669. *Organic Fluorine Compounds. Part XX.* Some Reactions of 1-Chloro-3-fluoropropan-2-ol and Epifluorohydrin.*

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In 1-chloro-3-fluoropropan-2-ol the chlorine atom is much more prone to nucleophilic attack than the fluorine. The reactions with potassium cyanide, sodium ethoxide, and sodium phenoxide have been studied. Also in epifluorohydrin the oxide ring is opened by diethyl sodiomalonate without attack on the fluorine atom. Alkyl- and aryl-magnesium bromide with epifluorohydrin give 1-bromo-3-fluoropropan-2-ol; phenyl-lithium gives 1-fluoro-3-phenylpropan-2-ol.

The preparation of alkyl fluorolactates and fluoropyruvates is described.

The easy availability, from epichlorohydrin, of 1-chloro-3-fluoropropan-2-ol and epifluorohydrin [1,2] has led us to study the reactions of these compounds. The publication of similar experiments by Cherbuliez and his co-workers [3] prompts us to report our results.

* Part XIX, Bergmann and Shahak, *J.*, 1960, 5261.

[1] Bergmann and Cohen, *J.*, 1958, 2259.
[2] Pattison and Norman, *J. Amer. Chem. Soc.*, 1957, **79**, 2311.
[3] Cherbuliez, Yazgi, and Rabinowitz, *Helv. Chim. Acta*, 1960, **43**, 1135; Cherbuliez, de Picciotto, and Rabinowitz, *ibid.*, p. 1143.

The chlorine atom in 1-chloro-3-fluoropropan-2-ol is, as expected, much more reactive than the fluorine towards nucleophilic reagents. Sodium cyanide yields γ-fluoro-β-hydroxybutyronitrile; the yield is somewhat better than that reported for the reaction with potassium cyanide. This nitrile was converted by reaction with ethanol and hydrogen chloride into the corresponding ethyl ester and the latter dehydrated with phosphorus pentoxide to ethyl γ-fluorocrotonate. With sodium ethoxide and sodium phenoxide, the chloropropanol was converted into 1-ethoxy-3-fluoro- and 1-fluoro-3-phenoxy-propan-2-ol, respectively, which were then oxidised to the disubstituted acetones.

Analogously, the ethylene oxide ring in epifluorohydrin is more open to nucleophilic attack than the fluorine atom. Cherbuliez *et al.*[3] have already described, *inter alia*, the reaction with dimethylamine which ultimately led to *N*-acetyl-2-fluoromethylcholine. In addition to this reaction, which we carried out in almost the same way, we observed that diethyl sodiomalonate gives δ-fluoro-γ-valerolactone after acid hydrolysis of the primary product. This reaction is analogous to that of ethylene oxides in general, including epichlorohydrin.[4]

With methyl-, butyl-, or phenyl-magnesium bromide, 1-bromo-3-fluoropropan-2-ol was obtained; only in the case of phenylmagnesium bromide a small amount of the expected 1-fluoro-3-phenylpropan-2-ol was secured. When phenyl-lithium was used at −70°, a 52% yield of the phenylpropanol was obtained.

As to the formation of 1-bromo-3-fluoropropan-2-ol, the mechanism of such reactions with ethylene oxides have been discussed by Kharasch and Reinmuth; [5] as to the reaction with phenyl-lithium, it is worthy of note that epichlorohydrin with phenylmagnesium bromide also gives, together with 1-bromo-3-chloropropan-2-ol, 1-chloro-3-phenylpropan-2-ol,[6] and with butyl-lithium gives 1-chlorohexan-2-ol.[7]

The preparation of 1-fluoropropane-2,3-diol from epifluorohydrin and its oxidation to 3-fluorolactic acid with nitric acid,[2] in analogy with the known preparation of 3-chlorolactic acid,[8] have been described before. However, the fluorolactic acid can be prepared more easily if the diol is replaced by the isopropylidene derivative, which is obtained in excellent yield from glycerol.[9] 3-Fluorolactic acid is most easily isolated from the reaction product as its ethyl or butyl ester.

Ethyl 3-fluorolactate can be converted into ethyl fluoropyruvate by reaction with *N*-bromosuccinimide (1 mole); with an excess of this reagent, ethyl bromofluoropyruvate is obtained, in analogy to the formation of ethyl bromopyruvate from ethyl lactate.[10] It is worthy of note that both ethyl fluoropyruvate and bromofluoropyruvate give, with 2,4-dinitrophenylhydrazine, the osazone of ethyl mesoxaldehydate.[11] In the former case, the reaction is the same as for the 2-hydroxycarbonyl compounds; under appropriate conditions, the normal 2,4-dinitrophenylhydrazone of ethyl fluoropyruvate can be obtained.

Experimental

γ-Fluoro-β-hydroxybutyronitrile.—A stirred mixture of 1-chloro-3-fluoropropan-2-ol (40 g.), sodium cyanide (18 g.), and water (10 g.) was heated at 50—60° for 2 hr. To the cooled solution, a large excess of acetone was added and the filtered solution distilled. The *nitrile* (18 g., 49%) boiled at 125—128°/15 mm. (Found: C, 46·1; H, 6·4; F, 18·1. C_4H_6FNO requires C, 46·6; H, 5·8; F, 18·4%).

[4] Traube and Lehmann, *Ber.*, 1899, **32**, 720; 1901, **34**, 1971; Haller, *Bull. Soc. chim. France*, 1899, **21**, 564; *Compt. rend.*, 1906, **142**, 1471.
[5] Kharasch and Reinmuth, "Grignard Reactions of Non-metallic Substances," Prentice-Hall Inc., New York, 1954, p. 961.
[6] Fourneau and Tiffeneau, *Bull. Soc. chim. France*, 1907, **1**, 1227.
[7] Gilman, Hofferth, and Honeycutt, *J. Amer. Chem. Soc.*, 1952, **74**, 1594.
[8] Koelsch, *J. Amer. Chem. Soc.*, 1930, **52**, 1105.
[9] Bergmann and Shahak, *Chem. and Ind.*, 1958, 157.
[10] Stuckwisoh, Hammer, and Blau, *J. Org. Chem.*, 1957, **22**, 1678.
[11] Bergmann and Shahak, *J.*, 1960, 462, 3225.

Ethyl γ-Fluoro-β-hydroxybutyrate.—A slow stream of hydrogen chloride was passed for 1 hr. through a boiling mixture of the foregoing compound (33 g.), 95% ethanol (33 g.), and water (3·5 ml.). To the cooled solution, an excess of ether was added. After 6 hr. the ammonium chloride was filtered off and the ethereal solution distilled. The *ester* (32 g., 67%) boiled at 104—108°/18 mm. (Found: C, 47·8; H, 7·0. $C_6H_{11}FO_3$ requires C, 48·0; H, 7·3%).

Ethyl γ-Fluorocrotonate.—Phosphorus pentoxide (10 g.) was added in small portions to a solution of the hydroxy-ester (16 g.) in benzene (30 ml.), and the mixture refluxed for 15 min. The benzene solution was decanted from the brown precipitate and distilled. The *ester* (7 g., 50%) boiled at 66—67°/21 mm. (Found: C, 54·8; H, 6·8. $C_6H_9FO_2$ requires C, 54·5; H, 6·8%).

1-*Ethoxy*-3-*fluoropropan*-2-*ol.*—1-Chloro-3-fluoropropan-2-ol (25 g.) was refluxed in 2N-ethanolic sodium ethoxide (100 ml.) for 2 hr., filtered, and distilled. The *product* (6 g., 22%) had b. p. 71—72°/28 mm. and n_D^{29} 1·3995 (Found: C, 49·5; H, 9·0; F, 15·4. $C_5H_{11}FO_2$ requires C, 49·2; H, 9·0; F, 15·6%).

1-*Ethoxy*-3-*fluoroacetone.*—To a mixture of the foregoing alcohol (31 g.), sodium dichromate (41·5 g.), and water (70 ml.), a mixture of concentrated sulphuric acid (69·5 g.) and water (20 ml.) was added at 15—20° with stirring. After 2 hr. the solution was extracted with ether, and the ethereal solution dried and distilled. The *ketone* (18 g., 58%) boiled at 63—65°/25 mm. (Found: C, 50·0; H, 7·4; F, 15·9. $C_5H_9FO_2$ requires C, 50·0; H, 7·5; F, 15·8%).

1-*Fluoro*-3-*phenoxypropan*-2-*ol.*—During 3 hr., a mixture of 1-chloro-3-fluoropropan-2-ol (23 g.), phenol (19 g.), and sodium hydroxide (8·5 g.) in water (70 ml.) was refluxed. The product was extracted with ether, and the ethereal solution dried and distilled twice. The new *alcohol* (28 g., 89%) boiled at 110—111°/4 mm. and had n_D^{30} 1·5138 (Found: F, 11·2. $C_9H_{11}FO_2$ requires F, 11·2%).

1-*Fluoro*-3-*phenoxyacetone.*—To a solution of the foregoing compound (24 g.) in acetone (70 ml.), a mixture of chromic anhydride (15 g.), concentrated sulphuric acid (23 g.), and water (40 ml.) was added at 15—20°. After 3 hr. an excess of water was added and the product extracted with ether. The slightly yellow *ketone* (17 g., 68%) had b. p. 115—117°/4 mm. and n_D^{28} 1·5125 (Found: C, 63·6; H, 6·0; F, 11·7. $C_9H_9FO_2$ requires C, 64·3; H, 5·4; F, 11·3%).

δ-*Fluoro*-γ-*valerolactone.*—To a solution prepared from sodium (12 g.), ethanol (250 ml.) and diethyl malonate (80 g.), epifluorohydrin (38 g.) was added. After 2 hr. at 40—50°, the viscous product was poured into ice and hydrochloric acid. The solution was concentrated *in vacuo* and the concentrate extracted with ether. The extract was evaporated and the residue refluxed with 10% aqueous hydrochloric acid (100 ml.) for 5 hr.; the aqueous acid was distilled off *in vacuo* and the residue fractionated, giving the *lactone* (18 g., 33%), b. p. 127—129°/32 mm., n_D^{27} 1·4260 (Found: C, 50·6; H, 6·0; F, 16·0. $C_5H_7FO_2$ requires C, 50·8; H, 6·0; F, 16·1%).

1-*Fluoro*-3-*phenylpropan*-2-*ol.*—At −70°, and with stirring, a phenyl-lithium solution, prepared from lithium (4 g.) and bromobenzene (44 g.) in ether (100 ml.), was added during 30 min. to a solution of epifluorohydrin (19 g.) in ether (50 ml.). The temperature was raised to 0° in 2 hr. and the product poured into ice and dilute sulphuric acid. The *alcohol* (20 g., 52%) boiled at 115—120°/15 mm. (Found: C, 69·8; H, 7·0. $C_9H_{11}FO$ requires C, 70·1; H, 7·1%).

1-*Bromo*-3-*fluoropropan*-2-*ol.* Epifluorohydrin (14 g.) was added, dropwise and with stirring, to a Grignard solution [from magnesium (2·4 g.), bromobenzene (16 g.) and ether (120 ml.)] at 0°. The solution was stirred for 1 hr., then poured on ice and concentrated sulphuric acid (10 ml.). The ethereal layer was separated and the aqueous phase extracted three times with ether. The combined ether extracts were dried (Na_2SO_4) and gave, on distillation, fractions (*a*) 1-bromo-3-fluoropropan-2-ol, b. p. 78—80°/30 mm. (7·5 g., 27% based on epifluorohydrin), and (*b*) 1-fluoro-3-phenylpropan-2-ol, b. p. 125—130°/30 mm. (4·5 g., 16% based on epifluorohydrin), identical with the product obtained in the preceding experiment.

Ethyl and Butyl 3-*Fluorolactate from* 4-*Fluoromethyl*-2,2-*dimethyl*-1,3-*dioxolan.*—A mixture of this isopropylidene derivative[9] (67 g.), water (80 ml.), and concentrated hydrochloric acid (20 ml.) was gradually heated, with stirring, to 80—90°. At this point, an exothermic reaction set in, and the liquid became homogeneous. The mixture was refluxed for 20 min., then distilled through a Vigreux column until 60 ml. of distillate had collected. After dilution of the residue with water (100 ml.), a mixture of 70% nitric acid (140 ml.) and water (100 ml.) was added, with stirring, at such a rate that the temperature did not exceed 60° (5 hr.). The solution was left at room temperature for 48 hr., heated at 60° for 1 hr., and concentrated at 60°/30—40 mm. After addition of water (100 ml.), the distillation was repeated and continued to dryness. The remaining syrup is fluorolactic acid of 90—95% purity.

The syrup was distilled azeotropically with anhydrous ethanol (50 g.), benzene (150 ml.), and toluene-*p*-sulphonic acid (0·5 g.). When no more water collected, part of the solution (50 ml.) was distilled off through a Vigreux column and the residue neutralised with sodium hydrogen carbonate (5 g.), filtered, freed from solvents, and distilled at 30 mm. Ethyl fluorolactate (31—38 g., 45—56%) boiled at 96—98°/30 mm. It is colourless, water-soluble, and very quickly hydrolysed in water (Found: C, 44·3; H, 6·7; F, 13·7. Calc. for $C_5H_9FO_3$: C, 44·1; H, 6·6; F, 14·0%).

In the same manner, *butyl fluorolactate* (59 g., 72%) was obtained; it had b. p. 94—95°/3 mm. (Found: C, 51·1; H, 7·7; F, 11·3. $C_7H_{13}FO_3$ requires C, 51·2; H, 7·9; F, 11·6%).

2-Ethyl-4-hydroxymethyl-2-methyl-1,3-dioxolan.—Azeotropic condensation of glycerol (500 g.) and ethyl methyl ketone (430 g.) in benzene (500 ml.) in the presence of toluene-*p*-sulphonic acid (20 g.) was carried out with vigorous agitation. The resulting solution was washed with sodium carbonate solution and water, dried, and distilled. The *product* (700 g., 80%) boiled at 72—73°/2 mm. or 126—128°/30 mm. (Found: C, 57·8; H, 9·4. $C_7H_{14}O_3$ requires C, 57·5; H, 9·6%).

2-Ethyl-4-fluoromethyl-2-methyl-1,3-dioxolan.[9]—The foregoing product was converted into the toluene-*p*-sulphonate, with benzene as reaction medium instead of ethanol,[12] as follows: The hydroxymethyl compound (146 g.) in benzene (100 ml.) was added slowly and with stirring to a suspension of sodium hydride (24 g.) in benzene (600 ml.). The mixture was refluxed for 30 min. and at 25° toluene-*p*-sulphonyl chloride (190 g.) in benzene (300 ml.) added with stirring. When the organic chloride had disappeared (test with alcoholic silver nitrate solution), the mixture was poured into cold water, and the benzene layer dried and concentrated *in vacuo* (first 10, then 1 mm.) at $\geqslant$80°. The toluene-*p*-sulphonate (quantitative yield) formed an oil which could not be distilled without decomposition and was used in its crude state for the fluorination.

In a 3-necked one-litre flask, fitted with stirrer, bent condenser, dropping funnel, gas-inlet, and thermometer, the toluene-*p*-sulphonate (300 g.) was added to a mixture of carefully dried potassium fluoride (90 g.) and anhydrous diethylene glycol (300 ml.), and the mass heated quickly until reaction set in, and then brought slowly to 150°. After 5 min. at this temperature, a current of air was passed through the mass for 10 min. The distillate was dissolved in ether and washed successively with 10% hydrochloric acid, sodium hydrogen carbonate solution, and water. Distillation of the dried product gave at 146—147°/760 mm. the fluorine compound (123 g., 84%; larger batches gave somewhat lower yields) (Found: C, 56·9; H, 8·7; F, 12·5. Calc. for $C_7H_{13}FO_2$: C, 56·8; H, 8·8; F, 12·8%).

Ethyl Fluoropyruvate from Ethyl Fluorolactate.—A mixture of ethyl fluorolactate (20·4 g.), *N*-bromosuccinimide (26·7 g.), and carbon tetrachloride (150 ml.) was refluxed for 1 hr. The cold solution was filtered and distilled in a short column. The ester (4·5 g., 22·5%) boiled at 82—83°/25 mm. (Found: C, 45·0; H, 5·4; F, 14·1. Calc. for $C_5H_7FO_3$: C, 44·8; H, 5·2; F, 14·2%).

Reaction with 2,4-dinitrophenylhydrazine gave first *ethyl fluoropyruvate 2,4-dinitrophenylhydrazone*, m. p. 125—126° (from dilute alcohol) (Found: C, 42·3; H, 3·8; F, 6·0; N, 17·5; OEt, 13·7. Calc. for $C_{11}H_{11}FN_4O_6$: C, 42·0; H, 3·5; F, 6·1; N, 17·5; OEt, 14·3%). This was converted, especially at elevated temperature, into the ethyl mesoxaldehydate osazone, m. p. 250° (from acetic acid) (Found: C, 41·8; H, 3·0; N, 22·4. Calc. for $C_{17}H_{14}N_8O_{10}$: C, 41·6; H, 2·8; N, 22·8%).

Ethyl Bromofluoropyruvate from Ethyl Fluorolactate.—A mixture of ethyl fluorolactate (20·4 g.), *N*-bromosuccinimide (53·5 g.), and carbon tetrachloride (250 ml.) was refluxed for 2 hr., then filtered, and the solution distilled. The ester (8 g., 25%) boiled at 100—101°/40 mm. (Found: C, 28·4; H, 3·1; F, 8·6. Calc. for $C_5H_6BrFO_3$: C, 28·2; H, 2·8; F, 8·9%). With 2,4-dinitrophenylhydrazine this gave ethyl mexosaldehydate osazone, m. p. 250°.

Infrared Spectra (Liquid Film).[13]—In epifluorohydrin, the fluorine bands were observed at 1020 and 1120, the nitrile band at 2300, and the hydroxyl peak at 3500 cm.$^{-1}$. For ethyl γ-fluoro-β-hydroxybutyrate, the following assignments were made: 3430 (OH), 1760 (ester C=O), 1100, 1015 cm.$^{-1}$ (C–F). For ethyl γ-fluorocrotonate, the carbonyl peak is shifted to 1705 cm.$^{-1}$; in the C–F region, there appear strong bands at 1033, 1085, and 1170 cm.$^{-1}$; the double bond absorbs at 1660 cm.$^{-1}$.

[12] Fichter and Schoenmann, *Helv. Chim. Acta*, 1936, **19**, 1411.
[13] For the C–F stretching frequency, see, *e.g.*, Klaboe and Nielsen, *J. Chem. Phys.*, 1960, **32**, 899.

The following bands were also allotted:

1-Ethoxy-3-fluoropropan-2-ol: 3400 (OH); in the C–F and C–O–C region: 1020 and 1085 cm.$^{-1}$.

1-Fluoro-3-phenoxypropan-2-ol: 3400 (OH); 1250 (Ar–O–C); in the C–F region: 1030, 1045, 1080, 1120, and 1180 cm.$^{-1}$.

1-Ethoxy-3-fluoroacetone: 1730 (C=O); 1025 and 1110 cm.$^{-1}$ (C–F and C–O–C).

1-Fluoro-3-phenoxyacetone: 1750 (C=O); 1240 (Ar–O–C); 1030, 1050, and 1120 cm.$^{-1}$ (C–F).

1-Fluoro-3-phenylpropan-2-ol: 3400 (OH), 1020 and 1100 broad with fine structure (C–F).

δ-Fluoromethyl-γ-valerolactone: 1790 (γ-lactone C=O), 1028, 1090, and 1120 (C–F).

1-Dimethylamino-3-fluoropropan-2-ol [3] has the hydroxyl peak at 3400 cm.$^{-1}$, shows a doublet at 2950 and 2800 cm.$^{-1}$ (hydrogen-bonded OH), and in the C–F region bands at 1015, 1040, and 1110 cm.$^{-1}$. In this region, the C–N frequency is also situated. The corresponding (2-acetoxy-3-fluoropropyl)trimethylammonium iodide shows bands at 1750 (ester C=O), and in the C–F region at 1030, 1050, 1080, and 1120 cm.$^{-1}$.

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