Reactions of Halogenomethanes in the Vapour Phase. Part 2.[1] Reactions of Chloroform with Indoles and Pyrrolo[2,3-*b*]pyridines at 550 °C

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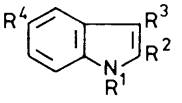
Vapour-phase reactions of chloroform with indole at 550 °C give mainly 3-chloroquinoline together with smaller proportions of 2-chloroquinoline and quinoline. *C*-Methylindoles similarly give the corresponding methylchloroquinolines and methylquinolines. The 2,3-cyclopentindole (20) gives mainly 3-chlorocarbazole and significant quantities of carbazole and 4-chlorocarbazole. In contrast, 1-methyl- and 1-benzyl-indole (7) afford mainly quinoline with some 3-chloroquinoline and in the case of (7) only, 2-phenylquinoline. Pyrrolo[2,3-*b*]pyridines (24) and (25) give mainly the corresponding 3-chloro-1,8-naphthyridines (26) and (27), though in low yield.

We have reported[1] the formation of both 2- and 3-chloropyridines when a mixture of chloroform and pyrrole or its methyl derivatives, is subjected to vapour-phase pyrolysis in a flow system. An obvious extension of this work was to investigate the reaction of indole and methylindoles under similar conditions. Such an investigation had interest since, at the time of the investigation, we did not know whether the interaction with chloroform would modify the benzene moiety in the indole nucleus. Also, if no attack occurs at the six-membered ring, we have in indole a molecule containing the pyrrole nucleus with two atoms of this heterocycle not susceptible to attack, though in any comparison with the reactions of pyrroles account must be taken of the different features causing stabilisation of the likely transition states in the two systems.

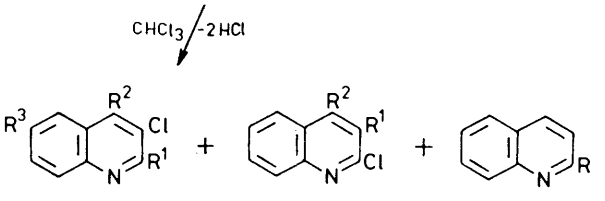
RESULTS AND DISCUSSION

Early investigations[2] with indole (1) in a vapour-phase pyrolysis system (followed by collection and analysis of the products in the manner described for pyrrole) quickly showed that 3-chloroquinoline (9) is formed (Scheme 1). A careful study was made of the variations in the yield of product caused by changing (*a*) the indole : chloroform ratio, and (*b*) the position and number of the preheater traps. The conditions found to be optimum for the reaction with indole were used for indole derivatives, though there is no reason to suppose that conditions were optimum in these cases.

Indole gave a total yield (42%) of quinolines considerably lower than that (86%) obtained for the formation of pyridines from pyrrole.[1] Careful analysis of the product showed it to consist of 3-chloroquinoline (9) (94%), 2-chloroquinoline (12) (4%), and quinoline (14) (2%); a markedly lower proportion of the 2-chloro-isomer than was obtained in the case of the 2-chloropyridine (24%) from pyrrole. A similar pattern was observed in the products from 2-methylindole (2), 3-methylindole (3), and 2,3-dimethylindole (4), *i.e.* <50% yield of quinolines, the majority of this product being the corresponding 3-chloroquinoline derivative; 2-chloroquinolines were either not detected or formed only a very small proportion of the total product. Until the recent development of the use of phase-transfer catalysts,[3] these reactions represented the best preparative conversion of indoles into the corresponding 3-chloroquinolines. After our work was completed, Patterson *et al.*[4] reported their investigation of similar reactions, using conditions similar to these we had described for the case of pyrrole, and their findings were largely very similar to ours. Thus, they reported a 2—5% impurity of 2-chloroquinoline in the crude 3-chloroquinoline obtained in 38.7% yield from indole. However, they did not detect 2-chloro-4-methylquinoline (13) as a very minor product from 3-methylindole.



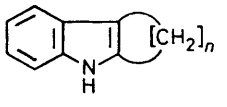
(1) $R^1 = R^2 = R^3 = R^4 = H$
(2) $R^1 = R^3 = R^4 = H, R^2 = Me$
(3) $R^1 = R^2 = R^4 = H, R^3 = Me$
(4) $R^1 = R^4 = H, R^2 = R^3 = Me$
(5) $R^1 = R^3 = H, R^2 = R^4 = Me$
(6) $R^1 = Me, R^2 = R^3 = R^4 = H$
(7) $R^1 = CH_2Ph, R^2 = R^3 = R^4 = H$
(8) $R^1 = R^2 = Me, R^3 = R^4 = H$



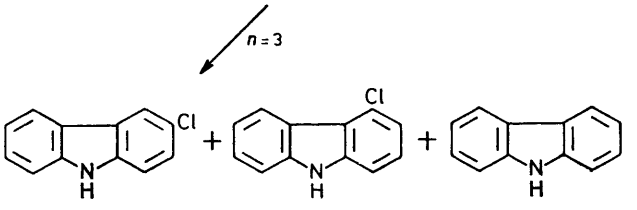
(9) $R^1 = R^2 = R^3 = H$
(10) $R^1 = R^3 = Me, R^2 = H$
(11) $R^1 = Me, R^2 = R^3 = H$
(12) $R^1 = R^2 = H$
(13) $R^1 = H, R^2 = Me$
(14) R = H
(15) R = Ph
(16) R = Me

Patterson *et al.*[5] have shown that under similar conditions, but in the absence of chloroform, 2-methylindole is largely unaffected, while 3-methylindole gave starting material containing a small quantity (3%) of 2-methylindole. We found that 2,5-dimethylindole (5) gave a 37% yield of 3-chloro-2,6-dimethylquinoline (10); a very similar result to that obtained with 2-methylindole. Thus, no products were isolated which resulted from attack at a methyl substituent.

The vapour-phase reactions of chloroform with indole derivatives having a ring fused across the 2,3-positions were also investigated. No products were isolated from the reactions of 2,3-cyclohepteno- (17), 2,3-cyclo-octeno- (18), and 2,3-cyclododeceno-indole (19); only charred material remained. In contrast, 2,3-cyclopentenoindole (20) gave a mixture of carbazole (23) (28%), 4-chloro-



(17) $n = 5$
(18) $n = 6$
(19) $n = 10$
(20) $n = 3$

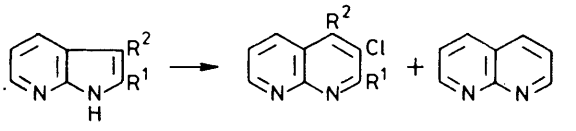


(21) (22) (23)

carbazole (22) (13%), and 3-chlorocarbazole (21) (59%), in 24% total yield. Thus it appears that ring-expansion to give an aromatic product may be necessary for either the reaction to occur or a product to be isolated.

A marked change in the pattern of the product composition was noted when NH was replaced by N-alkyl. For example, 1-methylindole (6) and chloroform yielded (25% total) mainly quinoline (77%) with minor proportions of 3-chloroquinoline (22%) and 2-chloroquinoline (1%). Patterson *et al.*[5] have shown that 1-methylindole alone is not isomerised at 550 °C in a flow system. In contrast, 1-benzylindole (7) does undergo isomerisation, together with other reactions, and these processes rapidly increase in importance in the temperature range 500—600 °C, so that at 500 °C 1-benzylindole was recovered (98%), whereas at 600 °C only 2% of the 1-benzylindole was recovered. In the presence of chloroform at 550 °C the major product from 1-benzylindole was quinoline (62%) together with 3-chloroquinoline (18%) and 2-phenylquinoline (15) (20%). Both quinoline and 2-phenylquinoline are minor products from the pyrolysis of 1-benzylindole alone, and quinoline is formed (but only as a trace component [5]) on pyrolysis of indole alone (indole is the likely major thermolysis product from 1-benzylindole [5]). Therefore it is very unlikely that the reaction products obtained from 1-alkylindoles and chloroform can be explained by thermolysis and subsequent reaction of the products to give the isolated quinolines. Pyrolysis of 1,2-dimethylindole (8) in the presence of chloroform yielded a smaller proportion of 3-chloro-2-methylquinoline (11) (42%) than was obtained (95%) with 2-methylindole. In addition, there were 3-chloroquinoline (9) (28%), 2-methylquinoline (16) (22%), and quinoline (14) (8%). Since these last three compounds were not detected in the reaction product from 2-methylindole, it seems likely that they are not formed from 3-chloro-2-methylquinoline, and they may be formed directly from 1,2-dimethylindole. However, the ratio of products is not altogether in accord with the result from 1-methylindole. This would lead to the expectation of a high proportion of 2-methylquinoline (also, possibly, quinoline) in the product from 1,2-dimethylindole, but does not indicate that the formation of 3-chloroquinoline is to be expected.

We obtained no products which could be attributed to secondary reactions at the heteroaromatic ring of the pyridine or quinoline products. It, therefore, seemed possible that ' azaindoles ' and other related heterocycles containing more than two nitrogen atoms might serve as a starting point for the vapour-phase synthesis of ' azaquinolines ' and other corresponding ring-expansion products. This was realised in part but the yield of products was low. For instance, pyrrolo[2,3-*b*]pyridine (24) gave only a 10% yield of a mixture which contained 1,8-naphthyridine (28) (33%) and 3-chloro-1,8-naphthyridine (26) (39%). Interestingly, the proportion of non-chlorinated ring-expansion product is high and is markedly different from the trace quantity of quinoline obtained from indole. Hydrogen chloride is a by-product of all the reactions with chloroform, and it may be that the interaction of the hydrogen chloride with the basic nitrogen atom in the starting material causes a significant change in the extent and course of the reaction. In the light of the result with ' 7-azaindole ', the isolation of 3-chloro-2,4-dimethylnaphthyridine (27) as the only product from 2,3-dimethylpyrrolo[2,3-*b*]pyridine (25) was unexpected.



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

EXPERIMENTAL

2,3-Dimethylindole,[6] pyrrolo[2,3-*b*]pyridine,[7] 2,3-dimethylpyrrolo[2,3-*b*]pyridine,[8] and 5,6,7,8-tetrahydro-5*H*-cyclopent[*b*]indole [9] were prepared by known routes. The thermal indolisation procedure [9] gave 2,3-cycloheptenoindole [10] (85%), 2,3-cyclo-octenoindole [11] (87%), and 2,3-cyclododecenoindole [12] (74%) (from the appropriate phenylhydrazone and digol) in considerably higher yields than have been obtained by acid-catalysed cyclisations. Other starting materials were obtained from commercial sources.

The general pyrolysis procedure was as described for pyrrole but, in the case of indole, the optimum conditions were found to be an indole : chloroform molar ratio of 1 : 3 at a contact time of 15 s, and only three trays with the highest one 14.5 cm from the top of the reaction tube. The products were separated and analysed with the instruments specified.[1] A comparison of g.l.c. retention time for each

compound was made with that of an authentic sample whenever possible. The support material in the g.l.c. columns was acid-washed and silanised Diatomite. The stationary phase (and concentration) for the analytical columns were: (A) Carbowax 20 M (10%); (B) OV-17 (3%); and (C) Apiezon L (10%): and for the preparative columns were: (1) Carbowax 20 M (20%); (2) OV-17 (10%); (3) OV-17 (15%); (4) OV-17 (20%); and (5) Apiezon L (25%).

The essential details of the experimental procedure for each pyrolysis experiment, and the separation, analysis, and identification of the components of the reaction mixture are given in the following order: the compound pyrolysed; the total yield of product (based on recovered starting material, if appropriate); the reference letter for the analytical g.l.c. column and the temperature used for the separation; the components of the mixture in the order of increasing retention time, the relative retention times, and the proportion of each component in the product. These are followed by details of the preparative g.l.c. conditions and the physical characteristics used to identify the components of the mixture.

Indole (1): 42%; A, 170 °C; quinoline, 1.00, 2%; 3-chloroquinoline, 1.55, 94%; and 2-chloroquinoline, 2.45, 4%. The compounds were separated by preparative g.l.c. on column 1 at 170 °C.

1-*Methylindole* (6): 25%; B, 160 °C; quinoline, 1, 77%; 3-chloroquinoline, 1.69, 22%; and 2-chloroquinoline, 2, 1%. These products were isolated by preparative g.l.c. on column 2 with temperature programming from 100 to 200 °C at 8 °C min^{-1}.

2-*Methylindole* (2): 46%; B, 220 °C; 2-methylindole, 1.00, 5%; and component 2, 1.22, 95%. The mixture was separated by preparative g.l.c. on column 4 at 220 °C. Component 2 was shown to be 3-chloro-2-methylquinoline (Found: M^+, 177.034 6. Calc. for $C_{10}H_8{}^{35}ClN$: M, 177.034 6); $\nu_{max.}$ (KBr) 3 050 (Ar–H), 2 920 (Me), 1 590 (quinoline ring), 748 (*o*-disubstituted benzene), 900, and 858 cm^{-1} (isolated H); τ($CDCl_3$) 7.20 (3 H, s, Me), 2.42 (3 H, m, 5-, 6-, and 7-H), 2.00 (1 H, q, 8-H), and 1.92 (1 H, s, 4-H).

1,2-*Dimethylindole* (8): 28%; C, 200 °C; quinoline, 1.00, 8%; 2-methylquinoline, 2.2, 22%; 3-chloroquinoline, 1.9, 28%; and 3-chloro-2-methylquinoline, 2.6, 42%. The components were isolated on column 5 with temperature programming from 125 to 225 °C at 8 °C min^{-1}.

3-*Methylindole* (3): 32%; B, 210 °C; 3-methylindole, 1.00, 2%; component 2, 1.58, 94%; and component 3, 1.96, 4%. The products were isolated by preparative g.l.c. on column 3 at 210 °C. Component 2 was 3-chloro-4-methylquinoline, m.p. 54—55 °C (lit.,[12] m.p. 54—55 °C) (Found: M^+, 177.034 7. Calc. for $C_{10}H_8{}^{35}ClN$: M, 177.034 6); $\nu_{max.}$ (KBr) 3 070 (Ar–H), (Me), 1 612 (quinoline ring), 753 (*o*-disubstituted benzene), 860, and 850 cm^{-1} (isolated H); τ($CDCl_3$) 7.27 (3 H, s, Me), 2.38 (2 H, m, 6- and 7-H), 1.98 (2 H, m, 5- and 8-H), and 1.24 (1 H, s, 2-H). Component 3 was identified as 2-chloro-4-methylquinoline by comparison of its g.l.c. retention time and i.r. spectrum with those of an authentic sample.

2,3-*Dimethylindole* (4): 35%; B, 190 °C; 2,3-dimethylindole, 1.00, 2%; 3-chloro-2,4-dimethylquinoline, 1.72, 98%. The chloro-compound had m.p. 74—75 °C (lit.,[13] m.p. 73 °C) (Found: M^+, 191.049 9. Calc. for $C_{11}H_{10}{}^{35}ClN$: M, 191.050 2); $\nu_{max.}$ (liq.) 3 070 (Ar–H), 2 955 (Me), 1 612 (quinoline ring), and 755 cm^{-1} (*o*-disubstituted benzene); τ($CDCl_3$) 7.32 (3 H, s, 4-Me), 7.22 (3 H, s, 2-Me), 2.47 (2 H, m, 6- and 7-H), and 2.09 (2 H, m, 5- and 8-H).

2,5-*Dimethylindole* (5): 37%; B, 170 °C; 2,5-dimethylindole, 1.00, 1%; component 2, 1.15, 1%; component 3, 1.55, 98%. Component 3 was purified on column 2 at 200 °C and shown to be 3-chloro-2,6-dimethylquinoline, m.p. 76—78 °C (lit.,[14] m.p. 82 °C) (Found: C, 68.5; H, 5.1; N, 7.0%; M^+, 191. Calc. for $C_{11}H_{10}ClN$: C, 68.9; H, 5.0; N, 7.0%; for $C_{11}H_{10}{}^{35}ClN$, M, 191); $\nu_{max.}$ (KBr) 3 006 (Ar–H), 2 950 (Me), 1 598 (quinoline ring), 852 and 840 (isolated CH), and 825 cm^{-1} (vicinal CH); τ($CHCl_3$) 7.38 (3 H, s, 6-Me), 6.78 (3 H, s, 2-Me), 2.16 (2 H, m, 5- and 7-H), 1.38 (1 H, s, 4-H), and 1.15 (1 H, d, $J_{8.7}$ 8.2 Hz, 8-H). We were unable to identify positively component 2, but it was shown to have an identical mass spectrum to that of component 3 and so is likely to be the 2-chloro-isomer.

2,3-*Cyclopentenoindole* (20): 24%; B, 230 °C; component 1.00, 1, 28%; component 2, 1.17, 13%; component 2, 1.17, 13%; component 3, 2.16, 59%. Component 3 was isolated by preparative g.l.c. on column 2 at 230 °C and components 1 and 2 were obtained as a mixture. G.c.–m.s. showed that component 1 did not contain chlorine and had M^+ 167. It was shown to be carbazole (expected M^+ 167) by comparison of the mass spectrum and g.l.c. retention time with those of an authentic sample. Component 3 was thought to be 3-chlorocarbazole and had m.p. 198 °C (lit.,[15] 199 °C) (Found: C, 71.8; H, 4.0; N, 6.8%; M^+, 201. Calc. for $C_{12}H_8ClN$: C, 71.6; H, 4.0; N, 7.0%. $C_{12}H_8{}^{35}ClN$, M, 201); $\nu_{max.}$ (KBr) 3 410 (NH); τ($CDCl_3$) 2.78 (1 H, s, 4-H), 2.60 (4 H, m, 2-, 5-, 6-, and 7-H), 2.00 (2 H, m, 1- and 8-H), and −1.3 (1 H, s, exchanged in D_2O, NH).

Component 2 was not isolated, but its mass spectrum was obtained by linked g.c.–m.s. and was shown to be almost identical with that of 3-chlorocarbazole. Comparison of the g.l.c. retention time of component 2 with those of 1-, 2-, and 4-chlorocarbazole (prepared by cyclisation of cyclohexanone *o*- and *m*-chlorophenylhydrazones [16] followed by dehydrogenation [15] of the corresponding chlorotetrahydrocarbazoles) showed component 2 to be 4-chlorocarbazole.

Pyrrolo[2,3-b]*pyridine* (24): 10%; B, 240 °C; pyrrolo-[2,3-*b*]pyridine, 1.00, 76%; component 2, 2.08, 2%; component 3, 3.17, 22%. The components were isolated by preparative g.l.c. on column 3 at 240 °C. Component 2 was identified as 1,8-naphthyridine by comparison of its g.l.c. retention time with that of an authentic sample. Component 3 was 3-chloro-1,8-naphthyridine, m.p. 149—150 °C (lit.,[17] m.p. 143—144 °C) (Found: M^+, 164. Calc. for $C_8H_5{}^{35}ClN_2$: M, 164); $\nu_{max.}$ (KBr) 3 050 (Ar–H) and 1 597 cm^{-1} (naphthyridine ring); τ($CDCl_3$) 1.79 (1 H, q, $J_{6.5}$ 8.3 and $J_{6,7}$ 5.5 Hz, 6-H), 1.37 (1 H, d, $J_{4.2}$ 2.4 Hz, 4-H), 0.97 (1 H, dd, $J_{5,6}$ 8.3 and $J_{5.7}$ 1.7 Hz, 5-H), 0.77 (1 H, d, $J_{2.4}$ 2.4 Hz, 2-H), and 0.60 (1 H, dd, $J_{7.5}$ 1.7 and $J_{7.6}$ 5.5 Hz, 7-H). An authentic sample of 2-chloro-1,8-naphthyridine was available, but this compound was not present in the pyrolysate.

2,3-*Dimethylpyrrolo*[2,3-b]*pyridine* (25): 57%; B, 230 °C: 2,3-dimethylpyrrolo[2,3-*b*]pyridine, 1.00, 87%; and component 2, 2.85 13%. The unknown was separated on column 2 at 230 °C to give 3-*chloro*-2,4-*dimethyl*-1,8-*naphthyridine*, m.p. 158—160 °C [Found: C, 62.2; H, 4.8; N, 14.4%; M^+, 192. $C_{10}H_9ClN$ requires C, 62.5; H, 4.7; N, 14.6%; M, 192 (for ^{35}Cl)]; $\nu_{max.}$ (KBr) 3 060 (Ar–H), 2 970 (Me), 1 598 (aromatic ring), and 804 cm^{-1} (3 adjacent H); τ($CDCl_3$) 7.22 (3 H, s, 4-Me), 7.1 (3 H, s, 2-Me), 2.55 (1 H, dd, $J_{6.5}$ 8.5 and $J_{6,7}$ 4.0 Hz, 6-H), 1.63 (1 H, dd,

$J_{5.6}$ 8.5 and $J_{5.7}$ 1.8 Hz, 5-H), and 0.85 (1 H, dd, $J_{7.6}$ 4 and $J_{7.5}$ 1.8 Hz, 7-H).

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