Synthesis of deuterated dextromethorphan derivatives

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Dedicated to Professor Csaba Szántay on the occasion of his 80th birthday

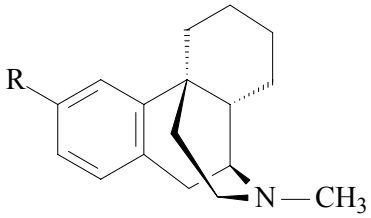
Abstract
Dextromethorphan is a widely used NMDA receptor antagonist and sodium channel blocker. Deuterated dextromethorphan and dextrorphan were synthesized via the N-desmethyl-dextromethorphan intermediate for pharmacokinetic study.

Keywords: Deuteration, dextromethorphan, dextrorphan, N-demethylation, methylation

Introduction

Dextromethorphan **1** is widely used as a cough suppressant.[1] It is an antagonist of the *N*-methyl-D-aspartate (NMDA) receptor and an agonist at sigma receptors.[1] Dextromethorphan **1** showed anticonvulsant activity and neuroprotective effect in cerebral ischemia.[2] It was studied for the treatment of pain and Parkinson's disease.[3] The main metabolite of **1** is dextrorphan[1] **2**, which is also an antagonist of the NMDA receptor. It was studied as a neuroprotective agent in the management of stroke.[4]

Dextromethorphan is often used as a component of drug combinations. Recently Richter patented the finding that **1** increased the effectiveness of the voltage gated sodium channel blocker tolperisone in animal models of various central nervous system disorders.[5] The mechanism of this effect is not quite clear, but possibly the serotonin uptake blocking effect of **1** plays a role.

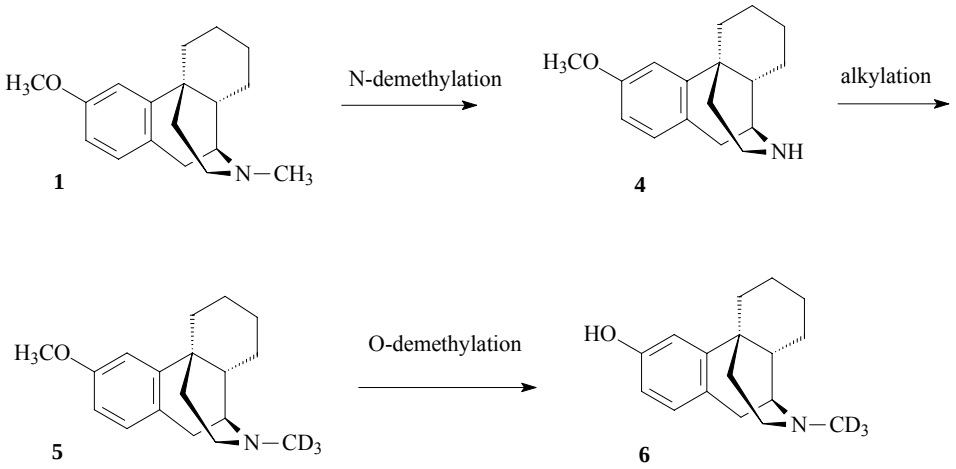


1 Dextromethorphan R = OCH_3,
2 Dextrorphan R = OH
3 R = OCD_3 derivative of **1**

Figure 1. Dextromethorphan, dextrorphan and CD_3O-derivative of dextromethorphan.

Results and Discussion

For pharmacokinetic studies we needed deuterated dextromethorphan and dextrorphan derivatives with three or more deuterium atoms. The isotopic enrichment and purity were required to be over 95% and 98%, respectively. The CD_3O-derivative of dextromethorphan **3** is a known compound, but its synthesis was not published.[6] Through N-desmethyl-dextromethorphan **4** intermediate we planned to prepare the N-CD_3-derivative of dextromethorphan **5** which can be an intermediate of N-CD_3-dextrorphan **6** in the following synthetic route (Scheme 1).

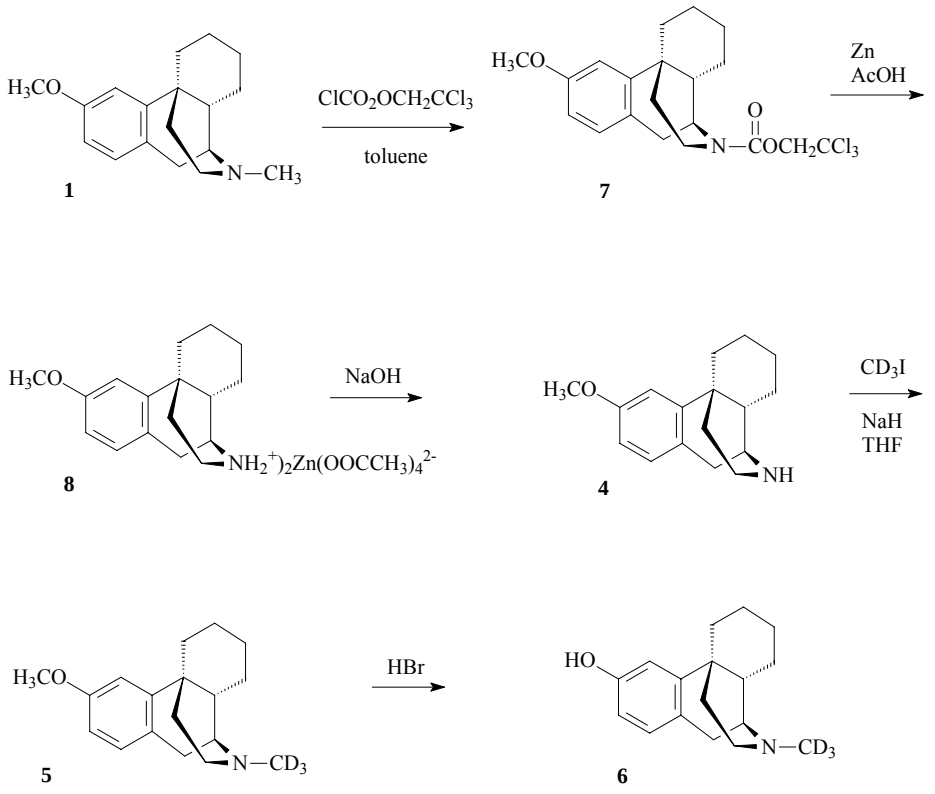


Scheme 1. The planned synthetic route.

N-Demethylation is an important question in the chemistry of alkaloids e.g. morphine alkaloids and morphinane derivatives. Several methods for it are known. The traditional method is the von Braun reaction[7] which is not suggested because of the toxicity of the reagent (cyanogen bromide). Photochemical N-demethylation is a quite special reaction with moderate yield.[8] The yield of the sodium sulfide or potassium thioacetate method is not high enough and

undesired side reactions could be noticed.[9] N-demethylation of the tertiary amine alkaloids e.g. certain opiate alkaloids using the non-classical Polonovski reaction resulted in the product in moderate yield only.[10]

Nowadays the chloroformate esters (methyl,[11] ethyl,[12-14] phenyl,[13,14] benzyl,[14] etc.) are preferred rather than the above mentioned reagents. We applied Peet's method[15] to N-demethylation under slightly modified conditions (Scheme 2). The crude trichloroethyl carbomate derivative **7** contained a small amount of starting material **1**, which can cause an impurity of the end-product. Purification by column chromatography resulted in the trichloroethyl carbomate in high quality (HPLC: >99% purity). The trichloroethoxy carbonyl group was removed by zinc in acetic acid. From the isolated zinc tetraacetate salt **8** the free base N-desmethyl-dextromethorphan **4** was gained smoothly by treatment with sodium hydroxide.



Scheme 2. Synthesis of N-CD_3-dextromethorphan **5** and N-CD_3-dextrorphan **6**.

Methylation of N-desmethyl-dextromethorphan **4** with iodomethane-d_3 was the crucial step in our synthetic work. At first the usual methods were tested.[16,17] Using potassium hydroxide in dimethylsulfoxide the conversion was moderate: 70-72 %. Modifying the conditions (sodium hydroxide, toluene, tetrabutylammonium bromide, potassium carbonate) one compound (Mw: 285) was obtained with 60% conversion. In the presence of potassium carbonate in dipolar-aprotic solvent, e.g. acetonitrile or DMF, the conversion was between 93-95 % according to GC-MS results. The quaternary salt was also obtained which is disadvantageous because it can be

easily transformed into a rearranged product.[18] In the presence of sodium hydride[19] in tetrahydrofuran the conversion of the methylation was more than 95%.

The most common reagents for O-demethylation are boron tribromide or hydrogen bromide. Both methods were studied. The latter transformed easily the N-CD_3-derivative of dextromethorphan into the corresponding N-CD_3-dextrorphan.

Scheme 2 summarizes our synthetic pathway.

The quality of our N-CD_3-derivative of dextromethorphan **5** and N-CD_3-dextrorphan **6** was checked by GC-MS, HPLC, NMR and MS measurements. The purity of the obtained N-CD_3-dextromethorphan was >99% by HPLC, and 97-98% by GC-MS. The GC-MS technique allowed to detect the N-CH, N-CH_2, and N-CH_3 contamination too.

The NMR spectrum of dextromethorphan hydrobromide showed a complex diastereomeric mixture because of α,β-protonation, which makes it difficult to determine possible N-CH_3, N-CH_2D and N-CHD_2 contamination. Figure 2 shows the ^{1}H NMR spectrum of the commercially available (Sigma-Aldrich) dextromethorphan hydrobromide.

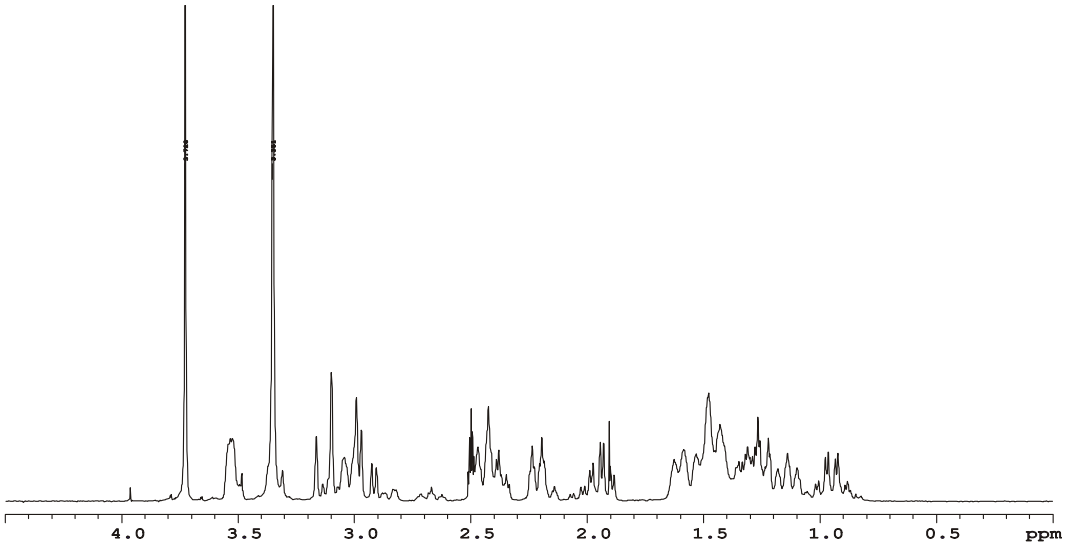


Figure 2. Partial ^{1}NMR spectrum of dextromethorphan hydrobromide monohydrate (Sigma D-2531) in DMSO-d_6 showing the aliphatic chemical shift region.

It is more advantageous to study the spectrum of the corresponding base, which is less ambiguous. Figure 3 shows the ^{1}H NMR spectrum of dextrorphan base **2** prepared from dextromethorphan **1** hydrobromide monohydrate (Sigma) by treatment with hydrogen bromide followed with aqueous ammonia. The N-methyl peak can be seen at ~ 2.3 ppm in DMSO-d_6.

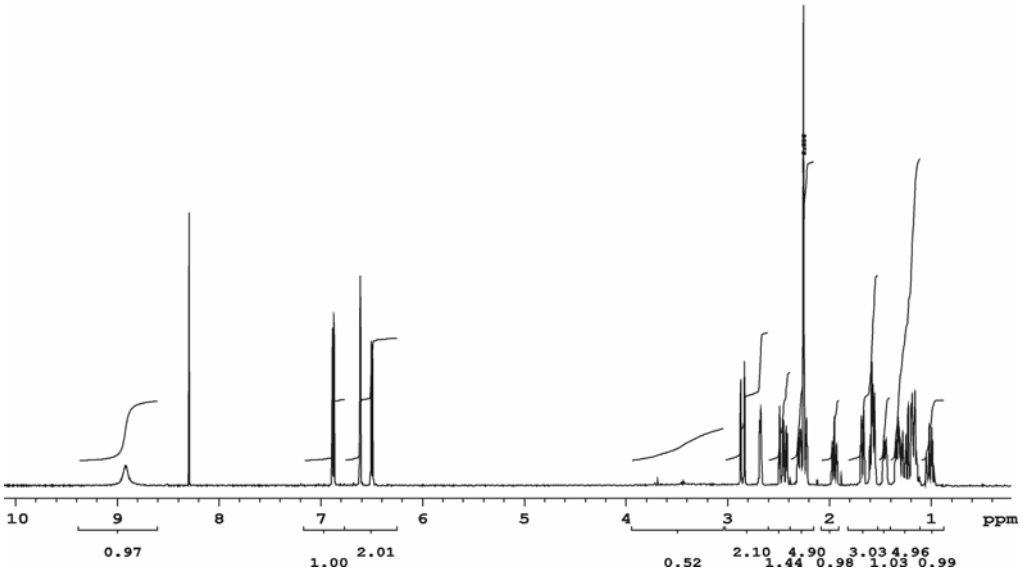


Figure 3. ^{1}H NMR spectrum of dextrorphan base reference compound in DMSO-d_6.

A simpler way to obtain the basic forms of these compounds is to dissolve them in a proper basic solvent or solvent mixture. Figure 4 shows the NMR spectrum of our N-CD_3-dextromethorphan HCl salt in pyridine-d_6: D_2O = 1:2 mixture (Figure 4 lower spectrum). When adding dextromethorphan to the sample, the peak at ~ 2.9 ppm increased (Figure 4 upper spectrum), which belongs to the N-CH_3 group. Integration of this peak showed that the N-CH_3 contamination is smaller than 5%.

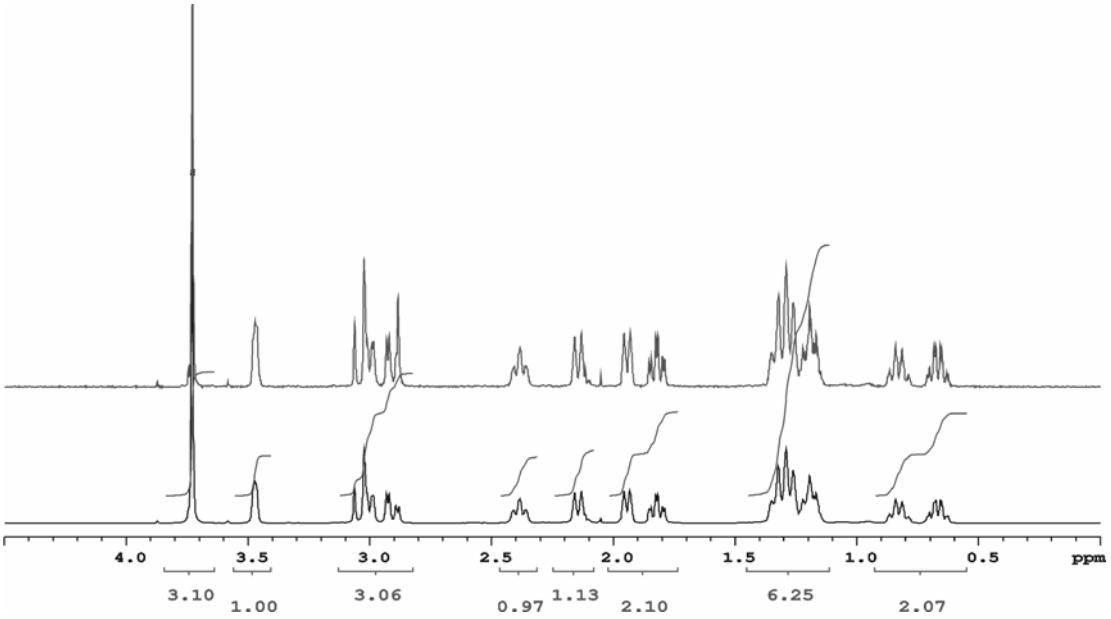


Figure 4. NMR spectra of N-CD_3-dextromethorphan HCl (bottom) and the spectrum used for standard addition (top) in pyridine-d_5 **:** D_2O=1:2 solvent mixture.

Our N-CD_3-dextrorphan samples were studied in a similar way. Adding dextrorphan hydrogen chloride salt to the sample in the NMR tube, N-CH_3 signal at ~2.3 ppm increased (Figure 5 above spectrum). After integration of this peak in the spectrum of our N-CD_3-dextrorphan sample it became evident that the rest of the N-CH_3 protons was < 5% (Figure 5 upper spectrum).

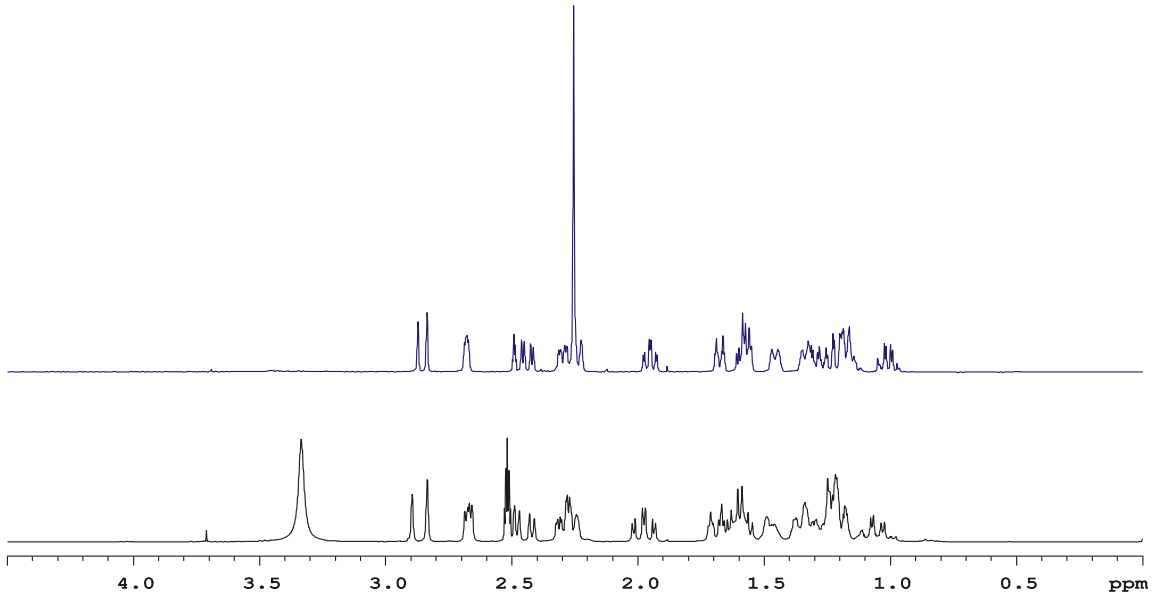


Figure 5. NMR spectra of N-CH_3-dextrorphan HCl reference (top), and N-CD_3-dextrorphan HCl (bottom) in DMSO-d_6.

The FAB MS spectrum of the commercially available dextromethorphan **1** hydrobromide monohydrate (Sigma D2351) is characterized by an intense protonated molecular ion at m/z MH^+ = 272 and M-H^+ = 270 (~8%). The M-$2H^+$ = 269 peak could not be detected (Figure 6).

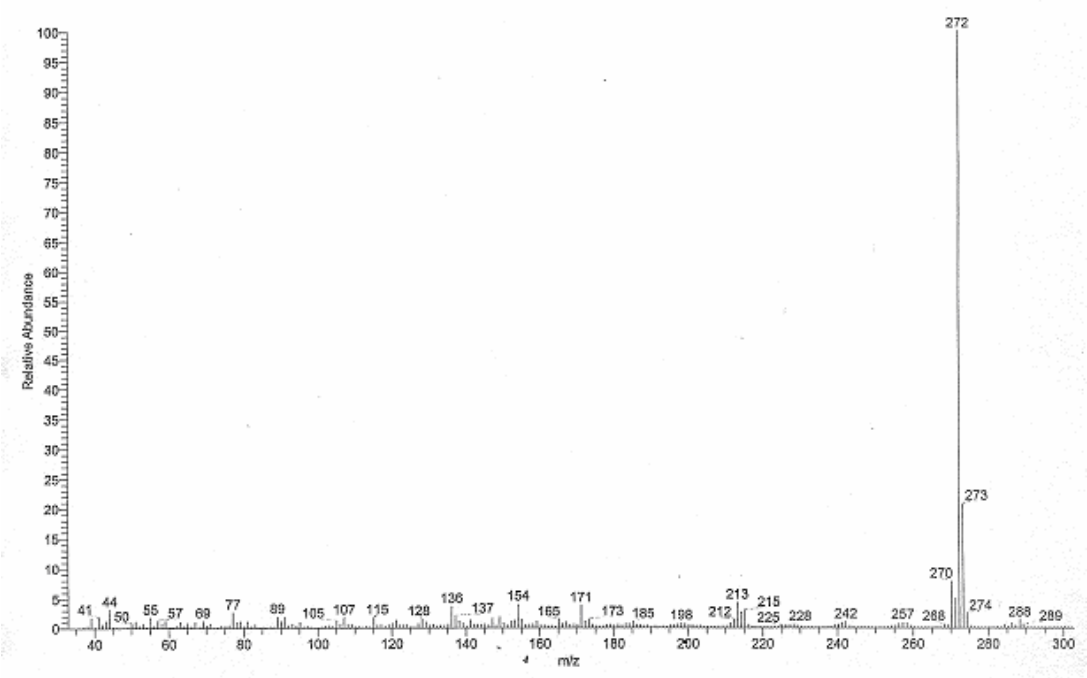


Figure 6. FAB MS spectrum of dextromethorphan hydrobromide monohydrate (Sigma D2351).

The FAB mass spectrum of the stable isotope labeled analog N-CD_3-dextromethorphan hydrochloride salt was dominated by peaks m/z M_1H^+ = 275 and M_1-H^+ = 273 due to the mass differences (Figure 7). The M_2H^+ = 272 contamination was ~2%.

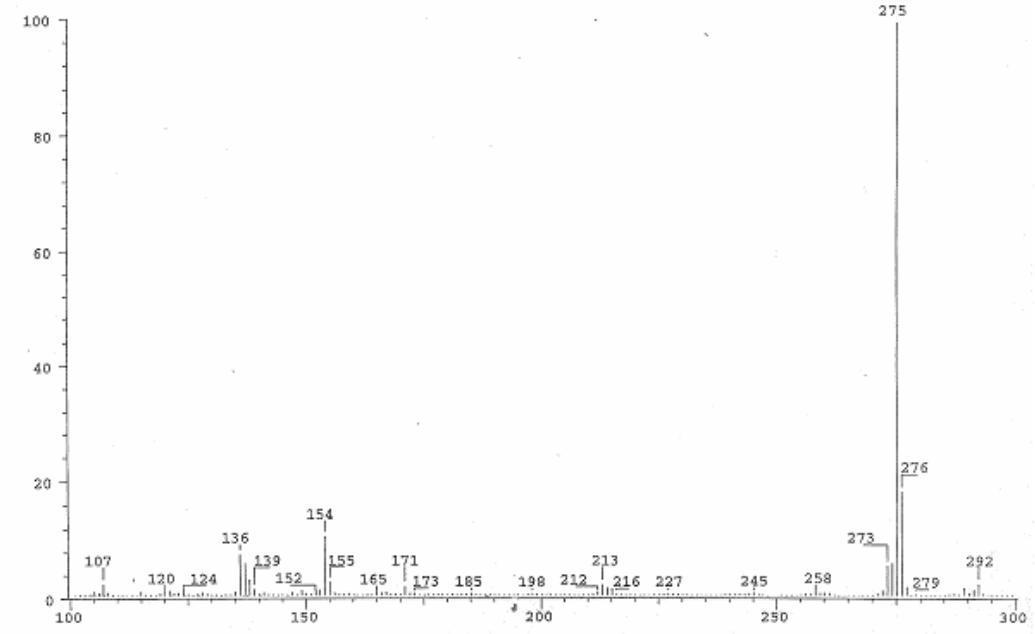


Figure 7. FAB spectrum of N-CD_3-dextromethorphan **5** hydrochloride salt.

The FAB MS spectrum of N-CD_3-dextromethorphan **5** base was not consistent with the above mentioned FAB results of the corresponding salt. The quaternary ion $=N^+(-CD_3)_2$, C_3^+ =292 could be observed beside the characteristic m/z M_1H^+ = 275 and M_1-H^+ = 273 peaks and the peak of the M_2H^+ = 272 increased significantly (~20 %; Figure 8).

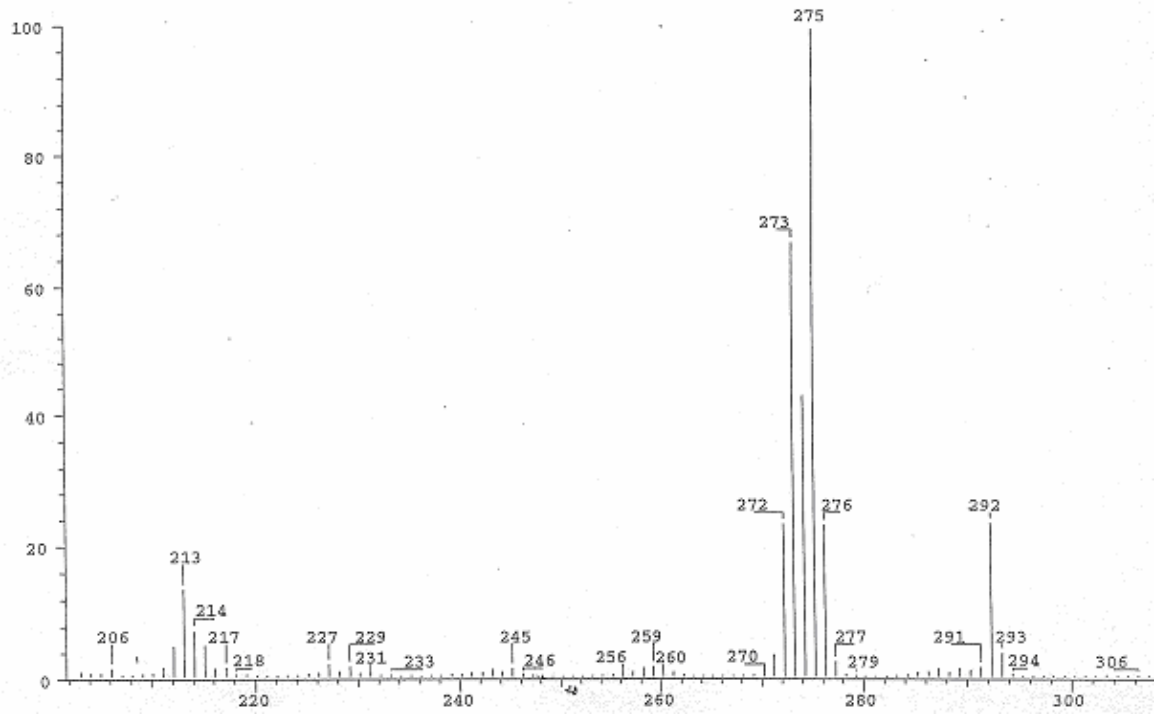


Figure 8. FAB MS spectra of the N-CD_3-dextromethorphan base.

The EI spectrum of N-CD_3-dextromethorphan **5** base was characterized by an intense molecular ion peak M_1=274, which was accompanied by the molecular ion peak of the N-CH_3-derivative as a contamination M_2=271 (~2-3%; Figure 9). In the case of N-CD_3-dextrorphan **6** analogue the quantity of the dextrorphan **2** contamination was established in a similar way by MS spectroscopy.

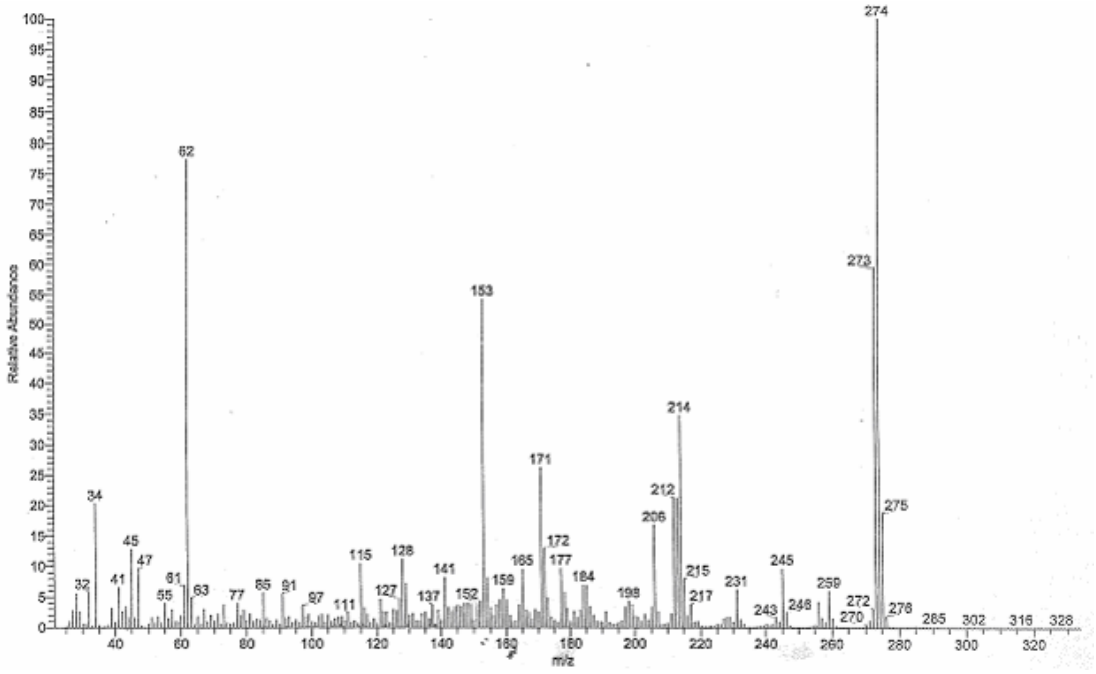


Figure 9. EI spectrum of N-CD_3-dextromethorphan **5** base.

Conclusions

For pharmacokinetic studies two new deuterated compounds, N-CD_3-dextromethorphan **5** and N-CD_3-dextrorphan **6** with isotopic enrichment between 97-98 % were synthesized.

Experimental Section

General Procedures. ^{1}H NMR spectra (499.97 MHz) were recorded on a Varian Inova-500 spectrometer at 30°C using an HCN indirect detection triple resonance probe. Deuterated solvents 99.95 atom % were purchased from Merck Gmbh®. Proton chemical shifts are referenced to the residual solvent signal (δ_{DMSO} = 2.50 ppm, δ_{C5D5N} = 7.19 ppm). Four scans were recorded and 20 second relaxation delay was applied to allow proper quantitation via the NMR integrals. Mass spectra were measured on a Finnigan MAT 95 XP instrument. A Fisons MD 800 instrument for GC-MS and a Thermo Separation Products instrument (UV 3000HR, P4000, AS1000, SN4000) for HPLC analysis were used.

1,3,4,9,10,10a-Hexahydro-6-methoxy-2*H*-10,4a-(iminoethano)phenantrene-11-carboxylic acid 2,2,2-trichloroethyl ester (7)

Dextromethorphan hydrobromide monohydrate (5.56 g, 15 mmoles) was dissolved in 60 ml of chloroform and a solution of 1.2 g sodium hydroxide in 60 mL of water. After stirring for 1 hour the organic layer was separated, dried (sodium sulfate), and evaporated in vacuum. The obtained oil was refluxed in 50 ml of toluene with 2.4 ml of 2,2,2-trichloroethyl chloroformate for 4 hours. The reaction was checked by TLC (Kieselgel 60, chloroform-methanol = 95:5, R_f = 0.7). After completion of the reaction the solvent was evaporated in vacuum. The residual oil was purified on a Kieselgel 60 (0.063-0.200) column (eluent: chloroform-methanol = 95:5), giving 6.0 g oil (13.86 mmoles, yield: 92.42 %). ^{1}H-NMR (300 MHz, $CDCl_3$, 30°C): δ 0.94-1.12 (m, 1H, CH); 1.16-1.72 (m, 9H, CH); 2.26-2.37 (m, 1H, CH); 2.54-2.76 (m, 2H, CH); 3.06 (dd, 1H, J=17.7 and 6.0 Hz, CH); 3.72 (s, 3H, OCH_3); 3.79-3.92 (m, 1H, CH), 4.32 (dd, 1H, J=4.6 and 4.4 Hz, CH); amide rotamers: [4.65 and 4.71 (d, 1H, J=12.3 Hz, CH_2) and 4.66 and 4.79 (d, 1H, J=12.0 Hz, CH_2)]; 6.66 (dd, 1H, J=8.4 and 3.0 Hz, Ar); 6.77 (d, 1H, J=3.0 Hz, Ar); amide rotamers: [6.95 and 6.96 (d, 1H, J=8.4 Hz, Ar)]; GC-MS: 98.0 %; MS: EI *m/e* 431 (M^+, 6.7%), 213 (100.0%).

3-Methoxymorphinan tetraacetatozincate (8)

The above prepared trichloroethyl ester derivative **7** (6.0 g, 13.86 mmoles) was dissolved in 57.5 ml of acetic acid and 5.89 ml of distilled water, to which 2.9 g of powered zinc was added. After 50 minutes stirring the completeness of the reaction was checked by TLC. Further 2.9 g of zinc was added to the reaction mixture. After 1 hour stirring the reaction mixture was filtered. The obtained white powder was washed three times with ether. Yield: 10.7 g crude product; mp 161-164°C; ^{1}H-NMR (300 MHz, $CDCl_3$, 30°C): δ 0.80-1.00 (m, 1H, CH); 1.08-1.42 (m, 5H, CH); 1.43-1.53 (m, 1H, CH); 1.54-1.76 (m, 2H, CH); 1.82 (s, 6H, CH_3COO^-), 1.80-1.89 (m, 1H, CH); 2.32-2.48 (m,2H, CH); 2.74-3.07 (m, 3H, CH); 3.39-3.46 (m, br, 1H, CH); 3.72 (s, 3H, OCH_3); 3.00-5.00 (s, vbr, 3H, NH^+ and H_2O), 6.75-6.82 (m, 2H, Ar); 7.07 (d, 1H, J=8.4 Hz, Ar); FAB-MS: C^+_1 = 258.

***N*-Desmethyl-dextromethorphan (4)**

The above prepared 10.7 g of 3-methoxymorphinan tetraacetatozincate **8** was partitioned between 300 ml of chloroform and 100 ml of 1N sodium hydroxide solution in water. The organic layer was separated, dried (sodium sulfate), evaporated in vacuum to yield: 3.1 g (12.04 mmoles, yield: 86.9%); GC-MS: 99.45%; ^{1}H-NMR (300 MHz, $CDCl_3$, 30°C): δ 1.00-1.12 (m, 1H, CH); 1.24-1.45 (m, 5H, CH); 1.46-1.69 (m, 3H, CH); 1.70-1.80 (m, 1H, CH); 2.14 (s, br, 1H, NH); 2.26-2.35 (m,1H, CH); 2.55-2.76 (m, 3H, CH); 3.02-3.16 (m, 3H, CH); 3.79 (s, 3H, OCH_3); 6.70 (dd, 1H, J=8.4 and 2.7 Hz, Ar); 6.81 (d, 1H, J=2.7 Hz, Ar); 7.03 (d, 1H, J=8.4 Hz, Ar); MS EI *m/e* 257 (M^+, 100.0%), 228 (M-29), 214 (M-43), 212 (M-45), 171 (M-(2x43)).

***N*-CD_3-Dextromethorphan (5)**

To the solution of the above prepared N-desmethyl-dextromethorphan **4** (3.1 g, 12.04 mmoles) in 265 ml of tetrahydrofuran 10.1 g of sodium hydride (60 % dispersion in mineral oil) was added. After 20 minutes stirring 1 ml (2.329 g= 16.067 mmoles) of iodomethane-d_3 was dropped into

the reaction mixture. The reaction was controlled by TLC. After 1 hour stirring at rt. the reaction mixture was poured into 180 ml of distilled water, which was extracted three times with 100 ml of diethyl ether. The organic layer was separated, dried (sodium sulfate), and evaporated in vacuum. The residue was crystallized in *n*-hexane. (Yield: 1.7 g, 6.195 mmoles, 51.5 %; mp 98-103°C). ^{1}H-NMR (300 MHz, DMSO, 30°C): δ 0.93-1.07 (m, 1H, CH); 1.11-1.40 (m, 5H, CH); 1.42-1.52 (m, 1H, CH); 1.53-1.66 (m, 2H, CH); 1.66-1.75 (m, 1H, CH); 1.93 (ddd,1H, J=12.3, 12.2 and 3.3 Hz, CH); 2.25-2.38 (m, 2H, CH); 2.48 (dd, 1H, J=17.7 and 5.7 Hz, CH); 2.68 (dd, 1H, J=5.7 and 3.3 Hz, CH); 2.90 (d, 1H, J=17.7 Hz, CH); 3.70 (s, 3H, OCH_3); 6.65 (dd, 1H, J=8.4 and 2.7 Hz, Ar); 6.72 (d, 1H, J=2.7 Hz, Ar); 7.00 (d, 1H, J=8.4 Hz, Ar); 8.85 (s, br, 1H, -OH); FAB-MS *m/z* 275 (M_1H^+); MS EI *m/z* 274 (M_1^+,100.0%), 271 (M_2^+, ~2-3%).

***N*-CD$_3$-Dextromethorphan (5) hydrochloride salt.** N-CD_3-dextromethorphan **5** (1.7 g) was dissolved in ethyl acetate-methanol mixture and was acidified with HCl in ethyl acetate to $p_H = 2$, *n*-hexane was added to the solution. The obtained crystals were filtered. Yield: 1.1 g (3.54 mmoles, 57.1%); mp 121-123 °C. ^{1}H-NMR (see Figure 4) (300 MHz, DMSO, 30°C): sum of protonated epimers: δ 0.87-1.03 (m, 1H, CH); 1.04-1.67 (m, 7H, CH); 1.88-2.05 (m, 1H, CH); 2.12-2.27 (m, 1H, CH); 2.33-2.49 (m, 2H, CH); 2.90-3.19 (m, 3H, CH); 3.50-3.56 (m, 1H, CH); 3.73 (s, 3H, OCH_3); 6.79-6.85 (m, 2H, Ar); 7.09-7.16 (m, 1H, Ar); 11.18 and 11.22 (s, 1H, NH^+); MS FAB *m/z* 275 (M_1H^+,100.0%), 272 (M_2H^+, 2%); GC-MS: 98.8%; HPLC: 99.4% (220 nm); isotopic enrichment 97 atom % D.

***N*-CD$_3$-Dextrorphan (6) hydrochloride salt.** N-CD_3-dextromethorphan **5** (1.25 g, 4.555 mmoles) was heated in 50 ml of hydrobromic acid (48%) at 110 °C for two hours. After cooling 125 ml of chloroform and 40 ml of ammonium hydroxide solution (25%) were added dropwise to the reaction mixture ($p_H = 9$). The organic layer was separated, dried (sodium sulfate), and evaporated in vacuum. The residue was dissolved in ethanol – ethyl acetate mixture. Acidifying the solution with HCl in ethyl acetate to $p_H = 2$, the obtained HCl salt of **6** was crystallized. Yield: 1.0 g (3.369 mmoles, 74.0 %); mp 122-127 °C. ^{1}H-NMR (see Figure 5) (300 MHz, DMSO, 30°C): sum of protonated epimers: δ 0.88-1.13 (m, 1H, CH); 1.10-1.67 (m, 7H, CH); 1.82-1.95 (m, 1H, CH); 2.09-2.19 (m, 1H, CH); 2.28-2.37 (m, 1H, CH); 2.40-2.49 (m, 1H, CH); 2.84-3.19 (m, 3H, CH); 3.50-3.56 (m, 1H, CH); 6.64 (dd, 1H, J=8.4 and 2.4 Hz, Ar); 6.71 (d, 1H, J=2.4 Hz, Ar); 7.00 (d, 1H, J=8.4 Hz, Ar); 9.22 (s, br, 1H, -OH); 10.69 and 10.71 (s, 1H, NH^+); MS: EI *m/e* 260 (M_1^+,100.0%), 257 (M_2^+, ~2-3%); GC-MS: 97.3 %; HPLC: 99.5 % (220 nm); isotopic enrichment 97 atom % D.

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