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NOTE

Synthesis of Racemic, S(+)- and R(-)-N-[methyl-^{3}H]3,4-Methylenedioxymethamphetamine.

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Summary

The synthesis of 3,4-methylenedioxymethamphetamine(MDMA), a serotonergic neurotoxin, labeled with tritium is described. Labeling was accomplished by N-alkylation of the free base of the corresponding desmethyl compound using [^{3}H]methyl iodide. The compound was purified by preparative HPLC. The radiochemical yield was about 60 % based on [^{3}H]methyl iodide. The radiochemical purity was more than 95 % from HPLC and TLC. Furthermore, S(+)- and R(-)-[^{3}H]MDMA were completely separated by analytical HPLC with chiral column.

Key words: [^{3}H]Labeling, 3,4-Methylenedioxymethamphetamine, Chiral separation

Introduction

3,4-Methylenedioxymethamphetamine(MDMA; "Ecstasy") is a psychedelic amphetamine analog and it was reported that MDMA was a selective neurotoxin of serotonergic nerve terminals in rat brain(1-5). MDMA produces a decrease in the concentration of 5-hydroxytryptamine(5-HT) and its major metabolite 5-hydroxyindoleacetic acid(5-HIAA), a decrease in the activity of tryptophan hydroxylase and reduction in the densities of 5-HT

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uptake sites labeled by [^{3}H]paroxetine in rat brain regions(1-5). It is, therefore, of great interest to study the pharmacological, metabolic and pharmacokinetic properties of MDMA. In the present study, we describe the synthesis of [^{3}H]MDMA. Interestingly, different pharmacological effects have been observed for the enantiomers of MDMA(2,6-8). Furthermore, we have separated S(+)-[^{3}H]MDMA and R(-)-[^{3}H]MDMA using analytical HPLC with chiral column.

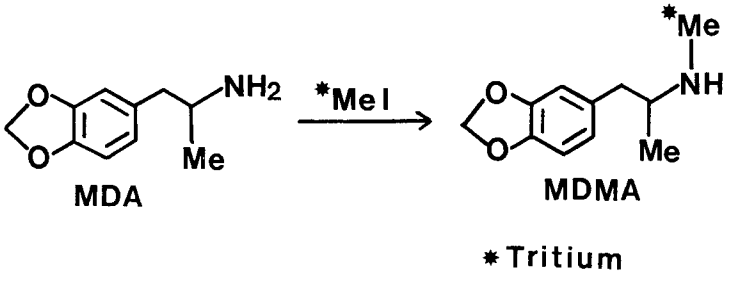

Fig.1 Synthesis of [^{3}H]MDMA

Results and Discussion

[^{3}H]Label was incorporated by N-alkylation of the free base of the corresponding desmethyl compound using [^{3}H]methyl iodide, as shown in Figure 1.

The incorporation of [^{3}H]methyl was accomplished within 5 min in a DMF/DMSO(75:25) mixture at 50 °C as described previously(9). The reaction mixture was separated by preparative HPLC. The total radiochemical yield was about 60 % based on [^{3}H]methyl iodide and the radiochemical purity was more than 95 % using HPLC and TLC. The specific activity of ^{3}H-MDMA was essentially the same as that of the starting [^{3}H]methyl iodide used(3.15 TBq/mmol).

Figure 2 shows the separation of racemic MDMA by HPLC with chiral column(SUMICHIRAL OA-4600). It was found that racemic MDMA

was completely separated under these conditions, since the retention times of S(+)-MDMA and R(-)-MDMA were 17.9 min and 20.0 min respectively. The optical resolution of these compounds was confirmed by measuring their optical rotations(S(+)-MDMA; +9.4°, R(-)-MDMA; -6.7° (0.1 % ethanol solution at 28 °C)). Furthermore, S(+)-[^{3}H]MDMA and R(-)-[^{3}H]MDMA could be obtained by using HPLC with the chiral column.

In conclusion, racemic [^{3}H]MDMA could be obtained by N-methylation of the free base of the desmethyl compound using [^{3}H]methyl iodide. S(+)-[^{3}H]MDMA and R(-)-[^{3}H]MDMA could be completely separated by HPLC with chiral column(SUMICHIRAL OA-4600). We are now in progress of performing distribution studies using racemic, S(+)- and R(-)-[^{3}H]MDMA in animals.

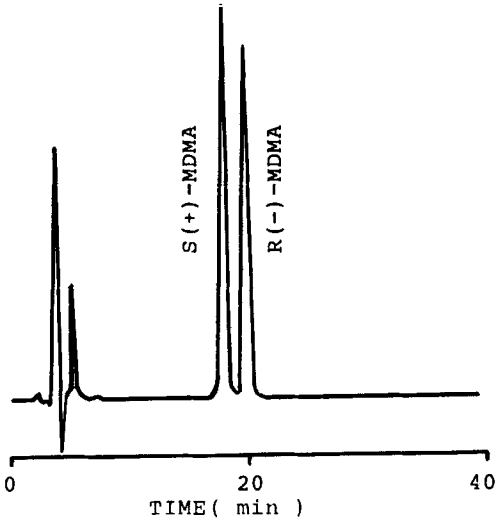

Fig. 2. Separation of S(+)- and R(-)-MDMA by HPLC with the chiral column

Experimental

[^{3}H]Methyl iodide(3.15 TBq/mmol) was purchased from Amersham Japan Ltd.(Tokyo). MDMA and desmethyl compound of MDMA, namely 3,4-methylenedioxyamphetamine(MDA) were synthesized from

3,4-methylenedioxyphenyl-2-propanone(Fluka AG, Switzerland) and methylamine and ammonium acetate respectively, as described by Braun et al(10). SUMICHIRAL OA-4600(5 μm, 4 mmI.D. x 25 cm) was purchased from Sumika Chemical Analysis Service Ltd.(Osaka). Other chemicals were purchased commercially.

Synthesis of [^{3}H]MDMA

[^{3}H]Methyl iodide(0.4 mL toluene solution) was added to a 3 mL reaction vial containing 5.0 mg of the free base of MDA in 0.5 mL DMF/DMSO(75:25) solvent mixture. The reaction mixture was heated at 50 °C for 5 min. The reaction solution was injected onto the HPLC(Column; TSKgel ODS-80Tm(10 μm, 7.8 mmI.D. x 30 cm), Mobile phase; H_2O:CH_3CN:Et_2NH=70:30:0.2, Flow rate; 4 mL/min, Detector; UV(254 nm)). The appropriate fractions were collected and evaporated. The radiochemical purity was determined by HPLC(Column; TSKgel ODS-80Tm(5 μm, 4.6 mmI.D. x 15 cm), Mobile phase; H_2O:CH_3CN:Et_2NH=60:40:0.2, Flow rate; 2 mL/min, Detector; UV(254 nm)) and TLC(silicagel; $CHCl_3$:MeOH:NH_4OH=9:1:0.1, Rf value=0.35).

Separation of [^{3}H]MDMA by HPLC with SUMICHIRAL OA-4600

[^{3}H]MDMA solution in $CHCl_3$ was injected onto the HPLC(Column; SUMICHIRAL OA-4600, Mobile phase; hexane:dichloroethane:ethanol:trifluoroacetic acid=60:35:5:0.25, Flow rate; 0.7 mL/min, Column temperature; RT, Detector; UV(254 nm)). The appropriate fractions were collected and evaporated. The radiochemical purity was determined by HPLC and TLC as described above.

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