586. *Toxic Fluorine Compounds containing the* C–F *Link. Part VIII. ω-Fluoro-carboxylic Acids and Derivatives containing an Oxygen Atom as a Chain Member.*

By F. J. Buckle and B. C. Saunders.

An oxygen atom has been introduced at selected points in the chain of certain ω-fluorocarboxylic acids (and derivatives) by methods depending ultimately upon the cyanoethylation of the appropriate fluoro-alcohol. These compounds, of the formula $F\cdot[CH_2]_m\cdot O\cdot[CH_2]_n\cdot CO_2H$, have been examined pharmacologically.

In view of the strong evidence for the β-oxidation of ω-fluoro-carboxylic acids (Part VI, this vol., p. 1471) *in vivo* and for the inhibition of β-oxidation when such compounds were " blocked " in the α- and in the β-position (Part VII, this vol., p. 2745) it was decided to investigate the effect of introducing an oxygen atom as a chain member at some appropriate point. For this purpose eleven compounds were synthesised and examined pharmacologically.

When 2-fluoroethyl alcohol was treated with 1 mol. of vinyl cyanide and aqueous potassium hydroxide 2-2'-*fluoroethoxyethyl cyanide*, $F\cdot[CH_2]_2\cdot O\cdot[CH_2]_2\cdot CN$, was obtained in good yield. This was readily hydrolysed by hydrochloric acid to β-2-*fluoroethoxypropionic acid*, the *acid chloride* of which on treatment with a large excess of diazomethane gave diazomethyl 2-2'-fluoroethoxyethyl ketone, $F\cdot[CH_2]_2\cdot O\cdot[CH_2]_2\cdot CO\cdot CHN_2$. This substance was a yellow oil which was stable up to about 60° and could be handled with safety. When distillation was attempted, however, it often decomposed explosively, so that further purification was not attempted. It was therefore converted immediately into *ethyl* γ-2-*fluoroethoxybutyrate*, $F\cdot[CH_2]_2\cdot O\cdot[CH_2]_3\cdot CO_2Et$, by warming it with absolute alcohol and dry silver oxide. Conversion of the diazoketone into the free acid or the amide under conditions of the Arndt–Eistert reaction could not be effected. Esterification of the fluoroethoxypropionic acid gave *ethyl* β-2-*fluoroethoxypropionate*, which reacted with phenylmagnesium bromide to give, not the expected diphenyl-2-2'-fluoroethoxyethylcarbinol, but the corresponding bromo-compound $Br\cdot[CH_2]_2\cdot O\cdot[CH_2]_2\cdot CPh_2\cdot OH$ as the result of halogen interchange.

The formation of the bromoethoxy-carbinol was unexpected as there seems to be no record in the literature of the substitution of one halogen for another by a Grignard reagent. Even with a deficiency of the Grignard reagent, the only product which could again be isolated was the bromoethoxy-carbinol. This replacement of an unreactive fluorine atom by the more reactive bromine is worthy of further investigation.

The reduction of 2-2′-fluoroethoxyethyl cyanide using Raney nickel and hydrogen was examined under a variety of conditions. Defluorination readily took place, but finally conditions were found which permitted the conversion of CN to $CH_2{\cdot}NH_2$ without the removal of the fluorine atom, giving 3-2′-*fluoroethoxypropylamine* as a stable distillable liquid.

Ethyl 2-fluoroethoxyacetate, $F{\cdot}[CH_2]_2{\cdot}O{\cdot}CH_2{\cdot}CO_2Et$, could not be prepared by the action of ethyl diazoacetate on pure redistilled 2-fluoroethyl alcohol, and the addition of a small quantity of concentrated hydrochloric acid had no effect, which is rather surprising in view of the known catalytic action of acids on the decomposition of the diazoacetic ester. Fluoroethyl alcohol which had, however, not been specially dried reacted immediately with ethyl diazoacetate with a vigorous evolution of nitrogen and the simultaneous disappearance of the yellow colour of the diazoacetic ester. The product obtained by distilling the reaction product had a low fluorine content, owing to the formation of ethyl glycollate from the water present in the undried fluoroethyl alcohol. This ester has a boiling point close to that of the required fluoroethoxy-ester. Accordingly the glycollate was removed by shaking the reaction product with water, and the ethyl 2-fluoroethoxyacetate was then obtained pure.

The reaction between 2-fluoroethyl alcohol and ethyl chloroformate was slow, but after the mixture had been heated at 100° for 10 hours the evolution of hydrogen chloride ceased and pure *ethyl 2-fluoroethyl carbonate*, $F{\cdot}[CH_2]_2{\cdot}O{\cdot}CO_2Et$, was obtained on distilling the product.

By warming together 2·5 mols. of 2-fluoroethyl alcohol and 1 mol. of ethylene oxide in the presence of concentrated sulphuric acid, 2-2′-*fluoroethoxyethanol* (2-*fluoro*-2′-*hydroxydiethyl ether*) was obtained in 25% yield, but there was no indication of the formation of any higher condensation product. When, however, a much larger excess of the alcohol (5 mols.) was used and the mixture heated in an autoclave at 140° for 4 hours with anhydrous sodium sulphate as catalyst, the yield of 2-2′-fluoroethoxyethanol increased to 70% and there was in addition a 15% conversion into 2-*hydroxy*-2′-2″-*fluoroethoxydiethyl ether*, $F{\cdot}[CH_2]_2{\cdot}O{\cdot}[CH_2]_2{\cdot}O{\cdot}[CH_2]_2{\cdot}OH$.

The following homologues were prepared from 3-fluoropropanol by suitable modifications of technique: 2-3′-*fluoropropoxyethyl cyanide*, $F{\cdot}[CH_2]_3{\cdot}O{\cdot}[CH_2]_2{\cdot}CN$, β-3-*fluoropropoxypropionic acid*, the *acid chloride* thereof, diazomethyl 2-3′-fluoropropoxyethyl ketone, and *ethyl* γ-3-*fluoropropoxybutyrate*.

Pharmacological examination was carried out by subcutaneous injection of the compound, in a suitable solvent, into mice. Methyl fluoroacetate was always injected, under the same conditions, into a batch of mice as a control (cf. Part I, *J.*, 1948, 1773). The β-carbon atom in β-2-fluoroethoxypropionic acid and in β-3-fluoropropoxypropionic acid is linked to the ether oxygen atom, and if β-oxidation of these compounds takes place *in vivo*, the hydrogen carbonate of the fluoro-alcohol will be formed. This would be expected to have approximately the same toxicity as the alcohol itself, since the latter would be produced either by hydrolysis or by elimination of carbon dioxide:

$$F{\cdot}[CH_2]_2{\cdot}O{\cdot}[CH_2]_2{\cdot}CO_2H \xrightarrow{\beta\text{-oxidation}} F{\cdot}[CH_2]_2{\cdot}O{\cdot}CO_2H \longrightarrow F{\cdot}[CH_2]_2{\cdot}OH$$

This was verified by showing that ethyl 2-fluoroethyl carbonate was as toxic as 2-fluoroethyl alcohol. Furthermore we found that β-2-fluoroethoxypropionic acid was indeed toxic, whereas β-3-fluoropropoxypropionic acid was non-toxic.* (3-Fluoropropanol is itself non-toxic.)

The actual L.D. 50 for β-2-fluoroethoxypropionic acid, however, was about 70 mg./kg. and was therefore considerably less than that for fluoroethyl alcohol, whereas the nitrile of the acid showed a toxicity (L.D. 50, 10—20 mg./kg.) of the same order as that of the alcohol. The cause of this difference may be due to different rates of absorption. 2-3′-Fluoropropoxyethyl cyanide was non-toxic in accordance with expectation.

In this connexion ethyl 2-cyanoethyl ether, $EtO{\cdot}[CH_2]_2{\cdot}CN$, was prepared and tested and found to be non-toxic, showing that the toxicity of the fluorine analogue was caused ultimately by the presence of the fluorine atom (as fluoroethoxyl) and not to another part of the molecule.

β-Oxidation of ethyl γ-2-fluoroethoxybutyrate and γ-3-fluoropropoxybutyrate will not lead to the formation of a hydrogen carbonate, but to a fluoroalkoxy-acetic acid. It was for

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* The designation non-toxic is used relatively to the highly toxic methyl fluoroacetate (Part I). At high concentrations (*e.g.*, several hundred mg./kg.) it is probable that some symptoms would be observed even with the " non-toxic " materials.

this reason that ethyl 2-fluoroethoxyacetate was prepared and examined. It was found to be non-toxic, and as expected the two butyric esters were also non-toxic.

2-Fluoro- and 2-hydroxy-2′-2″-fluoroethoxydiethyl ether were both toxic: the former had an L.D. 50 of 15—20 and the latter of 30—40 mg./kg. If the former is readily oxidised to the corresponding acid in the animal body, then we should expect it to be non-toxic in view of the non-toxicity of ethyl 2-fluoroethoxyacetate referred to above. It must be concluded then that the ether-alcohols exert some toxic action *per se*. Ethylene glycol monoethyl ether, was examined physiologically but was found to be completely non-toxic, showing that the activity of 2-fluoro-2′-hydroxydiethyl ether was again closely associated with the 2-fluoroethoxy-group in the molecule.

The L.D. 50 of 3-2′-fluoroethoxypropylamine was about 50 mg./kg.

Discussion.—No very precise conclusions, such as were readily made in previous Parts of this series, can be arrived at from the above toxicity determinations. Further evidence, however, for the process of β-oxidation of acids has been obtained, but not in such a clear-cut manner as with the compounds described in Parts VI and VII. Several additional factors, apart from β-oxidation, appear to be operating, owing to the presence of the ether linkage.

EXPERIMENTAL.

2-*Fluoro*-2′-*cyanodiethyl Ether* (2-2′-*Fluoroethoxyethyl Cyanide*).—2-Fluoroethyl alcohol (61 g., 0·95 mol.) was mixed with 40% aqueous potassium hydroxide (3 c.c.) and vinyl cyanide (50 g., 0·94 mol.) was added with stirring. The temperature rose to 37°, and the mixture was cooled in water and mechanically stirred for 17 hours. The product was neutralised with dilute hydrochloric acid, extracted with ether, dried (Na_2SO_4), filtered, and distilled. The *ether* was obtained as a colourless liquid, b. p. 103—104°/15 mm. (70 g., 64%), with a pleasant odour (Found: F, 16·6. C_5H_8ONF requires F, 16·2%).

β-2-*Fluoroethoxypropionic Acid*.—2-Fluoro-2′-cyanodiethyl ether (30 g., 0·26 mol.) was digested with concentrated hydrochloric acid on a boiling water-bath for 3 hours, and set aside overnight, whereupon a considerable quantity of ammonium chloride crystallised out. The mixture was diluted with water, extracted with ether, and dried (Na_2SO_4), and the ether removed. The product was a pale yellow liquid, which would not crystallise in ice–salt, was soluble in water, and gave a reddish precipitate with ferric chloride solution. The liquid was distilled and gave pure β-2-*fluoroethoxypropionic acid*, b. p. 133—134°/12 mm. (26·5 g., 75%) (Found: F, 13·7. $C_5H_9O_3F$ requires F, 13·9%).

Ethyl β-2-*Fluoroethoxypropionate*.—β-2-Fluoroethoxypropionic acid (25 g., 0·18 mol.) was heated on an oil-bath under reflux for 3 hours with absolute ethanol (75 c.c., 1·3 mols.) and concentrated sulphuric acid (5 c.c.), allowed to cool, diluted with water, and extracted 4 times with ether. The ethereal solution was dried (Na_2SO_4), and the *propionate* distilled as a colourless liquid, with a faint pleasant odour, of b. p. 92°/16 mm. (21 g., 67%) (Found: F, 11·2. $C_7H_{13}O_3F$ requires F, 11·6%).

3-2′-*Fluoroethoxypropylamine*.—(*a*) 2-Fluoro-2′-cyanodiethyl ether (10 g., 0·085 mol.) was mixed with saturated ammoniacal ethanol (200 c.c.) and hydrogenated with Raney nickel (1 g.) for 2 hours at 110° and a maximum pressure of 125 atms. The reduction product was filtered, most of the alcohol removed below 80°, and the residue fractionated through a Vigreux column; 3 g. of a fraction, b. p. 110—140°/760 mm., were obtained. This was redistilled, giving 2 fractions: (i) b. p. 78—128° (0·5 g.); (ii) b. p. 128—131° (1·2 g.); and a residue (1 g.). Fractions (i) and (ii) contained only traces of fluorine. Hydrogenolysis of the C–F link had therefore occurred under these conditions.

(*b*) 2-Fluoro-2′-cyanodiethyl ether (40 g., 0·34 mol.) in saturated ammoniacal ethanol (400 c.c.) was hydrogenated with Raney nickel (3 g.) for 3 hours at 90° and a maximum pressure of 75 atms. of hydrogen. The product was filtered, the alcohol removed, and the residue fractionated, first at atmospheric pressure and then at 12 mm., giving 3-2′-*fluoroethoxypropylamine* as a colourless oil (32·5 g., 77%), b. p. 164—167°/760 mm., with a faint fish-like odour (Found: F, 15·7. $C_5H_{12}ONF$ requires F, 15·7%).

β-2-*Fluoroethoxypropionyl Chloride*.—Thionyl chloride (50 g., 0·43 mol.) was placed in a flask fitted with a reflux water-condenser, dropping-funnel, and calcium chloride tube. β-2-Fluoroethoxypropionic acid (44 g., 0·32 mol.) was added slowly during 1 hour, and the product was heated on a steam-bath for a further hour, whereupon the evolution of hydrogen chloride ceased. The product was fractionated under reduced pressure, giving the *acid chloride* as a colourless mobile pungent liquid, b. p. 77—80°/11 mm. (39 g., 79%), which fumed in air [Found: equiv. by titration with N/10-sodium hydroxide (phenolphthalein), 153·8. $C_5H_8O_2ClF$ requires equiv., 154·5].

Ethyl γ-2-*Fluoroethoxybutyrate*.—β-2-Fluoroethoxypropionyl chloride (8 g., 0·05 mol.) in dry ether was added with continuous stirring to a solution of diazomethane (8·4 g., 0·2 mol.) in ether (350 c.c.), cooled in ice. Nitrogen was evolved, and after the addition was completed, the reaction mixture was set aside at room temperature overnight. The excess of diazomethane and ether was removed at <30° at a water-pump, leaving the yellow oily diazomethyl 2-2′-fluoroethoxyethyl ketone (7·5 g., 95%), which did not crystallise on cooling and scratching. As distillation tended to cause explosive decomposition, further purification or analysis was not attempted. The diazoketone was dissolved in absolute alcohol (150 c.c.) in a flask fitted with a reflux condenser and mechanical stirrer, and warmed to 50—60°.

Dry silver oxide was prepared by dissolving silver nitrate (10 g., 0·06 mol.) in water and adding sodium hydroxide (2·3 g., 0·06 mol.) dissolved in water, slowly with stirring. The silver oxide was filtered off and washed with water to remove sodium nitrate and then with alcohol and ether. The dry silver oxide so obtained was made into a slurry in absolute ethanol and added in small portions to the well-stirred alcoholic solution of the diazo-ketone. Vigorous evolution of nitrogen took place. After all the silver oxide had been added the mixture was heated under reflux on a steam-bath for 1¾ hours, during which time a silver mirror was formed. The mixture was allowed to cool and filtered, and the red residual oil was distilled twice in a vacuum, after removal of alcohol on a water-bath, giving the *ester* as a colourless, mobile, faint-smelling, liquid, b. p. 99—100°/12 mm. (3 g., 28%) (Found : F, 10·8. $C_8H_{15}O_3F$ requires F, 10·7%).

2-2′-*Fluoroethoxyethanol and* 2-*Hydroxy*-2′-2″-*fluoroethoxydiethyl Ether*.—Ethylene oxide (9 g., 0·2 mol.) was dissolved in 2-fluoroethyl alcohol (45 g., 0·76 mol.) in a flask cooled in ice–salt, and fitted with a spiral reflux condenser also cooled in ice–salt. Concentrated sulphuric acid (2 c.c., 0·035 mol.) was added carefully, the mixture was warmed to 50° for 10 minutes and allowed to cool, and concentrated aqueous potassium carbonate added until neutral to Congo-red. The solution was diluted with an equal volume of water and extracted continuously with ether for 4 hours. The ethereal extract was dried (Na_2SO_4), filtered, and distilled, 2 fractions being obtained : (i) b. p. 20°/16 mm., recovered fluoroethyl alcohol; and (ii) b. p. 76°/16 mm. (5·5 g., 25% on the ethylene oxide used). The experiment was repeated using different conditions. Ethylene oxide (13·3 g., 0·3 mol.) was dissolved in fluoroethyl alcohol (102 g., 1·6 mols.). The mixture became very hot and was cooled in ice–salt to 5° and then transferred to a steel autoclave with anhydrous sodium sulphate (0·5 g.) and heated at 130° for 4 hours. The reaction product was filtered from the catalyst and distilled, 3 fractions being obtained : (1) b. p. 22°/19 mm. (recovered fluoroethyl alcohol), (2) b. p. 79°/19 mm., and (3) b. p. 120—125°/19 mm. The last two fractions were redistilled, giving two pure mobile liquids : (*a*) 2-2′-*fluoroethoxyethanol*, b. p. 81°/22 mm. (22·5 g., 70% based on ethylene oxide) (Found : F, 17·3. $C_4H_9O_2F$ requires F, 17·6%); and (*b*) 2-*hydroxy*-2′-2″-*fluoroethoxydiethyl ether*, b. p. 132—133°/30 mm. (3·5 g., 15% based on ethylene oxide) (Found : F, 12·3. $C_6H_{13}O_3F$ requires F, 12·5%).

Attempted Barbier–Wieland Degradation of Ethyl β-2-*Fluoroethoxypropionate*.—Dry bromobenzene (15·7 g., 0·1 mol.) was dissolved in anhydrous ether (50 c.c.), and half of the solution was added to dry magnesium turnings (2·5 g., 0·1 atom) in a flask fitted with reflux condenser and calcium chloride tube. The reaction was started by the addition of a crystal of iodine, and when the initial ebullition had subsided the remainder of the ethereal bromobenzene solution was slowly added in 5-c.c. portions. After all the solution had been added, the reaction mixture was heated under reflux on a water-bath for 15 minutes. The solution was allowed to cool, and a solution of ethyl β-2-fluoroethoxypropionate (6 g., 0·036 mol.) in anhydrous ether (15 c.c.) was added slowly, with gentle shaking. A vigorous reaction took place, and a white solid separated, which later largely dissolved in the ether. Towards the end of the addition, a heavy oil separated from the ethereal layer. The reaction mixture was then heated on the water-bath for 15 minutes, allowed to cool, and poured into a cold mixture of dilute sulphuric acid (60 c.c.) and water (100 c.c.). The product was then steam-distilled for ½ hour, and a yellow residual oil was obtained, which solidified overnight. This was filtered off and twice recrystallised from ethanol in the form of white rosettes, m. p. 70·5—71·5°, which contained bromine but no fluorine. The aqueous solution remaining in the flask after steam-distillation contained fluorine, indicating that halogen interchange had taken place at some stage of the reaction. The crystalline solid of m. p. 70·5—71·5° was proved to be diphenyl-2-2′-bromoethoxyethylcarbinol, by analysis, molecular-weight determination, and mixed m. p. (Found : C, 60·9; H, 5·9; Br, 24·1%; *M*, 305. Calc. for $C_{17}H_{19}O_2Br$: C, 60·9; H, 5·6; Br, 23·9%; *M*, 335).

Condensation of Diazoacetic Ester with Fluoroethyl Alcohol.—Diazoacetic ester (0·057 mol.) was warmed under reflux with redistilled absolute 2-fluoroethyl alcohol (60 g., 0·94 mol.) for 4 hours. No evolution of nitrogen could be observed during this period, and distillation yielded no material with a b. p. higher than that of diazoacetic ester (47°/21 mm.). No condensation had taken place.

The experiment was repeated under the same conditions except that concentrated hydrochloric acid (3 c.c.) was also added, but again no nitrogen was evolved, and no high-boiling fraction was obtained.

The procedure was then repeated without the addition of hydrochloric acid, but using a crude fluoroethyl alcohol.

Diazoacetic ester (11·4 g., 0·1 mol.) was added slowly to undried fluoroethyl alcohol (10 g., 0·17 mol.), contained in a flask fitted with a reflux condenser. A vigorous evolution of nitrogen took place, and sufficient heat was generated to boil the solution. After about 5 minutes the yellow colour disappeared, and the mixture was heated on a steam-bath for ½ hour and then distilled. 2-Fluoroethyl alcohol distilled first, and the fraction of b. p. 78—83°/17 mm. was collected. This redistilled at 84—86°/23 mm (Found : F, 11·1. $C_6H_{11}O_3F$ requires F, 12·7%). The low fluorine content was caused by water in the crude fluoroethyl alcohol reacting with diazoacetic ester to form ethyl glycollate, b. p. 160°/760 mm. The product was therefore shaken with an equal volume of water to remove the ethyl glycollate which is moderately soluble in water, and the lower (non-aqueous) layer run off. The oil was diluted with ether, dried (Na_2SO_4), filtered, and distilled, the *ethyl* 2-*fluoroethoxyacetate*, b. p. 81°/21 mm., being collected as a colourless mobile liquid (Found : F, 12·25. $C_6H_{11}O_3F$ requires F, 12·7%).

Ethyl 2-*Fluoroethyl Carbonate*.—Ethyl chloroformate (11 g., 0·1 mol.) and redistilled 2-fluoroethyl alcohol (6·4 g., 0·1 mol.) were heated on a steam-bath under a reflux condenser fitted with a calcium chloride tube, until evolution of hydrogen chloride had ceased (10 hours), and the reaction product was distilled twice, the *carbonate* being obtained as a colourless liquid, b. p. 56—57°/14 mm. (Found : F, 14·1. $C_5H_9O_3F$ requires F, 14·0%).

3-*Fluoropropanol*.—This was prepared in a rotating autoclave by a technique similar to that described for fluoroethanol (Saunders, Stacey, and Wilding, this vol., p. 773). Quantities used were : triethylene chlorohydrin (127 g., 1·33 mols.), dry potassium fluoride (210 g., 3·6 mols.). Time of heating, 4 hours at 155—170°. B. p. 123—128°. Yield *ca.* 40%. The physical properties of this compound were first described by Kharasch (private communication).

2-3′-*Fluoropropoxyethyl Cyanide*.—Aqueous potassium hydroxide (40%; 2 c.c., 0·016 mol.) was added to 3-fluoropropanol (24 g., 0·3 mol.), and vinyl cyanide (16 g., 0·3 mol.) was added with stirring. The temperature rose as the addition proceeded, and was kept below 60°. The mixture was set aside overnight, then neutralised with dilute hydrochloric acid, and extracted with ether. The ethereal solution was dried (Na_2SO_4), filtered, and distilled under reduced pressure. 2-3′-*Fluoropropoxyethyl* *cyanide* was obtained as a colourless liquid, b. p. 105—108° (30·5 g., 76%), with a faint pleasant odour, insoluble in water (Found : F, 14·2. $C_6H_{10}ONF$ requires F, 14·5%).

β-3-*Fluoropropoxypropionic Acid.*—2-3′-Fluoropropoxyethyl cyanide (30 g., 0·23 mol.) was mixed with concentrated hydrochloric acid (100 g.), heated under a reflux condenser on a steam-bath for 4 hours, and set aside for 16 hours. The ammonium chloride which crystallised was dissolved by adding an equal volume of water, and the aqueous solution was extracted with ether. The ethereal solution was dried (Na_2SO_4), filtered, and distilled. The *acid* was obtained as a colourless water-soluble liquid, b. p. 144—150°/13 mm. (13 g., 32%), which did not crystallise at −10° (Found : F, 12·7. $C_6H_{11}O_3F$ requires F, 12·7%).

β-3-*Fluoropropoxypropionyl Chloride.*—β-3-Fluoropropoxypropionic acid (12·5 g., 0·083 mol.) was added dropwise to thionyl chloride (12·5 g., 0·1 mol.) in a flask fitted with reflux condenser and calcium chloride tube. The mixture was then heated until no more hydrogen chloride was given off (1 hour) and distilled under reduced pressure, the *acid chloride* being collected at 86—90°/13 mm. (8 g., 58%), as a pungent colourless liquid which fumed in air (Found : equiv., 169·9. $C_6H_{10}O_2ClF$ requires equiv., 168·5).

Ethyl γ-3-*Fluoropropoxybutyrate.*—β-3-Fluoropropoxypropionyl chloride (7·5 g., 0·045 mol.) in dry ether was added to a mechanically stirred solution of diazomethane (6·3 g., 0·15 mol.) in dry ether (300 c.c.), cooled in ice, and the ethereal solution set aside overnight. The ether and excess of diazomethane were then removed below 30° in a partial vacuum, leaving the diazomethyl 2-3′-propoxyethyl ketone as a yellow oil.

The diazo-ketone was dissolved in absolute alcohol (100 c.c.) and warmed to 55—60° in a flask fitted with a mechanical stirrer and reflux condenser. Pure silver oxide (from 7 g. of silver nitrate), made into a slurry with absolute alcohol, was added in small portions to the stirred alcoholic solution. Nitrogen was evolved, and after the addition of silver oxide the mixture was heated under reflux with stirring on a steam-bath for 1 hour, during which time silver was slowly deposited as a mirror. The product was cooled and the silver and oxide removed by filtration. The alcohol was removed from the filtrate, and the residual red oil was fractionated under reduced pressure, giving the *ethyl* γ-3-*fluoropropoxybutyrate* as a colourless liquid, b. p. 110—111°/14 mm. (1·5 g., 10%) (Found : F, 9·7. $C_9H_{17}O_3F$ requires F, 9·9%).

We express our thanks to Imperial Chemical Industries, Ltd. (Widnes), for a grant, and to Magdalene College for a Research Studentship held by one of us (F. J. B.) during the course of this work.

University Chemical Laboratory, Cambridge. [*Received, July* 18*th*, 1949].