Preparation and Preliminary Biodistribution of "No Carrier Added" Fluorine-18 Fluoroethanol

Timothy J. Tewson and Michael J. Welch

Washington University School of Medicine, St. Louis, Missouri

No-carrier-added [^{18}F] fluoroethanol has been prepared by two routes. The first involves fluoride-ion displacement on α-p-toluene sulfonyl ethyl glycolate followed by reduction of the α-fluoroethyl acetate. The second involves a ring-opening reaction on glycol sulfite to give an α-fluorosulfinic acid derivative that is hydrolyzed to fluoroethanol. The specific activity was measured as 10^5 Ci/millimole, and the stable fluorine-19 was traced to the cesium hydroxide used to trap the H^{18}F. Following intracarotid injection, the labeled fluoroethanol was not trapped in the brain, and thus is not a microsphere analog as has been suggested. Tomographic images of the myocardium were obtained using the fluoroethanol as a tracer.

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Following the development of positron emission tomography (*1*), several radiotracers have been developed for the noninvasive measurement of regional metabolic rates (*2–5*). There is also interest in the measurement of blood flow, however, methods proposed for this application are either invasive or suffer from severe limitations (*6*).

A radioagent that is suitable for the measurement of blood flow by a static technique should have the properties of labeled microspheres: that is, be totally removed from the blood by a single capillary transit, and remain trapped for longer than the total time required for the measurement. Microspheres have been used with success in animals (*7*), but the blocking of the capillaries, which is essential for the method's success, makes them unsuitable for use in humans.

Fluorine-18 fluoroethanol is a promising candidate for such an agent, as alcohols generally are efficiently extracted (*8*), and substitution of fluorine for hydrogen is unlikely to affect this. Second, the toxicity of fluoroethanol is due to its metabolism to fluorocitrate, which is a potent inhibitor of aconitase ($k_i = 6.5 \times 10^{-9} M$) (*9*), the enzyme responsible for the isomerization of citrate to cis-aconitate and isocitrate in the Krebs cycle. More recent studies have indicated that the toxicity of fluorocitrate at very low levels is due to inhibition of the mitochondrial transport system (*10*) by binding of the fluorocitrate, but in either case the metabolism and loss of fluoride is slow (*11*).

The toxic doses of fluoroethanol and fluoroacetate are identical (*12*), suggesting that the alcohol is metabolized to the acid. Synthetic fluorocitrate has approximately 25% the toxicity of either the alcohol or the acid, but because of the presence of two asymmetric centers, four isomers are formed. Limited studies with biosynthetically prepared isomers of fluorocitrate show that it has the same toxicity on a molar basis as either fluoroethanol or fluoroacetate (*12*). Thus, within the limitations of the method, toxicity studies show that the metabolism of fluoroethanol to fluorocitrate is complete. The enzymes responsible for metabolizing ethanol to acetic acid—and thus presumably fluoroethanol to fluoroacetate—have been shown to be present in the brain, with a reasonably uniform distribution, albeit at low levels (*13*), and fluoroethanol has been shown to be a substrate for at least one of the alcohol dehydrogenase fractions in human liver, ADH (*14*). It is reasonable to assume that any metabolically viable tissue will have some mitochondrial tricarboxylic acid cycle activity, and thus will have the

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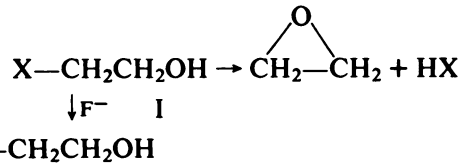
For reprints contact: T. J. Tewson, PhD, Mallinckrodt Institute of Radiology, Washington Univ. School of Medicine, 510 S. Kingshighway, St. Louis, MO 63110.

final metabolic activity necessary to trap the label permanently in the tissue. The available data suggest, therefore, that the metabolic reactions required for the successful application of fluoroethanol as a microsphere analog will occur. In the absence of in vivo kinetic data, it is not possible to predict whether the reactions will occur fast enough to trap the extracted activity totally and so serve as an agent to measure blood flow.

The preparation of [^{18}F] fluoroethanol has been described by two techniques (*15,16*), but in each case the yield and specific activity were low. In view of the toxicity of fluoroacetate (0.05 mg/kg in the dog) (*12*), one of the metabolites of fluoroethanol, material of higher specific activity is desirable.

We have recently described a cyclotron target system for producing anhydrous "carrier-free" cesium[^{18}F]-fluoride (*3*), and have applied this intermediate to synthesize high-specific-activity [^{18}F] fluoroethanol.

Formation of a carbon-fluorine bond with cesium fluoride requires the nucleophilic displacement of a good leaving group by the fluoride ion. However, the fluoride ion is not a good nucleophile, and in the accompanying equation the use of a substrate such as I, where X is a good leaving group, is far more likely



to give ethylene oxide by an intramolecular reaction than to give fluoroethanol by an intermolecular reaction. To avoid this problem, the substrate for the displacement reaction must contain a non-nucleophilic group that is inert to the conditions for the formation of the carbon-fluorine bond, and can readily be converted to the hydroxyl group after forming the carbon-fluorine bond. We took two different approaches to the problem, both of which were successful. First, in a modification of a published procedure (*15*), α-(p-toluenesulfonyl) ethyl glycolate (**2**) was allowed to react with cesium fluoride to give α-fluoro-ethyl acetate, which on reduction gave fluoroethanol (Fig. 1).

Second, glycol sulfite (**4**) was allowed to react with cesium fluoride to give the unisolated sulfinic acid derivative (**5**), which on aqueous hydrolysis gave fluoroethanol (Fig. 2).

MATERIALS AND METHODS

Preparation of α-(p-toluenesulfonyl) ethyl glycolate (2). Ethyl glycolate* (10.4 g, 0.1 moles) in pyridine/methylene chloride at 0°C was added to p-toluene sulphonic anhydride (39.4 g, 0.11 moles) (*17*) in methylene chloride at 0°C. The solution was kept at 0°C for 24 hr; washed with 1 *N* hydrochloric acid, then with saturated

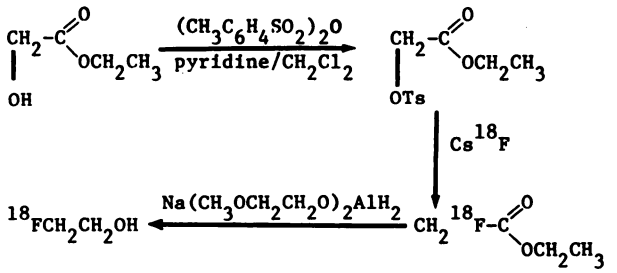


FIG. 1. Synthetic route to [^{18}F]-fluoroethanol via tosylate displacement.

sodium bicarbonate solution; dried with magnesium sulfate, and the methylene chloride removed under vacuum. Distillation (120°C, 0.1 torr) and crystallization (ether, pet. ether) gave α-(p-toluenesulfonyl) ethyl glycolate (**2**) in 60% yield (15.5 g). The melting point was 48–49°C, the reported melting point being 47.5–48°C (*18*). The NMR spectrum showed a four-proton AB quartet at 7.5 δ for the aromatic protons; a two-proton singlet at 4.55 δ for the acetoxy methylene protons; a two-proton quartet with J = 7 Hz at 4.2 δ for the ethyl methylene protons; a three-proton singlet at 2.45 δ for the aromatic methyl; and a three-proton triplet with J = 7 Hz at 1.3 δ for the ethyl methyl protons. We used p-toluene sulphonic anhydride instead of the more usual and convenient p-toluene sulphonyl chloride, since the latter gave rise to large amounts of α-chloroethylacetate, which made purification of the tosylate difficult and tedious.

Reaction of α-(p-toluenesulfonyl) ethyl glycolate (2) with cesium fluoride and cesium[^{18}F]fluoride. α-(p-toluenesulfonyl) ethyl glycolate (12.9 g, 0.05 moles) was stirred with cesium fluoride (8.4 g, 0.055 moles) in freshly distilled hexamethylphosphoric triamide (HMPA) (25 ml) in a flask equipped with a distilling head and condenser. The temperature was raised to 160°C and, after a small forerun, α-fluoroethyl acetate (**3**) (5.9 g) distilled over (bp 119–121°C) in 55% yield. The material was identical by gas chromatography (GC), infrared spectroscopy (IR), and liquid chroma-

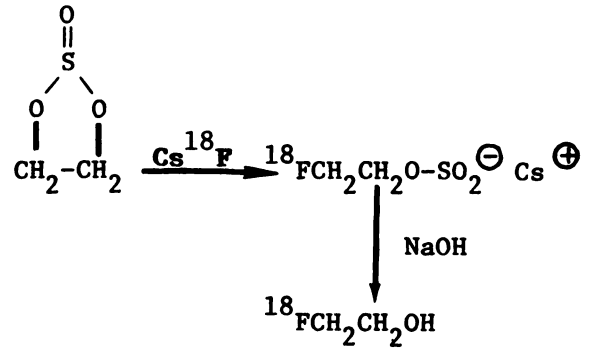


FIG. 2. Synthetic route to [^{18}F]-fluoroethanol via sulfite ring opening.

tography (LC) to authentic material.*

Cesium[^{18}F]fluoride is produced by bombarding neon containing 15% hydrogen with 6.3-MeV deuterons (5.3-MeV after passage through the window) and passing the H^{18}F over a silver-wool plug containing cesium hydroxide (2–5 mg), as has been described previously (*3*), where the H^{18}F reacts to form Cs^{18}F.

Initial experiments with cesium[^{18}F]fluoride were performed by adding the silver-wool plug containing the activity to a solution of **2** (50 mg) in HMPA (1 ml) and heating to 160°C for 30 min in a reaction analogous to that with Cs^{19}F. α-Fluoroethylacetate was formed, incorporating 70% of the available fluorine-18 activity and identical with authentic material on radiogas chromatography and radioliquid chromatography. However, the solvent HMPA proved to be troublesome in the reduction to fluoroethanol (*vide infra*) in that it activated the reducing agent, causing loss of fluorine as fluoride, and was itself slowly reduced to phosphines, which were difficult to separate from the final product. Subsequent reactions were performed by adding **2** (50 mg) in ether (2 ml) to the silver-wool plug, warming under vacuum to remove the ether, and heating the reaction vessel to 160°C in the absence of solvent. Yields are lower (~40% of the available activity) but the difficulties in the reduction are removed.

Reduction of α-[^{18}F]fluoroethylacetate to [^{18}F] fluoroethanol. The reaction vessel from the previous step was cooled in ice and ether, and sodium dihydro bis-(2-methoxyethoxy)-aluminate (0.2 ml of a 70% w/v solution in benzene) (*15*) were added. The solution was kept at 0°C for 30 min, the solvents removed under vacuum, and excess reducing agent destroyed by the addition of 1 *M* sulfuric acid solution. The solution was distilled to remove the aluminum salts, neutralized, passed down an alumina column to remove unreacted fluoride, and finally purified on a reverse-phase chromatography column (*vide infra*) to remove traces of organic solvents and ethylene glycol that might remain. One to two millicuries of activity are obtained starting from 25–30 mCi of Cs^{18}F, and the material is identical to authentic fluoroethanol by both gas and liquid radiochromatography.

This reaction sequence does provide usable quantities of [^{18}F] fluoroethanol, but the yield is somewhat low and the extensive manipulations required are undesirable.

Reaction of glycol sulfite with cesium fluoride and cesium[^{18}F]fluoride. Glycol sulfite (1.08 g, 0.01 moles) and cesium fluoride (1.7 g, 0.011 moles) were stirred under reflux and warmed to 160°C in an oil bath. After 30 min the reaction mixture became solid, was cooled in an ice bath, and sufficient 1 *N* sodium hydroxide was added to produce a neutral solution. Analysis by both gas and liquid chromatography showed that a high yield of fluoroethanol was being produced. The reaction was repeated using the silver-wool plug containing 25 mCi of cesium[^{18}F]fluoride, which was heated with glycol sulfite at 160°C for 30 min. The reaction was neutralized with 1 *N* sodium hydroxide solution and injected onto a chromatograph consisting of a short alumina column (to remove unreacted fluoride) and a reverse-phase column for final purification. Elution with water gave 11 mCi of [^{18}F] fluoroethanol in 2 ml of water. Radiogas and liquid chromatography showed only one radioactive compound, with retention characteristics identical to those of authentic fluoroethanol.

Analytical methods. Although no stable fluorine is deliberately introduced, either during bombardment or in the subsequent chemical synthesis, there is always the possibility that trace quantities of fluorine are unknowingly introduced during the entire sequence. The liquid chromatographic system used (a μ-Bondapak C_{18} column eluted with water for fluoroethanol and 15% ethanol/water for α-fluoroethyl acetate) involves a differential refractometer for mass detection and is far too insensitive to detect the traces of material that may be involved. However, the gas chromatograph uses a flame ionization detector (FID) that is sensitive down to the picomole level. The instrument† is fitted with a 1:1 effluent splitter that is connected to the FID and, by a heated umbilical tube, to a proportional gas counter (*19*), thus allowing simultaneous detection of both mass and radioactivity. The column used was a 20′ × ½″ carbowax 20M on chromosorb W 45/60, and was run at 120°C and 80 ml/min. Before the effluent reached the counter, carrier gas from the unused injection port was added to the effluent at 99 ml/min. The high flow rates were needed to maintain the FID in the range of maximum sensitivity (40 ml/min after the splitter) and to clear the column effluent through the 80-ml volume of the proportional counter as rapidly as possible. With this system, the fluoroethanol gives a well-retained, sharp peak that is well clear of any trace organic impurities liable to be found in deionized distilled water: namely, acetone, methanol, ethanol, chloroform, formaldehyde, or acetaldehyde. Under the conditions used, there is little decomposition of the products or byproducts of the reaction to cause baseline drift, so the system is suitable for operation at maximum sensitivity. The manufacturers claim a sensitivity of 2×10^{-13} moles of carbon sec^{-1} mv^{-1}, and this was confirmed with a series of standards of ethanol and fluoroethanol to ensure that the presence of fluorine did not interfere with the combustion process in the FID. The column was checked for "memory" effects by injection of large water samples following elution of authentic fluoroethanol, to determine whether trace amounts were retained on the column, and finally the radioactive solutions were re-analyzed after 24 hr to determine the effects of the ionization caused by nuclear decay on the detector. If the positrons from 10^4 d/sec (the approximate amount passing through the detector) are thermalized by reactions producing ions completely

within the confines of the detector, then the ion current produced would saturate the detector at the sensitivities used. This obviously cannot happen, since the FID is small (a cylinder approximately 1 cm in diameter and 1 cm long), and the positrons will have an average path length of 5 m in a gas at STP (*20*). Some ionizations will occur, however, and the effect on the detector is difficult to calculate.

The specific activity was measured by injection of 25-μl samples of an aqueous solution that had contained 5.5 mCi/ml of [^{18}F] fluoroethanol.

Animal experiments. The suitability of fluoroethanol as an agent to measure flow was assessed with a bolus intracarotid injection of 110 μCi of the compound into a paralyzed, anesthetized pigtail monkey (*Macaca nemestrina*). The cerebral activity was monitored by an externally mounted NaI(Tl) detector, and data were collected at 0.1-sec intervals and displayed by a classic LINC laboratory computer (*3*). Under these conditions, with a suitable agent for measuring flow, the count rate would rise to a maximum in less than a second and stay at this level for several minutes.

Positron images were obtained by i.v. injection of 6 mCi of fluoroethanol into a dog suitably positioned in PETT V (*21*). Blood samples were withdrawn and serial images obtained for an hour following injection.

RESULTS AND DISCUSSION

The two alternative synthetic routes provide access to labeled fluoroethanol in reasonable yields. The route through the tosylate (**2**) requires more manipulations, with the attendant exposure to the operators, but has the virtue of making both α-fluoroethylacetate and α-fluoroacetic acid available for biological studies, although these have not yet been pursued. The route through the glycol sulfite is a more convenient and higher-yielding route to fluoroethanol, and is a new synthetic sequence for the preparation of α-fluorohydrins, which may have applications to the synthesis of more complex fluorinated compounds.

The gas chromatographic analyses of the final product from the glycol sulfite procedure revealed a small mass peak due to stable fluoroethanol. This corresponded to approximately 1 pmole of fluoroethanol injected onto the instrument in a 25-μl sample. As the original solution had contained 5 mCi per ml, this corresponds to a specific activity of 1.25×10^5 Ci/millimole, which is an order of magnitude lower than the theoretical specific activity of fluorine-18 of 1.6×10^6 Ci/millimole. The chromatography column does have a small "memory" effect in that a 25-μl injection of water produces an observable but not quantifiable peak, and the ionization due to decay probably has an effect, since the sample injected 24 hr later produces a peak only 80% of the size of the original peak when the peak due to the standard remains unchanged. However, these artifacts can only account for at most 20–25% of the observed signal, and there is undoubtedly some stable fluorine present. In order to trace the source of this fluorine, we ran a series of experiments that eliminated steps in a sequential fashion. The same mass peak was seen whether the silver-wool/cesium-hydroxide plug was exposed to the target gases or not, eliminating the target as a source of a detectable quantity of fluorine-19. If the cesium hydroxide solution was not dried onto the silver wool, the mass signal virtually disappeared. Adding ten times as much cesium hydroxide increased the observed signal considerably.

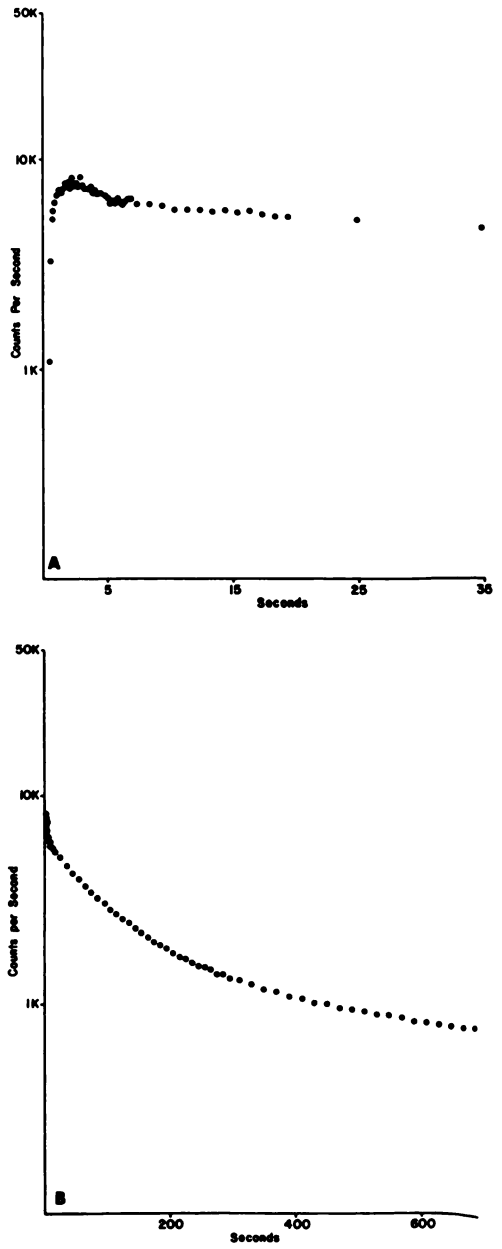


FIG. 3. Cerebral time-activity curves following intracarotid injection of [^{18}F] fluoroethanol. Both curves are from same injection but use different time scales for abscissae. (A) shows that initial extraction, though high, is not 100%; (B) shows that during 20 min most of the activity washes out of the brain.

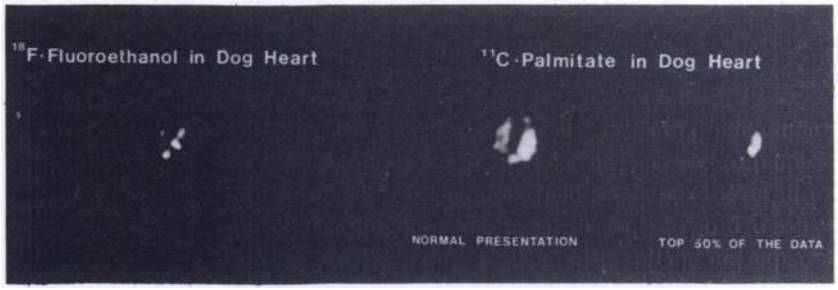


FIG. 4. Single-slice PETT V images of (L) canine myocardium obtained 30 min after injection of 6 mCi of [^{18}F] fluoroethanol; (R) images obtained from same animal at same level 2 hr earlier, 10 min after injection of [^{11}C] palmitic acid. Left-hand image uses normal display, that is, a window setting such that all data values are displayed. Right-hand image was obtained by setting window so that data values below 50% of maximum are rejected. Higher-contrast image shows more similarity to fluoroethanol image than normal display.

Subsequent chemical analysis of our present batch of cesium hydroxide[‡] with a fluoride glass electrode revealed the presence of 2 ppm of fluoride, which is sufficient to account for the observed [^{19}F] fluoroethanol. Whether the fluoride is an inevitable or a chance contamination of the cesium hydroxide has not yet been determined.

Animal experiments. Figure 3 shows the cerebral time-activity curve of [^{18}F] fluoroethanol following an intracarotid bolus injection in a pigtail monkey. Clearly the material does not have the characteristics of a microsphere analog, but is similar to a diffusible but nonmetabolized tracer, such as O-15-labeled water (*8*). The material does accumulate in tissue, however, as is shown by the myocardial images (Fig. 4) obtained on PETT V 30 min after the i.v. injection in the dog. The activity is rapidly cleared from the blood, as is shown in Fig. 5. The myocardial uptake can be estimated from the tomographic images, in that the cps/mCi per slice, obtained 30 min after injection, were approximately 30% higher than those obtained from the C-11 palmitic acid at 3 min after injection. The nature of the accumulation is more obscure, since fluoroethanol has been shown to affect the heart in vivo, but perfusion of the isolated heart with fluoroethanol solutions produces no obvious changes (*22*). Evaluation of these results will require a more complete study of both the kinetics and the biochemistry of fluoroethanol.

Although the chemical nature of the metabolic products, if any, has not yet been determined, certain deductions can be made from the available biological data. Rapid metabolism involving loss of fluorine as fluoride ion can probably be ruled out, since bone uptake is negligible in the rat at 60 min after injection, and no bone uptake is seen in the PETT V images of the dog (*23*). The metabolic pathway is shown in Fig. 6 (*12*). Once the metabolism reaches the fluoroacetyl CoA, it cannot leave the cell, so the washout must be occurring earlier than this. Fluoroacetate is rapidly washed out of the cells (*12*), but is then very poorly taken up again, so the blood curve should dip initially and then rise again as the extracted fluoroethanol is metabolized to fluoroacetate, which will re-enter the blood. Hence, the early oxidation steps are probably slow, or at least insufficiently fast to trap either the fluoroethanol or the fluoroacetaldehyde. This could be either because (a) the material enters a pool, and at the specific activity of the fluoroethanol used, a whole-body pool of 1 μmole of ethanol would constitute a ten-thousandfold dilution, or because (b) the fluoroethanol is a poor substrate for one of the two enzymes involved in the oxidation to fluo-

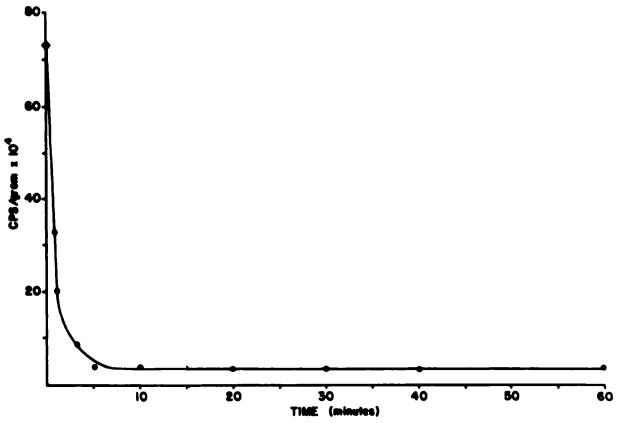


FIG. 5. Blood time-activity curve following injection of [^{18}F] fluoroethanol. Zero time point calculated assuming that blood represents 5% of animal's weight.

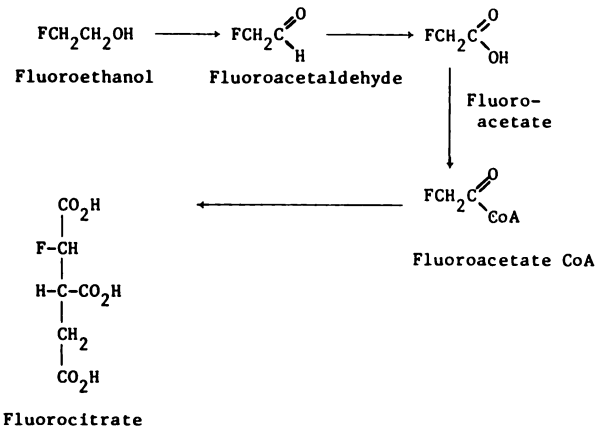


FIG. 6. Metabolic pathway of fluoroethanol to fluorocitrate.

roacetate. From the standpoint of oxidative metabolism, there is probably little or no difference between fluoroethanol or fluoroacetaldehyde, and the *a priori* assumption that the activity washes out in the same form as when it washed in is probably justified. Thus the tracer dynamics should be similar initially to those found with 2-fluoro-2-deoxy-glucose (*24*), in that the initial tissue extraction is followed by diffusion back into the blood and re-extraction in subsequent capillary transits. In the case of 2-fluoro-2-deoxy-glucose, the back-diffusion takes place because of dephosphorylation, by glucose-6-phosphatase, of the 2-fluoro-2-deoxy-glucose-6 phosphate, and thus the tracer accumulates in tissues deficient in this enzyme, such as the brain. However, in the case of fluoroethanol there is no evidence that a reversible metabolic reaction determines the rate at which the tracer leaves the tissue, but it seems that the rate at which it enters the metabolic pathway determines the amount that is trapped in the mitochondria.

FOOTNOTES

* Aldrich Rare Chemicals, Milwaukee, WI.
† Varian 3760,
‡ Alpha Ventron, Danvers, MA.

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