Synthesis and Antibacterial Activity of Thiazolo-, Oxazolo-, and Imidazolo[3,2-*a*][1,8]naphthyridinecarboxylic Acids

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Received July 10, 1989

It is known that thiazolo[3,2-*a*][1,8]naphthyridine derivatives (**3a**) exhibit good antibacterial activity. Accordingly, several analogues of **3a**, viz. oxazolo- and imidazolo[3,2-*a*][1,8]naphthyridine derivatives **3b** and **3c**, were synthesized and evaluated for antibacterial activity in vitro and for inhibitory activity against DNA gyrase of *Escherichia coli* K-12 C600. Compound **3a** exhibited antibacterial activity comparable to that of ofloxacin and enoxacin against Gram-positive and Gram-negative bacteria and displayed antibacterial activity superior to that of **3b** and **3c**. The antibacterial activities of **3b** and **3c** decreased in that order. DNA gyrase inhibitory activities of **3a-c** in *E. coli* K-12 C600 paralleled their in vitro antibacterial activity. It was found that enhancement of the DNA gyrase inhibitory activity of **3a** was dependent on a certain feature of the sulfur atom of the thiazole ring.

Introduction

Since the development of nalidixic acid as a useful therapeutic agent, a large number of analogues have been synthesized. Some of these are now in clinical use.[1] Analysis of the quantitative structure–activity relationship of a series of derivatives suggested that a set of N-1 alkyl groups, i.e., ethyl,[2] cyclopropyl,[3] and methylamino,[4] contributed to the appearance of potent activity.

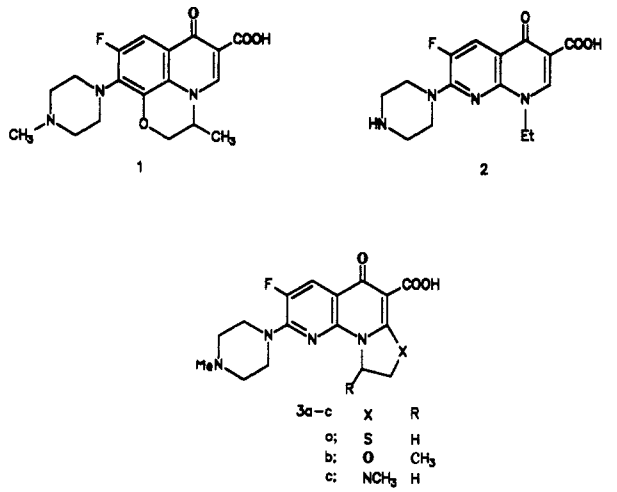
Recently, 7-fluoro-8-(4-methyl-1-piperazinyl)-5-oxo-1,2-dihydro-5*H*-thiazolo[3,2-*a*][1,8]naphthyridine-4-carboxylic acid[13] (**3a**, Chart I) has been reported to be a good antibacterial agent.[5] This suggests that substitution of a sulfur atom at the 2-position of 1,4-dihydro-4-oxonaphthyridine-3-carboxylic acids can lead to active compounds. However, there is little information regarding C-2 substituted derivatives with other heteroatoms, e.g., oxygen and nitrogen. One reason may be that there is no useful method for the introduction of a heteroatom at the 2-position of the 1,8-naphthyridine skeleton. Growing interest in naphthyridine analogues led us to synthesize several analogues of compound **3a**, viz., (±)-1-methyl-7-fluoro-8-(4-methyl-1-piperazinyl)-5-oxo-1,2-dihydro-5*H*-oxazolo[3,2-*a*][1,8]naphthyridine-4-carboxylic acid (**3b**) and 3-methyl-7-fluoro-8-(4-methyl-1-piperazinyl)-5-oxo-1,2-dihydro-5*H*-imidazolo[3,2-*a*][1,8]naphthyridine-4-carboxylic acid (**3c**).

In this paper, we report on the synthesis, antibacterial activity, and inhibition of DNA gyrase supercoiling activity of several azolo[3,2-*a*][1,8]naphthyridines (**3a-c**). The thiazolo[3,2-*a*][1,8]naphthyridine derivative (**3a**) was found to exhibit antibacterial activity superior to that of **3b** and **3c**. Thus, the sulfur atom of the thiazole ring appeared to play an important role in the enhancement of DNA gyrase inhibition.

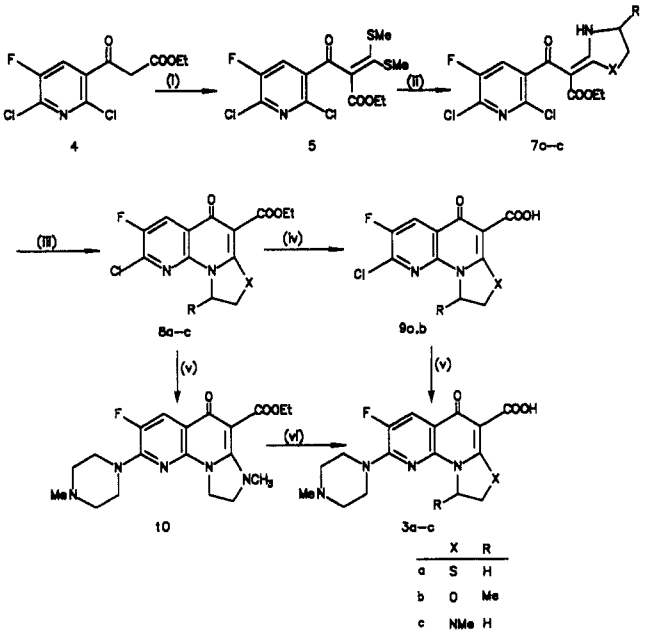
Chemistry

A method for the synthesis of thiazolo[3,2-*a*][1,8]-naphthyridinecarboxylic acid **3a** has recently been described.[5] However, it is not appropriate for the preparation of a different heterocyclic ring system, e.g., oxazolo[3,2-*a*][1,8]naphthyridinecarboxylic acid **3b** and imidazolo-[3,2-*a*][1,8]naphthyridinecarboxylic acid **3c**. Heretofore, a practical method for the preparation of **3b** and **3c** has

Chart I



Scheme I[a]



[a] (i) CS_2/MeI/NaH; (ii) $HXCH_2CH(R)NH_2$; (iii) *t*-BuOK; (iv) H_2SO_4; (v) $MeN(CH_2)_2NCH_2CH_2$; (vi) NaOH.

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0022-2623/90/1833-2012$02.50/0

Table I. In Vitro Antibiotic Activity of 1, 2, and 3a–c

compd	microorganism[a]											
	Sa(F)	Sa(I)	Se	Sf	Bs	Ec(K)	Ec(KC)	Kp	Pa	Pc	Ea	Ac
1	0.39	0.39	0.78	1.56	0.10	0.20	0.10	0.05	1.56	6.25	0.10	0.39
2	0.78	0.78	3.13	3.13	0.20	0.20	0.20	0.10	1.56	6.25	0.20	3.13
3a	0.39	0.39	1.56	6.25	0.10	0.20	0.20	0.05	1.56	3.13	0.20	0.39
3b	12.5	12.5	>25	>25	3.13	12.5	6.25	0.78	>25	>25	6.25	>25
3c	100	100	100	100	25	50	50	6.25	100	100	50	100

[a] Microorganism: Sa(F), *S. aureus* FDA207PJC-1; Sa(I), *S. aureus* IID 803; Se, *S. epidermidis* IAM 1296; Sf, *S. faecalis* IID 682; Bs, *B. subtilis* ATCC 6633; Ec(K), *E. coli* K-12 C600; Ec(KC), *E. coli* KC-14; Kp, *K. pneumoniae* PCI-602; Pa, *P. aeruginosa* E-2; Pc, *P. cepacia* IID 1341; Eac, *E. aerogenes* ATCC 13048; Ac, *A. calcoaceticus* AC54.

not existed. We have therefore developed an efficient method for the synthesis of several azolo[3,2-*a*][1,8]-naphthyridinecarboxylic acids (**3a–c**), as shown in Scheme I.

Ethyl 3-(2,6-dichloro-5-fluoro-3-pyridyl)-3-oxopropionate (**4**), sodium hydride, and carbon disulfide were stirred in *N*,*N*-dimethylacetamide for 1 h at room temperature. After addition of methyl iodide to the resultant solution, dimethyl ketene dithioacetal (**5**) was obtained in 58% yield after 3 h at room temperature. Condensation of **5** and several amines (**6a–c**) in hot toluene gave the corresponding heterocyclic compounds ethyl 3-(2,6-dichloro-5-fluoro-3-pyridyl)-2-(thiazolidin-2-ylidene)-3-oxopropionate (**7a**), (±)-ethyl 3-(2,6-dichloro-5-fluoro-3-pyridyl)-2-(4-methyloxazolidin-2-ylidene)-3-oxopropionate (**7b**), ethyl 3-(2,6-dichloro-5-fluoro-3-pyridyl)-2-(1-methylimidazolidin-2-ylidene)-3-oxopropionate (**7c**). Intramolecular condensation of **7a–c** under basic conditions gave the corresponding thiazolo-, oxazolo-, and imidazolo[3,2-*a*][1,8]naphthyridine-4-carboxylic acid derivatives **8a–c**. Condensation of **5** with 2 mequiv of amines **6a–c** yielded **8a–c** in a single step. Hydrolysis of the esters **8a,b** with sulfuric acid gave the corresponding carboxylic acids **9a,b**. Displacement of the 2-chloro group of **9a,b** with *N*-methylpiperazine yielded **3a** and **3b**, respectively. Because the hydrolysis of **8c** with acids caused undesired decarboxylation, **3c** was derived as shown in Scheme I. First, the displacement of **8c** with *N*-methylpiperazine gave **10**; **3c** was obtained by hydrolysis of **10** with 1 N sodium hydroxide.

Results and Discussion

Table I shows the in vitro antibacterial activities of compounds (**3a–c**), ofloxacin (OFLX, **1**),[6] and enoxacin (ENX, **2**)[7] against five Gram-positive bacteria (*Staphylococcus aureus* FDA 209P JC-1, *Staphylococcus aureus* IID 803, *Staphylococcus epidermidis* IAM 1296, *Streptococcus faecalis*, and *Bacillus subtilis* ATCC 6633) and seven Gram-negative bacteria (*E. coli* KC-14, *E. coli* K-12 C600, *Klebsiella pneumoniae* PCI-602, *Pseudomonas aeruginosa* E-2, *Pseudomonas cepacia* IID 1341, *Enterobacter aerogenes* ATCC 13048, and *Acinetobacter calcoaceticus* AC54). The in vitro effects of compounds **3a–c** having different azole rings attached to the 6-fluoro-7-piperazinyl-1,4-dihydro-4-oxoquinoline-3-carboxylic acid were compared to those of OFLX and ENX. Thiazolo-[3,2-*a*][1,8]naphthyridine derivative **3a** exhibited potent antibacterial activity comparable to that of OFLX and ENX, both of which are clinically used antibacterial agents.

Table II. Inhibitory Effect of Compounds 3a–c on DNA Gyrase Supercoiling Activity from *E. coli* K-12 C600

compd	IC_{50}, μg/mL
3a	0.52
3b	6.11
3c	>25
OFLX (1)	0.59

Oxazolo[3,2-*a*][1,8]naphthyridine derivative **3b** was more active than imidazolo[3,2-*a*][1,8]naphthyridine **3c**; however, **3b** was less active than **3a**.

Although the mechanism of bacterial killing by quinolones is unclear, DNA gyrase is a primary target of the quinolone agents and is central to the mechanism of action.[8] One possible mechanism is that the quinolones might cause DNA gyrase to damage DNA by introduction of a lesion which is either nonrepairable or which is rendered nonrepairable when altered by repair enzymes.[9,10] Accordingly, we compared the inhibitory effects of **3a–c** on DNA gyrase purified from *E. coli* K-12 C600. Compound **3a** exhibited the most inhibitory effect against DNA gyrase supercoiling activity; its value, 0.52, was similar to that of OFLX, 0.59 (Table II). The values for **3b** and **3c** were 6.11 and >25, respectively.

As noted above, the in vitro antibacterial activities of **3a–c** were correlated with their inhibitory effects on DNA gyrase. Interestingly, the sulfur atom of the thiazole ring appears to play an important role in the enhancement of DNA gyrase inhibitory activity. However, it remains unclear what features of the sulfur atom might contribute to the enhanced activity. Study of this problem is now in progress.

Experimental Section

Melting points were determined on a Yamato capillary melting point apparatus, Model MP-21, and all melting points are uncorrected. ^{1}H NMR spectra were determined at 100 MHz on a Nihon Denshi PS-100 NMR spectrometer using TMS as internal standard. IR spectra were recorded with a Hitachi IR 270-50 infrared spectrophotometer. All compounds were analyzed for C, H, and N, and the values were within ±0.4% of the calculated theoretical values.

In Vitro Antibacterial Activity. The MICs (minimum inhibitory concentrations) of compounds tested in this study were determined according to the method of Goto et al. by the serial 2-fold dilution technique using Mueller–Hinton agar.[11] The inoculum size was approximately 10^6 CFU/mL. The concentrations of compounds in the plates ranged from 0.006 to 100 μg/mL. The MIC of a compound was defined as the lowest

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concentration that prevented visible growth of bacteria after incubation at 37 °C for 18 h.

Ethyl 3-(2,6-Dichloro-5-fluoro-3-pyridyl)-2-[bis(methylthio)methylene]-3-oxopropionate (5). A 60% suspension of sodium hydride in oil (0.57 g, 14 mmol) was slowly added at room temperature to a solution of carbon disulfide (1.1 g, 14 mmol) and methyl iodide (2.5 g, 18 mmol) in *N,N*-dimethylacetamide (DMA, 20 mL), and the mixture was stirred for 1 h. Next, a solution of ethyl 3-(2,6-dichloro-5-fluoro-3-pyridyl)-3-oxopropionate (**4**;[12] 2.0 g, 7.1 mmol) in DMA (1 mL) was added dropwise to the mixture. The reaction mixture was stirred for 3 h, poured into ice/water (50 mL), and the mixture was extracted with ethyl acetate (120 mL). The organic phase was washed with water and dried over anhydrous sodium sulfate, and the solvent was evaporated. The residue was chromatographed on a column of silica gel with *n*-hexane/ethyl acetate (50/1, v/v) as eluent under medium pressure to give **5** (1.6 g, 58% yield) as a yellow oil. ^{1}H NMR ($CDCl_3$): δ 1.16 (t, 3 H), 2.40 (s, 6 H), 4.24 (q, 2 H), 7.90 (d, 1 H).

Ethyl 3-(2,6-Dichloro-5-fluoro-3-pyridyl)-2-(thiazolidin-2-ylidene)-3-oxopropionate (7a). A solution of **5** (0.24 g, 0.63 mmol) in toluene (5 mL) was added to a solution of cysteamine hydrochloride (71 mg, 0.63 mmol) and triethylamine (63 mg, 0.63 mmol) in toluene (15 mL). The mixture was heated under reflux for 2 h and the solvent was evaporated. Water was added to the residue and the mixture was extracted with ethyl acetate. The ethyl acetate extract was dried over anhydrous sodium sulfate, the solvent was evaporated, and the residue was recrystallized from ether to give **7a** (0.21 g, 84% yield) as pale yellow crystals. Mp: 172–175 °C. ^{1}H NMR ($CDCl_3$): δ 0.85 (t, 3 H), 3.10–3.40 (m, 2 H), 3.70–4.40 (m, 4 H), 7.41 (d, 1 H). MS: *m/e* (M^+) 365. Anal. ($C_{13}H_{11}FCl_2N_2O_3S$) H, N; C: calcd, 42.75; found, 43.18.

(±)-Ethyl 3-(2,6-Dichloro-5-fluoro-3-pyridyl)-2-(4-methyloxazolidin-2-ylidene)-3-oxopropionate (7b). A solution of **5** (0.43 g, 1.1 mmol) in toluene (5 mL) was added to a solution of (DL)-2-aminopropan-1-ol (84 mg, 1.1 mmol) in toluene (5 mL). The mixture was heated under reflux for 2.5 h and then the solvent was evaporated. The residue was chromatographed on a column of silica gel with chloroform to give **7b** (0.38 g, 93% yield) as pale yellow crystals. Mp: 159–163 °C. ^{1}H NMR ($CDCl_3$): δ 0.94 (t, 3 H), 1.45 (d, 3 H), 3.96 (q, 2 H), 4.10–4.90 (m, 3 H), 7.35 (d, 1 H). MS: *m/e* (M^+) 363. Anal. ($C_{14}H_{13}FCl_2N_2O_4$) C, N; H: calcd, 3.61; found, 4.11.

Ethyl 3-(2,6-Dichloro-5-fluoro-3-pyridyl)-2-(1-methylimidazolidin-2-ylidene)-3-oxopropionate (7c). A solution of **5** (0.50 g, 1.3 mmol) in toluene (5 mL) was added to a solution of *N*-methylethylenediamine (96 mg, 1.3 mmol) in toluene (5 mL). The mixture was heated under reflux for 4 h and then the solvent was evaporated. The residue was chromatographed on a column of silica gel with chloroform to give **7c** (0.42 g) as pale yellow crystals. Mp: 188–191 °C. ^{1}H NMR ($CDCl_3$): δ 0.92 (t, 3 H), 3.06 (s, 3 H), 3.87 (s, 4 H), 3.96 (q, 2 H), 7.44 (d, 1 H), 8.90 (b s, 1 H). Anal. ($C_{14}H_{14}FCl_2N_3O_3$) H, N; C: calcd, 46.43; found, 46.88.

Ethyl 7-Fluoro-8-chloro-5-oxo-1,2-dihydro-5*H*-thiazolo[3,2-*a*][1,8]naphthyridine-4-carboxylate (8a). A solution of **7a** (0.20 g, 0.50 mmol) in dioxane (1.5 mL) was added slowly to a suspension of potassium *tert*-butoxide (73 mg, 0.65 mmol) in dioxane (1.5 mL). The mixture was stirred at room temperature for 16 h and the solvent was evaporated. The residue was added to water and the mixture was extracted with chloroform. The $CHCl_3$ extract was washed with 15% aqueous NaCl, dried over anhydrous sodium sulfate, and then evaporated. The residue was recrystallized from ethanol/$CHCl_3$ to give **8a** (156 mg, 86% yield) as pale yellow crystals. Mp: 231 °C. ^{1}H NMR ($CDCl_3$): δ 1.45 (t, 3 H), 3.40 (t, 2 H), 4.42 (q, 2 H), 4.85 (t, 2 H), 8.35 (d, 1 H). Anal. ($C_{13}H_{10}FClN_2O_3S$): C, H, N.

(±)-Ethyl 1-Methyl-7-fluoro-8-chloro-5-oxo-1,2-dihydro-5*H*-oxazolo[3,2-*a*][1,8]naphthyridine-4-carboxylate (8b). A solution of **7b** (0.45 g, 1.20 mmol) in *N,N*-dimethylformamide (DMF, 2 mL) was added slowly to a suspension of sodium hydride (60 mg, 1.5 mmol) in DMF (2.5 mL). The mixture was heated at 132 °C for 1 h and the solvent was evaporated. The residue was added to water and the mixture was extracted with chloroform. The $CHCl_3$ extract was washed with 15% aqueous NaCl, dried over anhydrous sodium sulfate, and then evaporated. The residue was chromatographed on a column of silica gel to give **8b** (135 mg, 35% yield) as pale yellow crystals. Mp: 203 °C. ^{1}H NMR ($CDCl_3$): δ 1.36 (t, 3 H), 1.66 (d, 3 H), 2.35 (q, 2 H), 4.45–5.30 (m, 3 H), 8.26 (d, 1 H). Anal. ($C_{14}H_{12}FClN_2O_4$): C, H, N.

Ethyl 3-Methyl-7-fluoro-8-chloro-5-oxo-1,2-dihydro-5*H*-imidazolo[3,2-*a*][1,8]naphthyridine-4-carboxylate (8c). A solution of **7c** (0.47 g, 1.3 mmol) in dioxane (5 mL) was added slowly to a suspension of potassium *tert*-butoxide (0.15 g, 1.3 mmol) in dioxane (5 mL). The mixture was stirred at room temperature for 1.5 h and then heated at 80 °C for 2 h, and the solvent was evaporated. The oil obtained was poured into water and the mixture was extracted with chloroform. The $CHCl_3$ extract was washed with 15% aqueous NaCl, dried over anhydrous sodium sulfate, and then evaporated. The residue was recrystallized from ethanol to give **8c** (0.39 g, 92% yield) as pale yellow crystals. Mp: 205 °C. ^{1}H NMR ($CDCl_3$): δ 1.40 (t, 3 H), 3.00 (s, 3 H), 3.60–4.60 (m, 6 H), 8.07 (d, 1 H). Anal. ($C_{14}H_{13}FClN_3O_3$): C, H, N.

7-Fluoro-8-chloro-5-oxo-1,2-dihydro-5*H*-thiazolo[3,2-*a*][1,8]naphthyridine-4-carboxylic Acid (9a). A solution of **8a** (0.15 g, 0.41 mmol) in sulfuric acid (3 mL) was heated at 83 °C for 2.5 h. The mixture was then poured into ice/water (50 mL) and the precipitate that formed was collected and washed with water, ethanol, and ether. The solid thus obtained was recrystallized from ethanol/chloroform to give **9a** (76 mg, 55% yield) as white crystals. Mp: 259 °C dec. ^{1}H NMR ($CDCl_3$): δ 3.48 (t, 2 H), 4.80 (t, 2 H), 8.50 (d, 1 H), 15.04 (b s, 1 H). Anal. ($C_{11}H_6FClN_2O_3S$): C, H, N.

(±)-1-Methyl-7-fluoro-8-chloro-5-oxo-1,2-dihydro-5*H*-oxazolo[3,2-*a*][1,8]naphthyridine-4-carboxylic Acid (9b). A solution of **8b** (0.12 g, 0.36 mmol) in sulfuric acid (2 mL) was heated at 83 °C for 3 h. The mixture was then poured into ice/water (30 mL) and the precipitate that formed was filtered off and washed with water. The solid thus obtained was recrystallized from ethanol/chloroform to give **9b** (0.10 g, 91% yield) as white crystals. Mp: 238 °C dec. ^{1}H NMR ($CDCl_3$): δ 1.70 (d, 3 H), 4.42–5.30 (m, 3 H), 8.20 (d, 1 H), 14.8 (s, 1 H). Anal. ($C_{12}H_8FClN_2O_4$): C, H, N.

Ethyl 3-Methyl-7-fluoro-8-(4-methyl-1-piperazinyl)-5-oxo-1,2-dihydro-5*H*-imidazolo[3,2-*a*][1,8]naphthyridine-4-carboxylate (10). A solution of **8c** (75 mg, 0.23 mmol) and *N*-methylpiperazine (69 mg, 0.69 mmol) in ethanol was heated at 83 °C for 6.5 h. The mixture was concentrated under reduced pressure and the syrup thus obtained was chromatographed on a column of silica gel to give **10** (79 mg, 88% yield). Mp: 213 °C. ^{1}H NMR ($CDCl_3$): δ 1.36 (t, 3 H), 2.38 (s, 3 H), 2.40–2.80 (m, 4 H), 2.92 (s, 3 H), 3.50–4.50 (m, 10 H), 7.78 (d, 1 H). Anal. ($C_{19}H_{24}FN_5O_3$): C, H, N.

7-Fluoro-8-(4-methyl-1-piperazinyl)-5-oxo-1,2-dihydro-5*H*-thiazolo[3,2-*a*][1,8]naphthyridine-4-carboxylic Acid (3a). A solution of **9a** (70 mg, 0.2 mmol) and *N*-methylpiperazine (104 mg, 1 mmol) in DMF (3 mL) was stirred at 83 °C for 4 h and the mixture was concentrated under reduced pressure. The residue was added to water (30 mL) and extracted with chloroform. The $CHCl_3$ extract was then washed with 15% aqueous NaCl and dried over anhydrous sodium sulfate, and the solvent was evaporated. The residue was recrystallized from ethanol to give **3a** (58 mg, 68% yield) as pale yellow crystals. Mp: 267 °C. ^{1}H NMR ($CDCl_3$): δ 2.36 (s, 3 H), 2.57 (m, 4 H), 3.44 (t, 2 H), 3.88 (m, 4 H), 4.79 (t, 3 H), 7.96 (d, 1 H), 15.53 (s, 1 H). The melting point and ^{1}H NMR spectrum obtained were identical with those of **3a** in ref 5.

(±)-1-Methyl-7-fluoro-8-(4-methyl-1-piperazinyl)-5-oxo-1,2-dihydro-5*H*-oxazolo[3,2-*a*][1,8]naphthyridine-4-carboxylic Acid (3b). A solution of **9b** (0.40 g, 1.34 mmol) in acetonitrile (20 mL) was added to a solution of *N*-methylpiperazine (0.27 g, 2.7 mmol) and triethylamine (0.67 g, 6.7 mmol) in acetonitrile (10 mL). The mixture was heated at 93 °C for 2 h and the solvent was evaporated under reduced pressure. The residue was chromatographed on a column of silica gel to give **3b** (0.14 g, 29% yield) as pale yellow crystals. Mp: 219 °C. ^{1}H NMR ($CDCl_3$): δ 1.65 (d, 3 H), 2.36 (s, 3 H), 2.45–2.70 (m, 4 H), 3.70–4.00 (m, 4 H), 4.50–5.30 (m, 3 H), 7.96 (d, 1 H), 15.2 (b s, 1 H). MS:

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(13) The numbering used in the naming of these compounds is not systematic.

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]

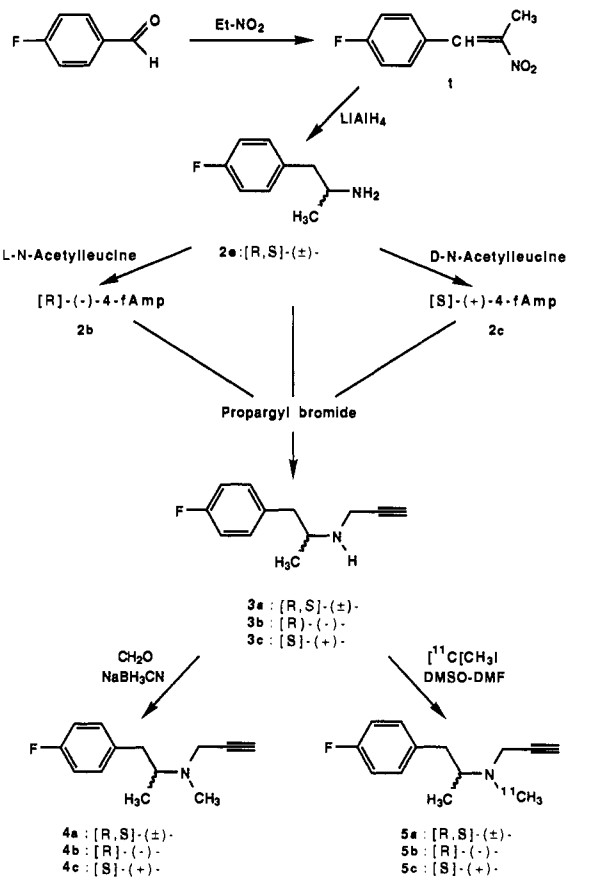
(*R*)-(−)-α-Methyl-β-phenyl-*N*-methyl-*N*-propynylethylamine ((*R*)-(−)-deprenyl) acts as a selective suicide inhibitor of MAO-B by forming a covalent bond to its active site. (*R*)-(−)-[*N*-^{11}C-*methyl*]deprenyl has been synthesized[6] and used to study MAO in vivo in animals[4,7] and in humans.[5] 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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0022-2623/90/1833-2015$02.50/0