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SYNTHESIS OF [^{14}C]AMIFLAMINE - AN MAO-A INHIBITOR

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SUMMARY

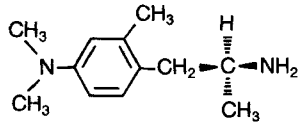
Amiflamine ((S)-(+)-2-(4-dimethylamino-2-methylphenyl)-1-methylethylamine) is a potent, selective, and reversible MAO-A inhibitor. Carbon-14 labelled amiflamine (8) with a specific activity of 8.1 mCi/mmol was prepared. The key-step in the synthesis is a Cu(I)-catalyzed reaction of an organometallic derivative obtained from compound (6) with $^{14}CH_3I$. Also described is the synthesis of the optically active compound (6).

Key-words: amiflamine, MAO-A inhibitor, Cu(I)-catalyzed alkylation, carbon-14 labelling.

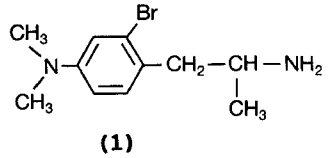
INTRODUCTION

Mitochondrial monoamine oxidase (MAO) is an enzyme that plays an important role in the regulation of transmitter amines (1). The discovery that MAO exists in two forms (2), namely MAO-A and MAO-B, have led to a resurgent search for new MAO-inhibitors with a view to obtaining more selective drugs. In general, MAO-inhibitors affecting the mood, i.e. potential antidepressive agents, should preferentially act on MAO-A (3).

(S)-(+)-2-(4-Dimethylamino-2-methylphenyl)-1-methylethylamine



Amiflamine



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(amiflamine) is a potent, selective, and reversible inhibitor of MAO-A (4-7). The present paper describes the synthesis of ^{14}C-labelled amiflamine.

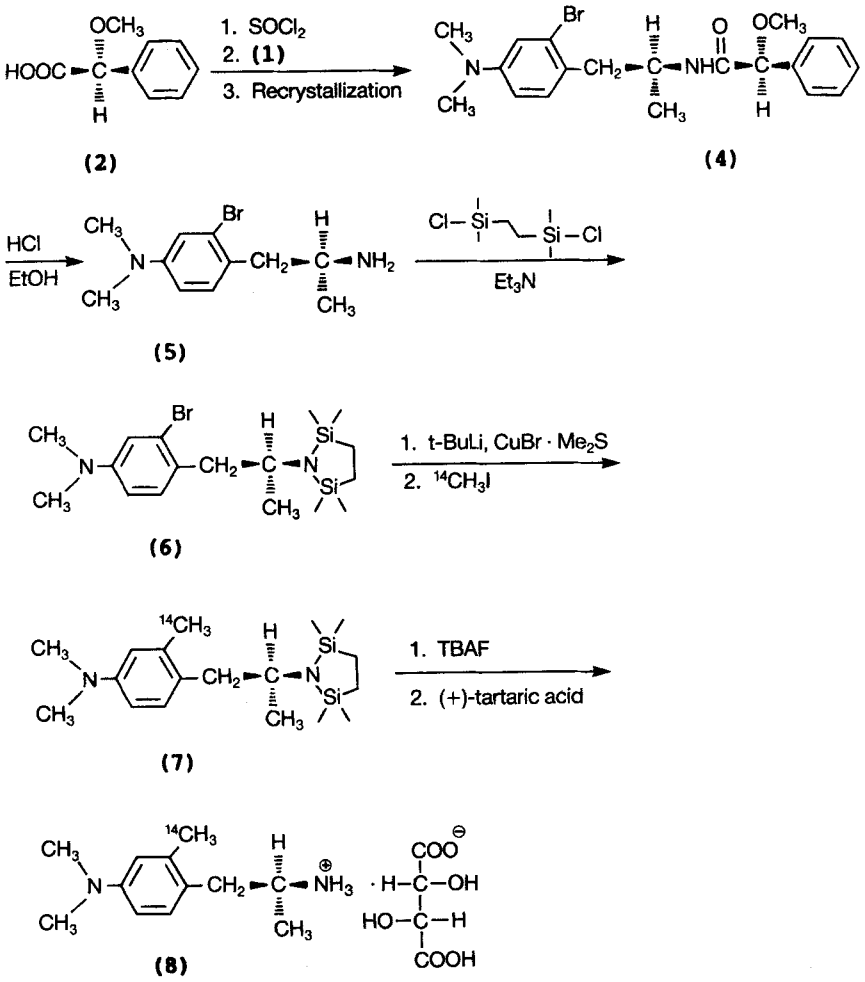
METHODS AND RESULTS

Compound (1), which is a 2-bromo analogue of amiflamine, was chosen as a potential starting material in the synthesis of carbon-14 labelled amiflamine. This choice was based on the following reasons: (i) N-protected (1) might be metalated, thereby providing an organometallic derivative which can react with $^{14}CH_3I$, (ii) compound (1) can be resolved before the introduction of carbon-14, and (iii) it would provide a derivative containing the label in a most likely metabolically stable position.

The use of stabase (2,2,5,5-tetramethyl-1-aza-2,5-disilacyclopentane) adducts as protecting groups for primary amines has recently been reported (8). We chose this methodology for compound (1). The obtained stabase adduct of (1) (cf. Scheme) was used in order to find the proper conditions for the metalation. This reaction was found to be a rather difficult one, however, the appropriate conditions were found to be: t-BuLi (2 equiv) in tetrahydrofuran (THF) at -70 °C (cf. reference 9). The desired lithiated derivative was formed in a yield of about 70% as determined by GLC of a H_2O quenched sample. The obtained lithiated derivative had, in our hands, low reactivity with methyl iodide. Therefore, the organolithium derivative was converted to an organocopper reagent by adding 20% of Cu(I)·Me_2S to the lithiated derivative. This reagent reacted smoothly with methyl iodide and N-protected racemic amiflamine was obtained in a yield of about 50% (cf. Scheme).

The next step in the synthetic strategy was to resolve compound (1) (Scheme). Amiflamine is easily obtained by resolution of 2-(4-dimethylamino-2-methylphenyl)-1-methylethylamine with L-(+)-tartaric acid (5). However, compound (1) could not be resolved with L-(+)-tartaric acid, (+)-di-benzoyl-L-tartaric acid, (+)-di-4-toluoyl-L-tartaric acid, or with (+)-mandelic acid. Instead, by reacting compound (1) with (S)-α-methoxyphenylacetic acid (2) using standard methods, a resolvable diastereomeric amide (3) was obtained. Compound (3) was purified by recrystallization from hexane to give the amide (4) with a diastereomeric purity of 97.4% de as determined by capillary GLC. Compound (4) was hydrolyzed by refluxing with EtOH/37% HCl for 14 days to give compound (5) in a yield of 94 %.

Scheme



The amine (5) was reacted with 1,2-bis(chlorodimethylsilyl)-ethane to give the stabase adduct (6). Compound (6) was metalated as described above, and the formed organolithium compound was transformed into an organocuprate which was allowed to react with 10 mCi of $^{14}CH_3I$. Compound (7) was then deprotected by the use of tetrabutylammonium fluoride trihydrate (TBAF) in THF and the obtained amine was converted to a hydrogen tartaric acid salt. After the addition of cold material and recrystallization, 1.0 mCi of the desired carbon-14 labelled amiflamine was obtained. The overall radiochemical yield was 10% and the specific activity was 8.1 mCi/mmol.

EXPERIMENTAL

Melting points were determined in open capillary tubes and are uncorrected. Optical rotations were obtained on a AA-100 polarimeter from Optical Activity Ltd. ^{1}H and ^{13}C NMR spectra were recorded at 199.5 MHz and 50.1 MHz, respectively, on a JEOL FX 200 spectrometer. GLC analyses were performed on a Carlo Erba 4200 chromatograph equipped with a 20 m SE-30 capillary column. Radiochemical purity was determined by scanning SiO_2 plates (Merck silica gel 60 0.2 mm), using a Berthold LB 283 TLC Linear Analyzer. Radioactivity was measured in a Packard Tri-Carb 460 C liquid scintillation spectrometer. [^{14}C]Methyl iodide (58 mCi/mmol) was purchased from Amersham, U.K., (S)-(+)-α-Methoxyphenylacetic acid, $[\alpha]_D^{20}$+ 146 ± 2° (c= 0.5, EtOH), from Fluka, Switzerland, and Cu(I)Br·Me_2S from Aldrich, West-Germany.

(2S)-N-((1S)-2-(2-Bromo-4-dimethylaminophenyl)-1-methylethyl)-2-methoxy-2-phenylacetamide (4). (S)-(+)-α-Methoxyphenylacetic acid ((2), 1.0 g, 6.0 mmol) was dissolved in CH_2Cl_2 (30 ml) and $SOCl_2$ (8 ml) was added. The reaction was stirred at 20 °C for 30 min. The mixture was then concentrated in vacuum. The crude residue, i.e. the acid chloride of (2), was dissolved in CH_2Cl_2 (30 ml) and this solution was then added to a mixture of 1M NaOH (60 ml), the (+)-hydrogen di-4-toluoyl-L-tartaric acid salt of (1) (3.86 g, 6 mmol), (10), and CH_2Cl_2 (30 ml). The reaction mixture was vigorously stirred for 15 min at 20 °C. The organic phase was separated, washed with water (2x20 ml), and dried (Na_2SO_4). Evaporation of the solvent gave 2.26 g of an oily residue which was purified on a silica gel column using EtOAc as the eluent to give 1.47 g (60%) of (2S)-N-(2-(2-bromo-4-dimethylaminophenyl)-1-methylethyl)-2-methoxy-2-phenylacetamide (3). This compound was recrystallized twice from hexane to yield 0.63 g (52% of theor.) of the title compound. M.p. 149 °C. The diastereomeric purity was 97.4% de, as determined by GLC. $[\alpha]_D^{22}$ +36.3° (c=0.40, EtOH). ^{1}H NMR ($CDCl_3$, TMS) δ 1.16 (d, ^{3}J= 6.6 Hz, 3H), 2.76- 3.00 (m, 2H), 2.91 (s, 6H), 3.30 (s, 3H), 4.14- 4.29 (m, 1H), 4.51 (s, 1H), 6.59 (dd, ^{3}J= 8.5 Hz, ^{4}J= 2.7 Hz, 1H), 6.75 (broad d, 1H), 6.87 (d, ^{4}J= 2.7 Hz, 1H), 7.06 (d, ^{3}J= 8.3 Hz, 1H), 7.28- 7.37 (m, 5H). ^{13}C NMR ($CDCl_3$, TMS) δ 20.36, 20.36, 40.40, 40.99, 46.14, 57.38, 83.85, 111.85, 116.08,124.98, 125.71, 126.93, 128.22, 128.44, 131.28, 137.31, 150.16, 169.81.

(S)-(+)-2-(2-Bromo-4-dimethylaminophenyl)-1-methylethylamine (5). 630 mg (1.56 mmol) of (4) was dissolved in EtOH (20 ml) and 37% HCl (20 ml) was added. The reaction mixture was heated under

reflux for 14 days. The reaction mixture was then cooled (ice), made alkaline (45% NaOH) and extracted with EtOAc. The organic phase was dried (Na_2SO_4) and the solvent evaporated to yield 377 mg (1.47 mmol, 94%) of (5). $[\alpha]_D^{22}$ + 27.1 ° (c= 0.76, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, TMS) δ 1.11 (d, ^{3}J= 6.4 Hz, 3H), 1.65 (broad s, 2H), 2.55 (dd, ^{2}J= 13.4 Hz, ^{3}J= 7.8 Hz, 1H), 2.70- 2.85 (m, 1H), 2.88 (s, 6H), 3.12- 3.28 (m, 1H), 6.59 (dd, ^{3}J= 8.55 Hz, ^{4}J= 2.7 Hz, 1H), 6.88 (d, ^{4}J= 2.7 Hz, 1H), 7.03 (d, ^{3}J= 8.55 Hz, 1H). ^{13}C NMR ($CDCl_3$, TMS) δ 23.25, 40.37, 45.38, 47.38, 111.72, 116.34, 125.56, 126.21, 131.47, 150.08.

(S)-(+)-2-(2-Bromo-4-dimethylaminophenyl)-1-methylethyl)-2,2-5,5-tetramethyl-1-aza-2,5-disilacyclopentane (6).To a solution of (5) (377 mg, 1.47 mmol) and Et_3N (420 µl, 3.0 mmol) in CH_2Cl_2(15 ml), at 20 °C and under argon, was added 323 mg (1.5 mmol) of 1,2-bis(chlorodimethylsilyl)ethane in CH_2Cl_2 (4 ml). The reaction mixture was stirred for 1 h. Et_2O (50 ml) was then added and the reaction mixture filtered. Evaporation of the solvent gave a crude product which was purified on a alumina column using Et_2O as the eluent. 293 mg (50 %) of (6) was obtained. $[\alpha]_D^{22}$ + 7.1 °(c= 0.62,dry CH_2Cl_2). ^{1}H NMR ($CDCl_3$, ref: $CHCl_3$= 7.25 ppm relative to TMS) δ 0.14 (s, 6H), 0.17 (s, 6H), 0.71 (s, 4H),1.05 (d, ^{3}J= 6.8 Hz, 3H), 2.67 (dd, ^{2}J= 13.1 Hz, ^{3}J= 10.4 Hz, 1H),2.80- 2.92 (m, 1H), 2.91 (s, 6H), 3.31- 3.42 (m, 1H), 6.61 (dd, ^{3}J= 8.55 Hz, ^{4}J= 2.70 Hz, 1H), 6.89 (d, ^{4}J= 2.70 Hz, 1H), 7.02 (d, ^{3}J= 8.55 Hz, 1H). ^{13}C NMR ($CDCl_3$, ref: $CHCl_3$= 77.2 ppm relative to TMS) δ 1.82, 2.01, 8.68, 23.86, 40.69, 46.53, 50.42, 112.01, 116.56,125.63, 127.48, 131.78, 150.15.

(S)-1-(2-(4-Dimethylamino-2-[methyl-^{14}C]phenyl)-1-methylethyl)-2,2,5,5-tetramethyl-1-aza-2.5-disilacyclopentane (7). A stirred solution of t-BuLi in pentane (1.65 M, 210 µl, 0.35 mmol) and THF (2.0 ml) under argon was cooled to -70 °C and a solution of (6) (70 mg, 0.175 mmol) in THF (1.0 ml) was then added with a syringe over a 10 min period. The solution was stirred for 30 min at -70 °C. CuBr·Me_2S (7 mg, 0.034 mmol) was then added and the mixture was stirred at -70 °C for 30 min. 10 mCi of $^{14}CH_3I$ (0.175 mmol) was then transferred, via a vacuum line, to the reaction mixture. After 1h at -70 °C the vacuum was broken by passing a stream of argon gas into the reaction vessel. The reaction mixture was allowed to reach room temperature and stirred for 48 h. The mixture was hydrolyzed with 2M NH_4OH (4 ml) and extracted with Et_2O (3x3 ml). The

combined extracts were washed with water (2x3 ml), dried (Na_2SO_4), and concentrated with a stream of nitrogen gas. The crude (7) was used in the next step without purification.

(S)-(+)-2-(4-Dimethylamino-2-[methyl-^{14}C]phenyl)-1-methylethylamine (+)-hydrogen tartrate (8). The crude product (7) was treated with TBAF (110 mg, 0.35 mmol) in THF (5 ml) for 48 h at 20 °C. The solvent was then removed by a stream of nitrogen gas and the residue was partitioned between 2M NH_4OH (3 ml) and Et_2O (3 ml). The aqueous phase was extracted with Et_2O (2x3 ml). The combined ether extracts were dried (Na_2SO_4) and (+)-tartaric acid (15 mg, 0.1 mmol) was added to the etheral solution. The solvent was then evaporated and 40 mg of unlabelled (8) was added to the residue. Two recrystallizations from 95% CH_3OH gave 43 mg (0.13 mmol) of (8). The specific activity was 8.1 mCi/mmol and the overall radiochemical yield was 10 %. The radiochemical purity was 95 % as determined by TLC (SiO_2, EtOAc: CH_3OH: conc. NH_4OH, 20: 20: 1.5, v/v/v) and scanning. The enantiomeric purity was >99 % ee, as indicated by GLC on the amide prepared from (8) and (S)-α-methoxyphenylacetic acid (2).

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10. The preparation of the dihydrochloride salt of (1) is described in reference 4.