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POLYHALOGENOAROMATIC COMPOUNDS

XXXV*. METAL—HALOGEN EXCHANGE BETWEEN n-BUTYLLITHIUM AND POLYHALOGENOBIPYRIDINES

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Summary

Metal—halogen exchange between n-butyllithium and 2,2′-dibromohexachloro-4,4′-bipyridine takes place at the 2- and 2′-positions; no rearrangement leading to 3-(5-)lithiobipyridines is observed. In the transition state for the metal—halogen exchange reaction the substrate probably has partial carbanionic character.

Introduction

Polychloroaromatic compounds normally react with organolithium compounds by metal—halogen exchange [2], which usually takes place at the position(s) most susceptible to nucleophilic substitution. The 4-substituted tetrachloropyridines are anomalous, however, since in most cases metal—halogen exchange occurs at the 3-position, whereas nucleophilic substitution takes place at the 2-position. We have considered two possible explanations for the anomaly. The first, that the reagent is 'directed' to the 3-position by co-ordination with the substituent, was rejected because no such effect has been observed in analogous pentachlorophenyl derivatives [2,3]; moreover, exchange at the 3-position occurs even with substituents such as *p*-trifluoromethylphenyl [4] and tetrachloro-4-pyridyl [5] which would be poor donor ligands. The second, that the 2-lithio compound is formed initially, and then rearranges to the 3-lithio compound, is also considered unlikely: in numerous experiments we have never observed any evidence for such behaviour; and the addition of ether to a solution of tetrachloro-2-pyridyllithium in a hydrocarbon solvent leads to decomposition, rather than rearrangement [6]. The experiments described here were designed

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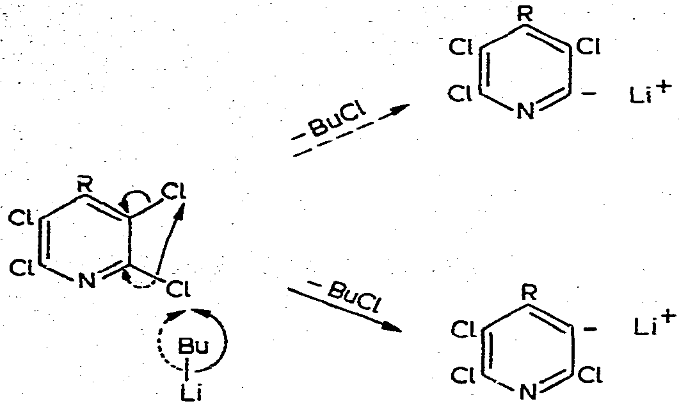
* For part XXXIV see ref. 1.

SCHEME 1



to test further the second hypothesis, and a possible extension of it: that attack at the 2-position is synchronous with migration of a chlorine atom from the 3- to the 2-position.

The mechanism of the metal—halogen exchange reaction may be envisaged as involving interaction between the carbanionic portion of the organolithium compound and the halogen [7]*. In the case of a 4-substituted tetrachloropyridine the predicted attack at C(2) would lead to the development of carbanionic character at that position (dotted arrows in Scheme 1). There is both theoretical [8] and experimental [9] evidence that a 2-pyridyl carbanion is less stable than a 3-pyridyl carbanion. It was therefore possible that *during the course of the metal—halogen exchange reaction* a chlorine atom could migrate from the 3- to the 2-position (solid arrows in Scheme 1).

Results and discussion

In order to test the hypotheses advanced above, and in the hope of shedding more light on the mechanism of the metal—halogen exchange reaction, some experiments directed at the synthesis of polyhalogeno-2-pyridyllithium intermediates have been carried out. We have already reported that metal—halogen exchange between n-butyllithium and octachloro-4,4′-bipyridine (I) (see Scheme 2) in diethyl ether gives first the 3-lithio (II) [5] and then the 3,3′-dilithio-intermediate (III) [10]. Metal—halogen exchange between n-butyllithium and pentachloropyridine, in hydrocarbon solvents, gives mainly the 2-lithio-derivative [6]. The low solubility of octachloro-4,4′-bipyridine in aliphatic hydrocarbons precluded reactions in these solvents, but in benzene, exchange occurred at room temperature; the ^{1}H NMR spectrum of the crude, hydrolysed product showed only a singlet at τ 2.65, corresponding to 3H-heptachloro-4,4′-bipyridine (IV) [5], with no signal at lower field attributable to the 2H-isomer (cf. ref. 6). Thus, even in a hydrocarbon solvent, the reaction proceeded either by

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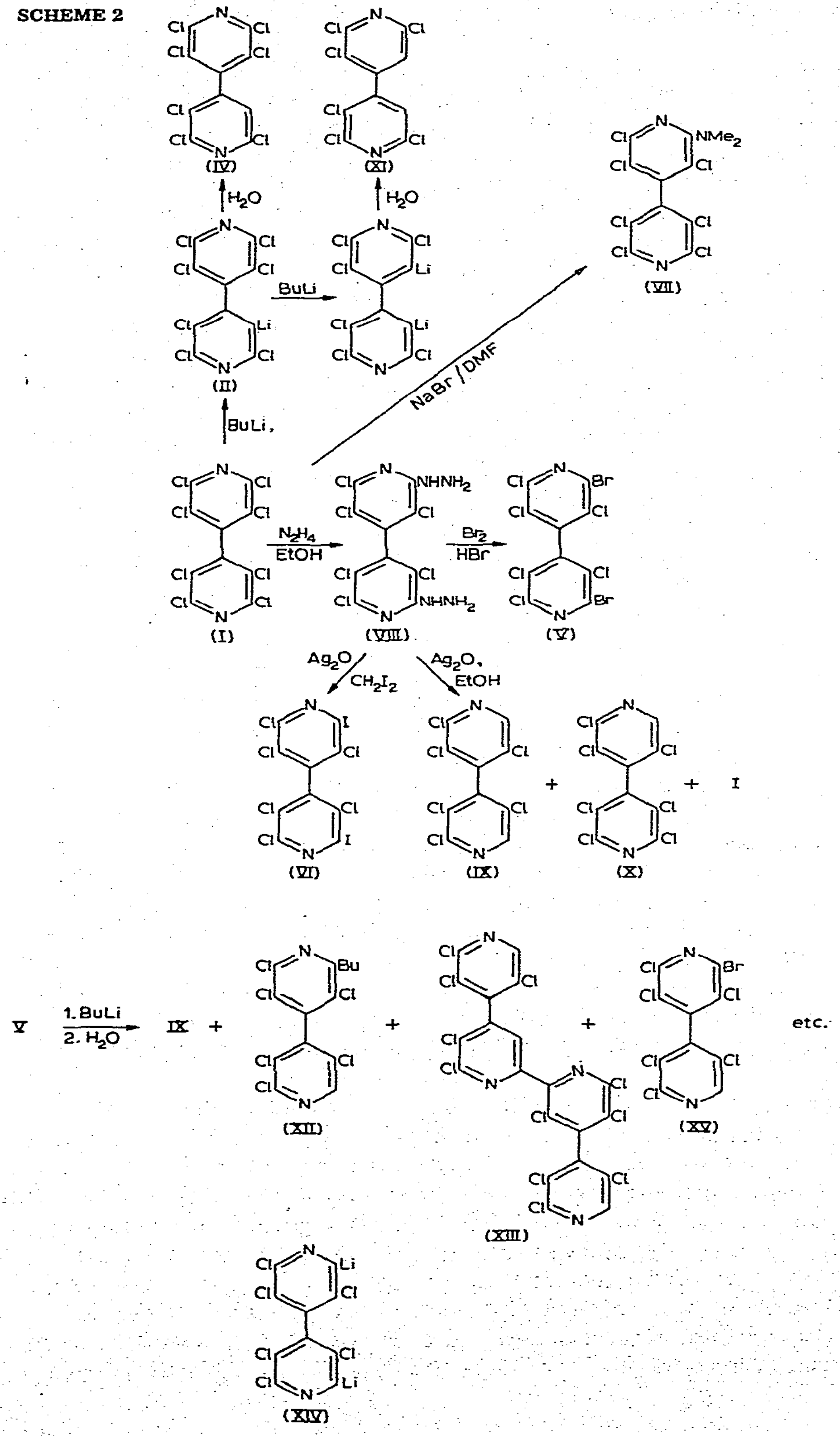
* There is growing evidence for some homolytic character in the reaction, but the extent to which such a pathway is followed is unknown.

SCHEME 2


(IV)
(XI)
H_2O
H_2O
(VII)
(II)
BuLi
BuLi,
NaBr / DMF
N_2H_4
EtOH
Br_2
HBr
(I)
(VIII)
(V)
Ag_2O
CH_2I_2
Ag_2O,
EtOH
+
+ I
(VI)
(IX)
(X)
V
1. BuLi
2. H_2O
IX +
+
+
etc.
(XII)
(XIII)
(XV)
(XIV)

direct exchange at a 3-position, or by the type of rearrangement postulated above.

It is known that metal—halogen exchange takes place at iodine or bromine in preference to chlorine [7], and 2,2′-dibromohexachloro-4,4′-bipyridine (V) and hexachloro-6,6′-diiodo-4,4′-bipyridine (VI) were therefore synthesised. The preparation and characterisation of the dibromo-compound (V) presented problems. Although pentachloropyridine reacts smoothly with sodium bromide in DMF to give 4-bromotetrachloropyridine [11], octachloro-4,4′-bipyridine (I) was inert under similar conditions, and under more vigorous conditions heptachloro-6-dimethylamino-4,4′-bipyridine (VII) was formed. On reaction with hydrazine hydrate in ethanol (cf. ref. 12), octachlorobipyridine (I) gave intractable mixtures of compounds; mass spectrometry indicated that under appropriate conditions, the dihydrazino-derivative (VIII) could be made the major product, and this was the key intermediate for the preparation of the dibromo-compound (V) and of 2H,2′H-hexachloro-4,4′-bipyridine (IX) and hexachloro-6,6′-diiodo-4,4′-bipyridine (VI). On reaction with bromine in hydrochloric acid [12], the dihydrazino-compound (VIII) gave mixtures of bromochlorobipyridines, which could not be separated, and which could be analysed only by mass spectrometry (^{1}H NMR spectroscopy was not applicable, all the mixtures had very similar IR spectra, and elemental analysis could only establish an average composition). When hydrobromic acid was used in place of hydrochloric acid, a product was obtained which showed a strong molecular ion at *m/e* 516 ($C_{10}Br_2Cl_6N_2$) as required for compound V, with only very weak signals at *m/e* 472 ($C_{10}BrCl_7N_2$) and 560 ($C_{10}Br_3Cl_5N_2$). Oxidation of the dihydrazino-compound (VIII) with silver oxide in ethanol [12] gave mixtures of octachloro-4,4′-bipyridine (I), 2H-heptachloro-4,4′-bipyridine (X) and 2H,2′H-hexachloro-4,4′-bipyridine (IX). The last two compounds (X and IX) were obtained as oils, which could not be adequately purified, but which were identified by mass measurement of their molecular ions. (A pure sample of compound (IX) had m.p. 96-97°C). Both showed a singlet in the ^{1}H NMR spectrum, at τ 1.45; this clearly distinguished them from the 3H- and 3H,3′H-compounds (IV and XI), which showed signals at τ 2.9 and 2.7, respectively [5,10]. Oxidation of the dihydrazino-compound (VIII) with silver oxide in iodomethane [12] gave mainly the hexachlorobipyridine (IX), with some iodo-compounds. The proportion of iodo-compounds was increased when the reaction was conducted in diiodomethane, and a small sample of pure hexachloro-6,6′-diiodo-4,4′-bipyridine (VI) was isolated, but the yield was so low that metal—halogen exchange experiments were not practicable.

When a hexane solution of n-butyllithium (2 equivalents) was added to a suspension of the dibromo-compound (V) in diethyl ether at —78°C, an intense red-brown colour developed rapidly. The mixture was kept at —78°C for 1 hour, allowed to warm to room temperature, hydrolysed and worked up, and the crude product was examined spectroscopically. Its ^{1}H NMR spectrum showed a singlet at τ 1.5 (2-H on pyridine ring) and multiplets in the aliphatic region, including one at τ 7.1, attributable to the α-methylene groups of butyl derivatives such as XII (n-butyltetrachloropyridines show triplets near τ 7.1 [6,13]); absorption near τ 2.7 (3-H on pyridine ring) was barely detectable. Its mass spectrum showed prominent ions at *m/e* 360 [M^+ for (IX)] and 373 [$(C_{10}HCl_6N_2 \cdot CH_2)^+$ fragment from (XII)] (both Cl_6 isotope pattern), and weaker ion peaks at much higher m/e (up to ca. 675, Cl_{11} isotope pattern). Attempts to separate the components of the mixture were unsuccessful, but the spectra indicated that it contained the hexachlorobipyridine (IX), together with compounds such as XII (which could arise by direct alkylation, or by reaction of a lithiobipyridine with bromobutane), and high molecular weight materials. The last could be compounds such as the quaterpyridine XIII, which could be formed via addition of a lithiobipyridine to a pyridine, and would show a molecular ion at m/e 684 (Cl_{11}), and NMR signals near τ 1.5 and 2.7. When the reaction was repeated, but hydrolysis was carried out at —78°C, the ^{1}H NMR spectrum of the crude product was similar but with only small 'butyl' signals. Chromatography on silica gave a pure sample (33% yield) of 2H,2'H-hexachloro-4,4'-bipyridine (IX), as well as starting material and mixtures containing 2H-2'-bromohexachloro-4,4'-bipyridine and high m.w. material, similar to that obtained previously.

It seems clear from these results that when metal—halogen exchange does take place at the 2-positions, no significant rearrangement occurs. The component of the hydrolysed products showing NMR absorption attributable to protons in the 3-position is not the simple hexachlorobipyridine (XI). It is also clear that hexachloro-6,6'-dilithio-4,4'-bipyridine (XIV) is much less stable than the 5,5'-dilithio isomer. The latter is stable in solution for several hours at room temperature [10], whereas the former has undergone a considerable amount of decomposition even during one hour at —78°C.

The hypothesis advanced in the introduction, like those previously put forward, must be rejected, and any fresh hypothesis must explain why metal—halogen exchange occurs directly at the 3-position. A reasonable postulate is that in the transition state for the reaction, the substrate has considerable carbanionic character with the additional negative charge being accomodated largely in the plane of the ring. Reaction would then be favoured at the position best able to bear the negative charge, which in the case of a 4-substituted pyridine, in which the substituent has no marked electronic effect, should be the 3-position [cf. refs. 8,9]. Furthermore a 3-pyridyl carbanion would be stabilised by an electron-withdrawing group in the 4-position, but destabilised by an electron-donating group in the 4-position. The fact that metal—halogen exchange at the 2- as well as at the 3-position of 4-substituted tetrachloropyridines has only been observed with electron-donating substituents [14-16], provides some support for this line of reasoning.

The orientation of nucleophilic substitution in polyhalogeno aromatic compounds is related to the stabilisation of Meisenheimer-type intermediates, where the additional negative charge is accommodated largely at the *o*- or *p*-positions [17,18]. It is thus largely fortuitous that in many cases nucleophilic substitution and metal—halogen exchange occur at the same position.

Experimental

n-Butyllithium was used as a 2.5 *M* solution in hexane. Calculated m/e values are based on ^{35}Cl and ^{79}Br.

Reactions of octachloro-4,4′-bipyridine

(a). With n-butyllithium. n-Butyllithium solution (0.50 ml) was added to a solution of octachloro-4,4′-bipyridine (0.50 g) in benzene (20 ml). After 10 min at room temperature water (10 ml) was added. The product (0.40 g), obtained by conventional work-up was a mixture of starting material and 3H-heptachloro-4,4′-bipyridine (IV) (τ 2.65), identified by comparison with authentic specimens.

(b). With sodium bromide in dimethylformamide. Octachloro-4,4′-bipyridine (2.16 g), sodium bromide (0.55 g) and dimethylformamide (100 ml) were heated under reflux during 7 hours. Conventional work-up gave heptachloro-6-dimethylamino-4,4′-bipyridine (VII) (1.2 g, 53%) m.p. 137-138°C (from light petroleum/chloroform), τ 6.85 (Found: C, 32.5; H, 1.6; N, 9.5. $C_{12}H_6Cl_7N_3$ calcd.: C, 32.8; H, 1.4; N, 9.55%).

(c). With hydrazine hydrate. Conditions giving the highest proportion of the dihydrazino-compound are described. Octachloro-4,4′-bipyridine (3.0 g), hydrazine hydrate (3.5 g) and ethanol (100 ml) were stirred under reflux during 9 hours. The suspension was cooled and filtered, and the solid product was washed with ethanol and water and dried. A typical product, hexachloro-6,6′-dihydrazino-4,4′bipyridine (VIII) (2.0 g, 67%) had m.p. ca. 225°C dec. (Found: N, 18.9%. $C_{10}H_6Cl_6N_6$ calcd.: 19.9%).

Reactions of hexachloro-6,6′-dihydrazino-4,4′-bipyridine

(a). With bromine. The dihydrazino-compound VIII (2.45 g) was suspended in concentrated hydrobromic acid (25 ml) at ca. 60°C, and the suspension was maintained at 60-70°C and stirred vigorously as a slight excess of bromine was added dropwise. The mixture was stirred at 60-70°C during 30 min, cooled, diluted with water and filtered. The solid (3.0 g) was purified by chromatography on silica and recrystallisation from chloroform/light petroleum to give 2,2′-dibromohexachloro-4,4′-bipyridine (V) (2.10 g), m.p. 241-242°C dec. subl., no ^{1}H NMR signal. M^+ at m/e 516 (Br_2Cl_6) with weak ($< 5\%$) M^+ at 472 ($BrCl_7$) and 560 (Br_3Cl_5). (Found: M^+ 515.6564. $C_{10}Br_2Cl_6N_2$ calcd.: M^+ 515.6560.)

(b). With silver oxide in ethanol. The dihydrazino-compound (VIII) (2.0 g), silver oxide (5.0 g) and ethanol (50 ml) were stirred under reflux during 90 min. The mixture was filtered hot, and the blue filtrate was evaporated. Chromatography of the brown, gummy residue (silica, benzene) gave mixtures (0.25 g) of octachloro-4,4′-bipyridine (M^+ 428, Cl_8) and 2H-heptachloro-4,4′-bipyridine (X) (τ 1.45; M^+ 394, Cl_7) and mixtures (0.34 g) of 2H-heptachloro-4,4′-bipyridine (X) (τ 1.45; found: M^+ 393.7947. $C_{10}HCl_7N_2$ calcd.; M^+ 393.7956) and 2H,2′H-hexachloro-4,4′-bipyridine (IX), the main product (τ 1.45; found: M^+ 359.8366. $C_{10}H_2Cl_6N_2$ calcd.: M^+ 359.8346).

(c). With silver oxide in methylene iodide. The dihydrazino-compound (VIII) (2.0 g), silver oxide (5.0 g) and methylene iodide (15 ml) were stirred at 50-70°C during 90 min. Chloroform (50 ml) was added, the mixture was filtered, and the solid was washed with hot chloroform. The combined filtrate and washings were evaporated under reduced pressure. Chromatography of the residue (silica, gradient elution with light petroleum/toluene) gave methylene iodide, white crystalline solids and oils (τ 1.45). Recrystallisation of the solid from carbon tetrachloride gave hexachloro-6,6′-diiodo-4,4′-bipyridine (VI) (0.18 g), m.p. 235-237°C subl. (Found: C, 19.3; N, 4.5%; M^+ 611.6295. $C_{10}Cl_6I_2N_2$ calcd.: C, 19.5; N, 4.6%; M^+ 611.6280.)

Reactions of 2,2'-dibromohexachloro-4,4'-bipyridine (V) with n-butyllithium

(a). To 2,2'-dibromohexachloro-4,4'-bipyridine (1.04 g) in diethyl ether (50 ml) at —75°C was added n-butyllithium solution (1.8 ml). The mixture was stirred at —75°C during 1 hour and as it warmed to room temperature during 20 min. Water (25 ml) was added. Conventional work-up gave an orange-brown gum (0.95 g), with spectroscopic properties described above. Chromatography on silica (20-40% chloroform in light petroleum) gave an oil (0.10 g) [τ 1.50(s), 7.1(t), 8-9(m); most intense M^+ at m/e 360 (Cl_6)] and an orange gum (0.40 g).

(b). To 2,2'-dibromohexachloro-4,4'-bipyridine (1.04 g) in diethyl ether (50 ml) at —75°C was added n-butyllithium solution (1.8 ml). The mixture was stirred at —75°C during 1 hour and methanol (5 ml) was added dropwise. After 5 min the mixture was allowed to warm to room temperature and worked up as before. The chromatographic separation gave the starting material, m.p. 239-241°C (0.04 g), a semi-solid mixture (0.07 g) of starting material (M^+ at m/e 516, Br_2Cl_6) and, mainly, 2H-2'-bromohexachloro-4,4'-bipyridine (M^+ at m/e 438, $BrCl_6$; τ 1.50); further 2H,2'H-hexachloro-4,4'-bipyridine (0.24 g; 33%), an oil which very slowly solidified, m.p. 96-97°C (from methanol), (τ 1.50, M^+ at m/e 360 (Cl_6); (Found: C, 32.6; H, 0.55; N, 7.7%. $C_{10}H_2Cl_6N_2$ calcd.: C, 33.1; H, 0.6; N, 7.7%), and an orange gum (0.28 g), comprising 2H,2'H-hexachloro-4,4'-bipyridine (M^+ at m/e 360, Cl_6, τ 1.50) and high m.w. material (ions up to m/e ca. 700, Cl_{10-14}; τ 2.7-3.0m, 7-9m).

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