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

Keywords: hydrazine, nicotinic hydrazide, isoniazid, isoniazid-enaminone, tuberculosis.

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 (isonicotinic acid 2-isopropylhydrazide) 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, pyroles, 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.

\[
\text{N} \quad + \quad \text{H}_2\text{O} \quad \rightarrow \quad \text{N} \quad + \quad \text{H}_2\text{N}-\text{NH}_2
\]

(eq. 1)

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 enaminone derivative 3a in the applied refluxed weak-acid catalyzed aqueous solution (Scheme 1 & Experimental), the probability of releasing free hydrazine -a carcinogen- from the enaminone 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 units 1,3-cyclohexanedione 2 and isoniazid 1a. In the second reaction, equation 1 has to be applied to release hydrazine from 1a.

![Scheme 1](image)

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 the 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=CH-), 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 Bruker 400 FTIR spectrophotometer (KBr pellet) at the Department of Chemistry, Faculty of Science at (New) Damietta, Mansoura University, Damietta branch, Egypt. $^1$H-NMR and $^{13}$C NMR spectra were performed on a Bruker (600 and 150 MHz, respectively) ultra shield Avance III III Spectrometer at the Faculty of Science, King Abdul-Aziz 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 $\text{N'}$(3-oxocyclohex-1-enyl)isonicotinohydrazide(3a) and $\text{N'}$(3-oxocyclohex-1-enyl)nicotinohydrazide(3b) (Scheme 1).

General procedure:

The hydrazide 1a (or 1b) (0.01 mol) 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 °C) till a solid was obtained. The solid product was, then, crystallized from ethanol: water (1: 4) mixture to give 3a, b, respectively.

$\text{N'}$(3-oxocyclohex-1-enyl)isonicotinohydrazide (3a).

Yellow fine crystals: Yield: 80%; m.p: 202-204 °C; IR (KBr, cm$^{-1}$): γ = 3243, 3178 (NH); 1677 (CO); $^1$H NMR (600 MHz, DMSO), δ, ppm = 10.81 (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-CH$_2$-), 3-oxocyclohex-1-enyl); $^{13}$C NMR (600 MHz, DMSO), δ, ppm = 150.46, 139.23, 121.23, 96.00 (-CO-CH=, enaminone), 36.56 (CH$_2$-CO), 25.60 (CH$_2$), 21.56 (CH$_2$-CH$_2$-CH$_2$). Anal. Calcd for $\text{C}_{12}\text{H}_{13}\text{N}_{2}\text{O}_2$: C, 62.3; H, 5.67; N, 18.17; Found: C, 62.22; H, 5.35; N, 17.93.

$\text{N'}$(3-oxocyclohex-1-enyl) nicotinohydrazide (3b)

Yellow fine crystals: Yield: 75%; m.p: 202-204 °C; IR (KBr, cm$^{-1}$): γ = 3243, 3178 (NH); 1677 (CO); $^1$H 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-CH$_2$-), 3-oxocyclohex-1-enyl); $^{13}$C NMR (600 MHz, DMSO), δ, ppm = 195.27 (CO, ketone), 164.01 (CO, hydrazide), 152.6, 148.30, 135.19, 127.93, 123.72, 96.00 (-CO-CH=, enaminone), 36.56 (CH$_2$-CO), 25.60 (CH$_2$), 21.57 (CH$_2$-CH$_2$-CH$_2$). Anal. Calcd for $\text{C}_{12}\text{H}_{13}\text{N}_{2}\text{O}_2$: (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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