Russian Journal of Organic Chemistry, Vol. 41, No. 1, 2005, pp. 67–69. Translated from Zhurnal Organicheskoi Khimii, Vol. 41, No. 1, 2005, pp. 70–72.

Synthesis of New 3-Phenoxypropan-2-ols with Various Heterocyclic Substituents

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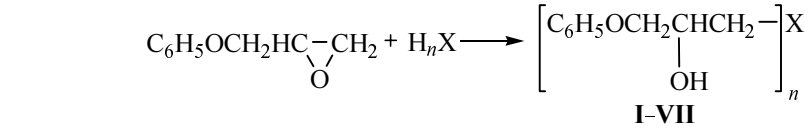
Received October 10, 2003

Abstract—1-Phenoxy-3-piperidinopropan-2-ol, 1-(5-methyl-1,3-benzothiazol-2-ylsulfanyl)-3-phenoxypropan-2-ol, 1-(2-hydroxy-3-phenoxypropyl)azepan-2-one, 1,1'-(6-chloro-1,3-benzothiazol-2-ylimino)bis(3-phenoxypropan-2-ol), 1-(1,3-benzothiazol-2-ylsulfanyl)-3-phenoxypropan-2-ol, 1,1'-(piperazine-1,4-diyl)bis(3-phenoxypropan-2-ol), and 1,3-bis(2-hydroxy-3-phenoxypropyl)barbituric acid were synthesized by condensation of 1,2-epoxy-3-phenoxypropane with the corresponding amines and thiols.

Condensation of 1,2-epoxy-3-phenoxypropane with piperidine, 5-methyl-1,3-benzothiazole-2-thiol, caprolactam, 6-chloro-1,3-benzothiazol-2-amine, 1,3-benzothiazole-2-thiol, piperazine, and barbituric acid afforded the corresponding 3-substituted 2-hydroxypropyl phenyl ethers **I**–**VII** (Table 1). Systems containing the above heterocyclic fragments, which are widely known pharmacophoric groups, attract interest from the viewpoint of their biological activity [1–3]. The effects of temperature, solvent nature, reaction time, and reactant ratio on the process were examined, and optimal conditions were found. It should be noted that opening of the oxirane ring in 1,2-epoxy-3-phenoxypropane occurs according to the Krasuskii rule, i.e., the hydroxy group appears at the least hydrogenized carbon atom. This reaction direction is also favored by steric factor, in keeping with our previous data [4, 5].

EXPERIMENTAL

The ^{1}H NMR spectra were recorded at 30°C on a Varian Mercury-300 spectrometer (300 MHz) using DMSO-d_6 as solvent (Table 2). The IR spectra of compounds **I**, **II**, and **V**–**VII** were measured on a Specord 75IR spectrophotometer from samples dispersed in mineral oil. The purity of the products was checked by TLC on Silufol UV-254 plates; development with iodine vapor.



I–**VII**

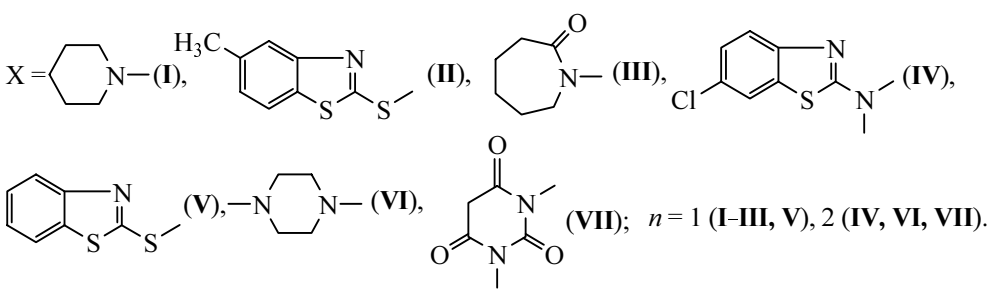


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Table 1. Yields, boiling or melting points, and elemental analyses of 3-phenoxypropan-2-ols **I**–**VII**

Comp. no.	Yield, %	bp, °C (*p*, mm) or mp, °C	TLC data				Found, %			Formula	Calculated, %		
			R_f	eluent composition			C	H	N		C	H	N
				acetone	chloroform	hexane							
I	65	55	0.53	2.0	1.0	0.1	71.55	8.77	5.69	$C_{14}H_{21}NO_2$	71.46	8.99	5.95
II	64	135	0.49	1.7	0.2	0.1	61.49	5.28	4.04	$C_{17}H_{17}NO_2S_2$	61.60	5.17	4.23
III	40	201–202 (2) n_D^{20} 1.5368	0.53	1.0	0.6	0.2	68.2	7.79	5.50	$C_{15}H_{21}NO_3$	68.42	8.04	5.32
IV	75	268–270 (0.5) n_D^{20} 1.5907	0.47	1.0	0.4	0.6	62.26	5.02	5.62	$C_{25}H_{25}ClN_2O_4S$	61.91	5.20	5.78
V	60	119–124 (0.5) n_D^{20} 1.5752	0.51	1.4	–	0.8	60.41	4.89	4.28	$C_{16}H_{15}NO_2S_2$	60.54	4.76	4.41
VI	65	140	0.57	2.0	0.1	–	68.52	7.53	7.39	$C_{22}H_{30}N_2O_4$	68.37	7.62	7.25
VII	63	360	0.45	3.0	0.1	–	61.49	5.48	6.65	$C_{22}H_{24}N_2O_7$	61.68	5.65	6.54

Table 2. IR and ^{1}H NMR spectra of compounds **I**–**VII**

Comp. no.	IR spectrum, ν, cm^{-1}				^{1}H NMR spectrum, δ, ppm
	C=N	C=C	C–O–Ph	OH	
I	–	1595	1250	3340	1.75 m (6H, $CH_2CH_2CH_2$), 2.4–2.6 m (6H, CH_2N), 3.8 d (2H, CH_2O), 4.1 br.s (1H, OH), 4.3 m (1H, CH), 6.90 m (3H, $H_{arom.}$), 7.23 m (2H, $H_{arom.}$)
II	1640	1590	1245	3450	1.21 s (3H, CH_3), 3.80 d (2H, CH_2O), 4.0 d (2H, CH_2S), 4.2 br.s (1H, OH), 4.5 m (1H, SH), 6.9–7.8 m (8H, $H_{arom.}$)
III	–	1600	1245	3265	2.0 m (6H, $CH_2CH_2CH_2$), 2.2 t (2H, CH_2CO), 3.25 d (2H, CH_2N), 3.3 t (2H, NCH_2, ring), 3.8 br.s (1H, OH), 4.1 d (2H, CH_2O), 4.4 m (1H, CH), 6.86 m (3H, $H_{arom.}$), 7.21 m (2H, $H_{arom.}$)
IV	1650	1605	1250	3400	3.60 d (4H, CH_2N), 3.8 br.s (2H, OH), 3.90 d (4H, CH_2O), 4.12 m (2H, CH), 7.0–8.1 m (13H, $H_{arom.}$)
V	1645	1600	1250	3395	3.70 br.s (2H, OH), 3.90 d (2H, CH_2O), 4.05 d (2H, CH_2S), 4.28 m (1H, CH), 6.85 t (3H, $H_{arom.}$), 7.2 t (2H, $H_{arom.}$), 7.75 m (4H, $H_{arom.}$)
VI	–	1610	1255	3430	2.5 m (12H, CH_2N), 3.02 br.s (2H, OH), 3.92 m (6H, $CHCH_2O$), 6.85 t (2H, $H_{arom.}$), 7.21 t (2H)
VII	–	1610	1250	3500	3.54 m (4H, CH_2O), 3.78 br.s (2H, OH), 3.85 m (4H, CH_2N), 4.08 m (2H, CH), 5.05 s (2H, CH_2CO), 6.95–7.51 m (10H, $H_{arom.}$)

1-Phenoxy-3-piperidinopropan-2-ol (1). A mixture of 6 g (0.04 mol) of 1,2-epoxy-3-phenoxypropane and 11.84 g (0.12 mol) of piperidine was heated for 6 h at 120–125°C. Excess piperidine was removed, and the residue was washed with hexane and recrystallized from hexane. The product is readily soluble in ethanol, chloroform, acetone, and DMSO and insoluble in heptane, water, and dioxane.

1-(5-Methyl-1,3-benzothiazol-2-ylsulfanyl)-3-phenoxypropan-2-ol (II). A mixture of 3.6 g (0.02 mol) of 5-methyl-1,3-benzothiazole-2-thiol and 3 g (0.02 mol) of 1,2-epoxy-3-phenoxypropane was heated for 7 h at 120–125°C. The product was washed with benzene. Compound **II** is readily soluble in ethanol, chloroform, DMF, and DMSO and insoluble in benzene, heptane, water, and dioxane.

1-(2-Hydroxy-3-phenoxypropyl)azepan-2-one (III). A mixture of 6 g (0.04 mol) of 1,2-epoxy-3-phenoxypropane, 9.04 g (0.08 mol) of caprolactam, and 0.1 ml of water was heated for 8 h at 120–125°C and

was then distilled under reduced pressure. Compound **III** is readily soluble in hot water, diethyl ether, ethanol, DMF, and DMSO and insoluble in hexane and cold water.

1,1'-(6-Chloro-1,3-benzothiazol-2-ylimino)bis(3-phenoxypropan-2-ol) (IV). 1,2-Epoxy-3-phenoxypropane, 15 g (0.1 mol), was added to a solution of 7.38 g (0.04 mol) of 6-chloro-1,3-benzothiazol-2-amine in 20 ml of anhydrous DMF, and the mixture was heated for 10 h at 95–100°C. The solvent was distilled off, and the residue was distilled under reduced pressure. Compound **IV** is readily soluble in chloroform, ethanol, DMF, and DMSO and insoluble in hexane and water.

1-(1,3-Benzothiazol-2-ylsulfanyl)-3-phenoxypropan-2-ol (V). 1,2-Epoxy-3-phenoxypropane, 6 g (0.04 mol), was added to a solution of 6.7 g (0.04 mol) of 1,3-benzothiazole-2-thiol in 5 ml of anhydrous DMF, and the mixture was heated for 4 h at 94–97°C. The solvent was distilled off, and the residue was distilled under reduced pressure. Compound **V** is readily soluble in chloroform, benzene, DMF, DMSO, hot ethanol, and hot water and insoluble in heptane, cold ethanol, and cold water.

1,1'-(Piperazin-1,4-diyl)bis(3-phenoxypropan-2-ol) (VI). 1,2-Epoxy-3-phenoxypropane, 18 g (0.12 mol), was added to a solution of 5.2 g (0.06 mol) of piperazine in 5 ml of anhydrous DMF, and the mixture was heated for 4 h at 94–97°C. The precipitate was separated and washed with ethanol. The product is readily soluble in hot ethanol, chloroform, and DMSO, and insoluble in cold ethanol, water, heptane, hexane, and diethyl ether.

1,3-Bis(2-hydroxy-3-phenoxypropyl)barbituric acid (VII). A mixture of 2.5 g (0.02 mol) of barbituric acid, 9 g (0.06 mol) of 1,2-epoxy-3-phenoxypropane, and 3 ml of DMF was heated for 4 h at 94–97°C. The precipitate was separated and washed with ethanol. The product is readily soluble in hot ethanol, water, chloroform, and DMSO and insoluble in cold ethanol, heptane, hexane, and diethyl ether.

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