Nucl. Med. Biol. Vol. 20, No. 8, pp. 939–944, 1993
Printed in Great Britain.

0969-8051/93 $6.00 + 0.00

High Yield Synthesis of High Specific Activity *R*-(−)-[^{11}C]Epinephrine for Routine PET Studies in Humans*

PULAK K. CHAKRABORTY, DAVID L. GILDERSLEEVE, DOUGLAS M. JEWETT, STEVE A. TOORONGIAN†, MICHAEL R. KILBOURN, MARKUS SCHWAIGER and DONALD M. WIELAND‡

Division of Nuclear Medicine, Department of Internal Medicine, University of Michigan Medical School, Ann Arbor, MI 48109-0552, U.S.A.

(Received 29 March 1993)

R-(−)-[^{11}C]Epinephrine ([^{11}C]EPI) has been synthesized from *R*-(−)-norepinephrine by direct methylation with [^{11}C]methyl iodide or [^{11}C]methyl triflate. The total synthesis time including HPLC purification was 35–40 min. The radiochemical yields (EOB) were 5–10% for [^{11}C]methyl iodide and 15–25% for [^{11}C]methyl triflate. Radiochemical purity was >98%; optical purity determined by radio-chiral HPLC was >97%. The [^{11}C]methyl triflate technique produces *R*-(−)-[^{11}C]epinephrine in quantities (80–170 mCi) sufficient for multiple positron emission tomography studies in humans. The two synthetic methods are generally applicable to the production of other *N*-[^{11}C]methyl phenolamines and *N*-[^{11}C]methyl catecholamines.

Introduction

N-[^{11}C]Methylation is a rapid radiosynthetic reaction adaptable to remote control. Many useful tracers have been synthesized in single-step processes from their normethyl precursors. Usually [^{11}C]methyl iodide is the reagent of choice, although *N*-[^{11}C]methylation has also been achieved by reductive alkylation using [^{11}C]formaldehyde (Mulholland *et al.*, 1988). Yields are generally good, especially when amides are methylated in the presence of strong bases such as sodium hydride. The technique, however, has not been generally applied to amines, especially chiral biogenic amines. The work reported here was prompted by our intent to synthesize [^{11}C]EPI to study the sympathetic nervous system of the human heart.

The first, and to our knowledge, the only synthesis of [^{11}C]EPI was reported by Soussain *et al.* in 1984. They employed phenylethanolamine-*N*-methyltransferase (PNMT) with *S*-adenosyl-L-[methyl-^{11}C]methionine (SAM) to methylate *R*-(−)-norepinephrine. The SAM itself was synthesized from [^{11}C]methyl iodide and L-homocysteine thiolactone. This elegant natural enzymatic approach, unfortunately, produced low yields (1.5 mCi) of [^{11}C]EPI with specific activities (< 200 Ci/mmol) so low as to preclude human studies. The authors briefly noted that low yields of [^{11}C]EPI were also obtained when direct methylation of *R*-(−)-norepinephrine with [^{11}C]methyl iodide or reductive alkylation with [^{11}C]formaldehyde were attempted.

Normally, direct methylation of primary amines with [^{12}C]methyl iodide is not a viable preparative route to the respective *N*-methylamines because of competitive polymethylation. However, it can be a successful radioalkylation route using [^{11}C]methyl iodide because the parent amine is present in large excess, thereby reducing the probability of polymethylation. Under neutral conditions, methylation of phenolamines with [^{11}C]methyl iodide produces *N*-[^{11}C]methyl products in acceptable yields without significant competing *O*-methylation of the phenol group. We have demonstrated this with the synthesis of *N*-[^{11}C]methyl-*meta*-hydroxyephedrine (MHED) from metaraminol free base by direct methylation

*Parts of this study were first reported in abstract form: Chakraborty P. K., Gildersleeve D. L., Toorongian S. A., Kilbourn M. R., Schwaiger M. and Wieland D. M. (1993) Synthesis of [^{11}C]epinephrine and other biogenic amines by direct methylation of normethyl precursors. *9th International Symposium on Radiopharmaceutical Chemistry*, 5–10 April 1992, Paris, France. *J. Labeled Cmpd. Radiopharm.* **32**, 172.

†Present address: Nuclear Medicine Department, SUNY at Buffalo, Buffalo, NY 14214, U.S.A.

‡All correspondence should be addressed to: Dr Donald M. Wieland, 3480 Kresge III Bldg, University of Michigan Medical School, Ann Arbor, MI 48109-0552, U.S.A.

with [^{11}C]methyl iodide (Rosenspire *et al.*, 1990). At present, MHED is routinely synthesized in our PET Center for clinical research studies in both nuclear cardiology (Schwaiger *et al.*, 1990, 1991) and nuclear oncology (Shulkin *et al.*, 1992). More recently we have radiolabeled other phenolamines by this approach including *para*-hydroxyephedrine and (+)-(1S,2S)-*threo*-MHED (Hutchins *et al.*, 1991; Haka *et al.*, 1990).

In view of the chemical instability of catecholamines, we anticipated that reaction of norepinephrine with [^{11}C]methyl iodide might give lower yields than those obtained from phenolamines such as metaraminol. This was, as reported here, indeed the case. However, an alternative pathway to [^{11}C]EPI was suggested by the work of Jewett (1992) who reported the synthesis of the more reactive methylating agent [^{11}C]methyl triflate. In view of the availability of [^{11}C]methyl triflate at our institution, we have applied this new reagent to the *N*-methylation of *R*-(−)-norepinephrine. Accordingly, we report here a rapid, high-yield synthesis of [^{11}C]EPI with a specific activity sufficiently high to permit positron emission tomography (PET) studies of this hormone in humans.

Materials and Methods

R-(−)-Norepinephrine hydrochloride samples were newly purchased from Aldrich Chemical Co., Milwaukee, Wis. and Fluka Chemical Co., Ronkonkoma, N.Y.; an older batch of the hydrochloride salt, no longer available, had been obtained from Schweizerhall, Piscataway, N.J. *R*-(−)-Epinephrine-D-bitartrate was newly purchased from RBI, Natick, Mass. Anhydrous dimethyformamide (DMF) and dimethyl sulfoxide (DMSO), 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl isothiocyanate (GITC), (±)-epinephrine, (±)-norepinephrine hydrochloride, (±)-normetanephrine hydrochloride, tetrabutylammonium hydroxide (1 M solution in methanol) and hydrazine hydrate were obtained from Aldrich Chemical Co. The [^{11}C]methyl iodide was prepared from [^{11}C]carbon dioxide produced by the ^{14}N(p, α)^{11}C reaction in a nitrogen target containing traces of oxygen under pressure (Marazano *et al.*, 1977). [^{11}C]Methyl triflate was prepared from [^{11}C]methyl iodide according to the procedure of Jewett (1992).

Synthesis of R-(−)-[^{11}C]epinephrine using [^{11}C]methyl iodide

R-(−)-Norepinephrine hydrochloride (1.0 mg) was weighed in a reaction vial and its free base generated *in situ* by the addition of 0.8–0.9 equivalents of tetrabutylammonium hydroxide (3.9 μL of 1 M solution in methanol). Following evaporation of the methanol with a nitrogen purge, the residue was dissolved in 0.25 mL of DMF/DMSO (3/1). The reaction vial was cooled to −35°C in a heating/cooling block to trap [^{11}C]methyl iodide as it was bubbled through the reaction mixture. After maximum radioactivity had accumulated, the vial was sealed and heated at 85°C for 5 min. The reaction mixture was then cooled to ambient temperature and purified by HPLC. Pure [^{11}C]EPI eluted at approx. 9 min from a strong cation exchange column (Optisil 10 μm SCX, 250 × 4.6 mm, Phenomenex, Inc., Torrance, Calif.) using 0.01 M NaH_2PO_4, (2.8 mL/min) as mobile phase. Column effluent was monitored with a radiation detector. A two-way valve was used to divert waste and to collect the desired radiolabeled products.

Radiochemical purity of the final product was determined independently on an analytical reversed-phase column (Ultremex 5 C18 IP, 250 × 4.6 mm; Phenomenex Inc.). The column was eluted with an aqueous solution of 0.1 M AcOH, 5 mM pentanesulfonate sodium salt and 1.5 mM EDTA disodium salt/CH_3OH (9:1, v/v) at a flow rate of 1 mL/min. Column effluent was monitored by an absorbance detector at 280 nm and radiation detector in series. The mass of both residual norepinephrine precursor and epinephrine in the final product was determined by comparison with standard curves obtained by injections of authentic samples of known concentration.

Synthesis of R-(−)-[^{11}C]epinephrine using [^{11}C]methyl triflate

The synthesis, purification and analysis of [^{11}C]EPI produced with [^{11}C]methyl triflate was identical to that described above for the synthesis of [^{11}C]EPI using [^{11}C]methyl iodide except for the substitution of [^{11}C]methyl triflate for [^{11}C]methyl iodide.

Assay of optical purity of R-(−)-[^{11}C]epinephrine

To a 100 μL aliquot of HPLC-purified *R*-(−)-[^{11}C]epinephrine in 0.01 M NaH_2PO_4 was added 135 μL of 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl isothiocyanate (GITC) in DMF (20 mg/mL). After the reaction mixture was warmed to 50°C for 10 min and then cooled to room temperature, 30 μL of hydrazine hydrate (5 μL/mL) in DMF was added to inactivate excess reagent. The mixture was analyzed by reversed-phase HPLC (Ultremex 5 C18 IP, 50 × 4.6 mm; Phenomenex) using 0.01 M KH_2PO_4/CH_3OH (67.5:32.5) as mobile phase at a flow rate of 1.0 mL/min. The retention times of the (+)- and (−)-epinephrine-GITC derivatives were determined by subjecting (±)-epinephrine to this procedure; optical identity of the peaks was determined by spiking (±)-epinephrine with authentic (−)-epinephrine before derivatization.

Assay of optical purity of R-(−)-norepinephrine

The optical purity of various commercial samples of *R*-(−)-norepinephrine was determined by chiral HPLC using a CrownPak CR(+) column (150 × 4.6 mm, Daicel, J. T. Baker, Phillipsburgh,

N.J.); with 23 mM perchloric acid (0.5 mL/min) as eluent. To determine if racemization of *R*-(−)-norepinephrine occurs during the course of the synthesis of [^{11}C]EPI, the following experiment was performed. To *R*-(−)-norepinephrine hydrochloride (1.0 mg) was added 0.8 equivalent of tetrabutylammonium hydroxide, 1 M in methanol (3.9 μL), in a sealed vial. The methanol was removed by nitrogen purge and the residual solid dissolved in 0.25 mL of DMF/DMSO (3/1). The vial was placed in a heating block, warmed for 5 min at 85°C and then returned to room temperature. After addition of 2 mL of milli-Q water, the solution was applied to a neutral alumina Sep-Pak and washed with 10 mL of water. Norepinephrine was eluted from the column with 1.0 M perchloric acid (1 mL). Optical analysis was performed by HPLC as described above.

Results and Discussion

Synthesis of R-(−)-[^{11}C]epinephrine

We have previously reported the synthesis of [^{11}C]MHED by direct methylation of metaraminol free base with [^{11}C]methyl iodide under neutral conditions (Rosenspire *et al.*, 1990). The yield and specific activity of the [^{11}C]MHED produced were sufficient to permit the use of this radiotracer in clinical trials. For the synthesis of [^{11}C]EPI, however, this method had to be modified because of the greater susceptibility of norepinephrine free base to air oxidation. This modification simply involved the *in situ* generation of free base norepinephrine from the hydrochloride salt under oxygen-free conditions. Tetrabutylammonium hydroxide (1 M in methanol) was chosen to partially neutralize the hydrochloride salt because the small amount of base required (0.8–0.9 eq.) to generate the free base could be added with reasonable accuracy, and the methanol could be removed by purging with nitrogen gas prior to redissolving the residue in DMF/DMSO (3:1).

In our initial syntheses of [^{11}C]EPI, [^{11}C]methyl iodide was used as the methylating agent. The specific activity of the product was 1000–2000 Ci/mmol (EOS) but only a 5–10% radiochemical yield (EOB, $N = 10$) could be achieved in a synthesis time of 35–40 min. Jewett (1992) reported the conversion of [^{11}C]methyl iodide to the more powerful methylating agent [^{11}C]methyl triflate. The availability of this carbon-11 precursor prompted us to apply it to the synthesis of [^{11}C]EPI in the hope of obtaining higher yields and possibly higher specific activities. Indeed, a yield of 15–25% (EOB, $N = 20$) with a specific activity of 900–2200 Ci/mmol (EOS) was obtained for [^{11}C]EPI (Fig. 1). At present, a typical production run produces 80–170 mCi of [^{11}C]EPI in 10 mL of final formulation. The amount of norepinephrine has ranged from 0.15 to 0.77 μg/mL; the amount of epinephrine present has ranged from 0.23 to 2.06 μg/mL.

HPLC purification and quality control of R-(−)-[^{11}C]epinephrine

We have previously reported that a C-18 reversed-phase column with 0.24 M monobasic sodium phosphate as mobile phase provided adequate resolution of metaraminol and MHED for the purification of [^{11}C]MHED (Rosenspire *et al.*, 1990). For the much more polar catecholamines, however, this system was

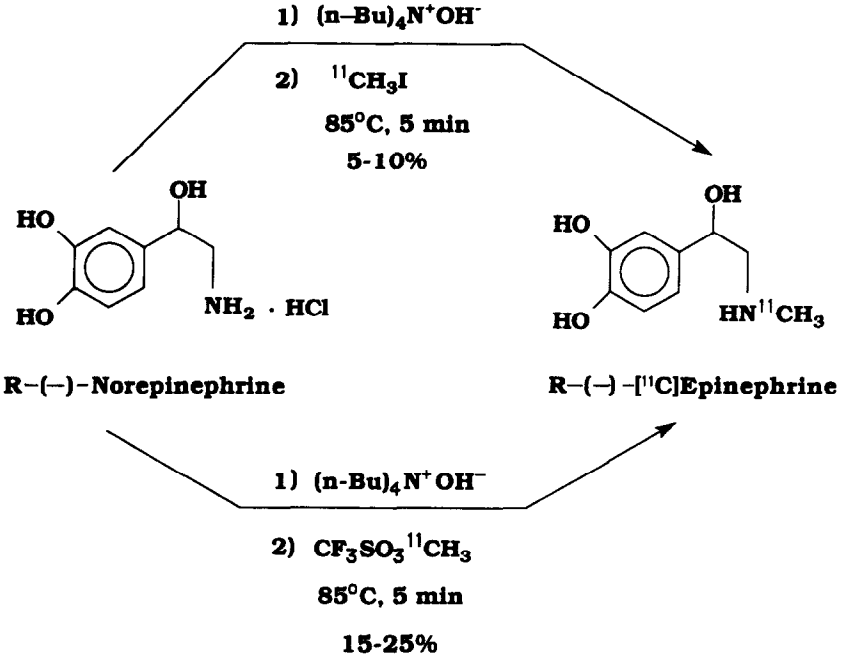

Fig. 1. Radiochemical syntheses of [^{11}C]EPI.

not sufficiently efficient to resolve [^{11}C]EPI from norepinephrine without the addition of ion-pair to the mobile phase, which would have complicated the purification methods. Switching to a strong cation exchange column with 0.01 M monobasic sodium phosphate as eluent did provide the necessary efficiency and resolution for the purification of [^{11}C]EPI. Under these conditions, norepinephrine eluted at ~5 min and epinephrine eluted at ~9 min. The unreacted norepinephrine and a large radioactive peak, which eluted at ~3 min, were diverted to waste. [^{11}C]EPI was collected through an in-line 0.22 μm sterile filter into a sterile vial in a total volume of 6.5–7.0 mL of eluent; 3.0–3.5 mL of 0.45 M sodium acetate buffer, pH 5.0, containing 0.3% sodium-L-ascorbate, was added to adjust both pH and ionic strength for i.v. injection.

The radiochemical and chemical purity of the final product were determined by a separate analytical HPLC system. The u.v. detection limit for both norepinephrine and epinephrine using this HPLC system was 25 pmol. A representative absorbance and radioactivity chromatogram are shown in Fig. 2. The most likely by-product in these labeling experiments would be 3-*O*-methyl norepinephrine [^{11}C]normetanephrine), potentially formed by methylation of the phenol group. However, [^{11}C]normetanephrine has not been detected in the crude product. Neither [^{11}C]metanephrine nor *N*-methyl[^{11}C]epinephrine would be an expected by-product since norepinephrine is present in vast excess of either [^{11}C]methyl iodide or [^{11}C]methyl triflate. The radiolytic stability of [^{11}C]EPI up to 1 h EOS in either the HPLC eluent or the formulation has been confirmed by analytical HPLC monitoring.

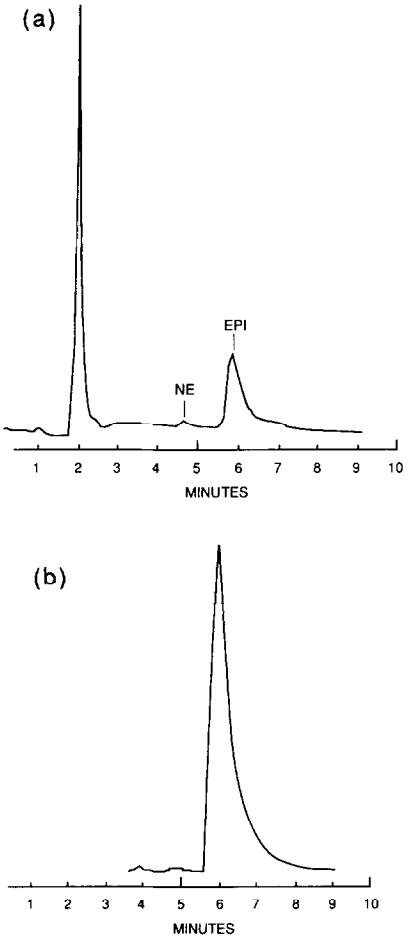

Fig. 2. Chemical and radiochemical purity of HPLC-purified [^{11}C]EPI determined by analytical HPLC. (a) Ultraviolet absorbance trace shows both norepinephrine (NE) and epinephrine (EPI); (b) radioactivity trace shows only [^{11}C]EPI. Traces are from a 1 mCi injection.

Optical purity of R-(−)-norepinephrine and R-(−)-[^{11}C]epinephrine

For research or clinical use of [^{11}C]EPI, the tracer must be enantiomerically pure. To achieve this goal, the precursor *R*-(−)-norepinephrine must also be optically pure. We have analyzed the enantiomeric purity of *R*-(−)-norepinephrine obtained from several commercial sources using a CrownPak CR(+) column. The *R*-(−)- and *S*-(+)-enantiomers of norepinephrine eluted at 12.4 and 13.5 min, respectively. *R*-(−)-norepinephrine hydrochloride obtained from both Fluka and Aldrich was found to have an enantiomeric purity >97% and was deemed suitable for use in the clinical synthesis of [^{11}C]EPI. Table 1 summarizes the results obtained for a number of commercial sources. The enantiomeric stability of *R*-(−)-norepinephrine under the reaction conditions used for the synthesis of [^{11}C]EPI was also confirmed by use of the CrownPak CR(+) column.

Unfortunately chiral HPLC with the CrownPak CR(+) column does not separate the enantiomers of epinephrine. However, Allgire *et al.* (1985) have reported the derivatization of epinephrine with the chiral reagent 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl isothiocyanate (GITC) in DMF. We have successfully formed the epinephrine–GITC derivative not only in DMF, but also in DMF/DMSO (3:1), and even in 0.01 M NaH_2PO_4. The diastereomeric GITC derivatives of (−)- and (+)-epinephrine were resolved by reversed-phase HPLC with u.v. detection at 254 nm. Figure 3 presents the HPLC chromatograms of the GITC-derivatized solutions of [^{11}C]EPI synthesized from *R*-(−)-norepinephrine obtained from two different commercial sources. The

Table 1. Optical purity of *R*-(−)-norepinephrine from commercial sources*

Company source	% (−)	% (+)
Aldrich Chemical	97	3
Fluka Chemical	97	3
RBI	91	9
Schweizerhall†	90	10

*Optical purity was determined by chiral HPLC using a CrownPak CR(+) column.
†This material was an old shelf sample; all other norepinephrine samples were recently purchased.

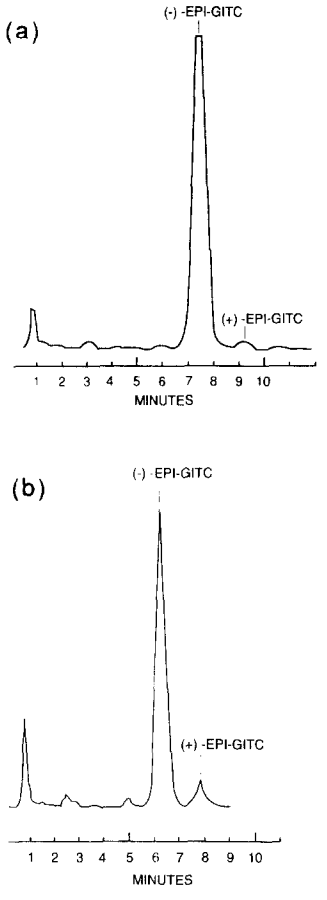

Fig. 3. Optical purity of [^{11}C]EPI determined by radio-HPLC. Radioactivity traces of crude solutions of [^{11}C]epinephrine–GITC derivatives synthesized using *R*-(−)-norepinephrine from Schweizerhall (a) and Fluka (b).

(−)- and (+)-epinephrine–GITC derivatives eluted at approx. 7.3 and 9.3 min, respectively. Underivatized epinephrine eluted at 0.8 min. Two unidentified, u.v.-absorbing peaks, eluting at 2.5 and 5.8 min, were also observed in the reaction mixture. We have also derivatized authentic racemic normetanephrine with GITC by the same procedure. Analysis of the products by the same HPLC system gave two peaks at ~10.7 and ~11.9 min, which are well resolved from the epinephrine-GITC derivatives. The isomeric identity of these two peaks was not determined.

The enantiomeric purity of [^{11}C]EPI was determined in both the crude reaction mixture and the final purified product. In both cases, HPLC analysis of the GITC-derivatized product showed a major and minor radioactive peak which co-eluted with the corresponding authentic (−)- and (+)-epinephrine-GITC derivatives. The radioactivity peak ratios were identical to the u.v. peak ratios obtained on chiral HPLC for the *R*-(−)-norepinephrine hydrochloride used as precursor. There was no radioactive peak corresponding to the (−)- or (+)-normetanephrine-GITC adducts. To rule out the possibility that other radioactive impurities might interfere with our determination of the enantiomeric purity, we performed an identical blank experiment, using [^{11}C]methyl triflate, in the absence of *R*-(−)-norepinephrine hydrochloride. HPLC analysis of the crude mixture showed that all radioactivity eluted in the first 2 min. These HPLC analyses provide strong evidence that no racemization occurred during either the ^{11}C-labeling procedure or purification of the [^{11}C]EPI. The chiral analyses also confirm our previous finding that, under these ^{11}C-methylation conditions, no *O*-^{11}C-methyl derivative (i.e. [^{11}C]normetanephrine) is formed.

Specific activity considerations

The methylation methods described above give a minimum specific activity of approx. 1000 Ci/mmol for [^{11}C]EPI. At this level, a 20 mCi i.v. injection of [^{11}C]EPI will contain 3.66 μg of carrier epinephrine. The i.v. dose of epinephrine known to induce a pressor response in adults is 100–250 μg administered "very slowly" (Harvey, 1990). Other sources suggest that this dose level can be administered over an approx. 1 min duration (McEnvoy, 1992). Since i.v. injections of radiotracers for PET studies are generally administered in 1 min or less, injection of 20 mCi of [^{11}C]EPI, 1000 Ci/mmol, is most likely below the anticipated dose range for a vasopressor effect. However, in view of the variability in patient pressor response to epinephrine (McEvoy, 1992), it will be important to closely monitor patient blood pressure and heart rate during i.v. administration of [^{11}C]EPI, especially if bolus injection times of considerably less than 1 min are employed. The presence of precursor norepinephrine is of equal concern since it has a pressor potency greater than epinephrine; approx. 2–10 μg/min is the recommended adult i.v. dose rate (McEvoy, 1992). Fortunately, in our most recent experience, norepinephrine levels have been kept below 1.0 μg/20 mCi of [^{11}C]EPI by careful attention to the HPLC purification. We continue to optimize this synthetic procedure to maximize both the specific activity and effective specific activity of the [^{11}C]EPI. Exclusion of ambient carbon sources, in particular traces of methanol that might be entrained in the tetrabutylammonium hydroxide, is very important in achieving this goal. For human PET studies at our institution, an i.v. injection of 10–20 mCi of [^{11}C]EPI is utilized. Upper dose limits of 9 μg for epinephrine and 1 μg for norepinephrine have been set for adults weighing 50 kg or more. Adherence to this limit assures that the patient will receive a subpharmacological dose of catecholamines. It is of paramount importance to obtain a specific activity as high as possible, preferably greater than 2500 Ci/mmol, a level which we have approached in our most recent syntheses.

The critical importance of specific activity has arisen previously with other catecholamines labeled with positron-emitting radioisotopes, such as 6-[^{18}F]fluorodopamine (6-FDA). Although dopamine is considerably less potent than epinephrine, the

extremely low specific activity (0.5–10 Ci/mmol) of 6-FDA produced by electrophilic fluorination (Goldstein *et al.*, 1990, 1991) places it outside the true tracer range needed for PET studies. The nucleophilic [^{18}F]fluoride method of 6-FDA preparation (Ding *et al.*, 1991a), however, provides 6-FDA in 100-fold higher specific activity and hence, the true tracer levels needed for cardiac PET studies. Similarly, high specific activity 6-[^{18}F]fluoronorepinephrine has been reported using the nucleophilic [^{18}F]fluoride approach (Ding *et al.*, 1991b). Thus, whether ^{11}C- or ^{18}F-labeled tracers are used to track endogenous catecholamines, attention must be paid to the compelling need to optimize the specific activity of the target tracer.

Summary

Simple, rapid, chiral syntheses of [^{11}C]EPI by direct methylation of *R*-(−)-norepinephrine with either [^{11}C]methyl iodide or [^{11}C]methyl triflate have been described. The latter method, due primarily to its higher yields, has been adopted for the routine clinical production of [^{11}C]EPI. These procedures appear to be generally applicable to the syntheses of other *N*-[^{11}C]methyl phenolamines and *N*-[^{11}C]methyl catecholamines.

Acknowledgements—This work was supported by National Institutes of Health Grants RO1 HL27555 and RO1 HL41047 and Department of Energy Grant DE-FG02-90ER6091. We thank Linder Markham for assistance in preparing the manuscript.

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