

## SYNTHESIS OF D<sub>3</sub>-SULPIRIDE AND ITS (R) AND (S) ISOMERS

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### SUMMARY

Racemic d<sub>3</sub>-sulpiride, (R)-(+)-d<sub>3</sub>-sulpiride and (S)-(-)-d<sub>3</sub>-sulpiride (with three deuterium atoms in the methoxy function ortho to the benzamide), as well as (R)-(+)-sulpiride and (S)-(-)-sulpiride were synthesized. The structures were characterized by melting points, IR, <sup>1</sup>H-NMR, GC-MS and polarimetry. The measured  $[\alpha]_D^{20}$  was 65° in 5% DMF.

**KEYWORDS** : benzamide, labelled compound, stable isotope, deuterium, sulpiride, 5-(aminosulfonyl)-N-[(1-ethyl-2-pyrrolidinyl) methyl]-2-methoxybenzamide, (R)-(+) isomer, (S)-(-) isomer.

### INTRODUCTION

Sulpiride, 5-(aminosulfonyl)-N-[(1-ethyl-2-pyrrolidinyl)methyl]-2-methoxy benzamide, is a potent, well known and widely prescribed neuroleptic [1,2]. It is a member of the orthomethoxybenzamide (o-anisamide) series known to possess antagonist activity at the dopaminergic receptor [3]. To date the racemate has always been prescribed in therapy, but it is now known, that the (S)-(-) isomer of sulpiride possesses greater anti-dopaminergic activity [4].

A recently published article [5] suggested the utilization of the isomers separately when differences in the pharmacokinetic parameters of more than five-fold between enantiomers is observed.

The overall objective of our study is to determine the influence of each isomer on the other in pharmacokinetics and metabolic transformations both in animals and man. That is, to investigate the existence of any possible advantages in separate administration of the (R)-(+)- or (S)-(-)- isomers of sulpiride.

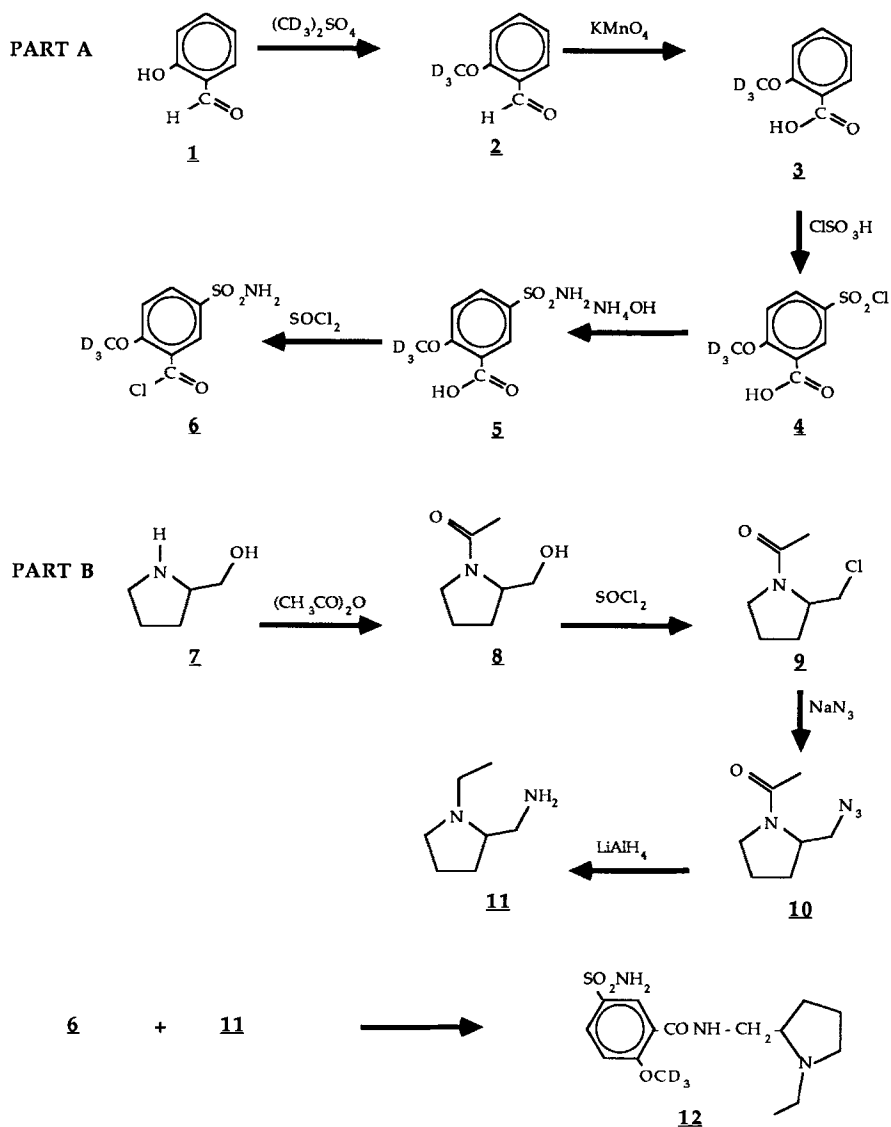
To accomplish this project it was necessary to have sufficient quantities of the purified isomers. We envisaged reconstitution of the racemate by mixing (R)-(+)-sulpiride with (S)-(-)-d<sub>3</sub>-sulpiride and (S)-(-)-sulpiride with (R)-(+)-d<sub>3</sub>-sulpiride. In addition, the stable isotope analogs will allow determination of the pharmacokinetics and the metabolism of each isomer separately [ (R)-(+)- or (S)-(-)- ], since these analogs could be used as internal standards for each other in the analytical procedure.

The traditional method of separating optical isomers starting from the racemate is to use optically active salts. This method has already been reported in the literature [6] using pyroglutamic acid and tartaric acid. Unfortunately, the application of this method gave very low yields in our hands, such that we were forced to separately synthesize the (R)-(+)- and (S)-(-)- isomers of both sulpiride and d<sub>3</sub>-sulpiride.

Syntheses of sulpiride radioactively labelled with <sup>14</sup>C at the carbonyl position [7], with <sup>3</sup>H in the aromatic ring [8], and with <sup>3</sup>H in the pyrrolidine moiety [9] have been previously reported. We required a stable isotope labelled analog since our ultimate intention involved administration of the labelled racemates in man. Administration of radioactive substances in man for non-therapeutic purposes is forbidden in France and many other countries.

O-demethylation of sulpiride's methoxy group is a known minor metabolic pathway in rats. There are no metabolites of sulpiride in man though it has been the object of several published investigations [10,11].

In the present paper we report the original syntheses of racemic d<sub>3</sub>-sulpiride, (R)-(+)-d<sub>3</sub>-sulpiride and (S)-(-)-d<sub>3</sub>-sulpiride and a new synthetic route to the previously reported substances (R)-(+)-sulpiride and (S)-(-)-sulpiride as shown in Fig. 1.

**Figure 1** : Synthetic Scheme for the Synthesis of d<sub>3</sub>-Sulpiride and Its Enantiomers**DISCUSSION**

We synthesized the five products: racemic d<sub>3</sub>-sulpiride, (R)-(+)-sulpiride, (S)-(-)-sulpiride, (R)-(+)-d<sub>3</sub>-sulpiride and (S)-(-)-d<sub>3</sub>-sulpiride, obtaining similar

yields when using either the commercial 1-ethyl-2-(aminomethyl)-pyrrolidine or the separately synthesized (R)-(+) and (S)-(-) isomers.

The first part of the synthesis, preparation of the substituted aromatic nucleus, was identical for the deuterated and non-deuterated except that the synthesis of the non-deuterated substances starts directly from commercially available *o*-methoxybenzoic acid. The deuterated substances start from *o*-hydroxybenzaldehyde which is trideuteromethylated by  $d_6$ -dimethyl sulfate and oxidized to *o*-trideuteromethoxybenzoic acid.

The second part of the synthesis was identical for all optically pure products. Starting from the commercially available (R)-(-)-pyrrolidinemethanol and (S)-(+)-pyrrolidinemethanol we easily acetylated the secondary amine to an amide using acetic anhydride, transformed the alcohol to a chloride using thionyl chloride and transformed the chloride to the azide using sodium azide. Care must be taken during reduction using lithium aluminum hydride not to exceed 50°C since the product of the reaction has a boiling point of 58°C. Racemic  $d_3$ -sulpiride was synthesized directly from the commercially available racemic 1-ethyl-2-(aminomethyl)-pyrrolidine (**11**).

We noted a change in the polarization of the successive intermediates during the syntheses. Starting from the (+) - pyrrolidinemethanol we obtained the (-) primary amine.

The enantiomers and the racemic mixture, identified by GC/MS, Fig. 2 and 3, yielded the same isotopic purity of 99.6% .

The measured  $[\alpha]_D^{20}$  was  $\pm 65^\circ$  in 5% DMF which corresponds to the literature value [6].

## EXPERIMENTAL

All the reagents and solvents used were either of synthetic or analytical grade and were purchased either from the Merck Chemical Company or the Aldrich Chemical Company. Sulpiride reference material was a kind gift from Laboratoires Delagrangre (Paris) .

All melting points were uncorrected and obtained using a Mettler Model FP61 apparatus. All IR spectra were obtained using a Beckman Model IR 4230 Infrared spectrophotometer. All  $^1\text{H-NMR}$  spectra were recorded using a Bruker Model AC200 Magnetic Resonance Spectrometer. Mass Spectra were obtained using a

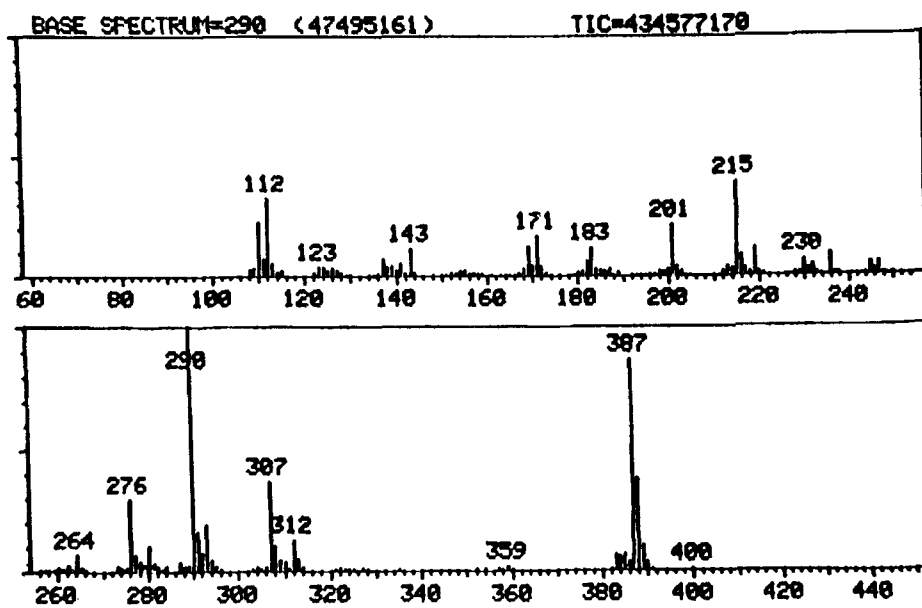


Figure 2 : GC-MS/CI(NH<sub>3</sub>) Spectrum of Trimethyl d<sub>3</sub>-Sulpiride after the Action of Trimethyl Anilinium Hydroxide.

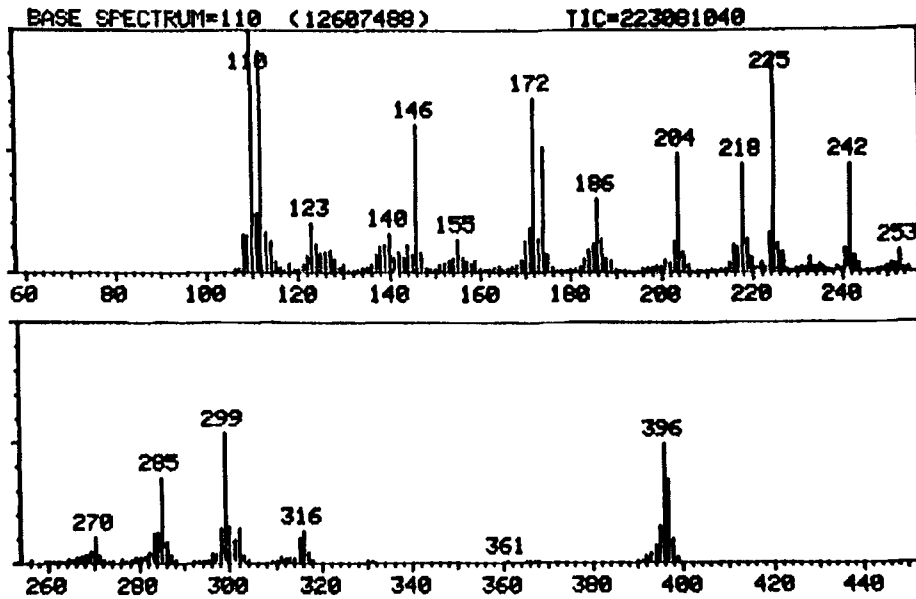


Figure 3 : GC-MS/CI(NH<sub>3</sub>) Spectrum of Nonadeuterotrimethyl d<sub>3</sub>-Sulpiride after the Action of Nonadeuterotrimethyl Anilinium Hydroxide.

Nermag Model R10-10B Quadrupole Mass Spectrometer. TLC plates were of Kieselgel 60F254 from the Merck Chemical Company.

#### A. 2-Trideuteromethoxy-5-(aminosulfonyl)-benzoylchloride (6)

##### 2-Trideuteromethoxybenzaldehyde (2)

A solution of salicylic aldehyde (**1**) (12.20 g, 0.10 moles) in acetone (100 ml) was treated with potassium carbonate (40 g, 0.30 moles) and  $d_3$ -dimethyl sulphate (11.50 ml, 0.11 moles) and the mixture heated under reflux for 5 hours. The mixture was then filtered, washed, and the organic phase was evaporated under reduced pressure. The residue was redissolved in chloroform and alkalinized by 0.1 N sodium hydroxide. This aqueous phase was extracted three times with chloroform, and the organic phases containing (**2**) were dried over anhydrous magnesium sulphate. After evaporation of the chloroform under reduced pressure the product (**2**) was recrystallized from hexane to yield (**2**) (10.44 g, 0.075 moles, 78.5 %) m.p. = 36-38°C. The IR spectrum showed absorptions at 3160  $cm^{-1}$  (C-H aromatic), 2880 and 2780  $cm^{-1}$  (CHO), 2270, 2240, 2180, 2130 and 2075  $cm^{-1}$  ( $OCD_3$ ), 1690  $cm^{-1}$  (C=O) and 1600  $cm^{-1}$  (C=C aromatic). The  $^1H$ -NMR spectrum (in  $CDCl_3$ ) showed signals at 10.55 (singlet, 1H, CHO), 7.85 ppm (multiplet, 1H, aromatic proton), 7.60 ppm (multiplet, 1H, aromatic proton) and 7.40 to 6.10 ppm (multiplet, 2H, aromatic protons).

##### 2-Trideuteromethoxybenzoic acid (3)

The aldehyde (**2**) (9.95 g, 0.07 moles) was dissolved in 10% sodium hydroxide (5.40 ml, 0.13 moles) and potassium permanganate (44 g, 0.28 moles) was added. The mixture was heated at 80°C for 15 minutes and immediately filtered and washed with water. After cooling at 20°C the filtrate was acidified by sulphuric acid, the precipitate was filtered, washed with water and dried to yield the acid (**3**) (8.50 g, 0.055 moles, 65%) m.p. = 106°C. The IR spectrum showed absorptions at 3400 to 3200  $cm^{-1}$  (OH acid), 2270, 2240, 2180, 2130 and 2075  $cm^{-1}$  ( $OCD_3$ ), 1730  $cm^{-1}$  (C=O acid) and 1600  $cm^{-1}$  (C=C aromatic). The  $^1H$ -NMR spectrum (in  $CDCl_3$ ) showed signals at 9.80 ppm (singlet, 1H, COOH), 9.20 ppm (multiplet, 1H, aromatic

proton), 7.60 ppm (multiplet, 1H, aromatic proton) and 7.30 to 6.90 ppm (multiplet, 2H, aromatic protons).

#### 2-Trideuteromethoxy-5-chlorosulfonylbenzoic acid (4)

The acid **(3)** (8.00 g, 0.05 moles) was added to cold ( 0°C ) chlorosulphonic acid (86 ml ,1.29 moles) .The mixture was heated at 60°C for 30 minutes, cooled and hydrolyzed by dropwise addition onto ice chips. The precipated product **(4)** was filtered, washed with water and thoroughly dried to yield **(4)** (9.42 g, 0.04 moles, 72% ) m.p. = 178°C. The IR spectrum showed absorptions at 3100 to 2800 cm<sup>-1</sup> (OH acid), 2270, 2240, 2180, 2130, 2075 cm<sup>-1</sup>(OCD<sub>3</sub>), 1710 cm<sup>-1</sup> (C=O acid), 1600 cm<sup>-1</sup> (C=C aromatic), 1370 and 1170 cm<sup>-1</sup> (SO<sub>2</sub>). The <sup>1</sup>H-NMR spectrum (in CDCl<sub>3</sub>) showed signals at 7.30 ppm (singlet, 1H, COOH), 7.00 ppm (multiplet, 1H, aromatic proton), 6.90 ppm (multiplet, 1H, aromatic proton) and 6.70 ppm (doublet, 1H, aromatic proton).

#### 2-Trideuteromethoxy-5-(aminosulfonyl)-benzoic acid (5)

The product **(4)** ( 8.50 g ,0.03 moles) from the previous reaction was added to cold ammonium hydroxide solution (38 ml , 0.05 moles , 28 % ) with stirring. The reaction mixture was acidified by 1N hydrochloric acid , and the product which precipitated was filtered, washed with water and dried to yield **(5)** (6.99 g, 0.03 moles , 89%) m.p. =220°C. The IR spectrum showed absorptions at 3360 to 3260 cm<sup>-1</sup> (NH<sub>2</sub>), 3100 to 2800 cm<sup>-1</sup> (OH acid), 2270, 2240, 2180, 2130 and 2075 cm<sup>-1</sup> (OCD<sub>3</sub>), 1710 cm<sup>-1</sup> (C=O acid), 1600 cm<sup>-1</sup> (C=C aromatic), 1330 and 1160 cm<sup>-1</sup> (SO<sub>2</sub>). The <sup>1</sup>H-NMR spectrum (in CDCl<sub>3</sub>) showed signals at 8.40 ppm (doublet, 1H, aromatic proton), 8.05 ppm (double doublet, 1H, aromatic proton), 7.10 (doublet, 1H, aromatic proton) and 6.30 ppm (singlet, 2H, NH<sub>2</sub>) .

#### 2-Trideuteromethoxy-5-(aminosulfonyl)-benzoyl chloride (6)

The product **(5)** (6.00 g, 0.03 moles ) was added in small portions to a cooled solution of thionyl chloride (93 ml ,1.28 moles) and the mixture was stirred for one hour at room temperature in a closed flask .

A few drops of dimethylformamide were added and the mixture was heated for two hours at 41°C. After cooling to 20°C the mixture was stirred for 12 hours,

the product which precipitated was filtered, washed with toluene and thoroughly dried to yield **(6)** (5.38 g ,0.02 moles , 82% ) m.p. = 150°C. The IR spectrum showed absorptions at 3310 and 3240  $\text{cm}^{-1}$  ( $\text{NH}_2$ ), 2270, 2240, 2180, 2130 and 2075  $\text{cm}^{-1}$  ( $\text{OCD}_3$ ), 1765  $\text{cm}^{-1}$  ( $\text{C}=\text{O}$ ), 1600  $\text{cm}^{-1}$  ( $\text{C}=\text{C}$  aromatic), 1330 and 1160  $\text{cm}^{-1}$  ( $\text{SO}_2$ ). The  $^1\text{H-NMR}$  spectrum (in  $\text{CDCl}_3$ ) showed signals at 8.40 ppm (doublet, 1H, aromatic proton), 8.05 ppm (double doublet, 1H, aromatic proton), 7.10 ppm (doublet, 1H, aromatic proton) and 6.30 ppm (singlet, 2H,  $\text{NH}_2$ ) .

**B. 1-Ethyl-2-(aminomethyl)-pyrrolidine [ R-(+) or S(-) ] (11)**

**1-Acetyl 2 - (hydroxymethyl)-pyrrolidine [R-(+) or S(-)] (8)**

2-(Hydroxymethyl)-pyrrolidine [ R(-) or S(+)] **(7)** ( 10.15 g , 0.10 moles) were dissolved in 100 ml methanol and acetic anhydride (9.50 ml , 0.10 moles) were added drop by drop with stirring. The mixture was heated at reflux for 6 hrs and after evaporation of the methanol under reduced pressure the residue was dissolved in chloroform and made alkaline with sodium carbonate. The mixture was then filtered, washed and the organic phase was dried over anhydrous magnesium sulphate, filtered and the chloroform evaporated to yield **(8)** [R-(+) or S(-)] ( 11.45 g , 0.08 moles , 80% ) .The IR spectrum showed absorptions at 3500 and 3200  $\text{cm}^{-1}$  (OH alcoholic), 2940 and 2880  $\text{cm}^{-1}$  (CH alkane) and 1620  $\text{cm}^{-1}$  ( $\text{C}=\text{O}$  amide). The  $^1\text{H-NMR}$  spectrum (in  $\text{CDCl}_3$ ) showed signals at 3.17 ppm (quintuplet, 1H,  $\text{H}_7$ ), 2.51 ppm (multiplet, 2H,  $\text{H}_1$ ,  $\text{H}_2$ ), 1.75 ppm (multiplet, 5H,  $\text{H}_3$ ,  $\text{H}_4$ ,  $\text{H}_5$ ,  $\text{H}_6$ , OH) and 1.10 ppm (singlet, 3H,  $\text{CH}_3$ ).

**1-Acetyl 2 - ( chloromethyl) - pyrrolidine [R-(+) or S(-)] (9)**

Thionyl chloride ( 56 ml , 0.77 moles) was added dropwise to a cooled solution of **(8)** [R-(+) or S(-)] (11,00 g ,0.08 moles) in chloroform (50 ml) containing pyridine (2 drops) . The mixture was then stirred for 4 hours at room temperature in a closed flask. After evaporation, and crystallisation from diisopropylether the product **(9)** [R-(+) or S(-)] (10.21 g, 0.06 moles, 82% ) was obtained. The IR spectrum showed absorptions at 2940 and 2880  $\text{cm}^{-1}$  (CH alkane) and 1630  $\text{cm}^{-1}$  ( $\text{C}=\text{O}$  amide). The  $^1\text{H-NMR}$  spectrum (in  $\text{CDCl}_3$ ) showed signals at 3.17 ppm



(quintuplet, 1H, H<sub>7</sub>), 2.51 ppm (multiplet, 2H, H<sub>1</sub>, H<sub>2</sub>), 1.75 ppm (multiplet, 4H, H<sub>3</sub>, H<sub>4</sub>, H<sub>5</sub>, H<sub>6</sub>,) and 1.10 ppm (singlet, 3H, CH<sub>3</sub>).

1-Acetyl 2- (azidomethyl) - pyrrolidine [R(-) or S(+)] (10)

Potassium iodid (0.97 g 0.01 moles) and sodium azide (7.60 g, 0.12 moles) were added to **(9)** [R-(+) or S(-)] (9.50 g, 0.06 moles) dissolved in DMF (95 ml) and the mixture heated at 110°C for 8 hours. The solvent was evaporated and the residue was dissolved in chloroform and the mixture was filtered, washed, dried (MgSO<sub>4</sub>) and the organic phase evaporated to yield the desired product **(10)** (7.44 g, 0.04 moles, 75%) . The IR spectrum showed absorptions at 2940 and 2880 cm<sup>-1</sup> (CH alkane), 2100 cm<sup>-1</sup> (N<sub>3</sub>) and 1630 cm<sup>-1</sup> (C=O amide). The <sup>1</sup>H-NMR spectrum (in CDCl<sub>3</sub>) showed signals at 3.17 ppm (quintuplet, 1H, H<sub>7</sub>), 2.51 ppm (multiplet, 2H, H<sub>1</sub>, H<sub>2</sub>), 1.75 ppm (multiplet, 4H, H<sub>3</sub>, H<sub>4</sub>, H<sub>5</sub>, H<sub>6</sub>) and 1.10 ppm (singlet, 3H, CH<sub>3</sub>).

1-Ethyl-2-(aminomethyl)-pyrrolidine [R-(+) or S(-)] (11)

The product **(10)** (7.00 g , 0.04 moles) was added to a cooled solution of lithium aluminium hydride (11.25 g , 0.03 moles) in tetrahydrofuran (80ml) and the mixture was heated at reflux for 16 hours and then cooled to 0°C. Water (11.25 ml a 15% aqueous solution of sodium hydroxide ( 11.25 g ) was carefully added followed by the dropwise addition of water (34 ml ) with stirring. The mixture was then filtered, washed, and the organic phase was dried over MgSO<sub>4</sub>, and the THF was evaporated . The residue was distilled to yield the product **(11)** [R-(+) or S(-)] (3.50 g, 0.03 moles, 65% ). The IR spectrum showed absorptions at 3380 and 3200 cm<sup>-1</sup> (NH<sub>2</sub>) and 2940 and 2860 cm<sup>-1</sup> (CH alkane). The <sup>1</sup>H-NMR spectrum (in CDCl<sub>3</sub>) showed signals at 3.17 ppm (quintuplet, 1H, H<sub>7</sub>), 2.70 ppm (multiplet, 3H, CH<sub>2</sub>NH<sub>2</sub>, H<sub>1</sub>), 2.30 ppm (multiplet, 3H, CH<sub>2</sub>CH<sub>3</sub>, H<sub>2</sub>), 1.71 ppm (multiplet, 4H, H<sub>3</sub>, H<sub>4</sub>, H<sub>5</sub>, H<sub>6</sub>), 1.55 ppm (singlet, 2H, NH<sub>2</sub>) and 1.10 ppm (triplet, 3H, CH<sub>3</sub>).

5-(Aminosulfonyl)-N-[(1-ethyl-2-pyrrolidinyl) methyl]-2-trideuteromethoxy benzamide [ Racemic, R-(+) or S-(-)] (12)

The amine **(11)** [ Racemic, R-(+) or S-(-) ] ( 2.54 g, 0.02 moles ) was dissolved in acetone and potassium carbonate ( 2.82 g, 0.02 moles) was added. The mixture was cooled to 0°C and the acid chloride **(6)** (5.00 g, 0.02 moles) added. The mixture was stirred for 2 hours at room temperature and then the acetone was evaporated and the residue redissolved in CHCl<sub>3</sub>/H<sub>2</sub>O. The organic phase was dried over MgSO<sub>4</sub>, filtered and evaporated. The product was recrystallized from diisopropylether/ethanol (50/50) to yield **(12)** [ Racemic, R-(+) or S-(-)] (2.06 g, 0.01 moles, 75%) m.p. = 179-180°C. The IR spectrum showed absorptions at 3370 cm<sup>-1</sup> (NH amide), 3280 and 3110 cm<sup>-1</sup> (NH<sub>2</sub>), 2270,2240, 2180, 2130 and 2075 cm<sup>-1</sup> (OCD<sub>3</sub>), 1620 cm<sup>-1</sup> (C = O amide), 1590 cm<sup>-1</sup> (C = C aromatic), 1330 and 1160 cm<sup>-1</sup> (SO<sub>2</sub>). The <sup>1</sup>H-NMR spectrum (in CDCl<sub>3</sub>) showed signals at 8.65 ppm (doublet, 1H, H<sub>1</sub>), 8.50 to 8.30 ppm (multiplet, 1H, NH), 8.00 ppm (double doublet, 1H, H<sub>2</sub>), 7.10 ppm (doublet, 1H, H<sub>3</sub>), 5.80 ppm (multiplet, 2H, NH<sub>2</sub>), 2.80 to 2.70 ppm (multiplet, 4H, H<sub>13</sub>, H<sub>14</sub>, H<sub>15</sub>, H<sub>16</sub>) and 1.15 ppm (triplet, 3H, H<sub>8</sub>, H<sub>9</sub>, H<sub>10</sub>).

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