358. *Toxic Fluorine Compounds containing the* C–F *Link. Part I. Methyl Fluoroacetate and Related Compounds.*

By B. C. Saunders and G. J. Stacey.

An account is given of the preparation and properties of methyl fluoroacetate, a convulsant poison with a delayed action. Unlike the other methyl halogenoacetates, it does not possess lachrymatory properties. Other fluorine compounds are described which are in general toxic if they contain the F·CH_2·CO· group, but non-toxic if they contain the ·COF group.

Triethyl-lead fluoroacetate combines the sternutatory properties associated with triethyl-lead salts with the convulsant action of the fluoroacetates.

The work described in this series of papers was carried out in Cambridge during the war, and was originally submitted by us to the Ministry of Supply in communications entitled "Fluoroacetates and related compounds". These communications were made available to American workers from the inception of the work. The present paper is concerned mainly with a description of methyl fluoroacetate, $CH_2F·CO_2Me$, and of certain other derivatives of fluoroacetic acid.

In this vol., p. 695 *et seq.* (see also McCombie and Saunders, *Nature*, 1946, **157**, 287, 776), we have described toxic fluorine compounds containing the >POF grouping. Such compounds possessed quick knock-out action and many of them were powerful miotics. Compounds of the

" fluoroacetate " series are characterised by the $\cdot CH_2F$ group. Many of them are highly toxic, with delayed action, but are completely devoid of miotic activity. The action is that of a convulsant poison.

Methyl fluoroacetate was first prepared by Swarts (*Bull. Soc. chim.*, 1896, **15**, 1134) in small yield by the action of silver or mercurous fluoride on methyl iodoacetate. The method is quite impracticable for large-scale work and therefore the preparation was reinvestigated in detail.* Methyl chloroacetate was used in place of the expensive iodoacetate, and a variety of fluorinating agents was tried. It was found that fluorination could be effected by heating methyl chloroacetate in a rotating autoclave with potassium fluoride at 220° for 4 hours. Sodium fluoride on the other hand was almost without action.

Methyl fluoroacetate (MFA) is a liquid of b. p. 104° and f. p. *ca.* — 32° and is almost odourless. During a 10-minute exposure to a lethal concentration of the vapour, small animals did not appear to be affected in any way. After exposure, no very obvious symptoms developed until some 30—60 minutes later (depending upon the concentration). The symptoms shown depended to some extent upon the species, but all animals suffered convulsions, from which a partial recovery was sometimes made. Finally, however, a recurrence of the convulsions would cause death.

The L.C. 50 for rabbits, rats, and guinea-pigs was of the order of 0·1 mg./l. Mice were more resistant. By intravenous injection into rabbits the L.D. 50 was 0·25 mg./kg. The L.D. 50 for subcutaneous injection into mice was found to be of the order of 7—10 mg./kg. MFA was also found to be toxic by absorption through the skin, but less so than by other routes. When placed on the clipped backs of rabbits the L.D. 50 was about 20 mg./kg. Free evaporation of the drops was permitted. The animals showed the usual symptoms.

It is noteworthy that a massive concentration of the vapour of methyl chloroacetate (1 : 1,000; 4·85 mg./l.) did not kill any animals.

MFA is practically odourless. When four of us were exposed to a concentration of 1 : 1,000,000 in a 10 m.^{3} chamber, we were unable to detect the compound. Even at 1 : 100,000 (30 seconds for reasons of safety) the compound was found to possess only a faint fruit-like odour indistinguishable from that of many harmless esters not containing fluorine.

The fluorine atom in methyl fluoroacetate (and in many other compounds containing the $CH_2F\cdot$ group described in this series of papers) is very firmly bound. When MFA was boiled with 20% alcoholic potassium hydroxide for 5 minutes, no free fluoride was formed. Even after some 20 hours, there was only about a 50% conversion into potassium fluoride. From the inception of this work we have found the most satisfactory sensitive qualitative test for fluorine in an organic compound to consist in the formation of "oily droplets" when it is heated with a mixture of concentrated sulphuric acid and potassium dichromate.

It was obviously of interest to determine whether other esters of fluoroacetic acid would prove to be more or less toxic than the methyl ester. In the fluorophosphonate series, for example, we found that esters of secondary alcohols were far more potent than those of primary alcohols; for instance, di*iso*propyl fluorophosphonate (I) was a compound of outstanding activity (Saunders and Stacey, this vol., p. 696). Accordingly ethyl, n-*propyl*, and iso*propyl*

$(CHMe_2\cdot O)_2POF$	$CHMeF\cdot CO_2Me$	$CMe_2F\cdot CO_2Me$
(I.)	(II.)	(III.)

fluoroacetates were prepared by heating the corresponding esters of chloroacetic acid in the rotating autoclave with potassium fluoride. The toxicity figures of these esters were very similar to those of methyl fluoroacetate.

In the fluorophosphonate series, we found that the diphenyl ester (this vol., p. 1011) was relatively non-toxic. *Phenyl fluoroacetate*, however, was toxic with an L.D. 50 of 6—10 mg./kg. for subcutaneous injection into mice. The symptoms were similar to those displayed by methyl fluoroacetate.

It was next important to determine the effect of altering the groups adjacent to the fluorine atom. Thus *methyl α-fluoropropionate* (II) and *α-fluoro*iso*butyrate* (III) were prepared. Both these compounds were non-toxic. The first, for example, at a concentration of 1 : 20,000 (0·24 mg./l.) killed 0/23 of a batch of 3 rabbits, 4 guinea-pigs, 6 rats, and 10 mice. The second at the same concentration killed only 2/23.

In Report No. 5 on fluoroacetates to the Ministry of Supply (May 30th, 1943) we described the

* Some of the early work in connexion with methyl fluoroacetate was carried out in collaboration with F/O Sporzynski, Prof. Briscoe, and Prof. Emeléus. We acknowledge with thanks their valuable help.

preparation of *methyl* 1 : 3-*difluoroacetoacetate*, $CH_2F{\cdot}CO{\cdot}CHF{\cdot}CO_2Me$, in 10% yield by the action of sodium on methyl fluoroacetate. Later (Report No. 10, July 14th, 1944), we reported that if the condensation were carried out in the presence of methyl alcohol, the yield of methyl difluoroacetoacetate could be increased to 23%, and allowing for recovered methyl fluoroacetate the overall yield was 35%.

Fluoroacetyl chloride, $CH_2F{\cdot}COCl$, was prepared as a useful fluoroacetylating agent in synthetic work. It was interesting to compare its toxicity with the isomeric chloroacetyl fluoride. The former possessed a toxicity comparable with that of methyl fluoroacetate, whereas the latter was relatively non-toxic. This is readily understandable in that fluoroacetyl chloride gives the toxic fluoroacetic acid, whereas chloroacetyl fluoride hydrolyses to chloroacetic acid and the relatively non-toxic (at the concentrations employed) hydrogen fluoride. Fluoroacetyl fluoride also possessed a toxicity comparable with that of fluoroacetyl chloride or of methyl fluoroacetate, again showing that the ·COF group contributed practically nothing. Acetyl fluoride was also non-toxic.

Goswami and Sarkar (*J. Indian Chem. Soc.*, 1933, 537) claim to have prepared methyl and ethyl fluoroformates by the action of thallium fluoride on the corresponding chloroformates. These fluoroformates were described as powerful lachrymators. We found that no reaction took place between potassium fluoride and ethyl chloroformate in boiling carbon tetrachloride or nitrobenzene. Ethyl fluoroformate could, however, be produced by the action of potassium fluoride on ethyl chloroformate by using the autoclave technique. It was found not to have the lachrymatory properties claimed for it, and was non-toxic in comparison with MFA. This non-toxicity was to be expected, as the fluoroformate contains the ·COF and not the $CH_2F{\cdot}$ group.

Chloromethyl esters are obtained quite readily by the action of paraformaldehyde on the appropriate acid chloride in the presence of a small quantity of zinc chloride as catalyst (Ulich and Adams, *J. Amer. Chem. Soc.*, 1921, **43**, 662). It therefore seemed worth while to try the action of paraformaldehyde on fluoroacetyl fluoride, but the only product which could be isolated was a low-melting solid which appeared from its reactions to be *methylene bisfluoroacetate*, $CH_2(O{\cdot}CO{\cdot}CH_2F)_2$. The compound was submitted for physiological tests and it was shown that the L.D. 50 for subcutaneous injection into mice was about 10 mg./kg. Subcutaneous injection into rats with doses of 2·5, 5, and 10 mg./kg. all killed 1/1.

Sodium fluoroacetate was prepared with the idea of obtaining a stable water-soluble compound containing the $CH_2F{\cdot}CO{\cdot}$ group, suitable for feeding experiments. The method of obtaining this salt is new, and is described in detail in the Experimental section. It consists essentially in adding cold aqueous sodium hydroxide to methyl fluoroacetate and evaporating the solution.

Fluoroacetic anhydride, which was readily prepared by the action of fluoroacetyl chloride on sodium fluoroacetate, was a mobile liquid of b. p. 89°/12 mm. It was rather more toxic by inhalation than MFA (weight for weight).

It has been shown that trialkyl-lead salts have marked sternutatory action when dispersed as a particulate cloud (McCombie and Saunders, *Nature*, 1947, **159**, 491). *Triethyl-lead fluoroacetate*, $CH_2F{\cdot}CO_2PbEt_3$, was therefore prepared with the idea of combining sternutatory action with " fluoroacetate-like " activity. The compound, a stable, highly crystalline material, was readily prepared by the action of fluoroacetic acid on tetraethyl-lead in the presence of silica gel. As a sternutator it proved to be similar in action to that of the majority of other triethyl-lead salts of organic acids. Eight observers were exposed for 10 minutes to a nominal concentration of 1 part in 10,000,000 (*i.e.*, 1·7 mg./m.^{3}) obtained by spraying an ether–alcoholic solution of the material. They all suffered from intense irritation of the nose and throat within the first minute, and five reported pains in the chest. Subcutaneous injection into mice gave an L.D. 50 of about 15 mg./kg. and produced the usual " fluoroacetate-like " symptoms.

Glycol bisfluoroacetate was prepared with a view to obtaining a toxic fluorine compound (containing the $CH_2F{\cdot}CO$ group) which would have a high b. p. and be soluble in oils and fats. [When it was sprayed into a chamber, 4/13 animals (rats, guinea-pigs, and rabbits) were killed at 1 : 40,000 for 10 mins. and exhibited the convulsions characteristic of MFA. This low toxicity may be due to low volatility.] The compound was found to be quite soluble in hot olive oil and to form in the cold a solution of sufficient concentration for animal feeding experiments. Injection of the solution (5 mg./c.c.) into the stomach with a catheter, showed that the L.D. 50 for rats was about 2·2 mg./kg.

Cholesteryl fluoroacetate was made in an attempt to discover whether a combination of fluoroacetic acid and some biologically important compound might give a product of increased toxicity and so give some clue as to the fate of fluoroacetic acid (or of MFA) in the body. This

compound, however, placed considerable limitations upon injection experiments owing to its low solubility in non-toxic solvents. It appeared, however, to be considerably less toxic than MFA.

In view of the well-known pharmacological action of aspirin, it was thought that the fluorine analogue, O-(*fluoroacetyl*)*salicylic acid*, might be of considerable interest. The compound was readily made by acylation of salicylic acid by fluoroacetyl chloride in the presence of pyridine. The L.D. 50 for subcutaneous injection into mice was approximately 15 mg./kg. After injection the mice went into a drugged sleep, and died overnight.

Experimental.

Methyl Fluoroacetate.—Methyl chloroacetate (108·5 g., 1 mol.) and neutral anhydrous potassium fluoride (70 g., 1·2 mols.) were mixed and heated (with glass marbles) in an inclined rotating autoclave at a constant temperature. A speed of about 280 r.p.m. together with the glass marbles ensured thorough mixing. At the end of a specified time the autoclave was allowed to cool and the contents were broken up and washed out with ether, and the inorganic salts filtered off. The filtrate was then placed in a flask with an efficient fractionating column 80 cm. long. The ether was distilled off slowly. The temperature then rose rapidly to 104°, and the fraction, b. p. 104—110°, was collected (methyl fluoroacetate). The temperature again rose rapidly to 125°, and the fraction, b. p. 125—132°, was collected (unchanged methyl chloroacetate). Below are tabulated the results of experiments employing different temperatures and times. For all subsequent work the conditions of experiment No. 5 were employed.

The fraction, b. p. 104—110°, on refractionation came over almost entirely at 104·5° (Found: F, 20·65. Calc. for $C_3H_5O_2F$: F, 20·65%) (for method of fluorine analysis see Chapman, Heap, and Saunders, *Analyst*, in the press). Methyl fluoroacetate is a mobile liquid of f. p. — 32°, $d_4^{20°}$ 1·1744, $n_D^{20°}$ 1·3679, soluble in water to the extent of about 15%. Hydrolysis according to the equation $CH_2F{\cdot}CO_2CH_3 + H_2O = CH_2F{\cdot}CO_2H + CH_3{\cdot}OH$ was found to be 50% complete at room temperature in about 14 days. The ester was completely miscible with alcohol, ether, acetone, light petroleum (b. p. 40—60°), carbon tetrachloride, benzene, glacial acetic acid, and 2 : 2′-dichlorodiethyl sulphide, and partly soluble in carbon disulphide.

Expt.	Temp.	Duration (hrs.).	B. p. 104—110° (g.).	B. p. 125—132° (g.).	Residue, b. p. >132° (g.).	Wt. of inorganic salts filtered off (g.).	Yield (actual), %.	Yield (net),* %.	Remarks.
1	140°	24	1·2	85·3	5·6	70	1·3	6·1	—
2	150	20	3·6	81·3	7·7	72	3·9	15·6	—
3	160	15	5·6	78·5	6·7	73	6·1	22·0	Press. *ca.* 2 atm.
4	190	10	35	40·5	9·1	86	38·0	60·7	Press. *ca.* 10 atm.
5	220	4	50·1	4·5	9·4	99	54·5	59·6	Press. *ca.* 12 atm.; about 1 atm. in cold at end of run
6	250	2	43·8	4·8	9·6	98	37·8	39·6	Press. *ca.* 30 atm.; 4 atm. in cold at end of run

* Allowing for recovery of methyl chloroacetate.

Highest actual yield at 220°
,, net ,, 190° (but of course more KF required per g. of MFA).

[N.B.—Because of the non-detectability of MFA by smell, respirators should be used when cleaning out the autoclave after a run.]

Ethyl Fluoroacetate.—Ethyl chloroacetate (122·5 g., 1 mol.) and dry potassium fluoride (70 g., 1·2 mols.) were heated in a rotating autoclave for 4 hours at 220°. The product was extracted with ether, the ether distilled off, and the residue fractionated. The fluoroacetate (20 g.) came over between 117° and 125°, the unchanged material (72·6 g.) between 125° and 144°, and a small residue (8·5 g.) was left. The fluoroacetate was redistilled and had b. p. 117—121°. It was chlorine-free (Found: F, 18·0. Calc. for $C_4H_7O_2F$: F, 17·9%).

n-*Propyl Fluoroacetate.*—The chloroacetate (cf. Shreiner, *Annalen*, 1879, **197**, 8, who gave very meagre details) was prepared as follows: Chloroacetic acid (567 g.) and *n*-propyl alcohol (540 g.) were refluxed for 6 hours with a stream of dry hydrogen chloride passing through the mixture. Two layers separated: the lower ester layer was treated with anhydrous sodium carbonate, filtered, and dried (Na_2SO_4) (A). The upper layer was saturated with sodium carbonate and separation into two layers took place; the lower of these was dried (Na_2SO_4) (B). A and B were combined and distilled; b. p. 156—158°; yield 450 g. (69·1%).

n-Propyl chloroacetate (1 mol.) and dry powdered potassium fluoride (1·2 mols.) were mixed and heated to 200° for 4½ hours in a rotating autoclave. The product was then extracted with dry ether and distilled through a 50-cm. fractionating column. The n-*propyl fluoroacetate* had b. p. 135—137° (Found: F, 15·62. $C_5H_9O_2F$ requires F, 15·8%).

iso*Propyl Fluoroacetate.*—The chloroacetate was prepared in a similar manner to the normal compound; b. p. 148·5°, yield 71%.

Thence the *fluoroacetate* was prepared by means of potassium fluoride in a rotating autoclave; b. p. 124°, yield 42% (Found: F, 15·61%).

Phenyl Fluoroacetate.—Phenol (18·8 g.) was dissolved in dry pyridine (15 c.c.) and fluoroacetyl

chloride (20 g., 5% excess) was added slowly, the temperature being kept at about 50°. The mixture was then heated on a water-bath for 10 minutes, and poured into water. Solid at once separated; yield 30 g. (100%). The *fluoroacetate* recrystallised from aqueous alcohol in lustrous colourless plates, m. p. 63·5—64·0° (Found: F, 12·45. $C_8H_7O_2F$ requires F, 12·34%).

Methyl α-Fluoropropionate.—Methyl α-bromopropionate was prepared in 73% yield by Walker's method (*J.*, 1895, **67**, 922). The bromopropionate (70 g.) and potassium fluoride (35 g.) were heated in a rotating autoclave at 200—210° for 7 hours. The mixture was then extracted with ether, filtered, the ether distilled off, and the residue fractionated. The following fractions were obtained: (*a*) 100—120°, (*b*) 120—140° (steady rise to small amount of unchanged bromo-ester). The first fraction on redistillation gave *methyl α-fluoropropionate*, b. p. 106·5—108·5° (Found: C, 45·6; H, 6·9; F, 18·0. $C_4H_7O_2F$ requires C, 45·3; H, 6·6; F, 17·9%).

Methyl α-Bromoisobutyrate.—Red phosphorus (12·5 g., 0·4 mol., dried over phosphoric oxide) and *iso*butyric acid (70·4 g., 0·8 mol.) were mixed, and bromine (319·6 g., 4 mols., dried over concentrated sulphuric acid) was added slowly. After the addition was complete, the mixture was heated under reflux on the water-bath for 5 hours. The water condenser was then replaced by a calcium chloride tube, and the mixture heated for another hour. It was then cooled and carefully mixed with methyl alcohol (128 g., 4 mols.). After addition to a saturated solution of sodium carbonate cooled in ice–salt, a heavy oil separated. The aqueous layer was extracted with ether, and the extract added to the oil. The mixture was washed in turn with 10% aqueous sodium bisulphite, aqueous sodium carbonate, and water, and then dried (Na_2SO_4). After removal of the ether the residual liquid came over almost entirely at 53—55°/21 mm.; yield 121·9 g. (84·2%).

Methyl α-Fluoroisobutyrate.—A mixture of methyl α-bromo*iso*butyrate (72·4 g., 0·4 mol.) and dry silver fluoride (76·2 g., 0·6 mol.) was refluxed, with stirring, for 3 hours. It was then cooled, and the solid filtered off. The solid was washed with ether, which on being added to the filtrate, precipitated more solid, necessitating further filtration. After drying (Na_2SO_4), the ether was distilled off, and more solid filtered off. The distillate of b. p. 24—30°/24 mm. was collected and redistilled at ordinary pressure; b. p. 108—109°. After a further distillation, the fraction of b. p. 108—109° was collected, but was still probably not quite pure. The *ester* contained fluorine (Found: C, 52·0; H, 7·5. $C_5H_9O_2F$ requires C, 50·0; H, 7·52%).

Ethyl 1:3-Difluoroacetoacetate.—(a) *Condensation using sodium in presence of methyl alcohol.* MFA (75 g.) and methanol (2 c.c.) were placed in a flask and sodium wire (7·5 g.) was added. The reaction began immediately and was complete within 30 minutes. It was necessary to control the reaction by cooling in ice–water. After all the sodium had reacted, a mobile liquid remained which was acidified with glacial acetic acid and then diluted with water to *ca.* 300 c.c. The liquid was extracted with ether, the extract dried (Na_2SO_4), and the ether distilled off. The residue was fractionally distilled, and the *difluoroacetoacetate* collected at 97°/14 mm.; yield 14 g. (23%). MFA recovered, 25 g.; overall yield of the difluoroacetoacetate, 35% (Found: C, 39·3; H, 4·06; F, 24·9, 24·84. $C_5H_6O_3F_2$ requires C, 39·5; H, 4·95; F, 25·0%).

(b) *Condensation using sodium.* Sodium wire (7·5 g.) was added to freshly distilled MFA (75 g.). The reaction began after 5—40 minutes and was moderated initially by cooling in ice. When no more sodium remained (*ca.* 100 minutes) the dark brown semi-solid mass was dissolved in water (300 c.c.), acidified with glacial acetic acid (5 c.c.), and extracted three times with a total of 250 c.c. of ether. The extract was dried (Na_2SO_4), and after the ether had been distilled off, the resulting liquid was fractionated under reduced pressure. Two fractions were obtained: (1) b. p. 30—35°/20 mm. (recovered MFA); (2) b. p. 103—105°/20 mm. (mainly difluoroacetoacetate). Fraction (1) was redistilled, giving MFA (25 g.) b. p. 103—105°/760 mm.; (2) was redistilled, giving the acetoacetate (9 g., 15%), b. p. 104°/20 mm. Yield of ester allowing for recovered MFA, 22·5%.

Notes. (i) Unless all the dark brown semi-solid was dissolved in water, the yield was reduced. (ii) The MFA in fraction (1) usually contained acetic acid which was removed by shaking with the minimum amount of saturated sodium carbonate solution. If excess of sodium carbonate was used some MFA was lost.

(c) *Condensation using sodium methoxide.* Sodium methoxide (20 g.) was added slowly to MFA (70 g.), and the mixture heated under reflux for 6 hours in an oil-bath. (The addition of MFA to the methoxide caused charring.) The resulting mixture was acidified, extracted with ether, the ether extract dried (Na_2SO_4), and the residue distilled. No appreciable quantity of difluoroacetoacetic ester was obtained.

Fluoroacetic Acid.—A few drops of phenolphthalein solution were added to a mixture of methyl fluoroacetate (46·0 g., 0·5 mol.) and water (100 c.c.) and then powdered barium hydroxide octahydrate (78·9 g., 0·25 mol.) was added in small portions, the mixture being mechanically stirred after each addition until the alkaline reaction had disappeared. The resultant liquid was then made acid, if necessary, by the addition of a few drops of methyl fluoroacetate, filtered, and the filtrate concentrated to about 100 c.c. on a water-bath. The liquid was cooled, and methylated spirit (500 c.c.) added in order to precipitate the barium fluoroacetate, which was filtered off, drained, and dried, but not recrystallised; yield 69·0 g. (95·0%).

Dry barium fluoroacetate (58 g., 0·2 mol.) was slowly added to 100% sulphuric acid (122·5 g., 1·25 mols.). On distillation under reduced pressure, using a wide air-condenser, the fluoroacetic acid came over between 83° and 100°/17 mm. and crystallised immediately. It was redistilled at atmospheric pressure and came over at 167—168·5°; yield 29·5 g. (94·2%); colourless needles, m. p. 31—32° (Found: F, 24·3. Calc. for $C_2H_3O_2F$: F, 24·4%). These yields are considerably higher than those obtainable by Swarts's original method (*loc. cit.*).

Fluoroacetyl Chloride.—Phosphorus pentachloride (93·8., 0·45 mol.) was placed in a 250-c.c. round-bottomed flask and cooled in ice–water. The flask was fitted with a reflux condenser and an inlet tube connected to a flask which could be rotated to allow the just molten fluoroacetic acid (31·2 g., 0·4 mol.) to be added in small quantities. At first the reaction was vigorous, but later, external cooling could be discontinued. After the addition was completed, the mixture was heated under reflux for

45 mins. in an oil-bath at 100°. The liquid was then distilled through a 30-cm. fractionating column, and the fraction of b. p. 72—80° collected. On redistillation, most of it came over at 71·5—73°/760 mm.; yield, 27 g. *Fluoroacetyl chloride* is a liquid with a pungent odour and is readily hydrolysed by water (Found: F, 19·7. C_2H_2OClF requires F, 19·7%).

Chloroacetyl Fluoride.—(*a*) A mixture of chloroacetyl chloride (113 g.) and dry potassium fluoride (69·6 g., 1·2 mols.) was heated for various times at various temperatures (see below) in a rotating autoclave. A slight pressure always remained in the apparatus at the end of the experiment, and the material was always charred, but excessive decomposition did not take place. The solid was extracted with xylene and fractionated, the fraction of b. p. 70—90° being collected and refractionated (Found: F, 19·6. Calc. for C_2H_2OClF: F, 19·7%).

200° for 45 mins.	Yield 32·0 g. (33·2%).	B. p. 73—75°/760 mm.	
200° ,, 20 ,,	,, 43·7 g. (45·2%).	,, 73—76/	,,
170° ,, 30 ,,	,, 53·7 g. (55·6%).	,, 73—76/	,,

(*b*) By heating chloroacetyl chloride under reflux with potassium fluoride in nitrobenzene for 6 hours a 6·8% yield of chloroacetyl fluoride was obtained.

(*c*) By heating chloroacetyl chloride, potassium fluoride, and benzoyl chloride at about 150° for 1 hour, a 15·8% yield of chloroacetyl fluoride was obtained. The compound had been prepared by Traube and Krahmer (*Ber.*, 1919, **52**, 1079) in 15% yield by the action of fluorosulphonic acid on chloroacetic acid.

Fluoroacetyl Fluoride.—(*a*) A mixture of fluoroacetic acid (23·4 g., 0·3 mol.) and dry potassium fluoride (23·2 g., 0·4 mol.) was placed in a flask fitted with dropping-funnel and reflux condenser through which water at 60° was passing. Fitted to the top of this condenser was a thermometer in a still-head which led to a long water-condenser and a trap, closed by a calcium chloride tube and cooled in an ice–salt mixture. The mixture in the flask was gently heated and stirred while benzoyl chloride (42·2 g., 0·3 mol.) was added from the dropping-funnel during 40 mins. Fuming and charring occurred and a small quantity of liquid collected in the trap, the thermometer in the still-head registering 32—40°. After all the benzoyl chloride had been added, the mixture was heated for a few minutes, but no more liquid distilled over and the benzoic acid present began to sublime. The *fluoride* collected was redistilled and had b. p. 50·5—51°; yield 4·1 g. (17·1%) (Found: F, 48·2. $C_2H_2OF_2$ requires F, 47·5%). It was advantageous to have a solvent (*e.g.*, nitrobenzene) present in the original mixture to facilitate mixing.

(*b*) A mixture of fluoroacetyl chloride (19·3 g., 0·2 mol.) and dry, powdered antimony trifluoride (17 g., 0·1 mol.) was heated gently under reflux for 3 hours. Some fuming occurred during this heating. The mixture was then cooled, the residual solid filtered off, and the filtrate distilled. A fraction was collected between 44° and 51° (mostly 50—51°) and a higher-boiling chloride was left behind; yield of product 10·3 g. (64·4%). On redistillation, the liquid had b. p. 50·5—51°, and was proved to be fluoroacetyl fluoride.

Ethyl Fluoroformate.—A mixture of ethyl chloroformate (108·5 g., 1 mol.) and dry potassium fluoride (69·6 g., 1·2 mols.) was heated in a rotating autoclave for 3 hours at 100—105°. After cooling, a pressure of 5 atm. still remained. The product was extracted with pure dry xylene and filtered. The filtrate was carefully fractionated using an 80-cm. column. Two fractions (*a*) and (*b*) were collected before the xylene started to come over: (*a*) b. p. 40—60°, 26 g.; (*b*) b. p. 60—105°, mainly unchanged chloroformate. The fraction (*a*) was twice redistilled, and *ethyl fluoroformate* of b. p. 55·5° was collected. This fraction was chlorine-free, and reacted vigorously with aqueous ammonia (Found: F, by refluxing with sodium in alcohol, 20·4, 20·8. $C_2H_5O_2F$ requires F, 20·65%).

Action of Paraformaldehyde on Fluoroacetyl Fluoride.—This was an attempt to obtaine fluoromethyl fluoroacetate. It seemed that none of this compound was formed but methylene bisfluoroacetate was isolated. Descudé (*Compt. rend.*, 1903, **136**, 1566) obtained some of the chloro-analogue together with some chloromethyl chloroacetate in the corresponding reaction with chloroacetyl chloride.

A mixture of paraformaldehyde (3·6 g., 0·12 mol.) and fluoroacetyl fluoride (9·6 g., 0·12 mol.), together with a few pieces of zinc chloride, was heated on the water-bath until the solid disappeared (about 3 hours). After cooling, the liquid was transferred to a distilling flask. At the beginning of distillation, it seemed that some gaseous decomposition products were being evolved. As the temperature rose, distillate began to come over and solidified on cooling. Distillation was continued up to 180°/15 mm., and the solid material thus obtained was recrystallised from light petroleum (b. p. 40—60°), it being found advantageous to use a continuous extraction apparatus owing to the low solubility of the product in this solvent. With benzene, the substance became deep purple during attempted recrystallisation. The *methylene bisfluoroacetate* consisted of small colourless needles, m. p. 57° (Found: F, 22·9. $C_5H_6O_4F_2$ requires F, 22·6%).

Sodium Fluoroacetate.—To methyl fluoroacetate (46·0 g., 0·5 mol.) suspended in water (100 c.c. containing a few drops of phenolphthalein), sodium hydroxide (0·5 mol., 20 g. in 100 c.c. water) was added slowly. The mixture was kept well stirred, and the rate of addition governed by the disappearance of the red coloration. When the addition of sodium hydroxide was complete, a few more drops of MFA were added to render the solution acid. It was then evaporated on the water-bath until crystallisation started, cooled, and the solid filtered off. More solid was obtained from the filtrate by the addition of alcohol; total yield 45·5 g. (91·0%) (Found: F, 19·0. Calc. for $C_2H_2O_2FNa$: F, 19·0%). This was characterised as p-*nitrobenzyl fluoroacetate* as follows. *p*-Nitrobenzyl bromide (0·9 g.), dissolved in alcohol (10 c.c.), was added to a solution of sodium fluoroacetate (0·3 g.) in the minimum amount of water. The mixture was heated under a reflux condenser for 2 hours and allowed to cool; the solid was collected by filtration, and crystallised from ethanol as long needles, m. p. 76° (Found: C, 50·9; H, 4·10; N, 6·7. $C_9H_8O_4NF$ requires C, 50·7; H, 3·8; N, 6·6%).

Fluoroacetic Anhydride.—Sodium fluoroacetate (15 g., 0·15 mol., dried in a vacuum over sulphuric acid) was placed in a Claisen flask, and fluoroacetyl chloride (12·1 g., 0·125 mol.) added slowly from a dropping-funnel; the heat developed was small. The mixture was then refluxed in an oil-bath at 110—120° for 1½ hours. The contents were distilled under reduced pressure, and initially the distillate

was collected in one fraction. This started to come over at 108°/41 mm. but when the temperature reached 110° the pressure began to fall, and finally a b. p. of 106° 32 mm. was recorded; yield 13·4 g. (77·7%). On redistillation, most of the liquid came over at 88—89°/12 mm. The *anhydride* was found to be chlorine-free (Found: F, 28·0. $C_4H_4O_3F_2$ requires F, 27·52%).

Triethyl-lead Fluoroacetate.—To fluoroacetic acid (2·3 g., 0·03 mol.) dissolved in absolute ether (5 c.c.) were added tetraethyl-lead (9·7 g., 0·03 mol.) and a few pieces of silica gel. After 5 mins. warming on a water-bath, a white solid began to crystallise out, and at the end of 15 mins. the mixture was almost solid. After standing at room temperature for a few hours, the white crystals (almost pure) were drained thoroughly at the filter-pump; yield, 8·8 g. (79·1%). Recrystallised from toluene containing a small quantity of ethyl alcohol, *triethyl-lead fluoroacetate* had m. p. 180·5° (decomp.) (Found: Pb, 55·5. $C_8H_{17}O_2FPb$ requires Pb, 55·8%). A slight yellow coloration developed at about 165°, but this disappeared before melting occurred.

Glycol Bisfluoroacetate.—Freshly distilled glycol (b. p. 194°, 5 g.) was placed in a small Claisen flask fitted with a water-condenser and a dropping-funnel in the two vertical arms, the side arm being closed. Fluoroacetyl chloride (16 g.) was added slowly from the dropping-funnel, the flask being kept cool. The product was then heated to 100° (oil-bath) and then distilled, two fractions being obtained; the first had b. p. 85—90°/22 mm. (unchanged glycol, 3 g.), and the second had b. p. 140—141°/11 mm. and was the required *ester* (5·3 g.) (Found: F, 21·1. $C_6H_8O_4F_2$ requires F, 20·9%). The compound is a stable, viscous, colourless liquid, insoluble in water, soluble in the usual organic solvents.

Cholesteryl Fluoroacetate.—Fluoroacetyl chloride (10 g.) was added to cholesterol (5 g.), and the mixture heated under reflux on a water-bath for 1 hour. The cholesterol dissolved and the solution developed a blue and then a red-brown coloration. After cooling, a mixture of water (25 c.c.) and alcohol (25 c.c.) was added to precipitate the product and to hydrolyse unchanged fluoroacetyl chloride (cooling required). The solid was then filtered off, washed well with water to remove fluoroacetic acid, and the *cholesteryl fluoroacetate* was recrystallised from ethyl alcohol; yield, (3·7 g., 62%), m. p. 144—144·5°. The condensation was also carried out in the presence of pyridine, and an identical product was obtained, m. p. 144·5°; mixed m. p. with cholesterol (m. p. 148°), 120—130°. The compound was insoluble in water or cold alcohol, readily soluble in chloroform, and more readily soluble than cholesterol in cold acetone. It was found to be chlorine-free (Found: F, 3·98, 4·10. $C_{28}H_{45}O_2F$ requires F, 4·17%). Hydrolysis with 0·1N-alcoholic soda showed it to contain one fluoroacetyl group; the product of hydrolysis had m. p. 146·5° and did not contain fluorine: it was therefore cholesterol.

O-(*Fluoroacetyl*)*salicylic Acid.*—Salicylic acid (10 g.) was dissolved in pyridine (7 c.c.) and then fluoroacetyl chloride (9·6 c.c.) was added in small portions, a considerable amount of heat being evolved. The product was heated on a boiling water-bath for 7 minutes, and then slowly poured into cold water (300 c.c.). The heavy oil which separated crystallised after vigorous stirring and scratching for 20 minutes (11 g., 85%). After being thoroughly dried in a desiccator it was recrystallised twice from benzene; m. p. 131·6 (5·3 g., 40%) (Found: F, 9·76. $C_9H_7O_4F$ requires F, 9·5%). The *acid* was slightly soluble in cold water, readily soluble in hot water and in cold dilute sodium hydroxide solution. It gave no coloration with ferric chloride (absence of phenolic hydroxyl group).

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UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, December 5th*, 1947.]