SYNTHESIS OF ^{14}C-LABELED FELBAMATE FROM PHENYLACETIC-(METHYLENE-^{14}C) ACID

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SUMMARY

A synthetic procedure for the preparation of 2-phenyl-1,3-propanediol-2-^{14}C dicarbamate, starting with phenylacetic-(methylene-^{14}C) acid was developed. The procedure from phenylacetic acid to 2-phenyl-1,3-propanediol dicarbamate has four steps via phenylmalonic acid and 2-phenyl-1,3-propanediol. The overall yield of all four steps was 28%.

Key Words: 2-Phenyl-1,3-propanediol-2-^{14}C dicarbamate, Phenylacetic-(methylene-^{14}C) acid, Phenylmalonic-(methine-^{14}C) acid, 2-Phenyl-1,3-propanediol-2-^{14}C

INTRODUCTION

Felbamate (2-phenyl-1,3-propanediol dicarbamate) is a new antiepileptic drug under development (1). In order to perform studies on the metabolic fate of this carbamate in animals and man, ^{14}C was needed to be placed in a metabolically stable position. The synthesis of unlabeled 2-phenyl-1,3-propanediol dicarbamate from diethyl phenylmalonate has been previously described (2) but was not suitable for labeling. A four-step procedure for the synthesis of ^{14}C-felbamate starting from phenylacetic-methylene-^{14}C acid was developed in our laboratories.

DISCUSSION

The synthesis of 2-phenyl-1,3-propanediol dicarbamate, which is described in the patent literature (2), involves reduction of diethyl phenylmalonate and

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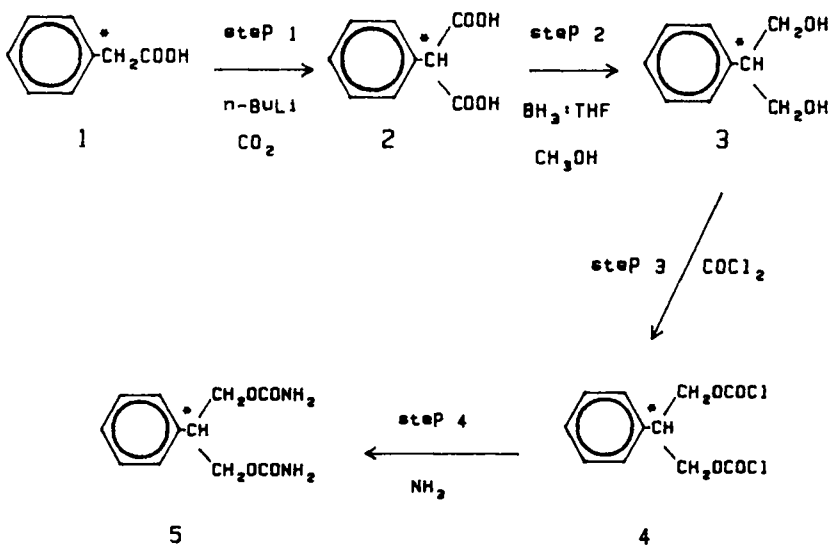
carbamation of 2-phenyl-1,3-propanediol via a three-step procedure. However, since diethyl phenylmalonate-(methine-^{14}C) was not commercially available, phenylacetic-(methylene-^{14}C) acid was selected as the starting material. The procedure involved four steps, i.e., carboxylation of phenylacetic acid [1] to 2-phenylmalonic acid [2], reduction of 2 to 2-phenyl-1,3-propanediol [3], conversion of 3 to its bis-chloroformate [4], and carbamation to the 2-phenyl-1,3-propanediol dicarbamate [5] (see scheme below). The optimal reaction conditions were initially determined using nonradioactive reactants on the same scale.

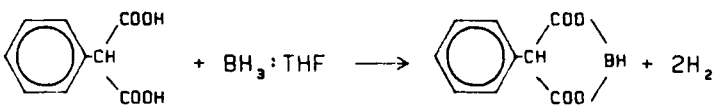
According to Barnes et. al. (3), organic carboxylic acids can be synthesized from a compound containing an acidic C-H bond by carboxylation utilizing n-butyl lithium and carbon dioxide. Thus, Step 1 was successfully carried out



by reaction of 1 with n-butyl lithium followed by introduction of excess carbon dioxide and maintained at dry-ice temperature for 5 h. The purification of 2 by recrystallization yielded 77% of the pure product [2] (Table 1). ^{1}H-NMR and HPLC analysis confirmed its structure.

Borane complexes such as borane-tetrahydrofuran (BH_3:THF) and borane-dimethyl sulfide (BH_3:SMe_2) have been reported to be excellent reducing agents for the reduction of carboxylic acids to the corresponding primary alcohols

(4,5). Therefore, the reduction of **2** (Step 2) was performed on a small scale with an excess of borane reagents. After the reduction was completed, the reaction mixture was decomposed with methanol at room temperature (6). The reaction progress was monitored by HPLC. As shown in Table I the reduction of 2 by either borane-tetrahydrofuran or borane-dimethyl sulfide with a 1.6 ratio of hydride to the compound gave only a 25% yield of **3** and a large amount of unreacted starting compound. The low yield of the product is probably due to formation of a sterically hindered borylene phenylmalonate intermediate [**6**] which prevents further reduction as indicated in the equation below:



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Consequently, a two-step or three-step reduction procedure was carried out with decomposition of the excess hydride and intermediate, **6**, by methanol after each step. This approach led to increased yields of the desired diol and consumption of all starting material (Table 2). Therefore, the optimal conditions were established to be a two-step reduction with 200% excess of hydride. The first step reduction provided 43% of product at 0° in 2 h and while the second reduction increased the yield to 72% of **3** by HPLC analysis, the crude product was further purified by using column chromatography giving 65% yield of the pure diol, **3**.

The phosgenation (Step 3) and carbamation (Step 4) have been reported to be carried out by the reaction of the **3** with phosgene in the presence of tetrahydrofuran (7) or antipyrine (8) followed by addition of anhydrous or aqueous ammonia. We have adapted the procedure to a small scale where **3** reacted with phosgene in toluene in the presence of antipyrine added as solution in chloroform. By recrystallization from acetone-hexane, a 72% yield of pure dicarbamate, **5**, was achieved.

Synthesis of 2-Phenyl-1,3-propanediol-2-^{14}C Dicarbamate [5]

The radiolabeling procedure was the same as described in the experimental

section except for small differences in weights and volumes. The starting material, 50 mCi, 1,3 g, of phenylacetic-(methylene-^{14}C) acid [**1**] supplied by Pathfinder Laboratories had a lower m.p. (71-73°C) than reported in the literature for the pure unlabeled material. The yields and m.p. of all intermediates for the radiolabeling procedure are listed in Table 2.

After the reduction in step 2 the crude **3** was further purified by column chromatography, which led to 0.55 g **3** (64.7%) of pure ^{14}C-labeled diol, **3**.

The conversion of the ^{14}C-diol, **3**, into the dicarbamate, **5**, gave 73.5% yield of the labeled drug. The purity was checked to be +98% by TLC and radioactivity scanning. No other radioimpurity could be detected. The overall weight yield was 28%, and the radioyield was 32% (16 mCi). The specific activity of this sample was determined to be 6.09 mCi/mM.

EXPERIMENTAL

Melting points are uncorrected. Thin-layer chromatography was performed on silica gel 60F 254 (EM Scientific) plates of 0.25 mm thickness and column chromatography with 70-270 mesh silica gel 60 (Brinkmann Instruments, Westbury, NY). Nuclear magnetic resonance spectra (NMR) were obtained in DMSO-d_6, $CDCl_3$, with a 60 MH_2 JEOL Model MH100 spectrometer. The HPLC instrument for product analysis was a liquid chromatograph, model 244, Waters Associates (Milford, MA). The starting material, phenylacetic-(methylene-^{14}C) acid, was purchased from Pathfinder Laboratories (St. Louis, MO).

Radioactivity determinations were carried out by liquid scintillation on a LS-9000 scintillation spectrometer (Beckman Instruments, Fullerton, CA) in Aquasol scintillation fluid (New England Nuclear, Boston, MA) using appropriate dilutions of compound solution or fractions collected from HPLC runs.

The radiopurity of intermediates and the final products were determined from the ratio of the dpm in the corresponding compound peak and the total dpm injected.

The peaks on thin-layer radiochromatograms were detected by a scanner, model 7201 (Packard Instruments, Downers Grove, IL).

Phenylmalonic Acid [2]

The reaction was carried out under N_2 atmosphere in a 250 mL RB flask with one side arm containing the N_2 outlet and a magnetic stirring bar. To this flask was added 1.31 g (9.54 mmol) of the acid **1** and 10 mL of dry THF at RT. The content was cooled to dry ice temperature under N_2 atmosphere and then 17 mL (37.4 mmol) of a 2.2 molar solution of n-butyllithium in hexane was slowly introduced to the flask during 20 min under stirring (giving an orange color). After additional stirring for 2 h at dry ice temperature, 14 g of solid CO_2 was slowly added in two portions (the orange color changed to light yellow). The reaction mixture was continuously stirred for another 2 h at dry ice temperature and for ½ h at RT. The mixture was decomposed by the addition of 2 N HCl under stirring. The organic layer was collected and the aqueous layer extracted twice with 30 mL of ethyl ether. The combined organic layers were dried over anhydrous magnesium sulfate and concentration under reduced pressure giving a light yellow oil. To the crude product was added 3 mL of ethyl ether and then 50 mL of hexane was introduced to precipitate the product. The crystalline substance was collected by filtration and dried, yielding 1.0 g (59%) of **2**, m.p. 143-145°C [Lit. (8) 152-153°C]. NMR (DMSO-d_6, δ ppm): 4.6 (1H, CH, s), 7.1-7.5 (5H, aromatic, m), and 10.2 (2H, 2COOH, bs).

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

The reaction was carried out under N_2 in a 250 mL RB flask with one side arm with the N_2 outlet connecting tube. To the pre-dried flask was added 1.0 g (5.55 mmol) of **2**, 0.4 mL of methanol, and 6 mL of dry THF at RT. The content of the flask was cooled to 0°C under N_2 and 61 mL (51.2 mmol) of a 0.84 M solution of borane:THF in THF was slowly introduced into the flask from a syringe under stirring (hydrogen evolution was observed). The reaction mixture was stirred at 0°C for 5½ h. Then 25 mL of dry methanol was slowly added at RT and the flask was kept overnight at RT. The excess solvent was distilled off under vacuum. To the residue was added 7 mL of THF and 60 mL (50.4 mmol) of a 0.84 M solution of borane: THF in THF at 0°C and after stirring for another 5½ h at 0°C 30 mL of dry methanol was slowly introduced into the flask. The reaction mixture was kept overnight at RT. The excess solvent was then removed as above

TABLE I

REACTION OF PHENYLMALONIC ACID WITH BORANE COMPLEX IN THF

Borane Complex	Ratio of H^- to CPD[b]	Reaction Temp (°C)	Reaction Time (h)	Yield of 3[a] (%)
H_3B:THF	1.6	0	4	25
H_3B:SMe_2	1.6	90	2	23
H_3B:THF	2.0	0	16	35
H_3B:THF[c]	3.0	0	4	36
	2.0	0	8	53
	2.0	0	10	70
H_3B:THF[d]	3.0	0	2	43
	3.0	0	2	72

[a] Yield by HPLC analysis

[b] 1 mmol of compound needs $6H^-$ for complete reduction.

[c] The reduction was repeated three times with recovered reaction mixture.

[d] The reduction was repeated two times with recovered reaction mixture.

to give 1.83 g of viscous oil. To the oily material 30 mL of ethyl ether was introduced and then extracted twice with a saturated potassium carbonate solution. The combined ether layers were dried over magnesium sulfate and concentrated by reduced pressure. To this was added toluene (to facilitate removal of the excess trimethyl borate) and the solvent evaporated under reduced pressure giving 1.06 g of material. This procedure was repeated after addition of another volume of toluene and 0.93 g of material was recovered (theoretical yield, 0.80 g). The crude product was then purified by column chromatography (2 x 30 cm) on 60 g of silica gel (6% H_2O) with a 1:1 mixture of hexane and acetone as eluting solvent. The fractions corresponding to the diol, **3**, were combined and the solvent distilled off by reduced pressure to give a colorless oily residue. To this was added 15 mL of toluene and the solvent was evaporated under reduced pressure, yielding 0.55 g (65%) of pure **3**

TABLE II

SYNTHESIS OF ^{14}C FELBAMATE FROM PHENYLACETIC ACID VIA THREE STEP EXPERIMENTS[a]

Product Yield	2 % (g), MP (°C)	3 % (g), MP (°C)	5 % (g), MP (°C)	Overall Yield (%)
Unlabeled Run[b]	77 (1.0), 152	65 (0.55), --	72 (0.62), 149	36
Labeled Run[c]	59 (1.0), 143	65 (0.55), --	74 (0.64), 147	28

[a] All the yields are isolation yields in each step.

[b] Starting material, 1.0 g of phenylacetic acid with MP 77-78°C was used.

[c] Starting material, 1.3 g of phenylacetic acid with MP 72-73°C was used.

as colorless crystals. NMR ($CDCl_3$, δ ppm): 3.0 (1H, CH, m), 3.0 (2H, 2OH, s), 3.9 (4H, $2CH_2$, d), and 7.4 (5H, aromatic, bs).

2-Phenyl-1,3-propanediol Dicarbamate [5]

This reaction was also carried out under N_2 in a 250 mL RB flask with a side arm with the N_2 outlet connecting tube. To the pre-dried flask was added 0.55 g (3.61 mmol) of **3** and 2 mL of dry THF at RT. To the reaction flask, kept at 0°C under N_2, 25 mL (27.5 mmol) of a 1.1 M solution of phosgene in toluene was slowly introduced and then 1.8 g (9.73 mmol) of antipyrine in 7 mL of CH_3Cl was added to the contents of the flask. The reaction was maintained overnight at RT. The precipitate of antipyrine hydrochloride was filtered off, and the clear solution containing **4** was collected in another 250 mL RB flask (containing a magnetic stirring bar and anhydrous NH_3 inlet). Then ammonia gas (NH_3) was bubbled into the solution under stirring for an additional 30 min at 0°C. The white precipitate was stirred for an additional 30 min at RT and then filtered. To the white solid in a 80 mL beaker was added 30 mL of distilled water and the contents stirred for 20 min at RT. Filtration gave a white solid which was washed with cold water and completely dried under vacuum at RT over-

night. To the crude white solid of **5**, m.p. 143-145°C, 40 mL of acetone (analytical grade) was added and refluxed under stirring for 20 min. The acetone solution was filtered and 120 mL of hexane was introduced into the clear solution giving a precipitate of the product. The contents of the flask were cooled to 0°C for 30 min and then filtered yielding 0.64 g (74%) of **5** as colorless crystals, m.p. 147°C [Lit. (7) 149-150°C]. NMR (DMSO-d_6, δ ppm): 3.3 (1H, CH, m), 4.2 (4H, $2CH_2$, d), 6.6 (4H, $2NH_2$, s), and 7.5 (5H, aromatic, s).

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