0.077 mole) in a small flask fitted to a micro-fractionation unit, the receiver of which was immersed in an ice-bath. An exothermic reaction took place spontaneously. The flask was then heated in an oil-bath at 110° and the product distilled at 15–20 mm. The temperature of the bath was slowly raised to 210° toward the end of the distillation. The nitrile was thus produced slowly but regularly (b.p. 50–51° (17 mm.)). The distillate was treated with anhydrous potassium carbonate overnight, to remove acidic impurities, and then redistilled twice, yielding 3-fluoropropionitrile (3.1 g., 71%).

Method II. 7-Fluoroheptanonitrile.—A mixture of sodium cyanide (12 g., 0.245 mole) and 6-fluorohexyl bromide (30 g., 0.164 mole) in 80% ethanol (33 ml.) was heated under reflux for 7.5 hours. The mixture was allowed to cool, and the precipitate of sodium bromide was filtered off and washed with a little alcohol. The majority of the alcohol was then distilled from the combined filtrate and washings on a water-bath. After cooling, the residue was diluted with an equal volume of water, and the organic layer separated. The aqueous layer was then extracted with ether, and the combined extract and organic layer were dried over anhydrous calcium chloride. Fractionation of the dried product through a 30-cm. Vigreux column gave 7-fluoroheptanonitrile (19.1 g., 90%).

Method III. 8-Fluoroöctanonitrile.—A mixture of 7-fluoroheptyl chloride (41.9 g., 0.275 mole), sodium iodide (41.3 g., 0.275 mole) and sodium cyanide (20.2 g., 0.412 mole) in 80% ethanol (60 ml.) was heated under reflux for 12 hours. After cooling and dilution with water, the mixture was extracted with ether. The combined extracts were washed successively with 10% sodium carbonate, concd. sodium thiosulfate and water. After drying over anhydrous sodium sulfate and removal of the ether, the residue on fractionation through a 30-cm. Vigreux column yielded 8-fluoroöctanonitrile (29.7 g., 76%).

Method IV. 7-Fluoroheptanonitrile.—A commercial sample of 7-bromoheptanonitrile, obtained from Columbia Organic Chemicals Co., Inc., 600 Capitol Place, Columbia, S. C., was redistilled before use, b.p. 143–145° (10 mm.) and $n^{25}D$ 1.4730. A mixture of 7-bromoheptanonitrile (44.5 g., 0.23 mole), anhydrous potassium fluoride (22.0 g., 0.38 mole) and diethylene glycol (80 g.) was heated at 115 ± 5° in a 200-ml. flask fitted with a precision-bore stirrer, thermometer, and vacuum-distillation assembly. The pressure in the system was reduced to 12 mm., and the crude fluoronitrile distilled at a slow, steady rate. Later, the temperature of the mixture was raised to 125° to ensure that most of the fluoronitrile had been collected. The distillate was diluted with ether, washed successively with water, 10% sodium carbonate and water, and dried over anhydrous sodium sulfate. After removal of the ether, fractionation of the residue gave 15.6 g. of 7-fluoroheptanonitrile. The residual mixture in the fluorination flask was heated at 125° for three hours at atmospheric pressure, in order to fluorinate any remaining bromonitrile. A further 2.0 g. of 7-fluoroheptanonitrile was thus obtained after the usual isolation procedure (dilution with an equal volume of water, extraction with ether, washing and drying the extracts, removal of ether and fractional distillation). The total yield of 7-fluoroheptanonitrile was 17.6 g. (58.3%).

In a large scale reaction under the same conditions, 7-fluoroheptanonitrile (62.6 g., 58%) was obtained from 7-bromoheptanonitrile (159 g., 0.84 mole).

ω-Fluoro-ω′-nitroalkanes.—The two methods listed in Table II are represented by the following typical examples.

Method I. 5-Fluoro-1-nitropentane.—In a 500-ml. flask, equipped with a reflux condenser protected by a calcium chloride drying-tube, were placed silver nitrite (30.0 g., 0.195 mole), 5-fluoroamyl bromide (30.0 g., 0.177 mole) and enough anhydrous ether to cover the surface of the solid. The mixture was heated under reflux for 24 hours. The solid was then filtered off and washed with a little anhydrous ether. The combined filtrate and washings were dried over sodium sulfate. After removal of the ether, the residue was fractionated through a Podbielniak column, yielding 5-fluoro-1-nitropentane (17.5 g., 73%).

Method II. 3-Fluoro-1-nitropropane.—3-Fluoropropyl iodide (54.73 g., 0.291 mole) was added dropwise to a stirred suspension of dry silver nitrite (60.70 g., 0.388 mole) in anhydrous ether (200 ml.) in absence of light.[21] Throughout the addition the temperature was maintained at 0°. When the addition was complete, the temperature was allowed to rise to room temperature and the stirring was continued for 48 hours. The mixture was filtered and the silver salts washed thoroughly with ether. After drying and removal of the ether, fractional distillation yielded 3-fluoro-1-nitropropane (23.62 g., 76%).

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LONDON, ONTARIO

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF WESTERN ONTARIO]

Toxic Fluorine Compounds. VI.[1] ω-Fluoroalkylamines

BY F. L. M. PATTISON, W. C. HOWELL AND ROBERT W. WHITE

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Representative members of the series of ω-fluoroalkylamines were synthesized, and their chemical, physical and toxicological properties determined. Confirmation was obtained for the mechanism of detoxication of aliphatic amines.

The value of the ω-fluorine atom in elucidating or confirming detoxication mechanisms has been outlined in previous reports.[2–4] Apart from the biochemical interest, the toxicity of some of the ω-fluoro compounds was so high that their potential value as new chemical warfare agents was constantly being examined. This communication deals with ω-fluoroalkylamines, and hence with the metabolic breakdown of simple, aliphatic amines.

Amine oxidase is a group specific enzyme that occurs at small concentrations in many animal tissues.[5] It catalyzes the oxidation of primary amines by the first of the reactions

(1) Issued as DRB Report No. SW-22. For part V, see ref. 4.

(2) F. L. M. Pattison, W. C. Howell, A. J. McNamara, J. C. Schneider and J. F. Walker, *J. Org. Chem.*, **21**, in press (1956).

(3) F. L. M. Pattison and W. C. Howell, *ibid.*, **21**, in press (1956).

(4) F. L. M. Pattison, W. J. Cott, W. C. Howell and R. W. White, THIS JOURNAL, **78**, 3484 (1956).

(5) E. Baldwin, "Dynamic Aspects of Biochemistry," Cambridge University Press, England, 1952, p. 165.

TABLE I

ω-FLUOROALKYLAMINES

Compound	Method[a]	Yield, %	B.p. °C.	Mm.	$n^{25}D$	L.D. 50 for mice (intraperitoneal), mg./kg.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
3-Fluoropropylamine	I	18	88.5–89	742	1.3884	46	46.76	46.56	10.39	10.14	18.18	17.98
4-Fluorobutylamine[b]	I	37	35–35.5	65	1.4036	...	52.74	52.54	11.06	11.26	15.38	15.14
N-4-Fluorobutylacetamide	IV	13	148–149	13	1.4418	16.5	54.13	54.30	9.02	9.21	10.52	10.37
5-Fluoroamylamine	II	62	61–61.5	40	1.4094	50	57.15	57.09	11.43	11.41	13.33	13.46
	III	10	67–67.5	50	1.4099							
6-Fluorohexylamine	I	37	52.5–53.5	9	1.4152	0.9					15.95[c]	15.7[c]
	II	78	54–55	13	1.4148							
7-Fluoroheptylamine	II	77.5	67.5–68	11	1.4200	50					14.27[c]	14.2[c]
8-Fluoroöctylamine	II	81	93–94	15	1.4253	0.76	65.31	65.12	12.25	12.45	9.52	9.84

[a] Methods of preparation: I, nitrocompound reduced by hydrogen and platinum catalyst; II, nitrile reduced by lithium aluminum hydride; III, nitrocompound reduced by lithium aluminum hydride; IV, 4-fluorobutyl isocyanate treated with methylmagnesium chloride. [b] Unstable at room temperature in sealed glass ampoule. [c] Fluorine, %.

$$RCH_2NH_2 + O_2 \longrightarrow RCH{=}NH + H_2O_2$$
$$RCH{=}NH + H_2O \longrightarrow RCHO + NH_3$$
$$RCHO + O \longrightarrow RCOOH$$

It is probable that the second reaction is not catalyzed but spontaneous, while the third reaction is a common enzymic oxidation. If this mechanism be applied to ω-fluoroalkylamines, it would be expected that the members containing an even number of carbon atoms would be toxic due to the formation of the corresponding ω-fluorocarboxylic acids. Confirmation of this is supplied by the results given below.

2-Fluoroethylamine, the only member of the series prepared previously, had been obtained from 2-aminoethylsulfnitrosamidic acid, $H_2NCH_2CH_2N(NO)SO_3H$, by treatment with 40% hydrofluoric acid,[6] and from 2-fluoroethyl bromide by the Gabriel synthesis[7] or by reaction with ammonia.[7] No mention was made of its toxicity.

The ω-fluoroalkylamines were prepared by the reduction of the corresponding ω-fluoronitriles or ω-fluoro-ω′-nitroalkanes. For the former, lithium aluminum hydride[8,9] was convenient and efficient, while for the latter, catalytic low-pressure hydrogenation[10] was satisfactory, but the one attempt with lithium aluminum hydride[8] was poor. Some results are shown in Table I. Yields were particularly low in the preparation of members containing five carbon atoms or less; this was due largely to loss of hydrogen fluoride, accompanied in the case of the four and five carbon members by ring closure giving piperidine and pyrrolidine. The above reductions provide proof of structure of the ω-fluoronitriles and ω-fluoro-ω′-nitroalkanes.

4-Fluorobutylamine was unstable even on standing at room temperature in a sealed glass ampoule. For this reason, its acetyl derivative, prepared in poor yield by the following route, was used for all pharmacological work.

$$F(CH_2)_4COOH \longrightarrow F(CH_2)_4COCl \xrightarrow{NaN_3} F(CH_2)_4NCO$$
$$\xrightarrow{CH_3MgCl} F(CH_2)_4NHCOCH_3$$

The ω-fluoroalkylamines are colorless liquids with an odor typical of aliphatic amines. They fume in moist air and deposit a white solid when exposed to the atmosphere. This has been shown to be the corresponding carbamate salt, formed by reaction with carbon dioxide of the air[11]; on treatment with dilute hydrochloric acid, carbon dioxide is liberated

$$2F(CH_2)_nNH_2 + CO_2 \longrightarrow F(CH_2)_nNHCOO^-{}^+H_3N(CH_2)_nF$$

Toxicities are shown in Table I. The results are consistent with the detoxication mechanism for aliphatic amines outlined above. The *a priori* evidence, provided by these crude toxicity figures, for the conversion *in vivo* of aliphatic amines to the corresponding acids thus furnishes a further example of the value of the ω-fluorine atom as a tool for elucidating biochemical transformations.[12,13]

Experimental[14]

The experimental details are subdivided according to the methods listed in Table I. A representative example is given below for each method.

Method I. 6-Fluorohexylamine.—A Parr low-pressure hydrogenation apparatus was first tested for leaks and then calibrated by the reduction of pure maleic acid (0.1 mole) as described by Adams and Voorhees.[17] By this method it was found that a pressure drop of 8 p.s.i. corresponded to the uptake of 0.1 mole of hydrogen.

In the reaction bottle was placed a solution of 6-fluoro-1-nitrohexane[4] (5 g., 0.033 mole) in 95% ethanol (30 ml.).

(6) W. Traube and E. Peiser, *Ber.*, **53B**, 1501 (1920).

(7) A. F. Childs, L. J. Goldsworthy, G. F. Harding, F. E. King, A. W. Nineham, W. L. Norris, S. G. P. Plant, B. Selton and A. L. L. Tompsett, *J. Chem. Soc.*, 2174 (1948).

(8) R. F. Nystrom and W. G. Brown, THIS JOURNAL, **70**, 3738 (1948).

(9) L. H. Amundsen and L. S. Nelson, *ibid.*, **73**, 242 (1951).

(10) D. C. Iffland and F. A. Cassis, Jr., *ibid.*, **74**, 6284 (1952).

(11) See, for example, J. Walker, "Chemistry of Carbon Compounds," Vol. IA, E. H. Rodd, Editor, Elsevier Publishing Co., Houston, Texas, 1951, p. 392.

(12) F. L. M. Pattison, *Nature*, **172**, 1139 (1953).

(13) F. L M. Pattison, *ibid.*, **174**, 737 (1954).

(14) (a) Microanalyses were performed by Mr. J. F. Alicino, Metuchen, N. J. Results are shown in Table I. The fluorine determinations were carried out in the authors' laboratory, either by the lead chlorofluoride method[15] or by the amperometric method[16] using aluminum chloride and Superchrome Garnet Y. (b) Boiling points are uncorrected.

(15) N. B. Chapman, R. Heap and B. C. Saunders, *Analyst*, **73**, 434 (1948).

(16) C. R. Castor and J. H. Saylor, *Anal. Chem.*, **24**, 1369 (1952).

(17) R. Adams and V. Voorhees, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 61.

To this was added platinum oxide catalyst (0.1 g.). The vessel was then attached to the hydrogenation apparatus and evacuated until the alcohol began to boil. Hydrogen was introduced into the system until a pressure of 60 p.s.i. was attained. The shaker was started and allowed to continue until a total pressure drop of 8 p.s.i. had occurred (*i.e.*, the theoretical drop for the reduction of 0.033 mole of nitrocompound to amine). The shaker was stopped and the system allowed to come to atmospheric pressure. The catalyst was allowed to settle and then most of the supernatant alcoholic amine solution was decanted off. The remaining amine solution was filtered, with care being taken to avoid sucking air over the dry platinum black. To the amine solution was added sufficient 85% phosphoric acid to render the solution acid to litmus. The mixture was cooled in an ice-bath, and the resulting precipitate filtered off. The precipitate was washed with cold ether, and then dissolved in excess 25% sodium hydroxide. The solution was then saturated with potassium carbonate, chilled and extracted with ether. After drying over sodium sulfate, the ether was removed and the residue distilled through a Podbielniak column. 6-Fluorohexylamine (1.43 g., 37%) was thus obtained as a colorless liquid.

Method II. 7-Fluoroheptylamine.—To a solution of lithium aluminum hydride (4.42 g., 0.116 mole) in anhydrous ether (200 ml.), contained in the usual apparatus, was added a solution of 7-fluoroheptanonitrile[4] (15 g., 0.116 mole) in anhydrous ether (130 ml.), dropwise and with stirring. Water was then added slowly to decompose the excess hydride. The complex was hydrolyzed by addition of excess 20% sodium potassium tartrate (*ca.* 290 ml.). The ether layer was separated and the aqueous phase extracted with ether. The combined extracts, after drying over anhydrous calcium sulfate, were fractionated through a 30-cm. Vigreux column. After removal of the ether, 7-fluoroheptylamine (12.0 g., 77.5%) was obtained as a colorless liquid.

Method III. 5-Fluoroamylamine.—To a solution of lithium aluminum hydride (6.8 g., 0.178 mole) in anhydrous ether (400 ml.), contained in the usual apparatus, was added 5-fluoro-1-nitropentane[4] (12.0 g., 0.089 mole) in anhydrous ether, dropwise and with stirring. Water was then added slowly to decompose the excess hydride. The complex was hydrolyzed by addition of excess 20% sodium potassium tartrate (*ca.* 225 ml.). Isolation and purification were carried out as under method II, using a Podbielniak column. 5-Fluoroamylamine (0.90 g., 10%) was obtained as a colorless liquid.

Method IV. N-4-Fluorobutylacetamide.—A suspension of methylmagnesium chloride was prepared by the procedure described by Kharasch and Reinmuth,[18] using magnesium turnings (3.9 g., 0.16 mole), preactivated with butyl chloride, in anhydrous ether (60 ml.), and gaseous methyl chloride. A solution of 4-fluorobutyl isocyanate[19] (10.0 g., 0.085 mole) in anhydrous ether (90 ml.) was added dropwise with stirring to the Grignard reagent. A vigorous exothermic reaction took place, accompanied by the formation of a precipitate. After standing overnight under an atmosphere of nitrogen, the reaction mixture was hydrolyzed by the addition of a minimum quantity of saturated aqueous ammonium chloride. The supernatant solution was decanted and the residue washed with several portions of ether. The combined ethereal solutions were dried over anhydrous magnesium sulfate. After removal of the ether, the residue on fractionation yielded N-4-fluorobutylacetamide (1.5 g., 13%) as a colorless liquid with a characteristic odor of mice. The material turned yellow after several weeks in a sealed glass ampoule.

Carbamate Salts.—The ω-fluoroalkylamines deposited white solids after a few minutes exposure to the atmosphere. These effervesced on treatment with dilute hydrochloric acid. The solid obtained from 8-fluoroöctylamine was analyzed without purification.

Anal. Calcd. for $C_{17}H_{36}F_2N_2O_2$: N, 8.28. Found: N, 8.29.

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(18) M. S. Kharasch and O. Reinmuth, "Grignard Reactions of Nonmetallic Substances," Prentice-Hall, Inc., New York, N. Y., 1954, p. 25.

(19) ω-Fluoroalkyl isocyanates will be described in a future publication.

LONDON, ONTARIO

[CONTRIBUTION FROM THE CHEMICAL RESEARCH LABORATORY, POLAROID CORPORATION]

The Properties of Some Fluorinated Vinyl Ethers[1]

BY RICHARD S. CORLEY, JOGINDER LAL AND MARSHALL W. KANE

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The preparation and characterization of $CH_3OCF{=}CFCl$ is reported. Some properties and reactions of this ether and of $C_6H_5OCF{=}CFCl$ are described. The alkyl vinyl ether, $CH_3OCF{=}CFCl$, was readily oxidizable by air and polymerized to a low molecular weight resin; the aryl vinyl ether, $C_6H_5OCF{=}CFCl$, did not autoxidize or polymerize.

Since the difficulty of polymerization of many fluorinated olefins may be due, at least in part, to the strong inductive effect of contiguous fluorine substituents on the double bond, we have examined the preparation and properties of two representative fluorinated olefins with substituents of opposite inductive effect, *viz.*, $CH_3O{-}CF{=}CFCl$ and the previously reported $C_6H_5O{-}CF{=}CFCl$.[2] These vinyl ethers were prepared by dehydrofluorination of the saturated ethers CH_3OCF_2CHFCl and $C_6H_5OCF_2CHFCl$.[2]

We prepared CH_3OCF_2CHFCl by base-catalyzed addition of methanol to chlorotrifluoroethylene, using a simplified version of the established technique,[3] and also by an anomalous Williamson synthesis in which sodium methoxide or potassium hydroxide was allowed to react in excess methanol with $CF_2ClCFCl_2$ in an attempt to prepare CH_3-

(1) This work was sponsored by the Signal Corps, Department of the Army; a summary of it was presented at the 124th National Meeting of the American Chemical Society, Chicago, Illinois, September 6–11, 1953.

(2) P. Tarrant and H. C. Brown, THIS JOURNAL, **73**, 5831 (1951).

(3) (a) J. T. Barr, K. E. Rapp, R. L. Pruett, C. T. Bahner, J. D. Gibson and R. H. Lafferty, Jr., *ibid.*, **72**, 4480 (1950); (b) W. T. Miller, Jr., E. W. Fager and P. H. Griswold, *ibid.*, **70**, 431 (1948); (c) J. D. Park, D. K. Vail, K. R. Lea and J. R. Lacher, *ibid.*, **70**, 1550 (1948).