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NOTE

Synthesis of Racemic, S(+)- and R(-)-N-[methyl-³H]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 [³H]methyl iodide. The compound was purified by preparative HPLC. The radiochemical yield was about 60 % based on [³H]methyl iodide. The radiochemical purity was more than 95 % from HPLC and TLC. Furthermore, S(+)- and R(-)-[³H]MDMA were completely separated by analytical HPLC with chiral column.

Key words: [³H]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 [³H]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 [³H]MDMA. Interestingly, different pharmacological effects have been observed for the enantiomers of MDMA(2,6-8). Furthermore, we have separated S(+)-[³H]MDMA and R(-)-[³H]MDMA using analytical HPLC with chiral column.

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R(-)-MDMA; -5.
S(+)-[³H]MDMA
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In conclusion
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[³H]methyl iodide
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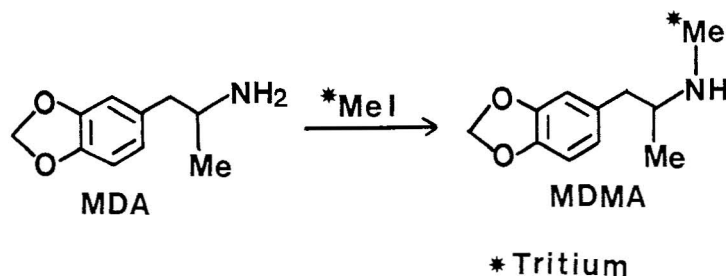


Fig.1 Synthesis of [³H]MDMA

Results and Discussion

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

The incorporation of [³H]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 [³H]methyl iodide and the radiochemical purity was more than 95 % using HPLC and TLC. The specific activity of ³H-MDMA was essentially the same as that of the starting [³H]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

Fig.

[³H]Methyl
Amersham Japan
namely 3,4-meth

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; $+9.4^\circ$, R(-)-MDMA; -6.7° (0.1 % ethanol solution at 28°C)). Furthermore, S(+)-[^3H]MDMA and R(-)-[^3H]MDMA could be obtained by using HPLC with the chiral column.

In conclusion, racemic [^3H]MDMA could be obtained by N-methylation of the free base of the desmethyl compound using [^3H]methyl iodide. S(+)-[^3H]MDMA and R(-)-[^3H]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(-)-[^3H]MDMA in animals.

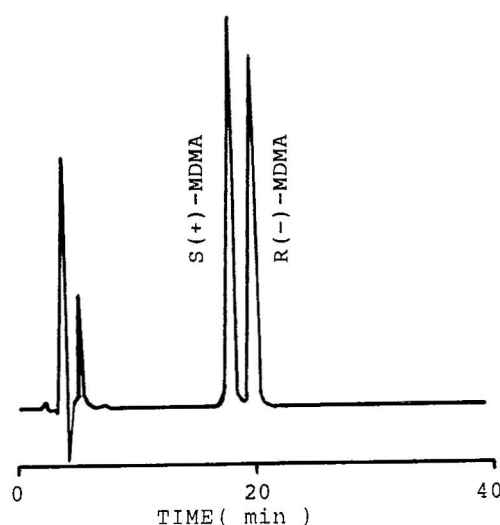


Fig. 2. Separation of S(+)- and R(-)-MDMA by HPLC with the chiral column

Experimental

[^3H]Methyl iodide (3.15 TBq/mmol) was purchased from Amersham Japan Ltd. (Tokyo). MDMA and desmethyl compound of MDMA, namely 3,4-methylenedioxymethamphetamine (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 μ m, 4 mmI.D. x 25 cm) was purchased from Sumika Chemical Analysis Service Ltd.(Osaka). Other chemicals were purchased commercially.

Synthesis of [³H]MDMA

[³H]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 μ m, 7.8 mmI.D. x 30 cm), Mobile phase; H₂O:CH₃CN:Et₂NH=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 μ m, 4.6 mmI.D. x 15 cm), Mobile phase; H₂O:CH₃CN:Et₂NH=60:40:0.2, Flow rate; 2 mL/min, Detector; UV(254 nm)) and TLC(silicagel; CHCl₃:MeOH:NH₄OH=9:1:0.1, R_f value=0.35).

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

[³H]MDMA solution in CHCl₃ 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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