SYNTHESIS OF 5-FLUOROALKYL-5-METHYLOXAZOLIDINE-2,4-DIONES AND THEIR ^{18}F-LABELED ANALOGS AS POTENTIAL INDICATORS OF TISSUE pH

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SUMMARY

5-Fluoromethyl-, 5-(2'-fluoroethyl)- and 5-(3'-fluoropropyl)-5-methyloxazolidine-2,4-diones (**4a,b,c**) were prepared as potential indicators of tissue pH, based on the fluorinative dehydroxylation with diethylaminosulfur trifluoride and/or the displacement reaction with fluoride ion. 5-(3'-[^{18}F]Fluoropropyl)-5-methyloxazolidine-2,4-dione (**4d**) was obtained by tosylate displacement in 14-16% radiochemical yield in a synthesis time of 40 min from start of the radiofluorination. The other two congeners labeled with ^{18}F resisted our efforts to prepare them using [^{18}F]fluoride ion.

Key Words: ^{18}F-labeling, 5-(3'-[^{18}F]fluoropropyl)-5-methyloxazolidine-2,4-dione, tosylate displacement, [^{18}F]fluoride ion

INTRODUCTION

5,5-Dimethyloxazolidine-2,4-dione (DMO) has been used as an indicator of intracellular pH due to its weak acidic characteristic and biochemical inertness (1). The measurement of regional brain-tissue pH in humans by positron emission tomography (PET) has been addressed by the preparation of DMO labeled with ^{11}C ($T_{1/2}$= 20.4 min), which is currently being applied to the study of cerebral ischemia and malignancy (2,3). Since tissue-plasma equilibration of [^{11}C]DMO requires a relatively long period (50-60 min), the originally injected radioactivity is considerably reduced at the time of PET measurements; large quantities of [^{11}C]DMO are needed for a PET study. Fluorine-18 is an another positron emitting radionuclide well suited for PET studies. The longer half-life of ^{18}F ($T_{1/2}$= 109.8 min) may be preferable, because the use of the fluorine-label allows more time for radiosynthetic procedure and a longer time span of investigation by PET. Thus it was of interest to develop ^{18}F-labeled analogs with similar physicochemical and biochemical properties. The ^{18}F-fluoroalkylation has recently drawn attention as a longer-lived alternative to the ^{11}C-alkylation in the design of positron emitting

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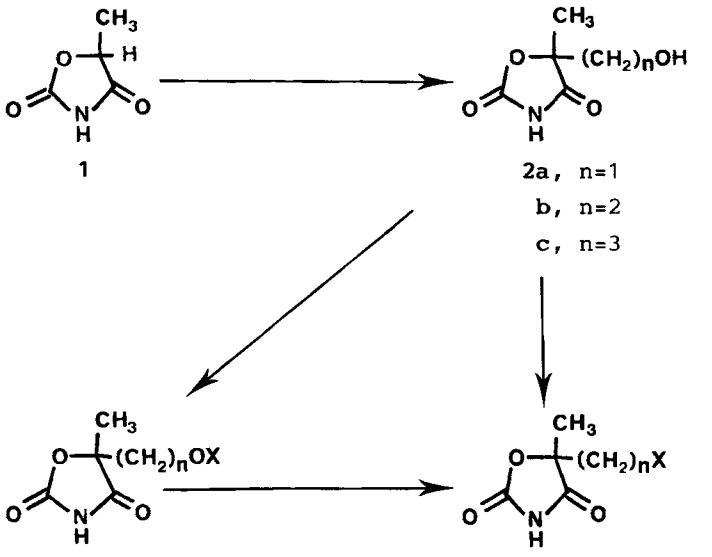
radiopharmaceuticals (4). Consequently, replacement of one of the methyl groups of DMO by the fluoroalkyl moiety seemed appropriate candidates for synthesis and evaluation as fluorine-containing derivatives of DMO. We describe here the synthesis of the three fluoroalkyl-substituted oxazolidine-2,4-diones as well as their radiochemical synthesis with ^{18}F.

RESULTS AND DISCUSSION

The strategy employed for the synthesis of nonradioactive 5-fluoroalkyl-5-methyloxazolidine-2,4-diones (**4a,b,c**) was based on the fluorinative dehydroxylation with diethylaminosulfur trifluoride (DAST)(5) and/or the substitution of a sulfonate ester group by fluoride ion. The latter process was adopted to work with ^{18}F because nucleophilic fluorination offers the only currently available method for no-carrier-added (NCA) reaction with ^{18}F (6). For these approaches, the hydroxyalkylated derivatives were required as immediate precursors. The synthetic route is outlined in Scheme 1. The hydroxymethyl (**2a**) was prepared according to the Stoughton's procedure as already described (7). The 2'-hydroxyethyl and 3'-hydroxypropyl substituents were introduced by alkylation of the dianion presumably formed by metalation of 5-methyloxazolidine-2,4-dione (**1**), with reference to that reported for the thiazolidine-2,4-dione nucleus (8). The dianion intermediate of **1** generated by means of three molar equivalents of lithium diisopropylamide was treated with a two-fold molar excess of tetrahydropyranyl (THP) protected 2-bromoethanol or 3-bromo-1-propanol in THF. Subsequent deprotection of the THP ethers with HCl gave the expected hydroxyethyl and hydroxypropyl (**2b** and **2c**), respectively, in 22 and 30% yields, together with several minor products that were not characterized; no attempt was made to improve the yield of this alkylation. Thus direct dehydroxylative fluorination of **2** with DAST in THF followed by aqueous workup gave the desired fluoroalkylated compounds (**4a,b,c**) in moderate yields. Although the fluoropropyl (**4c**) was isolated as single-spot material by TLC after purification on a silica gel column, ^1H-NMR analysis revealed the presence of minor impurity (δ 1.31 and 3.48 ppm) and difficulty was experienced in removing this impurity. Therefore, the hydroxypropyl (**2c**) was converted into the propyl tosylate (**3c**), whereas the corresponding triflate ester

Scheme 1



was difficult to prepare as pure material. The reaction of **3c** with tetramethylammonium fluoride in acetonitrile afforded a 57% yield of the fluoropropyl (**4c**) in pure form. On the other hand, attempted fluorination of the triflate (**3a**) of **2a** with a variety of fluoride ion sources failed to give the desired product. The structures of the fluorinated compounds were confirmed by elemental analyses, mass and ^{1}H-NMR spectra, in which the coupling patterns indicating the fluoroalkyl groups attached to the C_5 are consistent with those expected.

The dissociation constants of the fluorinated compounds were determined in aqueous solutions at 37°C and the values compared with those for DMO (pKa 6.13) and 5-ethyl-5-methyloxazolidine-2,4-dione (pKa 5.9) described in the literature (9,10). The pKa values decreased in the order of **4c** (pKa 5.97)> **4b** (pKa 5.95)> **4a** (pKa 5.52), indicating that the substitution of a fluoromethyl in place of a methyl in DMO has a significant acid-strengthening effect and that the influence of a fluorine atom two or three carbons removed from the C_5 of the ring is small.

The NCA [^{18}F]fluoride activity obtained from the ^{18}O(p,n)^{18}F reaction was con-

verted to the aminopolyether (Kryptofix 2.2.2) potassium complex ($[K/2.2.2]^{+18}F^-$) and tetra-n-butylammonium [^{18}F]fluoride (^{18}F-TBAF) as described earlier (11), which currently seem to be the most efficient form of [^{18}F]fluoride ion. Radiofluorinations of the methyl triflate (**3a**) and the ethyl tosylate (**3b**) were attempted using these [^{18}F]fluorinating agents under various experimental conditions. HPLC and TLC in all cases, however, revealed no labeled peaks other than [^{18}F]fluoride ion or only less than 1% incorporation of ^{18}F, although suspected from experiments with unlabeled materials. On the other hand, preliminary work using TLC indicated that the propyl tosylate (**3c**) was sufficiently reactive to allow a reasonable displacement with NCA [^{18}F]fluoride ion. Experiments were carried out under a variety of conditions to optimize the yield. The highest incorporation of ^{18}F occurred when the tosylate (**3c**)(9 μmol) in dry acetonitrile (300 μl) was heated for 10 min with $[K/2.2.2]^{+18}F^-$. Inevitable decomposition of the substrate occurred to some extent during the labeling reaction as evidenced by TLC analysis (12), probably because our drying conditions are insufficiently rigorous to remove all the water from the $[K/2.2.2]^{+18}F^-$ agent. This amount of the substrate (**3c**) was accordingly needed to obtain the maximum ^{18}F-labeling. Although HPLC purification using a reversed phase column was of limited success, a normal phase HPLC method involving addition of 3N HCl to the reaction mixture and subsequent ethyl acetate extraction allowed the selective separation of the desired product from all chemical and radiochemical impurities, as shown in Fig. 1. This technology offered the [^{18}F]fluoropropyl (**4d**) in 14-16% radiochemical yield after a processing time of 40 min from start of the radiofluorination. The use of ^{18}F-TBAF instead of $[K/2.2.2]^{+18}F^-$ and prolongation of reaction time led to no increased formation of **4d**. In addition, added carrier (1 μmol KF) had no effect in the yield. The specific activity of **4d** obtained here, starting from 1-2 mCi of the [^{18}F]fluorinating agent, was in the order of 50-90 Ci/mmol at end-of-synthesis. ^{18}F-Labeled 5-(3'-fluoropropyl)-5-methyloxazolidine-2,4-dione is thus now available for evaluation as an indicator of tissue pH in vivo. A synthesis of the ^{18}F-labeled fluoromethyl and fluoroethyl analogs with low specific activity may be achieved by the use of ^{18}F-labeled DAST (13), because the

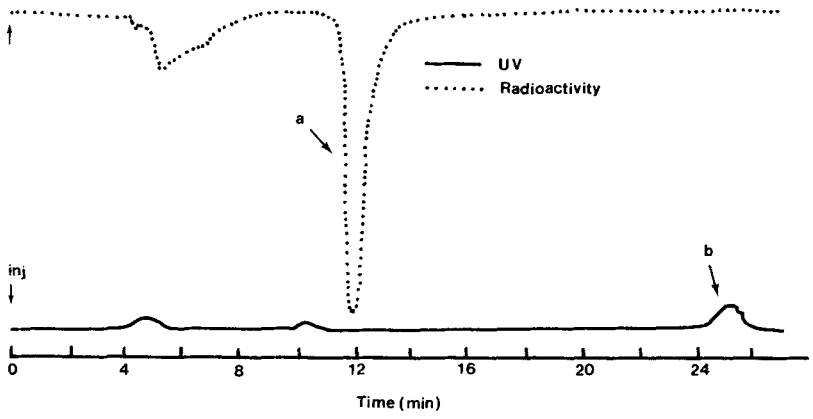


Fig. 1. HPLC separation of typical reaction mixture of 5-methyl-5-(3'-p-toluenesulfonyloxypropyl)-oxazolidine-2,4-dione (**3c**) with $[K/2.2.2]^{+18}F^-$ (see experimental for conditions). a: 5-(3'-[^{18}F]-fluoropropyl)-5-methyloxazolidine-2,4-dione (**4d**), b: substrate (**3c**)

unlabeled compounds (**4a** and **4b**) can be prepared by reacting the corresponding alcohols with DAST.

EXPERIMENTAL

All melting points are uncorrected. ^{1}H-NMR spectra were recorded on a JNM PS-100 or JEOL FX-100 spectrometer with tetramethylsilane as an internal reference and IR spectra were recorded on a JASCO IRA-1 spectrometer. Mass spectra (MS) were obtained with a JEOL DX-300 mass spectrometer using either electron-impact (EI) or fast atom bombardment (FAB) technique and UV spectra were obtained on a Hitachi 220A spectrometer. The elemental analyses were performed for C,H, and N by the staff of the microanalytical section of Kyushu University and results were within ±0.45% of the theoretical values. Column chromatography was performed on Kieselgel 60(70-230 mesh, Merck). TLC on silica gel 60F-254 (Merck) was used to monitor the reactions and to ascertain the purity of reaction products. Visualization of developed plates was effected by exposure to I_2. Analysis of radioactivity on TLC plates was performed with a Aloka radiochromatogram scanner. High pressure liquid chromatography (HPLC) was done using a Waters model M-45 fitted with a Whatman Partisil M9 10/50 column (attached a precolumn, silica gel 30 μ, 4 X 10 mm). The column was eluted with n-hexane/ethyl acetate (7:3, v/v)

at a flow rate of 6.0 ml/min. The radioactivity as well as the UV absorption (at 254 nm) of the effluent from the HPLC column were monitored. The radioactivity was also quantified with a Capintec radioisotope calibrator CRC-30. The radiochemical yields are expressed at the end of synthesis (not corrected for decay) relative to the amount of the [^{18}F]fluorinating agent measured as total radioactivity present in the reaction vessel.

The pKa values were determined as the pH at half neutralization from titration curves in distilled water at 37°C. A sufficient amount of compound was dissolved in water (20 ml) to give a concentration of 0.01 M. The titrant (0.05 N NaOH) was added and the pH changed followed with a Orion SA 720 pH meter.

Fluorine-18 was produced from 8% enriched [^{18}O]H_2O by the $^{18}O(p,n)^{18}F$ reaction as described previously (14). Aminopolyether (Kryptofix 2.2.2) supported potassium [^{18}F]fluoride ([K/2.2.2]$^{+18}F^-$) and tetra-n-butylammonium [^{18}F]fluoride (^{18}F-TBAF) were prepared by the addition of $K_2CO_3 \cdot 1.5H_2O$ (2.3 mg) and Kryptofix 2.2.2 (10.5 mg), and 10% tetra-n-butylammonium hydroxide in water (10 µl), respectively, to the irradiated water in a TPX (polymethylpentene) vessel and subsequent removal of the water by co-evaporation with acetonitrile as reported previously (11,15).

5-(2'-Hydroxyethyl)-5-methyloxazolidine-2,4-dione (2b)

Lithium diisopropylamide (LDA) was prepared in the following manner. A solution of n-butyllithium in n-hexane (1.62 M, 10 ml) was cooled to -20°C under argon followed by addition of diisopropylamine (1.6 g) via syringe. The temperature of the mixture was allowed to rise to 0°C where it was maintained for 20 min. The resulting solution of LDA was cooled to -78°C and a solution of 5-methyloxazolidine-2,4-dione (1)(16)(520 mg) in anhydrous THF (10 ml) was added dropwise from a syringe. After warming this solution to 0°C and stirring for 90 min, a solution of 2-bromoethyl-2-tetrahydropyranyl ether (3.34 g)[prepared from 2-bromoethanol and dihydropyran in dry methylene chloride containing a catalytic amount of pyridinium p-toluenesulfonate (17)] in anhydrous THF (15 ml) was added at -78°C and the reaction mixture then stirred at the same temperature for 3 hr, 0°C for 1 hr and finally at room temperature for 15 hr. The mixture was acidi-

fied to pH 3 with 3N HCl and stirred at room temperature for 4 hr. The product was extracted with ethyl acetate and the organic layers dried over Na_2SO_4. Removal of the solvent gave a syrup which was chromatographed on silica gel (n-hexane-ethyl acetate = 8:2) to give **2b** (157 mg, 22%) as colorless needles, after recrystallization from ethyl acetate-n-hexane, mp 106°C. IR(Nujol): 3300, 1800, 1720 cm^{-1}. ^{1}H-NMR(pyridine-d_5) δ: 1.65(3H, s, CH_3), 2.07-2.54(2H, m, CH_2), 3.99(2H, m, CH_2). MS(FAB) m/z: 160 $(M+1)^+$.

5-(3'-Hydroxypropyl)-5-methyloxazolidine-2,4-dione (**2c**)

To a freshly prepared LDA solution by mixing n-butyllithium in n-hexane (1.62 M, 7.4 ml) and diisopropylamine (1.25 g) was added a solution of 5-methyloxazolidine-2,4-dione (**1**)(16)(450 mg) in anhydrous THF (10 ml) at -78°C. After warming this solution to 0°C and stirred for 90 min, a solution of 3-bromopropyl-2-tetrahydropyranyl ether (2.3 g)[prepared from 3-bromo-1-propanol and dihydropyran in dry methylene chloride containing a catalytic amount of pyridinium p-toluenesulfonate (17)] in anhydrous THF (10 ml) was added at -78°C and the reaction mixture stirred at the same temperature for 30 min, and finally at room temperature for 4 hr. After the same workup as described in the synthesis of **2b** , the product was chromatographed on silica gel (n-hexane-ethyl acetate = 7:3) to give **2c** (205 mg, 30%) as colorless needles, after recrystallization from ethyl acetate-n-hexane, mp 86°C. IR(Nujol): 3350, 1810, 1740 cm^{-1}. ^{1}H-NMR(pyridine-d_5) δ: 1.59(3H, s, CH_3), 1.72-2.31(4H, m), 3.81(2H, t, J=6 Hz, CH_2). MS(FAB) m/z: 174 $(M+1)^+$.

5-Methyl-5-(trifluoromethanesulfonyloxymethyl)oxazolidine-2,4-dione (**3a**)

To an ice-chilled solution of the hydroxymethyl (**2a**)(7)(145 mg) in a mixture of methylene chloride and pyridine (16:1, 1 ml) was added slowly a solution of trifluoromethanesulfonic anhydride (423 mg) in methylene chloride (1 ml). The mixture was first stirred at 0°C for 20 min and then at room temperature for 80 min. To the mixture was added 0.3N HCl (10 ml) and the separated organic layer evaporated in vacuo. The residue was chromatographed on silica gel ($CHCl_3$) to yield **3a** (125 mg, 45%) as colorless needles, after recrystallization from ether-petroleum ether, mp 92-93°C. IR(Nujol): 1830, 1750 cm^{-1}. ^{1}H-NMR(acetone-d_6) δ: 1.70(3H, s, CH_3), 5.04(2H, s, CH_2), 10.95(1H, br, NH). MS(EI) m/z: 277 (M^+).

5-Methyl-5-(2'-p-toluenesulfonyloxyethyl)oxazolidine-2,4-dione (**3b**)

To a solution of p-toluenesulfonyl chloride (90 mg) in a mixture of methylene chloride (3 ml) and pyridine (150 µl) was added the hydroxyethyl (**2b**)(50 mg) at 0°C. The mixture was stirred at 0°C for 1 hr and then at room temperature for 24 hr. The reaction was quenched with ice-1N HCl and extracted with ethyl acetate, and evaporated to dryness in vacuo. The residue was chromatographed on silica gel ($CHCl_3$) to give **3b** (73 mg, 74%) as syrup. IR(Neat): 3450, 1800, 1740 cm^{-1}. ^{1}H-NMR($CDCl_3$) δ: 1.57(3H, s, CH_3), 2.15-2.38(2H, m, CH_2), 2.45(3H, s, CH_3), 4.16(2H, m, CH_2), 7.29-7.78(4H, m, aromatic), 7.95(1H, br, NH). MS(FAB) m/z: 314 $(M+1)^+$, 627 $(2M+1)^+$.

5-Methyl-5-(3'-p-toluenesulfonyloxypropyl)oxazolidine-2,4-dione (**3c**)

The hydroxypropyl (**2c**)(100 mg) was reacted with p-toluenesulfonyl chloride (154 mg) in a mixture of methylene chloride (5 ml) and pyridine (300 µl). After treatment as described in the synthesis of **3b**, the crude product was chromatographed on silica gel ($CHCl_3$) to give **3c** (134 mg, 71%) as syrup. IR(Neat): 1800, 1730 cm^{-1}. ^{1}H-NMR($CDCl_3$) δ: 1.55(3H, s, CH_3), 1.77-2.13(4H, m), 2.45(3H, s, CH_3), 4.03(2H, t, J=6 Hz, CH_2), 7.28-7.79(4H, m, aromatic). MS(FAB) m/z: 328 $(M+1)^+$, 655 $(2M+1)^+$.

5-Fluoromethyl-5-methyloxazolidine-2,4-dione (**4a**)

A solution of the hydroxymethyl (**2a**)(7)(1 g) in anhydrous THF (5 ml) was cooled to -20°C and a solution of DAST (1.11 g) in anhydrous THF (5 ml) was added dropwise. The mixture was stirred at the same temperature for 2 hr and at 40°C for 1.5 hr. Water was added and the aqueous phase was extracted with ethyl acetate. The organic extracts were dried over Na_2SO_4 and concentrated to give an oil, which was chromatographed on silica gel (n-hexane-ethyl acetate = 8:2) to afford **4a** (346 mg, 34%) as colorless needles, after recrystallization from ethyl acetate-n-hexane, mp 120°C. IR(Nujol): 1810, 1710 cm^{-1}. ^{1}H-NMR(acetone-d_6) δ: 1.55(3H, d, J=2.5 Hz, CH_3), 4.70(2H, dd, J=47, 2.5 Hz, CH_2F). MS(EI) m/z: 147 (M^+). TLC: R_f = 0.52(ethyl acetate), R_f = 0.38($CHCl_3$-ethyl acetate = 1:1).

5-(2'-Fluoroethyl)-5-methyloxazolidine-2,4-dione (**4b**)

The hydroxyethyl (**2b**)(220 mg) was dissolved in anhydrous THF (4 ml) and cooled to -20°C. A solution of DAST (306 mg) in anhydrous THF (1 ml) was added dropwise to this solution and the reaction mixture stirred at -20°C for 1 hr. The mixture was then allowed to rise to room temperature and stirred for 20 hr. The reaction was quenched with ice-water and extracted with ethyl acetate. The extracts were dried over Na_2SO_4 and evaporated to dryness in vacuo. The residue was chromatographed on silica gel (n-hexane-ethyl acetate = 7:3) to give **4b** (95 mg, 47%) as colorless needles, after recrystallization from ethyl acetate-n-hexane, mp 98-100°C. IR(Nujol): 1800, 1710 cm^{-1}. ^{1}H-NMR($CDCl_3$) δ: 1.65(3H, s, CH_3), 2.05-2.56 (2H, m, CH_2), 4.61(2H, dm, J=47 Hz, CH_2F), 7.86(1H, br, NH). MS(FAB) m/z: 162 $(M+1)^+$. TLC: R_f = 0.50(ethyl acetate), R_f = 0.39 ($CHCl_3$-ethyl acetate = 1:1).

5-(3'-Fluoropropyl)-5-methyloxazolidine-2,4-dione (**4c**)

Tetramethylammonium fluoride (226 mg)dried as previously described (18) was dissolved in dry acetonitrile (2 ml). A solution of the propyl tosylate (**3c**) (112 mg) in dry acetonitrile (1 ml) was added to this solution. The mixture was heated at 75°C for 3 hr. The solvent was removed and the residue dissolved in ice-water, made acidic with 1N HCl, and extracted with ethyl acetate. The extracts were dried over Na_2SO_4. Removal of the solvent gave a syrup which was chromatographed on silica gel (n-hexane-ethyl acetate = 8:2) to afford **4c** (35 mg, 57%) as syrup. IR(Neat): 3510, 1810, 1740 cm^{-1}. ^{1}H-NMR($CDCl_3$) δ: 1.60(3H, s, CH_3), 1.81-2.12(4H, m), 4.45(2H, dt, J=47, 6.0 Hz, CH_2F), 8.75(1H, br, NH). MS (FAB) m/z: 176 $(M+1)^+$. TLC: R_f = 0.52 (ethyl acetate), R_f = 0.34 ($CHCl_3$-ethyl acetate = 1:1).

Attempted radiofluorinations of the triflate (**3a**) and tosylate (**3b**)

To a solution of NCA ^{18}F-TBAF or $[K/2.2.2]^+{}^{18}F^-$ in dry acetonitrile (300-500 µl) in a TPX vessel was added the substrate **3a** or **3b** (1-5 mg) and the vessel capped. The mixture was heated at 60-80°C. The product was analyzed by TLC (silica gel, chloroform-ethyl acetate = 1:1) and/or HPLC (Whatman Partisil M9 10/50, n-hexane-ethyl acetate = 7:3, 6 ml/min). In all cases there was either

no measurable ^{18}F-incorporation or only less than 1% yield even with reaction times as long as 2 hr.

5-(3'-[^{18}F]Fluoropropyl)-5-methyloxazolidine-2,4-dione (**4d**)

The following is the procedure using optimum reaction conditions. A solution of the propyl tosylate (**3c**)(3 mg, 9 μmol) in dry acetonitrile (300 μl) was added to the [K/2.2.2]$^{+18}F^-$ (1-2 mCi) in a TPX vessel and the vessel capped. The reaction mixture was heated at 70°C for 10 min and cooled briefly in water prior to opening. To the mixture was added 3N HCl (100 μl) and extracted with ethyl acetate (500 μl x 3). The extract was evaporated and the residue was dissolved in a mixture of n-hexane and ethyl acetate (7:3, 2 ml) and injected onto a silica gel HPLC column (Whatman Partisil M9 10/50). Elution with n-hexane-ethyl acetate (7:3) at a flow rate of 6 ml/min gave the desired compound (**4d**)(R_T = 12.0 min) with radiochemical yields of 14-16% (not corrected for decay). The identity was verified by HPLC and TLC comparison with authentic sample. No chemical and radiochemical contamination was detected by HPLC and TLC. The entire procedure took 40 min from start of the radiofluorination. The specific activity of the product was 50-90 Ci/mmol at the end of radiosynthesis as estimated by UV spectroscopy (240 nm).

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REFERENCES

1) Roos A. and Boron W.F.—— Physiol. Rev. 61: 296 (1981).

2) Berridge M., Comar D., Roeda D. and Syrota A.— Int. J. Appl. Radiat. Isot. 33: 647 (1982); Ginos J.Z., Tibury R.S., Haber M.T. and Rottenberg D.A. — J. Nucl. Med. 23: 255 (1982): Diksic M. — Int. J. Appl. Radiat. Isot. 35: 1035 (1984); Ginos J.Z. — Int. J. Appl. Radiat. Isot. 36: 793 (1985).

3) Syrota A., Castaing M., Rougemont D., Berridge M., Baron J.C., Bousser M.G.

and Pocidalo J.J. — Ann. Neurol. 14: 419 (1983); Kearfott K.J., Junck L. and Rottenberg D.A. — J. Nucl. Med. 24: 805 (1983); Rottenberg D.A., Ginos J.Z., Kearfott K.J., Junck L. and Bigner D.D. — Ann. Neurol.(Suppl.) 15: S98 (1984); Syrota A., Samson Y., Boullais C., Wajnberg P., Loc'h C., Crouzel C., Maziere B., Soussaline F. and Baron J.C. — J. Cereb. Blood Flow Metabol. 5: 358 (1985).

4) Chi D.Y., Kilbourn M.R., Katzenellenbogen J.A., Brodack J.W. and Welch M.J. — Int. J. Appl. Radiat. Isot. 37: 1173 (1986); Shiue C.Y., Bai L.Q., Teng R.R. and Wolf A.P. — J. Label. Compd. Radiopharm. 24: 55 (1987).

5) Middleton J.W. — J. Org. CHem. 40: 574 (1975).

6) Berridge M.S. and Tewson T.J. — Appl. Radiat. Isot. 37: 685 (1986).

7) Yamaguchi T., Ichiki K., Sone H., Maeda M. and Kojima M. — Chem. Pharm. Bull. 26: 1623 (1978).

8) Taylor J.D. and Wolfe J.F. — Synthesis, 310 (1971).

9) Erlenmeyer H., Kleiber A. and Loebenstein A. — Helv. Chim. Acta 21: 1010 (1938); Erlenmeyer H. and Kleiber A. — Helv. Chim. Acta 22: 851 (1939).

10) Clark-Lewis J.W. — Chem. Rev. 58: 63 (1958).

11) Coenen H.H., Klatte B., Knochel A., Schuller M. and Stocklin G. — J. Label. Compd. Radiopharm. 23: 455 (1986); Block D., Klatte B., Knochel A., Beckmann R. and Holm U. — J. Label. Compd. Radiopharm. 23: 467 (1986).

12) The 2,4-oxazolidinedione ring is moderately stable towards acidic hydrolytic conditions whereas it undergoes ring fission by an excess of alkali, see ref. (10).

13) Straatmann M.G. and Welch M.J. — J. Nucl. Med. 18: 151 (1977).

14) Maeda M., Fukumura T. and Kojima M. — Appl. Radiat. Isot. 38: 307 (1987).

15) Haradahira T., Maeda M. and Kojima M. — J. Label. Compd. Radiopharm. 25: 497 (1988).

16) Stoughton R.W. — J. Amer. Chem. Soc. 63: 2376 (1941).

17) Miyashita M., Yoshikoshi A. and Grieco P.A. — J. Org. Chem. 42: 3773 (1977).

18) Haradahira T., Maeda M., Omae H., Yano Y. and kojima M. — Chem. Pharm. Bull. 32: 4758 (1984).