DIHYDROPYRAN DERIVATIVES

I. 2-(HYDROXYALKOXY)-3,4-DIHYDROPYRANS

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A number of 2-(hydroxyalkoxy)-3,4-dihydropyrans were synthesized by diene condensation of monovinyl ethers of glycols with acrolein, and some of their chemical transformations were studied. They were also subjected to initial pharmacological examination.

Compounds of the pyran series are widely used in organic synthesis and find application as glues, lubricants, plasticizers, and monomers in copolymerization [1, 2].

2-Alkoxy(aryloxy)-3,4-dihydropyrans were previously obtained by condensation of vinyl alkyl [3](aryl [4]) ethers with α,β-unsaturated aldehydes or ketones. We have investigated the diene condensation of monovinyl ethers of glycols with acrolein, which leads to the formation of the previously unknown 2-(hydroxyalkoxy)-3,4-dihydropyrans. The reaction proceeds in 4-5 h in the absence of a solvent and a catalyst at 145-155°C via the scheme

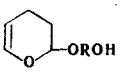
I-V

I R = $(CH_2)_2$; II R = $(CH_2)_3$; III R = $CH_2CH(CH_3)$; IV R = $(CH_2)_4$; V R = $(CH_2)_2O(CH_2)_2$

All of the synthesized compounds (I-V, Table 1) are high-boiling colorless liquids that are stable on storage.

The IR spectra of I-V contain frequencies at 1180 and 1215 cm^{-1}, which indicate the presence of C–O–C grouping in their molecules. The stretching vibrations of the C=C bond appear distinctly at 1654 cm^{-1}, while the stretching vibrations of the =CH– bond appear at 3065 cm^{-1}. The vibrations of the CH_2 group in the dihydropyran ring are characterized by bands at 2840-2860 and 2920 and 2940 cm^{-1} (ν CH) and at 1460 ± 20 cm^{-1} (δ CH). The presence of a hydroxyl group is confirmed by a broad band at 3430 cm^{-1}.

TABLE 1. 2-(Hydroxyalkoxy)-3,4-dihydropyrans (I-V)



Compound	R	bp, °C (mm)	d_4^{20}	n_D^{20}	MR_D found	MR_D calc.	Empirical formula	Found, % C	Found, % H	Calc., % C	Calc., % H	Yield, %
I	$-CH_2CH_2-$	70(3)	1,1129	1,4720	36,31	36,67	$C_7H_{12}O_3$	58,4	8,4	58,3	8,4	71,5
II	$-CH_2CH_2CH_2-$	107(8)	1,0797	1,4706	40,92	41,29	$C_8H_{14}O_3$	60,6	9,1	60,7	8,9	76,1
III	$-CH_2CH(CH_3)-$	69(5)	1,0650	1,4640	40,99	41,29	$C_8H_{14}O_3$	60,5	8,8	60,7	8,9	51,2
IV	$-CH_2CH_2CH_2CH_2-$	123 (10)	1,0571	1,4719	45,61	45,91	$C_9H_{16}O_3$	62,0	9,5	62,8	9,4	68,0
V	$-CH_2CH_2OCH_2CH_2-$	103(4)	1,1166	1,4726	47,25	47,55	$C_9H_{16}O_4$	57,5	8,5	57,4	8,6	58,0

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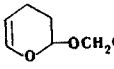
TABLE 2. Parameters of the PMR Spectra of the Synthesized Compounds

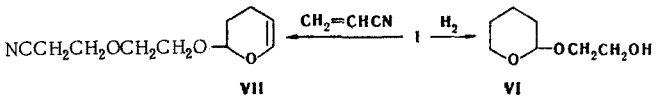
Compound	Chemical shifts, δ, ppm									Spin – spin coupling constants, J, Hz				
	H_6	H_5	$H_{3'}$, H_4	H_2	$-OCH_2$	$-CH_2$	OH	OH DMSO	other groups	5,6	2,3	2,3'	5,4	6,4
I	6,07	4,69	1,87	4,95	9,65	—	3,70	4,64		6,2	2,9	3,0	4,2	1,6
II	6,15	4,67	1,77	4,92	3,69	1,77	3,80	4,46		6,0	2,9	3,0	4,2	1,7
III	6,13	4,70	1,84	4,95	3,49	—	3,20	—	3,80 — CH 1,10 — CH_3	6,2	2,8	3,0	4,0	1,8
IV	6,12	4,67	1,80	4,90	3,51	1,57	4,20	4,43		6,2	2,8	3,0	4,1	1,7
V	6,11	4,68	1,80	4,95	3,55	—	4,68	4,62		6,2	2,9	3,0	4,0	1,8
VI	—	—	1,56	4,56	3,60	—	—	—		—	3,0	3,0	—	—
VII	6,15	4,71	1,86	4,97	3,65	2,54	—	—		6,3	2,9	3,0	4,2	1,8

The parameters of the PMR spectra of the synthesized compounds are presented in Table 2. The change in the length and character of the side chain is reflected in the magnitude of the chemical shifts, but the spin–spin coupling constants remain practically unchanged. The OCH_2 and CH_2 signals are weakly resolved multiplets. The signal splitting observed for H-2 is characteristic for the coupling of two equatorial and axial-equatorial vicinal protons [5], and the 2'-hydroxyalkoxy group in all of the studied compounds consequently occupies the axial position.

The extrapolated (to infinite dilution) chemical shifts of the hydroxyl protons of I-V in dimethyl sulfoxide (DMSO) are presented in Table 2. It is known [6] that these shifts can serve as a measure of the acid-base properties of hydroxyl-containing compounds. Withdrawal from the 

system lowers the acid properties of the hydroxyl group. The acidities of the hydroxyl hydrogens in I and V are practically identical.

Hydrogenation of the compounds described above in the presence of Raney nickel or palladium on $BaSO_4$ gives the corresponding tetrahydropyran derivatives (VI). Cyanoethylation proceeds with the participation of the hydroxyl group:



VII VI

A preliminary study of the physiological activity of the compounds showed that they are not toxic for white mice (LD_{50} = 1.5 g/kg). Except for a certain reduction in motor activity, expressed ataxia, a certain amount of salivation, and difficulty in breathing, no special changes were observed in the behavior of the test animals. No effect on the cardiovascular system was noted.

EXPERIMENTAL

The IR spectra of microlayers of the compounds were recorded with a UR-20 spectrometer (with NaCl and LiF prisms). The PMR spectra of 5% solutions in CCl_4 were recorded with a Tesla BS 487B spectrometer with an operating frequency of 80 MHz at 20°. Hexamethyldisiloxane (HMDS) was used as the internal standard. The starting hydroxyalkyl vinyl ethers were obtained by reaction of acetylene with the appropriate glycols under pressure in an autoclave [7].

Ethylene glycol monovinyl ether had bp 138° (715 mm) and n_D^{20} 1.4300. 1,2-Propylene glycol monovinyl ether had bp 47° (15 mm) and n_D^{20} 1.4312. Trimethylene glycol monovinyl ether had bp 164° (755 mm) and n_D^{20} 1.4390. Tetramethylene glycol monovinyl ether had bp 182° (755 mm) and n_D^{20} 1.4458. Diethylene glycol monovinyl ether had bp 96° (12 mm) and n_D^{20} 1.4480. The acrolein was distilled prior to the reactions and had bp 52-53° (720 mm) and n_D^{20} 1.3998. Hydroquinone (1%) was added to it as a polymerization inhibitor.

2-(2'-Hydroxyethoxy)-3,4-dihydropyran (I). A 0.25-liter rotating steel autoclave was charged with 11.2 g (0.2 mole) of acrolein, 0.1 g of hydroquinone, and 17.6 g (0.2 mole) of ethylene glycol monovinyl ether, and the mixture was heated at 145° for 4 h, after which it was distilled initially at atmospheric pressure (during which 0.4 g of acrolein with bp 53° and n_D^{20} 1.4010 was isolated) and then in vacuo to give 20.6 g (71.5%) of I.

The remaining compounds (II-V) were similarly synthesized.

2-(2'-Hydroxyethoxy)tetrahydropyran (VI). A hydrogenation vessel was charged with 3.6 g (0.025 mole) of I, 20 ml of alcohol, and 0.02 g of palladium on $BaSO_4$. After 600 ml (0.026 mole) of hydrogen had been absorbed, the mixture was filtered, the alcohol was removed by distillation, and the residue was fractionated in vacuo to give 3.4 g (92.7%) of VI with bp 83° (5 mm), d_4^{20} 1.0774, and n_D^{20} 1.4565. Found: C 57.5; H 9.7%; MR_D 36.91. $C_7H_{14}O_3$. Calculated: C 57.5; H 9.6%; MR_D 37.14.

2-(2'-Cyanoethoxyethoxy)-3,4-dihydropyran (VII). A mixture of 7.2 g (0.05 mole) of I, 2.65 g (0.05 mole) of acrylonitrile, and 0.05 g of sodium methoxide was placed in a glass ampul and heated at 140° for 8 h. It was then cooled and washed with water. The water layer was extracted with ether, and the ether extract was dried over K_2CO_3. The ether was removed by distillation, and the residue was vacuum distilled to give 3.7 g (37.2%) of VII with bp 144° (7 mm), d_4^{20} 1.0900, and n_D^{20} 1.4682. Found: N 7.2%; MR_D 50.32. $C_{10}H_{15}NO_3$. Calculated: N 7.1%; MR_D 50.46.

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