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SYNTHESIS OF 3-ALLYLOXY(2-HYDROXYPROPYL)-5,5-DIMETHYLHYDANTOIN, 1-ALLYLOXY-(2-HYDROXYPROPYL)-SUBSTITUTED BENZOTRIAZOLE AND BENZIMIDAZOLE, AND N-ALLYLOXY-(2-HYDROXYPROPYL)-SUBSTITUTED PYRROLIDONE, CAPROLACTAM, AND PHTHALIMIDE

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The reaction of 5,5-dimethylhydantoin, benzotriazole, benzimidazole, morpholine, pyrrolidone, caprolactam, and phthalimide with allyl glycidyl ether gave the corresponding heterylhydroxypropyl allyl ethers, the structures of which were confirmed by spectral data and elemental analysis.

Keywords: 3-allyloxy(2-hydroxypropyl)-5,5-dimethylhydantoin, 1-allyloxy(2-hydroxypropyl)-substituted benzotriazole, benzimidazole, N-allyloxy(2-hydroxypropyl)-substituted morpholine, pyrrolidone, caprolactam, phthalimide, oxide ring opening.

The condensation of allyl glycidyl ether with nitrogen heterocycles has been studied little. Heterocyclic derivatives of allyl glycidyl ethers are of great interest as monomers and also as starting materials for various chemical transformations. Derivatives of the heterocycles play an important role in bioorganic and pharmaceutical chemistry [1-3].

Consequently, the development of methods for the synthesis of hydroxypropyl allyl ethers with heterocyclic fragments is extremely urgent due to the prospects of the search for new biologically active substances in this series, since their molecules contain widely known highly active pharmacophoric fragments.

In the present work a single-stage method is proposed for the synthesis of 3-allyloxy(2-hydroxypropyl)-5,5-dimethylhydantoin (**1**) and the 1-allyloxy(2-hydroxypropyl) derivatives of benzotriazole (**2**), benzimidazole (**3**) morpholine (**4**), pyrrolidone (**5**), caprolactam (**6**), and phthalimide (**7**) and may be useful in preparative chemistry (Scheme 1, Tables 1 and 2).

The effects of temperature, reaction time, and the concentration of the initial compounds were investigated in order to determine the optimum conditions for the synthesis.

It was established that the product yields increase when the reaction is carried out in allyl glycidyl ether, also acting as solvent.

It should be noted that the reaction hardly occurs at all at temperatures below 90-100°C, while at higher temperatures strong resinification of the products is observed.

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TABLE 1. The Characteristics of the Synthesized Compounds

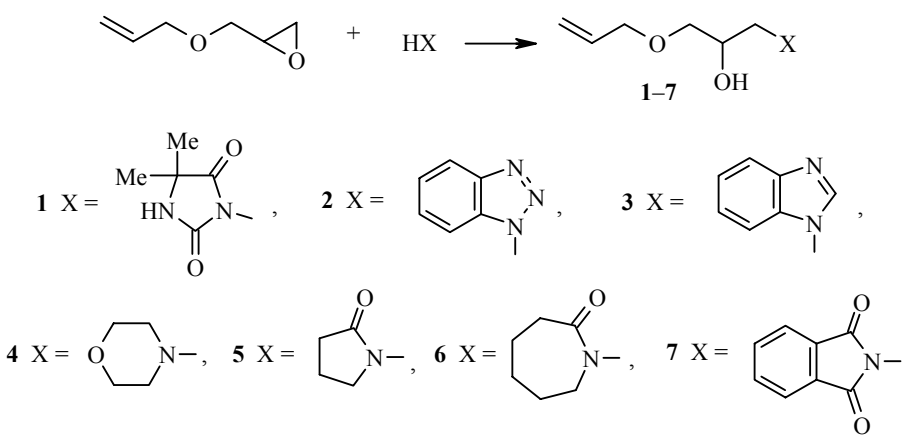
Compound	bp, °C (1 mm Hg)	n_D^{20}	Empirical formula	Found, % / Calculated, %			R_f (ratio of eluents)*	Yield, %
				C	H	N		
1	210-215	1.4970	$C_{11}H_{18}N_2O_4$	54.71 / 54.54	7.00 / 7.44	11.09 / 11.57	0.50 (1 : 1)	70
2	168-172	1.5591	$C_{12}H_{15}N_3O_2$	61.25 / 61.80	6.03 / 6.44	17.72 / 18.03	0.51 (0.7 : 2)	80
3	202-204	1.5660	$C_{13}H_{16}N_2O_2$	67.49 / 67.24	6.65 / 6.96	11.95 / 12.07	0.53 (0.6 : 1)	65
4	125-128	1.4790	$C_{10}H_{19}NO_3$	59.23 / 59.70	9.03 / 9.45	6.61 / 6.96	0.52 (0.7 : 2)	60
5	142-143	1.1990	$C_{10}H_{17}NO_3$	59.78 / 60.30	8.13 / 8.54	6.85 / 7.03	0.50 (0.6 : 2)	50
6	—*[2]	—	$C_{12}H_{21}NO_3$	62.98 / 63.44	8.85 / 9.25	5.91 / 6.17	0.55 (0.6 : 2)	50
7	182-184	1.5570	$C_{14}H_{15}NO_4$	63.91 / 64.37	5.29 / 5.75	5.01 / 5.36	0.56 (0.2 : 1 : 0.1)	70

* Eluents: acetone–chloroform (compounds **1**-**6**) and acetone–chloroform–hexane (compound **7**).
*[2] mp 145°C.

TABLE 2. The Spectral Characteristics of the Synthesized Heterocycles **1-7**

Compound	IR spectrum: ν, cm^{-1}				^{1}H NMR spectrum, δ, ppm. (SSCS, *J*, Hz)
	C=O	C=C	COC	OH	
1	1680, 1760	1630	1100	3300	1.20 (6H, s, CH_3); 3.18 (1H, dd, *J* = 13.8, *J* = 7.5, CH_2N); 3.30 (1H, dd, *J* = 13.8, *J* = 4.2, CH_2N); 3.80 (1H, m, CHOH); 3.98 (2H, dt, *J* = 5.4, *J* = 1.5, $CH_2CH=CH_2$); 4.11 (1H, dd, *J* = 14.3, *J* = 6.9, CH_2OAll); 4.34 (1H, dd, *J* = 14.3, *J* = 3.6, CH_2OAll); 4.58 (1H, d, *J* = 5.2, OH); 5.16 (1H, dq, *J* = 10.4, *J* = 1.5, $CH=CH_2$); 5.26 (1H, dq, *J* = 17.2, *J* = 1.5, $CH=CH_2$); 5.90 (1H, ddt, *J* = 17.2, *J* =10.4, *J* = 5.4, $CH=CH_2$); 9.50 (1H, s, NH)
2	—	1610, 1650	1100	3400	3.25 (2H, m, CH_2N); 3.98 (2H, dt, *J* = 5.4, *J* = 1.5, $CH_2CH=CH_2$); 4.15 (1H, m, CHOH); 4.62 (1H, dd, *J* = 14.3, *J* = 6.9, CH_2OAll); 4.78 (1H, dd, *J* = 14.3, *J* = 3.6, CH_2OAll); 5.07 (1H, d, *J* = 5.1, OH); 5.17 (1H, dq, *J* = 10.4, *J* = 1.5, $CH=CH_2$); 5.29 (1H, dq, *J* = 17.2, *J* = 1.5, $CH=CH_2$); 5.90 (1H, ddt, *J* = 17.2, *J* = 10.4, *J* = 5.4, $CH=CH_2$); 7.14 (1H, td, *J* = 7.2, *J* = 1.7, C_6H_4); 7.18 (1H, td, *J* = 7.2, *J* = 1.7, C_6H_4); 7.47 (1H, dd, *J* = 7.2, *J* = 1.7, C_6H_4); 7.60 (1H, dd, *J* = 7.2, *J* = 1.7, C_6H_4)
3	—	1610, 1650	1090	3300	3.22 (1H, dd, *J* = 9.5, *J* = 7.1, CH_2N); 3.39 (1H, dd, *J* = 9.5, *J* = 4.8, CH_2N); 3.95 (1H, m, CHOH); 3.98 (2H, dt, *J* = 5.4, *J* = 1.5, $CH_2CH=CH_2$); 4.16 (1H, dd, *J* = 14.3, *J* = 6.9, CH_2OAll); 4.34 (1H, dd, *J* = 14.3, *J* = 3.6, CH_2OAll); 5.07 (1H, br. s, OH); 5.17 (1H, dq, *J* = 10.4, *J* = 1.5, $CH=CH_2$); 5.29 (1H, dq, *J* = 17.2, *J* = 1.5, $CH=CH_2$); 5.90 (1H, ddt, *J* = 17.2, *J* = 10.4, *J* = 5.4, $CH=CH_2$); 7.35 (1H, td, *J* = 7.2, *J* = 1.7, C_6H_4); 7.40 (1H, td, *J* = 7.2, *J* = 1.7, C_6H_4); 7.78 (1H, dd, *J* = 7.2, *J* = 1.7, C_6H_4); 7.95 (1H, dd, *J* = 7.2, *J* = 1.7, C_6H_4); 7.95 (1H, s, imidazole)
4	—	1640	1100	3400	3.15–3.50 (6H, m, $N–CH_2$); 3.80 (1H, m, CHOH); 4.05–4.30 (6H, m, OCH_2); 3.95 (2H, dt, *J* = 5.4, *J* = 1.5, $CH_2CH=CH_2$); 4.60 (1H, d, *J* = 5.2, OH); 5.13 (1H, dq, *J* = 10.4, *J* = 1.5, $CH=CH_2$); 5.23 (1H, dq, *J* = 17.2, *J* = 1.5, $CH=CH_2$); 5.90 (1H, ddt, *J* = 17.2, *J* = 10.4, *J* = 5.4, $CH=CH_2$)
5	1680	1630	1080	3300	1.98 (2H, m, CH_2 in ring); 2.22 (2H, m, CH_2CO in ring); 3.14 (1H, dd, *J* = 13.8, *J* = 7.5, CH_2N); 3.26 (1H, dd, *J* = 13.8, *J* = 4.2, CH_2N); 3.30 (2H, m, CH_2OAll); 3.47 (2H, m, CH_2N in ring); 3.77 (1H, ddd, *J* = 7.5, *J* = 5.5, *J* = 4.2, CHOH); 3.96 (2H, dt, *J* = 5.4, *J* = 1.5, $CH_2CH=CH_2$); 4.55 (1H, d, *J* = 5.2, OH); 5.12 (1H, dq, *J* = 10.4, *J* = 1.5, $CH=CH_2$); 5.24 (1H, dq, *J* = 17.2, *J* = 1.5, $CH=CH_2$); 5.86 (1H, ddt, *J* = 17.2, *J* = 10.4, *J* = 5.4, $CH=CH_2$)
6	1680	1630	1080	3400	2.10 (6H, m, CH_2 in ring); 2.22 (2H, m, CH_2CO in ring); 3.14 (1H, dd, *J* = 13.8, *J* = 7.5, CH_2N); 3.26 (1H, dd, *J* = 13.8, *J* = 4.2, CH_2N); 3.30 (2H, m, CH_2OAll); 3.47 (2H, m, CH_2N in ring); 3.77 (1H, ddd, *J* = 7.5, *J* = 5.5, *J* = 4.2, CHOH); 3.96 (2H, dt, *J* = 5.4, *J* = 1.5, $CH_2CH=CH_2$); 4.55 (1H, d, *J* = 5.2, OH); 5.12 (1H, dq, *J* = 10.4, *J* = 1.5, $CH=CH_2$); 5.24 (1H, dq, *J* = 17.2, *J* = 1.5, $CH=CH_2$); 5.86 (1H, ddt, *J* = 17.2, *J* = 10.4, *J* = 5.4, $CH=CH_2$)
7	1700, 1770	1605, 1640	1100	3400	3.30 (2H, m, CH_2N); 3.98 (2H, dt, *J* = 5.4, *J* = 1.5, $CH_2CH=CH_2$); 4.20 (1H, m, CHOH); 4.63 (1H, dd, *J* = 14.3, *J* = 6.9, CH_2OAll); 4.76 (1H, dd, *J* = 14.3, *J* = 3.6, CH_2OAll); 4.60 (1H, br. s, OH); 5.12 (1H, dq, *J* = 10.4, *J* = 1.5, $CH=CH_2$); 5.24 (1H, dq, *J* = 17.2, *J* = 1.5, $CH=CH_2$); 5.90 (1H, ddt, *J* = 17.2, *J* = 10.4, *J* = 5.4, $CH=CH_2$); 7.82 (4H, m, C_6H_4)

Scheme 1



Opening of the ring by the action of the above-mentioned heterocycles takes place according the Krasuskii rule, i.e., the hydroxyl group is formed at the least hydrogenated carbon atom, and this is also promoted by steric factors [4, 5]. The presence of the allyl group was proved by bromination of the obtained products. The dibromo derivative of compound **6** is a brown crystalline substance melting at 90-92°C; it dissolves in alcohol and does not dissolve in diethyl ether, benzene, or hexane.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Varian Mercury-300 spectrometer (300 MHz) with DMSO-d_6 as solvent and HMDS as internal standard (δ 0.05 ppm). The IR spectra were recorded on a Specord IR-75 spectrometer. The individuality and the purity of the obtained compounds were monitored by TLC on Silufol UV-254 plates.

3-Allyl-(2-hydroxypropyl)-5,5-trimethylhydantoin (1). To 5,5-dimethylhydantoin (12.2 g, 100 mmol) we added in small portions allyl glycidyl ether (11.4 g, 100 mmol). The mixture was heated at 125-130°C for 6 h. It was then distilled under vacuum. Compound **1** dissolves readily in acetone, benzene, chloroform, DMF, and diethyl ether, is poorly soluble in ethanol, and does not dissolve in water or hexane.

1-Allyloxy(2-hydroxypropyl)benzotriazole (2). To 1,2,3-benzotriazole (4.8 g, 40 mmol) we added allyl glycidyl ether (6.86 g, 60 mmol), in which the benzotriazole dissolved completely. The mixture was heated at 125°C for 1.5 h. It was then distilled under vacuum. The product dissolved readily in acetone, chloroform, diethyl ether, ethanol, DMSO, and dioxane and did not dissolve in water or hexane.

1-Allyloxy(2-hydroxypropyl)benzimidazole (3). An equimolar mixture of benzimidazole (40 mmol) and allyl glycidyl ether was heated at 180-200°C for 3 h and was then distilled under vacuum. The product was a viscous substance, dissolved well in acetone and chloroform, was poorly soluble in ethanol and benzene, and did not dissolve in water or diethyl ether.

N-Allyloxy(2-hydroxypropyl)morpholine (4). An equimolar mixture of morpholine (40 mmol) and allyl glycidyl ether was heated at 130-140°C for 3 h and was then distilled under vacuum. The product was readily soluble in acetone, diethyl ether, and DMSO and did not dissolve in water, hexane, benzene, or chloroform

N-Allyloxy(2-hydroxypropyl)pyrrolidone (5). To allyl glycidyl ether (8.5 g, 75 mmol) we added pyrrolidone (12.8 g, 150 mmol) and water (0.05 ml). After heating at 180-200°C for 7 h the reaction mixture was distilled under vacuum. The product dissolved readily in acetone, DMSO, hot water, and diethyl ether and did not dissolve in hexane.

N-Allyloxy(2-hydroxypropyl)caprolactam (6). A mixture of allyl glycidyl ether (8.5 g, 75 mmol) and caprolactam (17.0 g, 150 mmol) was heated in the presence of water (0.05 ml) at 165°C for 4 h and then at 185°C for a further 5 h. The precipitate was washed with diethyl ether. A brown crystalline substance melting at 145°C was obtained. The product dissolved readily in ethanol, hot DMF, and DMSO and did not dissolve in water, chloroform, benzene, acetone, or hexane.

N-Allyloxy(2-hydroxypropyl)phthalimide (7). A mixture of phthalimide (14.7 g, 100 mmol) and allyl glycidyl ether (17.0 g, 150 mmol) was heated at 95-100°C for 1.5 h and then at 200°C for a further 1.5 h. The reaction mixture was distilled under vacuum. The product was readily soluble in acetone, benzene, chloroform, and DMF, dissolved poorly in ethanol and diethyl ether, and did not dissolve in water or hexane.

REFERENCES

1. M. D. Mashkovskii, *Drugs* [in Russian], Meditsina, Moscow, Vol. 2, (1973), p. 320.
2. G. A. Melent'eva, *Pharmaceutical Chemistry* [in Russian], Vol. 1, Meditsina, Moscow (1976), p. 312.
3. S. N. Ushakov, L. G. Bogomolova, and V. V. Davidenkov, *Urgent Problems of Blood Transfusion* [in Russian], Medgiz, Moscow (1954), p. 107.
4. E. G. Mesropyan, G. B. Ambartsumyan, and A. A. Avetisyan, *Zh. Org. Khim.*, **36**, 462 (2000).
5. E. G. Mesropyan, G. B. Ambartsumyan, E. V. Martirosyan, Zh. G. Boyadzhyan, and A. A. Avetisyan, *Arm. Khim. Zh.*, **38**, 252 (1986).