ISSN 1070-4280, Russian Journal of Organic Chemistry, 2006, Vol. 42, No. 12, pp. 1845–1847. © Pleiades Publishing, Inc., 2006.
Original Russian Text © E.G. Mesropyan, A.S. Galstyan, A.A. Avetisyan, 2006, published in Zhurnal Organicheskoi Khimii, 2006, Vol. 42, No. 12, pp. 1854–1856.

Syntheses on the Basis of 4-(Oxiran-2-ylmethyl)morpholine

E. G. Mesropyan, A. S. Galstyan, and A. A. Avetisyan

Erevan State University, ul. A. Manukyana 1, Erevan, 375049 Armenia
e-mail: mag_union@yahoo.com

Received December 9, 2005

Abstract—4-(Oxiran-2-ylmethyl)morpholine was synthesized and converted into new morpholino derivatives of propan-2-ols and butan-4-olides.

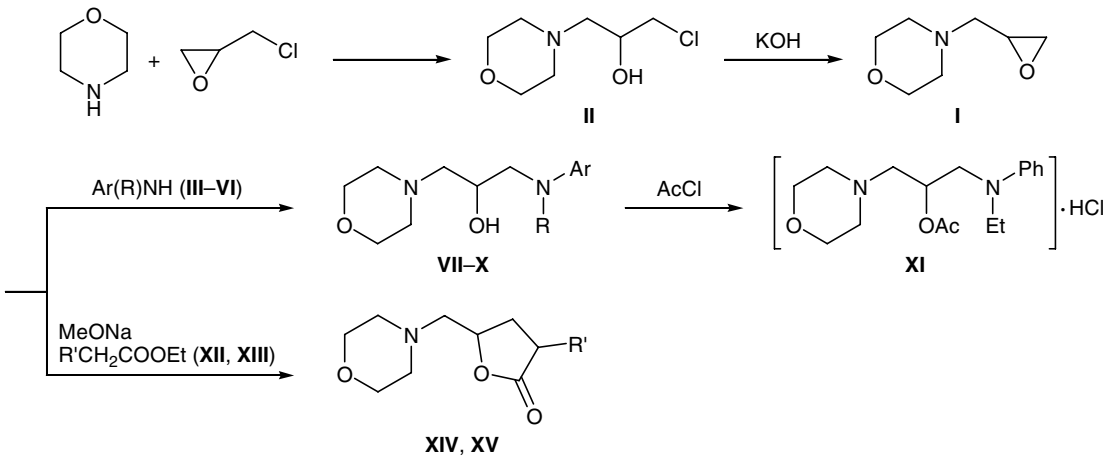
DOI: 10.1134/S1070428006120141

Systems containing a morpholine fragment attract interest as potential biologically active compounds. Many morpholine derivatives are tranquilizers, synthetic narcotic analgetics, and anticonvulsant and antituberculous agents, some of which have found application in medicine (e.g., Trioxazine, Dextromoramide, Ethmosine, Ofloxacin, etc.) [1]. 4-(Oxiran-2-ylmethyl)-morpholine may serve as a basis for the preparation of new derivatives of morpholine-containing vicinal amino alcohols as promising synthons in the design of natural and biologically active organic compounds [2–10]. Various vicinal amino alcohols are now used in medical practice; a number of these compounds are β-adrenergic blocking agents [1, 11, 12] exhibiting a specific effect on the stimulation of β-adrenoceptive systems.

We were the first to develop procedures for the synthesis of 4-(oxiran-2-ylmethyl)morpholine (**I**) from 1-chloro-2,3-epoxypropane and morpholine. These compounds reacted at an equimolar ratio in aqueous medium at 0–5°C to give in high yield 1-chloro-3-morpholinopropan-2-ol (**II**), and treatment of the latter with a base (KOH) in xylene at 0–5°C gave compound **I** (method *a*) in a satisfactory yield (76%, calculated on the initial chloroepoxypropane). It was more advantageous to use procedures *b* and *c* which required no isolation of alcohol **II** and ensured higher yields of the target product.

By condensation of morpholinomethyloxirane **I** with aniline (**III**), *p*-anisidine (**IV**), 1-naphthylamine (**V**), and phenyl(ethyl)amine (**VI**) at a reactant molar ratio of 1:3 we obtained the corresponding amino alcohols **VII**–**X** (Scheme 1). Treatment of alcohol **X** with acetyl chloride afforded 2-[ethyl(phenyl)amino]-1-(morpholinomethyl)ethyl acetate hydrochloride (**XI**).

Scheme 1.



III, **VII**, R = H, Ar = Ph; **IV**, **VIII**, R = H, Ar = 4-$MeOC_6H_4$; **V**, **IX**, R = H, Ar = 1-naphthyl; **VI**, **X**, R = Et, Ar = Ph; **XII**, **XIV**, R' = EtOCO; **XIII**, **XV**, R' = MeCO.

Compound **I** reacted with diethyl malonate in methanol in the presence of sodium methoxide to give ethyl 5-morpholino-2-oxotetrahydrofuran-3-carboxylate (**XIV**), and the reaction of **I** with ethyl acetoacetate under analogous conditions led to the formation of 3-acetyl-5-morpholinotetrahydrofuran-2-one (**XV**) (Scheme 1).

EXPERIMENTAL

The ^{1}H NMR spectra were recorded from solutions in DMSO-d_6 at 30°C on a Varian Mercury-300 spectrometer (300 MHz). The IR spectra were obtained on a Specord 75IR spectrophotometer from samples dispersed in mineral oil or from thin films. The purity of the products was checked by TLC on Silufol UV-254 plates; spots were visualized by treatment with iodine vapor.

1-Chloro-3-morpholinopropan-2-ol (II). Water, 25 ml, was added on cooling to 26.1 g (0.3 mol) of morpholine, the mixture was cooled to 0°C, 27.35 g (0.3 mol) of cold 1-chloro-2,3-epoxypropane was added, and the mixture was stirred for 4 h at 0–5°C. Removal of water left compound **II**. Yield 49.4 g (92%), bp 118–120°C (1.5 mm), n_D^{20} = 1.4936.

4-(Oxiran-2-ylmethyl)morpholine (I). *a.* Potassium hydroxide, 18.2 g (0.325 mol), was added in small portions on cooling to a solution of 49 g (0.27 mol) of alcohol **II** in 70 ml of xylene. The mixture was kept for 12 h at room temperature, and the solvent was removed to leave compound **I**. Yield 33.6 g (87%), bp 120°C (39 mm), 100°C (18 mm), n_D^{20} = 1.4685, d_4^{20} = 1.067, R_f 0.52 ($CHCl_3$–acetone–MeOH, 0.3:1.5:1.6). IR spectrum, ν cm^{-1}: 1105 (C–O), 1250 (C–N). ^{1}H NMR spectrum, δ, ppm: 3.6 t (4H, CH_2OCH_2), 2.96 m (1H, CH) 2.63 m (1H, C**H**$_2$OCH), 2.68–2.34 m (6H, CH_2N), 2.18 m (1H, C**H**$_2$OCH). Found, %: C 58.72; H 9.15; N 9.78. MR_D = 37.30. $C_7H_{13}NO_2$. Calculated, %: C 58.51; H 9.31; N 9.45. MR_D = 37.32.

b. Water, 30 ml, was added on cooling to 52.2 g (0.6 mol) of morpholine. The mixture was cooled to 0°C, 55.5 g (0.6 mol) of cold 1-chloro-2,3-epoxypropane was added, and the mixture was stirred for 4 h at 0–5°C. Xylene, 50 ml, was added, 60 g (1.07 mol) of potassium hydroxide was added in small portions, and the mixture was kept for 12 h at room temperature. The solvent was removed to obtain compound **I**. Yield 66.92 g (78%).

c. Water, 20 ml, was added on cooling to 87 g (1.0 mol) of morpholine, the mixture was cooled to 0°C, 92.5 g (1.0 mol) of cold 1-chloro-2,3-epoxypropane was added, and the mixture was stirred for 3 h at 0–5°C. Toluene, 50 ml, was added, potassium hydroxide, 100 g (1.8 mol), was added in small portions, the mixture kept for 18 h at room temperature and filtered, the filtrate was dried over $MgSO_4$, the solvent was removed, and the residue was distilled under reduced pressure. Yield 124 g (87%).

1-Morpholino-3-phenylaminopropan-2-ol (VII). A mixture of 8.37 g (0.09 mol) of aniline, 4.3 g (0.03 mol) of compound **I**, and 1 ml of ethanol was heated for 5.5 h at 85°C under continuous stirring. The mixture was cooled, and the precipitate was filtered off and recrystallized from ethanol. Yield 5.4 g (76%), mp 122–122.5°C. R_f 0.41 ($CHCl_3$–EtOH–hexane, 1.0:0.2:0.2). IR spectrum, ν, cm^{-1}: 3310 (NH), 3105 (OH), 3030 (CH_{arom}), 1600 ($C{=}C_{arom}$), 1590 (δNH). ^{1}H NMR spectrum, δ, ppm: 2.24–2.46 m (6H, CH_2N), 3.11 d.d (1H, C**H**$_2$NH), 3.34 d.d (1H, C**H**$_2$NH), 3.58 t (4H, CH_2O), 4.05 m (1H, C**H**OH) 4.81 d (1H, OH), 4.98 br.s (1H, NH), 6.52 t (1H, H_{arom}), 6.57 d (2H, H_{arom}), 7.05 t (2H, H_{arom}). Found, %: C 65.87; H 8.69; N 11.51. $C_{13}H_{20}N_2O_2$. Calculated, %: C 66.07; H 8.53; N 11.85.

1-(4-Methoxyphenylamino)-3-morpholinopropan-2-ol (VIII). *p*-Anisidine, 11.07 g (0.09 mol), was dissolved in 10 ml of ethanol, 4.3 g (0.03 mol) of compound **I** was added, and the mixture was heated for 6 h at 85–90°C under continuous stirring. The solvent was removed, and the residue was distilled under reduced pressure. Yield 6.55 g (82%), bp 195–197°C (0.5 mm), n_D^{20} = 1.5604, R_f 0.47 ($CHCl_3$–EtOH–hexane, 1.0:0.2:0.2). IR spectrum, ν cm^{-1}: 3480 (OH), 3325 (NH), 3030 ($C{-}H_{arom}$), 1610 ($C{=}C_{arom}$), 1580 (δNH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.24–2.46 m (6H, CH_2N), 3.04 d.d (1H, CH_2N, *J* = 13.8, 7.5), 3.25 d.d (1H, CH_2N, *J* = 13.8, 4.2), 3.67 s (3H, CH_3), 4.01 m (1H, C**H**OH), 4.62 br.s (1H, NH), 4.85 d (1H, OH), 6.55 d (2H, H_{arom}), 6.64 d (2H, H_{arom}). Found, %: C 63.41; H 8.62; N 10.26. $C_{14}H_{22}N_2O_3$. Calculated, %: C 63.14; H 8.33; N 10.52.

1-Morpholino-3-(1-naphthylamino)propan-2-ol (IX). 1-Naphthylamine, 12.87 g (0.09 mol), was dissolved in 25 ml of ethanol, 4.3 g (0.03 mol) of compound **I** was added, and the mixture was heated for 4 h at 85–90°C under continuous stirring. The solvent was removed, and the residue was distilled under reduced pressure. Yield 7.2 g (84%), bp 222–223°C (0.3 mm), n_D^{24} = 1.6166, R_f 0.52 ($CHCl_3$–EtOH–hexane, 1.0:0.2:0.2). IR spectrum, ν cm^{-1}: 3450 (OH), 3230 (NH),

3030 (C–H_{arom}), 1605 (C=C_{arom}), 1580 (δNH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.23–2.46 m (6H, CH_2N), 3.15 d.d (1H, CH_2N, *J* = 13.8, 7.5), 3.38 d.d (1H, CH_2N, *J* = 13.8, 4.2), 3.59 t (2H, CH_2O), 4.0 m (1H, C**H**OH), 4.80 br.s (1H, OH), 5.56 br.s (1H, NH), 6.54 d (1H, H_{arom}), 7.05 d (1H, H_{arom}), 7.25 t (1H, H_{arom}), 7.38 m (2H, H_{arom}), 7.67 t (1H, H_{arom}), 7.98 t (1H, H_{arom}). Found, %: C 71.01; H 7.56; N 9.99. $C_{17}H_{22}N_2O_2$. Calculated, %: C 71.30; H 7.74; N 9.78.

1-[Ethyl(phenyl)amino]-3-morpholinopropan-2-ol (X) was synthesized as described above for compound **VII** (the mixture was heated for 11 h at 90–95°C). After removal of the solvent, the residue was distilled under reduced pressure. Yield 5.2 g (67%), bp 168–170°C (0.5 mm), n_D^{18} = 1.5485, R_f 0.47 ($CHCl_3$–EtOH–hexane, 1:0.2:0.2). IR spectrum, ν, cm^{-1}: 3330 (OH), 3030 (C–H_{arom}), 1600 (C=C_{arom}). ^{1}H NMR spectrum, δ, ppm: 1.12 t (3H, $CH_2C\mathbf{H}_3$), 2.23–2.46 m (6H, CH_2N), 3.24–3.41 m (4H, C$\mathbf{H}_2$NPh), 3.58 t (4H, CH_2O), 3.98 m (1H, C**H**OH), 4.80 br.s (1H, OH), 6.60 t (1H, H_{arom}), 6.78 d (2H, H_{arom}), 7.13 t (2H, H_{arom}). Found, %: C 67.92; H 9.24; N 10.25. $C_{15}H_{14}N_2O_2$. Calculated, %: C 68.15; H 9.15; N 10.60.

2-[Ethyl(phenyl)amino]-(1-morpholinomethyl)-ethyl acetate hydrochloride (XI). A mixture of 3 g (0.0114 mol) of alcohol **X**, 0.89 g (0.0114 mol) of acetyl chloride, and 8 ml of toluene was kept for 1 h at room temperature, heated for 30 min at 90–95°C, and cooled, and the precipitate was filtered off, washed with toluene, and dried. Yield 3.4 g (87%), mp 134–135°C. IR spectrum, ν, cm^{-1}: 3030 (C–H_{arom}), 1740 (C=O), 1600 (C=C_{arom}). ^{1}H NMR spectrum, δ, ppm: 1.12 t (3H, $CH_2C\mathbf{H}_3$), 1.97 s (3H, CH_3CO), 2.31–2.50 m (6H, CH_2N), 3.24–3.41 m (4H, C$\mathbf{H}_2$NPh), 3.59 t (4H, CH_2O), 3.98 m (1H, C**H**OH), 6.60 t (1H, H_{arom}), 6.78 d (2H, H_{arom}), 7.13 t (2H, H_{arom}). Found, %: C 59.21; H 8.16; N 8.35. $C_{17}H_{26}N_2O_3\cdot$HCl. Calculated, %: C 59.55; H 7.94; N 8.17.

Ethyl 5-morpholino-2-oxotetrahydrofuran-3-carboxylate (XIV). Metallic sodium, 0.9 g (0.038 mol), was added in small pieces to a solution of 0.052 mol of diethyl malonate in 7 ml of methanol. When the mixture warmed up to 45°C, 5 g (0.035 mol) of compound **I** was added dropwise, and the mixture was kept for 18 h at room temperature, heated for 4 h at 50–55°C, neutralized with 15.4 ml of 31% hydrochloric acid, diluted with 100 ml of acetone, and filtered. The filtrate was dried over $MgSO_4$, the solvent was distilled off, and the residue was subjected to fractional distillation under reduced pressure. Yield 5.2 g (58%), bp 166°C (7 mm), n_D^{20} = 1.4890. IR spectrum, ν, cm^{-1}: 3440 (OH, enol), 1780 (C=O, lactone), 1740 (C=O, ester), 1650 (C=C, enol). ^{1}H NMR spectrum, δ, ppm: 1.5 t (3H, $OCH_2C\mathbf{H}_3$), 2.20 m (2H, 4-H, furan), 2.68 m (6H, CH_2N), 3.6 t (4H, CH_2OCH_2), 4.05 q (2H, $OC\mathbf{H}_2CH_3$), 4.2 m (1H, 5-H, furan), 5.5 t (1H, 3-H, furan). Found, %: C 55.86; H 7.14; N 5.31. $C_{12}H_{19}NO_5$. Calculated, %: C 56.02; H 7.44; N 5.44.

3-Acetyl-5-morpholinotetrahydrofuran-2-one (XV) was synthesized in a similar way. Yield 4.9 g (62%), bp 198–199°C (3 mm). IR spectrum, ν cm^{-1}: 1785 (C=O, lactone), 1720 (C=O, ketone). ^{1}H NMR spectrum, δ, ppm: 2.24 m (2H, 4-H, furan), 2.65 m (6H, CH_2N), 2.38 s (3H, CH_3CO), 3.6 t (4H, CH_2OCH_2), 4.20 m (1H, 5-H, furan), 5.4 t (1H, 3-H, furan). Found, %: C 58.36; H 7.24; N 5.88. $C_{11}H_{17}NO_4$. Calculated, %: C 58.14; H 7.54; N 6.16.

REFERENCES

1. Mashkovskii, M.D., *Lekarstvennye sredstva* (Drugs), Moscow: Novaya Volna, 2002, vol. 1, pp, 253–263, 368, 385; vol. 2, pp. 295, 303, 362.
2. Bergmeier, S.C., *Tetrahedron*, 2000, vol. 56, p. 2561.
3. Karpf, M. and Trussardi, R.J., *J. Org. Chem.*, 2001, vol. 66, p. 2044.
4. Inaba, T., Yamada, Y., Abe, H., Sagawa, S., and Cho, H., *J. Org. Chem.*, 2000, vol. 65, p. 1623.
5. Cristau, H.-J., Pirat, J.-L., Drag, M., and Kafarski, P., *Tetrahedron Lett.*, 2000, vol. 41, p. 9781.
6. Hudlicky, T., Abbod, K.F., Entwisle, D.A., Fan, R., Maurya, R., Thorpe, A.J., Bolonick, J., and Myers, B., *Synthesis*, 1996, p. 897.
7. Ger. Patent Appl. no. 19724186, 1998; *Ref. Zh., Khim.*, 2002, no. 19O116P.
8. Sabitha, G., Babu, R.S., Rajkumar, M., and Yadav, J.S., *Org. Lett.*, 2002, p. 343.
9. Mesropyan, E.G., Ambartsumyan, G.B., Avetisyan, A.A., Galstyan, A.S., and Arutyunova, I.R., *Russ. J. Org. Chem.*, 2005, vol. 41, p. 67.
10. Mesropyan, E.G., Ambartsumyan, G.B., Avetisyan, A.A., Galstyan, A.S., and Khachatryan, A.G., *Khim. Geterotsikl. Soedin.*, 2005, no. 8, p. 1135.
11. Shvaika, Ol., *Osnovi sintezu likars'kikh rechovii* (Principles of Synthesis of Drugs), Donets'k: Skhidnii Vidavnichii Dim, 2002.
12. Lukevits, E.Ya., Libert, L.I., and Voronkov, M.G., *Usp. Khim.*, 1970, vol. 29, p. 2005.