STEREOCHEMISTRY OF BROMOALKOXYLATION OF 6-PHENYL- Δ^2 -DIHYDROPYRAN AND SYNTHESIS OF 2-ALKOXY-6-PHENYL- Δ^3 -DIHYDROPYRANS

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 $2-A \operatorname{lkoxy-6-phenyl-}\Delta^3-\operatorname{dihydropyrans}$ were synthesized by bromoalkoxylation of 6-phenyl- $\Delta^2-\operatorname{dihydropyran}$ with N-bromosuccinimide in the presence of alcohols and subsequent dehydrobromination of the resulting 3-bromo-2-alkoxy-6-phenyltetrahydropyrans. The structural stereospecificity of the bromoalkoxylation and dehydrobromination reactions was studied by gas-liquid chromatography and PMR spectroscopy, and the configurations and preferred conformations of the compounds were also established.

Bromoalkoxylation of Δ^2 -dihydropyrans is widely used in the total synthesis of monosaccharides, amino sugars, and other biologically active compounds. In the present research we have investigated the stereochemistry of bromoalkoxylation of Δ^2 -dihydropyrans and subsequent dehydrobromination of the resulting bromoalkoxytetrahydropyrans [1]. The bromoalkoxylation of a Δ^2 -dihydropyran with a phenyl group in the 6 position by the action of N-bromosuccinimide (NBS) in methanol or tert-butyl alcohol gives alkoxybromides I, the isomeric composition of which was studied by gas-liquid chromatography (GLC) and PMR spectroscopy.

Bromination in methanol gave 2-methoxy-3-bromo-6-phenyltetrahydropyran (Ia) in 80% yield, which, according to GLC, is a mixture of two isomers (cis-Ia and trans-Ia). The ratio of the areas of the peaks of the isomers, which have greater and lesser retention times, is 1:4. The PMR spectrum of a mixture of the isomers of Ia has two signals in the region of an anomeric proton that also have an integral intensity ratio of 1:4. The doublet at δ 4.34 ppm (J=8.5 Hz) belongs to the anomeric proton of the isomer present in smaller amounts. The J value shows that the 2- and 3-H protons occupy a trans-diaxial position (cis-Ia). The signal of the anomeric proton of the isomer present in greater amounts lies at δ 4.80 ppm and, judging from its width ($W_{1/2} \sim 3$ Hz) is related to the equatorial proton. The signal of the 3-H proton for this isomer is a poorly resolved multiplet with $W_{1/2} \sim 7$ Hz. These data constitute unambiguous evidence for a trans-diaxial orientation of the bromine atom and the methoxy group in the isomer having a shorter retention time and formed in greater amount (trans-Ia). The PMR spectrum of a mixture of isomers Ia also contains two quartets at δ 4.44 and 4.68 ppm (in both, $J_{AX}=11$ Hz and $J_{BX}=2.5$ Hz), which are related to the axial 6-H proton in both the cis and trans isomers of Ia. (See scheme on following page.)

Bromoalkoxyltion of 6-phenyl- Δ^2 -dihydropyran in tert-butyl alcohol gave 2-tert-butoxy-3-bromo-6phenyltetrahydropyran (Ib) (71% yield), which, according to the GLC and PMR data, is the individual trans isomer. Thus a singlet of an equatorial anomeric proton at 5.18 ppm ($W_{1/2} \sim 3$ Hz), a poorly resolved multiplet of an equatorial 3-H proton at 3.96 ppm ($W_{1/2} \sim 7$ Hz), and a quartet of an axial 6-H proton at 4.85 ppm (J_{AX} =11 Hz and J_{BX} =2.5 Hz) are observed in the PMR spectrum.

Dehydrobromination of I with alcoholic alkali gives 2-alkoxy-6-phenyl- Δ^3 -dihydropyran (II). Only one isomer (IIb) is formed from the individual trans-Ib. The signal of the anomeric proton at 5.28 ppm in its PMR spectrum has a poorly resolved structure with J ~3 Hz (W_{1/2}~5.5 Hz), which indicates its pseudo-

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equatorial orientation. The triplet at 4.89 ppm with a width of 15 Hz at the extreme peaks is related to the axial 6-H proton. Thus, as expected, trans isomer Ib is converted to trans isomer IIb.

A mixture of isomers of 2-methoxy-6-phenyl- Δ^3 -dihydropyran (IIa) in a ratio of 1 : 6 was obtained by dehydrobromination of a mixture of isomers of bromomethoxytetrahydropyran Ia. It is known that the epimerization of 6-substituted 2-alkoxy- Δ^3 -dihydropyrans in the presence of boron trifluoride etherate leads practically entirely to the formation of trans isomers [2]. We found that similar treatment of a mixture of isomers IIa leads practically entirely to conversion of the isomer formed in smaller amounts to the isomer that is obtained in larger amounts and has a shorter retention time. We assigned a trans configuration to the latter. This was also confirmed by the PMR spectra, in which a triplet 6-H signal at 4.77 ppm that is partially overlapped by the signal of the 2-H proton at 4.80 ppm is observed. An approximate evaluation of the width gives $W_{1/2} \sim 5.5$ Hz for the signal of the 2-H proton and 14 Hz for the signal of the 6-H proton. Hydrogenation of this isomer gave 2-methoxy-6-phenyltetrahydropyran, in the PMR spectrum of which partial overlapping of the singlet of the anomeric proton at 4.7 ppm with the quartet of the 6-H proton at 4.6 ppm is observed. An accurate estimate of J is also impossible here, but an approximate estimate of the width of the signal of the anomeric proton as being 3 Hz and of the quartet as being 14 Hz is fully adequate for the qualitative assignment of the trans configuration.

EXPERIMENTAL

Analysis by GLC was performed with an LKhM-8MD chromatograph with a catharometer. A 1.0 by 4 mm column with 12.5% polyethylene glycol adipate (PEGA) on Chromatone-N was used; the helium flow rate was 25 ml/min. The PMR spectra of 30% solutions of all of the compounds in CCl_4 were recorded with a Varian XL-100 spectrometer with hexamethyldisiloxane as the internal standard. The physical constants and yields of the compounds and the results of elementary analysis are presented in Table 1.

<u>3-Bromo-2-alkoxy-6-phenyltetrahydropyrans (I)</u>. A 0.1-mole sample of NBS was added with stirring to a mixture of 0.1 mole of 6-phenyl- Δ^2 -dihydropyran and 1 mole of the appropriate alcohol (at -10° for methanol and at 25° for tert-butyl alcohol), and the resulting precipitate was removed by filtration. The filtrate was treated with ether and water, and the ether extract was dried with magnesium sulfate. The ether was removed by distillation, and the residue was vacuum distilled.

 $2-A \text{lkoxy-6-phenyl-}\Delta^3-\text{dihydropyrans (II)}$. A mixture of 0.05 mole of tetrahydropyran I, 0.3 mole of potassium hydroxide, and 0.5 mole of absolute alcohol was refluxed for 6 h (the bath temperature was 140-150°), after which the mixture was cooled and extracted thoroughly with ether. The extract was washed with water, dried with potassium carbonate, and vacuum distilled.

Com- pound	R	bp , °C (mm)	mp, °C	n _D 20	Empirical formula	Found, %			Calc., %			Yield.
						с	н	Br	с	н	Br	%
Ia	CH ₃	93-94		1,5510	$C_{12}H_{15}BrO_2$	53,0	5,7	30,0	53,2	5,6	29,5	80
Ib Ila	t-C₄H₃ CH₃	94—96	80—81 —	1,5322	C ₁₅ H ₂₁ BrO ₂ C ₁₂ H ₁₄ O ₂	57,3 75,8	6,9 7,3	25,2	57,5 75,8	6,8 7,4	25,5 —	71 75
IIb IIIa	t-C₄H9 CH3	(0,4) 	93—94 —	1,5130	$\begin{array}{c} C_{15}H_{20}O_2\\ C_{12}H_{16}O_2 \end{array}$	77,3 74,8	8,8 8,2		77,6 75,0	8,7 8,4	_	64 82

TABLE 1. Characteristics of the Compounds Obtained

 $\frac{\text{trans-2-Methoxy-6-phenyltetrahydropyran (IIIa).}}{\text{ml of methanol over Raney nickel at 20-25° and an initial pressure of 120 atm. The usual workup gave tetrahydropyran IIIa in 82% yield.}$

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