

164. *Toxic Fluorine Compounds Containing the C-F Link. Part II.*
2-Fluoroethanol and its Derivatives.

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A practicable method for the production of 2-fluoroethanol is described and an account is given of its highly toxic properties. A variety of compounds containing the 2-fluoroethyl group is described. The facile conversion of *fluoroethyl thiocyanate* into *fluoroethylsulphonyl chloride* has been effected. An example of the fluoroethylating action of 2 : 2'-*difluorodiethyl sulphate* is given.

In this work on compounds containing the C-F link, it was obviously desirable to prepare 2-fluoroethanol, both for toxicity tests on the compound itself, and as a starting material for the production of other fluorine compounds. Swarts (*Chem. Centr.*, 1914, I, 1551) was unable to obtain 2-fluoroethanol by the action of silver fluoride or mercuric fluoride on either ethylene chlorohydrin or ethylene bromohydrin. He obtained acetaldehyde in each case. He ultimately obtained fluoroethanol in very poor yield by the indirect method of hydrolysing fluoroacetin (from bromoacetin and mercuric fluoride) for 80 hours with dilute mineral acid.

In Report No. 3 on "Fluoroacetates and Allied Compounds" to the Ministry of Supply (March 31st, 1943) we described a very simple and efficient preparation of fluoroethanol (FEA) by heating together ethylene chlorohydrin and potassium fluoride in a rotating autoclave at 135° for 4 hours. Details of the method are described in the Experimental section. For large-scale work we found it advantageous to use nitrobenzene as a diluent, thereby enabling the reaction mixture to be stirred much more thoroughly and to render its removal (by suction or otherwise) from the autoclave more efficient.

Fluoroethanol is soluble in water and stable to moisture. As a lethal inhalant it produces convulsions in animals similar to those produced by methyl fluoroacetate (MFA). A concentration of 0.29 mg./l. (10 minutes' exposure) killed 62% of a batch of rabbits, guinea-pigs, and rats, and a concentration of 0.14 mg./l. killed 38%, all the deaths occurring within 12 hours. Mice were much more resistant, the L.C. 50 being about 1.1 mg./l.

1-Chloro-2-fluoroethane was found to be non-toxic. A concentration of 0.184 mg./l. failed to kill any animals whereas a similar concentration of fluoroethanol or of methyl fluoroacetate would have killed some 50% of a batch of rabbits, guinea-pigs, or rats. The chlorine atom in chlorofluoroethane was found to be very unreactive towards a variety of reagents, and this fact no doubt accounts for its non-toxic nature since it is unlikely that the animal body is able to hydrolyse it to the toxic fluoroethanol.

Under the conditions employed in our experiments no reaction occurred between chlorofluoroethane and potassium phthalimide or potassium thiocyanate. Magnesium (in ethereal suspension) did not react in the normal manner to give a Grignard reagent, although on prolonged heating, a certain amount of metal did go into solution to give a product which, on the addition of water, set to a jelly-like mass.

Attempts to prepare 2 : 2'-difluorodiethyl sulphide by the action of sodium sulphide on chlorofluoroethane resulted in the production of dithian together with other polymeric substances. Aniline either did not react at all or, under drastic conditions, gave *NN'*-diphenylpiperazine and *NN'*-diphenylethylenediamine.

Sodium phenoxide, however, reacted with chlorofluoroethane when they were heated together in alcoholic solution and gave *phenyl 2-fluoroethyl ether*, a solid which proved to be less toxic than MFA.

An attempt to prepare 1-bromo-2-fluoroethane by the partial fluorination of ethylene dibromide by means of antimony trifluoride was unsuccessful. The compound was best prepared by the action of phosphorus tribromide on FEA. Swarts (*Bull. Acad. roy. Belg.*, 1914, 7), who first prepared the compound by means of this reagent, poured the crude product into water, but he did not record the yield. Using his method, we obtained a 6% yield. We modified the method and were ultimately able to obtain consistent yields of about 50%. The compound was relatively non-toxic and the bromine atom rather unreactive, but considerably more reactive than the chlorine atom in chlorofluoroethane. For example bromofluoroethane was readily converted by means of potassium thiocyanate into *2-fluoroethyl thiocyanate*. As a lethal inhalant the toxicity of the thiocyanate was inferior to that of MFA. Toxicity by injection, however, appeared to be high. The results on this aspect of the work will be reported later.

The action of potassium cyanide on bromofluoroethane was examined, but under the conditions used, which were similar to those for the thiocyanate, no reaction took place.

By employing the method similar to that of Johnson and Douglass for converting SCN into SO_2Cl (*J. Amer. Chem. Soc.*, 1939, **61**, 381), fluoroethyl thiocyanate was readily converted by the action of chlorine water into 2-fluoroethylsulphonyl chloride, a stable liquid. When small animals were exposed to the vapour at a concentration of 0.5 mg./l. for 10 minutes, irritation and lachrymation were caused, but there were no deaths and all the animals recovered.

2-Fluoroethyl xanthate, $\text{F}\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{S}\cdot\text{CS}\cdot\text{OEt}$, was a yellow oil formed by the action of sodium xanthate on bromofluoroethane. The compound has an L.D. 50 of 50 mg./kg. for subcutaneous injection into mice, thus showing it to be considerably less toxic than MFA (Part I, *J.*, 1948, 1773).

The action of sulphuryl chloride on FEA was investigated, chiefly with a view to preparing 2 : 2'-difluorodiethyl sulphate, a compound which was expected to have applications analogous to those of diethyl sulphate. The method at first tried was similar to that recommended by Kharasch *et al.* (private communication, 1943) for the preparation of 2 : 2'-dichlorodiethyl sulphate. In this process, 2-fluoroethanol was added slowly to an excess of cooled sulphuryl chloride, the only product isolated being, however, 2-fluoroethyl chlorosulphonate, $\text{Cl}\cdot\text{SO}_2\cdot\text{O}\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{F}$. In the second experiment, conditions were reversed and sulphuryl chloride was added to slightly more than the theoretical quantity of FEA. The difluorodiethyl sulphate was obtained this time, but not in large yield.

On exposing animals for 10 minutes to 0.327 g./m.³ of the chlorosulphonate, irritation was observed and rats showed the same type of convulsions as with MFA. However, only 2/13 of a batch of rabbits, guinea-pigs, and rats died within 24 hours. The difluorodiethyl sulphate was non-irritant and less toxic.

2-Naphthyl 2-fluoroethyl ether was readily prepared by warming an alkaline solution of 2-naphthol with 2 : 2'-difluorodiethyl sulphate. Subcutaneous injection into mice of the propylene glycol solution showed that the compound had an L.D. 50 of approximately 60 mg./k. and was therefore much less toxic than MFA.

The reaction between FEA and manganese dioxide and sulphuric acid was investigated initially with a view to prepare the corresponding fluorinated acetal. It soon became apparent that the isolation of the hitherto undescribed fluoroacetaldehyde might be possible in this experiment, and accordingly attention was directed to that end. Evidence for the formation of fluoroacetaldehyde was obtained by the isolation of the 2 : 4-dinitrophenylhydrazone from the aqueous distillate. This fluorine-containing aqueous distillate also gave most of the usual aldehyde tests (*e.g.*, silver mirror with ammoniacal silver nitrate, slow pink coloration with Schiff's reagent, etc.). Analyses showed that the amount of aldehyde present in the distillate was only about 7%, but by suitable means of concentration (see p. 776) it was possible to obtain in small quantities a liquid of b. p. 89—93° containing about 80% of the aldehyde. Further dehydration gave a liquid of b. p. 57—65°, but this polymerised rapidly on standing.

By analogy with chloral and monochloroacetaldehyde it is to be expected that fluoroacetaldehyde might readily form a hydrate, and it is not improbable that, in the liquid of b. p. 89—93°, it was present largely in this form.

Toxicity determinations by subcutaneous injection into mice of a sample containing 80% of the aldehyde gave an L.D. 50 of 6 mg./kg. As the L.D. 50 for MFA is also 6 mg./kg., the two compounds are equally toxic, molecule for molecule, allowance being made for the presence of 20% of water in the aldehyde. This degree of toxicity is thus exactly in accordance with expectation.

EXPERIMENTAL.

2-Fluoroethanol.—Anhydrous ethylene chlorohydrin (226 g.) and dry finely-powdered potassium fluoride (200 g.) were heated in a rotating autoclave at 130—135° for 4 hours. After cooling, the product was extracted with ether, care being taken to grind up any solid crust as completely as possible with the ether. The solid was filtered off, and the ethereal filtrate shaken with dry sodium hydrogen sulphite for at least 1 hour to remove crotonaldehyde (formed as a by-product). The solution was again filtered and the ether distilled off through an efficient 30'' fractionating column. The residue was then carefully distilled, and the fraction of b. p. 103.5—105.5° collected; yield 75 g. (42%), b. p. 103.5°. Aldehydes were shown to be absent in pure fluoroethanol by Schiff's reagent. 2-Fluoroethanol is a colourless, almost odourless liquid, miscible with water in all proportions (Found : F, 29.2. Calc. for $\text{C}_2\text{H}_5\text{OF}$: F, 29.7%); f. p. -43°, d_4^{15} 1.1150, d_4^{15} 1.1095, d_4^{20} 1.1040; vapour pressure 5.55, 14.3, and 40 mm. at 0°, 15°, and 30°, respectively.

Notes on the preparation. (a) Some crotonaldehyde is produced in the reaction and this has nearly the same b. p. as that of fluoroethanol. It is therefore necessary to remove the aldehyde with solid sodium hydrogen sulphite.

(b) About 250 c.c. of nitrobenzene could, with advantage, be added as a diluent in the above reaction. The crude product was then much more easily removed from the autoclave. This was particularly useful for large-scale runs, for the reaction product could then be poured as a slurry from the autoclave. It must be emphasised, however, that nitrobenzene is not a suitable diluent for all fluorinations of the

above type; for example, at the higher temperature required in the preparation of methyl fluoroacetate (Part I, *loc. cit.*) explosions are likely to occur when nitrobenzene is used as diluent.

(c) The yields obtained with sodium fluoride (in place of potassium fluoride) were very small.

(d) Zinc fluoride and antimony fluoride did not react to any appreciable extent to give the alcohol, when heated with ethylene chlorohydrin for several hours without an autoclave.

Derivatives.—Phenylurethane. A mixture of phenyl isocyanate (1.2 g.) and FEA (0.64 g.) in dry light petroleum (25 c.c., b. p. 100—120°) was heated under reflux for 30 minutes, and filtered hot; an oil separated, and on standing in a refrigerator overnight this solidified, and when it was again dissolved in light petroleum and chilled, it again separated as an oil. The oil solidified to the colourless *urethane*, m. p. 36° (Found: N, 7.7. $C_8H_{10}O_2NF$ requires N, 7.9%).

1-Naphthylurethane. A mixture of 1-naphthyl isocyanate (1.7 g.) and FEA (0.64 g.) in dry light petroleum was heated as above. The liquid was filtered hot and on cooling the *urethane* crystallised; recrystallised from light petroleum (b. p. 100—120°), it had m. p. 128° (Found: N, 6.04. $C_{13}H_{12}O_2NF$ requires N, 6.2%).

3:5-Dinitrobenzoate. A mixture of 3:5-dinitrobenzoyl chloride (2 g.) and FEA (2 g.) was heated on a water-bath for 30 minutes. On cooling, the product solidified and was recrystallised from warm alcohol (10 c.c.). The white 3:5-dinitrobenzoate recrystallised from alcohol in fine, elongated, rectangular prisms, m. p. 86° (Found: C, 41.8; H, 2.94. $C_9H_7O_6N_2F$ requires C, 41.9; H, 2.74%).

1-Chloro-2-fluoroethane.—Fluoroethanol (32.1 g., 0.5 mol.) was placed in a flask, and thionyl chloride (59.5 g., 0.5 mol.) added slowly down a reflux condenser. Heat was evolved at first, but external cooling was not necessary. After the addition was complete, the mixture was heated under reflux for 30 mins. in an oil-bath at 90°. It was then fractionated through a 50-cm. column, the fraction, b. p. 51—55°, being collected. This was shaken with aqueous sodium carbonate to remove hydrochloric acid and sulphur dioxide, and then dried (Na_2SO_4) and distilled; yield 18.2 g. (44%) (Found: Cl, 43.14. Calc. for C_2H_4ClF : Cl, 43.02%). The compound was proved to contain fluorine.

Reaction with aniline. A mixture of aniline (13.9 g., 0.15 mol.) and chlorofluoroethane (6.6 g., 0.08 mol.) was gently heated under reflux for 18 hours. Much solid separated, and the product was extracted with boiling benzene, and the solution filtered and allowed to stand. The solid (insoluble in water) which separated was recrystallised from aqueous alcohol and gave a solid, m. p. 65° (not sharp), free from chlorine and fluorine. This product was proved to be *NN'*-diphenylethylenediamine (m. p.s given in literature vary from 59° to 65°).

The benzene filtrate was evaporated and a white solid remained. This distilled at 236—240°/16 mm. and was recrystallised from chloroform-alcohol; m. p. 159—162°. This compound, which contained nitrogen but not fluorine, was *NN'*-diphenylpiperazine which has m. p. 164—165°, b. p. 230—235°/12 mm. Under less vigorous conditions than the above, very little reaction took place.

In another experiment aniline and chlorofluoroethane were heated together in a sealed tube at 200° for 2 hours, but complete breakdown to intractable material took place.

Non-reaction with silver cyanide. A mixture of silver cyanide (13.4 g.) and chlorofluoroethane (8.3 g.) was heated under reflux for 8 hours, but there were no signs of reaction and on distillation unchanged chlorofluoroethane was obtained.

Reaction with sodium phenoxide. The phenoxide was prepared from sodium (4.6 g., 0.2 mol.) in alcohol (75 c.c.), to which was added phenol (18.8 g., 0.2 mol.) also dissolved in alcohol (25 c.c.). The mixture was then evaporated to dryness under reduced pressure, and the residual white solid powdered and dried; yield 22 g.

A mixture of sodium phenoxide (11.6 g., 0.1 mol.) and chlorofluoroethane (8.3 g., 0.1 mol.), dissolved in alcohol (30 c.c.), was heated under reflux for 18 hours. After removal of the solid which separated, the alcohol was distilled off, and the residual oil poured into water. The suspension was extracted with ether, and the extract washed with aqueous sodium hydroxide and then with water, and dried ($CaCl_2$). After removal of the ether, the residue distilled at 97—98°/22 mm.; yield 3.4 g. (24.3%). On redistillation the *phenyl ether* came over at 92.5—93°/17 mm. and solidified to colourless crystals, m. p. 41—41.5° (Found: F, 13.0. C_8H_9OF requires F, 13.56%).

Bromofluoroethane.—To FEA (38.4 g., 0.6 mol.) contained in a flask placed in ice-water, phosphorus tribromide (57.2 g., 0.2 mol.) was added slowly down a reflux condenser. There was no vigorous reaction and the drops of phosphorus tribromide disappeared on shaking. The mixture was then heated in an oil-bath at 100° for 10 minutes and hydrogen bromide was copiously evolved. The product was fractionated, and the fraction of b. p. 71—90° was collected, washed with aqueous sodium carbonate solution, then with water, dried ($CaCl_2$), and distilled, b. p. 71—74°; yield 36.6 g. (57%) (Found: F, 15.0. Calc. for C_2H_4BrF : F, 14.96%).

2-Fluoroethyl Thiocyanate.—A mixture of bromofluoroethane (50.8 g., 0.4 mol.), potassium thiocyanate (38.8 g., 0.4 mol.), ethyl alcohol (90 c.c.), and water (15 c.c.) was heated under reflux on a water-bath for 6 hours and allowed to stand overnight. After the potassium bromide had been filtered off, the alcohol and most of the water were distilled off below 83°. The residual liquid was then distilled under reduced pressure, almost the whole coming over at 78—79°/20 mm. The *thiocyanate* so obtained was further purified by redistillation; yield 32.9 g. (78.2%); b. p. 77.5—78.5°/19 mm. (Found: N, 12.9. C_3H_4NSF requires N, 13.3%).

2-Fluoroethylsulphonyl Chloride.—Fluoroethyl thiocyanate (the product from 0.4 mol. of bromofluoroethane) was suspended in water, cooled to 0°, and a rapid stream of chlorine passed in until a permanent green colour was obtained. The oil was then separated, extracted with ether, washed with aqueous sodium hydrogen sulphite, aqueous sodium hydrogen carbonate, and then with water, and dried ($CaCl_2$). The ether was distilled off and nearly the whole of the residue came over between 81.5° and 84.5°/13 mm.; yield 35.3 g. (*i.e.*, 60.6% based on bromofluoroethane). The chlorine content of the *sulphonyl chloride* was determined by boiling with excess of dilute, halogen-free sodium hydroxide solution for 30 minutes [Found: Cl, 22.8 (Volhard), 22.6 (gravimetrically). $C_3H_4O_2SFCl$ requires Cl, 24.2%].

2-Fluoroethyl Xanthate.—Metallic sodium (10 g.) was dissolved in ethyl alcohol (250 c.c.), and carbon disulphide added until the solution was acid to phenolphthalein. The solution was then concentrated

until crystallisation commenced. Ether (5 vols.) was then added, and the sodium xanthate filtered off. Sodium xanthate (28.8 g., 0.2 mol.) was dissolved in ethyl alcohol (35 c.c.), bromofluoroethane (25.4 g., 0.2 mol.) added, and the solution heated under reflux for 2 hours, sodium bromide being precipitated. The mixture was then filtered and the filtrate distilled, the fraction of b. p. 200—210° being collected (18 g., 55%). The xanthate on redistillation gave a pale yellow liquid, b. p. 208—210°, soluble in alcohol, insoluble in water, and with an unpleasant odour (Found: F, 11.75. C_5H_9OSF requires F, 11.31%).

2-Fluoroethyl Chlorosulphonate.—FEA (32.0 g., 0.5 mol.) was added down a reflux condenser to sulphuryl chloride (37.2 g., 0.0275 mol.*), contained in a flask cooled in ice-water. Hydrogen chloride was evolved towards the end of the addition, and finally the mixture was gently heated under reflux for 45 minutes, whereupon darkening occurred. The liquid was then distilled under reduced pressure, and a fraction collected below 80°/18 mm., but chiefly in the range 76—80°/18 mm. The black residual liquid would not distil. The fluoroethyl chlorosulphonate was refracted at 76—78.5°/16 mm.; yield 5.5 g. For analysis, a portion of the thrice-distilled liquid, b. p. 80°/18 mm., was used [Found: Cl, 23.0 (Stepanow); F, 12.4. $C_2H_4O_2ClFS$ requires Cl, 21.8; F, 11.7%].

2 : 2'-Difluorodiethyl Sulphate.—Sulphuryl chloride (33.8 g., 0.25 mol.) was added slowly down a reflux condenser to FEA (38.4 g., 0.6 mol.) placed in a flask cooled in ice. After the addition was complete, the mixture was gently warmed for 45 mins. during which time it darkened slightly. It was then distilled under reduced pressure and a fraction of b. p. below 70°/18 mm. (largely unchanged FEA) was collected. A second fraction came over with much fuming at about 144° and the pressure rose to 60 mm.; a solid charred residue was left. The second fraction redistilled at 144—147°/17 mm.; yield ca. 9 g. The compound was chlorine-free, contained fluorine, and after hydrolysis with aqueous sodium hydroxide solution, it gave a positive test for sulphate ion. For purposes of analysis the 2 : 2'-difluorodiethyl sulphate was redistilled at 145°/18 mm. (Found: F, 20.4. $C_4H_8O_4SF_2$ requires F, 20.0%).

2-Naphthyl 2-Fluoroethyl Ether.—Fluoroethyl sulphate (5.7 g., 0.03 mol.) was added to 2-naphthol (3.6 g., 0.025 mol.) dissolved in sodium hydroxide solution (16 c.c., 10%). No reaction took place in the cold, but after 15 minutes' heating under reflux a yellow oil was produced, which solidified on cooling. The ether was filtered off, washed with sodium hydroxide solution and then with water, and recrystallised from aqueous ethyl alcohol, forming small colourless plates, m. p. 49.5—50° (3.5 g., 78%) (Found: F, 9.75. $C_{12}H_{11}OF$ requires F, 10.0%).

Fluoroacetaldehyde.—Manganese dioxide (69.6 g., 0.9 mol.), sulphuric acid (78.4 g., 0.8 mol.), water (45.0 g., 2.5 mols.) and FEA (64.1 g., 1.0 mol.) were mixed. After a time, the whole became warm spontaneously and liquid began to distil over. This was allowed to proceed, and finally external heat was applied to drive over as much liquid as possible up to 98°. At this stage about 50 g. of distillate had been obtained containing about 6% of aldehyde (determined gravimetrically by means of 2 : 4-dinitrophenylhydrazine). This distillate was concentrated by acidifying it with sulphuric acid, passing a stream of carbon dioxide through the boiling solution, and allowing the vapours to pass up a condenser sloping at an angle of about 45° and having water at 70—75° in its jacket. The condensate (10 g.) thus collected in a carbon dioxide-alcohol trap was again analysed and was found to have an aldehyde content of 30%.

Further concentration of the aqueous solution was carried out as follows. The liquid was distilled slowly through a nearly horizontal tube (slanting downwards away from the flask) containing fine granules of calcium chloride and a small quantity of anhydrous copper sulphate at the far end. The tube was heated in a steam jacket and the issuing vapour was condensed in a carbon dioxide-alcohol trap. Liquid distilled over between 92° and 98°, after which the distillate seemed to be almost entirely water. Repeated distillation of the small quantity of liquid which passed over into the trap did not give a fraction of sharp b. p., even after further drying with calcium chloride. Finally, the liquid, b. p. 89—93°, was selected for analysis (Found: F, 24.1. $C_2H_3OF \cdot H_2O$ requires F, 23.7%).

Gravimetric analyses of the aldehyde group by means of 2 : 4-dinitrophenylhydrazine (Iddles and Jackson, *Ind. Eng. Chem. Anal.*, 1934, **6**, 454) gave the following results, the values being calculated on the assumption that the only aldehyde present was fluoroacetaldehyde: purity of sample, 79, 82, 82.5%. In the first estimation rather less dinitrophenylhydrazine reagent was used than in the second and the third. A check analysis was carried out by the bisulphite-iodine method (Parkinson and Wagner, *ibid.*, p. 434), and this, with the same assumption, indicated a similar percentage of aldehyde. Alternatively, if the hydrate is not present as such, the fluorine content indicates that the liquid contains 78.6% of fluoroacetaldehyde, assuming that none of the impurities contains fluorine.

A more complete removal of water was then attempted. The liquid was distilled slowly over anhydrous copper sulphate, heated in a steam jacket. Distillation was continued until the temperature reached 95°. The liquid which was collected in the trap was rather viscous. It was kept over calcium chloride and was then redistilled several times until a small quantity of liquid of b. p. 57—65° was obtained. On standing, this became more and more viscous and its odour was distinct from the original aldehydic smell. Finally it set to a white solid. The action of heat on the solid gave a liquid of b. p. ca. 60° which went through the same changes on standing. The viscous liquid contained fluorine and slowly gave a precipitate with 2 : 4-dinitrophenylhydrazine. On warming with aqueous sodium hydroxide, the solution became reddish-brown and the characteristic resinous odour associated with aldehydes was obtained.

A sample of the 2 : 4-dinitrophenylhydrazone of the fluoroacetaldehyde was isolated from the distillate of b. p. 89—93°. It was recrystallised from alcohol or from benzene-light petroleum (b. p. 60—80°) as small, orange-red needles. The m. p. was variable † and readings of from 141.5° to 147° were obtained for different samples (Found, for a sample of m. p. 147°: F, 7.34. $C_8H_7O_4N_4F$ requires F, 7.84%).

* These molar proportions were originally used with a view to preparing 2 : 2'-difluorodiethyl sulphate (see p. 774).

† There is a possibility of polymorphism, particularly as polymorphic forms of acetaldehyde 2 : 4-dinitrophenylhydrazone are known (Bryant, *J. Amer. Chem. Soc.*, 1933, **55**, 3201; Martin, Synde, and Bell, *Biochem. J.*, 1941, **35**, 294).

The use of potassium dichromate (in place of manganese dioxide) and sulphuric acid as oxidising agent for the fluoroethanol was attended with even less success as the aqueous distillate from the reaction mixture contained only about 1% of aldehyde.

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