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Syntheses of Potential Degradation Products of Phenylephrine in OTC Products

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Abstract: Compound **1** and **2** are potential major degradants in over the counter (OTC) products containing phenylephrine HCl and dexbrompheniramine maleate or chlorpheniramine maleate. Compound **2** matches the unknown peak in the solution of stressed active and excipient and thus was identified as the correct degradation product. Whether the degradation product is racemic or chiral is not known. This article describes synthesis of both compounds. Compound **2** will be useful as an analytical standard for quantitative analysis of the major degradant in OTC products of phenylephrine HCl and dexbrompheniramine maleate or chlorpheniramine maleate.

Keywords: Chlorpheniramine; Degradants; Maleate; Michael addition; Phenylephrine

INTRODUCTION

The decongestant phenylephrine is used in many over-the-counter (OTC) products for treatment of the common cold. A novel degradation product was isolated from pharmaceutical formulations containing phenylephrine HCl and chlorpheniramine maleate and was assigned structure **1**.[1] Compound **1** is presumably formed by reaction of phenylephrine with maleic acid with a hydroxyl group migration or with malic acid with a removal of water. We observed a compound with the same molecular weight and similar high pressure liquid chromatography (HPLC) retention time and ultra violet (UV) spectrum in formulations containing phenylephrine

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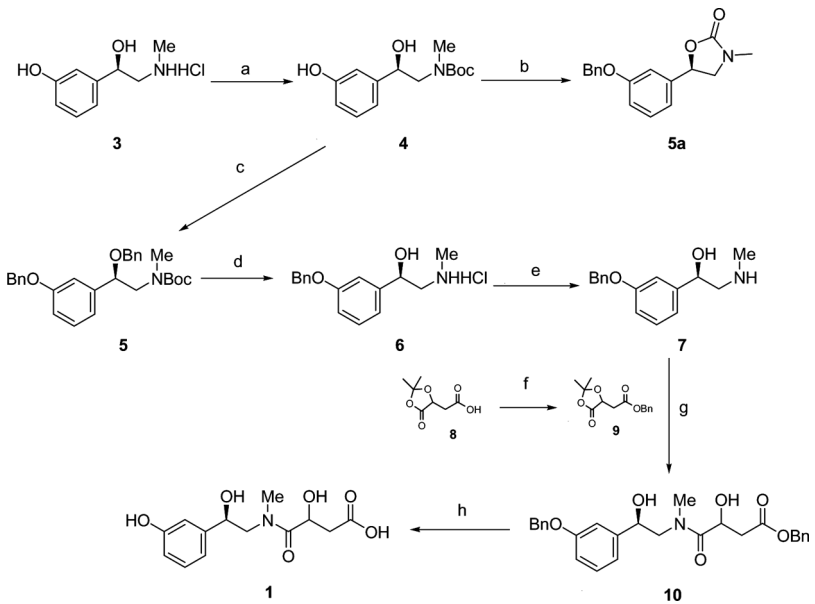
HCl and dexbrompheniramine maleate. We synthesized compound **1** and found the NMR spectrum to be different from that reported.[2] Reaction of phenylephrine and maleic acid could also give structure **2**. We synthesized compound **2** and found this structure to be correct.[2]

RESULTS AND DISCUSSION

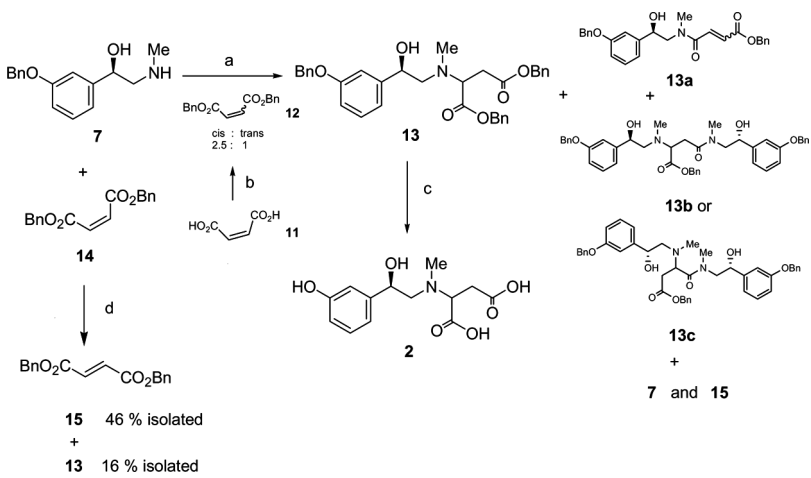
The synthesis of compound **1** is shown in Scheme 1. (*R*)-(–)-Phenylephrine hydrochloride (**3**)[3] was treated with Boc_2O in the presence of 1 N NaOH to give compound **4**. An attempt to protect both hydroxyl groups of **4** with 2 equivalents of benzyl bromide and 2 equivalents of NaH in N, N-dimethyl formamide (DMF) gave **5a**[3b, 4] instead. [One equivalent of NaH and 1 equivalent of benzyl bromide under the same condition afforded 63% of compound **5a**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.90 (s, 3H), .21 (dd, 1H, $J = 8.4$, 8.8 Hz), 3.90 (t, 1H, $J = 8.8$ Hz), 5.08 (s, 2H), 5.42 (t, 1H, $J = 8.0$ Hz), 6.90–7.00 (m, 3H), 7.30–7.43 (m, 6H).



Scheme 1. Synthesis of compound 1: Reagents and conditions: (a) 1N NaOH/THF (1:1), Boc_2O, 1 h, 100%; (b) 2 eq. NaH, 2 eq. BnBr, DMF, rt, 18 h, 56%; (c) 2 eq. Cs_2CO_3, 2 eq. BnBr, 3 h, 100%; (d) 4N HCl in dioxne, 3 h, 76%; (e) 1N NaOH, 1 h, 100%; (f) 1 eq. Cs_2CO_3, 1 eq. BnBr, DMF, 3 h, 59%; (g) DMF, 105°C, 12 h, 34%; and (h) MeOH, Pd/C, H_2, rt 18 h, 98%.

MS, m/z284 ($M^+ + 1$, 75%).] No product **5** was detected. Use of 2 equivalents of Cs_2CO_3 and 2 equivalents of benzyl bromide in DMF gave **5** in quantitative yield. Compound **5** was treated with 4 N HCl in dioxane to remove the Boc protecting group. To our surprise, the benzyl group of the secondary alcohol was also cleaved off to give **6** in 83% isolated yield. The amino alcohol **7** was obtained quantitatively after basification of **6**. Compound **9**[5] was prepared by reacting racemic compound **8** with benzyl bromide in the presence of NaH in DMF. Following the procedure of A. Khalaj,[6] heating a mixture of **7** and **9** in DMF at 103 to 105°C for 12 h afforded compound **10** in 34% isolated yield. The benzyl protecting group of **10** was removed by hydrogenolysis with H_2 and Pd/C in MeOH to give compound **1**.

The synthesis of compound **2** is shown in Scheme 2. Maleic acid **11** was treated with benzyl bromide in the presence of Cs_2CO_3 in DMF at 60°C to give a mixture of dibenzyl maleate and dibenzyl fumarate **12**, in a ratio of 2.5 to 1. Compound **7** reacted with the maleate–fumarate mixture **12** in DMF at 45°C for 65 h to give compound **13** in 20% isolated yield. The low yield of **13** was caused by several factors. The major factor was the competition between isomerization of dibenzyl maleate **14** to dibenzyl fumarate **15** versus the desired Michael addition of **7** to dibenzyl maleate. This competition was confirmed by reacting pure dibenzyl



Scheme 2. Synthesis of compound 2: Reagents and conditions: (a) DMF, 1 1/2 h, 20%; (b) 2 eq. Cs_2CO_3, 2 eq. BnBr, DMF, rt, 5 h, 80%; (c) MeoH, H_2, rt 18 h, 96%; (d) DMF, 42°C, 1 h, 16% of **13**.

maleate **14** with amine **7** in the same fashion as described previously. Dibenzyl fumarate **15** and compound **13** were isolated in 46% and 16% yield, respectively. It seems that amine **7** only reacted with dibenzyl maleate **14**. By-products **13a** and **13b** or **13c** and starting material **7** were identified from their $M^+ + 1$ ions in the mass spectrum of the crude reaction. These side reactions also contributed to the poor yield. Compound **2** was obtained after removal of all benzyl groups of **13** by hydrogenation in MeOH with Pd/C in 90% yield.

CONCLUSION

Structures of compounds **1** and **2** were determined by two-dimensional nuclear magnetic resonance (2D NMR) as described previously.[2] All protons and carbon resonances in the spectra were assigned, and the connectivities between proton and carbon nuclei were confirmed by 2D NMR techniques such as heteronuclear single-quantum correlation (HSQC), heteronuclear single-quantum correlation total correlation spectroscopy (HSQCTOCSY), and HMBC. The NMR spectrum of compound **1** is more complicated than compound **2** because both diastereomers have two rotomers. Therefore, four sets of peaks in the NMR spectrum were observed for compound **1**, and only two sets of peaks were observed for compound **2**. Compound **2** matches the major unknown peak in the solution of stressed active and excepient, and compound **1** does not.[2]

Two new potential degradants were synthesized. These two compounds were fully characterized by MS and NMR. Both compounds are adducts of phenylephrine and maleic acid. The Michael addition product, compound **2**, is the correct structure of the degradation product found in OTC pharmaceutical preparations. The stereochemistry of isolated degradant is not known.[1]

EXPERIMENTAL

General

Starting materials, reagents, and solvents were purchased from commercial suppliers and used without further purifications. Because compound **8** is not available as a racemate from Aldrich, a 1:1 mixture of R and S is used. Melting points were determined with a Thomas-Hoover Uni-Melt apparatus and are uncorrected. Column chromatography was performed on silica gel, 230–400 mesh. Chemical shifts (δ) are reported in parts per million. All ^{1}H NMRs were recorded with a Varian 400-MHz spectrometer with solvents indicated. Mass spectra were obtained with either Waters-ZQ

mass spectrometer or JUL Mstation magnetic factor mass spectrometer. Mass spectra were used only to detect mass ions. CHN analyses were performed by QTI Technologies Inc., Whitehouse, New Jersey.

tert-Butyl[(2R)-2-hydroxy-2-(2-hydroxyphenyl)ethyl]carbamate (4)

To a stirred solution of (R)-(−)-phenylephrine hydrochloride **3** (10 g, 49.3 mmol) in 1 N NaOH and THF (1:1) (100 mL), Boc_2O (10.75 g, 49.3 mmol) was added. The reaction mixture was stirred at rt for 1 h. Solvents were removed, and the residue was dissolved in CH_2Cl_2 (100 mL) and washed with water (50 mL). The aqueous was extracted again with layer CH_2Cl_2 (100 mL). The combined CH_2Cl_2 phases was dried over $MgSO_4$, filtered, and concentrated to give **4** as a glassy foam (12 g, 97%): ^{1}H NMR ($CDCl_3$) of two rotamers with 3:2 ratio. δ 6.7–7.3 (4 H), 4.8–4.9 (1 H), 3.3–3.6 (2 H), 2.8–2.9 (3 H), 1.4–1.5 (9 H); MS m/z 290 ($M^+ + Na$). $[\alpha]^{21}{}_D = +25.2^\circ$ (C = 1.0 MeOH).

(5R)-5-[3-(Benzyloxy)phenyl]-3-methyl-1,3-oxazolidin-2-one (5a)

NaH (60%) (659 mg, 10 mmol) was added portionwise to a solution of **4** (2.0 g, 7.5 mmol) in DMF (20 mL). This was stirred at rt for 30 min or until no gas evolution. To this was then added BnBr (3.76 g, 21.9 mmol) via a syringe. The reaction was stirred at rt overnight. The reaction mixture was diluted with water (50 mL) and extracted with Et_2O (2 × 200 mL). Et_2O layer was washed with water (2 × 50 mL), dried over $MgSO_4$, filtered, and then concentrated. The crude mixture was purified with a silica-gel column, eluted with 10 to 50% EtOAc in hexane to afforded **5a** (1.13 g, 53%) as white crystalline solid: mp 57–59°C; MS m/z 284 ($M^+ + H$). Anal. calc. for $C_{17}H_{17}NO_3$: C, 72.07; H, 6.05; N, 4.94. Found: C, 72.06; H, 6.07; N, 4.96.

tert-Butyl{(2R)-2-(benzyloxy)-2-[3-(benzyloxy)phenyl]ethyl}-methylcarbamate (5)

Cs_2CO_3 (3.25 g, 10 mmol) was added to a solution of **4** (1.0 g, 3.74 mmol) and BnBr (1.71 g, 10 mmol) in DMF (10 mL). The reaction was stirred at rt for 3 h. The reaction was filtered, diluted with Et_2O (100 mL), washed with water (3 × 30 mL), dried over with $MgSO_4$, and concentrated to give **5** (1.8 g > 100%) as a yellowish oil: ^{1}H NMR ($CDCl_3$) δ 7.2–7.5 (11 H), 7.1 (1 H), 6.8–7.0 (2 H), 5.1 (s, 2 H), 4.9 (1 H), 4.5 (s, 2 H), 3.3–3.6 (br, 2 H), 2.8 (br, 3 H), 1.5 (s, 9 H); MS m/z 470 ($M^+ + Na$).

(1R)-1-[3-(Benzyloxy)phenyl]-2-(methylamino)ethanol, hydrochloride (6)

HCl (4N) in dioxane (150 mL) was added to a solution of **5** (24 g, 53.6 mmol) in dioxane (100 mL) at rt. After stirring for 2 h, solvents were removed, and the residue was triturated with Et_2O (250 mL). The solids were filtered to give **6** (12 g, 76%) as a white solid: ^{1}H NMR (D_2O) δ 6.8–7.4 (9 H), 5.0 (s, 2 H), 4.8 (m, 1 H), 3.1 (m, 2 H), 2.6 (s, 3 H).

(1R)-1-[3-(Benzyloxy)phenyl]-2-(methylamino)ethanol (7)

NaOH (1N) (50 mL) was added to a solution of **6** (12 g, 41 mmol) in water (55 mL). After stirring for 15 min, the reaction was diluted with water (100 mL) and then extracted with CH_2Cl_2 (2 × 500 mL). CH_2Cl_2 phase was washed with brine, dried over $MgSO_4$, filtered, and then concentrated to give **7** (10.5 g, 100%) as a white solid: mp 91–93°C; ^{1}H NMR ($CDCl_3$) δ 7.3–7.4 (m, 5 H), 7.2 (t, $J = 8$ Hz, 1 H), 7.1 (s, 1 H),7.0 (dd, $J = 8$, 2 Hz, 1 H), 6.9 (dd, $J = 8$, 2 Hz, 1 H), 5.1 (s, 2 H), 4.7 (m, 1 H), 2.6–2.9 (m, 2 H), 2.4 (s, 3 H); MS m/z 258 ($M^+ + H$), 240 ($M^+ + H\text{-}H_2O$). Anal. calc. for $C_{16}H_{19}NO_2$: C, 74.68; H, 7.44; N, 5.44. Found: C, 74.29; H, 7.49; N, 5.44.

2,2-Dimethyl-5-oxo-1,3-dioxolane-4-acetic Acid Benzyl Ester (9)

BnBr (15.7 g, 91.8 mmol) was added to a solution of 1:1 mixture of (R) and (S) of 2.2, dimethyl-5-oxo-1,3-dioxolane-4-acetic acid **8** (16 g, 91.8 mmol) in DMF (100 mL). After stirring for 5 min, Cs_2CO_3 (30 g, 91.8 mmol) was added. The reaction was stirred at rt for 3 h and at 45°C for 30 min. The reaction was filtered. The filtrate was diluted with Et_2O (500 mL, washed with water (3 × 300 mL) and brine (1 × 100 mL), dried over $MgSO_4$, and then filtered. Solvents were evaporated. The crude product was chromatographed on a silica column, and eluted with 20% EtOAc in hexane to give **9** (14.2 g, 59%) as a white solid: mp 42–44°C; ^{1}H NMR ($CDCl_3$) δ 7.4 (m, 5 H), 5.2 (m, 2 H), 4.7 (m, 1 H), 3.0 (dd, 4, 15 Hz, 1 H), 2.9 (dd, 8, 15 Hz, 1 H), 1.6 (s, 3 H), 1.5 (s, 3 H). Anal. calc. for $C_{14}H_{16}O_5$: C, 63.63; H, 6.10. Found: C, 63.44; H, 6.13.

Benzyl-4-[{(2R)-2-[3-(benzyloxy)phenyl]-2-hydroxyethyl}(methyl)amino]-3-hydroxy-4-oxo-butanoate (10)

A solution of **7** (11 g, 42.8 mmol) and **9** (8.3 g, 31.4 mmol) in DMF (150 mL) was heated at 104°C for 12 h. DMF was evaporated, and the

residue was diluted with EtOAc (500 mL), washed with water (3×300 mL), dried over $MgSO_4$, filtered, and then concentrated. The crude product was chromatographed on a silica-gel column and eluted with 30–60% of EtOAc in hexane to give **10** (5.0 g, 34%) as a yellowish gum: ^{1}H NMR ($CDCl_3$) of 2 diastereomers and 2 rotamers with 3:1 ratio δ 6.9–7.5 (14 H), 5.2 (s, 2 H), 5.1 (s, 2H), 4.7–5.1 (2 H), 3.2–3.9 (2 H), 2.9–3.1 (3 H), 2.5–2.8 (2 H); MS m/z 486 ($M^+ + Na$), (FAB) m/z 464 ($M^+ + H$), 446 ($M^+ + H–H_2O$).

3-Hydroxy-4-{[(2R)-2-hydroxy-2-(3-hydroxyphenyl)ethyl](methyl)amino}-4-oxo-butanoic Acid (1)

Compound **10** was dissolved in MeOH (200 mL), and 10% Pd/C (1 g) was added under an N_2 atmosphere. The reaction was hydrogenated with a balloon filled with H_2 overnight. After purging with N_2, catalyst was removed by filtration, and solvents were removed under reduced pressure to afford **1** (3.0 g, 98%) as a white gum: ^{1}H NMR (CD_3OD) of 2 diastereomers and 2 rotamers d 7.2 (1 H), 6.9 (2 H), 6.7 (1 H), 4.8–5.0 (2 H), 3.4–3.9 (2 H), 2.9–3.1 (4 s, 3 H), 2.4–2.9 (2 H); MS *m/z* 306 ($M^+ + Na$), 284 ($M^+ + H$), 266 ($M^+ + H–H_2O$). $[\alpha]^{22}_D = -6.8^\circ$ (C = 1.0, MeOH).

Z and *E* But-2-enedioic acid Dibenzyl Ester (12)

Cs_2CO_3 (65 g, 200 mmol) was added to a solution of maleic acid **11** (11 g, 94.8 mmol) and BnBr (34 g, 199 mmol) in DMF (300 mL). The reaction was stirred at 60°C for 5 h and then stirred at rt overnight. Solids were filtered, and the filtrate was evaporated on rota-evaporator. The residue was dissolved in EtOAc (500 mL), washed with water (2×250 mL), dried over $MgSO_4$, filtered, and then concentrated to give **12** (22.3 g, 75%, Z/E = 2.5) as a brown oil. A portion of this mixture (15 g) was chromatographed on a silica-gel column, eluted with 5 to 20% of EtOAc in hexane to give E isomer **15** (4 g) as an off-white solid (less polar) and Z isomer **14** (10 g) as a clear oil (more polar). **14**: ^{1}H NMR ($CDCl_3$) δ 7.38 (m, 10 H), 6.29 (s, 2 H), 5.15 (s, 4 H); **15**: ^{1}H NMR ($CDCl_3$) δ 7.39 (m, 10 H), 6.92 (s, 2 H), 5.22 (s, 4 H).

Dibenzyl-N-{(2R)-2-[3-(benzyloxy)phenyl]-2-hydroxyethyl}-N-methylaspartate (13)

Compound **12** (1.5 g, 5.1 mmol) was added to a stirred solution of **7** (1.3 g, 5.1 mmol) in DMF (14 mL) at rt. The reaction was heated at

45°C for 1.5 hours. The reaction was chilled in an ice bath and then diluted with Et_2O (100 mL), washed with water (2 ×), dried over $MgSO_4$, filtered, and concentrated. The crude product was passed through a silica-gel column and eluted with 10–30% EtOAc in hexane to provide **13** (540 mg, 20%) as a yellowish thick oil: ^{1}H NMR ($CDCl_3$) of 2 diastereomers in the ratio 2.5 to 1, δ 6.8–7.6 (19 H), 5.0–5.2 (6 H), 4.6–4.8 (1 H), 4.0 (1 H), 3.6–3.9 (br, 1 H), 2.5–3.0 (4 H), 2.4–2.5 (2 s, 3 H); MS *m/z* 554 ($M^+ + H$).

N-{(2R)-2-Hydroxy-2-(3-hydroxyphenyl)ethyl]}-N-methylaspartic Acid (2)

Compound **13** (634 mg, 1.15 mmol) was dissolved in MeOH (50 mL), and 10% Pd/C (60 mg) was added under an N_2 atmosphere. The reaction was hydrogenated overnight with a balloon filled with H_2. After purging with N_2, catalyst was removed by filtration. Solvents were removed under reduced pressure to give **2** (335 mg, 96%) as a white glassy foam: ^{1}H NMR (D_2O) of 2 diastereomers, δ 6.7–7.2 (4 H), 5.0 (1 H), 4.2 (1 H), 3.2–3.4 (2 H), 3.2 and 2.8 (2 s, 3 H), 2.8 (2 H); MS m/z 284 $M^+ + H$), 266 ($M^+ + H–H_2O$).

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