Polyhalogenoaromatic Compounds. Part XXXIV.[1] Reactions of Pentachloropyridine and 3,5-Dichlorotrifluoropyridine with Aliphatic Diamines

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The reactions of pentachloropyridine or 3,5-dichlorotrifluoropyridine with aliphatic diamines gave *N*-mono- and/or *NN'*-bis-(tetrahalogeno-4-pyridyl)diamines, depending on the reagents and the conditions. None of the *N*-monosubstituted compounds underwent cyclisation by intramolecular nucleophilic substitution at the 3-position of the pyridine ring, but the *N*-(dichlorotrifluoro-4-pyridyl) derivatives of nonane-1,9-diamine and dodecane-1,12-diamine cyclised *via* intramolecular attack at the 2-position.

POLYHALOGENOPYRIDINES undergo substitution by a variety of nucleophiles; in the cases of pentachloropyridine and 3,5-dichlorotrifluoropyridine, reaction takes place at the α- and/or γ-positions, depending on the nucleophile and on the solvent.[2] Very few reactions with difunctional nucleophiles have been reported. The products of such reactions are of interest both because of their possible biological activity [3] and because the initial products could undergo intramolecular nucleophilic substitution to yield novel heterocyclic systems. We describe here the reactions of pentachloropyridine and 3,5-dichlorotrifluoropyridine with aliphatic diamines, and experiments designed to cyclise some of the products.

Pentachloropyridine reacted with ethane-1,2-diamine in boiling ethanol to give a mixture of products which was almost insoluble in all the common organic solvents and could not be separated by chromatography or by fractional crystallisation. It was, however, separated into two components by repeated extraction with concentrated hydrochloric acid. The soluble component was purified as its hydrochloride and regenerated with alkali. Its n.m.r. spectrum confirmed the presence of an $-NH\cdot CH_2\cdot CH_2\cdot NH_2$ side chain; the same compound was obtained by a similar reaction between 4-bromotetrachloropyridine and ethane-1,2-diamine, and it is therefore formulated as the 4-substituted derivative (1). No useful n.m.r. spectrum was obtained for the component insoluble in hydrochloric acid; its elemental analytical figures were in approximate agreement with the constitution $C_{12}H_6Cl_8N_4$, and its mass spectrum showed the molecular ion at *m/e* 486, with the appropriate isotope pattern for eight chlorine atoms. The compound is therefore formulated as the *NN'*-disubstituted compound (2)

The proportions of compounds (1) and (2) varied according to the proportions of the starting materials, but even with 3 mol. equiv. of diamine the yield of compound (1) was only 58%.

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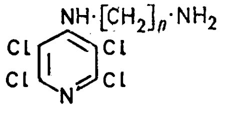
[1] Part XXXIII, B. Iddon, A. W. Thompson, and H. Suschitzky, preceding paper.

[2] B. Iddon and H. Suschitzky, in ' Polychloroaromatic Compounds,' ed. H. Suschitzky, Plenum Press, London, 1974, ch. 2.

[3] M. B. Green, in ' Polychloroaromatic Compounds,' ed. H. Suschitzky, Plenum Press, London, 1974, ch. 4.

The reaction of pentachloropyridine with dodecane-1,12-diamine gave an even more intractable mixture, which yielded no pure sample of the monosubstituted compound (3), and only a small one of the disubstituted compound (4).* Similarly, the only pure compound obtained by the reaction of dodecane-1,12-diamine with pentachloropyridine *N*-oxide was the *NN'*-disubstituted compound (6). Deoxygenation of the di-*N*-oxide (6) with phosphorus trichloride gave compound (7), isomeric with compound (4). Pentachloropyridine *N*-oxide normally undergoes substitution by amines in the 2-position,[5] and although the m.p. of compound (7) was close to that of compound (4), the chemical shifts for the protons α to the amino-groups differed: the signal for compound (7) was at higher field. (The protons α to the amino-group absorb at τ 6·17 for tetrachloro-4-ethylaminopyridine and at τ 6·47 for tetrachloro-2-ethylaminopyridine;[6] *cf.* ref. 4.)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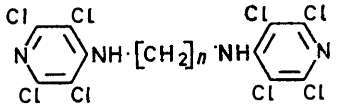
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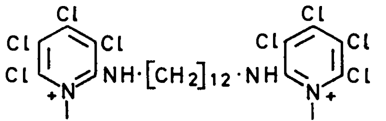
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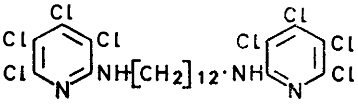
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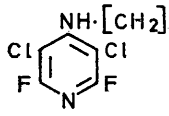
In the reactions of 3,5-dichlorotrifluoropyridine with aliphatic diamines, a similar tendency towards the formation of *NN'*-disubstituted compounds was noted, and they were the only products isolated when the diamine was added to a solution of the pyridine. Nevertheless when the dichlorotrifluoropyridine was added to a solution of an excess of the diamine in ethanol, the monosubstituted compounds could be obtained.

The properties of the monosubstituted compounds (8)—(11) and the *NN'*-disubstituted compounds (12)—(15) are listed in Tables 1 and 2. Compounds (8)—(11) are unstable (see later): compounds (8) and (11) decomposed sufficiently slowly to permit them to be characterised by elemental analysis, *etc.*, but compounds (9) and (10) were rapidly decomposing oils. However, the degree of substitution of the diamines was established by ^{1}H n.m.r. spectroscopy. The disubstituted compounds (12)—(15) were characterised by elemental analysis and by their ^{1}H n.m.r. and mass spectra. The position of substitution in these compounds and, by implication, in the monosubstituted compounds also, was established by their ^{19}F n.m.r. spectra, which in each case showed a singlet at low field, due to the equivalent 2- and 6-fluorine atoms.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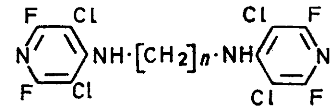
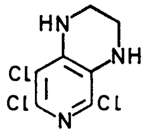
(11) n = 12


(12) n = 2
(13) n = 6
(14) n = 9
(15) n = 12

All attempts to cyclise compound (1) failed: it was heated neat, and in solution in dimethylformamide or *NN*-dimethylaniline, with or without potassium carbonate present. Under mild conditions the starting material was recovered, and under more vigorous conditions tars were obtained. Our failure to obtain any of the desired product (16) provides a further example of the reluctance of polychloropyridines to undergo nucleophilic substitution at the 3-position.[2,7] However, although the mass spectrum of compound (1) did not show a molecular ion (*m*/*e* 273), a prominent ion at *m*/*e* 237 (M^+ — HCl) was observed, suggesting that cyclisation may have occurred in the mass spectrometer.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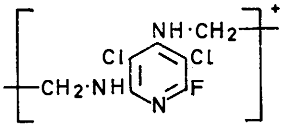
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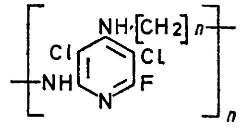
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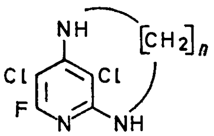
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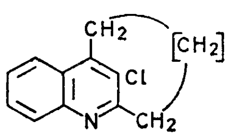
(20) = 12


(21)

The *N*-(dichlorodifluoropyridyl) compounds (8)—(11) polymerised at room temperature. The polymers were not fully characterised, but their mass spectra

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* The reaction of hexane-1,6-diamine with 2 mol. equiv. of pentachloropyridine to give the disubstituted compound (5) is reported in a Thesis,[4] which also describes the preparation of compound (1); however the position of substitution was not rigorously established in either case.

[4] S. A. Majid, Ph.D. Thesis, Manchester (U.M.I.S.T.), 1967.

[5] S. M. Roberts and H. Suschitzky, *J. Chem. Soc.* (*C*), 1968, 1537.

[6] S. M. Roberts, personal communication.

[7] N. J. Foulger and B. J. Wakefield, *J.C.S. Perkin I*, 1974, 871.

showed prominent peaks at *m/e* 221 (two chlorine atoms), attributable to the fragment (17); they probably contain the repeating unit (18), and arise *via* intermolecular nucleophilic substitution. Compounds (8) and (9) gave only polymer even when they were heated in dilute solution. On the other hand, compounds (10) and (11) also gave low yields of the bicyclic compounds (19) and (20), respectively, arising *via* intramolecular nucleophilic substitution. Compounds (19) and (20) were characterised by their ^{1}H n.m.r. spectra, and by accurate mass measurement of their molecular ions. Although their yields were low, the method described here is a useful one, since only two stages are required. It is not, however, suitable for the synthesis of lower homologues, although a chain of as few as six methylene groups can be accommodated in a similar situation [compound (21)], albeit with considerable strain.[8]

EXPERIMENTAL

^{1}H N.m.r. spectra were recorded at 60 MHz, with tetramethylsilane as internal standard. Calculated *m/e* values for the mass spectra are given in terms of the ions containing only ^{35}Cl; the appropriate patterns of isotope peaks were observed.

TABLE 1

N-(3,5-Dichloro-2,6-difluoro-4-pyridyl)alkanediamines

Compound	M.p. (°C)	Yield (%)	Formula	Found C (%)	Found H (%)	Found N (%)	Found M^+	Required C (%)	Required H (%)	Required N (%)	Required M^+
(8)	72—74	61	$C_7H_7Cl_2F_2N_3$	34·9	2·8	17·0		34·7	2·9	17·3	
(9)	(Oil)	Quant.[a]	$C_{11}H_{15}Cl_2F_2N_3$		[b]			44·3	5·1	14·1	
(10)	(Oil)	40 [a]	$C_{14}H_{21}Cl_2F_2N_3$		[b]			49·4	6·2	12·3	
(11)	(Oil)	84 [a]	$C_{17}H_{27}Cl_2F_2N_3$	53·2	7·0	10·4		53·4	7·1	11·0	
(12)	154—155	73	$C_{12}H_6Cl_4F_4N_4$	34·4	1·6	13·3	424	34·0	1·4	13·2	424
(13)	131—132	70	$C_{16}H_{14}Cl_4F_4N_4$	40·4	3·0	11·7	480	40·0	2·9	11·7	480
(14)	59	62	$C_{19}H_{20}Cl_4F_4N_4$	43·7	3·7	10·35	520	43·7	3·9	10·7	520
(15)	67—68	54	$C_{22}H_{26}Cl_4F_4N_4$	46·0	4·7	9·9	562	46·8	4·6	9·9	562

[a] Crude. [b] Satisfactory analysis not obtained; see text.

N-*Mono- and* NN′-*Bis-(tetrachloro-*4-*pyridyl)ethane-*1,2-*diamine*.—(*a*) Ethane-1,2-diamine (1·5 g, 0·025 mol) was added to pentachloropyridine (5·0 g, 0·02 mole) dissolved in ethanol (150 ml) and the mixture was stirred under reflux during 4·5 h. The solution was cooled, diluted with water (150 ml), and filtered. The filtrate was made alkaline (sodium hydroxide) and filtered. The combined precipitate was washed with water, and then repeatedly extracted with warm concentrated hydrochloric acid. Basification of the extract gave N-*(tetrachloro-*4-*pyridyl)ethane-*1,2-*diamine* (2·0 g, 32%), m.p. 111—113°, τ [$(CD_3)_2CO$] 3·6 (s, exch.), 6·0 (t), 6·5 (t), and 7·2 (s, exch.); $\nu_{max.}$ 3450, 3400, and 1585 cm^{-1} (Found: C, 30·5; H, 2·6; N, 15·0. $C_7H_7Cl_4N_3$ requires C, 30·6; H, 2·5; N, 15·3%); *hydrochloride*, m.p. 245° (decomp.), τ (D_2O) 5·95 (t) and 6·65 (t) (Found: C, 27·4; H, 2·6; Cl, 56·6; N, 14·0. $C_7H_8Cl_5N_3$ requires C, 27·0; H, 2·6; Cl, 56·9; N, 13·5%).

The residue left after extraction with hydrochloric acid was NN′-*bis(tetrachloro-*4-*pyridyl)ethane-*1,2-*diamine* (2·0 g, 41%), m.p. 190° (decomp.) (Found: C, 30·2; H, 1·5; N, 11·2%; M^+, 486. $C_{12}H_6Cl_8N_4$ requires C, 29·4; H, 1·25; N, 11·4%; *M*, 486).

(*b*) A similar experiment, but with ethane-1,2-diamine (4·0 g, 0·066 mol), gave the *N*-substituted compound (3·6 g, 58%) and the *NN′*-disubstituted compound (1·0 g, 20%).

(*c*) An experiment similar to (*b*) but with 4-bromotetrachloropyridine[9] (5·92 g) gave the *N*-substituted compound (60%) and the *NN′*-disubstituted compound (27%).

Isomeric NN′-*Bis(tetrachloropyridyl)dodecane-*1,12-*diamines*.—(*a*) Pentachloropyridine (5·0 g, 0·02 mol), dodecane-1,12-diamine (4·0 g, 0·02 mol), and ethanol (50 ml) were stirred and heated under reflux during 5 h. The solution was cooled and poured into 2M-sodium hydroxide (100 ml), and the crude product was obtained by extraction with ether. Fractionation by extraction with hydrochloric acid, partition with organic solvents, *etc.*, gave a fraction (insoluble in acid, soluble in chloroform) which on chromatography (silica; chloroform–light petroleum) and repeated recrystallisation (benzene–light petroleum) gave NN′-*bis(tetrachloro-*4-*pyridyl)dodecane-*1,12-*diamine* (0·54 g,) m.p. 76—77°, τ ($CDCl_3$) 4·90 (2H, t, exch.), 6·24 (4H, q), and 8·70br (20H, s) (after exchange with D_2O the signal at τ 6·24 was a triplet) (Found: C, 42·4; H, 4·3; N, 9·0%; M^+, 626. $C_{22}H_{26}Cl_8N_4$ requires C, 41·9; N, 4·2; N, 8·9%; *M*, 626).

(*b*) Pentachloropyridine *N*-oxide (5·34 g, 0·02 mol), dodecane-1,12-diamine (4·0 g, 0·02 mol), and ethanol (50 ml) were stirred at room temperature during 48 h. The solvent was evaporated off and the residue was extracted with chloroform. Conventional work-up of the extract, followed by repeated recrystallisation (chloroform–ethanol) gave NN′-*bis(tetrachloro-*2-*pyridyl)dodecane-*1,12-*diamine di-*N^{pyr}-*oxide* (1·50 g), m.p. 125°, τ ($CDCl_3$) 2·5br (exch.), 6·20 (q), and 8·70br (s); highest mass peaks in mass spectrum at *m/e* 626 (*M* − 32) (Found: C, 39·2; H, 3·7; N, 8·6. $C_{22}H_{26}Cl_8N_4O_2$ requires C, 39·9; H, 4·0; N, 8·5%).

Treatment of the di-*N*-oxide with phosphorus trichloride in boiling chloroform overnight, followed by conventional work-up and chromatography (alumina; light petroleum) gave NN′-*bis(tetrachloro-*2-*pyridyl)dodecane-*1,12-*diamine*, m.p. 90° (from light petroleum), τ ($CDCl_3$) 4·85br (2H, exch.), 6·51 (4H, q; t after exchange), and 8·68br (20H, s) [Found: C, 41·5; H, 4·6%; M^+ ($^{35}Cl_7{}^{37}Cl$), 627·9628. $C_{22}H_{26}Cl_8N_4$ rquires C, 41·9; H, 4·2%; *M* ($^{35}Cl_7{}^{37}Cl$), 627·9639.]

Reactions of 3,5-*Dichlorotrifluoropyridine with Diamines*.—(*a*) The diamine (0·03 mol) in ethanol (25—50 ml) was heated to 50—70° and stirred rapidly as 3,5-dichlorotrifluoropyridine (0·01 mol) in ethanol (20 ml) was added dropwise during 20 min. The solution was poured on ice, and the mixture was extracted with ether. The extract was quickly washed with water, dried ($MgSO_4$), and evaporated to leave the *N*-(dichlorotrifluoro-4-pyridyl)diamine [(8)—(11); see Tables 1 and 2].

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[8] W. E. Parham, R. W. Davenport, and J. B. Biasotti, *Tetrahedron Letters*, 1969, 1163; *J. Org. Chem.*, 1970, **35**, 3775.

[9] Ya. N. Ivashchenko, L. S. Sologub, S. D. Moshchitskii, and A. V. Kirsanov, *Zhur. obshchei Khim.*, 1969, **39**, 1195.

(*b*) The diamine (0·01 mol) was added to a stirred ice-cold solution of 3,5-dichlorotrifluoropyridine (0·01 mol) in ethanol (25 ml). The mixture was stirred at room temperature overnight. The solvent was evaporated off and the residue was washed with hydrochloric acid and recrystallised, to give the *NN'*-bis(dichlorotrifluoro-4-pyridyl)diamine [(12)—(15); see Tables 1 and 2].

TABLE 2

N.m.r. spectra

	τ [a]					
Compd.	NH [c]	α-H_2	$[CH_2]_n$	α'-H_2	NH_2 [c]	^{19}F δ [b]
(8)	3·9br	6·10 (q)		7·00 (t)	8·6 (s)	
(9)	5·5br	6·2 (t)	8·5br	6·6 (t)	*d*	
(10)	1·8br	6·25 (q)	8·7br	6·7br	5·0br	
(11)	*d*	6·1 (t)	8·6br	6·5 (t)	*d*	
(12)	3·5br	5·75 (d)				4·05
(13)	4·9br	6·15 (q)	8·45br			5·2
(14)	4·8br	6·15 (q)	8·6br			5·3
(15)	4·8br	6·20 (q)	8·7br			5·3

[a] In $CDCl_3$ [compounds (8)—(10) and (13)—(15)], $(CD_3)_2CO$ [compound (12)] or $(CD_3)_2SO$ [compound (11)]; integration showed the appropriate relative intensities. [b] Recorded at 56·5 HMz; δ in p.p.m. downfield from trifluoroacetic acid (external reference); signals were singlets. [c] Exchangeable. [d] Not observed.

Cyclisation Procedures.—(*a*) The *N*-(tetrahalogeno-4-pyridyl)diamines were heated in dimethylformamide (or *NN*-dimethylaniline) at various concentrations and temperatures, and in some experiments in the presence of anhydrous potassium carbonate. Conventional work-up gave starting material or polymer or tars in every case.

(*b*) Ethanol (1 l) was stirred and heated to reflux while *N*-(3,5-dichloro-2,6-difluoro-4-pyridyl)dodecane-1,12-diamine (2·0 g, 5·2 mmol) in ethanol (300 ml) was added dropwise during 2·5 h. Most of the solvent was evaporated off and the residue was poured on ice. The resulting mixture was extracted with ether. The extract was dried and evaporated and the residue (0·7 g) was distilled (Kugelrohr) to give 19,20-*dichloro*-18-*fluoro*-2,15,17-*triazabicyclo*[14.3.1]*eicosa*-1(20),16,18-*triene* (20), b.p. 175—180° at 3·5 mmHg, τ ($CDCl_3$) 6·25 (4H, m; br t after exchange) and 8·6br (20H) (Found: M^+, 361·1487. $C_{17}H_{26}Cl_2FN_3$ requires *M*, 361·1486).

In a similar experiment, *N*-(3,5-dichlorotrifluoro-4-pyridyl)nonane-1,9-diamine gave 16,17-*dichloro*-15-*fluoro*-2,12,14-*triazabicyclo*[11.3.1]*heptadeca*-1(17),13,15-*triene* as an oil, τ ($CDCl_3$) 6·25 (4H, m; br t after exchange) and 8·6br (14H) (Found: M^+, 319·1025. $C_{14}H_{20}Cl_2FN_3$ requires *M*, 319·1013).

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