

Short Note

(Benzoylamino)methyl 4-Hydroxybenzoate

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Abstract: (Benzoylamino)methyl 4-hydroxybenzoate (“Benzamidomethylparaben”) (3) was obtained from a reaction of 4-hydroxybenzoic acid (2) with a dioxane suspension of (benzamidomethyl)triethylammonium chloride (1). The phenolic group in 2 cannot be benzamidomethylated with 1 in aqueous media.

Keywords: benzamidomethyl; paraben; 4-hydroxybenzoic acid; preservative

Parabens such as methylparaben, ethylparaben, propylparaben, isopropylparaben, butylparaben and isobutylparaben are chemical compounds derived from 4-hydroxybenzoic acid (2) [1]. For almost one century they have been successfully used as antimicrobial preservatives in foods and beverages, pharmaceuticals and cosmetics [2]. In addition, parabens have been reported to have anticonvulsive, vasodilating, analgesic, and anesthetic effects in animals [3,4].

Considering toxicity, many results so far are inconclusive. Once entering the human body, parabens do not accumulate, but are rapidly absorbed, metabolized and excreted. Numerous acute toxicity studies as well as subchronic and chronic oral studies confirm their low toxicity, non-sensitivity and non-irritability [1,5,6]. Estrogen agonist properties of parabens have been documented with a wide variety of assay systems *in vitro* and *in vivo* [7,8]. However, research data related to the vulnerability of the paraben exposure in estrogen-sensitive period of implantation indicated that parabens may not be as potent as previously reported [6]. In addition, some of the parabens have also been shown to possess androgen antagonist activity, to act as inhibitors of sulfotransferase enzymes and to possess genotoxic activity, especially when multiple daily doses of parabens, combined with other ingredients, are applied [9–15].

So, in view of the long history of use of parabens and of these inconclusive data, there remains a need for detailed research and evaluation of their biological properties and it is continuously performed [16–18]. In parallel, the search for new ways of synthesis [19] or new parabens continues [20].

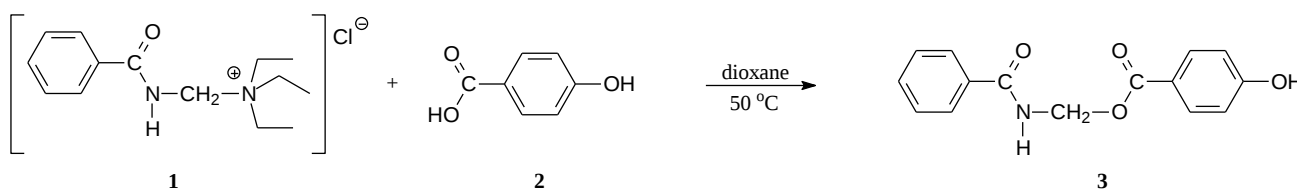
In this paper, we present the synthesis of a new paraben compound, *i.e.*, “benzamidomethylparaben” [(benzoylamino)methyl 4-hydroxybenzoate]. The benzamidomethyl group can be found in many molecules with biological activity or it intermediates within the synthesis of different biologically active compounds [21–25] such as the 2-benzamidomethyl-3-oxybutanoates, which are used as intermediates in the preparation of (2*R*,3*S*)-2-benzamidomethyl-3-hydroxybutanoates [26–28] as chiral building blocks for the synthesis of biologically active carbapenems [29–31].

We have already reported [32] that phenols can be easily benzamidomethylated with (benzamidomethyl)triethylammonium chloride (**1**) in aqueous media (pH > 9), giving high yields of the corresponding ethers. Also, carboxylic acids give moderate yields of the corresponding esters in reactions with acetone or dioxane suspensions of **1** in the presence of a small amount of triethylamine (TEA) [33].

According to our research, 4-hydroxybenzoic acid (in which both a phenolic group and a carboxylic group are present) cannot be benzamidomethylated with **1** in aqueous media. The carboxylic group as a weak nucleophile in aqueous media does not react, but it deactivates the phenolic group in the molecule of **2**. However, when the same reaction was performed in a dioxane suspension of **1** in the presence of TEA, a moderate to high yield of benzamidomethyl paraben (**3**) was obtained (Scheme 1).

For further evaluation, the biological properties of the newly synthesized compound, benzamidomethylparaben, will be investigated. Knowing that an ester chain is necessary for antimicrobial activity [1,2] and considering the fact that it is preserved in the molecule, one can expect that this compound could be used as preservative.

Scheme 1. Synthetic route to the title compound **3**.



Experimental

Compound **1** is not commercially available and it was synthesized as described previously [32].

(Benzoylamino)methyl 4-hydroxybenzoate (“Benzamidomethylparaben”) (**3**)

Finely powdered (benzamidomethyl)triethylammonium chloride (0.997 g, 3.68 mmol) was suspended in dioxane (30 mL). Triethylamine (0.2 mL) and 4-hydroxybenzoic acid (0.608 g, 4.40 mmol) were added to the suspension. The mixture was stirred at 50 °C for 4 h and left to cool at room temperature. After cooling, water was added to the mixture until occurrence of a precipitate. The typical yield of crude colorless crystals with m.p. of 148–154 °C was 75%. Purification was performed

firstly by dissolving the product in dioxane (or acetone), followed by precipitation with water and then by recrystallization from CHCl_3 .

Melting point: 165–166 °C.

FT-IR (KBr): 3385 cm^{-1} (νNH); 3320 cm^{-1} (νOH); 1689 cm^{-1} ($\nu\text{OC=O}$); 1663 cm^{-1} Amide I; 1527 cm^{-1} Amide II

^1H -NMR (300 MHz, $\text{DMSO-}d_6$): δ/ppm 10.37 (s, 1H, OH); 9.63 (t, $J = 6.5$ Hz, 1H, NH); 7.96–6.85 (m, 9H, Ar); 5.56 (d, $J = 6.7$ Hz, 2H, $\text{N-CH}_2\text{-O}$).

^{13}C -NMR (75 MHz, $\text{DMSO-}d_6$): δ/ppm 167.11 (C=O); 165.36 (C=O); 65.31 (CH_2); Ar: 162.25, 133.25, 132.11, 131.64, 128.57, 127.66, 120.18, 115.50.

Anal. Calcd. (found) for $\text{C}_{15}\text{H}_{13}\text{NO}_4$: C, 66.41 (66.29); H, 4.83 (4.86); N, 5.16 (5.31).

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