SYNTHESIS OF DEUTERIUM-LABELED FELBAMATE FROM DIETHYL PHENYLMALONATE

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SUMMARY

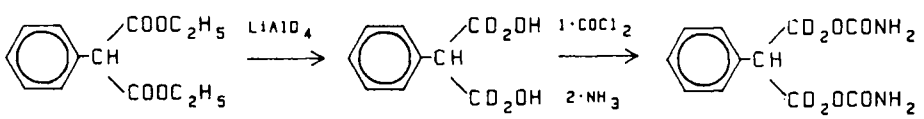
A synthesis of felbamate-d_4 (2-phenyl-1,3-propanediol-1,1,3,3-d_4 dicarbamate) starting from diethyl phenylmalonic acid ester and lithium aluminum deuteride was developed. The procedure has three steps from the starting material to felbamate-d_4 via the intermediate, 2-phenyl-1,3-propanediol-1,1,3,3-d_4. The final overall yield was 44%. The isotope purity was 99.2%.

Key Words: Felbamate-d_4 (2-phenyl-1,3-propanediol-1,1,3,3-d_4 dicarbamate), diethyl malonic acid ester, lithium aluminum deuteride, 2-phenyl-1,3-propanediol-1,1,3,3-d_4

INTRODUCTION

Felbamate (2-phenyl-1,3-propanediol dicarbamate) is a new antiepileptic drug under development (1). To study clinical drug interactions with concommitant medication and possible changes in pharmacokinetics under chronic drug administration, deuterated felbamate was needed.

A simple three-step synthesis for the preparation of 2-phenyl-1,3-propanediol-1,1,3,3-d_4 dicarbamate [3] (felbamate-d_4) from diethyl phenylmalonate [1] via 2-phenyl-1,3-propanediol-1,1,3,3-d_4 [2] was developed and is shown below:



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DISCUSSION

The general method for the synthesis of felbamate starting from **1** via a three-step procedure has been described (2). The procedure involved reduction of **1** with lithium aluminum hydride, followed by phosgenation of the diol to the corresponding bischloroformate and then carbamation of this intermediate to felbamate. However, the yield in the first step was reported to be only 30-50% (2,3).

Recently, selective reductions of various organic acid esters with metal hydride were described utilizing a new technique and giving a higher yield of the corresponding primary alcohols (4). Consequently, in order to make the deuterated intermediate, **2**, in the first step, the readily available lithium aluminum deuteride was selected as a reducing agent. However, the optimal reduction conditions were initially determined using unlabeled lithium aluminum hydride (see Table 1). We have applied this new reduction procedure to the synthesis of **2**. It has the following important advantages over the previous one: (i) the amount of deuteride, $3D^-$/ester, is sufficient for the reduction to the alcohol stage; (ii) a steady increase in the concentration of the reactants caused by the solvent distilling off results in an increase of the rate of the reduction; (iii) the higher temperature (135°) also increases the rate of the reduction; (iv) the added xylene serves as a heat transfer material and keeps the contents in the fluid state. Thus, the reduction in the first step was successfully carried out by the procedure described above. The purification of **2** by recrystallization provided a 68% yield (see Table I). ^{1}H-FTNMR, CI-MS, and TLC analysis confirmed its structure. The isotope purity of the deuterated diol, **2**, was estimated by ^{1}H-FTNMR from the integration of the methylene peak at 3.8 ppm (δ) in deuterochloroform to be 99.6%. The purity by CI-MS from the peaks at m/e 121 and 117 was 99.4%.

Felbamate has been reported (5,6) to be prepared by the reaction of **2** with phosgene in the presence of antipyrine or tetrahydrofuran followed by addition of anhydrous ammonia. The preparation of **3** was performed on a 0.25 mole scale of **2** and the reagent mentioned above. By recrystallization from

the solvent mixture of acetone, toluene, and ethyl ether (1:3:1), a 64% yield of the deuterated **3** was obtained (see Table I). The structure and purity of the compound was confirmed by ^{1}H-FTNMR, CI-MS, and TLC analysis. In a similar manner the isotope purity was determined by ^{1}H-FTNMR from the integration of the methylene peak at 4.15 ppm (δ) to be 99.2% and CI-MS from the intensity of the ions m/e = 182 and 178 to be 99.8%.

EXPERIMENTAL

Melting points (MP) are uncorrected. Thin layer chromatography (TLC) was performed on silica gel 60F 254 (EM Scientific) plates of 0.25 mm thickness. Proton nuclear magnetic resonance spectra (^{1}H-NMR) were recorded on a 90 MHz FX-90Q fourier transform FT-NMR spectrometer (JEOL USA, Inc., Peabody, MA). The following FT-NMR conditions were used: Solvent, deuterochloroform ($CDCl_3$) and dimethylsulfoxide-d_6 (DMSO-d_6); temperature, ambient; tube, 5 mm,; reference, tetramethylsilane (TMS). The starting materials, diethyl phenylmalonic acid ester and lithium aluminum deuteride, were purchased from Aldrich Chemical Co. (Milwaukee, WI). The isotope purity was determined by the comparison of ^{1}H-FTNMR spectra of the deuterated compounds with that of the unlabeled substrates. Mass spectrometry was performed in a VG 7070 mass spectrometer (VG Analytical, Manchester, England) with direct probe insertion of the samples.

2-Phenyl-1,3-propanediol-1,1,3,3-d_4 [2]

The reaction apparatus consisted of a predried 1000 mL three-necked round bottom flask containing a nitrogen inlet and outlet, a magnetic stirring bar, and a distillation set-up. To 225 mL of a solution of lithium aluminum deuteride (24.7 mmol, 990 mmol of D^-) in ethyl ether under nitrogen 32.37 mL (150 mmol) of **1** was added dropwise to 10 mL of xylene with a hypodermic syringe at 0°C. The reaction mixture was stirred at room temperature for 30 min and then heated to 50°C to distill off 95% of the solvent, ether. The contents of the reaction mixture was continuously heated to 130° for 2½ h without stirring. After cooling to room temperature, 100 mL of ethyl acetate in 300 mL of THF was slowly added at 0°C. Then 300 mL of a mixture of ethyl

ether and THF (1:1) was added followed by the slow addition of 2N HCl until a clear homogeneous solution was obtained. The separated organic layer was extracted two times with a mixture of ether and THF. The combined organic layers were washed with a saturated solution of potassium carbonate and dried over anhydrous magnesium sulfate. Filtration and concentration gave a yellowish oily material. This material was recrystallized from a mixture of ether, toluene, and hexane (1:1:5). Filtration provided 15.63 g (68%) of a colorless solid corresponding to **2** with a m.p. of 51-53°C. The isotope purity was determined by ^{1}H-FTNMR and CI-MS to be 99.6% and 99.4%, respectively. TLC analysis on SiO_2 in acetone and hexane (1:1) showed only one spot. ^{1}H-FTNMR ($CDCl_3$; δ ppm): 7.22 (5H, aromatic, s), 3.38 (2H, 2OH, s), and 2.95 (1H, benzylic, s); CI (Isobutane) MS, *m+1/e* (relative intensity): 157 (7.1), 139 (17.8), 121 (100), and 106 (60.5).

2-Phenyl-1,3-propanediol-1,1,3,3-d_4 Dicarbamate [**3**]

This reaction was also carried out under a N_2 atmosphere in a 2000 mL three-necked round bottom flask containing a mechanical overhead stirring bar with N_2 inlet and outlet connecting tubes. To the predried flask 40 g (256 mmol) of **2** was added to 70 mL of THF at room temperature. To the contents of the flask, kept at 0°C under N_2, 1,299 mL (1.429 mole) of 1.1M solution of phosgene in toluene was slowly added to 130.2 g (692 mmol) of antipyrine in 180 mL of chloroform. The reaction was maintained overnight at room temperature. The reaction mixture was then filtered giving a clear filtrate. The solution was transferred to another 2000 mL round bottom flask equipped with a mechanical overhead stirring bar and inlet and outlet connecting tubes for ammonia gas. The contents of the reaction flask were cooled to 0°C under nitrogen, and anhydrous ammonia was bubbled into the solution under stirring for 2 h at 0°C. The heterogeneous mixture was stirred overnight at room temperature and filtered providing a colorless solid. The resulting solid was slurried with distilled water for stirring. Filtration gave a solid, which was washed with cold water and completely dried overnight under vacuum at room temperature. The crude product was recrystallized from a mixture of acetone, toluene, and ether (1:3:1), and filtration provided 38.61 g (64%) of

a colorless solid of **3**, m.p. 148-150°C. The isotope purity was 99.2% by ^{1}H-FTNMR and 99.8% by CI-MS determination. TLC analysis of the sample on SiO_2 in acetone:hexane (2:1) showed only one spot. ^{1}H-FTNMR (DMSO-d_6, δ ppm): 7.28 (5H, aromatic, s), 3.17 (1H, benzylic, s), and 6.44 (4H, $2NH_2$, s); CI (Isobutane) MS, m+1/e; relative intensity: 243 (1.6), 182 (100), 138 (8.7), 121 (23.8), and 106 (7.6).

TABLE 1: SYNTHESIS OF FELBAMATE-d_4 FROM DIETHYL PHENYLMALONIC ACID ESTER VIA A THREE-STEP PROCEDURE[a]

Experiment	**2** % (g), M.P. (°C)	**3** % (g), M.P. (°C)
Unlabeled Experiment	70 (4.4)[b], 52-54	72 (0.86)[c], 149-150
Labeling Experiment	68 (16)[d], 51-53	64 (38.6)[e], 148-150

[a] All the yields are isolation yields
[b] Starting material, 75 mmol of diethyl phenylmalonate was used.
[c] Starting material, 4.9 mmol of 2-phenyl-1,3-propanediol was used.
[d] Starting material, 150 mmol of diethyl phenylmalonate was used.
[e] Starting material, 256 mmol of 2-phenyl-1,3-propanediol-1,1,3,3-d_4 was used.

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