Ethyl 2,2-Dimethyltetrahydro-4-pyranylpropiolate (III). A 31-g (0.06 mole) sample of phosphorane II was placed in a Claisen flask, and the flask was evacuated to 1-3 mm and heated gradually with a bath to 200-250 deg C. The product that distilled was collected in a receiver cooled with a mixture of dry ice and acetone. The fraction that boiled up to 200 deg C (1-3 mm) was collected. The reaction product contained admixed triphenylphosphine oxide. Redistillation gave 10 g (75.2%) of acid III with bp 126 deg°C (3 mm), n_D^{20} 1.4770, and d_4^{20} 1.0492. IR spectrum: 2250 ($C \equiv C$) and 1720 ($C=O$) cm^{-1}. Found: C 68.6; H 8.6%; MR_D 56.627. $C_{12}H_{18}O_3$. Calculated: C 68.5; H 8.6%; MR_D 56.711.

Ethyl β-Diethylamino-β-(2,2-dimethyltetrahydro-4-pyranyl)acrylate (IV). A 3-g (0.04 mole) sample of diethylamine was added in the cold to 6 g (0.03 mole) of III in 50 ml of absolute ethanol, after which the mixture was refluxed for 1 h. The ethanol was removed by distillation, and the product was vacuum fractionated to give 4.2 g (50%) of IV with bp 140-141 deg C (2 mm), n_D^{20} 1.4880, and d_4^{20} 1.0130. IR spectrum: 1580 ($C=C$) and 1690 cm^{-1} ($C=O$). Found: C 67.8; H 10.3; N 4.9%; MR_D 80.601. $C_{16}H_{29}NO_3$. Calculated: C 67.8; H 10.3; N 4.9%; MR_D 80.658.

Ethyl β-(2,2-Dimethyltetrahydro-4-pyranyl)-β-oxopropionate (V). A 3.5-g (0.013 mole) sample of IV was dissolved in a small amount of ether, and a saturated solution of 3 g of oxalic acid in ethanol-ether (1:10) containing traces of water was added with vigorous stirring. The mixture was then stirred for 12 h, after which the precipitated amine salt was removed by filtration, and the filtrate was evaporated to half its original volume and washed twice with water. The ether solution was dried with magnesium sulfate, and the solvent was removed by vacuum distillation to give 2 g (71.7%) of acid V with bp 130-131 deg C (2 mm), n_D^{20} 1.4710, and d_4^{20} 1.0868. IR spectrum: 1720 (ketone $C=O$), 1750 ($C=O$ in $COOC_2H_5$), 1660 (enol $C=C$), and 3400 cm^{-1} (enol OH). Found: C 63.1; H 8.8%; MR_D 58.712. $C_{12}H_{20}O_4$. Found: C 63.1; H 8.8%; MR_D 58.724.

LITERATURE CITED

1. R. A. Kuroyan, F. V. Dangyan, N. S. Arutyunyan, and É. S. Marashyan, Arm. Khim. Zh., 29, 447 (1976).

THREE-DIMENSIONAL STRUCTURES OF 2-ALKYL-4-FORMYLTETRAHYDROPYRANS

A. P. Engoyan, R. A. Kuroyan,
and K. S. Lusararyan

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The three-dimensional structures of a number of diastereomeric 2-alkyl-4-formyltetrahydropyrans were studied by means of ^1H and ^{13}C NMR spectroscopy. It is shown that the 2,2-dialkyl derivatives are mixtures of two configurational isomers in which the formyl group is equatorially oriented. 2-Monoalkyl-4-formyltetrahydropyrans exist in the form of mixtures of two diastereomeric forms that have different orientations (axial and equatorial) of the formyl group; the alkyl group in both isomers is equatorially oriented.

2-Alkyl-4-formyltetrahydropyans are the starting compounds in the synthesis of new biologically active substances that have a coronary-dilating effect. Since the physiological activity of organic compounds depends to a considerable extent on the geometry of the molecules, the isolation of each isomer and the determination of its activity are of great interest. In this case it is more convenient to separate the isomers of the starting compounds and subsequently synthesize biologically active compounds with a definite configuration. For this reason, in the present research we undertook a study of the three-dimensional structures of 2-alkyl-4-formyltetrahydropyrans and of the corresponding carboxylic acids and their methyl esters by means of ^1H and ^{13}C NMR spectroscopy.

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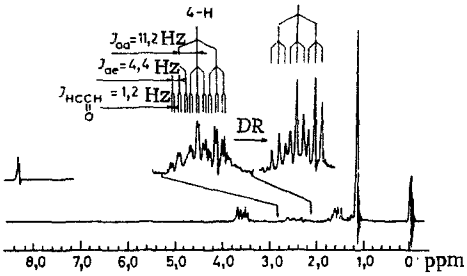
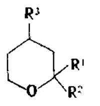


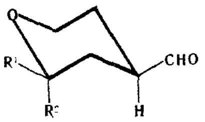
Fig. 1. PMR spectrum of 2,2-dimethyl-4-formyltetrahydropyran in CCl_4 (60 MHz).

TABLE 1. Parameters of the ^1H and ^{13}C NMR Spectra of 2-Alkyl-4-formyltetrahydropyrans

No.	R^1	R^2	PMR				^{13}C NMR, δ, ppm					
			$\delta_{2\text{-}CH_3}$, ppm	δ CHO, ppm	J_{4a3a}, J_{4a5a}, Hz	J_{4a3e}, J_{4a5e}, Hz	$C_{(2)}$	$C_{(3)}$, $C_{(5)}$	$C_{(4)}$	$C_{(6)}$	C=O	2-CH_3
I	CH_3	CH_3	1,15	9,5	11,2	4,40						
I II	CH_3	C_2H_5	1,08 1,03	9,5	11,4	4,20	71,0		42,3 42,6	58,1 58.6	200,7	17,8 ?
II			1,10	9,5	11,5	4,08	71,0	31,5 24,0	46,2	65,0	200,7	20,1
IV	H	CH_3	1,05	9,7			68,5	30,3 22,8	42,7	62,7	202,3	19,9
II IV	H	n-C_3H_7		9,5 9,7	11,6	4,12						
II			0,82	9,5			80,0	24,4 26,5	46,4	65,3	200,2	16,3 (Me) 31,5 (CH)
IV	H	i-C_3H_7	0,80	9,7			77,5	23,2 25,5	42,8	63,1	201,7	16,5 (Me) 31,3 (CH)



R^1,R^2=H, Alk;
R^3=CHO, COOH, COOCH$_3$



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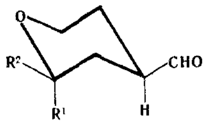

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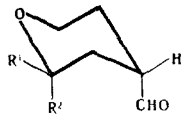
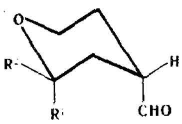


III



IV

The 2,2-dimethyl-4-formyltetrahydropyran (R^1 = R^2 = CH_3, R^3 = CHO) molecules can exist in two different forms with equatorially and axially oriented aldehyde groups (I and III). The signal of the proton attached to C_4 appears in the PMR spectrum of this compound in the form of a multiplet with three spin–spin coupling constants (SSCC) (Table 1 and Fig. 1). The splitting of 1.2 Hz is due to coupling with the aldehyde proton, since it vanishes in the case of double resonance with irradiation at the frequency of this proton (Fig. 1). The other two SSCC (11.2 and 4.4 Hz) correspond to axial–axial and axial–equatorial couplings of 4-H with the protons attached to the adjacent C_3 and C_5 carbon atoms. It follows from these data that the 4-H proton is axially oriented, the formyl group is equatorially oriented, and the three-dimensional structure of the molecule is described by structure I.

When one methyl group is replaced by an ethyl group (R^1 = CH_3, R^2 = C_2H_5, R^3 = CHO), one should evidently expect that the numbers of cis and trans isomers will be close, since the conformational energies of the methyl and ethyl groups are approximately identical. In fact, two sets of signals of equal intensities are observed in the PMR spectrum of this compound for the methyl and ethyl groups and the 4-H proton. In addition, as in the case of the 2,2-dimethyl-substituted compound, the signal of the formyl proton appears in the form of a single doublet (Table 1). However, when the shift reagent Eu(DPM)$_3$ is added gradually to the solution, this signal also is split into two doublets with identical SSCC (1.15 Hz). Similar data were obtained for the corresponding ester (R^3 = $COOCH_3$), in the spectrum of which the singlet signal of the methoxy group is split into two equal-intensity peaks when Eu(DPM)$_3$ is added. In the ^{13}C NMR spectrum the signals of all of the carbon atoms except the C_2 atom and the carbonyl carbon atom are doubled (Table 1). The latter fact indicates that the formyl group has an identical orientation in both forms.

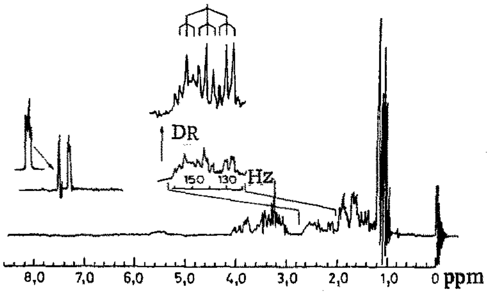


Fig. 2. PMR spectrum of 2-methyl-4-formyltetrahydropyran in CCl_4 (60 MHz).

The signal of the 4-H proton in the PMR spectrum is the superimposition of two similar multiplets, the SSCC of which are similar to the SSCC in the PMR spectrum of the preceding compound and consequently constitute evidence in favor of an equatorial orientation of the formyl group in both isomers. Thus it may be concluded that 2-methyl-2-ethyl-4-formyltetrahydropyran exists in solution in the form of a mixture of two diastereomers of the I and II type, which are evidently formed in approximately equal amounts during their synthesis [1].

An axial orientation of the formyl group in the molecules of the two compounds examined above is markedly hindered because of steric 1,3 interaction with the axial group attached to C_2. Moreover, this sort of interaction will not develop in 2-monoalkyl-4-formyltetrahydropyrans if the 2-alkyl group occupies an equatorial position. In fact, secondary resonance absorption corresponding to an axial orientation of this group is observed in addition to the signal of an equatorial carbonyl group in the ^{13}C NMR spectra of the 2-monosubstituted derivatives ($R^1 = H$, $R^2 = CH_3$, n-C_3H_7, iso-C_3H_7; $R^3 = CHO$). In addition to this, the signals of all of the carbon atoms are also doubled (Table 1).

The formyl proton in the PMR spectra of the 2-monoalkyl derivatives appear in the form of a doublet (δ 9.5 ppm) and a multiplet at 9.7 ppm, which are related, respectively, to equatorial and axial formyl groups (Fig. 2). The complication of the latter signal is probably due to both long-range spin–spin coupling with the axial 3-H and 5-H protons via a W-shaped path [2] and to virtual coupling [3]. Two singlets of equal intensity are observed in the PMR spectrum of the corresponding ester.

An analysis of the PMR spectrum in the region of absorption of the 4-H proton indicates the presence of a multiplet with SSCC of 1.0-1.15, 4.1, and 11.5 Hz, which correspond to an axial orientation of this proton, and a less intense broad signal (Fig. 2). Since the total width of the latter is less than 20 Hz, an SSCC corresponding to an axial–axial interaction is excluded; this signal is consequently related to an equatorial 4-H proton.

Other protons of the 2-monoalkyl derivatives also give two signals, and the ratio of their areas corresponds to the ratio of the integral intensities of the resonance absorptions of the formyl proton. The addition of a shift reagent leads to an increase in the differences in the chemical shifts of the signals; however, additional splitting of the peaks of the formyl proton is not observed, and this indicates an identical orientation of the 2-alkyl group in both forms.

The PMR spectra of the monosubstituted derivatives at 100 MHz were recorded for the determination of the orientation of the 2-alkyl group. A portion of the spectrum of 2-isopropyl-4-formyltetrahydropyran is presented in Fig. 3. The resonance absorption of the 2-H proton is observed at 2.8-3.2 ppm and is the superimposition of two identical multiplets of different intensities with SSCC of 2.3, 6.0, and 11.3 Hz. The J value of 6.0 Hz corresponds to coupling of 2-H with the CH proton of the isopropyl group, and the other two correspond to axial–equatorial and axial–axial coupling of 2-H with the protons attached to C_3; this constitutes evidence in favor of an equatorial orientation of the 2-alkyl group in both isomers.

Thus on the basis of all of the data it may be concluded that 2-monoalkyl-4-formyltetrahydropyrans exist in the form of mixtures of two isomers of the II and IV type.

It follows from an analysis of the PMR spectrum that the axial 6-H proton shows up in the form of two multiplets (Fig. 3) in which $[J_{66}^{gem}] = J_{6a5a} = 11.5$ Hz; however, $J_{6a5e} = 3.25$ Hz for the IV isomer, and $J_{6a5e} = 2.75$ Hz for the II isomer. The equatorial 6-H proton of the II isomer resonates in the form of a multiplet with $J_{66}^{gem} = -11.5$ Hz, $J_{6e5e} = 1.80$ Hz, and $J_{6e5a} = 4.50$ Hz. The larger J_{6e5a} value as compared with the J_{6a5e} value is in agreement with the vicinal SSCC of the protons attached to the α- and β-carbon atoms [4].

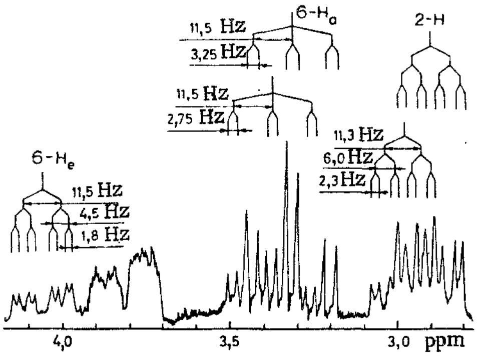


Fig. 3. PMR spectrum of 2-isopropyl-4-formyltetrahydropyran in CCl_4 (100 MHz).

EXPERIMENTAL

The PMR spectra of solutions of the compounds in CCl_4 and $CDCl_3$ were recorded with T-60 and XL-100 spectrometers with tetramethylsilane as the standard. The ^{13}C spectra of the pure substances were recorded with a WP-80 NMR spectrometer (20.1 MHz) with hexamethyldisiloxane as the standard.

The synthesis of the investigated aldehydes is described in [1].

2-Methyl-2-ethyltetrahydropyran-4-carboxylic Acid. An aqueous solution of potassium permanganate (1.9 g of $KMNO_4$ in 100 ml of water) was added gradually with stirring at no higher than 20 deg C to 2.8 g of 2-methyl-2-ethyl-4-formyltetrahydropyran, and stirring was continued for 5 h, after which the mixture was allowed to stand overnight. It was then filtered, and the filtrate was evaporated to dryness. The residue was acidified and extracted with ether, and the extract was dried with magnesium sulfate. The ether was removed, and the residue was distilled in vacuo to give 2.96 g (96%) of the acid with bp 135 deg C (4 mm) and n_D^{20} 1.4670. Found: C 62.4; H 9.1%; $C_9H_{16}O_3$. Calculated: C 62.8; H 9.4%.

2-Isopropyltetrahydropyran-4-carboxylic Acid. Similarly, 4.63 g (94%) of this acid, with bp 131 deg C (4 mm) and n_D^{20} 1.4635, was obtained from 4.2 g of 2-isopropyl-4-formyltetrahydropyran. Found: C 62.7; H 9.4%. $C_9H_{16}O_3$. Calculated C 62.8; H 9.4%.

Methyl 2-Methyl-2-ethyltetrahydropyran-4-carboxylate. A mixture of 3.44 g of the acid, 20 ml of absolute methanol, and a few drops of sulfuric acid was refluxed for 15 h, after which the methanol was removed by distillation, and the residue was extracted with ether. The extract was washed with water and dried with magnesium sulfate, and the ether was removed. The residue was distilled in vacuo to give 3.43 g (92%) of the ester with bp 79 deg C (5 mm) and n_D^{20} 1.4490. Found: C 64.4; H 9.5%. $C_{10}H_{18}O_3$. Calculated: C 64.5; H 9.7%.

Methyl 2-Isopropyltetrahydropyran-4-carboxylate. Similarly, the reaction of 3.44 g of acid gave 3.35 g (90%) of the ester with bp 76 deg C (4 mm) and n_D^{20} 1.4460. Found: C 64.3; H 9.6%. $C_{10}H_{18}O_3$. Calculated: C 64.5; H 9.7%.

LITERATURE CITED

1. R. A. Kuroyan, N. S. Arutyunyan, S. A. Minasyan, and S. A. Vartanyan, Arm. Khim. Zh., 30, 516 (1977).
2. B. I. Ionin and B. A. Ershov, Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry [in Russian], Khimiya, Leningrad (1967), p. 120.
3. J. I. Musher and E. J. Corey, Tetrahedron, 18, 791 (1962).
4. H. Booth, Tetrahedron Lett., No. 7, 411 (1965).