195. *Toxic Fluorine Compounds containing the C–F Link. Part III. Fluoroacetamide and Related Compounds.*

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An account is given of the preparation of fluoroacetamide and of a number of hitherto undescribed *N*-substituted derivatives. Fluoroacetamide, a stable crystalline compound, can be conveniently used as an analytical reference substance for the determination of fluorine in organic compounds.

Fluoromethyl cyanide is very readily converted into *fluoroacetimino ethyl ether hydrochloride* and the *2-fluoroethyl* and the *phenyl* analogue.

The toxic action of these compounds is discussed.

Fluoroacetamide was first mentioned by Swarts (*Bull. Soc. chim.*, 1896, **15**, 1134), but he gave no exact details for its preparation. In 1943 (Ministry of Supply Contract) we prepared this compound in high yield by the action of ammonia on methyl fluoroacetate. It is a highly crystalline stable compound of sharp m. p., and it has proved useful for the identification of methyl fluoroacetate (MFA). Because of its stability and the fact that it can be obtained in a highly purified condition, it has proved to be of great value as an analytical standard for organic compounds containing fluorine. It has the advantage, too, that it contains nitrogen which can be determined independently. Being a solid, it was not possible to assess its toxicity by inhalation in comparison with MFA, but intravenous injection into rabbits showed that the two compounds were about equally toxic and produced the same type of convulsions.

By distilling the amide with phosphoric oxide at ordinary pressure, fluoromethyl cyanide was obtained as a colourless, mobile liquid. This compound had been obtained by Swarts (*Bull. Soc. chim. Belg.*, 1922, **31**, 364), who claimed that it was necessary to distil the amide with phosphoric oxide under reduced pressure and to collect the distillate at –50°. We have shown that neither of these elaborations is necessary. The toxicity of fluoromethyl cyanide on inhalation proved to be less than that of methyl fluoroacetate. The cyanide, however, did show the interesting property of being much more toxic to rabbits than to guinea-pigs, rats, and mice. The preparation of free fluoroacetic acid from methyl fluoroacetate *via* the barium salt was described in Part I (*J.*, 1948, 1773). An alternative and very convenient method for preparing the free acid consists in treating fluoroacetamide with nitrous fumes, the pure acid being produced in 90% yield. The two methods may be summarised thus :

$$\mathrm{F{\cdot}CH_2{\cdot}CO_2Me} \xrightarrow{90{\cdot}7\%} \underset{\text{(crude)}}{\mathrm{(F{\cdot}CH_2{\cdot}CO_2)Ba}} \xrightarrow{82{\cdot}7\%} \underset{\text{(pure)}}{\mathrm{F{\cdot}CH_2{\cdot}CO_2H}} \quad \textit{Overall yield } 75{\cdot}0\%$$

$$\mathrm{F{\cdot}CH_2{\cdot}CO_2Me} \xrightarrow{100\%} \underset{\text{(crude)}}{\mathrm{F{\cdot}CH_2{\cdot}CO{\cdot}NH_2}} \xrightarrow{90{\cdot}0\%} \underset{\text{(pure)}}{\mathrm{F{\cdot}CH_2{\cdot}CO_2H}} \quad \textit{Overall yield } 90{\cdot}0\%$$

It is noteworthy that the L.D. 50 by intravenous injection for fluoroacetic acid, methyl fluoroacetate, and the amide are almost identical (0·25 mg./kg. for rabbits).

N-*Methylfluoroacetamide* and its *N*-nitroso-derivative were prepared by standard methods and found to have toxicities which indicated the ready hydrolysis of these compounds by the animal body to fluoroacetic acid.

The group $\mathrm{Cl{\cdot}CH_2{\cdot}CH_2{\cdot}N{<}}$ occurs in the powerful vesicant $\mathrm{CH_3{\cdot}N(CH_2{\cdot}CH_2Cl)_2}$. It was decided therefore to introduce this group into the fluoroacetamide molecule in the hope of combining vesicant properties with the delayed convulsant action of the fluoroacetates. For this purpose N-2-*hydroxyethylfluoroacetamide* (I) was prepared by the action of monoethanolamine on methyl fluoroacetate and was readily converted into N-2-*chloroethylfluoroacetamide* (II) by the action of thionyl chloride.

$$\mathrm{CH_2F{\cdot}CO_2Me + NH_2{\cdot}CH_2{\cdot}CH_2{\cdot}OH} \longrightarrow \underset{\text{(I.)}}{\mathrm{CH_2F{\cdot}CO{\cdot}NH{\cdot}CH_2{\cdot}CH_2{\cdot}OH}} \longrightarrow \underset{\text{(II.)}}{\mathrm{CH_2F{\cdot}CO{\cdot}NH{\cdot}CH_2{\cdot}CH_2Cl}}$$

N-2-Chloroethylfluoroacetamide was also prepared by the direct action of 2 mols. of fluoroacetyl chloride on ethanolamine, although we carried out this reaction with the intention of preparing 2-(fluoroacetamido)ethyl fluoroacetate, $\mathrm{CH_2F{\cdot}CO_2CH_2{\cdot}CH_2{\cdot}NH{\cdot}CO{\cdot}CH_2F}$. Injection of (II) into mice showed that the L.D. 50 was similar to that of fluoroacetamide or of fluoroacetic acid, and the symptoms produced appeared to be identical in each case; (II), however, showed no vesicant action. It is probable then that hydrolysis of the molecule occurs *in vivo*, resulting in the formation of fluoroacetic acid and the relatively harmless 2-chloroethylamine.

By reactions similar to the above we also prepared NN-*di*-(2-*hydroxyethyl*)*fluoroacetamide* and NN-*di*-(2-*chloroethyl*)*fluoroacetamide*.

It was hoped that the action of bromine and potassium hydroxide solution on fluoroacetamide might give rise to the hitherto undescribed fluoromethylamine. Under the conditions employed, no fluoromethylamine was obtained, but a crystalline solid containing both fluorine and nitrogen was produced. Analysis and general reactions showed that it was N-*fluoroacetyl*-N′-*fluoromethylurea*. This reaction then is exactly analogous to Hofmann's preparation of the corresponding chloro-compound from chloroacetamide (*Ber.*, 1885, **18**, 2735). Toxicity by injection into mice showed an L.D. 50 of about 60 mg./kg.

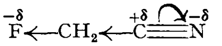
We then directed our attention to the properties of fluoromethyl cyanide, as it seemed likely, on theoretical grounds, that it would undergo certain addition reactions very readily. Alcohol and dry hydrogen chloride readily converted it into *fluoroacetimino ethyl ether hydrochloride* (III), which was converted into the *amidine* (IV) by means of alcoholic ammonia. Similar condensation of the cyanide with 2-fluoroethanol and phenol yielded *fluoroacetimino*-2-*fluoroethyl ether hydrochloride* (V; $\mathrm{R = CH_2{\cdot}CH_2F}$) and the corresponding *imino phenyl ether hydrochloride*

(V; R = Ph) respectively. Analogous experiments were carried out with methyl cyanide, and it was established that the rate of formation of the imino ether hydrochlorides was much slower with this than with the fluoro-substituted analogue; *e.g.*, on a 0·1M. scale separation of (III) occurred within 10 minutes, and the mixture became very hot although cooled in ice, but with methyl cyanide, although absorption of hydrogen chloride was just as fast, the solution became only very slightly warm and no solid separated for several hours. This difference in reactivity was even more noticeable in the condensations with phenol.

$F{\cdot}CH_2{\cdot}C(OEt){:}\overset{+}{N}H_2\overset{-}{Cl}$
(III.)

$F{\cdot}CH_2{\cdot}C(NH_2){:}\overset{+}{N}H_2\overset{-}{Cl}$
(IV.)

$F{\cdot}CH_2{\cdot}C(OR){:}\overset{+}{N}H_2\overset{-}{Cl}$
(V.)



$\overset{-\delta}{F}\leftarrow CH_2\leftarrow \overset{+\delta}{C}\equiv \overset{-\delta}{N}$
(VI.)

This enhanced reactivity of fluoromethyl cyanide is undoubtedly due to the inductive effect of the fluorine atom which produces an electron deficit on the carbon atom linked to the nitrogen, and presumably increases still further the polarity of the carbon–nitrogen bond, so that the electron displacements can be pictured as (VI). The increased polarity of the CN bond will obviously facilitate polar addition of hydrogen chloride and alcohols (or phenols).

Compounds (III), (IV), and (V; R = $CH_2{\cdot}CH_2F$ and R = Ph) were tested pharmacologically by subcutaneous injection into mice. Results obtained are shown in the accompanying table.

Compound.	Toxicity towards mice.
(III)	Comparable with that of methyl fluoroacetate
(V; R = Ph)	,, ,, ,,
(IV)	,, ,, ,,
(V; R = $CH_2{\cdot}CH_2F$)	Comparable with that of 2-fluoroethyl fluoroacetate

It was to be expected that the imino ether hydrochlorides would be hydrolysed in the body to give the corresponding fluoroacetate and ammonium chloride, and the toxicities should be roughly the same as those of the fluoroacetates. The results show this to be the case. The compound (V; R = $CH_2{\cdot}CH_2F$) was expectedly more toxic than the other compounds, as this would form 2-fluoroethyl fluoroacetate on hydrolysis, which is known to be twice as toxic as methyl or ethyl fluoroacetate (McCombie and Saunders, *Nature*, 1946, **158**, 382).

EXPERIMENTAL.

Fluoroacetamide.—Pure methyl fluoroacetate (20 g.) was cooled in ice-water and excess of aqueous ammonia (20 c.c., *d* 0·88) was added. The crystalline precipitate (15 g.) which separated was filtered off after an hour and dried. It was practically pure. It could be recrystallised from chloroform, or from chloroform–light petroleum (b. p. 100°), forming long needles, m. p. 108°. Further crops of crystals were obtained from the original ammoniacal filtrate by evaporation under reduced pressure (1 g.) and finally by evaporation to dryness (2·7 g.). The last specimen (dried in a vacuum over sulphuric acid) was not so pure as the others; total yield 16·7 g. (100%). The amide was obtained in very pure condition by sublimation; m. p. 108° (Found: C, 31·0; H, 4·9; N, 18·2; F, 24·7. Calc. for C_2H_4ONF: C, 31·2; H, 5·2; N, 18·2; F, 24·7%). This can serve as an analytical standard (*Analyst*, 1948, **73**, 434).

Fluoromethyl Cyanide.—A mixture of fluoroacetamide (10 g., dried in a vacuum over concentrated sulphuric acid) and phosphoric oxide (17·5 g.) was placed in a flask fitted with a water-condenser, and heated in an oil-bath to 110° at which temperature the reaction started. The bath was then kept at 160° until the cyanide ceased to distil; yield 5 g. (65·2%). This product was distilled through a column and practically the whole of it came over at 80°/760 mm. (Found: N, 23·3. Calc. for C_2H_2NF: N, 23·7%).

Fluoroacetic Acid (*New Method*).—Nitrous fumes, prepared from nitric acid and arsenous oxide, and dried over calcium chloride and phosphoric oxide, were passed into crystalline fluoroacetamide (10 g.) cooled in ice. Heat was evolved and the mixture liquefied as the reaction proceeded. The passage of nitrous fumes was continued for about an hour after the mixture had completely liquefied. The black liquid thus obtained was heated to boiling while a stream of dry nitrogen was passed through in order to remove excess of nitrous fumes. Excess of phosphoric oxide (6 g.) was added with cooling, and the mixture set aside overnight. Dry nitrogen was again passed through at the b. p. until the nitrous fumes were completely removed. In this way, water and nitric acid were completely eliminated. The product was then distilled at ordinary pressure, and the fraction of b. p. 164·5—165° collected. This solidified to a mass of fine needles; m. p. 31°; yield 9 g. (90%) (Found: F, 24·3. Calc. for $C_2H_3O_2F$: F, 24·3%).

N-*Methylfluoroacetamide.*—Methyl fluoroacetate (10 g.) was cooled in ice-water, and excess of methylamine added (10 g. of 33% aqueous solution). No solid separated overnight, and the solution was therefore submitted to vacuum distillation and the solid residue dried in a vacuum over concentrated sulphuric acid. The impure product (100% yield) recrystallised from chloroform–light petroleum (b. p. 100°) in long deliquescent needles, and was dried over sulphuric acid, calcium chloride and paraffin wax; m. p. 64°; yield of recrystallised *amide*, 7·5 g. (75%) (Found: C, 39·9; H, 6·7; N, 15·2. C_3H_6ONF requires C, 39·6; H, 6·1; N, 15·4%).

N-*Nitroso*-N-*methylfluoroacetamide.*—Nitrous fumes were passed into *N*-methylfluoroacetamide (12 g.), and the excess then driven off by heating the product in a stream of nitrogen. The residue was fractionated under reduced pressure; b. p. 84°/14 mm.; yield 7 g. The compound contained nitrogen and fluorine and gave the Liebermann nitroso-reaction.

NN-*Di*-(2-*chloroethyl*)*fluoroacetamide.*—Methyl fluoroacetate (20 g.) and diethanolamine (23 g.) were mixed, and after a time the mixture became homogeneous with only slight evolution of heat. As the crude *NN*-di-(2-hydroxyethyl)fluoroacetamide thus obtained decomposed on distillation (142°/0·2 mm.), it was used without further treatment for the next stage. The crude hydroxy-amide was dissolved in chloroform (100 c.c.), and thionyl chloride dissolved in chloroform (100 c.c.) was added down a reflux condenser. [The amount of thionyl chloride used was 88 g., *i.e.*, rather more than sufficient (10% excess) to react with both hydroxyl groups of the amide and with the methyl alcohol formed in the first part of the reaction.] After the addition was complete, the mixture was heated under reflux for 4 hours. Most of the chloroform was distilled off at room pressure. At 0·1 mm. a fraction was obtained of b. p. 111°. This was redistilled, and NN-*di-(2-chloroethyl)fluoroacetamide* was obtained as a colourless viscous liquid of b. p. 102°/0·04 mm.; yield 17·5 g. (40%) (Found: Cl, 35·3; N, 7·1. $C_6H_{10}ONCl_2F$ requires Cl, 35·15; N, 6·9%).

N-2-*Hydroxyethylfluoroacetamide*.—Methyl fluoroacetate (10 g.) and ethanolamine (6·5 g.) were carefully mixed. Considerable heat was evolved, and the mixture was then allowed to cool spontaneously. The methyl alcohol (theoretical yield) was distilled off at room pressure, and the residue then fractionated under reduced pressure. The *amide* was obtained as a viscous, colourless distillate; b. p. 114°/0·1 mm.; yield 12 g. (91·4%). It solidified to a white solid, m. p. *ca.* 21° (Found: N, 11·5. $C_4H_8O_2NF$ requires N, 11·6%).

N-2-*Chloroethylfluoroacetamide*.—(i) Thionyl chloride (9·5 g.), dissolved in dry chloroform (10 c.c.), was slowly run down a reflux condenser into the hydroxy-amide (9·5 g.), also dissolved in dry chloroform (10 c.c.). The mixture was left for some hours, and the chloroform distilled off in the cold at 15 mm. The solid residue thus obtained was distilled and had b. p. 77°/0·3 mm. The N-2-*chloroethylfluoroacetamide* solidified and was recrystallised from chloroform; m.p. 65°. It sublimed slowly on heating. Yield 9·5 g. (87·1%) (Found: N, 9·7; Cl, 25·0. C_4H_7ONClF requires N, 10·0; Cl, 25·4%).

(ii) [This experiment was originally designed to afford 2-(fluoroacetamido)ethyl fluoroacetate.] Fluoroacetyl chloride (16 g., 0·16 mol.) was slowly added to monoethanolamine (5 g., 0·08 mol.) in a flask fitted with a condenser and calcium chloride tube. There was an initial vigorous reaction which subsided when about half of the acid chloride had been added. The flask was then heated in an oil-bath to 70°, which caused a further copious evolution of hydrogen chloride. Finally, the temperature of the oil-bath was raised to 100° to complete the reaction. The product was then distilled (b. p. 125—130°/17 mm.), forming a colourless liquid which crystallised to a white solid (8·9 g.; 70% based on monoethanolamine used). The crystals thus obtained were recrystallised from benzene and dried in an Abderhalden apparatus at 1 mm./40—60°; m. p. 64·5° [Found: C, 34·6; H, 5·4; N, 10·2; F, 13·66; *M* (Rast), 144. C_4H_7ONClF requires C, 34·3; H, 5·0; N, 10·0; F, 13·6%; *M*, 139·5].

Action of Bromine and Potassium Hydroxide on Fluoroacetamide.—(i) Fluoroacetamide (11 g.) and bromine (25 g., 7·5 c.c.) were mixed in a flask immersed in cold water. Potassium hydroxide (10% aqueous solution) was added with shaking until the mixture became pale yellow. The product was then run into potassium hydroxide (30 g.), dissolved in water (55 c.c.). The mixture (the temperature of which was not allowed to rise above 70°) was slowly distilled into dilute hydrochloric acid. The distillate on evaporation gave mainly ammonium chloride, but traces of fluorine were detected, probably due to ammonium fluoride.

(ii) The above experiment was repeated but with only 20 g. of potassium hydroxide. The gas evolved during the distillation was collected in liquid air. A white solid was obtained which, on removal from the liquid air, slowly evaporated without liquefying. It proved to be mainly carbon dioxide contaminated with traces of hydrogen fluoride. The non-volatile residue was extracted with ether, dried (Na_2SO_4), filtered, and the ether distilled off. N-*Fluoromethyl*-N′-*fluoroacetylurea* was obtained as a solid which recrystallised from benzene in small, colourless, well-defined needles; m. p. 84° (Found: C, 31·85; H, 4·3; F, 25·6. $C_4H_6O_2N_2F_2$ requires C, 31·6; H, 3·9; F, 25·0%). When heated with sodium hydroxide, it evolved ammonia.

Fluoroacetimino Ethyl Ether Hydrochloride.—Dry fluoromethyl cyanide (6 g., 0·1 mol.) was mixed with absolute alcohol (4·6 g., 0·1 mol.) in a flask protected by a calcium chloride tube, and cooled in ice–salt. Dry hydrogen chloride was passed into the mixture, which in spite of external cooling, became very hot, and a solid began to separate. The mixture became a solid mass within 5 minutes, the gain in weight then being 3·5 g. (0·097 mol. of hydrogen chloride). The solid mass was ground, washed with dry ether, and the *hydrochloride* dried in a vacuum (Found: Cl′, 24·85. C_4H_9ONClF requires Cl′, 25·1%).

Fluoroacetamidine Hydrochloride.—The foregoing hydrochloride (6 g., 0·05 mol.) was ground in a dry mortar with absolute alcohol (2 c.c.) and stirred mechanically with 9% absolute alcoholic ammonia (25 c.c.; 0·13 mol. of NH_3) for 3 hours. A faint pink colour developed, the ammonium chloride formed was filtered off, and the filtrate evaporated on a steam-bath. A dark brown colour developed, and on cooling a mass of crystals separated. The *hydrochloride* was recrystallised twice from absolute alcohol, yielding colourless needles, m. p. 161—162° (decomp.) (Found: F, 16·32. $C_2H_6N_2ClF$ requires F, 16·9%). The *picrate* was prepared by mixing cold saturated alcoholic solutions of picric acid and the amidine hydrochloride; it separated as yellow needles in a few minutes, and was recrystallised twice from alcohol; m. p. 222—224° (decomp.) (Found: C, 31·45; H, 2·3; N, 22·6. $C_8H_8O_7N_5F$ requires C, 31·5; H, 2·6; N, 22·95%).

Fluoroacetimino 2-*Fluoroethyl Ether Hydrochloride*.—Dry fluoromethyl cyanide (6 g., 0·1 mol.) and redistilled fluoroethyl alcohol (6·4 g., 0·1 mol.) were mixed in a flask cooled in ice and salt and fitted with an inlet tube, the exit tube being protected from moisture by a calcium chloride tube. Dry hydrogen chloride was passed in with occasional shaking for 7 minutes, the mixture then becoming very hot and solidifying to a mass of white crystals. The gain in weight was 3·0 g. (0·08 mol. of hydrogen chloride). The mixture could not be broken up sufficiently to allow thorough mixing of the product, and the excess of fluoroethyl alcohol and fluoromethyl cyanide was removed by grinding the product to a fine powder with dry ether; the *hydrochloride* was filtered off and dried (Found: Cl, 21·4. $C_4H_8ONClF_2$ requires Cl, 21·9%).

Fluoroacetimino Phenyl Ether Hydrochloride.—Phenol (9·4 g., 0·1 mol.) was dissolved in dry fluoromethyl cyanide (5·9 g., 0·1 mol.), and dry hydrogen chloride passed into the mixture for 15 minutes, under the same conditions as above. The gain in weight was 3·6 g. (0·1 mol. of hydrogen chloride). The mixture became very viscous and after a few minutes deposited white rosettes of crystals, the whole mass becoming solid in a few hours. The crystalline *ether hydrochloride* was broken up, ground with dry ether, filtered off, and dried (Found: Cl, 19·2. C_8H_9ONClF requires Cl, 18·9%).

An analogous experiment was performed with dry methyl cyanide (4·1 g., 0·1 mol.) and phenol (9·4 g., 0·1 mol.), but after ½ hour the amount of hydrogen chloride absorbed was only 0·1 g. (0·28 mol.), and only a very few crystals were deposited after 14 hours.

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