925. *Polyfluoroheterocyclic Compounds. Part IV.*[1] *Compounds Derived from 4-Aminotetrafluoropyridine*

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4-Aminotetrafluoropyridine is a very weak base but it can be oxidised to the 4-nitro-compound and diazotised in 80% hydrofluoric acid. The diazonium salt, with cuprous bromide, is converted into 4-bromotetrafluoropyridine but its reactions with *NN*-dimethylaniline and with water are complex. 4-Bromotetrafluoropyridine gives 4,4′-octafluorobipyridyl, using the Ullmann technique, and the bromo-compound is also readily converted into a Grignard reagent at low temperature. Carbonation of the Grignard reagent gives tetrafluoroisonicotinic acid and reaction of the former with pentafluoropyridine gives 4,4′-octafluorobipyridyl. Nucleophilic reagents attack 4-bromotetrafluoropyridine at the 2-position and a number of derivatives have been prepared.

In previous Papers in this Series [1,2] we have shown that nucleophilic attack on pentafluoropyridine occurs principally at the 4-position and this has been confirmed by other workers.[3] Thus, 4-aminotetrafluoropyridine was readily obtained by the reaction between

[1] Part III, R. D. Chambers, J. Hutchinson, and W. K. R. Musgrave, *J.*, 1964, 5634.
[2] R. D. Chambers, J. Hutchinson, and W. K. R. Musgrave, *J.*, 1964, 3736.
[3] R. E. Banks, J. E. Burgess, W. M. Cheng, and R. N. Haszeldine, *J.*, 1965, 576.

aqueous ammonia and pentafluoropyridine, and the present Paper shows that the compound is a useful intermediate in the preparation of many other 4-substituted tetrafluoropyridines.

4-Aminotetrafluoropyridine is a considerably weaker base than aminopentafluorobenzene since the latter formed a hydrochloride when hydrogen chloride was passed through a dry ethereal solution, whereas the former gave no hydrochloride under the same conditions. Also, in this context, 4-aminotetrafluoropyridine was difficult to oxidise to the 4-nitro-compound but the oxidation was achieved by heating under reflux for 22 hr. with peroxytrifluoroacetic acid (reactions of 4-nitrotetrafluoropyridine will be reported later [4]).

Diazotisation of negatively substituted aromatic amines usually requires special conditions but diazotisation of 4-aminotetrafluoropyridine was further complicated by the possibility of loss of fluoride ion from the diazonium salt, a difficulty which has been encountered by other workers using fluorinated aromatic amines.[5,6] Only starting material was recovered from the attempted diazotisation of 4-aminotetrafluoropyridine using a medium of concentrated sulphuric acid but using 80% hydrofluoric acid, which has been used previously to offset the loss of fluoride ion,[7] successful reaction was achieved. A temperature of $-25°$ to $-20°$ was maintained during the diazotisation and, after the addition of cuprous bromide, 4-bromotetrafluoropyridine was obtained in 61% yield. Dilution of a solution of the diazonium salt with water immediately produced a tarry material rather than 4-hydroxytetrafluoropyridine and this decomposition probably involves nucleophilic displacement of fluoride ion from the diazonium salt. The reaction of the diazonium salt with *NN*-dimethylaniline gave the expected azo-dye, which was isolated by column chromatography, but other unidentified highly coloured materials were also produced in the reaction.

Ullmann coupling of 4-bromotetrafluoropyridine to 4,4′-octafluorobipyridyl was achieved using copper powder either in a sealed tube at 230° or in *NN*-dimethylformamide at reflux temperature. This bipyridyl was also obtained by a Grignard reaction; 4-bromotetrafluoropyridine formed a Grignard reagent with magnesium in tetrahydrofuran, at low temperature to avoid polymerisation,[8] and this reacted with pentafluoropyridine to give 4,4′-octafluorobipyridyl. Pentafluorophenylmagnesium bromide also reacted with pentafluoropyridine to give 4-(pentafluorophenyl)tetrafluoropyridine whereas the former reagent will not react with hexafluorobenzene under the same conditions, and these present observations are consistent with our earlier observations on the increased susceptibility of pentafluoropyridine over hexafluorobenzene to nucleophilic attack. Reactions of other polyfluoropyridylmagnesium halides with polyfluoropyridines obviously provide a route to a number of polyfluorobipyridyls. Tetrafluoro-4-pyridylmagnesium bromide was carbonated, giving, in good yield, the isonicotinic acid (the ionisation constant of which is recorded and discussed elsewhere [9]), and reacted normally with ethyl methyl ketone to give the corresponding alcohol.

Nucleophilic reagents, *i.e.*, aqueous ammonia, potassium hydroxide, and sodium methoxide, all reacted with 4-bromotetrafluoropyridine with the exclusive replacement of fluorine, rather than bromine, giving 4-bromo-2-amino-, -2-hydroxy-, and -2-methoxy-trifluoropyridines. The reaction with sodium methoxide also gave some 4-bromo-2,6-dimethoxydifluoropyridine, and the monomethyl ether from the same reaction was demethylated using hydriodic acid to give the -2-hydroxy-compound.

These results are consistent with other work on nucleophilic aromatic substitution,[10]

[4] R. D. Chambers, J. Hutchinson, and W. K. R. Musgrave, unpublished results.
[5] H. H. Hodgson and J. Nixon, *J.*, 1931, 2272.
[6] E. J. Forbes, R. D. Richardson, and J. C. Tatlow, *Chem. and Ind.*, 1958, 630.
[7] G. M. Brooke and W. K. R. Musgrave, *J.*, 1965, 1864.
[8] R. D. Chambers, F. G. Drakesmith, and W. K. R. Musgrave, forthcoming publication.
[9] Part V, following Paper.
[10] G. G. Yakobson, T. D. Rubina, and N. N. Vorozhtsov, *Doklady Akad. Nauk S.S.S.R.*, 1961, **141**, 1395 (*Chem. Abs.*, 1962, **56**, 12,782); L. A. Wall, W. J. Pummer, J. E. Fearn, and J. M. Antonucci, *J. Res. Nat. Bur. Stand.*, 1963, **67A**, 481.

where preferential replacement of fluorine occurs. Thus we have observed, in each case, substitution in the 2-position in 4-bromotetrafluoropyridine and this is significant because, so far, very few polyfluoropyridine derivatives have been obtained with functional groups in the 2-position. 4-Bromo-2,3,5-trifluoromethoxy- and 4-bromo-3,5-difluorodimethoxy-pyridine both formed Grignard reagents and these were hydrolysed to give 2,3,5-trifluoro-6-methoxy- and 3,5-difluoro-2,6-dimethoxy-pyridine, respectively. Coupling did not occur when 2-amino-4-bromotrifluoropyridine was refluxed with copper powder in *NN*-dimethylformamide but instead, the bromine was replaced by hydrogen to give 2-amino-3,5,6-trifluoropyridine, which was also produced in the reaction between 2,3,5,6-tetrafluoropyridine and ammonia.

Experimental

Oxidation of 4-Aminotetrafluoropyridine.—A mixture of methylene dichloride (10 ml.), trifluoroacetic anhydride (2·5 ml.), and *ca.* 90% hydrogen peroxide (1 ml.) was stirred and heated under reflux for 15 min.[11] A solution of 4-aminotetrafluoropyridine (0·94 g., 5·7 mmoles) in methylene dichloride (5 ml.) was then added to the refluxing solution and the mixture immediately became yellow and changed to bright green after 10 min. Hydrogen peroxide (0·5 ml.) was added after a further 20 min., and then again after 3 hr., together with trifluoroacetic anhydride (0·5 ml.). After 7—8 hr. the solution had become yellow. When the solution had been heated for a total of 22 hr., water was added, the methylene dichloride layer was separated, washed three times with water, dried ($MgSO_4$), and the solvent was distilled off through a short Vigreux column. Distillation of the residual liquid (from P_2O_5) afforded the pale yellow *tetrafluoro-4-nitropyridine* (0·7 g., 56%) (Found: C, 31·0; F, 38·9. $C_5F_4N_2O_2$ requires C, 30·6; F, 38·8%), b. p. 152—154°, n_D^{20} 1·4459.

Preparation of 4-Bromotetrafluoropyridine from 4-Aminotetrafluoropyridine.—To a stirred solution of the amine (12 g., 72·0 mmoles) in aqueous hydrofluoric acid (80 ml., 80% w/w) was added sodium nitrite (12 g.) at −20° over 30 min.[7] A solution of cuprous bromide in hydrobromic acid (made by dissolving the cuprous bromide produced from hydrated cupric sulphate (60 g.), potassium bromide (40 g.), and hydrated sodium sulphite (20 g.) in hydrobromic acid (60 ml., 48% w/w) was added dropwise over 30 min. to the diazotised amine, the temperature being maintained at −25° to −20°. After a further 30 min., during which time the temperature rose to that of the room, the mixture was diluted with water and extracted with ether. The extracts were dried and the solvent was removed by distillation. Distillation of the residual liquid (from P_2O_5) gave *4-bromotetrafluoropyridine* (11·0 g., 61%) (Found: C, 26·4; Br, 35·3; F, 33·1. C_5BrF_4N requires C, 26·1; Br, 34·8; F, 33·0%), b. p. 134—135°; n_D^{20} 1·4579.

Preparation of 2,3,5,6-Tetrafluoropyridinediazonium Fluoride and Reaction with NN-Dimethylaniline.—To a stirred solution of the amine (1·0 g., 6 mmoles) in hydrofluoric acid (12 ml., 80% w/w) was added sodium nitrite (0·6 g.) at −20° over 15 min. The solution was cooled to −50° to −45° and *NN*-dimethylaniline (0·8 g., 6·6 mmoles) was added dropwise. After the mixture had been stirred at this temperature for 30 min., water (50 ml.) was added which precipitated a dark red solid. The precipitate (0·78 g.) was filtered from the solution, dried, dissolved in benzene, and chromatographed on an alumina column. Two main red bands were obtained from the column (leaving several other yellow bands) and the second of these (0·175 g.) was isolated, washed with cold light petroleum, and recrystallised from light petroleum–benzene to give a 4-(NN-*dimethylphenylazo*)*tetrafluoropyridine* (Found: C, 51·8; F, 25·8. $C_{13}H_{10}F_4N_4$ requires C, 52·3; F, 25·5%), m. p. 209—210°.

Reaction between 4-Bromotetrafluoropyridine and Copper.—(*a*) 4-Bromotetrafluoropyridine (4·0 g., 1·7 mmoles) was sealed under vacuum in a Carius tube with copper powder (3 g.) and heated to 230° for 48 hr. The tube was cooled, opened, and the contents were transferred to a sublimation apparatus. Sublimation under reduced pressure and recrystallisation from light petroleum (40—60°)–benzene afforded *octafluoro-4,4′-bipyridyl* (Found: C, 39·6; F, 50·9. $C_{10}F_8N_2$ requires C, 40·0; F, 50·7%), m. p. 81—82°, crude yield 50%.

(*b*) 4-Bromotetrafluoropyridine (1·6 g., 7·0 mmoles), *NN*-dimethylformamide (6 ml.) and copper powder (2 g.) were stirred and heated under reflux for 5 hr. After this time the reaction

[11] G. M. Brooke, J. Burdon, and J. C. Tatlow, *J.*, 1961, 802.

mixture was poured into water, and extracted with methylene dichloride. The extracts were washed with water and dried, and the solvent was removed by distillation. The residue was sublimed under reduced pressure and the sublimate identified by its infrared spectrum as octafluoro-4,4′-bipyridyl (0·45 g., 40%).

Preparation and Reactions of 2,3,5,6-*Tetrafluoropyridylmagnesium Bromide.*—A three-necked flask fitted with stirrer, dropping funnel, and condenser, and containing magnesium (0·4 g.) and dry tetrahydrofuran (9 ml.), was purged with dry nitrogen and cooled to −20°. A solution of 4-bromotetrafluoropyridine (2·0 g., 8·7 mmoles) in dry tetrahydrofuran (1 ml.) was added and after a few minutes the reaction commenced. The mixture was allowed to warm to −10° to 0° and maintained at this temperature for 1 hr. before further reactants were added.

(*a*) *Carbonation.* The Grignard reagent was formed as above and dry carbon dioxide was bubbled through the solution for 2 hr. at −10°. Dilute sulphuric acid was added and the mixture was extracted with ether. The extracts were dried, the solvent was removed by distillation, and from the residue a white crystalline solid (1·0 g., 59%) was sublimed under reduced pressure. Recrystallisation from hexane afforded tetrafluoroisonicotinic acid (Found: C, 36·7; F, 39·2%; Equiv., 192. Calc. for $C_6HF_4NO_2$: C, 36·9; F, 39·0%; Equiv., 195), m. p. 104—105° (lit.,[3] 98—100°).

(*b*) *Reaction with ethyl methyl ketone.* To the Grignard reagent from 4-bromotetrafluoropyridine (1·45 g., 6·3 mmoles) was added ethyl methyl ketone (0·6 g., 8·3 mmoles) at −10°. The mixture was stirred at this temperature for 30 min. then at room temperature for 1½ hr. before being hydrolysed with dilute sulphuric acid and then extracted with ether. Solvent was distilled from the dried extracts, and the use of preparative-scale gas–liquid chromatography (g.l.c.) afforded a pure sample of 2-*hydroxy*-2-(2,3,5,6-*tetrafluoropyridyl*)*butane* (Found: C, 48·4; H, 4·0; F, 34·1. $C_9H_9F_4NO$ requires C, 48·5; H, 4·1; F, 33·8%), n_D^{20} 1·4524. This compound distilled under reduced pressure (12—13 mm.) with a bath temperature of 80—82°.

(*c*) *Reaction with pentafluoropyridine.* To the Grignard reagent from 4-bromotetrafluoropyridine (1·0 g., 4·7 mmoles) was added pentafluoropyridine (0·75 g., 4·5 mmoles) at −35° to −40°. After a few minutes the solution became dark blue-green and remained this colour while the mixture was stirred for 1 hr. at −35° to −40°. The mixture was then hydrolysed with dilute sulphuric acid and extracted with ether, and solvent was distilled from the dried extracts to leave a brown crystalline material. Sublimation under reduced pressure afforded octafluoro-4,4′-bipyridyl (0·91 g., 68%) identified by its infrared spectrum.

Reactions between 4-*Bromotetrafluoropyridine and Nucleophilic Reagents.*—(*a*) *Aqueous ammonia.* A Carius tube containing 4-bromotetrafluoropyridine (2·0 g., 8·7 mmoles) and aqueous ammonia (4 ml., *d* 0·88) was heated to 85° for 2 hr. and then on cooling the tube to room temperature the organic layer became solid. Water was added to the mixture which was extracted with ether; distillation of the dried ether solution afforded an orange crystalline material (1·7 g., 86%) which was sublimed under reduced pressure and recrystallised from light petroleum(40—60°)–benzene to give 2-*amino*-4-*bromotrifluoropyridine* (Found: C, 26·5; Br, 35·4. $C_5H_2BrF_3N_2$ requires C, 26·4; Br, 35·3%), m. p. 116—117°. The fluorine-19 n.m.r. spectrum consisted of three chemically shifted peaks of equal intensity at 152·4 (5-F), 137·8 (3-F), and 92·2 (6-F) p.p.m. from CCl_3F. These values are consistent with those expected for 2-amino-4-bromotrifluoropyridine.[1,2]

(*b*) *Potassium hydroxide in t-butanol.* A mixture of 4-bromotetrafluoropyridine (1·0 g., 4·3 mmoles), potassium hydroxide (0·6 g.), and t-butyl alcohol (10 ml.) was stirred and heated under reflux for 2 hr. after which time water was added and the alcohol was distilled off. The aqueous solution was acidified and extracted with methylene dichloride. Removal of solvent from the dried extracts afforded a pale yellow solid which was sublimed under reduced pressure to give a white solid (0·93 g.) which on recrystallisation from light petroleum–benzene afforded pure 4-*bromo*-2,3,5-*trifluorohydroxypyridine* (Found: C, 26·3; Br, 35·1; F, 25·0. C_5HBrF_3NO requires C, 26·0; Br, 35·4; F, 25·4%), m. p. 130—131°. The fluorine-19 n.m.r. spectrum consisted of three chemically shifted peaks of equal intensity at 146·3 (3-F), 135·7 (5-F), and 92·2 (2-F) p.p.m. from CCl_3F. These values are consistent with those expected for 4-bromo-2,3,5-trifluorohydroxypyridine.[1,2]

(*c*) *Sodium methoxide.* (i) To a stirred solution of 4-bromotetrafluoropyridine (1·0 g., 4·3 mmoles) in dry methanol (10 ml.) was slowly added, at 0°, a solution made from sodium (0·1 g., 4·3 mg.-atoms) and dry methanol (3 ml.). The reaction mixture was allowed to warm to room temperature and so maintained for 30 min. before water was added. Oily

droplets were precipitated which were extracted into methylene dichloride. Removal of the solvent from the dried extracts afforded a pale yellow liquid (0·95 g.) which was shown by analytical g.l.c. to contain traces of solvent and starting material and also a single product peak. The product, obtained pure by preparative g.l.c., was 4-*bromo*-2,3,5-*trifluoromethoxypyridine* (Found: C, 29·8; Br, 33·0; F, 23·5. $C_6H_3BrF_3NO$ requires C, 29·7; Br, 32·7; F, 23·4%), b. p. 193—194°, n_D^{20} 1·4886. The fluorine-19 n.m.r. spectrum consisted of three chemically shifted peaks of equal intensity at 145·1 (3-F), 135·2 (5-F), and 92·2 (2-F) p.p.m. from CCl_3F. These values are consistent with those expected for 4-bromo-2,3,5-trifluoromethoxypyridine.[1,2]

(ii) To a stirred solution of 4-bromotetrafluoropyridine (1·0 g., 4·3 mmoles) in dry methanol (8 ml.) was added a solution made from sodium (0·3 g., 13·0 mg.-atoms) in dry methanol (4 ml.). The reaction mixture was heated under gentle reflux for 30 min., and then treated as above. Analytical g.l.c. showed the solid product (0·95 g.) to contain a trace of 4-bromo-2,3,5-trifluoromethoxypyridine and another compound with longer retention time. Reduced-pressure sublimation and recrystallisation from light petroleum afforded 4-*bromo*-3,5-*difluorodimethoxypyridine* (Found: C, 32·9; Br, 31·2; F, 14·8. $C_7H_6BrF_2NO_2$ requires C, 33·1; Br, 31·5; F, 15·0%), m. p. 120·5—121·5°. The fluorine-19 n.m.r. spectrum consisted of a single peak at 144·2 p.p.m. from CCl_3F which is consistent with that expected for 4-bromo-3,5-difluorodimethoxypyridine.[1,2]

Demethylation of 4-*Bromo*-2,3,5-*trifluoromethoxypyridine using Hydriodic Acid.*—A mixture of 4-bromo-2,3,5-trifluoromethoxypyridine (0·3 g., 1·4 mmoles) and hydriodic acid (3 ml., 54—56% w/w) was maintained at 120° for 4 hr. The reaction mixture was then cooled, made alkaline, and extracted with methylene dichloride. Solvent was distilled from this extract and analytical-scale g.l.c. showed the residue (0·2 g.) to consist of a trace of solvent and starting material. The aqueous layer was acidified and extracted with methylene dichloride. Distillation of solvent from this extract gave 4-bromo-2,3,5-trifluorohydroxypyridine (0·05 g.), identified by its infrared spectrum.

Preparation and Hydrolysis of 2,3,5-*Trifluoro*-6-*methoxypyridylmagnesium Bromide.*—A three-necked flask fitted with stirrer, dropping funnel, and condenser, and containing magnesium (0·3 g.) and dry tetrahydrofuran (6 ml.), was purged with dry nitrogen and cooled to 0°. A solution of 4-bromo-2,3,5-trifluoromethoxypyridine (0·9 g., 3·72 mmoles) in dry tetrahydrofuran (4 ml.) was added and the mixture was allowed to warm to room temperature. An exothermic reaction commenced but the reaction vessel was quickly cooled and the reaction mixture was not allowed to rise above room temperature before 1½ hr. Dilute sulphuric acid was added after this time and the mixture was extracted with ether. Distillation of most of the solvent from the dried extracts gave a small amount of liquid which was shown by analytical-scale g.l.c. to contain a single compound, which was not starting material, together with traces of solvents. A pure sample of the product was obtained by preparative-scale g.l.c. and found to be 2,3,5-*trifluoro*-6-*methoxypyridine* (Found: C, 44·0; H, 2·2. $C_6H_4F_3NO$ requires C, 44·2; H, 2·4%), b. p. 146°, n_D^{20}, 1·4513.

Preparation and Hydrolysis of 3,5-*Difluoro*-2,6-*dimethoxypyridylmagnesium Bromide.*—The reaction was carried out as above but using 4-bromo-3,5-difluorodimethoxypyridine (0·9 g., 3·5 mmoles). The product (0·50 g., 80%) was 3,5-*difluoro*-2,6-*dimethoxypyridine* (Found: C, 48·0; H, 4·0. $C_7H_7F_2NO_2$ requires C, 47·8; H, 3·8%), m. p. 87°.

2-*Amino*-4-*bromotrifluoropyridine and Copper in* NN-*Dimethylformamide.*—A mixture of 2-amino-4-bromotrifluoropyridine (0·40 g., 1·76 mmoles), copper powder (0·6 g.), and *NN*-dimethylformamide (10 ml.) was stirred and heated under gentle reflux for 2 hr. After this time the product was cooled and poured into water and then the mixture was extracted with ether and solvent was distilled from the dried extract to give a pale brown solid (0·12 g., 46%). Sublimation under reduced pressure and recrystallisation (light petroleum–benzene) afforded 2-*amino*-3,5,6-*trifluoropyridine* (Found: C, 40·3; H, 2·0. $C_5H_3F_3N_2$ requires C, 40·4; H, 2·0%), m. p. 94·5—95·5°. The fluorine-19 n.m.r. spectrum consisted of three chemically shifted peaks of equal intensity at 155·6 (5-F), 142·1 (3-F), and 94·4 (6-F) p.p.m. from CCl_3F. The peak at 94·4 p.p.m. was broad but those at 155·6 and 142·1 p.p.m. were octets, showing that each of the fluorine atoms in these positions couples with three other nuclei.

2,3,5,6-*Tetrafluoropyridine and Aqueous Ammonia.*—Aqueous ammonia (1 ml.; *d* 0·88) and 2,3,5,6-tetrafluoropyridine (0·35 g., 2·3 mmoles) were sealed in a Carius tube and heated to 100° for 1 hr. When the tube was cooled the organic layer became solid and water was added to the mixture which was then extracted with methylene dichloride. Distillation of the dried

solution afforded a white solid (0·25 g., 72%) which was sublimed under reduced pressure and identified by its infrared spectrum as 2-amino-3,5,6-trifluoropyridine.

Pentafluorophenylmagnesium Bromide and Pentafluoropyridine.—Pentafluorophenylmagnesium bromide was made in dry tetrahydrofuran (12 ml.) from bromopentafluorobenzene (2·0 g., 8·1 mmoles) and magnesium (0·6 g.). The solution was cooled to −10° and pentafluoropyridine (1·4 g., 8·3 mmoles) was added. The temperature was allowed to rise to 0° and this was maintained for 3 hr. before dilute sulphuric acid was added and the mixture extracted with ether. Solvent was distilled from the dried extracts leaving a dark brown tacky solid from which a white solid (1·2 g.) was sublimed under reduced pressure. Further sublimation and then recrystallisation from light petroleum–benzene afforded 4-(*pentafluorophenyl*)-*tetrafluoropyridine* (Found: C, 41·5; F, 54·3. $C_{11}F_9N$ requires C, 41·6; F, 53·9%), m. p. 98·5—99·5°. The fluorine-19 n.m.r. spectrum showed five chemically shifted peaks in the ratio 2 : 2 : 2 : 1 : 2 at 140·8, 149·0, 138·7, 137·0, and 89·8 p.p.m. from CCl_3F. These values are consistent with those expected for this compound.[1,2]

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