# Polyhalogenoaromatic Compounds. Part 39.[1] Synthesis of the Bromo- and Iodo-tetrachloropyridines

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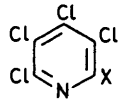
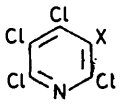
Nucleophilic substitution of pentachloropyridine by bromide or iodide is an unsatisfactory route to tetrachlorohalogenopyridines. We report syntheses of all the bromotetrachloropyridines and tetrachloroiodopyridines *via* the corresponding pyridylhydrazines or pyridyl-lithium or -magnesium derivatives.

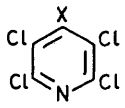
Of the six possible bromotetrachloropyridines and tetrachloroiodopyridines, (1)—(6), only the 4-halogeno-compounds (5) and (6) have been reported.[2,3] We



(1) X = Br
(2) X = I
(10) X = $NHNH_2$
(11) X = $NH_2$
(12) X = H
(13) X = NHMe



(3) X = Br
(4) X = I
(14) X = H



(5) X = Br
(6) X = I
(8) X = MgCl
(15) X = Li
(16) X = Cu

required these compounds in order to study their photochemistry and their reactions with copper. The 4-bromo-compound (5), which is also a key intermediate in establishing the orientation of substituted tetrachloropyridines, was apparently easily prepared by the reaction of sodium bromide with pentachloropyridine in dimethylformamide (DMF).[2] However, investigation of the product of such a reaction by g.l.c.[4] and by $^{13}C$ n.m.r. spectroscopy revealed the presence of much pentachloropyridine and traces of 2-bromotetrachloropyridine (1). We were not able to isolate pure samples of the 4-bromo-compound (5) from the mixtures, so variations on the reaction were tried. Typical results are summarised in Table 1. That the reaction with sodium bromide in

Table 1

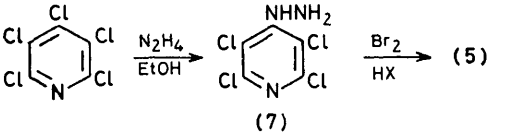
Reactions of pentachloropyridine with bromide

| Source of bromide ion | Solvent | Reaction time | Yields of products (%) [a] pentachloropyridine | 4-bromo (5) | 2-bromo (1) |
|---|---|---|---|---|---|
| NaBr | DMF | 1 h | 68 | 31 | 1 |
| $CaBr_2$ | HMPT | 2 h | 66 | 23 | 12 |
| KBr | MeCN [b] | 18 days | 100 | 0 | 0 |
| HBr [c] | AcOH | 19 h | 55 | 9 | 36 |

[a] By g.l.c. [b] Containing 18-crown-6. [c] The higher proportion of the 2-bromo-compound from this reaction suggested that substitution in protonated pentachloropyridine was occurring (*cf.* F. Mutterer and C. D. Weis, *Helv. Chim. Acta*, 1976, **59**, 229).

DMF is reversible was demonstrated by treating the 4-bromo-compound with sodium chloride, which after 1 h gave pentachloropyridine (48%). It was clearly not possible to obtain pure 4-bromotetrachloropyridine by these routes. Earlier work in this laboratory[3] had suggested that the 4-bromo-compound (5) could be prepared *via* the 4-hydrazino-compound (7) as shown in the Scheme. Further investigation showed that the original procedure required modification, since the use of an excess of hydrazine in the first stage led to some polysubstitution, and the use of hydrochloric acid in the second stage gave some pentachloropyridine (*cf.* ref. 5); the procedure described in the Experimental section gave pure 4-bromotetrachloropyridine in fair yield. A third route, which gave pure 4-bromotetrachloropyridine by a ' one-pot ' reaction in fair yield, involved the preparation of tetrachloro-4-pyridylmagnesium chloride (8) in THF,[6] followed by reaction with bromine at −75 °C.

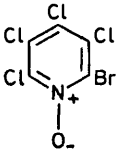
We have confirmed the earlier observation[7] that pentachloropyridine does not react to any great extent with sodium iodide in acetone or DMF; nor did reaction occur with potassium iodide in acetonitrile in the presence of 18-crown-6-ether. Similarly, the reaction of



(7)

Scheme

pentachloropyridine *N*-oxide with bromide gave a maximum of *ca.* 25% of 2-bromotetrachloropyridine *N*-oxide (9) (with calcium bromide in DMF or HMPT) (*cf.*



(9)

ref. 8). When a large excess of calcium bromide was used, di- and tri-substitution occurred.

In the light of these observations, the remaining pentahalogenopyridines (1)—(4) and (6) were prepared by adaptation of the hydrazine and organometallic routes, as summarised below.

Pentachloropyridine *N*-oxide with hydrazine gave poor yields of tetrachloro-6-hydrazinopyridine (10), accompanied by 2-aminotetrachloropyridine (11) as well as the 2,3,4,5-tetrachloropyridine (12) previously reported.[3] The hydrazine (10) gave 2-bromotetrachloropyridine (1)

in 60% yield on treatment with bromine in hydrobromic acid but with silver oxide in iodomethane tetrachloro-6-iodopyridine (2) was obtained in only 10% yield, other products being tetrachloro-6-methylaminopyridine (13) (34%) and 2,3,4,5-tetrachloropyridine (12) (9%). The iodo-compound (2) was obtained in better yield (23%) by treatment of 2,3,4,5-tetrachloropyridine (12) with lithium di-isopropylamide followed by iodine.

3-Bromotetrachloropyridine (3) and tetrachloro-5-iodopyridine (4) were prepared by metallation of 2,3,4,6-tetrachloropyridine (14) with n-butyl-lithium [9] followed by reaction with bromine and iodine, respectively.

Tetrachloro-4-iodopyridine (6) was prepared in 74% yield by reaction of tetrachloro-4-pyridyl-lithium (15) (from metal–halogen exchange between 4-bromotetrachloropyridine and n-butyl-lithium) and iodine; similar yields have been reported *via* the Grignard reagent (8) and the copper derivative (16) [4] while the hydrazine route gave lower yields.[3]

## EXPERIMENTAL

All experiments involving organometallic compounds were carried out using dry solvents and reagents, under dry, oxygen-free nitrogen. For prolonged reactions in dimethylformamide it was necessary to use pure (>99%) material, dried and stored over molecular sieve, to avoid side-reactions involving dimethylamine.

Mass spectroscopic data refer to ions containing $^{35}Cl$ and/or $^{79}Br$ only; the appropriate isotopic distribution pattern was observed in every case. N.m.r. data refer to $Me_4Si$ as internal standard; the $^{13}C$ n.m.r. spectra of compounds (1)—(6) are given in Table 2. Gas chromatographic analyses employed a 5 m × 6 mm column packed with 20% L.A.C. 466 + 2% phosphoric acid on Chromosorb WAW 60/80, hydrogen as carrier gas, and a katharometer detector.

TABLE 2

$^{13}C$ N.m.r. spectra of pentahalogenopyridines

| | $^{13}C$ Chemical shift (p.p.m.) Carbon number [a] | | | | |
|---|---|---|---|---|---|
| Compound | 2 | 3 | 4 | 5 | 6 |
| (1) | 138.0 | 132.4 | 144.0 | 130.0 | 146.7 |
| (2) | 115.5 | 136.9 | 141.4 | 130.6 | 146.5 |
| (3) | 148.2 | 120.6 | 147.0 | 128.7 | 147.1 |
| (4) | 152.2 | 99.4 | 148.7 | 127.8 | 150.8 |
| (5) [b] | 146.5 | 129.7 | 137.1 | 129.7 | 146.5 |
| (6) | 143.2 | 135.0 | 121.9 | 135.0 | 143.2 |

[a] In order to facilitate comparison, the position bearing bromine or iodine is given the lowest possible number, regardless of alphabetical order. [b] B. Iddon, O. Meth-Cohn, H. Suschitzky, J. A. Taylor, and B. J. Wakefield, *Tetrahedron Letters*, 1976, 627.

*Reactions of Pentahalogenopyridines with Halide.*—Most of the reactions were carried out under the following general conditions. The pentahalogenopyridine (*ca.* 0.01 mol) and the halide (1 mol equiv. unless otherwise stated) were dissolved and heated in the solvent (15—25 ml). The reaction mixture was cooled, poured into water (100—200 ml), and filtered. The precipitate was washed with water, dried, and analysed by g.l.c. For the experiments involving crown ethers the solvent was acetonitrile (50 ml) containing 18-crown-6 (0.2 ml); after the reaction the solvent was evaporated off and the residue was washed with water and dried before analysis. The products from the reactions of pentachloropyridine *N*-oxide were deoxygenated before analysis by treatment with titanium(III) chloride in boiling methanol.

The results of these experiments are given in Table 1 and in the Discussion. An experiment carried out as described in reference 2 gave a product, m.p. 144—145° (from light petroleum, b.p. 100—120°). G.l.c. showed this product to contain pentachloropyridine (68%), 4-bromotetrachloropyridine (31%), and 2-bromotetrachloropyridine (1%). The presence of pentachloropyridine was also revealed by $^{13}C$ n.m.r. spectroscopy, and by an i.r. absorption at $\nu_{max.}$ 820 $cm^{-1}$. Chromatography (3 m silica column, light petroleum as eluant) gave a little pure pentachloropyridine and fractions enriched in 4-bromotetrachloropyridine (maximum proportion 74%, m.p. 151°).

*4-Bromotetrachloropyridine.*—(*a*) A mixture of pentachloropyridine (10.0 g; 0.04 mol), hydrazine hydrate (2.0; 0.04 mol), sodium carbonate (4.25 g; 0.04 mol), and ethanol (100 ml) was heated under reflux during 5 h, and then poured into water (300 ml) and filtered. The precipitate was washed with water and boiling light petroleum and dried to give tetrachloro-4-hydrazinopyridine, m.p. 163—164° (lit.,[3] 160—162°). A suspension of tetrachloro-4-hydrazinopyridine (2.45 g) in hydrobromic acid (50% w/v) was stirred at 60 °C as bromine (slight excess) was added dropwise. After stirring at this temperature for a further 30 min the mixture was poured into water and filtered. Chromatography of the dried precipitate (silica, chloroform–light petroleum 1 : 9) gave 4-bromotetrachloropyridine (2.0 g, 68%), m.p. 156—158° (lit., 146—148°,[2] 150—152°,[3]), $M^+$ 293.

(*b*) A solution of pentachloropyridine (12.6 g) in THF (100 ml) was added dropwise to a suspension of magnesium (1.32 g) in a small volume of THF at −10 °C. The mixture was stirred overnight at room temperature, then cooled to −75 °C as bromine (9.0 g) was added dropwise with stirring. The mixture was allowed to warm to room temperature, poured into aqueous sodium thiosulphate, and filtered. Purification as in (*a*) gave 4-bromotetrachloropyridine (9.0 g, 61%), m.p. 155—157°.

*2-Bromotetrachloropyridine.*—A solution of pentachloropyridine *N*-oxide (3.0 g) and hydrazine hydrate (1.7 g) in ethanol (100 ml) was heated under reflux during 2 h, and then poured into water (300 ml). The solution was extracted with chloroform (3 × 100 ml) and the combined extracts were dried and evaporated and the residue was recrystallised from light petroleum to give crystals (1.3 g), m.p. 150—152° (lit.,[3] m.p. for tetrachloro-6-hydrazinopyridine 153—154°). Chromatography (silica, chloroform) gave (i) 2,3,4,5-tetrachloropyridine (0.2 g, 8%), identified by i.r.; (ii) 2-aminotetrachloropyridine (0.9 g, 37%), m.p. 175—176° (lit.,[10] 174—175°); and (iii) *tetrachloro-6-hydrazinopyridine* (1.06 g, 38%), m.p. 202—204° (from light petroleum), $M^+$ 245 (Found: C, 24.6; H, 1.3; N, 16.9. $C_5H_3Cl_4N_3$ requires C, 24.3; H, 1.2; N, 17.0%). Treatment of tetrachloro-6-hydrazinopyridine (0.7 g) with bromine, as described above for tetrachloro-4-hydrazinopyridine, gave *2-bromotetrachloropyridine* (0.50 g, 60%), m.p. 137—138° (from ethanol), $M^+$ 293 (Found: C, 20.3; N, 4.3. $C_5BrCl_4N$ requires C, 20.3; N, 4.7%), and 2,3,4,5-tetrachloropyridine (0.01 g, 2%).

*Tetrachloro-6-iodopyridine.*—(*a*) A mixture of tetrachloro-6-hydrazinopyridine (3.0 g), silver oxide (7.0 g), and iodomethane (20 ml) was stirred at room temperature for 15 min

and then under reflux for 90 min. The mixture was extracted with ethanol and chloroform, and the combined organic extracts were filtered and evaporated. Chromatography of the residue (silica, gradient elution with chloroform–light petroleum) gave (i) *tetrachloro-6-iodopyridine* (0.4 g, 10%), m.p. 128—129° (from ethanol), $M^+$ 341 (Found: C, 17.5; N, 4.05. $C_5Cl_4IN$ requires C, 17.5; N, 4.1%); (ii) 2,3,4,5-tetrachloropyridine (0.24 g, 9%); and (iii) tetrachloro-6-methylaminopyridine (1.0 g, 34%), m.p. 120° (lit.,[11] 106°) (from aqueous ethanol), $\nu_{max.}$ 3 430 $cm^{-1}$, $\tau$ 4.8br (exch, NH) and 6.9 (d, Me), $M^+$ 244.

(*b*) A solution of lithium di-isopropylamide from di-isopropylamine (0.73 g) and n-butyl-lithium (1 equiv.) in diethyl ether (50 ml) was added to a solution of 2,3,4,5-tetrachloropyridine (1.7 g) in diethyl ether (50 ml) at −75 °C. The mixture was stirred at −75 °C during 1 h, iodine (2.29 g) was added in one portion, and stirring was continued for 1 h. The mixture was poured into aqueous sodium thiosulphate. Conventional work-up and chromatography (silica, gradient elution with chloroform–light petroleum) gave (i) tetrachloro-6-iodopyridine (0.64 g, 23%), m.p. 128—129°, and (ii) 2,3,4,5-tetrachloropyridine (0.05 g, 4%).

*3-Bromotetrachloropyridine and Tetrachloro-5-iodopyridine.*—(*a*) To a solution of 2,3,4,6-tetrachloropyridine (2.15 g) in diethyl ether (100 ml) at −75 °C was added n-butyl-lithium in hexane (1.2 equiv.). The solution was stirred for 1 h and then also while bromine (2.4 g) was being added dropwise. The mixture was allowed to warm to room temperature and then poured into aqueous sodium thiosulphate. Conventional work-up and chromatography (silica, light petroleum) gave *3-bromotetrachloropyridine* (1.7 g, 58%), m.p. 131—133° (from light petroleum), $M^+$ 293 (Found: C, 20.5; N, 4.7. $C_5BrCl_4N$ requires C, 20.3; N, 4.7%).

(*b*) In an otherwise similar experiment, iodine (2.45 g) was added in one portion in place of the bromine. The products were *tetrachloro-5-iodopyridine* (2.03 g, 60%), m.p. 110—111° (from ethanol), $M^+$ 341 (Found: C, 17.5; N, 4.0. $C_5Cl_4IN$ requires C, 17.5; N, 4.1%), and starting material (0.85 g, 40%).

*Tetrachloro-4-iodopyridine.*—To a stirred suspension of 4-bromotetrachloropyridine (5.88 g) in diethyl ether (100 ml) at −75 °C was added n-butyl-lithium (1 mol equiv.) in hexane. Stirring was continued for 1 h, iodine (5.08 g) was added in one portion, and the mixture was allowed to warm to room temperature and poured into aqueous sodium thiosulphate. Conventional work-up and chromatography (silica, chloroform–light petroleum 1 : 9) gave tetrachloro-4-iodopyridine (5.0 g, 74%), m.p. 201—202° (lit.,[3] 202°).

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