314. *Toxic Fluorine Compounds containing the* C–F *Link. Part VI. ω-Fluorocarboxylic Acids and Derivatives.*

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The synthesis of hitherto undescribed ω-fluorocarboxylic acids and esters, of the type $F\cdot[CH_2]_n\cdot CO_2R$, is described. It has been established that if n is odd, the compound is toxic and causes fluoroacetate-like symptoms in animals. If n is even no such toxic properties are shown. This remarkable alternation of properties is discussed in the light of the β-oxidation theory of long-chain carboxylic acids. This theory does not, however, account for all the facts observed.

The toxicity is often greatly enhanced if $R = CH_2\cdot CH_2F$ compared with R = Me or Et. This difference is less obvious when the chain is long ($n = 7$) and is negligible with the ω-fluorodecoates ($n = 9$).

Previous investigations in this series of papers (Saunders *et al.*, Parts I to V) have shown that any compound which can give rise to fluoroacetic acid (or the fluoroacetate ion) either by hydrolysis or by oxidation (or both) is toxic. The toxic grouping is thus $F\cdot CH_2\cdot CO$, and any substitution in this radical destroys the toxicity. We had reached this conclusion by May 1943 (McCombie and Saunders, Report No. 5 on Fluoroacetates to Ministry of Supply, May 30, 1943; also Carpenter, Kilby, McCombie, and Saunders, Report to Ministry of Supply, January 8, 1944). American workers later showed (private communication) that esters of β-fluoropropionic acid were non-toxic, whereas esters of γ-fluorobutyric acid were toxic. In 1944 (Saunders, Ministry of Supply Meeting, June 1, 1944, and Report No. 11 on Fluoroacetates to Ministry of Supply, August 8, 1944) we reported the synthesis of *ethyl 5-fluoropentanecarboxylate*, $F\cdot[CH_2]_5\cdot CO_2Et$ (I). This was a stable, colourless, liquid and we showed that it possessed very potent toxic properties of the " fluoroacetate " type. By subcutaneous injection of the propylene glycol solution into mice the L.D. 50 was 4 mg./kg. Methyl fluoroacetate (II) may be taken as a convenient standard (Part I, *J.*, 1948, 1773) and has an L.D. 50 of about 6 mg./kg. for saline solutions, and 15 mg./kg. for propylene glycol solutions.* Therefore ethyl 5-fluoropentanecarboxylate was about 7 times as toxic as methyl fluoroacetate (molecule for molecule).

In Part IV (this vol., p. 916) it was shown that 2-fluoroethyl fluoroacetate was about twice as toxic as methyl fluoroacetate (MFA) by inhalation. By analogy then it seemed that *2-fluoroethyl 5-fluoropentanecarboxylate* (III) might be a compound of exceptionally high toxicity. This proved to be correct, for its L.D. 50 for subcutaneous injection into mice was 2·5 mg./kg., *i.e.*, it is about 11 times as toxic as MFA (per molecule) by this route and in propylene glycol as solvent.

The comparison of the toxicities of compounds I, II, and III by intravenous injection into rabbits also revealed a similar gradation, as shown herewith:

	L.D. 50, mg./kg.
Methyl fluoroacetate (II)	0·25
Ethyl 5-fluoropentanecarboxylate (I)	0·2—0·5
2-Fluoroethyl 5-fluoropentanecarboxylate (III)	0·1—0·2

The very high toxicity of ethyl 5-fluoropentanecarboxylate and its derivatives and the " fluoroacetate-like " symptoms produced seemed to be of particular interest since by a process of β-oxidation in the animal body 5-fluoropentanecarboxylic acid would readily give rise to the toxic fluoroacetic acid. Similar remarks apply to γ-fluorobutyric acid and its derivatives prepared by American workers. The non-toxicity of β-fluoropropionic acid and its derivatives may, on the other hand, be due to the inability of this acid to give the toxic fluoroacetic acid by a process of β-oxidation.

In order to prove that fluorine was responsible for the lethal action in (I) and (II), the intermediate bromo-esters were examined physiologically. Ethyl 5-bromopentanecarboxylate was found to be entirely without toxic action, and the toxicity of the *2-fluoroethyl* ester was of a low order, the L.D. 50 being about 75 mg./kg.

We then set out to determine whether this remarkable alternation in toxic properties could be observed among other ω-fluorocarboxylic acids.

Ethyl δ-fluorovalerate (IV) was found to be completely non-toxic, a subcutaneous injection of 160 mg./kg. killing 0/2 mice, with complete absence of any symptoms of poisoning. Intramuscular injection of 40 mg./kg. into rats similarly produced no symptoms.

* This difference in toxicities when using saline and propylene glycol should be noted when comparing potencies.

In striking contrast to this we showed that *ethyl 7-fluoroheptanecarboxylate* (V) was highly toxic and that the *2-fluoroethyl* ester (VI) was slightly more toxic.

Ethyl 9-fluorononanecarboxylate (VII) was found to be even more toxic than ethyl 5-fluoropentanecarboxylate by injection into rabbits, the L.D. 50 for propylene glycol solution of (VII) being 0·2 mg./kg.* Mice and rats were slightly more resistant, but exhibited convulsions of the general fluoroacetate type. On account of the high boiling point of the material, no inhalation experiments were attempted. *2-Fluoroethyl 9-fluorononanecarboxylate* (VIII) was found to be no more toxic than the corresponding ethyl ester by injection into mice. Each had an L.D. 50 of about 10 mg./kg. This apparent anomaly is discussed later.

Ethyl 10-fluorodecanecarboxylate (IX) when injected into mice caused no deaths at a concentration of 100 mg./kg., and produced no symptoms of any kind. Therefore it was non-toxic. In accordance with expectation *ethyl 11-fluoroundecanecarboxylate* (X) proved to be toxic.

The results obtained for injection into mice of propylene glycol solutions are summarised in the following table.

Value of n in acid $F\cdot[CH_2]_n\cdot CO_2H$.	L.D. 50, mg./kg. (propylene glycol as solvent). Me or Et ester.	2-Fluoroethyl ester.	Value of n in acid $F\cdot[CH_2]_n\cdot CO_2H$.	L.D. 50, mg./kg. (propylene glycol as solvent). Me or Et ester.	2-Fluoroethyl ester.
1	15 (Me)	8·5	5	4 (Et)	2·5
2	Non-toxic (American workers)	—	7	9 (Et)	7
			9	10 (Et)	10
			10	>100 (Et) ∴ Non-toxic	—
3	Toxic (American workers)				
4	>160 (Et) ∴ Non-toxic	—	11	<20 (Et)	—

It is thus apparent that, in this series of ω-fluorocarboxylic esters, if n is odd the compound is highly toxic, whereas if n is even it is non-toxic. This striking alternation in toxicity would seem to provide a useful verification of the theory of β-oxidation of fatty acids in the animal body.

The theory of β-oxidation was first put forward by Knoop (*Beitr. Chem. Physiol. Path.*, 1904, **6**, 150; 1906, **11**, 411) and was based essentially on the following evidence. The ω-phenyl derivatives of the fatty acids containing from one to five carbon atoms were administered to dogs, and the urine was subsequently analysed for the presence of derivatives of these acids. In all cases the final acid produced by breakdown was excreted as its glycine derivative. Those fatty acids containing an odd number of carbon atoms were excreted as hippuric acid, and those with an even number as phenylaceturic acid, $CH_2Ph\cdot CO\cdot NH\cdot CH_2\cdot CO_2H$. These results led Knoop to postulate that fatty acids were oxidised by a route which involved the loss of two carbon atoms at each stage, owing to oxidation occurring at the β-carbon atom. He suggested, but without evidence, that the β-oxidation took place by the following steps:

$$R\cdot CH_2\cdot CH_2\cdot CO_2H \xrightarrow{-H_2} R\cdot CH{:}CH\cdot CO_2H \xrightarrow[-H_2]{+H_2O} R\cdot CO\cdot CH_2\cdot CO_2H \xrightarrow{+H_2O} R\cdot CO_2H + CH_3\cdot CO_2H$$

It will readily be seen in our series of ω-fluorocarboxylic acids, that when n is odd, β-oxidation would yield the toxic fluoroacetic acid, whereas when n is even, the compound will be oxidised only as far as the non-toxic β-fluoropropionic acid. The pharmacological results obtained are in complete accord with this hypothesis, and provide verification, of a kind not hitherto achieved, of the process of β-oxidation in the living animal body. Recently, however, Weinhouse, Medes, and Floyd (*J. Biol. Chem.*, 1944, **153**, 689) have inoculated rat-liver slices with one or two fatty acids containing isotopic carbon, and have obtained some evidence for a process of β-oxidation.

Certain aspects of our results, however, while not invalidating the β-oxidation theory of the ω-fluorocarboxylic acids, do indicate that β-oxidation is not the only factor concerned with the alternation of toxic properties.

Ethyl 9-fluorononanecarboxylate is toxic in accordance with expectation, but the magnitude of the toxicity (L.D. 50 for injection into rabbits 0·2 mg./kg.) is *greater* (molecule for molecule) than that of methyl fluoroacetate (L.D. 50, 0·25 mg./kg.). On the basis of the β-oxidation theory alone, the toxicity of the former ester should be *less* than that of the latter, because of the long chain of CH_2 groups which must be burned away in the body before fluoroacetic acid is

* The ester (VII) would probably be even more toxic in saline solution.

produced. It may be, however, that because of its long chain, the higher ester would have a higher fat : water partition coefficient and therefore would pass more readily than the lower ester through the cell membranes, and there break down giving a higher intracellular concentration of fluoroacetic acid.

Reference has already been made to the fact that 2-fluoroethyl 9-fluorononanecarboxylate was no more toxic than the corresponding ethyl ester by injection into mice. This was contrary to expectation, and was investigated in the following manner. One set of mice was injected with ethyl 9-fluorononanecarboxylate in the usual way; a second set of mice had exactly the same injections of this ester and then, almost simultaneously, injections of fluoroethyl alcohol were made corresponding to the amount which would have been liberated had 2-fluoroethyl 9-fluorononanecarboxylate been injected instead. The mice of the second set therefore contained the same amount of fluorine as if they had been injected with the latter ester. The results are tabulated as follows :

	Wt. of nonanecarboxylate alone, mg./kg.		
	20	8	6
Ethyl 9-fluorononanecarboxylate alone	6/6 killed	4/6 killed	4/6 killed
Ditto + fluoroethyl alcohol	6/6 killed	5/6 killed	1/6 killed

This showed the fluoroethyl alcohol had no very marked effect, and this observation was in line with the fact that the ethyl and the 2-fluoroethyl ester had the same toxicity.

Two points are tentatively put forward to account for this similarity of toxicity : (1) As the homologous series of ω-fluoro-esters is ascended, the proportion of fluoroethyl alcohol obtainable from the 2-fluoroethyl esters must decrease. It is suggested that a point will be reached when the amount of fluoroethyl alcohol derived from the 2-fluoroethyl ester will be too small to make any apparent difference in the toxicity. The L.D. 50 of 2-fluoroethyl 9-fluorononanecarboxylate liberates only about 0·05 mg. of fluoroethyl alcohol in the mouse. This, if injected alone, would have no action. (2) 2-Fluoroethyl 5-fluoropentanecarboxylate was found to be nearly twice as toxic as the corresponding ethyl ester, weight for weight; but if its action were due solely to hydrolysis *in vivo* the toxicity should be the same. Similar remarks apply to 2-fluoroethyl fluoroacetate. It thus seems possible that the molecule may exert some action *per se*, independently of any subsequent degradation. It might further be suggested that if the toxic action of these 2-fluoroethyl esters is indeed dependent primarily upon the molecule as a whole (as distinct from its hydrolysis products) then the action may be related to the terminal fluorine atoms of the molecule. If this is so, there may be an optimum stereochemical distance apart of the fluorine atoms for the maximum action of the molecule in this way. It is significant that the difference in activity between the ethyl and the 2-fluoroethyl esters is greater with the shorter chains. With the fluoroheptanecarboxylates the difference is slight, and it disappears entirely with the nonanecarboxylates.

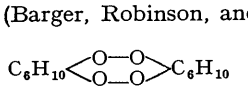
Although our results support the β-oxidation theory, one point must not be overlooked, namely, that fluoroacetic acid is perhaps not the actual toxic agent and has to be converted into some other compound before exerting any activity. American workers (private communication) showed that both methyl γ-fluorobutyrate and methyl γ-fluorocrotonate, $F{\cdot}CH_2{\cdot}CH{:}CH{\cdot}CO_2Me$, were highly toxic, and moreover, we showed that the crotonate was much more rapid in its lethal action than fluoroacetate at equivalent concentrations. However, this is purely hypothetical and is not yet supported by any direct experimental evidence.

Synthetic Methods employed in this Series of Compounds.—As direct chlorination or bromination of a carboxylic acid gives invariably the α-substituted acid, such methods are useless for the preparation of the ω-substituted acids required for the present investigation; *ad hoc* methods have therefore had to be found for the preparation of each individual ω-fluorocarboxylic acid and its derivatives.

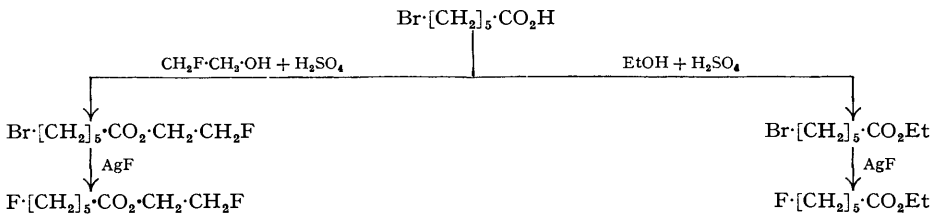
Ethyl δ-fluorovalerate (IV) was prepared in an impure state (67% purity by fluorine analysis) from ethyl δ-bromovalerate, and in a pure condition from ethyl δ-iodovalerate by fluorination with the silver fluoride. It may be noted that difficulty was experienced in converting allylacetic acid into δ-bromovaleric acid. The conditions of the experiment were varied between wide limits both in the presence and the absence of peroxides. Conflicting results had previously been obtained by other workers in this field (Boorman, Linstead, and Rydon, *J.*, 1933, 568, 1974; Kharasch and McNab, *Chem. and Ind.*, 1935, **54**, 98). δ-Iodovaleric acid was prepared by Carter's method (*J. Amer. Chem. Soc.*, 1928, **50**, 1968) who converted it into the ethyl ester using a solution of dry hydrogen chloride in alcohol. We found that under these conditions a large part of the iodo-acid was converted into the chloroester. We therefore carried out the esterification using sulphuric acid and showed that if the

molar ratios of sulphuric acid, iodo-acid, and ethyl alcohol were 1 : 4 : 32, neglible interchange took place. The fluorination of the iodo-ester was achieved by the use of pure dry silver fluoride in the absence of a solvent.

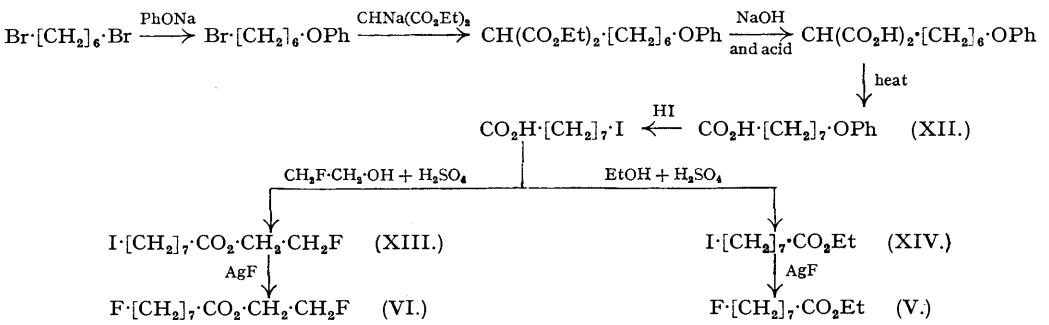
The starting point for the 5-fluoropentanecarboxylic esters was *cyclo*hexanone, which was oxidised to 5-hydroxypentanecarboxylic acid by Robinson and Smith's method (*J.*, 1937, 373). This was then converted into the bromo-acid by means of hydrogen bromide and sulphuric acid (Barger, Robinson, and Smith, *J.*, 1937, 718). By employing certain modifications described in the Experimental section, the yields have been increased. It may be noted that a solid of m. p. 130°, probably di*cyclo*hexylidene peroxide (XI), could usually be isolated during the preparation of 5-hydroxypentanecarboxylic acid. The isolation of this compound may throw light on the mechanism of the oxidation of *cyclo*hexanol (cf. Waters, *Ann. Reports*, 1945, **42**, 147; Milas, Harris, and Pangiotakos, *J. Amer. Chem. Soc.*, 1939, **61**, 2430).


(XI.)

5-Bromopentanecarboxylic acid was converted into the appropriate esters as follows:



The 7-fluoroheptanecarboxylates were synthesised from hexamethylene dibromide according to the following scheme. All the *compounds* beyond hexamethylene dibromide are new.

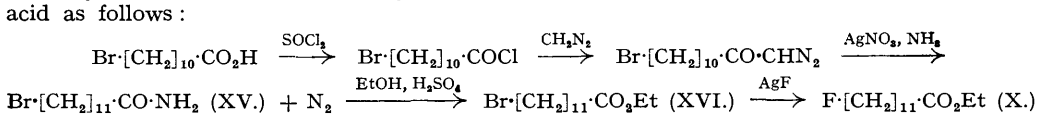


The splitting of (XII) took place very smoothly with constant-boiling hydriodic acid to give the pure iodo-acid. The fluorination of (XIII) was more facile than that of (XIV). In fact with the latter acid, hydrogen iodide was eliminated to some extent with the production of ethyl hept-6-enecarboxylate, which was effectively removed only by conversion into the dibromide with bromine, followed by distillation.

Ethyl and *2-fluoroethyl 9-bromononanecarboxylate* and ethyl and 2-fluoroethyl 9-fluorononanecarboxylate were all prepared from 9-bromononanecarboxylic acid, made by the action of hydrogen bromide and sulphuric acid on 9-acetoxynonanecarboxylic acid, which in turn was obtained by a four-stage synthesis from sebacic acid.

Ethyl 10-fluorodecanecarboxylate was readily prepared by the fluorination of the corresponding bromo-ester, prepared by esterifying the acid with ethyl alcohol and sulphuric acid.

Ethyl 11-fluoroundecanecarboxylate was synthesised from 10-bromodecanecarboxylic acid as follows:



The alcoholysis of (XV) to (XVI) was effected by boiling with absolute alcohol and sulphuric acid for 10 hours. The standard technique was adopted for the fluorination.

Experimental.

Ethyl δ-Bromovalerate.—δ-Bromovaleric acid (29 g., 0·16 mol.) was heated under reflux at 110° on an oil-bath for 8 hours with absolute alcohol (60 g., 1·2 mols.) and concentrated sulphuric acid (3 c.c.); the mixture was allowed to cool, diluted with water, extracted with ether, the ethereal solution dried (Na_2SO_4), and the product distilled under reduced pressure after removal of the ether; b. p. 104—106°/13 mm.; yield 27 g. (79%).

Reaction between Silver Fluoride and Ethyl δ-Bromovalerate.—Silver fluoride (17 g., 1·34 mols., dried over P_4O_{10} at 100°) was ground to a fine powder, and added slowly to ethyl δ-bromovalerate (14 g., 0·68 mol.) in a flask cooled in ice. A white cloudiness soon appeared, and the mixture was heated in a water-bath at 50° for 10 minutes, and kept at room temperature for 3 hours, with occasional shaking, by which time an orange coloration had developed. The mixture was diluted with ether, filtered, and distilled under reduced pressure. Impure ethyl δ-fluorovalerate (about 1 g.) was obtained as a colourless liquid, b. p. 70—88°/12 mm. (Found: F, 8·7. Calc. for $C_7H_{13}O_2F$: F, 12·87%).

Ethyl δ-Iodovalerate.—δ-Iodovaleric acid (60 g., 0·26 mol.) was heated on a sand-bath under reflux for 4 hours with an 8% solution of dry hydrogen chloride in absolute ethanol (300 c.c.). A deep red colour soon developed. The reaction mixture was cooled, diluted with an equal volume of water, extracted with ether, washed with sodium thiosulphate solution to remove iodine, dried (Na_2SO_4), the ether removed, and the product fractionated; yield 29·5 g.; b. p. 93—100°/13 mm. This was redistilled at 90—91°/12 mm. (Found: C, 50·8; H, 8·0. Calc. for $C_7H_{13}O_2I$: C, 32·8; H, 5·1%. Calc. for $C_7H_{13}O_2Cl$: C, 51·1; H, 7·9%).

Analysis for halogen by Stepanow's method assuming it to be chlorine gave Cl, 22·06 (Calc. for $C_7H_{13}O_2Cl$: Cl, 21·53%). It was therefore apparent that the Fischer–Speier method of esterification very readily substituted chlorine for iodine in the molecule as well as esterifying the acid; sulphuric acid was therefore used in place of hydrochloric acid in subsequent esterifications.

δ-Iodovaleric acid (36 g., 0·156 mol.) was heated under reflux on an oil-bath at 110° for 6 hours with absolute alcohol (84 c.c., 1·08 mols.) and concentrated sulphuric acid (3·6 c.c.). A deep red colour developed. The mixture was cooled, diluted with water, extracted with ether, shaken with sodium carbonate to remove excess of unchanged acid, and worked up as above. The ester (27 g., 69%) distilled at 108—118°/20 mm. (Found: I, 49·0. Calc. for $C_7H_{13}O_2I$: I, 49·2%).

Ethyl δ-Fluorovalerate.—Silver fluoride (34 g., 0·26 mol.) was slowly added (1 hour) with shaking to ethyl δ-iodovalerate (34 g., 0·13 mol.), the reaction flask being cooled in ice. After all the silver fluoride had been added, the flask was heated on a water-bath at 45—50° for 20 minutes, cooled, dry ether added, and the product filtered. The ethereal filtrate was washed with water to remove hydrogen fluoride, dried (Na_2SO_4), filtered, the ether removed, and the residue fractionated. Three fractions were collected: (1) b. p. 35—70°/10 mm., *ca.* 3 c.c.; (2) b. p. 70—90°/10 mm., *ca.* 2 c.c.; (3) b. p. 90—115°/10 mm. (mainly 110—115°), *ca.* 8 c.c. (recovered iodovalerate). Fraction (3) was refluorinated with silver fluoride (8 g.) by the same procedure as before. The fraction of b. p. 35—70°/10 mm. was collected (2 c.c.) and mixed with fraction (1) from the initial fluorination. The mixture was refractionated and a well-defined fraction of b. p. 56—60°/16 mm. (1·5 c.c.) was collected. The *ethyl δ-fluorovalerate* thus obtained was a colourless liquid with a pleasant fruit-like odour (Found: F, 12·53. $C_7H_{13}O_2F$ requires F, 12·87%).

5-*Hydroxypentanecarboxylic Acid* (cf. Robinson and Smith, *J.*, 1937, 373; Barger, Robinson, and Smith, *ibid.*, p. 718).*—To water (240 c.c.) and sulphuric acid (710 c.c.), cooled with stirring to below 15°, potassium persulphate (500 g.) was added, followed by alcohol (1000 c.c.), the temperature throughout being kept below 15°. The mixture was cooled to 10° and *cyclo*hexanone (100 c.c.) in alcohol (150 c.c.) was added during 2½ hours. After the addition, the stirring was continued at 10° for 15 minutes, and then for one hour without the cooling-bath. The mixture was then diluted to 7 l., filtered, saturated with ammonium sulphate, filtered again, and finally thoroughly extracted with ether. The extract was dried (Na_2SO_4), and the ether distilled off completely on a steam-bath. The residue was cooled and filtered if necessary from the solid (m. p. 130°) which may have separated out. The residue in the flask was 5-hydroxypentanecarboxylic acid (and traces of its lactone) and was sufficiently pure for the next stage.

5-*Bromopentanecarboxylic Acid.*—The above hydroxy-acid was added to a cold mixture of constant-boiling hydrobromic acid (550 c.c.) and sulphuric acid (125 c.c.) contained in a flask. The mixture was kept at room temperature for 2 hours with occasional shaking. The flask was then fitted with a reflux condenser and heated on a steam-bath for 6 hours. The product was then cooled, diluted with an equal volume of water, saturated with ammonium sulphate, and extracted with ether. After drying (Na_2SO_4), the ether was distilled off, and the residue consisted of the required acid. (If the acid were required pure it could be distilled at 160°/14 mm., but this was not necessary in preparing the ethyl and the 2-fluoroethyl ester.)

Ethyl 5-Bromopentanecarboxylate.—The foregoing crude bromo-acid was esterified with ethyl alcohol (108 c.c.) and sulphuric acid (5·3 c.c.) for 10 hours in an oil-bath at 110°. The product was cooled, diluted with an equal volume of water, and extracted with ether. The extract was dried (Na_2SO_4), the ether distilled off, and the residue fractionated, the fraction of b. p. 120—130°/15 mm. being collected; yield 61 g. (*i.e.*, 30% based on the *cyclo*hexanone used).

Ethyl 5-Fluoropentanecarboxylate.—The above ester (10 g., 0·045 mol.) was placed in a flask fitted with a reflux condenser and calcium chloride tube, and finely-powdered silver fluoride (11·4 g., 0·09 mol.) was added. A slight precipitate of silver bromide was produced almost immediately. The flask was heated to 50° for 30 minutes and then cooled. The contents were extracted with ether, and the extract filtered and dried (Na_2SO_4). The ether was distilled off, and the residue distilled under reduced pressure.

* Soon after the completion of our work (Report by Saunders to Ministry of Supply Meeting, London, June 1, 1944), Brown and Partridge (*J. Amer. Chem. Soc.*, 1944, **66**, 839) described similar modifications which confirmed our findings.

The fraction of b. p. 80—85°/14 mm. was redistilled, and the clear colourless *fluoro*-ester, b. p. 82—84°/14 mm., was collected; yield of twice distilled material, 2 g. (27%) (Found: C, 59·3; H, 9·5; F, 11·2. $C_8H_{15}O_2F$ requires C, 59·2; H, 9·25; F, 11·7%).

2-*Fluoroethyl* 5-*Bromopentanecarboxylate*.—5-Bromopentanecarboxylic acid was purified by distillation (b. p. 165—170°/20 mm.) and after recrystallisation from light petroleum had m. p. 35°. This acid (38 g.), fluoroethyl alcohol (30 g.), and sulphuric acid (2·5 c.c.) were thoroughly mixed and heated under reflux in an oil-bath at 120° for 5—6 hours. The mixture was cooled, diluted with water, and extracted with ether, and the extract dried (Na_2SO_4). After distillation of the ether, most of the residue came over at 144—146°/14 mm.; yield 25·1 g.(53%). Refractionation gave the 2-*fluoroethyl* ester as a colourless liquid, b. p. 142°/13 mm., containing fluorine (Found: Br, 33·7. $C_8H_{14}O_2BrF$ requires Br, 33·2%).

This ester could also be prepared satisfactorily from unpurified bromo-acid. The crude bromo-acid (from *cyclo*hexanone 95 g., 1 mol.) was mixed with fluoroethyl alcohol (120 c.c.) and concentrated sulphuric acid (5 c.c.) and heated to 110—115° for about 10 hours. The product was cooled, diluted with an equal volume of water, and extracted with ether. The ether extract was dried (Na_2SO_4) and after distillation of the ether, the fraction of b. p. 138—143°/13 mm. was collected; yield 70 g. from 95 g. of *cyclo*hexanone (*i.e.*, 30%).

2-*Fluoroethyl* 5-*Fluoropentanecarboxylate*.—The foregoing bromo-ester (20 g., 0·083 mol.) and silver fluoride (21·6 g., 0·17 mol.) were kept at room temperature with occasional shaking for 15 minutes, then warmed to 40° for an hour with shaking. The product was cooled, extracted with ether, and the extract filtered, washed with an equal volume of water, and dried (Na_2SO_4). The subsequent fractionation was carried out in an atmosphere of nitrogen or dry carbon dioxide, by aid of a water-pump. The following fractions were obtained: (1) up to 106°/14 mm.; (2) 106—115/14 mm.; (3) 115—120°/14 mm. Fractions (2) and (3) were combined and refluorinated using silver fluoride (8 g.). The product was again extracted with ether, washed with water, dried, and distilled in an atmosphere of dry carbon dioxide. The following fractions were obtained: (1) 85—105°/12 mm.; (2) 107—108°/12 mm.; (3) 109—120°/12 mm. Fraction (2) was finally redistilled in an atmosphere of dry carbon dioxide, and the 2-*fluoroethyl* 5-*fluoropentanecarboxylate*, b. p. 103—105°/14 mm., was collected as a colourless liquid (Found: F, 19·5. $C_8H_{14}O_2F_2$ requires F, 21·0%).

Investigation of the Solid of m. p. 130°.—The solid (see p. 1475) was recrystallised to constant m. p. from methanol. It was a colourless, odourless, crystalline material, insoluble in water, alkali, and hydrochloric acid. It contained no nitrogen, halogen, or sulphur. It reacted vigorously with concentrated sulphuric acid in the cold, with much charring, and it liberated iodine when boiled with acidified potassium iodide solution [Found: C, 63·4; H, 8·52; O, 28·08 (by diff.). C_3H_5O requires C, 63·2; H, 8·77; O, 28·03%]. The molecular weight was determined in a semimicro-ebullioscopic apparatus (Found: *M*, 216, 223. $C_{12}H_{20}O_4$ requires *M*, 228). From the positive peroxide test by means of potassium iodide, it is very probable that the compound is *di*cyclo*hexylidene peroxide* (XI).

6-*Phenoxyhexyl Bromide*.—Hexamethylene dibromide (244 g., 1 mol.), water (400 c.c.), and phenol (77 g., 0·82 mol.) were placed in a 2-l. 3-necked flask fitted with stirrer, dropping-funnel, and reflux condenser. The stirrer was started, the mixture heated to boiling, and 30% sodium hydroxide (106 c.c.) added through the dropping-funnel during 20 minutes. The mixture was heated under reflux for 8 hours with vigorous stirring, and allowed to cool. The upper layer was discarded, and the lower layer fractionated under reduced pressure, two fractions being obtained: (1) up to 174°/13 mm., mostly recovered hexamethylene dibromide; (2) 174—180°/13 mm. (112 g., 79% net), 6-*phenoxyhexyl bromide* (Found: Br, 31·16. $C_{12}H_{17}OBr$ requires Br, 31·13%). The bromide was obtained as a colourless viscous liquid with a faint phenolic smell. The first fraction was shaken with 10% sodium hydroxide to remove phenol, and dried ($CaCl_2$). On distillation 100 g. of hexamethylene dibromide were recovered.

Ethyl 6-*Phenoxyhexylmalonate*.—Sodium (9·5 g., 0·42 atom) was dissolved in absolute alcohol (150 c.c., dried over magnesium ethoxide) in a 1-l. flask fitted with reflux condenser, stirrer, and dropping-funnel, and ethyl malonate (67 g., 0·42 mol.) was added with stirring. 6-Phenoxyhexyl bromide (108 g., 0·42 mol.) was slowly added with stirring, and after the addition was complete, the mixture was gently heated under reflux with stirring for 3 hours, during which a heavy white precipitate of sodium bromide was formed. The flask and contents were allowed to cool, water was added to dissolve the sodium bromide, and the non-aqueous layer was collected in ether and dried (Na_2SO_4). After removal of the ether, alcohol, and malonic ester with a water pump, the residual colourless viscous *ethyl* 6-*phenoxyhexylmalonate* was distilled by use of a mercury pump; yield 81 g. (51%); b. p. 155—158°/2 × 10^{-3} mm. (Found: C, 67·8; H, 8·46. $C_{19}H_{28}O_5$ requires C, 67·7; H, 8·34%).

6-*Phenoxyhexylmalonic Acid*.—The above ester (80 g., 0·24 mol.) was heated under reflux on an oil-bath with 20% sodium hydroxide solution (250 c.c.) until the mixture was homogeneous (4 hours); it was then cooled, and acidified strongly with dilute sulphuric acid. The thick white precipitate formed was filtered off, washed with a small quantity of cold water, recrystallised from water, separated, and dried in a vacuum over phosphoric oxide. The *acid* crystallised in short white needles (60 g., 88%), m. p. 162—163° (decomp.) (Found: C, 63·97; H, 7·06. $C_{15}H_{20}O_5$ requires C, 64·28; H, 7·14%).

7-*Phenoxyheptanecarboxylic Acid*.—6-Phenoxyhexylmalonic acid (60 g., 0·23 mol.) was heated in a round-bottom flask at 230°, with occasional stirring, until no more effervescence took place (2½ hours). The liquid so obtained solidified on cooling and was broken up, and recrystallised (animal charcoal) from light petroleum (b. p. 60—80°), forming colourless plates; yield of purified *acid*, 35 g. (58%); m. p. 69—70° (Found: C, 71·6; H, 8·6. $C_{14}H_{20}O_3$ requires C, 71·2; H, 8·47%).

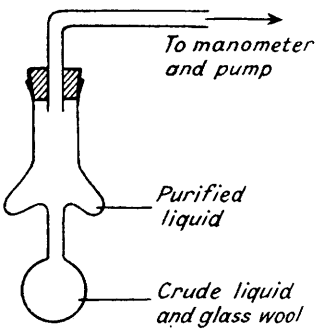
7-*Iodoheptanecarboxylic Acid*.—The phenoxy-acid (5 g., 0·021 mol.) was heated under reflux on an oil-bath at 160—170° with constant-boiling hydriodic acid (20 c.c., redistilled; *d* 1·7) for 6 hours. The product was cooled, extracted three times with ether, and the ethereal solution extracted twice with saturated sodium carbonate, this serving the double purpose of destroying the free iodine present and extracting the iodo-acid as its sodium salt. The aqueous solution so obtained was acidified with concentrated hydrochloric acid, and the white granular precipitate formed was filtered off, dried over phosphoric oxide, and recrystallised from light petroleum (b. p. 60—80°). The *iodo-acid* crystallised

in colourless rosettes (4 g., 70%), m. p. 43—44° (Found : I, 47·23. $C_8H_{15}O_2I$ requires I, 47·04%).

The experiment was repeated on a larger scale using 28 g. (0·12 mol.) of the phenoxy-acid, and 110 c.c. of constant-boiling hydriodic acid. The total yield of iodo-acid obtained in the two experiments was 27 g. (71%).

Ethyl 7-Iodoheptanecarboxylate.—The above acid (12 g., 0·44 mol.) was dissolved in absolute ethanol (80 g., 1·77 mols.), concentrated sulphuric acid (5·5 g., 0·054 mol.) was added, and the mixture was heated under reflux for 6 hours on an oil-bath at 110—120°. The product, which had become red, was cooled and poured into a large volume of water. The oil which separated was collected in ether, and the aqueous solution extracted twice with ether. The combined ethereal extracts were shaken twice with saturated sodium carbonate solution to remove iodine and hydriodic acid, then dried (Na_2SO_4) and distilled under reduced pressure. The *ethyl* ester was obtained as a colourless, mobile liquid (11·2 g., 83%) with a faint pleasant smell; b. p. 114°/1 mm. (Found : I, 42·6. $C_{10}H_{19}O_2I$ requires I, 43·0%).

Ethyl 7-Fluoroheptanecarboxylate.—Silver fluoride (9·7 g., 0·076 mol.) was added slowly to the iodo-ester (10·2 g., 0·034 mol.) in a 50-c.c. round-bottom flask. The mixture slowly became warm and a yellow precipitate began to form. The mixture was continuously stirred, and the silver halide ground to expose fresh silver fluoride to the iodo-ester. It was not necessary to cool the reaction vessel, and after 30 minutes the heavy yellow precipitate of silver iodide which had been formed turned brick-red, presumably owing to formation of silver iodofluoride. The reaction mixture was cooled in ice and extracted with dry ether, and the extract washed with water, dried (Na_2SO_4), and distilled under reduced pressure. A fraction was collected of b. p. 100—108°/12 mm. (2 g.), which contained fluorine and decolorised bromine-water in the cold, indicating the presence of an olefinic bond (Found : F, 5·7. Calc. for $C_{10}H_{19}O_2F$: F, 10·0%). It appeared that a considerable proportion of ethyl hept-6-ene-carboxylate had been formed during the fluorination. As this ester would be very hard to remove from the fluoro-ester by fractional distillation owing to similarity of b. p., it was decided to brominate the olefinic ester, for the dibromo-ester should have a much higher b. p. than the desired fluoro-ester. Bromine (dried with concentrated sulphuric acid) in carbon tetrachloride was therefore added dropwise to the ester mixture, until a faint brown colour just remained. The carbon tetrachloride and excess of bromine were then removed by distillation, and the residual colourless liquid (*ca.* 1 g.) was distilled. The volume of liquid was too small to allow the use of a normal distillation flask, so the method described below was adopted. The distillation flask used was as shown in the diagram, the liquid to be distilled being placed in the bulb (of about 3 c.c. capacity) with glass-wool. The bulb was placed in an oil-bath, and the apparatus connected to a vacuum pump. When the oil-bath was heated, the liquid distilled into the upper, pear-shaped bulb from which it could be removed. (The efficiency of the flask had first been determined by distillation of a 4 : 1 mixture of benzene and toluene.) The b. p. of each fraction was determined by the method of Emich (*Monatsh.*, 1917, **38**, 219).



Three fractions were obtained from the crude *ethyl 7-fluoroheptanecarboxylate*. The third fraction (0·2 g.) distilled at an oil-bath temperature of 145—150°/12 mm., and contained fluorine. The ester was thus obtained as a colourless mobile liquid with a pleasant fruity smell; b. p. 191° (Found : C, 63·1; H, 9·9. $C_{10}H_{19}O_2F$ requires C, 63·2; H, 10·0%).

2-Fluoroethyl 7-Iodoheptanecarboxylate.—7-Iodoheptanecarboxylic acid (13 g., 0·48 mol.) was dissolved in 2-fluoroethyl alcohol (110 g., 1·73 mol.), and concentrated sulphuric acid (5·5 g., 0·054 mol.) was added. The mixture was heated under reflux for 6 hours on an oil-bath at 120—130°. The product was allowed to cool, poured into a large volume of water, and the deep red, oily, lower layer which separated was run off. The aqueous solution was twice extracted with ether, and the ethereal extracts united with the crude ester. The extract was washed twice with 20% sodium carbonate solution, and dried (Na_2SO_4). After filtration, and removal of the ether, the residual oil was distilled. The *fluoroethyl* ester was obtained as a colourless mobile liquid (9·5 g., 62·5%) with a very faint pleasant odour; b. p. 122—124°/0·8 mm. (Found : I, 39·9. $C_{10}H_{18}O_2IF$ requires I, 40·2%).

2-Fluoroethyl 7-Fluoroheptanecarboxylate.—Silver fluoride (9 g., 0·07 mol.) was added slowly to the foregoing ester (8·5 g., 0·027 mol.) in a 50-c.c. round-bottom flask. The mixture slowly became warm, with simultaneous formation of a yellow precipitate; it was stirred with a glass rod, and the silver halide ground continuously to expose fresh silver fluoride. After about 30 minutes the precipitate became red, and dry ether was added. The mixture was filtered, and the heavy precipitate thoroughly extracted with dry ether. The ethereal extract was washed with water to remove hydrofluoric acid, dried (Na_2SO_4), the ether removed, and the residual oil distilled, the fraction of b. p. 128—130°/13 mm. being collected (1·1 g., 21%). *2-Fluoroethyl 7-fluoroheptanecarboxylate* was obtained as a colourless mobile liquid with a pleasant fruit-like smell, very similar to that of the ethyl ester (Found : F, 17·84. $C_{10}H_{18}O_2F_2$ requires F, 18·27%).

9-Bromononanecarboxylic Acid.—Sebacic acid (202 g., 1·0 mol.) and ethyl sebacate (150 g., 0·58 mol.) were converted into ethyl hydrogen sebacate by the method of Swann, Oehler, and Buswell (*Org. Synth.*, Coll. Vol. II, 276); yield 147 g. (65%). The latter ester (115 g., 0·5 mol.) was converted into crystalline potassium ethyl sebacate in theoretical yield (134 g.). This salt (134 g.) was reduced to crude 9-hydroxynonanecarboxylic acid by the method of Grun and Wirth (*Ber.*, 1922, **55**, 2208). The crude product, which contained sebacic acid, was heated in a flask to 100°, and acetic anhydride (250 c.c.) was added a few c.c. at a time as a vigorous reaction took place after each addition. The contents of the flask were cooled and diluted with water (2 vols.), and the solution extracted three times with light petroleum (b. p. 60—80°). After drying (Na_2SO_4), and removal of solvent, the residue consisted of crude 9-acetoxynonanecarboxylic acid. This was shaken with a cooled mixture of constant-boiling hydrobromic acid (400 c.c.) and concentrated sulphuric acid (96 c.c.), and set aside overnight. The mixture

was then heated on a water-bath for 4 hours, cooled, diluted with an equal volume of water, and extracted with ether. The extract was dried (Na_2SO_4) and after removal of ether, the residue was distilled and 9-bromononanecarboxylic acid was obtained as a colourless liquid, b. p. 145—155°/0·4 mm. It solidified to a colourless solid, m. p. 42° (yield 15 g.; 12% based on the ethyl hydrogen sebacate used). This acid had been prepared by a different method by Chuit and Hausser (*Helv. Chim. Acta*, 1929, **12**, 474), who gave m. p. 42°, b. p. 163—165°/2 mm.

Ethyl 9-*Bromononanecarboxylate*.—The bromo-acid (12·5 g., 0·05 mol.), ethyl alcohol (15 c.c.), and concentrated sulphuric acid (2·0 c.c.) were heated under reflux for 2 hours, cooled, diluted with an equal volume of water, and extracted with ether. The extract was dried (Na_2SO_4), the ether removed, and the residue distilled under reduced pressure. The *ethyl* ester distilled at 162—164°/10 mm. as a colourless liquid (10 g., 72%) (Found: Br, 28·7. $C_{12}H_{23}O_2Br$ requires Br, 28·7%).

Ethyl 9-*Fluorononanecarboxylate*.—The bromo-ester (10 g., 0·036 mol.) and pure, dry, finely-powdered silver fluoride (10 g., 0·08 mol.) were warmed to 80° for 20 minutes, during which a yellow precipitate of silver bromide separated. The contents of the flask were cooled and extracted with ether. The extract was washed and dried (Na_2SO_4). The ether was removed, and the residue on distillation yielded the following fractions: (1) 130—145°/10 mm.; (2) 145—150°/10 mm.; (3) 150—165°/10 mm. All three fractions contained fluorine. The first fraction contained no bromine, but the second and third contained traces. The two higher fractions were accordingly refluorinated with silver fluoride (4 g.), and, after isolation as above, were combined with the first fraction and the whole redistilled. The *ethyl* 9-*fluorononanecarboxylate*, b. p. 135—138°/10 mm., was collected as a colourless, pleasant-smelling liquid (1·5 g., 20%) (Found: F, 8·4. $C_{12}H_{23}O_2F$ requires F, 8·7%).

2-*Fluoroethyl* 9-*Bromononanecarboxylate*.—The acid (10 g., 0·04 mol.), fluoroethyl alcohol (20 c.c.), and concentrated sulphuric acid (2·0 c.c.) were heated under reflux for 1 hour. The mixture was cooled, diluted with an equal volume of water, and extracted 3 times with ether. The extract was dried (Na_2SO_4), filtered, and distilled. After removal of the ether, nearly all the *ester* came over at 184—188°/11 mm., as a colourless liquid (10·4 g., 87%) melting just below room temperature (Found: Br, 26·6. $C_{12}H_{22}O_2BrF$ requires Br, 26·9%).

2-*Fluoroethyl* 9-*Fluorononanecarboxylate*.—The bromo-ester (9·4 g., 0·03 mol.) and silver fluoride (13 g., 0·1 mol.) were warmed at 75° for 15 minutes. The mixture was then cooled, extracted with ether, and filtered. The extract was washed and dried (Na_2SO_4), the ether removed, and the residue on distillation gave a fraction, b. p. 142—150°/12 mm., which contained fluorine and a slight trace of bromine. About 4 g. of unchanged bromo-ester were recovered. This was fluorinated by means of silver fluoride (5 g.), and the product isolated as before and added to the above fraction. The combined liquids were redistilled and the *ester* of b. p. 145—149°/12 mm. was collected as a colourless, pleasant-smelling liquid, which was bromine-free (1·3 g., 17%) (Found: F, 14·6. $C_{12}H_{22}O_2F_2$ requires F, 16·0%).

Ethyl 10-*Bromodecanecarboxylate*.—The corresponding acid (10 g., 0·038 mol.) and ethyl alcohol (10 c.c.) were heated under reflux with concentrated sulphuric acid (1·0 c.c.) for 1½ hours. The mixture was cooled, an equal volume of water added, and the whole extracted three times with ether. The extract was dried (Na_2SO_4). After removal of the ether, the *ester* distilled at 137°/0·15 mm. (9·0 g., 81%) (Found: Br, 27·0. $C_{13}H_{25}O_2Br$ requires Br, 27·2%).

Ethyl 10-*Fluorodecanecarboxylate*.—The bromo-ester (8 g., 0·027 mol.) and silver fluoride (8 g., 0·06 mol.) were heated at 75° with constant shaking. Separation of silver bromide occurred almost immediately and after 30 minutes the reaction appeared to be complete. The product was cooled, extracted with ether, filtered, and the ethereal extract washed with water. After drying (Na_2SO_4) and removal of the ether, the *fluoro*-ester, b. p. 82—84°/0·02 mm., 140—141°/11 mm., was obtained (1·2 g., 19%) (Found: F, 7·8. $C_{13}H_{25}O_2F$ requires F, 8·2%).

10-*Bromodecanecarboxyl Chloride*.—The corresponding acid (26·5 g., 0·1 mol.) and pure thionyl chloride (18 g., 0·15 mol.) were heated on a boiling water-bath for 1½ hours. The mixture was then directly distilled under reduced pressure. The *acid chloride* was obtained as a colourless liquid, b. p. 174—175°/10 mm. (23·5 g., 83%) (Found: total halogen, 40·7. $C_{11}H_{20}OClBr$ requires total halogen, 40·6%).

10-*Bromo*-1-*diazoacetyldecane*.—The foregoing chloride (9·1 g., 0·033 mol.) in dry ether was added to diazomethane (8·4 g., 0·2 mol.) in dry ether (350 c.c.) with mechanical stirring and efficient cooling in a tared flask at 0—5°. The solution was kept overnight in a refrigerator, and the *diazo-ketone* was isolated by evaporation under reduced pressure, a water-bath at a temperature of less than 30° being used. It was obtained as a yellow solid, m. p. *ca.* 30° (12·5 g., 98%).

11-*Bromoundecanecarboxyamide*.—The diazo-ketone (12·5 g., 0·043 mol.) was dissolved in warm, freshly-distilled dioxan (100 c.c.) and then treated with 20% aqueous ammonia (30 g., 0·35 mol.) and 10% aqueous silver nitrate (6 c.c.) under reflux in a large flask on a boiling water-bath. A vigorous effervescence occurred at once, and the clear yellow solution turned brown and opaque. The solution was heated for 25 minutes and then filtered hot. On cooling, a colourless, micro-crystalline solid was deposited. This was recrystallised from aqueous alcohol (charcoal). The pure *amide* (5·7 g., 49%) had m. p. 105°, and evolved ammonia on being heated with soda–lime (Found: N, 5·24. $C_{12}H_{24}ONBr$ requires N, 5·04%).

Ethyl 11-*Bromoundecanecarboxylate*.—The above amide (3·5 g., 0·013 mol.) was heated under reflux with absolute ethyl alcohol (20 c.c.) and concentrated sulphuric acid (6 c.c.) for 10 hours in an oil-bath at 130—140°. The product was cooled and extracted three times with ether. The extracts were thoroughly washed with water and dried (Na_2SO_4). After removal of the ether, the residue was fractionally distilled and the *ester* was obtained as a clear colourless liquid (1·8 g., 47%), b. p. 130—132°/2·5 × 10^{-2} mm. Redistillation gave a b. p. of 127°/9 × 10^{-3} mm. (Found: Br, 25·6. $C_{14}H_{27}O_2Br$ requires Br, 26·0%).

Ethyl 11-*Fluoroundecanecarboxylate*.—The bromo-ester (5 g., 0·017 mol.) and silver fluoride (5 g., 0·039 mol.) were gently heated in a water-bath at 80° for 15 minutes. Silver bromide was formed. The mixture was cooled and extracted with ether, and the ethereal extracts were washed twice with

water and dried (Na_2SO_4). After removal of the ether, the residue was fractionated, yielding a colourless liquid, b. p. 151°/11 mm., which contained F and no Br. The higher fraction, b. p. 155—180°/11 mm., was refluorinated by means of silver fluoride (3 g., 0·023 mol.) and 25 minutes' heating at 90°. The product was isolated as before and dried (Na_2SO_4). To the residue, after removal of the ether, was added the fraction of b. p. 151°/11 mm., and the combined liquids were fractionated. The *fluoro*-ester was obtained as a clear, colourless liquid (0·5 g., 12%), b. p. 152—153°/11 mm. (Found: F, 7·3. $C_{14}H_{27}O_2F$ requires F, 7·7%).

Preparation of Silver Fluoride.—Commercial silver fluoride was usually found to be unsuitable for the fluorinations mentioned in this paper. It was therefore prepared according to Moissan's method (*Bull. Soc. chim.*, 1891, **5**, 456, 880) from freshly prepared silver carbonate (from 106 g. of anhydrous sodium carbonate and 340 g. of silver nitrate) and 40% hydrofluoric acid (100 g.). The reaction was carried out in a large platinum dish. Recrystallisation from water was carried out in the dark and gave silver fluoride which contained water. In order to remove the last traces of water two methods were found to be successful: (*a*) The crystals were added to three times their volume of pure, dry benzene, which was then slowly distilled: the water–benzene azeotrope distilled first, and then pure benzene; the last traces of liquid were finally removed by connecting the distilling-flask to a water-pump and heating it to 140°. (*b*) The crystals were dried for several weeks in a vacuum over fresh phosphoric oxide in the dark. The former method had the advantage of speed. The pure silver fluoride was obtained as a brown powder, which was finely ground in a mortar before use. It was stored in a bottle covered with black paper. The yield varied between 125 g. and 150 g. (50—60% based on silver nitrate used).

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