

TOXIC FLUORINE COMPOUNDS CONTAINING THE C-F LINK—X*

RUPTURE OF THE C-F LINK BY ALKALI AND OTHER REAGENTS

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Abstract—The reactivity of the carbon fluorine bond in certain ω -fluorocarboxylic acids and esters with respect to nucleophilic attack has been examined. Heating under reflux with 30 per cent sodium hydroxide hydrolyses this type of compound and on this basis a method of fluorine analysis is suggested.

Phenyl magnesium bromide converts methyl fluoroacetate and fluoroacetyl chloride into 1:2:2-triphenylethanol. The so-called unreactive fluorine atom in methyl γ -fluorobutyrate is also removed by this reagent giving 2:2-diphenyltetrahydrofuran.

It has frequently been stated, in general terms, that the carbon and fluorine atoms in fluoroacetates and related compounds are very firmly bound.¹ By comparison with the corresponding chloro-, bromo- and iodo-compounds this is true, nevertheless we have collected a number of instances where the C-F link is easily ruptured, particularly by nucleophilic reagents. Attention is first drawn to the action of sodium hydroxide on fluoroacetates with a view to the development of a simple analytical method for the determination of the fluorine content.

Hitherto recommended methods for breaking down "fluoroacetates" have included:—

- (a) Fusion with sodium in an evacuated tube at 400°.^{2,3}
- (b) Fusion in a stainless steel bomb with sodium peroxide.³
- (c) For volatile compounds: heating with oxygen at 1250° in a platinum tube and absorbing the resulting hydrofluoric acid in water.⁴

After breakdown by a suitable method, the subsequent determination of fluoride can be carried out by any standard method, e.g. precipitation as lead chlorofluoride³ or titration with thorium nitrate.

When methyl fluoroacetate or fluoroacetic acid is heated under reflux with 10 per cent aqueous sodium hydroxide solution for one hour no fluoride ion is produced. Rather surprisingly little serious attention has been paid to the action of boiling concentrated (e.g. 30 per cent) aqueous alkali on the stability of the C-F link in these compounds. We have therefore investigated the reaction in detail by heating the fluoro compound under reflux with a large excess of 30 per cent sodium hydroxide solution for 1 hr. The free fluoride was then determined by precipitation as lead chlorofluoride followed by a Volhard volumetric estimation.³ Almost the whole of the fluorine was removed under these conditions. In some instances the fluorine was eliminated within 15 min.

* Part IX, *J. Chem. Soc.* 1929 (1953).

¹ B. C. Saunders, *Phosphorus and Fluorine* p. 115. Cambridge University Press (1957).

² P. J. Elvin and W. B. Ligett, *Industr. Engng. Chem. (Anal.)* **14**, 449 (1942).

³ N. B. Chapman, R. Heap and B. C. Saunders, *Analyst* **73**, 434 (1948).

⁴ O. I. Milner, *Industr. Engng. Chem. (Anal.)* **22**, 315 (1950).

After heating for 1 hr the results with fluoroacetamide were as follows:—

° F in various analyses	Av. % F and deviation	Calc. for $\text{CH}_2\text{F}\cdot\text{CONH}_2$
24.51, 24.22, 24.42.	24.42 ± 0.24	24.68%
24.28, 24.43, 24.35.		
24.34, 23.97, 24.72.		
24.93.		

Fluoroacetamide can be obtained in a highly purified condition⁵ and good analyses were obtained. With methyl fluoroacetate, 2-fluoroethanol, 3-fluoropropanol, β -fluoropropionic acid, and benzyl fluoroacetate the results tended to be low (about 1 per cent below the calculated value). The reason for this is at present being investigated. So far, however, it can be readily seen that boiling 30 per cent sodium hydroxide solution is capable of removing virtually the whole of the fluorine. Furthermore these preliminary experiments show that this reaction could form the basis of a rapid analytical method which moreover is safe with toxic and volatile materials. The indications at present are that the large excess of ions may to some extent interfere with the delicacy of the lead chlorofluoride method. Hence although excess of 30 per cent sodium hydroxide solution seems to remove all the fluoride, it may be better to use it in conjunction with some other method, e.g. distillation as hydrofluorosilicic acid and determination of fluoride in the distillate with thorium nitrate. This is at present being examined.*

Trifluoroacetic acid when heated under reflux for 1 hr with 30 per cent sodium hydroxide solution gave no fluoride ion.

Hoffmann⁶ made observations on the reactivity of the halogen atoms in a series of 1-bromo- and 1-chloro- ω -fluoroalkanes using N-sodium ethoxide in alcohol and N-potassium hydroxide in 70 per cent alcohol. He made conclusions about the behaviour of the C-F link when not influenced by neighbouring groups. In general there was great resistance to nucleophilic attack, the highest percentage of fluorine hydrolysed was 11 per cent compared with 82 per cent of bromine and 52 per cent of chlorine in a wide range of experiments under standard conditions. Also, as the fluorine atom becomes further separated from the other halogen atom in the molecule, so resistance to hydrolysis increases. The presence of the C-F bond increases the strength of the C-Cl and C-Br bonds in the 1-halo-2-fluoroethanes.

It is evident from the above that any reaction at the C-F link would have to be carried out with some strong nucleophilic reagent to have any chance of success. The obvious choice was the Grignard reagent. It is known that phenyl magnesium bromide converts methyl chloroacetate into 1:1-diphenyl-2-chloroethanol in small yield together with traces of diphenyl.⁷ We have shown that when methyl fluoroacetate reacted

* Work being carried out at present (D. L. E. Bronnert and B. C. Saunders) indicates that some F⁻ is probably retained on the walls of the flask in which the hydrolysis is carried out. This accounts for the low results often obtained. Using 1/20 of the above quantities (cf. Belcher and Macdonald⁵) the results tended to be rather erratic. Further work is necessary to establish the range of applicability of the method.

⁵ R. Belcher and A. M. G. Macdonald, *Mikrochim. Acta* 510 (1957).

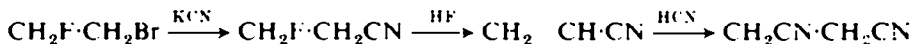
⁶ F. W. Hoffmann, *J. Org. Chem.* XIV, 105 (1949).

⁷ Shigeki Horie, *Mem. Inst. Sci. Ind. Res. Osaka Univ.* 7, 143 (1950).

under reflux, without cooling, with 3 moles of phenyl magnesium bromide, 1:2:2-triphenylethanol* was produced. This facile rupture of the C F link was unexpected and separate experiments showed that at least 77.5 per cent of the fluorine was eliminated as fluoride ion. When the reaction was carried out at 0°, 1:1-diphenyl-2-fluoroethanol was obtained. Three moles of phenyl magnesium bromide reacted with 1 mole of fluoroacetyl chloride, without cooling, to give 1:2:2-triphenylethanol.

Saunders *et al.*⁹ demonstrated the difference in reactivity of the fluorine and bromine atoms in 1-fluoro-2-bromoethane. For instance the latter reacted with potassium thiocyanate to give 2-fluoroethyl thiocyanate in 78 per cent yield. We have now shown, however, that ethanolic potassium cyanide will remove both the halogen atoms from 1-fluoro-2-bromoethane giving ethylene dicyanide in 50 per cent yield.

Since alcoholic potassium cyanide solution does not convert methyl fluoroacetate to methyl cyanoacetate (but yields only potassium fluoroacetate) and in view of Hoffmann's experiments cited above, the following mechanism is suggested for the action of potassium cyanide on 1-fluoro-2-bromoethane:

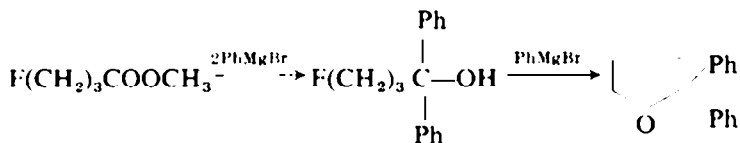


This emphasises the fact that the C F bond is weakened when the carbon is β to a positive carbon atom.

The ease with which the β -fluorine atom can be lost is demonstrated by the difficulty in preparing β -fluoropropionic acid by any kind of substitution reaction. We have also shown that whereas boiling 10 per cent sodium hydroxide solution did not remove any fluorine from methyl fluoroacetate in 1 hr it removed all the fluorine from β -fluoropropionic acid under the same conditions. Even on allowing β -fluoropropionic acid to stand at room temperature for 24 hr with 10 per cent aqueous sodium hydroxide, removal of 94.6 per cent of the fluorine took place.

It was considered that, in the next homologue, γ -fluorobutyric acid, the fluorine was too far removed from the carboxyl group to undergo facile elimination as hydrogen fluoride.

Methyl γ -fluorobutyrate was allowed to react with 3 equivalents of phenyl magnesium bromide in the cold followed by heating under reflux. A crystalline solid, m.p. 65-66° was obtained. The compound was fluorine-free, did not contain a hydroxyl group and showed no signs of unsaturation. Infra-red spectra proved the absence of a hydroxyl group, but showed a strong band at 1050 cm^{-1} in agreement with the C—O—C stretching frequency found in tetrahydrofuran and related compounds. Moreover the analysis and reactions agreed with that of 2:2-diphenyltetrahydrofuran and the following pathway for the reaction is suggested:



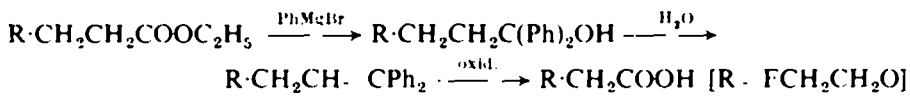
* One might expect that 1:1:2-triphenylethanol would be formed, but this is not so. A mixed m.p. showed that our product (1:2:2-triphenylethanol) and the compound obtained by reducing 1-bromo-1:1-diphenylacetophenone were identical (cf. Boyle *et al.*⁹).

⁹ J. S. W. Boyle, A. McKenzie and W. Mitchell, *Ber. Dtsch. Chem. Ges.* **70**, 2156 (1937).

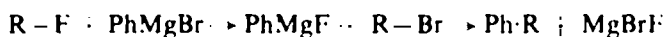
⁹ B. C. Saunders, G. J. Stacey and I. G. E. Wilding, *J. Chem. Soc.* 773 (1949).

Under the same conditions phenyl magnesium bromide and methyl γ -chlorobutyrate failed to produce the diphenyltetrahydrofuran.

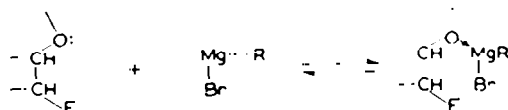
In the course of our systematic investigations of toxic organo-fluorine compounds,¹⁰ we attempted to degrade ethyl β -2-fluoroethoxypropionate by the Barbier Wieland reaction as follows:



The first product actually obtained was diphenyl-2:2'-bromoethoxyethyl carbinol as a result of halogen interchange. This appeared to be the first recorded example of the exchange of fluorine by bromine. Later Hoffmann found that the reaction of aliphatic-bound fluorine with a Grignard reagent could be summarised as follows:



In view of this, it is difficult to state categorically whether the ether linkage β to the C-F bond has a specific influence on the halogen interchange. Doubtless, the fact that the Grignard reagent can co-ordinate with the ether linkage, thus bringing the halogen into close proximity, helps the reaction.



In any case it was of interest to determine whether the lower homologue of the series would also undergo the reaction with the same ease. Accordingly ethyl 2-fluoroethoxy acetate was allowed to react with three equivalents of phenyl magnesium bromide. A fluorine-free compound, m.p. 64-6°, was obtained. Analysis and other evidence, including infra-red spectra, showed it to be diphenyl 2-bromoethoxymethyl carbinol, $\text{BrCH}_2\text{CH}_2\text{O}\cdot\text{CH}_2\text{C}(\text{Ph})_2\text{OH}$.

EXPERIMENTAL

Determination of fluorine in a C-F compound. An amount of the compound, such as to contain about 200 mg of fluorine was weighed into a 25 ml round-bottomed flask. Pure sodium hydroxide (10 ml, 30 per cent aqueous solution) was added and the mixture heated under reflux for 1 hr. The solution was then made up to 100 ml, and the fluoride ion determined in 25 ml by the lead chlorofluoride method.³ Results for fluoroacetamide appear on p. 38.

Reaction between phenyl magnesium bromide and methyl fluoroacetate. Bromobenzene (15.7 g) was dissolved in dry ether (50 ml) and half of the solution added to magnesium turnings (2.5 g). After the initial reaction had subsided, the remainder of the bromobenzene was added slowly and the mixture heated under reflux for 15 min, then cooled in ice-water, and a solution of methyl fluoroacetate (3.2 g) in dry ether (15 ml) added with stirring. A vigorous action ensued and a white solid separated which was soon replaced by a heavy oil. The mixture was heated under reflux for 15 min, poured on to a mixture of ice (100 g) and 10 per cent sulphuric acid (60 ml) and

¹⁰ F. J. Buckle and B. C. Saunders, *J. Chem. Soc.* 2774 (1949).

then steam-distilled. On cooling overnight at 0°, the oil which had distilled over solidified (0.514 g) and was readily sublimed at 40°/0.5 mm and recrystallised from ethanol, m.p. 68–9°. Mixed m.p. with authentic diphenyl, 69–70°.

The yellow oil left in the flask after steam distillation was extracted with ether and dried (Na₂SO₄). The aqueous layer contained fluoride (see below), the ethereal layer was fluorine-free. The ethereal layer was evaporated and a viscous oil (6.24 g) remained. On warming the oil with light petroleum (b.p. 40°–60°) and then cooling to 0°, yellow waxy crystals (1.5 g) separated. These were recrystallised from light petroleum (b.p. 40°–60°) and had m.p. 86°. (Found: C, 87.6; H, 6.7. Calc. for C₂₀H₁₈O: C, 87.6; H, 6.6 per cent). Mixed m.p. with authentic 1:2:2-triphenylethanol (m.p. 87°) gave no depression.

The product (100 mg) was heated under reflux for 30 min with acetic anhydride (2 ml) and poured into water. The oil which separated solidified and was recrystallised from benzene-light petroleum (b.p. 60–80°) mixture. The 1:2:2-triphenylethylacetate thus obtained had m.p. 158° and could be sublimed. (Found: C, 83.7; H, 6.2. C₂₂H₂₀O₂ requires C, 83.5; H, 6.4 per cent).

Analysis of the aqueous solution for fluoride ion. Methyl fluoroacetate (2.57 g) was allowed to react with phenyl magnesium bromide as above. The product was not steam distilled, but extracted with ether. The aqueous solution was made up to 500 ml. This solution (25 ml) and concentrated sulphuric acid (25 ml) were mixed and steam distilled in the presence of powdered glass. Fluoride was determined in the filtrate by titration with thorium nitrate.¹¹ (Found: F⁻ in 500 ml = 0.41 g. Total fluorine in methyl fluoroacetate = 0.53 g therefore the amount of fluorine converted to F⁻ by Grignard reaction = 77.5 per cent).

Reaction between phenyl magnesium bromide and methyl fluoroacetate at 0°. The Grignard reagent [bromobenzene (15.7 g), magnesium (2.5 g), ether (50 ml)] was placed in a freezing mixture and methyl fluoroacetate (3.2 g) added dropwise with vigorous stirring so that the temperature did not rise above 0°. The product was acidified, and on standing overnight a yellow oil and white crystals were obtained. The latter (1:1-diphenyl-2-fluoroethanol) were recrystallised from carbon tetrachloride and then from light petroleum (b.p. 60–80°). Yield 2.8 g m.p. 71–2°. (Found: C, 77.2; H, 5.8. Calc. for C₁₄H₁₃OF: C, 77.8; H, 6.0 per cent).

Reaction between phenyl magnesium bromide and fluoroacetyl chloride. To the Grignard reagent from bromobenzene (47.1 g), cooled to 0°, fluoroacetyl chloride (9.65 g) in ether (100 ml) was added with stirring. A vigorous reaction followed and an orange-coloured oil separated. The mixture was then heated under reflux for 15 min, poured onto ice (180 g) and dilute sulphuric acid (180 ml) and the ether layer separated, dried (Na₂SO₄) and distilled. A red oil (19.2 g) remained. (The aqueous layer gave a positive test for fluoride ion.) On stirring the oil with light petroleum, crystallisation slowly took place and the solid was recrystallised from ethanol and had m.p. 145–151° (1 g). This was sublimed at 120°/0.2 mm giving a residual solid, m.p. 120° and a liquid sublimate which ultimately crystallised and was recrystallised from light petroleum (b.p. 40–60°). M.p. and mixed m.p. with authentic 1:2:2-triphenylethanol, 85°.

Action of potassium cyanide on bromofluoroethane. Bromofluoroethane (50 g), potassium cyanide (26 g), ethanol (90 ml) and water (15 ml) were heated under reflux

¹¹ B. C. Saunders, *Phosphorus and Fluorine* p. 115. Cambridge University Press (1957).

for 6 hr. The mixture was cooled, allowed to stand for 2 hr. Solid was filtered off and ethanol removed from the filtrate and the residue fractionated:

(1) B.p. below 20°/21 mm (7.23 g). F(-). CN(-).

(2) B.p. 25°/21 mm (2.5 g). F(-). CN(-).

(3) B.p. 116-120°/2 mm, with charring. (8.0 g of solid). F(-). CN(-). Sublimed readily giving crystals m.p. 53-54°. (Found: N, 34.9. Calc. for $C_2H_4N_2$: N, 35.0 per cent). Mixed m.p. with authentic succinonitrile showed no depression.

Action of potassium cyanide on methyl fluoroacetate. Methyl fluoroacetate (27.6 g), potassium cyanide (18.3 g), methanol (90 ml) and water (5 ml) were heated under reflux for 1 hr, and the mixture filtered. The methanol was slowly distilled off until crystals began to separate. These were dissolved in water giving a cloudy solution which was centrifuged, purified with charcoal and concentrated. The potassium fluoroacetate that separated was recrystallised from ethanol. (Found: C, 20.9; H, 1.8. Calc. for $C_2H_2O_2FK$: C, 20.7; H, 1.7 per cent).

Action of phenyl magnesium bromide on methyl γ -fluorobutyrate. The Grignard reagent [bromobenzene (16.5 g), magnesium (2.6 g) and ether (50 ml)] was cooled to 0° and methyl γ -fluorobutyrate¹² (4.2 g) in ether (10 ml) was added with stirring, and then heated under reflux for 15 min. The mixture was cooled and acidified with dilute sulphuric acid. The ether layer was separated, and the aqueous layer extracted with ether (2 \times 10 ml). The ether layers were washed with sodium bicarbonate solution, water and dried ($MgSO_4$). After distilling off the ether, the residue (8.6 g) was distilled.

Two fractions were obtained:

(1) B.p. 80°/0.9 mm and was diphenyl m.p. 67.5°.

(2) B.p. 110-130°/0.9 mm and solidified (2.3 g). This was fluorine-free and recrystallised from ethanol as needles, m.p. 65.5°. The 2:2-diphenyltetrahydrofuran thus obtained had mixed m.p. 40-45° with diphenyl. (Found: C, 85.95; H, 7.3. $C_{16}H_{10}O$ requires C, 85.7; H, 7.1 per cent).

Action of phenyl magnesium bromide on ethyl 2-fluoroethoxyacetate. Ethyl 2-fluoroethoxyacetate¹⁰ (5 g) in dry ether (15 ml) was added slowly to the Grignard reagent [from magnesium (2.4 g) and bromobenzene (15.7 g)]. The mixture was boiled under reflux for 25 min, cooled, poured on to ice (100 g) and dilute sulphuric acid (80 ml), and steam-distilled. Diphenyl (0.5 g) came over.

The aqueous residue was extracted with ether, dried ($MgSO_4$) and the ether distilled off and the product recrystallised from ethanol and then from light petroleum (b.p. 40-60°). The diphenyl 2-bromoethoxymethyl carbinol thus obtained had m.p. 64-6°. (Found: C, 59.5; H, 5.1. $C_{12}H_{17}OBr$ requires C, 59.8; H, 5.3 per cent).

One of us (P. M.-S.) acknowledges with thanks a D.S.I.R. maintenance grant.

¹² Private communication from (the late) M. S. Kharasch.