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Research Article

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Synthesis and characterization of dimer impurity of Felbamate, an anti-epileptic drug substance

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ABSTRACT

Felbamate is an anticonvulsant drug used in the treatment of epilepsy. Dimer impurity of Felbamate substance was synthesized and characterized. Structure of Felbamate dimer was verified by synthesis, comparison of the spectra and chromatographic (HPLC) retention data.

Keywords: Synthesis, characterization, dimer, anticonvulsant, retention time, monograph

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INTRODUCTION

Felbamate marketed under the brand name Felbatol is an anti-epileptic drug [1]. Felbamate is approved for adjunctive or monotherapy in adults with partial seizures with or without secondary generalization [2, 3]. Felbamate´s mechanism of action is not known, but it has been reported as an allosteric antagonist at the NR2B subunit of the NMDA glutamate receptor and also as $GABA_A$ receptor agonist.

The control of pharmaceutical impurities is currently a critical issue to the pharmaceutical industry. The International Conference on Harmonization (ICH) has formulated a workable guideline regarding the control of impurities. Now a days in order to improve safety and efficacy of drug, there is a tremendous upsurge for the impurity identification and profiling for the pharmaceuticals products. Identification, characterization and quantification of any impurity by analytical method is very important in order to minimize toxicity of any drug [4-7]. As per regulatory guidelines for any products it is important to fix the limit for any specified and unspecified impurity in the product.

Felbamate chemically known as 2-phenylpropane-1,3-diyl dicarbamate (**1**); **Fig. 1** is typically synthesized from commercially available diethyl phenyl malonate in two steps. Diethyl phenyl malonate converted into corresponding diol as a key intermediate using several reagents, among which sodium borohydride is preferred, subsequent transformation into the corresponding carbamate can be carried out using phosgene, chloroformate, cyanate derivatives, and urethane exchange method [8].

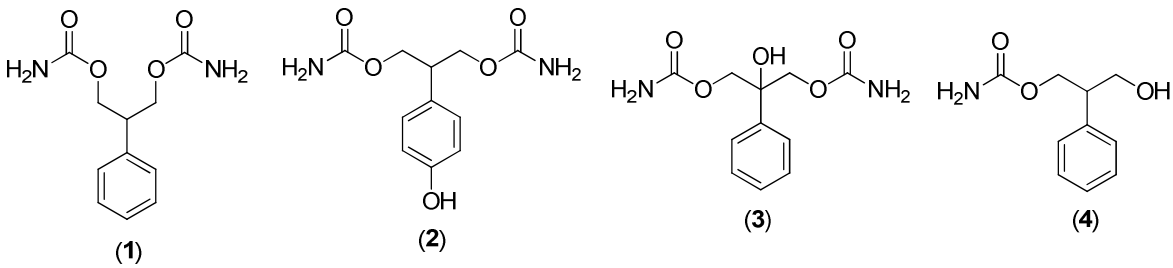
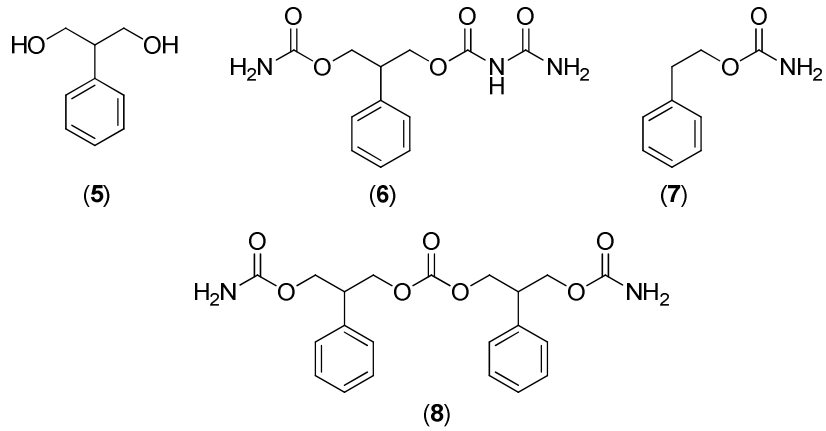


Fig. 1: Felbamate and their metabolites

Synthesis of Felbamate metabolites *i.e.* 2-(4-hydroxyphenyl)-1,3-propanediol dicarbamate (**2**), 2-phenyl-2-hydroxy-1,3-propanediol dicarbamate (**3**), and 2-phenyl-1,3-propanediol monocarbamate (**4**); **Fig. 1** is well documented [9, 10]. In USP monograph total five impurities **Fig. 2** related to Felbamate API are 2-phenylpropane-1,3-diol (**5**), impurity A *i.e.* 3-hydroxy-2-phenylpropyl carbamate (**4**), 3-carbamoyloxy-2-phenylpropyl allophanate (**6**), impurity B *i.e.* phenethyl carbamate (**7**), and dimer *i.e.* 3,3'-carbonylbis- (oxy)*bis*(2-phenylpropane-3,1-diyl) dicarbamate (**8**). Source of all these impurities are unreacted starting material, degradation or metabolic. Whereas dimer impurity is process related impurity, objective of this work was to synthesize the same in pure form with complete characterization.



(**5**) (**6**) (**7**)

(**8**)

Fig. 2: Felbamate USP related substances

EXPERIMENTAL SECTION

Thin-layer chromatography (TLC) were run on silica gel 60 F254 pre-coated plates (0.25 mm, Merck, Art. 5554) and spots were visualized inside an UV cabinet under short UV. Infrared spectra were recorded on IR Affinity-1, Shimadzu. ^{1}H-NMR spectra were recorded on Bruker Advance III 400 MHz with TMS as an internal standard. Mass spectra were obtained using LC-MS API-2000, ABSciex. All solvents and reagents were purchased from Aldrich (India) and S. D. Fine Chemicals, Mumbai. The solvents and reagents were used without purification. 2-Phenyl-1,3-propanediol monocarbamate (**4**) one of starting material was synthesized as per literature [10].

Experimental procedures

Synthesis of 3,3'-Carbonylbis-(oxy)bis(2-phenylpropane-3,1-diyl) dicarbamate (8):

Step 1: To a solution of 3-hydroxy-2-phenylpropyl carbamate (**4**) (1.0 g, 5 mmole) and triethylamine (1.2 mole equiv.) in dichloromethane (15 ml) was added phenyl chloroformate (1.1 mole equiv.) at 0-5 °C. Reaction mixture was allowed to come to room temperature and maintain for 3 h. Reaction progress was monitored by TLC. Reaction mixture was diluted with water (10 ml). Organic layer washed with water (4×10 ml) and dried over sodium sulfate, filtered, concentrated under reduced pressure to obtain crude product (**9**) (2.60 g) as viscous oil.

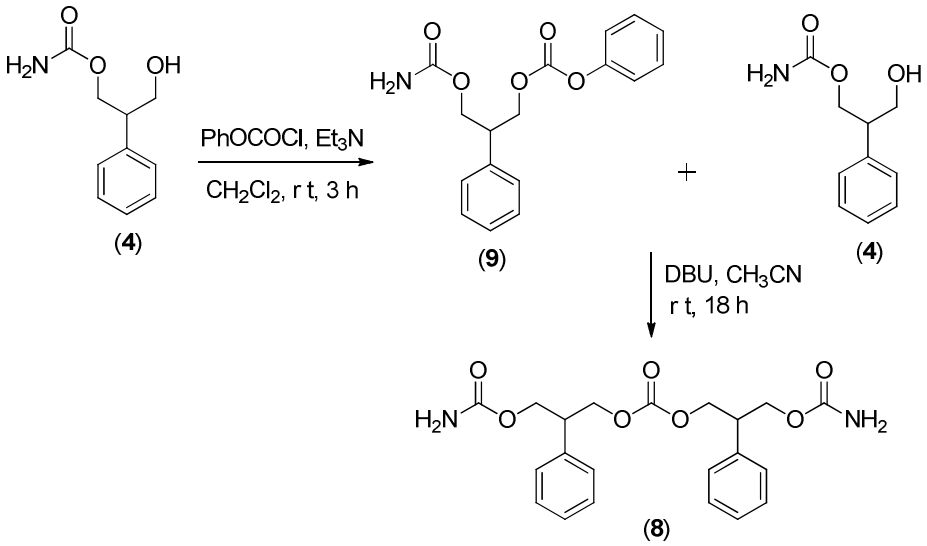
Step 2: To a solution of crude product (**9**) (2.60 g, 5 mmole) in acetonitrile (20 ml) was added DBU (1.5 mole equiv.) dropwise at room temperature and maintain for 15 min. To this reaction mixture was added solution of 3-hydroxy-2-phenylpropyl carbamate (**4**) (1 mole equiv.) in acetonitrile (5 ml) at room temperature maintain for 18 h. Reaction progress was monitored by TLC. The reaction mixture was diluted with dichloromethane (20 ml) and water (20 ml). Organic layer was separated, dried over sodium sulphate, filtered and concentrated under reduced pressure to obtain crude product (2.90 g) as gummy semi solid. The crude reaction mixture was purified by flash column chromatography in dichloromethane:methanol as gradient to obtain (0.700 g; 33%) as a white colored solid product. HPLC Purity= 98.84%. IR (cm^{-1}): 3437, 3327, 3261, 3200, 1730, 1701, 1697, 1612, 1456, 1419, 1356, 1263, 1064, 966, 700. ^{1}H-NMR ($CDCl_3$) δ 7.31-7.24 (dd, *J*= 6.8 and 1.6 Hz, 4H, Ar-H), 7.24-7.21 (dd, *J*= 8.0 and 4.4 Hz, 2H, Ar-H), 7.13-7.19 (dd, *J*= 7.2 and 3.2 Hz 4H, Ar-H), 5.23 (bs, 4H, CH), 4.67-4.23 (m, 4H), 3.30-3.24 (m, 2H). Mass: 417 ($M+H^+$) and 415 ($M-H^-$).

RESULTS AND DISCUSSION

As per USP monograph Felbamate dimer (**8**) is having relative retention time (RRT) 9.1 and relative response factor 1.0 with acceptance criteria NMT 0.15%. Synthesis of dimer impurity is not reported in literature. Considering crucial role of this impurity as per regulatory requirement we have decided to synthesize the same which was confirmed with HPLC RRT using HPLC method as per USP monograph and complete characterization.

Phenylchloformate is known reagent for urea derivative synthesis. Felbmate dimer (**8**) is a mixed anhydride type of compound. Phenylchloroformate derivative is reactive chemical intermediate used in synthesis of various pharmaceutical and agrochemical products.

Phenylmonocarbamate (**4**) was synthesized as per literature [10] which was treated with phenyl chloroformate under basic condition to obtain intermediate 3-(phenoxycarbonyl- oxy)-2-phenylpropyl carbamate (**9**), which was further reacted with another mole equivalent of phenylmonocarbamate (**4**) specifically with DBU as a base leads to dimer impurity, 3,3'-carbonylbis-(oxy)bis(2-phenylpropane-3,1-diyl) dicarbamate (**8**); **Scheme 1**. Synthesis of Felbamate dimer (**8**) was tried using different mild bases having less pKa such as pyridine, triethyl amine, Hünig's base and methyl picoline under different reaction conditions but reaction was not going forward. Inorganic base such as potassium carbonate or sodium hydride was not preferred considering instability of intermediate in presence of such strong base.



Scheme 1: Synthetic reaction scheme for Felbamate dimer impurity (8)

CONCLUSION

Felbamate dimer impurity 3,3'-carbonylbis-(oxy)bis(2-phenylpropane-3,1-diyl) dicarbamate (**8**) is synthesized independently for its use in pharmaceutical industry for method development and validation. Various bases were tried, DBU worked well for final reaction between phenylmonocarbamate (**4**) and 3-(phenoxycarbonyloxy)-2-phenyl- propyl carbamate (**9**) to get Felbamate dimer (**8**).

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