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THE SYNTHESIS OF ^{13}C LABELLED N,N'-DIMETHYL 2-NAPHTHALENEETHANIMIDAMIDE MONOHYDROCHLORIDE, A POTENTIAL PSYCHOTHERAPEUTIC AGENT

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SUMMARY

N,N'-Dimethyl 2-naphthaleneethanimidamide monohydrochloride (DL-588) is a potential psychotherapeutic agent for which a sample of carbon-13 labelled material was required for metabolism studies. The sample of 90% ^{13}C enriched DL-588 was prepared starting with 90% ^{13}C enriched potassium cyanide in three steps. 2-(Bromomethyl)naphthalene was treated with the ^{13}C potassium cyanide under phase transfer catalysis. The resulting ^{13}C-2-napthylacetonitrile was converted to the imidate ester hydrochloride under Pinner reaction conditions (1). This intermediate was treated with excess methylamine in ethanol at 55° to give the title compound in an overall yield of 68%. The effects of ^{13}C labelling on the ^{1}H NMR spectra of the final product and intermediates are discussed.

Keywords: N,N'-Dimethyl 2-naphthaleneethanimidamide monohydrochloride, Carbon-13 labeling, ^{1}H-^{13}C NMR coupling constants

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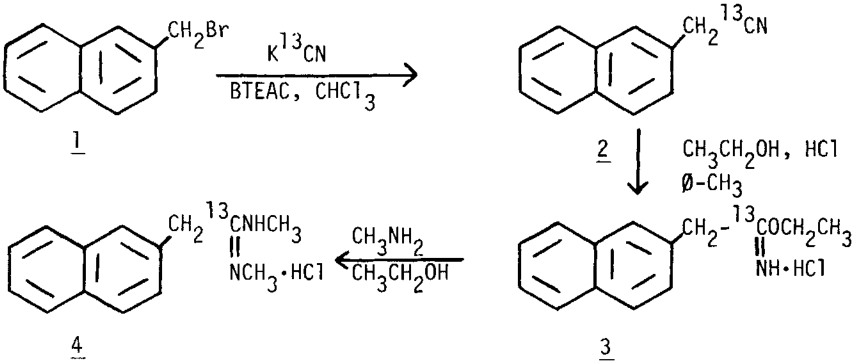
N,N'-Dimethyl 2-naphthaleneethanimidamide monohydrochloride (DL-588) is a new nontricyclic potential antidepressant agent (2,3) which is currently undergoing clinical evaluation. In conjunction with a program to study the metabolism of DL-588, a sample of ^{13}C-labelled material was required. The sequence used for the preparation of ^{13}C-labelled DL-588 (4) is outlined below.

Synthetic Scheme:



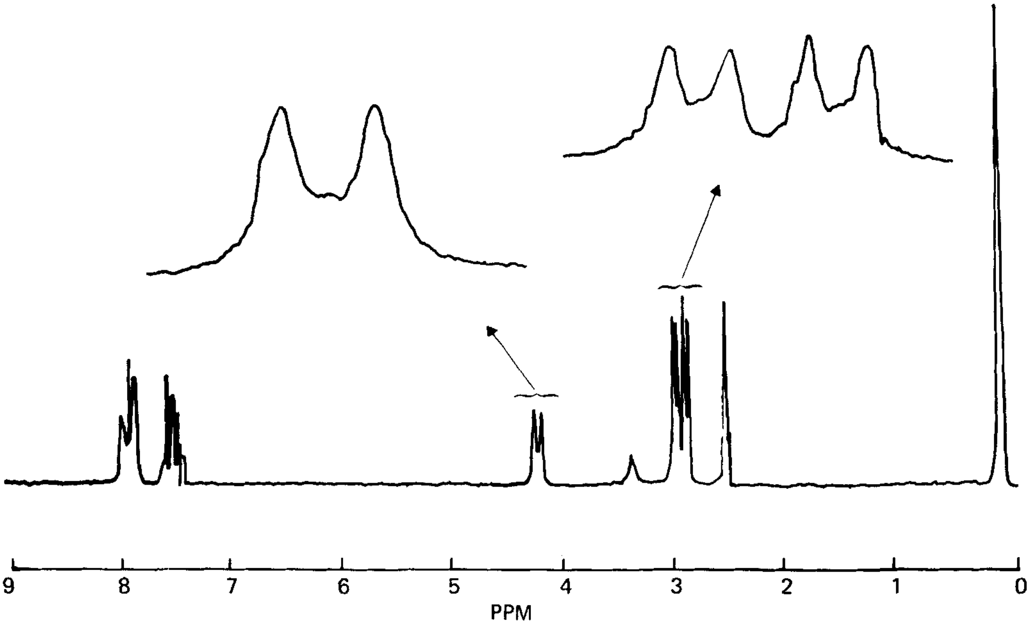
Treatment of a chloroform solution of 2-(bromomethyl)naphthalene (1) with an aqueous solution of 90% ^{13}C-enriched potassium cyanide in the presence of benzyltriethylammonium chloride (BTEAC) afforded ^{13}C-labelled 2-naphthylacetonitrile (2) in 90% yield. The infrared spectrum (KBr) of 2 displayed a sharp peak at 2197 cm^{-1} for the stretching vibration of the ^{13}C≡N group and a sharp peak at 2254 cm^{-1} for the stretching vibration of the ^{12}C=N group in an area ratio of 10:1, respectively. The ^{1}H 100 MHz NMR spectrum (CDCl$_3$) of 2 showed a coupling between the

^{13}C and the protons of the adjacent methylene group of 10.4 Hz. Careful integratiion of a 50 Hz sweep width detail of the methylene signals indicated a ^{13}C-enrichment of 89.5%.

The reaction of 2 with anhydrous ethanol and anhydrous hydrogen chloride in toluene gave ^{13}C-labelled ethyl 2-naphthaleneethanimidate hydrochloride (3) in 89% yield. The infrared spectrum (KBr) of 3 displayed a strong band at 1619 cm^{-1} for the stretching vibration of the ^{13}C=N bond (the stretching vibration of the ^{12}C=N bond is 1627 cm^{-1}). The ^{1}H 100 MHz NMR spectrum (DMSO-d_6) of 3 showed a coupling between the ^{13}C and the protons of the adjacent methylene group of 6.8 ± 0.2 Hz. The ^{13}C was also observed to couple with the methylene protons of the ethyl group with a coupling constant of 2.5 ± 0.2 Hz.

In the final step, 3 was treated with an excess of methylamine in absolute ethanol at 55°C to give ^{13}C-DL-588 (4) in 85% yield. The infrared spectrum (KBr) of 4 displayed a strong band at 1637 cm^{-1} for the stretching vibration of ^{13}C=N bond (the stretching vibration of the ^{12}C=N bond is 1659 cm^{-1}). The ^{1}H 100 MHz NMR spectrum (DMSO-d_6) of ^{13}C-DL-588 (4) is shown in Figure 1. The ^{13}C is observed to couple with the protons of the adjacent methylene group with a coupling constant of 6.3 ± 0.2 Hz. The ^{13}C is also coupled to the protons of both of the N-methyl groups with coupling constants of 4.0 ± 0.2 Hz for the upfield methyl signal and 4.1 ± 0.2 Hz for the downfield methyl signal.

Figure 1
100 MHz PMR Spectrum (DMSO-d_6) of ^{13}C-DL-588-US (4) with 50 Hz sweep width detail of the methylene group and the methyl groups



EXPERIMENTAL

Capillary melting points are corrected. The infrared spectra were determined as KBr pellets using a Perkin Elmer 180 infrared spectrometer. The nuclear magnetic resonance spectra were determined using a Varian XL-100 spectrometer. The elemental analyses were performed by the Michigan Division Analytical Laboratories.

Carbon-13 Labelled 2-Naphthylacetonitrile (2).

In a 125 ml, three-neck flask equipped with a magnetic stirrer and a reflux condenser were placed 14.5 g (65.6 mmol) of 2-(bromomethyl)-

naphthalene, 3.2 g (14 mmol) of benzyltriethylammonium chloride, and 40 ml of chloroform. A solution of 5.0 g (75.7 mmol) of 90 atom percent carbon-13 labelled potassium cyanide (Merck Sharpe and Dohme Canada Ltd., Montreal, Lot A-1356) in 20 ml of warm water was added to the pale yellow reaction solution and rinsed with and additional 5 ml of water. The reaction mixture was heated at 90°C (bath temperature) for 12 hrs (the progress of the reaction was followed by thin layer chromatography). The organic layer was then separated and washed with three 100 ml portions of water. The organic layer was dried over anhydrous sodium sulfate, and the chloroform removed _in vacuo_ leaving a light tan solid. The solid was dissolved in 700 ml of boiling hexane, and the solution filtered away from a small amount of dark, insoluble material. The light yellow solution was concentrated to 500 ml and cooled slowly to 0°C. The resulting white crystals (8.92 g), mp 83-85°C, were collected by filtration. The filtrate was concentrated to 100 ml and additional white crystals (0.76 g), mp 78-80.5°C were obtained. An additional 0.25 g, mp 80-82°C, was obtained by purifying the filtrate on three 20 x 20 preparative thin layer chromatography plates (2 mm thick, Merck Silica Gel 60 E-254). The plates were developed with chloroform: hexane (1:1) and the slower moving band was the desired product. Total yield of **2**: 9.93 g (90%).

Anal. Calcd for $^{12}C_{11.1}\ ^{13}C_{0.9}H_9N$: C, 86.28; H, 5.39; N, 8.33. Found: C, 86.3; H, 5.57; N, 8.19.

Carbon-13 Labelled Ethyl 2-Naphthaleneethanimidate Hydrochloride (3).

In a 100 ml, three-neck flask equipped with a magnetic stirrer, a thermometer, a gas inlet tube, and a reflux condenser fitted with a drying tube were placed 9.13 g (0.0546 mol) of carbon-13 2-naphthylacetonitrile and 34 ml toluene. To the above mixture 3.0 g (0.065 mol) of absolute ethanol was added. The reaction mixture was then cooled to 0°C, and anhydrous hydrogen chloride was sparged in until the temperature reached 7°C. A total of 3.3 g (0.090 mol) of hydrogen chloride was sparged in. The reaction mixture was then warmed to 30°C, at which time it became homogeneous. After 1 hr a heavy precipitate began to form. The reaction was then allowed to stir for an additional 16 hrs. The slurry was carefully poured into a sintered glass funnel, and the flask and filter cake washed with 200 ml of fresh toluene. The solid was air-dried and then vacuum dried at 50°C for 2.5 hrs to give 12.10 g (89.5% yield) of 3.*

Anal. Calcd for $^{12}C_{13.1}\,^{13}C_{0.9}ClH_{16}NO$: C, 67.44; H, 6.43; N, 5.59. Found: C, 66.8; H, 6.51; N, 5.78.

Carbon-13 Labelled N,N'-Dimethyl 2-Naphthaleneethanimidamide Monohydrochloride (DL-588, 4).

In a 100 ml, three-neck flask equipped with a magnetic stirrer, a thermometer, a pressure-equalizing addition funnel, and a reflux condenser fitted with a drying tube were placed 11.95 g (0.048 mol) of carbon-13 labelled ethyl 2-naphthaleneethanimidate hydrochloride.

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* A well defined melting point for this compound cannot be obtained because of thermal degradation to give the corresponding amide.

A solution of 21.20 g (0.683 mol) of methylamine in 35 ml of absolute ethanol was then prepared. The solution of methylamine in ethanol was then rapidly added (the temperature quickly rose to 65°C, and then dropped to 30°C as all of the solution was added). The reaction mixture was then heated to 50°C, and controlled at 50-53°C for 21 hrs. The progress of the reaction was monitored by HPLC (Partisil SCX; 9:1 MeOH/0.1N $NaClO_4$; 254 nm). The reaction mixture was then cooled to 2°C, and the white, crystalline product filtered off. The reaction flask and the product cake were washed with 50 ml of toluene. The product was dried at 50°C for 2 hrs to give 10.2 g (85% yield) of 4. This material was recrystallized from 50 ml of absolute ethanol (with hot filtration). The solid was filtered off, and the crystallization flask and product cake were washed with 50 ml of toluene. The product was then air-dried and vacuum dried at 60°C for 6 hrs to give 8.97 g (88% recovery) of 4, mp 225.5-227°C (lit.[3] mp 223.5-224.5°).

Anal. Calcd for $^{12}C_{13.1}\,^{13}C_{0.9}H_{17}ClN_2$: C, 67.7; H, 6.87; N, 11.22. Found: C, 67.40; H, 7.03; N, 11.28.

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