THE SYNTHESIS OF PYRROLO[1,2-*a*]PYRAZIN-1(2*H*)-ONES AND PYRROLO[1,2-*b*]PYRIDAZIN-6(5*H*)-ONES

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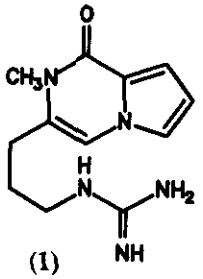
Abstract

The pyrrolo[1,2-*a*]pyrazin-1(2*H*)-ones (10), (11), (12) and (13) and the pyrrolo[1,2-*b*]pyridazin-6(5*H*)-one (18) were prepared either a) directly by Chichibabin quaternisation-cyclisation of the corresponding methoxymethylpyrazine or pyridazine or b) by hydrogen halide hydrolysis of methoxypyrrolo[1,2-*a*]pyrazines and methoxypyrrolo[1,2-*b*]pyridazines. Protonation studies and some reactivity of the systems are discussed.

INTRODUCTION

Pyrrolo[1,2-*b*]pyridazinone,[1] pyrrolo[1,2-*a*]pyrazinone, pyrrolo[1,2-*a*]pyrimidinone and pyrrolo[1,2-*c*]pyrimidinone can all be considered as azaindolizinones where an amide function is incorporated into the six membered ring of the indolizine system. These systems are of interest due to their association with biologically active molecules .[2] For example they are isoelectronic with and isosterically resemble the purine base guanine.[3] In addition, derivatives of the pyrrolo[1,2-*a*]pyrimidinone system have been investigated[4] due to their similarity to the 10 π quinolone antibacterial agents. More recently, interest has been focussed on the synthesis of the pyrrolo[1,2-*a*]pyrazin-1(2*H*)-one system because it is the heterocyclic framework of the natural insect feeding deterrent, peramine (1).[5] The most common synthetic route to pyrrolo[1,2-*a*]pyrazine and pyrrolo[1,2-*b*]pyridazines is by the Chichibabin quaternisation of an α-methyldiazine with an α-haloketone, followed by base cyclisation.[6] A similar Chichibabin procedure has been utilised to obtain pyrrolo[1,2-*a*]pyrimidinones and pyrrolo[1,2-*c*]pyrimidinones from hydroxy and methoxy derivatised pyrimidines.[7] In this paper we report the application of the Chichibabin quaternisation-cyclisation to the synthesis of

pyrrolo[1,2-*a*]pyrazin-1(2*H*)-ones (2) and pyrrolo[1,2-*b*]pyridazin-6(5*H*)-ones (3).



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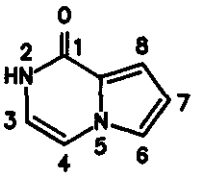

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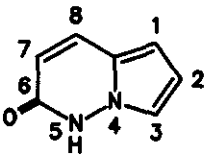
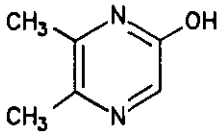


(3)

RESULTS AND DISCUSSION

Initially, it was attempted to prepare the desired pyrrolo[1,2-*a*]pyrazinone system by the quaternisation of the hydroxypyrazine (4) with an α-haloketone followed by cyclisation by base. However, despite using a variety of α-haloketones and quaternising conditions this direct approach was unsuccessful due to the failure of the pyrazine to quaternise.



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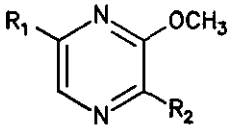
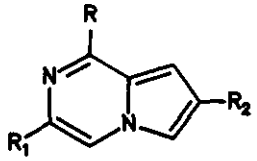
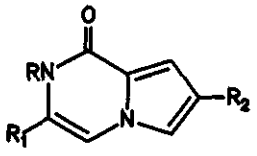


(5) R_1=H, R_2=CH_3
(6) R_1=R_2=CH_3

A second approach involved using the methoxy(methyl) pyrazines (5) and (6)[8]; these readily reacted with bromoacetone to give quaternary salts. These salts, when refluxed in dilute sodium bicarbonate, gave, in addition to the expected cyclisation products 1-methoxy-7-methylpyrrolo[1,2-*a*]pyrazine (7) and 3,7-dimethyl-1-methoxypyrrolo[1,2-*a*]pyrazine (8) small quantities of 7-methylpyrrolo[1,2-*a*]pyrazin-1(2*H*)-one (10) and 3,7-dimethylpyrrolo[1,2-*a*]pyrazin-1(2*H*)-one (11) respectively.



(7) R=OCH_3, R_1=H, R_2=CH_3
(8) R=OCH_3, R_1=R_2=CH_3
(9) R=OCH_3, R_1=CH_3, R_2=Ph
(27) R=Cl, R_1=H, R_2= CH_3
(28) R=NH_2, R_1=H, R_2=CH_3
(29) R=Cl, R_1=CH_3, R_2=Ph

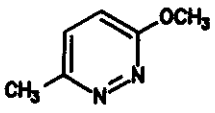


(10) R=R_1=H, R_2=CH_3
(11) R=H, R_1=R_2=CH_3
(12) R=H, R_1=CH_3, R_2=Ph
(13) R=R_1=CH_3, R_2=Ph

On reflux with aqueous hydrochloric acid the methoxymethylpyrrolo[1,2-*a*]pyrazines (7) and (8) were readily hydrolysed to the corresponding pyrrolo[1,2-*a*]pyrazin-1(2*H*)-ones (10) and (11). Similarly, when 3,6-dimethyl-2-methoxypyrazine (6) was quaternised with phenacyl bromide and then treated with dilute aqueous sodium bicarbonate it gave as the major product 1-methoxy-3-methyl-7-phenylpyrrolo[1,2-*a*]-pyrazine (9) which could be hydrolysed to 3-methyl-7-phenylpyrrolo[1,2-*a*]pyrazin-1(2*H*)-one (12). Cyclisation, however, with a more concentrated sodium bicarbonate solution at room temperature gave an orange precipitate which was shown to be mainly the isomeric 2,3- dimethyl-7-phenylpyrrolo[1,2-*a*]pyrazin-1(2*H*)-one (13). The formation of **13** is envisaged to arise by rearrangement[9] of the quaternary salt (14) to the *N*-methylpyrazinone (15) prior to cyclisation.

The two isomers (9) and (13), although showing similar ^{1}H-nmr spectral patterns differed most significantly in the chemical shift of their methyl signals; the lowest field methyl of the former occurred at δ 4.06 whereas for the latter it occurred at higher field at δ 3.38.[7] Reflux of the aqueous solution from which **13** was isolated gave a buff coloured precipitate which was identified as the previously isolated 3-methyl-7-phenylpyrrolo-[1,2-*a*]pyrazin-1(2*H*)-one (12).

When 3-methoxy-6-methylpyridazine (16), obtained by methoxylation of 3-chloro-6-methylpyridazine[10] was subjected to Chichibabin quaternisation-cyclisation with bromoacetone it gave solely 6-methoxy-2-methyl-pyrrolo[1,2-*b*]pyridazine (17).



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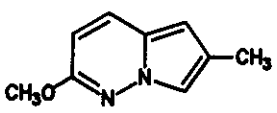

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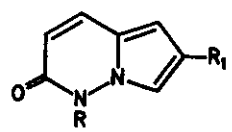
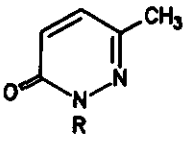
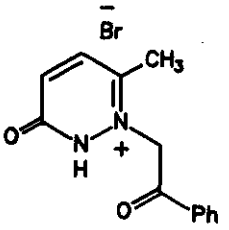


(18) R=H, R_1=CH_3
(19) R_1=Ph

Only after prolonged reflux with aqueous hydrobromic acid was **17** converted to the pyrrolo[1,2-*b*]pyridazin-6(5*H*)-one (18). Thus, the methyl ether linkage of 6-methoxypyridazine is considerably more resistant to cleavage than the ether linkage of the 1-methoxypyrrolo[1,2-*a*]pyrazines (7), (8) and (9). Attempts to synthesise the pyrrolo[1,2-*b*]pyridazin-6(5*H*)-one (19, R=H) more directly by reacting 6-methylpyridazin-3(2*H*)-one (20) with phenacyl bromide was unsuccessful. The reaction did not lead to isolation of the quaternary salt (23) but gave the neutral *N*-phenacylpyridazinone (21). When **20** was treated with methyl iodide it similarly gave the *N*-methylpyridazinone (22) which could not be converted to the *N*-methylpyrrolo[1,2-*b*]pyridazinone (19, R=Me) by subsequent α-haloketone quaternisation-cyclisation.

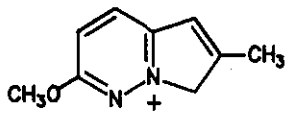


(20) R=H
(21) R=CH_2COPh
(22) R=CH_3



(23)

The methoxypyrrolo[1,2-*b*]pyridazine and methoxypyrrolo[1,2-*a*]pyrazine systems as represented by **17** and **7** and the pyrrolo[1,2-*b*]pyridazinone and pyrrolo[1,2-*a*]pyrazinone systems (18) and (10) respectively showed contrasting protonation and deuterium exchange patterns. A comparison of the $CDCl_3$ and *CF_3COOH spectra of the methoxypyrrolo[1,2-b]pyridazine* (17), besides showing in the latter a downfield shift of corresponding signals, more significantly showed the emergence of a 2H methylene singlet at δ 3.90 and the disappearance of the signal ascribed to H-3. This suggests **17** to C-3 protonate to give the conjugate acid (24).[11] A similar comparison of the $CDCl_3$ and CF_3COOH spectra of the 1-methoxypyrrolo[1,2-*a*]-pyrazine (7) showed, in the latter, no 2H methylene signal but merely a downfield shift of the spectral pattern suggesting *N*-protonation to occur.[12]



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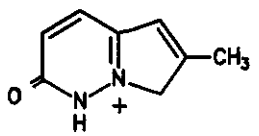

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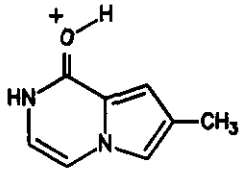
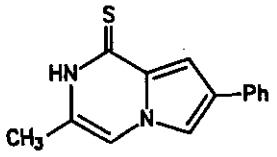


(26)

When the $CDCl_3$ and CF_3COOH spectra of the pyrrolo[1,2-*b*]pyridazinone (18) were compared the CF_3COOH spectra again showed an overall downfield shift of signals; the disappearance of the H-3 signal and the emergence of a 2H methylene signal. In contrast, the pyrrolo[1,2-*a*]pyrazinone (10) showed little change other than a downfield shift of signals for the CF_3COOH spectrum relative to the corresponding signals of the $CDCl_3$ spectrum. Thus protonation is inferred to occur at C-3 in the pyrrolo[1,2-*b*]pyridazinone (18) to give the conjugate acid cation (25), whereas in the pyrrolo[1,2-*a*]pyrazinones it is inferred to occur on the exocyclic carbonyl oxygen to give the resonance stabilised cation (26). Deuterium exchange studies on the methoxypyrrolo[1,2-*b*]pyridazine (17), methoxypyrrolo[1,2-*a*]pyrazine (7), pyrrolo[1,2-*b*]pyridazinone (18) and pyrrolo[1,2-*a*]pyrazinone (10) support the above conclusions. Thus, the $CDCl_3$ solution of the pyrrolo[1,2-*b*]pyridazines (17) and (18) when triturated with CF_3COOD were shown from their ^{1}H-nmr spectrum to differentially exchange their H-3 signals, whereas the pyrrolo[1,2-*a*]pyrazines (7) and (10) showed no such deuterium exchange.

The 7-methylpyrrolo[1,2-*a*]pyrazin-1(2*H*)-one (10), when treated with phosphoryl chloride yielded the 1-chloro-7-methylpyrrolo[1,2-*a*]pyrazine (27).[13] This chlorine was found to be readily displaceable, by using aqueous ammonia to give the 1-aminopyrrolo[1,2-*a*]pyrazine (28) and by sodium methoxide to give the 1-methoxypyrrolo[1,2-*a*]pyrazine (7). In addition 1-chloro-3-methyl-7-phenylpyrrolo[1,2-*a*]pyrazine (29) was easily converted to 3-methyl-7-phenylpyrrolo[1,2-*a*]pyrazin-1(2*H*)-thione (30) using thiourea.[14] The pyrrolo[1,2-*a*]pyrazin-1(2*H*)-thione (30) could alternatively be prepared directly from the pyrrolo[1,2-*a*]-pyrazin-1(2*H*)-one (12) using Lawesson's reagent.[15] In contrast, attempts to synthesise the corresponding pyrrolo[1,2-*b*]pyridazin-6(5*H*)-thione (31) from **18** using Lawesson's reagent were unsuccessful as were attempts to chlorinate **18** using phosphoryl chloride.



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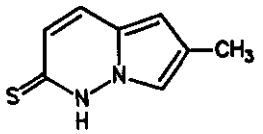

(31)

EXPERIMENTAL

Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. Ultraviolet light absorption data refers to solutions in ethanol unless otherwise stated and were measured using a Perkin Elmer Lambda 2 spectrophotometer and 10 mm silica cells. Inflections and shoulders are given in parenthesis. Infrared spectra were recorded with a Perkin Elmer 781 or a Nicolet 5ZDXFT-IR spectrophotometer and are for nujol mulls unless otherwise stated. ^{1}H-Nmr spectra refer to solutions in deuteriochloroform unless otherwise stated and were recorded on a Perkin Elmer RB12B using tetramethylsilane as internal standard. Values given are on the δ scale (TMS = δ 0.00) and refer to singlet absorptions unless otherwise stated. Approximate coupling constants are in Hertz. Integration values and signal assignments are in parenthesis. For multiplets d = doublet, dd = double doublet, t = triplet, q = quartet and m = complex multiplet. Signals marked with an asterix are broadened and/or weakly split. Mass spectroscopic data were obtained from a VG 70-250SE spectrometer. Mass data and elemental analysis were performed by the analytical laboratories of ICI Pharmaceuticals Division.

Reaction between 2-methoxy-3-methylpyrazine and bromoacetone

2-Methoxy-3-methylpyrazine (5) (4.5 g, 0.036 mol) and bromoacetone (3.0 g, 0.036 mol), when mixed together, gave a salt which upon addition of excess 10% sodium bicarbonate solution gave a red oil. The latter oil was subjected to vacuum distillation (50°C, 18 mm) to yield 1-methoxy-7-methylpyrrolo[1,2-*a*]-pyrazine (7), 0.62 g (10.5%) as a pale yellow oil; ir 760, 1160, 1330, 1370, 1520, 1620, 3100 cm^{-1}; ^{1}H-nmr 2.26 (3H, CH_3-7), 4.00 (3H, OCH_3-1), 6.65* (1H, H-8), 7.00 (1H, d, J = 4.6 Hz, H-3), 7.07* (1H, H-6), 7.35 (1H, d, J = 4.6 Hz, H-4). Anal. Calcd for $C_9H_{10}N_2O$: C, 66.7; H, 6.2; N, 17.3. Found: C, 66.3; H, 6.3; N, 16.9.

The residual solid from the distillation was subjected to vacuum sublimation (95°C, 18 mm) to give 7-methylpyrrolo[1,2-*a*]pyrazin-1(2*H*)-one (10), 0.081 g (1.5%) as pale yellow needle like crystals; mp 170-171°C (from ethyl acetate/toluene); ir 710, 760, 900, 1200, 1650, 3020, 3160 cm^{-1}, ^{1}H-nmr 2.25 (3H, CH_3-7), 6.50 (1H, d, J = 7.6 Hz, H-3), 6.96 (1H, d, J = 7.6 Hz, H-4), 6.97 (2H, H-6 and H-8), 10.50 (1H,

N-H). Anal. Calcd for $C_8H_8N_2O$: C, 64.8; H, 5.4; N, 18.9. Found: C, 65.1; H, 5.5; N, 19.2. Mass spectrum, mass calcd for $C_8H_8N_2O$: 148. Found: m/z (base peak) 148.

Hydrolysis of 1-methoxy-7-methypyrrolo[1,2-*a*]pyrazine

1-Methoxy-7-methylpyrrolo[1,2-*a*]pyrazine (7) (0.1 g, 0.62 mmol) in conc. hydrochloric acid (20 ml) was heated on a water bath for 0.5 h. The mixture was evaporated to dryness and the resulting solid was dissolved in water (25 ml) and then basified with 10% aqueous sodium bicarbonate. After extraction with chloroform (3 x 15 ml) and evaporation of the solvent gave a crude solid, which on sublimation (18 mm, 110°C) produced 7-methylpyrrolo[1,2-*a*]pyrazin-1(2*H*)-one (10), 50 mg (55%), as colourless needle crystals; mp 170-171°C (from ethyl acetate/toluene); λ_{max} (226), 230, 285, (315); log ε 4.59, 4.61, 4.02, 3.49; ir 970, 1160, 1370, 1520, 1620, 3100 cm^{-1}; ^{1}H-nmr 2.25 (3H, CH_3-7), 6.50* (1H, H-8), 6.97 (3H, m, H-6, H-4 and H-3). Anal. Calcd for $C_8H_8N_2O$: C, 64.8; H, 5.4; N, 18.9. Found: C, 65.1; H, 5.5; N, 19.2. Mass spectrum, mass calcd for $C_8H_8N_2O$: 148. Found m/z 148 (base peak).

Reaction between 3,6-dimethyl-2-methoxypyrazine and bromoacetone

3,6-Dimethyl-2-methoxypyrazine (6) (1.4 g, 9.8 mmol) and bromoacetone (1.1 g, 9.8 mmol) was left to react at 45°C for 10 days. The resulting dark red solid was dissolved in water (50 ml) and extracted with ether (3 x 15 ml). Excess solid sodium bicarbonate was added to the aqueous layer to yield a dark red oil. Vacuum distillation (62°C, 18 mm) of the latter gave 3,7-dimethyl-1-methoxypyrrolo[1,2-*a*]pyrazine (8), 0.2 g (12%), as a pale yellow oil; λ_{max} (205), (228), 230, 290 (broad), 312 nm; log ε 4.24, 4.57, 4.58, 3.73, 3.60; ir 750, 800, 1180, 1305, 1490, 1540, 1640, 3120 cm^{-1}; ^{1}H-nmr 2.25 (6H, CH_3-7, CH_3-3), 4.00 (OCH_3-1), 6.51* (1H, H-8), 6.95* (1H, H-6), 7.14 (1H, H-4). Anal. Calcd for $C_{10}H_{12}N_2O$: N, 15.9. Found: N, 15.4.

The residual solid from the distillation was then subjected to vacuum sublimation (18 mm, 100°C) to afford 3,7-dimethylpyrrolo[1,2-*a*]pyrazin-1(2*H*)- one (11), 0.016 g (1.2%), as yellow crystals; mp 209-210°C (from ethyl acetate/toluene); ir 630, 810, 880, 1180, 1650, 3140 cm^{-1}; ^{1}H-nmr 2.16 (CH_3-7), 2.21 (3H, CH_3-3), 6.61 (1H, H-8), 6.87 (2H, H-6, H-4), 9.90 (1H, br, N-H). Anal. Calcd for $C_9H_{10}N_2O$: C, 66.7; H, 6.2; N, 17.3. Found: C, 66.9; H, 6.5; N, 17.1. Mass spectrum, mass calcd for $C_9H_{10}N_2O$: 162. Found: M^+ (base peak)

162, 161 (M-1, 42), 147 (M-15, 14), 132 (M-30, 8), 93 (M- 69, 18).

Reaction between 3,6-dimethyl-2-methoxypyrazine and phenacyl bromide using 2 equivalents sodium bicarbonate

3,6-Dimethyl-2-methoxypyrazine (6) (1.0 g, 7.0 mmol) and phenacyl bromide (1.4 g, 7.0 mmol) was left to react at 55°C for 14 days. To the resulting salt was added sodium bicarbonate (1.18 g, 14 mmol) in water (20 ml) to yield a crude which after vacuum sublimation (112°C, 18 mm) gave 1-methoxy-3-methyl-7-phenylpyrrolo[1,2-*a*]pyrazine (9), 0.5 g (32%), as pale yellow crystals; mp 134°C (from ethyl acetate/ toluene); ^{1}H-nmr 2.28 (3H, CH_3-3), 4.06 (3H, OCH_3-1), 6.96 (1H, H-8), 7.22-7.90 (7H, m, Ph-7, H-6, H-4). Anal. Calcd for $C_{15}H_{14}N_2O$: C, 75.6; H, 5.9; N, 11.8. Found: C, 75.8; H, 6.0; N, 11.8.

Reaction of 3,6-dimethyl-2-methoxypyrazine with phenacyl bromide using excess of sodium bicarbonate.

3,6-Dimethyl-2-methoxypyrazine (6) (3.71 g, 26.9 mmol) and phenacyl bromide (5.35 g, 26.9 mmol) were heated together at 55°C for 10 days. The reaction mixture was taken up in water (200 ml) and extracted with chloroform. To the aqueous solution was added solid sodium bicarbonate (20 g, 238 mmol) and the mixture was stirred for 1 h. An orange solid precipitated out and was filtered off. This was sublimated (160°C, 18 mm) to give 2,3-dimethyl-7-phenylpyrrolo[1,2-*a*]pyrazin-1(2*H*)-one (13), 1.0 g (15.6%), as yellow crystals; mp 170-172 °C (from ethyl acetate/toluene); λ_{max} 219, 252, 259, 266, 269, (272), 278, (309) nm; log ε 4.22, 4.42, 4.42, 4.46. 4.42, 4.39, 4.37, 3.89; ir 692, 752, 1058, 1198, 1222, 1315, 1352, 1407, 1430, 1627, 1674 cm^{-1}; ^{1}H-nmr 2.12 (3H, CH_3-3), 3.38 (3H, N-CH_3), 6.72 (1H, H-8), 7.18-7.65 (7H, m, Ph-7, H-6 and H-4). Anal. Calcd for $C_{15}H_{14}N_2O$: C, 75.6; H, 5.9; N, 11.8. Found: C, 75.6; H, 6.0; N, 11.3.

The basic aqueous solution was then refluxed for 30 min to give a buff precipitate which was then filtered off. Sublimation (202°C, 18 mm) gave 3-methyl-7-phenylpyrrolo[1,2-*a*]pyrazin-1(2*H*)one (12), 0.41 g (6.8%), as a cream solid; mp 280 °C (from ethyl acetate); λ_{max} 221, 260, 266, 273 nm; log ε 4.25, 4.48, 4.50, 4.45; ir 690, 752, 1320, 1420, 1603, 1648, 3415 cm^{-1}; ^{1}H-nmr (DMSO-d_6) 2.05 (3H, CH_3-3), 7.08- 7.80 (8H, m, Ph-7, H-8, H-6 and H-4), 10.60 (1H, bs, N-H). Anal. Calcd for $C_{14}H_{12}N_2O$: C, 75.0; H, 5.4; N, 12.5. Found: C, 75.0; H, 5.5; N, 12.2.

Preparation of 3-methoxy-6-methylpyridazine

3-Chloro-6-methylpyridazine (2.0 g, 15.6 mmol) was refluxed in methanol (40 ml) with sodium methoxide (4.0 g, 74 mmol) for 2 h. After cooling, the methanol was evaporated, the solid was taken up in water and then extracted with ether. Evaporation of the solvent yielded a yellow oil which was vacuum distilled (46°C, 18 *mm*) to give 3-methoxy-6-methylpyridazine (16), 1.29 g (66.8%), as a colourless oil; ^{1}H-nmr 2.58 (3H, CH_3-6), 4.08 (3H, OCH_3), 6.88 (1H, d, J = 9 Hz, H-5) 7.24 (1H, d, J = 9 Hz, H-4).

Reaction of 3-methoxy-6-methylpyridazine with bromoacetone

Bromoacetone (2.14 g, 15.6 mmol) was added slowly to 3-methoxy-6-methylpyridazine (16) (1.29 g, 10.4 mmol). Heat was evolved after 2 min therefore the flask was cooled in a water bath at room temperature. The reaction mixture was then heated at 60°C overnight and the resultant solid dissolved in water (250 ml). This solution was extracted with chloroform (which was discarded), solid sodium bicarbonate (25 g, 0.3 mol) added and then refluxed for 30 min. After cooling, the aqueous solution was extracted with chloroform and this was evaporated to give an oil. Vacuum distillation (54°C, 18 mm) gave 6-methoxy-2-methylpyrrolo-[1,2-*b*]pyridazine (17), 0.5 g (29.7%), as a colourless oil which rapidly darkened; λ_{max} (217), 228, 238, 246, 318, 353 nm; log ε (4.04), 4.06, 4.08, 4.09, 3.57, 3.68; ir 791, 1028, 1100, 1211,1280, 1313, 1355, 1552, 1650, 2860-3010 cm^{-1}; ^{1}H-nmr 2.27 (3H, CH_3-2), 3.89 (3H, OCH_3), 6.15 (1H, d, J = 10 Hz, H-8), 6.23 (1H, H-1), 7.36 (1H, H-3), 7.45 (1H, d, J = 10 Hz, H-7). Anal. Calcd for $C_9H_{10}N_2O$: C, 66.7; H, 6.2; N, 17.3. Found: C, 66.5; H, 6.4; N, 17.0.

Reaction of 6-methoxy-2-methylpyrrolo[1,2-*b*]pyridazine with concentrated hydrobromic acid.

6-Methoxy-2-methypyrrolo[1,2-*b*]pyridazine (17) (0.3 g, 1.85 mmol) was refluxed in concentrated hydrobromic acid (10 ml) for 48 h. The solution was cooled, basified with 10% sodium hydroxide and extracted with ethyl acetate. Purification by column chromatography on silica gel (ethyl acetate as an eluent) gave 2-methylpyrrolo[1,2-*b*]pyridazin-6(5*H*)-one (18), 0.12 g (43.8%); mp 148-150°C (from ethyl acetate/toluene); λ_{max} 219, 231, 239, 246, (307), 322, 356 nm; log ε 4.03, 4.06, 4.07, 4.08, 3.46, 3.56, 3.63; ir 720, 756, 791, 857, 1039, 1118, 1191, 1286, 1320, 1556, 1642, 3384 cm^{-1}; ^{1}H-nmr 2.21 (3H, CH_3-2), 6.19 (1H, d, J = 9.3 Hz, H-8),

6.22 (1H, H-1), 7.33 (1H, H-3), 7.68 (1H, d, J = 9.3 Hz, H-7). Anal. Calcd for $C_8H_8N_2O$: C, 64.9; H, 5.4; N, 18.9. Found: C, 64.5; H, 5.0; N, 18.4.

Reaction of 6-methylpyridazin-3(2*H*)-one with phenacyl bromide

6-Methylpyridazin-3(2*H*)-one (20) (3.0 g, 27.3 mmol), phenacyl bromide (5.9 g, 29.6 mmol) and sodium bicarbonate (6.0 g, 71.4 mmol) were refluxed together in acetonitrile (75 ml) for 14 h. The solvent was evaporated and the solid was extracted with chloroform. The crude product was purified by column chromatography on silica gel (ethyl acetate as an eluent) to give 6-methyl-2-phenacylpyridazin-3(2*H*)-one (21), 5.9 g (95%), as a colourless solid; mp 158°C (from ethyl acetate/toluene); ir 691,763, 854, 913, 1159, 1182, 1223, 1332, 1394, 1420, 1523, 1586, 1655, 1701 cm^{-1}; ^{1}H-nmr 2.28 (3H, CH_3), 5.59 (2H, CH_2), 6.94 (1H, d, J = 9.3 Hz, H-5), 7.43 (1H, d, J = 9.3 Hz, H-4), 7.52-8.15 (5H, m, Ph). Anal. Calcd for $C_{13}H_{12}N_2O_2$: C, 68.4; H, 5.3; N, 12.3. Found: C, 68.0; H, 5.3; N, 12.4.

Reaction of 7-methylpyrrolo[1,2-*a*]pyrazin-1(2*H*)-one with phosphoryl chloride

7-Methylpyrrolo[1,2-*a*]pyrazin-1(2*H*)-one (10) (0.143 g, 0.966 mmol) together with phosphoryl chloride (25 ml, 0.27 mol) were refluxed for 3 h. After evaporation of the excess phosphoryl chloride under reduced pressure and basification with 10% aqueous sodium bicarbonate solution the mixture was extracted with chloroform (3 x 25 ml). Evaporation of the solvent yielded a deep red oil as the crude. Vacuum sublimation on the crude (79°C, 18 mm) gave 1-chloro-7-methylpyrrolo[1,2-*a*]pyrazine (27), 0.150 g (93%), as colourless crystals; mp 28°C (from ethyl acetate / toluene); λ_{max} (216.5), 226.5, (238), (244.5), 290, 300, (335) nm, log ε 4.43, 4.47, 4.31, 4.19, 3.57, 3.64, 3.47; ^{1}H-nmr 2.31 (3H, CH_3-7), 6.66 (1H, H-8), 7.20 (1H, d, J = 4.5 Hz, H-4), 7.63 (1H, d, J = 4.5 Hz, H-3). Anal. Calcd for $C_8H_7ClN_2$: C, 57.7; H, 4.2; Cl, 21.3; N, 16.8. Found: C, 57.8; H, 4.1; Cl, 21.6; N, 17.1. Mass spectrum, mass calcd for $C_8H_7ClN_2$: 166 Found: m/z 166 (base peak).

Reaction of 1-chloro-7-methylpyrrolo[1,2-*a*]pyrazine with sodium methoxide

1-Chloro-7-methylpyrrolo[1,2-*a*]pyrazine (27) (0.03 g, 0.18 mmol) was added to a solution of sodium methoxide (5.0 g, 93 mmol) in methanol (50 ml) and the mixture was boiled under reflux for 10 h. Excess

methanol was evaporated and water (20 ml) was added to the residue. The resulting solution was extracted with chloroform (3 x 15 ml). Evaporation of the solvent gave a yellow oil which on vacuum distillation (50°C, 18 mm) produced 1-methoxy-7-methylpyrrolo[1,2-*a*]pyrazine (7), 0.02 g (68%), as a colourless oil; ir 760, 1100, 1160, 1330, 1370, 1620, 3100 cm^{-1}; ^{1}H-nmr 2.26 (CH_3-7), 4.00 (OCH_3-1), 6.65* (1H, H-8), 7.00 (1H, d, J=4.6 Hz, H-6), 7.07* (1H, H-6), 7.35 (1H, d, J=4.6 Hz, H-4). Anal. Calcd for $C_9H_{10}N_2O$: C, 66.6; H, 6.2; N, 17.3. Found: C, 66.3; H, 6.3; N, 16.7.

Reaction of 1-chloro-7-methylpyrrolo[1,2-*a*]pyrazine with ammonia

1-Chloro-7-methylpyrrolo[1,2-*a*]pyrazine (27) (0.04 g, 0.24 mmol) was added to a solution of conc. ammonia (10 ml). The mixture was heated in an autoclave at 180°C for 48 h. After cooling (-15°C), the solution was made strongly alkaline with potassium hydroxide pellets and extracted with chloroform (3 x 10 ml). Evaporation of the solvent gave 1-amino-7-methylpyrrolo[1,2-*a*]pyrazine (28), 0.02 g (57%) as white needle like crystals; mp 135°C (from ethyl acetate / toluene); λ_{max} 206, (213), 227, 285, (304); log ε 4.31, 4.25, 4.37, 3.78, 3.64; ir 760, 1630, 1650, 3300, 3440 cm^{-1}; ^{1}H-nmr 2.29 (3H, CH_3-7), 4.49 (2H, NH_2-1), 6.27 (1H, H-8), 6.99 (1H, d, J = 4.9 Hz, H-4), 7.08 (1H, H-6), 7.28 (1H, d, J = 4.9 Hz, H-3). Anal. Calcd for $C_8H_9N_3$: C, 65.3; H, 6.1; N, 28.6. Found: C, 65.1; H,6.4; N, 28.7. Mass spectrum, mass calcd for $C_8H_9N_3$: 147. Found: M^+ (base peak) 147, 146 (M^+-1, 38), 119 (M^+-28, 25).

Synthesis of 3-methyl-7-phenylpyrrolo[1,2-*a*]pyrazin-1(2*H*)- thione (30)

The synthesis of **32** was effected by two routes;

(i) 3-Methyl-7-phenylpyrrolo[1,2-*a*]pyrazin-1(2*H*)-one (12) (0.3 g, 1.34 mmol) was refluxed in phosphoryl chloride (30 ml, 322 mmol) for 2 h. Evaporation of the solvent gave a green residue which was decomposed with ice (50 g) and then made alkaline with 10% sodium bicarbonate solution to pH 8. A gold coloured precipitate was filtered off which was sublimated (124°C, 18 mm) to give 1-chloro-3-methyl-7-phenylpyrrolo-[1,2-*a*]pyrazine (29), 0.26 g (80.1%); mp 156-157°C (from ethyl acetate / toluene); λ_{max} (222), 255, 264, (268), (276), 292, 328 nm; log ε 4.14, 4.32, 4.31, 4.30, 4.17, 3.48, 3.64; ir 749, 1215, 1253, 1343, 1421, 1615 cm^{-1}; ^{1}H-nmr 2.35 (3H, CH_3-3), 7.19 (1H, H-8), 7.25-7.65 (7H, m, Ph-7, H-6 and H-4). Anal. Calcd for

$C_{14}H_{11}ClN_2$: C, 69.3; H, 4.6; Cl, 14.6; N, 11.5. Found: C, 68.8; H, 4.7; Cl, 14.7; N, 11.3.

1-Chloro-3-methyl-7-phenylpyrrolo[1,2-*a*]pyrazine (29) (0.24 g, 0.99 mmol) and thiourea (0.48 g, 6.32 mmol) were refluxed in ethanol (8 ml) for 4 h. The reaction mixture was cooled, the solid was filtered off and washed with ethanol. Purification by column chromatography on silica gel (ethyl acetate as an eluent) gave 3-methyl-7-phenylpyrrolo[1,2-*a*]pyrazin-1(2*H*)-thione (30), 0.15 g (62.6%), as a yellow solid; mp 286°C (decomp.) (from ethyl acetate / toluene); λ_{max} (240), 259, 280, 302, 369, (382) nm; log ε 4.18, 4.22, 4.25, 4.04, 3.09, 3.99 ir 689, 755, 1052, 1189, 1240, 1318, 1340, 1429, 1528, 1555, 3068, 3104 cm^{-1}; ^{1}H-nmr (DMSO-d_6) 2.16 (3H, CH_3-3). 7.24-7.77 (7H, m, Ph-7, H-8 and H-4), 7.94 (1H, d, J = 1.3 Hz, H-6), 12.18 (1H, br s, N-1). Anal. Calcd for $C_{14}H_{12}N_2S$: C, 70.0; H, 5.0; N, 11.7. Found: C, 69.5; H, 5.2; N, 11.3.

(ii) 3-Methyl-7-phenylpyrrolo[1,2-*a*]pyrazin-1(2*H*)-one (12) (0.3 g, 1.34 mmol) and Lawesson's reagent (0.6 g, 1.48 mmol) were refluxed in toluene (20 ml) for 4 h. The mixture was cooled, filtered and washed with toluene. After evaporation of the toluene the residue was subjected to column chromatography on silica gel (ethyl acetate as an eluent) to give a compound having an identical pmr spectrum to 3-methyl-7-phenyl-pyrrolo[1,2-*a*]pyrazin-1(2*H*)-thione (32) prepared by method (i). Yield was 0.21g, 65.3%.

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