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Synthesis of 4,6-difluoro-5-hydroxy-(α-methyl)tryptamine and 4,6-difluoro-5-hydroxy-(β-methyl)tryptamine as potential selective monoamine oxidase B inhibitors

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Abstract

Condensation of 4-nitro-1-pentanal and 4-nitropentanal 3-methylbutanal with 3,5-difluoro-4-methoxyphenylhydrazine afforded 4,6-difluoro-5-methoxy-3-(2′-nitro)propylindole **4a** and 4,6-difluoro-5-methoxy-3-(1′-methyl-2′-nitro)ethylindole **4b**, respectively, in one step. Reduction of the nitro group with lithium aluminum hydride followed by removal of the methyl ether with boron tribromide produced the title compounds. They were inactive as MAO B inhibitors. © 1998 Elsevier Science S.A. All rights reserved.

Keywords: Monoamine oxidase; Serotonin (5HT); Enzyme selectivity; Fischer indole synthesis

1. Introduction

The flavin-linked monoamine oxidases (MAO) that oxidize monoamines to carbonyl compounds have many important physiological roles. MAO inactivates catecholamine and indolamine neurotransmitters, intestinal MAO metabolizes pressor amines found in food, vascular MAO protects organs from circulating pressor amines, and liver MAO controls blood levels of amines. The mood elevating effect of MAO inhibitors has provided impetus to the examination of such inhibitors as drugs for the treatment of depressive illnesses. An important aspect of this research was prompted by the discovery in 1968 of two forms of MAO – MAO A and MAO B – which have different substrate and inhibitor selectivities. For example, 5-hydroxytryptamine (serotonin, 5-HT) is oxidized preferentially by MAO-A, whereas less polar amines such as phenethylamine, tyramine and dopamine are metabolized mainly by MAO-B. Design of selectively acting compounds that can function as reversible or irreversible inhibitors of the different isozymes has been an important goal of medicinal chemists [1].

Consideration of the potential protective role of MAO-B in serotonergic neurons, through degradation of extraneous amines [2], has made the selective inhibition of MAO-B in these neurons a target for pharmacological and potential therapeutic studies. To explore the effects of such inhibition, a drug is required that can be taken up readily into the serotonergic neuron, but which has a preference for interaction with the MAO-B rather than for MAO-A, the enzyme for which 5-HT is a preferred substrate. The identification of structural parameters which favor recognition by 5-HT uptake mechanisms but which reverses substrate selectivity for MAO enzymes represents a major challenge to the development of such an agent.

As seen frequently with other enzyme substrates, introduction of halogen can have significant effects on the interactions of compounds with the MAO enzymes. For example, ring fluorination of 5-HT [3] causes this predominantly MAO A substrate to be metabolized significantly by the MAO B enzyme [4]. The trend in selectivity seen with fluorinated analogues of 5-HT and other biogenic amines, including dopamine and tyramine, appears to reflect greater lipophilicity of the fluorinated analogues.

We have also shown that fluorine enhances the uptake of 5-HT into platelets [5], an observation that suggests that fluorinated analogues of 5-HT may also be good substrates for serotonergic neuron uptake mechanisms. In this regard, fluorinated analogues of other biogenic amines, for example, fluorinated norepinephrines, are taken up into neurons and serve as false neurotransmitters [6].

Although many reversible competitive inhibitors selective for MAO A have been developed, including a large number

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of α-methylamines, very few effective MAO B-selective inhibitors have been reported. These α-substituted amines apparently derive their MAO selectivity from steric hindrance to binding to the B enzyme [1]. Recent studies, however, suggest that β-alkylation may favor B-selectivity. For example, *p*-chloro-β-methylphenylethylamine has a 618-fold selectivity for MAO B [7].

Taken together, these considerations indicate that a fluorinated analogue of 5-HT with appropriate side chain modification may meet the criteria outlined above for selective MAO-B inhibitors that can be targeted to serotonergic neurones. β-Methyl-4,6-difluoroserotonin (**1b**) was our initial synthetic goal. α-Methyl-4,6-difluoroserotonin (**1a**) was also targeted as an analogue to study more fully the effects of side chain methylation on MAO activity.

2. Chemistry

The Fischer indole synthesis was used to construct the indole nucleus. The alumina-catalyzed condensation of acrolein with nitroethane, as described by Ballini and Petrini, provided 4-nitropentanal **2a** [8]. Using the same procedure, condensation of nitromethane with crotonaldehyde afforded 4-nitro-3-methyl-butanal **2b**. Condensation of the aldehydes **2a** and **2b** with 3,5-difluoro-4-methoxyphenylhydrazine (**3**), prepared according to the procedure of Hunsberger and coworkers [9] from 3,5-difluoro-4-anisidine [3], was carried out under conditions that produced 4,6-difluoro-5-methoxy-3-(2′-nitro)propylindole **4a** and 4,6-difluoro-5-methoxy-3-(1′-methyl-2′-nitro)ethylindole **4b**, respectively, without isolation of the intermediate hydrazones. This one step procedure was superior in terms of convenience and overall yield compared to the sequence that involved isolation of the hydrazones. The corresponding tryptamines **5a** and **5b** were formed by lithium aluminum hydride reduction of **4a** and **4b**, respectively. Demethylation with boron tribromide produced the title compounds **1a** and **1b** (Scheme 1).

3. Biological results and discussion

4,6-Difluoro-5-hydroxytryptamines **1a,b**, as well as the precursor 4,6-difluoro-5-methoxytryptamines **5a,b**, were examined as inhibitors of the MAO B-catalyzed oxidation of ^{14}C-phenylethylamine. At concentrations as high as 10 mM no significant inhibition was observed with either of the analogues. Under the conditions used, 10 nm pargyline produced approximately 80% inhibition.

4. Experimental details

Proton NMR spectra were performed on a Varian 220 spectrometer. Chemical ionization mass spectra were obtained on a Finnigan/extrel Model 1015 mass spectrometer with ammonia as reagent gas.

4.1. *3,5-Difluoro-4-methoxyphenylhydrazine* 3

To a stirred suspension of 3,5-difluoro-4-methoxyaniline [3] (3.18 g, 20 mmol) in 8 ml of concentrated HCl was added dropwise 20 mmol of sodium nitrite in 7 ml of cold water with stirring. After the mixture was stirred for 0.5 h at 0°C, a solution of 60 mmol stannous chloride dihydrate in 14 ml of cold concentrated HCl was added dropwise. The slurry produced was refrigerated overnight, filtered and the precipitate was washed with brine, followed by 2:1 petroleum ether/ethyl ether. The filtered solid was then added to excess concentrated aqueous NaOH and the hydrazine was extracted into ether. The ether extract was washed with brine, dried over anhydrous sodium sulfate and evaporated to give the hydrazine **3** as a pale yellow solid, mp 61–62°C (3.10 g, 89%). ^{1}H-NMR ($CDCl_3$) d 3.55 (broad s, 2H), 3.88 (s, 3H), 5.17 (broad s, 1H), 6.39 (d, *J*=5.3 Hz, 2H); MS (CI, NH_3): *m/z* 175 $[M+1]^+$, 192 $[M+18]^+$, 209 $[M+35]^+$.

4.2. *4-Nitropentanal* 2a

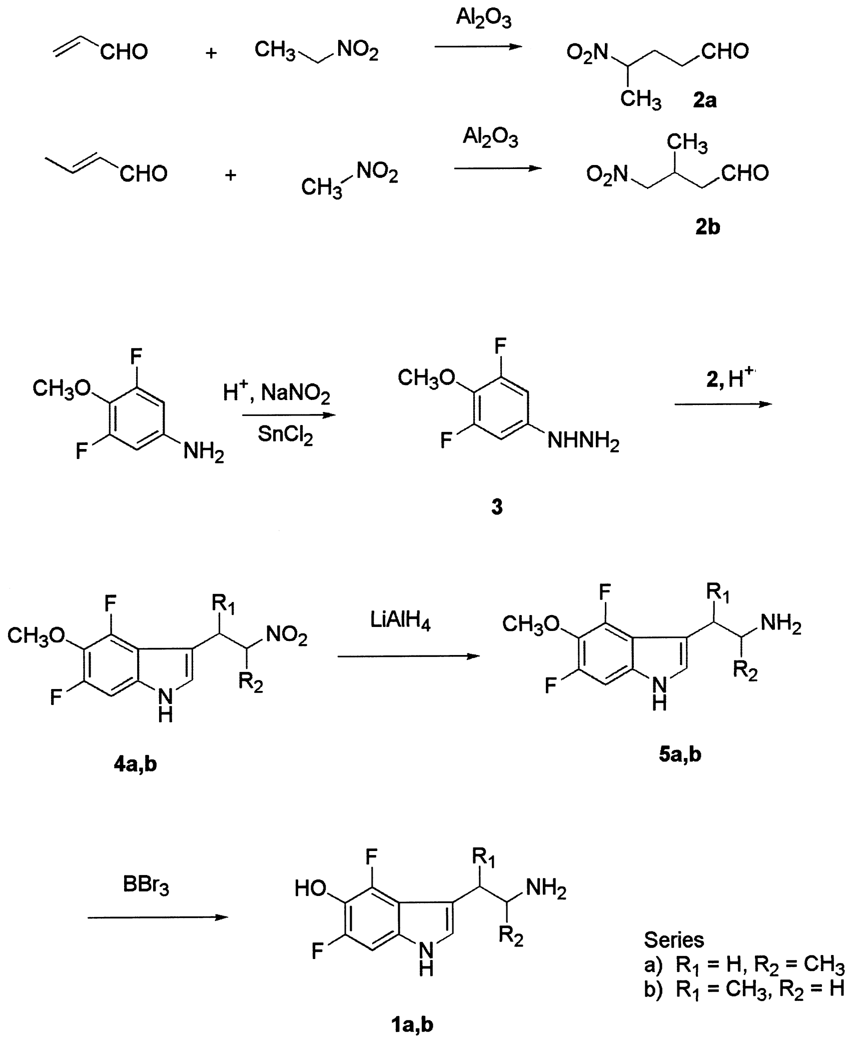
Nitroaldehyde **2a** was prepared by alumina-catalyzed condensation of acrolein with nitroethane according to the literature procedure [8]. From 3.59 ml (50 mmol) of nitroethane and 3.34 ml (50 mmol) of acrolein there was obtained 1.79 g of **2a** (27%) as a yellow oil. The ^{1}H-NMR ($CDCl_3$) was in complete agreement with that reported [8]. MS (CI, NH_3): *m/z* 148 $[M+17]^+$, 131 $[M]^+$, 116 $[M-15]^+$.

4.3. *4-Nitro-3-methylbutanal* 2b

The literature procedure used to prepare **2a** was adapted to the preparation of **2b**. To a two-necked round bottom flask containing nitromethane (3.05 g, 50 mmol) was added crotonaldehyde (3.5 g, 50 mmol) at 0°C and the mixture was stirred with a mechanical stirrer for 5 min. Chromatographic alumina (Neutral, Brockman Activity 1, 80–200 mesh, 10 g) was added and stirring was continued for 5 h at room temperature. The alumina was filtered, washed with ether and the filtrate was evaporated under reduced pressure to give a pale yellow oil. 4-Nitro-3-methylbutanal was obtained in 18% yield after silica gel chromatographic purification (hexane/ethyl acetate [4/1]). ^{1}H-NMR ($CDCl_3$) δ 1.12 (d, *J*=6.90 Hz, 3H), 2.48–2.92 (m, 3H), 4.33–4.46 (m, 2H), 9.78 (s, 1H); MS (CI, NH_3): *m/z* 148 $[M+17]^+$, 131 $[M^+]$, 116 $[M-15]^+$.

4.4. *4,6-Difluoro-5-methoxy-3-(2′-nitro)propylindole* 4a

To a stirred solution of 3,5-difluoro-4-methoxyphenylhydrazine 3 (1.33 g, 7.6 mmol) in 30 ml of 90% formic acid was added 4-nitropentanal **2a** (1.00 g, 7.6 mmol) at room temperature. After stirring for 2 h at room temperature, the



Scheme 1.

solution was refluxed for 1 h. After the reaction mixture was cooled, it was diluted with water and extracted with $CHCl_3$ (3×50 ml). The $CHCl_3$ extract was washed with brine, dried over anhydrous Na_2SO_4, and the solvent was evaporated by rotary evaporation. The resulting brown oil was purified by silica gel chromatography [hexane/ethyl acetate (4/1)] to afford **4a** as a yellow oil (1.22 g, 59%). ^{1}H-NMR ($CDCl_3$) δ 1.62 (d, J=6.6 Hz, 3H), 3.24 (dd, J=5.3, 14.8 Hz, 1H), 3.43 (dd, J=8.7, 14.8 Hz, 1H), 3.98 (s, 3H), 4.94 (m, 1H), 6.89 (dd, J=1.5, 10.3 Hz, 1H), 6.92 (d, J=2.6 Hz, 1H), 8.08 (broad s, 1H); MS (CI, NH_3): m/z 271 $[M+1]^+$, 288 $[M+18]^+$.

4.5. *4,6-Difluoro-5-methoxy-3-(1′-methyl-2′-nitro)ethyl indole* **4b**

A similar procedure was performed using 4-nitro-3-methylbutanal **2b** as the aldehyde component for reaction with **3**. The product was obtained in 39% yield after purification. ^{1}H-NMR ($CDCl_3$) δ 1.47 (d, J=7.1 Hz, 3H), 3.91 (m, 1H), 3.98 (s, 3H), 4.54 (dd, J=7.8, 11.8 Hz, 1H), 4.77 (dd, J=7.8, 11.8 Hz, 1H), 6.91 (dd, J=1.4, 10.2 Hz, 1H), 6.99 (d, J=2.3 Hz, 1H), 8.15 (broad s, 1H); MS (CI, NH_3): m/z 288 $[M+18]^+$, 271 $[M+1]^+$.

4.6. *4,6-Difluoro-5-methoxy-3-(α-methyl)tryptamine* **5a**

To a suspension of $LiAlH_4$ (902 mg, 23.7 mmol) in 30 ml of anhydrous THF was added a THF solution of **4a** (3.0 mol) at 0°C with stirring. After the addition, the mixture was refluxed for 30 min, and cooled to 0°C, 0.90 ml of water was added dropwise with stirring until decomposition was complete. This was followed by dropwise addition of 15% NaOH (0.90 ml), followed by the dropwise addition of 2.7 ml of water [10]. After the reaction mixture was stirred for 1 h at 0°C, it was filtered. The solution was evaporated to obtain the crude product which was purified by silica gel chromatography [methanol/ethyl acetate (65/35)] to afford **5a** as yellow crystals (344 mg, 54%). ^{1}H-NMR (MeOH-d_4) d 1.11 (d, J=6.4 Hz, 3H), 2.61 (dd, J=7.6, 14.1 Hz, 1H), 2.69 (dd, J=5.8, 14.0 Hz, 1H), 3.17 (m, 1H), 3.87 (s, 3H), 6.92 (dd, J=1.4, 10.7 Hz, 1H), 7.01 (s, 1H); MS (CI, NH_3): m/z 241 $[M+1]^+$.

4.7. *4,6-Difluoro-5-methoxy-3-(β-methyl)tryptamine* **5b**

A similar procedure as described above for the preparation of **5a** was used to prepare **5b** in 43% yield starting with **4b**. ^{1}H-NMR (MeOH-d_4) δ 1.33 (d, J=6.9 Hz, 3H), 2.85 (m, 1H), 2.97 (m, 1H), 3.23 (m, 1H), 3.88 (s, 3H), 6.94 (d, J= 10.7 Hz, 1H), 7.06 (s, 1H); MS (CI, NH_3): m/z 241 $[M+1]^+$.

4.8. *4,6-Difluoro-5-hydroxy-3-(methyl)tryptamine* **1a**

To a solution of **5a** (229 mg, 0.95 mmol) in anhydrous CH_2Cl_2 (20 ml) cooled to −78°C was added a solution of 1 M boron tribromide (2.0 ml, 2.0 equivalent) in anhydrous CH_2Cl_2 with stirring. The temperature gradually warmed to room temperature and the reaction was stirred overnight. Excess methanol was added and the resulting trimethylborate and solvent were evaporated to dryness. Hot isopropanol was added and the insoluble salt was filtered and washed with hot isopropanol. The combined filtrate was evaporated to afford a brown oil which was purified by a preparative TLC (20×20 cm, 500 mm thickness, Analtech, Newark, DE) eluting with NH_4OH/iPrOH/EtOAc (35/25/40). The product fraction was extracted from silica gel with methanol. The product **1a** (95 mg, 42% yield) was obtained as a partially crystalline yellow solid. ^{1}H-NMR (MeOH-d_4) δ 1.28 (d, J=6.5 Hz, 3H), 3.02 (m, 2H), 3.53 (m, 1H), 6.92 (d, J=10.5 Hz, 1H), 7.05 (s, 1H); MS (CI, NH_3): m/z 244 $[M+18]^+$, 227 $[M+1]^+$.

4.9. *4,6-Difluoro-5-hydroxy-3-(β-methyl)tryptamine* **1b**

A procedure similar to that described above for **1a** was used to prepare **1b** from **5b** in 47% yield. ^{1}H-NMR (MeOH-d_4) δ1.41 (d, J=6.9 Hz, 3H), 3.11 (dd, J=6.6, 12.5 Hz, 1H), 3.24 (dd, J=7.9, 12.5 Hz, 1H), 3.38 (m, 1H), 6.93 (d, J=10.5 Hz, 1H), 7.10 (s, 1H); MS (CI, NH_3): m/z, 244 $[M+18]^+$, 227 $[M+1]^+$.

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