). 5-Bromo-3-methylaminopyrazin-2-amine reacted similarly to give 6-bromo-1-methyl- (4; $R^1 = Br$, $R^2 = H$) and 6-bromo-1,2-dimethyl-1*H*-imidazo[4,5-*b*]pyrazines (4; $R^1 = Br$, $R^2 = Me$), which with sodium 2-dimethylaminoethanethiolate in ethanol at reflux formed *N*,*N*-dimethyl-2-(1′-methyl-1′*H*-imidazo[4,5-*b*]pyrazin-6′-ylthio)ethylamine (4; $R^1 = SCH_2CH_2NMe_2$, $R^2 = H$) and *N*,*N*-dimethyl-2-(1′,2′-dimethyl-1′*H*-imidazo[4,5-*b*]pyrazin-6′-ylthio)ethylamine (4; $R^1 = SCH_2CH_2NMe_2$, $R^2 = Me$).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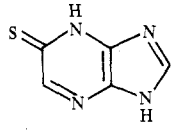
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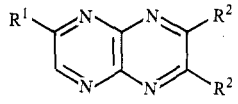
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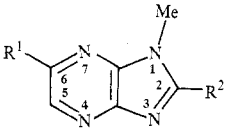
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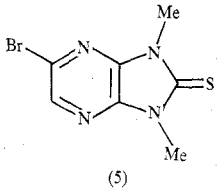
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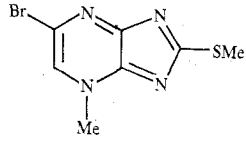
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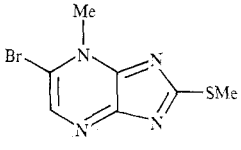
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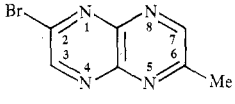
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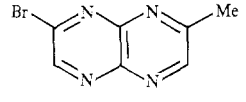
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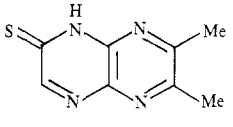
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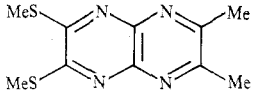
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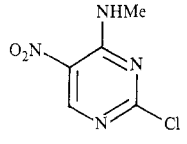
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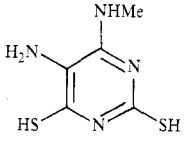
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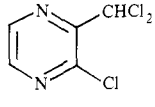
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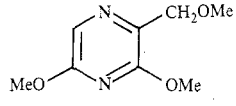
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5-Bromo-3-methylaminopyrazin-2-amine when refluxed with potassium ethyl xanthate in pyridine and the product methylated directly with diazomethane gave 5-bromo-1,3-dimethyl-1*H*-imidazo[4,5-*b*]pyrazine-2(3*H*)-thione (5) and 6-bromo-1-methyl-2-methylthio-1*H*-imidazo[4,5-*b*]pyrazine (4; $R^1 = Br$, $R^2 = SMe$). The structures of the products were established by analysis and ^1H n.m.r. spectra. The

1,3-dimethyl compound (5) gave a single methyl peak at δ 3·78 and the 1-methyl-2-methylthio compound (4; R^1 = Br, R^2 = SMe) gave peaks at δ 2·86 for the *S*-methyl group and δ 3·73 for the *N*-methyl group.

When a similar ring closure was applied to 5-bromopyrazine-2,3-diamine and the product methylated with diazomethane, five dimethylated products were obtained. These were again identified from analyses and considerations of the ^{1}H n.m.r. spectra. 5-Bromo-1,3-dimethyl-1*H*-imidazo[4,5-*b*]pyrazine-2(3*H*)-thione (5) and 6-bromo-1-methyl-2-methylthio-1*H*-imidazo[4,5-*b*]pyrazine (4; R^1 = Br, R^2 = SMe) were identical with the products isolated above. 5-Bromo-1-methyl-2-methylthio-1*H*-imidazo[4,5-*b*]pyrazine (1; R^1 = Me, R^2 = SMe) gave a *S*-methyl peak at δ 2·85 and *N*-methyl at 3·73 [similar to its *N*-methyl analogue (4; R^1 = Br, R^2 = SMe)]. 6-Bromo-4-methyl-2-methylthio-4*H*-imidazo[4,5-*b*]pyrazine (6) gave peaks at δ 2·81 and 4·19, the latter being typical of an *N*-methyl group in a six-membered ring.[5] A small amount of another product gave an ^{1}H n.m.r. spectrum with a *S*-methyl group at δ 2·81 and a *N*-methyl group at 4·29. This product was assigned the orientation 5-bromo-4-methyl-2-methylthio-4*H*-imidazo[4,5-*b*]pyrazine (7) because the methyl group on N4 adjacent to the electron-withdrawing bromo substituent was downfield of that in the 7-methyl isomer.

5-Bromopyrazine-2,3-diamine with diacetyl in ethanol formed 2-bromo-6,7-dimethylpyrazino[2,3-*b*]pyrazine (3; R^1 = Br; R^2 = Me) but similar condensations with benzil could be effected only in refluxing ethanolic hydrogen chloride, and it gave 2-ethoxy-6,7-diphenylpyrazino[2,3-*b*]pyrazine (3; R^1 = OEt; R^2 = Ph). 5-Bromopyrazine-2,3-diamine with pyruvaldehyde in ethanol at 20° gave one product only, identified from considerations of its ^{13}C n.m.r., as 2-bromo-6-methylpyrazino-[2,3-*b*]pyrazine (8). The fully coupled ^{13}C n.m.r. spectrum of the product showed doublets for both C4a and C8a, consistent with the structure 2-bromo-6-methylpyrazino[2,3-*b*]pyrazine, whereas that of the isomer, 2-bromo-7-methylpyrazino[2,3-*b*]-pyrazine (9) would be expected to show a quartet for C4a and a singlet for C8a. The fully coupled spectrum of 2-bromo-6,7-dimethylpyrazino[2,3-*b*]pyrazine (3; R^1 = Br, R^2 = Me), as expected, gave a doublet for C4a and a singlet for C8a.

2-Bromo-6,7-dimethylpyrazino[2,3-*b*]pyrazine with sodium methoxide gave 2-methoxy-6,7-dimethylpyrazino[2,3-*b*]pyrazine (3; R^1 = OMe, R^2 = Me), and with potassium hydrogen sulfide afforded the thione (10) because methylation with methyl iodide gave 2,3-dimethyl-6-methylthiopyrazino[2,3-*b*]pyrazine (3; R^1 = SMe, R^2 = Me). Alkylation of 6,7-dimethylpyrazino[2,3-*b*]pyrazine-2(1*H*)-thione (10) with 2-dimethylaminoethyl chloride (hydrochloride) gave an oil which showed the expected ^{1}H n.m.r. spectrum. The product (like 2,3-dimethyl-6-methylthiopyrazino[2,3-*b*]-pyrazine) darkened considerably in the air. It decomposed on addition of ethanolic hydrogen bromide and was not pursued further for identification or biological testing.

Treatment of 2-bromo-6,7-dimethylpyrazino[2,3-*b*]pyrazine (3; R^1 = Br, R^2 = Me) with 0·4 M sodium methylmercaptide in methanol at 20° gave 2,3-dimethyl-6-methylthiopyrazino[2,3-*b*]pyrazine (3; R^1 = SMe, R^2 = Me) as a major product, but with 2 M sodium methylmercaptide the bromo compound gave instead 2,3-dimethyl-6,7-bismethylthiopyrazino[2,3-*b*]pyrazine (11). (The last compound was not formed when 2,3-dimethyl-6-methylthiopyrazino[2,3-*b*]pyrazine was treated with methanolic 2 M sodium methylmercaptide.)

[5] Barlin, G. B., and Fenn, M. D., *Aust. J. Chem.*, 1983, **36**, 633.

Anomalous substitution products have been reported in the reaction of *N*-methyl-2-chloro-5-nitropyrimidin-4-amine (12) with sodium hydrogen sulfide[6] which formed not only the expected 5-amino-4-methylaminopyrimidin-2(1*H*)-thione but also 5-amino-6-methylaminopyrimidin-2,4-(1*H*,3*H*)-dithione[6] (13); in the reaction of 2-chloro-3-dichloromethylpyrazine[2] (14) with 3 equiv. of methoxide ions to give 2,6-dimethoxy-3-methoxymethylpyrazine[7] (15); and in the reaction of 2-trichloromethylpyrazine[7] with 3 equiv. of methoxide ions to give 2-dimethoxymethyl-5-methoxypyrazine, 2,3,5-trimethoxy-6-methylpyrazine and 2,3-dimethoxy-5-methoxymethylpyrazine.[7] Tetraazanaphthalenes are also known to form covalent adducts.[8]

Biological Activities

N,*N*-Dimethyl-2-(1′-methyl-1′*H*-imidazo[4,5-*b*]pyrazin-6′-ylthio)ethylamine (4; $R^1 = SCH_2CH_2NMe_2$, $R^2 = H$) and *N*,*N*-dimethyl-2-(1′,2′-dimethyl-1′*H*-imidazo-[4,5-*b*]pyrazin-6′-ylthio)ethylamine (4; $R^1 = SCH_2CH_2NMe_2$, $R^2 = Me$) were tested as amplifiers of phleomycin at 3·3 mM as outlined previously.[9] Both showed a low activity of one star only, comparable to that shown by 1-methyl-2-methylthio-1*H*-imidazo[4,5-*b*]pyrazine and *N*,*N*-dimethyl(1′*H*-imidazo[4,5-*b*]pyrazin-2′-ylthio)ethylamine.[1]

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. ^{1}H n.m.r. spectra were recorded at 90 MHz and 30° with a Jeol FX90Q Fourier transform spectrometer with tetramethylsilane [in $CDCl_3$ and $(CD_3)_2SO$] as internal standard.

5-Bromo-3-methylaminopyrazin-2-amine

3,5-Dibromopyrazin-2-amine[2] (0·3 g) and ethanolic methylamine (7·0 ml; 33%) were heated in an autoclave at 100° for 17 h, then evaporated to dryness under reduced pressure. The oily residue was dissolved in a little ethanol, and a portion treated with a little concentrated sulfuric acid. On chilling, a crystalline solid separated and was collected and was recrystallized from warm ethanol to give *5-bromo-3-methylaminopyrazin-2-amine*, m.p. 193° (Found: N, 18·9. $C_5H_9BrN_4O_4S$ requires N, 18·6%).

5-Bromo-3-hydrazinopyrazin-2-amine

A mixture of 3,5-dibromopyrazin-2-amine[2] (0·15 g) in water (16·0 ml) with hydrazine hydrate (0·2 ml) was warmed on a steam bath for 1·25 h. (T.l.c. showed some unchanged dibromopyrazine.) The mixture was chilled and the dark solid filtered off, washed well with water and dried at 20° to give *5-bromo-3-hydrazinopyrazin-2-amine* (0·030 g) which decomposed without melting (Found: C, 23·3; H, 2·6; N, 34·4. $C_4H_6BrN_5$ requires C, 23·5; H, 3·0; N, 34·3%).

*5-Bromo-1*H*-imidazo[4,5-*b*]pyrazine* (*1*; $R^1 = R^2 = H$)

5-Bromopyrazine-2,3-diamine[3] (0·15 g) and diethoxymethyl acetate (2·0 ml; Aldrich) were heated in an oil bath at 143° for 3 h, then evaporated to dryness under reduced pressure. The oily

[6] Brown, D. J., *J. Appl. Chem.*, 1957, **7**, 109.
[7] Grabowski, E. J. J., Tristram, E. W., Tull, R., and Pollak, P. I., *Tetrahedron Lett.*, 1968, 5931.
[8] Armarego, W. L. F., *J. Chem. Soc.*, 1963, 4304.
[9] Brown, D. J., Buttler, B. B., Cowden, W. B., Grigg, G. W., Kavulak, D., and Podger, D. M., *Aust. J. Chem.*, 1981, **34**, 2423.

product was dissolved in aqueous sodium hydroxide by warming briefly on a steam bath. After cooling, the mixture was adjusted by addition of acetic acid to pH 6, and the solid (0·156 g) filtered off and washed with water. It was recrystallized from water with charcoal filtration to give *5-bromo-1*H-*imidazo*[*4,5*-b]*pyrazine*, m.p. 196–198° (Found: C, 30·1; H, 1·6; N, 28·2. $C_5H_3BrN_4$ requires C, 30·2; H, 1·5; N, 28·1%). ^{1}H n.m.r. [$(CD_3)_2SO$]: δ 8·48, s, H2; 8·72, s, H6.

*5-Bromo-2-methyl-1*H-*imidazo*[*4,5*-b]*pyrazine* (*1*; $R^1 = H$, $R^2 = Me$)

5-Bromopyrazine-2,3-diamine (0·1 g) and acetic anhydride (2·0 ml) were refluxed for 2 h, then evaporated to dryness under reduced pressure. The residue was dissolved in 1 M sodium hydroxide by warming gently, and the mixture adjusted with acetic acid to pH 5 to give a whitish precipitate. This product was recrystallized from water with charcoal filtration to give *5-bromo-2-methyl-1*H-*imidazo*[*4,5*-b]*pyrazine* (0·033 g), m.p. 285–287° (dec.) (Found: C, 33·7; H, 2·3; N, 26·1. $C_6H_5BrN_4$ requires C, 33·8; H, 2·3; N, 26·3%). ^{1}H n.m.r. [$(CD_3)_2SO$]: δ 2·59, s, 2-Me; 8·43, s, H6.

*6-Bromo-1-methyl-1*H-*imidazo*[*4,5*-b]*pyrazine* (*4*; $R^1 = Br$, $R^2 = H$)

Crude 5-bromo-3-methylaminopyrazin-2-amine (from 0·2 g 3,5-dibromopyrazin-2-amine with ethanolic methylamine at 100° for 17 h) and diethoxymethyl acetate (2·5 ml) were refluxed for 3·5 h. The mixture was evaporated under reduced pressure and the product subjected to t.l.c. (silica; chloroform) and recrystallized from cyclohexane to give *6-bromo-1-methyl-1*H-*imidazo*-[*4,5*-b]*pyrazine* (0·92 g), m.p. 156·5–157° (Found: C, 33·8; H, 2·4; N, 26·7. $C_6H_5BrN_4$ requires C, 33·8; H, 2·4; N, 26·3%). ^{1}H n.m.r. ($CDCl_3$): δ 3·99, s, 1-Me; 8·45, s, H2; 8·56, s, H5.

*6-Bromo-1,2-dimethyl-1*H-*imidazo*[*4,5*-b]*pyrazine* (*4*; $R^1 = Br$, $R^2 = Me$)

Crude 2-amino-5-bromo-3-methylaminopyrazine (from 5·0 g 2-amino-3,5-dibromopyrazine with ethanolic methylamine at 100° for 17 h), acetic anhydride (20 ml) and triethyl orthoacetate (20 ml) were refluxed for 48 h. The mixture was evaporated to dryness under reduced pressure, then evaporated with ethanol, and the product was chromatographed in chloroform over alumina (25 cm by 5 cm diameter). The material in the early fractions was recrystallized from cyclohexane to give *6-bromo-1,2-dimethyl-1*H-*imidazo*[*4,5*-b]*pyrazine* (0·856 g), m.p. 167–168° (Found: C, 37·3; H, 3·1; N, 24·2. $C_7H_7BrN_4$ requires C, 37·0; H, 3·1; N, 24·7%). ^{1}H n.m.r. ($CDCl_3$): δ 2·69, s, 2-Me; 3·82, s, 1-Me; 8·47, s, H5.

N,N-*Dimethyl-2-*(*1'-methyl-1'*H-*imidazo*[*4,5*-b]*pyrazin-6'-ylthio*)*ethylamine*
(*4*; $R^1 = SCH_2CH_2NMe_2$, $R^2 = H$)

6-Bromo-1-methyl-1*H*-imidazo[4,5-*b*]pyrazine (0·50 g), 2-dimethylaminoethanethiol hydrochloride (2·5 g) and ethanolic sodium ethoxide (from 0·83 g sodium and 50 ml ethanol) were warmed briefly to dissolve the bromo compound and allowed to stand at 20° for 72 h. The mixture was diluted with water and extracted with chloroform to give an oil which was chromatographed in chloroform over alumina (30 cm by 2·5 cm diameter). The product crystallized from light petroleum (b.p. 60–80°) to give N,N-*dimethyl-2-*(*1'-methyl-1'*H-*imidazo*-[*4,5*-b]*pyrazin-6'-ylthio*)*ethylamine* (0·444 g), m.p. 88–90° (Found: for material dried at 20° for 6 h over phosphorus pentoxide: C, 50·6; H, 6·3; N, 29·3. $C_{10}H_{15}N_5S$ requires C, 50·6; H, 6·4; N, 29·5%). ^{1}H n.m.r. ($CDCl_3$): δ 2·33, s, Me_2N; 2·67, t, *J* 7 Hz, CH_2N; 3·39, t, *J* 7 Hz, CH_2S; 3·89, s, 1'-Me; 8·11, s, H2; 8·40, s, H5'.

N,N-*Dimethyl-2-*(*1',2'-dimethyl-1'*H-*imidazo*[*4,5*-b]*pyrazin-6'-ylthio*)*ethylamine*
(*4*; $R^1 = SCH_2CH_2NMe_2$, $R^2 = Me$)

A mixture of 6-bromo-1,2-dimethyl-1*H*-imidazo[4,5-*b*]pyrazine (0·40 g), 2-dimethylaminoethanethiol hydrochloride (2·0 g) and ethanolic sodium ethoxide (from 0·76 g sodium and 50 ml ethanol) was refluxed for 1·75 h. The ethanol was evaporated, the residue diluted with water, and extracted with chloroform and the product chromatographed in chloroform over alumina (25 cm by 2·5 cm diameter). The oil obtained was treated with 10% ethanolic hydrogen bromide and then ether to give N,N-*dimethyl-2-*(*1',2'-dimethyl-1'*H-*imidazo*[*4,5*-b]*pyrazin-6'-ylthio*)*ethylamine*

1·9 hydrobromide (0·580 g), m.p. 242–244° (from methanol/ether) (Found: C, 32·5; H, 4·9. $C_{11}H_{17}N_5S.1·9HBr$ requires C, 32·6; H, 4·7%). ^1H n.m.r. of free base ($CDCl_3$): δ 2·32, s, Me_2N; 2·64, s, 2′-Me; 2·70, t, *J* 7 Hz, CH_2N; 3·35, t, *J* 7 Hz, CH_2S; 3·78, s, 1′-Me; 8·28, s, H5. HBr (in D_2O): δ 2·88, s, 2′-Me; 3·00, s, Me_2N; 3·65, complex, SCH_2CH_2N; 3·96, s, 1′-Me; 8·54, s, H5.

6-Bromo-1-methyl-2-methylthio-1H-imidazo[4,5-b]pyrazine (*4*; R^1 = Br, R^2 = *SMe*) *and 5-Bromo-1,3-dimethyl-1H-imidazo[4,5-b]pyrazine-2(3H)-thione* (*5*)

Crude 5-bromo-3-methylaminopyrazine-2-amine (from 0·2 g 3,5-dibromopyrazin-2-amine with ethanolic methylamine at 100° for 17 h) and potassium ethyl xanthate (1·0 g) in pyridine (3·0 ml) were refluxed for 12 h. The mixture was evaporated to dryness under reduced pressure, then evaporated twice with water, the residue acidified with dilute hydrochloric acid, then adjusted with 1 M sodium hydroxide to pH 5 and evaporated to dryness.

The residue was broken up, suspended in ethanol (10 ml) and ethereal diazomethane (from 3·1 g nitrosomethylurea) added with swirling and the mixture allowed to stand for 1 h. This mixture was evaporated to near dryness, the residue extracted with chloroform (twice) and the product obtained subjected to t.l.c. (alumina, chloroform).

The band at higher R_F was extracted with chloroform and the product crystallized from cyclohexane with charcoal filtration to give *5-bromo-1,3-dimethyl-1H-imidazo[4,5-b]pyrazine-2(3H)-thione* (0·003 g), m.p. 177–178° (Found: C, 32·7; H, 2·6; N, 21·4. $C_7H_7BrN_4S$ requires C, 32·4; H, 2·7; N, 21·6%). ^1H n.m.r. ($CDCl_3$): δ 3·78, s, 1,3-Me_2; 8·21, s, H6.

The band at lower R_F after extraction with chloroform and recrystallization of the product from cyclohexane with charcoal filtration gave *6-bromo-1-methyl-2-methylthio-1H-imidazo[4,5-b]pyrazine* (0·002 g), m.p. 160·5–161° (Found: C, 32·4; H, 2·7; N, 21·5%). ^1H n.m.r. ($CDCl_3$) δ 2·86, s, MeS; 3·73, s, 1-Me; 8·44, s, H5.

5-Bromopyrazine-2,3-diamine with Potassium Ethyl Xanthate Followed by Diazomethane

A mixture of 5-bromopyrazine-2,3-diamine (0·5 g) and potassium ethyl xanthate (2·5 g) in pyridine (7·5 ml) was refluxed for 24 h. The mixture was evaporated to dryness under reduced pressure and the residue evaporated twice with water. The residue was diluted with water, acidified with 10 M hydrochloric acid, then adjusted with 1 M potassium hydroxide to pH 5, and the solution evaporated to dryness. The residue was broken up, suspended in ethanol (25 ml), swirled as ethereal diazomethane solution (from 6·18 g nitrosomethylurea) was added, and the mixture allowed to stand at 20° for 3 days.

The reaction mixture was evaporated to dryness and extracted with chloroform to give a product (0·673 g) which was subjected initially to t.l.c. (alumina; chloroform).

The bands at lower R_F were subjected to further separation in the same system and those at higher R_F to further t.l.c. (alumina; benzene). The following products were obtained in order of decreasing R_F: 5-Bromo-1,3-dimethyl-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-thione (5) (0·011 g), m.p. 177–178° (from cyclohexane), identical with the product obtained above. *5-Bromo-1-methyl-2-methylthio-1H-imidazo[4,5-b]pyrazine* (1; R^1 = Me, R^2 = SMe) (0·038 g), m.p. 158–159° (from cyclohexane) (Found: C, 32·7; H, 2·75; N, 21·5%). ^1H n.m.r. ($CDCl_3$): δ 2·85, s, MeS; 3·73, s, 1-Me; 8·23, s, H6. 6-Bromo-1-methyl-2-methylthio-1*H*-imidazo[4,5-*b*]pyrazine (4; R^1 = Br, R^2 = SMe) (0·087 g), m.p. 158·5–159° (from cyclohexane), identical with the product obtained above. *6-Bromo-4-methyl-2-methylthio-4H-imidazo[4,5-b]pyrazine* (6) (0·027 g), m.p. 220–221° (from benzene) (Found: C, 32·5; H, 2·7; N, 21·2%). ^1H n.m.r. ($CDCl_3$): δ 2·81, s, MeS; 4·19, s, 4-Me; 7·49, s, H5.

A small amount of another product (0·002 g), m.p. 163–163·5° (from benzene), was also obtained at slightly higher R_F than the last named compound from t.l.c. (alumina; twice developed with chloroform). The ^1H n.m.r. ($CDCl_3$): δ 2·81, s, MeS; 4·29, s, 4-Me; 8·23, s, H6, indicated by comparison with its isomers that it may be 5-bromo-4-methyl-2-methylthio-4*H*-imidazo[4,5-*b*]-pyrazine (7).

2-Bromo-6,7-dimethylpyrazino[2,3-b]pyrazine (*3*; *R* = *Br*)

5-Bromopyrazine-2,3-diamine[3] (0·5 g) and diacetyl (0·6 g) in ethanol (50 ml) were allowed to stand at 20° for 16 h. The ethanol was evaporated at 40–50° and 20 mmHg, and the product

recrystallized from light petroleum (b.p. 40–60°) with charcoal filtration to give *2-bromo-6,7-dimethylpyrazino[2,3-b]pyrazine* (0·487 g), m.p. 115–116° (Found: C, 40·4; H, 3·1; N, 23·1. $C_8H_7BrN_4$ requires C, 40·2; H, 2·95; N, 23·4%). ^1H n.m.r. ($CDCl_3$): δ 2·84, s, 2·85, s, 6,7-Me_2; 9·03, s, H3. ^{13}C n.m.r. ($CDCl_3$): δ 23·43, 6,7-Me_2; 141·45, C2; 143·51, C4a; 144·46, C8a; 150·14, C3; 158·97, C7; 159·76, C6.

2-Ethoxy-6,7-diphenylpyrazino[2,3-b]pyrazine (*3*; *R* = *OEt*)

A mixture of 5-bromopyrazine-2,3-diamine (0·040 g), benzil (0·100 g) and ethanolic hydrogen chloride (3·0 ml; 2 M) was refluxed for 10 h. The solvent was evaporated and the residue diluted with water, made alkaline with sodium hydroxide solution and extracted with chloroform. The product was subjected to t.l.c. (alumina; chloroform, and alumina; benzene) which separated unchanged benzil at higher R_F, and the product at lower R_F was recrystallized from cyclohexane to give yellow crystals of *2-ethoxy-6,7-diphenylpyrazino[2,3-b]pyrazine* (0·003 g), m.p. 233–234° (Found: C, 73·6; H, 5·0. $C_{20}H_{16}N_4O$ requires C, 73·2; H, 4·9%). ^1H n.m.r. ($CDCl_3$): δ 1·53, t, *J* 5·5 Hz, CH_3CH_2; 4·71, q, *J* 5·5 Hz, CH_3CH_2; 7·37, complex, 6,7-Ph_2; 8·73, s, H3.

2-Bromo-6-methylpyrazino[2,3-b]pyrazine (*8*)

2,3-Diamino-5-bromopyrazine (0·3 g) and pyruvaldehyde (0·6 g) in ethanol (75 ml) was allowed to stand at 20° for 16 h. It was then evaporated to dryness on the rotary evaporator at 20° and the product subjected to t.l.c. (alumina; chloroform) and recrystallized from cyclohexane to give *2-bromo-6-methylpyrazino[2,3-b]pyrazine* (0·214 g), m.p. *c.* 170° (with darkening from 160°) (Found: C, 37·5; H, 2·2; N, 25·1. $C_7H_5BrN_4$ requires C, 37·4; H, 2·2; N, 24·9%). ^1H n.m.r. ($CDCl_3$): δ 2·91, s, 6-Me; 9·01, s, H7; 9·11, s, H3. ^{13}C n.m.r. ($CDCl_3$): δ 22·78, 6-Me; 141·83, C2; 144·32, C4a; 144·43, C8a; 150·58, C7; 151·44, C3; 159·30, C6.

2-Methoxy-6,7-dimethylpyrazino[2,3-b]pyrazine (*3*; R^1 = *OMe*, R^2 = *Me*)

A mixture of 2-bromo-6,7-dimethylpyrazino[2,3-*b*]pyrazine (0·050 g) and methanolic sodium methoxide (2·0 ml; 0·136 M) was allowed to stand at 20° for 2·5 h, then diluted with water and adjusted with dilute hydrochloric acid to pH 5·4. The mixture was evaporated to dryness under reduced pressure, the residue extracted with chloroform, and the product subjected to t.l.c. (alumina; chloroform) and recrystallized from light petroleum (b.p. 60–80°) to give *2-methoxy-6,7-dimethylpyrazino[2,3-b]pyrazine* (0·020 g), m.p. 108–110° (Found: for sample dried at 90° for 30 min: C, 56·4; H, 5·3; N, 29·2. $C_9H_{10}N_4O$ requires C, 56·8; H, 5·3; N, 29·5%). ^1H n.m.r. ($CDCl_3$): δ 2·78, s, 2·80, s, 6,7-Me_2; 4·20, s, MeO; 8·64, s, H3.

2,3-Dimethyl-6-methylthiopyrazino[2,3-b]pyrazine (*3*; R^1 = *SMe*, R^2 = *Me*)

(A) 2-Bromo-6,7-dimethylpyrazino[2,3-*b*]pyrazine (0·050 g) and methanolic potassium hydrogen sulfide (2·5 ml; 0·47 M) were allowed to stand at 20° for 16 h, the mixture acidified with dilute hydrochloric acid and evaporated to dryness. The residue was dissolved in aqueous sodium hydroxide and shaken with methyl iodide (0·2+0·1 ml) for 10 min. The reaction mixture was extracted with chloroform and the product subjected to t.l.c. (alumina; chloroform and silica; ethyl acetate) and recrystallized from light petroleum (b.p. 60–80°) to give *2,3-dimethyl-6-methylthiopyrazino[2,3-b]pyrazine* (0·019 g), m.p. 107–108° (Found, for sample dried at 20° and 20 mmHg for 3 h: C, 52·9; H, 4·9; N, 27·0. $C_9H_{10}N_4S$ requires C, 52·4; H, 4·9; N, 27·2%). ^1H n.m.r. ($CDCl_3$): δ 2·78, s, 2·79, s, 2,3-Me_2; 2·81, s, MeS; 8·77, s, H7.

(B) A mixture of 2-bromo-6,7-dimethylpyrazino[2,3-*b*]pyrazine (0·020 g) and methanolic sodium methoxide (2·5 ml; 0·4 M), in which had been absorbed methanethiol (0·129 g), was allowed to stand at 20° for 1·25 h. It was then diluted with water, adjusted with dilute hydrochloric acid to pH 6·8 and evaporated under reduced pressure. The residue was extracted with chloroform and the ^1H n.m.r. in $CDCl_3$ showed it to consist mostly of 2,3-dimethyl-6-methylthiopyrazino[2,3-*b*]-pyrazine, identical with that obtained in (A).

Alkylation of 6,7-Dimethylpyrazino[2,3-b]pyrazine-2(1H)-thione (10) with Dimethylaminoethyl Chloride

Crude 6,7-dimethylpyrazino[2,3-*b*]pyrazine-2(1*H*)-thione (prepared as in Method A, for 2,3-dimethyl-6-methylthiopyrazino[2,3-*b*]pyrazine) was alkylated in dilute aqueous sodium hydroxide

by shaking with 2-chloro-*N,N*-dimethylethylamine (hydrochloride). The product was extracted with chloroform and purified by t.l.c. (alumina; chloroform) to give an oil showing the expected ^{1}H n.m.r. ($CDCl_3$): δ 2·33, s, Me_2N; 2·79, s, 2·81, s, 6,7-Me_2; 2·74, t, J 7 Hz, CH_2N; 3·59, t, CH_2S; 8·75, s, H 3 which decomposed on treatment with ethanolic hydrogen bromide.

Similar behaviour was observed with the 6-(3′-dimethylaminopropyl)thio analogue.

*2,3-Dimethyl-6,7-bis(methylthio)pyrazino[2,3-*b*]pyrazine*

Methanethiol was passed into an ice-cold solution of methanolic sodium methoxide (2·0 ml; 2 M) until the weight gain was 0·5 g. 2-Bromo-6,7-dimethylpyrazino[2,3-*b*]pyrazine (0·050 g) was added and the mixture was allowed to stand at 20° for 4 h. It was diluted with water, adjusted with hydrochloric acid to pH 7·2 and evaporated to dryness. The residue was extracted with chloroform and the crude product subjected to t.l.c. (alumina; chloroform) and recrystallized from cyclohexane to give *2,3-dimethyl-6,7-bis(methylthio)pyrazino[2,3-*b*]pyrazine* (0·010 g), m.p. 240–242° (Found: C, 47·2; H, 4·7; N, 21·9. $C_{10}H_{12}N_4S_2$ requires C, 47·6; H, 4·8; N, 22·2%). ^{1}H n.m.r. ($CDCl_3$): δ 2·77, s, 2·80, s, 2,3-Me_2, 6,7-$(MeS)_2$. The ^{1}H n.m.r. of the crude product indicated the presence of traces of 2,3-dimethyl-6-methylthiopyrazino[2,3-*b*]pyrazine. 2,3-Dimethyl-6-methylthiopyrazino[2,3-*b*]pyrazine (0·004 g) with methanolic sodium methanethiolate (0·5 ml; sample prepared above) at 20° for 4 h did not give any 2,3-dimethyl-6,7-bis(methylthio)pyrazino-[2,3-*b*]pyrazine.

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