Tetrahedron, 1960, Vol. 10, pp. 160 to 163. Pergamon Press Ltd. Printed in Northern Ireland

TOXIC FLUORINE COMPOUNDS CONTAINING THE C—F LINK—XI*

LABILITY OF THE FLUORINE ATOM IN 2-FLUOROETHANOL

D. L. E. BRONNERT and B. C. SAUNDERS
University Chemical Laboratory, Lensfield Road, Cambridge

(*Received* 30 *March* 1960)

Abstract—It has been shown that 2-fluoroethanol, often described as a chemically unreactive compound, will react with a number of nucleophilic reagents.

In Part X of this series[1] we gave experimental evidence to show that, although the C—F link in fluoroacetic acid is often correctly described as strong, there are many reactions in which this bond is easily broken. Thus whereas boiling 10 per cent aqueous sodium hydroxide is without effect on the C—F link in fluoroacetic acid, boiling 30 per cent aqueous sodium hydroxide will give a quantitative elimination of F^-. Similarly Grignard reagents will rupture certain C—F links giving well-defined products. Thus methyl fluoroacetate reacts with phenyl magnesium bromide to give triphenylethanol and methyl γ-fluorobutyrate gives 2,2-diphenyltetrahydrofuran.

It has often been stated that the C—F link in 2-fluoroethanol is a firm one, although very little precise evidence has been produced in support of this observation. It is claimed that in fluoroethanol, "the fluorine atom is unaffected by all but the most drastic treatment".[2] McCabe and Warner[3] observed that the reaction between fluoroethanol and hydroxyl ion is so slow that the solvent media effects were studied only at 60°. They were, however, able to show the presence of ethylene oxide in the resulting solution. Without giving any details of concentrations used, Swarts[4,5] made passing reference to the fact that 2-fluoroethanol is attacked by alkali whereas sodium fluoroacetate gave no F^- under the conditions of his experiment.

Our interest in the reactivity of the fluorine atom in 2-fluoroethanol was stimulated by the observation that a pure sample of the compound, left in a bottle for several years, gave the iodoform reaction in the cold and a positive test for the fluoride ion. Freshly distilled fluoroethanol does not give the iodoform reaction.[6] Moreover ethylene chlorohydrin, left under similar conditions and for a similar period does not give an immediate iodoform reaction in the cold nor does it give a positive test for chloride ion.

The evidence accumulated so far points to the fact that iodoform is produced from

---

* Part X: P. Mirosevic-Sorgo and B. C. Saunders, *Tetrahedron* **5**, 38 (1959).

[1] P. Mirosevic-Sorgo and B. C. Saunders, *Tetrahedron* **5**, 38 (1959).

[2] F. L. M. Pattison, *Toxic Aliphatic Compounds* p. 24. Elsevier, Amsterdam (1959).

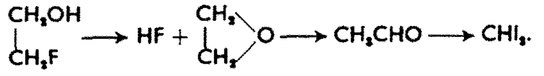
[3] C. L. McCabe and J. C. Warner, *J. Amer. Chem. Soc.* **70**, 4031 (1948).

[4] F. Swarts, *Bull. Acad. Roy. Belg.* 7 (1914).

[5] F. Swarts, *J. Chim. Phys.* **17**, 3 (1919).

[6] C. C. Price and W. G. Jackson, *J. Amer. Chem. Soc.* **69**, 1065 (1947).

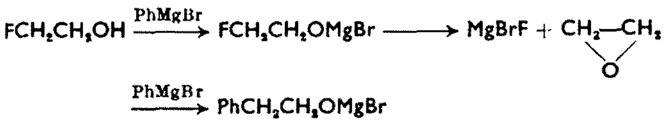
acetaldehyde formed by the rearrangement of ethylene oxide obtained by the dehydrofluorination of fluoroethanol:



Support for this mechanism is also provided by an earlier observation by Saunders and Stacey,[7] who noted that, in the preparation of fluoroethanol from ethylene chlorohydrin and potassium fluoride, crotonaldehyde is always produced as an impurity. This is readily explained on the basis of the initial production of acetaldehyde according to the above equation.

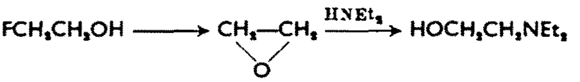
Details are given in the Experimental of a procedure that has enabled us to demonstrate the presence of both ethylene oxide and acetaldehyde in the reaction product obtained by action of very concentrated sodium hydroxide solution on fluoroethanol. It has also been shown that fluoroethanol is sensitive to *cold* aqueous alkali. When, for example, fluoroethanol was allowed to stand at room temperature for 12 hours with 10 per cent sodium hydroxide solution, 80 per cent of the fluoride appeared as fluoride. In these circumstances, the C—F link in methyl fluoroacetate was not affected.[1]

On heating 2-fluoroethanol with phenyl magnesium bromide in ether, the fluorine atom was eliminated and phenylethanol resulted. The reaction most probably follows the course.



On heating 2-fluoroethanol with sodium phenoxide, 2-phenoxyethanol was obtained. Using similar conditions sodium thiophenoxide gave a 64 per cent yield of 2-hydroxyethyl phenyl sulphide, and sodium sulphide gave a 60 per cent yield of di(2-hydroxyethyl) sulphide. Attempts to obtain ethylene cyanhydrin from 2-fluoroethanol and sodium cyanide were not successful for under mild conditions no reaction occurred, whereas heating under reflux resulted in a vigorous reaction with the evolution of ammonia owing to the hydrolysis of the cyanhydrin first formed. Under these conditions 60 per cent of the fluorine of the fluoroethanol appeared as fluoride ion.

When a mixture of diethylamine and 2-fluoroethanol was heated for as long as 24 hours no reaction took place. However, when the amine and fluoroethanol were allowed to react in the presence of 0·5 mole of sodium hydroxide for only 40 minutes 2-hydroxyethyl diethylamine was obtained in 40 per cent yield. It is evident that in this case ethylene oxide is first formed by the action of the alkali on fluoroethanol, and subsequently reacts with diethylamine.



Thioglycollic acid reacted very readily with fluoroethanol when heated together under reflux in the presence of alkali, the product being hydroxyethylthioglycollic acid.

---

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

No significant reactions were observed between 2-fluoroethanol and potassium phthalimide, sodium *p*-toluenesulphonate, potassium thiocyanate, sodiom diethyl malonate, piperidine and thiourea.

It may be concluded that aliphatic fluorine compounds containing the C—F link are in general relatively unstable if they are able to lose hydrogen fluoride and form an intermediate oxide-ring compound. It can be expected that compounds which, like 2-fluoroethanol, have fluorine and hydroxyl groups on adjacent carbon atoms will lose hydrogen fluoride fairly readily.

In this connexion the relative instability of fluoroacetid acid to concentrated alkali should be considered in relation to the work of Grunwald and Winstein[8] who suggested "α-lactone" formation for other monohalogeno-carboxylic acids.

EXPERIMENTAL

All experiments were carried out in a fume-cupboard fitted with a powerful fan.

The action of concentrated sodium hydroxide solution on 2-fluoroethanol. 2-Fluoroethanol (32 g, 0·5 mole) was placed in a three-necked flask fitted with a stirrer and reflux condenser. The outlet of the condenser was fitted with glass tubing leading to an acetone-solid carbon dioxide trap. Conc sodium hydroxide solution (40 g, 1·0 mole in 40 ml water) was added dropwise with vigorous stirring. When about half of the sodium hydroxide solution had been added, a very vigorous reaction ensued. When this had moderated, the remainder of the sodium hydroxide solution was added during 10 min. The liquid (6 g) that collected in the trap was shown to be a mixture of ethylene oxide and acetaldehyde as follows. To the liquid (1 g) were added (a) cold conc hydrochloric acid (5 ml) and (b) 2,4-dinitrophenylhydrazine reagent (5 ml). The first reagent yielded ethylene chlorohydrin identified as its 1-naphthylurethane, m.p. 100° (lit. 101°). (Found: C, 62·2; H, 5·0; N, 5·4. Calc. for $C_{13}H_{12}ClNO_2$: C, 62·3; H, 4·85; N, 5·6%). The second reagent (b) yielded acetaldehyde 2,4-dinitrophenylhydrazone, m.p. 148° (lit. 148°, 168°). (Found: C, 42·7; H, 3·9; N, 25·5. Calc. for $C_8H_8N_4O_4$: C, 42·9; H, 3·6; N, 25·0%).

Reaction between 10% *aqueous sodium hydroxide solution and 2-fluoroethanol.* 2-Fluoroethanol (1·2 g) and 10% aqueous sodium hydroxide solution (20 ml) were mixed and allowed to stand overnight at 20°. The solution was then made up to 100 ml with distilled water and aliquot portions of 10 ml were titrated using thorium nitrate solution.[9] Results showed that 84·5 ± 0·5% of fluoroethanol had been hydrolysed to F^-.

Reaction between phenyl magnesium bromide and 2-fluoroethanol. Phenyl magnesium bromide was made from bromobenzene (157 g, 1 mole) and magnesium (24·3 g) in ether (500 ml). After allowing to cool, fluoroethanol (19·3 g, 0·3 mole) in ether (100 ml) was added slowly with stirring. A vigorous reaction took place causing the ether to boil. After all the fluoroethanol had been added and the reaction had subsided, the mixture was heated under reflux for 30 min and set aside overnight. The product was poured on to ice (1 kg) and conc hydrochloric acid (200 ml). After stirring, the aqueous layer (A) was separated, and the ethereal layer was dried ($MgSO_4$) and the ether distilled off. The residue was distilled under reduced pressure and gave small quantities of diphenyl, bromobenzene and terphenyl and a fraction of b.p. 108–115°/20 mm (5 g, 13·5%). This proved to be 2-phenylethanol and was converted into its 1-naphthylurethane, m.p. 118·5–119·5° (lit. 119°). (Found: C, 79·2; H, 6·3; N, 4·85. Calc. for $C_{19}H_{17}NO_2$: C, 79·4; H, 6·0; N, 4·8%).

A fluoride determination on the aqueous layer (A), using the thorium nitrate method,[9] showed that 82% of the fluoroethanol had been converted to F^-.

Sodium phenoxide and 2-fluoroethanol. Phenol (47 g, 0·5 mole) was dissolved in a slight excess of sodium hydroxide solution (70 ml, 30%), and fluoroethanol (32 g, 0·5 mole) was added. The mixture was heated under reflux. After about 10 min the reaction became very vigorous and the heating was discontinued for a few minutes. Sodium fluoride gradually separated. When the reaction had subsided, the heating was continued, making a total of 30 min in all. After allowing to cool overnight, the liquid was decanted and extracted with ether (2 × 200 ml) and dried ($MgSO_4$). The ether was

[8] E. Grunwald and S. Winstein, *J. Amer. Chem. Soc.* **70**, 841 (1948).

[9] B. C. Saunders, *Some aspects of the Chemistry and Toxic Action of Organic Compounds Containing Phosphorus and Fluorine* p. 210. Cambridge University Press, London (1957).

removed and the residue distilled giving a fraction of b.p. 135–160°/40 mm. This was refractionated and then had b.p. 83–85°/0·3 mm (38 g, 55%). (Found: C, 69·9; H, 7·1. Calc. for $C_8H_{10}O_2$: C, 69·6; H, 7·3%). This 2-phenoxyethanol was converted into its 1-naphthylurethane, m.p. 124°. (Found: C, 73·7; H, 6·2; N, 4·8. Calc. for $C_{19}H_{17}NO_3$: C, 74·2; H, 5·7; N, 4·6%).

Sodium thiophenoxide and 2-fluoroethanol. The conditions employed were similar to those given in the previous reaction. Thiophenol (22 g, 0·2 mole) dissolved in sodium hydroxide solution (27 ml, 30%) and 2-fluoroethanol (12·8 g, 0·2 mole) were used. 2-Hydroxyethyl phenyl sulphide was obtained as a fraction of b.p. 100–102°/0·3 mm (19·3 g, 63·5%). (Found: C, 61·8; H, 6·6; S, 20·85. Calc. for $C_8H_{18}OS$: C, 62·3; H, 6·5; S, 20·8%). This was converted into its 1-naphthylurethane, m.p. 69–70°. (Found: C, 71·1; H, 5·9; N, 4·5. Calc. for $C_{19}H_{17}NO_2S$: C, 70·6; H, 5·3; N, 4·3%).

Sodium sulphide and 2-fluoroethanol. Sodium sulphide (80 g of $Na_2S,9H_2O$, 0·5 mole) was dissolved in water (100 ml) and 2-fluoroethanol (32 g, 0·5 mole) added. The mixture was heated under reflux. Heating was discontinued after a few minutes to prevent the violent reaction from getting out of control. Solid was precipitated. When the reaction had moderated, the heating was continued; the total time being ½ hr. After allowing to cool, the liquid (A) was decanted from the solid (B), and water evaporated from (A) under reduced pressure (30–40 mm) on a boiling water bath. The solid and liquid remaining from (A) were added to the original solid (B, also dried) and extracted with hot absolute ethanol (2 × 300 ml), and filtered (the solid residue was predominantly sodium fluoride). The ethanol was distilled off and the fraction, b.p. 160–163°/13 mm of di(2-hydroxyethyl) sulphide was collected and redistilled at b.p. 110°/0·05 mm (18·2 g, 59·6%). (Found: C, 39·3; H, 8·4; S, 25·6. Calc. for $C_4H_{10}O_2S$: C, 39·3; H, 8·3; S, 26·2%).

Sodium cyanide and 2-fluoroethanol. Water (10 ml) and sodium cyanide (25 g, 0·51 mole) were stirred together and 2-fluoroethanol (32 g, 0·5 mole) was added. The mixture was heated under reflux and stirred vigorously. After about 15 min the reaction became violent and heating was discontinued. The mixture continued to boil without further heating for about ½ hr, ammonia being evolved. The mixture, after cooling was extracted with water and ether. The ethereal layer was dried (Na_2SO_4) and shown to contain no ethylene cyanohydrin. A fluoride determination on the aqueous layer showed that at least 60% of the total fluorine had been converted to F^-.

Diethylamine and 2-fluoroethanol. 2-Fluoroethanol (32 g, 0·5 mole) and diethylamine (73 g, 1 mole) were placed in a flask fitted with a very efficient reflux condenser. Sodium hydroxide (20 g, 0·5 mole) in water (20 ml) was added. After about 5 min the mixture began to boil without the application of external heating and continued to do so for 45 min, sodium fluoride separated out meanwhile. After cooling, the mixture was extracted with benzene (200 ml) filtered and dried (K_2CO_3). After distilling off the benzene, the 2-hydroxyethyl diethylamine, b.p. 50–60°/15 mm was collected. It redistilled at b.p. 58–62°/15 mm (23·8 g, 41%). The picrate was recrystallized from ethanol and had m.p. 78° (lit. 79°). (Found: N, 16·2. Calc. for $C_{12}H_{18}N_4O_8$: N, 16·2%).

Thioglycollic acid and 2-fluoroethanol. A mixture of thioglycollic acid (9·4 g, 0·1 mole), sodium hydroxide (8 g, 0·2 mole) in water (80 ml) and 2-fluoroethanol (6·4 g, 0·1 mole) was heated under reflux for 1 hr. After cooling and filtering, copper acetate (9·1 g, 0·5 mole) in water (200 ml) was added. After 12 hr the liquid was decanted from the magnificent dark blue crystals of copper hydroxyethylthioglycollate which had separated. These were washed with water and dried *in vacuo* and were still contaminated with traces of copper thioglycollate. (13·8 g, 82·5%) (Found: C, 27·95; H, 4·3; S, 19·95. Calc. for $C_8H_{14}O_6S_2Cu$: C, 28·8; H, 4·2; S, 19·2%).

Acknowledgement—One of us (D. L. E. B.) is indebted to the Department of Scientific and Industrial Research for a maintenance allowance.