SYNTHESIS OF 2-ALKOXY-Δ^3-DIHYDROPYRANS FROM Δ^2-DIHYDROPYRANS

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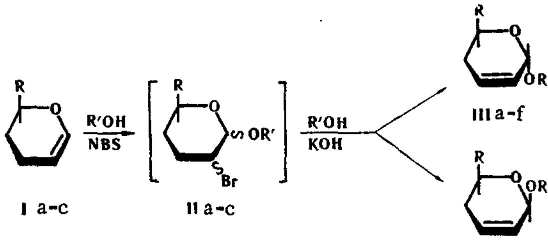
UDC 547.451+547.811

Some 2-alkoxy-Δ^3-dihydropyrans can be easily obtained by bromoalkoxylation with N-bromosuccinimide in the presence of alcohols of various Δ^2-dihydropyrans and subsequent dehydrobromination of the resulting alkoxybromides with alcoholic alkali. The stereospecificity of this transformation was studied in the case of 6-substituted Δ^2-dihydropyrans.

In connection with the development of methods for the total synthesis of racemic sugars and their derivatives, interest in 2-alkoxy-Δ^3-dihydropyrans, 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-Δ^3-dihydropyrans are presently known: diene condensation of 1-alkoxy-1,3-butadienes with carbonyl-containing compounds [4, 5] and conversion of Δ^2-dihydropyrans to the corresponding 2-alkoxy-3-bromotetrahydropyrans with subsequent dehydrobromination of them to give 2-alkoxy-Δ^3-dihydropyrans [6, 7]. An alcohol solution of N-bromosuccinimide (NBS) has been used as the bromoalkoxylating 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 Δ^2-dihydropyrans to the corresponding 2-alkoxy-Δ^3-dihydropyrans (Ia-c), which were subsequently the starting materials for the synthesis of alkyl glycosides of racemic 4-desoxy sugars and their derivatives.

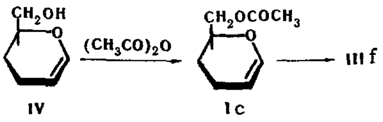


I, III a R=H; b R=CH_3; c R=CH_2OCOCH_3

By reaction with NBS in the presence of alcohols, dihydropyrans Ia-c were converted to the corresponding 2-alkoxy-3-bromotetrahydropyrans (IIa-c), which, without isolation, were converted to dihydropyrans IIIa-f (Table 1) by dehydrobromination with an alcohol of alkali at 130-160° C.

In connection with the fact that two geometrical isomers of the dihydropyrans (IIIe-f) can be formed from 6-substituted Δ^2-dihydropyrans Ib,c, we studied the stereospecificity of such transformations.

We obtained starting dihydropyran Ic by acetylation of alcohol IV.



M. V. Lomonosov Moscow Institute of Fine Chemical Technology. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 2, pp. 171-173, February, 1975. Original article submitted January 6, 1974.

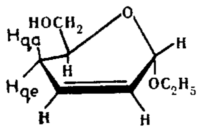
TABLE 1. 2-Alkoxy-Δ^3-dihydropyrans (IIIa-f)

Compound	R	R′	bp, °C (mm)	n_D^{20}	Yield, %
IIIa[6]	H	CH_3	139—140 (760)	1,4446	45
IIIb[6]	H	C_2H_5	153—155 (760)	1.4456	48
IIIc[7]	H	$CH_2C_6H_5$	137—140 (10)	1,5225	50
IIId	H	$C_8H_{12}O_2$*	117—118 (14)	1.4862	37
IIIe[8]	CH_3	$CH_2C_6H_5$	99—101 (0.5)	1,5236	50
IIIf[9]	$HOCH_2$	C_2H_5	83—84 (0,7)	1.4666	46

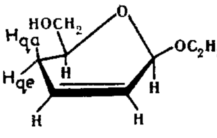
* (trans-2-Ethoxy-Δ^3-dihydro-6-pyranyl)methyl.

The three-dimensional structure of dihydropyrans IIIe,f was established by means of their PMR spectra. The PMR spectrum of benzyloxy derivative IIIe coincided completely with the PMR spectrum of trans-2-benzyloxy-6-methyl-Δ^3-dihydropyran, 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 dihydropyran IIIe 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 IIIf 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 IIIf is ~15 : 85.



trans-isomer IIIf



cis-isomer IIIf

The PMR spectrum of the principal stereoisomer of IIIf contains the signal of a 2-H proton at 5.04 ppm ($J_{2,3}$ = 3.0 Hz) and multiplet signals of 5_{qe}-H and 5_{qa}-H protons at 1.88 and 2.20 ppm ($J_{5_{qe}6}$ = 3.8 Hz and $J_{5_{qa}6}$ = 10.0 Hz, respectively). On the basis of the literature data [11, 12], the J_{vic} values attest to pseudoaxial orientation of the ethoxy group and equatorial orientation of the hydroxymethyl group for the predominant isomer of IIIf in the mixture, and this in turn proves the trans orientation of these groups.

Thus bromoalkoxylation of 6-substituted Δ^2-dihydropyrans Ib,c and subsequent dehydrobromination of the resulting bromides IIb,c give primarily trans isomers of 2-alkoxy-Δ^3-dihydropyrans (IIIe,f). This fact provides a possibility for the realization of stereospecific syntheses of various alkyl glycosides of racemic 4-desoxyhexoses.

EXPERIMENTAL

2-Methoxy-Δ^3-dihydropyran (IIIa). 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 Δ^2-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 %) of dihydropyran IIIa with bp 139-140° and n_D^{20} 1.4446.

trans-2-Ethoxy-6-[(Δ^3-dihydro-2-pyranyl)hydroxy]methyl-Δ^3-dihydropyran (IIId). 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 Δ^2-dihydropyran Ia and 18 g (0.11 mole) of trans-2-ethoxy-6-hydroxymethyl-Δ^3-dihydropyran (IIIf) 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

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

36 g of potassium hydroxide in 85 ml of anhydrous ethanol. The mixture was heated at 130-140° for 8 h, after which it was cooled to room temperature and poured over ice. The aqueous mixture was extracted with ether (five 200-ml portions), and the combined ether extracts were dried with potassium carbonate and filtered. The ether was removed from the filtrate by distillation, and the residue was fractionated to give 8.5 g (37%) of dihydropyran IIId with bp 93-94° (0.076 mm) and n_D^{20} 1.4815. Found: C 64.4; H 8.4%. $C_{13}H_{20}O_4$. Calculated: 65.0%; H 8.4%.

6-Acetoxymethyl-Δ^2-dihydropyran (Ic). A solution of 48.5 g of 6-hydroxymethyl-Δ^2-dihydropyran (IV) in 65 ml of dry pyridine was cooled to 0°, and 63.5 ml of acetic anhydride was added to it. The next day, the mixture was poured over ice, and the aqueous mixture was extracted with chloroform (three 200-ml portions). The combined extracts were dried with magnesium sulfate and filtered. The ether was removed from the filtrate by distillation, and the oily residue was fractionated to give 59 g (84%) of dihydropyran Ic with bp 84-86° (16 mm) and n_D^{20} 1.4590. Found: C 61.2; H 7.8%. $C_8H_{12}O_3$. Calculated: C 61.5, H 7.9%.

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