m/e (M^+) 362, (M^+ - 44) 318. Anal. ($C_{17}H_{19}FN_4O_4$): C, H, N.

3-Methyl-7-fluoro-8-(4-methyl-1-piperazinyl)-1,2-dihydro-5-oxo-5*H*-imidazolo[3,2-*a*][1,8]naphthyridine-4-carboxylic Acid (3c). A suspension of **10** (79 mg, 0.2 mmol) in 10% aqueous NaOH (3 mL) was heated at 100 °C for 1 h. The reaction mixture was washed with chloroform (20 mL) and adjusted to pH 7.0 with 30% aqueous hydrochloric acid. The neutral solution was extracted with chloroform (30 mL). The extract was washed with 15% aqueous NaCl, dried over anhydrous sodium sulfate, and evaporated under reduced pressure. The residue was recrystallized from ethanol to give **3c** (59 mg, 80% yield) as white crystals. Mp: 220 °C. ^{1}H NMR ($CDCl_3$): δ 2.35 (s, 3 H), 2.40–2.70 (m, 4 H), 3.28 (s, 3 H), 3.50–4.50 (m, 8 H), 7.63 (d, 1 H), 15.0 (s, 1 H). Anal. ($C_{17}H_{20}FN_5O_3$): C, H, N.

Synthesis of (*R*)-(−)- and (*S*)-(+)-4-Fluorodeprenyl and (*R*)-(−)- and (*S*)-(+)-[*N*-^{11}C-*methyl*]-4-Fluorodeprenyl and Positron Emission Tomography Studies in Baboon Brain

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(*R*)-(−)- and (*S*)-(+)-α-methyl-β-4-(fluorophenyl)-*N*-methyl-*N*-propynylethylamine ((*R*)-(−)- and (*S*)-(+)-4-fluorodeprenyl) were synthesized via the reaction of 4-fluorobenzaldehyde with nitroethane followed by reduction with lithium aluminum hydride to produce racemic 4-fluoroamphetamine, which was resolved by recrystallization with L- or D-*N*-acetylleucine to yield (*R*)-(−)-4-fluoroamphetamine or (*S*)-(+)-4-fluoroamphetamine in >96% enantiomeric excesses and in yields of 42 and 39%, respectively. Alkylation with propargyl bromide gave (*R*)-(−)- or (*S*)-(+)-4-fluoronordeprenyl which was reductively methylated (Borch conditions) to produce (*R*)-(−)- or (*S*)-(+)-4-fluorodeprenyl. Alkylation of (*R*)-(−)- or (*S*)-(+)-4-fluoronordeprenyl with carbon-11 labeled methyl iodide gave (*R*)-(−)- or (*S*)-(+)-[*N*-^{11}C-*methyl*]-4-fluorodeprenyl in a radiochemical yield of 30–40%. Comparative PET studies of the two labeled enantiomers in baboons showed a significantly lower retention of radioactivity in the striatum for the (*S*)-(+) enantiomer relative to the (*R*)-(−) enantiomer.

The mitochondrial-bound enzyme monoamine oxidase (MAO), which catalyzes the oxidative deamination of endogenous and exogenous amines, has been subdivided into two types, MAO-A and MAO-B on the basis of substrate and inhibitor selectivity.[1]

Two different approaches for studies of functional MAO activity in the living brain involving positron emission tomography (PET) have been recently described. One approach employs the carbon-11 labeled substrate, *N,N*-dimethylphenethylamine, and relies on the metabolic trapping of the labeled dimethylamine in the brain tissue[2,3] and the other employs a labeled suicide inactivator to label covalently the enzyme in vivo.[4,5]

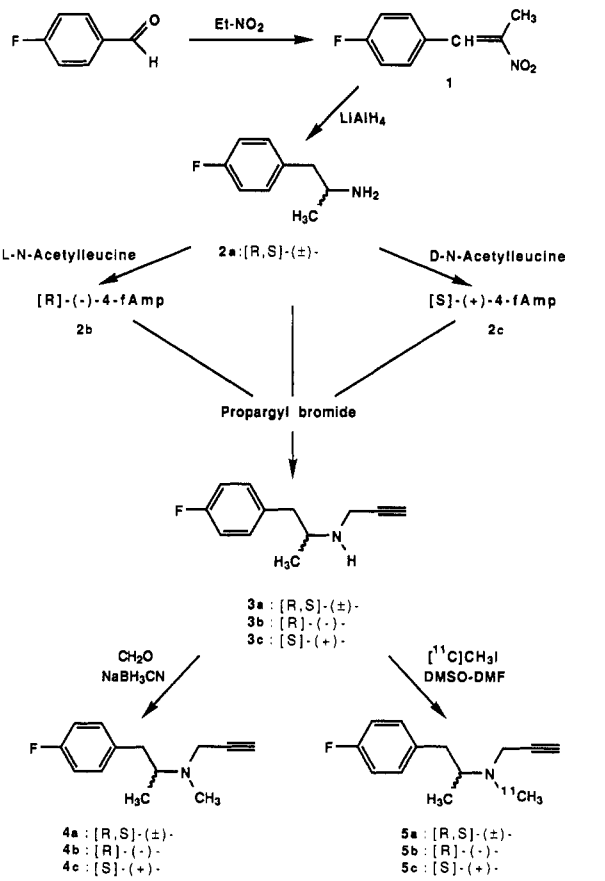
(*R*)-(−)-α-Methyl-β-phenyl-*N*-methyl-*N*-propynylethylamine ((*R*)-(−)-deprenyl) acts as a selective suicide inhibitor of MAO-B by forming a covalent bond to its active site. (*R*)-(−)-[*N*-^{11}C-*methyl*]deprenyl has been synthesized[6] and used to study MAO in vivo in animals[4,7] and in humans.[5] In addition, mechanistic PET studies using deuterium substituted (*R*)-(−)-[*N*-^{11}C-*methyl*]deprenyl have identified catalysis by MAO as being the rate-limiting step in the retention of radioactivity in baboon brain after the injection of (*R*)-(−)-[*N*-^{11}C-*methyl*]deprenyl.[8]

As part of our interest in the development of a fluorine-18 labeled derivative of (*R*)-(−)-deprenyl, we have assessed the effect of fluorine substitution on deprenyl by synthesizing (*R*)-(−)-, (*S*)-(+)-, and (*R,S*)-(±)-4-fluorodeprenyl (**4b**, **4c**, and **4a**), labeling these compounds in the *N*-methyl group with carbon-11 ($t_{1/2}$ = 20.4 min) and comparing their regional uptake in baboon brain by using PET.

Results and Discussion

1. Syntheses. The synthetic pathway used in the preparation of pure (*R*)-(−)- and (*S*)-(+)-4-fluorodeprenyl (**4b**, **4c**) is a five-step reaction (Scheme I) consisting of the classical Knoevenagel condensation between 4-fluoro-

Scheme I. Synthetic Pathways Used in the Preparation of Pure (*R*)-(−)- and (*S*)-(+)-4-Fluorodeprenyl and (*R*)-(−)- and (*S*)-(+)-[*N*-^{11}C-*methyl*]-4-Fluorodeprenyl



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† Liege University.

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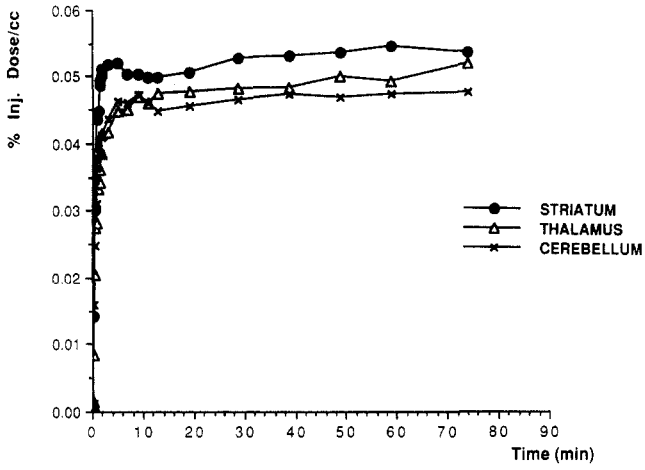

Figure 1. Brain uptake of (*R*)-(−)-[*N*-^{11}C-*methyl*]-4-fluorodeprenyl (**5b**) in baboon.

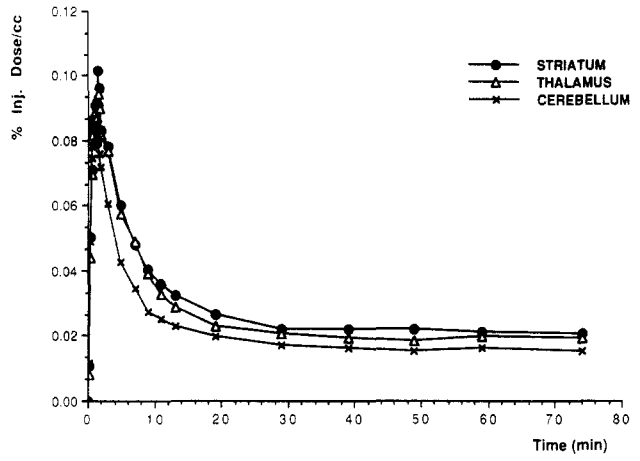

Figure 2. Brain uptake of (*S*)-(+)-[*N*-^{11}C-*methyl*]-4-fluorodeprenyl (**5c**) in baboon.

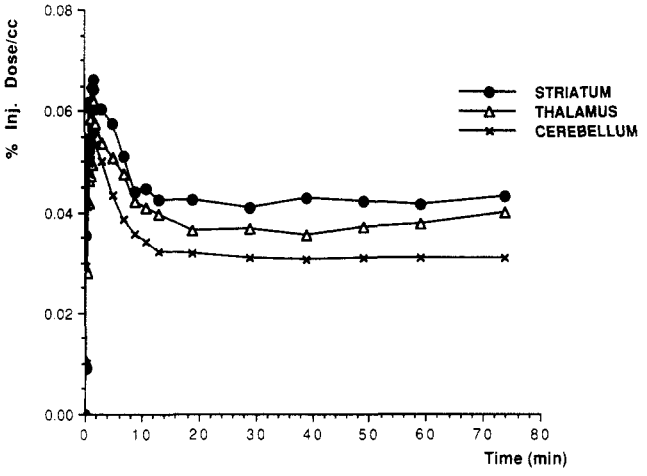

Figure 3. Brain uptake of (*R,S*)-(±)-[*N*-^{11}C-*methyl*]-4-fluorodeprenyl (**5a**) in baboon.

benzaldehyde and nitroethane followed by reduction with $LiAlH_4$ to get the racemic mixture of 4-fluoroamphetamine (4-fAmp, **2a**).

All attempts to resolve **2a** by crystallization of the salt with L-(+)-tartaric acid failed; even after three crystallizations, no resolution was observed. In contrast, resolution with L- and D-*N*-acetylleucine, previously used for 4-chloroamphetamine,[9] led to rapid and clean separation of the two enantiomers. After one crystallization with L-*N*-acetylleucine and one recrystallization from methanol, (*R*)-(−)-4-fAmp (**2b**) was obtained with an enantiomeric excess >97% in a yield of 48%. The same procedure applied to the remainder; using D-*N*-acetylleucine led to (*S*)-(+)-4-fAmp (**2c**) with an enantiomeric excess >96% in a yield of 39%. The enantiomeric excess was checked by HPLC after derivatization with 1-[(4-nitrophenyl)-sulfonyl]prolyl chloride (NPSP-Cl) synthesized as previously described.[10] The diastereomeric NPSP-amides of 4-fAmp were easily separated on a silica gel column and direct integration of the UV-detector signal gave the diastereomeric ratio and the enantiomeric excess. The conditions used led to a total baseline resolution of the enantiomers.

(*R*)-(−)- or (*S*)-(+)-4-fluoronordeprenyl (**3b** or **3c**) was prepared by alkylation of **2b** or **2c** with propargyl bromide. The enantiomeric excess of 4-fluoronordeprenyl was checked in the same way as that of 4-fAmp. Derivatization with NPSP-Cl and injection onto a C18 HPLC column led to very good separation of the two diastereomeric amides of 4-fluoronordeprenyl.

The direct methylation of 4-fluoronordeprenyl with methyl iodide led to poor and nonreproducible yield of 4-fluorodeprenyl (30%). The method proposed by Borch[11] using formaldehyde and $NaBH_3CN$ cleanly produced 4-fluorodeprenyl with a yield >90% after a 15-min reaction at room temperature.

(*R*)-(−)-, (*S*)-(+)-, (*R,S*)-(±)-[*N*-^{11}C-*methyl*]-4-fluorodeprenyl (**5b**, **5c**, and **5a**) were prepared by alkylation with carbon-11 labeled iodomethane, the production of which has been described elsewhere,[12-14] by using well-known techniques of carbon-11 alkylation. Each compound was obtained in an overall yield of 30–40% EOB (end of cyclotron bombardment) corrected within a reaction time of 40 min in very high radiochemical and chemical purity after HPLC purification.

2. Baboon Blood Kinetics. The baboon blood total plasma radioactivity clearances following the injection of (*R*)-(−)-, (*S*)-(+)-, and (*R,S*)-(±)-[*N*-^{11}C-*methyl*]-4-fluorodeprenyl (**5b**, **5c**, and **5a**) were very rapid and similar in each case, indicating a fast organ uptake. The peak of

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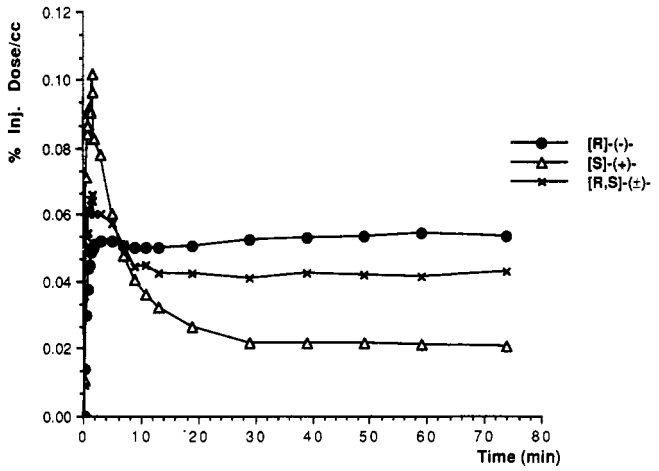

Figure 4. Striatal uptake of the three forms of (*N*-^{11}C-*methyl*)-4-fluorodeprenyl (**5a**, **5b**, and **5c**) in baboon.

blood activity ranged from 0.08 to 0.11% injected dose/cm^3 at 0.5 min after injection and decreased rapidly to reach 0.01% injected dose/cm^3 at 1.5 min (data not shown).

The amount of unchanged tracer in baboon plasma has been measured 1, 10, 30, and 60 min after injection, the results were 96%, 50%, 20%, 14% for **5b**; 98%, 61%, 30%, 22% for **5c**; and 96%, 43%, 16%, 15% for **5a**.

3. Baboon Brain Kinetics. The distribution of radioactivity in the striatum, cerebellum, and thalamus in the baboon brain are depicted in Figures 1–3 for (*R*)-(−)-, (*S*)-(+)-, and (*R,S*)-(±)-[*N*-^{11}C-*methyl*]-4-fluorodeprenyl (**5b**, **5c**, and **5a**), respectively. The time–activity profiles are markedly different in the three cases. **5a** and **5c**, although initially taken up in the region of interest, are cleared rapidly to yield a lower plateau. The striatal uptake for the three forms of 4-fluorodeprenyl are shown in Figure 4. The absolute striatal uptake at 60 min was 0.041% dose/cm^3 for **5a**, 0.021% for **5c**, and 0.053% for **5b**. The value for the carbon-11 labeled (*R*)-(−)-enantiomer of 4-fluorodeprenyl is very similar to that of carbon-11 labeled (*R*)-(−)-deprenyl itself (0.057% dose/cm^3).[8] The similarity of uptake with the unsubstituted compound, along with the stereoselectivity of uptake, which is similar to results with (*R*)-(−)- and (*S*)-(+)-[^{11}C]deprenyl in human brain[5] and with the known potencies of (*S*)-(+)- and (*R*)-(−)-deprenyl as MAO inhibitors,[15] suggests that (*R*)-(−)-deprenyl labeled with ^{18}F will be a good tracer for PET studies of MAO.

The brain kinetics in baboons is also consistent with the known in vitro and in vivo MAO activity of (*R*)-(−)-4-fluorodeprenyl (**4b**) reported previously.[19] The in vitro IC_{50} for **4b** is 4.17×10^{-8} M for brain and the selectivity for MAO-B relative to MAO-A is 580.67 (ratio of IC_{50}'s for liver). Although the fate of the label in the brain has not been determined for (*R*)-(−)-[*N*-^{11}C-*methyl*]-4-fluorodeprenyl (**5b**), it has been determined in mouse brain for the (*R*)-(−)-[*N*-^{11}C-*methyl*]deprenyl with the major products, labeled protein (48%) and labeled methamphetamine (26%), being the products of MAO-catalyzed oxidation.[8]

Experimental Section

1. Chemistry. 4-Fluorobenzaldehyde, nitroethane, $LiAlH_4$ (1.0 M in THF), 4-nitrobenzenesulfonyl chloride, propargyl bromide (80% in toluene), and $NaBH_3CN$ were purchased from Aldrich Chemical Co. L-*N*-Acetylleucine, D-*N*-acetylleucine, and L-proline were obtained from Sigma Chemical Co.

Melting points were taken on a Fisher-Johns apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Brucker 300-MHz instrument in $CDCl_3$; the chemical shifts were reported in parts per million (δ) downfield from tetramethylsilane as internal reference; optical rotations were determined on HCl salts with use of a Rudolf polarimeter.

Hydrochloride salts of amines were prepared by gradual addition of a solution of dry HCl in ether to an ethereal solution of the amine followed by centrifugation.

Preparative scale purification was achieved by conventional liquid column chromatography (250 mm × 10 mm) with silica gel 60 (230–400 mesh) from Merck. Fractions from the liquid chromatography column were monitored by thin-layer chromatography by using plastic plates precoated with silica gel 60F (Merck). The plates were developed with the same solvent as had been used to elute the column.

HPLC analyses were done by using one of the three configurations: configuration I, silica gel column (250 mm × 10 mm) from IBM with chloroform–hexane (80–20%), at a flow rate of 4 mL/min; configuration II, C18 Spherisorb 5 ODS (250 mm × 4.6 mm) with methanol–0.05 N ammonium formate (70–30%) at a flow rate of 1 mL/min; configuration III, C18 Spherisorb 5 ODS (250 mm × 10 mm) with methanol–0.05 N ammonium formate (70–30%) at a flow rate of 5 mL/min. The UV detector was set with a 10-mm analytical cell at 254 nm.

Specific activities were determined by HPLC assay of an aliquot of the labeled product with comparison to a standard curve generated from solutions of known concentration.

1-(4-Fluorophenyl)-2-nitropropene (1). 4-Fluorobenzaldehyde (12.4 g, 0.1 mol), nitroethane (15 g, 0.2 mol), 10 mL of absolute EtOH, and 500 μL of butylamine were heated under reflux for 5 h. The reaction mixture was allowed to cool to room temperature overnight while crystallization occurred. The crude yellow product was filtered and recrystallized from CH_3OH to afford 10 g (55%) of pale yellow crystals of 1: mp 64–66 °C (lit.[16] mp 64–66 °C); ^{1}H NMR δ 8.05 (s, 1 H, ArC*H*=C), 7.41–7.46 (m, 2 H, aromatic H's), 7.12–7.18 (m, 2 H, aromatic H's), 2.44 (s, 3 H, CH_3).

(*R,S*)-(±)-α-Methyl-β-(4-fluorophenyl)ethylamine ((*R,S*)-(±)-4-fAmp) (2a). $LiAlH_4$ (1 M in THF) (200 mL, 0.2 mol) was added to a stirred solution of 1 (18.1 g, 0.1 mol) in 200 mL of dry THF. The mixture was stirred at room temperature for 4 h. The excess of $LiAlH_4$ was destroyed carefully with water. The resulting cake was filtered off and washed twice with 100 mL of warm THF. The filtrate was concentrated under reduced pressure. The crude residue was dissolved in ether and washed three times with 0.1 N HCl. The combined acidic fractions were basified with NH_4OH, and the crude compound was extracted with ether. The organic layer was dried over $MgSO_4$ and concentrated. The residue was distilled twice to afford 8 g (52%) of **2a** as a colorless liquid: bp 78 °C at 10 mmHg (lit. bp 95–96 °C at 17 mmHg[18], 96 °C at 19 mmHg[20]); mp (hydrochloride salt) 152–154 °C (lit. mp 152–154 °C,[17,20] 156–157 °C[18]); ^{1}H NMR δ 7.1–7.16 (m, 2 H, aromatic H's), 6.9–7.08 (m, 2 H, aromatic H's), 3.08–3.19 (m, 1 H, C*H*CH_3), 2.42–2.53, 2.61–2.72 (m, 2 H, ArCH_2), 1.23 (s, 2 H, NH_2), 1.10 (d, 3 H, J = 6 Hz, $-CH_3$).

Resolution of (*R,S*)-(±)-4-fAmp (2a). L-*N*-Acetylleucine sodium salt (0.01 mol) (prepared by addition of 1 N NaOH to a suspension of L-*N*-acetylleucine (1.73 g, 0.01 mol) in 5 mL of water until pH 7) was added slowly to a stirred solution of **2a** hydrochloride salt (3.78 g, 0.02 mol) in 10 mL of water. Crystals formed overnight and were removed by filtration, washed with a small amount of cold water, and recrystallized from absolute CH_3OH. A small amount of diasteromeric salt was hydrolyzed for an enantiomeric excess check after derivatization. The mother liquors which were rich in (*S*)-(+)-4-fAmp (**2c**) were combined, made strongly alkaline with 5 N NaOH, and washed three times with ether. The organic layer was washed with water and dried over $MgSO_4$, and HCl was passed through the solution until the precipitation of hydrochloride salt was complete. The same procedure was applied with D-*N*-acetylleucine sodium salt. The

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diastereomeric salt of each enantiomer was dissolved in 20 mL of water, made strongly alkaline with 5 N NaOH, and extracted with ether. The organic layer was washed with water and dried over $MgSO_4$, and the hydrochloride salt was prepared.

The solution of 3.78 g (0.02 mol) of **2a** led to 0.79 g (42%) of **2b** hydrochloride salt in >97% ee: mp 195–198 °C; $[\alpha]^{25}_D = -17.8°$ (c = 19 g/100 mL of water), and 0.74 g of **2c** hydrochloride salt in >96% ee: mp 195–198 °C; $[\alpha]^{25}_D = +19.9°$ (c = 19 g/100 mL of water).

Derivatization Procedure for 4-fAmp and 4-Fluorononordeprenyl. Freshly prepared NPSP-Cl solution (1 mL, 0.0335 M) in THF, 1 mL of 4-fAmp HCl salt of 4-fluorononordeprenyl HCl salt (0.0053 M) solution in water, 2 mL of THF, and 0.7 mL of 10% $NaHCO_3$ were placed in a 5-mL screwcap vial. The vial was sealed and heated at 65 °C for 1 h. After cooling, the reaction mixture was extracted with 3 × 10 mL of $CHCl_3$. The organic layer was dried over $MgSO_4$ and concentrated. The residue was dissolved in 2 mL of HPLC solvent and used directly for HPLC analysis.

The diastereomeric NPSP-amides of 4-fAmp were separated by using HPLC configuration I: t_R 9.9 min for NPSP-amide of **2c** and 11.6 min for NPSP-amide of **2b**. The diastereomeric NPSP-amides of 4-fluorononordeprenyl were separated by using configuration II: retention t_R 9 min for NPSP-amide of **3c** and 10 min for NPSP-amide of **3b**.

α-Methyl-β-(4-fluorophenyl)-*N*-propynylethylamine (4-Fluorononordeprenyl) (3a, 3b, and 3c). The procedure was the same for the racemic mixture and for the pure isomers. A mixture of 4-fAmp (265 mg, 1.73 mmol) and propargyl bromide (80% in toluene, 107 mg, 0.9 mmol) in 2.5 mL of CH_3CN and K_2CO_3 (250 mg, 1.81 mmol) in 400 μL of water was stirred in a 5-mL vial. After 3 h, all the propargyl bromide had reacted as verified by HPLC (configuration II). Additional propargyl bromide (80% in toluene, 50 mg, 0.45 mmol) was added, and the reaction mixture was checked every 30 min. When a second product (presumed to be the dipropargylated fluoroamphetamine) became important (about 8%), the reaction was stopped by decanting the CH_3CN from the gummy KBr adhering to the wall of the vial. The CH_3CN solution was dried by passing through a small column of K_2CO_3 (30 mm × 5 mm) and evaporated. The residue was dissolved in 0.5 mL of ether–hexane (1:1) and applied to the silica gel column (250 mm × 10 mm). The eluting solvent was ether–hexane (1:1). A forecut of 20 mL was discarded, and 1 mL fractions were taken; 4-fluorononordeprenyl eluted in fractions 35–45 mL. After evaporation of the solvent, 160 mg (62%) of 4-fluorononordeprenyl was obtained: mp (hydrochloride salt) 196–198 °C for **3a**, 172–174 °C for **3c**, and 170–171 °C for **3b**; $[\alpha]^{25}_D = +11.7°$ (c = 22 g/100 mL of water) for **3c** and −10.4° (c = 22 g/100 mL of water) for **3b**; ^{1}H NMR δ 6.93–7.19 (m, 4 H, aromatic H's), 3.36–3.51 (m, 2 H, $-CH_2NH-$), 3.07–3.18 (sex, 1 H, $CHCH_3$), 2.57–2.72 (m, 2 H, $ArCH_2$), 2.18 (t, 1 H, J = 2.5 Hz, $C{\equiv}CH$), 1.49 (s, 1 H, –NH–), 1.04 (d, 3 H, J = 6 Hz, CH_3); t_R (HPLC configuration II) 4.8 (propargyl bromide), 7.8 (4-fAmp), 8.8 (toluene), 9.3 (4-fluorononordeprenyl), 10.9 min (by-product presumed to be the dipropargylated amine).

α-Methyl-β-(4-fluorophenyl)-*N*-methyl-*N*-propynylethylamine (4-Fluorodeprenyl) (4a, 4b and 4c). 4-Fluorononordeprenyl (100 mg, 0.52 mmol) and formaldehyde (37% in water, 80 mg, 2.67 mmol) in 500 μL of CH_3CN were treated with $NaBH_3CN$ (52 mg, 0.83 mmol). The reaction mixture was stirred for 15 min at room temperature then diluted with 1 mL of 0.1 N KOH and extracted three times with ether. The organic layer was passed through a K_2CO_3 column (30 mm × 5 mm) and evaporated. The residue was dissolved in 0.5 mL of ether–hexane (1:1) and applied to the silica gel column (250 mm × 10 mm). The eluting solvent was ether–hexane (1:1). 4-Fluorodeprenyl eluted in fractions 28–35 mL; after evaporation of the solvent, 100 mg (93%) of 4-fluorodeprenyl was obtained (care was taken when evaporating solutions of 4-fluorodeprenyl as this compound showed similar volatility as deprenyl[21]): mp (hydrochloride salt) 142–145 °C for **4a** (lit.[19] mp 130–133 °C), 164–166 °C for **4c**, 162–164 °C for **4b**; $[\alpha]^{25}_D = +10.3°$ (c = 24 g/100 mL of water) for **4c** and −9.4° (c = 24 g/100 mL of water) for **4b** (lit.[19] $[\alpha]^{25}_D = -10.9°$); ^{1}H NMR δ 6.93–7.19 (m, 4 H, aromatic H's), 3.42 (d, 2 H, J = 2.3 Hz, $-NCH_2-$), 2.89–3.04 (m, 2 H, $ArCH_2$), 2.37–2.43 (m, 4 H, $NCH_3 + CHCH_3$), 2.24 (t, 1 H, J = 2.5 Hz, $C{\equiv}CH$), 0.95 (d, 3 H, J = 7 Hz, $CHCH_3$); t_R (HPLC configuration II) 9.3 min (4-fluorononordeprenyl), 15.2 min (4-fluorodeprenyl).

[*N*-^{11}C-*methyl*]-4-Fluorodeprenyl (5a, 5b, 5c). The procedure was the same for the three forms using the corresponding desmethyl precursor (free base). Carbon-11 labeled carbon dioxide was obtained as previously described.[22] It was purged through 0.3 mL of 1 M $LiAlH_4$ in THF, and when the trapping was complete, the mixture was heated, and the THF was evaporated with a stream of N_2. To the residue was added 0.5 mL of 58% HI. The vessel was closed and heated to 160 °C under reflux. After a vigorous reflux had been established, the vessel was opened to a stream of N_2 which carried the [^{11}C]iodomethane into a cooled solution (−40 °C) of 0.3 mL of CH_3CN and 0.2 mL of a mixture DMF–DMSO (4:1) containing 2 μL of desmethyl precursor free base. The solution was heated in the closed vessel at 130 °C for 5 min. Then 0.5 mL of water was added and the solution injected onto an HPLC column. The fraction containing the [*N*-^{11}C-*methyl*]-4-fluorodeprenyl was evaporated in the presence of 2% HCl in ethanol. To the residue was added 2 mL of ethanol, and this was evaporated. The residue was dissolved in 3 mL of saline–water (3:1) and passed through a 22 μm millipore filter into a vial containing 0.1 mL of $NaHCO_3$. The radiochemical yield was 30–40% (EOB corrected) with a synthesis time of 40 minutes. The specific activity was about 600 mCi/μmol (22.2 GBq/μmol) EOB. The total mass of [*N*-^{11}C-*methyl*]-4-fluorodeprenyl was 30 μg, t_R (HPLC configuration III) was 9.2 min ([*N*-^{11}C-*methyl*]-4-fluorodeprenyl).

2. PET Baboon Studies. A young adult (12.6 kg) female baboon (*Papio anubis*) was anesthetized with ketamine (10 mg/kg) and subsequently maintained under isofluorane/nitrous oxide anesthesia for one study as described previously.[8] The same animal was used for three experiments. A minimum interval of two weeks was respected between studies. In the first study, the animal was treated with an iv bolus injection of 6.3 mCi (0.233 GBq) of (*R,S*)-(±)-[*N*-^{11}C-*methyl*]-4-fluorodeprenyl (**5a**) (20 μg) in 2.5 mL of saline solution, in the second study, with 11.2 mCi (0.414 GBq) of (*R*)-(−)-[*N*-^{11}C-*methyl*]-4-fluorodeprenyl (**5b**) (30 μg) in 2.5 mL of saline, and in the third study, with 13.8 mCi (0.510 GBq) of (*S*)-(+)-[*N*-^{11}C-*methyl*]-4-fluorodeprenyl (**5c**) (26 μg) in 2.5 mL of saline. PET scans were made continually for 90 min from the time of radiotracer injection. The PET instrument used for these studies was a CTI-931; 15 slices, whole body tomograph with approximately 6.5-mm resolution in all directions.

Regions of interest corresponding to the corpus striata, thalamus, and cerebellum were selected directly on the PET image (transverse slices) with the aid of neuroanatomical photographs of transverse sections extending through the rostral/caudal extent of the baboon brain. References included the external auditory meatus, laterally, and the orbital foramen, anteriorly.

3. Baboon Plasma Analyses. A complete arterial blood curve was obtained for each study. Samples were either withdrawn manually by using the sampling schedule described previously[8] or via an automatic blood sampling instrument (Ole Dich, Denmark) at a rate of 8.0 mL/min. The automated blood sampling instrument was only used for the first 2 minutes and allowed 48 samples to be taken during this interval. Samples were taken at successively longer time intervals up to 80 min postinjection. Samples were centrifuged and aliquots of plasma were counted for total carbon-11 in a sodium iodide well counter.

Samples of arterial plasma withdrawn at 1, 10, 30, and 60 min were analyzed for unchanged [*N*-^{11}C-*methyl*]-4-fluorodeprenyl by using the HPLC (configuration II) method described previously.[7]

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Acknowledgment. The authors are grateful to Payton King for his assistance in performing the baboon experiments and to David Schlyer, Robert MacGregor, Yu-Shin Ding, Bernard Bendriem, and John Gatley for their advice and help with these studies. They are also grateful to the National Institutes of Health (Grant No. NS-15380) and to the Department of Energy, Office of Health and Environmental Research for financial support.

1,2-Dihydro-1-oxopyrrolo[3,2,1-*kl*]phenothiazine-2-carboxamides and Congeners, Dual Cyclooxygenase/5-Lipoxygenase Inhibitors with Antiinflammatory Activity

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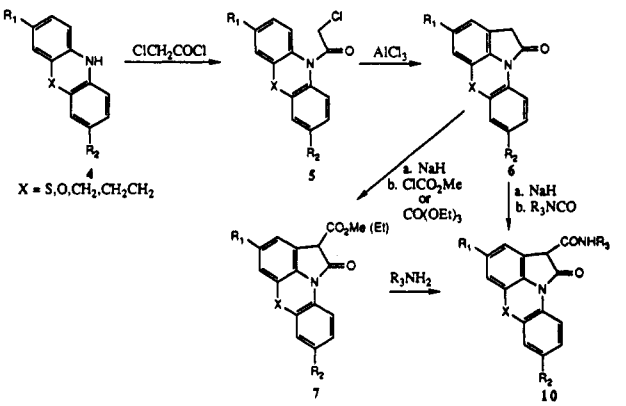
A series of 1,2-dihydro-1-oxopyrrolo[3,2,1-*kl*]phenothiazine, 1,2-dihydro-1-oxopyrrolo[3,2,1-*kl*]phenoxazine, and 1,2-dihydro-1-oxopyrrolo[3,2,1-*de*]acridine-2-carboxamides were prepared by reaction of 1,2-dihydro-1-oxopyrrolo[3,2,1-*kl*]phenothiazine or other corresponding phenoxazine and acridan ethyl or methyl esters with appropriate amines. Several members of this family were found to be potent, dual inhibitors of cyclooxygenase and 5-lipoxygenase pathways of arachidonic acid metabolism and to have in vivo antiinflammatory activity in the rat foot edema assay. Structure–activity relationships within this family of compounds are described. 1,2-Dihydro-*N*-(2-thiazolyl)-1-oxopyrrolo[3,2,1-*kl*]phenothiazine-1-carboxamide (**34**) was found to be one of the best compounds to display potent cyclooxygenase/5-lipoxygenase inhibition of arachidonic acid metabolism. Its IC_{50}s against the enzymes sourced from rat basophillic leukemia-1 (RBL-1) cells were 0.07 and 1.4 μM, respectively. It was active in the rat foot edema test for antiinflammatory effect (48% inhibition at 33 mg/kg po) and in the mouse phenylbenzoquinone induced writhing test for analgesic effect (93% inhibition at 32 mg/kg po).

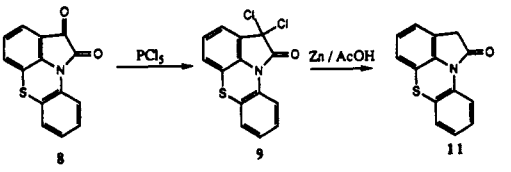
Currently available non-steroidal, cyclooxygenase-inhibiting antiinflammatory drugs, which block arachidonic acid (AA) metabolism to prostaglandins, provide relief to arthritic patients by virtue of their analgesic and antiedema properties. The discovery of the 5-LO pathway of AA metabolism[1] and the participation of the LO metabolite leukotriene B_4[1] as a mediator in the inflammatory response[2-5] offers an opportunity to explore dual CO/LO inhibitors as potentially superior drugs for treatment of inflammatory diseases. Already several dual inhibitors have been discovered,[6-10] some of which are undergoing clinical evaluation.

The work of Kadin,[11] Lombardino,[12] and McManus[13] has established amide structures with pK_a's equal to or lower than typical carboxylic acids as a rich source of antiinflammatory agents. Upon establishing a convenient assay for cellular CO/LO activity, it was found that oxindolecarboxamide **1**[13] was a dual inhibitor of AA metabolism. This lead was pursued within our Central Research Laboratories with the objective of obtaining sufficiently potent and safe dual inhibitors with in vivo rat foot edema (RFE) activity for clinical investigation. One avenue of pursuit has already yielded a novel clinical candidate, **2**, now designated tenidap.[14] We describe here our efforts along another chemical approach leading to a new series of

Scheme I



Scheme II



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