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Stereochemical Transformations of Some Seven-Membered Pyridoxine Dimethyl Ketals

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Abstract — According to the data of single crystal X-ray diffraction analysis and computational methods, the seven-membered rings of acylated pyridoxine acetonides have C_2 symmetry. Two stereochemical transformations in solutions, enantiotopomerization of P-, M-conformations with spiral chirality of *twist-boat* forms and diastereotopomerization of structures that differ in the configuration of the phenolic oxygen substituents, were revealed by dynamic ^{1}H NMR spectroscopy.

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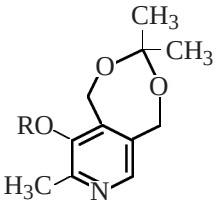
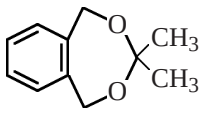
Seven-membered cyclic acetals with a planar fragment (1,3-dioxacyclohept-5-enes and phthalyl acetals) present an example of the existence of two forms in solution, *chair* and *twist* [1]. Previous studies revealed certain regular trends in the steric structure and reactivity of compounds of this series [1–4].

Proceeding with a systematic study of conformationally nonuniform seven-membered heterocycles, we examined 1,5-dihydro-3,3,8-trimethyl-[1,3]dioxepino[5,6-*c*]pyridin-9-ols, the seven-membered acetals derived from vitamin B_6, which are also of independent interest from the synthetic viewpoint. Information on the structure of this class of compounds concerns only a few examples considering the crystal structure of three monoalkyl-substituted pyridoxine acetals in which the acetal ring has the *chair* form with the parameters only slightly differing from those of the related phthalyl acetals [5, 6].



I



II

I, R = H (**a**), CH_3CO (**b**), *p*-$NO_2C_6H_4CO$ (**c**), *p*-FC_6H_4CO (**d**).

In this work we studied steric structure of acetonides **I**: **Ib**–**Id**, by X-ray structural analysis, and **Ib**, also by dynamic ^{1}H NMR spectroscopy. Ketals **Ia**–**Id** were also studied by ab initio calculations in the STO-3G basis set.

To gain information on the structure of ketals in the crystal phase, three compounds **Ib**–**Id** containing along with the acetyl group also two benzoyl groups were examined. The choice of the two latter compounds which contain nitro group or fluorine atom in the *para* position relative to the benzoyl group was governed by the possibility of formation in such compounds of intermolecular structures due to stacking effect and hydrogen bonding with the halogen atom [7].

Ketals **Ib**–**Id** in a crystal exist as *twist* forms (Figs. 1–3).

For comparison of the geometric parameters of the pyridoxine dimethyl ketals we chose 2,2-dimethyl-1,3-dioxa-5,6-benzocycloheptene **II** which has the *twist* form in the crystal [8]. Table 1 lists the bond lengths, bond angles, and torsion angles in molecules of **Ib**–**Id** and **II**.

The comparison shows that the acetal fragments of ketals **Ib**–**Id** and of model ketal **II** are fairly similar (Table 1). The lengths of the respective bonds are the same within experimental errors. The bond angles also practically coincide, except the $O^3C^4C^5$ angle which in **II** is 2.6° larger than in **Ib**–**Id**. The differences in

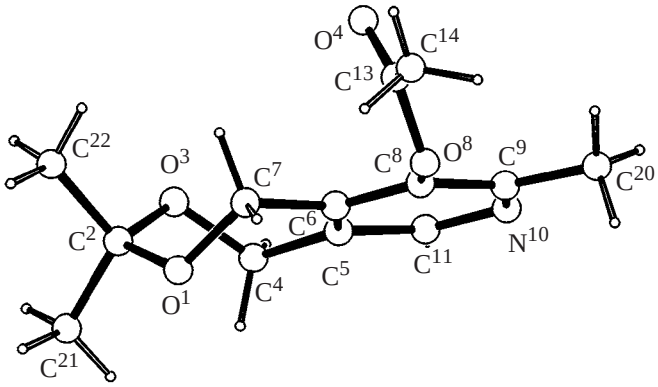


Fig. 1. Crystal structure of compound **Ib**.

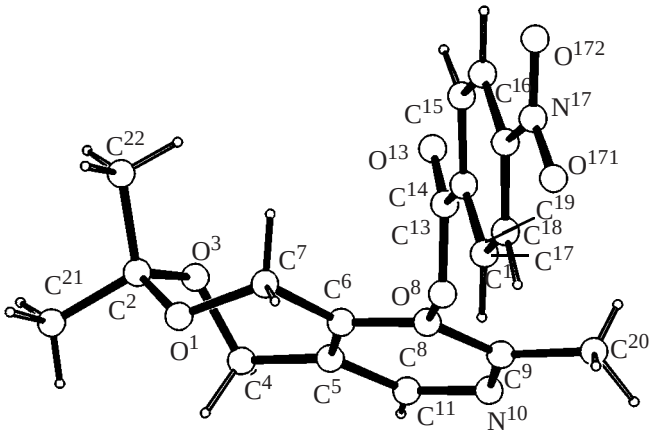


Fig. 2. Crystal structure of compound **Ic**.

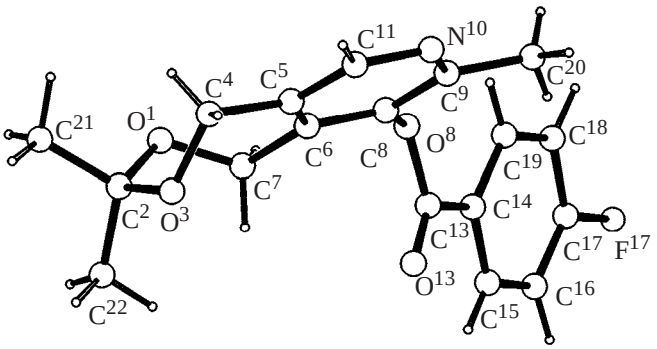


Fig. 3. Crystal structure of compound **Id**.

the torsion angles describing the molecular conformation are more substantial, reaching 15° ($C^5C^6C^7O^1$).

The acetyl fragment at the C^8 atom in all the structures is practically orthogonal to the plane of the pyridine ring ($C^6C^8O^8C^{13}$ torsion angle is within the range 77°–83°), in good agreement with published data [6]. The carbonyl oxygen atom in all the cases is oriented toward the pyridine ring, that is, the carbonyl group is in eclipsed conformation with respect to the C^8–O^8 bond (the $C^8O^8C^{13}O^{13}$ torsion angle is maximal in **Ic**: 16.06°). The endocyclic O^1–C^7 bond is located on the other side of the pyridine ring relative to the O^8–C^{13} bond.

X-ray structural analysis revealed no significant intermolecular interactions in the crystal of **Ib**. In the crystal of **Ic**, there are fairly strong π–π pair interactions between the benzyl fragments. The crystal packing of **Id** appears as a set of π-bonded heteroaromatic stacks. Features of crystal packing of **Ic** and **Id** will be considered in detail elsewhere.

Table 1. Selected geometric parameters of compounds **Ib**–**Id** and **II**

Bond length, Å	**Ib**	**Ic**	**Id**	**II**
O^1–C^2	1.431(2)	1.434(2)	1.421(3)	1.425(2)
O^3–C^2	1.427(2)	1.424(2)	1.432(2)	1.425(2)
O^1–C^7	1.428(2)	1.422(2)	1.418(3)	1.432(2)
O^3–C^4	1.428(2)	1.429(2)	1.425(2)	1.432(2)
C^6–C^7	1.515(2)	1.513(2)	1.507(3)	1.506(3)
C^5–C^4	1.501(2)	1.502(3)	1.496(3)	1.510(3)
C^5–C^6	1.394(2)	1.399(2)	1.394(3)	1.400(3)
Bond angle, deg	**Ib**	**Ic**	**Id**	**II**
$C^2O^1C^7$	115.9(1)	116.5(1)	116.4(2)	114.7(1)
$C^2O^3C^4$	114.4(1)	115.0(1)	114.6(2)	114.7(1)
$O^1C^2O^3$	108.9(1)	109.4(1)	109.1(2)	109.6(2)
$O^3C^4C^5$	111.6(1)	110.6(2)	111.9(2)	113.2(2)
$C^4C^5C^6$	122.8(1)	122.3(2)	123.1(2)	122.1(2)
$C^5C^6C^7$	122.8(1)	123.4(2)	122.7(2)	122.3(2)
$O^1C^2C^{21}$	105.3(1)	105.0(2)	105.8(2)	105.2(2)
$O^3C^2C^{22}$	105.8(1)	105.6(2)	104.9(2)	105.2(2)
$O^1C^7C^6$	112.7(1)	114.0(1)	113.2(1)	112.5(2)
Torsion angle, deg	**Ib**	**Ic**	**Id**	**II**
$C^5C^6C^7O^1$	31.6(2)	–22.2(2)	29.3(3)	37.2(3)
$O^3C^4C^5C^6$	38.3(2)	–43.8(2)	36.9(3)	37.3(3)
$C^2O^3C^4C^5$	–91.5(2)	91.5(2)	–90.0(2)	–89.3(2)
$C^4O^3C^2O^1$	47.6(2)	–39.8(2)	46.6(2)	47.1(2)
$C^7O^1C^2O^3$	49.9(2)	–56.7(2)	50.6(2)	49.1(2)
$C^2O^1C^7C^6$	–87.3(2)	82.8(2)	–86.6(2)	–90.5(2)
$C^7O^1C^2C^{21}$	171.0(1)	–177.1(2)	171.8(2)	170.6(2)
$C^4O^3C^2C^{22}$	169.2(1)	–161.7(2)	168.4(2)	168.5(2)
$C^8O^8C^{13}O^{13}$	3.0(2)	16.1(3)	–1.5(3)	–
$C^6C^8O^8C^{13}$	–77.6(2)	–82.8(2)	79.47(0.20)	–

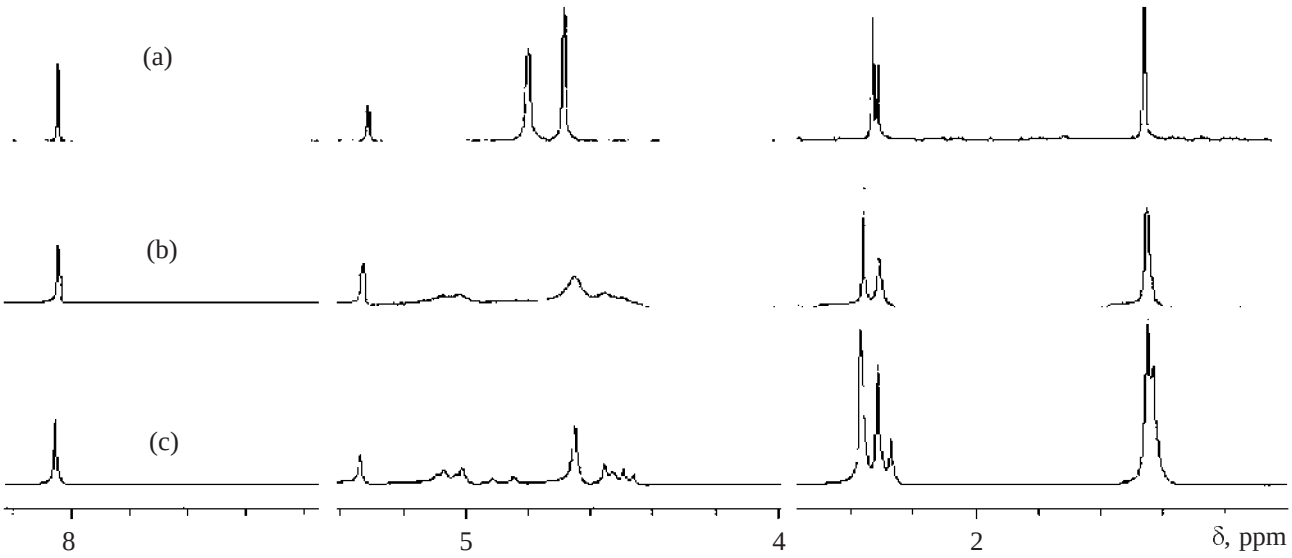


Fig. 4. ^{1}H NMR spectra of 1,5-dihydro-3,3,8-trimethyl-9-acetoxy[1,3]dioxepino[5,6-*c*]pyridine (**Ib**). Solvent CS_2/CD_2Cl_2, 1:L1. Temperature, °C: (a) 25, (b) –67, and (c) –97.

The very low solubility of ketal **Ia** did not allow us to study it by dynamic ^{1}H NMR spectroscopy. A study of acetonide **Ib** by this method confirmed non-chair structure of its seven-membered ring (Fig. 4).

Within the framework of slow exchange in the NMR scale, for the *twist* form of unsymmetrical pyridoxine dimethyl ketals, taking into account symmetry relationships, we should expect for the methyl group a singlet (local symmetry of acetal ring C_2), as in the case of benzo derivative **II** [8], or two singlets of equal intensity due to anisotropic influence of the substituted pyridine fragment. In the *chair* (or *boat*) conformation with C_s symmetry of the seven-membered rings, the methyl groups a priori should be nonequivalent and give signals of equal intensity. The observed changes in the spectral pattern are rather complicated, suggesting the occurrence of two dynamic processes differing significantly in the activation characteristics.

Below –67°C (Fig. 4b), one of conformation processes becomes slow in the NMR scale, as seen from transformation of singlet signals of the methylene groups into two multiplets of equal intensity. In the process, the signal of *gem*-dimethyl groups remains singlet: 1.44 ($2CH_3$), 2.30 (CH_3), 2.35 (CH_3CO), 4.64 (CH_2), 3.77 and 4.21 (CH_2, *AB* quadruplet, $-^2J_{AB}$ 14.2 Hz), 8.04 (H). These data correspond to the conformational equilibrium of the *twist* forms. Note that, according to ab initio calculations in the STO-3G basis set, the *chair* conformation of ketals **Ib**–**Id** is less advantageous by 3.8 kcal mol^{-1}. Similar pattern is observed with compound **Ia** where the *twist* form is by 3.37 kcal mol^{-1} more favorable than the *chair* form.

A further decrease in temperature (Fig. 4c) leads to changes in signals of all methyl groups. At –97°C, benzyl protons give two pairs of overlapping multiplets differing in the intensity. Simultaneously, the singlets of aromatic hydrogen atom and of acetyl and acetal methyl groups transform each into two slightly nonequivalent singlets in 2.5/1 ratio (ΔG_{176} 320 cal mol^{-1}): major form, 1.45 ($2CH_3$), 2.32 (CH_3), 2.37 (CH_3CO), 4.65 (CH_2), 4.52 and 5.04 (CH_2, *AB* quadruplet, $-^2J_{AB}$ 15.0 Hz), 8.05 (H); minor form, 1.43 ($2CH_3$), 2.27 (CH_3), 2.36 (CH_3CO), 4.88 and 4.52 (CH_2, *AB* quadruplet, $-^2J_{AB}$ 17.2 Hz), 4.50 and 5.06 (CH_2, *AB* quadruplet, $-^2J_{AB}$ 15.5 Hz), 8.04 (H).

Thus, the first observed process (–67°C) should be considered as the conformational enantiotopomerization of P- and M-*twist* conformations with a spiral chirality element at fast rotation of the acetyl fragment (Fig. 5, $\mathbf{A} \rightleftarrows \mathbf{A}'$). A similar phenomenon of axial chirality of conformers of seven-membered sulfur-containing *twist* forms of spirobisdithiepins was recently reported by Edmir et al. [9]. The spectral pattern at lower temperature, when in the NMR time scale the rotation of an irregular substituent around the C_{sp^2}–O bond is hindered, is indicative of simultaneous occurrence of a second process, diastereotopomerization of diastereomeric structures differing in the configuration of the substituent at phenolic oxygen atom (Fig. 5, $\mathbf{B} \rightleftarrows \mathbf{B}'$). Diastereotopomerization processes were repeatedly detected previously by

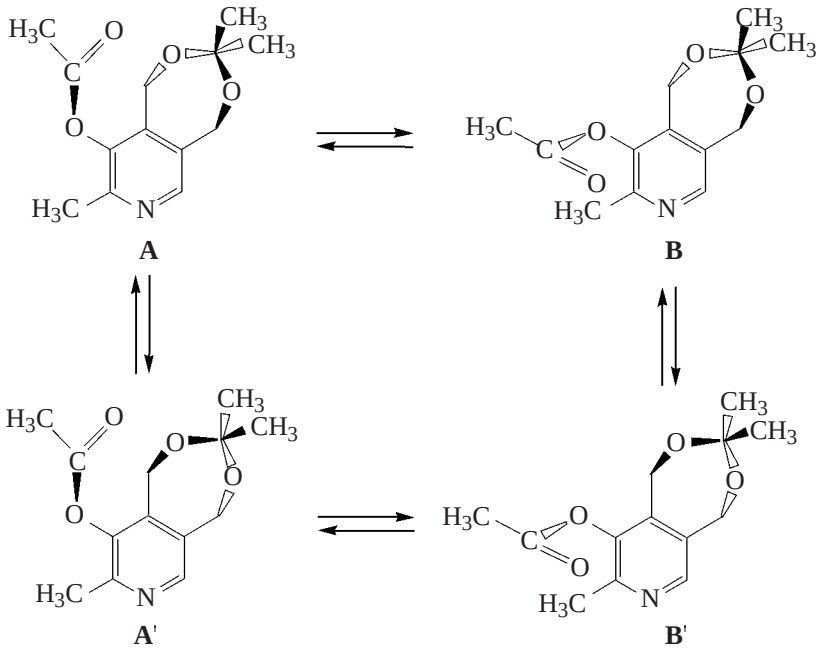


Fig. 5. Scheme of conformational transformations of compound **Ib**.

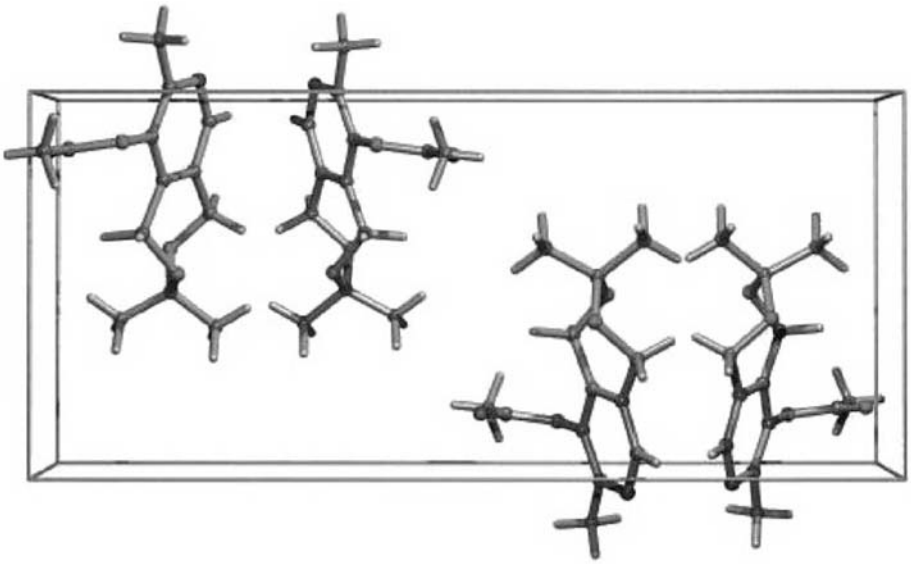


Fig. 6. Structure of unit cell of compound **Ib**.

dynamic NMR spectroscopy (see, e.g., [10–12] and references therein).

It is interesting that the crystal lattice of compound **Ib** (centrosymmetrical space group, Fig. 6) also contains molecules of two enantiomeric *twist* forms involved, as we assume, in dynamic conformational processes in solution.

The presented examples of these certainly rare cases of stereochemical transformations in the series of seven-membered acetals should be further studied in more detail with taking into account all thermodynamic and activation characteristics. This will be the subject of further papers.

EXPERIMENTAL

Quantum-chemical ab initio calculations were performed using HyperChem 7 program with full geometry optimization without symmetry restrictions. For all stationary points we calculated the matrix of second derivatives. All the considered structures have positive frequencies.

Table 2. Parameters of crystals of compounds **Ib**–**Id** and conditions of X-ray experiments

Parameter	**Ib**	**Ic**	**Id**
Color, habit	Transparent, needles	Transparent, prismatic	Transparent, prismatic
Crystal system	Monoclinic	Monoclinic	Monoclinic
Space group	$P2_1/c$	$P2_1/n$	$P2_1/a$
Unit cell parameters	a 6.243(1), b 22.101(9), c 9.797(4) Å, β 92.37(4)°	a 7.620(2), b 20.999(7), c 10.883(2) Å, β 99.52(2)°	a 13.277(1), b 7.912(2), c 15.949(2) Å, β 105.882(7)°
Unit cell volume, Å^3	1350.5(5)	1717.6(8)	1611.3(3)
Z	4	4	4
Molecular weight	251.28	358.34	331.33
ρ_{calc}, g cm^{-3}	1.24	1.39	1.36
μ, mm^{-1}	0.724	0.098	0.098
F(000)	536	752	696.0
Radiation (λ, Å)	CuK_α, λ 1.54184	MoK_α, λ 0.71073	MoK_α, λ 0.71073
Range of θ, deg	$0 \le \theta \le 64.78$	$0 \le \theta \le 26.29$	$0 \le \theta \le 24.64$
Range of Miller indices	$-6 \le h \le 0$, $-24 \le k \le 0$, $-11 \le l \le 10$	$-9 \le h \le 9$, $-26 \le k \le 0$, $0 \le l \le 13$	$-15 \le h \le 13$, $0 \le k \le 8$, $0 \le l \le 18$
Number of measured reflections	2096	3791	3094
Number of reflections with $I > 3\sigma(I)$	1609	2120	2088
Absorption corrections	None		
Conditions of setting and refinement of hydrogen atoms	Revealed from differential series, refined anisotropically		
Final R and R_W	0.034, 0.044	0.035, 0.047	0.042, 0.055
Goodness of fit and Δ/σ	1.566/0.099	1.528/0.022	1.906/0.046
Number of unique reflections and refined parameters	1609/231	2120/307	2088/289

The ^{1}H NMR spectra were recorded on a Varian Unity-300 spectrometer (300 MHz) with VTC 4 temperature-control block (Oxford Instruments Ltd.), solvent $CDCl_3$ and acetone-d_6, internal reference HMDS. The spectrometer operated in the internal stabilization mode with the ^{2}H resonance signal. In recording ^{1}H NMR spectra, we used 10°–15° pulses with delay dl = 1–2 s; spectrum width sw = 15 ppm, number of scans nt from 10 to 100.

X-ray structural analysis. The X-ray study was performed in the Division of X-ray Structural Studies of the Center of Collective Use of the Spectral Analytical Center on the basis of Laboratory of Diffraction Methods of the Arbuzov Institute of Organic and Physical Chemistry, Kazan Scientific Center, Russian Academy of Sciences.

The X-ray analysis was performed on Enraf–Nonius CAD-4 automatic four-circle diffractometers. The structures were solved by the direct method using SIR program [13]. All the calculations were performed using MolEN program package [14] on a DEC Alpha Station200 computer. The parameters of crystals and conditions of X-ray diffraction experiment are given in Table 2. The atomic coordinates and their thermal parameters for compounds **Ib**–**Id** are deposited in the Cambridge Crystallographic Data Centre, http//www.ccdc.cam.ac.uk; deposit nos. 642008–642010, respectively.

1,5-Dihydro-3,3,8-trimethyl[1,3]dioxepino-[5,6-*c*]pyridin-9-ol (Ia) was prepared according to [15], mp 184.5–186°C (published: 184–185°C). ^{1}H NMR spectra ($CDCl_3$), δ, ppm: 1.49 s (6H, $2CH_3$), 2.42 s (3H, CH_3), 4.79 s (2H, CH_2), 4.95 s (2H, CH_2), 7.82 s (1H, CH).

1,5-Dihydro-3,3,8-trimethyl-9-acetoxy[1,3]dioxepino[5,6-*c*]pyridine (Ib). To a mixture of 0.3 g of acetal **Ia** and 0.168 g of triethylamine in 10 ml of dichloromethane, stirred at room temperature, we

added 0.169 g of acetic anhydride, and stirring was continued for 1 h. Then 10 ml of water was added, and the mixture was stirred for 20 min. The organic layer was separated, washed with three portions of water, and dried over sodium sulfate. The product was recrystallized from diethyl ether. Yield 0.3 g (75%), mp 65°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.47 s (6H, $2CH_3$), 2.34 s (3H, CH_3), 2.35 s (3H, CH_3), 4.72 s (2H, CH_2), 4.82 s (2H, CH_2), 8.10 s (1H, CH). Found, %: C 62.30; H 7.27; N 5.33. $C_{13}H_{17}NO_4$. Calculated, %: C 62.14; H 6.81; N 5.57.

1,5-Dihydro-3,3,8-trimethyl-9-(4-nitrobenzoyloxy)[1,3]dioxepino[5,6-*c*]pyridine (Ic) was prepared according to [16], mp 163°C (published: 164–166°C). ^{1}H NMR spectrum (acetone-d_6), δ, ppm: 1.42 s (6H, $2CH_3$), 2.33 s (3H, CH_3), 4.78 s (2H, CH_2), 5.00 s (2H, CH_2), 8.17 s (1H, CH), 8.36–8.64 m (4H, $C_6H_4NO_2$).

1,5-Dihydro-3,3,8-trimethyl-9-(4-fluorobenzoyloxy)[1,3]dioxepino[5,6-*c*]pyridine (Id) was prepared similarly to acetal **Ic** from 3 g (14 mmol) of acetal **Ia** and 2.29 g (14 mmol) of *p*-fluorobenzoyl chloride. Yield 3.8 g (80%), mp 99–100°C (from diethyl ether). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.45 s (6H, $2CH_3$), 2.39 s (3H, CH_3), 4.77 s (2H, CH_2), 5.00 s (2H, CH_2), 8.16 s (1H, CH), 7.05–8.26 m (4H, C_6H_4F). Found, %: C 65.57; H 5.53; N 5.20. $C_{18}H_{18}NO_4F$. Calculated, %: C 65.24; H 5.48; N 4.23.

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