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THE SYNTHESIS OF ^{13}C LABELLED N,N'-DIMETHYL 1-CHLORO-2-NAPHTHALENEETHANIMIDAMIDE MONOHYDROCHLORIDE, A POTENTIAL PSYCHOTHERAPEUTIC AGENT

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SUMMARY

N,N'-Dimethyl 1-chloro-2-naphthaleneethanimidamide monohydrochloride is a potential psychotherapeutic agent for which a sample of carbon-13 labelled material was required for metabolism studies. A sample of 90% enriched N,N'-dimethyl 1-chloro-2-naphthaleneethanimidamide monohydrochloride was prepared from 90% carbon-13 enriched potassium cyanide and 2-methylnaphthalene in five steps. Chlorination of 2-methylnaphthalene with sulfuryl chloride gave 1-chloro-2-methylnaphthalene in 69% yield. Bromination of 1-chloro-2-methylnaphthalene with N-bromosuccinimide in carbon tetrachloride in the presence of catalytic benzoyl peroxide afforded 2-(bromomethyl)-1-chloronaphthalene in 59% yield. Treatment of 2-(bromomethyl)-1-chloronaphthalene with ^{13}C potassium cyanide in aqueous ethanol afforded ^{13}C-1-chloro-2-naphthylacetonitrile in 89% yield. The nitrile was converted to the imidate ester hydrochloride in 89% yield under Pinner reaction conditions (1). This intermediate was treated with excess methylamine in ethanol at 40-55°C to give the title compound in an overall yield of 27% from 2-methylnaphthalene. The effects of the ^{13}C labelling on the infrared and ^{1}H and ^{13}C NMR spectra of the intermediates and the final product are discussed.

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

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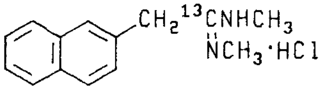
In a previous paper we reported the preparation of ^{13}C-labelled N,N'-dimethyl 2-naphthaleneethanimidamide monohydrochloride (DL-588, 1)(2). As part



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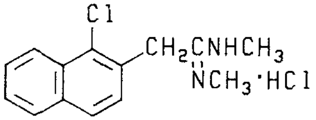
of a study of this novel, nontricyclic antidepressant agent (3,4), the 1-chloro derivative, N,N'-dimethyl 1-chloro-2-naphthaleneethanimidamide monohyrochloride (2), was selected for further evaluation. In conjunction with a program to



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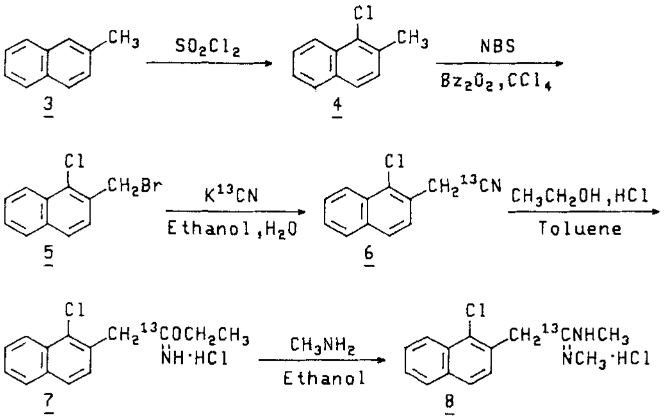
study the metabolism of 2, a sample of ^{13}C-labelled material was required. The sequence of reactions used for the synthesis of ^{13}C-labelled N,N'-dimethyl 1-chloro-2-naphthaleneethanimidamide monohydrochloride (8) is outlined below.

SYNTHETIC SCHEME



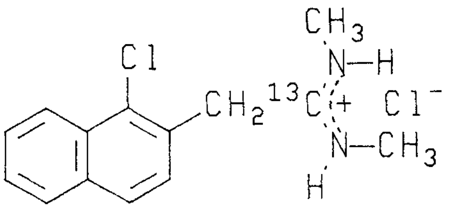
Chlorination of 2-methylnaphthalene (3) with sulfuryl chloride gave 1-chloro-2-methylnaphthalene (4) in 69% yield (5,6). The 15 MHz ^{13}C NMR spectrum ($CDCl_3$) of 4 displayed a signal at 20.64 ppm for the methyl group.

In the second step, 1-chloro-2-methylnaphthalene (4) was brominated with N-bromosuccinimide (NBS) in carbon tetrachloride in the presence of a catalytic amount of benzoyl peroxide to afford 2-(bromomethyl)-1-chloronaphthalene (5) in 59% yield. The infrared spectrum of 5 (10% split in CCl_4 and CS_2 solution) displayed bands at 1210 cm^{-1} (CH_2 wag) and at 589 cm^{-1} (ν_{C-Br}) indicative of the presence of a CH_2Br group attached to a naphthalene ring. The out-of-plane hydrogen deformations which support the indicated ring substitution appear at 813 cm^{-1} and 748 cm^{-1}. The 15 MHz ^{13}C NMR spectrum of 5 displayed a signal at 31.32 ppm for the methylene group.

Treatment of an ethanol solution of 2-(bromomethyl)-1-chloronaphthalene (5) with an aqueous solution of 90% ^{13}C-enriched potassium cyanide followed by a four hour period of reflux afforded ^{13}C-labelled 1-chloro-2-naphthylacetonitrile (6) in 89% yield. The infrared spectrum (KBr) of 6 displayed a strong, sharp peak at 2198 cm^{-1} for the stretching vibration of the $^{13}C{\equiv}N$ group and a sharp peak at 2252 cm^{-1} for the stretching vibration of the $^{12}C{\equiv}N$ group. From the absorbance at these two frequencies, the percent carbon-13 enrichment was calculated to be 90.3%. In addition, infrared bands at 800 cm^{-1} and 770 cm^{-1}, resulting from out-of-plane bending modes, confirmed the substitution of the naphthalene ring in the 2-position. The 100 MHz ^{13}C NMR spectrum ($CDCl_3$) of 6 displayed a coupling between the ^{13}C and the protons of the adjacent methylene group of 10.7 ± 0.2 Hz. Integration of this doublet with respect to the singlet observed for the ^{12}C compound indicated a carbon-13 enrichment of 90.2%. The 15 MHz ^{13}C NMR spectrum ($CDCl_3$) of 6 displayed a coupling between the ^{13}C and the methylene carbon with a ^{13}C-C coupling constant of 59 ± 2 Hz.

The reaction of 6 with anhydrous ethanol and anhydrous hydrogen chloride in toluene gave ^{13}C-labelled ethyl 1-chloro-2-naphthaleneethanimidate hydrochloride (7) in 89% yield. The infrared spectrum (KBr) of 7 displayed a strong band at 1639 cm^{-1} for the stretching vibration of the $^{13}C{=}N$ bond. The 100 MHz ^{1}H NMR spectrum (DMSO-d_6) of 7 displayed a coupling between the ^{13}C and the protons of the adjacent methylene group of 7.2 ± 0.3 Hz. The ^{13}C was also observed to couple with the methylene protons of the ethyl group with a coupling constant of 2.7 ± 0.5 Hz. The 15 MHz ^{13}C NMR spectrum of 7 displayed a coupling between the ^{13}C and the methylene carbon with a ^{13}C-C coupling constant of 50.8 ± 2 Hz. The ^{13}C was also observed to couple with the methylene carbon of the ethyl group with a coupling constant of 3.9 ± 1 Hz and the methyl carbon of the ethyl group with a coupling constant of 2.9 ± 1 Hz.

In the final step, 7 was treated with a large excess of anhydrous methylamine in absolute ethanol at 40-55°C to give carbon-13 labelled N,N'-dimethyl 1-chloro-2-naphthaleneethanimidamide monohydrochloride (8) in 85% yield. The infrared spectrum (KBr) of 8 displayed a strong, sharp peak at 1630 cm^{-1} for the stretching vibration of the $^{13}C{=}N$ bond and a sharp peak at 1661 cm^{-1} for the stretching vibration of the $^{12}C{=}N$ bond. From the absorbance at these two frequencies, the percent carbon-13 enrichment was calculated to be 90.1%. The 90 MHz ^{1}H NMR spectrum (methanol-d_4) of 8 displayed a coupling of the ^{13}C with the protons of the adjacent methylene group with a coupling constant of 6.8 ± 0.3 Hz and with both the upfield and downfield methyl groups with a coupling constant of 3.8 • 0.3 Hz. These spectral data suggest that in solution 8 exists as the structure depicted in 9, which is in agreement with the solution structure proposed by Newman, et. al. (7) for amidinium salt 10. The 15 MHz ^{13}C NMR spectrum (methanol-d_4) of 8 showed coupling between the ^{13}C and the adjacent methylene carbon with a ^{13}C-C coupling constant of 46.9 • 2 Hz.



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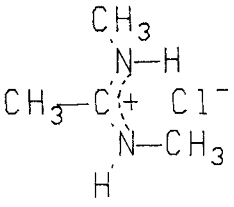

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The ^{13}C was also observed to couple with both of the methyl groups with a coupling constant ≤2 Hz.

EXPERIMENTAL

Capillary melting points are corrected. The infrared spectra were determined using a Perkin Elmer infrared spectrometer. The ^{1}H nuclear magnetic resonance spectra were determined using a Varian XL-100 spectrometer. The ^{13}C nuclear magnetic resonance spectra were determined using a JEOL FX spectrometer. The elemental analyses were performed by Steve Konopnicki of the Analytical Laboratory, Michigan Applied Science and Technology Laboratories.

1-Chloro-2-methylnaphthalene (4).

A 5 liter, three-neck flask equipped with a mechanical stirrer, a reflux condenser fitted with a a drying tube vented to a counter-current scrubber, and a Claisen adapter fitted with a thermometer and an addition funnel was charged with 504.0 g (3.54 mol) of 2-methylnaphthalene (Note: the 2-methylnaphthalene had been previously melted). To this, 300 ml of sulfuryl chloride (technical) was added dropwise over a period of 1 hour. Occassional ice-bath cooling was used to keep the reaction temperature between 20-45°C. After the addition was complete, the reaction mixture was allowed to stir at ambient temperature over night. The reaction was quenched by pouring it over crushed ice. The resulting mixture was diluted with 200 ml of methylene chloride and the layers allowed to separate. The organic layer was drained off and washed with a solution of 130 ml of 20% sodium hydroxide in 250 ml of water. An additional 500 ml of methylene chloride were added to the organic layer. The organic layer was washed with 500 ml water and dried over anhydrous sodium sulfate. In a similar fashion, an additional 2,517.0 g of 2-methylnaphthalene were chlorinated. The methylene chloride layers from these reactions were combined, and the methylene chloride removed in vacuo leaving 3,631.0 g (96.8% yield) of crude 1-chloro-2-methylnaphthalene. This material was distilled through a 2 inch, 15 plate Oldershaw column to give 2,593.0 g (69% yield) of 1-chloro-2-methylnaphthalene, bp 79-82°C/0.5 mm.

Analysis. Calc'd for $C_{11}H_9Cl$: C, 74.79; H, 5.14. Found: C, 74.75; H, 5.19.

2-(Bromomethyl)-1-chloronaphthalene (5).

A 5 liter, three-neck flask equipped with a mechanical stirrer, a thermometer, and a reflux condenser fitted with a drying tube was charged with 530.0 g (3.00 mol) of 1-chloro-2-methylnaphthalene (4), 2,250 ml of carbon tetrachloride, and 540.0 g (3.00 mol) of N-bromosuccinimide. To this mixture, 1.0 g of benzoyl peroxide was added, and the mixture heated to reflux with good agitation. The reaction was stirred at reflux for 19 hours. The reaction mixture was then cooled slowly to room temperature and then cooled to approximately 15°C with an ice-bath. The succinimide was filtered off and washed with carbon tetrachloride. The carbon tetrachloride was removed in vacuo from the combined filtrates leaving a pale yellow solid. The solid was recrystallized, with hot filtration, from 1,200 ml of absolute ethanol. The resulting white crystals were separated by filtration, air-dried, washed with 300 ml of ice-cold, absolute ethanol, air-dried, and vacuum dried at 50°C to give 450.0 g (59% yield) of 2-(bromomethyl)-1-chloronaphthalene, mp 82-83.5°C.

Analysis. Calc'd for $C_{11}H_8BrCl$: C, 51.70; H, 3.15. Found: C, 51.80; H, 3.29.

Carbon-13 Labelled 1-Chloro-2-naphthylacetonitrile (6).

A 250 ml, three-neck flask equipped with a magnetic stirrer, a reflux condenser, a pressure-equalizing addition funnel, and a thermometer was charged with 17.3 g (0.0677 mol) of 2-(bromomethyl)-1-chloronaphthalene and 100 ml of absolute ethanol. The resulting solution was heated to 70°C and a solution of 5.0 g (0.0756 mol) of 90% carbon-13 enriched potassium cyanide (Merck, Sharp, and Dohme, Canada Limited; Lot B-1490) was added dropwise with stirring. After the addition was complete, the reaction was heated at reflux for 4 hours. The reaction was cooled slowly to 3°C, and the resulting crystalline solid was collected by filtration. The solid was washed with 40 ml of 50% ethanol, air-dried and vacuum dried at 60°C to give 12.2 g (89% yield) of the title compound 6, mp 106-107.5°C.

Analysis. Calc'd for ${}^{12}C_{11.1}{}^{13}C_{0.9}H_8ClN$: C, 71.60; H, 3.98; N, 6.91. Found: C, 71.40; H, 4.08; N, 6.87.

Carbon-13 Labelled Ethyl 1-Chloro-2-naphthaleneethanimidate Hydrochloride (7).

A solution of 12.1 g (0.0579 mol) of carbon-13 labelled 1-chloro-2-naphthylacetonitrile in 250 ml of toluene was prepared. This solution was warmed and then filtered into a 500 ml, three-neck flask equipped with a magnetic stirrer, a gas inlet tube, a thermowell, and a drying tube. The solution was then cooled to 5°C, and 3.2 g (0.0695 mol) of absolute ethanol and 10.0 g (0.274 mol) of anhydrous hydrogen chloride were added. The reaction mixture was warmed to room temperature and stirred for 42 hours. The flask was purged with dry nitrogen for 1 hour. The slurry was then cooled to 5°C and the white solid collected by filtration. The solid was washed with 100 ml of toluene, air-dried, and vacuum dried at 50°C to give 14.5 g of the title compound 7.*

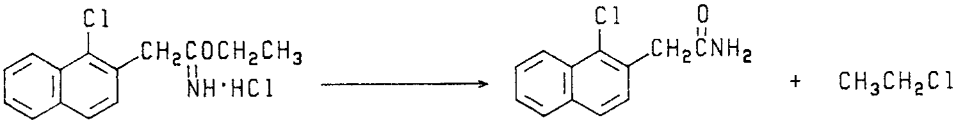
Analysis. Calc'd for $^{12}C_{13.1}{}^{13}C_{0.9}H_{14}ClNO \cdot HCl$: C, 59.16; H, 5.32; N, 4.93. Found: C, 58.40; H, 5.42; N, 5.32.

The reaction liquors yielded a 0.7 g second crop of 7 (89% total yield).*

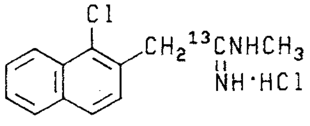
Analysis. Calc'd for $^{12}C_{13.1}{}^{13}C_{0.9}H_{14}ClNO \cdot HCl$: C, 59.16; H, 5.32; N, 4.93. Found: C, 58.60; H, 5.31; N, 5.25.

Carbon-13 Labelled N,N'-Dimethyl 1-Chloro-2-naphthaleneethanimidamide Monohydrochloride (8).

A 500 ml, three-neck flask equipped with a magnetic stirrer, a thermowell, a gas inlet tube, and a reflux condenser fitted with a drying tube was charged



with 14.8 g (0.0519) of carbon-13 labelled ethyl 1-chloro-2-naphthaleneethanimidate hydrochloride and 250 ml of absolute ethanol. The resulting slurry was cooled with an ice bath and saturated with anhydrous methylamine. The reaction mixture became homogeneous after the methylamine addition and was heated to 40°C for 22 hours. HPLC analysis (Partisil^{R} 10 SCX; 9:1 MeOH/0.1 N $NaClO_4$; 280 nm; 2.0 ml/min) showed that the reaction was 97% complete. The reaction was heated to 55°C and held at that temperature for 23 hours. HPLC analysis showed that the reaction was 99.6% complete. The reaction was heated at reflux for 4 hours. HPLC analysis at the end of the reflux period showed that the reaction was complete (no peak was observed for the monomethyl compound 11).



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

The reaction mixture was then cooled to 5°C. The resulting white, crystalline solid was collected by filtration, washed with 50 ml of absolute ethanol, air-dried, and vacuum dried at 55°C to give 12.25 g (83% yield) of 8, mp 307-308°C.

Analysis. Calc'd for $^{12}C_{13.1}{}^{13}C_{0.9}H_{15}ClN_2 \cdot HCl$: C, 59.50; H, 6.58; N, 9.86. Found: C, 59.40; H, 5.73; N, 9.97.

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