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# Synthesis of Carbamate Derivatives of 2,3-Dihydro-4*H*-1,4-benzoxazine

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**Abstract**—Alkylation of methyl 2-hydroxyphenylcarbamates with 1,2-dibromoethane in acetone in the presence of $K_2CO_3$ gave the corresponding methyl 6(7)-R-2,3-dihydro-4*H*-1,4-benzoxazine-4-carboxylate. Alkylation of methyl 2-hydroxyphenylcarbamates with chloromethyloxirane was accompanied by recyclization of the oxirane ring with formation of methyl 6(7)-R-3-hydroxymethyl-2,3-dihydro-4*H*-1,4-benzoxazine-4-carboxylates.

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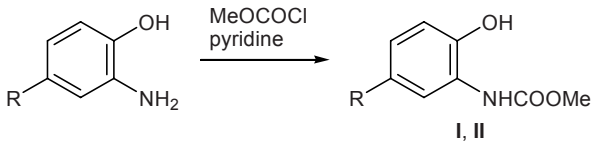
The chemistry of hydroxyphenylcarbamates has been poorly studied. On the other hand, these compounds, as well as their alkyl and acyl derivatives, attract considerable interest as intermediate products in the synthesis of nitrogen-containing heterocycles possessing a wide potential of biological activity. In continuation of our studies on the synthesis of O-alkyl derivatives of aromatic carbamates [1, 2], in the present work we examined alkylation of methyl 2-hydroxyphenylcarbamate (**I**), methyl 2-hydroxy-5-nitrophenylcarbamate (**II**), and dimethyl 2-hydroxybenzene-1,4-diyldicarbamate (**IV**) with 1,2-dibromoethane and chloromethyloxirane.

*ortho*-Hydroxyphenylcarbamates **I** and **II** were synthesized by acylation of the corresponding aminophenols with methyl chloroformate in pyridine (Scheme 1). Dimethyl 2-hydroxybenzene-1,4-diyldicarbamate (**IV**) was obtained by hydrolysis of dimethyl 2-acetoxybenzene-1,4-diyldicarbamate (**III**) which was prepared in turn by reaction of dimethyl cyclohexa-2,5-diene-1,4-diylidenedicarbamate [3] with glacial acetic acid (Scheme 2).

The alkylation of carbamates **I**, **II**, and **IV** with 1,2-dibromoethane and chloromethyloxirane in acetone in the presence of potassium carbonate afforded the corresponding 2,3-dihydro-4*H*-1,4-benzoxazine carbamate derivatives **V**–**X** whose structure was consistent with their elemental compositions and $^1$H and $^{13}$C NMR and IR spectra (Scheme 3). For example, the $^1$H NMR spectrum of benzoxazine **V** contained a three-proton multiplet at δ 7.39–7.22 ppm due to aromatic protons, a doublet at δ 6.68 ppm ($J$ = 7.9 Hz) from 5-H, a two-proton multiplet at δ 4.21–4.15 ppm from 2-H, and a five-proton multiplet at δ 3.92–3.76 ppm from the $NCH_2$ and $OCH_3$ protons.

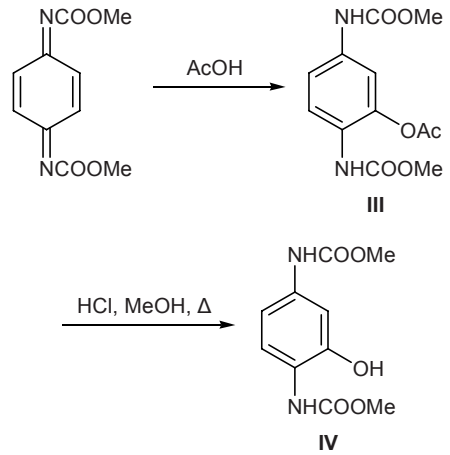
**Scheme 1.**




**I**, **II**

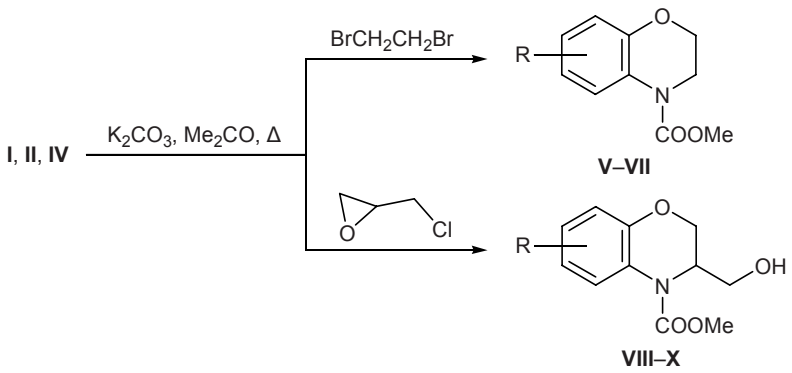
**I**, R = H; **II**, R = $O_2N$.

**Scheme 2.**




It is well known that 2,3-epoxypropyl phenylcarbamate is capable of undergoing recyclization through intramolecular interaction between the epoxide and carbamate moieties to produce oxazolidin-2-one deriv-

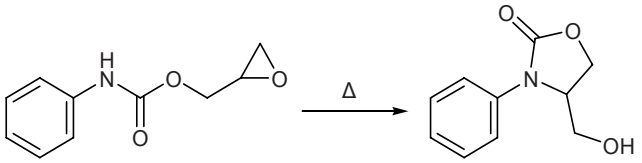
**Scheme 3.**



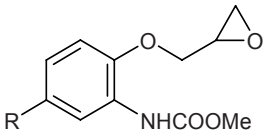

**V**, **VIII**, R = H; **VI**, **IX**, R = 6-$O_2N$; **VII**, **X**, R = 7-MeOCONH.

atives having a hydroxymethyl substituent [4] (Scheme 4). The results of our studies showed that recyclization of the oxirane ring with participation of the carbamate group in the *ortho* position with respect to the oxiranylmethoxy group could give rise to 2,3-dihydro-4*H*-1,4-benzoxazine system.

**Scheme 4.**




The alkylation of methyl 2-hydroxyphenylcarbamates **I**, **II**, and **IV** with chloromethyloxirane was also accompanied by recyclization of the oxirane ring with formation of methyl 6(7)-R-3-hydroxymethyl-2,3-dihydro-4*H*-1,4-benzoxazine-4-carboxylates **VIII**–**X**. Presumably, in this case 1,4-benzoxazine system is formed via intermediate 2,3-epoxypropoxyphenyl carbamate **A** which then undergoes heterocyclization.




**A**

The heterocyclization involves nucleophilic attack by the carbamate nitrogen atom on the positively charged carbon atom in the oxirane ring. As a result, six-membered heteroring having a hydroxymethyl substituent is built up. The IR spectrum of **VIII** lacked NH absorption in the region 3400–3300 $cm^{-1}$, but a broad absorption band was present at 3200–3600 $cm^{-1}$ due to stretching vibrations of the hydroxy group. No absorption bands typical of oxirane ring (865, 910, 1220 $cm^{-1}$) were observed, while the spectrum contained bands assignable to carbonyl group and benzene ring. Compound **VIII** displayed in the $^1H$ NMR spectrum a multiplet signal at δ 4.38 ppm (3-H) and multiplets at δ 3.76 and 3.70 ppm due to protons in the 3-$CH_2$ and OH groups, respectively. In addition, signals from protons in the other molecular fragments were present. The hydroxymethyl group in compounds **VIII**–**X** gave a signal in the region $\delta_C$ 61.84–62.04 ppm in the $^{13}C$ NMR spectrum.

## EXPERIMENTAL

The $^1H$ NMR spectra were measured on a Bruker DRX-500 spectrometer at 500.13 MHz from solutions in DMSO-$d_6$ using tetramethylsilane as internal reference. The $^{13}C$ NMR spectra were recorded with complete decoupling from protons on a Bruker WM-400 instrument (100 MHz) from solutions in acetone-$d_6$. The IR spectra (3800–400 $cm^{-1}$) were obtained on a Specord M82 spectrophotometer from samples prepared as KBr pellets. The purity of the products was checked by TLC on Silufol UV-254 plates.

**Methyl 2-hydroxyphenylcarbamate (I).** Methyl chloroformate, 7.7 ml (0.1 mol), was added dropwise over a period of 1.5 h to a solution of 10.9 g (0.1 mol) of *o*-aminophenol in 46 ml of anhydrous pyridine under stirring and cooling. The mixture was stirred for an additional 0.5 h, left to stand for 13 h at room temperature, poured onto ice, carefully acidified with concentrated hydrochloric acid (according to Congo Red), and extracted with ethyl acetate (4×50 ml). The extract was washed with 100 ml of a saturated aqueous solution of sodium chloride and water (2×50 ml) and dried over sodium sulfate. The solvent was removed under reduced pressure, and the residue crystallized. The product was purified by reprecipitation from 2%

aqueous sodium hydroxide with 2% hydrochloric acid, followed by recrystallization from ethanol. Yield 14.4 g (86%), colorless crystals, mp 119–122°C. IR spectrum, ν, $cm^{-1}$: 3396, 3300 (NH, OH); 1704, 1680 (C=O); 1604, 1540, 1460 (C–$C_{arom}$). $^1$H NMR spectrum, δ, ppm: 9.65 s (1H, OH), 8.23 s (1H, NH), 7.50 d (1H, 6-H, *J* = 9.8 Hz), 6.91 t (1H, 4-H, *J* = 8.0 Hz), 6.84 d (1H, 3-H, *J* = 8.0 Hz), 6.76 t (1H, 5-H, *J* = 8.0 Hz), 3.66 s (3H, OMe). Found, %: C 57.18; H 5.61; N 8.41. $C_8H_9NO_3$. Calculated, %: C 57.49; H 5.39; N 8.38.

**Methyl 2-hydroxy-5-nitrophenylcarbamate (II)** was synthesized in a similar way from 15.4 g (0.1 mol) of 2-amino-4-nitrophenol in 46 ml of anhydrous pyridine and 7.7 ml (0.1 mol) of methyl chloroformate. Yield 17.6 g (83%), light yellow crystals, mp 222–223°C (from benzene). IR spectrum, ν, $cm^{-1}$: 3384, 3248 (NH, OH); 1708 (C=O); 1628, 1596 (C–$C_{arom}$); 1544, 1352 ($NO_2$). $^1$H NMR spectrum, δ, ppm: 11.51 s (1H, OH), 8.75 s (1H, NH), 8.62 s (1H, 6-H), 7.89 d (1H, 4-H, *J* = 10.0 Hz), 7.02 d (1H, 3-H, *J* = 10.0 Hz), 3.70 s (3H, OMe). Found, %: C 44.99; H 3.82; N 12.94. $C_8H_8N_2O_5$. Calculated, %: C 45.28; H 3.77; N 13.21.

**Dimethyl 2-acetoxybenzene-1,4-diyldicarbamate (III).** Glacial acetic acid, 5 ml, was added to 0.5 g (2.5 mmol) of *N*,*N*′-bis(methoxycarbonyl)-1,4-benzoquinone diimine [3]. The mixture spontaneously warmed up and crystallized in a few minutes. Recrystallization from chloroform gave 0.55 g (98%) of compound **III** as a colorless crystalline substance, mp 205–206°C. IR spectrum, ν, $cm^{-1}$: 3300 (NH); 1720, 1690 (C=O); 1600, 1520 (C–$C_{arom}$). Found, %: C 51.44; H 4.83; N 10.13. $C_{12}H_{14}N_2O_6$. Calculated, %: C 51.06; H 4.97; N 9.93.

**Dimethyl 2-hydroxybenzene-1,4-diyldicarbamate (IV).** A solution of 0.5 g (2.5 mmol) of compound **III** in 20 ml of methanol containing 1 ml of concentrated hydrochloric acid was heated for 40 min under reflux. Excess alcohol was removed under reduced pressure, and the residue was recrystallized from ethanol. Yield 0.35 g (73%), colorless crystals, mp 217°C. IR spectrum, ν, $cm^{-1}$: 3356, 3295 (NH, OH); 1712, 1684 (C=O); 1624, 1568, 1524 (C–$C_{arom}$). $^1$H NMR spectrum, δ, ppm: 9.63 s (1H, OH), 8.45 s and 8.18 s (1H each, NH), 7.32 d (1H, 5-H, *J* = 10.0 Hz), 7.12 s (1H, 3-H), 6.78 d (1H, 6-H, *J* = 10.0 Hz), 3.65 s (3H, OMe), 3.62 s (3H, OMe). Found, %: C 49.87; H 4.89; N 12.01. $C_{10}H_{12}N_2O_5$. Calculated, %: C 50.00; H 5.00; N 11.67.

**Methyl 2,3-dihydro-4*H*-1,4-benzoxazine-4-carboxylate (V).** A mixture of 3.34 g (0.02 mol) of compound **I**, 2.8 g (0.02 mol) of potassium carbonate, 1.7 ml (0.02 mol) of 1,2-dibromoethane, and 7 ml of acetone was heated for 5 h at 70°C. The mixture was cooled, diluted with 25 ml of water, and extracted with diethyl ether (3×30 ml). The extract was washed with 100 ml of 10% aqueous sodium hydroxide and water (2×50 ml) and dried over potassium carbonate. The solvent was removed, and the residue crystallized. Recrystallization from ethyl acetate–hexane (1:3 by volume) gave 2.9 g (74%) of compound **V** as colorless crystals, mp 172–173°C. IR spectrum, ν, $cm^{-1}$: 1730, 1760 (C=O); 1615, 1530 (C–$C_{arom}$). $^1$H NMR spectrum, δ, ppm: 7.39–7.22 m (3H, $H_{arom}$), 6.68 d (1H, 5-H, *J* = 7.9 Hz), 4.21–4.15 m (2H, $OCH_2$), 3.92–3.76 m (5H, $NCH_2$, OMe). $^{13}$C NMR spectrum, $\delta_C$, ppm: 46.74 ($C^3$), 54.24 ($OCH_3$), 69.75 ($C^2$), 112.77 ($C^8$), 120.42 ($C^5$), 123.30 ($C^7$), 124.32 ($C^6$), 132.52 ($C^{10}$), 153.14 ($C^9$), 154.28 (C=O). Found, %: C 61.94; H 5.42; N 7.37. $C_{10}H_{11}NO_3$. Calculated, %: C 62.18; H 5.70; N 7.25.

Compounds **VI**–**X** were synthesized in a similar way.

**Methyl 6-nitro-2,3-dihydro-4*H*-1,4-benzoxazine-4-carboxylate (VI)** was synthesized using 2.12 g (0.01 mol) of compound **II**, 1.40 g (0.01 mol) of potassium carbonate, and 0.85 ml (0.01 mol) of 1,2-dibromoethane. Yield 1.86 g (78%), light yellow crystals, mp 110–111°C (from chloroform). IR spectrum, ν, $cm^{-1}$: 1725, 1758 (C=O); 1610, 1575 (C–$C_{arom}$); 1530, 1350 ($NO_2$). $^1$H NMR spectrum, δ, ppm: 7.85 s (1H, 5-H), 7.69 d (1H, 7-H, *J* = 8.7 Hz), 7.21 d (1H, 8-H, *J* = 8.7 Hz), 4.25–4.13 m (2H, $OCH_2$), 3.89–3.73 m (5H, $NCH_2$, OMe). $^{13}$C NMR spectrum, $\delta_C$, ppm: 46.73 ($C^3$), 54.28 ($OCH_3$), 69.68 ($C^2$), 111.52 ($C^5$), 114.25 ($C^8$), 119.75 ($C^7$), 134.01 ($C^{10}$), 144.08 ($C^6$), 150.65 ($C^9$), 153.90 (C=O). Found, %: C 50.21; H 3.92; N 11.34. $C_{10}H_{10}N_2O_5$. Calculated, %: C 50.42; H 4.20; N 11.77.

**Methyl 7-methoxycarbonylamino-2,3-dihydro-4*H*-1,4-benzoxazine-4-carboxylate (VII)** was obtained using 2.40 g (0.01 mol) of bis-carbamate **IV**, 1.40 g (0.01 mol) of potassium carbonate, and 0.85 ml (0.01 mol) of 1,2-dibromoethane. Yield 2.2 g (84%), colorless crystals, mp 181–182°C (from ethyl acetate–hexane, 1:3 by volume). IR spectrum, ν, $cm^{-1}$: 3410 (NH); 1725 (C=O); 1610, 1530 (C–$C_{arom}$). $^1$H NMR spectrum, δ, ppm: 7.60 br.s (1H, NH), 7.51 s (1H, 8-H), 7.32 d (1H, 6-H, *J* = 8.2 Hz), 6.82 d (1H, 5-H, *J* = 8.2 Hz), 4.15–4.24 m (2H, $OCH_2$), 3.93 m (1H, $NCH_2$), 3.81 s (3H, 4-$CO_2$Me), 3.76–3.73 m (1H,

$NCH_2$), 3.71 (3H, $NHCO_2C\mathbf{H}_3$). $^{13}C$ NMR spectrum, $\delta_C$, ppm: 46.74 ($C^3$), 52.68 ($NHCO_2\mathbf{Me}$), 54.24 ($NCO_2\mathbf{Me}$), 69.75 ($C^2$), 112.05 ($C^8$), 114.01 ($C^6$), 115.49 ($C^5$), 125.71 ($C^{10}$), 136.61 ($C^7$), 154.28 ($N\mathbf{C}O_2Me$), 155.18 ($C^9$, $NH\mathbf{C}O_2Me$). Found, %: C 54.41; H 5.07; N 10.26. $C_{12}H_{14}N_2O_5$. Calculated, %: C 54.14; H 5.26; N 10.53.

**Methyl 3-hydroxymethyl-2,3-dihydro-4*H*-1,4-benzoxazine-4-carboxylate (VIII)** was synthesized using 1.67 g (0.01 mol) of compound **I**, 1.4 g (0.01 mol) of potassium carbonate, and 0.95 ml (0.01 mol) of chloromethyloxirane. Yield 1.45 g (65%), colorless crystals, mp 53–54°C (from hexane). IR spectrum, ν, $cm^{-1}$: 3200–3600 (OH); 1725 (C=O); 1610, 1540 (C–$C_{arom}$). $^1H$ NMR spectrum, δ, ppm: 7.31–7.22 m (2H, 6-H, 7-H), 6.72 d (1H, 5-H, $J$ = 7.8 Hz), 6.65 d (1H, 8-H, $J$ = 7.8 Hz), 4.49 d.d (1H, 2-$H_A$, $J$ = 2.0, 12.0 Hz), 4.38 m (1H, 3-H), 3.94 m (1H, 2-$H_B$), 3.85 s (3H, OMe), 3.76 m (1H, $C\mathbf{H}_2OH$), 3.70 m (1H, OH), 3.61 m (1H, $C\mathbf{H}_2OH$). $^{13}C$ NMR spectrum, $\delta_C$, ppm: 52.70 (OMe), 56.65 ($C^3$), 62.02 ($CH_2OH$), 63.24 ($C^2$), 112.27 ($C^8$), 119.24 ($C^5$), 123.53 ($C^7$), 123.80 ($C^6$), 132.02 ($C^{10}$), 152.03 ($C^9$), 153.87 (C=O). Found, %: C 58.98; H 5.62; N 6.30. $C_{11}H_{13}NO_4$. Calculated, %: C 59.19; H 5.83; N 6.28.

**Methyl 3-hydroxymethyl-6-nitro-2,3-dihydro-4*H*-1,4-benzoxazine-4-carboxylate (IX)** was synthesized using 2.12 g (0.01 mol) of carbamate **II**, 1.4 g (0.01 mol) of potassium carbonate, and 0.95 ml (0.01 mol) of chloromethyloxirane. Yield 1.85 g (69%), light yellow crystals, mp 135–137°C (from chloroform). IR spectrum, ν, $cm^{-1}$: 3200–3600 (OH); 1740 (C=O); 1624, 1596 (C–$C_{arom}$); 1544, 1348 ($NO_2$). $^1H$ NMR spectrum, δ, ppm: 8.69 s (1H, 5-H), 7.96 d (1H, 7-H, $J$ = 7.5 Hz), 7.25 d (1H, 8-H, $J$ = 7.5 Hz), 4.51 d.d (1H, 2-$H_A$, $J$ = 2.0, 12.0 Hz), 4.35–4.05 m (3H, 3-H, 2-$H_B$, $C\mathbf{H}_2OH$), 3.76 m (1H, $C\mathbf{H}_2OH$), 3.73 s (3H, OMe), 3.47 m (1H, OH). $^{13}C$ NMR spectrum, $\delta_C$, ppm: 52.68 (OMe), 56.65 ($C^3$), 61.84 ($CH_2OH$), 63.24 ($C^2$), 110.52 ($C^5$), 113.73 ($C^8$), 120.02 ($C^7$), 133.38 ($C^{10}$), 143.55 ($C^6$), 149.50 ($C^9$), 154.74 (C=O). Found, %: C 49.01; H 4.56; N 10.31. $C_{11}H_{12}N_2O_6$. Calculated, %: C 49.25; H 4.48; N 10.45.

**Methyl 3-hydroxymethyl-7-methoxycarbonylamino-2,3-dihydro-4*H*-1,4-benzoxazine-4-carboxylate (X)** was synthesized using 2.40 g (0.01 mol) of carbamate **IV**, 1.4 g (0.01 mol) of potassium carbonate, and 0.95 ml (0.01 mol) of chloromethyloxirane. Yield 1.84 g (62%), white powder, mp 88–90°C (from ethyl acetate–petroleum ether, 1:3 by volume). IR spectrum, ν, $cm^{-1}$: 3200–3600 (OH); 1725 (C=O); 1610, 1575 (C–$C_{arom}$). $^1H$ NMR spectrum, δ, ppm: 7.81 br.s (1H, NH), 7.40 s (1H, 8-H), 7.22 d (1H, 6-H, $J$ = 7.8 Hz), 6.82 d (1H, 5-H, $J$ = 7.8 Hz), 4.50–4.46 m (2H, 2-H, 3-H), 3.94 m (1H, 2-H), 3.85 s (3H, $NCO_2Me$), 3.80–3.73 m (1H, $C\mathbf{H}_2OH$), 3.71 s (3H, $NHCO_2\mathbf{Me}$), 3.70–3.61 m (2H, $CH_2OH$). $^{13}C$ NMR spectrum, $\delta_C$, ppm: 52.63 ($NHCO_2\mathbf{Me}$), 56.65 ($C^3$), 52.70 ($NCO_2\mathbf{Me}$), 62.02 ($CH_2OH$), 63.28 ($C^2$), 111.54 ($C^8$), 113.45 ($C^6$), 114.35 ($C^5$), 125.10 ($C^{10}$), 136.85 ($C^7$), 154.01 ($C^9$), 154.76 ($N\mathbf{C}O_2Me$), 154.97 ($NH\mathbf{C}O_2Me$). Found, %: C 52.56; H 5.68; N 9.38. $C_{13}H_{16}N_2O_6$. Calculated, %: C 52.70; H 5.41; N 9.46.

## REFERENCES

1. Velikorodov, A.V., Bakova, O.V., and Mochalin, V.B., *Russ. J. Org. Chem*., 2002, vol. 38, p. 63.
2. Velikorodov, A.V., *Russ. J. Org. Chem*., 2004, vol. 40, p. 188.
3. Maksimova, T.N. and Velikorodov, A.V., *Zh. Org. Khim*., 1986, vol. 22, p. 1092.
4. Farrissey, M.J., Jr. and Nashu, A.M., *J. Heterocycl. Chem*., 1970, vol. 7, p. 331.