

Synthesis of Substituted Phenyl *N*-(2-hydroxybenzyl)-*N*-Methylcarbamates

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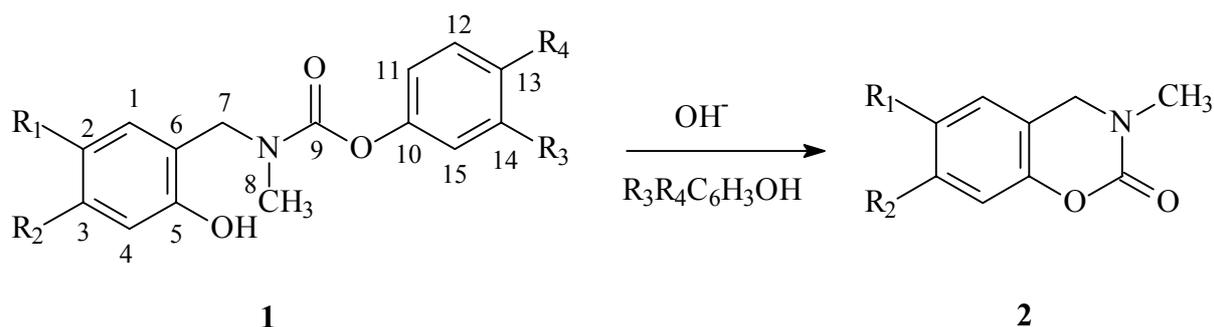
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Abstract: Thirteen previously unreported substituted phenyl *N*-(2-hydroxybenzyl)-*N*-methylcarbamates were prepared by the reaction of substituted 2-hydroxybenzyl-*N*-methylamines with phenyl chlorocarbonates. They were identified by their ¹H- and ¹³C-NMR spectra.

Keywords: Carbamates syntheses, NMR-spectra

Introduction

Carbamates are widely used nowadays. Apart from the use of polyurethanes in plastics they are also common components of agrochemicals [1] or drugs used for treatment of Alzheimer's disease [2]. Their ability to cyclise to heterocyclic compounds is widely used in organic syntheses [3]. The aim of this work is to synthesise substituted phenyl *N*-(2-hydroxybenzyl)-*N*-methylcarbamates **1** which are to be used for studying kinetics and mechanism of their intramolecular cyclization to 3-methyl-4*H*-1,3-benzoxazin-2(3*H*)-ones (Scheme 1)

Scheme 1 - Preparation of 3-methyl-4*H*-1,3-benzoxazin-2(3*H*)-ones

Results and Discussion

A report that has been published recently surveys a number of papers concerned with the preparation of carbamates [4]. The selection of methods for preparation of carbamates such as structure **1** is limited both by the methyl group substitution on the nitrogen and by the presence of the nucleophilic hydroxyl group in the aromatic part of the benzylamine molecule. That is the reason why it is not possible to use an isocyanate as an intermediate for the syntheses. Taking into account the presence of the hydroxy group in the desired products, we thus chose to use phenyl chlorocarbonates (Scheme 2) in ether in the presence of TEA for phenoxy-carbonylation of the substituted 2-hydroxybenzyl-*N*-methyl amines:

Scheme 2

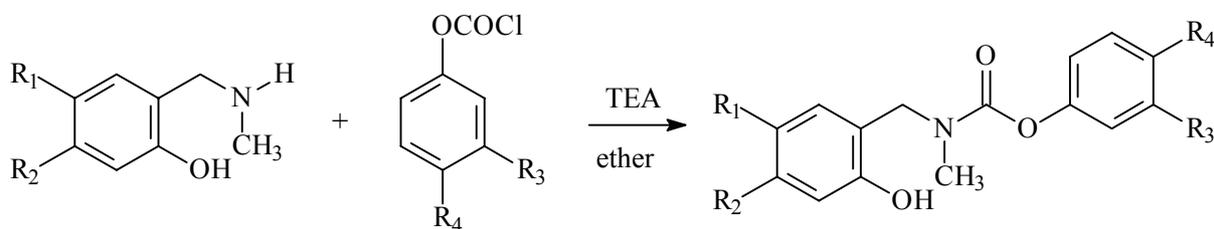


Table 1

	R ₁	R ₂	R ₃	R ₄		R ₁	R ₂	R ₃	R ₄
1a	H	Cl	H	H	1h	H	NO ₂	H	H
1b	H	Cl	Cl	H	1i	H	NO ₂	NO ₂	H
1c	H	Cl	NO ₂	H	1j	NO ₂	H	H	H
1d	Br	H	H	H	1k	NO ₂	H	H	Cl
1e	Br	H	H	Cl	1l	NO ₂	H	Cl	H
1f	Br	H	Cl	H	1m	NO ₂	H	NO ₂	H
1g	Br	H	NO ₂	H					

The reaction proceeds at room temperature and its progress can be followed by TLC. The reaction required some 30 minutes for all derivatives **1a-m** (see Table 1). The excess of TEA was removed after the saturation of the reaction mixture with hydrogen chloride and filtration of eliminated TEA·HCl. The required carbamates were obtained after the distilling off the solvent. They were purified by crystallisation from the mixture of heptane/propan-2-ol. The identification of compounds **1a-m** formed in this way was carried out by means of their elemental analysis and ¹H- and ¹³C-NMR spectra. The carbamates show three characteristic signals in their ¹³C-NMR spectra: ~ 157 ppm that corresponds to the C-OH carbon; ~ 156 ppm that corresponds to the carbamate carbonyl and ~ 150 ppm that corresponds to the C-10 carbon.

Conclusions

Thirteen previously undescribed substituted phenyl *N*-(2-hydroxybenzyl)-*N*-methylcarbamates **1a-m** were prepared by the reaction of substituted 2-hydroxybenzyl-*N*-methylamines with phenyl chlorocarbonates in ether in the presence of TEA. The structure of the compounds was confirmed by ¹H- and ¹³C-NMR spectra, which are also discussed.

Acknowledgements

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Experimental

General

Melting points were measured on Koffler instrument and they are not corrected ¹H- (360 MHz) and ¹³C-NMR (90.56 MHz) spectra in CDCl₃ were recorded using Bruker AMX 360 spectrometer. The ¹³C-NMR chemical shifts were referred to the solvent signal and this were recalculated in the δ-scale (δ-76.90 ppm). The δ (¹H) chemical shifts were referred to the internal hexamethyldisiloxane (δ 0.05) standard. Coupling constants *J*(H, H) are given in Hz. TLC chromatography was carried out on Silufol UV-254 plates (Kavalier, Czech republic), mobile phase 10:1 chloroform-heptane.

Phenyl *N*-(2-hydroxybenzyl)-*N*-methyl carbamates **1** (General method):

Substituted phenyl chlorocarbonate (5 mmol) was dissolved in dry diethyl ether (5 mL) and mixed within 20 minutes with substituted 2-(aminonethyl)phenol (5 mmol) and TEA (6 mmol) in diethyl ether (10 mL) at a temperature of 10 °C. Then the reaction mixture was stirred at the room temperature for 30 min. The mixture was saturated with dry hydrogen chloride and after the cooling (10 °C), the eliminated TEA·HCl was filtered off. Diethyl ether was distilled off under vacuum and the evaporation residue was crystallised from a 4:1 mixture of heptane/propan-2-ol.

Yields and physicochemical properties:

Phenyl N-(4-chloro-2-hydroxybenzyl)carbamate (1a). Yield 61%; m.p. 110.5-112.0°C; Calculated for C₁₅H₁₄ClNO₃ (291.2): 61.76 % C, 4.81% H, 4.80% N; found 61.73% C, 4.81% H, 4.95% N; ¹H-NMR: 8.93 (br, 1H, OH), 7.35 (m, 2H, H-12), 7.21 (m, 1H, H-13), 7.08 (m, 2H, H-11), 7.05 (d, *J*=8.1, 1H, H-1), 6.95 (s, 1H, H-4), 6.82 (dd, *J*=2.1, *J*=8.0, 1H, H-2), 4.37 (s, 2H, H-7), 3.11 (s, 3H, H-8); ¹³C-NMR: 157.1 (C-5), 156.7 (C-9), 150.8 (C-10), 135.4 (C-3), 131.8 (C-1), 129.3 (C-12), 125.8 (C-13), 121.4 (C-11), 120.3 (C-6), 119.6 (C-4), 118.0 (C-2), 49.5 (C-7), 34.2 (C-8).

3-Chlorophenyl N-(4-chloro-2-hydroxybenzyl)carbamate (1b). Yield 55%; m.p. 101-103° C; Calculated for C₁₅H₁₃ClNO₃ (325.3): 55.24 % C, 4.02% H, 4.29% N; found 55.19% C, 4.10% H, 4.47% N; ¹H-NMR: 8.75 (br, 1H, OH), 7.29 (m, 1H, H-14), 7.21 (m, 1H, H-15), 7.14 (m, 1H, H-11), 7.06 (d, *J*=8.1, 1H, H-1), 7.01 (m, 1H, H-13), 6.96 (s, 1H, H-4), 6.84 (dd, *J*=1.8, *J*=8.0, 1H, H-2), 4.38 (s, 2H, H-7), 3.11 (s, 3H, H-8); ¹³C-NMR: 156.7 (C-5), 156.6 (C-9), 151.2 (C-10), 135.6 (C-12), 134.6 (C-3), 131.9 (C-1), 130.0 (C-14), 126.1 (C-13), 122.1 (C-11), 120.0 (C-6), 119.8 (C-15), 119.8 (C-4), 118.1 (C-2), 49.5 (C-7), 34.3 (C-8).

3-Nitrophenyl N-(4-chloro-2-hydroxybenzyl)carbamate (1c). Yield 81%; m.p. 123-126° C; Calculated for C₁₅H₁₃ClN₂O₅ (336.3): 53.50 % C, 3.89% H, 8.32% N; found 53.64% C, 3.92% H, 8.31% N; ¹H-NMR: 8.53 (br, 1H, OH), 8.08 (d, *J* = 8.0, 1H, H-13), 8.00 (m, 1H, H-11), 7.54 (m, 1H, H-14), 7.47 (d, *J*=8.2, 1H, H-15), 7.08 (d, *J*=8.1, 1H, H-1), 6.91 (d, *J*=1.4, 1H, H-4), 6.84 (dd, *J*=2.0, *J*=8.0, 1H, H-2), 4.41 (s, 2H, H-7), 3.14 (s, 3H, H-8); ¹³C-NMR: 156.4 (C-5), 156.0 (C-9), 151.0 (C-10), 148.5 (C-12), 135.6 (C-3), 131.9 (C-1), 129.9 (C-14), 127.9 (C-15), 120.6 (C-13 + C-6), 119.9 (C-4), 117.9 (C-2), 117.1 (C-11), 49.5 (C-7), 34.3 (C-8).

Phenyl N-(5-bromo-2-hydroxybenzyl)carbamate (1d). Yield 72%; m.p. 113-115° C; Calculated for C₁₅H₁₄BrNO₃ (336.4): 53.61 % C, 4.17% H, 4.17% N; found 53.47% C, 4.20% H, 4.29% N; ¹H-NMR: 8.76 (br, 1H, OH), 7.31 (m, 3H, H-3 + H-12 + H-14), 7.24 (s, 1H, H-1), 7.18 (m, 1H, H-13), 7.07 (m, 2H, H-11 + H-15), 6.78 (d, *J*=8.5, 1H, H-4), 4.33 (s, 2H, H-7), 3.08 (s, 3H, H-8); ¹³C-NMR (CDCl₃): 157.0 (C-5), 155.0 (C-9), 150.8 (C-10), 133.3 (C-3), 132.8 (C-1), 129.3 (C-12 + C-14), 125.8 (C-13), 123.9 (C-6), 121.4 (C-11 + C-15), 119.5 (C-4), 111.2 (C-2), 49.4 (C-2), 29.6 (C-8).

4-Chlorophenyl N-(5-bromo-2-hydroxybenzyl)carbamate (1e). Yield 79%; m.p. 124 - 126° C; Calculated for C₁₅H₁₃BrClNO₃ (370.4): 48.62% C, 3.51% H, 3.78% N; found 48.66% C, 3.52% H, 3.77% N; ¹H-NMR: 8.65 (br, 1H, OH), 7.32 (m, 3H, H-3 + H-12+ H-14), 7.26 (d, *J*=2.4, 1H, H-1), 7.04 (m, 2H, H-11 + H-15), 6.83 (d, *J*=8.6, 1H, H-4), 4.37 (s, 2H, H-7), 3.13 (s, 3H, H-8); ¹³C-NMR: 156.6 (C-5), 154.9 (C-9), 149.2 (C-10), 133.3 (C-3), 132.9 (C-1), 131.1 (C-13), 129.2 (C-12 + C-14), 123.6 (C-6), 122.7 (C-11 + C-15), 119.5 (C-4), 111.2 (C-2), 49.5 (C-7), 34.4 (C-8).

3-chlorophenyl N-(5-bromo-2-hydroxybenzyl)carbamate (1f). Yield 54%; m.p. 130 -134° C; Calculated for C₁₅H₁₃BrClNO₃ (370.4): 48.62% C, 3.51% H, 3.78% N; found 48.38% C, 3.51% H, 3.97% N; ¹H-NMR: 8.62 (br, 1H, OH), 7.33 (dd, J=2.3, J=8.7, 1H, H-3), 7.27 (m, 2H, H-14 + H-1), 7.21 (m, 1H, H-15), 7.14 (t, J = 2.00, 1H, H-11), 7.01 (m, 1H, H-13), 6.84 (d, J=8.6, 1H, H-4), 4.37 (s, 2H, H-7), 3.13 (s, 3H, H-8); ¹³C-NMR: 156.5 (C-5), 155.0 (C-9), 151.2 (C-10), 134.6 (C-12), 133.4 (C-3), 133.1 (C-1), 130.0 (C-14), 126.1 (C-13), 123.5 (C-11), 119.8 (C-15), 119.7 (C-4), 111.2 (C-2), 49.6 (C-7), 34.5 (C-8).

3-Nitrophenyl N-(5-bromo-2-hydroxybenzyl)carbamate (1g). Yield 74%; m.p. 147°C (dec); Calculated for C₁₅H₁₃BrClN₂O₅ (416.5): 47.27% C, 3.41% H, 7.35% N; found 47.44% C, 3.50% H, 7.26% N; ¹H-NMR: 8.41 (br, 1H, OH), 8.11 (m, 1H, H-13), 8.02 (t, J=2.2, 1H, H-11), 7.56 (t, J=8.1, 1H, H-14), 7.49 (m, 1H, H-15), 7.35 (dd, J=2.3, J=8.6, 1H, H-3), 7.29 (d, J=2.4, 1H, H-1), 6.85 (d, J=8.6, 1H, H-4), 4.41 (s, 2H, H-7), 3.18 (s, 3H, H-8); ¹³C-NMR: 155.0 (C-9), 154.9 (C-5), 150.9 (C-10), 148.5 (C-12), 133.4 (C-3), 133.2 (C-1), 129.9 (C-14), 127.9 (C-15), 123.3 (C-6), 120.7 (C-13), 119.7 (C-4), 117.2 (C-11), 111.4 (C-2), 49.7 (C-7), 34.6 (C-8).

Phenyl N-(4-nitro-2-hydroxybenzyl)carbamate (1h). Yield 49%; m.p. 147.5 – 150 °C; Calculated for C₁₅H₁₄N₂O₅ (302.3): 59.62% C, 4.63% H, 9.27% N; found 59.44% C, 4.63% H, 9.38% N; ¹H-NMR: 9.25 (br, 1H, OH), 7.75 (s, 1H, H-4), 7.70 (d, J=8.2, 1H, H-1), 7.37 (m, 2H, H-12 + H-14), 7.30 (d, J=8.1, 1H, H-2), 7.23 (m, 1H, H-13), 7.10 (m, 2H, H-11 + H-15), 4.96 (s, 2H, H-7), 3.16 (s, 3H, H-8); ¹³C-NMR: 157.2 (C-5), 156.7 (C-9), 150.8 (C-10), 149.3 (C-3), 131.4 (C-1), 129.4 (C-12 + C-14), 128.6 (C-6), 125.9 (C-13), 121.4 (C-11 + C-15), 114.3 (C-2), 113.0 (C-4), 49.5 (C-7), 34.7 (C-8).

3-Nitrophenyl N-(4-nitro-2-hydroxybenzyl)carbamate (1i). Yield 84%; m.p. 137°C (dec.); Calculated for C₁₅H₁₃N₃O₇ (347.4): 51.89% C, 3.74% H, 12.11% N; found 51.96% C, 3.76% H, 12.16% N; ¹H-NMR: 8.95 (br, 1H, OH), 8.13 (d, J=8.1, 1H, H-13), 8.02 (m, 1H, H-11), 7.78 (d, J=1.90, 1H, H-4), 7.73 (dd, J=2.0, J=8.3, 1H, H-2), 7.59 (m, 1H, H-14), 7.49 (dd, J=1.0, J=8.7, 1H, H-15), 7.32 (d, J=8.3, 1H, H-1), 4.53 (s, 2H, H-7), 3.20 (s, 3H, H-8).

Phenyl N-(5-nitro-2-hydroxybenzyl)carbamate (1j). Yield 73%; m.p. 146 (dec.); Calculated for C₁₅H₁₄N₂O₅ (302.3): 59.62% C, 4.63% H, 9.27% N; found 59.73% C, 4.65% H, 9.43% N; ¹H-NMR: 9.50 (br, 1H, OH), 8.11 (m, 2H, H-1 + H-3), 7.37 (m, 2H, H-12 + H-14), 7.21 (t, J=7.4, 1H, H-13), 7.10 (m, 2H, H-11 + H-15), 6.97 (d, J=8.8, 1H, H-4), 4.47 (s, 2H, H-7), 3.17 (s, 3H, H-8); ¹³C-NMR: 162.2 (C-5), 157.5 (C-9), 150.7 (C-10), 140.2 (C-2), 129.4 (C-12 + C-14), 127.2 (C-3), 126.4 (C-1), 126.0 (C-13), 122.0 (C-6), 121.3 (C-11 + C-15), 118.2 (C-4), 49.7 (C-7), 34.5 (C-8).

4-Chlorophenyl N-(5-nitro-2-hydroxybenzyl)carbamate (1k). Yield 88%; m.p. 144.5-147.0° C; Calculated for C₁₅H₁₃ClN₂O₅ (336.3): 53.50 % C, 3.89% H, 8.32% N; found 53.20% C, 3.86% H, 8.58% N; ¹H-NMR: 9.47 (br, 1H, OH), 8.16 (dd, J=2.7, J=9.0, 1H, H-3), 8.11 (d, J=2.7, 1H, H-1), 7.34

(m, 2H, H-12 + H-14), 7.06 (m, 2H, H-11 + H-15), 7.00 (d, $J=8.9$, 1H, H-4), 4.47 (s, 2H, H-7), 3.18 (s, 3H, H-8).

3-Chlorophenyl N-(5-nitro-2-hydroxybenzyl)carbamate (1l). Yield 71%; m.p. 117-119°C; Calculated for $C_{15}H_{13}ClN_2O_5$ (336.3): 53.50 % C, 3.89% H, 8.32% N; found 53.44% C, 3.89% H, 8.44% N; 1H -NMR: 9.54 (br, 1H, OH), 8.09 (m, 2H, H-1 + H-3), 7.28 (t, $J=8.1$, 1H, H-14), 7.19 (d, $J=8.1$, 1H, H-13), 7.14 (s, 1H, H-11), 7.02 (d, $J=8.0$, 1H, H-15), 6.91 (d, $J=9.1$, 1H, H-4), 4.54 (s, 2H, H-7), 3.15 (s, 3H, H-8); ^{13}C -NMR: 161.9 (C-5), 156.8 (C-9), 150.9 (C-10), 140.1 (C-2), 134.5 (C-12), 130.0 (C-14), 1287.0 (C-13), 127.0 (C-1), 126.4 (C-3), 126.2 (C-11), 121.9 (C-15), 121.7 (C-6), 119.6 (C-4), 49.6 (C-7), 34.5 (C-8).

3-Nitrophenyl N-(5-nitro-2-hydroxybenzyl)carbamate (1m). Yield 90%; m.p. 151-154°C; Calculated for $C_{15}H_{13}N_3O_7$ (347.4): 51.89% C, 3.74% H, 12.11% N; found 52.18% C, 3.83% H, 12.22% N; 1H -NMR: 9.52 (br, 1H, OH), 8.14 (m, 3H, H-3 + H-1 + H-13), 8.03 (t, $J=2.2$, 1H, H-11), 7.58 (t, $J=8.1$, 1H, H-14), 7.50 (m, 1H, H-15), 7.01 (d, $J=8.9$, 1H, H-4), 4.51 (s, 2H, H-7), 3.23 (s, 3H, H-8); ^{13}C -NMR: 161.9 (C-5), 156.5 (C-9), 150.9 (C-10), 148.6 (C-12), 140.4 (C-2), 130.0 (C-14), 127.8 (C-15), 127.2 (C-1), 126.6 (C-3), 121.6 (C-6), 120.9 (C-13), 118.3 (C-4), 117.2 (C-11), 49.9 (C-7), 34.7 (C-8).

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Sample availability: Available from the authors.

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