2,5-Dihydro-3-azido-5-oxo-1,2,4-triazines and Related Compounds. Syntheses and Structure Elucidation

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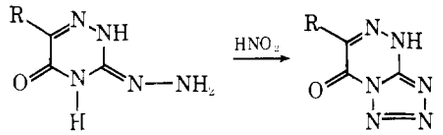
Several 3-azido-2,5-dihydro-5-oxo-1,2,4-triazines were prepared by treating the corresponding 3-hydrazino derivatives with nitrous acid. The azidotriazines spontaneously cyclized into a tetrazolo isomer. These transformations were studied using nuclear magnetic resonance and infrared spectroscopic methods. The tetrazolo isomers which could cyclize either into the N-2 or N-4 positions were proven to be tetrazolo[1,5-*b*]-2,5-dihydro-5-oxo-1,2,4-triazines by a ^{13}C NMR spectroscopic study.

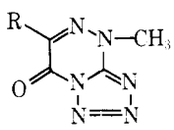
Dornow, Menzel, and Marx[1,2] have reported the oxidation of some 6-substituted 3-hydrazino-2,5-dihydro-1,2,4-triazines, which they considered as having structure **1**, with nitrous acid. Without an unequivocal structure proof, they assigned the tetrazolo[1,5-*c*]-1,2,4-triazine structure **2** (**a** and **b**) to these oxidation products.



1 **2a, b**

a, R = CH_3
b, R = C_6H_5

Treatment of one of the oxidation products (**2a**) with diazomethane afforded an *N*-methyl derivative which was stated to be isomeric with compound **3a**. The open-chain isomer **4a** was not considered as a possibility.



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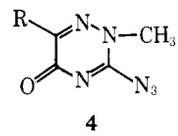
a, R = CH_3
b, R = H



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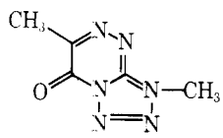
a, R = CH_3
b, R = H

These authors suggested that the diazomethane reaction product might conceivably have structure **5** or **6**.



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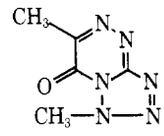

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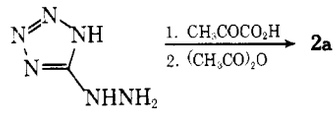
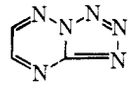
Further proof in support of structure **2a**, the initial cyclization product, was offered based upon the following interconversion:



In view of the fact that we have shown that 3-azido-1,2,4-triazines cyclize spontaneously to form tetrazolo[1,5-*b*]-1,2,4-triazines (**7**) rather than the isomeric compounds of type



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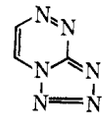

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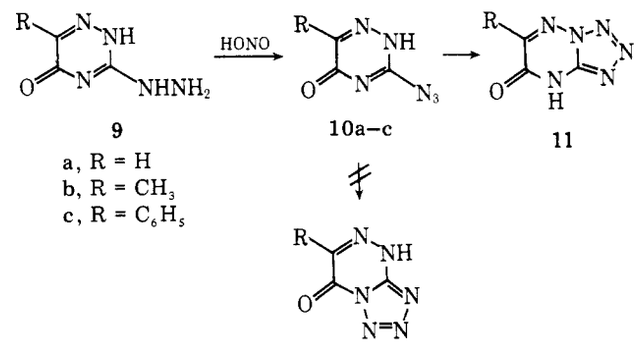
8,[3] we decided to reexamine the structures proposed by Dornow, Menzel, and Marx.

Our synthetic approach involved the nitrous acid oxidation of 3-hydrazino-2,5-dihydro-5-oxo-1,2,4-triazines (**9a–c**) (cf. Scheme I). The initial product of the oxidation, the azido

Scheme I



9

a, R = H
b, R = CH_3
c, R = C_6H_5

10a–c **11**

2

compounds **10a–c**, can, in principle, cyclize to form either compounds of general structure **2** or **11a–c**.

The infrared spectrum of the oxidation product of **9a** obtained either in the solid state or in chloroform solution showed the presence of absorption due to the azido group (2160–2120 cm^{-1}), as well as absorption due to the presence of a tetrazolo ring (1100–1000 cm^{-1}) (cf. Table I). The azido asorption is time dependent in solution and disappears within 2 h at room temperature. On the other hand, oxidation of the 6-methyl (**9b**) and the 6-phenyl (**9c**) derivatives affords only one product, devoid of any azido absorption in the solid state (the compounds are insoluble in chloroform). It now remains to establish whether cyclization of the azido compounds (**10a–c**) occurs to form the tetrazolo derivatives **2** or **11**.

We had selected to compare the ^1H NMR spectra of the triazolo derivatives **12a** and **13a**[4] (in dimethyl sulfoxide) with the ^1H NMR spectrum of the oxidation product of the hydrazino-1,2,4-triazine **9a**. Unfortunately, the chemical shift difference of the six-membered ring proton between **12a** and **13a** is insignificant and thus no comparisons could be made. Thus, we took recourse to an analysis of the ^{13}C NMR spectra of some of these compounds (cf. Table III).

In order to identify the absorptions due to C-3 and C-6 in compound **12a**, we obtained the ^{13}C spectrum of its 6-methyl derivative (**12b**). It is well known that replacement of a proton by a methyl group on a sp^2 carbon causes the latter to become more deshielded by approximately 9 ppm.[5] Consequently, the shift of the 145.0-ppm peak in compound **12a** to 154.0 ppm in its 6-methyl derivative (**12b**) identifies this peak as being due to C-6. The remaining resonance peaks are, as expected, not significantly affected in going from the "parent" com-

Table I. Infrared Absorption Spectra (cm^{-1}) of Some Substituted 1,2,4-Triazines

Compd	"Phase"	C=O	C=N	Azido bands	Tetrazolo bands
3a	Nujol	1720	1604, 1534		1090, 1068, 992, 978
	$CHCl_3$	1670		2170, 2180	
3b	Nujol	1728	1600, 1515		1090, 1068, 982, 968
	$CHCl_3$	1660		2170	
11a	Nujol	1702	1620, 1554	2170, 2180	1080, 1060, 970, 950
	$CHCl_3$	1702	1615, 1550		1085, 1060, 964, 948
11b	Nujol	1700	1630, 1570		1080, 1060, 960
11c	Nujol	1700	1638, 1570		1085, 1060, 970, 950
15a	Nujol	1700	1625, 1570		1090, 1040, 985, 965
15b	Nujol	1695	1620, 1570		1105, 1060, 978, 965
15c	Nujol	1700	1620, 1552		1100, 1060, 960
	$CHCl_3$	1700	1615, 1545		
10a	Nujol			2170, 2180	
	$CHCl_3$			2170, 2180	

Table II. ^1H NMR Spectra (δ ppm) of Some 1,2,4-Triazines

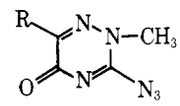
Compd	Solvent[a]	R_1	R_2	R_3	R_4	R_5	R_6	R_8
3a	Me_2SO-d_6				4.02		2.33	
3a	$CDCl_3$				4.15		2.51	
3b	$CDCl_3$				4.24		7.27	
3b	Me_2SO-d_6				4.09		9.01	
4a	$CDCl_3$		3.77				2.27	
4b	$CDCl_3$		3.70				7.58	
10c	Me_2SO-d_6						7.99	
11a	Me_2SO-d_6						8.22	
	Acetone-d_6						8.12	
11b	Me_2SO-d_6						2.36	
11c	Me_2SO-d_6						9.03–9.20 (m)	
							8.60–8.72	
12a	Me_2SO-d_6			9.10			7.89	
12b	Me_2SO-d_6			9.03			2.27	
13a	Me_2SO-d_6		8.40				7.87	
13b	Me_2SO-d_6		8.37				2.37	
14	$CDCl_3$	9.85			4.15		2.50	
15a	Me_2SO-d_6						2.37	3.52
15b	Me_2SO-d_6						9.03–9.20 (m)	3.63
							8.60–8.72	
15c	Acetone-d_6						8.18	4.63
	$CDCl_3$						8.48	4.28

[a] Dilute solutions in indicated solvents. A Varian HA-100 NMR spectrometer was used to obtain these spectra.

pound **12a** to its 6-methyl derivative (**12b**).[2] Since the bridgehead carbon is expected to have the longest relaxation time (lowest intensity peak) and remains a singlet in the coupled ^{13}C spectrum it is readily identified as having a chemical shift of 144 ppm. The oxygen bearing carbon will be the most deshielded one in the ring system (155.8 ppm) and is identifiable on that basis. Similar reasoning can be used to assign the ^{13}C peaks in compounds **13a** and **13b**.[4] These arguments can now be employed to unequivocally differentiate between structures **2** and **11**. Clearly, the ^{13}C resonances [^{13}C δ (ppm) 144, 145, 152] of the tetrazolotriazine are consistent with the N-2 cyclized structure **11** when compared to its "deaza" N-2 cyclized analogue **12a** [^{13}C δ (ppm) 145, 144, 156] rather than with the N-4 cyclized compound **13a** [^{13}C δ (ppm) 131, 148, 151].

Thus, as is the case in the 3-azido-1,2,4-triazines, cyclization occurs onto N-2 in these compounds as well. The one unique feature of this ring system as compared to the nonoxo form **7** lies in the observation that the initial azido form of these compounds has finite stability (2 h) even in dimethyl sulfoxide (cf. Table II).

The propensity toward cyclization of the 3-azido-1,2,4-triazines into N-2 rather than N-4 prompted us to examine the derivative **4a,b**, where cyclization into N-2 is impossible:



4

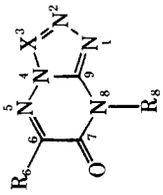
a, R = CH_3
b, R = H

These compounds were prepared from the known 2-methyl-3-methylthio-2,5-dihydro-5-oxo-1,2,4-triazines by converting them successively to the 3-hydrazino derivatives and oxidation of the latter to compounds **3a,b** or **4a,b**. The infrared spectrum of the oxidation products obtained in the solid state did not show any absorption in the azido group region. Thus, the compounds exist, in the solid state at least, as the tetrazolo derivative **3a,b**.

However, the ^1H NMR spectrum of a solution of compound **3a** in deuteriochloroform shows the presence of two species in the ratio of 2:1. In order to establish which set of peaks (δ 2.27, 3.77 or 2.51, 4.15) corresponds to the open (**4a**) and which to the closed (**3a**) form, recourse was taken to a spectral comparison with compound **14**.

Clearly, the lower intensity set of peaks (δ 4.15, 2.51) correspond to the N-4 cyclized isomer **3a**, while the high-intensity peaks (δ 2.27 and 3.77) correspond to the open-chain form **4a**. In fact, a comparison of the ^{13}C chemical shifts of **3b** with

Table III. ^{13}C NMR Spectra (Chemical Shifts in δ, ppm)[a]

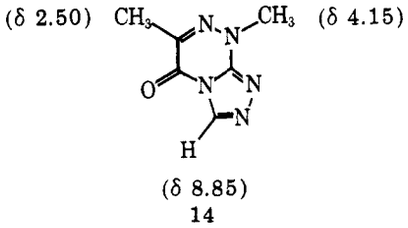


X = CH, N

X = CH, N

Compd	Solvent	C_2	C_3	C_4	C_5	C_6	C_7	C_8	C_9	R_2	R_5	R_6	R_7	R_8
3a	$CDCl_3$			147.0			141	154.5			42.0		16.5	
3b	Me_2SO-d_6			145.5			131.0	149.0			41.5			
4a	$CDCl_3$		150.5			151.0						17.0		
					161.5					41.0				
11a	Me_2SO-d_6					145.0	152.0		144.0					
11b	Me_2SO-d_6					154.0	152.0		144.0			18.0		
12a	Me_2SO-d_6		134.0			144.0	155.8		145.0					
12b	Me_2SO-d_6		135.0			154.0	155.0		144.5			18.0		
13a	Me_2SO-d_6	149.0		148.0			131.0	151.0					17.5	
13b	Me_2SO-d_6	148.5		148.0			139.0	152.0						30
15c	Me_2SO-d_6					152	151		145			18		

[a] ^{13}C spectra were taken with a Hitachi Perkin-Elmer R-26 spectrometer, δ (ppm) from Me_4Si. The spectra of the amino compounds were obtained as 1.5 M solutions in Me_2SO-d_6; all of the others were obtained as 1.5 M solutions in $CDCl_3$. The pulse intervals were 16 s, and a pulse angle of 50° with a total of about 500 scans per spectrum. All spectra were wide-band proton decoupled.



(δ 2.50) (δ 4.15) (δ 8.85)

14

those of compound **13a** conclusively prove the mode of cyclization (cf. Table III). These data also unequivocally establish that in the absence of an *N*-methyl group on N-2, cyclization does indeed take place at that position. This equilibrium in $CDCl_3$ is shifted slightly in greater favor of the azido form, when a hydrogen is present at C-6, when the ratio becomes 2.1:1. Interestingly, the ^1H NMR spectra of these compounds in dimethyl sulfoxide show the presence of *only* the closed species.

Conclusions

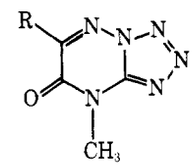
This study has established the following facts:

1. 3-Azido-5-oxo-2,5-dihydro-1,2,4-triazines in dimethyl sulfoxide or deuteriochloroform exist as the N-2 cyclized isomers (**11**).

2. The presence of a 5-oxo group in the 1,2,4-triazines does not alter the direction of cyclization.

3. The structure assigned to these oxidation products (**2a,b**) by others is incorrect.

4. The N-methylation product assigned either structure **5** or **6** is, in fact, the N-4 methylated compound (**15a**).



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a, R = CH_3
b, R = C_6H_5
c, R = H

5. When N-2 in 3-azido-5-oxo-2,5-dihydro-1,2,4-triazines is N-methylated, an equilibrium exists between the azido (**4**) and the N-4 cyclized tetrazolo isomers (**3**).

Experimental Section[6]

7,8-Dihydro-7-oxotetrazolo[1,5-*b*]-1,2,4-triazine (**11**). To a 25-mL Erlenmeyer flask was added 2,5-dihydro-5-oxo-3-hydrazino-1,2,4-triazine (254 mg, 2 mmol) and 5 N HCl (6 mL). The solution was cooled to 0–5 °C and aqueous $NaNO_2$ (140 mg in 1 mL of H_2O) was added dropwise. The solution was stirred for an additional 1 h while maintaining the temperature at 0–5 °C. The crude tetrazole was separated by extraction with $CHCl_3$. The dried (Na_2SO_4) $CHCl_3$ extracts were evaporated to dryness and the residue recrystallized from absolute methanol to afford 7,8-dihydro-7-oxotetrazolo[1,5-*b*]-1,2,4-triazine (**11a**) (114 mg, 39%, mp 170–172 °C, mass spectrum mol wt 138).

7,8-Dihydro-8-methyl-7-oxotetrazolo[1,5-*b*]-1,2,4-triazines (15) (General Procedure). A solution of the appropriate 7,8-dihydro-7-oxotetrazolo[1,5-*b*]-1,2,4-triazine (3 mmol), dimethyl sulfoxide (5 mL), anhydrous K_2CO_3 (0.5 g), and CH_3I (0.57 g, 4 mmol) was stirred at room temperature for 24 h. The Me_2SO was removed by distillation (90 °C, 0.3 mm) to afford a dark brown residue. The residue was washed with water, filtered, and recrystallized from absolute ethanol (**15a**, mp 210–212 °C, 36%; **b**, 199–200 °C, 73%, **c**, 153–155 °C, 31%).

4,7-Dihydro-4-methyl-7-oxotetrazolo[5,1-*c*]-1,2,4-triazine (3b). A solution of 2,5-dihydro-2-methyl-3-hydrazino-5-oxo-1,2,4-triazine (423 mg, 3 mmol) and 5 N HCl (9 mL) was cooled to 0–5 °C and aqueous $NaNO_2$ (207 mg) in 2 mL of H_2O was added dropwise. The solution was stirred for an additional 30 min while maintaining the temperature at 0–5 °C. The solution was extracted with $CHCl_3$. The dried (Na_2SO_4) $CHCl_3$ extracts were evaporated to dryness and the residue was sublimed (110 °C, 0.5 mm) to afford 4,7-dihydro-4-methyl-7-oxotetrazolo[5,1-*c*]-1,2,4-triazine (0.29 g, 64%, mp 150–151 °C, mass spectrum mol wt 152).

Registry No.—**3a,** 61788-10-1; **3b,** 61788-11-2; **4a,** 61788-12-3; **4b,** 61788-13-4; **9a,** 21383-22-2; **9b,** 38736-23-1; **9c,** 61788-14-5; **10a,** 61788-15-6; **10c,** 61788-16-7; **11a,** 61788-17-8; **11b,** 61788-18-9; **11c,** 61788-19-0; **12a,** 874-40-8; **12b,** 19542-10-0; **13a,** 57351-74-3; **13b,** 57250-39-2; **14,** 25623-69-2; **15a,** 61788-20-3; **15b,** 61788-21-4; **15c,** 61788-22-5; 2,5-dihydro-2-methyl-3-hydrazino-5-oxo-1,2,4-triazine, 39214-97-6.

References and Notes

(1) A. Dornow, H. Menzel, and P. Marx, *Chem. Ber.*, **97,** 2185 (1964).
(2) A. Dornow, H. Menzel, and P. Marx, *Chem. Ber.*, **97,** 2647 (1964).
(3) M. M. Goodman, J. L. Atwood, R. Carlin, W. Hunter, and W. W. Paudler, *J. Org. Chem.*, **41,** 2860 (1976).
(4) J. Daunis, R. Jacquir, and F. Viallefont, *Bull. Soc. Chim. Fr.*, 2492 (1969).
(5) G. C. Levy and G. L. Nelson, "Carbon-13 Nuclear Magnetic Resonance for Organic Chemists", Wiley-Interscience, New York, N.Y., 1972.
(6) Mass spectra were recorded with a Hitachi Perkin-Elmer RMU-6M instrument on all new compounds. Their molecular ions and fragmentation patterns are consistent with the indicated structures. A Varian HA-100 instrument was used to record the ^{1}H NMR spectra. Melting points are corrected. Elemental analyses on all new compounds were performed by Atlantic Microlab. Inc., Atlanta, Ga., and the Analytical Services Laboratory, Department of Chemistry, The University of Alabama, and are within the accepted standards for C, H, and N analyses.

Selective N-Oxidations of Chlorinated Pyrazines and Quinoxalines

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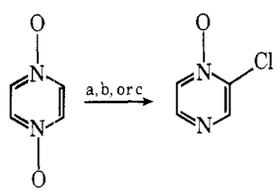
Chlorinated pyrazines and quinoxalines are specifically oxidized on the nitrogen adjacent to the halogen-bearing carbon by means of Caro's acid (peroxysulfuric acid) in concentrated sulfuric acid. This procedure affords the first simple, direct, and high-yield synthesis of 2-chloropyrazine 1-oxides. The use of lanthanide induced shift (LIS) reagents to unambiguously identify isomers was complicated by the presence of two nonequivalent coordination sites. The role of the strong-acid reaction medium in determining the steric course of oxidation is discussed.

Aromatic diazines in which the basicity of the ring nitrogens is severely reduced by electron-withdrawing substituents such as halogens are often resistant to N-oxidation by the usual peroxycarboxylic acid reagents.[2-4] The peracetic acid oxidations of chloropyrazines and chloroquinoxalines occur in such a manner that the most basic and least hindered nitrogen atom is oxidized exclusively.[2-5] In other words, N-oxidation of a pyrazine bearing a halogen substituent takes place on the nitrogen farthest removed from that substituent, e.g., 2-chloropyrazine → 2-chloropyrazine 4-oxide. Several 2-chloro 1-oxide isomers of pyrazine and quinoxaline have been prepared, but generally in low yield and indirectly from the bis *N*-oxide (eq 1).[6-11] Furthermore, dihalogenated py-



(1)

a, $POCl_3$
b, aq HCl, $h\nu$
c, $C_6H_5SO_2Cl$ or $SOCl_2$

razines are notoriously difficult to oxidize; 2,6-dichloropyrazine 4-oxide is obtained in only 4% yield by direct oxidation.[12]

Quite recently, several new oxidizing systems (peroxydichloromaleic acid,[13] CF_3CO_2H–H_2SO_4–90% H_2O_2,[14] and H_2SO_4–60% H_2O_2[15]) have been found to effect the oxidation of polyhalogenated diazines. The success of these novel reagents prompted us to extend the application of one of them to mono- and dichlorinated pyrazines and quinoxalines.

In terms of simplicity, cost, and availability of reagents, the oxidation procedure of Kyriacou appeared to be the method of choice for large-scale applications.[15] The handling of 60–90% hydrogen peroxide, however, presented serious safety implications. The conditions employed in such strong-acid oxidations, viz., sulfuric acid and hydrogen peroxide, suggest that the actual oxidizing agent is Caro's acid (peroxysulfuric acid). This being the case, this same intermediate could be generated from potassium persulfate and sulfuric acid, thus avoiding the use of potentially hazardous concentrated peroxide. Duplication of the previously reported oxidations of tetrachloropyrazine, substituting persulfate for peroxide, verified this hypothesis.

With a modified procedure which consisted of dissolving the halogenated diazine in sulfuric acid and of slowly adding potassium persulfate at 10 °C, a series of chlorinated pyrazines and quinoxalines were successfully converted to their *N*-oxides in high yield (see Experimental Section). Somewhat unexpectedly, however, the monochloropyrazines afforded the 2-chloro 1-oxide isomers in high purity. To verify the structural assignments of these derivatives, the 2-chloro 4-oxide isomers were prepared by known routes for comparison of physical and spectral properties. With the exception of the *N*-oxide isomers of 2,6-dichloropyrazine, all isomers could be distinguished by well-separated melting points. 2,6-Dichloropyrazine 1-oxide (mp 122–123.5 °C) and 2,6-dichloropyrazine 4-oxide (mp 119–121 °C) gave a typical mixture melting point depression (mp 85–90 °C).

The IR and NMR spectra of each pair of isomers are substantially different. All of the *N*-oxides display an N–O stretching frequency in the region of 1350–1260 cm^{-1}, but isomer identification by this method (1-oxides exhibit a deviation to lower frequencies than the corresponding 4-oxides)[8,9] was deemed tenuous because more than one substituent was present in most cases. The NMR spectra, however, are more informative (see Table I). Based on an examination of these data and on the shielding effects of the *N*-oxide function,[9] the following corollary can be formulated: *a given ring proton will generally resonate at higher field in 2-chloropyrazine 4-oxides than in the corresponding 1-oxide isomers.* While this criterion is useful in distinguishing between a pair of isomers, its utility is limited in that both isomers should be available for direct comparison.

In an attempt to develop a method to unambiguously identify a single isomer, the effects of lanthanide induced