Reactions of Halogenomethanes in the Vapour Phase. Part 4.[1] The Reactions of Imidazoles with Chloroform at 550 °C, and a Comparison with their Liquid-phase Reactions with Trichloroacetate Ion or Hexachloroacetone and Base

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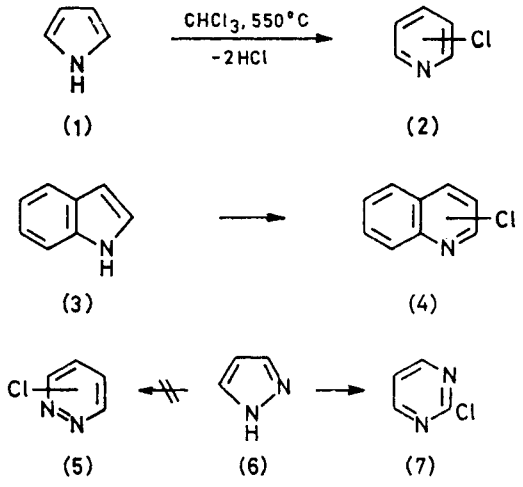
1-Unsubstituted imidazoles and chloroform at 550 °C in a flow system give mainly 5-chloropyrimidines, together with 4-chloropyrimidines and chloropyrazines. The effects of methyl substituents on the ratio of products is considered. The liquid-phase reactions of 2-methyl- and 2,4,5-trimethyl-imidazole under conditions in which dichlorocarbene is said to be formed in basic or neutral conditions were studied, and compared with the gas-phase reactions with chloroform.

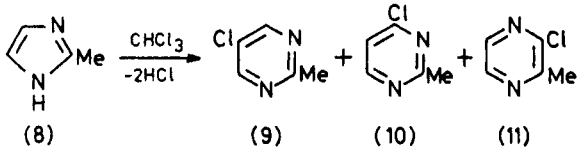
We have shown that both pyrroles [2] (1) and indoles [3] (3) undergo ring-expansion reactions with chloroform at 550 °C in a flow system to give chloropyridines (2) and chloroquinolines (4), respectively. The major products may be visualised as being formed by insertion of a carbon atom from chloroform into either a C–N or C–C bond of the five-membered ring. Pyrazole (6) also undergoes ring-expansion under these conditions but, in marked contrast to the previous cases, only one product [a pyrimidine (7)] is formed,[1] *i.e.* insertion of the carbon atom occurs in the N–N bond but not in the C–N or C–C



bonds, which would produce a pyridazine (5). In order to study further the regio-specificity of chloroform (or an intermediate species) in these high-temperature processes, we have investigated the corresponding reactions of imidazoles.[4] Also, two of these compounds have been subjected to liquid-phase reactions under conditions in which dichlorocarbene is usually thought to be an intermediate.

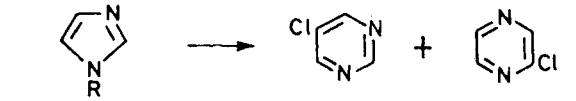
RESULTS AND DISCUSSION

In our earlier investigations we used two different reactor systems: one vertical [2] and one nearly horizontal.[1] The yield of product from 2-methylimidazole (8) (Scheme 1) depended on the type of reactor used: the vertical and horizontal reactors gave yields of 19 and 44%, respectively. However, the composition of the reaction products was very similar. In each case the major product (55 and 60%, respectively) was 5-chloro-2-methyl-



pyrimidine (9) and the second major product was 2-chloro-3-methylpyrazine (11). The product from the vertical reactor additionally contained 4-chloro-2-methylpyrimidine (10) (5%). Thus, insertion occurs into both the C–C bond [to give (9)] and the C–N bonds [to give (10) and (11)], though the first is the dominant process. In contrast, 2-methylimidazole with either hexachloroacetone [5] and sodium ethoxide at ambient temperature, or sodium trichloroacetate [6] at elevated temperature, gave (in 5 and 7% yield, respectively) 5-chloro-2-methylpyrimidine only.

That the methyl group has a significant effect on the course of the pyrolysis reaction is shown by comparison of the results obtained with 2-methylimidazole and imidazole (12). In the latter case, the product consisted of a greater proportion of C–C bond insertion product, *i.e.* 5-chloropyrimidine (14), together with 2-chloropyrazine (15) (10%). Pyrolysis of 1-trimethylsilylimidazole (13) under these conditions gave a high

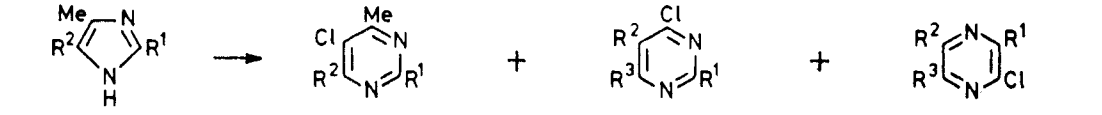


overall yield (65%) and an increased proportion of 2-chloropyrazine (18%). Interestingly, in the cases of (12) and (13) no 4-chloropyrimidine was detected, *i.e.* insertion into the N–C-4 bond does not occur.

Mixtures of 5-chloro- and 4-chloro-pyrimidines and

chloropyrazines (Table) were obtained when 4(5)-methyl- (16), 2,4(5)-dimethyl- (17), and 4,5-dimethyl-imidazole (18) were separately pyrolysed with chloroform. In the cases of (16) and (17) the proportion of 4-chloropyrimidine formed from insertion into the N–C-4 bond is increased compared with imidazole. This is a similar trend to that formed in the comparison of the results from 2-methyl-imidazole and imidazole, *i.e.* the presence of a methyl group increases the proportion of N–CMe bond insertion. However, 2,4(5)-dimethyl- (17) and, more unexpectedly, 4,5-dimethyl-imidazole (18) show an increased proportion (20%) of chloropyrazines formed by insertion into the N–C-2 bond compared with that from imidazole (10%). Thus, the effect of the methyl substituent is not always to facilitate insertion into the N–CMe bond. In general, the *C*-methyl-substituted imidazoles gave lower overall yields than that obtained with imidazole.

The pyrolysis of 2,4,5-trimethylimidazole (19) with chloroform gave an unexpectedly high yield (92%) of chloropyrimidine (23) (98%) and the pyrazine (34) (2%); the latter was not detected in an earlier investigation [7] when less sensitive analytical techniques were used. A larger proportion of the pyrazine (34) (5%) and some 4-chloropyrimidine (28) (5%), together with the 5-chloropyrimidine (23) (91%), were formed when (19) was treated with hexachloroacetone and base. This result is as expected if (28) and (34) are formed by attack on the heterocyclic anion, while the 5-chloropyrimidine is formed from the molecule.



(16) $R^1 = R^2 = H$
(17) $R^1 = Me, R^2 = H$
(18) $R^1 = H, R^2 = Me$
(19) $R^1 = R^2 = Me$

(20) $R^1 = R^2 = H$
(21) $R^1 = Me, R^2 = H$
(22) $R^1 = H, R^2 = Me$
(23) $R^1 = R^2 = Me$

(24) $R^1 = R^2 = H, R^3 = Me$
(25) $R^2 = H, R^1 = R^3 = Me$
(26) $R^1 = R^3 = Me, R^2 = H$
(27) $R^1 = H, R^2 = R^3 = Me$
(28) $R^1 = R^2 = R^3 = Me$

(29) $R^1 = R^3 = H, R^2 = Me$
(30) $R^1 = R^2 = H, R^3 = Me$
(31) $R^1 = R^2 = Me, R^3 = H$
(32) $R^1 = R^3 = Me, R^2 = H$
(33) $R^1 = H, R^2 = R^3 = Me$
(34) $R^1 = R^2 = R^3 = Me$

The reaction products were usually isomers and the structure of the novel compounds was deduced mainly from spectroscopic evidence. The mass spectrum showed the presence or absence of chlorine (ratio of M^+, $M^+ + 1$, and $M^+ + 2$ peaks) and the molecular formula. ^1H N.m.r. spectra in $CDCl_3$ indicated the presence or absence of methyl substituents and the inter-relationship of any ring protons, but not necessarily the position of these protons on the nucleus. A combination of chemical-shift and coupling-constant data was used to assign the positions of the protons. The ^1H n.m.r. spectra were also obtained in trifluoroacetic acid and the large downfield shift of 5-H in the protonated pyrimidines was characteristic and useful. This may be explained in terms of shielding caused by a reduction in the anisotropy of the nitrogen atom upon protonation.[8] The small downfield shift (0.29 p.p.m.) observed for 5-Me in the spectrum of (26) in trifluoroacetic acid compared with that in $CDCl_3$ agrees with the similarly small downfield shift (0.29—0.36 p.p.m.) for 3-Me in chloropicolines compared with those for the 2- (0.31—0.37 p.p.m.) and 4-Me (0.36—0.45 p.p.m.) substituents. The range of values of these shifts overlap but it is noteworthy that, when there is more than one Me substituent on the pyridine nucleus,

The yield and composition of the diazines formed from imidazoles and chloroform at 550 °C

		5-Chloropyrimidine (%)		4-Chloropyrimidine (%)		Chloropyrazine (%)	
Imidazole	Yield (%)						
(12)	43	(14)	90			(15)	10
(13)	65	(14)	82			(15)	18
(8)	44	(9)	55	(10)	5	(11)	40
(16)	38	(20)	55	(24)	36	(29)	6
						(30)	3
(17)	35	(21)	43	(25)	33	(31)	12
				(26)	4	(33)	6
(18)	30	(22)	62	(27)	18	(33)	20
(29)	92	(23)	70	(28)	17	(34)	13

ring-expansion products. This is unlikely to be due to a greater vulnerability to electrophilic attack since the dimethylimidazoles (17), (18), and (19) give rise to slightly lower total yields than the methylimidazoles (8) and (16), and imidazole. When the results from the trimethylimidazole and imidazole are compared, the 3-methyl substituents are seen to cause the following effects: a decrease in the proportion of the 5-chloropyrimidine; an increase in the proportion of the 4-chloropyrimidine; and little change in the proportion of the chloropyrazine, though this contrasts with the results from other methyl-substituted imidazoles with the exception of 4(5)-methylimidazole (16). Our re-investigation of the reaction of 2,4,5-trimethylimidazole with trichloroacetate gave a product (12%) containing the 5-

the 3-Me substituent always has the smallest shift upon protonation.

EXPERIMENTAL

I.r., ^{1}H n.m.r., and mass spectra were obtained with the instruments described previously.[2] The analytical g.l.c. was performed on a stationary phase of OV 17 (3%) on Chromosorb G. Preparative g.l.c. used: (A), Apiezon L (25%); (B), Carbowax 20 M (20%); (C), OV 17 (15%); and (D), OV 17 (20%). The starting materials and authentic samples were from commercial sources unless otherwise indicated by a reference to a preparative route.

Pyrolysis Experiments.—The general procedure was similar to that described previously using the vertical [2] or nearly horizontal [1] reactor system. The molar ratio of imidazole : chloroform was in the range 1 : 5—1 : 7. The products were obtained by basification of the acidic mixture and separate continuous extraction with two solvents: in all cases ether was used first, and then either chloroform or dichloromethane. The mixtures were analysed by g.l.c. and separated by preparative g.l.c. In some cases we were unable to isolate each compound, and in these instances the composition of the fraction was deduced from its n.m.r. spectrum.

The assignment of a known structure was confirmed, wherever possible, by comparison of at least two items of data (m.p., g.l.c. retention time, i.r., ^{1}H n.m.r., or mass spectrum) with those either obtained by us from an authentic sample or in the literature.

2-Methylimidazole (20 g) in the vertical reactor gave an oil (6.1 g, 19%) from the ether extract and this was separated on column A at 100 °C into 5-chloro-2-methylpyrimidine [9] (55%), compound A (5%), and 2-chloro-3-methylpyrazine [10] (40%). Compound A was 4-chloro-2-methylpyrimidine [11] (Found: M^+, 128. Calc. for $C_5H_5{}^{35}ClN_2$: M, 128); τ ($CDCl_3$) 7.28 (3 H, s, Me), 2.82 (1 H, d, J 5.5 Hz, 5-H), and 1.49 (1 H, d, J 5.5 Hz, 6-H).

Imidazole (13.6 g) and chloroform (5 mol equiv.) in the vertical reactor gave a maximum yield (43%) of diazines when six trays [2] were in the tube. The products were separated by preparative g.l.c. (column A at 120 °C) into 5-chloropyrimidine (90%), m.p. 36—37 °C (lit.,[12] m.p. 36.5 °C) and chloropyrazine (10%).

1-Trimethylsilylimidazole (14 g) in the vertical reactor gave an oil (7.4 g, 65%) from ether which was separated on column C into 5-chloropyrimidine (82%) and chloropyrazine (18%).

4(5)-Methylimidazole [13] (8.4 g) in the vertical reactor yielded a product (5.1 g, 38%) from ether. Preparative g.l.c. on column A at 90 °C gave two fractions: fraction 1 was 5-chloro-4-methylpyrimidine [14] (55%) (Found: M^+, 128. Calc. for $C_5H_5{}^{35}ClN_2$: M, 128); $\nu_{max.}$ 3 045 (aromatic CH), 2 920 (aliphatic CH), and 1 390 cm^{-1} (pyrimidine ring); τ ($CDCl_3$) 7.39 (3 H, s, 4-Me), 1.41 (1 H, s, 6-H), and 1.05 (1 H, s, 2-H): fraction 2 was shown (g.l.c. on column C at 120 °C) to be composed of three compounds and analysis of its n.m.r. spectrum indicated them to be: 4-chloro-6-methylpyrimidine [15] (36%); τ ($CDCl_3$) 7.47 (3 H, s, 6-Me), 2.86 (1 H, s, 5-H), and 1.14 (1 H, s, 2-H); 2-chloro-5-methylpyrazine [16] (6%), τ ($CDCl_3$) 7.46 (3 H, s, 5-Me), 1.78 (1 H, d, J 1.5 Hz, 6-H), and 1.54 (1 H, d, J 1.5 Hz, 3-H); 2-chloro-6-methylpyrazine [17] (3%); τ ($CDCl_3$) 7.46 (3 H, s, 6-Me), 1.65 (1 H, d, J 0.5 Hz, 5-H), and 1.60 (1 H, d, J 0.5 Hz, 3-H).

2,4(5)-Dimethylimidazole [13] (2.2 g) afforded an ether extract which yielded an oil (1.15 g, 35%), which was separated into three fractions by g.l.c. on column A at 100 °C: 5-*chloro*-2,4-*dimethylpyrimidine* (43%) (Found: M^+, 142. $C_6H_7{}^{35}ClN_2$ requires M, 142); $\nu_{max.}$ (film) 3 040 (aromatic CH), 2 960 (aliphatic CH), and 1 380 cm^{-1} (pyrimidine ring); τ ($CDCl_3$) 7.45 (3 H, s, 4-Me), 7.35 (3 H, s, 2-Me), and 1.55 (1 H, s, 6-H); 4-chloro-2,6-dimethylpyrimidine [18] (33%) (Found: M^+, 142. Calc. for $C_6H_7{}^{35}ClN_2$: M, 142); $\nu_{max.}$ (film) 3 060 (aromatic CH), 2 960 (aliphatic CH), and 1 394 cm^{-1} (pyrimidine ring); τ ($CDCl_3$) 7.53 (3 H, s, 6-Me), 7.34 (3 H, s, 2-Me), and 2.97 (1 H, s, 5-H). Analysis of the ^{1}H n.m.r. spectrum of the third fraction showed it to contain three components: 3-chloro-2,5-dimethylpyrazine (12%), τ ($CDCl_3$) 7.45 (3 H, s, 5-Me), 7.34 (3 H, s, 2-Me), and 1.77 (1 H, s, 6-H); 4-chloro-2,5-dimethylpyrimidine (8%), τ ($CDCl_3$) 7.50 (3 H, s, 5-Me), 7.34 (3 H, s, 2-Me), and 1.55 (1 H, s, 6-H); and 2-chloro-3,5-dimethylpyrazine (4%), τ ($CDCl_3$) 7.50 (3 H, s, 5-Me), 7.39 (3 H, s, 3-Me), and 1.95 (1 H, s, 6-H).

4,5-Dimethylimidazole [19] (9.0 g) afforded a residue (3.99 g, 30%) on evaporation of the ethereal extract which was separated by preparative g.l.c. on column D at 125 °C into: 5-*chloro*-4,6-*dimethylpyrimidine* (62%) (Found: M^+, 142.030 1. $C_6H_7{}^{35}ClN_2$ requires M, 142.029 8); $\nu_{max.}$ (film) 2 920 (aliphatic CH) and 1 386 cm^{-1} (pyrimidine ring); τ ($CDCl_3$) 7.40 (6 H, s, 4- and 6-Me), and 1.11 (1 H, s, 2-H); 4-*chloro*-5,6-*dimethylpyrimidine* (18%) (Found: M^+, 142.029 7. $C_6H_7{}^{35}Cl$ requires M, 142.029 8); $\nu_{max.}$ (film) 3 040 (aromatic CH), 2 920 (aliphatic CH), and 1 396 cm^{-1} (pyrimidine ring); τ ($CDCl_3$) 7.63 (3 H, s, 5-Me), 7.44 (3 H, s, 6-Me), and 1.33 (1 H, s, 2-H); and 2-*chloro*-5,6-*dimethylpyrazine* (20%) (Found: M^+, 142.029 5. $C_6H_7{}^{35}ClN_2$ requires M, 142.029 8); $\nu_{max.}$ (film) 3 045 (aromatic CH), 2 950 (aliphatic CH), and 1 390 cm^{-1} (pyrazine ring); τ ($CDCl_3$) 7.48 (6 H, s, 5- and 6-Me) and 1.70 (1 H, s, 3-H).

2,4,5-Trimethylimidazole [20] (8 g) in the horizontal reactor gave a semi-solid residue (8.8 g, 91%) from chloroform which was separated into two fractions by preparative g.l.c. on column C at 110 °C: fraction 1 was 5-chloro-2,4,6-trimethylpyrimidine [7] (70%). Fraction 2 was separated into two components by preparative g.l.c. on column C at 90 °C to give 2-chloro-3,5,6-trimethylpyrazine (13%), m.p. 56—57 °C (lit.,[16] 57 °C), and 4-*chloro*-2,5,6-*trimethylpyrimidine* (17%) (Found: C, 54.2; H, 5.8; N, 17.6%; M, 156.045 8. $C_7H_9{}^{35}ClN_2$ requires M, 156.045 4); $\nu_{max.}$ (film) 2 930 cm^{-1} (aliphatic CH); τ ($CDCl_3$) 7.69 (3 H, s, 5-Me), 7.5 (3 H, s, 6-Me), and 7.38 (3 H, s, 2-Me).

Liquid-phase Reactions with (a) *Sodium Trichloroacetate or* (b) *Hexachloroacetone and Base.*—*2-Methylimidazole.* (*a*) The heterocycle (4.1 g), sodium trichloroacetate (15 g), and dimethoxyethane (80 cm^3) were refluxed for 18 h. Removal of the sodium chloride and the solvent yielded the product (3.9 g), which comprised 2-methylimidazole (93%) and 5-chloro-2-methyl-pyrimidine (7%).

(*b*) 2-Methylimidazole (4.5 g), sodium methoxide (10.8 g), hexachloroacetone (26 g), and methylene chloride (150 cm^3) were mixed and allowed to react in the usual way.[5] The residue after evaporation of the solvent was extracted with ether, and this ether-soluble product was chromatographed on neutral alumina to give 5-chloro-2-methylpyrimidine (0.42 g). The portion of the residue not soluble in ether was crystallised from ethanol (charcoal) to give 2-methylimidazole (3.9 g).

2,4,5-Trimethylimidazole. (*a*) The imidazole (6 g), sodium trichloroacetate (28 g), and 1,2-dimethoxyethane (200 cm^3) were refluxed for 22 h. The product was analysed by g.l.c.

as 5-chloro-2,4,6-trimethylpyrimidine (98%) and 2-chloro-3,5,6-trimethylpyrazine (2%).

(*b*) Sodium methoxide (7.5 g) was added to a mixture of 2,4,5-trimethylimidazole (3.5 g), hexachloroacetone (18 g), ether (200 cm^3), and dichloromethane (50 cm^3). Removal of the sodium chloride and solvents yielded a residue which was chromatographed on neutral alumina with ether. The eluate yielded a product (0.3 g) which was shown by g.l.c. to be 5-chloro-2,4,6-trimethylpyrimidine (88%), 2-chloro-3,5,6-trimethylpyrazine (5%), 4-chloro-2,5,6-trimethylpyrimidine (4%), and trimethylimidazole (3%). Finally, elution with chloroform yielded more 2,4,5-trimethylimidazole (2.4 g).

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