

### DIMEPHOSPHONE ANALOGUES. 3. MOLECULAR AND CRYSTAL STRUCTURE OF DIMEPHOSPHONE PYRIDINOYLHYDRAZONES EXHIBITING ANTIPHTHISIC ACTIVITY

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Molecular and crystal structures of dimephosphone nicotinoylhydrazone and dimephosphone iso-nicotinoylhydrazone exhibiting antiphthisic activity are studied. In contrast to aroylhydrazones of arylaldehydes, existing in the crystalline state as a mixture of two amide conformers, the studied hydrazones exist in the crystalline state in the single geometrical form  $E_{C=N}E_{N-N}Z_{N-C(O)}$ .

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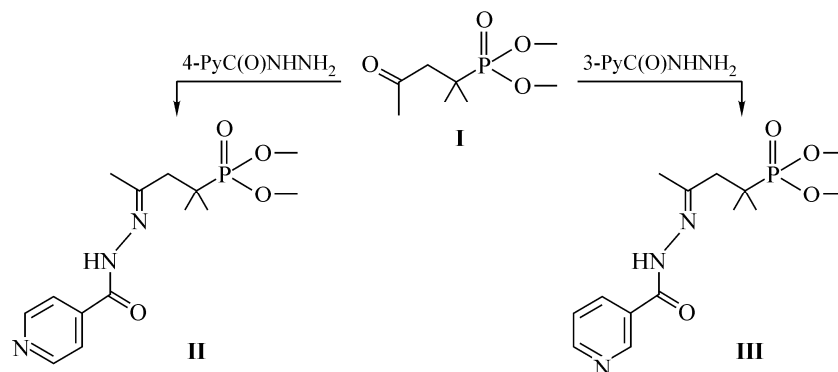
**Keywords:** dimephosphone pyridinoylhydrazones, dimephosphone nicotinoylhydrazone, dimephosphone iso-nicotinoylhydrazone, structure of acylhydrazones, geometrical isomers, amide conformers, X-ray crystallography, biological activity, toxicity, antiphthisic activity.

Dimephosphone is a widely used medication [1-3]. It is a metabolic type drug and is able to normalize biochemical, homeostatic and neurological processes in the body, thus being successfully applied for the treatment of acidoses of different ethiology, strokes, respiratory diseases, and many other disorders [1, 2]. The drug form “Dimephosphone” is an aqueous solution of 2-dimethoxyphosphoryl-2-methylpentan-4-one (dimethyl ether of 2-methyl-4-oxopent-2-yl phosphonic acid, ketone **I**), which is also liquid, thus causing some troubles in processing and transportation. It makes topical the preparation of dimephosphone analogues suitable for the development of dry drug forms. A successful synthesis of crystalline dimephosphone oxime preserving the pharmacological properties of the precursor [4] has stimulated us to prepare nicotinoylhydrazone (**III**) and iso-nicotinoylhydrazone (**II**) of dimephosphone using the known Scheme 1 [5].

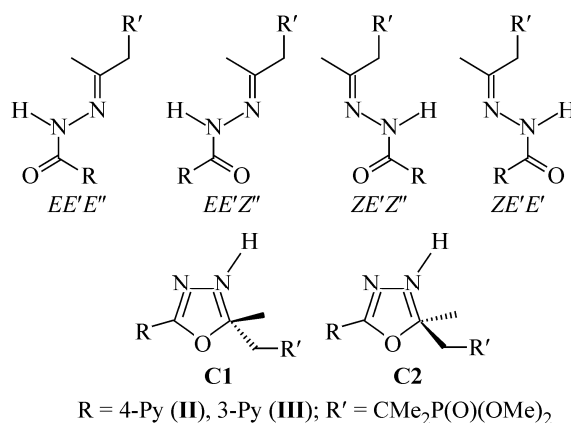
Pyridinoylhydrazones **II** and **III** belong to acylhydrazones of asymmetric ketones, which can be realized as different geometrical isomers relative to the double imine C=N bond and/or different amide conformers relative to the amide (O)C–N(H) bond both in the solid state and solution [5-10]. Since the internal rotational barrier for the N–N bond is low, four geometrical forms are usually considered:  $E_{C=N}E_{N-N}Z_{N-C(O)}$  (abbreviated as  $EE'Z''$ ,  $EE'E'$ ,  $ZE'Z''$ , and  $ZE'Z''$ , Scheme 2). Commonly the  $E_{C=N}$ -isomer is preferable, but a possible intramolecular hydrogen bond (IMHB) between the NH group of the hydrazone fragment and the proton acceptor in the ylidene fragment (here the phosphoryl group) can also stabilize the *Z*-isomer at the double C=N bond, as observed in the molecules of aroylhydrazones of 2-pyridylaldehydes [10]. Moreover, cyclic tautomers can be found among acylhydrazones (**C1** or **C2**, Scheme 2) [11].

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Scheme 1. Synthesis of iso-nicotinoyl- and nicotinoylhydrazones of dimephosphone (**II** and **III** respectively).



Scheme 2. Possible geometrical isomers of dimephosphone hydrazones.

Nicotinoylhydrazones and iso-nicotinoylhydrazones of arylaldehydes, extensively characterized by X-ray crystallography, usually have the form  $E_{C=N}E_{N-N}Z_{N-C(O)}$  regardless of the presence of the hydroxyl group able to form IMHB in the ylidene moiety [12-14].

As indicated by IR, <sup>1</sup>H and <sup>13</sup>C NMR spectroscopy, pyridinoylhydrazones **II** and **III**, in contrast to nicotinoyl- and iso-nicotinoylhydrazones of aromatic aldehydes [7], exist in the crystalline state in only one geometrical form. Solutions exhibit, as a rule, the signals of two, and, on prolonged storage, sometimes three forms, one always dominating.

The ratio of the existing forms depends on solvent polarity and solution storage time. A comparison of the experimental spectral characteristics with the literature data has not provide grounds for an unambiguous judgment on the spatial arrangement of prepared acylhydrazones **II** and **III** either in the crystalline state, or in solution. Therefore, we have studied the molecular and crystal structures of pyridinoylhydrazones **II** and **III** by single crystal X-ray diffraction.

## EXPERIMENTAL

**Iso-nicotinoylhydrazone of dimephosphone** (iso-nicotinoylhydrazone of dimethyl ester of 4-keto-2-methylpent-2-yl phosphonic acid, **II**) C<sub>14</sub>H<sub>22</sub>N<sub>3</sub>O<sub>4</sub>P was obtained as colorless (white in bulk) crystals or ecru-colored crystalline powder, m.p. 110-115°C. X-ray quality crystals were grown from methanol.

**Nicotinoylhydrazone of dimephosphone** (nicotinoylhydrazone of dimethyl ester of 4-keto-2-methylpent-2-yl phosphonic acid, **III**) C<sub>14</sub>H<sub>22</sub>N<sub>3</sub>O<sub>4</sub>P was obtained as ecru-colored small-sized crystals, m.p. 134-136°C. X-ray quality crystals were grown from benzene.

**TABLE 1.** Interactions in the Crystals of Compounds **II** and **III**

D–H···A	D–H, Å	H···A, Å	D···A, Å	DHA, deg	Symmetry code
<b>II</b>					
N(1)–H(1)···O(1)′	0.80(3)	2.19(3)	2.961(3)	165(3)	$x, 1/2-y, 1/2+z$
C(4)–H(42)···O(1)′	0.96	2.58	3.325(4)	134	$x, 1/2-y, 1/2+z$
C(7)–H(73)···O(4)″	0.96	2.36	3.300(4)	165	$x, 3/2-y, -1/2+z$
C(8)–H(83)···O(1)	0.96	2.59	2.950(5)	102	—
<b>III</b>					
N(1)–H(1)···O(1)′	0.85(3)	2.07(3)	2.894(2)	162(3)	$x, 1/2-y, -1/2+z$
C(4)–H(42)···O(1)′	0.96	2.44	3.213(3)	138	$x, 1/2-y, -1/2+z$
C(7)–H(72)···O(4)″	0.96	2.44	3.233(4)	140	$x, 3/2-y, 1/2+z$
C(11)–H(11)···N(1)	0.93	2.56	2.874(3)	100	—

**X-ray diffraction study** of the crystals of compounds **II** and **III** was carried out on an automated Bruker Smart APEX II CCD diffractometer: graphite monochromator;  $\lambda\text{MoK}\alpha = 0.71073 \text{ \AA}$ ;  $\omega$ -scanning; temperature 293 K. Semi-empirical absorption correction was applied with SADABS [15]. The structures were solved by the direct method with SIR [16] and subsequently refined in isotropic and anisotropic approximations using SHELXL-97 [17]. In the structures of **II** and **III**, H(1) hydrogen atoms at the N(1) nitrogen atom were located from difference Fourier maps and refined isotropically. Other hydrogen atoms of the structures were set in geometrical positions and refined as riding atoms. All calculations were performed using WinGX [18] and APEX2 programs [19]. Illustrations and analysis of intermolecular interactions were carried out using PLATON [20] and ORTEP [21]. The single crystals of compounds **II** and **III** have been studied at the Federal Spectral Analytical Common Access Center of the A.E. Arbusov Institute of Organic and Physical Chemistry, Kazan Scientific Center, Laboratory of Diffraction Methods. The parameters of intra- and intermolecular interactions (hydrogen bonds) are given in Table 1.

Crystals of compound **II**: colorless, prismatic, monoclinic;  $\text{C}_{14}\text{H}_{22}\text{N}_3\text{O}_4\text{P}$ ;  $M = 327.32$ ;  $a = 11.256(7) \text{ \AA}$ ,  $b = 10.559(6) \text{ \AA}$ ,  $c = 15.130(9) \text{ \AA}$ ,  $\beta = 109.733(7)^\circ$ ;  $V = 1693(2) \text{ \AA}^3$ ,  $d_x = 1.285 \text{ g/cm}^3$ ,  $Z = 4$ , space group  $P2_1/c$ . Scanning range  $1.92^\circ < \theta < 26.00^\circ$ ,  $\mu(\text{MoK}\alpha) = 1.83 \text{ cm}^{-1}$ . 3313 independent reflections were measured, 2310 with  $I \geq 2\sigma$ . Final convergence factors are  $R = 0.0546$  and  $R_w = 0.1429$  for 2310 reflections with  $F > 2\sigma(F^2)$ . The structure has been deposited to the Cambridge structural database (CCDC 876127; <http://www.ccdc.cam.ac.uk>).

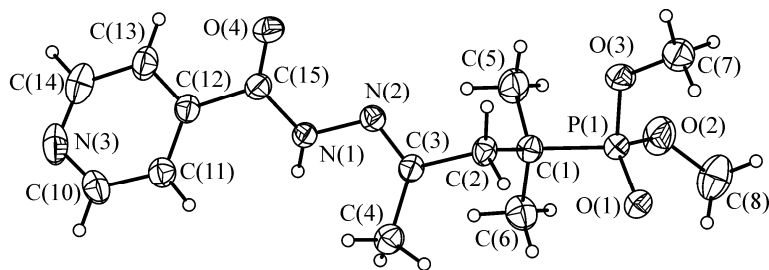
Crystals of compound **III**: ecru-colored, prismatic, monoclinic;  $\text{C}_{14}\text{H}_{22}\text{N}_3\text{O}_4\text{P}$ ;  $M = 327.32$ ;  $a = 10.496(2) \text{ \AA}$ ,  $b = 10.600(2) \text{ \AA}$ ,  $c = 14.986(3) \text{ \AA}$ ,  $\beta = 90.732(2)^\circ$ ;  $V = 1667.2(6) \text{ \AA}^3$ ,  $d_x = 1.304 \text{ g/cm}^3$ ,  $Z = 4$ , space group  $P2_1/c$ . Scanning range  $1.94^\circ < \theta < 28.00^\circ$ ,  $\mu(\text{MoK}\alpha) = 1.86 \text{ cm}^{-1}$ . 3963 independent reflections were measured, 2692 with  $I \geq 2\sigma$ . Final convergence factors are  $R = 0.0564$  and  $R_w = 0.1470$  for 2692 reflections with  $F > 2\sigma(F^2)$ . The structure has been deposited to the Cambridge structural database (CCDC 876126; <http://www.ccdc.cam.ac.uk>).

## RESULTS AND DISCUSSION

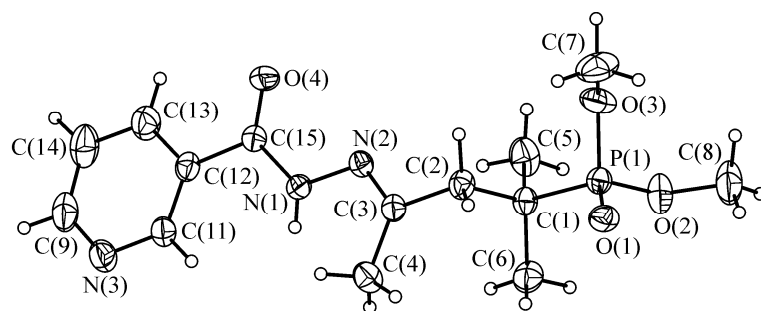
According to the structural data, in the crystals the molecules of pyridinoylhydrazones **II** and **III** exist in the form  $E_{\text{C}=\text{N}}E_{\text{N}-\text{N}}Z_{\text{N}-\text{C}(\text{O})}$ , i.e., they are *E*-configuration at the double C(3)=N(2) bond and the *Z'*-conformation at the amide N(1)–C(15) bond. The geometry of the molecules of hydrazones **II** and **III** is illustrated in Figs. 1, 2 respectively.

The retrieval of similar molecules from CSD [22] gave about 200 structures of nicotinoylhydrazones of asymmetric ketones, existing, as a rule, as  $E_{\text{C}=\text{N}}E_{\text{N}-\text{N}}E_{\text{N}-\text{C}(\text{O})}$  isomers [23-26].

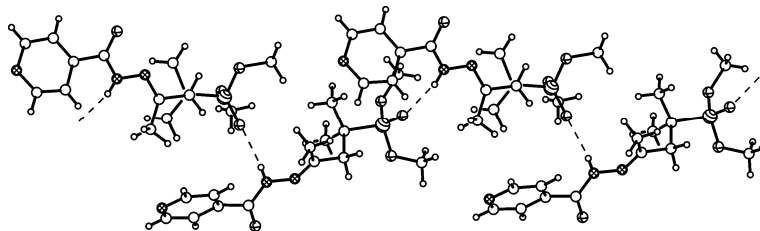
The corresponding bond lengths and angles in the molecules of **II** and **III** are similar within uncertainty and are close to the geometrical parameters of similar molecules found in CSD. Different conformations of the phosphoryl moiety



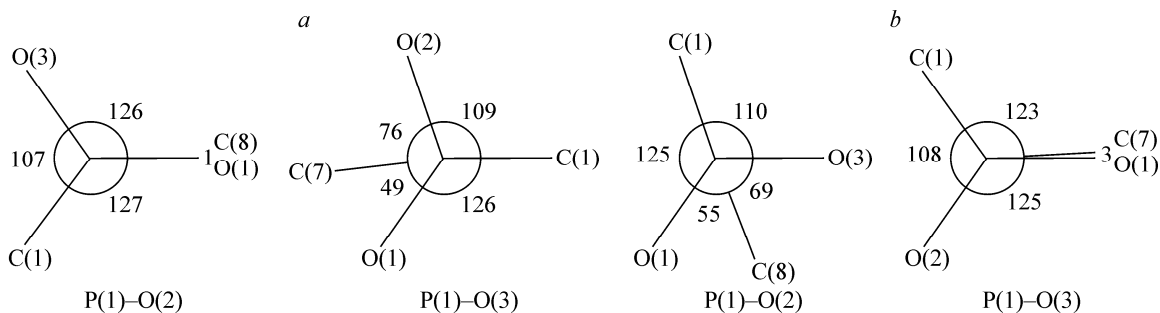
**Fig. 1.** Geometry of the molecule of **II** (isomer  $E_{C=N}E_{N-N}Z_{N-C(O)}$ ) in the crystal. Thermal ellipsoids are drawn at the 30% probability level.



**Fig. 2.** Molecular geometry of **III** ( $E_{C=N}E_{N-N}Z_{N-C(O)}$  isomer) in the crystal. Thermal ellipsoids are drawn at the 30% probability level.



**Fig. 3.** Chains of the molecules of compound **II** formed by the classical  $N(1)-H(1)\cdots O(1)'$  hydrogen bond.



Scheme 3. Newman projections along the P(1)-O(2) and P(1)-O(3) bonds for compound **II** (a) and **III** (b).

can be noted in the molecules of **II** and **III** (Newman projections in Scheme 3). As shown in Scheme 3, C(8) and O(1) atoms are eclipsed in compound **II** (Fig. 3a), while in **III** they are in the *gauche* conformation with an angle of  $55.0(3)^\circ$ . Similarly, in the molecule of **III** the C(7) and O(1) atoms are in the eclipsed conformation along the P(1)-O(3) bond, while in the molecule of **II** it is *gauche* (angle  $48.6(3)^\circ$ ).

In both molecules, the N(1)N(2)C(2)C(3)C(4) fragment is planar (within  $0.024(2)$  Å and  $0.023(2)$  Å for **II** and **III** respectively), thus indicating conjugation in the iso-nicotinoylhydrazone and nicotinoylhydrazone moieties of the molecules.

This is also supported by small dihedral angles between the N(1)N(2)C(2)C(3)C(4) plane and that of the pyridine substituent. In the molecule of **II** this angle is somewhat larger and is 11.3(2)°, while in **III** it is 3.4(1)°, so the pyridine substituent in the molecule of **III** can be considered as coplanar to N(1)N(2)C(2)C(3)C(4).

The molecular packing in the crystals of **II** and **III** is primarily determined by classic N–H···O hydrogen bonds (the N<sup>1</sup>–H<sup>1</sup>···O<sup>1</sup> parameters are given in Table 1), giving rise to the formation of chains running along the 0z direction in the crystals of both compounds (illustrated in Fig. 3 with the chain of molecules of **II**). Short C–H···O contacts also can be noted, which organize the molecules of arylcarbonylhydrazones **II** and **III** in layers parallel to the *b*0*c* plane of the crystal (parameters are given in Table 1).

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