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Synthesis and Characterization of [1-^{14}C] N-Methylneodecanamide

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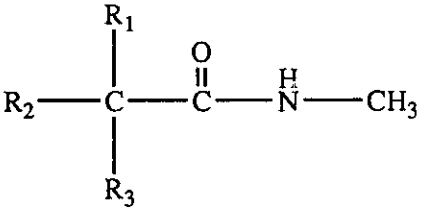
SUMMARY

[1-^{14}C] N-methylneodecanamide (MNDA), a potent insect-repellent, was synthesized from [1-^{12}C] neodecanoic acid (NDA) by an exchange variant of the Koch reaction, followed by conversion to the acyl halide and methylamination. The product had all the characteristics of authentic commercial MNDA, and the radiocarbon was distributed among the isomers in the same proportions as the isomers were among the mass.

INTRODUCTION

N-Methylneodecanamide (MNDA), a highly effective insect repellent, was discovered at the Colgate-Palmolive Piscataway Technology Center in the mid 1980's [1-4].



where R1+ R2 + R3 = 8 Carbon Atoms

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It is a complex mixture of branched tertiary amides prepared from neodecanoic acid (NDA), which is manufactured using the well known Koch reaction[5-7]. Gas chromatography shows over 19 isomers, not all of which are from R-group branching at the α-carbon, for there is branching elsewhere in some of the R-groups; the sidechain is a mixture of isomers with an average C-number of 9. Proton NMR, however, shows that there is almost no α-proton in any of the components.

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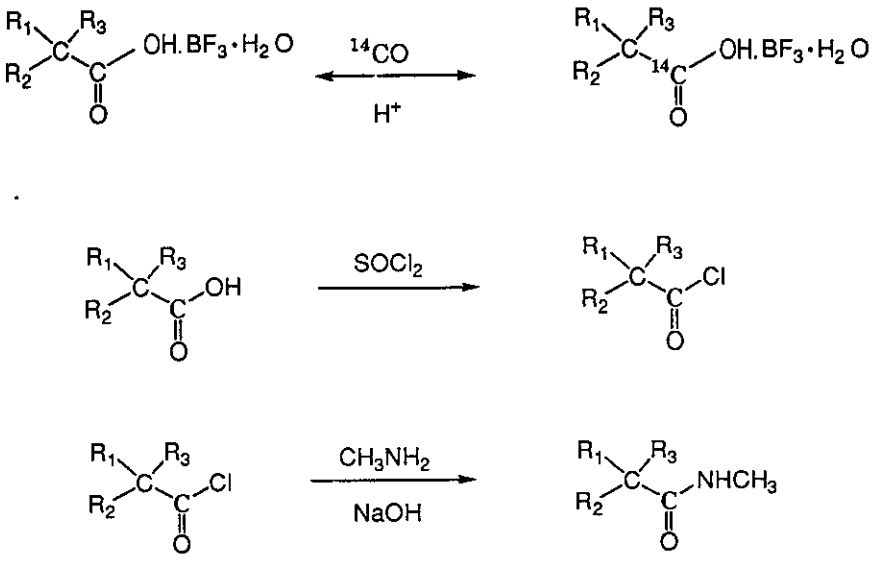
Extensive preclinical and environmental safety testing done during the last few years supports the safety of MNDA used in cleaning products[8], but some regulatory approvals require pharmacokinetics and metabolic profile, and thus MNDA radiolabeled with ^{14}C.

MNDA is best labeled at the carboxyl carbon, a site near the core of the molecule which is relatively stable to metabolism. (The amide methyl group is an inappropriate location; it would be metabolically cleaved and quickly eliminated[9].) Since pharmacokinetic testing using just a few MNDA structural isomers could be misleading, it was important to prepare [1-^{14}C]-NDA having ^{14}C distributed among the isomers in the same way that the isomers are distributed among the mass. The preparation of the radiolabeled NDA might be carried out by the Koch reaction of nonene with ^{14}C-carbon mon-oxide, but a procedure involving ^{14}CO at high pressure seemed exceedingly costly and difficult. Instead, an exchange between ^{14}CO and pre-existing NDA-BF_3-H_2O was used:

Figure 1
Synthesis of [1-^{14}C]-MNDA



Exchange reactions using ^{13}C-carbon monoxide showed that the resulting isomer distribution was similar to that of commercial NDA and that about 20% of the ^{12}C-carboxyl carbons were exchanged with ^{13}C. If ^{14}C-carbon monoxide were used in place of ^{13}C-carbon monoxide under the same reaction conditions, the resulting specific activity from similar incorporation would be adequate for pharmacokinetic testing. ^{13}C-NDA from one trial was converted to ^{13}C-MNDA and the isomer profile of this material was similar to that of commercial MNDA.

SYNTHESIS OF [1-^{14}C] MNDA

Commercial [1-^{12}C]-neodecanoic acid (5.6 grams, 32.6 mmoles) was placed into a 500 mL thick-walled glass reactor along with the $BF_3 \cdot H_2O$ (3 grams, 35 mmoles). The mixture was stirred with a magnetic stirrer, and two separate ^{14}C-carbon monoxide charges of 1 Curie each were allowed to exchange with it for 48 hours at 70 °C and 1.3 atmospheres, by introducing the gas from cylinders and removing it back to them as waste after the exchange. After each reaction, the product was transferred to a separatory funnel. The reactor was washed with 20 mL of water and then 20 mL of hexane and the washes transferred to the separatory funnel; the aqueous phase was back-washed with 20 mL of hexane, the organic phases combined, and the hexane removed in vacuo. Following the second exchange, 5.7 grams (33.1 mmoles) of [1-^{14}C]-NDA was recovered. The ^{13}C-NMR of the product was like that of commercial NDA, and scintillation counting showed about 50 μCi/mg radioactivity was incorporated, and the second and third step was begun. These sides were adapted from a literature procedure for preparing [1-^{14}C]-*N,N*-diethyl-*m*-toluamide, another insect repellent[10].

In the same 500 mL reaction vessel, equipped with a soda lime trap, [1-^{14}C]-neodecanoic acid (5.6 g, 32.6 mmoles) was mixed with thionyl chloride (5.6 mL, 71.5 mmoles), and the mixture chilled in an ice bath for 15 minutes and mixed with magnetic stirring. The mixture turned brown and became less viscous. After 30 minutes, 0.15 mL of dimethylformamide was added (catalyst). The mixture became darker and fumed, and the soda lime in the trap discolored. The mixture was allowed to come to ambient temperature and was mixed for 4.5 - 5 hours. During this time the soda lime trap was refilled twice. By the second refill, discoloration had stopped, but another 1 mL of thionyl chloride had to be added and the mixture warmed to 54 °C for another 3 hours before the IR showed just a trace of free carboxylic acid. ^{13}C - NMR showed an acid chloride signal at 178 ppm and no evidence of free carboxylic acid at 184 ppm. The thionyl chloride was removed in vacuo (10 microns) for 1 hour; 5.4 g (28.4 mmole) of [1-^{14}C] neodecanoyl chloride was recovered as a dark oil.

Sodium hydroxide (50%, 5.0 grams) and deionized water (5.0 grams) were placed in a 250 mL separatory funnel, and chilled in an ice bath for 15 minutes. Methylamine (40%, 4.4 g, 56.8 mmoles) was then added, and the [1-^{14}C]-NDCl (5.4 g , 28.4 mmoles) was transferred to the separatory funnel in 0.5 mL portions. Two mole-equivalents of amine were used to maximize yield. The funnel was shaken after each addition, venting regularly. Fuming was evidence of reaction and formation of product. The organic (MNDA) and aqueous phases were allowed to separate for one hour, the lower aqueous phase was drained off, and the organic phase washed twice with water, allowing to separate overnight. At the end of the final water wash, four drops of 0.5 M HCl brought the pH to 6. The final wash was allowed to settle for 3 hours before separation.

The preliminary instrumental analysis of the organic phase was consistent with authentic MNDA. The infrared spectrum showed fingerprint bands at 3450 cm^{-1} (N-H) , 1635 cm^{-1} (secondary amide I band, carbonyl) and 1540 cm^{-1} (secondary amide II band, C-N). The ^{13}C-NMR showed a secondary amide

signal at 178 ppm and no signals consistent with acid chloride or carboxylic acid. The preliminary yield was 5.70 grams (30.7 mmoles) at about 50 μCi/mg.

CHARACTERIZATION of [1-^{14}C] -MNDA

Based on cold trials, the product was estimated to contain about 6% water, as the only major impurity. Other potential impurities are NDA, NDCl, and methylamine and are probably minor based on the infrared and chromatographic data presented below.

Specific Activity:

Liquid scintillation counts on dilutions of solutions made up in hexane gave a specific activity of about 40 uCi/mg, slowly increasing as residual water separates from the oil. This specific activity suggests that the exchange reaction came to equilibrium at about 10 to 15% substitution.

Thin-Layer Chromatography:

Samples were spotted with authentic MNDA on ordinary 250 μ analytical silica gel G TLC plates, and developed in the systems

1% acetic acid/30% ethanol/69% hexane
1% acetic acid/10% methylethylketone/89% hexane

Infra-Red Spectroscopy:

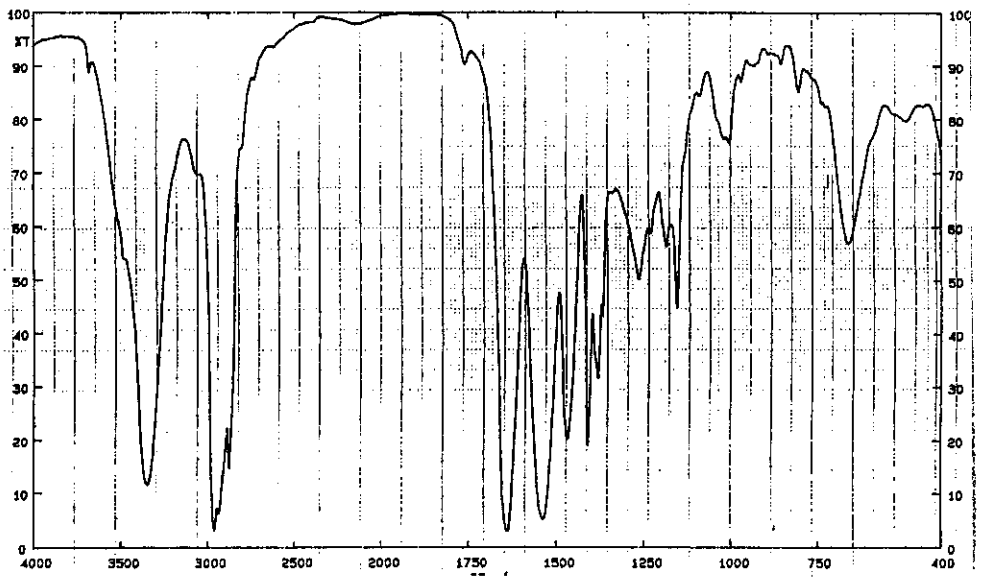


FIGURE 2. Approximately 10 μL of [1-^{14}C]-MNDA between KBr plates; Perkin-Elmer Model 1750 Fourier Transform Infrared Spectro-photometer. Fingerprint absorbances are consistent with commercial ^{12}C-MNDA. A trace of unreacted NDCl noted at 1800 cm^{-1}. Given the known impurity of water, we anticipate that this will convert to ^{14}C NDA in time.

The plates were then exposed to Kodak X-O-Mat AR film overnight, and MNDA control samples later visualized by charring with sulfuric acid/ $K_2Cr_2O_7$. They showed that over 95% of the radioactive materials comigrated with components found in authentic MNDA, and no activity was detectable migrating with neodecanoic acid.

NMR:

Both proton and ^{13}C spectra were taken in $CDCl_3$ (10 mg/mL) on a Bruker 300 MHz / 52 MM. The proton NMR is the same as that of commercial MNDA, with a broad multiplet at 1.1 ppm integrating for 19 protons, a doublet at 2.8 ppm (amide methyl) integrating for three, and a small singlet at 5.6 ppm (=N-H) integrating for 1. A tiny multiplet at about 2.0 indicated a trace impurity of material with α-protons.

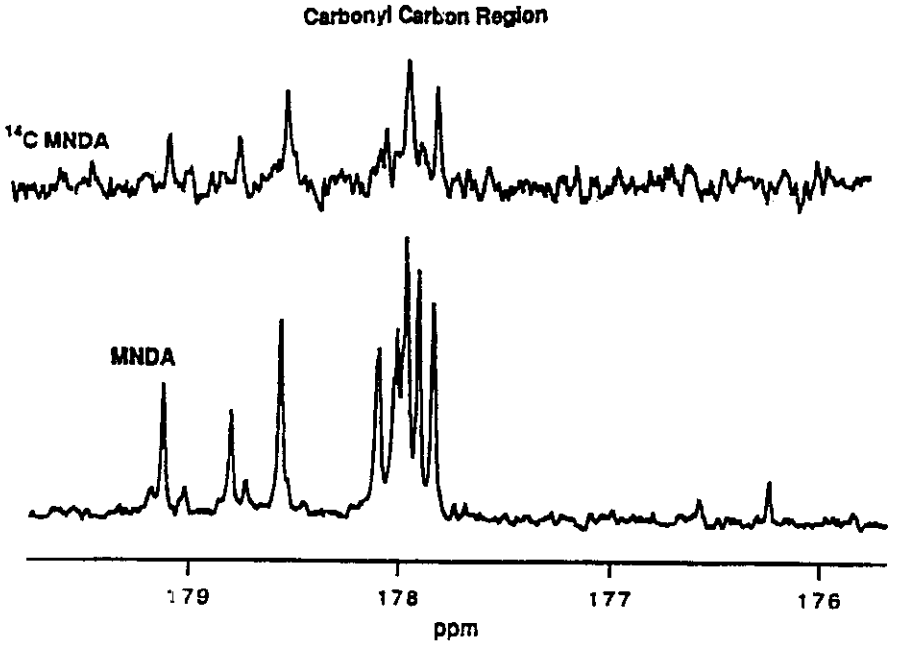


FIGURE 3: Expanded view of the ^{13}C-NMR spectrum of the carbonyl region of ^{14}C MNDA and normal MNDA

Gas Chromatography:

Hewlett-Packard 5890 Series II GC with HP 5921A atomic emission detector. Column: DB-5, 60 m, 0.25 mm ID, 0.25 mm df.; carrier gas: He 99.9999% Reagent gases for the AED were oxygen (99.995%) and hydrogen (99.999%) Oven program: 90 °C for 47 min, 0.5 °C/min to 120 °C, held for 13 min, 10 °C/min to 300 °C. Injector port temp: 250 °C; split ratio: 10:1; flow rate: 0.53 mL/min; transfer line temp: 300 °C. Isotope-specific chromatograms were obtained by monitoring the appropriate emission wavelength: ^{12}C at 343 nm, ^{14}C at 341 nm.

The molecular emission trace from the labeled MNDA is consistent with its having the same isomer profile as normal. Classical GC/FID of the radiolabeled product gave a distribution profile showing about 18 separate peaks virtually identical with that of authentic MNDA.

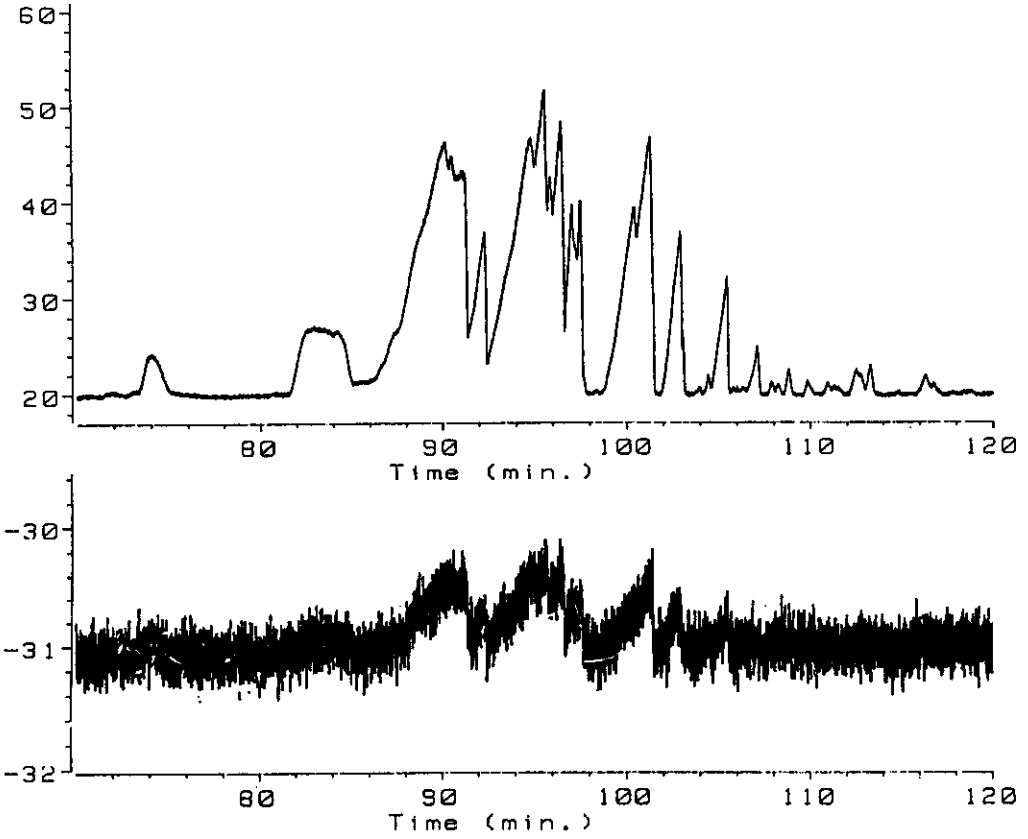


FIGURE 4: GLC/AED The upper trace is the isomer profile of ^{12}C MNDA seen by following the ^{12}C emission; the lower trace is the ^{14}C emission from the ^{14}C MNDA.

HPLC:

(Courtesy of XenoBiotic Laboratories, Inc.)

Column: Zorbax XDB C_8, 4.6 X 250 mm, SN: PX1406. Simultaneous detectors, UV @ 195 nm, and radioactivity monitor, 50 µL Raytest Ramona cell. Solvent gradient: 68% water/acetonitrile (71 min), 34 min to 100% acetonitrile (30 min) at a flow rate of 0.85 mL/min

The radioactivity trace follows the UV trace almost perfectly, indicating that the radioactivity present in the sample of ^{14}C-MNDA is almost exclusively associated with the molecule in the same proportion as the structural isomers.

The intensity of the ions produced from LC/MS on a similar system showed m/z 186 the strongest intensity indicating the sample contains predominantly MNDA at molecular weight 185. The m/z 186 trace yielded a very similar profile to the UV and reconstructed ion chromatogram

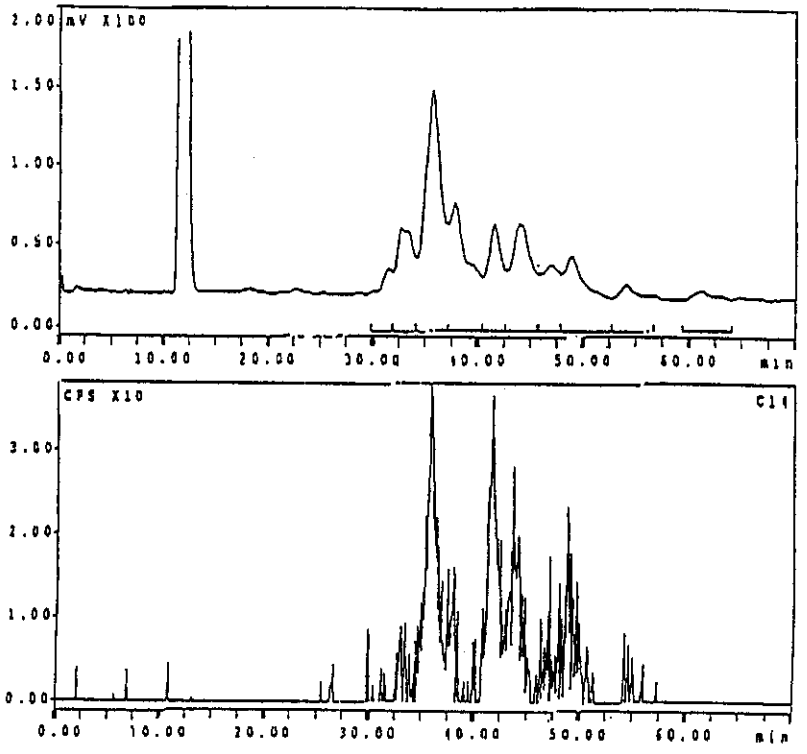


FIGURE 5: HPLC of ^{14}C MNDA. The upper trace is the 217 nm absorbance, showing the distribution of components approximately by mass; the lower trace is the radioactivity, showing the distribution of activity among them.

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