Triazine Chemistry VIII. 2,5-Dihydro-5-oxo-1,2,4-triazines

Jaekeun Lee and William W. Paudler

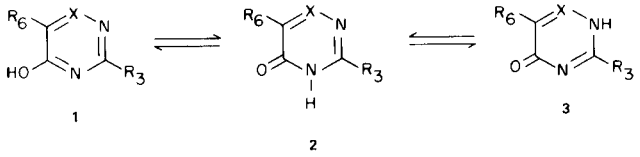
Department of Chemistry, Clippinger Laboratories,
Ohio University, Athens, Ohio 45701

Received June 2, 1972

2,5-Dihydro-5-oxo-1,2,4-triazine and some of its alkylated derivatives have been prepared. Nmr spectroscopic analysis has established that the 2,5-dihydro-5-oxo tautomers are preferred over the 4,5-dihydro-5-oxo ones. This preference, and the behavior of 1,2,4-triazines in some other chemical reactions has been interpreted in terms of electron-electron repulsions between the lone pairs of electrons of N_1 and N_2 in this ring system.

We have recently commented on the chemistry of 2,3-dihydro-3-oxo-1,2,4-triazines (1), the synthesis of 1,6-dihydro-6-oxo-1,2,4-triazines (2) and have shown that these compounds exist largely, if not entirely, in the dihydro-oxo- rather than in the hydroxy- forms. Furthermore, we have established that 3-oxo-1,2,4-triazines undergo facile covalent hydration across the N_4-C_5 bond, that they exist essentially completely as the 2,3-dihydro, rather than the 3,4-dihydro tautomers, and that they are subject to methyl-methylene tautomerism when a tautomerizable alkyl group is present at C_5.

When one examines the tautomeric possibilities of "5-hydroxy-1,2,4-triazines," structures **1** (X = N), **2** (X = N) and **3** (X = N) must be considered.

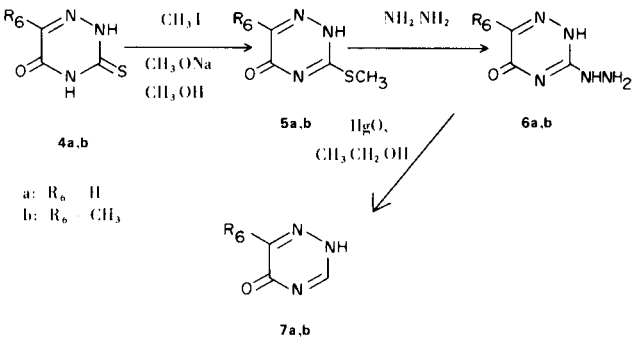


1 2 3

These compounds, with X = N, may also be considered as aza analogs of "4-hydroxypyrimidine" (**1**, X = CH) and thus lend themselves ideally to an examination of the effect that the replacement of a sp^2 carbon atom (**1**, **2**, **3** with X = CH) by a sp^2 nitrogen atom (**1**, **2**, **3** with X = N) has upon these equilibria.

The major effect that one would anticipate from this substitution is that caused by the expected decrease of the basicity of N_2 when X = CH is changed to X = N in **1**, **2** and **3**.

Only *C*-alkylated and *C*-arylated derivatives of "5-hydroxy-1,2,4-triazine" have, so far, been described. J. Gut and coworkers (5) have concluded that, in a series of substituted "5-hydroxy-1,2,4-triazines" (**1** (X = N); $R_3 = CH_3$, $R_6 = H$; $R_3 = C_6H_5$, $R_6 = H$; $R_3 = R_6 = CH_3$; $R_3 = C_6H_5$, $R_6 = CH_3$) the *para*-quinonoid structure predominates whereby the 3 ⇌ 2 equilibrium constant was estimated to vary between 2.6 to 4.6. This conclusion was based upon an examination of the infrared and ultraviolet spectra. We have now prepared the parent "5-hydroxy-1,2,4-triazine" (**4** (X = N), $R_3 = R_6 = H$) by the following sequence:

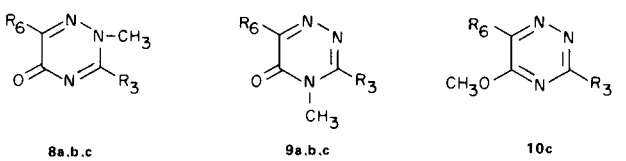


4a,b 5a,b 6a,b 7a,b

a: R_6 = H
b: R_6 = CH_3

The structure proofs of compounds **5**, **6**, and **7** rest upon the correct elemental analyses, mass spectral and pmr data and are self-evident from an examination of the data presented in the experimental section and in the Tables.

In order to examine the tautomeric behavior of the parent compound (**7a**) and the related 3-methyl (**7b**) as well as 3,6-dimethyl derivatives, we judged it necessary to prepare compounds **8**, **9** and **10**.

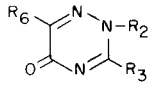
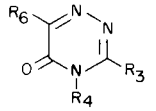
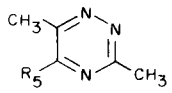
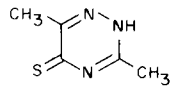


8a,b,c 9a,b,c 10c

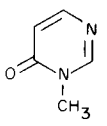
a: R_3 = R_6 = H
b: R_3 = H, R_6 = CH_3
c: R_3 = R_6 = CH_3

TABLE I

Pmr Spectral Data for Various 2,5-Dihydro-5-oxo-1,2,4-triazines

Structure		Chemical Shift in (τ) R_2	R_3	R_4	R_5	R_6	Solvent	Compound No.
	$R_2 = R_3 = R_6 = H$	-----	1.28	-----	-----	2.26	DMSO	**7a**
	$R_2 = R_6 = H, R_3 = NHNH_2$	-----	-----	-----	-----	2.18	DMSO	**6a**
	$R_2 = R_6 = H, R_3 = SCH_3$	-----	7.48	-----	-----	2.36	DMSO	**5a**
	$R_3 = R_6 = H, R_2 = CH_3$	6.21	2.21	-----	-----	1.28	DMSO	**8a**
		6.18	2.26	-----	-----	1.64	$CDCl_3$	
	$R_2 = R_3 = H, R_6 = CH_3$	-----	1.38	-----	-----	7.81	DMSO	**7b**
	$R_2 = R_6 = CH_3, R_3 = H$	6.21	1.64	-----	-----	7.70	$CDCl_3$	**8b**
	$R_2 = H, R_6 = CH_3, R_3 = NHNH_2$	-----	-----	-----	-----	7.96	DMSO	**6b**
	$R_2 = H, R_6 = CH_3, R_3 = SCH_3$	-----	7.50	-----	-----	7.86	DMSO	**5b**
	$R_2 = H, R_3 = R_6 = CH_3$	-----	7.68	-----	-----	7.82	DMSO	
	$R_2 = R_3 = R_6 = CH_3$	6.25	7.58	-----	-----	7.84	DMSO	**8c**
		6.22	7.55	-----	-----	7.75	$CDCl_3$	
	$R_3 = R_6 = H, R_4 = CH_3$	-----	1.55	6.58	-----	1.38	DMSO	**9a**
		-----	1.76	6.50	-----	1.57	$CDCl_3$	
	$R_3 = H, R_4 = R_6 = CH_3$	-----	1.87	6.52	-----	7.51	$CDCl_3$	**9b**
	$R_3 = R_4 = R_6 = CH_3$	-----	7.51	6.59	-----	7.70	DMSO	**9c**
		-----	7.47	6.52	-----	7.58	$CDCl_3$	
	$R_5 = OCH_3$	-----	7.35	-----	6.00	7.48	$CDCl_3$	**10**
	$R_5 = SCH_3$	-----	7.29	-----	7.46	7.46	$CDCl_3$	**16**
		-----	7.62	-----	-----	7.60	DMSO	**15**

Since it has been known for some time that the treatment of "4-hydroxypyrimidine" (**1** (X = CH), $R_3 = R_6 = H$) with methyl iodide in methanolic sodium methoxide affords the 3-methyl-3,4-dihydro-4-oxo-pyrimidine (**11**) (4) as the, apparently, sole product, an application of



11

this alkylation procedure to the various "5-hydroxy-1,2,4-triazines" (**1** (X = N)) is a logical extension.

When this reaction was employed with compound **7a**, two isomeric monomethyl derivatives were obtained in the ratio of 6:4. The pmr spectra of these compounds (see Table I) indicate that the two ring-protons (at C_3 and C_6) are still present in both isomers. Consequently, we are either dealing with a 5-methoxy and a *N*-methylated, or with two *N*-methylated derivatives. The chemical shifts of the methyl protons in these two compounds (τ 6.21 and 6.50, respectively) clearly show that neither of the compounds is a methoxyl derivative (the methyl protons in 3-methoxy-1,2,4-triazine absorb at τ 4.85, for example). Thus, we are dealing with the *N*-methylated derivatives **8a** and **9a**.

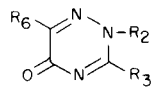
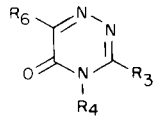
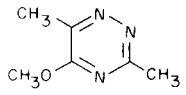
A comparison of the uv spectra (Table II) of these isomers with those of 1,2-dihydro-1-methyl-2-oxo-pyridine and 1,4-dihydro-1-methyl-4-oxo-pyridine allows one to conclude that the major *N*-methylated isomer is the N_2 methyl derivative **8a** and that the minor one is the N_4 methylated compound **9a**.

Similarly, alkylation of the "5-hydroxy-6-methyl-1,2,4-triazine" **7b** (or general structure (**1** (X = N), $R_3 = H$, $R_6 = CH_3$)) affords a mixture of the N_2-methyl and the N_4-methyl isomers in a ratio of 4:1. The latter compound is identical to an unequivocally prepared sample (5). Thus, the presence of a methyl group at C_6 decreases the amount of N_4-alkylated product with respect to the N_2-alkylated isomer.

Clearly, the presence of the "extra" nitrogen atom in the 1,2,4-triazine ring system has a drastic effect upon

TABLE II

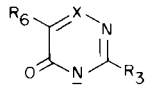
UV Spectral Data for Various 2,5-Dihydro-5-oxo-1,2,4-triazines

Structure		λ max, mμ (ε x 10^3)	λ min, mμ (ε x 10^3)	Solvent	Compound No.
	$R_2 = R_3 = R_6 = H$	280 (3.45) 228 (11.42)	248 (1.33)	EtOH	**7a**
	$R_3 = R_6 = H, R_2 = CH_3$	260 (4.67) sh 242 (11.40)		EtOH	**8a**
	$R_2 = R_3 = H, R_6 = CH_3$	273 (4.47) 230 (10.15)	250 (3.00	EtOH	**7b**
	$R_3 = H, R_2 = R_6 = CH_3$	265 (6.48) sh 244 (11.83)		EtOH	**8b**
	$R_2 = H, R_3 = R_6 = CH_3$ (a)	260 (4.53) sh 232 (8.90)		EtOH	
		240 (8.38) 260 (4.31) sh		$CHCl_3$	
	$R_2 = R_3 = R_6 = CH_3$	255 (7.29) sh 243 (10.00)		EtOH	**8c**
		248 (10.95) 260 (7.46) sh		$CHCl_3$	
	$R_3 = R_6 = H, R_4 = CH_3$	273 (3.71) 218 (5.67)	238 (1.60)	EtOH	**9a**
	$R_3 = H, R_4 = R_6 = CH_3$	272 (4.52) 218 (5.67)	238 (1.23)	EtOH	**9b**
	$R_3 = R_4 = R_6 = CH_3$	273 (5.19) 218 (5.19)	237 (1.04)	EtOH	**9c**
		275 (5.07)	240 (1.54)	$CHCl_3$	**9c**
		330 (0.34) 262 (4.73)	290 (1.71)	$CHCl_3$	**10**
		318 (0.34) 262 (5.16) 212 (6.71)	290 (1.72) 230 (1.20)	EtOH	

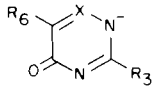
(a) Lit. (5) 237 (log ε 4.01) sh 260 (log ε 3.78).

the course of the alkylation when compared to 3,4-dihydro-4-oxo-pyrimidine. In the latter case, the nitrogen adjacent to the oxo function is exclusively alkylated, while in the former case alkylation at *both* the *ortho* and the *para* situated nitrogen atoms (with respect to the oxo group) occurs, with the *para* situated nitrogen being preferentially alkylated.

This difference in behavior can be accounted for by considering the relative stabilities of the two anions which must be involved in the base-catalyzed *N*-alkylation. The presence of the nitrogen atom at X in structures **12** and **13** would be expected to decrease the basicity of N_2 in relation to N_4, and consequently the N_2 methylated



12 (X = N)



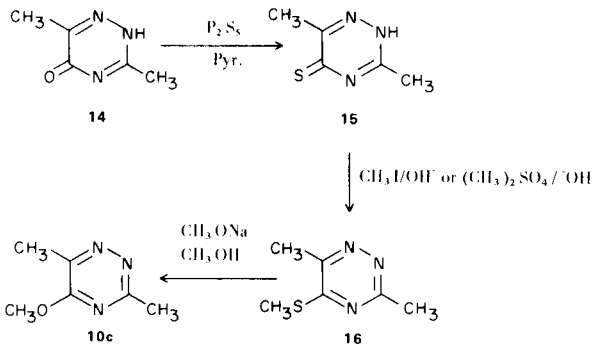
13 (X = N)

isomer should be preferred over the N_4-methylated one. On the other hand, in the pyrimidine case (**12** and **13**; X = CH) the relative anion stabilities would be controlled by the *o*-quinonoid: *p*-quinonoid stability ratio only. A ratio that certainly would be counteracted by N_1 in the 2,5-dihydro-5-oxo-1,2,4-triazine instances.

In order to examine the **1** ⇌ **2** ⇌ **3** (X = N) equilibrium it now remained to prepare a 5-methoxy-1,2,4-triazine as a reference compound for structure **1** (X = N).

The 5-methoxy-3,6-dimethyl-1,2,4-triazine (**10c**) was prepared by the following sequence:

Gut and coworkers (3) applied infrared spectroscopy to obtain the **2** ⇌ **3** (X = N) equilibrium constants. When we examined the uv and pmr spectra of a series of 5-oxo-1,2,4-triazines we found, to no great astonishment, that the spectra of these compounds are strongly solvent dependent (see Table II). This dependency reflects substantial intermolecular hydrogen bonding between the solute and

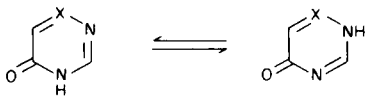


14 15 10c 16

solvent in ethanol and apparent solute-solute interactions in chloroform. Thus, this type of spectral technique is not applicable in these instances to any quantitative estimations of the **2** ⇌ **3** (X = N) equilibrium constants.

However, hydrogen bonding effects are not expected significantly to affect the chemical shifts of the ring protons in these compounds since they are significantly far removed from the bonding site. Thus, an examination of the pmr spectra of the various compounds offers a more reliable means of estimating the **2** ⇌ **3** (X = N) equilibrium constants. A comparison of the pmr spectra of the various 2,5-dihydro-5-oxo-1,2,4-triazines with those of the corresponding N_2 methylated isomers (see Table I), reveals that the chemical shifts of H_6, where present, or of the protons of the C_6-CH_3 group where no H_6 is present, are essentially the same. If the N_4-H tautomer (**2** (X = N)) were to make a significant contribution to the equilibrium **2** ⇌ **3** (X = N), the proton chemical shifts for H_6 or for the C_6-methyl group protons would be expected to lie at values intermediate between those of the N_2 and the N_4 methylated isomers. Since this is not the case, we conclude that the **1** ⇌ **2** ⇌ **3** (X = N) equilibrium is at least 95% in favor of the N_2-H tautomer **3** (X = N).

We must now ask why the equilibrium **2** ⇌ **3** (x = CH) with a ratio of 70:30 is so drastically altered (to, at least



2 (X = CH) 3 (X = CH)

5:95) when X = N, as compared to the X = CH case.

An explanation for this is readily found, when one considers that in tautomer **2** (X = N) there would be a considerable amount of electron-electron repulsion between the unshared electron pairs on N_1 and N_2. This repulsion is readily relieved by the formation of the N_2-H tautomer **3** (X = N), and accounts for the apparent "anomalous" behavior of these 2,5-dihydro-5-oxo-1,2,4-triazines which are more stable as *para*-quinoid than as *ortho*-quinonoid (2, X = N) structures.

This electron-electron repulsion between the N_1-N_2 unshared electron pairs in 1,2,4-triazines also accounts for the following observations:

TABLE III

Analytical Data for Various Dihydro-5-oxo-1,2,4-triazines

Compound	No.	M.P. °C	Yield (%)	Elemental Analyses					
				Calcd.			Found		
				N	C	H	N	C	H
$C_5H_7N_3OS$	**5b**	228	81	26.75	38.22	4.46	26.91	38.38	4.50
$C_4H_5N_3OS$	**5a**	213	49	29.37	33.57	3.50	29.62	33.78	3.61
$C_4H_7N_5O$	**6b**	239	79	49.65	34.04	4.96	49.52	34.14	5.11
$C_3H_5N_5O$	**6a**	247	47	55.12	28.35	3.94	55.38	28.47	4.19
$C_4H_5N_3O$	**7b**	212 (a)	31	37.84	43.24	4.50	37.99	43.35	4.45
$C_3H_3N_3O$	**7a**	196	64	43.30	37.11	3.09	43.25	37.21	3.15
$C_5H_7N_3O$	**8b**	146	18	33.60	48.50	5.60	33.57	48.23	5.65
$C_4H_5N_3O$	**8a**	125	~10	37.84	43.24	4.50	37.51	43.35	4.58
$C_5H_7N_3O$	**9b**	100.5 (b)	<5	33.60	48.50	5.60	33.65	48.50	5.51
$C_4H_5N_3O$	**9a**	118.5	<5	37.84	43.24	4.50	37.56	43.58	4.51
$C_6H_9N_3O$	**8c**	82	30.2	30.22	51.80	6.47	30.35	51.91	6.49
$C_6H_9N_3O$	**9c**	139	17.6	30.22	51.80	6.47	29.18	51.75	6.59
$C_5H_7N_3S$	**15**	228	63	29.79	42.55	4.96	29.83	42.54	5.09
$C_6H_9N_3O$	**10**	81.5	15	30.22	51.80	6.47	30.50	52.03	6.92

(a) Lit. (5) 211~212. (b) Lit. (5) 105~108.

(1) *N*-oxidation and *N*-alkylation occur at N_1; rather than the expected N_4 position.

(2) The 3-oxo isomers exist as 2,3-dihydro, rather than 3,4-dihydro structures as might be expected on the basis of nitrogen basicities.

(3) When forced into a structural situation that would demand the presence of this repulsion, the compound tautomerizes, if possible, to remove this repulsion (*cf.* the behavior of 4,5-dimethyl, 3,4-dihydro-3-oxo-1,2,4-triazines).

We are in the process of obtaining some quantitative measurements of these repulsion forces in 1,2,4-triazines and in pyridazines.

EXPERIMENTAL

3-Hydrazino-2,5-dihydro-5-oxo-1,2,4-triazine (**6a**).

Hydrazine (0.6 g. of a 95% solution) was added to a solution of 1.2 g. (8.4 mmoles) of 3-methylthio-5-hydroxy-1,2,4-triazine (**5a**) in a mixture of 10 ml. of absolute methanol and 10 ml. of tetrahydrofuran. The resulting solution was refluxed on a steam-bath for 8 hours and the reaction mixture was cooled to room temperature. The precipitated 3-hydrazino-2,5-dihydro-5-oxo-1,2,4-triazine (**6a**) (0.78 g., 47% of theory, m.p. 247) was collected.

2,5-Dihydro-5-oxo-1,2,4-triazine (**7a**).

Yellow mercuric oxide (10 g.) was added to 150 ml. of absolute ethanol in which 1.3 g. (10 mmoles) of finely powdered 3-hydrazino-2,5-dihydro-5-oxo-1,2,4-triazine had been suspended. The resulting vigorously stirred mixture was refluxed on a steam-bath for 24 hours. The hot filtrate was concentrated to dryness and the residue was recrystallized from absolute ethanol to afford light yellow crystals (0.62 g., 64% of theory, m.p. 196°) of the 2,5-dihydro-5-oxo-1,2,4-triazine (**7a**).

2-Methyl-2,4-dihydro-5-oxo-1,2,4-triazine (**8a**) and 4-Methyl-4,5-dihydro-5-oxo-1,2,4-triazine (**9a**).

To a methanolic solution (15 ml.) of 100 mg. (1 mmole) of 2,5-dihydro-5-oxo-1,2,4-triazine (**7a**) was added 1 ml. of methyl iodide and sufficient sodium methoxide to make the solution basic. The reaction mixture was then refluxed with stirring for 24 hours, evaporated to dryness and the residue was dissolved in 15 ml. of water. The water solution was then extracted with chloroform (3 x 15 ml.) and the dried, (anhydrous calcium carbonate) combined extracts were evaporated to dryness to yield a brown oil. This oil was subjected to preparative scale TLC (alumina, as developing solvent, ethylacetate:hexane:methanol = 2:2:1 by volume) to yield 10 mg. (10% of theory) of 2-methyl-2,5-dihydro-5-oxo-1,2,4-triazine (**8a**) (m.p. 125-125°) and 5 mg. of 4-methyl-4,5-dihydro-5-oxo-1,2,4-triazine (**9a**) (m.p. 118.5°).

3,6-Dimethyl-5-thio-1,2,4-triazine (**15**) and 3,6-Dimethyl-5-methylthio-1,2,4-triazine (**16**).

These compounds were prepared in the same manner as described for the synthesis of 6-methyl-5-thio-1,2,4-triazine (**3**) and 6-methyl-5-methylthio-1,2,4-triazine (**5b**) (3).

3,6-Dimethyl-5-methoxy-1,2,4-triazine (**10**).

To a solution of 3,6-dimethyl-5-methylthio-1,2,4-triazine (243 mg., 1.57 mmoles) in 20 ml. of absolute methanol was added 110 mg. (2 mmoles) of sodium methoxide. The reaction mixture was stirred at room temperature for 20 hours and evaporated to dryness. The residue was sublimed at 40° (0.05 mm. to yield 33 mg. (15% of theory) of 3,6-dimethyl-5-methoxy-1,2,4-triazine (**10**) (m.p. 81.5°).

REFERENCES

(1) W. W. Paudler and J. Lee, *J. Org. Chem.*, 36, 3921 (1971).

(2) W. W. Paudler and J. Lee, *J. Org. Chem. (D)*, 1636 (1971).

(3) W. E. Taft and R. G. Shepherd, *J. Med. Chem.*, 10, 883 (1967).

(4) R. Fusco and S. Rossi, *Tetrahedron*, 3, 209 (1958).

(5) V. Uchytilova, P. Fiedler, M. Prystas and J. Gut, *Collect. Czech. Chem. Commun.*, 36, 1955 (1971).

(6) F. H. S. Curd and D. N. Richardson, *J. Chem. Soc.*, 1853 (1955).

(7) S. F. Mason, *ibid.*, 674 (1958).

(8) A recent publication by J. Daunis, R. Jacquier and P. Viallefont (*Bull. Soc. Chim. France*, 3658 (1971)) mentions the tautomeric equilibrium **16** ⇌ **17** as favoring structure **17**.

16 **17**

(9) The nmr spectra were obtained with a Varian HA-100 spectrometer. Elemental analyses were done by Mrs. Victoria Gindlesperger of this department. Melting points were determined on a Thomas-Hoover Capillary Melting Point apparatus and are corrected. Uv spectra were obtained with a Cary 14 instrument.