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THE NUCLEAR MAGNETIC RESONANCE SPECTRA OF PYRAZINES

BENZYLIC COUPLING IN SUBSTITUTED METHYLPYRAZINES

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Abstract—The coupling constants arising from benzylic coupling between ring-Me protons and ortho-, meta-, and para-situated ring protons for methylpyrazine and for a number of chloro-and methoxyl-substituted pyrazines were found to have the magnitudes $^4J_o = 0{\cdot}55 - 0{\cdot}66$ Hz; $^5J_m = 0{\cdot}28 - 0{\cdot}34$ Hz; $^6J_p = 0{\cdot}65 - 0{\cdot}74$ Hz. The signs were found by selective decoupling experiments to be negative, positive and negative respectively. On the basis of the Me replacement technique, within its inherent limitations, the para-benzylic coupling appears to be π-electron transmitted, whereas a σ-electron contribution of ~ 30% appears likely for the meta-benzylic coupling.

STUDIES of benzylic[1,2] coupling have embraced data from many different aromatic ring systems, although little detailed information concerning benzylic coupling in 6-membered nitrogen heterocycles has been available. In the present work the range of aromatic systems studied is extended to include the substituted pyrazines, a group of compounds in which considerable interest has recently been shown from the point of view of both natural occurrence and characterisation.[3] Furthermore, although structural elucidation of a number of pyrazines has been much facilitated by the work of Bothner-By and Cox[4,5] on the measurement of the ring proton coupling constants, the assignment of the benzylic coupling constants as proposed by these authors needs to be revised on the basis of the present work.[6] This paper is concerned with results involving coupling to "free" rotating Me groups only. The effect of substituents at the benzylic carbon atom will be discussed elsewhere.

Apart from the potential utility of benzylic coupling constants in the structure determination of novel pyrazines, the relative insensitivity of these constants to reactions involving the nitrogen lone pairs[4] provides a means of assigning the signals of the ring protons, for example, in studies involving protonation* or complex formation† in disubstituted pyrazines. In the discussion section the compatibility of the results with ideas of the nature of the coupling mechanism is examined.

RESULTS

Determination of the magnitude of the long-range coupling constants. The benzylic coupling constants were obtained directly from a first-order analysis of the splittings

* The invariance of long range couplings in pyrazines upon protonation of the N atoms has been noted by Bothner-By and Cox.[4] On the basis of this observation and the results of the present work it is the signal of proton 6 (not proton 5) of 2-methoxy-3-methylpyrazine which undergoes the greater downfield shift in an acid medium.[4]

† See results section for details of the complex formation of pyrazines with lanthanide shift reagents.

of the ring Me group signals, which do not show the broadening which characterises the ring proton signals. Correlation of a splitting with the particular ring proton concerned was then achieved by specific ring deuteration, or by observation of the corresponding long range splittings of the aromatic proton signals and assigning these to specific protons on the basis of the ring coupling constants in the case of mono-substituted pyrazines or chemical shift data in the case of di- and tri-substituted pyrazines as described below. The data are collated in Table 1.

(i) *Methylpyrazine.* At 60 MHz the spectrum of methylpyrazine in carbon tetrachloride is not first order (Figs 1(a) and (c)) and therefore first order analysis of the splitting of the Me signal is not possible. Addition of the lanthanide shift reagent, tris dipivalomethanato europium III ($Eu(DPM)_3$),[7] however, results in large differential chemical shifts and even a quantity as small as 0·025 molar equivalents is sufficient to give a spectrum which can be analysed on a first order basis.* Assignment of the

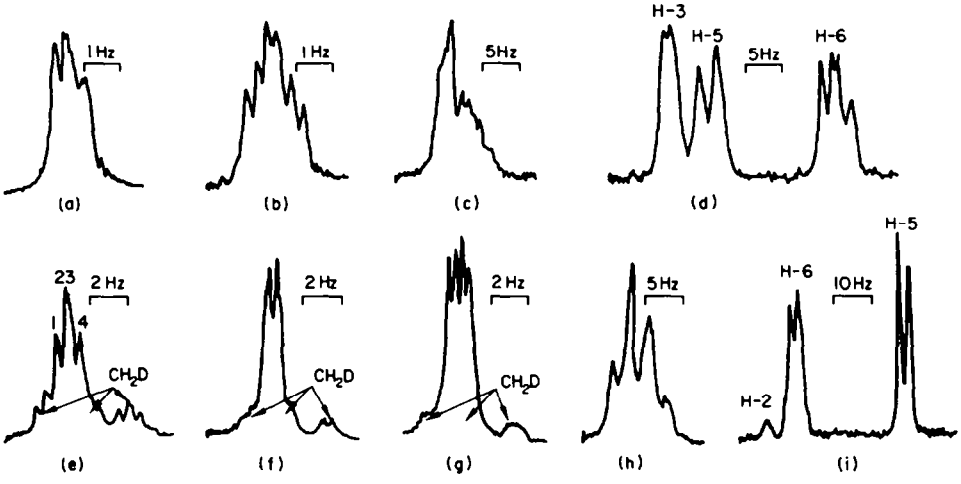


FIG 1. Spectra of methylpyrazines: (a) methylpyrazine: methyl protons (b) methylpyrazine + Eu shift reagent: methyl protons (c) methylpyrazine: ring protons (d) methylpyrazine + Eu shift reagent: ring protons (e) 2-deutero-6-methylpyrazine: methyl protons (f) 2-deutero-3-methylpyrazine: methyl protons (g) 2-deutero-3-methylpyrazine + Eu shift reagent: methyl protons (h) 2-deutero-3-methylpyrazine: ring protons (i) 2-deutero-3-methylpyrazine + Eu shift reagent: ring protons.

ring proton signals on the basis of the ring proton coupling constants[5] shows that protons 3 and 5 undergo a considerably greater shift than proton 6, as would be expected on the grounds of relative inhibition to complex formation at nitrogen-1 by the presence of a 2-Me group. For the Me signals (Fig 1(b)) the close values of ^4J_o and ^6J_p result in effective overlapping of lines so that six instead of eight lines are resolved. Irradiation of proton 6 resulted in the appearance of a triplet for the Me signal, the

* The complex formed with methylpyrazine is not very soluble in carbon tetrachloride, necessitating a fairly low concentration at normal probe temperature ($\sim 36°$). Other pyrazines did not present solubility problems.

TABLE 1. BENZYLIC COUPLING CONSTANTS IN SUBSTITUTED METHYLPYRAZINES

Compound	Solvent	Mole proportion of $Eu(DPM)_3$	^5J_m	^4J_o	^6J_p	$\frac{\delta_{AB}\dagger}{J_{AB}}$
2-Methylpyrazine	CCl_4	0·025	0·29 ± 0·03	$\lvert^4J_o\rvert + \lvert^6J_p\rvert$ = 1·20 ± 0·02		
2-Deutero-6-methylpyrazine	CCl_4	—	—	$\lvert^4J_o\rvert + \lvert^6J_p\rvert$ = 1·20 ± 0·05 0·55	0·65	
2-Deutero-3-methylpyrazine	CCl_4	0·025	(+)0·29 ± 0·02	—	(−)0·65 ± 0·02	13.6
2-Methoxy-3-methylpyrazine	CCl_4	—	0·22 ± 0·03	—	0·65 ± 0·02	1·8
	CCl_4	0·06	(+)0·29 ± 0·02	—	(−)0·71 ± 0·02	11·2
	$DMSO-d_6$	—	$\lvert^5J_m + {}^6J_p\rvert$ = 0·42 ± 0·02			0·36
2-Deutero-5-methoxy-6-methylpyrazine	CCl_4	—	—	—	(−)0·72 ± 0·02	—
2-Methoxy-5-methylpyrazine	CCl_4	—	(+)0·29 ± 0·02	(−)0·66 ± 0·03		9·5
2-Deutero-3-monodeuteromethyl-6-methoxypyrazine	CCl_4	—	0·28 ± 0·03	—	—	—
2-Chloro-3-methylpyrazine	CCl_4	—	(+)0·32 ± 0·04	—	(−)0·69 ± 0·04	3·8
	CCl_4	0·05	(+)0·34 ± 0·02	—	(−)0·70 ± 0·03	9·8
	CCl_4	0·10	(+)0·35 ± 0·03	—	(−)0·70 ± 0·03	18·8
2-Deutero-5-chloro-6-methylpyrazine	CCl_4	—	—	—	(−)0·72 ± 0·03	—
2-Methoxy-6-methylpyrazine	CCl_4	—	—	$\lvert^4J_o\rvert + \lvert^6J_p\rvert$ = 1·40 ± 0·02		7
		0·025	—	$\lvert^4J_o\rvert + \lvert^6J_p\rvert$ = 1·39 ± 0·02		5·5
	$benzene-d_6$	—	—	$\lvert^4J_o\rvert + \lvert^6J_p\rvert$ = 1·40 ± 0·02		
2-Methoxy-6-methylpyrazine	$benzene-d_6$	—	—	0·66* ± 0·03	0·74* ± 0·03	38
2-Chloro-6-methylpyrazine	CCl_4		—	$\lvert^4J_o\rvert + \lvert^6J_p\rvert$ = 1·36 ± 0·02		8
	$benzene-d_6$	—	—	$\lvert^4J_o\rvert + \lvert^6J_p\rvert$ = 1·33 ± 0·02		41
	$benzene-d_6$	—	—	0·60* ± 0·03	0·73* ± 0·02	41
2-Chloro-3,5-dimethyl pyrazine	CCl_4	—	$\lvert^6J_m\rvert$ = 0·24 ± 0·03	0·60 ± 0·03	0·70 ± 0·03	—

* Values obtained by separate decoupling of ring protons.

† Ring protons of disubstituted pyrazines denoted by A and B.

two inner lines being unresolved. These are just resolved in the single resonance spectrum of the Me group of 2-deutero-6-methylpyrazine (Fig 1(e)) from which the values for $|^4J_o|$ and $|^6J_p|$ were measured. Since insufficient resolution of the inner lines could lead to errors[8] in estimating $|^4J_o|$ and $|^6J_p|$ an independent value for $|^6J_p|$ was obtained from the splitting of the Me signal of 2-deutero-3-methylpyrazine in the presence of the europium shift reagent. Fig 1(f–i) shows the effect on the spectrum of the addition of the shift reagent. $|^4J_o|$ could then be obtained by difference from the value for $|^4J_o| + |^6J_p|$ given by the separation of lines 1 and 4 of the methyl signal of 2-deutero-6-methylpyrazine (Fig 1(e)). The two sets of values of $|^4J_o|$ and $|^6J_p|$ thus obtained were in agreement.

(ii) *Disubstituted pyrazines.* With the exception of the 2,3-isomers, the disubstituted pyrazines listed in Table 1 give rise to ABX_3 spectra in carbon tetrachloride solution, the X_3 part of which may be analysed on a first-order basis (i.e. AMX_3) with error less than the precision of measurement. Of the 2,3-isomers, 2-chloro-3-methylpyrazine is a borderline case since ABX_3[9] calculations show that for coupling constants of this magnitude the error involved in making a first order analysis is $\backsim$ 0·02 Hz for $\delta_{AB}/J_{AB} \backsim 4$. For 2-methoxy-3-methylpyrazine in carbon tetrachloride ($\delta_{AB}/J_{AB} \backsim 1{\cdot}8$) it will be seen from the results in Table 1 that a first-order treatment of the Me splitting introduces small errors in the magnitude of the coupling constants thereby obtained. Addition of 0·06 molar equivalents of the europium shift reagent resulted in a spectrum which could be treated as first-order ($\delta_{AB}/J_{AB} \sim 11{\cdot}2$). The values of the coupling constants obtained from the latter spectrum were used to calculate the corresponding X spectrum for the uncomplexed pyrazine with $\delta_{AB}/J_{AB} = 1{\cdot}8$, and the line separation of the calculated spectrum agreed with the values given in the Table to within 0·01 Hz (i.e. well within the standard deviation of the measurements). From this, and from inspection of the other results in Table 1 it is apparent that complex formation with low concentrations of the europium shift reagent has a negligible effect on the magnitude of the benzylic coupling constants, and that the use of this reagent provides a valid means of obtaining the long range coupling constants. For the 2,6-disubstituted pyrazines the change from carbon tetrachloride to benzene solvent, made in order to facilitate (larger δ_{AB}) decoupling of the ring protons (Table 1), also had little effect on the magnitude of the couplings.

Assignment of the long range coupling constants. The unambiguous assignment of the measured benzylic coupling constants for the disubstituted pyrazines presents some difficulty. Although the Me splittings were easily correlated with the ring proton splittings it was still necessary to assign the latter to a particular ring proton. One solution to the problem involves the assumption of the approximate additivity of substituent effects deduced from the spectra of the corresponding monosubstituted pyrazines. It is known that such simple correlations must be approached with caution, particularly where the effects of *ortho* substituents have to be considered, and where a heterocyclic nucleus is involved.[10] However, it is apparent that for the disubstituted pyrazines discussed in the present work, a simple empirical estimation (Experimental) of ring proton chemical shifts is successful in enabling ring proton assignments to be made. Nevertheless, since the resulting assignments for the 2,3-isomers were in conflict with the data of Bothner-By and Cox,[4] it seemed desirable to make the assignments unambiguous where possible by means of specific ring deuterations. For the 2,3- and 2,5-substituted pyrazines, routes for synthesis were available which could be

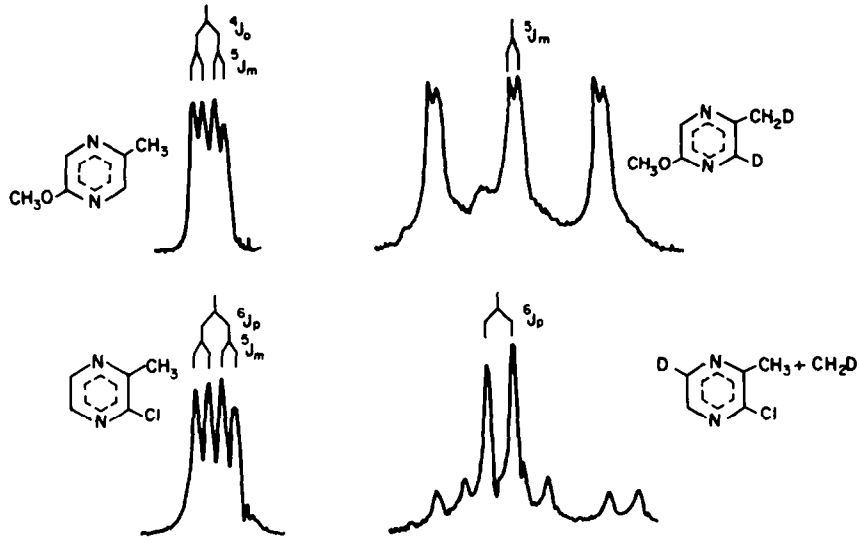


FIG 2. Comparison of ring Me signals for undeuterated and deuterated pyrazines.

adapted for preparation of the deuterated derivatives, and which did not require separation of positional isomers (see section on the synthesis of the compounds). The unambiguously assigned Me signal splittings in these deuterated compounds (Fig 2 and Table 1) confirmed the validity of the corresponding chemical shift assignments.

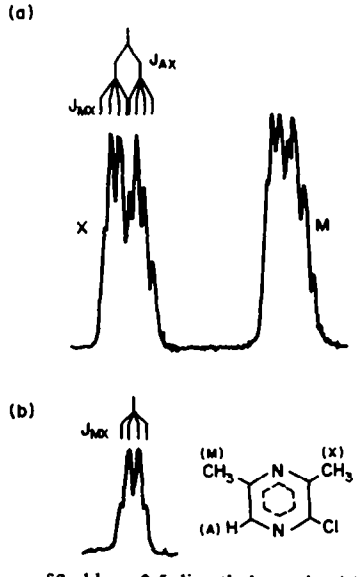


FIG 3. Me group spectrum of 2-chloro-3,5-dimethylpyrazine (a) normal spectrum (b) low field methyl signal (X) with decoupling irradiation of the ring proton (A).

Trisubstituted pyrazines. The spectrum of 2-chloro-3,5-dimethylpyrazine (Fig 3) reveals the existence of an appreciable homobenzylic coupling constant $^6J_m^{CH_3,CH_3}$, each Me signal appearing as a (slightly overlapped) doublet of quartets (Fig 3(a)). Irradiation at the frequency of the ring proton signal removed the benzylic coupling leaving the homobenzylic coupling, as shown by the quartet splitting of the low field Me signal (Fig 3(b)). For this compound assignment of the Me group signals is made on the assumption that the Me group *ortho* to the chlorine substituent will be deshielded relative to the Me group *para* to this substituent. On the basis of this assignment the measured benzylic coupling constants $|^4J_o|$ and $|^6J_p|$ were identical to those obtained from the spectra of 2-chloro-3-methylpyrazine and 2-chloro-6-methylpyrazine. The Me signals in the spectrum of 2-methoxy-3,5-dimethylpyrazine were insufficiently separated in carbon tetrachloride, even in the presence of the europium shift reagent, to allow convenient measurement of $|^6J_m|$ for this compound.

Determination of the signs of the long range coupling constants. The ABX_3 spectra exhibited by the disubstituted pyrazines are insufficiently well-resolved in the AB part to give an indication of the relative signs of J_{AX} and J_{BX} on the basis of line intensities as discussed by Kowalewski and Kowalewski.[9] Since these pyrazines exhibited relatively loosely coupled ABX_3 spectra, however, the signs of J_{AX} and J_{BX} relative to that of J_{AB} were readily determined by selective decoupling experiments. The use of this method as applied to ABX_3 (or AKX_3) systems has been described, for example, by Hoffman, Gestblom *et al.*[11,12] Fig 4 shows the spectrum of 2-chloro-3-methylpyrazine and the corresponding collapse of the X_3 lines when the four quartets in the AB part are separately irradiated.

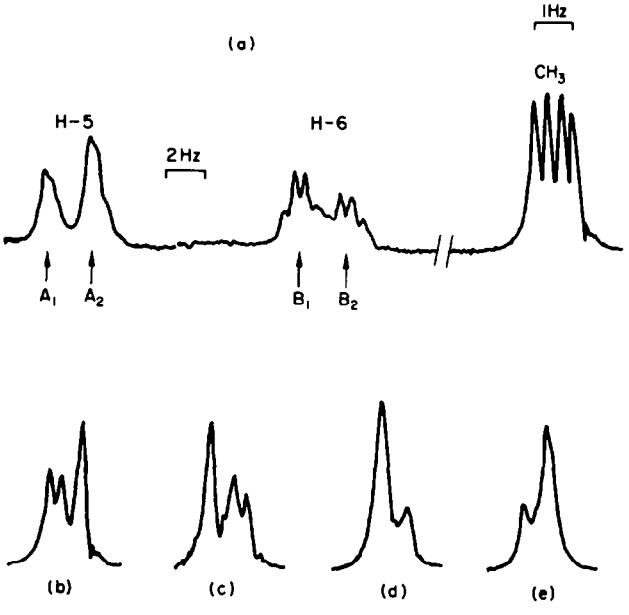


FIG 4. Selective decoupling of the ABX_3 spin system of 2-chloro-3-methylpyrazine. (a) Normal spectrum. (b–e) Me signals with irradiation at (b) A_1 (c) A_2 (d) B_1 (e) B_2.

The pattern of collapse shows that ^6J_p has opposite sign to J_{AB} and that ^5J_m has the same sign as J_{AB}. Similar decoupling experiments performed on 2-methoxy-3-methylpyrazine and 2-deutero-3-methylpyrazine gave identical results. Since J_{AB} (^3J_o) is taken to be positive[5] the absolute signs of ^6J_p and ^5J_m are thus negative and positive respectively.*

An analogous experiment performed on 2-methoxy-5-methylpyrazine gave an identical sequence of collapse for the X_3 lines to that described for the 2,3-isomer. In this case, therefore, the results showed that ^5J_m has the same sign as the ring coupling constant ^5J_p, and ^4J_o has the opposite sign. Bothner-By and Cox have established[5] that ^5J_p is of the same sign (positive) as ^3J_o and thus the absolute signs of ^5J_m and ^4J_o are positive and negative respectively.

In summary, therefore, the three long range couplings in the disubstituted pyrazines (and also methypyrazine) ^4J_o, ^5J_m and ^6J_p are shown to have the absolute signs, negative, positive and negative respectively.

DISCUSSION

The mechanism of spin-spin coupling in aromatic molecules is commonly discussed in terms of separable π- and σ-electron contributions, i.e. $J_{NN'} = J^{\pi}_{NN'} + J^{\sigma}_{NN'}$.[14] Thus aromatic ring proton coupling is considered to occur predominantly by way of the σ-electron orbital framework, at least in the *ortho* and *meta* cases,[1,15] whereas most aspects of benzylic coupling have been considered to be satisfactorily explained on the basis of a π-electron mechanism. These conclusions have been supported by theoretical calculations,[16–20] which have predicted signs and orders of magnitude, and also by observations of the influence of ring substituents on the coupling constants.[1,15] However, while there appears to be universal acceptance of a π-electron dominated mechanism for the transmission of the *para*-benzylic coupling various authors have also taken into account the possibility of appreciable σ-electron contributions to the other benzylic coupling constants, particularly in the *meta* case *via* the extended planar zig-zag configuration.[1,11,21–25]

TABLE 2. BENZYLIC COUPLING IN OTHER AROMATIC COMPOUNDS

Compound	^4J_o	^5J_m	^6J_p	Ref.
Toluene	−0·75	+0·36	−0·62	15
2,3,4,5-Tetrachlorotoluene 2,3,4,6-Tetrachlorotoluene 2,3,5,6-Tetrachlorotoluene	±0·63	±0·36	±0·63	29
2-Bromo-5-chlorotoluene	−0·63	+0·40	−0·58	26
4,6-Dibromo-2,3-dimethylaniline	–	+0·36	−0·61	25
4,6-Dibromo-2,5-dimethylaniline	−0·76	+0·38	—	25
3,4-Dibromo-2,6-dimethylaniline	−0·77	—	−0·57	25
2-Fluoro-3-methylpyridine	−0·85	+0·40	−0·7	23

* The fact that ^6J_p and ^5J_m are of opposite sign may, in some cases, also be inferred from the change in the appearance of the X_3 signals where tight coupling is introduced into the AB part of the spectrum by a change in solvent.[13]

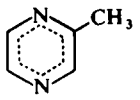
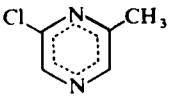
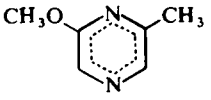
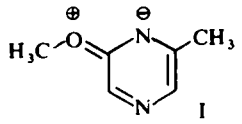
A feature of benzylic coupling often emphasised is the apparent insensitivity of the coupling constants to the effects of ring substitution.[1] In Table 2, benzylic coupling constants for several substituted toluenes and a substituted pyridine are quoted from the literature. The similarity of the signs and magnitudes for ^5J_m is remarkable and those for ^6J_p only slightly less so, although a wider variation is found for ^4J_o.

While detailed comparisons with such a heterogeneous series of compounds is obviously not possible, it is evident from a general comparison of Tables 1 and 2 that formal introduction of N atoms into the aromatic ring has a significant effect, particularly on the values of ^4J_o and ^5J_m. It is also interesting that, in comparison with the present work, recently published data for the benzylic coupling constants of a number of fluoro-methylpyridines[23b] show a change of ^4J_o and ^5J_m from "toluene-like" values to "pyrazine-like" values when the N atom is adjacent to the *ortho* or *meta* coupling path. Unfortunately, direct comparison of the results is again made difficult by the presence of the F atom in the substituted pyridines. The comparison of data for toluene[15] (Table 2) and methylpyrazine is perhaps of more direct significance. All three benzylic coupling constants are of the same sign in both molecules, but ^4J_o and ^5J_m are appreciably smaller in magnitude in methylpyrazine, while ^6J_p is of the same order*. In view of the fact that ^5J_m probably involves appreciable σ-electron coupling, it is possible that the smaller value for methylpyrazine compared to that for toluene may reflect some influence of the polarization of the σ-bond framework of the former compound since the assumed (see also later discussion) π-electron transmitted *para*-benzylic coupling is of the same order for both molecules. Schaefer *et al.*[23] have in fact suggested that the benzylic coupling constants observed for 2-fluoro-methylpyridines demonstrate that the N atom primarily polarizes the σ-bonds in the molecule. Certainly, recent MO calculations[28] have shown that σ-polarization in pyridine is important, and indeed provides the dominant contribution to the reduced electron density on the C atoms α to the N atom.

Although appreciable σ-contributions have also been suggested for ^4J_o[25] there is evidence to show that ^4J_o bears a relation to π-bond order.[27, 29, 30] Indeed, extended HMO calculations[31] for pyrazine show increased σ- and decreased π-bond order for the 2,3-bond relative to benzene, so that the latter factor may be responsible for the relative decrease in ^4J_o. Discussion of the *para* coupling is more difficult. In the terms adopted by Schaefer[23a] in connection with 2-fluoro-3-methylpyridine it is tempting to ascribe the similar values of ^6J_p in toluene and methylpyrazine to a relatively unaffected π-contribution to the long range coupling on formal introduction of the N atoms, but quantitative support for the relative effects of the changes in σ- and π-electron densities and bond orders for the six bond path is lacking.

* The magnitude of ^4J_o reported for toluene [15] (−0·746Hz) has been questioned by Nair *et al.*[27] on the basis of Me splitting and Me bandwidth measurements for 2-bromotoluene and 2-deuterotoluene respectively. However, as shown by the results in this paper, treatment of Me splittings as first order effects is not satisfactory when there is strong coupling in the aromatic proton spectrum (e.g. the bandwidth as measured by us for the ring Me resonances in 2-methoxy-3-methylpyrazine in DMSO-d_6 is only 0·4Hz greater than the line width of the TMS internal reference, but the coupling constants involved are −0·71 and +0·29 Hz). Thus it appears to us that there is not enough evidence from the measurements made for 2-bromo and 2-deuterotoluenes by themselves to cast doubt on the above mentioned value of ^4J_o for toluene. Further experiments e.g. with tetradeutero toluenes, might be carried out to yield the benzylic couplings by direct measurement of Me splittings.

It is also possible from the data in Table 1 to compare the benzylic coupling constants for 2-methylpyrazine with those for its chloro and methoxyl substituted derivatives. Substitution at the 6-position leads to an increase in the magnitude of both ^4J_o and ^6J_p.

^4J_o	0·55	0·60	0·66
^6J_p	0·65	0·73	0·74

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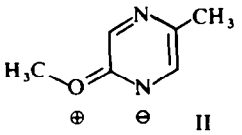


II

Similar behaviour of ^4J_o has been noted for other compounds. Blears, Danyluk and Schaefer[30] have pointed out that in substituted toluenes a range of values from − 0·6 to − 0·87 Hz could be adequately attributed to a 20% variation in the square of the bond order of the intervening ring bond. The large magnitude of $^4J_o^{CH_3,H}$ in 2-fluoromethylpyridines relative to toluene derivatives was thus discussed[23] in terms of the increase in bond order due to the resonance electron donor properties of the F atom. For the pyrazines also, the increasing magnitude of ^4J_o with increasing π-electron donor strength of the substituent is qualitatively in accordance with increase in the bond order of the 2,3 bond, expected from the increasing importance of the contribution of a structure of type I to the resonance hybrid. A similar resonance situation exists for a π-donor substituent in the 5-position, with structure II as an important contributor. Similar values of ^4J_o might therefore be expected for the 2,5- and 2,6-methoxyl substituted isomers, and identical values were observed. Comparison of the chloro derivatives was not possible because of the inaccessibility of 2-chloro-5-methylpyrazine.

The interpretation of ^6J_p on the basis of the above reasoning is difficult, since substitution of 2-methylpyrazine by chloro and methoxyl substituents (in either the 3- or 6-position) leads to increased, but *similar*, values for the magnitude of ^6J_p. More experimental data and information concerning π-bond orders in these systems is required for a detailed discussion of substituent effects. Nevertheless, evidence to support the contention that ^6J_p is transmitted predominantly *via* a π-electron mechanism can be adduced for the pyrazines. The criterion of Me substitution for estimating the π-electron contributions to long range coupling constants[32] can be invoked in conjunction with data from the work of Cox and Bothner-By, and from the present work. Using this criterion, a π-electron transmitted benzylic coupling constant is expected to be unchanged in magnitude but of opposite sign when the ring proton is replaced by a Me group, whereas a σ-contribution is expected to be significantly attenuated by the interpolation of an extra bond in the coupling path. In other words, corresponding benzylic and "homo"[2] (or "inter"[1]) benzylic couplings will have similar magnitudes for π-electron transmitted couplings. Thus, for 2-chloro-3-methypyrazine the benzylic coupling constant $|^6J_p| = 0{\cdot}70 \pm 0{\cdot}03$ Hz (CCl_4, present work), 0·68 Hz ($CDCl_3$, ref 4) whereas the homobenzylic coupling constant

for 2-chloro-3,6-dimethylpyrazine $|^7J_p| = 0{\cdot}72$ Hz ($CDCl_3$, ref 4). The unchanged relative magnitude (within probable experimental error) is therefore consistent on the basis of this method with a π-dominated coupling, although the sign of ^7J_p is not known. Similar conclusions have been reached for substituted toluenes.[25]

The Me group replacement technique as applied to toluenes has suggested a σ-contribution to ^5J_m of about one third or greater.[25] A similar contribution is demonstrable for pyrazines since substitution of 2-chloro-3-methylpyrazine by a Me group at the 5-position results in a reduction in the magnitude of the *meta* long range coupling by nearly one third (for 2-chloro-3-methylpyrazine $|^5J_m| = 0{\cdot}34 \pm 0{\cdot}02$ Hz, whereas for 2-chloro-3,5-dimethylpyrazine $|^6J_m| = 0{\cdot}24 \pm 0{\cdot}03$ Hz). However, as pointed out in connection with the results for toluene,[25] some σ-electron contribution to ^6J_m may also have to be taken into consideration.

Synthesis of compounds

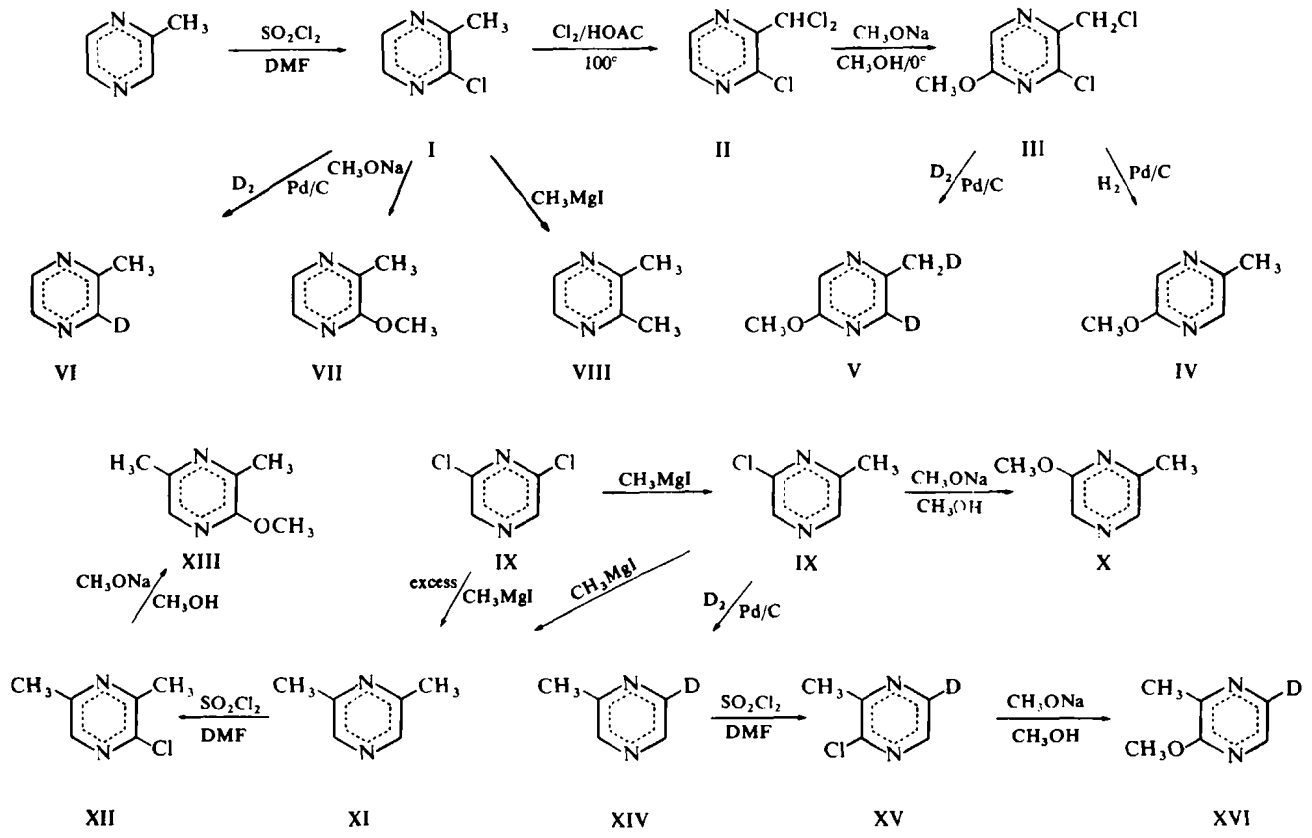
The most facile route to specifically deuterated pyrazines is by deuterolysis of the corresponding halogenated derivative. Unfortunately, the methods at present available for nuclear halogenation suffer in general from a lack of specificity. However, the reaction of chloropyrazine with a number of chlorinating agents in a water-soluble, polar, organic solvent containing various amounts of water has been reported to give 2,3- or 2,6-dichloropyrazine specifically.[33] In the presence of at least 0·02 mole per cent of water 2,6-dichloropyrazine was obtained, but less than this amount resulted in 2,3-orientation. This reaction has now been applied to alkylpyrazines in general.[34] Thus, the chlorination of methylpyrazine with sulphuryl chloride (which functions both as chlorinating and dehydrating agent) in the presence of dimethyl formamide gave 2-chloro-3-methylpyrazine (I, 33%).

It was necessary for the structures of the materials prepared during this investigation to be unambiguous. Where the method of synthesis left any doubt as to the configuration of the product, it was converted to a material of known structure (Scheme).

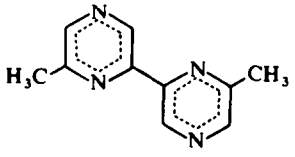
2-Chloro-3-methylpyrazine (I) was converted to compound II in excellent yield in a similar manner to that previously described.[35] Although other routes to 2-chloro-6-methylpyrazine (IX) are known,[36] they give rise to either a mixture of isomers or are not unequivocal, and therefore necessitated the use of the depicted route. The deuterolysis and hydrogenolysis of the chloropyrazines was effectively catalysed by palladium, both on charcoal (5%) and alumina (5%), although the reactions appeared to be faster with the former catalyst.

A basic medium for the latter reactions was necessary since the ring chlorine could not be displaced in neutral medium. The hydrogenolysis of a mixture of 2-chloro-3- and 6-methylpyrazine in the presence of sodium hydroxide (1–2 molar equivalents) in methanol results in termination of the reaction at about 88% of the theoretical uptake of hydrogen, and the formation of a small quantity of the corresponding methoxylated pyrazines. In the presence of barium hydroxide, the reaction was very slow and gave a poor yield of the required product. The same result was obtained with sodium isopropoxide in isopropanol and, in addition, some poisoning of the catalyst was observed. The latter system was, however, successful with the more reactive compound III, and less alkoxylated product was formed. The preferred conditions for the deuterolysis of compound IX were found to be sodium methoxide/methanol-d_1/dioxan.

SCHEME


CH3
SO2Cl2
DMF
Cl
Cl2/HOAC
100°
CHCl2
CH3ONa
CH3OH/0°
CH2Cl
CH3O
I
II
III
D2
Pd/C
CH3ONa
CH3MgI
H2
Pd/C
CH2D
D
OCH3
VI
VII
VIII
V
IV
H3C
XIII
IX
X
excess
XII
XI
XIV
XV
XVI

Very careful precautions were observed to exclude all traces of moisture from apparatus, reactants and catalyst, since this was shown to be a major cause of proton contamination in the deuterated products. Virtually no hydrogen/deuterium exchange occurred in the synthesis of V but despite the above precautions the isotopic purity of compound XIV ranged from 93 to 97% Since the NMR spectrum shows evidence of deuterium exchange in the Me group to the extent of ~ 16% (Fig 1(e)) it is possible that the Me group is the source of proton contamination. Deuterolysis of compound I gave a product with only ~ 85% deuterium at the 3 position and ~ 8% exchange in the Me group. In this case the proximity of the Me group and the Cl atom could presumably facilitate such exchange on the catalyst surface. Certainly, the relatively large amount of contamination of VI appears to rule out proton exchange occurring via the solvent system, which contained an excess of methanol-d_1. However, the relatively low yields obtained in these reactions, and the isolation in one instance (during the synthesis of XIV) of compound XVII, partially deuterated in the methyl groups, indicate that other modes of exchange may be operating. All new compounds reported had satisfactory mass-spectral molecular weights, and fragmentation patterns consistent with their structures. Purity was verified by GLC and the NMR spectrum.



XVII

EXPERIMENTAL

NMR measurements. All results reported in this paper, with the exception of some of the selective decoupling experiments, were obtained using a Varian Associates A–60A 60 MHz spectrometer equipped with a V–6058A spin decoupler. The sweep ranges were calibrated with the usual Varian reference sample, and chemical shifts are considered accurate to only ±0·02 ppm. Chemical shifts were measured on the δ scale in parts per million (ppm) relative to TMS internal standard. Dissolved O_2 was removed from all samples by bubbling N_2 through the solns. Where sufficient compound was available, soln concentrations were approximately 10 mole %. Coupling constants (J) were measured directly from spectra recorded using the 50 Hz sweep width with a sweep rate of 0·05 or 0·02 Hz/second. A linewidth for the internal TMS standard of 0·2–0·25 Hz was usually achieved under the conditions used. The values given in Table 1 are averages of 10–20 measurements made with an equal number of upfield and downfield scans. Quoted error figures are standard deviations. Frequency sweep selective decoupling experiments were performed using a JEOL PS 100 spectrometer.

Substituent-induced chemical shifts. For the purpose of obtaining substituent-induced shifts to enable assignment of ring proton chemical shifts in the disubstituted pyrazines (particularly the 2,6-isomers, see results section) the spectra of a number of monosubstituted pyrazines were analysed. Data have been reported for methylpyrazine in deuterochloroform solution, and for other monosubstituted pyrazines in dimethyl sulphoxide solution.[5] For the present work data were required for CCl_4 solns.

Although the spectra of chloropyrazine and methoxypyrazine could be analysed sufficiently accurately as ABX systems, the ring proton spectrum of methylpyrazine in CCl_4 is too complex at 60 MHz for direct analysis (Fig 1(c)). However, since measurements of high accuracy were not required, the spectrum of methylpyrazine was conveniently analysed by making use of the two deuterated derivatives, 2-deutero-3-methylpyrazine and 2-deutero-6-methylpyrazine. Chemical shifts for these compounds and for chloro- and methoxypyrazines are given in Table 3, together with the effective shifts due to the presence of the ring substituent at the *ortho*, *meta* and *para* positions. Shifts for the ring protons in the disubstituted

TABLE 3. CHEMICAL SHIFT DATA*

Compound	δ ring protons 3	5	6	δo, m, p† = δ ortho	δ monosubst. pyrazine − δ meta	δ pyrazine δ para
2-Deutero-3-methylpyrazine		8·30	8·37	−0·14	−0·15	−0·22
2-Deutero-6-methylpyrazine	8·38	8·30				
2-Methoxypyrazine	8·19	8·07	8·02	−0·33	−0·50	−0·45
2-Chloropyrazine	8·57	8·45	8·34	+0·05	−0·18	−0·07

* For carbon tetrachloride solutions.

† Negative sign indicates upfield shift from pyrazine (δ = 8·52).

pyrazines were then estimated assuming additivity of the individual substituent shifts, and the results are given in Table 4.

Synthesis of compounds. Analytical GLC was performed on a Pye 104 instrument with 9 ft glass columns packed with Apiezon L (3% + 0·3% FFAP on Chromosorb G, 100–200 mesh), FFAP (3% on Chromosorb G) or ethylene glycol adipate (EGA 3% on Chromosorb G). Preparative GLC was performed on a 20 ft column of EGA (7% on Chromosorb G, 60–80 mesh). All solvents were reagent grade or better. Solvents used for deuterolysis work were thoroughly dried, and purified by fractional distillation. Pd catalysts (5% on alumina or charcoal) employed for deuterolyses were obtained from Johnson-Matthey Chemicals Ltd.

Methylpyrazine and chloropyrazine were purchased from R. N. Emanuel Ltd. and the latter compound was used to prepare methoxypyrazine in the same way as described below for 2-methoxy-3-methylpyrazine. 2,6-Dichloropyrazine was obtained from Aldrich Chemical Co. Inc.

2-Chloro-3-dichloromethylpyrazine (II). A soln of 2-chloro-3-methylpyrazine (16 g, 0·12 mole) in glacial AcOH (250 ml) was heated to 100°. Cl_2 gas was passed into the soln at this temp (250 ml/min) until GLC analysis on aliquots of the mixture showed the absence of starting material. The total quantity of Cl_2 added was 13 litres (0·54 mole) at 20°. The mixture was cooled and water (250 ml) was added followed by NaOH aq (270 ml, 45%, temp < 10°). The ppt thus obtained was filtered, washed with water, dried and recrystallised from light petroleum to give colourless plates (18·6 g, 76%), mp. 46–47° [Lit[37] mp. 45·5–46·5°]. It has been found[37] that this material is a potent skin irritant, a fact which we can confirm.

2-Chloro-3-chloromethyl-6-methoxypyrazine (III). 2-Chloro-3-dichloromethylpyrazine (19·75 g, 0·1

TABLE 4. COMPARISON OF OBSERVED AND ESTIMATED RING PROTON CHEMICAL SHIFTS FOR THE DISUBSTITUTED PYRAZINES

Compound	ring proton	δ obs ppm ±0·02	δ calc ppm ±0·02	δ_{AB} obs* ppm ±0·02	δ_{AB} calc* ppm ±0·02
2-Methoxy-3-methylpyrazine	5	7·88	7·92	0·09	0·12
	6	7·79	7·80		
2-Chloro-3-methylpyrazine	5	8·30	8·30	0·16	0·18
	6	8·14	8·12		
2-Methoxy-5-methylpyrazine	3	8·05	8·04	0·22	0·17
	6	7·83	7·87		
2-Methoxy-6-methylpyrazine	3	7·96	7·97	0·05	0·04
	5	7·91	7·93		
2-Chloro-6-methylpyrazine	3	8·34	8·35	0·05	0·05
	5	8·29	8·30		

All shifts measured for carbon tetrachloride solution.

* δ_{AB} = chemical shift between ring protons.

mole) was dissolved in MeOH (25 ml) and added during 10 min to a soln of Na (2·3 g, 0·1 g. at. in MeOH (25 ml) at a temp of 0 ± 5°. This temp was maintained for a further hr when GLC analysis showed the reaction to be complete. Water (150 ml) was added and the mixture was extracted with light petroleum (5 × 25 ml). The combined extracts were dried ($MgSO_4$) and evaporated to give a colourless liquid (18·7 g, 97%).

2-Chloro-3-methylpyrazine (I). Sulphuryl chloride (405 g, 3·0 mole) was added during 2 hr to a soln of methylpyrazine (188 g, 2·0 mole) in DMF (169 g, 2·32 mole) whilst the temp was maintained at 45 ± 5°. The mixture was stirred for a further 2 hr at room temp when water (500 ml, temp <40°) was added and the pH of the soln adjusted to 8·0–9·0 with 45% NaOH aq (temp <40°). The alkaline mixture was steam distilled and the distillate was extracted with chloroform (3 × 100 ml). The combined extracts were dried ($MgSO_4$) and the solvent was removed under vacuum at 40°. GLC analysis of the crude product (139 g) showed the major component to be 2-chloro-3-methylpyrazine with a trace only of the 2,6-isomer. Fractionation of a portion (91 g) on a 30 cm glass helices-packed column gave the pure material (55·5 g, 33% total yield), bp. 85°/40 mm.

2-Methoxy-3-methylpyrazine (VII). Na (58·3 g, 2·53 g.at.) was dissolved in MeOH (600 ml) and crude 2-chloro-3-methylpyrazine (217 g, 1·69 mole) was added to the refluxing soln during 2 hr. The mixture was heated under reflux for a further 4 hr, filtered to remove NaCl, and evaporated to remove MeOH. Water (200 ml) was added and the soln was extracted with light petroleum (4 × 100 ml, bp. 40–60°). The combined extracts were dried ($MgSO_4$) and evaporated. Standardised GLC analysis on the crude product (169 g) showed it to contain 2-methoxy-3-methylpyrazine (106 g, 27% based on methylpyrazine). Fractionation on a 70 cm glass helices-packed column gave the pure material (103 g, 26%), bp. 87°/60 mm.

2-Chloro-6-methylpyrazine (IX). Recrystallised 2,6-dichloropyrazine (11·9 g, 0·08 mole) was dissolved in anhyd ether (25 ml) and added at 10 ± 2° to Me Mg I (0·48 mole) in ether (100 ml), during 50 min. The mixture was stirred at the same temp for 1 hr when excess Grignard was decomposed with 10% HCl. The soln was made alkaline (pH 9) with NaOH aq and steam distilled. The distillate was extracted with ether (6 × 50 ml), the extracts were dried ($MgSO_4$) and evaporated to a white solid (9·0 g). Chromatography on silica gel (400 g) and elution with ether/light petroleum (1:9) gave unreacted starting material (9% recovery) and 2-chloro-6-methylpyrazine (6·35 g, 62%). Further elution with ether gave 2,6-dimethylpyrazine (1·3 g, 15%).

2-Methoxy-6-methylpyrazine (X). CCl_4 (1·1 litre) was saturated at 40° with Cl_2 gas and alternate additions of 2-methylpyrazine (18·8 g) containing 1% water and Cl_2 (1000 ml/min) were made whilst the temp was maintained, with cooling, at 45 ± 5°. The reaction was complete after the addition of 225·6 g (2·4 mole) of methylpyrazine and 78 litres of Cl_2. The yellow ppt of 2-chloro-3- and 6-methylpyrazine hydrochloride was filtered, dissolved in water, made alkaline with NaOH aq (45%) and steam-distilled. The distillate was extracted with CCl_4 (2 × 50 ml) and the combined extracts were washed to neutrality with water, dried ($MgSO_4$) and evaporated to a pale yellow oil (294 g) comprising (by GLC analysis using an internal standard) 2-chloro-6-methylpyrazine (28%), 2-chloro-3-methylpyrazine (69%) and unconverted methylpyrazine (3%). This material was methoxylated as before with NaOMe (5·03 mole). The crude product (229 g) was fractionated through a glass helices-packed column (80 cm) and gave 2-methoxy-3-methylpyrazine (75 g, 25%), bp. 89°/60 mm, and 2-methoxy-6-methylpyrazine (12 g, 4%), bp. 80°/45 mm. A mixture of the two isomers (109 g) bp. 89–92°/60 mm was also obtained.

2,3-Dimethylpyrazine (VIII). 2-Chloro-3-methylpyrazine (3·21 g, 0·025 mole) was added at 10 ± 2° during 1 hr to MeMgI (0·1 mole) in ether (25 ml) prepared in the usual way. After stirring the mixture for a further 1 hr, excess Grignard was decomposed with dil HCl. The soln was made alkaline with NaOH aq and extracted with ether (4 × 25 ml). The crude product (2·2 g) was distilled to give a colourless oil (1·95 g), bp. 72–100°/10 mm. Separation of the product (0·7 g, 26%) from starting material (0·7 g, 22% recovery) was effected by preparative GLC. The product was shown to be identical with authentic 2,3-dimethylpyrazine obtained via the decarboxylation of 5,6-dimethylpyrazine-2,3-dicarboxylate.

2-Chloro-3,5-dimethylpyrazine (XII). This was prepared by the chlorination of commercial 2,6-dimethylpyrazine (5 g, 0·05 mole) with sulphuryl chloride/DMF, as described. The crude product (4·3 g) contained the required chloride (1·4 g, 43%) together with recovered starting material (2·8 g, 56%).

2-Methoxy-3,5-dimethylpyrazine (XIII). The crude product obtained above (1·5 g) was methoxylated essentially as before and gave 2-methoxy-3,5-dimethylpyrazine (0·21 g), isolated by preparative GLC.

Synthesis of deuterated pyrazines

2-Deutero-6-methylpyrazine (XIV). A number of experiments were performed using the following

procedure: 2-chloro-6-methylpyrazine (1 molar eqt) was added to a soln of NaOMe, prepared from Na (1 g, at. eqt) and MeOD (25 ml/g of Na) followed by the addition of dioxan (62·5 ml/g of Na). The mixture was deuterolysed over Pd/C catalyst (5%, 0·1 g/g of the chloropyrazine) at room temp and pressure. After the uptake of the theoretical quantity of deuterium the (very slow) deuterolysis was stopped and the mixture was filtered. The catalyst was washed with several small portions of MeOH and the washings were added to the filtrate. Analysis by GLC (E.G.A. on Chromosorb G at 150°) of a number of experiments showed the presence of 2-deutero-6-methylpyrazine together with a small quantity (1–5%) of a component having the same retention time as 2-methoxy-6-methylpyrazine. 2-Deutero-6-methylpyrazine (40–50%) of isotopic purity 93–97% deuterium at position 6 was separated from this mixture by preparative GLC (20 ft. column of E.G.A. on Chromosorb G at 120°). The isotopic purity was assessed by NMR analysis and 97% isotopically pure material was used for subsequent reactions. The true yield is probably considerably higher as the GLC trapping efficiency would not be expected to be greater than 85% at this dilution.

During a hydrogenation employing the isopropanol/isopropoxide solvent/base system a small quantity ($\sim$ 3% theoretical yield) of a solid by-product precipitated from the filtered mixture at low temp. This was shown by its NMR and mass spectra to be XVII. On the evidence of the NMR spectrum of the crude product this material (partially deuterated in the Me groups) was also present in the deuterolysis experiments under the conditions given above.

2-Deutero-5-chloro-6-methylpyrazine (XV). 2-Deutero-6-methylpyrazine (250 mg, 0·0026 mole) was chlorinated with sulphuryl chloride/DMF as before. Compound XV (12 mg) was isolated by preparative GLC, together with residual starting material (75 mg).

2-Deutero-5-methoxy-6-methylpyrazine (XVI). The crude product (180 mg, 0·0014 mole) from the above chlorination reaction was methoxylated as before, to give XVI (18 mg isolated by preparative GLC).

2-Deutero-3-monodeuteromethyl-6-methoxypyrazine (V). 2-Chloro-3-chloromethyl-5-methoxypyrazine (0·5 g, 0·0026 mole) was deuterolysed over 5% Pd on alumina catalyst (1·2 g) in the presence of sodium isopropoxide prepared from Na (0·131 g, 0·057 g.at.) and isopropanol-d_1 (27 ml), the quantity of isopropanol-d_1 being sufficient to keep the Na derivative in soln at room temp. Very slow uptake of deuterium continued after 1 molar equivalent (126 ml) of deuterium had been absorbed, and the deuterolysis was terminated after the uptake of 129 ml of deuterium. The mixture was processed as before and separation of the deuterated pyrazine was effected by direct preparative GLC (20 ft. column of Apiezon L at 150°). The yield of 2-monodeuteromethyl-3-deutero-5-methoxypyrazine was 140 mg (43%).

2-Methoxy-5-methylpyrazine (IV). The hydrogenolysis procedure used was identical to that described for the preceding deuterolysis except for the use of hydrogen and isopropanol in place of deuterium and isopropanol-d_1.

2-Deutero-3-methylpyrazine (VI). 2-Chloro-3-methylpyrazine (1·0 g) was deuterolysed following a procedure identical to that described above for 2-chloro-6-methylpyrazine. The yield of 2-deutero-3-methylpyrazine was 350 mg (47%) with isotopic purity 85% at the 3-position.

Determination of isotopic purity. The percentage incorporation of deuterium at specific ring positions in 2-methylpyrazine was measured before proceeding to the chlorination and methoxylation reactions. Since the protons of the Me group undergo some deuterium exchange the Me signal could not be used as an integration standard. Rather than use a separate internal standard it was found convenient to add a sufficient quantity of europium shift reagent to give a first-order spectrum (e.g. Fig 1(i)) and to integrate the residual proton signal at the replacement position against the remaining ring signals due to both deuterated and undeuterated material.

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