926. *Polyfluoroheterocyclic Compounds. Part V.*[1] *Catalytic Reduction of Perfluoro- and Chlorofluoro-pyridines and the Preparation of Polyfluoropyridinecarboxylic Acids*

By R. D. CHAMBERS, F. G. DRAKESMITH, and W. K. R. MUSGRAVE

Chlorine in 3-chlorotetrafluoro- and 3,5-dichlorotrifluoro-pyridines is replaced by hydrogen, using hydrogen and a palladium catalyst. Similarly, reduction of pentafluoropyridine gives 2,3,5,6-tetrafluoropyridine, by replacement of fluorine. The hydro-compounds react readily with butyl-lithium in hexane and carbonation of the resultant lithio-derivatives yields perfluoronicotinic or -isonicotinic acids and, using hexane–tetrahydrofuran, trifluoropyridine-3,5-dicarboxylic acid. pK_a values for the acids have been determined and are compared with the values for other acids.

IN previous Papers in this Series we have described a useful route to pentafluoropyridine and chlorofluoropyridines[2] and some nucleophilic substitution reactions of these compounds.[3] We describe here their catalytic reduction to produce hydrofluoropyridines, their subsequent metallation with alkyl-lithiums, and carbonation of the lithio-derivatives to give polyfluoronicotinic acids.

The reductions were carried out by passing the fluoropyridines in a stream of hydrogen over a heated catalyst consisting of palladium on activated charcoal, a system which has been used previously for the replacement of aromatic chlorine by hydrogen.[4] Chlorine in 3-chlorotetrafluoropyridine and in 3,5-dichlorotrifluoropyridine was replaced by hydrogen in preference to fluorine, at 250 and 280°, respectively, and the corresponding hydro-compounds were obtained in ~75% yield, the temperatures quoted being the optimum conditions found for these compounds. However, the 2,4,5,6-tetrafluoropyridine was accompanied by a small amount (~5%) of 2,5,6-trifluoropyridine resulting from replacement of the 4-fluorine in the starting material. Following from this observation, the replacement of the 4-fluorine in pentafluoropyridine by hydrogen was achieved at 300° in ~30% yield and the product also contained ~5% of 3,4,5,6-tetrafluoropyridine. Using higher catalyst temperatures resulted in increased decomposition. The preferential

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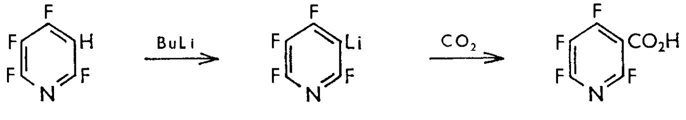
[1] Part IV, preceding Paper.
[2] R. D. Chambers, J. Hutchinson, and W. K. R. Musgrave, *J.*, 1964, 3573.
[3] R. D. Chambers, J. Hutchinson, and W. K. R. Musgrave, *J.*, 1964, 3736.
[4] R. E. Florin, W. J. Pummer, and L. A. Wall, *J. Res. Nat. Bur. Stand.*, 1959, **62**, 119.

replacement of the 4-fluorine in pentafluoropyridine in this reaction is interesting because it has already been shown that 4-fluorine is the most susceptible to nucleophilic displacement[3] and the present result suggests that this preference also applies to free-radical displacements.

Recently, Tamborski and his co-workers[5] have shown that hydrogen in polyfluorobenzenes is sufficiently acidic to react with alkyl-lithiums, leading to metallation. We have found that hydrogen in polyfluoropyridines is also acidic in this context and the lithio-derivatives may be obtained in a similar way. Therefore, the hydro-compounds are valuable synthetic intermediates. Thus, butyl-lithium reacted with 2,3,4,6-tetrafluoropyridine in n-hexane at −60°; a dense white precipitate was formed, presumably the lithio-derivative, and when carbon dioxide was passed through the mixture and then the mixture acidified, tetrafluoronicotinic acid was obtained in 62% yield. Similarly, tetrafluoroisonicotinic acid and 2,4,6-trifluoronicotinic acid were obtained from 2,3,5,6-tetrafluoropyridine and 2,4,6-trifluoropyridine, respectively. Attempts to form a dilithio-compound from 2,4,6-trifluoropyridine, using n-hexane as solvent, were unsuccessful because the monolithio-derivative was precipitated before further reaction with butyl-lithium could occur. However, the use of tetrahydrofuran as solvent increased the solubility of the intermediates and, on carbonation, a mixture of mono- and di-carboxylic acids was obtained.



Strengths of polyfluoropyridinecarboxylic acids

Acid	pK_a	Equiv. wts. Found	Equiv. wts. Calc.
Benzoic	4·21[6]		
Pentafluorobenzoic	3·38 *	208	212
Pyridine-3-carboxylic	4·824[6]		
Tetrafluoropyridine-3-carboxylic	3·45	191	195
2,4,6-Trifluoropyridine-3-carboxylic	3·55	175	177
Trifluoropyridine-3,5-dicarboxylic	3·33	223·6	221
Pyridine-4-carboxylic	4·835[6]		
Tetrafluoropyridine-4-carboxylic	3·21	192	195

* This disagrees with the value of 0·8 given by Tatlow and his co-workers[7] but Professor Tatlow has informed us that the published value is incorrect.

Values of pK_a for the acids which have been prepared are recorded in the Table, together with the values for benzoic, pentafluorobenzoic, and pyridinecarboxylic acids. The most significant feature of these results is that, whereas nicotinic and isonicotinic acids are significantly weaker than benzoic acid, the corresponding tetrafluoro-nicotinic and -isonicotinic acids are of similar strength to that of pentafluorobenzoic acid and this difference between the two series must be due to the considerably reduced basic character of the nitrogen atom in polyfluoropyridine systems. It can be seen that the presence of several fluorine atoms is the most important feature affecting the strength of the polyfluoropyridinecarboxylic acids since the differences in strength between the various acids are quite small. However, the position of the carboxyl groups relative to fluorine is obviously important because tetrafluoropyridine-4-carboxylic acid is a stronger acid than the corresponding 3-carboxylic acid and is also stronger than trifluoropyridine-3,5-dicarboxylic acid. This suggests that fluorine *para* to carboxyl has an acid-weakening effect in these

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[5] R. J. Harper, E. J. Soloski, and C. Tamborski, *J. Org. Chem.*, 1964, **29**, 2385.

[6] G. Kortüm, W. Vogel, and K. Andrussow, "Dissociation Constants of Organic Acids in Aqueous Solution," Butterworths, London, 1961.

[7] B. Gething, C. R. Patrick, and J. C. Tatlow, *J.*, 1961, 1574.

systems, although the basic character of nitrogen will also be influenced by the group in the 4-position and this will also affect the strength of the acid, but the importance of the latter effect cannot yet be estimated.

EXPERIMENTAL

^{19}F and ^{1}H Chemical shifts are recorded with reference to $CFCl_3$ and Me_4Si, respectively, as internal standards.

Reduction.—(*a*) 3-*Chlorotetrafluoropyridine.* 3-Chlorotetrafluoropyridine (4 g., 21·6 mmoles) was dropped at a rate of 0·1 g./min. into a flask heated to 200° and through which a stream of hydrogen (50 ml./min.) was passing. The chlorotetrafluoropyridine vaporised immediately and was carried in the gas stream through a silica tube (1 in. diam. × 12 in.); the central 6 in. of this tube was heated by an electric furnace and was packed with palladised charcoal (10% Pd, 90% C) which was held in position by glass-wool plugs and heated to 250°. Product emerging from the catalyst was condensed in a trap cooled by liquid air and then dried by distillation under vacuum from P_2O_5. This material (2·5 g.) was then separated by gas–liquid chromatography (g.l.c.), using tritolyl phosphate as stationary phase, and shown to contain approximately 80% of 2,4,5,6-*tetrafluoropyridine*, b. p. 89—90° (Found: C, 40·1; F, 49·9. C_5HF_4N requires C, 39·7; F, 50·3%). The fluorine-19 n.m.r. spectrum confirmed that migration of fluorine to the 3-position had not occurred during the process. The spectrum showed four chemically shifted groups of peaks, of equal intensity, two of which are broad and at low field (indicating the proximity to the ^{14}N nucleus); $\delta = 67{\cdot}6$ (2-F, shifted to lower field due to adjacent hydrogen); 83·3 (6-F); 113·1 (5-F); 99·2 p.p.m (4-F). Also present in the product (~5%) was 2,5,6-*trifluoropyridine*, b. p. 115—116° (Found: C, 45·2; F, 42·6. $C_5H_2F_3N$ requires C, 45·1; F, 42·9%). The fluorine-19 n.m.r. spectrum showed three chemically shifted peaks of equal intensity, two of which were broad and to low field, indicating the proximity to the ^{14}N nucleus; $\delta = 74{\cdot}40$ (2-F), 88·69 (6-F), and 147·4 (5-F).

(*b*) 3,5-*Dichlorotrifluoropyridine.* Using the same technique as that employed in the previous experiment, 3,5-dichlorotrifluoropyridine (5 g., 25 mmoles) was flash-distilled at 240° and passed in a stream of hydrogen (80 ml./min.) over the catalyst at 280°. The product (2·5 g., 75%), b. p. 94—95°, was 2,4,6-*trifluoropyridine* (Found: C, 44·7; F, 43·3. $C_5H_2F_3N$ requires C, 45·1; F, 42·9%). The fluorine-19 n.m.r. spectrum confirmed that no migration of fluorine had taken place. The spectrum was approximately the AXX′ part of an APP′XX′ system and contained two chemically shifted groups of peaks of intensity 2 : 1 and the peak due to the 2- and 6-fluorine atoms was broadened owing to the ^{14}N nucleus. The peak due to the 4-fluorine was a triplet of triplets, showing the coupling that would be expected from an *ortho*-proton and a *meta*-fluorine atom; $\delta = 65{\cdot}05$ (2- and 6-F), 93·15 (4-F), $J = 19{\cdot}7 \pm 0{\cdot}2$ c./sec. $= J_{FF}$ *meta*; $J = 7{\cdot}6 \pm 0{\cdot}2$ c./sec. $= J_{FH}$ *ortho*. Also, the proton spectrum showed a pair of triplets, demonstrating the same *ortho* H–F coupling constant as indicated above; $\delta = 6{\cdot}61$ p.p.m., $J = 1{\cdot}2 \pm 0{\cdot}1$ c./sec. $= J_{HF}$ *para* $= J_{HH}$ *meta*; $J = 7{\cdot}5 \pm 0{\cdot}1$ c./sec. $= J_{HF}$ *ortho*.

(*c*) *Pentafluoropyridine.* Pentafluoropyridine (5 g.) was flash-distilled at 180° during 2 hr. in a stream of hydrogen (60 ml./min.) over the catalyst at 320°. The product (2·6 g.), condensed out, dried as described above, and then separated by g.l.c., contained 2,3,5,6-*tetrafluoropyridine* (30% yield), b. p. 98—99° (Found: C, 39·9%; *M*, 152. C_5HF_4N requires C, 39·7; *M*, 151), 3,4,5,6-tetrafluoropyridine (~5% yield), b. p. 87—88° (Found: C, 39·5; F, 50·2. C_5HF_4N requires C, 39·7; F, 50·3%), and another minor component which was probably 2,4,5,6-tetrafluoropyridine. The 2,3,5,6-tetrafluoropyridine gave an infrared spectrum which was identical with the spectrum of a sample obtained by the reaction of $LiAlH_4$ on pentafluoropyridine;[8] and the fluorine-19 n.m.r. spectrum was typical of that of the PP′XX′ part of an APP′XX′ system. This can only occur if the system has a two-fold axis of symmetry, *i.e.*, the substituent is in the 4-position. Two chemically shifted groups of peaks of equal intensity were obtained $\delta = 92{\cdot}28$ (2-, 6-F) broad and 140·97 p.p.m. (3-, 5-F). The fluorine-19 n.m.r. spectrum of 3,4,5,6-trifluoropyridine showed four chemically shifted groups of peaks of equal intensity only one of which was broad and at low field $\delta = 83{\cdot}9$ (6-F, broad), 140·5 (4-F), 157·9 (5-F), and 148·8 p.p.m. (3-F, shifted to lower field owing to adjacent hydrogen). The proton spectrum showed only one complex chemically shifted group of peaks.

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[8] J. Hutchinson, unpublished result.

Metallation and Carbonation.—(*a*) *Preparation of* 2,4,5,6-*tetrafluoronicotinic acid*. Butyl-lithium (3·3 mmoles) in hexane (1 ml.) was added to a stirred solution of 2,4,5,6-tetrafluoropyridine (0·5 g., 3·3 mmoles) in hexane (5 ml.) at −60° and under an atmosphere of dry nitrogen. After 15 min. a dense white precipitate had formed and while the temperature was maintained at −60°, dry carbon dioxide was passed into the reaction mixture for 30 min. Then the mixture was allowed to warm up to room temperature while the introduction of CO_2 continued. Water (5 ml.) was added and the mixture stirred; the white precipitate dissolved, then on the addition of dilute hydrochloric acid (5 ml.), a further white precipitate was formed which quickly redissolved. The mixture was extracted with ether, the organic ethereal layer separated and dried ($MgSO_4$), and then solvent removed by distillation leaving 2,4,5,6-*tetrafluoronicotinic acid* (0·4 g., 62%) which, after vacuum sublimation and recrystallisation (hexane) had m. p. 121—122° (Found: C, 37·1; F, 38·6%; Equiv., 191. $C_6HF_4NO_2$ requires C, 36·9; F, 38·98%; Equiv., 195).

(*b*) *Preparation of* 2,3,5,6-*tetrafluoroisonicotinic acid*. Butyl-lithium (3·3 mmoles) in hexane (1 ml.) was added to 2,3,5,6-tetrafluoropyridine (0·5 g., 3·3 mmoles) in hexane (18 ml.) at −55°, as described above. After 20 min. a precipitate had formed and then the temperature was lowered to −60° before carbonation as above. After the mixture had reached room temperature, water (5 ml.) was added, followed by dilute hydrochloric acid (5 ml.). Then the mixture was extracted with ether, the ethereal solution dried ($MgSO_4$), and when solvent was removed by distillation, 2,3,5,6-tetrafluoroisonicotinic acid (0·32 g., 50%) was obtained which, after vacuum sublimation and recrystallisation (hexane), had m. p. 102—103° (Found: Equiv., 192); the infrared spectrum and m. p. were identical with those of an authentic specimen of the acid.[1]

(*c*) *Preparation of* 2,4,6-*trifluoronicotinic acid*. 2,4,6-Trifluoropyridine (0·425 g., 3·2 mmoles) was dissolved in dry hexane (6 ml.), cooled to −60°, and butyl-lithium (6·4 mmoles) in hexane (2 ml.) was added. The reaction mixture was maintained at −60° and carbonated as described in (*a*). Water (5 ml.) followed by dilute hydrochloric acid (20 ml.) was added and then the organic layer was separated. The aqueous layer was further extracted with ether, the organic layers combined and dried ($MgSO_4$), and the solvent distilled leaving a crystalline residue of 2,4,6-*trifluoronicotinic acid* (0·4 g., 65%) which, after sublimation under vacuum and recrystallisation (hexane), had m. p. 125—126° (Found: C, 40·3; F, 32·2%; Equiv., 175. $C_6HF_3NO_2$ requires C, 40·6; F, 32·3%; Equiv., 177).

(*d*) *Preparation of* 2,4,6-*trifluoropyridine*-3,5-*dicarboxylic acid*. 2,4,6-Trifluoropyridine (0·85 g., 6·4 mmoles) in dry tetrahydrofuran (3 ml.) was added slowly to a stirred solution of butyl-lithium (19·2 mmoles) in hexane (6 ml.) and tetrahydrofuran (10 ml.) at −75°. After 5 min. a dense pale orange precipitate formed and the temperature was maintained at −75° for a further 15 min. and then dry carbon dioxide, diluted with an equal volume of nitrogen, was passed into the mixture. Initially a dark crimson colour was formed which became dark brown and the reaction mixture solidified to a stiff paste. Continued passage of carbon dioxide caused the dark coloration to disappear and as the temperature was allowed to rise to that of the room, the reaction mixture became fluid. Water (5 ml.) was added, followed by dilute hydrochloric acid (50 ml.), and the organic layer was removed. The aqueous layer was extracted with ether (2 × 25 ml.), the organic layer dried ($MgSO_4$), and the solvent removed by distillation leaving a solid (0·6 g.). When this solid was heated to 50° under high vacuum a white solid sublimed (~0·25 g.), and both the m. p. and infrared spectrum of this compound were identical with those of an authentic specimen of 2,4,6-trifluoronicotinic acid. The remaining solid was heated to 140° also under high vacuum when it was observed to sublime slowly, and gave 2,4,6-*trifluoropyridine*-3,5-*dicarboxylic acid*, m. p. 218° (decomp.) (Found: C, 38·2; F, 25·5%; Equiv., 111·8. $C_7H_2F_3NO_4$ requires C, 38·1; F, 25·7%; Equiv., 110·5).

pk_a *Values*.—Equivalent weights and pK_a values of the carboxylic acids in aqueous solution were determined by potentiometric titration against standard sodium hydroxide solution, using an E.I.L. pH meter and calomel and glass electrodes. pK_a was given by the pH value at half-equivalence point according to the Henderson equation.

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University Science Laboratories, South Road, Durham. [*Received, March 24th,* 1965.]