196. *Toxic Fluorine Compounds Containing the* C–F *Link. Part IV.* (a) *2-Fluoroethyl Fluoroacetate and Allied Compounds.* (b) *2 : 2′-Difluorodiethyl Ethylene Dithioglycol Ether.*

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2-Fluoroethyl fluoroacetate (I) is a stable liquid of high toxicity. It is about twice as potent (weight for weight) as either fluoroethanol or methyl fluoroacetate. The synthesis and examination of six related esters is described, none of which is as toxic as (I).

The synthesis of 2 : 2′-difluorodiethyl ethylene dithioglycol ether ("sesqui-fluoro H") is described. It is a liquid which is neither vesicant nor produces " fluoroacetate-like " symptoms in the animal body.

In view of the fact that fluoroethanol is as toxic as methyl fluoroacetate (or as fluoroacetic acid), it seemed worth while preparing a compound in which the " active " parts of these molecules were combined, in the hope of obtaining a compound of increased potency. Such a compound is *2-fluoroethyl fluoroacetate* (I), first prepared and described by us in 1943 (Report No. 4 on Fluoroacetates by McCombie and Saunders, to the Ministry of Supply, April 15, 1943). This ester was readily prepared by the action of fluoroacetyl chloride (Part I, *J.*, 1948, 1773) on fluoroethanol (Part II, this vol., p. 773). It is a stable, mobile liquid possessing an extremely faint odour.

.In accordance with expectation, 2-fluoroethyl fluoroacetate was found to possess greatly enhanced toxic properties. The L.C. 50 by inhalation for rabbits was 0·05 mg./l. This shows that it is about twice as toxic (weight for weight) as fluoroethanol or methyl fluoroacetate. This seems to indicate that the toxicity of 2-fluoroethyl fluoroacetate cannot be due entirely to that of its hydrolysis products according to the equation $CH_2F{\cdot}CO_2{\cdot}CH_2{\cdot}CH_2F + H_2O = CH_2F{\cdot}CO_2H + CH_2F{\cdot}CH_2{\cdot}OH$, for if this were the case the L.C. 50 would be approximately equal to that of either fluoroethanol or methyl fluoroacetate. 2-Fluoroethyl fluoroacetate must therefore possess toxic properties *per se* and this may be connected with the two " active " ends of the molecule. Subcutaneous injection into mice also showed the compound to be about twice as toxic as methyl fluoroacetate. With other animals this difference was not always so apparent.

In order to determine whether this increase in toxicity was necessarily bound up with the presence of two fluorine atoms in the molecule, a series of structurally related esters was prepared and examined. The first obvious simplification was to investigate 2-fluoroethyl acetate (II). [Ethyl fluoroacetate has been shown to have toxic properties almost identical with those of the methyl ester (" MFA "), Part I, *loc. cit.*] By inhalation, (II) produced all the usual " fluoroacetate-like " symptoms, and appeared to be just slightly less toxic than methyl fluoroacetate.

2-Chloroethyl fluoroacetate (III), at a concentration of 0·31 mg./l., killed 92% of a batch of rabbits, guinea-pigs, and rats, and at 0·10 mg./l., 54%. These (and other figures obtained) indicate that the compound was more toxic than MFA, but not as toxic as (I).

It is of interest that (III) and *2-fluoroethyl chloroacetate* (IV) have identical boiling points. The toxicities of these two isomers were also found to be almost identical.

The synthesis of 2-fluoroethyl fluoroacetate mentioned above entails a double fluorination, depending ultimately upon the conversion of chlorohydrin into fluoroethanol and of methyl chloroacetate into methyl fluoroacetate. Attempts were therefore made to prepare (I) by direct fluorination of 2-chloroethyl chloroacetate. By the action of potassium fluoride in a rotating autoclave under pressure on the chloro-ester, only low yields of (I) were obtained. Although the conditions of fluorination were varied considerably, yields higher than about 14% were not obtained. Even then the product was slightly contaminated with the partly fluorinated esters. It seems, therefore, that the double fluorination method is much more satisfactory.

Phenyl fluorothiolacetate (V) had an L.D. 50 of about 80 mg./kg. for subcutaneous injection into mice, hence its toxicity was about one-tenth of that of MFA.

2-*Chloroethyl fluorothiolacetate* (VI) was prepared in the hope that it might combine vesicant properties (cf. " mustard gas ") with the convulsant properties of the fluoroacetates. It was an unpleasant-smelling oil which, however, was devoid of vesicant action. The L.D. 50 for subcutaneous injection into mice was 17·5 mg./kg. It was therefore less toxic than MFA. By inhalation the toxicity was even lower, though this may have been due to its relative nonvolatility (b. p. 100°/29 mm.).

In view of the irritant action exerted by some vinyl and allyl compounds, *allyl fluoroacetate* (VII) was prepared and examined. It proved to be nearly as toxic by inhalation as MFA, and in addition it had an irritant effect on the animals submitted to it. Slow breathing and gasping were shown towards the end of the exposure. Typical " fluoroacetate-type " convulsions were also observed. Subcutaneous injection of a normal saline solution into mice showed that the L.D. 50 was 6 mg./kg., this figure being very close to that for MFA.

The above may be conveniently summarised in the following table :

Ester.	Formula.	Toxicity compared with methyl fluoroacetate.
Ethyl fluoroacetate	$CH_2F{\cdot}CO_2Et$	Similar
2-Chloroethyl fluoroacetate	$CH_2F{\cdot}CO_2CH_2{\cdot}CH_2Cl$ (III.)	Rather higher
2-Fluoroethyl acetate	$CH_3{\cdot}CO_2{\cdot}CH_2{\cdot}CH_2F$ (II.)	Less
2-Fluoroethyl chloroacetate	$CH_2Cl{\cdot}CO_2{\cdot}CH_2{\cdot}CH_2F$ (IV.)	Rather higher
2-Fluoroethyl fluoroacetate	$CH_2F{\cdot}CO_2{\cdot}CH_2{\cdot}CH_2F$ (I.)	Twice
Phenyl fluorothiolacetate	$CH_2F{\cdot}CO{\cdot}SPh$ (V.)	Low
2-Chloroethyl fluorothiolacetate	$CH_2F{\cdot}CO{\cdot}S{\cdot}CH_2{\cdot}CH_2Cl$ (VI.)	Lower by injection ; considerably lower by inhalation
Allyl fluoroacetate	$CH_2F{\cdot}CO_2C_3H_5$ (VII.)	Very slightly less

In view of the powerful vesicant action of 2 : 2′-dichlorodiethyl ethylene dithioglycol ether (" sesqui-H "), we decided in 1943 (Report No. 8 on Fluoroacetates by McCombie and Saunders) to prepare the corresponding fluorine analogue. Earlier workers had failed to achieve the synthesis of this compound. Our preparation consisted in treating bromofluoroethane with sodium hydrogen sulphide. The resulting fluoroethanethiol (VIII) was not isolated, but was converted directly into the sodium mercaptide (IX). This was heated under reflux with an alcoholic solution of bromofluoroethane, and 2 : 2′-*difluorodiethyl ethylene dithioglycol ether* (1 : 8-difluoro-3 : 6-dithiaoctane) (X) thus obtained.

$$\text{(VIII.)}\quad CH_2F{\cdot}CH_2{\cdot}SH \longrightarrow CH_2F{\cdot}CH_2{\cdot}SNa \quad \text{(IX.)}$$

$$2CH_2F{\cdot}CH_2{\cdot}SNa + CH_2F{\cdot}CH_2Br \longrightarrow CH_2F{\cdot}CH_2{\cdot}S{\cdot}CH_2{\cdot}CH_2{\cdot}S{\cdot}CH_2{\cdot}CH_2F \quad \text{(X.)}$$

This reaction is very interesting in view of the unreactivity of the halogen atoms in bromofluoroethane toward many reagents (Part II, *loc. cit.*). It may well be, however, that the reaction is not as simple as that represented above.

In order to prove the identity of (X), it was synthesised in a different manner. Ethylene dibromide was converted into ethylene dithiol, which was then heated with bromofluoroethane in the presence of sodium hydroxide. The yield by this method was small and quantities of dithian were also produced.

EXPERIMENTAL.

2-*Fluoroethyl Fluoroacetate.*—Fluoroacetyl chloride (9·7 g., 0·1 mol.), prepared by the method given in Part II (*loc. cit.*), was added slowly to fluoroethyl alcohol (8·0 g., 0·125 mol.) ; heat was evolved and external cooling was applied. When the addition was complete, the mixture was heated under reflux for 30 minutes, in an oil-bath at 110—120°. The product was then cooled in ice-water and poured into about 15 c.c. of ice-cold 20% aqueous sodium carbonate. The oil which separated was removed, the aqueous layer extracted with ether, the extracts added to the oil, and the whole washed with water and dried (Na_2SO_4). After distillation of the ether, the residue was fractionated and nearly all of it came over at 92—95°/67 mm. ; yield 9·6 g. (77·4%). On redistillation the 2-*fluoroethyl fluoroacetate* had b. p. 90·5—91°/58 mm. (Found : F, 31·1. $C_4H_6O_2F_2$ requires F, 30·6%). It is an almost odourless, mobile liquid, $d_{4^\circ}^{10^\circ}$ 1·3047, $d_{4^\circ}^{15^\circ}$ 1·2975, $d_{4^\circ}^{20^\circ}$ 1·2906, $d_{4^\circ}^{25^\circ}$ 1·2836 ; f. p. −25·4° ; vap. press. : 0°, 0·45 mm. ; 15°, 1·28 mm. ; 30°, 3·29 mm.

2-*Chloroethyl Fluoroacetate.*—Fluoroacetyl chloride (19·3 g., 0·2 mol.) was added slowly to ethylene chlorohydrin (18·1 g., 0·225 mol.) without external cooling. The product was then warmed under reflux in an oil-bath at 100° for 30 minutes, cooled, and carefully added to ice-cold sodium carbonate (25 c.c., 20%). The oil which formed was separated, the aqueous layer extracted with ether, and the ethereal extracts added to the oil, the whole being washed once before being dried (Na_2SO_4). After distillation of the ether, the residual liquid distilled at 104—106°/56 mm. This was redistilled, and the fraction of b. p. 78·5°/15 mm. was collected; yield 21·6 g. (76·9%). 2-*Chloroethyl fluoroacetate* is a colourless mobile liquid, almost insoluble in water, and possessing a very faint odour; b. p. 178—179°/760 mm.; f. p. −8·7° ± 0·5° (Found: C, 34·2; H, 3·86; Cl, 25·1. $C_4H_6O_2ClF$ requires C, 34·2; H, 4·12; Cl, 25·23%); $d_{4°}^{10°}$ 1·3361, $d_{4°}^{15°}$ 1·3295, $d_{4°}^{20°}$ 1·3230, $d_{4°}^{25°}$ 1·3160; vap. press. at 15°, 0·85 mm.

2-*Fluoroethyl Chloroacetate.*—To fluoroethyl alcohol (16·0 g., 0·25 mol.), placed in a flask under reflux, chloroacetyl chloride (33·8 g., 0·2 mol.) was added slowly, very little external cooling being necessary. When the addition was complete, the mixture was heated under reflux on the water-bath for 30 minutes, cooled, and added to aqueous sodium carbonate (25 c.c., 20%). The heavy oil which separated was run off, and the aqueous layer extracted with carbon tetrachloride, the extracts added to the oil, and the whole washed once with water, and dried ($CaCl_2$). The carbon tetrachloride was distilled off, and the 2-*fluoroethyl chloroacetate* distilled under reduced pressure; almost all of it came over at 78—79°/15 mm.; yield 26·1 g. (92·8%); b. p. 178°/760 mm. (b. p. of 2-chloroethyl fluoroacetate is 178—179°/760 mm.) (Found: F, 14·1. $C_4H_6O_2ClF$ requires F, 13·52%).

2-Fluoroethyl chloroacetate was also prepared as follows: Chloroacetic acid (20 g., 0·2 mol.), fluoroethyl alcohol (25 g., 0·4 mol.), and sulphuric acid (2·5 c.c.) were heated under reflux for 6 hours at 120°. The product was cooled, diluted with water, the oily layer separated, and the aqueous layer extracted with ether. The oil and the ether extracts were combined, dried (Na_2SO_4), filtered, and the ether distilled off; almost the entire residue had b. p. 179—181°; yield 23 g.

Fluorination of 2-*Chloroethyl Chloroacetate.*—A mixture of 2-chloroethyl chloroacetate (105 g., 0·67 mol.) and dry, powdered potassium fluoride (116 g., 2 mols.) was heated in a rotating autoclave. The period of heating and the temperature were varied. On cooling, the viscous brown material was extracted with acetone or acetone–ether, the low-boiling solvent distilled off, and the residual liquid fractionated. As no very definite fractions were obtained, the distillate was collected between certain limits, designed to separate as far as possible the difluorinated from the monofluorinated compounds formed. The first distillation was carried out under reduced pressure, up to the temperature of the b. p. of the unchanged ester. This distillate was then fractionated under ordinary pressure. The accompanying table gives some of the results obtained.

Reference data. 2-Chloroethyl chloroacetate, b. p. 202°. 2-Chloroethyl fluoroacetate, b. p. 178—179°. 2-Fluoroethyl chloroacetate, b. p. 178°. 2-Fluoroethyl fluoroacetate, b. p. 158°.

		Final fractionation.					
Temp. of reaction.	Time of heating, hrs.	Temp. (a.)	Yield, g.	Temp. (b.)	Yield, g.	Temp. (c.)	Yield, g.
200—210°	6	Up to 152°	3·6	152—170°	10·7	170—173°	1·9
225	2½	Up to 150	4·5	150—168 (mainly 158—165)	10·9	168—185 (mainly 174—176)	15·4
180—185	10	Up to 150	1·9	150—168	2·2	168—190 (mainly 174—178)	25·5
250—260	3	← ill defined →					
225—230	7	← ill defined →					

The middle fraction (*b*) in each of the above distillations was essentially 2-fluoroethyl fluoroacetate. The compound, however, could not be obtained pure, being always slightly contaminated with the chloro-esters. The best yield was 10·9 g. (13·4%).

2-*Fluoroethyl Acetate.*—Acetyl chloride (24·5 g.) was added slowly to fluoroethyl alcohol (20 g.). Much heat was evolved, and when the reaction subsided, the mixture was heated under reflux for 30 minutes and then distilled. 2-Fluoroethyl acetate was obtained in almost theoretical yield; b. p. 118—119°/760 mm. (Found: F, 18·21. Calc. for $C_4H_7O_2F$: F, 17·92%).

Phenyl Fluorothiolacetate (S-*Fluoroacetylthiophenol*).—A mixture of thiophenol (5 g.) and fluoroacetyl chloride (5 g.; *i.e.*, a slight excess) was heated in an oil-bath, the temperature being raised slowly (1 hour) to 220° and then kept there for 20 minutes. The mixture darkened as the temperature rose. The product was then distilled under reduced pressure, and the fraction of b. p. 120—140°/18 mm. was collected. On standing overnight, this solidified to colourless needle-shaped crystals. The *fluorothiolacetate* was recrystallised from a small volume of alcohol and ice-cooled before being collected; m. p. 36·5—37·5°; b. p. 132°/18 mm.; yield of recrystallised material, 1·7 g. (21%) (Found: S, 18·97; F, 10·95. C_8H_7OSF requires S, 18·82; F, 11·17%). The compound was insoluble in cold water and very soluble in alcohol and in acetone.

2-*Chloroethyl Fluorothiolacetate.*—Fluoroacetyl chloride (10 g., 0·1 mol.) was added to chloroethylthiol (10 g., 0·1 mol.). No reaction occurred in the cold: the mixture was therefore heated at 150° for 30 minutes under reflux. The temperature was then slowly raised to 190° and the heating stopped when no more hydrogen chloride was evolved. On distillation a colourless liquid, b. p. 104—105°/33 mm., was obtained; yield 13·5 g. (63%). The 2-*chloroethyl fluorothiolacetate* thus obtained had an unpleasant odour. It was insoluble in water, soluble in ethyl alcohol, ether, or acetone (Found: Cl, 22·28; F, 11·75; S, 20·40. C_4H_6OSClF requires Cl, 22·67; F, 12·14; S, 20·45%).

Allyl Fluoroacetate.—Fluoroacetyl chloride (20 g., 0·2 mol.) was added slowly from a dropping-funnel to allyl alcohol (11·6 g., 0·2 mol.) in a flask, cooled in ice, and fitted with a reflux condenser. Hydrogen chloride was evolved in the cold and there was a slight rise in temperature. When the evolution of hydrogen chloride ceased, the mixture was heated at 130° (oil-bath) until no more gas came off. The resulting liquid was distilled, and the fraction, b. p. 136—137°/760 mm., was collected and found to be chlorine-free; yield 10·5 g. (46%). *Allyl fluoroacetate* immediately decolourised bromine water in the cold. It was insoluble in water, but readily soluble in alcohol, ether, or acetone (Found : F, 16·45. $C_5H_7O_2F$ requires F, 16·1%).

2 : 2'-*Difluorodiethyl Ethylene Dithioglycol ether*.—(1) Sodium (6·9 g., 0·3 mol.) was dissolved in ethyl alcohol (120 c.c.), and the resultant solution saturated with a stream of hydrogen sulphide (washed with water and dried by passage through calcium chloride). The solution of sodium hydrogen sulphide so obtained was added, in small portions, with shaking, to 1-bromo-2-fluoroethane (38·1 g., 0·3 mol.) dissolved in alcohol (30 c.c.). The whole was then heated under reflux on the water-bath for 15 minutes, cooled, and filtered. To the filtrate was added, slowly, a solution of sodium (4·6 g., 0·2 mol.) in ethyl alcohol (80 c.c.). and the whole added to a solution of 1-bromo-2-fluoroethane (25·4 g., 0·2 mol) in ethyl alcohol (30 c.c.). The mixture was heated under reflux for 15 minutes, cooled, and filtered. The alcohol was distilled from the filtrate under reduced pressure : during the process, a quantity of solid separated. The residual liquid was distilled and came over at 142—146°/22 mm. (Usually a small quantity of dithian sublimed over as well and there was also a higher-boiling liquid left.) The distillate was redistilled, and the fraction, b. p. 138—139°/17 m., was collected; yield 10·4 g. After three distillations the 2 : 2'-*difluorodiethyl ethylene dithioglycol ether* was obtained free from dithian and then had b. p. 139°/17 mm. (Found : S, 35·0; F, 20·9. $C_6H_{12}S_2F_2$ requires S, 34·4; F, 20·4%).

(2) Sodium (14·4 g., 0·625 mol.) was dissolved in alcohol (250 c.c.), and the solution saturated with hydrogen sulphide and added, in small quantities at a time, to ethylene dibromide (49·0 g., 0·25 mol.) in alcohol (30 c.c.). The mixture was heated under reflux for 1½ hours, allowed to cool, and then filtered. To the filtrate was added 1-bromo-2-fluoroethane (63·5 g., 0·5 mol.), followed by powdered sodium hydroxide (20·0 g., 0·5 mol.), the latter in small portions because a moderate amount of heat was generated by the reaction. The mixture was refluxed for 1½ hours, allowed to cool, and then filtered from a large quantity of organic sulphur-containing impurity. The alcohol was distilled off from the filtrate, under reduced pressure, and the residual liquid was fractionated. A considerable quantity of dithian volatilised over. The liquid displayed no constant b. p., but the fraction, b. p. 139—145°/24 mm., was collected and dried (Na_2SO_4). Further redistillations gave 2 : 2'-difluorodiethyl ethylene dithioglycol ether, b. p. 132—138°/15 mm., free from dithian. The yield was small, and it was evident that this method of preparation was inferior to the previous one.

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