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Supramolecular packing and polymorph screening of *N*-isonicotinoyl arylketone hydrazones with phenol and amino modifications

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ABSTRACT

Thirteen structural variants based on the (*E*)-*N*′-(1-arylethylidene)pyridohydrazide template were prepared, investigated and screened for possible polymorphic behaviour. Four variants showed from Differential Scanning Calorimetry Scans thermal events indicative of new solid-state phases. The thirteen variants included substituents R = −OH or $-NH_2$ placed at *ortho*, *meta* and *para* positions on the phenyl ring; and shifting the pyridyl nitrogen between positions 4-, 3- and 2-. The crystal structures of twelve of the compounds were determined to explore their supramolecular structures. The outcomes of these modifications demonstrated that the pyridyl nitrogen at the 2- position is 'locked' by forming a hydrogen bond with the amide hydrogen; while placing the pyridyl nitrogen at positions 3- and 4- offers a greater opportunity for hydrogen bonding with neighbouring molecules. Such interactions include O–H···N, N–H···N, O–H···O, N–H···O, N–H···π, π···π stacking, as well as other weaker interactions such as C–H···N, C–H···O, C–H···N(pyridyl). When OH or NH_2 donors are placed in the *ortho* position, an intramolecular hydrogen bond is formed between the acceptor hydrazone nitrogen and the respective donor. The *meta*- and *para*-positioned donors form an unpredictable array of supramolecular structures by forming hydrogen-bonded chains with the pyridyl nitrogen and carbonyl acceptors respectively. In addition to the intramolecular and chain hydrogen bond formation demonstrated throughout the crystal structures under investigation, larger order hydrogen-bonded rings were also observed in some of the supramolecular aggregations. The extent of the hydrogen-bonded ring formations range from two to six molecular participants depending on the specific crystal structure.

1. Introduction

Crystal engineering is the attempt at pre-meditated control and design of crystal structures from organic species [1,2]. This is often accomplished by varying the structure of a designated molecule and then observing the resultant crystal structure [3–10]. The compounds of interest in this study are a series of modified geometric *N*-isonicotinoyl arylketone hydrazones, which are pyridine-based derivatives of the drug isoniazid, a first line treatment against *Mycobacterium tuberculosis*. In recent studies [11,12], researchers evaluated the antimicrobial activity of various analogues of *N*-isonicotinoyl arylaldehyde hydrazones, which exemplifies the great importance in understanding organic molecular structures of this type. Additionally, research data on geometric isomers of *N*-isonicotinoyl arylaldehyde hydrazones have been used to study supramolecular structures arising from multiple hydrogen bonding nodes [13]. However, for the present study, the hydrogen bonding patterns and supramolecular aggregates arising when *N*-isonicotinoyl arylketone hydrazones are modified with R = −OH or $-NH_2$ at the *ortho*, *meta* and *para* positions of the phenyl ring (as shown in Scheme 1) will be followed. The molecules of interest contain a number of hydrogen bonding functional groups (as well as other weaker intermolecular interactions) resulting from the presence of the pyridine ring, linked by a highly polar hydrazone group to the modified phenyl ring (Scheme 2). The interactions observed are O–H···N, N–H···N, O–H···O, N–H···O, N–H···π, π···π stacking and other weaker interactions such as C–H···N, C–H···O, C–H···N (pyridyl) (see Scheme 3).

In an attempt to extend the variety of supramolecular aggregates, the skeletal backbone of the molecule was altered by shifting the pyridyl nitrogen to the 3- position from the 4- position. The intention behind these modifications was to observe the hydrogen

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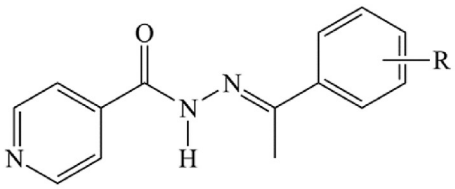
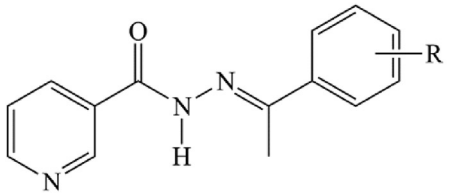


I - III R = 2-OH, 3-OH, 4-OH
VII - IX R = 2-NH_2, 3-NH_2, 4-NH_2

I: 1-(2-hydroxyphenyl)ethanone isonicotinoyl hydrazone
II: 1-(3-hydroxyphenyl)ethanone isonicotinoyl hydrazone
III: 1-(4-hydroxyphenyl)ethanone isonicotinoyl hydrazone

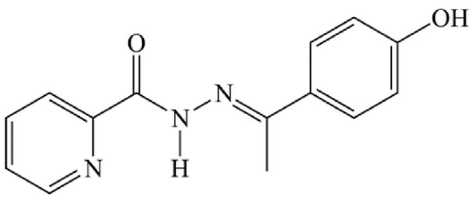
VII: 1-(2-aminophenyl)ethanone isonicotinoyl hydrazone
VIII: 1-(3-aminophenyl)ethanone isonicotinoyl hydrazone
IX: 1-(4-aminophenyl)ethanone isonicotinoyl hydrazone



IV - VI R = 2-OH, 3-OH, 4-OH
X - XII R = 2-NH_2, 3-NH_2, 4-NH_2

IV: 1-(2-hydroxyphenyl)ethanone nicotinoyl hydrazone
V: 1-(3-hydroxyphenyl)ethanone nicotinoyl hydrazone
VI: 1-(4-hydroxyphenyl)ethanone nicotinoyl hydrazone

X: 1-(2-aminophenyl)ethanone nicotinoyl hydrazone
XI: 1-(3-aminophenyl)ethanone nicotinoyl hydrazone
XII: 1-(4-aminophenyl)ethanone nicotinoyl hydrazone



XIII: 1-(4-hydroxyphenyl)ethanone picolinoyl hydrazone

Scheme 1. The thirteen compounds chosen to study the effects of modification and placement of pyridyl nitrogen on the supramolecular aggregates.

bond patterns manifested during crystallization when the hydrogen bond nodes are shifted around to different regions of the molecule. A third additional pyridyl isomer was also investigated in which the pyridyl nitrogen was placed in the 2- position (Scheme 1) to establish whether this position for the pyridyl nitrogen could be useful for forming hydrogen bond nodes with neighbouring donors. Overall the compounds were found to generate one, two, and three dimensional aggregates with no distinctive predilection for a single direction-specific intermolecular interaction, as will be discussed below. Even minor alterations to the skeletal backbone by shifting the pyridyl nitrogen one position in the ring can give rise to disparate supramolecular aggregates. Further, no isostructural or isomorphoric variations were observed in the compounds, as the unit cell parameters deviate significantly for each structure and space groups are not identical. Even unit cell parameters of structures with identical modifications in the phenyl ring when the pyridyl nitrogen is shifted about its own respective ring, do not correlate well. As a result one cannot predict crystal structures even for such structurally similar compounds.

In addition to structure prediction amongst the compounds **I** – **XIII**, a preliminary assessment was performed to identify the polymorphic capacity of these compounds. The driver behind this was to determine if the modification and/or position of the hydrogen bond donor either disrupts or enhances the polymorphic capacity observed, when compared to the highly polymorphic parent compound isonicotinic acid-(1-phenylethylidene) hydrazide (IPH) [14]. Selected compounds are presented that show either interesting or promising thermal behaviour, when heating and cooling cycles are applied from 25 °C to the compound's respective melting point and cooled back down to 25 °C.

2. Experimental

2.1. Syntheses and crystallizations

Isoniazid (0.100 g, 0.729 mmol) and its pyridyl isomers were respectively mixed with the appropriate substituted acetophenone in an equimolar ratio, and dissolved in absolute ethanol (15 ml); these mixtures were then stirred at room temperature for 18 h. The crude residue was filtered, and then washed with cold ethanol. Crystallization was achieved by slow evaporation of various solvents (see Table 1). Multiple crystallization attempts for **XI** were not successful and suitable crystals for structure determination were never obtained. The melting points for each compound determined from DSC experiments are included in Table 1.

2.2. Data collection, structure solution and refinement

The Bruker D8 VENTURE PHOTON CMOS area detector diffractometer, equipped with a graphite monochromated Mo $K\alpha_1$ radiation (50 kV, 30 mA), was used to collect all the intensity data. Crystal structures were collected at 173 K and to achieve satisfactory thermal ellipsoids. The program *SAINT+*, vers. 6.02 [15] was used to integrate the data and the program *SADABS* [16] was used to make empirical absorption corrections. Space group assignments were made using *XPREP* [15] on all compounds. In all cases, the structures were solved in the *WinGX* [17] suite of programs by direct methods using *SHELXS-97* [18] and refined using full-matrix least-squares/difference Fourier techniques on F^2 using *SHELXL-97* [18]. All non-hydrogen atoms were refined anisotropically. Thereafter, all hydrogen atoms attached to N atoms were located in the difference Fourier map and their coordinates refined freely with