**Enaminones in heterocyclic syntheses: part 5: isoniazid-enaminone a new organic synthon and tuberculostatic candidate.**

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**Abstract**: condensation of nicotinic, isonicotinic acid hydrazides **1a,b** with1,3-cyclohexanedione **2**, in water, using acetic acid as catalyst, afforded enaminone derivatives **3a,b.**

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**Introduction**

Isoniazid (isonicotinic acid hydrazide) **1a** is used as a veterinary antiactinomycotic agent and, most important, as a primary drug for the treatment of all types of tuberculosis [1-4a] and is, normally, given in high doses over long periods of time [2, 5]. Also, iproniazid (isonicotinicacid 2-isopropyl hydrazide) is applied as antidepressant [4b, 6].

Isoniazid **1a** itself has been reported to be carcinogenic in mice [2, 7] but the carcinogenic activity is probably due to the release of free hydrazine (H2NNH2) by the hydrolysis of **1a** according to **equation 1** [1, 2, 7]. Hydrazine, one of isoniazid’s principle degradation products (**equation 1**) is a known carcinogen [1-3] and considerably, is more toxic than isoniazid [1, 2, 4c]. A very recent review [1] reported that “hydrazines cause DNA damage and gene mutations [8, 9]; hydrazine, methylhydrazine and related hydrazides (isoniazid is a hydrazide derivative of hydrazine) are known human carcinogens [10]; and hydrazines, hydrazides and hydrazones all show conventional structural alerts for genotoxic potential [11]”.

On the other hand, Enaminones have proven to be versatile synthons for the synthesis of various heterocycles and natural products [12-14]. They are involved in the synthesis of, for example, pyridines, pyrimidines, pyrroles, indolizidines, quinolizidines and perhydroindoles, many of which are common motifs in alkaloid structures [12, 13]. Enaminones are, also, frequently employed as building blocks for the preparation of highly functionalized mono-, bi- or larger- cyclic compounds of biological interest. In addition, some enaminones have been recognized as potential anticonvulsant [12, 15a-c] and analeptic [15d] compounds, with low toxicity.

Most of the syntheses of enaminones [12, 13], (especially, *via* condensation of 1,3-dicarbonyl compounds with ammonia, primary or secondary amines [16-21]; or with hydrazines [22]) are, usually, carried out in dry organic solvents, with continuous removal of water as a reaction by-product. However, we, herein, present a synthesis- in water- of the new enaminones **3a, b** (Scheme 1, Experimental). This work is in continuation of our recent interest in the field of (*Green Chemistry*), especially, in the direction of applying water -the safest and most economic solvent- in place of hazardous and expensive solvents in synthetic organic reactions [23, 24]. It is, also, in continuation of the work of one of our team on enaminones [25-28].

When isoniazid **1a** was allowed to react with the highly enolisable 1,3-cyclohexanedione **2**, through two hours of reflux conditions in water, in the presence of catalytic amount of acetic acid, the new enaminone derivative **3a** was obtained as a yellow fine crystalline matter in 80% yield of isolated product (Scheme 1,Experimental).



In the light of forming and, hence, stability of the enaminones **3a** in the applied refluxed weak-acid catalyzed aqueous solution (Scheme 1 & Experimental), the probability of releasing free hydrazine -a carcinogen- from the enaminones **3a** should be eliminated under conditions comparable to, or softer than the applied synthetic conditions of **3a**. Moreover, a hypothetical assumption of splitting off free hydrazine from the enaminone derivative **3a** is
 **-**in our opinion**-** very much retarded since this splitting involves two consecutive reactions to occur. In the first assumed reaction, (**equation 2**), the enaminone **3a** has to be forced to be hydrolyzed -by water- into its building unites 1,3-cyclohexanedione **2** and isoniazid **1a**. In the second reaction, **equation 1** has to be applied to release hydrazine from **1a**. Similar to **1a**, the nicotinic acid hydrazide **1b** was allowed to react with **2**, under the same experimental

conditions to afford the new enaminone **3b** as yellow fine crystals (Scheme 1& Experimental).

The structures of **3a,b** were established on basis of satisfactory elemental and spectral (IR,
1H NMR, 13C NMR) analyses (Experimental). For example, the IR spectrum of **3a** showed stretching bands in the regions of 3229, 3170 and 1681 cm-1 for the –NH- and –CO- functional groups, respectively; its 1H NMR (DMSO), showed singlet signal (s) in the regions of δ 10.83, 9.15 and 4.96 ppm for the proton (s) of the hydrazide nitrogen -CONH-, enaminone nitrogen (=C-NH-) and the ene (or vinylic) moiety
(-CH=C-), respectively; and its 13C NMR (DMSO) showed signal (s) in the regions of δ 195.30, 164.00 and 96.00 ppm for the ketonic carbonyl, hydrazide carbonyl carbon and the ene-methine (-CH=) carbon (i.e., C-2 in the 3-oxocyclohex-1-enyl moiety), respectively.





In the light of the above mentioned findings and results and as each of the new derivatives **3a,b** gathers or combines -in its chemical structure- between the functionality of cyclic enaminone and
2-substituted-hydrazide, it is worthy to suggest future studies to explore the potentiality of these new derivatives **3a, b** in both the fields of biological activity -especially, towards the different types of tuberculosis- and organic synthesis.

**Experimental**

Melting points were obtained on a Gallenkamp melting point apparatus (open capillary tubes) and were uncorrected; IR spectra were performed on a Jasco 4100 FTIR spectrophotometer (KBr pellet) at the Department of Chemistry, Faculty of Science at (New) Damietta, Mansoura University, Damietta branch, Egypt. 1H NMR and 13C NMR spectra were performed on a BRUKER (600 and 150 MHz, respectively) ultra shield Avence III Spectrometer at the Faculty of Science, King Abd-Elaziz University, Jeddah, K.S.A, using (TMS) as an internal stander and DMSO as a solvent. Chemical shifts were expressed as δ ppm. Microanalytical data were performed on a PERKIN-ELMER 2400 C, H, N Elemental Analyzer at the Microanalytical Unit, Cairo University, EGYPT.

**3.1. Synthesis of N'-(3-oxocyclohex-1-enyl) isonicotinohydrazide (3a) and N'-(3-oxocyclohex-1-enyl)nicotinohydrazide(3b) (Scheme 1).**

**General procedure:**

The hydrazide **1a (or 1b)**(0.01mol) was dissolved in 30 ml of hot distilled water, while stirring. 1,3-cyclohexanedione **2** (0.01 mol) was, then, added, in portions, in the presence of 2 drops glacial acetic acid as a catalyst. A after complete addition of **2,** heating, while stirring, continued for two additional hours. The reaction solvent -water- was, then, removed using a rotary evaporator system. The evaporation residue was cooled to room temperature and, next, triturated with petroleum ether (40-60 oC) till a solid was obtained. The solid product was, then, crystallized from ethanol: water (1: 4) mixture to give **3a, b**, respectively.

**N'-(3-oxocyclohex-1-enyl)isonicotinohydrazide (3a).**

Yellow fine crystals: Yield: 80%; m.p: 186-8 oC; **IR** (KBr, cm-1): γ = 3229, 3170 (NH); 1681 (CO); **1H NMR** (600 MHz, DMSO), δ, ppm = 10.83 (1H, s ,
-CONH-, hydrazide), 9.15 (1H, s, =C-NH-, enaminone), 8.80 (2H, d, H-2, H-6, pyridyl), 7.78 (2H, d, H-3, H-5, pyridyl), 4.96 (1H, s, -CO-CH=, enaminone), 2.41, 2.14, 1.87 (6H, 3x m,3x-CH2-,
3-oxocyclohex-1-enyl); **13C NMR** (150 MHz, DMSO), δ, ppm = 195.30 (**C**O, ketone), 164.00 (**C**O, hydrazide), 150.46 139.23, 121.23, 96.00
(-CO-**C**H=, enaminone), 36.55 (**C**H2-CO), 25.60 (**C**H2), 21.56 (CH2-**C**H2-CH2).

Anal.Calcd for C12H13N3O2 (Mol.Wt: 231.25):
C, 62.3; H, 5.67; N, 18.17; Found: C, 62.22; H, 5.35; N, 17.93.

**N'-(3-oxocyclohex-1-enyl) nicotinohydrazide (3b)**

Yellow fine crystals: Yield: 75%; m.p: 202-204 oC; **IR** (KBr, cm-1): γ = 3243, 3178 (NH); 1677 (CO);
 **1H NMR** (600 MHz, DMSO), δ, ppm = 10.71 (1H, s ,-CONH-, hydrazide), 9.12 (1H, s, =C-NH-, enaminone), 9.03 (1H, s, pyridyl), 8.77 (1H, d, pyridyl), 8.23 (1H, d, pyridyl), 7.56 (1H, m, pyridyl), 4.97 (1H, s, -CO-CH=, enaminone), 2.41, 2.14, 1.87 (6H, 3x m, 3x-CH2-, 3-oxocyclohex-1-enyl);
**13C NMR** (600 MHz, DMSO), δ, ppm = 195.27 (**C**O, ketone), 164.01 (**C**O, hydrazide), 152.6, 148.30, 135.19, 127.93, 123.72, 96.00 (-CO-**C**H-, enaminone), 36.56 (**C**H2-CO), 25.69 (**C**H2), 21.57 (CH2-**C**H2-CH2).

Anal. Calcd for C12H13N3O2 (Mol.Wt: 231.25):
C, 62.3; H, 5.67; N, 18.17; Found: C, 62.32; H, 5.55; N, 18.06.

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