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Preparation of N-[^{11}C]methyl-2,5-dimethoxy-4-methylamphetamine

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In order to evaluate the neurobiological mechanism causing the psychogenic effects of N-methyl-2,5-dimethoxy-4-methylamphetamine (MDOM), the ^{11}C labelled analogue was prepared for application in in vivo PET studies by the reaction of 2,5-dimethoxy-4-methylamphetamine (DOM) with [^{11}C]CH_3I. The radiochemical yield was determined in dependence on time, temperature, solvent and amount of substrate. The best conditions for fast labelling reactions with ^{11}C on a preparative scale were found to be a reaction time of 10 miutes at 110 °C using 1 mg DOM in acetonitrile thus obtaining radiochemical yields of 80% (based on produced [^{11}C]CH_3I).

Introduction

Amphetamines exhibit psychogenic properties that can be very different from each other. The differences depend, for example, on type and position of substituents at the benzene ring. The 2,4,5-trisubstitution pattern has been found to provide a maximum of hallucinogenic activity, especially in those compounds where the 4-position is occupied by a substituent such as iodine, bromine or a methyl group.

2,5-dimethoxy-4-methylamphetamine 1 (DOM) is a well known example of amphetamine derivatives belonging to the class of psychedelics. DOM is a potent 5-HT_2 receptor agonist with virtually no dopaminergic character. The N-methyl-derivative of DOM, N-methyl--2,5-dimethoxy-4-methylamphetamine 2 (MDOM), has been reported to show a higher K_i value for the 5-HT_2 binding site in rat frontal cortical homogenates[1] but, in general, little is known about the compound, thus leaving the mechanism of action still unclear. So psychotropic effects have been described only in anecdotal reports and with controversal character.[2] Moreover, a full receptor profile for MDOM and other N-methylated hallucinogenes, belonging to the amphetamine class, has not been established, yet.

For in vivo PET studies the compound was planned to be labelled with ^{11}C ($T_{1/2}$ = 20 min) by ^{11}C-methylation of the free base thus forming N-[^{11}C]methyl-2,5--dimethoxy-4-methylamphetamine 2 (MDOM).

Experimental

For applying the labelling procedure, first two compounds had to be prepared: 2,5-dimethoxy--4-methylamphetamine, DOM, as the starting material for the labelling reaction and N-methyl-2,5-dimethoxy--4-methylamphetamine, MDOM, as the reference compound for the product according to procedures described elsewhere.[2] As analytical data was scarcely available it was determined as presented below.

2,5-dimethoxy-4-methylamphetamine hydrochloride (DOM) 1 (Fig. 1a)

DOM was obtained as the hydrochloride in a yield of 59% and the melting point was 89 °C which was in accordance with the literature.[2] The product was finally characterized by NMR and MS using a Bruker WM 400 spectrometer (250 MHz for ^{1}H, 62.9 MHz for ^{13}C) and a Hewlett Packard mass spectrometer MSD 5970 (quadrupole) at 70 eV and a source temperature of 220 °C. The NMR data for characterizing the compound was the following: ^{1}H-NMR ($CDCl_3$): δ 8.3 (bs, 2H, NH_2) 6.7 (s, 2H, ArH), 3.8 (s, 6H, OCH_3 and OCH_3), 3.0 (m, 3H, $CHCH_2$), 2.2 (s, 3H, $ArCH_3$), 1.3 (d, 3H, $CHCH_3$); ^{13}C-NMR ($CDCl_3$): δ 151.5, 151.2 (C-2- and C-5), 126.4 (C-4), 121.7 (C-1), 114.1, 113.8 (C-3 and C-6), 56.2, 55.8 (OCH_3 and OCH_3), 48.3 (CH_2), 36.5 (CH), 18.4 ($CHCH_3$), 16.2 ($ArCH_3$). EI-MS: m/z 209 (10%), 166 (100%), 151 (60%), 135 (15%), 91 (20%).

N-methyl-2,5-dimethoxy-4-methylamphetamine (MDOM) 2 (Fig. 1b)

MDOM was prepared in a yield of 63% as a yellowish oil. For characterizing the compound ^{1}H-, ^{13}C-NMR and EI-MS was applied. The NMR spectra were recorded as mentioned above while the electron impact mass spectra were obtained using a TSQ 70, Finnigan MAT with a direct inlet and a source temperature of 200 °C. ^{1}H-NMR ($CDCl_3$): δ 6.7 (d, 2H, ArH), 3.8 (2s, 6H, OCH_3 and OCH_3), 2.8 (m, 1H, CH), 2.6 (m, 2H, CH_2), 2.4 (s, 3H, NCH_3), 2.2 (s, 3H, $ArCH_3$), 1.7 (bs, 1H, NH), 1.1 (d, 3H, $CHCH_3$); ^{13}C-NMR ($CDCl_3$): δ 151.4, 151.3 (C-2 and C-5), 125.6, 125.1 (C-1 and C-4), 113.9, 1138 (C-3 and C-6), 56.0, 56.0, 55.1 (OCH_3, OCH_3 and $NHCH_3$), 37.9 (CH_2), 33.9 (CH), 19.7 ($CHCH_3$), 16.1 ($ArCH_3$). EI-MS: *m/z* = 224 (25%), 166 (20%), 151 (5%), 135 (5%), 91 (7%), 77 (5%), 58 (100%).

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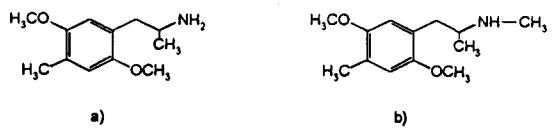

Fig. 1. Structures of DOM 1 and MDOM 2

Labelling procedure

[^{11}C]CO_2 was produced at the cyclotron of the PET-Center (PETtrace, GE Medical Systems) via the $^{14}N(p,\alpha)^{11}C$ reaction, trapped on molecular sieve 4 Å and converted to [^{11}C]methane in presence of Ni catalyst (Shimalite-Ni reduced 80/100, Shimadzu). [^{11}C]methane was reacted with elemental iodine at 760 °C, thus producing [^{11}C]CH_3I in 40% radiochemical yield (EOB) based on produced [^{11}C]CO_2 in 12.5 minutes. The activity was trapped in a 10 ml Reactivial, containing 5 ml of solvent (CH_3CN or DMF). 1 ml portions of the [^{11}C]CH_3I solution were added to a solution of DOM in CH_3CN or DMF, the vial was sealed, and heated for different reaction times at temperatures of 70, 90 and 110 °C. After cooling to room temperature an aliquot of the reaction mixture was analysed by HPLC (Econosil 10 µm, 250 mm × 4.6 mm, Alltech, MeOH/0.15M NH_4NO_3-buffer at pH 9.9, 987.5/12.5 v/v, flow 2 ml/min). Under these conditions the k' values for CH_3I, DOM and MDOM were 0.25, 1.63 and 3.50, respectively. The specific activity was determined to be 300 GBq/µmol (8000 Ci/mmol) at EOB. The calculation of the radiochemical yields was based on the time at which the production of [^{11}C]CH_3I was finished.

Table 1. Dependence of radiochemical yield on reaction temperature in DMF and CH_3CN; reaction conditions: 2 mg (9.6 µmol) DOM, 1 ml DMF or CH_3CN, reaction time 8 minutes, $n = 3 \pm$ sd

Temperature, °C	Radiochemical yield, %	
	CH_3CN	DMF
40	Not determined	57 ± 6
70	47 ± 4	75 ± 4
90	67 ± 9	76 ± 4
110	78 ± 8	68 ± 4
130	84 ± 4	62 ± 4

Table 2. Dependence of radiochemical yield on amount of precursor, DOM, reaction conditions: 90 °C, 1 ml CH_3CN reaction volume, 8-minute reaction time, $n = 3 \pm$ sd

Amount of precursor DOM, mg (µmol)	Radiochemical yield, %(± sd)
0.10 (0.48)	8 ± 6
0.25 (1.19)	18 ± 4
0.50 (2.39)	26 ± 11
1.00 (4.78)	52 ± 4
2.00 (9.56)	67 ± 9
3.00 (14.33)	78 ± 4

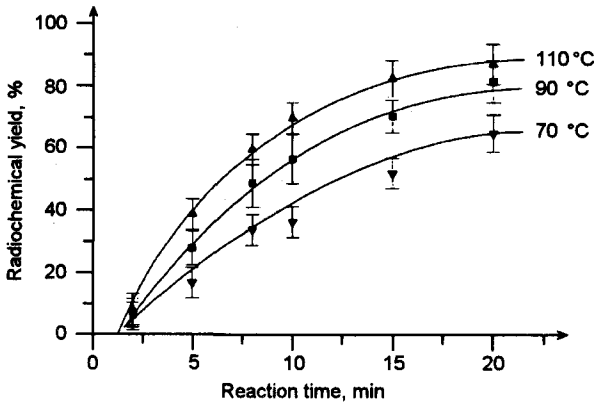

Fig. 2. Dependence of radiochemical yield on reaction time at 70, 90 and 110 °C (reaction conditions: 3 mg DOM (14.3 µmol), 3 ml CH_3CN, $n = 3$)

Results and discussion

For the [^{11}C]methylation reaction of 2,5-dimethoxy-4-methylamphetamine, DOM, the yield of MDOM was determined in dependence on reaction temperature in CH_3CN and DMF (Table 1). In all of those experiments the reaction time was 8 minutes. In DMF a yield of 75% was obtained already at 70 °C, whereas in acetonitrile higher temperatures were necessary, so at 110 °C the amount of product was 78%. Best results were observed in CH_3CN at 130 °C yielding 84% product.

The dependence of the radiochemical yield on the amount of precursor was determined in a range between 0.1 mg and 3.0 mg of starting material, i.e., DOM at a reaction time of 8 minutes and 90 °C in acetonitrile. As shown in Table 2 the yield strongly depends on the amount of precursor, it clearly increases from 8% at 0.1 mg to 52% at 1.0 mg while the following increase is slower reaching the maximum of 78% at 3.0 mg.

The product yield was determined for reaction times between 2 and 20 minutes in acetonitrile at 70, 90 and 110 °C. The experiments were performed with 1.0 mg DOM. As shown in Table 2, higher yields are found using more than 1 mg precursor, but the particular condition is clearly preferred because it assures an efficient and fast HPLC purification important for routine preparations. As can be seen in Fig. 2 a yield of 80% is reached at a temperature of 110 °C after a reaction time of 15 minutes, this is a very feasible condition for the labelling with ^{11}C.

With regard to the half-life of ^{11}C, the best condition for preparing MDOM is to perform the methylation during 10 minutes at a temperature of 110 °C using 1 mg DOM and acetonitrile as solvent. Under those conditions separation of the product is efficiency performed by using a fairly

small HPLC column. Thus [^{11}C]MDOM can be obtained in a small peak volume which is easily evaporated and the product redissolved in isotonic phosphate buffer for injection. In preparative runs ($n = 4$), 200 MBq of [^{11}C]MDOM were obtained from 2 GBq [^{11}C]CH_3I in solution suitable for injection after a total synthesis time of 60 minutes.

References

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