SYNTHESIS OF 2-ALKOXY-\(\Delta^3\)-DIHYDROPYRANS FROM \(\Delta^3\)-DIHYDROPYRANS

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Some 2-alkoxy-\(\Delta^3\)-dihydropyran can be easily obtained by bromoalkoxylation with N-bromo-succinimide in the presence of alcohols of various \(\Delta^3\)-dihydropyran and subsequent dehydrobromination of the resulting alkoxybromides with alcoholic alkali. The stereospecificity of this transformation was studied in the case of 6-substituted \(\Delta^3\)-dihydropyran.

In connection with the development of methods for the total synthesis of racemic sugars and their derivatives, interest in 2-alkoxy-\(\Delta^3\)-dihydropyran, which are substrates for the synthesis of alkyl glycosides of racemic 4-desoxy- and 3-amino-3,4-didesoxy sugars [1-3], has grown in the last decade. Two principal methods for the synthesis of 2-alkoxy-\(\Delta^3\)-dihydropyran are presently known: diene condensation of 1-alkoxy-1,3-butadienes with carbonyl-containing compounds [4, 5] and conversion of \(\Delta^3\)-dihydropyran to the corresponding 2-alkoxy-3-bromotetrahydropyran with subsequent dehydrobromination of them to give 2-alkoxy-\(\Delta^3\)-dihydropyran [6, 7]. An alcohol solution of N-bromosuccinimide (NBS) has been used as the bromoalkoxylation agent, and an alcohol solution of potassium hydroxide has been used as the dehydrobrominating agent [7].

In an extension of the research in [7] we have investigated the conversion of various \(\Delta^3\)-dihydropyran to the corresponding 2-alkoxy-\(\Delta^3\)-dihydropyran (Ia-c), which were subsequently the starting materials for the synthesis of alkyl glycosides of racemic 4-desoxy sugars and their derivatives.

By reaction with NBS in the presence of alcohols, dihydropyran Ia-c were converted to the corresponding 2-alkoxy-3-bromotetrahydropyran (IIa-c), which, without isolation, were converted to dihydropyran IIIa-f (Table I) by dehydrobromination with an alcohol of alkali at 130-160°C.

In connection with the fact that two geometrical isomers of the dihydropyran (IIIe-f) can be formed from 6-substituted \(\Delta^3\)-dihydropyran Ib,c, we studied the stereospecificity of such transformations.

We obtained starting dihydropyran Ic by acetylation of alcohol IV.

TABLE 1. 2-Alkoxy-Δ³-dihydropyrans (IIa-f)

<table>
<thead>
<tr>
<th>Compound</th>
<th>R</th>
<th>R'</th>
<th>bp, °C (mm)</th>
<th>αD</th>
<th>Yield, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIa</td>
<td>H</td>
<td>CH₃</td>
<td>139-140 (760)</td>
<td>1.4446</td>
<td>45</td>
</tr>
<tr>
<td>IIb</td>
<td>H</td>
<td>C₂H₅</td>
<td>153-155 (780)</td>
<td>1.4456</td>
<td>48</td>
</tr>
<tr>
<td>IIc</td>
<td>H</td>
<td>C₆H₁₃</td>
<td>137-140 (10)</td>
<td>1.5225</td>
<td>50</td>
</tr>
<tr>
<td>IId</td>
<td>C₆H₅O₂⁻</td>
<td>CH₃CH₂C₆H₅</td>
<td>117-118 (11)</td>
<td>1.482</td>
<td>37</td>
</tr>
<tr>
<td>IIe</td>
<td>CH₃</td>
<td>C₆H₁₃</td>
<td>99-101 (0.5)</td>
<td>1.5235</td>
<td>50</td>
</tr>
<tr>
<td>IIf</td>
<td>HOCH₂</td>
<td>C₆H₅</td>
<td>83-84 (0.7)</td>
<td>1.4666</td>
<td>46</td>
</tr>
</tbody>
</table>

* (trans-2-Ethoxy-Δ³-dihydro-6-pyranyl)methyl.

The three-dimensional structure of dihydropyrans IIe,f was established by means of their PMR spectra. The PMR spectrum of benzyloxy derivative IIe coincided completely with the PMR spectrum of trans-2-benzyloxy-6-methyl-Δ³-dihydropyranyl, which we had previously obtained by a different method [10]. The complete coincidence of the physicochemical constants of these compounds made it possible to conclude that dihydropyranyl IIe obtained in this study is the trans isomer.*

Triplet signals of protons of a methyl fragment of an ethoxy group are present in the PMR spectrum of dihydropyran IIf at 1.26 and 1.3 ppm; this indicates the presence of two geometrical isomers in the mixture. The ratio of the cis and trans isomers of IIf is ~ 15 : 85.

The PMR spectrum of the principal stereoisomer of IIf contains the signal of a 2-H proton at 5.04 ppm (J₂₃ = 3.0 Hz) and multiplet signals of 5Q₆-H and 5QA-H protons at 1.88 and 2.20 ppm (J₅QA₆ = 3.8 Hz and J₂QA₆ = 10.0 Hz, respectively). On the basis of the literature data [11, 12], the Jvic values attest to pseudodiagonal orientation of the ethoxy group and equatorial orientation of the hydroxymethyl group for the predominant isomer of IIf in the mixture, and this in turn proves the trans orientation of these groups.

Thus bromoalkylation of 6-substituted Δ³-dihydropyrans Ib,c and subsequent dehydrobromination of the resulting bromides IIb,c give primarily trans isomers of 2-alkoxy-Δ³-dihydropyrans (IIe,f). This fact provides a possibility for the realization of stereospecific syntheses of various alkyl glycosides of racemic 4-deoxyhexoses.

EXPERIMENTAL

2-Methoxy-Δ³-dihydropyran (IIa). An 8-g (0.045 mole) sample of NBS was added in small portions with stirring to a cooled (to -10°) solution of 4 g (0.048 mole) of Δ²-dihydropyran Ia in 25 ml of anhydrous methanol at such a rate that the temperature of the reaction mixture did not exceed 0°. The resulting solution was then stirred at room temperature for 2 h, after which 35 ml of anhydrous methanol and 11 g of potassium hydroxide were added, and the mixture was stirred at 130° for 6 h. The mixture was then cooled to room temperature and poured over ice. The aqueous mixture was extracted with ether (three 150-ml portions), and the combined ether extracts were dried with potassium carbonate and filtered. The ether was removed by distillation, and the residue was fractionated to give 2.3 g (45 ½) of dihydropyran IIa with bp 139-140° and αD 20 1.4446.

trans-2-Ethoxy-6-[(Δ³-dihydro-2-pyranyl)hydroxy)methyl]-Δ³-dihydropyran (IId). A 17-g (0.096 mole) sample of NBS was added with stirring in small portions to a cooled (to -10°) solution of 8 g (0.095 mole) of Δ²-dihydropyran Ia and 18 g (0.11 mole) of trans-2-ethoxy-6-hydroxymethyl-Δ³-dihydropyran (IIf) in 25 ml of carbon tetrachloride while maintaining the temperature of the reaction mixture at no higher than 0°. The mixture was then stirred at room temperature for 2 h and allowed to stand overnight. It was then diluted with 800 ml of ether and washed with aqueous sodium bicarbonate solution. The ether extract was dried with potassium carbonate and filtered, and the ether was removed from the filtrate by distillation. The residue was dissolved in 15 ml of anhydrous ethanol, and the solution was added with stirring to a solution of

* The cis configuration was erroneously assigned to this compound in [8].