Polyhalogenoaromatic Compounds. Part XIX.[1] Metal–Halogen Exchange Reactions of n-Butyl-lithium with Tetrabromo-4-pyridyl and Tetrachloro-2-pyridyl Derivatives

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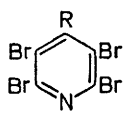
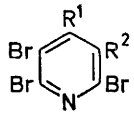
The reaction of n-butyl-lithium with tetrabromo-4-methoxypyridine, tetrabromo-4-dimethylaminopyridine, and tetrabromo-4-piperidinopyridine led to the corresponding tribromo-3-pyridyl-lithium derivatives. When heated in the presence of furan, tribromo-4-methoxy-3-pyridyl-lithium gave an adduct of 5,6-dibromo-4-methoxy-2-pyridine. The reaction of n-butyl-lithium with tetrachloro-6-methoxypyridine, tetrachloro-6-dimethylaminopyridine, tetrachloro-6-pyrrolidinopyridine and tetrachloro-6-piperidinopyridine led to the corresponding trichloro-4-pyridyl-lithium derivatives. When heated in the presence of furan, each of these lithium compounds gave only one of the two possible pyridyne adducts; evidence is presented that the 2-substituted 3-pyridyne was involved in each case. Factors governing the position of metal–halogen exchange in polyhalogeno-benzenes and -pyridines are discussed.

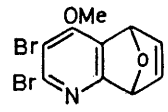
RECENT reports have described metal–halogen exchange reactions of n-butyl-lithium with hexachlorobenzene,[2] hexabromobenzene,[3] pentachlorophenyl derivatives,[4] pentachloropyridine,[5,6] pentabromopyridine,[3] and tetrachloro-4-pyridyl derivatives.[6–9] The position of substitution in these compounds is somewhat unpredictable and in order to obtain further information we have examined the reaction of n-butyl-lithium with the tetrabromo-4-pyridyl derivatives (1)—(3) and the tetrachloro-2-pyridyl derivatives (12)—(15).



(1) R = OMe
(2) R = NMe_2
(3) R = $C_5H_{10}N$
(4) R = OH



(5) R^1 = OMe, R^2 = H
(6) R^1 = NMe_2, R^2 = H
(7) R^1 = $C_5H_{10}N$, R^2 = H
(8) R^1 = OMe, R^2 = Li
(9) R^1 = NMe_2, R^2 = Li
(10) R^1 = $C_5H_{10}N$, R^2 = Li



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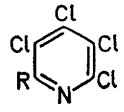


(12) R = OMe
(13) R = NMe_2
(14) R = C_4H_8N
(15) R = $C_5H_{10}N$

Tetrabromo-4-methoxypyridine (1) was prepared in high yield from tetrabromo-4-hydroxypyridine (4), dimethyl sulphate, and potassium carbonate in acetone. However, when the reaction period was prolonged, an additional product was found, whose empirical formula corresponded to a tribromo-4-methoxypyridine, and whose ^{1}H n.m.r. spectrum showed a singlet at τ 3·05, attributable to a proton at the 3-position.[5b] The additional product was therefore 2,3,6-tribromo-4-methoxypyridine (5), which presumably arose by a process analogous to that proposed by Collins and Suschitzky[10] for the debromination of hexabromobenzene by sodium methoxide in ethyl methyl ketone. Tetrabromo-4-dimethylaminopyridine (2) and tetrabromo-4-piperidinopyridine (3) were prepared as mixtures with the 2-substituted compounds by the reaction of the amines with pentabromopyridine.[11] During the separation of the mixtures, small amounts of debrominated materials were detected, but the compounds were not isolated.

The tetrabromo-4-pyridyl derivatives (1)—(3), readily underwent metal–halogen exchange reactions with n-butyl-lithium in diethyl ether; in each case, hydrolysis of the product led to a tribromo-3-pyridyl derivative, whose ^{1}H n.m.r. spectrum showed a singlet between τ 3·0 and 3·3 attributable to a proton at the 3-position of a pyridine ring. The product derived from tetrabromo-4-methoxypyridine (1) was identical with the compound (5) obtained as a by-product during methylation of tetrabromo-4-hydroxypyridine (4), and the products derived from the amines (2) and (3) must be the analogous 2,5,6-tribromo-4-dialkylaminopyridines (6) and (7). The 4-substituted tetrabromopyridines (1)—(3) thus behave like the corresponding tetrachloropyridines, in undergoing metal–halogen exchange *ortho* to the substituent,[7,8] rather than the corresponding pentachlorophenyl derivatives, where little or no exchange *ortho* to the substituent occurs.[4] The fact that tetrabromo-4-methoxypyridine (1) undergoes metal–halogen exchange with n-butyl-lithium is noteworthy, as with tetrachloro-4-methoxypyridine the product is 4-butyltetrachloropyridine, and only the more sterically demanding t-butyl-lithium reacts by metal–halogen

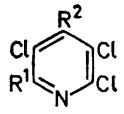
[1] Part XVIII, F. Binns and H. Suschitzky, *J. Chem. Soc.* (*C*), preceding paper.
[2] M. D. Rausch, F. E. Tibbets, and H. B. Gordon, *J. Organometallic Chem.*, 1966, **5**, 493.
[3] D. J. Berry and B. J. Wakefield, *J. Chem. Soc.* (*C*), 1969, 2342.
[4] D. J. Berry, I. Collins, S. M. Roberts, H. Suschitzky, and B. J. Wakefield, *J. Chem. Soc.* (*C*), 1969, 1285.
[5] (*a*) J. D. Cook, B. J. Wakefield, and C. J. Clayton, *Chem. Comm.*, 1967, 150; (*b*) J. D. Cook and B. J. Wakefield, *J. Organometallic Chem.*, 1968, **13**, 15.
[6] S. S. Dua and H. Gilman, *J. Organometallic Chem.*, 1968, **12**, 299.
[7] J. D. Cook and B. J. Wakefield, *Chem. Comm.*, 1968, 297; *idem*, *J. Chem. Soc.* (*C*), 1969, 1973, 2376.
[8] R. A. Fernandez, H. Heaney, J. M. Jablonski, K. G. Mason, and T. J. Ward, *J. Chem. Soc.* (*C*), 1969, 1908.
[9] E. Ager, B. Iddon, and H. Suschitzky, *Tetrahedron Letters*, 1969, 1507; *J. Chem. Soc.* (*C*), 1970, 193.
[10] I. Collins and H. Suschitzky, *J. Chem. Soc.* (*C*), 1969, 2337.
[11] I. Collins and H. Suschitzky, *J. Chem. Soc.* (*C*), 1970, 1523.

exchange.[8] For tetrabromo-4-methoxypyridine (1) the *substrate* is more sterically crowded, and in addition bromine is more susceptible to metal–halogen exchange than chlorine.[12] An analogous case of steric hindrance to nucleophilic displacement of a 4-substituent has recently been reported: piperidine replaces the nitro-group in tetrachloro-4-nitropyridine, but a bromine atom in tetrabromo-4-nitropyridine.[11,13]

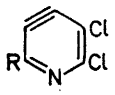
All of the tribromo-3-pyridyl-lithium compounds (8)—(10) are potential precursors for 2-pyridynes, but when they were heated in the presence of furan, we were able to isolate an adduct only in the case of the methoxy-derivative (8), which gave the expected 2,3-dibromo-5,8-epoxy-5,8-dihydro-4-methoxyquinoline (11).

The 2(6)-substituted tetrachloropyridines (12)—(15) were prepared by the reaction of the appropriate nucleophiles with pentachloropyridine. For the amino-derivatives (13)—(15) the required isomer was the major product,[14] but in the reaction of pentachloropyridine with potassium methoxide in methanol, the 2(6)-isomer is reported to form only 15% of the product.[14b] We have found, however, that with magnesium methoxide in methanol, the proportion of 2(6)-isomer is raised to approximately 25%.*

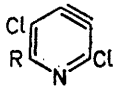
On reaction with n-butyl-lithium in diethyl ether, followed by hydrolysis, all the tetrachloro-2-pyridyl derivatives (12)—(15) gave trichloropyridines.† The n.m.r. signals for the pyridine ring protons were near τ 2·4, suggesting that the protons were located at the 4-position. A proton at the 3-position would have



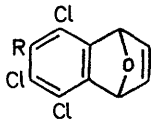
(16) R^1 = OMe, R^2 = H
(17) R^1 = NMe_2, R^2 = H
(18) R^1 = C_4H_8N, R^2 = H
(19) R^1 = $C_5H_{10}N$, R^2 = H
(20) R^1 = OMe, R^2 = Li
(21) R^1 = NMe_2, R^2 = Li
(22) R^1 = C_4H_8N, R^2 = Li
(23) R^1 = $C_5H_{10}N$, R^2 = Li



(24) R = OMe
(25) R = NMe_2
(26) R = C_4H_8N
(27) R = $C_5H_{10}N$



(28) R = OMe
(29) R = NMe_2
(30) R = C_4H_8N
(31) R = $C_5H_{10}N$



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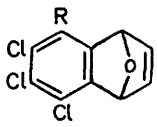


(33)

given a signal at much higher field, and one at the 2-position one at much lower field; we considered it unlikely that metal–halogen exchange had taken place at the 5-position. The structures of the methoxy-(16), dimethylamino- (17) and pyrrolidino- (18) compounds were confirmed by comparison with the compounds formed by the reaction of 2,3,5,6-tetrachloropyridine with the appropriate nucleophiles. The piperidino-compound (19) was identical with an authentic specimen.[15]

We can summarise the results of our studies on metal–halogen exchange reactions of polyhalogenoaromatic compounds as follows. In the majority of systems (pentachlorophenyl derivatives,[4] pentahalogenopyridines,[3,5,6] tetrachloro-2-pyridyl derivatives) metal–halogen exchange takes place mainly at the same position as nucleophilic substitution, and steric effects and the electronic effects of substituents apparently outweigh co-ordination of the reagent by substituents. The tetrahalogeno-4-pyridyl compounds are anomalous. In the majority of 4-substituted tetrachloropyridines, metal–halogen exchange occurs at the 3-position, whereas nucleophilic substitution takes place at the 2-position. Only in the cases of tetrachloropyridine-4-thiolate[9] and tetrachloropyridine-4-phenolate,[16] where the substituent is exceptionally electron-donating, is any metal–halogen exchange at the 2-position observed. The reasons for the anomalous behaviour of the 4-substituted tetrachloropyridines are obscure. It is known, however, that metal–halogen exchange reactions are reversible,[12,17] and it is possible that in some cases we have observed the products of thermodynamically, rather than kinetically, controlled reactions; this hypothesis will unfortunately be extremely difficult to test, in view of the high rate of the reactions even at low temperatures.

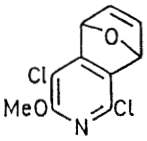
The 2-substituted trichloro-4-pyridyl-lithium compounds (20)—(23) are potential precursors for pyridynes, and when they were heated in the presence of furan, adducts were obtained. These could have been derived from the 2-substituted 3-pyridynes (24)—(27) or the 6-substituted 3-pyridynes (28)—(31). In each case, only one adduct was isolated, and it was difficult to distinguish between the alternative structures. The related benzyne adducts, (32) and (33) (R = OMe, NMe_2, C_4H_8N, or $C_5H_{10}N$) could be distinguished by their n.m.r. spectra; the signals for the bridgehead protons of the adducts of type (32) were superimposed, whereas for those of type (33) the signals were separated by approximately 0·25 p.p.m.[4] For the methoxy-pyridyne adduct, the signals for the bridgehead protons were almost superimposed, suggesting that it had the structure (34). However, for the other adducts, the signals for the bridgehead protons were separated by 0·13 to 0·29 p.p.m., suggesting that they had the structures (35)—(37). In the absence of any obvious reason

* Experiments carried out by J. Worth.

† In one run, the methoxy-derivative (12) gave a mixture containing some butylated material; we were unable to repeat this result.

[12] H. Gilman and R. G. Jones, *Org. Reactions*, 1951, **6**, 339.
[13] S. M. Roberts and H. Suschitzky, *J. Chem. Soc.* (*C*), 1968, 2844.
[14] (*a*) S. M. Roberts and H. Suschitzky, *Chem. Comm.*, 1967, 893; (*b*) W. T. Flowers, R. N. Haszeldine, and S. A. Majid, *Tetrahedron Letters*, 1967, 2503; (*c*) S. M. Roberts and H. Suschitzky, *J. Chem. Soc.* (*C*), 1968, 1537.
[15] S. M. Roberts, Ph.D. Thesis, Salford, 1969.
[16] J. D. Cook, Ph.D. Thesis, Salford, 1969.
[17] H. J. S. Winkler and H. Winkler, *J. Amer. Chem. Soc.*, 1966, **88**, 964.

why the elimination of lithium chloride should occur exclusively in one direction for the methoxy-compound, and in the other direction for the others, some chemical confirmation of the proposed structures was desirable.



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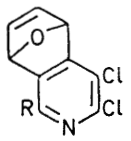
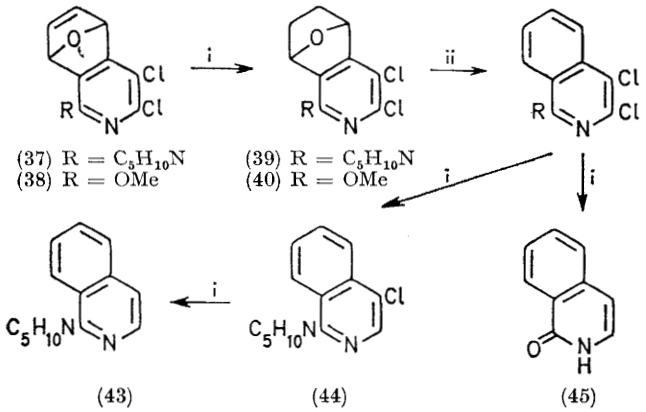


(35) R = NMe_2
(36) R = C_4H_8N
(37) R = $C_5H_{10}N$
(38) R = OMe

Accordingly, the methoxypyridyne adduct and the piperidinopyridyne adduct were degraded to mono-substituted isoquinolines, by the route shown in the Scheme. The ^1H n.m.r. spectrum of the product from the piperidino-derivative showed *ortho* -coupled doublets (J 6 Hz) at τ 1·90 and 2·90, confirming that it was



(37) R = $C_5H_{10}N$
(38) R = OMe

(39) R = $C_5H_{10}N$
(40) R = OMe

(43) (44) (45)

SCHEME

Reagents: i, N_2H_4 + Pd/C; ii, HBr/HOAc.

1-piperidinoisoquinoline (44) rather than the 3-piperidino-isomer. The product from the methoxy-derivative also showed doublets (J 7 Hz) at τ 2·7 and 3·35, and melted at 204—205°, indicating that it was 1-isoquinolone (45). The n.m.r. spectrum of the methoxypyridyne adduct was thus misleading, as it in fact had structure (38) rather than structure (34), and all the 2-substituted trichloro-4-pyridyl-lithium compounds (20)—(23) gave adducts derived from 2-substituted 3-pyridynes (24)—(27).

EXPERIMENTAL

All experiments involving organometallic compounds were conducted in dry solvents, under dry, oxygen-free nitrogen. n-Butyl-lithium was in the form of a commercially available 2·25M-solution in hexane. ^1H N.m.r. spectra were recorded at 60 MHz with tetramethylsilane as internal standard and deuteriochloroform as solvent, unless otherwise stated.

Tetrabromo-4-hydroxypyridine.—This compound, prepared by a literature method, had m.p. 255—257° (lit.,[18] m.p. 257—258°).

Methylation of Tetrabromo-4-hydroxypyridine.—(*a*) Tetrabromo-4-hydroxypyridine (8·22 g), dimethyl sulphate (2·5 ml), anhydrous potassium carbonate (5·60 g) and dry acetone (100 ml) were heated under reflux for 36 h. The mixture was evaporated to dryness. Water (500 ml) was added to the residue, and the organic products were isolated *via* chloroform extraction, and separated by chromatography on silica; 40% benzene–light petroleum eluted tetrabromo-4-methoxypyridine (4·25 g, 50%), m.p. 143—144° (from 10% benzene–light petroleum) (lit.,[15] 143°), and 75% benzene–light petroleum eluted 2,3,6-*tribromo*-4-*methoxypyridine* (1·79 g, 26%), m.p. 153—154° (from 10% benzene–light petroleum), τ 3·05 (s, 1H) and 4·00 (s, 3H) (Found: C, 21·3; H, 1·2; N, 4·1. $C_6H_4Br_3NO$ requires C, 20·8; H, 1·15; N, 4·05%).

(*b*) A similar experiment, with the reaction period shortened to 2 h, gave tetrabromo-4-methoxypyridine (7·1 g, 84%).

2,3,5,6-*Tetrabromo*-4-*dimethylaminopyridine and* 2,3,5,6-*tetrabromo*-4-*piperidinopyridine.*—These compounds were prepared, and separated from the 2-dialkylamino-isomers, as previously described.[11] Large-scale preparations from pentabromopyridine (70 g) gave, as chromatographic fractions between the 2- and 4-isomers, complex mixtures (*ca.* 2·0 g) containing debrominated products.

Reaction of n-Butyl-lithium with Tetrabromo-4-pyridyl Derivatives.—(a) *With tetrabromo-4-methoxypyridine.* n-Butyl-lithium solution (5·0 ml) was added to a stirred suspension of tetrabromo-4-methoxypyridine (4·25 g) in diethyl ether (100 ml) at −75°. The mixture was stirred whilst being allowed to warm to −10° during 40 min., and then at −10° to −5° during 30 min. Water (100 ml) was added to the mixture and the material recovered from the ether layer was purified by chromatography on silica. Elution with 65% benzene–light petroleum gave 2,3,6-tribromo-4-methoxypyridine (1·10 g, 32%) identical (i.r., mixed m.p.) with the compound described above.

A second reaction was carried out as described above, except that before hydrolysis, the solution was re-cooled to −75°, furan (80 ml) was added, and the mixture was heated under reflux for 5 h. Chromatography of the products (silica) gave 2,3,6-tribromo-4-methoxypyridine (0·170 g, 5%) (eluted with 70% benzene–light petroleum), and 2,3-*dibromo*-5,8-*epoxy*-5,8-*dihydro*-4-*methoxyquinoline* (0·40 g, 12%), m.p. 139—140° (from 30% benzene–light petroleum), τ 2·88 (s, 2H, olefinic H), 3·78 (s, 1H, bridgehead H), 4·48 (s, 1H, bridgehead H), and 5·94 (s, 3H, OCH_3) (Found: C, 36·2; H, 2·2; N, 4·45. $C_{10}H_7Br_2NO$ requires C, 36·05; H, 2·1; H, 4·2%).

(b) *With tetrabromo-4-dimethylaminopyridine.* Under similar conditions to those described under (a) above, tetrabromo-4-dimethylaminopyridine (1·0 g) gave 2,3,6, *tribromo*-4-*dimethylaminopyridine* (0·31 g, 38%), m.p. 98—99° (from light petroleum), τ 3·30 (s, 1H, 3-H) and 6·95 (s, 6H, NMe_2) (Found: C, 23·6; H, 1·8; N, 7·9. $C_7H_7Br_3N_2$ requires C, 23·4; H, 1·95; N, 7·8%).

(c) Similarly, tetrabromo-4-piperidinopyridine (1·0 g) gave 2,3,6-*tribromo*-4-*piperidinopyridine* (0·35 g, 41%), m.p. 66—68° (from light petroleum), τ 3·08 (s, 1H, 3-H), 6·85br (s, 4H, α-CH_2), and 8·30br (s, 6H, other CH_2) (Found: C, 30·25; H, 2·9; N, 6·9. $C_{10}H_{11}Br_3N_2$ requires C, 30·1; H, 2·75; N, 7·0%).

Tetrachloro-6-*methoxypyridine.*—Magnesium (2·60 g) was

[18] H. Pfanz and H. Dorn, *Arch. Pharm.*, 1956, **289**, 651.

dissolved in dry methanol (160 ml) and a solution of pentachloropyridine (20·0 g) in methanol (40 ml) was added to it; the mixture was heated under reflux for 4 h. The solvent was removed *in vacuo*, water (50 ml) was added to the residue, and the products were isolated *via* ether extraction and were separated by chromatography on silica. Light petroleum eluted tetrachloro-6-methoxypyridine (2·16 g, 13·3%), m.p. 90° (lit.,[14c] m.p. 91°), and 10% benzene–light petroleum eluted tetrachloro-4-methoxypyridine (9·43 g, 48%) m.p. 114—116° (lit.,[19] m.p. 117—119°).

The crude product from a similar experiment showed ^{1}H n.m.r. signals (C_6D_6) at τ 6·43 and 6·61, in the ratio 3 : 1.

2,3,5-*Trichloro*-6-*methoxypyridine*.—2,3,5,6-Tetrachloropyridine (1·0 g) was added to a solution of sodium (0·106 g) in methanol (60 ml), and the solution was heated under reflux for 4 h. The solvent was removed *in vacuo*, water (50 ml) was added to the residue, and product was isolated *via* ether extraction *etc.*, and purified by chromatography on silica. Light petroleum eluted 2,3,5-*trichloro*-6-*methoxypyridine* (0·47 g, 41%), identical (mixed m.p., ^{1}H n.m.r.) with the compound described below.

2,3,5-*Trichloro*-6-*dimethylaminopyridine*.—2,3,5,6-tetrachloropyridine (1·10 g), ethanolic dimethylamine (0·50 g in 2·0 ml), and benzene (30 ml) were heated under reflux for 16 h. Removal of solvent followed by chromatography on silica (eluant 20% benzene–light petroleum) gave 2,3,5-*trichloro*-6-*dimethylaminopyridine* (0·84 g., 74%), b.p. 88°/0·2 mmHg (Found: C, 37·1; H, 3·2; N, 12·35. $C_7H_7Cl_3N_2$ requires C, 37·25; H, 3·1; N, 12·4%).

2,3,5-*Trichloro*-6-*pyrrolidinopyridine*.—A similar experiment, with pyrrolidine (0·80 g) in place of dimethylamine, gave the 6-*pyrrolidino-derivative* (0·89 g, 73%), m.p. 46—47° (from ethanol) (Found: C, 43·1; H, 3·5; N, 11·2. $C_9H_9Cl_3N_2$ requires C, 42·9; H, 3·6; N, 11·1%).

Reactions of n-Butyl-lithium with Tetrachloro-2-pyridyl Derivatives.—(a) *With tetrachloro*-6-*methoxypyridine*. n-Butyl-lithium solution (2·4 ml) was added to a stirred suspension of tetrachloro-6-methoxypyridine (1·45 g) in diethyl ether (150 ml) at −75°. The mixture was stirred as it warmed to room temperature during 1 h, and then for a further 30 min. Water (50 ml) was added to the residue, and the product, recovered from the ether layer, was purified by chromatography on silica (eluant light petroleum) and vacuum sublimation, to yield 2,3,5-trichloro-6-methoxypyridine (1·10 g, 88·2%), m.p. 52—53°, τ (CCl_4) 2·35 (1H, s) and 5·96 (3H, s) (Found: C, 33·8; H, 2·0; N, 6·5%; M^+, 211. $C_6H_4Cl_3NO$ requires C, 33·9; H, 1·9; N, 6·6%; *M*, 211).

(b) *With tetrachloro*-6-*dimethylaminopyridine*. n-Butyl-lithium solution (5·0 ml) was added to a solution of tetrachloro-6-dimethylaminopyridine (2·60 g) in diethyl ether (100 ml) at −75°. The solution was allowed to warm to −35° and was stirred during ½ h. Water (50 ml) was added. The ether layer was dried and evaporated to dryness. Chromatography of the residue (silica, 20% benzene–light petroleum) gave 2,3,5-trichloro-6-dimethylaminopyridine (1·90 g, 84%), τ 2·43 (1H, s, 4-H) and 6·92 (6H, s, NMe_2) identical (i.r.) to the compound described above.

(c) *With tetrachloro*-6-*pyrrolidinopyridine*. In a similar experiment, tetrachloro-6-pyrrolidinopyridine (2·86 g) gave 2,3,5-trichloro-6-pyrrolidinopyridine (1·93 g, 77%), τ 2·52 (1H, s, 4-H), 6·3 (4H, m, α-CH_2), and 8·1 (4H, m, β-CH_2) identical (i.r., mixed m.p.) to the compound described above.

(d) *With tetrachloro*-6-*piperidinopyridine*. In a similar experiment tetrachloro-6-piperidinopyridine (3·00 g) gave 2,3,5-trichloro-6-piperidinopyridine (2·20 g, 82%), b.p. 135°/0·4 mmHg, τ 2·39 (1H, s, 4-H), 6·7 (4H, m, α-CH_2), and 8·3 (6H, m, β,γ-CH_2), identical (i.r.) to an authentic specimen.[19]

3,4-*Dichloro*-5,8-*epoxy*-5,8-*dihydro*-1-*methoxyisoquinoline*.—To a solution of 2,3,5-trichloro-6-methoxy-4-pyridyl-lithium, from tetrachloro-6-methoxypyridine (1·50 g), in diethyl ether (100 ml) at −75°, was added furan (50 ml). The mixture was stirred at −75° during 30 min. and then under reflux during 3 h. Water (50 ml) was added to the mixture and the products were obtained by ether extraction and chromatography on silica. 20% Chloroform–light petroleum eluted successively 2,3,5-trichloro-6-methoxypyridine (0·44 g, 34%) and 3,4-*dichloro*-5,8-*epoxy*-5,8-*dihydro*-1-*methoxyisoquinoline* (0·47 g, 32%), which was purified by preparative t.l.c., m.p. 73—74·5°, τ (CCl_4) 2·93 (2H, m, 6,7-H), 4·23 (2H, m, 5,8-H), and 6·08 (3H, s, OMe) (Found: C, 49·0; H, 3·1; N, 5·7%; M^+ 243. $C_{10}H_7Cl_2NO_2$ requires C, 49·2; H, 2·85; N, 5·7%; *M* 243).

The adduct (3·40 g), hydrazine hydrate (10 ml), 5% palladium on charcoal (1 g) and ethanol (50 ml) were heated under reflux during 2 h. The solution was filtered hot, evaporated to low volume, and poured into water. The resulting solution was extracted with chloroform, and the extract was washed with dilute hydrochloric acid, dried, and evaporated to dryness. Chromatography of the residue (silica, 60% benzene–light petroleum) gave 3,4-*dichloro*-5,8-*epoxy*-5,6,7,8-*tetrahydro*-1-*methoxyisoquinoline* (2·90 g, 85%), m.p. 92° (from ethanol), τ 4·45 (2H, m, 5,8-H), 6·02 (3H, s, OMe), 7·8—8·9 (4H, complex m, 6,7-H) (Found: C, 48·4; H, 3·7; N, 5·5. $C_{10}H_9Cl_2NO_2$ requires C, 48·8; H, 3·65; N, 5·7%).

The tetrahydroisoquinoline (2·80 g) and 45% (w/v) hydrogen bromide in acetic acid (25 ml) were heated under reflux for 2 h. The mixture was poured into water (100 ml), and the suspension was filtered, to give 3,4-dichloroisoquinolone (1·60 g, 66%), m.p. 257—258° (from ethanol), τ [$(CD_3)_2SO$] 1·65 (1H, d, 8-H), and 2·05 (3H, m, 5,6,7-H) (Found: C, 50·2; H, 2·2; N, 6·3. $C_9H_5Cl_2NO$ requires C, 50·5; H, 2·35; N, 6·55%).

3,4-Dichloro-1-isoquinolone (1·50 g), hydrazine hydrate (10 ml), 5% palladium on charcoal (1·0 g), and ethanol (30 ml) were heated under reflux for 3 h. The solution was filtered hot, evaporated to low volume, and diluted with water (50 ml). The product, recovered by chloroform extraction *etc.*, recrystallised from ethanol to give 1-isoquinolone (0·80 g, 78%), m.p. 204—205° (lit.,[20] 208°), τ [$(CD_3)_2SO$] 1·65 (1H, dt, 8-H), 2·1—2·6 (3H, complex m, 5,6,7-H), 2·71 (1H, d, 3-H), 3·35 (1H, d, 4-H), and 6·51br (1H, s, NH, $J_{3,4}$ 7 Hz).

3,4-*Dichloro*-1-*dimethylamino*-5,8-*epoxy*-5,8-*dihydroisoquinoline*.—To a solution of 2,3,5-trichloro-6-dimethylamino-4-pyridyl-lithium, from tetrachloro-6-dimethylaminopyridine (5·20 g), in diethyl ether (200 ml) at −70°, was added furan (100 ml) during 10 min. The solution was heated under reflux during 3 h and was then diluted with water (100 ml). The ether layer was separated, dried, and evaporated. Chromatography of the residue (silica, 20% light petroleum–benzene) gave 3,4-*dichloro*-1-*dimethyl*-

[19] A. Roedig, K. Grohe, and D. Klatt, *Chem. Ber.*, 1966, **99**, 2818.

[20] D. Bain, W. H. Perkin, jun., and R. Robinson, *J. Chem. Soc.*, 1914, **105**, 2392.

amino-5,8-*epoxy*-5,8-*dihydroisoquinoline* (3·0 g, 58%), m.p. 59—60° (from light petroleum), τ 2·90 (2H, m, 6,7-H), 3·93 (1H, m, bridgehead H), 4·22 (1H, m, bridgehead H), 6·92 (6H, m, NMe_2) (Found: C, 51·8; H, 3·7; N, 10·6. $C_{11}H_{10}Cl_2N_2O$ requires C, 51·5; H, 3·9; N, 10·9%).

3,4-*Dichloro*-5,8-*epoxy*-5,8-*dihydro*-1-*pyrrolidinoisoquinoline*.—A similar experiment with tetrachloro-6-pyrrolidinopyridine (5·7 g) gave the *adduct* (3·70 g, 65%), m.p. 149—150° (from light petroleum), τ 2·94 (2H, m, 6,7-H), 3·98 (1H, m, bridgehead H), 4·25 (1H, m, bridgehead H), 6·5 (4H, m, α-CH_2), 8·1 (4H, m, β-CH_2) (Found: C, 55·3; H, 4·4; N, 9·95. $C_{13}H_{12}Cl_2N_2O$ requires C, 55·15; H, 4·2; N, 9·9%).

3,4-*Dichloro*-5,8-*epoxy*-5,8-*dihydro*-1-*piperidinoisoquinoline*.—A similar experiment with tetrachloro-6-piperidinopyridine (6·00 g), gave the *adduct* (3·80 g, 64%), m.p. 68—69° (from light petroleum), τ (CCl_4) 2·92 (2H, m, 6,7-H), 4·17 (1H, m, bridgehead H), 4·30 (1H, m, bridgehead H), 6·6br (4H, s, α-CH_2) and 8·4br (6H, s, β,γ-CH_2) (Found: C, 56·3; H, 4·65; N, 9·6. $C_{14}H_{14}Cl_2N_2O$ requires C, 56·6; H, 4·7; N, 9·4%).

The adduct (6·50 g), hydrazine hydrate (20 ml), 10% palladium on charcoal (2·0 g), and ethanol (50 ml) were heated under reflux for 30 min. The solution was filtered, evaporated, and worked up by extraction with chloroform *etc.* Chromatography of the product (silica, 20% light petroleum–benzene) gave 3,4-*dichloro*-5,8-*epoxy*-5,6,7,8-*tetrahydro*-1-*piperidinoisoquinoline* (4·00 g, 61%), m.p. 73—74° (from ethanol), τ 4·5 (2H, s, bridgehead H), 6·5br (4H, s, α-CH_2), and 7·7—8·6 (10H, complex, m, β,γ-CH_2) (Found: C, 56·2; H, 5·3; N, 9·3. $C_{14}H_{16}Cl_2N_2O$ requires C, 56·1; H, 5·35; N, 9·4%).

A solution of the tetrahydroisoquinoline (3·9 g) in 45% (w/v) hydrogen bromide in acetic acid (70 ml) was heated under reflux for 2 h, cooled, and then neutralised with sodium carbonate. The product was obtained by chloroform extraction *etc.*, and chromatography on silica (eluant 10% chloroform–light petroleum), which gave 3,4-*dichloro*-1-*piperidinoisoquinoline* (2·0 g, 55%), m.p. 141—142° (from ethanol), τ 1·7—2·6 (4H, complex m, ArH), 6·6br (4H, s, α-CH_2), and 8·3br (6H, s, β,γ-CH_2) (Found: C, 59·8; H, 5·1; N, 10·1. $C_{14}H_{14}Cl_2N_2$ requires C, 59·75; H, 5·0; N, 9·95%).

3,4-Dichloro-1-piperidinoisoquinoline (1·0 g), 10% palladium on charcoal (0·5 g), hydrazine hydrate (7 ml), and ethanol (25 ml) were heated under reflux for 2½ h. The solution was filtered and evaporated. Water (50 ml) was added to the residue, and the product was obtained by extraction with chloroform *etc.*, and chromatography on alumina. 10% Chloroform–light petroleum eluted starting material (0·45 g), followed by 4-*chloro*-1-*piperidinoisoquinoline* (0·28 g, 58%), m.p. 87—88° (from ethanol), τ 1·75 (1H, s, 3-H), 1·80—2·60 (4H, m, 5,6,7,8-H), 6·67br (4H, s, α-CH_2), and 8·25br (6H, s, β,γ-CH_2) (Found: C, 67·9; H, 6·0; N, 11·3. $C_{14}H_{15}ClN_2$ requires C, 68·2; H, 6·1; N, 11·35%).

In a similar experiment, after the initial period under reflux, 10% palladium on charcoal (0·5 g) and hydrazine hydrate (7 ml) was added, and the mixture was heated under reflux during a further 3 h, and then set aside for 48 h. The mixture was worked up as before. 10% Chloroform–light petroleum eluted traces of starting material and the 4-chloro-compound, and 15% chloroform–light petroleum eluted 1-*piperidinoisoquinoline* (0·23, 31%) as an oil, τ 1·90 (1H, d, 3-H), 2·0—2·75 (4H, m, 5,6,7,8-H), 2·90 (1H, d, 4-H), 6·65br (4H, s, α-CH_2), and 8·30br (6H, s, β,γ-CH_2, $J_{3,4}$ 6 Hz); the *hydrochloride* had m.p. 178—179° (decomp.) (Found: C, 67·3; H, 6·7; N, 11·1. $C_{14}H_{17}ClN_2$ requires C, 67·6; H, 6·85; N, 11·25%).

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