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Reactions of Vinyl 2,3-Epoxypropyl Ethers with 4,5-Dihydro-1*H*-pyrazoles

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Abstract—Reactions of vinyl 2,3-epoxypropyl ether and 2-(vinyloxy)ethyl 2,3-epoxypropyl ether with 4,5-dihydro-1*H*-pyrazoles give, respectively, 3-vinyloxy-1-(4,5-dihydro-1*H*-pyrazol-1-yl)propan-2-ols and 3-(2-vinyloxyethoxy)-1-(4,5-dihydro-1*H*-pyrazol-1-yl)propan-2-ols in 70–91% yield.

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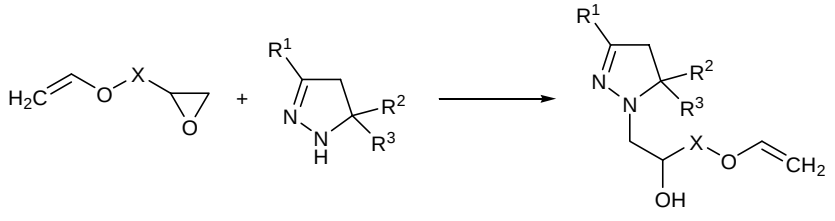
Vinyl ethers derived from nitrogen-containing alcohols are promising as monomers for the preparation of strongly basic anion exchangers and as starting compounds for the synthesis of biologically active substances [1]. 4,5-Dihydropyrazoles are also known to exhibit versatile biological activity [2]. Taking into account the above stated, in the present work we synthesized vinyl ethers containing a 4,5-dihydropyrazole ring, which attract undoubted interest from the viewpoint of studying their biological activity.

Vinyl 2,3-epoxypropyl ethers **Ia** and **Ib** were heated with 3 equiv of substituted 4,5-dihydro-1*H*-pyrazoles **IIa**–**IIe** for 2.5–4 h at 95–100°C. The progress of reactions was monitored by GLC until complete disappearance of initial epoxy derivative **Ia** or **Ib** from the reactions mixture. The yields of compounds **IIIa**–**IIIg** were 70–91% (Scheme 1). Comparison of the product yields and reaction times with those in analogous reactions of 2,3-epoxypropyl 2-(vinyloxy)ethyl ether with morpholine, diallylamine, and diethylamine [3] shows that 4,5-dihydropyrazole behave as typical secondary amines.

The IR spectra of dihydropyrazolyl-substituted alcohols **IIIa**–**IIIg** contain absorption bands at 1605–1610 (ν C=C), 1625–1630 (ν N=C), 3040–3115 [ν_{as}(=C–H)], and 3310–3420 cm^{-1} (ν OH). In the ^{1}H NMR spectra of **IIIa**–**IIIg**, signals from protons in the vinyloxy group appear as three doublets of doublets at δ 3.97–4.01 (*cis*-CH=), 4.09–4.26 (*trans*-CH=), and 6.44–6.50 ppm (OC**H**=CH_2) (^2J = 2.0–2.1, $^3J_{cis}$ = 6.7–6.9, $^3J_{trans}$ = 14.0–14.3 Hz). The ^{1}H NMR spectra of compounds containing asymmetric carbon atoms both in the substituent on the nitrogen and in the pyrazole ring were complicated due to the presence of different diastereoisomers. However, in some cases we succeeded in assigning proton signals to particular stereoisomers and determined the corresponding coupling constants.

Scheme 1.



Ia, **Ib** **IIa**–**IIe** **IIIa**–**IIIg**

I, X = CH_2 (**a**), $(CH_2)_2OCH_2$ (**b**); **II**, $R^1 = R^2 = R^3$ = H (**a**); $R^1 = R^2$ = H, R^3 = Me (**b**); $R^1 = R^2 = R^3$ = Me (**c**); $R^1 = R^2$ = Et, R^3 = Me (**d**); $R^1 = R^2$ = H, R^3 = Ph (**e**); **III**, X = CH_2, $R^1 = R^2 = R^3$ = Me (**a**); $R^1 = R^2$ = Et, R^3 = Me (**b**); X = $(CH_2)_2OCH_2$, $R^1 = R^2 = R^3$ = H (**c**); $R^1 = R^2$ = H, R^3 = Me (**d**); $R^1 = R^2 = R^3$ = Me (**e**); $R^1 = R^2$ = Et, R^3 = Me (**f**); $R^1 = R^2$ = H, R^3 = Ph (**g**).

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were recorded at 26°C on a Bruker DPX-400 spectrometer at 400 and 100 MHz, respectively, using $CDCl_3$ as solvent and HMDS as internal reference. The IR spectra were obtained on a Specord 75IR spectrometer; samples were examined as thin films (neat).

1-(4,5-Dihydro-1*H*-pyrazol-1-yl)-3-(vinyloxy)propan-2-ols IIIa and IIIb and 1-(4,5-dihydro-1*H*-pyrazol-1-yl)-3-(2-vinyloxyethoxy)propan-2-ols IIIc–IIIg (*general procedure***).** A mixture of 0.05 mol of 2,3-epoxypropyl ether **Ia** or **Ib** and 0.15 mol of dihydropyrazole **IIa**–**IId** was heated for 2.5–4 h at 97–100°C. The product was isolated by distillation under reduced pressure.

1-(3,5,5-Trimethyl-4,5-dihydro-1*H*-pyrazol-1-yl)-3-(vinyloxy)propan-2-ol (IIIa). Yield 77%, bp 115–118°C (2 mm), d_4^{20} = 1.0123, n_D^{20} = 1.4771. IR spectrum, ν, cm^{-1}: 520, 535, 570, 590, 615, 660, 750, 765, 815, 825, 860, 905, 960, 980, 995, 1090, 1100, 1145, 1165, 1195, 1240, 1270, 1320, 1360, 1380, 1430, 1460, 1605, 1625, 2875, 2915, 2930, 2970, 3040, 3080, 3115, 3410. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.12 s (6H, 5-Me), 1.90 s (3H, 3-Me), 2.39 s (2H, 4-H), 2.76 d.d (1H, H_A in $NCH_AH_BCH_X$, $^2J_{AB}$ = 12.5, $^3J_{AX}$ = 2.8), 2.90 d.d (1H, H_B in $NCH_AH_BCH_X$, $^2J_{AB}$ = 12.5, $^3J_{BX}$ = 7.5), 3.76 m (2H, $OCH_AH_BCH_C$, $^2J_{AB}$ = 11.6, $^3J_{AC}$ = 5.6), 3.98 d.d (*cis*-CH=CO, ^2J = 2.0, $^3J_{cis}$ = 6.8), 4.14 m (1H, C**H**OH), 4.19 d.d (1H, *trans*-CH=CO, ^2J = 2.0, $^3J_{trans}$ = 14.3), 4.47 br.s (1H, OH), 6.48 d.d (1H, C=CHO, $^3J_{cis}$ = 6.8, $^3J_{trans}$ = 14.3). Found, %: C 62.09; H 9.59; N 13.78. $C_{11}H_{20}N_2O_2$. Calculated, %: C 62.23; H 9.50; N 13.20.

1-(3,5-Diethyl-5-methyl-4,5-dihydro-1*H*-pyrazol-1-yl)-3-(vinyloxy)propan-2-ol (IIIb). Yield 70%, bp 128–132°C (2 mm), d_4^{20} = 1.0006, n_D^{20} = 1.4828. IR spectrum, ν, cm^{-1}: 525, 535, 580, 640, 645, 680, 705, 800, 860, 945, 980, 1060, 1075, 1185, 1255, 1275, 1305, 1335, 1360, 1445, 1605, 1625, 2870, 2925, 2960, 3040, 3110, 3395. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.87 t (1.5H, 5-CH_2CH_3 in diastereoisomer **A**, ^3J = 7.4), 0.89 t (1.5H, 5-CH_2CH_3 in diastereoisomer **B**, ^3J = 7.4), 1.01 s (3H, 5-Me), 1.09 t (3H, 3-CH_2CH_3, ^3J = 7.4), 1.54 m (2H, 5-CH_2), 1.85–2.55 m (5H, 3-CH_2, 4-H, OH), 2.78–2.85 m (1H, H_A in NCH_AH_B-CH_X), 2.89 d.d (0.5H, H_B in $NCH_AH_BCH_X$, diastereoisomer **A**, $^2J_{AB}$ = 12.4, $^3J_{BX}$ = 2.7), 2.98 d.d (0.5H, H_B in $NCH_AH_BCH_X$, diastereoisomer **B**, $^2J_{AB}$ = 12.4, $^3J_{AX}$ = 2.7), 3.67–3.86 m (2H, OC**H**$_2$CH), 3.95–4.23 m (3H, CH_2=CO, C**H**OH), 6.49 d.d (0.5H, C=CHO in diastereoisomer **A**, $^3J_{cis}$ = 6.8, $^3J_{trans}$ = 14.2), 6.50 d.d (0.5H, C=CHO in diastereoisomer **B**, $^3J_{cis}$ = 6.8, $^3J_{trans}$ = 14.2). Found, %: C 65.05; H 10.14; N 11.43. $C_{13}H_{24}N_2O_2$. Calculated, %: C 64.97; H 10.07; N 11.66.

1-(4,5-Dihydro-1*H*-pyrazol-1-yl)-3-(2-vinyloxyethoxy)propan-2-ol (IIIc). Yield 78%, bp 162–165°C (3 mm), d_4^{20} = 1.0751, n_D^{20} = 1.4918. IR spectrum, ν, cm^{-1}: 450, 535, 600, 650, 690, 810, 830, 865, 960, 1025, 1075, 1110, 1185, 1280, 1310, 1355, 1370, 1425, 1445, 1605, 1625, 2860, 2905, 3105, 3360. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.60–3.35 m (6H, 4-H, 5-H, 1-CH_2), 3.52–3.86 m (6H, OCH_2), 4.00 d.d (1H, *cis*-CH=CO, ^2J = 2.1, $^3J_{cis}$ = 6.9), 4.15–4.25 m (2H, C**H**OH, *trans*-CH=CO), 5.53 br.s (1H, OH), 6.48 d.d (1H, C=CHO, $^3J_{cis}$ = 6.9, $^3J_{trans}$ = 14.3), 6.84 m (1H, 3-H). Found, %: C 56.12; H 8.50; N 13.54. $C_{10}H_{18}N_2O_3$. Calculated, %: C 56.06; H 8.47; N 13.07.

1-(5-Methyl-4,5-dihydro-1*H*-pyrazol-1-yl)-3-(2-vinyloxyethoxy)propan-2-ol (IIId). Yield 74%, bp 181–185°C (7 mm), d_4^{20} = 1.0709, n_D^{20} = 1.4885. IR spectrum, ν, cm^{-1}: 540, 615, 695, 765, 815, 880, 905, 965, 1030, 1075, 1125, 1190, 1250, 1270, 1315, 1340, 1375, 1425, 1440, 1610, 1625, 2875, 2920, 2960, 3060, 3115, 3355–3430. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.27 t (3H, 5-Me, ^3J = 5.7), 1.96 br.s (1H, OH), 2.22–2.34 m (2H, 4-H), 2.66–3.17 m (3H, 1-CH_2, 5-H), 3.54–3.80 m (4H, OC**H**$_2$CH, =CHOCH_2C**H**$_2$O), 3.83–3.86 m (2H, =CHOC**H**$_2$CH_2O), 3.99 d.d (0.5H, *cis*-CH=CO in diastereoisomer **A**, ^2J = 2.1, $^3J_{cis}$ = 6.8), 4.00 d.d (0.5H, *cis*-CH=CO in diastereoisomer **B**, ^2J = 2.1, $^3J_{cis}$ = 6.8), 4.12–4.26 m (2H, C**H**OH, *trans*-CH=CO), 6.48 d.d (1H, C=CHO, $^3J_{cis}$ = 6.8, $^3J_{trans}$ = 14.3), 6.77 m (1H, 3-H). Found, %: C 57.94; H 8.85; N 12.18. $C_{11}H_{20}N_2O_3$. Calculated, %: C 57.87; H 8.83; N 12.27.

1-(3,5,5-Trimethyl-4,5-dihydro-1*H*-pyrazol-1-yl)-3-(2-vinyloxyethoxy)propan-2-ol (IIIe). Yield 91%, bp 148–152°C (3 mm), d_4^{20} = 1.0241, n_D^{20} = 1.4765. IR spectrum, ν, cm^{-1}: 525, 560, 610, 655, 690, 760, 820, 855, 875, 900, 965, 980, 990, 1030, 1095, 1115, 1160, 1190, 1230, 1265, 1310, 1355, 1375, 1425, 1440, 1610, 1625, 2865, 2920, 2960, 3040, 3065, 3115, 3405. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.13 s (6H, 5-Me), 1.91 t (3H, 3-Me, ^4J = 1.0), 2.39 q (3H, 4-H, OH, ^4J = 1.0), 2.76 d.d (1H, H_A in $NCH_AH_BCH_X$, $^2J_{AB}$ = 12.4, $^3J_{AX}$ = 3.1), 2.89 d.d (1H, H_B in $NCH_AH_BCH_X$, $^2J_{AB}$ = 12.4, $^3J_{BX}$ = 7.5), 3.59 m (2H, OC**H**$_A$**H**$_B$$CH_C$O, $^2J_{AB}$ = 11.7, $^3J_{AC}$ = 5.6, $^3J_{BC}$ = 1.8), 3.74 m (2H, CH_2=CHOCH_2C**H**$_2$O), 3.83 m (2H, CH_2=CHOC**H**$_2$-

CH_2O), 3.98 d.d (1H, *cis*-CH=CO, ^2J = 2.1, $^3J_{cis}$ = 6.8), 4.08 m (1H, C**H**OH), 4.18 d.d (1H, *trans*-CH=CO, ^2J = 2.1, $^3J_{trans}$ = 14.3), 6.47 d.d (1H, C=CHO, $^3J_{cis}$ = 6.8, $^3J_{trans}$ = 14.3). ^{13}C NMR spectrum, δ, ppm: 16.06 (5-Me), 22.72 (3-Me), 49.47 (C^4), 50.80 (1-CH_2), 65.93 (C^5), 67.40 (=CHO**C**H_2CH_2O), 69.85 (=CHO-CH_2**C**H_2O), 70.19 (**C**HOH), 73.33 (O**C**H_2CHOH), 86.28 (=CH_2), 150.50 (OCH=), 151.45 (C^3). Found, %: C 60.99; H 9.34; N 10.74. $C_{13}H_{24}N_2O_3$. Calculated, %: C 60.91; H 9.44; N 10.93.

1-(3,5-Diethyl-5-methyl-4,5-dihydro-1*H*-pyrazol-1-yl)-3-(2-vinyloxyethoxy)propan-2-ol (IIIf). Yield 82%, bp 99–102°C (2 mm), d_4^{20} = 1.0215, n_D^{20} = 1.4811. IR spectrum, ν, cm^{-1}: 540, 600, 665, 695, 715, 775, 810, 835, 875, 920, 940, 955, 970, 995, 1035, 1095, 1100, 1130, 1195, 1240, 1260, 1285, 1315, 1370, 1455, 1615, 1625, 2875, 2935, 2970, 3045, 3120, 3430. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.88 t (3H, 5-CH_2C**H**$_3$, ^3J = 7.6), 1.00 s (1.5H, 5-Me in diastereoisomer **A**), 1.01 s (1.5H, 5-Me in diastereoisomer **B**), 1.08 t (1.5H, 3-CH_2C**H**$_3$ in diastereoisomer **A**, ^3J = 7.5), 1.09 t (1.5H, 3-CH_2C**H**$_3$ in diastereoisomer **B**, ^3J = 7.5), 1.46–1.61 m (2H, 5-CH_2), 1.84–2.54 m (5H, 3-CH_2, 4-H, OH), 2.77 d.d (0.5 H, H_A in $NCH_AH_BCH_X$, diastereoisomer **A**, $^2J_{AB}$ = 12.5, $^3J_{AX}$ = 2.9,), 2.79 d.d (0.5H, H_A in $NCH_AH_BCH_X$, diastereoisomer **B**, $^2J_{AB}$ = 12.5, $^3J_{BX}$ = 6.2), 2.88 d.d (0.5H, H_B in $NCH_AH_BCH_X$, diastereoisomer **A**, $^2J_{AB}$ = 12.5, $^3J_{AX}$ = 6.2, $^3J_{BX}$ = 2.9), 2.94 d.d (0.5H, H_B in $NCH_AH_BCH_X$, diastereoisomer **B**, $^2J_{AB}$ = 12.5, $^3J_{BX}$ = 6.2, $^3J_{AX}$ = 2.9), 3.60 m (2H, OC**H**$_2$-CHOH), 3.70–3.76 m (2H, CH_2=CHOCH_2C**H**$_2$O), 3.81–3.85 m (2H, CH_2=CHOC**H**$_2$CH_2O), 3.98 d.d (0.5H, *cis*-CH=CO in diastereoisomer **A**, ^2J = 2.0, $^3J_{cis}$ = 6.8), 3.99 d.d (0.5H, c*is*-CH=CO in diastereoisomer **B**, ^2J = 2.0, $^3J_{cis}$ = 6.8), 4.01–4.14 m (1H, C**H**OH), 4.18 d.d (0.5H, *trans*-CH=CO in diastereoisomer **A**, ^2J = 2.0, $^3J_{trans}$ = 14.3), 4.19 d.d (0.5H, *trans*-CH=CO in diastereoisomer **B**, ^2J = 2.0, $^3J_{trans}$ = 14.3), 6.47 d.d (1H, C=CHO, $^3J_{cis}$ = 6.8, $^3J_{trans}$ = 14.3). Found, %: C 63.16; H 9.97; N 10.04. $C_{15}H_{28}N_2O_3$. Calculated, %: C 63.35; H 9.92; N 9.85.

1-(5-Phenyl-4,5-dihydro-1*H*-pyrazol-1-yl)-3-(2-vinyloxyethoxy)propan-2-ol (IIIg). Yield 72%, bp 179–182°C (2 mm), d_4^{20} = 1.1012, n_D^{20} = 1.5402. IR spectrum, ν, cm^{-1}: 520, 615, 640, 690, 740, 805, 820, 930, 950, 985, 1025, 1075, 1115, 1190, 1240, 1255, 1280, 1310, 1350, 1375, 1440, 1480, 1575, 1610, 1625, 2870, 2920, 3025, 3060, 3110, 3420. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.59–3.23 m (5H, 4-H, OH, 1-CH_2), 3.47–3.88 m (6H, OC**H**$_2$CH, OCH_2CH_2O), 3.95–4.24 m (4H, 5-H, CH_2=CO, C**H**OH), 6.42 d.d (0.5H, C=CHO in diastereoisomer **A**, $^3J_{cis}$ = 6.9, $^3J_{trans}$ = 14.1), 6.44 d.d (0.5H, C=CHO in diastereoisomer **B**, $^3J_{cis}$ = 6.9, $^3J_{trans}$ = 14.1), 6.82 s (1H, 3-H), 7.28–7.45 m (5H, Ph). Found, %: C 66.72; H 7.18; N 9.53. $C_{16}H_{22}N_2O_3$. Calculated, %: C 66.18; H 7.64; N 9.65.

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