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Synthesis of N-Aryl Derivatives of Vicinal Aminoalcohols

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Abstract—Synthesis was performed of substituted 2-propanols based on glycidyl phenyl and glycidyl allyl ethers, Also some acetic acid esters were prepared.

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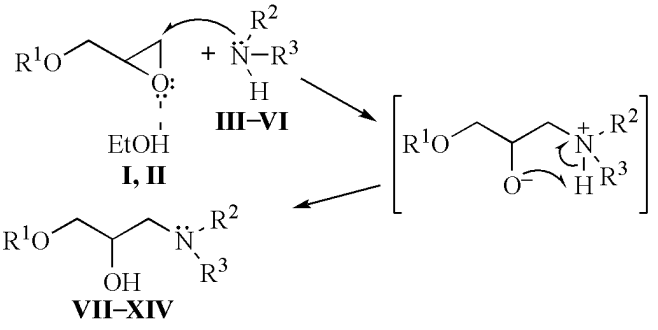
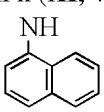
Reactions of epoxy compounds with amines is one among the most convenient preparation methods for vicinal aminoalcohols used as building blocks in designing molecules of natural and biologically active organic substances [1–15].

Various vicinal aminoalcohols and their derivatives both at the hydroxy group and nitrogen atom exhibiting versatile activity are included in the composition of existing drugs [16–19].

The goal of this study was a synthesis of new N-aryl derivatives of vicinal aminoalcohols, potential biologically active substances.

We investigated the reactions of glycidyl ethers **I** and **II** with various aromatic amines: aniline (**III**), *p*-anisidine (**IV**), 1-naphthylamine (**V**), and *N*-ethylaniline (**VI**). Optimum reaction conditions were developed. The reaction was established to occur in the presence of ethanol at a molar reagents ratio 1:3.



R^1 = All (**I, VII–X**), Ph (**II, XI–XIV**); NR^2R^3 = NHPh (I**II, VII, XI**), *n*-NHC_6H_4OMe (**IV, VIII, XII**),  (**V, IX, XIII**), NEtPh (**VI, X, XIV**).

The ring opening occurred as expected [20–23] exclusively in keeping with Krasusky rule yielding a single isomeric product as was proved by ^{1}H NMR spectra.

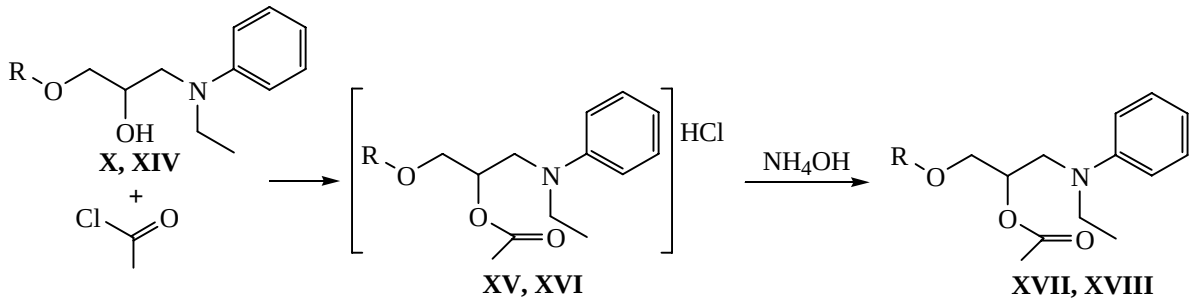
The reaction of 1-(*N*-phenyl-*N*-ethylamino)-3-phenoxypropan-2-ol and 1-allyloxy-3-(*N*-phenyl-*N*-ethylamino)propan-2-ol with acetyl chloride in toluene led to the formation of hydrochlorides of 1-[(*N*-ethyl-*N*-phenylamino)methyl]-2-phenoxyethyl acetate (**XVI**) and 1-[(*N*-ethyl-*N*-phenylamino)methyl]-2-allyloxyethyl acetate (**XV**), which by treating with ammonium hydroxide were converted into free bases **XVII** and **XVIII** (see Scheme).

EXPERIMENTAL

^{1}H NMR spectra were registered at 30°C on a spectrometer Varian Mercury-300 at operating frequency 300 MHz, solvent DMSO-d_6. IR spectra were recorded on a spectrophotometer Specord 75IR from thin films and mulls in mineral oil. The homogeneity and purity of compounds obtained were checked by TLC on Silufol UV-254 plates, development in iodine vapor.

1-Allyloxy-3-phenylaminopropan-2-ol (VII). A mixture of 8.37 g (0.09 mol) of aniline, 3.42 g (0.03 mol) of epoxide **I**, and 1 ml of ethanol was heated at 75–80°C for 5.5 h at constant stirring. On removing ethanol and excess aniline in a vacuum (20 mm Hg) the residue was subjected to distillation. Yield 4.5 g (72%), bp 171–172°C (3.5 mm Hg), n_D^{26} 1.5477, R_f 0.51 [$CHCl_3$–$Me_2C(O)$, 1:0.4]. IR spectrum, ν, cm^{-1}: 3340 (OH), 3280

Scheme.



R = All (**XV, XVII**), Ph (**XVI, XVIII**).

(NH), 3030 (Ar), 1650 (All), 1600 (Ar), 1590 (NH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.11 d.d (1H, $\underline{CH_2}$N, *J* 13.8, 7.5), 3.34 d.d (1H, $\underline{CH_2}$N, *J* 13.8, 4.2), 3.48 m (2H, $\underline{CH_2}$OAll), 4.0 m (1H, $\underline{CH}$OH), 4.04 d.t (2H, $\underline{CH_2}$CH=CH_2, *J* 5.4, 1.5), 4.81 br.s (1H, OH), 4.98 br.s (1H, NH), 5.16 d.q (1H, CH=$\underline{CH_2}$, *J* 10.4, 1.5), 5.26 d.q (1H, CH=$\underline{CH_2}$, *J* 17.2, 1.5), 5.90 d.d.t (1H, $\underline{CH}$=CH_2, *J* 17.2, 10.4, 5.4), 6.52 t, 6.57 d, 7.05 t (5H_{arom}, PhN). Found, %: C 69.23; H 8.32; N 6.38. $C_{12}H_{17}NO_2$. Calculated, %: C 69.54; H 8.27; N 6.76.

1-Allyloxy-3-(4-methoxyphenylamino)propan-2-ol (VIII). To a solution of 11.07 g (0.09 mol) of *p*-anisidine in 10 ml of ethanol was added 3.42 g (0.03 mol) of epoxide **I**. The mixture was heated for 8 h at 85–90°C while continuous stirring. On removing ethanol in a vacuum (20 mm Hg) the residue was distilled to obtain compound **VIII**. Yield 5.8 g (81%), bp 179–180°C (1 mm Hg), n_D^{21} 1.5472, R_f 0.48 [$CHCl_3$–$Me_2C(O)$, 1:0.4]. IR spectrum, ν, cm^{-1}: 3480 (OH), 3320 (NH), 3030(Ar), 1645 (All), 1610 (Ar), 1580 (NH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.04 d.d (1H, $\underline{CH_2}$N, *J* 13.8, 7.5), 3.25 d.d (1H, $\underline{CH_2}$N, *J* 13.8, 4.2), 3.48 m (2H, $\underline{CH_2}$OAll), 3.67 s (3H, CH_3), 4.01 m (1H, $\underline{CH}$OH), 4.04 d.t (2H, $\underline{CH_2}$CH=CH_2, *J* 5.4, 1.5), 4.62 br.s (1H, NH), 4.85 br.s (1H, OH), 5.16 d.q (1H, CH=$\underline{CH_2}$, *J* 10.4, 1.5), 5.26 d.q (1H, CH=$\underline{CH_2}$, *J* 17.2, 1.5), 5.90 d.d.t (1H, $\underline{CH}$=CH_2, *J* 17.2, 10.4, 5.4), 6.55 d, 6.64 (4H_{arom}, $NC_6\underline{H_4}$OMe). Found, %: C 65.99; H 7.83; N 5.56. $C_{13}H_{19}NO_3$. Calculated, %: C 65.80; H 8.07; N 5.90.

1-Allyloxy-3-(naphthalen-1-ylamino)propan-2-ol (IX). To a solution of 12.87 g (0.09 mol) of 1-naphthylamine in 25 ml of ethanol was added 3.42 (0.03 mol) of epoxide **I**. The mixture was heated for 4 h at 85–90°C while continuous stirring. On removing ethanol in a vacuum (20 mm Hg) the residue was subjected to fractional distillation to obtain compound **IX**. Yield 6.65 g (79%), bp 197°C (0.3 mm Hg), n_D^{25} 1.6060, R_f 0.48 [$CHCl_3$–PhMe–$Me_2C(O)$–CCl_4, 1:0.6:0.4:0.4]. IR spectrum, ν, cm^{-1}: 3550 (OH), 3410 (NH), 3051 (Ar), 1650 (All), 1610 (Ar), 1580 (NH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.15 d.d (1H, $\underline{CH_2}$N, *J* 13.8, 7.5), 3.38 d.d (1H, $\underline{CH_2}$N, *J* 13.8, 4.2), 3.48 m (2H, $\underline{CH_2}$OAll), 4.0 m (1H, $\underline{CH}$OH), 4.04 d.t (2H, $\underline{CH_2}$CH=CH_2, *J* 5.4, 1.5), 4.80 br.s (1H, OH), 5.16 d.q (1H, CH=$\underline{CH_2}$, *J* 10.4, 1.5), 5.26 d.q (1H, CH=$\underline{CH_2}$, *J* 17.2, 1.5), 5.56 br.s (1H, NH), 5.90 d.d.t (1H, $\underline{CH}$=CH_2, *J* 17.2, 10.4, 5.4), 6.54 d, 7.05 d, 7.25 t, 7.38 m, 7.67 t, 7.98 t (7H_{arom}, naphthalene). Found, %: C 74.35; H 7.55; N 5.11. $C_{16}H_{19}NO_2$. Calculated, %: C 74.68; H 7.44; N 5.44.

1-Allyloxy-3-(*N*-phenyl-*N*-ethylamino)propan-2-ol (X) was obtained in the same way as compound **VII**. The mixture was heated for 10 h at 80–85°C. Yield 6.2 g (88%), bp 152–154°C (1.5 mm Hg), n_D^{22} 1.5390, R_f 0.47 [$CHCl_3$–PhMe–$Me_2C(O)$–CCl_4, 1:0.6:0.5:0.4]. IR spectrum, ν, cm^{-1}: 3340 (OH), 3030 (Ar), 1650 (All), 1600 (Ar). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.13 t (3H, $CH_2\underline{CH_3}$), 3.23–3.40 m (4H, $\underline{CH_2}$N), 3.48 m (2H, $\underline{CH_2}$OAll), 3.98 m (1H, $\underline{CH}$OH), 4.04 d.t (2H, $\underline{CH_2}$CH=CH_2, *J* 5.4, 1.5), 4.82 br.s (1H, OH), 5.16 d.q (1H, CH=$\underline{CH_2}$, *J* 10.4, 1.5), 5.26 d.q (1H, CH=$\underline{CH_2}$, *J* 17.2, 1.5), 5.90 d.d.t (1H, $\underline{CH}$=CH_2, *J* 17.2, 10.4, 5.4), 6.60 t, 6.78 d, 7.13 t (5H_{arom}, PhN). Found, %: C 71.69; H 8.67; N 6.24. $C_{12}H_{17}NO_2$. Calculated, %: C 71.46; H 8.99; N 5.95.

1-Phenoxy-3-phenylaminopropan-2-ol (XI) was obtained in the same way as compound **VII**. The mixture was heated for 5 h at 80–85°C. Yield 5.8 g (79%), bp 212°C (3 mm Hg), n_D^{20} 1.5970, R_f 0.52 [$CHCl_3$–PhMe–$Me_2C(O)$, 1:0.6:0.2]. IR spectrum, ν, cm^{-1}: 3350 (OH), 3290 (NH), 3030 (Ar), 1600 (Ar), 1590 (NH). ^{1}H NMR spectrum, δ, ppm: 3.11 d.d (1H, $\underline{CH_2}$NH), 3.34 d.d (1H, $\underline{CH_2}$NH), 3.93 d.d (2H, $\underline{CH_2}$OPh), 4.05 m (1H, $\underline{CH}$OH),

4.81 d (1H, OH), 4.98 br.s (1H, NH), 6.52 t, 6.57 d, 7.05 t (5H_{arom}, PhN), 6.87 t, 6.89 d, 7.23 t (2H_{arom}, PhO). Found, %: C 73.85; H 7.23; N 5.51. $C_{15}H_{17}NO_2$. Calculated, %: C 74.05; H 7.04; N 5.76.

1-(4-Methoxyphenylamino)-3-phenoxypropan-2-ol (XII) was obtained in the same way as compound **VIII**. The mixture was heated for 8 h at 85–90°C. On removing excess *p*-anisidine the residue was dissolved in hot ethanol. On cooling the precipitated crystals were filtered off, washed with ethanol, and dried. Yield 6.25 g (75%), mp 86°C (ethanol), R_f 0.43 [$CHCl_3$–PhMe–$Me_2C(O)$, 1:0.6:0.4]. IR spectrum, ν, cm^{-1}: 3255 (NH), 3170 (OH), 3030 (Ar), 1600 (Ar), 1590 (NH). ^{1}H NMR spectrum, δ, ppm: 3.04 d.d (1H, $\underline{CH}_2$NH), 3.25 d.d (1H, $\underline{CH}_2$NH), 3.67 s (3H, OCH_3), 3.93 d.d (2H, $\underline{CH}_2$OPh), 4.01 m (1H, $\underline{CH}$OH), 4.62 br.s (1H, NH), 4.81 d (1H, OH), 6.55 d, 6.64 d (4H_{arom}, $NC_6\underline{H}_4$OMe), 6.85 t, 6.89 d, 7.23 t (5H_{arom}, PhO). Found, %: C 70.53; H 7.25; N 4.85. $C_{16}H_{19}NO_3$. Calculated, %: C 70.31; H 7.01; N 5.12.

1-(Naphthalen-1-ylamino)-3-phenoxypropan-2-ol (XIII) was prepared similarly to compound **IX**. The mixture was heated for 5 h at 80–85°C. Yield 6.3 g (72%), bp 232–233°C (0.3 mm Hg), mp 62°C, R_f 0.62 [$CHCl_3$–PhMe–$Me_2C(O)$, 1:0.6:0.4]. IR spectrum, ν, cm^{-1}: 3550 (OH), 3410 (NH), 3051 (Ar), 1620 (Ar), 1580 (NH). ^{1}H NMR spectrum, δ, ppm: 3.15 d.d (1H, $\underline{CH}_2$NH), 3.38 d.d (1H, $\underline{CH}_2$NH), 3.93 m (2H, $\underline{CH}_2$OPh), 4.01 m (1H, $\underline{CH}$OH), 4.8 br.s (1H, OH), 5.56 br.s (1H, NH), 6.54 d, 7.05 d, 7.25 t, 7.38 m, 7.67 t, 7.98 t (7H_{arom}, naphthalene), 6.85 t, 6.89 d, 7.23 t (5H_{arom}, PhO). Found, %: C 77.53; H 6.74; N 5.01. $C_{19}H_{19}NO_2$. Calculated, %: C 77.79; H 6.53; N 4.77.

1-(*N*-Phenyl-*N*-ethylamino)-3-phenoxypropan-2-ol (XIV) was obtained in the same way as compound **VII**. The mixture was heated for 12 h at 90–95°C. Yield 7.95 g (98%), bp 193°C (1.5 mm Hg), n_D^{20} 1.5830, R_f 0.45 [$CHCl_3$–PhMe– $Me_2C(O)$, 1:0.6:0.2]. IR spectrum, ν, cm^{-1}: 3510 (OH), 3030 (Ar), 1600 (Ar). ^{1}H NMR spectrum, δ, ppm: 1.12 t (3H, $CH_2\underline{CH}_3$), 3.24–3.41 m (4H, $C\underline{H}_2N$), 3.93 d.d (2H, $\underline{CH}_2$OPh), 3.98 m (1H, $\underline{CH}$OH), 4.83 br.s (1H, OH), 6.60 t, 6.78 d, 7.13 t (5H_{arom}, PhN), 6.85 t, 6.89 d, 7.23 t (5H_{arom}, PhO). Found, %: C 75.52; H 8.06; N 5.43. $C_{17}H_{21}NO_2$. Calculated, %: C 75.25; H 7.80; N 5.16.

1-[(N-Ethyl-N-phenylamino)methyl]-2-allyloxyethyl acetate (XVII). A mixture of 6.05 g (0.026 mol) of propan-2-ol **X**, 2.02 g (0.026 mol) of acetyl chloride, and 10 ml of toluene was maintained for 18 h at room temperature and then heated for 4 h at 90–95°C, the mixture obtained was treated with 8% ammonia solution (till pH 10), then the oily layer was separated from the water one, washed with water till neutral washings, and dried with $MgSO_4$. The solvent was removed, and the residue was subjected to a vacuum distillation. Yield 5 g (69%), bp 171°C (6 mm Hg), n_D^{20} 1.5207, R_f 0.57 ($CHCl_3$–PhMe–CCl_4, 1:0.6:0.4). IR spectrum, ν, cm^{-1}: 3030 (Ar), 1740 (C=O), 1650 (All), 1600 (Ar). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.13 t (3H, $CH_2C\underline{H}_3$), 1.97 s (3H, $\underline{CH}_3CO$), 3.23–3.40 m (4H, $C\underline{H}_2N$), 3.48 m (2H, $C\underline{H}_2$OAll), 3.98 m (1H, $C\underline{H}$OH), 4.04 d.t (2H, $C\underline{H}_2CH{=}CH_2$, *J* 5.4, 1.5), 5.16 d.q (1H, $CH{=}C\underline{H}_2$, *J* 10.4, 1.5), 5.26 d.q (1H, $CH{=}C\underline{H}_2$, *J* 17.2, 1.5), 5.90 d.d.t (1H, $C\underline{H}{=}CH_2$, *J* 17.2, 10.4, 5.4), 6.60 t, 6.78 d, 7.13 t (5H_{arom}, PhN). Found, %: C 68.95; H 8.56; N 5.39. $C_{16}H_{23}NO_3$. Calculated, %: C 69.29; H 8.36; N 5.05.

1-[(*N*-Ethyl-*N*-phenylamino)methyl]-2-phenoxyethyl acetate (XVIII). A mixture of 4.65 g (0.017 mol) of propan-2-ol **XIV**, 1.35 g (0.017 mol) of acetyl chloride, and 10 ml of toluene was maintained for 18 h at room temperature and then heated for 4 h at 90–95°C, the mixture obtained was cooled. The separated precipitate was filtered off, washed with ether, and dried. Yield of compound **XVI** 5.35 g (90%), mp 125°C, R_f 0.62 [$CHCl_3$–PhMe–$Me_2C(O)$, 1.0:0.6:0.4]. IR spectrum, ν, cm^{-1}: 3030 (Ar), 1740 (C=O), 1600 (Ar). ^{1}H NMR spectrum, δ, ppm: 1.12 t (3H, $CH_2\underline{CH}_3$), 1.97 s (3H, $\underline{CH}_3CO$), 3.24–3.41 m (4H, $\underline{CH}_2N$), 3.93 d.d (2H, $\underline{CH}_2$OPh), 3.98 m (1H, $\underline{CH}$O), 6.62 t, 6.80 d, 7.16 t (5H_{arom}, PhN), 6.85 t, 6.89 d, 7.23 t (5H_{arom}, PhO), 12.7 br.s (1H, HCl). Found, %: C 65.56; H 7.23; N 4.32. $C_{19}H_{23}NO_3{\cdot}HCl$. Calculated, %: C 65.23; H 6.91; N 4.00. To obtain free base **XVIII** a dispersion of 1.75 g (0.005 mol) of compound **XVI** in 3 ml of benzene was treated with 8% ammonia solution (till pH 10), then the oily layer was separated from the water one, washed with water till neutral washings, and dried with $MgSO_4$. The solvent was removed, and the residue was subjected to a vacuum distillation. Yield 1.3 g (83%), bp 193°C (1.8 mm Hg), n_D^{26} 1.5578.

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