

## SYNTHESIS OF <sup>14</sup>C-FELBAMATE

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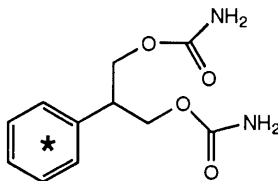
### Summary

**<sup>14</sup>C-Felbamate**, 2-[ring-U-<sup>14</sup>C]phenyl-1,3-propanediol-dicarbamate, (1), was synthesized. The carbon label was introduced into Felbamate using uniformly labelled diethyl 2-phenylmalonate as the starting material.

**Key Words:** Felbamate, 2-phenyl-1,3-propanediol dicarbamate, diethyl 2-phenylmalonate, 2-phenyl-1,3-propanediol.

### Introduction

Felbamate\* is currently marketed for use in the treatment of Lennox-Gastaut Syndrome.

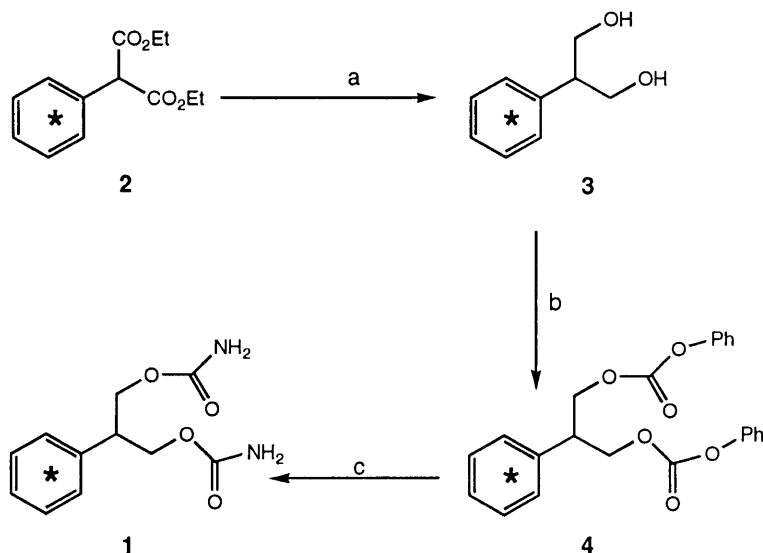


**Felbamate**

This compound was originally developed by Carter Wallace and licensed to Schering Plough Corporation for international marketing. In order to perform further drug metabolism and clinical studies, additional **<sup>14</sup>C-Felbamate** was essential. This paper describes the synthesis of 2-[ring-U-<sup>14</sup>C]phenyl-1,3-propanediol dicarbamate.

## Discussion

A four step procedure for the synthesis of  $^{14}\text{C}$ -Felbamate using phenyl-[2- $^{14}\text{C}$ ]acetic acid as the starting material was developed in the Carter Wallace laboratories and has been published.<sup>(1)</sup> In our paper, we describe the synthesis of Felbamate in three steps using commercially available diethyl 2-[ring-U- $^{14}\text{C}$ ]phenylmalonate (**2**) as the starting material, scheme 1.



**SCHEME 1**

- a) DiBAL-H,  $-10^{\circ}\text{C}$  to rt temp  
 b)  $\text{CH}_2\text{Cl}_2$ , pyridine, phenylchloroformate  
 c)  $\text{NH}_3$ , MeOH

The first step in our synthesis involved the reduction of the diester (**2**) to the diol (**3**). The preparation of **3** from **2** using lithium aluminum hydride (LAH) has been reported in the literature, however the yields were only in the range of 30-50%.<sup>(2)</sup>

Enolizable 1,3 dicarbonyl compounds have been reported in the literature to yield the enolate as well as the desired reduction product when reacted with hydrides. Once the enolate is formed, it becomes resistant to reducing agent thus accounting for the low yields.<sup>(3,4)</sup>

Choi and co-workers investigated the reduction of diethyl phenylmalonate using various metal hydrides to give the corresponding diol **3**. Of all the reducing reagents they employed, Choi reported that diisobutylaluminum hydride was the only reagent to afford pure diol with no evidence of metalation occurring.<sup>(5)</sup>

**Table 1**

<u>Reaction Number</u>	<u>Reagent</u>	<u>Reaction Temperature</u>	<u>Reagent Equivalents</u>	<u>Diol Yields</u>
1	DIBAL-H	0°C.	5.5	38%
2	DIBAL-H <sup>f</sup>	0°C.	11	39%
3	DIBAL-H <sup>f</sup>	room temperature	11	0%
4 <sup>b</sup>	DIBAL-H	-5° to 0° to r.t.	5.7	45% <sup>d</sup>
5 <sup>b</sup>	DIBAL-H <sup>a</sup>	-10° to r.t.	5.7	52% <sup>e</sup>
6 <sup>b</sup>	DIBAL-H	-10° to r.t.	5.7	56% <sup>e</sup>
7 <sup>b</sup>	DIBAL-H	-10° to r.t.	5.7	59% <sup>e</sup>
8 <sup>e</sup>	DIBAL-H	-10° to r.t.	5.7	59% <sup>e</sup>
9 <sup>e</sup>	DIBAL-H <sup>a</sup>	-10° to r.t.	5.7	59% <sup>e</sup>
10 <sup>c</sup>	DIBAL-H	-10° to r.t.	5.7	56% <sup>d</sup>

a) fresh bottle; b) ester diluted, 1:1; c) ester diluted, 2:1; d) column chromatography purification; e) trituration purification; f) DIBAL-H added in two portions

Initial DiBAL-H reactions following the procedure published by Choi produced the diol in only 38% yield. Extensive studies were conducted in an effort to maximize the yield of this reduction. Optimization of the reaction conditions was determined using unlabelled diethyl 2-phenylmalonate. The results are illustrated in **Table 1**.

Examination of **Table 1** indicates that yields approach 60% when the diester is added to 5.7 equivalents of DiBAL-H at -10°C and gradually allowing the reaction to warm to ambient temperature. Adding the diester at 0°C using 5.5 or 11 equivalents had no effect on the yield, while running the reaction at ambient temperature failed to give any of the desired diol.

The next step in the Carter Wallace synthesis required the diol to be reacted with phosgene gas to produce the dicarbamoyl chloride which was reacted with gaseous ammonia to yield the product. Due to the hazardous nature of phosgene gas, we felt that its use, especially in a radiochemical synthesis, was not acceptable.

Phenylchloroformate and 4-nitrophenylchloroformate are excellent phosgene synthons. Reactions using these chloroformates with an alcohol produce an activated carbonate ester which can be isolated. This ester is reacted with ammonia to give the carbamate. A series of experiments using these reagents were conducted to find the optimum conditions and the results are listed in **Table 2**.

The results in **Table 2** indicate that using 4-nitrophenylchloroformate in the presence of triethylamine produced Felbamate in very low yields. Running

**Table 2**

Reaction Number	Reaction Solvent	Reaction Base	Reaction Temperature <sup>1</sup>	Reaction Reagent	Felbamate Yield <sup>2</sup>
1a	Et <sub>2</sub> O/THF	Triethylamine 2.8x	0°C.	4-NPCF*	16%
2a	THF	Triethylamine 2.8x	0°C.	4-NPCF*	44%
3a	CH <sub>2</sub> Cl <sub>2</sub>	Triethylamine 4x	0°C.	4-NPCF*	22%;
4a	CH <sub>2</sub> Cl <sub>2</sub>	Pyridine, 5.6x	reflux, 1 hr.	PCF** 2.3x	65%
5b	CH <sub>2</sub> Cl <sub>2</sub>	Pyridine, 5.6x	reflux, 3 hr.	PCF** 2.8x	57%
6c	CH <sub>2</sub> Cl <sub>2</sub>	Pyridine, 5.6x	reflux, 1 hr.	PCF** 2.8x	63%.
7b	CH <sub>2</sub> Cl <sub>2</sub>	Pyridine 10x	reflux, 1 hr.	PCF** 2.8x	49%
8b	CH <sub>2</sub> Cl <sub>2</sub>	Pyridine 10x	reflux, 1 hr.	PCF** 4x	19%
9b	CH <sub>2</sub> Cl <sub>2</sub>	Pyridine 10x	reflux, 1 hr.	PCF** 4x	18%
10c	CH <sub>2</sub> Cl <sub>2</sub>	Pyridine 10x	reflux, 1 hr.	PCF** 4x	18%
11a	CH <sub>2</sub> Cl <sub>2</sub>	Pyridine 10x	reflux, 1 hr.	PCF** 4x	61%
12a	CH <sub>2</sub> Cl <sub>2</sub>	Pyridine 10x	room temp.	PCF** 4x	60%

\*nitrophenylchloroformate

\*\*phenylchloroformate

1) The column heading: "reaction temperature" are the conditions for the conversion of the diol to the activated ester.

2) The column with the heading "Felbamate yield" is the overall yield for the two step process of forming the activated ester, and then conversion of this ester to Felbamate by stirring with methanolic ammonia over night.

a) from diol standard; b) from triturated diol; c) from diol purified by column chromatography

the reaction in various solvents such as methylene chloride and tetrahydrofuran had little effect on the yield. However using phenylchloroformate as the phosgene synthon in the presence of pyridine, produced yields that were in the 60% range.

### Synthesis of 2-[ring-U- $^{14}\text{C}$ ]-phenyl-1,3-propanediol-dicarbamate (1)

Diethyl 2-[ring-U- $^{14}\text{C}$ ]phenylmalonate, **2**, was obtained from Amersham Corporation at a specific activity of 45 mCi/mmol. Radiolabelled **2** and unlabelled material were dissolved in tetrahydrofuran. The temperature was lowered to  $-10^\circ\text{C}$  and the solution was treated with DiBAL-H. The crude diol obtained was purified by column chromatography.

Phenylchloroformate was reacted with diol, **3**, in methylene chloride. After one hour, the reaction appeared complete by thin layer chromatography analysis. Work-up and removal of the solvent, gave an off-white solid. This crude carbonate, **4**, was stirred over night with methanolic ammonia. Removal of the solvent produced crude Felbamate, **1**. The crude radiolabelled material was combined with unlabelled Felbamate and recrystallized from methanol giving a batch of Felbamate with a specific activity of  $65.5\ \mu\text{Ci}/\text{mg}$ . High pressure liquid chromatography of the product when compared to that of the reference standard was found to have chemical and radiochemical purities of 98.3% and 99.1%, respectively.

## Experimental

### Materials

Diethyl 2-[U- $^{14}\text{C}$ ]phenylmalonate was purchased from Amersham Corporation and used without further purification. All reagents and solvents were used without purification. The reactions were carried out under an argon atmosphere.

### Thin Layer Chromatography

Thin layer chromatography was performed on Whatman LK6DF (silica gel 60) 5 x 20 cm, 0.25 mm plates. Analysis of radioactive material was obtained from a Bioscan System 200 imaging scanner. Column chromatography used 0.063 mesh silica gel 60 obtained from EM Science.

### High Pressure Liquid Chromatography

High pressure liquid chromatography was used for radiochemical and chemical purity. A Waters 600E system controller was used with a Waters 712 WISP auto-injector. The chemical purity was determined using the Waters 490 programmable multiwavelength detector while radiochemical purity was obtained from a Radiomatic Flow 1 detector. Radiomatic Flo-Scint III liquid scintillation cocktail was used. The following systems were used:

- 1) Zorbax SB-C18, 3.5 micron, 75 x 4.6 mm I.D., 254 nm, MeOH:CH<sub>3</sub>CN:TEA:AcOH:H<sub>2</sub>O (6.3: 12.6: 1.0: 1.5: 78.4) for 3 min, linear gradient for 7 min to 100% acetonitrile at a flow rate of 1 mL/min.
- 2) Keystone PVA-Sil, 150 x 4.6 mm I.D., 254 nm, Hexane:Ethanol (95:5) linear gradient for 15 min to 100% Etanol at 2.0 mL/min.

### Liquid Scintillation Counting

Radioactivity measurements were performed using a Packard 2000CA TRICARB liquid scintillation analyzer.

### 2-[ring-U-<sup>14</sup>C]phenyl-1,3-propanediol [3]

To a 100 mL round bottom flask fitted with an argon inlet tube, a magnetic stir bar, a 50 mL dropping funnel and a thermometer was added DiBAL-H (17 mL, 1.0M solution in tetrahydrofuran). The temperature was lowered to -10°C using a dry ice/acetone bath. A mixture of diethyl 2-[ring-U-<sup>14</sup>C]phenylmalonate (100 mCi, 531 mg, 2.22 mmol) and unlabelled (163.7 mg, 0.68 mmol) diethyl 2-phenylmalonate dissolved in dry tetrahydrofuran (35 mL) was added dropwise, maintaining the temperature at -10°C. After the addition was complete, the cooling bath was removed and the reaction allowed to warm to ambient temperature. The reaction was monitored by TLC; after 4 h there was no evidence of starting material. The temperature was lowered to -10°C and the reaction was quenched slowly with methanol (4 mL) followed by 2N hydrochloric

acid (8 mL). The homogeneous solution was extracted with diethyl ether (2 x 30 mL). The aqueous layer was made alkaline (pH=9-10) using saturated potassium carbonate solution. The aqueous layer was extracted with diethyl ether (2 x 30 mL) and the combined ether layers washed with water (30 mL), dried over magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure to obtain crude diol. The diol was purified by silica gel chromatography using 4% methanol in methylene chloride as the eluent to yield 0.22g, 50 mCi (50%) of pure diol, **3**, which co-chromatographed with an authentic sample on hplc.

**2-[ring-U-<sup>14</sup>C]phenyl-1,3-propane-diphenyl dicarbonate [4]**

To a 50 mL round bottom flask fitted with an argon inlet tube was added diol, **3**, (0.22 g, 1.44 mmol, 50 mCi), dry pyridine (0.93 mL, 11.91 mmol) and methylene chloride (5 mL). The reaction was stirred at ambient temperature while phenylchloroformate (0.54 mL, 4.76 mmol) dissolved in methylene chloride (5 mL) was added slowly via syringe. The reaction temperature rose to reflux during addition. After the addition was complete, the reaction was stirred for 1 h. Additional phenylchloroformate (0.27 mL, 2.38 mmol) in methylene chloride (0.5 mL) was added and the reaction stirred for 0.5 h. The reaction was quenched by adding ice to the reaction flask. The mixture was transferred to a separatory funnel and the layers separated. The methylene chloride was washed with 2N hydrochloric acid (2 x 5 mL), brine (10 mL) and dried over magnesium sulfate. The solid was filtered and the filtrate concentrated under reduced pressure to give 0.77g of crude carbonate, **4**. Compound **4** was used without further purification.

**2-[ring-U-<sup>14</sup>C]phenyl-1,3-propanediol-dicarbamate (<sup>14</sup>C-Felbamate [1])**

To a 100 mL round bottom flask was added the crude carbonate, **4**, (0.77g) and methanolic ammonia (50 mL). The reaction was sealed and stirred for 20 h. The solvent was removed under reduced pressure to give crude Felbamate. The crude solid was slurried in hexane (25 mL) for 0.5 h, the solvent decanted and the residue dried to yield 0.206g, 30 mCi, (60% from **2**) of pure Felbamate. The hplc analysis using systems 1 and 2 indicated that the radiolabelled material was 98.4% pure as compared to that of the reference standard with no minor component containing more than 1% of the total radioactivity.

## References

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