Nuclear Chlorination of Alkylpyrazines

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A series of monoalkylpyrazines have been chlorinated specifically in the 3-position with sulphuryl chloride in the presence of *NN*-dimethylformamide; the nucleus of symmetrical 2,6-dialkylpyrazines is also readily chlorinated. The structures of the by-products from some of the reactions have been assigned. The reaction of isobutylpyrazine with phosphoryl chloride and phosphorus pentachloride was also investigated and gave specifically 2-chloro-5-isobutylpyrazine in 25% yield.

THE identification of a number of alkoxy(alkyl)pyrazines isolated from a variety of natural sources (such as oil of galbanum,[1] bell peppers,[2] green peas,[3] roasted coffee,[4] and oil of petitgrain [5]) has required the synthesis of several groups of model compounds with unambiguous structures. Halogeno-compounds are convenient starting materials for the preparation of such alkoxy-derivatives but until now their application has been restricted by the general lack of specific halogenating agents. For this reason the halogeno-intermediates required have often been derived from hydroxy- or amino-pyrazines.[6-8] Amongst the agents suitable for direct nuclear halogenation which have been investigated are chlorine in carbon tetrachloride,[9] bromine in acetic acid,[8,10] bromine in aqueous hydrobromic acid,[11] a mixture of phosphorus pentabromide and phosphoryl bromide,[12] phosgene,[13] sodium hypoiodite,[6] phosphoryl chloride (for pyrazine *N*-oxides [14]), and chlorine or sulphuryl chloride in a number of solvents.[15] In using the last-named reagents, the presence of water has been shown to affect the position of substitution in the nucleus. For instance, the chlorination of chloropyrazine with chlorine in the presence of a water-soluble polar organic solvent containing at least 0·02 mol percent of water gives 2,6-dichloropyrazine, whilst less than this amount of water results in preferential formation of the 2,3-isomer.[15] Similarly, the chlorination of chloropyrazine with sulphuryl chloride in the presence of *NN*-dimethylformamide affords specifically, 2,3-dichloropyrazine;[15] in this instance the sulphuryl chloride functions as both chlorinating and dehydrating agent.

We have investigated this last procedure for the chlorination of 2-alkylpyrazines and found it to lead specifically to the 3-chloro-derivative (see Table 1); no other isomers were detected by g.l.c. under conditions which are known to separate the 2,3- and 2,6-isomers. The chlorination of some 2,6-dialkylpyrazines was also studied but these were mainly of the symmetrical type and specificity in these cases was thereby ensured [see, however, isopropyl(methyl)pyrazine below].

The conversion of the chloro-derivatives cited in Table 1 into the corresponding methyl ethers is virtually quantitative and also facilitates the isolation of the products and by-products. For this reason the yields and n.m.r. data quoted in the Table are those of the methyl ethers. The n.m.r. spectra substantiated the structures unambiguously and also confirmed that the isolated materials did not contain any noticeable amounts of other isomers. It may be seen that in general the yield of 2-alkyl-3-chloropyrazine increases with increasing complexity of the 2-alkyl group. It is interesting that the chlorination of an unsymmetrical 2,6-dialkylpyrazine (*viz.* 2-isopropyl-6-methylpyrazine) results in the preferential formation of the chloro-derivative on the more hindered side.

The chlorination and subsequent methoxylation of isopropylpyrazine yielded, in addition to the 3-methoxy-derivative, by-products (I) and (II) (*ca.* 50% yield). On similar treatment, isobutylpyrazine gave the 3-methoxy-derivative and by-products (III) and (IV) (*ca.* 10% yield) (see Table 2 for n.m.r. data). The formation of these by-products could account for the relatively low yields of the 3-methyl ethers obtained starting with these pyrazines.

In many cases the crude chlorinated product contained a dark polymer-like material, from which the chloro-derivative could be easily separated by steam-distillation. The degree of by-product formation (*e.g.*, as a result of polychlorination of the nucleus or side-chain chlorination) seemed dependent upon the molar ratios of reactants and, to a lesser extent, the temperature of reaction (see later).

[1] A. F. Bramwell, J. W. K. Burrell, and G. Riezebos, *Tetrahedron Letters*, 1969, 3215.
[2] (*a*) R. G. Buttery, R. M. Seifert, R. E. Lundin, D. G. Guadagni, and L. C. Ling, *Chem. and Ind.*, 1969, 490; (*b*) R. G. Buttery, R. M. Seifert, D. G. Guadagni, and L. C. Ling, *J. Agric. Food Chem.*, 1969, **17**, 1322.
[3] K. E. Murray, J. Shipton, and F. B. Whitfield, *Chem. and Ind.*, 1970, 897.
[4] P. Friedel, V. Krampl, T. Radford, J. A. Renner, F. W. Shephard, and M. A. Gianturco, *J. Agric. Food. Chem.*, 1971, **19**, 530.
[5] R. J. H. Duprey and J. F. Janes, *Amer. Perfumer*, 1971, **86**, No. 9, 53.
[6] A. Hirschberg and P. E. Spoerri, *J. Org. Chem.*, 1961, **26**, 1907.
[7] A. E. Erickson and P. E. Spoerri, *J. Amer. Chem. Soc.*, 1946, **48**, 400.
[8] R. C. Ellingson and R. L. Henry, *J. Amer. Chem. Soc.*, 1949, **71**, 2798.
[9] U.S.P.s 3,096,331, 1963 and 3,113,132, 1963, but see also W. B. Lutz, S. Lazarus, S. Klutchko, and R. I. Meltzer, *J. Org. Chem.*, 1964, **29**, 415.
[10] B.P.s 928,151, 1963 and 928,152, 1963.
[11] H. Brachwitz, E.Ger.P. 66,877, 1969 (*Chem. Abs.*, 969, **71**, 124,498*d*).
[12] K. H. Schaaf and P. E. Spoerri, *J. Amer. Chem. Soc.*, 1949, **71**, 2043.
[13] B.P. 927,974, 1963.
[14] B. Klein, N. E. Hetman, and M. E. O'Donnell, *J. Org. Chem.*, 1963, **28**, 1682.
[15] U.S.P. 3,291,802, 1966.

The reaction of s-butylpyrazine with sulphuryl chloride–*NN*-dimethylformamide was thoroughly investigated and the optimum conditions (with respect to the yields based on pyrazine consumed) for the formation of the 3-chloro-compound were ascertained. The most favourable molar ratio of the pyrazine to sulphuryl chloride appeared to be 1 : 1·2, and any amount of *NN*-dimethylformamide in excess of 0·25 mol. equiv. seemed to be superfluous but not detrimental to the reaction. It was also found that temperatures between 0 and 45° gave essentially the same yields (*ca.* 40% based on converted starting material over 1—3 h).

Apart from the main product, the chlorination of s-butylpyrazine with an excess of sulphuryl chloride in the presence of *NN*-dimethylformamide gave compounds (*ca.* 50% total yield) to which structures analogous to those obtained with isobutyl- and isopropylpyrazine [see (IVa and b) and (II)] were tentatively assigned by g.l.c.–m.s. By chlorination of 2,6-di-s-butylpyrazine, compounds (V) and (VI) (*ca.* 25% total yield) were isolated, and analogous products with an unsaturated side-chain were also obtained from s-butylpyrazine using an excess of sulphuryl chloride.

Addition of aluminium chloride–sulphur monochloride (1%), which is known to catalyse the nuclear chlorination of toluene by sulphuryl chloride,[16] failed to

[16] I. L. Finar, 'Organic Chemistry,' Vol. 1, 3rd edn., Longmans, 1959, p. 519.

TABLE 1

The chlorination of alkylated pyrazines with sulphuryl chloride and *NN*-dimethylformamide; n.m.r. data for the methoxy-derivatives of the principal products (δ/p.p.m.; *J*/Hz)

Starting material	Yield (%) [a]	δ (ring protons)	*J* (±0·1 Hz) (ring protons)	δ (OMe)	δ (Substituents other than OMe)
2-Methylpyrazine	29 [b]	7·88 7·93	2·85	3·94	Me: 2·41
2-Isopropylpyrazine	21 [b]	7·83 7·98	2·85	3·94	Pr^i: 1·22 (6H, d, *J* 7), 3·31 (1H, sept, *J* 7)
2-Isobutylpyrazine	26 [b]	7·83 7·96	2·85	3·93	Bu^i: 0·93 (6H, d, *J* 6·5), 2·18 (1H, complex m), *ca.* 2·64 (2H, complex d)
2-s-Butylpyrazine	41 [b]	7·83 7·99	2·75	3·94	Bu^s: 0·82 (3H, t, *J* 7), 1·19 (3H, d, *J* 7), 1·3—2·1 (2H, complex m), 3·13 (1H, sext, *J* 7)
2-(1-Ethylpropyl)pyrazine	48 [b]	7·83 8·02	2·70	3·93	Et_2CH: 0·76 (6H, t, *J* 7), *ca.* 1·4—2·0 (4H, complex m), 2·97 (1H, m, *J* 7)
2,6-Dimethylpyrazine	31 [b]	7·97 [d]			Me: 2·47, 2·57
2,6-Diethylpyrazine	17 [b]	7·66		3·91	Et: 1·23 (3H, t, *J* 7), 1·26 (3H, t, *J* 7), 2·69 (2H, q, *J* 7), 2·76 (2H, q, *J* 7)
2,6-Di-s-butylpyrazine	30 [b]	7·66		3·93	Bu^s: 0·83 (6H, t, *J* 7), 1·22 (3H, d, *J* 7), 1·26 (3H, d, *J* 7), *ca.* 1·4—2·0 (4H, complex m), 2·71 (1H, sext, *J* 7), 3·14 (1H, sext, *J* 7)
2-Isopropyl-6-methylpyrazine	28 [b] 14 [c]	7·67 7·68		3·91 3·91	Me: 2·38; Pr^i: 1·23 (6H, d, *J* 7), 3·29 (1H, sept, *J* 7) Me: 2·40; Pr^i: 1·26 (6H, *J* 7), 2·95 (1H, sept, *J* 7)
2-Isopropyl-3-methoxy-6-methylpyrazine	24 [c]			3·91	Me: 2·30; Pr^i: 1·17 (6H, d, *J* 7), 3·20 (1H, sept, *J* 7)

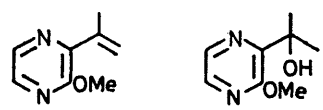
[a] All reactions were carried out under comparable conditions (see experimental section). [b] Product chlorinated at the 3-position. [c] Product chlorinated at the 5-position. [d] Data are for the chloride.

TABLE 2

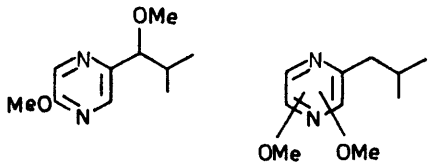
N.m.r. spectra of by-products (δ/p.p.m., *J*/Hz)

Compound	δ (ring proton)	*J* (±0·1 Hz) (ring protons)	δ (OMe)	δ (Substituents other than OMe)
(I)	7·87 8·07	2·65	3·98	$CH{:}CMe{\cdot}$: 2·17 (3H, d, *J* 0·85; d, *J* 1·50), 5·52 (1H, m, *J ca.* 1·5), 6·05 (1H, m, *J ca.* 1·5)
(II)	7·99 8·01	2·85	4·02	$Me_2C(OH)$: 1·49 (6H) 4·76 (1H)
(III)	8·03 8·09	1·50	side chain 3·25 ring 3·94	$Pr^iCH(OMe)$: 0·83 (3H, d, *J* 7), 0·90 (3H, d, *J* 7), *ca.* 2·03 (1H, m, 2-H), 3·94 (1H, d, *J* 6, 1-H)
(IVa)	7·30		3·90 3·92	Bu^i: 0·93 (6H, d, *J* 6·5), *ca.* 2·00 (1H, complex m), *ca.* 2·43 (2H, complex d)
(IVb)	7·64		3·88 3·91	Bu^i: 0·90 (6H, d, *J* 6·5), *ca.* 2·03 (1H, complex m), *ca.* 2·53 (2H, complex d)
(V)	8·20 8·53	<0·5		$CH_2{:}CEt$: 1·5 (3H, t, *J* 7), 2·63 (2H, q, *J* 7, m, *J ca.* 1·5), 5·29 (1H, d, *J ca.* 1·5, t, *J ca.* 1·5), 5·80 (1H, m, $J \leqslant 1$) Bu^s: 0·85 (3H, t, *J* 7), 1·31 (3H, d, *J* 7), *ca.* 1·4—2·0 (2H, complex m), 2·78 (1H, sext, *J* 7)
(VI)	8·15 8·43	<0·5		$MeCH{:}CMe$: 1·87 (3H, d, *J* 7, m, *J ca.* 1·5), 2·08 (3H, m, *J ca.* 1·5), 6·49 (1H, q, *J* 7, q, *J ca.* 1·5) Bu^s: 0·84 (3H, t, *J* 7), 1·28 (3H, d, *J* 7), *ca.* 1·4—2·0 (2H, complex, m), 2·77 (1H, sext)

increase the yield of 2-chloro-3-methylpyrazine. Attempts to retard that part of the side-chain chlorination which might have resulted from a free radical

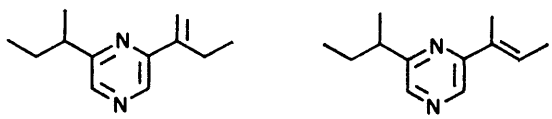


(I) (II)



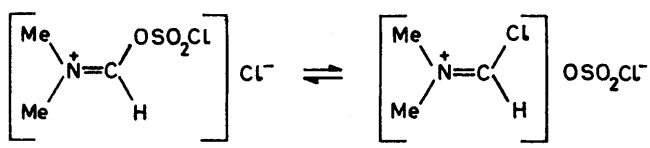
(III) (IV a,b) (2 isomers)

mechanism by the addition of sulphur or iron(III) chloride had no apparent effect, as did performing the reaction in the absence of light.

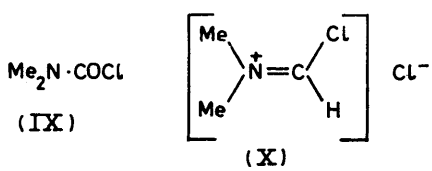


(V) (VI)

A further study of the mechanism of the chlorination was based on the work of Hasserodt,[17] who suggested that the complex formed when sulphuryl chloride reacts with *NN*-dimethylformamide gave an equilibrium mixture of the species (VII) and (VIII). Elimination of sulphur dioxide to give the acid chloride (IX) is believed to progress *via* the cation of species (VII) by pyrolysis, which may be base-catalysed; a similar elimination of sulphur trioxide *via* the cation (VIII) is assumed to give the chloride (X). Although the temperatures applied in our work were not conducive to the reaction (VII) ⟶ (IX), the presence of base (*i.e.* the pyrazine derivative) means that at least five species might have been responsible for the actual



(VII) (VIII)



(IX) (X)

chlorination, *viz.* the cations of (VII) and (VIII), the acid chloride (IX), and the anions Cl^- and OSO_2Cl^-.

The acid chloride (IX) was prepared,[17] but did not effect any detectable chlorination of s-butylpyrazine under the given conditions. The cation of species (VIII) has been shown to be present in the complex formed between thionyl chloride and *NN*-dimethylformamide; however, the use of this complex under conditions identical to those of our experiments, gave no chlorination. Species (VIII) represents an especially active salt of chlorosulphonic acid, the anion of which was prepared by the neutralisation of chlorosulphonic acid with trimethylamine [this base was selected to give a cation which would resemble that of the salt (VIII)].

This product however, did not chlorinate s-butylpyrazine and, since the chloride ion is unlikely to be the chlorinating agent, it would appear reasonable that the cation of species (VII) is mainly responsible for the chlorination.

During an investigation of the use of other dipolar aprotic solvents in place of *NN*-dimethylformamide for the chlorination of s-butylpyrazine, it was shown that (*a*) no specific chlorination occurs in the absence of a dipolar aprotic solvent, (*b*) *N*-methylpyrrolid-2-one and acetic anhydride were less efficient (yielding 28 and 15% of the 3-chloro-derivative respectively), and (*c*) with acetonitrile and *NN*-dimethylacetamide the conversions were extremely low.

An interesting change in the selectivity of the reaction with temperature was noticed with isobutylpyrazine. In this case an increase in the temperature of the reaction from 45 to 75° resulted in an increase in the yield of the 2,5-isomer from 1 to 13%, although the yield of the 2,3-isomer remained virtually unchanged (at 0° the 2,5-isomer was not detected).

During the course of our investigation of other potentially-specific chlorinating agents, it was found that the reaction of isobutylpyrazine with a mixture of phosphoryl chloride and phosphorus pentachloride gave 2-chloro-5-isobutylpyrazine (25%) with no detectable quantities of the other isomers. A similar result was obtained with s-butylpyrazine, but in this case the yield was very low (*ca.* 1%) although the majority of the starting material was consumed. The scope of this reaction has not yet been investigated but it could provide a means for the specific preparation of the 2,5-isomers.

The structures of the compounds were established from n.m.r. data (see Tables 1 and 2).

EXPERIMENTAL

N.m.r. spectra were obtained at 60 MHz with a Varian A60A instrument for carbon tetrachloride solutions. Analytical g.l.c. was performed with a Pye 104 instrument with 9 ft glass columns packed with Apiezon L (3% + 0·3% FFAP on Chromosorb G, 100—120 mesh), FFAP (3% on Chromosorb G) or E.G.A. (3% on Chromosorb G). All solvents were reagent grade or better. Appropriate mass spectral data were obtained for all compounds,

[17] U. Hasserodt, *Chem. Ber.*, 1968, **101**, 113.

and are listed in Supplementary Publication No. SUP 20444.*

2-Isobutylpyrazine, 2-s-butylpyrazine, 2-isopropylpyrazine, and 2-(1-ethylpropyl)pyrazine were prepared by the alkylation of 2-methylpyrazine according to the general method described in the literature.[18] 2-Isopropyl-6-methyl- and 2,6-di-s-butyl-pyrazine were prepared by the alkylation of 2-methyl- and 2-s-butyl-pyrazine, respectively, with acetone and ethyl methyl ketone.[19]

The following experimental procedure may be regarded as typical of the technique employed for the chlorination of alkylpyrazines.

2-Chloro-3-s-butylpyrazine.—Sulphuryl chloride (397 g, 2·94 mol) was added dropwise to a stirred mixture of 2-s-butylpyrazine (400 g, 2·94 mol) and *NN*-dimethylformamide (249 g, 3·41 mol) during 2 h. The rate of addition was such as to maintain the temperature of the reaction at 45 ± 5°. The reaction was exothermic and a cooling bath at *ca.* 20° was employed. When the reaction was complete, the mixture was cooled to below 40° and water (600 ml) was added cautiously, whilst keeping the temperature below 40°.† The pH was adjusted to 7·0—8·0 with aqueous sodium hydroxide (450 ml, 50% w/w), the temperature again being maintained below 40°. The alkaline mixture was steam-distilled and the distillate was extracted with chloroform (3 × 50 ml). The combined extracts were dried and evaporated *in vacuo* to give the crude product (350 g) which was shown (g.l.c.) to contain 2-chloro-3-s-butylpyrazine (173 g, 34%) and unchanged s-butylpyrazine (80 g, 20%). These components were easily separated by distillation, but in general the steam-distilled product was methoxylated directly.

2-Methoxy-3-s-butylpyrazine.—The crude 2-chloro-3-s-butylpyrazine (350 g) was heated under reflux with a solution of sodium methoxide (3·1 mol) in methanol (500 ml) for 5 h. The mixture was filtered to remove sodium chloride and the excess of methanol was removed *in vacuo* prior to the addition of water (100 ml) and extraction with light petroleum (3 × 50 ml). The combined extracts were washed to neutrality with water (6 × 50 ml), dried, and, after removing the solvent, the crude product (292 g) was obtained. This contained (g.l.c.) 2-methoxy-3-s-butylpyrazine (160 g, 33%) and 2-s-butylpyrazine (76 g, 19%). Fractionation through a column (90 cm) packed with glass helices gave 2-s-butylpyrazine (64 g, 16%) and 2-methoxy-3-s-butylpyrazine (151 g, 31%).

2-Isobutyl-5-methoxypyrazine.—2-Isobutylpyrazine (68 g, 0·5 mol) was added dropwise to a stirred mixture of phosphorus pentachloride (109 g, 0·55 mol) and phosphoryl chloride (300 ml, 1·2 mol) and the mixture was heated at 95 ± 5° for 8 h. The mixture was quenched by the cautious, dropwise addition of water (150 ml), whilst maintaining the temperature at 20° with external cooling.‡ The pH of the mixture was adjusted to 9·0 with aqueous sodium hydroxide (50% w/w) before steam-distillation and extraction of the distillate with ether. The combined extracts were dried and the solvent was removed *in vacuo* to give the crude product. G.l.c. showed that only one positional isomer had been formed, *i.e.* 2-chloro-5-isobutylpyrazine.

The crude chloro-derivative was methoxylated as described already. Fractionation of the crude product (145 g) through a column (100 cm, glass helices) gave 2-isobutyl-5-methoxypyrazine (17 g, 21% yield) and 2-isobutylpyrazine (17 g, 25% recovery).

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* For details of Supplementary Publications, see Notice to Authors No. 7 in the index issue of *J. Chem. Soc.* (*A*), 1970.

† This method of quenching was found to be more convenient than addition to water.

‡ Vigorous reaction is often preceded by a long induction period when the mixture is poured cautiously into iced water.

[18] J. D. Behun and R. Levine, *J. Org. Chem.*, 1961, **26**, 3379.
[19] A. F. Bramwell, L. S. Payne, G. Riezebos, P. Ward, and R. D. Wells, *J. Chem. Soc.* (*C*), 1971, 1627.