Formation of Certain Substituted 5*H*-Pyrrolo[2,3-*b*]pyrazines by Thermal Cyclisation of Pyrazinylhydrazones and a Route to 5*H*-Pyrazino[2,3-*b*]indole; a Synthesis of 5*H*-Pyrrolo[2,3-*b*] pyrazine and Some of its Properties

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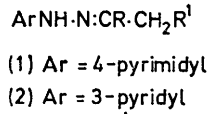
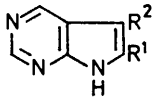
Thermal (non-catalytic) cyclisation of the pyrazinylhydrazones (6a—i) caused ring closure on to the carbon atom of the pyrazine nucleus to give the 3-substituted and 2,3-disubstituted 5*H*-pyrrolo[2,3-*b*]pyrazines (7a—g), (8), and (9), respectively. 6,7,8,9-Tetrahydro-5*H*-pyrazino[2,3-*b*]indole (7g) was dehydrogenated to the parent pyrazino[2,3-*b*]indole (15). Pyrrolo[2,3-*b*]pyrazine (7h) has been obtained from 2-amino-3-methylpyrazine and some of its properties have been investigated.

WE have shown that pyridylhydrazones may be cyclised to yield pyrrolopyridines (azaindoles).[1,2] The presence



(1) Ar = 4-pyrimidyl
(2) Ar = 3-pyridyl



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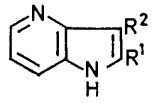

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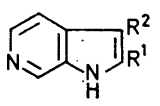


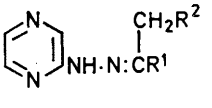
(5)

of an additional nitrogen atom in the nuclei of pyrimidine, pyrazine, and pyridazine as compared with pyridine might be expected to reduce the ease of cyclisation of their heteroarylhydrazones as compared with the corresponding pyridylhydrazones. There appeared to be some evidence [3] to support this idea: although some successful cyclisations of 4-pyrimidylhydrazones (1) to pyrrolo[2,3-*d*]pyrimidines (3) have been reported, the conversion was generally not as smooth as in the case of the corresponding 2-pyridylhydrazones. This finding has recently been extended and confirmed.[4] The mechanism of the thermal cyclisation is not established but it has been suggested that it may be a concerted process.[4,5]

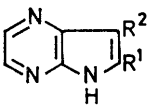
3-Pyridylhydrazones (2) give mainly pyrrolo[3,2-*b*]-pyridines (4), formed by cyclisation on to the 2-position, with only small quantities of pyrrolo[2,3-*c*]pyridines (5) produced by reaction at the 4-position. This indicates that cyclisation on to the position adjacent to a ring nitrogen atom is the favoured process and led us to think that pyrazinylhydrazones (6a—i) might cyclise at the 3-position to give derivatives of pyrrolo[2,3-*b*]pyrazine. The pyrrolo[2,3-*b*]pyrazine nucleus had only once been reported [6] when this work was done.

Hydrazinopyrazine was readily converted into a series of solid hydrazones (6a—i). Ammonia was evolved when solutions of these pyrazinylhydrazones in diethylene glycol were refluxed, and elemental analysis of the products was consistent with the presence of either the pyrrolo[2,3-*b*]pyrazine or the isomeric imidazo[1,2-*a*]-pyrazine (10) ring system. However, the i.r. spectra of all the isolated products showed absorption in the region 3 125—3 200 cm^{-1} attributable to NH. Also, the n.m.r. spectra showed only two remaining signals due to protons of the pyrazine nucleus, and a low-field signal removable on addition of D_2O, thus confirming the assignment of the pyrrolo[2,3-*b*]pyrazine structures (7a—i), (8), and (9) to these new compounds.

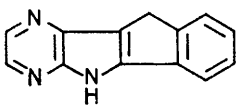
The parent pyrrolo[2,3-*b*]pyrazine (7h) was obtained in 74% yield from 2-amino-3-methylpyrazine (11). Treatment with triethyl orthoformate gave the unstable ethyl *N*-(3-methylpyrazin-2-yl)formimidate (12) (66%) which, when heated with *N*-methylaniline at 180 °C



(6)a; R^1 = H, R^2 = Me
b; R^1 = H, R^2 = Ph
c; R^1 = R^2 = Me
d; R^1 = Ph, R^2 = Me
e; R^1 = Me, R^2 = Ph
f; R^1 = R^2 = Ph
g; R^1R^2 = $[CH_2]_4$
h; $R^2CH_2{\cdot}CR^1$ = indan-1-ylidene
i; $R^2CH_2{\cdot}CR^1$ = 1,2,3,4-tetrahydro-1-naphthylidene



(7)a; R^1 = H, R^2 = Me
b; R^1 = H, R^2 = Ph
c; R^1 = R^2 = Me
d; R^1 = Ph, R^2 = Me
e; R^1 = Me, R^2 = Ph
f; R^1 = R^2 = Ph
g; R^1 and R^2 = $[CH_2]_4$
h; R^1 = R^2 = H
i; R^1 = H, R^2 = CHO
j; R^1 = H, R^2 = NO_2
k; R^1 = H, R^2 = Br



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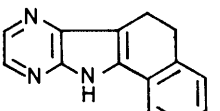
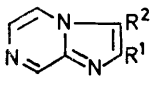


(9)

readily gave N^1-methyl-N^2-(3-methylpyrazin-2-yl)-N^1-phenylformamidine (13). The amidine (13) was then treated with sodium *N*-methylanilide at 180 °C. Recently, Yakhontov [7] has reported the preparation of (7h),

[1] A. H. Kelly and J. Parrick, *Canad. J. Chem.*, 1966, **44**, 2455.
[2] A. H. Kelly and J. Parrick, *J. Chem. Soc.* (*C*), 1970, 303.
[3] P. A. Crooks and B. Robinson, *Canad. J. Chem.*, 1969, **47**, 2061.
[4] T. D. Duffy and D. G. Wibberley, *J.C.S. Perkin II*, 1974, 1921.
[5] T. L. Gilchrist and R. C. Storr, 'Organic Reactions and Orbital Symmetry,' Cambridge University Press, 1972, p. 234.
[6] S. Klutchko, H. V. Hansen, and R. I. Meltzer, *J. Org. Chem.*, 1965, **30**, 3454.
[7] V. A. Azimov and L. N. Yakhontov, *Khim. geterotsikl. Soedinenii*, 1973, 858.

in unspecified yield, by a conventional Madelung synthesis from 2-formamido-3-methylpyrazine (14) and base.



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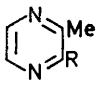
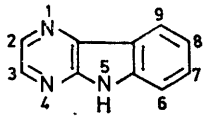


(11) R = NH_2
(12) R = N:CH·OEt
(13) R = N:CH·NMePh
(14) R = NH·CHO



(15)

The ^{1}H n.m.r. spectrum of pyrrolo[2,3-*b*]pyrazine (7h) showed two pairs of doublets: one (*J* 2.6 Hz) at lower field attributed to the 5- and 6-H and one at higher field (*J* 3.5 Hz) from the 2- and 3-H. It seems likely that the 3-H signal is at highest field [δ 6.77 in $(CD_3)_2SO$] and the 2-H signal at 7.95, but assignment of the doublets centred at 8.43 and 8.30 is uncertain. By analogy with indole it would be expected that the 5-H would show as the higher field signal.[8] All the pyrrolo[2,3-*b*]pyrazines studied gave a doublet in each of the ranges 8.23—8.53 and 8.03—8.32 ($J_{5,6}$ 2.3—2.7 Hz) and showed a broad peak (NH) in the range 11.57—12.60.

The u.v. spectra of pyrrolopyrazine and the alkyl derivatives show only two maxima, *e.g.* (7h) has maxima at 218 (log ε 4.07) and 309 nm (3.80), corresponding to the I and III bands of indole. The absorption maximum corresponding to band II of indole is apparently absent, and this corresponds with the findings for pyrrolopyridines, for which it has been suggested[9] that bands II and III overlap.

Pyrrolo[2,3-*b*]pyrazine-3-carbaldehyde (7i) was obtained by treatment of 1*H*-pyrrolo[2,3-*b*]pyrazine (7h) with hexamethylenetetramine, and was identical with the compound obtained by treatment of 2-amino-3-methylpyrazine with the Vilsmeier reagent.[6] Mononitro- and -bromo-derivatives of (7h) were also obtained, and their ^{1}H n.m.r. spectra show the compounds to be 2- or 3-substituted derivatives, but do not allow an unambiguous assignment of structure. On the evidence from the formylation experiment and more general considerations, it is likely these products are the 3-substituted isomers (7j and k).

The pyrazinoindole (15) was obtained by dehydrogenation of the tetrahydro-derivative (7g).

EXPERIMENTAL

I.r. and n.m.r. spectra were recorded as previously described.[10] U.v. spectra were measured for ethanolic solutions with a Unicam SP 800 spectrometer.

* For details of Supplementary Publications see Notice to Authors No. 7, *J.C.S. Perkin I*, 1975, Index issue.

[8] P. J. Black and M. L. Heffernan, *Austral. J. Chem.*, 1965, **18**, 353.

Details of the pyrazinylhydrazones, their cyclisation, and the properties of the pyrrolo[2,3-*b*]pyrazines (7a—g), (8), and (9) are given in Supplementary Publication No. SUP 21746 (6 pp.).*

Ethyl N-(3-*Methylpyrazin*-2-*yl*)*formimidate* (12).—2-Amino-3-methylpyrazine [11] (8.0 g), triethyl orthoformate (22 g), and ethanolic hydrogen chloride (6M; 0.75 ml) were heated slowly to 145 °C, and ethanol was collected as the temperature rose from 115 to 145 °C over 5 h. The excess of triethyl orthoformate was distilled off and the residue distilled under reduced pressure to give ethyl *N*-(3-methylpyrazin-2-yl)formimidate (8.0 g, 66%), b.p. 106—108° at 8 mmHg, $\nu_{max.}$ (liq.) 1 636 cm^{-1} (C:N), δ(CCl_4) 8.12 (1 H, d, *J* 2.0 Hz, 5-H), 7.98 (1 H, d, *J* 2.0 Hz, 6-H), 8.37 (1 H, s, N:CH), 4.40 (2 H, q, *J* 7.0 Hz, CH_2), 2.52 (3 H, s, 3-CH_3), and 1.40 (3 H, t, *J* 7.0 Hz, CH_3). The formimidate was unstable and no elemental analysis was obtained.

N^1-*Methyl*-N^2-(3-*methylpyrazin*-2-*yl*)-N^1-*phenylformamidine* (13).—The formimidate (12) (8.0 g) and *N*-methylaniline (10.4 g) were heated slowly at 180 °C. Ethanol began to distil off at 110 °C and was collected over 2 h. The excess of methylaniline was distilled off (b.p. 88° at 14 mmHg). The residue solidified on cooling and was triturated with petroleum (b.p. 40—60°) to give the *amidine* (13) (9.9 g, 91%), which crystallised from benzene–petroleum (b.p. 40—60°) as needles, m.p. 83—83.5° (Found: C, 69.3; H, 6.2; N, 24.5. $C_{13}H_{14}N_4$ requires C, 69.0; H, 6.2; N, 24.8%), δ($CDCl_3$) 8.94 (1 H, s, CH), 8.07 (2 H, s, 5- and 6-H), 7.30 (5 H, m, Ph), 3.58 (3 H, s, N·CH_3), 2.67 (3 H, s, 3-CH_3).

5H-*Pyrrolo*[2,3-b]*pyrazine* (7h).—Freshly prepared sodamide (3.2 g) was added to dry *N*-methylaniline (17.8 g) with stirring under a stream of nitrogen, and the suspension was brought slowly to boiling. The mixture was refluxed for 40 min and then a warm solution of the amidine (13) (9.0 g) in methylaniline (10 ml) was added over 15 min. The excess of methylaniline was distilled off at atmospheric pressure. Water was added to the cooled residue and the mixture stirred for 1 h. After filtration, the solution was continuously extracted with ether overnight. The dried extract was evaporated and a small quantity of *N*-methylaniline distilled off under reduced pressure. The residue crystallised from benzene to give 5H-*pyrrolo*[2,3-*b*]*pyrazine* (3.52 g, 74%), m.p. 155—156° (sublimes) (Found: C, 60.2; H, 4.2; N, 35.3%; *M*, 119. $C_6H_5N_3$ requires C, 60.5; H, 4.20; N, 35.3%; *M*, 119), $\nu_{max.}$ (KBr) 3 180 cm^{-1} (NH), $\lambda_{max.}$ 218 (log ε 4.07) and 309 nm (3.80), δ[$(CD_3)_2SO$] 12.13 (1 H, s, exchanged in D_2O, NH), 8.43 (1 H, d, *J* 2.6 Hz, 5- or 6-H), 8.30 (1 H, d, *J* 2.6 Hz, 5- or 6-H), 7.95 (1 H, d, *J* 3.5 Hz, 2-H), and 6.77 (1 H, d, *J* 3.5 Hz, 3-H).

Details of the 3-formyl-, 3-nitro-, and 3-bromo-5*H*-pyrrolo[2,3-*b*]pyrazines are given in the Supplementary Publication.

5H-*Pyrazino*[2,3-b]*indole* (15).—6,7,8,9-Tetrahydro-5*H*-pyrazino[2,3-*b*]indole (1.7 g), chloranil (4.9 g), and xylene (150 ml) were refluxed for 10 h. The solution was cooled and the precipitate collected and dissolved in dilute sodium hydroxide solution. Extraction of this solution with ether yielded 5H-*pyrazino*[2,3-b]*indole* (0.44 g). A further quantity (0.2 g) was obtained when the xylene filtrate was diluted with ether, washed with alkali, and then water, and evaporated. The combined solids (40%) were crystallised

[9] R. E. Willette, *Adv. Heterocyclic Chem.*, 1968, **9**, 27.

[10] B. A. J. Clark, M. M. S. El-Bakoush, and J. Parrick, *J.C.S. Perkin I*, 1974, 1531.

[11] H. Gainer, M. Kokorudz, and W. K. Langdon, *J. Org. Chem.*, 1961, **26**, 2360.

from benzene; m.p. 241—243° (Found: C, 70.6; H, 4.2; N, 24.6%; *M*, 169. $C_{10}H_7N_3$ requires C, 71.0; H, 4.1; N, 24.8%; *M*, 169), $\lambda_{max.}$ 214 (log ε 4.36), 244 (3.95), 261 (4.00), and 319 nm (3.92), δ[$(CD_3)_2SO$] 12.20 (1 H, s, exchanged in D_2O, NH), 8.50 (1 H, d, *J* 2.6 Hz, 2- or 3-H), 8.37 (2 H, m, 2- or 3-H and 9-H), and 7.40 (3 H, m, 6-, 7-, and 8-H).

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