SYNTHESIS OF 4-FLUORO-2,3-DIMETHYL-1-PHENYL-3-PYRAZOLINE-5-ONE (4-FLUOROANTIPYRINE) AND ^{18}F-LABELED ANALOG BY DIRECT FLUORINATION OF ANTIPYRINE WITH MOLECULAR FLUORINE

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SUMMARY

A facile procedure for preparing 4-fluoroantipyrine is reported. Treatment of antipyrine with molecular fluorine gives 4-fluoroantipyrine (3) and 4,4-difluoro-3-hydroxy-2,3-dimethyl-1-phenylpyrazolidin-5-one (2). The product distribution depends on the ratio of antipyrine and molecular fluorine. The same procedure is used to prepare [^{18}F]-4-fluoroantipyrine with high specific activity.

Key Words: Antipyrine, 4-fluoroantipyrine, 4,4-difluoro-3-hydroxy-2,3-dimethyl-1-phenylpyrazolidin-5-one, 4,4-difluoro-3-methyl-1-phenyl-2-pyrazolin-5-one, ^{18}F-4-fluoroantipyrine, cerebral blood flow.

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INTRODUCTION

Labeling of biologically active compounds with positron emitting nuclides where the labeling nuclides are non- or in minimally bioactive positions so as not to significantly alter the biochemical characteristics of the compounds, has become especially attractive with the advent of the new positron emission tomographs. The transport and localization of these compounds in a particular organ can serve as a probe for metabolism in vivo. Antipyrine (1), a lipophilic compound, has been shown to have high uptake by the brain and has been used to estimate the water content of an organ or of the whole body (1-3). Its radioactive analog, ^{14}C-antipyrine has been investigated as a tracer for estimating regional cerebral blood flow using autoradiography in animals. However, its uptake by cerebral tissues has been shown to be diffusion and flow limited thereby limiting its usefulness as a tracer (4). 4-Iodoantipyrine, becasue of its higher partition coefficient, has been shown to be a satisfactory non-volatile tracer for the measurement of regional cerebral blood flow and iodo[^{14}C]antipyrine has been used for this purpose in animals (5). Radioiodinated antipyrines [^{123}I and ^{131}I] have been used to study the symmetry of brain perfusion using the gamma camera (6) and single photon tomography (7). However, there are several disadvantages for radioiodinated 4-iodoantipyrine: 1) it is unstable in vivo (8-10), and 2) the half-life for radioactive iodine is relatively long ($t_{\frac{1}{2}}$ = 13.1 hrs for ^{123}I; $t_{\frac{1}{2}}$ = 8 days for ^{131}I). Use of ^{131}I in particular, results in a high radiation burden to the individual. Fluorine-18, however, has attractive properties for use in nuclear medicine: 1) it is a positron emitter and has a useful half-life (109.8 min), 2) the C-F bond is strong, resulting in stability of the label, and 3) the substitution of fluorine for hydrogen in a biologically active compound frequently does not alter the biological characteristics of the parent compound (11,12). Indeed, several ^{18}F-labeled compounds have been proven to be good radiopharmaceuticals (13). Therefore, it was of interest to synthesize ^{18}F-labeled 4-fluoroantipyrine and study its biological activities.

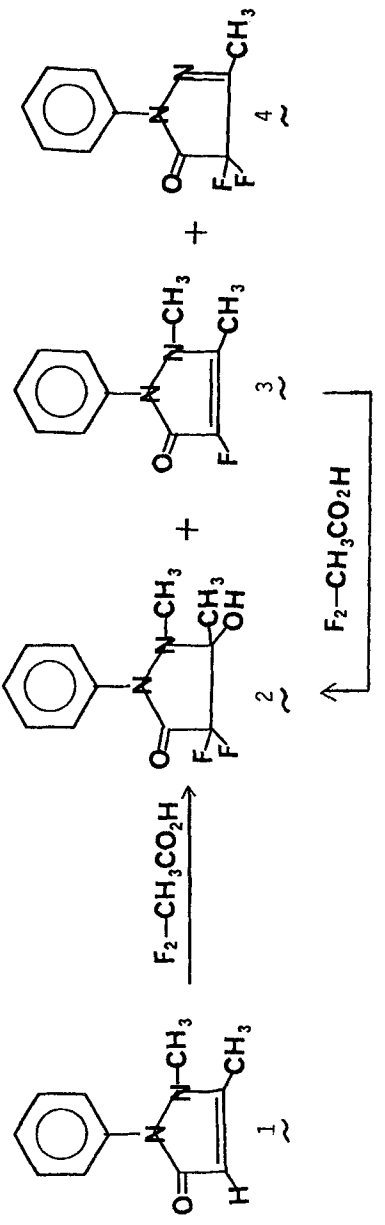
RESULTS AND DISCUSSION

Recently, ^{18}F-labeled 4'-fluoroantipyrine has been synthesized by a Schiemann reaction, but its ultimate application is limited by its low specific activity (14). An attempt was made to synthesize 4-fluoroantipyrine (3) by a Schiemann-type reaction starting 4-aminoantipyrine. The product isolated from this reaction was antipyrylazopyrazopyrazolone instead of the desired 4-fluoroantipyrine (15). Compound 3, however, has been synthesized by the electrophilic fluorination of antipyrine with fluoroxytrifluoromethane (16). This method, however, is not suitable for the synthesis of high specific activity of ^{18}F-labeled 4-fluoroantipyrine. Since the reactions of molecular fluorine are often similar to those of CF_3OF, and we are able to produce high specific activity $^{18}F\text{-}F_2$(17), we have synthesized compound 3 by direct fluorination of antipyrine with moelcular fluorine.

The reaction of antipyrine with moelcular fluorine in glacial acetic acid gave 4,4-difluoro-3-hydroxy-2,3-dimethyl-1-phenylpyrazolidin-5-one (2)(16), 4-fluoroantipyrine (3) (16), and an unidentified product (possibly 4,4-difluoro-3-methyl-1-phenyl-2-pyrazolin-5-one (4) as reported by Airey) (Scheme I) (16). The ratio of 3 to 2 depends on reaction conditions (Table 1). In the presence of excess fluorine, compound 2 becomes the major product. This is presumably due to the addition of fluorine to the compound 3 formed, since under the same reaction conditions, fluorine reacts with compound 3 to give compound 2. The mechanism of this reaction probably involved electrophilic substitution of fluorine at C-4 followed by electron shift as suggested by Airey et al. (16).

The structures of these compounds were verified by comparison with the reported (16) nmr and ms properties.

The sequence described here provides a convenient method for the synthesis of 4-fluoroantipyrine and is especially suited for the syntehsis of ^{18}F-labeled 4-fluoroantipyrine of high specific activity. Although the specific activity of 3 depends on total irradiation dose, typically, 0.44 mCi of 3 at delivery can be obtained from 4.19 mCi of $^{18}F\text{-}F_2$ with a specific activity of 0.16 mCi/mg.



SCHEME 1

EXPERIMENTAL

Melting points were determined on a Fischer-Jones melting point apparatus and were corrected. NMR spectra were measured on a JEOL MH-100 spectrometer and TMS used as an internal standard. Mass psectra were determined on a Hitachi Perkin-Elmer RMU-7 mass spectrometer. GLPC analyses were carried out on a Hewlett Packard 5830A gas chromatograph using a thermal conductivity detector. Radiochemical purities of the products were determined by thin-layer chromatography (TLC) on silica gel (Eastman) in the following solvent systems: petroleum ether:ethyl ether (1:1 by volume) (A) and ethyl acetate (B).

Reactions of Antipyrine (1) with Molecular Fluorine

In a typical reaction,2.4 mmol of 1.9% F_2/N_2 was bubbled into a solution of antipyrine (572 mg, 3.04 mmol) in 30 mL of glacial acetic acid held at room temperature. The light brown solution was then evaporated to dryness. GLPC (10% SE-30 on chromosorb w, 80/100 mesh, 6 ft. x 0.125 in. column 190°, 40 ml He/min) analysis of the residue showed peaks at 1.33, 2.42, 6.99, and 8.93 min in the area ratio of 0.96:9.7:31.72:57.67. The first peak is probably 4,4-difluoro-3-methyl-1-phenyl-2-pyrazolin-5-one (4). The other peaks corresponded to 4,4-difluoro-3-hydroxy-2,3-dimethyl-1-phenylpyrazolidin-5-one (2), 4-fluoroantipyrine (3), and antipyrine (1), respectively. The residue was then dissolved in a small amount of ethyl acetate and passed through a silica gel column. The column was eluted with ethyl acetate and fractionated to give 4,4-difluoro-3-hydroxy-2,3-dimethyl-1-phenylpyrazolidin-5-one (2) (13.67 mg), m.p. 154-156°C (lit. (16) 158.5-159.5°C); NMR spectrum ($CDCl_3$) was identical with previously reported values (16) and showed peaks at δ7.4-8.0 (m,5H,Ph), 4.6 (br,1H,OH), 2.8 (t,J=2Hz,3H, N-CH_3), 1.68 (d,J=3Hz,3H,C-CH_3); the mass spectrum gave a correct M^+ at m/e 242 and M^+-H_2O at 224; followed by 4-fluoro-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one (3) (84.92 mg), m.p. 132-134°C (lit. (16) 135-136°C); NMR ($CDCl_3$) δ7.64 (S,5H,Ph), 3.04 (d,J=2Hz,3H,N-CH_3), 2.28 (d,J=2Hz,3H,C-CH_3); M^+ 206 and antipyrine (342 mg).

The product distribution in the reaction of antipyrine with molecular fluorine at different concentration was analyzed by GLPC and is lsited in Table I.

Table I. Distribution of Products in the Reaction of Antipyrine with Molecular Fluorine in Glacial Acetic Acid at 25°C as a Function of $[F_2]$/[Antipyrine]

$[F_2]$/[Antipyrine]	0.27	0.79	1.06	1.79	4.06
% unreacted antipyrine 1	88.17	62.13	48.85	18.13	6.23
% 4,4-difluoro compound 2	1.46	9.20	14.23	33.06	49.48
% 4-fluoroantipyrine 3	10.20	27.44	34.00	45.24	22.43

Fluorination of 4-Fluoro-2,3-Dimethyl-1-Phenyl-3-Pyrazolin-5-One (3)

The 4-fluoroantipyrine (3) (4.7 mg, 0.23 mmol) in acetic acid (8 mL) was treated with molecular fluorine (0.48 mmol) at room temperature. GLPC analysis of the reaction mixture gave the difluoro adduct (2) and starting material (3).

[^{18}F]-4-Fluoroantipyrine (3)

The target, consisting of neon containing 0.1% of fluorine carrier (∿ 50 μmol) was irradiated with deuterons at the Brookhaven National Laboratory 60" cyclotron. The ^{18}F-labeled fluorine was produced from the $^{20}Ne(d,\alpha)^{18}F$ nuclear reaction. Typically, for a 3 min irradiation at a beam current of 5 μA, the yield of ^{18}F-F_2 is 4.19 mCi (75.6% recovery). The ^{18}F-F_2 was slowly purged from the target chamber into the solution of 11.58 mg (61.5 μM) of antipyrine (1) in 5 mL of glacial acetic acid in a reaction vessel held at room temperature. After all the gas had bubbled through, the reaction mixture was transferred to a round bottom flask and evaporated *in vacuo* to dryness. The residue was dissolved in a small amount of ethyl acetate and passed through a silica gel column (1 x 12 cm), eluted with ethyl acetate (50 mL) and evaporated to dryness. The residue containing compounds 2, 3, and possibly 4 was dissolved

in solvent (A) and passed through another silica gel column (1 x 12 cm), eluted with solvent (A) (150 mL) to remove compounds 2 and 4. Compound 3 which remained on the column was eluted with ethyl acetate (30 mL) and evaporated to dryness to give 2.8 mg (0.44 mCi at the time of delivery) of product (22.1% chemical yield and 13.7% radiochemical yield in a synthesis time of 87 min from EOB). Thin-layer chromatography showed that compound 3b had R_f 0.21 on solvent (A) and R_f 0.71 on solvent (B).

In an alternative method of purification, the reaction mixture was separated by preparative GLPC. The fluorination mixture was first passed through a silica gel column, eluted with ethyl acetate, and evaporated to dryness. The mixture (compounds 2, 3, and 4) was then dissolved in methanol and separated by preparative GLPC (10% SE-30 on chromosorb w, 80/100 mesh, 5 ft. x 0.25 in. column, 190°C, 40 ml He/min.). The peak corresponded to ^{18}F-4-fluoroantipyrine (3b) was collected.

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