REACTION OF ALCOHOLS AND SOME NITROGEN-CONTAINING COMPOUNDS WITH 2-ETHOXY-Δ^3-DIHYDROPYRANS

V. B. Mochalin, A. N. Kornilov,
A. N. Vul'fson,
and I. S. Varpakhovskaya

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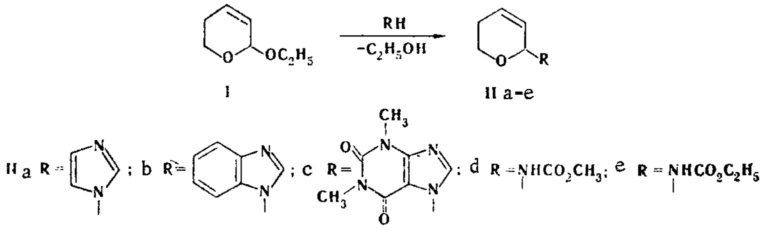
The ethoxy group is replaced by the corresponding residue when 2-ethoxy-Δ^3-dihydropyrans are heated with compounds having a labile hydrogen atom (alcohols, imidazoles, and urethanes). The stereochemical principles of the reaction of 6-substituted 2-ethoxy-Δ^3-dihydropyrans with benzyl alcohol were studied.

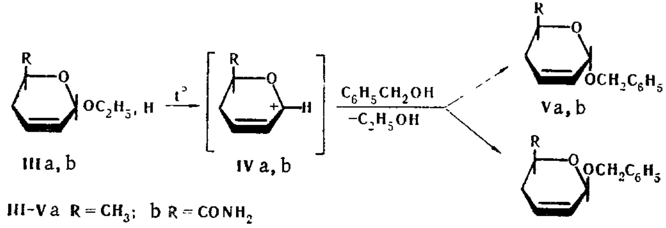
2-Ethoxy-Δ^3-dihydropyrans are convenient starting materials for the synthesis of ethyl glycosides of racemic 4-desoxy sugars [1]. 2-Benzyloxy-Δ^3-dihydropyrans [2], synthesized by transacetalization of 2-ethoxy-Δ^3-dihydropyrans with benzyl alcohol, can similarly be used for the synthesis of benzyl glycosides.

We have studied the possibility of the utilization of the exchange of the ethoxy group of 2-ethoxy-Δ^3-dihydropyrans for other substituents for the synthesis of dihydropyran compounds with nitrogen-containing groups attached to the C_2 atom of the dihydropyran ring, which are unique models of nucleosides. It was found that imidazole, its analogs, and urethanes are capable of replacing the ethoxy group of 2-ethoxy-Δ^3-dihydropyran (I) to give N-(Δ^3-dihydro-2-pyranyl)-substituted imidazoles IIa-c and carbamates IId-e [3].



The reaction was accomplished by heating 2-ethoxy-Δ^3-dihydropyran (I) with compounds having a labile hydrogen atom at 130-200° C with simultaneous removal of the resulting ethanol by distillation. In individual cases, catalytic amounts of anhydrous zinc chloride were added to the reaction mixtures.

In [2] it was shown that some 6-substituted 2-ethoxy-Δ^3-dihydropyrans react with benzyl alcohol to give individual isomers of 6-substituted 2-benzyloxy-Δ^3-diphydropyrans. In connection with the fact that Mochalin and co-workers did not unambiguously prove the configuration of the compounds, we undertook a study of the three-dimensional structures of these dihydropyrans.



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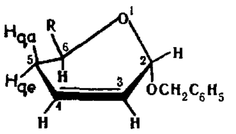
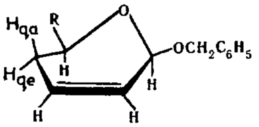
We used mixtures of the cis and trans isomers of 2-ethoxy-6-methyl- and 6-carbamoyl-Δ^3-dihydropyrans (IIIa and IIIb) [4, 5] as the starting materials. The ratio of the cis and trans isomers in the mixtures of IIIa and IIIb was established previously as 1 : 1 for IIIa [4] and ~1 : 1 for IIIb [5]. In the reaction of the corresponding mixtures of isomers IIIa and IIIb with benzyl alcohol, the cis or trans isomers of 6-substituted dihydropyrans Va and Vb, as well as mixtures of them, can theoretically be obtained. However, the reaction of various geometrical isomers of amide IIIb with benzyl alcohol gives individual isomer Vb, to which Mochalin and co-workers assigned a cis configuration [2].

We carried out transacetalization by the method described in [2], as a result of which we isolated Va and Vb, respectively.



trans V a, b



cis V a, b

We isolated Vb in a yield exceeding the previously described yields [2] for the reaction of individual geometrical isomers of IIIb with benzyl alcohol.

The three-dimensional structures of the dihydropyrans (Va and Vb) formed in the transacetalization reactions were established by means of their PMR spectra.

The PMR spectrum of dihydropyran Va contains a doublet of the 2-H protons at 4.90 ppm with a spin-spin coupling constant [SSCC] of the vicinal 2-H and 3-H protons ($J_{2,3}$ = 2 Hz) and a multiplet at 3.95 ppm of the 6-H proton with a SSCC of the 5-H and 6-H protons ($J_{5q\alpha,6}$ = 12.8 Hz and $J_{5qe,6}$ = 6.6 Hz). On the basis of the literature data [6, 7], these SSCC attest to a pseudoaxial orientation of the benzyloxy group and an equatorial orientation of the methyl group; this in turn constitutes evidence for a trans orientation of the benzyloxy group relative to the methyl group. The absence of signals affiliated with the possible cis isomer of Va attests to the specificity of the transacetalization reaction leading to predominantly the trans isomer of Va.

The PMR spectrum of amide Vb contains a doublet of the 2-H proton at 5.16 ppm with a SSCC of the vicinal 2-H and 3-H protons ($J_{2,3}$ = 1.6 Hz) and a quartet of a 6-H proton at 4.41 ppm with an SSCC of the 5-H and 6-H protons ($J_{5qa,6}$=10.8 and $J_{5qe,6}$=4.5 Hz). On the basis of [6, 7], these SSCC also attest to a pseudoaxial orientation of the benzyloxy group and an equatorial orientation of the carbamoyl group; this in turn confirms the trans orientation of the benzyloxy group relative to the carbamoyl group. The absence in the spectrum of signals affiliated with the possible cis isomer of Vb attests to the specificity of the transacetalization reaction leading to predominantly the trans isomer of Vb.

Thus individual trans isomers of 6-substituted 2-benzyloxy-Δ^3-dihydropyrans Va,b are formed in the transacetalization of 6-substituted 2-ethoxy-Δ^3-dihydropyrans IIIa,b with benzyl alcohol.*

The formation of individual isomers of Va,b form a mixture of isomers of IIIa,b and the fact that aprotic acids catalyze replacement of the ethoxy group in I by other substituents with conversion of it to IIc-e constitutes evidence in favor of the formation of cations of IVa and IVb, as well as of IV (R = H), as intermediates. The high stereospecificity of the conversions of the cations of IVa,b in target products Va,b may be explained by an anomeric effect leading to the formation of predominantly trans isomers at high temperatures [8].

EXPERIMENTAL

The PMR spectra of 30% solutions of Va and Vb in deuterochloroform were recorded with a Varian HR-100 spectrometer with tetramethylsilane as the internal standard.

1-(Δ^3-Dihydro-2-pyranyl)imidazole (IIa). A 2.56-g (0.02 mole) sample of dihydropyran I and 1.58 g (0.023 mole) of imidazole were mixed in a Wurtz flask, and the mixture was heated at 130-150° for 1 h with simultaneous removal of the liberated ethanol by distillation. The mixture was then cooled to room temperature and filtered through a thin layer of aluminum oxide to remove the excess imidazole. The filtrate was fractionated to give 1.8 (60%) of imidazole IIa as a yellow viscous syrup with bp 138-140° (0.06 mm). Found: C 63.9; H 7.0; N 19.2%. $C_8H_{10}N_2O$. Calculated: C 64.0; H 6.7; N 18.7%.

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*The cis configuration was erroneously assigned to these compounds in [2].

1-(Δ^3-Dihydro-2-pyranyl)benzimidazole (IIb). This compound was similarly obtained from I and benzimidazole at 160-175°. The reaction mixture was dissolved in methylene chloride, and the unchanged benzimidazole was removed by filtration. The filtrate was evaporated, and the residue was chromatographed with a 300 × 25 column filled with activity II aluminum oxide with elution by hexane and ether. The solvent was removed from the appropriate fractions by distillation to give crystals of benzimidazole IIb with mp 85-86° (from ether) to 70% yield. Found: C 71.9; H 6.3; N 13.9%. $C_{12}H_{12}N_2O$. Calculated: C 72.0; H 6.0; N 14.0%.

7-(Δ^3-Dihydro-2-pyranyl)theophylline (IIc). As in the preparation of IIa, this compound was obtained from I and theophylline at 180-200° with the addition of catalytic amounts of fused zinc chloride. The reaction mixture was diluted with methylene chloride and filtered. The filtrate was evaporated, and the residue was recrystallized from carbon tetrachloride to give crystals of IIc with mp 194.5-195.0° (from carbon tetrachloride) in 49% yield. Found: C 54.7; H 5.3; N 21.4%. $C_{12}H_{14}N_4O_3$. Calculated: C 55.0; H 5.4; N 21.4%.

Methyl N-(Δ^3-Dihydro-2-pyranyl)carbamate (IId). A mixture of 12 g (0.094 mole) of I and 8.3 g (0.11 mole) of methylurethane was heated in a Wurtz flask at 135-145° for 10 min in the presence of 0.1 g of anhydrous zinc chloride with removal of the liberated ethanol by distillation. The reaction mixture was cooled and dissolved in 500 ml of ether. The ether solution was washed successively with saturated sodium bicarbonate solution and water and dried with magnesium sulfate. The ether was removed by vacuum distillation to give 8.1 g (55%) of IId with mp 64-65° (from ether). Found: C 53.4; H 7.2; N 8.8%. $C_7H_{11}NO_3$. Calculated: 53.5; H 7.1; N 8.9.

Ethyl N-(Δ^3-Dihydro-2-pyranyl)carbamate (IIe). As in the preparation of IId, this compound, with mp 80-81° (from ether), was obtained from I and ethylurethane in 67% yield. Found: C 55.9; H 8.0; N 8.1%. $C_8H_{13}NO_3$. Calculated: C 56.1; H 7.6; N 8.2 %.

trans-2-Benzyloxy-6-methyl-Δ^3-dihydropyran (Va). This compound was obtained by the method in [2] from a mixture of cis- and trans-2-ethoxy-6-methyl-Δ^3-dihydropyrans (IIIa) and benzyl alcohol at 190°. The yield of product with bp 99-101° (0.5 mm) and n_D^{20} 1.5236 [bp 99-101° (0.2 mm) [2] and n_D^{20} 1.5126] was 60%.

trans-2-Benzyloxy-6-carbamoyl-Δ^3-dihydropyran (Vb). This compound was obtained by the method in [2] from a mixture of cis- and trans-2-ethoxy-6-carbamoyl-Δ^3-dihydropyrans (IIIb) and benzyl alcohol at 190°. The yield of product with mp 161-162° (from CCl_4) [mp 161-5° (from dioxane)] was 64%.

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