Polyhalogeno-aromatic Compounds. Part XVI.¹ The Preparation and Reactions of Polyhalogenophenyl- and Polyhalogenopyridyl-hydrazines

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A series of polyhalogenophenyl- and polyhalogenopyridyl-hydrazines have been prepared, usually from the appropriate perfluoro-, perchloro-, or perbromo-compound and hydrazine hydrate. Treatment with silver oxide or copper sulphate or with a base (sodium hydroxide or hydrazine hydrate) led to replacement of the hydrazinomojety and, in most cases, also to that of the ortho- or para-halogen atom by hydrogen, yielding the corresponding polyhalogeno-compounds. The loss of the hydrazino-group is due to the established oxidative elimination of such moieties via a diazohydride. The accompanying elimination of the halogen ortho- or para- to the hydrazino-group is interpreted as an HX elimination (X = F, Cl, or Br) from a tautomeric form of the polyhalogenohydrazine. The use of these hydrazines in indole synthesis has been found to be very restrictive.

It has previously been observed that pentafluorophenylhydrazine undergoes an unusual reaction with bases² or Fehling's solution³ to produce 1,2,4,5-tetrafluorobenzene. In view of our current studies of polyhalogenoaromatic systems, other than those of fluorine, it was of interest to find out whether polychcloro- and polybromohydrazines would show an analogous behaviour and also to explore their synthetic utility. We prepared tetrafluoro-, tetrachloro-, dichlorodifluoro-, and tetrabromo-hydrazinopyridine as well as pentachloro- and pentabromo-phenylhydrazine, by the following methods.

Tetrafluoro-4-hydrazinopyridine (Ia) was made as reported 4 from pentafluoropyridine and hydrazine hydrate in cold ethanol. In a similar manner, 3-chlorotetrafluoropyridine (Ib) and 3,5-dichlorotrifluoropyridine (Ic) were converted into 3-chlorotrifluoro-4-hydrazinopyridine (Id) and 3,5-dichlorodifluoro-4-hydrazinopyridine (Ie), respectively.

The reaction between pentachloropyridine 1-oxide and hydrazine hydrate in boiling ethanol gave 2,3,4,5-tetrachloropyridine (IIa) and tetrachloro-6-hydrazinopyridine (IIb) as a mixture, from which the latter was obtained pure by recrystallisation. No product arising from substitution at the 4-position was detected indicating the intermediacy of tetrachloro-6-hydrazinopyridine 1-oxide (III), which is deoxygenated intramolecularly with simultaneous oxidative decomposition of the hydrazinomoiety yielding 2,3,4,5-tetrachloropyridine (IIa) whereas intermolecular deoxygenation by the excess of reagent would give the hydrazine (IIb). A similar reaction with pentachloropyridine gave a mixture of tetrachloro-4-hydrazinopyridine (IIc) and the 6-isomer (IIb) (4:1). The former was separated by recrystallisation and found to be stable to light and air contrary to earlier reports.⁵ With excess of hydrazine hydrate in hot ethanol, pentachloropyridine gave trichloro-4,6-dihydrazinopyridine (IId).

Pentabromopyridine and hydrazine hydrate gave tetrabromo-4-hydrazinopyridine (IVa) and tetrabromo-6-hydrazinopyridine (IVb) (2:1) as an inseparable

D. G. Holland, G. J. Moore, and C. Tamborski, J. Org. Chem., 1964, **29**, 1562; 3042.

J. H. Birchall, R. N. Haszeldine, and A. R. Parkinson, J. Chem. Soc., 1962, 4966.

mixture.⁶ The isomer ratios were determined by oxidation with ethanolic silver oxide 6 (cf. below and Table 1).



Hexachlorobenzene was unreactive towards hydrazine hydrate in boiling ethanol. Pentachlorophenylhydrazine (Va) was obtained in low yields from the reaction of pentachloronitrobenzene and a slight excess of hydrazine hydrate in ethanol-dioxan. The major product was 4,5,6,7-tetrachloro-1-hydroxybenzotriazole (VI) as reported,⁷ but also a little of the hydrazine was formed by

⁴ R. E. Banks, J. E. Burgess, W. M. Cheng, and R. N. Haszeldine, J. Chem. Soc., 1965, 575.

- ⁵ A. Roedig and K. Grohe, Chem. Ber., 1965, 98, 923.
 ⁶ I. Collins and H. Suschitzky, J. Chem. Soc. (C), 1970, 1523.
 ⁷ D. E. Burton, A. J. Lambie, D. W. J. Lane, G. T. Newbold,
- and A. Percival, J. Chem. Soc. (C), 1968, 1268.

¹ Part XV, E. Ager, B. Iddon, and H. Suschitzky, J. Chem. Soc. (C), 1970, 1530.

nucleophilic displacement of the nitro-group and obtained from the mother liquors. Alternatively, pentachlorophenylhydrazine (Va) was prepared in good yield by diazotisation of pentachloroaniline (Vb) with nitrosyl sulphuric acid and subsequent reduction with stannous chloride in hydrochloric acid.

Pentabromophenylhydrazine (VIIa) was also prepared by the reduction of the appropriate diazonium salt with stannous bromide in hydrobromic acid. Neither hexabromobenzene nor pentabromofluorobenzene (VIIb) would react with hydrazine hydrate (molar ratio 1:2) in hot ethanol but in hot sulpholane both gave 1,2,3,4-tetrabromobenzene (VIIc). A similar result was observed when either polybromo-compound was made to react with an excess of hydrazine hydrate in

TABLE 1

Reactions of polyhalogenophenyl- and polyhalogenopyridylhydrazines with bases and oxidising agents

Hydra-				Pro-	
zine	Reagent	Solvent	Temp.	ducts	Ratios a
(Ia)	CuSO,	H,O	100°	(If)	
(Id)	CuSO₄	H_2O	100	(Ig)	1
• • •	-	-		(Iĥ)	3
(Ie)	$CuSO_4$	H_2O	100	(Ii)	1
				(Ij)	4
(IIb)	$CuSO_4$	H ₂ O	100	(IIa)	
(IIb)	Ag_2O	EtOH	78	(IIa)	2
(11c)	$CuSO_4$	H_2O	100	(11e)	3
					7
(IIc)	Cu ₂ O	H,O	100	(11e)	1
()	A = 0	THOIT	70		10
(110)	Ag_2O	Dell	18	(IIe)	1
(110)	Ag_2O	геп	80	(IIC)	1
(110)	1~0	Mot	19	(IIg)	1
(110)	Ag ₂ O	MET	42	(IIE)	3
(IIc)	MnO	PeH	80		ĩ
(110)	MIO_2	1 011	00	$(\Pi \sigma)$	1
(IIc)	H.O.	CF.CO.H	72	(III)	•
	NaOH	H ₀ O	100	(TTi)	
(IId)	CuSO.	H ₂ O	100	dīb	
(IVa) b	Ago	EtOH	78	(ÌVc)	1
(1.1.4)				(ÌVd)	3
(IVb) »	Ag ₉ O	EtOH	78	(IVe)	
(Va)	Ag ₂ O	EtOH	78	(Vc)	2
· · /	0.			(Vd))	1 ¢
				(Ve)∫	1.
(Va)	Ag ₂ O	$C_{5}H_{5}N$	115	(Vc)	4
				(Vd)	2ª
				(Ve)	14
(Va)	Ag₂O	C_5D_5N	115	(Vd)	2 d
				(Ve)	1 a
177.)	1 - 0	34-1	49	(VI)	4 *
(Va)	Ag_2O	Mei	42	(Ve)	2
(37-)	0	ИO	100	(vg)	3 9
(va)	CuSO ₄	$\Pi_2 O$	100		э
					10
(Va)	NaOH	н.0	100		
(Va)	N.H. H.O	Sulpholane	140	(V_{c})	2
(,,,,)		Sarphonano	·	(Vd)	3
(VIIa)	N,H,H,O	EtOH	78	(VIIc)	-
	~ ~ ~ ~ ~				

• The ratios of the recovered products were determined by ¹H n.m.r., in deuteriochloroform the total yields were 60—70%. • Reacted as a mixture. • Both products absorbed at $\tau 2.46$ and the ratio was not determined. • Analysed by g.l.c. on polyethyleneglycol adipate at 180°. • Mass spectral analysis showed that 1,2,3,4-tetrachloro-5-deuteriobenzene (Vf) was the major component (>85%), m/e 215 (M^+ , C₆HCl₄D), a small amount of 1,2,3,4-tetrachlorobenzene (Vc) was also present, m/e 214 (M^+ , C₆H₂Cl₄). No peak was apparent at m/e 216 (M^+ , C₆Cl₄D₂). hot ethanol or over a prolonged period at room temperature when a stoicheiometric amount of nitrogen was evolved. The 1,2,3,4-tetrabromobenzene (VIIc) was characterised by conversion into the known 2,3,4,5-tetrabromonitrobenzene (VIId) with hot concentrated nitric acid.⁸

We confirmed that pentabromophenylhydrazine (VIIa) and hydrazine hydrate in hot ethanol also gave 1,2,3,4-tetrabromobenzene (VIIc), whereas it remained unchanged in hot ethanol alone. This indicates that hexabromobenzene or pentabromofluorobenzene (VIIb) form the hydrazine (VIIa) initially when treated with excess of hydrazine hydrate. Indeed, it was observed that pentabromofluorobenzene (VIIb) reacted with sodium methoxide, ammonia, and cyclohexylamine with exclusive replacement of the fluorine atom to yield pentabromoanisole (VIIe), pentabromoaniline (VIIf), and *N*-pentabromophenylcyclohexylamine (VIIg), respectively.

The above polyhalogenophenyl- and polyhalogenopyridyl-hydrazines were made to react with bases (aqueous sodium hydroxide or hydrazine hydrate) and also with oxidising agents (ethanolic silver oxide or aqueous copper sulphate). All these reagents produced similar results which are set out in Table 1. For instance, pentachlorophenylhydrazine (Va) and hot aqueous sodium hydroxide solution gave 1,2,4,5-tetrachlorobenzene (Vd) and with hydrazine hydrate in hot sulpholane, a mixture of 1,2,3,4-tetrachlorobenzene (Vc) and 1,2,4,5-tetrachlorobenzene (Vd). It should be noted that when heated alone in sulpholane the phenylhydrazine (Va) was unchanged. Treatment of the hydrazine (Va) with silver oxide in ethanol or with aqueous copper sulphate resulted in a mixture of the tetrachlorobenzenes [(Vc) and (Vd)] and pentachlorobenzene (Ve). The outcome of these reactions was essentially analogous in the 4-hydrazinopyridines (cf. Table 1).

We have considered several mechanisms to rationalise the results. Replacement of the hydrazino-group by



hydrogen to yield pentahalogenobenzene or tetrahalogenopyridine by oxidation is in accordance with the usual

8 I. Collins and H. Suschitzky, J. Chem. Soc. (C), 1969, 2337.

behaviour of hydrazines 3,9 which deaminate *via* an intermediate diazohydride (RN=NH) with liberation of nitrogen. Simultaneous loss of the *para*-halogen atom has previously been observed when pentafluorophenylhydrazine (VIII) is made to react with aqueous sodium hydroxide or hydrazine hydrate² or Fehling's solution or aqueous copper sulphate³ to afford 1,2,4,5-tetrafluorobenzene (IX). Tamborski² has ascribed this reaction to a path involving tautomerism followed by elimination of HF as shown in Scheme 1.



This mechanism is equally applicable to our polyhalogenophenylhydrazines since the electron-withdrawing properties of fluorine, which render the α -proton of the hydrazino-group mobile, are similar in the other halogenohydrazines. We propose that silver oxide and copper sulphate, apart from acting as oxidising agents, behave as bases catalysing the prototropy. Basicity of silver oxide is, of course, well established 10 and copper sulphate is reduced in the course of the reaction to cuprous oxide which then acts as a base. Indeed, when tetrachloro-4-hydrazinopyridine (IIc) was treated with cuprous oxide in hot water the major product was 2,3,6-trichloropyridine (IIf), that is the product expected from attack by a basic reagent. The mechanism leading to a mixture of pentachlorobenzene (Ve) and tetrachlorobenzenes [(Vc) and (Vd)] with the oxidising agents as well as with the basic reagents, is therefore similar involving oxidative deamination and HCl elimination. The reported reaction of pentafluorophenylhydrazine (VIII) with Fehling's solution³ to give 1,2,4,5-tetrafluorobenzene (IX) is explicable on the same basis since the reagent contains an oxidising agent as well as sodium hydroxide.

The observation that pentabromophenylhydrazine (VIIa) gives 1,2,3,4-tetrabromobenzene (VIIc) and no 1,2,4,5-tetrabromo-isomer as expected by analogy could be due to the large size of the bromine atoms which prevents coplanarity of the molecule (X) the precursor of the latter tetrabromo-compound, but allows adoption of the *o*-quinonoid intermediate (XI). 1,4-Elimination of HBr followed by oxidation as shown (Scheme 2) led to the observed product (VIIc).

⁹ F. D. Chattaway and M. Aldridge, J. Chem. Soc., 1911, **99**, 404.



Certain features of the reactions deserve comment. (a) In only one case was a fluorine atom ortho to the hydrazino-group removed [see (f) below]. A small amount of 1,2,3,4-tetrafluorobenzene was, however, formed from pentafluorophenylhydrazine (VIII) with sodium hydroxide.² In the case of 3-chlorotrifluoro-4-hydrazinopyridine (Id) or 3,5-dichlorodifluoro-4-hydrazinopyridine (Ie), copper sulphate oxidation yields some dechlorinated products [(Ih) and (Ij), respectively].

(b) The action of aqueous sodium hydroxide solution on tetrachloro-4-hydrazinopyridine (IIc) yielded tetrachloro-4-hydroxypyridine (IIi). This lends support to the intermediacy of the imino-amine tautomer (XII) which is possibly stabilised as the sodium salt (Scheme 3). A similar result is obtained by the action of peroxytrifluoroacetic acid.

(c) Tetrachloro-6-hydrazinopyridine (IIb) gives only 2,3,4,5-tetrachloropyridine (IIa) on oxidation with aqueous copper sulphate or silver oxide in ethanol. The corresponding bromopyridine (IVb) reacts similarly. This is presumably due to hydrogen bonding of the hydrazino-group to the ring nitrogen atom (XIII) and tautomerism in the *ortho*-position involving the pyridine nitrogen and not the carbon atom [as in (XIV)].



(d) Reactions with silver oxide in aprotic media (benzene and methyl iodide) only give products arising from oxidation of the hydrazino-moiety and halogen atoms are never replaced. For instance, pentachloro-

¹⁰ J. W. Laist, 'Comprehensive Inorganic Chemistry,' Van Nostrand, New York, 1965, vol. II, p. 146.

phenylhydrazine (Va) and silver oxide in methyl iodide afford pentachlorobenzene (Ve) and pentachloroiodobenzene (Vg). The results indicate that in these reactions the basic properties of the silver oxide are suppressed and prototropy is thus prevented. The apparent anomaly, where pyridine is used as solvent and dehalogenation takes place, can be explained by the pyridine acting as the base in the reaction and not the silver oxide.

(e) Trichloro-4,6-dihydrazinopyridine (IId) reacts with hot copper sulphate solution to give 2,3-dichloropyridine (IIj) as the sole product. This indicates the intermediacy of the quinonoid form (XV) and excludes a stepwise decomposition which would yield some 2,5-dichloropyridine.



(f) Decomposition of tetrafluoro-4-hydrazinopyridine (Ia) with sodium hydroxide solution gives 2,3-difluoro-6-pyridone (XVI); this reaction provides the only case where an *ortho*-fluorine atom is exclusively replaced by hydrogen. The result can be rationalised as shown in Scheme 4.



(g) A mixture of 2,3-dichloro-6-piperidinopyridine (XVII) and 2,5-dichloro-6-piperidinopyridine (XVIII) was obtained by the action of piperidine on tetrachloro-4-hydrazinopyridine (IIc). Again, as in Scheme 4, substitution by the nucleophile precedes decomposition since 2,3,6-trichloropyridine (IIf) reacts with piperidine to yield (XVII) and (XVIII) in a different ratio, namely 1:3. As before, the electron-releasing substituent favours elimination of the adjacent halogen atom so that the 2,3-dichloro-isomer (XVII) predominates over the 2,5-isomer (XVIII).

(h) The reaction of pentachlorophenylhydrazine (Va) with silver oxide in deuteriopyridine gave mainly

1,2,3,4-tetrachloro-5-deuteriobenzene (Vf). This illustrates that one hydrogen atom is derived from the solvent (presumably a radical process) and one from the hydrazino-moiety itself.

(i) The treatment of pentachlorophenylhydroxylamine (Vh) with aqueous sodium hydroxide solution gave pentachloroaniline (Vb) as the only product; no tetrachlorobenzenes were detected. Thus the hydroxylamine does not react in an analogous way to the hydrazine with sodium hydroxide.

Other mechanisms were considered to account for the replacement of an *ortho*-halogen atom by hydrogen. The formation of a tetrahalogenobenzyne [e.g. (XIX)] was ruled out since in an excess of hydrazine and/or ethanol products such as (VIIh and VIIi) would be expected. A 'nuisance effect' due to the presence of the ionic diazohydride [e.g. (XX)] could feasibly cause nucleophilic substitution of the *ortho*-halogens by



analogy with our previous observations.¹¹ This is, however, unlikely because the ease of replacement would be in the order $F \gg Cl > Br$, whereas the reverse is observed. In the nucleophilic substitution of hexabromobenzene, we have reported several instances involving nucleophilic attack on halogen.⁸ A similar mechanism involving intramolecular attack by nitrogen on bromine during the decomposition of the polybromohydrazines (as shown in Scheme 5) cannot be completely ignored.



Tetrachloro-4-hydrazinopyridine (IIc) was pyrolysed at 160° in sand for 2 hr. to give 4-aminotetrachloropyridine (IIk) and 2,3,5,6-tetrachloropyridine (IIe). The mixture of the tetrabromohydrazines (IVa and IVb) likewise gave 2-, and 4-aminotetrabromopyridine (IVf and IVg) and 2,3,5,6-tetrabromopyridine (IVc) but no 2 3,4,5-tetrabromopyridine (IVe) was detected. When

¹¹ H. Suschitzky, Angew. Chem. Internat. Edn., 1967, 6, 596.

hexachlorobenzene was treated with hydrazine hydrate (molar ratio 1:1) at 200° for 24 hr. in sulpholane, some pentachloroaniline (Vb) was obtained accompanied by much starting material. The course of the decomposition is similar to that described for phenylhydrazine⁹ and pentafluorophenylhydrazine,³ and this probably accounts for the trace quantities of polyhalogenoaminopyridines observed in the mass spectra of crude products from the oxidation of tetrafluoro-, 3-chlorotrifluoro-, and 3,5-dichlorodifluoro-4-hydrazinopyridine.

Some of the polyhalogenohydrazino-compounds were studied as possible synthetic intermediates. Reaction of tetrachloro-4-hydrazinopyridine (IIc) with silver oxide or manganese dioxide in dry benzene, gave tetrachloro-4-phenylpyridine (IIg) as described above, undoubtedly owing to homolytic substitution of the solvent by the tetrachloropyridyl radical (XXI). The method is not of synthetic value, however, since the product is much contaminated with 2,3,5,6-tetrachloropyridine (IIe), from which it is difficult to separate.

Treatment of pentachlorophenylhydrazine (Va) or tetrachloro-4-hydrazinopyridine (IIc) with bromine in dilute hydrochloric acid gave bromopentachlorobenzene (Vi) and the unknown 4-bromotetrachloropyridine (III), respectively. Reaction of the latter compound with piperidine in benzene gave tetrachloro-4-piperidinopyridine (IIm) and 4-bromotrichloro-6-piperidinopyridine (IIn) (1:2) while in ethanol the ratio of products was 2:3, respectively. By comparison pentachloropyridine reacts with piperidine in benzene and ethanol to give 4%and 37%, respectively, of (IIm)¹² indicating that the bromine atom in 4-bromotetrachloropyridine (III) is more easily replaced than the 4-chlorine atom in pentachloropyridine. The bromotetrachloro-compound (III) reacted with n-butyl lithium in diethyl ether to give 2,3,5,6-tetrachloropyridine (IIe) exclusively.

Oxidation of pentachlorophenylhydrazine (Va) with silver oxide in methyl iodide gave pentachlorobenzene (Ve) and pentachloroiodobenzene (Vg) (1:1) as described above. Similarly, tetrachloro-4-hydrazinopyridine (IIc) yielded the tetrachloro-compound (IIe) and tetrachloro-4-iodopyridine (IIh) (1:3). The latter compound was treated with piperidine, in ethanol, to afford tetrachloro-4-piperidinopyridine (IIm) and trichloro-4-iodo-6-piperidinopyridine (IIo) (1:9). The iodine atom is thus not very readily replaced by a nucleophile. Tetrachloro-4-iodopyridine (IIh) when heated with copper bronze at 200° afforded octachloro-4,4'-bipyridyl (XXII).

The polyhalogenohydrazines condensed readily with ketones to give the corresponding polyhalogenohydr-Acetophenone pentachlorophenylhydrazone azones. (XXIIIa) when heated with polyphosphoric acid at 200° for 30 min., gave 4,5,6,7-tetrachloro-2-phenylindole (XXIV). This cyclisation must involve loss of chlorine 12 S. M. Roberts and H. Suschitzky, J. Chem. Soc. (C), 1968, 1537.

which, surprisingly, does not attack the 3-position of the indole (XXIV). Characterisation followed from its elemental analysis, n.m.r. [deuteriochloroform, $\tau 2 \cdot 1 - 2 \cdot 6$ multiplet (phenyl group), τ 1.33 broad singlet, removed by deuterium oxide (NH), $\tau 3.12$ doublet (3-H) J 2.5 Hz] and its mass spectrum $[m/e \ 331 \ (M^+)]$.

However, the pentachlorophenylhydrazones of acetone (XXIIIb), propiophenone (XXIIIc) and cyclohexanone (XXIIId) could not be made to cyclise when heated with various reagents [polyphosphoric acid, (PPA) acetic acid, zinc chloride] under many conditions. Invariably pentachloroaniline (Vb) accompanied by much tar and sometimes by pentachlorobenzene (Ve) was obtained.



Polyfluoroindoles have been prepared by cyclisation of tetrafluorophenylhydrazones (XXV)¹⁴ and also by intramolecular nucleophilic substitution with suitable intermediates [e.g. (XXVI)¹⁵ and (XXVII)¹⁶]. We attempted to cyclise acetophenone pentafluorophenylhydrazone (XXVIII) and its bromo-analogue (XXIX) with PPA at 156° but without success. Only tar and starting material were recovered.



EXPERIMENTAL

Preparation of Hydrazines.—(a) By nucleophilic substitution reactions. (i) Pentafluoro-, 3-chlorotetrafluoro-, and 3,5-dichlorotrifluoropyridine (1 mol.) were each treated with hydrazine hydrate (2 mol.) in ethanol at 0° for 3hr. Water (200 ml.) was added and the hydrazine was recovered by filtration or extraction with chloroform. Details are set out in Table 2. (ii) Pentachloropyridine (10 g.) was treated

¹⁵ G. M. Brooke and R. J. D. Rutherford, J. Chem. Soc. (C),

¹³ B. Robinson, Chem. Rev., 1963, **63**, 373; 1969, **69**, 227.

¹⁴ T. D. Petrova, V. P. Mamaev, and G. G. Yakobson, *Izvest. Akad. Nauk S.S.S.R., Ser. khim.*, 1969, 679.

<sup>1967, 1189.
1967, 1189.
&</sup>lt;sup>16</sup> V. P. Petrov, V. A. Barkhasch, G. S. Shchegoleva, T. D. Petrova, T. I. Savchenko, and G. G. Yakobson, *Doklady Akad. Nauk S.S.S.R.*, 1968, **178**, 864; V. P. Petrov and V. A. Barkhasch, C. M. Barkhasch, *Value Velace*, 1969, **29**, 1615. Zhur. obshchei Khim., 1969, 39, 1615.

with hydrazine hydrate (12 g.) in ethanol (100 ml.) at reflux for 4 hr. Water (200 ml.) was added and the residue was filtered off and dried. Recrystallisation from light petroleum (b.p. 80-100°) gave tetrachloro-4-hydrazinopyridine (cf. Table 2). (iii) The reaction between pentabromopyridine and hydrazine hydrate has been described previously by us.⁶ The product was a mixture of tetrabromo-4- and 6-hydrazinopyridine which could not be separated. (iv) Pentachloropyridine 1-oxide (1.5 g.), hydrazine hydrate (0.85 g.) and ethanol (50 ml.) were heated under reflux together for 2 hr. The solution was poured into water (150 ml.) and the precipitate was extracted with chloroform, which was dried (MgSO₄) and evaporated to give a residue (0.9 g.). Recrystallisation from light petroleum (b.p. 80-100°) yielded tetrachloro-6-hydrazinopyridine (36%) (cf. Table 2). The mother liquors were evaporated and the

Reactions of the Polyhalogeno-hydrazines.-(a) Oxidations with silver oxide. (i) In a typical reaction, tetrachloro-4-hydrazinopyridine (3 g.) was stirred in ethanol (50 ml.) at room temperature with silver oxide (7 g.) and the suspension was stirred and heated under reflux for 1.5 hr. The mixture was filtered and the filtrate was evaporated under reduced pressure to give a brown solid (1.3 g.). Recrystallisation gave 2,3,5,6-tetrachloropyridine (49%), m.p. 89° (ethanol) (lit.,¹⁸ m.p. 90°). (ii) Details of the similar reactions with other polyhalogenohydrazines are set out in Tables 1 and 3. (iii) The reaction was repeated as in (i) with benzene in place of ethanol. Careful sublimation of the brown residue obtained gave 2,3,5,6-tetrachloropyridine, identical (m.p. and i.r.) to that previously obtained. Recrystallisation of the residue afforded tetrachloro-4-phenylpyridine, m.p. 136° (aqueous ethanol) (lit., m.p. 135.5-

TABLE 2 Polyhalogeno-phenyl- and ridal bad

		Forynaioge	eno-pnei	тут-а	па -руг	nayi-nyarazines				
	M.p.		Found (%)				Required (%)			
Hydrazine	Found	Lit.	<u>с</u>	H H	N	Formula	c	H	N	Ref.
(Ia)	$53-54^{\circ}$	$57-58^{\circ}$				$C_5H_3F_4N_3$				4
(Id)	136	139 - 140				C ₅ H ₃ ClF ₃ N ₃				а
(Ie)	96	91 - 92				$C_5H_3Cl_2F_2N_3$				
(IIb)	152 - 154		24.8	1.5	17.0	$C_5H_3Cl_4N_3$	24.3	$1 \cdot 2$	17.0	
(IIc)	160 - 162	152 - 156	$24 \cdot 8$	1.5	17.3	$C_5H_3Cl_4N_3$	24.3	$1 \cdot 2$	17.0	5
(IId)	180		24.6	$2 \cdot 2$	28.6	C ₅ H ₄ Cl ₅ N ₅	24.8	$2 \cdot 5$	28.9	
(Va)	179 - 180		26.0	1.0	9.8	C.H.Cl.N.	25.7	1.1	10.0	
(VIIa)	212 - 214		14.8	0.8	$5 \cdot 1$	C ₆ H ₃ Br ₅ N ₂	14.3	0.4	5.6	
	^a Nethe	rlands Pat. (3,611,766	(Cher	n. Abs.,	1968, 68, 59,438).				

solid obtained (0.3 g.) was sublimed, under reduced pressure, to afford 2,3,4,5-tetrachloropyridine (0.1 g.), m.p. 24° (lit.,¹⁷ m.p. 21-22°). The presence of the tetrachloropyridine was also detected in the crude product by n.m.r. spectroscopy. (v) Pentachloropyridine (5 g.) was treated with hydrazine hydrate (6 g.) in ethanol (60 ml.) as described above to yield trichloro-4,6-dihydrazinopyridine (1.5 g.) (cf. Table 2). (vi) Pentachloronitrobenzene (5 g.) was heated under reflux with hydrazine hydrate (4.2 g.) in 1:1 ethanol-dioxan (75 ml.) for 6 hr. The cool mixture was filtered to isolate 4,5,6,7-tetrachloro-1-hydroxybenzotriazole, m.p. 206° (decomp.) [lit.,7 m.p. 209-210° (decomp.)]. The filtrate was poured into water (100 ml.) and the precipitate was filtered off and recrystallised from ethanol to give pentachlorophenylhydrazine (19%) (cf. Table 2).

(b) Via the amine.--(i) Pentachloroaniline (10 g.) was stirred in acetic acid (50 ml.) at 55-60° and a solution of sodium nitrite (2.9 g.) in sulphuric acid $(d \ 1.84; 24 \text{ ml.})$ was slowly added. The mixture was held at this temperature for 20 min. and then cooled in an ice-salt mixture to 5°. An ice-cold solution of stannous chloride dihydrate (35 g.) in hydrochloric acid (d 1.18; 30 ml.) was dripped in at such a rate that the temperature did not rise above 15°. When the addition was complete, the mixture was stirred at room temperature for 30 min. The residue was filtered off, washed with a small amount of water, basified with ammonia solution ($d \ 0.88$), filtered, and dried at 80° . Pentachlorophenylhydrazine (9.4 g., 89%) was obtained by Soxhlet extraction of the residue with chloroform; the details are in Table 2. (ii) By a similar procedure to the above, pentabromoaniline was diazotised and reduced with stannous bromide dihydrate in hydrobromic acid (d 1.47). Pentabromophenylhydrazine was obtained in 87.5% yield.

17 C. R. Kolder and H. J. den Hertog, Rec. Trav. chim., 1953, 72, 853.

136°). A similar reaction was observed with manganese dioxide as the oxidising agent. (iv) The reaction was repeated as in (i) with methyl iodide as solvent. The residue obtained was boiled with ethanol (50 ml.) and allowed to

TABLE 3

¹H and ¹⁹F Chemical shifts ^a in CDCl₃ (δ scale) for the decomposition products of the polyhalogenohydrazines Ring positions

				-8 P.					
Dere	$\overline{2}$	3	4		5	i		6	
duct	t F	F	Ĥ	Ĥ	<u>~</u>	Ĥ	F	ਜ	
(If	91.6	140.7		7.7	140.7		91.6		h
(Ìg				7.9	142.7		89.0		Ď
ίIň	j́ 87∙8	146.0		7.84		6.9	70.1		ь
(Ii) 72.7			8·04			72.7		b
(Ij) 70·2			7.94		6.84	70.2		Ь
(IIa)							8.34	
(11e)			7.9					
(11f)		7.23 €	7.73 •					J 8 Hz
(IVc)			8.09					
(IVd)		7.32 •	7·73 •					J 8 Hz
(IVe)							7.58	
(Vc) 7.28	đ							
(Vd) 7.54	đ							
(Ve) 7.54	d							
(VIIc) 7.47	d							
a	Refere	ence to	CFCl _a f	for 19F	resona	ances	and	Me₄Si	for ¹ H

resonances. ^b Coupling constants were as expected for these compounds. · Signals were doublets. · Signals were singlets.

cool, the mixture was filtered to give tetrachloro-4-iodopyridine (48%), m.p. 178-180° (ethanol-chloroform) (Found: C, 17.3; H, 0.2; N, 4.1. C₅Cl₄IN requires C, 17.5; H, 0.0; 18 H. J. den Hertog and J. de Bruyn, Rec. Trav. chim., 1951,

70, 182. ¹⁹ J. D. Cook and B. J. Wakefield, J. Chem. Soc. (C), 1969, 2376.

H, $4 \cdot 1\%$). Evaporation of the ethanol gave almost pure 2,3,5,6-tetrachloropyridine (15%). An identical reaction with pentachlorophenylhydrazine gave pentachloroiodobenzene (23%), m.p. 206-207° (ethanol) (lit., 20m.p. 207- 208°) and pentachlorobenzene (35°_{\circ}).

(b) Oxidations with aqueous copper sulphate. The required hydrazine (2 g.) was suspended in water (50 ml.) and a solution of copper sulphate pentahydrate (8 g.) in water (50 ml.) was slowly added; the mixture was heated under reflux for 2 hr. Extraction of the cooled mixture with chloroform followed by evaporation of solvent under reduced pressure gave a residue, the constituents of which were identified from a study of its n.m.r. spectrum. Purification was effected by recrystallisation or distillation of the crude products. Details are set out in Tables 1 and 3.

(c) Oxidation of (IIc) with peroxytrifluoroacetic acid. The tetrachloro-4-hydrazinopyridine (1 g.), 30% hydrogen peroxide (3 ml.), and trifluoroacetic acid (20 ml.) were heated together under reflux for 8 hr. The mixture was poured into ene and 1,2,4,5-tetrachlorobenzene (cf. Table 1). When the hydrazine was heated alone, in sulpholane, complete recovery of starting material was achieved. (ii) In a similar manner, pentabromophenylhydrazine afforded 1,2,3,4-tetrabromobenzene (89%), m.p. 62° (lit.,⁸ m.p. 62-63°). The hydrazine when heated under reflux in ethanol was recovered unchanged. (iii) The reaction between hexabromobenzene and ethanolic hydrazine hydrate has been described by us,8 the product was 1,2,3,4-tetrabromobenzene. A similar reaction with pentabromofluorobenzene gave the tetrabromocompound, both when the mixture was boiled or stirred for a prolonged period at room temperature; the evolution of nitrogen gas was also observed.

(f) Reactions with bromine. (i) Bromine (3 ml.) was slowly added to a stirred suspension of pentachlorophenylhydrazine (2 g.) in 6M-hydrochloric acid at 60°; the reaction was maintained at this temperature for 30 min. Water (100 ml.) was added to the cooled mixture and pentachlorobromobenzene (quant.) was filtered off, m.p. 239-

TABLE 4

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		Required (%)						
Hydrazone	M.p.	c	H	N	Formula	ć	H	N
(XXIIIa)	148°	43 ·9	$2 \cdot 4$	7.3	C14H9Cl5N2	44 ·0	$2 \cdot 4$	$7 \cdot 3$
(XXIIIb)	98	33.8	$2 \cdot 1$	8.7	$C_{9}H_{7}Cl_{5}N_{2}$	33.7	$2 \cdot 2$	8.8
(XXIIIc)	106	45.1	$2 \cdot 7$	$7 \cdot 1$	$C_{15}H_{11}Cl_5N_2$	$45 \cdot 4$	$2 \cdot 8$	7.1
(XXIIId)	105	40 ·0	$3 \cdot 0$	7.8	$C_{12}H_{11}Cl_5N_2$	40·0	$3 \cdot 1$	7.8
(XXVIII)	149 - 150	56.3	$3 \cdot 0$	9.3	$C_{14}H_9F_5N_2$	56.0	3.0	9.3
(XXIX)	176 - 177	27.3	$1 \cdot 2$	$4 \cdot 2$	$C_{14}H_9Br_5N_2$	27.8	1.5	$4 \cdot 6$

water (100 ml.) and extracted with chloroform. The residue obtained after evaporation of the dried solvent $(MgSO_4)$ was triturated with cold 4m-sodium hydroxide solution to leave 2,3,5,6-tetrachloropyridine (0.1 g.). Acidification of the basic solution with hydrochloric acid $(d \ 1.18)$ gave tetrachloro-4-hydroxypyridine (0.4 g.), m.p. 230° (ethanol) (lit.,²¹ m.p. 231°).

(d) Reactions with aqueous sodium hydroxide. (i) Pentachlorophenylhydrazine (1.5 g.) was heated under reflux with 6M-sodium hydroxide solution (50 ml.) for 4 hr. The cooled solution was acidified with hydrochloric acid $(d \ 1.18)$ and extracted with chloroform. Evaporation of the dried extract (MgSO₄) gave 1,2,4,5-tetrachloropyridine (0.8 g., 67%). (ii) Tetrachloro-4-hydrazinopyridine was similarly treated to afford tetrachloro-4-hydroxypyridine (63.3%) which was identical (m.p. and i.r.) to an authentic sample. (iii) With the above conditions, tetrafluoro-4-hydrazinopyridine gave 2,3-difluoro-6-pyridone (68%), m.p. 147° (Found: C, 46.2; H, 2.1. C₅H₃F₂NO requires C, 45.8; H, $2\cdot 3\%$; its n.m.r. spectrum shows resonances at δ 91.4 (2-F) and δ 155.9 p.p.m. (3-F) (relative to CFCl₃), and δ 7.69 (4-H) and δ 6.56 p.p.m. (5-H) (relative to Me₄Si); the mass spectrum had m/e 131 (M^+). (iv) Pentachlorophenylhydroxylamine was treated with sodium hydroxide solution to give pentachloroaniline (64%) which was identical (m.p. and i.r.) to an authentic specimen.²²

(e) Reactions with hydrazine hydrate. (i) Pentachlorophenylhydrazine (1 g.) and hydrazine hydrate (1 ml.) were heated in sulpholane (25 ml.) at 140-150° for 5 hr. The cooled reaction mixture was diluted with water (100 ml.) to precipitate a mixture (0.6 g.) of 1,2,3,4-tetrachlorobenz-

20 C. Willgerodt and K. Wilcke, Ber., 1910, 43, 2746.

²¹ H. J. den Hertog, J. Mass, C. R. Kolder, and W. P. Combé, *Rec. Trav. chim.*, 1955, **74**, 59.

240° (dimethyl sulphoxide), (lit.,²³ m.p. 236°). (ii) Likewise, tetrachloro-4-hydrazinopyridine gave 4-bromotetrachloropyridine (83%), m.p. 150-152° (ethanol-chloroform) (Found: C, 20.7; H, 4.8; C₅BrCl₄N requires C, 20.3; H, 4·7%).

(g) Hydrazone formation. The required hydrazine and ketone were made to react in ethanol. The solvent was evaporated off and the hydrazone (quant.) was washed with light petroleum (b.p. 40-60°). The details are in Table 4.

(h) Reaction with piperidine. Tetrachloro-4-hydrazinopyridine (4 g.), and piperidine (2.8 g.) were heated together in boiling dioxan (50 ml.). The residue obtained by evaporation was separated by chromatography on silica gel with light petroleum (b.p. 60-80°) and gave 2,3-dichloro-6-piperidinopyridine (42%) and 2,5-dichloro-6-piperidinopyridine (28%) (cf. below).

Pyrolyses of Polyhalogeno-hydrazines.-(a) Tetrachloro-4-hydrazinopyridine (2 g.) was heated at 160-170° in dry sand (20 g.) for 2 hr. The sand was extracted, in a Soxhlet extractor, with benzene for 8 hr. Evaporation of the solvent gave a residue which was chromatographed on silica gel. Light petroleum (b.p. 60-80°) gave 2,3,5,6-tetrachloropyridine (0.1 g.) and light petroleum-benzene (1:1) afforded 4-aminotetrachloropyridine (0.7 g.), m.p. 220° (lit.,¹² m.p. 220°).

(b) The mixture of tetrabromo-4- and -6-hydrazinopyridine was treated as above to yield 2,3,5,6-tetrabromopyridine (0.3 g.), and a mixture of 2-, and 4-aminotetrabromopyridine (0.2 g.), which were identical (i.r.) to authentic specimens.6

²² D. J. Berry, I. Collins, S. M. Roberts, H. Suschitzky, and B. J. Wakefield, J. Chem. Soc. (C), 1969, 1285.
 ²³ M. Lerer, C. Fabre and G. Hugel, Bull. Soc. chim. France,

1957, 173.

Reaction between 2,3,6-Trichloropyridine and Piperidine.-2,3,6-Trichloropyridine (4 g.), piperidine (4.4 ml.), and dioxan (100 ml.) were heated under reflux for 16 hr. The cooled reaction mixture was diluted with water (100 ml.) and extracted with chloroform which on evaporation gave an off-white solid. Chromatography on silica gel with light petroleum (b.p. 60-80°) as eluant gave 2,3-dichloro-6-piperidinopyridine (0.6 g., 12%), b.p. $140^{\circ}/0.6$ mm. (Found: C, 52.2; H, 5.5. C₁₀H₁₂Cl₂N₂ requires C, 52.0; H, 5.2%); its n.m.r. spectrum (deuteriochloroform) showed τ 2.59 (d, 4-H), 3.55 (d, 3-H, J 8.5 Hz), 6.86 (s, α -CH₂), and 8.26 (s, β , γ -CH₂). Further elution gave 2,5-dichloro-6-piperidinopyridine (1.8 g., 33%), b.p. 200°/4 mm. (Found: C, 51.5; H, 5.5%); its n.m.r. spectrum had resonances at τ 2.59 (d, 4-H), 3.35 (d, 3-H, J 8 Hz), 6.83 (s, α -CH₂), and 8.28 (s, β , γ -CH₂).

Reactions of 4-Bromotetrachloropyridine.—(a) With piperidine. (i) A solution of 4-bromotetrachloropyridine (1 g.) and piperidine ($5\cdot 8$ g.) in benzene (30 ml.) was set aside for 72 hr. at room temperature and then washed with water, dried (MgSO₄), and evaporated. The residue was chromatographed on silica gel with light petroleum (b.p. 60—80°) to afford 4-bromotrichloro-6-pipieridinopyridine (0.45 g., 39%), m.p. 64—65° (aqueous ethanol) (Found: C, $35\cdot 0$; H, $3\cdot 0$; N, $8\cdot 4$. $C_{10}H_{10}BrCl_3N_2$ requires C, $34\cdot 9$; H, $2\cdot 9$; N, $8\cdot 2\%$). Further elution yielded tetrachloro-4-piperidinopyridine ($0\cdot 2$ g., 20%), m.p. 81° (lit., 12 m.p. 81°). (ii) The reaction was repeated with ethanol as the solvent to give 4-bromotrichloro-6-piperidinopyridine ($0\cdot 6$ g., $52\cdot 5\%$) and tetrachloro-6-piperidinopyridine ($0\cdot 33$ g., $32\cdot 5\%$).

(b) With n-butyl lithium. The pyridine (1 g.) was dissolved in diethyl ether (50 ml.) and cooled to -75° , in an atmosphere of nitrogen. n-Butyl-lithium (molar ratio 1:1) (0.002 moles/cm³ in cyclohexane) was added with stirring. The solution was stirred at this temperature for 30 min. before being allowed to warm to room temperature; it was then stirred for a further 16 hr. at this temperature. Water (20 ml.) was slowly added and the ethereal phase was separated, the aqueous layer was extracted with ether, and the combined extracts were dried (MgSO₄). Evaporation under reduced pressure gave 2,3,5,6-tetrachloropyridine (76%) m.p. 89° (lit.,¹⁸ m.p. 90°).

Reactions of Tetrachloro-4-iodopyridine. (a) With piperidine. The amine (1 g.), tetrachloro-4-iodopyridine (2 g.) and ethanol (50 ml.) were heated together under reflux for 16 hr. The solvent was evaporated off, and the residue was chromatographed on silica gel with light petroleum (b.p. 60—80°) as eluant, to give trichloro-4-iodo-6-piperidinopyridine (1.8 g., 78%), m.p. 45° (ethanol) (Found: C, 30.2; H, 2.6; N, 7.0. $C_{10}H_{10}Cl_3IN_2$ requires C, 30.7; H, 2.6; N, 7.2%). Further elution gave tetrachloro-4-piperidinopyridine (0.2 g.).

(b) With copper bronze. An intimate mixture of tetrachloro-4-iodopyridine (2 g.) and copper bronze (6 g.) were heated at 200—210° for 20 hr. in a sealed tube. The mixture was extracted with diethyl ether, the solvent was dried (MgSO₄), and evaporated to give octachloro-4,4'-bipyridyl (0.5 g., 40%), m.p. 211° (ethanol) (lit.,²⁴ m.p. 210°); it had an identical i.r. spectrum to an authentic specimen.²⁴

Preparation of Pentabromofluorobenzene.-This was made

by modifying the reported method.²⁵ Sulphuric acid (d, 1.93, 150 g.), bromine (15 g.), iodine (0.25 g.), and iron powder (0.25 g.) were stirred and heated together at 60°. Bromine (33 g.) and fluorobenzene (9.6 g.) were added dropwise, separately, during 1 hr. and the reaction was held at 60° for 3 hr.; the mixture was then cooled and excess of bromine was blown off with air. The mixture was poured onto crushed ice (2 kg.) to give pentabromofluorobenzene (34.6 g., 70.7%), m.p. 196° (ethanol), (lit.,²⁵ m.p. 197°).

Reactions of Pentabromofluorobenzene.—(a) With sodium methoxide. Pentabromofluorobenzene (3 g.), M-methanolic sodium methoxide (6·2 ml.) and pyridine (100 ml.) were heated together under reflux for 0·5 hr. The solvent was evaporated off and washed with water to give pentabromoanisole (2·1 g., 57%), m.p. 173—174° (benzene) (lit.,²⁶ m.p. 174°).

(b) With ethanolic ammonia. Saturated ethanolic ammonia (500 ml.) and pentabromofluorobenzene (10 g.) were heated together at 150° for 3 hr. in a 1-1 stirred autoclave. Pentabromoaniline (4.6 g.) was filtered off, m.p. $254-256^{\circ}$ (decomp.) (lit.,²⁷ m.p. $256-257^{\circ}$). The filtrate was evaporated and the residue was triturated with cold ethanol to leave more bromo-amine (1.9 g.).

(c) With cyclohexylamine. The amine (50 ml.), pentabromofluorobenzene (5 g.), and benzene (100 ml.) were heated together under reflux for 6 hr. The residue obtained by evaporation of the reaction mixture under reduced pressure was chromatographed on silica with light petroleum (b.p. $60-80^{\circ}$) to give starting material (2.7 g.). Light petroleum-benzene (1:1) eluted N-pentabromophenylcyclohexylamine (1.7 g., 63%), m.p. 89° (light petroleum) (lit., $89-90^{\circ}$).

Reactions of Polyhalogenophenylhydrazones with Cyclising Agents.—(a) (i) Acetophenone pentachlorophenylhydrazone (1 g.) was heated at 200° for 0.5 hr. in polyphosphoric acid (20 g.). The mixture was treated with ice and the residue was filtered off and dried. Chromatography on silica gel with light petroleum (b.p. 60-80°)-benzene (1:1) afforded 4,5,6,7-tetrachloro-2-phenylindole (0.7 g., 81%), m.p. 194° (light petroleum-benzene) (Found: C, 50.9; H, 2.4. $\dot{C}_{14}H_7Cl_4N$ requires C, 50.8; H, 2.1%); ν_{max} 3430 cm.⁻¹ (NH), its n.m.r. spectrum (deuteriochloroform) showed bands at $\tau 2.1$ —2.6 (m, Ph), 1.33br (s, NH, exchangeable), and 3.12 (d, J 2.5 Hz, 3-H); the mass spectrum showed M^+ at m/e 331. (ii) When the reaction was repeated, with a separate batch of polyphosphoric acid, the polychloroindole was obtained in lower yield, contaminated with pentachloroaniline.

(b) Unsuccessful attempts were made to cyclise other polyhalogenophenylhydrazones (cf. Table 4) with anhydrous zinc chloride, PPA, and acetic acid, by heating them in diethylene glycol or in a mixture of ethylene glycol and zinc powder. In all cases the main product was pentachloroaniline accompanied by tar and, occasionally, pentachlorobenzene.

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²⁷ P. Jacobson and A. Loeb, Ber., 1900, 33, 702.

 ²⁴ J. D. Cook, Ph.D. Thesis, University of Salford, 1969, p. 89.
 ²⁵ N. N. Vorozhtsov, G. G. Yakobson and N. I. Krizhechkovskaya, J. Gen. Chem. (U.S.S.R.), 1961, **31**, 1561.

²⁶ A. Bonneaud, Bull. Soc. chim. France, 1910, 7, 776.