NN-Dimethyl-2-fluoro-2-phenylethylamine: Preparation and Solvolysis in Aqueous Acetone

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Anhydrous potassium fluoride and ethyl α-bromophenylacetate in *NN*-dimethylformamide at 145—150° gave the corresponding α-fluoro-ester (53%), which was converted by alkaline hydrolysis and acidification, followed by reaction with thionyl chloride, into α-fluorophenylacetyl chloride (not isolated) and thence into the corresponding amide or *NN*-dimethylamide by conventional reactions. Diborane reduced the *NN*-dimethylamide to *NN*-dimethyl-2-fluoro-2-phenylethylamine (53%), also obtained by the action of dimethylamine on 1-bromo-2-fluoro-2-phenylethane. Reduction of the *NN*-dimethylamide with lithium aluminium hydride in ether gave a mixture of products.

THE 2-halogenoalkylamines, of which the *NN*-dialkyl-2-halogeno-2-phenylethylamines (I; X = Cl, Br, or I; R = alkyl) are typical, have been extensively studied as potent antagonists of adrenaline and noradrenaline.[1]

There is now abundant evidence [1] that their pharmacological activity is due to the derived ethyleniminium ion (II; X = Cl, Br, or I; R = alkyl), which is readily produced under physiological conditions.

The relatively few 2-fluoroalkylamines which have been reported are mainly of the type $Ar{\cdot}CH_2{\cdot}NR{\cdot}CH_2{\cdot}CH_2F$ (Ar = 1- or 2-naphthyl, R = alkyl) [2] or $R{\cdot}NH{\cdot}CH_2{\cdot}CH_2F$ [R = H, or $CH_2{\cdot}CH_2X$ (X = Cl, Br, or F)],[3] in which the fluorine atom is attached to a primary carbon atom. The former compounds are inactive as antagonists of adrenaline and noradrenaline, probably owing to their observed inability to form ethyleniminium ions in aqueous acetone at ordinary temperatures.[2] The solvolysis in deuterium oxide of several of the second group of compounds has been shown [4,5] by nuclear magnetic resonance (n.m.r.) studies to proceed *via* the corresponding ethyleniminium ions, which, however, are produced much more slowly than from the corresponding chloro-compounds. We now describe the preparation and report briefly on the solvolysis of *NN*-dimethyl-2-fluoro-2-phenylethylamine, which we believe to be the first example of a fluorine-containing compound in which the fluorine atom is situated β- to a dialkylamino-group and α- to an aryl group.

Early attempts [6] to replace the bromine atom in *NN*-dimethyl-2-bromo-2-phenylethylamine by fluorine by using various metallic fluorides gave intractable mixtures of products. Moreover, the usual procedure of halogenating an amino-alcohol (I; X = OH, R = Me) was inapplicable owing to the difficulty of replacing the hydroxyl group by fluorine. It was desirable to use as a precursor a compound containing the fluorine atom in the correct environment, and another functional group from which the dimethylamino-group could be obtained. We chose ethyl α-fluorophenylacetate, which could be obtained in good yield from the corresponding bromo-ester by reaction with potassium fluoride in *NN*-dimethylformamide. Alkaline hydrolysis followed by acidification gave α-fluorophenylacetic acid, which Pattison and his co-workers [7] have since obtained by the decarboxylation of α-fluorophenylmalonic acid. Conversion into the acid chloride, followed by treatment with dimethylamine, gave *NN*-dimethyl-α-fluorophenylacetamide. We attempted selectively to reduce it to *NN*-dimethyl-2-fluoro-2-phenylethylamine (I; X = F, R = Me) with lithium aluminium hydride in refluxing ether (overnight), but extensive hydrogenolysis of the C–F bond occurred to give a high yield of *NN*-dimethyl-2-phenylethylamine (I; X = H, R = Me). Reduction for shorter periods gave a complex mixture of products, consisting mainly of starting material and the product of hydrogenolysis. Other workers [3b,c] have observed similar hydrogenolysis of C–F bonds by lithium aluminium hydride, but usually in the presence of aluminium chloride. Reduction with diborane,[8] however, pro-

[1a] J. D. P. Graham, in "Progress in Medicinal Chemistry," ed. G. P. Ellis and G. B. West, Butterworths, London, 1962, vol. II, ch. 4. [b] N. B. Chapman and J. D. P. Graham, "Drugs Affecting the Peripheral Nervous System," ed. Alfred Burger, Marcel Dekker, New York, 1967, vol. 1, ch. 9.

[2] N. B. Chapman and J. W. James, *J. Chem. Soc.*, 1954, 2103.

[3] See, *e.g.*, the following Papers, and the references cited therein: (*a*) A. P. Martinez, W. W. Lee, and L. Goodman, *Tetrahedron*, 1964, **20**, 2763; (*b*) G. R. Pettit and R. L. Smith, *Canad. J. Chem.*, 1964, **42**, 572; (*c*) Z. B. Papanastassiou and R. J. Bruni, *J. Org. Chem.*, 1964, **29**, 2870.

[4] K. P. L. Levins and Z. B. Papanastassiou, *J. Amer. Chem. Soc.*, 1965, **87**, 826.

[5] G. R. Pettit, J. A. Settepani, and R. A. Hill, *Canad. J. Chem.*, 1965, **43**, 1792.

[6] R. D. Strickland, Ph.D. Thesis, Hull, 1962.

[7] F. L. M. Pattison, R. L. Buchanan, and F. H. Dean, *Canad. J. Chem.*, 1965, **43**, 1700.

[8] H. C. Brown and P. Heim, *J. Amer. Chem. Soc.*, 1964, **86**, 3566.

ceeded smoothly and gave the required fluoroamine (I; X = F, R = Me) in good yield. It was isolated as the hydrochloride, since the free base proved somewhat unstable.

After the above preparative work had been completed, Pattison, Peters, and Dean [9] described the preparation of 1-bromo-2-fluoro-2-phenylethane (III) by reaction of styrene with *N*-bromoacetamide in liquid hydrogen fluoride. We have found that the bromine atom can be quantitatively replaced by treatment with dimethylamine to give the required fluoroamine (I; X = F, R = Me) directly. This observation also serves to confirm the structure assigned by the Canadian workers to compound (III), mainly by analogy with the direction of addition of iodine monochloride to styrene.

$Ph{\cdot}CHF{\cdot}CH_2Br$ (III)

The n.m.r. spectra of some of the above compounds are summarised in the Table.

N.m.r. results and assignments for compounds of the type Ph·CHF·CO·R

Compound	Chemical shift (τ value)	Coupling constant (c./sec.)	Assignment
R = OEt	3·9d	J_{HF} = 46	**H**–C–F
	2·3s		Arom. H
	8·55t, 5·5q	J = 6	Me, CH_2
R = OH (In $CDCl_3$)	4·25d	J_{HF} = 48	**H**–C–F
	2·6s		Arom. H
	−1·15s		OH
R = NMe_2	4·0d	J_{HF} = 48	**H**–C–F
	2·7s		Arom–H
	7·1, 7·15		Non-equivalent Me

s = Singlet; d = doublet; t = triplet; q = quartet.

In the n.m.r. spectrum of *NN*-dimethyl-2-fluoro-2-phenylethylamine the resonance due to the proton geminal to the fluorine atom was well resolved and, as expected for part of an ABCX system, consisted of two series of lines, [centred at τ 4·55, (J_{HF} = 48 c./sec.)], each of which consisted of two doublets. The complex pattern due to the non-equivalent methylene protons could not be completely assigned owing to masking by the methyl signal (τ 7·75).

The proton magnetic resonance spectrum of 1-bromo-2-fluoro-2-phenylethane (III) could be analysed completely and was very similar to that of methyl 3-bromo-2-fluoropropanoate,* which has been studied in detail.[10] Its ^{19}F magnetic resonance spectrum was, however, surprisingly complex.

The mass spectrum † of *NN*-dimethyl-2-fluoro-phenylethylamine (I; X = F, R = Me) showed the molecular ion (*m/e* 167), which underwent cleavage of the carbon–carbon bond adjacent to the nitrogen atom to give the base peak at *m/e* 58 ($CH_2 : \overset{+}{N}Me_2$) and an ion at *m/e* 109 ($Ph{\cdot}\overset{+}{C}HF$). A further intense peak at *m/e* 147 ($[Ph{\cdot}CH : CH{\cdot}NMe_2]^{+\cdot}$) was formed by loss of HF from the molecular ion.

Solvolysis of *NN*-dimethyl-2-fluoro-2-phenylethylamine in 1 : 1 acetone–water at 37° was studied by determining the concentration of ethyleniminium ion in the usual way.[2] Some 12—13% of the theoretical maximum amount of ethyleneiminium ion was formed within 5 min. of liberation of the amine from its hydrochloride and this value declined to about 1% after about 4·5 hr. These observations (by Mr. B. A. Gore) stand in sharp contrast to the behaviour of the corresponding chloro-compound, which yields 100% of ethyleniminium ion immediately on liberation from its hydrochloride, and the behaviour of primary fluoro-compounds referred to on p. 528.

Preliminary pharmacological examination of the compound by Dr. J. D. P. Graham and H. Al Katib, Department of Pharmacology, Welsh National School of Medicine, Cardiff, shows that it is a very weak antagonistic of noradrenaline and the antagonism is probably unspecific.

EXPERIMENTAL

N.m.r. spectra were obtained on a Perkin-Elmer spectrometer operating at 40 Mc./sec. Unless otherwise stated, spectra were obtained in carbon tetrachloride as solvent with tetramethylsilane added as internal standard. Infrared spectra were determined on a Unicam SP 200 spectrophotometer.

Ethyl α-Bromophenylacetate.[11]—Prepared in 65% yield from phenylacetic acid, this had b. p. 148—151°/12 mm. (lit.,[11] 141—142°/10 mm.), $\nu_{max.}$ (liquid film) 1740 $cm.^{-1}$ (ester C=O).

Ethyl α-Fluorophenylacetate.—An efficiently stirred mixture of finely powdered anhydrous potassium fluoride (12 g.; dried *in vacuo* for several days at 140°), ethyl α-bromophenylacetate (40 g.), and *NN*-dimethylformamide (100 ml.; dried over molecular sieves) was maintained at 145—150° with exclusion of moisture for 4 hr. A further portion of potassium fluoride (8 g.) was then added, and the mixture was maintained at 145—150° for a further 4 hr. The cooled mixture was diluted with water and shaken with ether. Evaporation of the ether from the dried ($MgSO_4$) extracts, followed by fractionation of the residue, gave the *fluoro-ester* (16·5 g., 53%) as a colourless liquid, b. p. 116—117°/18 mm. (Found: C, 66·1; H, 6·15. $C_{10}H_{11}FO_2$ requires C, 65·9; H, 6·1%), $\nu_{max.}$ (liquid film) 1750 $cm.^{-1}$ (ester C=O).

When the above reaction was carried out in ethylene glycol as solvent the yields of fluoro-ester were less reproducible, and varied from 0 to 40%.

α-Fluorophenylacetic Acid.—The fluoro-ester (16 g.) was heated under reflux for 30 min. with an excess of 10% aqueous sodium hydroxide (40 ml.). The cooled solution was shaken once with ether, and the aqueous layer was then acidified with conc. hydrochloric acid. The acid, isolated with ether in the usual manner, had m. p. 61—70°

* We thank Professor F. L. M. Pattison for drawing our attention to this similarity.

† We are grateful to Dr. D. H. Williams of Cambridge University for obtaining this spectrum, and for his helpful comments.

[9] F. L. M. Pattison, D. A. V. Peters, and F. H. Dean, *Canad. J. Chem.*, 1965, **43**, 1689.

[10] J. B. Stothers, J. D. Talman, and R. R. Fraser, *Canad. J. Chem.*, 1964, **42**, 1530.

[11] V. M. Rodionov, N. N. Suvorov, and K. S. Mikhailov, *Chem. Abs.* 1954, **48**, 579d.

[from light petroleum (b. p. 60—80°)]. Several recrystallisations from carbon tetrachloride gave the pure acid (9 g., 64%) as large plates, m. p. 80—81° (lit.,[7] 83—85°) [Found: C, 62·4; H, 4·6%; Equiv. (titration), 153. Calc. for $C_8H_7FO_2$: C, 62·35; H, 4·6%; Equiv., 154], $\nu_{max.}$ (KBr) 1700 and 1750 cm.$^{-1}$; ($CHCl_3$) 1735 cm.$^{-1}$ (acid C=O).

Amides of α-Fluorophenylacetic Acid.—The fluoro-acid (9 g.) and redistilled thionyl chloride (20 ml.) were heated under reflux for 1 hr. Excess of thionyl chloride was then removed under reduced pressure, the residue was diluted with dry benzene (25 ml.), and an excess of a solution of dimethylamine in benzene was cautiously added until no further reaction occurred. After 1 hr. the benzene solution was washed with water, dried ($MgSO_4$), and evaporated. Crystallisation of the residue from ether–light petroleum (b. p. 40—60°) gave NN-*dimethyl-α-fluorophenylacetamide* (6·5 g., 60%), m. p. 60—61°. A specimen for analysis was obtained as long needles, m. p. 61°, by sublimation at 100°/15 mm. (Found: C, 66·35; H, 6·7; N, 7·75. $C_{10}H_{12}FNO$ requires C, 66·25; H, 6·7; N, 7·75%), $\nu_{max.}$ (CCl_4) 1650 cm.$^{-1}$ (tertiary amide C=O).

α-Fluorophenylacetamide, prepared from the crude acid chloride and aqueous ammonia (*d* 0·88) was obtained as colourless leaflets, m. p. 129—130° (from water) (Found: C, 63·15; H, 5·3; N, 8·85. C_8H_8FNO requires C, 62·8; H, 5·3; N, 9·15%), $\nu_{max.}$ (KBr) 1665 cm.$^{-1}$ (amide C=O).

Reduction of NN-*Dimethyl-α-fluorophenylacetamide.*—(*a*) *With lithium aluminium hydride.* The *NN*-dimethylamide (2·0 g.) and lithium aluminium hydride (0·45 g.) were stirred and heated under reflux overnight in dry ether (100 ml.). The basic product, obtained in the usual manner, was *NN*-dimethyl-2-phenylethylamine, isolated as the hydrochloride (1·65 g., 80%), m. p. and mixed m. p. 204—205°.

(*b*) *With diborane.* Diborane, prepared by the method of Papanastassiou and Bruni[3c] from sodium borohydride (0·48 g.) and boron trifluoride etherate (2·6 g.), was passed in a stream of nitrogen during 1·5 hr. through a stirred solution of the *NN*-dimethylamide (1 g.) in dry tetrahydrofuran (4·6 ml.) at room temperature. After being kept for a further 2 hr., the product was mixed cautiously with absolute ethanol (4 ml.), and a stream of dry hydrogen chloride was passed through the solution. It was then evaporated to dryness under reduced pressure and the residue was shaken with ethereal hydrogen chloride. The resultant white precipitate was filtered off and crystallised from dry ethanol to give NN-*dimethyl-2-fluoro-2-phenylethylamine hydrochloride* (0·72 g., 53%) as colourless needles, m. p. 189—190° (Found: C, 58·95; H, 7·5; N, 6·95; Cl, 17·4. $C_{10}H_{15}ClFN$ requires C, 59·0; H, 7·4; N, 6·9; Cl, 17·4%). A specimen of the free base was prepared from the hydrochloride [Found: *M* (mass spectrum), 167. $C_{10}H_{14}FN$ requires *M* 167].

Reaction of 1-*Bromo-2-fluoro-2-phenylethane* (III) *with Dimethylamine.*—1-Bromo-2-fluoro-2-phenylethane (III) (6·5 g.), prepared by the method of Pattison *et al.*,[9] and dimethylamine (3·2 g.), in dry benzene (30 ml.), were heated together at 100° in a sealed tube for 8 hr. The precipitate of dimethylamine hydrobromide (3·8 g., 95%), m. p. and mixed m. p. 133—134°, was filtered off. The filtrate was washed with water, dried ($MgSO_4$), and evaporated under reduced pressure. The residue was treated with ethereal hydrogen chloride to give the hydrochloride of the amine (I; X = F, R = Me) (4·5 g., 69%), m. p. 190—191°, undepressed by admixture with the salt prepared by the previous method. The infrared spectra of the two samples were identical.

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