SYNTHESIS OF LIDOCAINE-d_3

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SUMMARY

A simple two step synthetic procedure has been developed for the preparation of deuterated lidocaine. The deuterium was incorporated into the 6'-methyl group which is a metabolically stable position. The overall yield of the synthetic procedure was 41.3%.

Key Words: Lidocaine, Synthesis, Deuterium, Mass Spectrum

INTRODUCTION

Lidocaine is an antiarrhythmic agent used widely by intravenous infusion to treat patients who have had an acute myocardial infarction or cardiac surgery. Its metabolism is complex (1,2) with less than 5 percent of the dose being excreted as unchanged drug. During studies designed to optimize therapy with lidocaine we have examined the pharmacokinetics of both lidocaine and two of its biologically active metabolites, 2-(ethylamino)-N-(2',6'-dimethylphenyl)acetamide and 2-(amino)-N-(2',6'-dimethylphenyl)-acetamide. These studies required the use of isotopically labeled lidocaine and detection of the label with mass spectrometry. The incorporation of the isotope into the drug is ideal when it does not alter endogenous biotransformation. To reduce cost we wished to use deuterium, which must not be placed at a site in the molecule where metabolism occurs since the primary isotope effects of deuterium may be large (3). Since lidocaine's metabolism is complex and involves most functional groups the only possibilities were to incorporate deuterium into the 2'- and/or 6'-methyl groups on the aniline moiety where metabolism is negligible. We therefore chose to label the

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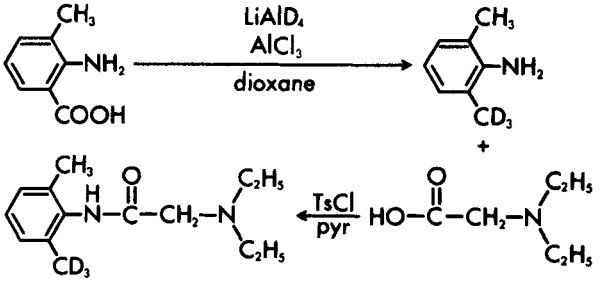
6'-position and herein describe the synthesis of lidocaine-d_3 [2-(diethylamino)-N-(2'-methyl-6'-methyl-d_3-phenyl)acetamide].

The synthetic route for lidocaine-d_3 is shown in scheme I and involved the reduction of 2-amino-3-methylbenzoic acid with lithium aluminum deuteride and aluminum chloride to convert the carboxyl group to a methyl-d_3 group (4-6). The product, 2-methyl-6-methyl-d_3-aniline, was then combined with N,N-diethylglycine in the presence of p-toluenesulfonyl chloride to form an amide linkage to yield lidocaine-d_3 (7).



Scheme I. Synthesis of lidocaine-d_3.

DISCUSSION

The synthetic scheme used to prepare lidocaine-d_3 is a simple two step procedure which procedes in good overall yield, 41.3%, based on 2-amino-3-methylbenzoic acid. The first step of the synthesis, direct reduction of the carboxyl group of 2-amino-3-methylbenzoic acid to a methyl group, proceded in a yield of 51.3%. This represents a maximized yield resulting from trial experiments using unlabeled compounds. The molar ratio of lithium aluminum hydride to 2-amino-3-methylbenzoic acid was varied from 1 to 10, and the molar ratio of aluminum chloride to lithium aluminum hydride was varied from 0.5 to 5 in model reactions. The maximum yield of 51.3% was obtained using the procedure in the experimental section. To maximize deuterium incorporation the exchangeable hydrogen atoms in 2-amino-3-methylbenzoic acid were replaced with deuterium by dissolving the compound in ethanol-d and then evaporating to dryness on a rotary evaporator with a hot water bath. Replacement of the

hydrogen atoms with deuterium atoms prior to reduction substantially increased the amount of label in the final product. The 2,6-dimethylaniline formed was purified partially by fractional distillation, and used in the second step of the reaction without extensive purification to minimize loses.

The second step of the synthesis, formation of an amide linkage between 2,6-dimethylaniline and N,N-diethylglycine, was achieved using p-toluenesulfonyl chloride in a yield of 80.5% based on 2,6-dimethylaniline. This maximized yield was obtained by comparing reactions in which the ratio of N,N-diethylglycine to 2,6-dimethylaniline was varied from 1 to 10. As expected the maximum yield resulted at a ratio of 10 which represents a 10-fold molar excess of the N,N-diethylglycine. The use of a large excess of N,N-diethylglycine presents no problem since its cost is relatively low, and it is easily removed from the target lidocaine by simple basic extraction. Comparison of ratios of p-toluenesulfonyl chloride to 2,6-dimethylaniline of 1 and 4 in the reaction revealed that a higher yield was obtained with the ratio of 4. This ratio was therefore used in the final synthetic procedure described.

An overall yield of 41.3% results when the two steps are combined. The lidocaine-d_3 produced by this procedure was purified by silica gel preparative layer chromatography using four successive elutions with different solvent systems. These elutions were necessary to produce completely pure lidocaine, which was to be given to volunteers, but such extensive purification may not be necessary in certain instances (e.g., when the deuterated material is used as an internal standard). Administration of lidocaine-d_3 prepared by the procedure described to six volunteers has resulted in no observable physiological effects different from those produced by unlabeled lidocaine.

EXPERIMENTAL

Materials and Methods

N,N-diethylglycine (ICN Pharmaceuticals, Inc., Plainview, N.Y.), p-toluenesulfonyl chloride, 2-amino-3-methylbenzoic acid, and ethyl alcohol-d (Aldrich Chemical Co., Milwaukee, Wis.), lithium aluminum deuteride (Merck & Co., Inc., Rahway, N.J.), and deuterium oxide (Stohler Isotope Chemicals,

Rutherford, N.J.), were all used as obtained from the vendors. Structures and isotopic purity were established by nuclear magnetic resonance (NMR) spectroscopy and mass spectrometry (MS). NMR spectra were recorded in 5 mm tubes in $DCCl_3$ with an EM 390 90 MHz NMR spectrometer (Varian, Palo Alto, Calif.). Electron impact mass spectra were recorded using a gas chromatograph-mass spectrometer-computer system (Finnigan 3300 quadrupole mass spectrometer and Finnigan 6000 data system, Sunnyvale, Calif.) at 70 eV ionizing energy. A 6' x 1/8" I.D. glass gas chromatographic column packed with 3% OV-17 on 100/120 mesh Gas Chrom Q (Supelco, Bellefonte, Pa.) was used to determine purity. Preparative layer chromatography plates of 20 x 20 cm x 2 mm silica gel GF (Analtech, Newark, Del.) were used for purification.

Synthesis of Lidocaine-d_3

To a 2-l flask with magnetic stirrer was added 1-l dioxane and 10 g (0.264 mol) lithium aluminum deuteride. To this was carefully added 5 g (0.033 mol) 2-amino-3-methylbenzoic acid. After stirring 15 min 8.9 g (0.067 mol) aluminum chloride was carefully added (some gas was liberated), and the resulting mixture was refluxed for 16 hr. The mixture was cooled and then decomposed by the sequential addition of ethyl acetate, ethanol, and finally 20% aqueous potassium hydroxide until the solution was strongly basic (pH > 12 by pH paper). The mixture, which still contained solid material, was extracted three times with 500-ml portions of ether. The ether extracts were combined, dried over anhydrous granular sodium sulfate, and reduced to an oily residue with a rotary evaporator using a water aspirator. The oil resulting was distilled at atmospheric pressure to yield four fractions. The two highest boiling fractions, 185°-200°C and 200°-207°C, were combined (total volume was 4 ml) and dissolved in 250 ml dry pyridine. Diethylglycine (22.4 g, 0.134 mol) was added and mixed, p-toluenesulfonyl chloride (12.8 g, 0.067 mol) was added, and the mixture was refluxed for 2 hr. The mixture was evaporated to approximately one-half its original volume on a rotary evaporator. The amount of lidocaine in the mixture was determined by GC-MS using mepivacaine as an internal standard and was found to be 7.8 g (41.3% yield). The mixture was then added

to 250 ml of 5% aqueous potassium hydroxide and was extracted twice with 500 ml ether. The ether was evaporated to yield a glassy-like residue. The lidocaine present in this material was isolated in pure form by repeated preparative layer chromatography on silica gel GF. In each case the starting material or appropriate band was appplied to and eluted from the plates with ethanol. The solvents used for development and approximate R_f values for lidocaine were ethyl ether (< 0.1), ethylacetate (0.4), chloroform (0.2), chloroform:methanol, 9:1 (0.7). The product resulting was white, crystalline lidocaine.

The chemical purity of the final product was established by GC, NMR, GC-MS, and MS using probe introduction. The amount of deuterium incorporated into the final product was established by NMR and GC-MS. In the NMR spectrum the only changes readily apparent when spectral comparison with lidocaine is made is the diminished size and integration of the signal at 2.2 ppm due to the two methyl groups in the aniline moiety. Other signals in the NMR spectrum at 8.9 ppm (broad, amide proton), 7.1 ppm (singlet, three aromatic protons), 3.3 ppm (singlet, two methylene protons of glycine moiety), 2.8 ppm (quartet, 4 methylene protons in ethyl groups), and 1.1 ppm (triplet, 6 methyl protons in ethyl groups) were indistinguishable from signals in the spectrum of unlabeled lidocaine. The mass spectrum of lidocaine-d_3 exhibited a shift of the molecular ion from $^m/_e$ 234 to $^m/_e$ 235,236, and 237 (3.8:15.3:100.0). All mass spectral fragments were in agreement with the deuterium atoms being in the aniline portion of the molecule as expected.

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