Russian Journal of Organic Chemistry, Vol. 40, No. 2, 2004, pp. 188–190. Translated from Zhurnal Organicheskoi Khimii, Vol. 40, No. 2, 2004, pp. 215–217.

Synthesis of Methyl-*N*-[4-(3-R-amino-2-hydroxypropoxy)phenyl]carbamates

A. V. Velikorodov

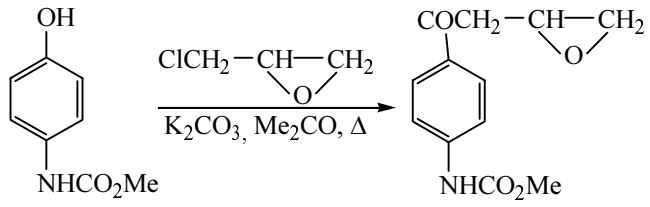
Astrakhan State University Astrakhan, 414056 Russia
e-mail: avelikorodov@mail.ru

Received April 27, 2003

Abstract—By alkylation of methyl-*N*-(4-hydroxyphenyl)carbamate with (chloromethyl)oxirane in acetone in the presence of K_2CO_3 methyl-*N*-[4-(2,3-epoxypropoxy)phenyl]carbamate was prepared. The aminolysis of the latter effected by benzylamine, morpholine, piperidine, and pyrrolidine occurs in keeping with Krasusky rule to afford methyl-N-[4-(3-R-amino-2-hydroxypropoxy)phenyl]carbamates.

In extension of our research on the synthesis of O-alkyl derivatives of aromatic carbamates [1] we report here the results obtained in alkylation of methyl-*N*-(4-hydroxyphenyl)carbamate **I** with (chloromethyl)oxirane and in the study of the possibility to use the product for syntheses of new derivatives with potential β-adrenoblockador activity. Some compounds containing aminohydroxyalkyl moiety already found application in therapeutical practice, for example, Atenolol, Pindolol, Anaprilin, and Buphetanol [2, 3].

We established that the alkylation of carbamate **I** with with (chloromethyl)oxirane in acetone in the presence of potassium carbonate gave rise to methyl-*N*-[4-(2,3-epoxypropoxy)phenyl]carbamate **II** whose composition and structure are consistent with elemental analysis and IR spectrum.



I **II**

In the IR spectrum of compound **II** in contrast to that of carbamate **I** are present absorption bands at 1250, 1020 and 840 cm^{-1} corresponding to pulsating, symmetric, and asymmetrical vibrations of the oxirane ring.

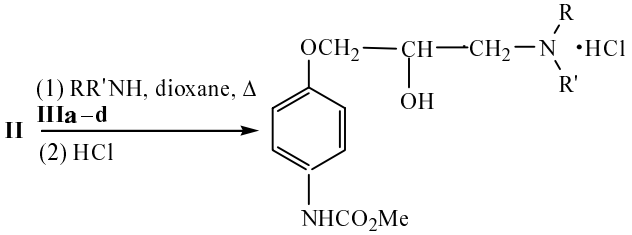
We investigated carbamate **II** aminolysis with benzylamine **IIIa**, morpholine **IIIb**, pyrrolidine **IIIc**, and piperidine **IIId**. The reaction was carried out by heating an equimolar reagents mixture in dioxane to 50°C for 6 h.

The oxirane ring can presumably open in two fashions: either in keeping with the Krasusky rule from the side of the α-carbon of the three-membered ring, or against the rule affording an isomeric reaction product. The oligomerization also cannot be ruled out [4].

It is known [5] that an oxirane containing at the ring a substituents with a negative inductive effect reacts with a nucleophilic reagent to afford only a product of the regular structure. Our results support this statement: the heterocycle opening occurs exclusively along Krasusky rule furnishing the product as a single isomer as confirmed by the ^{1}N NMR spectra.

The position of one-proton signals (one in the region 4.00–4.07 and another at 3.70 ppm) in agreement with published data [6, 7] proved that the opening of the oxirane ring happened according to the Krasusky rule.

The regioselectivity of the reaction presumably originates from the structural features of the epoxide: the terminal carbon atom is sterically available for the nucleophiles attack, and also to the oxirane ring a substituent with a negative inductive effect is linked. The latter apparently destabilizes the alternative transition state that would lead to a product of the *anti*-Krasusky addition [8].



IVa–d

III, IV, R = H, R' = $PhCH_2$ (**a**); R, R' = $(CH_2)_2O(CH_2)_2$ (**b**); R, R' = $(CH_2)_4$ (**c**), R, R' = $(CH_2)_5$ (**d**).

The treating of amines **IVa–d** solutions in a mixture methylene chloride–dioxane (1:1 by volume) with

hydrogen chloride solution in ether afforded the respective amine hydrochlorides as colorless crystalline compounds, well soluble in water.

Methyl-*N*-[4-(2,3-epoxypropoxy)phenyl]carbamate (II). A mixture of 3.34 g (0.02 mol) of carbamate **I**, 2.8 g (0.02 mol) of potassium carbonate, 1.9 ml (0.02 mol) of (chloromethyl)oxirane and 3 ml of acetone was heated for 5 h at 70°C, then was cooled, diluted with water (25 ml), and extracted with ethyl ether (3×30 ml). The extract was washed with 10% water solution of sodium hydroxide (100 ml) and with water (2×50 ml), and dried with potassium carbonate. The solvent was removed, the residue crystallized. On recrystallization from a mixture chloroform–petroleum ether, 2:1, we obtained 3.88 g (87%) of colorless crystalline compound **II**, mp 98°C. IR spectrum, ν, cm^{-1}: 3330 (NH), 1705 (C=O), 1605, 1545, 1530 (C⎓C arom), 1250, 1020, 840 (oxirane). Found, %: C 58.97; N 5.64; N 6.14. $C_{11}N_{13}NO_4$. Calculated,%: C 59.19; N 5.83; N 6.28.

Methyl-*N*-[4-(3-benzylamino-2-hydroxypropoxy)phenyl]carbamate (IVa). A mixture of 2.23 g (0.01 mol) of carbamate **II**, 1.16 ml (0.01 mol) of freshly distilled benzylamine **IIIa**, and 5 ml of dioxane was heated at 50°C for 6 h, the solvent was removed, the residue was washed with hexane (2×10 ml). On recrystallization from a mixture carbon tetrachloride–petroleum ether, 3:1, we obtained 2.70 g (82%) of amine **IVa**, mp 86°C. IR spectrum, ν, cm^{-1}: 3420, 3350 (NH), 3245 (OH), 1715 (C=O), 1610, 1550, 1525 (C⎓C). ^{1}N NMR spectrum, δ, ppm: 8.47 br. s (1N, N<u>H</u>CO_2Me), 7.40 d (2H arom, *J* 7.8 Hz), 7.33 d (2H arom, *J* 8.7 Hz), 7.20 t (3N arom, *J* 7.02 Hz), 6.94 d (2H arom, *J* 8.7 Hz), 4.07 m (C<u>H</u>OH), 3.98 d, (1N, OCN_2, *J* 4.7 Hz), 3.82 d (2N, C<u>N</u>$_2$Ph, *J* 13 Hz), 3.78 d (1N, OCN_2, *J* 3.3 Hz), 3.70 c (3H, OMe), 3.21 m (2N, NH, OH), 2.79 d. d (1N, C<u>N</u>$_2$N, *J* 7.5, 13.2 Hz), 2.66 d. d (1N, C<u>N</u>$_2$N, *J* 7.5, 13.2 Hz). Found, %: C 65.21; N 6.88; N 8.22. $C_{18}H_{22}N_2O_4$. Calculated, %: C 65.46; N 6.67; N 8.49.

Compound **IVa** (1 g, 3.03 mmol) was converted in the corresponding hydrochloride by treating in a mixture dioxane–methylene chloride, 1:1, with hydrogen chloride solution in ether. The arising colorless crystalline reaction product was separated and dried in air. We obtained 1.09 g (98%) of methyl-*N*-[4-(3-benzylamino-2-hydroxypropoxy)-phenyl]carbamate hydrochloride, mp 192°C. Found, %: C 58.63; N 6.07; N 7.51. $C_{18}H_{22}N_2O_4$·HCl. Calculated, %: C 58.94; N 6.28; N 7.64.

Carbamates **IVb–d** and their hydrochlorides were obtained by similar procedures.

Methyl-*N*-[4-(2-hydroxy-3-morpholinopropoxy)-phenyl]carbamate (IVb). Yield 2.67 g (86%), mp 82°C (from a mixture carbon tetrachloride–petroleum ether, 3:1). IR spectrum, ν, cm^{-1}: 3310–3260 (NH, OH), 1735 (C=O), 1620, 1565, 1525 (C⎓C arom). ^{1}N NMR spectrum, δ, ppm: 8.47 br. s (1N, N<u>H</u>CO_2Me), 7.33 d (2N arom, *J* 8.7 Hz), 6.93 d (2N arom, *J* 8.7 Hz), 4.00 m (2N, OCN_2, C<u>N</u>ON), 3.81 d (1N, OCN_2, *J* 3.3 Hz), 3.70 s (4N, OMe, CNO<u>N</u>), 3.60 m (4N, O$(CN_2)_2$), 2.60 d.d (1N, NCH_2, *J* 7.6, 13.2 Hz), 2.40 d. d (1N, NCH_2, *J* 7.6, 13.2 Hz), 2.26 m [4N, N$(CH_2)_2$]. Found, %: C 58.21; N 6.88; N 8.86. $C_{15}H_{22}N_2O_5$. Calculated, %: C 58.07; N 7.10; N 9.03.

Methyl-*N*-[4-(2-hydroxy-3-morpholinopropoxy)-phenyl]carbamate hydrochloride, yield 1.1 g (99%), mp 199°C. Found, %: C 52.17; N 6.37; N 7.99. $C_{15}H_{22}N_2O_5$·HCl. Calculated, %: C 51.95; N 6.64; N 8.08.

Methyl-N-[4-(2-hydroxy-3-pyrrolidinopropoxy)-phenyl]carbamate (IVc). Yield 2.38 g (81%), mp 92°C (from a mixture chloroform–petroleum ether, 2:1). IR spectrum, ν, cm^{-1}: 3320–3260 (NH, OH), 1735 (C=O), 1620, 1560, 1525 (C⎓C arom). ^{1}N NMR spectrum, δ, ppm: 8.47 br. s (1N, N<u>H</u>CO_2Me), 7.33 d (2N arom, *J* 8.7 Hz), 6.93 d (2N arom, *J* 8.7 Hz), 4.00 m (2N, OCN_2, C<u>N</u>ON), 3.83 d (1N, OCN_2, *J* 3.3 Hz), 3.70 s (4N, OMe, CNO<u>N</u>), 2.62 m (5N, β-N of pyrrolidine, NCH_2), 2.39 d. d (1N, NCH_2, *J* 7.5, 13.2 Hz), 1.78 m (4N, α-N of pyrrolidine). Found, %: C 60.94; N 7.54; N 9.27. $C_{15}H_{22}N_2O_4$ .Calculated, %: C 61.23; N 7.48; N 9.52.

Hydrochloride of methyl-*N*-[4-(2-hydroxy-3-pyrrolidino-propoxy)phenyl]carbamate Hydrochloride yield 1.10 g (98%), mp 150–151°C. Found,%: C 54.25; N 7.01; N 8.23. $C_{15}H_{22}N_2O_4$·HCl. Calculated, %: C 51.46; N 6.96; N 8.47.

Methyl-*N*-[4-(2-hydroxy-3-piperidinopropoxy)-phenyl]carbamate (IVd). Yield 1.47 g (71%), mp 111°C (from a mixture carbon tetrachloride–petroleum ether, 3:1). IR spectrum, ν, cm^{-1}: 3320–3260 (NH, OH), 1730 (C=O), 1620, 1565, 1525 (C⎓C arom). ^{1}N NMR spectrum, δ, ppm: 8.47 br. s (1N, N<u>H</u>CO_2Me), 7.33 d (2N arom, *J* 8.7 Hz), 6.93 d (2N arom, *J* 8.7 Hz), 4.00 m (2N, OCN_2, C<u>N</u>ON), 3.81 d (1N, OCN_2, *J* 3.3 Hz), 3.70 s (4N, OMe, CNO<u>N</u>), 2.60 d.d (1N, NCH_2, *J* 7.5, 13.2 Hz), 2.40 d. d. (1N, NCH_2, *J* 7.5, 13.2 Hz), 2.24 m (4N, β-N of piperidine), 1.30 м (6N, 3CN_2 of piperidine). Found, %: C 62.13; N 8.03; N 9.16. $C_{16}H_{24}N_2O_4$. Calculated, %: C 62.34; N 7.79; N 9.09.

Hydrochloride a methyl-*N*-[4-(2-hydroxy-3-piperidinopropoxy)phenyl]carbamate, yield 1.10 g (98%), mp 152°C. Found, %: C 55.50; N 7.31; N 8.01. $C_{16}H_{24}N_2O_4 \cdot HCl$. Calculated, %: C 55.73; N 7.26; N 8.13.

^1H NMR spectra were registered on spectrometer VXR-400 (400.13 MHz) in acetone-d_6, internal reference TMS. IR spectra were measured on spectrophotometer IKS-29 in the range 4000–400 cm^{-1} from mulls in mineral oil.

The purity of compounds obtained was checked by TLC on Silufol UV-254 plates

Methyl-*z*-(4-hydroxyphenyl)carbamate **I** was prepared by procedure described in [1].

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