**Condensation of Phenylacetaldehyde, Benzaldehyde and Ammonia.**—After concentration of the ethanolic solution of the condensation products, 9.70 g. of solid, m.p. 110–160°, was collected from the residue diluted with an equal volume of ether. The crude basic material during the ether extraction yielded an additional 10.35 g., m.p. 90–145°. The rest of the material was distilled. The first fraction, b.p. 106–107° (14 mm.), $n^{20}D$ 1.5393, weighed 2.13 g. and was identified as benzyl alcohol by its infrared spectrum. (This material was apparently carried through the acid extraction in the third layer which resulted here as in all other cases.) The α-naphthylurethan melted at 133–134° after crystallization from ligroin (literature data for benzyl alcohol: b.p. 93° (10 mm.), $n^{20}D$ 1.5396; α-naphthylurethan, m.p. 134°). Fraction 2, b.p. 107–207° (14 mm.), $n^{20}D$ 1.5943, weighed 3.30 g. and yielded 0.22 g. of 3,5-diphenylpyridine, m.p. 135–137°, and 0.56 g. of 3,5-diphenylpyridine picrate, m.p. 203–205°. The higher boiling material, collected at 207–290° (14 mm.), weighed 59.45 g. and formed a solid or glass. By judicious crystallization of this material as well as the solids mentioned above from ethanol, ether and ligroin (b.p. 60–71°) three crystalline fractions were obtained. The least soluble one melted at 256–257° after final crystallization from ligroin. The total amount of this material was 5.13 g.

*Anal.* Calcd. for $C_{23}H_{17}N$: C, 89.87; H, 5.57; equiv. wt., 307. Calcd. for $C_{24}H_{19}N$: C, 89.68; H, 5.96; equiv. wt., 321. Found: C, 89.62; H, 5.50; equiv. wt., 320.

The ultraviolet spectrum of this material showed a maximum at 240 mμ (ε 27,000 for a molecular wt. of 321) and a shoulder at 280 mμ (ε 8,800).

The picrate decomposed at 232°.

*Anal.* Calcd. for $C_{29}H_{20}N_4O_7$: C, 64.92; H, 3.76. Calcd. for $C_{30}H_{22}N_4O_7$: C, 65.45; H, 4.03. Found: C, 65.37; H, 3.82.

The material of intermediate solubility proved to be 3,5-diphenylpyridine, m.p. 135–137°, undepressed by admixture of an authentic sample. The total amount of this material isolated was 17.51 g. (including the material obtained from fraction 2); in addition, 4.92 g. of 3,5-diphenylpyridine picrate, m.p. 205-207°, undepressed by admixture with an authentic sample, was isolated in addition to the picrate isolated from fraction 2.

The most soluble material, after final crystallization from ligroin (b.p. 60–71°), melted at 123–124°. This material is a triphenylpyridine, probably the 2,3,5-isomer.

*Anal.* Calcd. for $C_{23}H_{17}N$: C, 89.87; H, 5.57; equiv. wt., 307. Found: C, 89.81; H, 5.47; equiv. wt., 314.

The ultraviolet spectrum showed a maximum at 249 mμ (ε 23,900) and a shoulder at 280 mμ (ε 17,000).

The total amount of this material isolated was 25.73 g. In addition there was isolated 5.10 g. of triphenylpyridine picrate, m.p. 230–233°. The analytical sample of this picrate was prepared from the parent base and melted at 232–234° after crystallization from acetone.

*Anal.* Calcd. for $C_{29}H_{20}N_4O_7$: C, 64.92; H, 3.76. Found: C, 64.95; H, 3.69.

The original ethanol distillate of this condensation was worked up in the usual way. After the pentane had been removed, the temperature of the distillate rose rapidly to 106°. The material collected at 106–109° weighed 0.89 g. and was identified as toluene by its 2,4-dinitro derivative. No benzene was isolated.

NOTRE DAME, INDIANA

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

# Toxic Fluorine Compounds. V.[1] ω-Fluoronitriles and ω-Fluoro-ω′-nitroalkanes

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

RECEIVED JANUARY 9, 1956

Representative members of the series of ω-fluoronitriles, $F(CH_2)_nCN$, and ω-fluoro-ω′-nitroalkanes, $F(CH_2)_nNO_2$, were synthesized and their chemical, physical and toxicological properties determined. Evidence was obtained for the mode of breakdown *in vivo* of aliphatic nitriles and nitroalkanes.

## Introduction

In earlier reports on the study of toxic fluorine compounds we have described some ω-fluoroalcohols[2] and ω-fluorohalides,[3] all of which exhibited the alternation in toxicity characteristic of the ω-fluorocarboxylic acids. We next turned our attention to other series of aliphatic compounds containing an ω-fluorine atom, which are, in most cases, accessible from the intermediate ω-fluorohalides. This paper deals with two such series, the ω-fluoronitriles and the ω-fluoro-ω′-nitroalkanes.

No member of the ω-fluoro-ω′-nitroalkane series has been prepared previously. Of the members of the ω-fluoronitrile series, fluoroacetonitrile has been fully described,[4,5] 3-fluoropropionitrile has been prepared[6] since the completion of our work, and 4-fluorobutyronitrile has been listed with its physical constants but with no details of its preparation.[7]

Fluoroacetonitrile has been reported to be non-toxic,[4,8] a fact implying that the nitrile is not hydrolyzed *in vivo* to the toxic fluoroacetic acid. This observation conforms to the reported metabolic breakdown of nitriles to hydrogen cyanide and the next lower acid[9]; the fluoroacetonitrile would thus be expected to form the relatively non-toxic fragments derived from the hypothetical fluoroformic acid. A simple means of confirming this breakdown mechanism was to examine the toxicological properties of the higher ω-fluoronitriles. The results and conclusions are discussed below. In addition to their biological interest, the ω-fluoronitriles proved to be important intermediates in the preparation of other series, such as ω-fluoroalkylamines and ω-fluorocarboxylic acids.

(1) Issued as DRB Report No. SW-21. For part IV, see ref. 3.

(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. J. Buckle, R. Heap and B. C. Saunders, *J. Chem. Soc.*, 912 (1949).

(5) F. Swarts, *Bull. soc. chim. Belg.*, **31**, 364 (1922).

(6) H. Kitano, K. Fukui, R. Nozu and T. Osaka, *J. Chem. Soc. Japan, Ind. Chem. Sec.*, **58**, 224 (1955).

(7) C. E. Redemann, S. W. Chaikin, R. B. Fearing, G. J. Rotariu, J. Savit and D. van Hoesen, THIS JOURNAL, **70**, 3604 (1948).

(8) E. Gryszkiewicz-Trochimowski, A. Sporzynski and J. Wnuk, *Rec. trav. chim.*, **66**, 419 (1947).

(9) R. T. Williams, "Detoxication Mechanisms: The Metabolism of Drugs and Allied Organic Compounds," Chapman and Hall Ltd., London, 1947, p. 125.

TABLE I

ω-FLUORONITRILES

| Nitrile | Formula | Method of prepn.[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 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Fluoroaceto-[b] | $FCH_2CN$ | I | 75 | 79–80 | 742 | 1.3313 | 25 | | | | | | |
| 3-Fluoropropio-[c] | $F(CH_2)_2CN$ | I | 71 | 44–45 | 12 | 1.3679 | 10 | 49.32 | 49.47 | 5.48 | 5.57 | 19.18 | 19.11 |
| 4-Fluorobutyro-[d] | $F(CH_2)_3CN$ | II[e] | 81 | 58.5–59 | 16 | 1.3867 | 16 | 55.17 | 55.34 | 6.90 | 7.01 | 16.09 | 15.91 |
| 5-Fluorovalero- | $F(CH_2)_4CN$ | II | 82 | 71.5–72 | 14 | 1.3962 | 1.0 | | | | | 18.81[f] | 18.6[f] |
| | | III | 76 | 70–71.5 | 13 | | | | | | | | |
| 6-Fluorohexano- | $F(CH_2)_5CN$ | II[e] | 83 | 83.5–84 | 11 | 1.4055 | 50 | | | | | 16.52[f] | 16.2[f] |
| | | III | 87 | 85–86 | 12 | | | | | | | | |
| 7-Fluoroheptano- | $F(CH_2)_6CN$ | II | 90 | 97–98 | 12 | 1.4118 | 2.7 | | | | | 14.72[f] | 15.0[f] |
| | | IV | 58 | 96–98 | 9 | | | | | | | | |
| 8-Fluoroöctano- | $F(CH_2)_7CN$ | II | 61 | 117–118 | 10 | 1.4166 | >100 | 67.14 | 66.90 | 9.79 | 9.52 | 9.79 | 9.57 |
| | | III | 76 | 122–123 | 15 | | | | | | | | |
| 12-Fluorododecano- | $F(CH_2)_{11}CN$ | II | 91.5 | 114–115 | 0.9 | 1.4320 | 80 | 72.36 | 72.06 | 11.05 | 10.95 | 7.03 | 7.36 |

[a] Methods of preparation: I, dehydration of corresponding amide; II, ω-fluoroalkyl bromide and sodium cyanide; III, ω-fluoroalkyl chloride, sodium iodide and sodium cyanide; IV, direct fluorination of ω-bromonitrile. [b] Buckle, Heap and Saunders[4] report b.p. 80° (760 mm.); Redemann, *et al.*,[7] report b.p. 78° (752 mm.) and $n^{20}D$ 1.3224. [c] Kitano, *et al.*,[6] report b.p. 99–103° (180 mm.). [d] Redemann, *et al.*,[7] report b.p. 98° (100 mm.); using the conversion formula and the constants provided by these authors, b.p. (16 mm.) is 57.5°. 4-Fluorobutyronitrile was prepared by Dr. M. S. Kharasch (no details given). [e] Ethylene glycol as solvent (100° for one hour). [f] Fluorine, %.

It has been shown[10,11] that when nitroethane is administered intravenously to rabbits, the main metabolic products are acetaldehyde and nitrous acid. Assuming that the ω-fluoro-ω′-nitroalkanes follow the same metabolic pathway, the expected products would be the corresponding aldehydes. Since the ω-fluoroaldehydes are readily oxidized *in vivo* to ω-fluoroacids, of which only the even members are toxic, it seemed reasonable to predict that the even-numbered ω-fluoro-ω′-nitroalkanes would be more toxic than the odd members. The toxicological results given below confirm this argument. As well as being of intrinsic biological interest, the ω-fluoro-ω′-nitroalkanes were of some value in preparing ω-fluoroalkylamines by reduction. Their conversion to ω-fluoroaldehydes by the Nef reaction,[12] in simulation of the biological breakdown, also has been examined and will be reported in a future paper.

## Methods of Preparation

The most convenient method for preparing ω-fluoronitriles was by the reaction of ω-fluoroalkyl halides with sodium cyanide in aqueous alcohol.[13,14] After a series of experiments to determine the optimum conditions, it was established that maximum yields are obtained using a 50% excess of sodium cyanide in 80% ethanol (200 ml. per mole of alkyl halide). When this method was unsuitable, dehydration of the corresponding amides proved to be convenient and satisfactory. Some yields are shown in Table I.

Considerable difficulty was encountered in the preparation of 3-fluoropropionitrile by standard replacement reactions. The following were unsuccessful: the action of alkali cyanides on 2-fluoroethyl chloride, bromide,[15] iodide, methanesulfonate and *p*-toluenesulfonate; the action of silver fluoride on 3-bromo- and 3-chloropropionitrile; and the action of potassium fluoride on 3-chloropropionitrile, 3-bromopropionitrile and 2-cyanoethyl methanesulfonate. In many of these reactions acrylonitrile was the only product isolated. Ultimately, 3-fluoropropionitrile was obtained[16] in 71% yield by dehydration of 3-fluoropropionamide.

The ω-fluoro-ω′-nitroalkanes were prepared[17] by the classical procedure of Victor Meyer[18] as modified by later workers[19–21]

$$F(CH_2)_nX + AgNO_2 \longrightarrow F(CH_2)_nNO_2 + AgX$$

ω-Fluoroalkyl chlorides were shown to be completely inert in this reaction, hence ω-fluoroalkyl bromides and iodides were used exclusively. The former were treated with silver nitrite in boiling anhydrous ether for 24 hours, and the latter with silver nitrite in anhydrous ether at 0° and then at room temperature for 48 hours. Petroleum ether (45–55°) recently has been described[22] as being a suitable solvent for the reaction, but yields were generally inferior to those obtained in ether.

It is known that silver nitrite undergoes decomposition on heating, forming silver nitrate and metallic silver. Both these products are undesirable in the reaction with ω-fluoroalkyl halides, since the former can give rise to ω-fluoroalkyl nitrates[23] and the latter to Wurtz-type couplings. Other possible contaminants include[24,25] alcohols, ketones and nitrites, some of which are inseparable from the nitro compound by distillation. All of these side reactions are minimized at low temperatures, and consequently the second of the above methods of preparation was

(10) W. Machle, E. W. Scott and J. Treon, *J. Ind. Hyg. Toxicol.*, **24**, 5 (1942).
(11) E. W. Scott, *ibid.*, **24**, 226 (1942).
(12) J. U. Nef, *Ann.*, **280**, 263 (1894).
(13) D. T. Mowry, *Chem. Revs.*, **42**, 189 (1948).
(14) H. B. Hass and J. R. Marshall, *Ind. Eng. Chem.*, **23**, 352 (1931).
(15) Previously reported to give none of the desired product, B. C. Saunders, G. J. Stacey and I. G. E. Wilding, *J. Chem. Soc.*, 773 (1949).
(16) F. L. M. Pattison, Interim Report No. 9 to Defence Research Board (January, 1955).
(17) F. L. M. Pattison, Interim Reports to Defence Research Board, Nos. 5 and 6 (Jan. and June, 1953).
(18) V. Meyer and O. Stuber, *Ber.*, **5**, 203 (1872).
(19) R. B. Reynolds and H. Adkins, THIS JOURNAL, **51**, 279 (1929).
(20) A. I. Vogel, *J. Chem. Soc.*, 1833 (1948).
(21) N. Kornblum, B. Taub and H. E. Ungnade, *ibid.*, **76**, 3209 (1954).
(22) C. W. Plummer and N. L. Drake, *ibid.*, **76**, 2720 (1954).
(23) F. L. M. Pattison and G. M. Brown, *Can. J. Chem.*, **34**, in press (1956).
(24) N. Kornblum, N. N. Lichtin, J. T. Patton and D. C. Iffland, THIS JOURNAL, **69**, 307 (1947).
(25) N. Kornblum, J. T. Patton and J. B. Nordmann, *ibid.*, **70**, 746 (1948).

TABLE II

ω-FLUORO-ω′-NITROALKANES

| Compound | Method of prepn.[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-Fluoro-1-nitropropane | I | 39 | 69.5–70 | 19 | 1.4030 | 92 | 33.64 | 33.65 | 5.61 | 5.77 | 13.08 | 13.23 |
| | II | 76 | 72–74 | 20 | | | | | | | | |
| 4-Fluoro-1-nitrobutane | I | 58 | 78–79 | 11 | 1.4110 | 11 | 39.67 | 39.44 | 6.61 | 6.56 | 11.57 | 11.48 |
| | II | 76[b] | 79–80 | 12 | | | | | | | | |
| 5-Fluoro-1-nitropentane | I | 73 | 98–99 | 12 | 1.4170 | 90 | 44.45 | 44.40 | 7.41 | 7.38 | 10.37 | 10.06 |
| | II | 70 | 96–97 | 9 | | | | | | | | |
| 6-Fluoro-1-nitrohexane | I | 54 | 106–106.5 | 9 | 1.4217 | 12.5 | 48.32 | 48.31 | 8.05 | 8.22 | 9.40 | 9.33 |
| | | | | | | | | | | | 12.76[c] | 12.7[c] |

[a] Methods of preparation: I, ω-fluoroalkyl bromide and silver nitrite in boiling ether; II, ω-fluoroalkyl iodide and silver nitrite in ether at 0° and then at room temperature. [b] 4-Fluorobutanol (b.p. 60° (15 mm.) and $n^{25}D$ 1.3970) was also isolated in 13% yield. [c] Fluorine, %.

found to be the more efficient. Yields by both methods are shown in Table II.

## Properties

The members of both homologous series are stable, colorless, mobile liquids. The fluorine atom is inert to most reagents, and the standard reactions of nitriles and nitro compounds thus occur in the usual way. Physical constants and toxicities of the members of both series are shown in Tables I and II.

It can be seen that the nitriles and nitro compounds show a pronounced alternation in toxicity, and, as predicted above, it is the odd-numbered nitriles[26] and the even-numbered nitro compounds that are the toxic members. These figures thus confirm the postulated metabolism of nitriles and nitro compounds.

One of the most important objectives in our study of fluorine compounds has been to elucidate the biochemical breakdown of simple aliphatic groupings *in vivo*. In this, we have used the ω-fluorine atom as a "tag": by reference to the previously described[27,28] toxic properties of the fluorinated "tail," it has become possible to deduce the metabolism of the functional "head." This is clearly illustrated in the case of the nitriles. It can be seen: (a) that the nitriles are not hydrolyzed appreciably *in vivo* by the standard chemical route (RCN → RCOOH), since the toxic odd members would give rise to nontoxica cids, whereas this is plainly not the case; (b) that they are not reduced *in vivo* to the corresponding amines (RCN → $RCH_2NH_2$), since the toxic odd members would give rise to amines containing an odd number of carbon atoms, and these have been shown to be non-toxic[27]; but (c) that, on the contrary, the most satisfactory way of explaining the high toxicity of the odd members is to accept the less plausible theory of C–CN rupture, possibly proceeding by an α-oxidation mechanism,[29] giving the toxic even-numbered fluoroacids and hydrogen cyanide.

(26) In this report, the carbon atom of the nitrile group is considered as part of the chain.

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

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

(29) See, for example, C. H. Fawcett, R. C. Seeley, F. Taylor, R. L. Wain and F. Wightman, *Nature*, **176**, 1026 (1955).

## Experimental[30]

**ω-Fluoronitriles.**—The four methods listed in Table I are represented by the following typical examples.

**Method I. 3-Fluoropropionitrile.**[33] (a) **3-Fluoropropionyl Chloride.**—In a two-necked flask, fitted with a dropping funnel and a condenser protected by drying tubes, was placed thionyl chloride (42.8 g., 0.36 mole). 3-Fluoropropionic acid[34] (30 g., 0.326 mole) was added dropwise over a half-hour, with slight warming, and the mixture was then allowed to stand overnight at room temperature. The product was distilled directly through a small Vigreux column, yielding 3-fluoropropionyl chloride (27.8 g., 77%), a colorless, corrosive liquid of b.p. 52° (70 mm.) and $n^{25}D$ 1.4049.

*Anal.* Calcd. for $C_3H_4OFCl$: Cl, 32.13. Found: Cl, 32.33.

(b) **3-Fluoropropionamide.**[35]—A 500-ml. round-bottomed flask was fitted with a rubber stopper through which passed a dropping funnel, drawn to a fine tip and a sintered glass gas delivery tube. A groove was cut in the stopper to permit the escape of ammonia, and the dropping funnel was protected by a drying tube. Anhydrous benzene (120 ml.) was placed in the flask, immersed in an ice-bath, and a solution of 3-fluoropropionyl chloride (10 g., 0.09 mole) in anhydrous benzene (25 ml.) in the dropping funnel. Anhydrous ammonia was passed through the benzene at a moderate rate, and the acid chloride solution was added dropwise over approximately one hour. The passage of ammonia was continued for a further half-hour. The mixture was then heated to dissolve the amide, and the ammonium chloride removed by filtration of the hot solution through a preheated sintered glass büchner funnel. The benzene solution was concentrated, and the amide precipitated by the addition of petroleum ether (30–50°). After several recrystallizations from an anhydrous mixture of benzene–petroleum ether (30–50°), and drying in a vacuum desiccator over calcium chloride, 3-fluoropropionamide (4.3 g., 52%) was obtained as a colorless solid, m.p. 40.5–41°.

*Anal.* Calcd. for $C_3H_6ONF$: N, 15.38. Found: N, 15.11.

(c) **3-Fluoropropionitrile.**—3-Fluoropropionamide (5.5 g., 0.060 mole) was mixed with phosphorus pentoxide (11 g.,

(30) (a) The majority of the microanalyses were performed by Mr. J. F. Alicino, Metuchen, N. J., and some by Dr. Rob. Dietrich, Zürich, Switzerland. Results are shown in Tables I and II. The fluorine determinations were carried out in the authors' laboratory, either by the lead chlorofluoride method[31] or by the amperometric method[32] using aluminum chloride and Superchrome Garnet Y. (b) Boiling points are uncorrected.

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

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

(33) Prepared by G. J. O'Neill.

(34) F. L. M. Pattison, J. B. Stothers and R. G. Woolford, THIS JOURNAL, **78**, 2255 (1956).

(35) Adapted from the method of G. E. Philbrook, *J. Org. Chem.*, **19**, 623 (1954).

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

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[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.

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