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SYNTHESIS, CRYSTAL STRUCTURE, AND CONFORMATION OF N-ISONICOTINOYLPHTHALIMIDE

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The reaction of phthalic acid anhydride with isonicotinoylhydrazide is carried out under severe conditions with the formation of cyclic phthalic acid imide N-isonicotinoylphthalimide. The structure of the compound is determined by ^{1}H and ^{13}C NMR spectroscopy and from the data of two-dimensional (^{1}H–^{1}H) COSY and (^{1}H–^{13}C) HMQC spectra. The spatial structure and conformation of N-isonicotinoylphthalimide is investigated by single crystal XRD and a semi-empirical quantum chemical method. It is found that π-conjugation between the phenyl and carbonyl groups is practically absent in the free N-isonicotinoylphthalimide molecule and a rotation of the pyridine ring relative to the amide group in the crystal is determined by the π–π interaction between the pyridine rings.

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INTRODUCTION

The biological activity of compounds and the mechanism of their membrane penetration into cells are due to stereochemical and some physicochemical properties. Despite a large number of studies in this area, there is still no unambiguous answer to the question which molecular parameters are most important in the manifestation of a biological response. From the analysis of publications, it follows that planar and three-dimensional molecules can have a selective activity in the composition of highly effective antibacterial drugs [1-4].

The antibacterial properties of chemical compounds depend on their ability to contact with the bacterial cell membrane and overcome the membrane barrier, on the target binding rate, and disruption of cellular metabolism, which ultimately causes the bacterial cell death. Whilst there are many synthesized drugs successfully used in pharmacological practice, the general laws determining the efficiency of antibacterial properties have not been studied, which makes it necessary to synthesize new drugs using the similarity principle, directing efforts to reduce the overall toxicity and achieve a selective action. Meanwhile, the knowledge of structure–function correlations contributes to the search for new effective

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drugs and allows one to understand the resistance emergence mechanisms of prokaryotes to many known antibacterial drugs during their long-term use.

In this regard, isonicotinic acid hydrazide (GINA) used in medical practice and its various N-substituted amides, which occupy a leading place in treating different forms of tuberculosis, are of particular interest [5-10]. Based on this compound, many different derivatives have been synthesized with a wide variation in the antitubercular activity and toxicity. Previously, based on isonicotinic acid hydrazide, we synthesized a number of new derivatives [11, 12], which showed a pronounced antimicrobial activity against gram-positive (*Staphylococcosaureus, Bacillussubtilis*) strains. In continuation of this work, N-isonicotinoylphthalimide (**1**) was obtained and its spatial structure was determined.

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra were recorded on a JNN-ECA Jeol 400 spectrometer (399.78 MHz and 100.53 MHz respectively) using the DMSO-d_6 solvent. Chemical shifts were measured relative to the signals from residual protons or carbon atoms of deuterated DMSO.

The reaction course and the purity of the obtained compounds were controlled by thin-layer chromatography on Silufol UV-254 plates in isopropyl alcohol–benzene–ammonia systems (10:5:2). The plates were exposed to iodine vapor. The reaction product was isolated by recrystallization from ethanol. The melting point was measured on a SMF-38 melting point apparatus. All solvents used in the work were purified and absolutized according to standard procedures [13].

Synthesis of N-isonicotinoylphthalimide. A mixture of isonicotinic acid hydrazide (0.01 mol) and phthalic anhydride (0.01 mol) in 25 mL of DMF was stirred at 120 °C in a flask with a Dean–Stark trap for 3.5 h. After cooling to room temperature the reaction mixture was diluted with 0.1 L of distilled water, vigorously stirred, and leaved for 24 h. The deposited white precipitate was filtered off, rinsed with ethanol, and dried at room temperature. The product yield is 32%, m.p. is 220-221 °C.

^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.85, d (2H, H12, H16, ^{3}J 5.0), 8.82, d (2H, H13, H15, ^{3}J 6.0), 7.92-7.95, m (2H, H6, H7), 7.97-8.00, m (2H, H5, H8), 11.72, br. s (1H, H3).

^{13}C NMR spectrum, δ, ppm: 121.96 (C12, C16), 124.52 (C5, C8), 129.94 (C4, C9), and 136.03 (C6, C7), 138.20 (C11), 151.32 (C13, C15), 164.73 (C10), and 165.62 (C1, C3).

The calculations were performed within the MOPAC2009 software by the semi-empirical quantum chemical method using the PM6 parametrization [14].

Single crystal X-ray diffraction analysis (XRD) of N-isonicotinoylphthalimide was performed on an Xcalibur Ruby diffractometer (Oxford Diffraction) (CuK_α, graphite monochromator, ω-scanning, $4.59° \le \theta \le 75.96°$) at 297 K. 4779 reflections were measured, including 2494 independent ($R_{int} = 0.0307$). The crystals are monoclinic, $a = 8.6184(4)$ Å, $b = 19.2541(10)$ Å, $c = 7.4815(4)$ Å, $\beta = 99.030(5)°$, $V = 1226.1(1)$ Å^3, $Z = 4$ ($C_{14}H_9N_3O_3$), space group $P2_1/c$, $d_{calc} = 1.448$ g/cm^3, $\mu = 0.879$ mm^{-1}. The initial set of measured intensities was processed and the absorption correction was applied using the CrysAlisPro program (multiscan, $T_{min} = 0.930$, $T_{max} = 1.000$) [15].

The structure was determined by a direct method. The positions of non-hydrogen atoms were refined in the anisotropic approximation by full-matrix LSM. The hydrogen atom of the amine group was determined from the difference maps and its position was refined in the isotropic approximation; the other hydrogen atoms were placed in geometrically calculated positions refined in the isotropic approximation with fixed positional and thermal parameters (riding model). 1895 independent reflections with $I \ge 2\sigma(I)$ were used in the calculations; the number of refined parameters was 185. The final divergence factors are $R_1 = 0.0495$, $wR_2 = 0.1182$ (for the reflection with $I \ge 2\sigma(I)$), $R_1 = 0.0668$, $wR_2 = 0.1324$ (for all reflections), GOOF = 1.057. The residual density peaks are $\Delta\rho = 0.203$ e/Å^3 and –0.335 e/Å^3. The structure was determined and refined using the SHELXS [16] and SHELXL-2018/3 [17] software. The XRD data in the form of a CIF file have been deposited with the Cambridge Crystallographic Data Centre (CCDC 1979530).

RESULTS AND DISCUSSION

It is known from publications (for example, [18]) that the interaction of cyclic anhydrides of dicarboxylic acids with primary and secondary amines under severe conditions (high temperature, presence of catalysts and dehydrating agents) results in the formation of cyclic acid imides. It was noted that the cyclization process occurs through the formation of dicarboxylic acid monoamides that convert into cyclic acid imides.

Thus, it was of interest to study the acylation reaction of isonicotinic acid hydrazide by phthalic anhydride under severe conditions. Moreover, a combination of the pyridine ring, the peptide bond, and the imide moiety in one molecule can produce practical substances, since a manifestation of some types of biological activity requires a volumetric structure, while the others requires its planarity.

The reaction of phthalic acid anhydride with isonicotinoylhydrazide was carried out in a 1:1 reagent ratio in the DMF solvent according to the known procedure [19] (Fig. 1). The DMF solvent velocity impedes the ion motion, hence, intermediate ions do not form, in contrast to the reaction under mild conditions.

The ^{1}H NMR spectrum of compound **1** is characterized by two proton doublet of doublet signals in the aromatic spectral region at 7.85 ppm and 8.82 ppm typical of pyridine protons: H12, H16 with ^{3}J 5.0 Hz and H13, H16 with ^{3}J 6.0 Hz respectively. The H6, H7 and H5, H8 aromatic protons of the phthalimide framework appeared as two double proton multiplets in a range of 7.92-7.95 ppm and 7.97-8.00 ppm respectively. The amide H3 proton resonated in the form of a broadened single proton singlet at 11.72 ppm.

In the ^{13}C NMR spectrum of compound **1** the pyridine carbon atoms appeared at 121.96 ppm (C12, C16), 138.20 ppm (C11), and 151.32 ppm (C13, C15). The carbon atoms of the aromatic core resonated at 124.52 ppm (C5, C8), 129.94 ppm (C4, C9), and 136.03 ppm (C6, C7). In the most downfield part of the spectrum, the carbonyl carbon atoms were observed at 164.73 ppm (C10) and 165.62 ppm (C1, C3).

The structure of compound **1** was also confirmed by two-dimensional (^{1}H–^{1}H) COSY and (^{1}H–^{13}C) HMQC NMR spectroscopy, which allows one to determine homo- and heteronuclear spin-spin couplings. In the ^{1}H–^{1}H COSY spectra there are spin-spin correlations through three proton bonds of the neighboring methine groups H6,7–H5,8 (7.92, 8.03 and 7.98, 7.91) and H3,5–H2,6 (7.84, 8.82 and 8.81, 7.85). In the ^{1}H–^{13}C HMQC spectra the proton couplings with the carbon atoms through one bond were established for all pairs in the compound: H12,16–C12,16 (7.85, 122.01), H6,7–C6,7 (7.93, 136.03), H5,8–C5,8 (7.97, 124.56), and H13,15–C13,15 (8.81, 151.28).

The spatial structure of the **1** molecule determined by single crystal XRD is depicted in Fig. 2.

From our data it follows that the bond lengths and bond angles in compound **1** are nearly normal [20]. The phthalimide ring is planar within ±0.013 Å. The amide group is almost perpendicular relative to it; the dihedral angle is 91.3°. According to the published data, the rotation between the phthalimide ring and the amide group is somewhat less. For instance, in N,N-phthaloylpicoloylhydrazide (**2**), being an isomer of compound **1** (pyridine ring is attached at *meta*-position), it is 73.4° and 79.7° for two crystallographically independent molecules respectively [21].

Also, in **1** the carbonyl O3 atom deviates from the pyridine ring plane (the O3C10C11C16 torsion angle of 15.1(3)°), while in **2** this angle is 1.4° (–1.6)°. It is known that phenylaldehydes and phenylketones are characterized by the conjugation of π-orbitals of the phenyl and carbonyl groups [22]. For example, in the crystal structures of acetophenone [23] and 2-bromo-1-phenylethanone [24] the O = C(sp^2)–C(*ar*)–C(*ar*) torsion angle is 1.4° and –1.6° respectively. Substitution of the amide keto group weakens this interaction caused by the conjugation of the carbonyl π-orbital and the lone pair of the

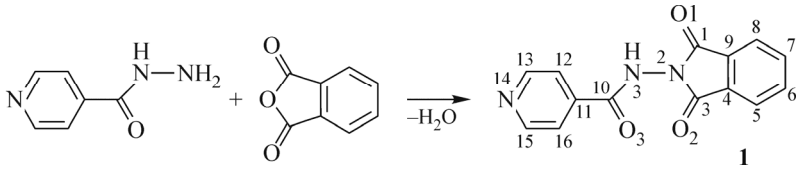

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Fig. 1. Synthesis scheme of N-isonicotinoylphthalimide (**1**).

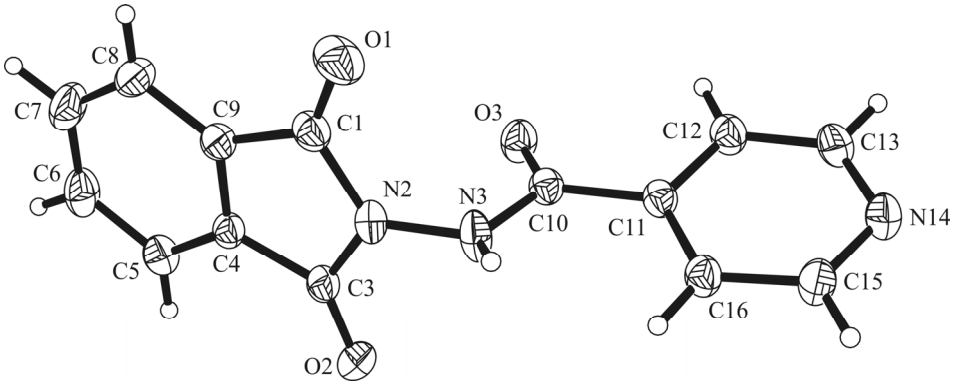

Fig. 2. Structure of N-isonicotinoylphthalimide (**1**) (thermal ellipsoids are shown at a 30% probability level).

planar trigonal nitrogen atom. As a result, the C(*ar*)–C(sp^2) bond length increases from 1.488 Å in phenylketones to 1.500 Å in phenylamides [20]. Thus, the respective C10–C11 bond length is 1.496(2) Å in **1** and 1.499 Å and 1.498 Å in **2**. In these molecules, the amide nitrogen atom has a planar trigonal configuration. The sum of bond angles of this atom is 357.4° in **1**, 360.0° and 359.9° in **2** respectively. Generally, the rotation about the C(*ar*)–C(sp^2) bond in the compounds containing the NR_2–NH–C(O)–Ph fragment reaches sufficiently large values. For example, in the crystal structures of N-(4-oxo-2-(trifluoromethyl)-1,3-thiazolidine-3-yl)benzamide [25], N-(2,4-dihydroxy-5-oxo-3-(3-oxo-3,4-dihydroquinoxaline-2-yl)-2-phenyl-2,5-dihydro-1H-pyrrol-1-yl)benzamide [26], 4-chlorine-N-(2-methyl-2,3-dihydro-1H-indole-1-yl)-3-sulfamoylbenzamide hydrate [27], and N-(2,4-dihydroxy-5-oxo-3-(3-oxo-3,4-dihydroquinoxaline-2-yl)-2-phenyl-2,5-dihydro-1H-pyrrol-1-yl N,N-dimethylformamide [28] the O3C10C11C16 torsion angle is 34.3°, 35.2°, 41.3°, and 46.7° respectively. It should be noted that in these structures the phenyl ring does not contain *meta*-substituents, which excludes the influence of a steric factor on the rotation about the C(*ar*)–C(sp^2) bond. For example, in the crystal structure of N',N'-dibenzyl-2-*m*-chlorobenzohydrazine the mutual repulsion of chloride and oxygen atoms brings this angle to –79.8° [29].

On the other hand, in the crystal structures containing the NR_2–NH–C(O)–Ph fragment the conjugation between the carbonyl group and the phenyl ring sometimes persists. Thus, in the structure of N-(5-benzoyl-2-oxo-4-phenyl-1,2-dihydropyrimidine-1-yl)benzamide [30] the respective C(*ar*)–C(sp^2) bond length is 1.489 Å and the sum of bond angles of the amide nitrogen atom is 359.3°. Moreover, in N-(3-methyl-5-phenyl-4H-1,2,4-triazole-4-yl)benzamide monohydrate [31] this C(*ar*)–C(sp^2) bond length is 1.490 Å, and the sum of bond angles of the amide nitrogen atom decreases to 249.5°, which is indicative of a weakening of the conjugation between the carbonyl π-orbital and the lone pair of the planar trigonal nitrogen atom.

To determine the rotation of the pyridine ring relative to the amide group in the free molecule of **1**, quantum chemical calculations with the full geometry optimization were performed. The comparison of the metrics of **1** with the single crystal XRD data showed their satisfactory agreement (Table 1). It is found that in this case, the π-conjugation between the pyridine ring and the carbonyl group in **1** is practically absent. The minimum formation heat when rotated about the C1–C11 bond is observed at the O3C10C11C16 torsion angle of 70° and 250° with a transition barrier of 36.5 kJ/mol. Such a large difference in the pyridine ring rotation relative to the amide group in the **1** molecule in the free and crystalline states is explained by the influence of intermolecular interactions between the pyridine rings in the latter one. Thus, in the crystal packing of **1** molecules, the π–π conjugation between the pyridine rings is observed (*Cg*–*Cg* = 3.742(1) Å, α = 5.1(1)°). In addition, there is the C–H···π interaction between the pyridine and phenyl rings C13–H···*Cg* (*x*+1, -*y*+1/2, *z*+1/2) (the C–H distances 0.93 Å, H···*Cg* 2.87 Å).

In the crystal, the **1** molecules are linked by intermolecular N3–H···O2 hydrogen bonds (*x*, –*y*+1/2, *z*+1/2) (N–H distances 0.89(2) Å, H···O 2.01(2) Å, N···O 2.896(2) Å, the O–H···O angle of 172(2)°) forming stacks with parallel pyridine rings along the *c* axis (Fig. 3). In addition, the oxygen atoms (potential acceptors) form shortened C–H···O contacts:

TABLE 1. Bond Lengths (Å) and Bond Angles (deg) in the R_2N–NH–C(O)–C(*ar*) Fragment in the **1** Molecule from the Experimental XRD Data and Quantum Chemical Calculations

Bond length	XRD	PM6	Bond angle	XRD	PM6
N2–N3	1.381	1.391	N2N3C10	116.9	119.8
N3–C10	1.365	1.422	N2N3H3	116.8	113.2
C10–C11	1.496	1.502	C10N3H3	123.7	121.4
C10–O3	1.213	1.209	N3C10C11	115.8	111.9
N3–H3	0.895	1.027	N3C10O3	121.8	122.4
			O3C10C11	122.4	125.6

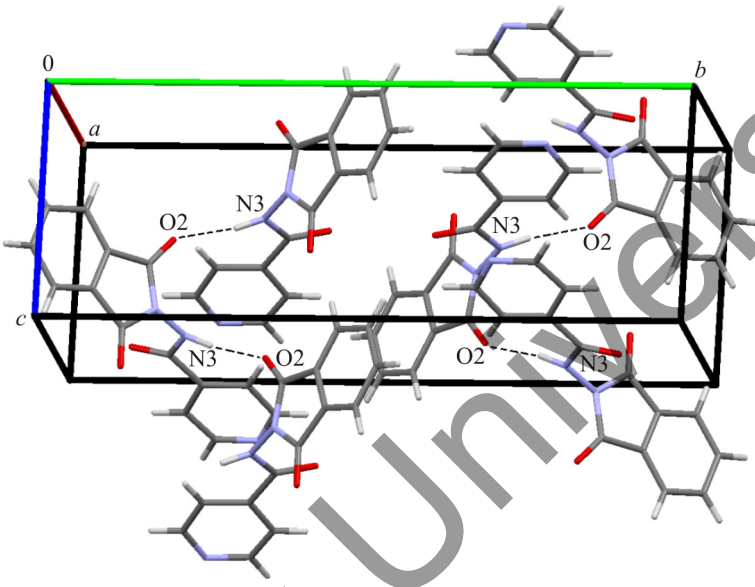

Fig. 3. Crystal packing of N-isonicotinoylphthalimide (**1**) molecules.

C5–H···O1 (*x*, *y*, *z*–1) (C–H distances 0.93 Å, H···O 2.55 Å, C···O 3.460(3) Å, the C–H···O angle 165°), C6–H···O3 (–*x*+1, –*y*+1, –*z*) (C–H distances 0.93 Å, H···O 2.52 Å, C···O 3.390(3) Å, the C–H···O angle 155°), C8–H···O3 (–*x*+1, –*y*+1, –*z*+1) (C–H distances 0.93 Å, H···O 2.54 Å, C···O 3.327(2) Å, the C–H···O angle 143°), and C12–H···O2 (*x*, –*y*+1, *z*+1/2) (C–H distances 0.93 Å, H···O 2.50 Å, C···O 3.286(2) Å, the C–H···O angle 142°).

Hence, the study revealed that the reaction of phthalic acid anhydride with isonicotinoylhydrazide under severe conditions results in the formation of cyclic phthalic acid imide N-isonicotinoylphthalimide. It was found that the π-conjugation between the phenyl and carbonyl groups is practically absent in the free N-isonicotinoylphthalimide molecule and a rotation of the pyridine ring relative to the amide group in the crystal is due to the π–π conjugation between the pyridine rings.

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CONFLICT OF INTERESTS

The authors declare that they have no conflict of interests.

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