Polyhalogenoaromatic Compounds. Part 48.[1] Reactions of Tetrachloro-4-cyanopyridine with Mono- and Di-functional Nucleophiles

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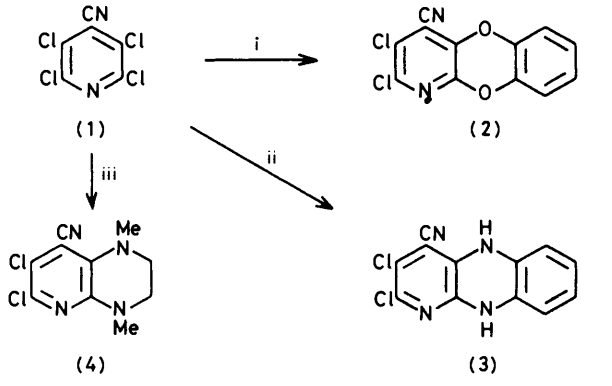
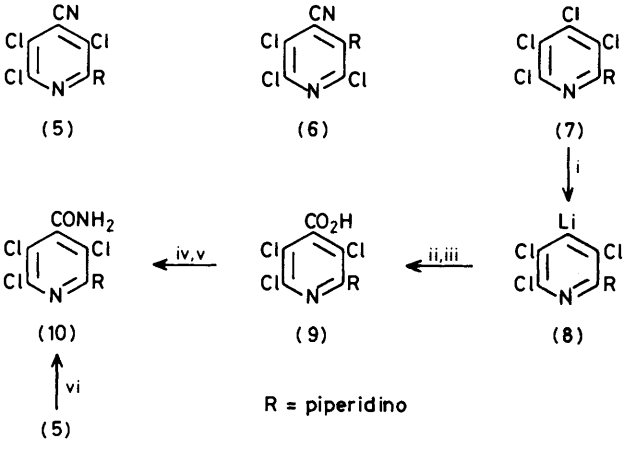
Nucleophiles react with tetrachloro-4-cyanopyridine by replacement of chlorine rather than by reactions involving the cyano-group. With *o*-dihydroxybenzene, *o*-phenylenediamine, and *NNN'N'*-tetramethylethanediamine, new heterocycles (2,3,4) are formed by replacement of 2- and 3-Cl. With piperidine 2,3,5-trichloro-4-cyano-6-piperidinopyridine (5) and 3,5-dichloro-4-cyano-2,6-dipiperidinopyridine (12) are obtained. Other monofunctional nucleophiles similarly give 2(6)-substituted trichloro-4-cyanopyridines.

Polyhalogenopyridines readily undergo nucleophilic substitution at the 2- and/or 4-positions, and 2- and 4-substituted polychloropyridines are thus readily available.[2] 3-Substituted polychloropyridines are of interest because of their possible biological activity (*cf.* nicotine, *etc.*) and as potential intermediates to build up fused rings with bidentate nucleophiles. Some success in obtaining 3-substituted polychloropyridines has been achieved by metal-halogen exchange of 4-substituted tetrachloropyridines,[3] and by photosubstitution,[4] but a polychloropyridine derivative in which the 3-position could be activated towards simple nucleophilic substitution would be useful and experimentally convenient. Tetrachloro-4-nitropyridine and tetrachloro-4-pyridylsulphonyl derivatives are known, but react with nucleophiles mainly by displacement of the 4-substituent.[5,6] Tetrachloro-2- and -4-cyanopyridines are now available by high temperature vapour-phase chlorination of cyanopyridines.[7] Some reactions of the 4-cyano-compound (1) with ambident nucleophiles (Scheme 1) showed that both the 2- and 3-positions were indeed activated towards these reagents, so that new heterocycles could be formed without attack on, or loss of, the cyano-group. For example, under basic conditions pyrocatechol gave the benzodioxinopyridine (2)† in up to 92% yield. Similarly, *o*-phenylenediamine gave the pyrido[2,3-*b*]quinoxaline (3), and *NNN'N'*-tetramethylethylenediamine gave the pyrido[2,3-*b*]pyrazine (4) (presumably with loss of chloromethane).

In none of the reactions with ambident nucleophiles represented in Scheme 1 was any uncyclised intermediate observed, so we did not know whether the initial attack took place at the 2- or the 3-position. We therefore investigated the reaction of tetrachloro-4-cyanopyridine (1) with a simple amine, piperidine. With a deficiency of the amine, a trichloro-4-cyanopiperidinopyridine (up to 78%) was the only product observed. With an excess of the amine, a dichloro-4-cyano-dipiperidinopyridine was also obtained. The ^{13}C n.m.r. spectrum of the monopiperidino-derivative was compared with those predicted for the two possible isomers (5) and (6) by our simple additivity method.[8] As shown in the Table, the predicted spectrum for the 2-piperidino-isomer (5) corresponded much more closely to the experimental spectrum. However, stronger evidence was required, particularly since no 3-dialkylaminotetrachloropyridine was available as a reference compound. Our 'classical' proof of structure is summarised in Scheme 2. We have previously shown that the reaction of tetrachloro-6-piperidinopyridine (7) with n-butyllithium gives the 4-lithio-compound (8).[9] Reaction of this



Scheme 1. *Reagents*: i, pyrocatechol; ii, *o*-phenylenediamine; iii, *NNN'N'*-tetramethylethanediamine



Scheme 2. *Reagents*: i, BuLi; ii, CO_2; iii, H_3O^+; iv, $SOCl_2$; v, NH_3; H_2SO_4/H_2O

intermediate (8) with carbon dioxide gave the 4-carboxylic acid (9), which was converted into its amide (10). The amide proved to be identical with that obtained by partial hydrolysis of the product from tetrachloro-4-cyanopyridine and piperidine, which was, therefore, the 2(6)-piperidino-compound (5). The nitrile (5) could not be hydrolysed to the carboxylic acid (9); under a variety of acidic conditions only the amide (10) was obtained, and with, for example, potassium hydroxide in ethanol the ethoxy-amide (11) was formed.

The dipiperidino-derivative was the 2,6-disubstituted

† **CAUTION** Since this compound bears some structural resemblance to the notoriously toxic chlorinated dibenzodioxins it must be handled with great caution, as must all polychloro-compounds.

Table. Predicted and observed ^{13}C n.m.r. spectra

Compound	δ/p.p.m.[a] C-2	C-3	C-4	C-5	C-6
(1), observed	147.0	131.8	125.3	131.8	147.0
Δ for 3-piperidino-group [b]	+10.3	−10.4	+10.3	+1.3	+9.4
(6), predicted	136.7	142.2	115.0	130.5	137.6
Δ for 2-piperidino-group [8]	−10.4	+10.3	+1.3	+9.4	+1.5
(5), predicted	157.4	121.5	124.0	122.4	145.5
Compound from reaction of (1) with piperidine, observed	155.9	120.5 [c]	124.8	121.4 [c]	145.0

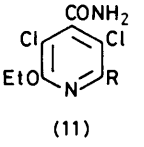
[a] For convenience in comparison ring carbons are numbered starting at the side bearing a piperidino-group, despite alphabetical order. [b] Assumed analogous to that of 2-piperidino-group.[8] [c] Assignments could be interchanged.

isomer (12), since its ^{13}C n.m.r. spectrum showed only three signals for the pyridine ring carbon atoms.

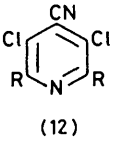
Reactions of tetrachloro-4-cyanopyridine (1) with several other monofunctional nucleophiles were carried out. The position of the substituent has not been proved by synthesis in every case, but it is reasonably assumed that substitution occurs in the 2-(6-) position, by analogy with the product from piperidine. The other compounds prepared were (13) (with aniline), (14) (with benzylamine), (15) (with hydrazine), (16) (with *NN'*-dimethylhydrazine), and (17) (with sodium nitrite in dimethyl sulphoxide followed by hydrolysis; *cf.* ref. 10). The morpholino-derivative (18) has also been prepared and its structure established.[11]

It is noteworthy that in the polychloropyridines, the presence or absence of infrared absorption at *ca.* 2 250 cm^{-1} is not diagnostic for the presence or absence of a cyano-group. For example the band is absent in tetrachloro-4-cyanopyridine (although three peaks are present in the Raman spectrum, at 2 232, 2 243, and 2 257 cm^{-1}) and in the 2-piperidino-compound (5) but is just observable, at 2 240 cm^{-1}, in the di-piperidino-compound (12). Compounds which show the band clearly are indicated in the Experimental section.

Since this work was completed, it has been reported that 3-chloro-4-cyanopyridine undergoes nucleophilic displacement of chlorine, although in some cases attack on the cyano-group was observed.[12]

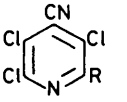


(11)



(12)

R = Piperidino



(13) R = NHPh
(14) R = $NHCH_2Ph$
(15) R = $NHNH_2$
(16) R = NMeNHMe
(17) R = OH
(18) R = Morpholino

Experimental

N.m.r. spectra were recorded at 60 MHz or 90 MHz (^1H), or 20 MHz (^{13}C) with Me_4Si as internal standard. Mass spectra refer to ions containing ^{35}Cl only; the appropriate isotope clusters were observed. Light petroleum was the fraction, b.p. 60—80 °C. Tetrachloro-4-cyanopyridine was a gift from I.C.I. Ltd., or was made by one of us (R. S. D.) using facilities at I.C.I. Ltd., Blackley.

Reactions of Tetrachloro-4-cyanopyridine.—(i) *With o-dihydroxybenzene.* A mixture of tetrachloro-4-cyanopyridine (1.0 g, 4.13 mmol), *o*-dihydroxybenzene (0.46 g, 4.18 mmol), sodium carbonate (0.70 g) and isopropyl alcohol (20 ml) was heated and stirred under reflux during 27 h. The mixture was cooled and poured into water. Filtration gave 2,3-*dichloro*-4-*cyanopyrido*[2,3-b][1,4]*benzodioxin* (2) (1.06 g, 92%), m.p. 237—240 °C, $\nu_{max.}$ 2 230w cm^{-1} (Found: C, 51.7; H, 1.6; N, 10.2%; M^+, 278. $C_{12}H_4Cl_2N_2O_2$ requires C, 51.6; H, 1.4; N, 10.0%; M^+, 278).

(ii) *With* o-*diaminobenzene* (o-*phenylenediamine*). A mixture of *o*-diaminobenzene (0.90 g, 8.3 mmol), tetrachloro-4-cyanopyridine (2.0 g, 8.3 mmol) and dioxan (20 ml) was stirred and heated under reflux during 40 h. The mixture was filtered, poured into diethyl ether, and again filtered, the small amount of insoluble material being discarded. The ether solution was concentrated, and the precipitated solid was recrystallised from ethyl acetate–chloroform to give 2,3-*dichloro*-4-*cyano*-5,10-*dihydropyrido*[2,3-b]*quinoxaline* (3) (0.42 g, 18%; 38% allowing for recovered starting material), m.p. 234—235 °C (decomp.), $\nu_{max.}$ 2 230w cm^{-1} (Found: C, 51.8; H, 2.2; N, 20.25, $C_{12}H_6Cl_2N_4$ requires C, 52.0; H, 2.2; N, 20.2%). Starting material (1.05 g, 52.5%) was recovered from the ethereal mother-liquor by evaporation and chromatography on silica.

(iii) *With* NNN'N'-*tetramethylethane*-1,2-*diamine* (*TMEDA*). A mixture of TMEDA (1.84 g, 15.8 mmol), tetrachloro-4-cyanopyridine (4.0 g, 16.5 mmol), and dioxan (50 ml) was stirred and heated under reflux during 65 h. The solvent was evaporated and the residue was triturated with diethyl ether. The insoluble material was purified by recrystallisation and chromatography on silica to give 6,7-*dichloro*-8-*cyano*-1,4-*dimethyl*-2,3-*dihydropyrido*[2,3-b]*pyrazine* (4) (0.61 g), m.p. 147—150° (from methanol), $\nu_{max.}$ 2 200w cm^{-1}; δ [$(CD_3)_2SO$] 3.0 (s, 3H), 3.3 (s, 3H) and 3.5 (s, 4H) (Found: C, 46.7; H, 3.9; N, 21.8. $C_{10}H_{10}Cl_2N_4$ requires C, 46.7; H, 3.9; N, 21.8%). Concentration of the ethereal extract gave further crops of pyridopyrazine (0.41 g, total yield 24%). Starting material (1.14 g, 28.5%) was recovered from the combined mother liquors.

(iv) *With piperidine.* (a) Tetrachloro-4-cyanopyridine (5.28 g, 22.0 mmol) was dissolved in hot toluene (50 ml). A solution of piperidine (2.0 g, 23.5 mmol) in ethanol (20 ml) was added

during 1 h and the mixture was heated under reflux during 48 h. Evaporation of the solvent, recrystallisation from ethanol, and column chromatography (silica, gradient elution with toluene and light petroleum) gave starting material ($\lambda_{max.}$ 325 nm) and 2,3,5-*trichloro*-4-*cyano*-6-*piperidinopyridine* (5) (1.76 g, 61%), m.p. 90—92 °C, $\lambda_{max.}$ 375 and 285 nm; ^{1}H δ ($CDCl_3$) 1.7 (m, 6H) and 3.3 (m, 4H); for ^{13}C δ see Table (Found: C, 45.4; H, 3.5; N, 14.4%; M^+, 288. $C_{11}H_{10}Cl_3N_3$ requires C, 45.5; H, 3.5; N, 14.5%; M^+, 288).

(b) A similar experiment, but with toluene as solvent, anhydrous potassium carbonate present, and a reflux time of 24 h gave the same compound (71%).

(c) Tetrachloro-4-cyanopyridine (4.8 g, 20 mmol), piperidine (6.72 g, 80 mmol), and ethanol (20 ml) were heated under reflux during 48 h. The solvent was evaporated, and the product was worked up as described in (a) to give a 3,5-*dichloro*-4-*cyano*-2,6-*dipiperidinopyridine* (12) (1.72 g, 51%), m.p. 110—112 °C (from ethanol), $\lambda_{max.}$ 390 and 285 nm; $\nu_{max.}$ 2 240vw cm^{-1}; δ_H 1.7 (m) and 3.3 (m); δ_C 24.6 (piperidino C-4), 25.5 (piperidino C-3, 5), 49.6 (piperidino C-2, 6), 111.9 (CN), 113.1 (C-3, 5), 124.3 (C-4), and 155.0 (C-2, 6) (Found: C, 56.5; H, 6.0; N, 16.6%; M^+, 338. $C_{16}H_{20}Cl_2N_4$ requires C, 56.5; H, 5.9; N, 16.5%; M^+, 338).

(v) *With aniline.* A mixture of tetrachloro-4-cyanopyridine (1.2 g, 5 mmol), aniline (0.93 g, 10 mmol), and ethane-1,2-diol (50 ml) was heated under reflux during 90 min. The solution was cooled and poured slowly into ice-water. The resulting mixture was kept at 0 °C during 30 min and then filtered. The resulting solid was dried and recrystallised from ethanol to give bright yellow 2-*anilino*-3,5,6-*trichloro*-4-*cyanopyridine* (13) (0.57 g, 38%), m.p. 175—178 °C, δ_C 112.3 (CN), 116.7 and 117.9 (C-3, 5), 122.0, (anilino C-2, 6), 122.9 (C-4), 124.2 (anilino C-3, 4, 5), 138.4 (anilino C-1), 144.1 (C-6), and 149.9 p.p.m. (C-2) (Found: C, 48.9; H, 2.1; N, 13.6%; M^+, 297. $C_{12}H_6Cl_3N_3$ requires C, 48.3; H, 2.0; N, 14.0%; M^+, 297).

(vi) *With benzylamine.* A mixture of tetrachloro-4-cyanopyridine (3.0 g, 12.4 mmol), benzylamine (1.5 g, 14 mmol), and ethanol (25 ml) was stirred under reflux during 49 h. The mixture was evaporated to dryness and the residue digested with boiling chloroform. The chloroform solution was dried and evaporated, and the residue recrystallised twice from chloroform to give 2-*benzylamino*-3,5,6-*trichloro*-4-*cyanopyridine* (14) (1.18 g, 30%), m.p. 148—149 °C; $\nu_{max.}$ (HCBD mull) 2 243 cm^{-1}; ^{1}H δ 4.6 (d, 2H), 5.6br (1H), and 7.35 (s, 5H) (Found: C, 50.0; H, 2.6; N, 13.4%; M^+, 311. $C_{13}H_8Cl_3N_3$ requires C, 49.95; H, 2.6; N, 13.4%; M^+, 311).

(vii) *With hydrazine.* A mixture of tetrachloro-4-cyanopyridine (1.21 g, 5 mmol) and hydrazine hydrate (0.5 g, 10 mmol) was stirred at room temperature during 2 h. The mixture was poured into water and the resulting precipitate was recovered by filtration, dried, and recrystallised from ethanol to give pale green *trichloro*-4-*cyano*-6-*hydrazinopyridine* (15) (0.96 g, 82%), m.p. 184—186 °C, $\lambda_{max.}$ 3 390, 3 330, and 3 170 cm^{-1} (Found: C, 30.45; H, 1.3; N, 23.4%; M^+, 236. $C_6H_3Cl_3N_4$ requires C, 30.35; H, 1.3; N, 23.6%; M^+, 236).

(viii) *With* NN′-*dimethylhydrazine.* A mixture of tetrachloro-4-cyanopyridine (2.0 g, 8.3 mmol), *NN*′-dimethylhydrazine dihydrochloride (1.10 g, 8.3 mmol), sodium hydrogencarbonate (1.39 g, 16.5 mmol), and dioxan (20 ml) was stirred under reflux during 23 h. The products were recovered by evaporation under reduced pressure and chromatography on alumina. Light petroleum eluted starting material (0.42 g, 21%). Light petroleum–chloroform (3 : 1) eluted 2,3,5-*trichloro*-4-*cyano*-6-NN′-*dimethylhydrazinopyridine* (16) (0.65 g, 30%), m.p. 107—109 °C (from light petroleum, then methanol); $\nu_{max.}$ 2 240w; ^{1}H δ 2.7 (s, 3H), 3.25 (s, 3H), and 3.95 broad (1H) [Found: C, 36.2; H, 2.5; N, 21.1. $C_8H_7Cl_3N_4$ requires C, 36.2; H, 2.7; N, 21.0%]

(ix) *With sodium nitrite.* A mixture of tetrachloro-4-cyanopyridine (4.0 g, 16.5 mmol), sodium nitrite (8 g), and dimethyl sulphoxide (10 ml) was stirred at room temperature during 2 h. The mixture was poured into water and filtered. The precipitate was starting material (0.8 g, 20%). The solution was acidified with hydrochloric acid, and the resulting precipitate was recovered by filtration and identified as 2,3,5-*trichloro*-4-*cyano*-6-*hydroxypyridine* (17) (0.61 g, 16.5%), m.p. 227—229 °C (from chloroform), $\nu_{max.}$ (HCBD mull) 3 000br cm^{-1} (Found: C, 32.0; H, 0.6; N, 12.6. $C_6HCl_3N_2O$ requires C, 32.25. H, 0.45; N, 12.5%)

2,3,5-*Trichloro*-6-*piperidinopyridine*-4-*carboxaminde*.—(a) To a solution of tetrachloro-6-piperidinopyridine (prepared as described [13]) (3.0 g) in dry diethyl ether (100 ml) at −70 °C was added n-butyl-lithium (6.4 mmol) in hexane (10 ml). The mixture was kept at −35 °C during 30 min and then re-cooled to −70 °C. Dry carbon dioxide was bubbled through the solution as it warmed to room temperature, and then during a further 3 h. 4M-Hydrochloric acid was added, and the ethereal layer was separated and evaporated to dryness. The residue (1.0 g) was added to thionyl chloride (4 ml) and the mixture was heated under reflux during 30 min. The excess of thionyl chloride was distilled off. The residue was diluted with diethyl ether and ammonia was passed into the solution during 30 min. The ether was evaporated, and the residue recrystallised from ethanol to give 2,3,5-*trichloro*-6-*piperidinopyridine*-4-*carboxamide* (10) (0.6 g, 63%), m.p. 193—195 °C (Found: C, 42.9; H, 4.0; N, 13.6%; M^+, 306. $C_{11}H_{12}Cl_3N_3O$ requires C, 42.8; H, 3.9; N, 13.6%; M^+, 306).

(b) Trichloro-4-cyano-6-piperidinopyridine (5) (1 g, 4.0 mmol), sulphuric acid (30 ml), and ethanol (20 ml) were heated at 70 °C during 3 h. Conventional work-up gave the carboxamide (0.66 g, 67%), identical (i.r. and mixed m.p.) with the compound described in (a) above.

In another experiment, trichloro-4-cyano-6-piperidinopyridine (5) was heated with 50% potassium hydroxide in ethanol at 70 °C during 30 min. The product was 3,5-*dichloro*-2-*ethoxy*-6-*piperidinopyridine*-4-*carboxamide* (11), m.p. 153—155 °C, $\nu_{max.}$ 3 380, 3 180, and 1 660 cm^{-1}; ^{1}H δ ($CDCl_3$) 1.4 (t, 3H), 1.65 (m, 6H), 3.3 (m, 4H), 4.4 (q, 2H) and 5.8—6.1br (2H) (Found: C, 48.9; H, 5.4; N 13.0%; M^+ 317. $C_{13}H_{17}Cl_2N_3O$ requires C, 49.1; H, 5.4; N, 13.2%; M^+ 317).

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References

1 Part 47, J. H. Brady, A. D. Redhouse, and B. J. Wakefield, *J. Chem. Res.*, 1982, (*S*) 137; (*M*), 1541.
2 ' Polychloroaromatic Compounds,' ed. H. Suschitzky, Plenum, London, 1974.
3 J. D. Cook and B. J. Wakefield, *J. Chem. Soc. C*, 1969, 1973.
4 J. Bratt, B. Iddon, A. G. Mack, H. Suschitzky, J. A. Taylor, and B. J. Wakefield, *J. Chem. Soc., Perkin Trans. 1*, 1980, 648.
5 S. M. Roberts and H. Suschitzky, *J. Chem. Soc. C*, 1968, 2844.
6 E. Ager, B. Iddon, and H. Suschitzky, *J. Chem. Soc., Perkin Trans. 1*, 1972, 133.
7 R. M. Bimber, U.S. 3 325 503 (1967) (*Chem. Abstr.*, 1968, **68**, 68896); W. H. Taplin, U.S. 3 420 833 (1969) (*Chem. Abstr.*, 1969

71, 3279); N. Hughes, A. Nelson, and R. S. Dainter, unpublished work.
8 B. Iddon, A. G. Mack, H. Suschitzky, J. A. Taylor, and B. J. Wakefield, *J. Chem. Soc., Perkin Trans. 1*, 1980, 1370.
9 D. J. Berry, B. J. Wakefield, and J. D. Cook, *J. Chem. Soc. C*, 1971, 1227.
10 J. Bratt and H. Suschitzky, *J. Chem. Soc., Perkin Trans. 1*, 1973 1689.
11 K. Walocha, unpublished work (University of Salford).
12 J. L. LaMattina and R. L. Taylor, *J. Org. Chem.*, 1981, **46**, 4179.
13 S. M. Roberts and H. Suschitzky, *J. Chem. Soc. C*, 1968, 1537

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