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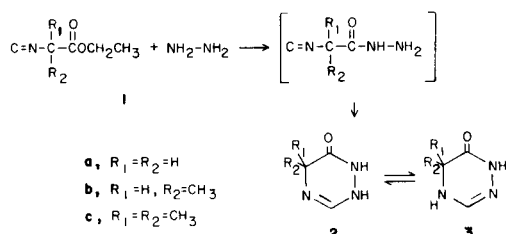
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The novel synthesis of 4,5-dihydro-1,2,4-triazin-6-(1H)ones, **2**, from 2-isocyanoacetates is described. This synthetic method allows the first synthesis of the unsubstituted parent ring system and, in general, gives **2** substituted in only the five position. The assignment of tautomeric structures (**2** or **3**) to the triazinone products was resolved by spectroscopic means.

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Pursuant to our studies on the preparation and reaction of 2-isocyanoacetamides (**1**) we investigated the reaction of hydrazine with ethyl 2-isocyanoacetates **1**. The substituted 2,2,2-(trifluoroethyl)hydrazine yielded the expected product,  $\alpha$ -isocyano[2,2,2-trifluoroethyl]acetylhydrazide. However, the same reaction with simple hydrazine yielded directly 4,5-dihydro-1,2,4-triazin-6-(1H)ones. These compounds could arise by immediate cyclization of the expected acyclic product as shown. Cyclization *via* simple alpha-addition would be expected to yield **2** while tautomerization would give **3** (Scheme 1).

Scheme 1



The acyclic product ( $\text{R}_1, \text{R}_2 = \text{H}$ ) shown in brackets was isolated by Ugi (3). We have found that while this intermediate can be isolated under sharply defined conditions, otherwise, it is easily induced to undergo cyclization to give the triazinone **3a**.

The previously unreported parent compound **3a** was isolated as a water soluble (pH 1-14) white solid having the calculated molecular weight by both VPO and mass spectrometry. An amide carbonyl band was present in the ir, and micro analysis confirmed the empirical formula. The possibility of isomerization of the double bond about the 3 position was next considered. As shown in Scheme 1, either **2** or **3** or a mixture of these could arise from the reaction.

Camparini, *et al.* (4), isolated this ring system, although substituted in both the 3- and 5-position, by the reaction of iminoesters with hydrazine. They draw the tautomeric structure **3** for 3-phenyl-5-methyl-4,5-dihydro-1,2,4-triazin-6-(1H)one and cite as evidence the fact that the 5-proton,

split into a quartet by the 5-methyl group, is additionally coupled to the adjacent N-H ( $J = 1.5$  Hz). A recent publication by Saegusa, Ito, *et al.* (5), describes the first and unusual synthesis of 5-methyl-4,5-dihydro-1,2,4-triazin-6-(1H)one, compound **3b**, by the palladium dichloride catalyzed reaction of alanine hydrazide with *t*-butyl isocyanide. These investigators also favored the **3** isomer but no mention was made regarding coupling of the 5-proton with the adjacent N-H, a condition presumably necessary for this assignment. Further, these investigators purified the material by distillation while we isolated **3b** as a solid, m.p. 143-146°. An attempt to fully define the structure by single crystal X-ray was unsuccessful.

Therefore, a careful analysis of the pmr spectra (100 MHz, FT nmr) of our compounds was undertaken. The spectra of **3b** reveals that the 5-proton which is coupled to the 5-methyl group ( $q, J = 6.6$  Hz) is also split by the adjacent N-H ( $J = 1.3$  Hz). Experiments show that this fine splitting can be removed by irradiating the N-H found at  $\delta$  7.0. Likewise, **3a** exhibits this fine splitting of the 5 methylene singlet ( $J = 1.2$  Hz). All three compounds show an unsymmetrical doublet at  $\delta$  6.8-6.9 for the hydrogen in the 3-position. This absorption is too close to the 4-N-H for irradiation experiments but the doublet is unaffected by irradiation of all other protons in the molecule. In addition, this doublet, as well as the fine splitting of the 5-hydrogens in **3a** and **3b**, is collapsed in the deuterium oxide nmr of these compounds.

The observed coupling combined with irradiation and deuterium oxide experiments are consistent for **3a** and **3b** only if the tautomeric structure **3** is assigned, where both the 5- and 3-hydrogens are split by an N-H found in position 4. Compound **3c**, which has no 5-hydrogen can be assigned structure **3** only by analogy of the 3-proton doublet observed with compounds **3a** and **3b**.

## EXPERIMENTAL

## General.

Melting points were determined on a Laboratory Devices Melt-Temp apparatus and are uncorrected. Nuclear magnetic resonance (nmr) spec-

tra were recorded on Varian T-60 and JEOL FX-100 spectrometers using tetramethylsilane as an internal standard. Chemical shifts are reported in parts per million (ppm) downfield ( $\delta$ ) relative to TMS. Combustion analyses were performed by Atlantic Microlabs, Galbraith Laboratories, or the Monsanto Physical Science Center. Infrared spectra were recorded from a Perkin-Elmer Infracord.

#### 2-(2,2,2-Trifluoroethyl)- $\alpha$ -isocynoacetylhydrazide.

To 0.033 mole of 70% aqueous 2,2,2-trifluoroethylhydrazine was added 0.03 mole (3.4 g.) of ethyl 2-isocynoacetate. After the resulting solution was allowed to stand for three days, water was added to the reaction mixture. The product was separated by filtration and recrystallized from toluene to give 1.2 g. (22%) of a white solid, m.p. 112-114° (sealed tube); ir (chloroform): 4.7, 5.7  $\mu$ ; nmr (deuteriochloroform, DMSO- $d_6$ ):  $\delta$  3.5 (complex multiplet with coupling to both fluorine and hydrogen, 2,  $\text{CF}_3\cdot\text{CH}_2$ ), 4.2 and 4.5 (2 singlets, ratio of 3:1, 2,  $\text{CNCH}_2$ ), 5.4 (br t, 1, N-H), 9.8 (br s, 1, NH).

*Anal.* Calcd. for  $\text{C}_5\text{H}_8\text{F}_3\text{N}_3\text{O}$ : C, 33.16; H, 3.34; N, 23.20. Found: C, 33.55; H, 3.32; N, 22.96.

#### 4,5-Dihydro-1,2,4-triazin-6-(1H)one (3a).

A mixture of 0.1 mole of ethyl 2-isocynoacetate in 25 ml. of water was cooled to 0-5° and 0.1 mole of 95% hydrazine was added dropwise. The mixture was allowed to stand overnight, water was removed and the residue extracted with boiling acetonitrile. The product crystallized from this solvent to yield 3.4 g. (34%) of white solid, m.p. 176-178° (decomposes in a sealed tube); ir (Nujol) 6.2  $\mu$ ; nmr (DMSO- $d_6$ ):  $\delta$  3.7 (d, 2, J = 1.2 Hz,  $\text{CH}_2$ ), 6.8 (d, 1, J = 3.9 Hz, CH); 6.9 (br s, 1, NH), 10.0 (br s, 1, NH).

*Anal.* Calcd. for  $\text{C}_5\text{H}_5\text{N}_3\text{O}$ : C, 36.16; H, 5.09; N, 42.41. Found: C, 36.16; H, 5.30; N, 42.59.

#### 4,5-Dihydro-1,2,4-triazin-6-(1H)one (3a).

$\alpha$ -Isocynoacetylhydrazide (1.0 g.) was dissolved in 5 ml. of water and 2-3 drops of hydrazine hydrate was added as a catalyst. The reaction was stirred overnight and filtered through clay. The water was removed *in vacuo* and the solid residue was recrystallized from acetonitrile to give 0.4 g. of white solid, compound 3a.

#### 5-Methyl-4,5-dihydro-1,2,4-triazin-6-(1H)one (3b).

To a solution of 1.6 g. (0.05 mole) of hydrazine in 15 ml. of water was added 6.35 g. (0.05 mole) of ethyl 2-isocynoacetate. After standing overnight, the water was removed by a rotary vacuum evaporator. The residue was taken up in 2-propanol. 1.2 g. (20%) of white solid was recovered by filtration, m.p. 143-146° (decomposes in a sealed tube); nmr (DMSO- $d_6$ ):  $\delta$  1.2 (d, 3, J = 6.4 Hz,  $\text{CH}_3$ ), 3.8 (q, 1, J = 6.6 Hz and J = 1.3 Hz,  $\text{CH}_2\text{CH}$ ), 6.8 (d, 1, J = 3.9 Hz, =CH), 6.9 (br s, 1, NH), 10.0 (br s, 1, NH).

*Anal.* Calcd. for  $\text{C}_6\text{H}_7\text{N}_3\text{O}$ : C, 42.47; H, 6.24; N, 37.15. Found: C, 42.53; H, 6.24; N, 37.26.

#### 5,5-Dimethyl-4,5-dihydro-1,2,4-triazin-6-(1H)one (3c).

A mixture of 7.05 g. (0.05 mole) of ethyl 2-isocynoacetate in 20 ml. of water was cooled to 0-5° and 1.75 g. (0.055 mole) of 95% hydrazine was added dropwise. After stirring overnight at room temperature, the water was removed *in vacuo*. The residue was recrystallized from ethyl acetate to yield 2.8 g. (43%) of white solid, m.p. 163-166° (sealed tube); nmr (deuteriochloroform, DMSO- $d_6$ ):  $\delta$  1.4 (s, 6,  $\text{CH}_3, \text{CH}_3$ ), 6.8 (br s, 1, N-H), 7.0 (d, 1, J = 3.8 Hz, =CH), 9.9 (br s, 1, NH); ir ( $\text{CH}_3\text{CN}$ ) 6.0  $\mu$ .

*Anal.* Calcd. for  $\text{C}_7\text{H}_9\text{N}_3\text{O}$ : C, 47.24; H, 7.09; N, 33.07. Found: C, 47.46; H, 6.71; N, 33.10.

## REFERENCES AND NOTES

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