ARYLOXYDIHYDROPYRANS. XII*. CONFIGURATION AND CONFORMATIONS OF 8-(3,4-DIHYDRO-2-PYRANYLOXY)QUINOLINE DERIVATIVES

M. V. Sigalov, V. K. Voronov,
M. A. Andriyankov, and G. G. Skvortsova

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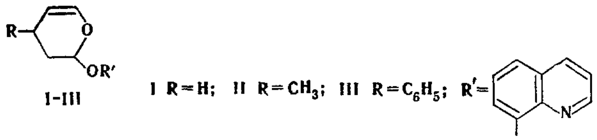
The configuration and conformations of stereoisomeric 4R-8-(3,4-dihydro-2-pyranyloxy)quinolines were studied by means of their PMR spectra. It was established that the trans isomers of the investigated compounds have primarily a "half-chair" conformation and display an anomeric effect. A "sofa" conformation is proposed for the labile cis isomers.

The anomeric effect has been quite adequately studied in a number of saturated and unsaturated heterocyclic compounds [2]. There have been publications involving the study of the anomeric effect in a series of 2-alkoxychromans and dihydropyrans [3,4]. Aryloxydihydropyrans have not been subjected to conformational study.

In the present research we investigated the configuration and conformations of 8-(3,4-dihydro-2-pyranyloxy)quinolines (I-III) by PMR spectroscopy:



I-III I R=H; II R=CH$_3$; III R=C$_6$H$_5$;

TABLE 1. Parameters of the PMR Spectra of 8-(3,4-Dihydro-2-pyranyloxy)quinolines*

Compound	R	Isomer	Chemical shifts, δ, ppm					SSCC, Hz					n, %
			H_2	H_3	H_4	H_5	H_6	H_2H_{3a}	H_2H_{3e}	H_4H_5	H_4H_6	H_3H_5	
I	H	—	6,04		1,5—2,8	4,87	6,14	2,5	2,5		2,0 (Ha) 1,2 (He)		100
IIa	CH$_3$	trans	5,96	1,57 (a) 2,3 (e)	2,3	4,71	6,10	2,5	2,5	2,0	2,4	2,0	100
II b	CH$_3$	cis	5,86	1,99 (a) 2,3 (e)	2,3	4,56	6,15	6,5	2,5	2,4	1,9	1,0	53
IIIa	C$_6$H$_5$	trans	5,99	1,95 (a) 2,53 (e)	2,5	4,90	6,26	2,5	2,5	2,0	2,5	2,0	100
IIIb	C$_6$H$_5$	cis	5,89	2,24 (a) 2,53 (e)	2,5	4,70	6,30	8,5	2,5	2,0	2,0	1,2	30

*The spectra were obtained with a Tesla BS 487B spectrometer (80 MHz). Compounds II and III were studied in the form of a mixture of the isomers (10-15% solutions in CCl$_4$).

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*See [1] for communication XI.

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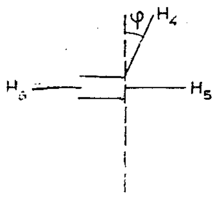
The synthetic method and the physicochemical constants of I-III were presented in [1]. The PMR spectral parameters of the investigated compounds are presented in Table 1.

The signals of all of the protons of the dihydropyran ring (and also of the pyridine ring when $R = C_6H_5$) in the PMR spectra of II and III are doubled, and this constitutes evidence that both products are mixtures (1:1) of stereoisomers. In the establishment of the configuration and conformation of the isomers we were guided by the stereochemical dependences of the vicinal [5], allyl [6], and long-range [7] spin–spin coupling constants (SSCC).

We selected the orientation of the substituent in the 4 position of the dihydropyran ring from the allyl $^4J_{H_4H_6}$ constants, which are 2.0 and 2.5 Hz for the isomers of III. This constant [6] can be realized for a φ angle close to zero:



This indicates an equatorial (or pseudoequatorial) orientation of the phenyl group. The methyl groups attached to C_4 in the isomers of II are also equatorially oriented.

The signal of the proton in the 2 position in the spectrum of I is a triplet, whereas in the spectrum of III this proton resonates in the form of two signals – a triplet and a quartet (Fig. 1). Inasmuch as the equatorial configuration of the substituent in the 4 position was established for both isomers of III, the triplet is related to the trans isomer, and the quartet is related to the cis isomer. The spectrum of II is similar to the spectrum presented in Fig. 1*.

The vicinal $^3J_{H_2H_3}$ constants found from the spectra (Table 1) make it possible to assert that a distinct anomeric effect is observed in dihydropyran I and the trans isomers of dihydropyrans II and III, since the ^3J value of 2.5 Hz corresponds to equatorial–equatorial and equatorial–axial interactions [8], i.e., the 8-quinolyloxy group is axially oriented.

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*The assignment of the remaining lines in the spectra to individual isomers was made by means of the double-resonance method and on the basis of the shift induced by the paramagnetic shift reagent $Eu(DPM)_3$. More nearly complete data from a study of the PMR spectra of I-III in the presence of $Eu(DPM)_3$ will be published separately.

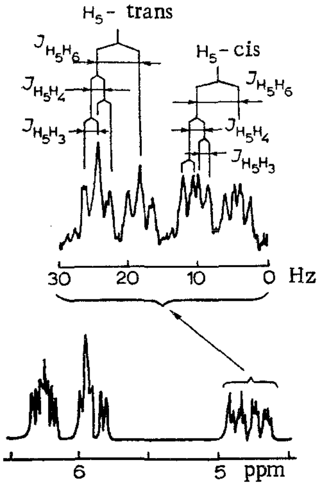
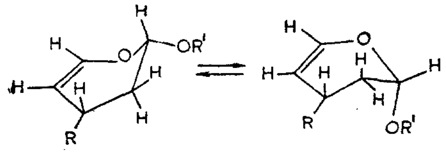


Fig. 1. Fragment of the PMR spectrum of III (mixture of trans and cis isomers).

The vicinal ${}^3J_{H_2H_3}$ constants for the cis isomers of II and III provide evidence that either an equilibrium mixture of the conformers or the primary conformation of a compressed half-chair exists in this case. The size of the substituent in the 4 position determines primarily the position of the conformational equilibrium, whereas in the second case it determines the degree of compression of the half-chair conformation. The second of these assumptions is not confirmed by the temperature dependence of the spectrum. An increase in the temperature to 75° in CCl_4 leads to a decrease in the ${}^3J_{H_2H_{3a}}$ constant of 1 Hz. This corresponds to an increase in the fraction of the axial conformation of $\sim$10%. The equilibrium is shifted to favor the equatorial conformer as the temperature is lowered. Using the "average" standard J_{aa}, J_{ae}, and J_{ee} values presented in [3] we made a semiquantitative estimate (of course, with a low degree of accuracy) of the position of the conformational equilibrium, which is characterized by the population (n) of the axial conformer. The results of this estimate show that (Table 1): 1) I, IIa, and IIIa exist exclusively in the conformation with an axial aryloxy group; 2) the cis isomers constitute an equilibrium mixture of the conformers, evidently because of the counteraction of the anomeric effect and the steric interactions in the axial conformation.

At first glace, the magnitudes of the allyl ${}^4J_{H_4H_6}$ constants contradict the second assertion, since the different positions of the conformational equilibria in IIb and IIIb should undoubtedly be reflected in different ${}^4J_{H_4H_6}$ values of these isomers, if it is assumed that the allyl constant is determined primarily by angular factors. In fact, one observed just the opposite. This contradiction can be eliminated if a "sofa" conformation with planar atoms in the $C_3-C_4-C_5-C_6-O$ fragment of the dihydropyran ring rather than a "half-chair" conformation is assumed for the dihydropyran ring in IIb and IIIb. This conformation is satisfied by all of the SSCC. Inversion of the conformation in this case occurs during rotation about the $O-C_2$ and C_2-C_3 bonds:



Insofar as the trans isomers are concerned, there is no basis to reject the "half-chair" conformation peculiar to cyclohexene and dihydropyran systems.

An independent confirmation of the conclusions drawn above regarding the configuration and conformations of the investigated compounds can be obtained from an examination of the form of the signal of the H-5 proton in the spectra of dihydropyrans II and III. In the case of trans isomers IIa and IIIa this signal is a doublet ($J_{H_5H_6}$ = 6 Hz), each component of which is split into a triplet (see the scheme of the spin–spin splitting in Fig. 1), which is due to coupling with H-4 (2.0 Hz) and with H-3e (2.0 Hz). The stereochemical dependence of the vicinal SSCC with an allyl double bond [9,10] shows that this value is characteristic for angles close to 90°, i.e., it confirms the axial orientation of the proton and the equatorial orientation of the substituent in the 4 position. The H_5-H_{3e} interaction is an interaction through four σ bonds, which in unstrained cyclic compounds is usually realized through a planar zigzag fragment of the W form. This indicates fixation of a primary conformation of the "half-chair" type.

In cis isomers IIb and IIIb each component of the H-5 doublet is a doublet of doublets, rather than a triplet, because of a decrease in the ${}^4J_{H_3H_5}$ constant. This form of signal constitutes evidence that the long-range spin–spin coupling of the H-5 proton is realized with only one of the H-3 protons. Examination of a three-dimensional model shows that inversion of the conformations in the case of realization of the "sofa" form of the dihydropyran ring indicates that the planar W-shaped orientation of the H-3 and H-5 protons occurs only for one of the H-3 protons, and the second proton does not couple with H-5 at any time. The decrease in the magnitude of the long-range SSCC in the spectra of the cis isomers is also in agreement with this. The higher symmetry of the "half-chair" form indicates that, because of ring inversion, the H-3 protons alternately occupy the equatorial position and should be responsible for triplet splitting of the H-5 signal.

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MANNICH REACTION IN A NUMBER OF SIX-MEMBERED HETEROCYCLIC γ-KETONES. X*. STEREOCHEMISTRY OF THE REDUCTION AND PHENYLATION OF 2,2-DIMETHYL-5-DIMETHYLAMINOMETHYL-4-OXOTETRAHYDROPYRAN

E. T. Golovin, B. M. Glukhov,
and L. S. Botsman

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2,2-Dimethyl-5-dimethylaminomethyl-4-oxotetrahydropyran was subjected to reduction with lithium aluminum hydride, sodium borohydride, aluminum isopropoxide, and lithium in liquid ammonia, to catalytic hydrogenation over Raney nickel, and phenylation with phenyllithium. The quantitative ratios in the resulting mixtures of stereoisomeric 2,2-dimethyl-5-dimethylaminomethyl-4-hydroxytetrahydropyrans and their dependence on the character of the reducing agents were established by means of gas—liquid chromatography and PMR spectroscopy. The individual geometrical isomers of the amino alcohols were isolated, and their three-dimensional structures were studied by means of their PMR and IR spectra.

In addition to its theoretical interest, the investigation of the stereochemical principles of the reduction and phenylation of variously substituted β-amino ketones, readily obtained by Mannich reaction from six-membered heterocyclic γ-ketones, is of value for the development of stereospecific methods for the synthesis of esters of the corresponding secondary and tertiary γ-amino alcohols and clarification of the dependence of their physiological activities on their three-dimensional structures.

Up until now, we have studied the stereochemistry of the indicated reactions in the case of sterically unhindered cyclic amino ketones [2-4]. In the present communication we describe the reduction and phenylation of 2,2-dimethyl-5-dimethylaminomethyl-4-oxotetrahydropyran (I) [5], which contains two methyl groups in the meta position with respect to the carbonyl group, one of which is axially oriented. It is well known [6] that this sort of

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*See [1] for communication IX.

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