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REACTION OF PHENYL GLYCIDYL ETHER WITH SOME HETEROCYCLES

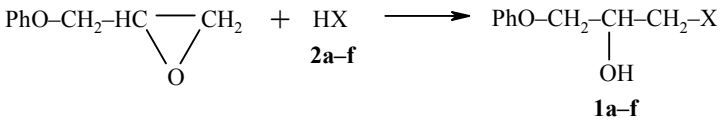
E. G. Mesropyan, G. B. Ambartsumyan, A. A. Avetisyan, and A. S. Galstyan

The respective hydroxypropyl phenyl ethers were obtained by the reaction of 5,5-dimethylhydantoin, morpholine, benzotriazole, benzimidazole, pyrrolidone, and phthalimide with phenyl glycidyl ether. 8-(2-Hydroxy-3-phenoxy) quinoline was synthesized by O-alkylation.

Keywords: benzimidazole, benzotriazole, 8-hydroxyquinoline, 5,5-trimethylhydantoin, morpholine, pyrrolidone, phenyl glycidyl ether, phthalimide, Krasuskii rule.

The development of methods for the synthesis of compounds with heterocyclic fragments is currently of some importance due to the prospects of finding new biologically active substances containing widely known highly active pharmacophoric fragments among them [1-3].

With this end in view a single-stage method was proposed for the synthesis of the N-(2-hydroxy-3-phenoxypropyl)-5,5-dimethyl derivatives of hydantoin (**1a**), morpholine (**1b**), benzotriazole (**1c**), benzimidazole (**1d**), pyrrolidone (**1e**), and phthalimide (**1f**), which can also be used in preparative chemistry.



1,**2a** X = 4,4-dimethyl-2,5-dioxoimidazolidin-1-yl, **b** X = morpholino,
c X = benzotriazol-1-yl, **d** X = benzimidazol-1-yl,
e X = 2-oxopyrrolidino, **f** X = phthalimido.

It should be noted that the opening of the oxide ring by the action of the heterocycles **2a-f** takes place according to the Krasuskii rule, i.e., the hydroxyl group is formed at the least hydrogenated carbon atom, which is also favored by steric factors [4, 5].

For the synthesis of the quinoline derivative we prepared 2-hydroxy-1-phenoxy-3-chloropropane by the reaction of phenyl glycidyl ether with hydrogen chloride. The product was converted into 8-(2-hydroxy-3-phenoxypropoxy)quinoline (**1g**) by reaction with the potassium derivative of 8-hydroxyquinoline in isopropyl alcohol.

Erevan State University, Erevan 375049, Armenia; e-mail: mag_union@yahoo.com. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 6, pp. 817-820, June, 2008. Original article submitted February 5, 2006.

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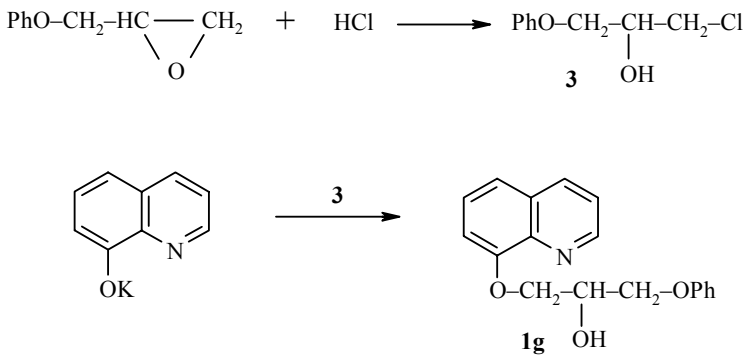

EXPERIMENTAL

The ^{1}H NMR spectra were obtained in DMSO on a Varian Mercury-300 spectrometer (300 MHz) with HMDS as internal standard (δ 0.05 ppm). The IR spectra were recorded in thin layers in vaseline oil on a Specord IR-75 spectrophotometer. The individuality and the purity of the products were monitored by TLC on Silufol UV-254 plates; the eluants were acetone–chloroform–hexane (for **1a**,**c**,**f**), acetone–chloroform (for **1b**,**d**,**g**), and acetone–hexane (for **1e**) (Tables 1-3).

3-(2-Hydroxy-3-phenoxypropyl)-5,5-dimethylhydantoin (1a). 5,5-Dimethylhydantoin (5.12 g, 0.04 mol) we added in small portions a solution of phenyl glycidyl ether (6 g, 0.04 mol) in of DMF (5 ml). The mixture was heated at 165-175°C for 4 h. The obtained crystals were recrystallized from water; mp 128°C, R_f 0.56 (3.6:0.3:0.1 acetone–chloroform–hexane).

TABLE 1. The Characteristics of the Synthesized Compounds

Compound	Empirical formula	Found, % / Calculated, %			Yield, %
		C	H	N	
1a	$C_{14}H_{18}N_2O_4$	60.60 / 60.43	6.52 / 6.47	9.92 / 10.07	68
1b	$C_{13}H_{19}NO_3$	65.66 / 65.82	8.15 / 8.02	6.02 / 5.91	86
1c	$C_{15}H_{15}N_3O_2$	67.04 / 66.91	5.39 / 5.58	15.30 / 15.61	63
1d	$C_{16}H_{16}N_2O_2$	71.49 / 71.64	5.86 / 5.97	10.53 / 10.45	58
1e	$C_{13}H_{13}NO_3$	66.23 / 66.38	7.34 / 7.23	6.04 / 5.96	69
1f	$C_{17}H_{15}NO_4$	68.49 / 68.69	5.60 / 5.05	4.65 / 4.71	85
1g	$C_{19}H_{17}NO_3$	74.08 / 74.27	5.72 / 5.54	4.41 / 4.56	88

TABLE 2. The IR Spectra of Compounds **1a-g**

Compound	ν, cm^{-1}			
	C=O	C=C	C–O–Ph	OH
1a	1695-1745	1595	1240	3340
1b	—	1590	1235	3250
1c	—	1600	1250	3500
1d	—	1605	1245	3400
1e	1680	1600	1240	3440
1f	1700, 1770	1610	1250	3520
1g	—	1600, 1570	1250	3400

TABLE 3. The ^{1}H NMR Spectra of Compounds **1a-g**

Com-pound	Chemical shifts, δ, ppm. (*J*, Hz)
1a	1.35 (6H, s, CH_3); 3.51 (1H, dd, *J* = 14.3, *J* = 6.9, CH_2O); 3.56 (1H, dd, *J* = 14.3, *J* = 3.6, CH_2O); 3.78 (1H, br. s, OH); 3.81 (1H, dd, *J* = 13.8, *J* = 7.5, CH_2N); 3.87 (1H, dd, *J* = 13.8, *J* = 4.2, CH_2N); 4.08 (1H, m, CH); 6.86 (1H, tt, *J* = 7.2, *J* = 1.1, C_6H_5); 6.88 (2H, m, C_6H_5); 7.21 (2H, m, C_6H_5); 8.06 (1H, s, NH)
1b	2.4-2.6 (6H, m, CH_2N); 3.60 (4H, t, *J* = 6.0, CH_2O in cycle); 3.90 (1H, dd, *J* = 14.3, *J* = 6.9, CH_2O); 3.96 (1H, dd, *J* = 14.3, *J* = 3.6, CH_2O); 4.00 (1H, m, CH); 4.30 (1H, br. s, OH); 6.86 (1H, tt, *J* = 7.2, *J* = 1.1, C_6H_5); 6.88 (2H, m, C_6H_5); 7.21 (2H, m, C_6H_5)
1c	3.80 (1H, br. s, OH); 3.98 (1H, dd, *J* = 14.3, *J* = 6.9, CH_2O); 4.02 (1H, dd, *J* = 14.3, *J* = 3.6, CH_2O); 4.38 (1H, m, CH); 4.78 (1H, dd, *J* = 13.8, *J* = 7.5, CH_2N); 4.83 (1H, dd, *J* = 13.8, *J* = 4.2, CH_2N); 6.85-8.00 (9H, m, Ar)
1d	3.88 (1H, dd, *J* = 13.8, *J* = 7.5, CH_2N); 4.93 (1H, dd, *J* = 13.8, *J* = 4.2, CH_2N); 4.29 (1H, dd, *J* = 14.3, *J* = 6.9, CH_2O); 4.32 (1H, dd, *J* = 14.3, *J* = 3.6, CH_2O); 4.48 (1H, m, CH); 4.2 (1H, br. s, OH); 6.85–7.6 (9H, m, Ar); 8.05 (1H, c, NH)
1e	2.00 (2H, m, CH_2 in cycle); 2.20 (2H, m, CH_2CO in cycle); 3.22 (1H, dd, *J* = 13.8, *J* = 7.5, CH_2N); 3.27 (1H, dd, *J* = 13.8, *J* = 4.2, CH_2N); 3.3 (2H, m, CH_2N in cycle); 3.8 (1H, br. s, OH); 4.08 (1H, dd, *J* = 14.3, *J* = 6.9, CH_2O); 4.13 (1H, dd, *J* = 14.3, *J* = 3.6, CH_2O); 4.4 (1H, m, CH); 6.86 (1H, tt, *J* = 7.2, *J* = 1.1, C_6H_5); 6.88 (2H, m, C_6H_5); 7.21 (2H, m, C_6H_5)
1f	3.64 (1H, br. s, OH); 3.75 (1H, dd, *J* = 14.3, *J* = 6.9, CH_2O); 3.79 (1H, dd, *J* = 14.3, *J* = 3.6, CH_2O); 3.91 (1H, dd, *J* = 13.8, *J* = 7.5, CH_2N); 3.97 (1H, dd, *J* = 13.8, *J* = 4.2, CH_2N); 4.18 (1H, m, CH); 6.85-7.95 (9H, m, Ar)
1g	3.95 (1H, br. s, OH); 3.5-3.8 (4H, m, CH_2O); 4.10 (1H, ddd, *J* = 7.5, *J* = 5.5, *J* = 4.2, CH); 6.9-8.0 (11H, m, Ar)

4-(2-Hydroxy-3-phenoxypropyl)morpholine (1b). Morpholine (10.44 g, 0.12 mol) we added of phenyl glycidyl ether (6 g, 0.04 mol). The mixture was heated on a boiling water bath for 3 h. The excess of morpholine was removed, and the residue was distilled under vacuum; mp 60°C; bp 176-178°C (4 mm Hg); n_D^{20} 1.5358, R_f 0.52 (4:1.5 acetone–chloroform).

1-(2-Hydroxy-3-phenoxypropyl)benzotriazole (1c). An equimolar mixture of benzotriazole and phenyl glycidyl ether (0.04 mmol) was heated on a boiling water bath for 4 h. The precipitate was washed with diethyl ether; mp 101-103°C, R_f 0.46 (0.4:1:0.4 acetone–chloroform–hexane).

1-(2-Hydroxy-3-phenoxypropyl)benzimidazole (1d). An equimolar mixture of benzimidazole and phenyl glycidyl ether (0.04 mmol) was heated on a water bath for 4 h. The mixture was then dissolved in hot ethanol (25 ml). After cooling crystals of compound (**1d**) separated; mp 122°C, R_f 0.46 (1.2:1 acetone–chloroform).

1-(2-Hydroxy-3-phenoxypropyl)pyrrolidin-2-one (1e). An equimolar mixture of 2-pyrrolidone and phenyl glycidyl ether (0.04 mol of each) was heated at 160°C for 2 h. The product was then distilled under vacuum and recrystallized from hexane; mp 80-82°C; bp 200-205°C (1 mm Hg); R_f 0.49 (1:1 acetone–hexane).

N-(2-Hydroxy-3-phenoxypropyl)phthalimide (1f). A mixture of phenyl glycidyl ether (6 g, 0.04 mol) and of phthalimide (5.88 g, 0.04 mol) was heated at 170-175°C for 4 h. Ethanol, in which the initial substances are soluble, was then added, and the product was precipitated. The obtained crystals were recrystallized from aqueous ethanol (1:4); mp 112-113°C; R_f 0.51 (0.4:1:0.6 acetone–chloroform–hexane).

8-(2-Hydroxy-3-phenoxypropoxy)quinoline (1g). To a solution of dry KOH (3.36 g, 0.06 mol) in isopropyl alcohol (30 ml) we added of 8-hydroxyquinoline (8.5 g, 0.06 mol), dissolved in isopropyl alcohol (30 ml). The mixture was heated on a water bath for 30 min. A solution of the chloride (**3**) (11.19 g, 0.06 mol) (obtained by the reaction of phenyl glycidyl ether with hydrogen chloride, bp 110°C (0.5 mm Hg), n_D^{20} = 1.5415, yield 98%) in isopropyl alcohol (20 ml) was then added drop by drop, and the mixture was

heated on a water bath. The product was filtered, the filtrate was chromatographed on a column of aluminum oxide (35×2 cm) with isopropyl alcohol as eluant, the solvent was evaporated, and the quinoline **1g** was obtained; n_D^{20} 1.6182, R_f 0.6 (2.2:0.1 acetone–chloroform).

Compounds **1a-g** are readily soluble in DMSO, alcohol, acetone, and chloroform, and some of them (**1b**,**d**,**e**) are soluble in benzene. They are insoluble in ether, heptane, and water.

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