# SYNTHESIS OF CARBOXY-$^{14}$C FUROSEMIDE

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SUMMARY

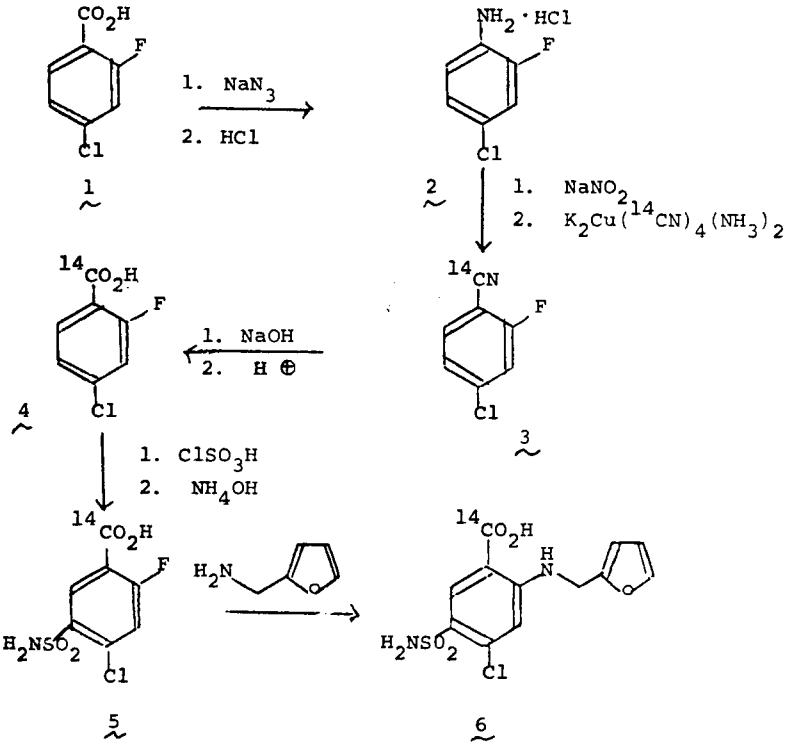
*A modification of the Sandmeyer reaction which requires only a moderate excess of cyanide-$^{14}$C was utilized for the preparation of 4-chloro-2-fluorobenzonitrile-7-$^{14}$C (3). After hydrolysis, the resulting acid (4) was converted to carboxy labelled furosemide (6) by existing methods. This procedure is potentially useful for insertion of $^{14}$C in compounds that fail to undergo conventional carbonation reactions.*

## Introduction and Discussion

Furosemide (6) has been prepared from 4-chloro-2-fluorobenzoic acid (1) after chlorosulfonation, amidation and selective replacement of fluorine with furfurylamine[1-3]. Metabolic studies with sulfur-35 labelled furosemide have been reported[4,5] and this labelled compound could be readily prepared by the reported synthetic sequence. We were interested in labeling furosemide with carbon-14 in a position such that the label would be metabolically stable. To avoid the multiplicity of radiochemical steps required if the benzene ring were to be labelled, we chose to label the carboxyl group.

To parallel the nonradioactive synthesis, the dihalogenated benzoic acid (4) was selected as the labelled starting material and we considered the possibility of using the

available nonlabelled acid (1) as a precursor. By a Schmidt reaction, (1) was converted to the aniline (2) which was diazotized and subjected to a modified Sandmeyer reaction to yield the labelled nitrile (3). Without purification, the nitrile was hydrolyzed to the desired acid (4). Subsequent reactions to yield the sulfonamide (5) and furosemide-7-$^{14}$C (6) were carried out as described [1]. On a 2 mmole scale of $K^{14}CN$ (52 mCi/mmole), 4.68 mCi of 6 were obtained. Dilution with nonradioactive material was effected during the sequence and final specific activity was 36.4 μCi/mg.




The Sandmeyer reaction, involving cyanide-$^{14}$C, is usually considered to be too radiochemically inefficient to be useful since it requires large excesses of cyanide. However,

in this instance, we were able to carry out the sequence (2 ⟶ 4) in approximately 25% radiochemical yield using potassium-cupric-diammino-cyanide[6]. This yield does not compare favorably with carbonation procedures, however, the related 2,4-dichlorobromobenzene has been reported not to undergo carbonation after butyl lithium exchange[7]. And in considering alternative approaches to 4, this modified Sandmeyer reaction becomes quite attractive.

## Experimental

Melting points are uncorrected. All solvents used were distilled. Radioactivity was measured by the liquid scintillation technique using a Packard Tricarb Model 2010 spectrometer. Radiochemical purity was determined on thin layer chromatograms with a Packard Model 7201 Radiochromatogram Scanner System.

4-Chloro-2-fluoroaniline hydrochloride (2) - A solution of 870 mg (5 mmole) of 4-chloro-2-fluorobenzoic acid [1] in 2 ml of 100% $H_2SO_4$ and 4 ml of chloroform was stirred and heated to 40° and sodium azide (425 mg, 7.5 mmole) was slowly added. After the addition was complete, stirring and heating were maintained until $N_2$ evolution ceased (1 hr) whereupon the mixture was cooled (25°) then poured into a solution of 3.2 g NaOH in 25 ml of water. This was extracted with three 20 ml portions of ether which were combined, dried, ($K_2CO_3$), filtered and concentrated in vacuo to a 10 ml volume. To this solution, ethereal HCl (saturated) was added and the resulting solid was filtered and dried to a constant weight of 725 mg (80%) of product, mp 222° (sublimes), which was homogeneous by tlc ($SiO_2$, ammonia saturated ethyl acetate, $R_f$ 0.68). The NMR spectrum (60 MHz in DMSO) was compatible.

Anal: Calcd for $C_6H_5ClFN \cdot HCl$: C, 39.6; H, 3.3; N, 7.7; Cl, 39.0; F, 10.4. Found: C, 39.5; H, 3.3, N, 7.8; Cl, 38.9; F, 10.2.

4-Chloro-2-fluorobenzonitrile-7-$^{14}C$ (3) - To a solution of $K^{14}CN$ (145 mg, 2.0 mmole, 104 mCi) in 2 ml of water was added

67 µl (1 mmole) of concentrated ammonia solution. To this was added a solution of $CuSO_4 \cdot 5H_2O$ (125 mg, 0.5 mmole, in 2 ml water) as described[6]. The resulting mixture was cooled to 0°, treated with 5 ml of toluene[8] and then, with stirring, a solution of the diazonium salt of 2 [prepared by adding 75 mg of $NaNO_2$ to a solution of the hydrochloride of 2 (183 mg, 1 mmole) in 2.5 ml of 1N HCl] was added dropwise. After the addition, stirring was continued at 0° for 0.5 hr, at 25° for 0.5 hr then at 50° for 1.5 hr. The reaction mixture was then steam distilled and the distillate was extracted with three 20 ml portions of ether which were combined, dried ($MgSO_4$), filtered and concentrated in vacuo to an orange oil which solidified on standing (178 mg).

4-Chloro-2-fluorobenzoic-7-$^{14}$C acid (4) - The crude nitrile obtained above was treated with 5 ml of 10% NaOH solution and the resulting mixture was stirred at 100° for 16 hr. After cooling, the alkaline mixture was extracted with two 10 ml portions of ether. The aqueous solution was then acidified (3 ml conc. HCl) and extracted with three 20 ml portions of ether which were combined, dried ($MgSO_4$), filtered and concentrated in vacuo yielding 86.5 mg (0.49 mmole) of 4. By tlc ($SiO_2$; 1% acetic acid in acetonitrile), purity was estimated to be greater than 95% and no further purification was effected.

4-Chloro-2-fluoro-5-sulfamoylbenzoic-7-$^{14}$C acid (5) - The crude sample of 4 obtained above was diluted with 176 mg (1 mmole) of nonradioactive carrier to an approximate specific activity of 17 mCi/mmole. After adding 865 µl of freshly distilled chlorosulfonic acid, the resulting mixture was stirred magnetically and heated to 155° as described[1]. Heating was continued for 2 hr after which time the solution was cooled and then added to about 6 g of ice. After the product solidified, the mixture was filtered and the precipitate washed with water until the washings were neutral. The precipitate was then added, at 0°, to 2.9 ml of concentrated ammonia solution and allowed to stir at 25° for 16 hr. The pH of the solution was adjusted to 2 with conc. HCl and the mixture was

continuously extracted with ether for 3 hr yielding 171.8 mg (0.675 mmole, 45% crude) of 5 of approximately 95% radiochemical purity (tlc; $SiO_2$, 1% acetic acid in acetonitrile). Continuing the extraction for 20 hours yielded an additional 20 mg of material of less than 50% radiochemical purity which was not used in subsequent reactions.

4-Chloro-N-furfuryl-5-sulfamoylanthranilic-7-$^{14}C$ acid (6, Furosemide-7-$^{14}C$) - To the crude 5 contained in a 10 ml round bottom flask, 340 mg of freshly distilled furfurylamine was added and with stirring, the resulting solution was heated to 95° and held at this temperature for two hours. After cooling to 70°, 3 ml of water was added and the mixture was filtered. The insoluble material was digested for several minutes with 5 ml of boiling water and again filtred. The combined filtrates were chilled in an ice bath and treated with 3 ml of glacial acetic acid. The resulting precipitate was filtered, washed with 5-6 ml of ice water and dried to a constant weight of 136 mg which was dissolved in 3 ml of acetone and applied to a column of 68 g of silica gel (E. Merck #7734) packed in acetonitrile: acetic acid, 99.5:0.5. The column was eluted with this solvent mixture in 3 ml fractions. Fractions 22-50, containing pure furosemide, were combined and concentrated *in vacuo* to a residue of 74.5 mg. Earlier fractions were rechromatographed and yielded an additional 54.3 mg for a total of 128.8 mg (57%); specific activity was found to be 36.4 μCi/mg.

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