SYNTHESIS OF THE FIRST MONOSUBSTITUTED 1,2,4-TRIAZINE DI-N-OXIDE. ^{13}C NMR OF 1,2,4-TRIAZINE N-OXIDES AND USE OF HYDROGEN/DEUTERIUM ISOTOPE SHIFTS FOR THE ASSIGNMENTS OF SOME DIHYDRO-1,2,4-TRIAZINE TAUTOMERS

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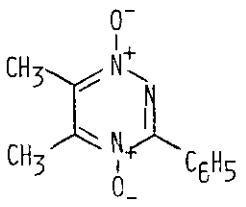
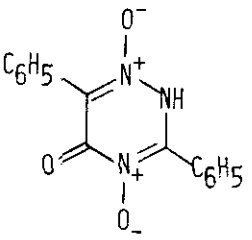
Abstract - 3-Amino-1,2,4-triazine 2,4-dioxide (4) was prepared by oxidation of 3-amino-1,2,4-triazine 2-oxide (3) with hydrogen peroxide in polyphosphoric acid, the first 1,2,4-triazine 2,4-dioxide ever reported. Same starting material gave ring contracted products as well as ring C-oxidation under a variety of reaction conditions employed in the attempted synthesis of the title compound (4). ^{13}C nmr proved to be a method of choice for structural assignments of isomeric N-oxides. H/D isotope shifts unequivocally established the structures of compounds which could conceivably exist as several tautomers.

In general, 1,3-diazines and polyazines are very susceptible to ring oxidation, degradation, ring contraction, nucleophilic ring opening, and many other rearrangements.[1-4] The high reactivity of these systems under very mild reaction conditions imposes severe limitations on their synthesis.

When key positions are blocked, such as $C_4(C_6)$ in pyrimidines (C_5 in 1,2,4-triazines), one can oxidize ring nitrogen atom(s) with moderate success. For instance, 3-phenyl-5,6-dimethyl-1,2,4-triazine 4-oxide (1a) was oxidized with peracetic acid to the 3-phenyl-5,6-dimethyl-1,2,4-triazine 1,4-dioxide (1b).[5] However, 3,6-diphenyl-1,2,4-triazine 4-oxide (2a), under same reaction conditions, is first oxidized to 3,6-diphenyl-1,2,4-triazin-5-one 4-oxide (2b), which is then further oxidized to 3,6-diphenyl-1,2,4-triazin-5-one 1,4-dioxide (2c).[5] To our knowledge, compounds 1b and 2c are the only other 1,2,4-triazine di-N-oxides reported to date.



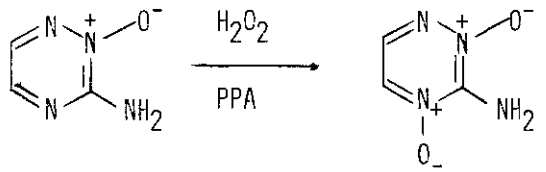
1B



2c

When 3-amino-1,2,4-triazine 2-oxide (3) was treated with concentrated hydrogen peroxide (90%) in polyphosphoric acid, it afforded 3-amino-1,2,4-triazine 2,4-dioxide (4). This was quite unexpected since Stanovnik and Tisler obtained only 3-nitropyridazines under similar reaction conditions.[6] Possible explanation for this could be that the exocyclic nitrogen atom of the amino group in 3 is much less basic than the equivalent nitrogen in aminopyridazines. This, in turn, could be attributed to the greater π-deficiency of 1,2,4-triazine ring (smaller $^{\pi}\Delta$ value) relative to pyridazine.[7-9] In such a case 1,2,4-triazine acts as a powerful -I group to an extent that the ring oxidation is preferred.

The preparative method used is described in literature.[6] It is absolutely essential that the suspension of 3 in polyphosphoric acid is cooled before the addition of hydrogen peroxide (See experimental). The peroxide was added dropwise over a period of 4h and temperature maintained at 24°C by external cooling (water bath). The reaction mixture was left standing at room temperature for 48h and worked up to yield a bright yellow solid. The elemental analysis, mass spectrum, ^{1}H and ^{13}C nmr established the structure of 4 to be that of 3-amino-1,2,4-triazine 2,4-dioxide (see also the NMR section).

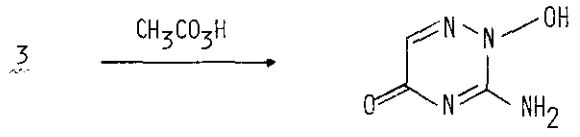


3 4

The reason why the five position in 3 is <u>not</u> oxidized is not yet clear. We have observed earlier that low-temperature, "solid-state" chemical reactions with strong oxidizing reagents could be carried out without decomposing the 1,2,4-triazine ring.[10] Polyphosphoric acid /H_2O_2 medium may have similar advantages.

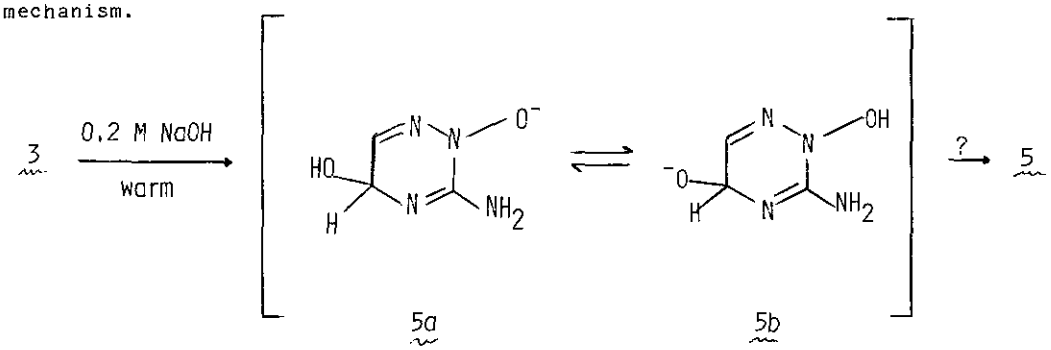
It prevents covalent hydration by absorbing any water formed during the reaction, yet it is strong enough oxidant to allow the oxidation of sites of relatively low basicity such as ring nitrogen atoms.

Oxidation of 3 with perocetic acid or trifluoroperacetic acid at 60°C for 1h produced a white solid (mp>300°C). Elemental analysis and ^{1}H mmr {d_6-DMSO: δ 5.10 ppm (broad, 1H) and δ 7.05 ppm ($2H_s$) exchange in D_2O; δ 8.08 ppm (1H)] prompted us to assign the structure of this product as that of 2-N-hydroxy-3-amino-2,5-dihydro-1,2,4-triazin-5-one (5). Interestingly enough, the same



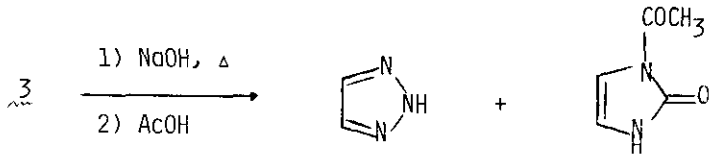
5

product was obtained by careful hydrolysis of 3 with 0.2M warm sodium hydroxide. Compound 3 was heated gently in the presence of NaOH for 15 min, cooled and neutralized with glacial acetic acid according to the procedure used for hydrolysis of 3-amino-1,2,4-triazine (6).[11] Refrigeration of the neutralized reaction mixture precipitated a reddish-brown solid which was filtered and recrystallized from water to yield white crystals with physical properties identical to those of compound 5. The addition across the C_5-N_4 bond compared to the nucleophilic substitution at C_3 may be explained in terms of intermediates 5a and 5b where the oxygen at N_2 is able to better stabilize the negative charge relative to the charge carried by $N_2(N_4)$ during the hydrolysis of 6. Nevertheless, the addition of hydroxide ion to C_5 of 3 and subsequent reduction to 5 without the loss of N_2-oxide oxygen atom (as OH or H_2O) suggests a more complex mechanism.



5a 5b

In contrast to the above, when 3 was dissolved in water and treated with excess sodium hydroxide, vigorous exothermic reaction ensued with liberation of ammonia. Dark, wine-red reaction mixture was acidified as before to yield 1,2,3-triazole (7) as the major product and trace amounts of 1-acetyl-2,3-dihydro-2-imidazolone (8).

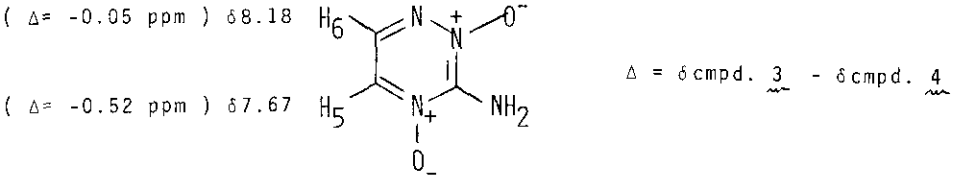


3 → major 7 + minor 8

Both products were expected since ring degradation and ring contraction of the 5-phenyl analogue of 3 were reported.[12,13]

NMR DATA

Proton nmr spectrum of 4 showed two doublets at δ 7.67 and 8.18 ppm assigned to H_5 and H_6, respectively. The doublet at a higher field (H_5) is shielded by 0.52 ppm as compared to compound 3, whereas H_6 remains virtually unchanged. This is exactly what we would expect if N-oxidation occurred at the four position.[14]



However, as pointed out by a referee, we cannot exclude the possibility of 1,2-dioxide formation, since oxidation of N_1 of 3 would cause similar upfield shift in the nmr spectrum (i.e. δ 8.19 → 8.18, Δ = -0.01 ppm; δ 8.23 → 7.67, Δ = -0.56 ppm). Therefore, we sought other means to obtain more decisive data for unambiguous structural assignment of the 2,4-dioxide (4).

One such method is to examine the ^{13}C spectrum of 4 since ^{13}C chemical shift changes caused by N-oxidation would be more pronounced and more evident. ^{13}C chemical shifts of few 1,2,4-triazine N-oxides have been reported.[14,15] Table I lists the ^{13}C chemical shifts of some model 1,2,4-triazines, 3-aminoderivatives, their methyl analogues and their N-oxides. Of the three carbon resonances observed in the proton-decoupled ^{13}C spectrum of 1,2,4-triazine 1-oxide (9), the

one at the lowest field at 158.5 ppm was assigned to C_3 carbon by virtue of it being adjacent to two ring nitrogen atoms and slight broadening of the signal due to additional quadrupolar relaxation by ^{14}N nuclei. The other two resonances at 152.7 and 129.7 ppm were assigned to C_5 and C_6, respectively, based on the anticipated large shielding effect of C_6 ($\Delta \approx -21.1$ ppm) by the N-oxide group[14] relative to the parent 1,2,4-triazine (10).[16] Analysis of the ^{13}C spectra and chemical shifts of 5-methyl (11) and 5,6-dimethyl-1,2,4-triazine 1-oxide (12) confirms these assignments. It is well known that methyl group substituent chemical shift changes (SCS effects) are very small and that only the methyl substituted carbon is significantly affected (8-10 ppm).[17-19] Therefore, the chemical shift of C_3 carbon in 9 should not change significantly from those of 11 and 12. Indeed, we find this to be the case (Table I). Similarly, C_6 signal of the parent N_1-oxide (9) is the only other signal which has the chemical shift almost identical to C_6 carbon of 5-methyl derivative (11). Thus, all our original assignments of compound 9 are correct.

The literature ^{13}C chemical shifts[14] reported for N_2-oxide (13) seem to be incorrect since ^{13}C chemical shift changes ($\Delta^{13}C$) do not match the predicted values. However, if the assignments of C_3 and C_5 are reversed, the $\Delta^{13}C$ of -14.5, -17.1 and -7.8 ppm for C_3, C_5 and C_6, resepctively, fall well within the predicted ranges. The authors must have inadvertedly made an error since C_5 and C_6 resonances overlapped. ($\Delta^{13}C$ for C_3, C_5 and C_6 would be -28.1, -6.6 and -7.8 ppm which are undoubtedly incorrect).

Table I. ^{13}C NMR Chemical Shifts of Some 1,2,4-Triazines, 3-Amino-1,2,4-triazines and Their N-Oxides.

Cmpd. No.	Position Of N-Oxide	Substituent(s) R_3	R_5	R_6	^{13}C Chemical Shifts (δ ppm)[a,b] R_3	R_5	R6	Other
10	None[c]	H	H	H	158.1	149.6	150.8	-
9	N_1-oxide	H	H	H	158.5	152.7	129.7	-
11	N_1-oxide	H	CH_3	H	158.7	166.1	129.1	21.3
12	N_1-oxide	H	CH_3	CH_3	155.9[d]	164.0	139.6	22.0, 5-Me; 13.0, 6-Me
13	N_2-oxide	H	H	H	143.5	132.5	146.0	-
					132[e]	143[e]	143	-
14	None	NH_2[f]	H	H	163.3	149.8	140.6	-
					161[g]	148	139	-

Table I. (Cont.)

Cmpd. No.	Position Of N-Oxide	Substituent(s) R_3	R_5	R_6	^{13}C Chemical Shifts (δ ppm)[a,b] R_3	R_5	R6	Other
15	None	NH_2[f]	CH_3	H	162.7	159.6	140.8	20.9
					161[g]	157	139	20
16	None	NH_2[f]	H	CH_3	162.0	147.8	150.2	17.8
17	None	NH_2[f]	CH_3	CH_3	162.1	158.9	147.1	21.1, 5-Me; 18.0, 6-Me
18	None	NH_2[f]	C_6H_5	H	163.0	154.8	137.2	133.9 (C_1'), 127.2 (C_2', C_6'), 129.0 (C_3', C_5'), 131.7 (C_4')
19	None	NH_2[f]	H	C_6H_5	162.2	147.8	147.7	134.4 (C_1'), 124.9 (C_2', C_6'), 128.8 (C_3', C_5'), 130.7 (C_4')
20	None	NH_2[f]	C_6H_5	C_6H_5	161.7	156.1	148.6	136.5 (C_1''), 136.2 (C_1'), 129.8, 129.1, 128.9 and 128.1 (phenyl).
21	N_1-oxide	NH_2[f]	H	H	165.0	155.9	120.7	-
					162[g]	153	119	-
22	N_1-oxide	NH_2[f]	CH_3	H	166.0	164.3	119.4	20.8
23	N_1-oxide	NH_2[f,t]	CH_3	CH_3	164.3	162.1	127.6	21.7, 5-Me; 11.9, 6-Me
24	N_2-oxide	NH_2[f]	H	H	151.6	132.4	134.9	-
					151[g]	132	134	-
25	N_2-oxide	NH_2[f]	CH_3	CH_3	148.9	140.2	144.2	17.7, 5-Me; 20.0, 6-Me
26	N_2-oxide	NH_2[f]	C_6H_5	H	150.3	141.2	133.6	130.2 (C_1'), 128.9 and 126.2 (phenyl).
27	N_2-oxide[h]	NH_2[f]	C_6H_5	C_6H_5	149.4	140.9	142.4	134.8 (C_1'), 135.9 (C_1''), 128.2 and 129.2 (phenyl).
28	N_4-oxide	NH_2	CH_3	CH_3	154.4	143.0	148.7	12.6, 5-Me; 19.2, 6-Me.

a. All spectra were recorded as 1.2 - 1.5 M solutions in $CDCl_3$ unless indicated otherwise. b. δ (ppm) downfield from TMS and using the solvent as double reference standard; $CDCl_3$ = 77.0 ppm. c. Date taken from ref. 16. d. The upfield shift of 2.6 ppm is ascribed to steric effects. e. The two assignments in ref. 14 should be reversed. f. Spectra were obtained in hexadeuterio-dimethylsulfoxide; d_6-DMSO = 39.5 ppm. g. Data taken from ref. 14. h. Data reported in ref. 20.

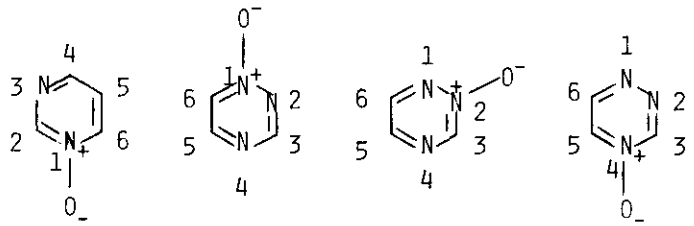
3-Amino-2,3,4-triazines and the corresponding N_1- and N_2-oxides also give ^{13}C spectra which are easily interpreted. Here too, in order to avoid any ambiguities of our assignments, we prepared some aminomethyl and phenyl derivatives which are also included in Table I. The ^{13}C signals can quickly by classified into two groups, substituted and proton-bearing carbons, by comparing proton-coupled and proton-decoupled ^{13}C spectra. Furthermore, amino-substituted carbon sites are easily discernible since amino groups cause an increase in signal broadening (3-5 Hz) and ^{13}C relaxation times. (In some instances interpulse delays had to be increased from one to four seconds in order for C_3 carbon to be observed). Thus, by comparing the ^{13}C carbon spectra of C-methylated derivatives we could easily make the assignments in the same manner as discussed for the N_1-oxide. The 3-amino group causes the upfielded shift of C_6 and it deshields the substituted ipso carbon (C_3). This is in accordance with the established chemical shift changes for the benzene series and other heterocycles.[17-19] The assignments of 3-aminophenyl derivatives have already been determined by us and are reported elsewhere.[20]

^{13}C chemical shifts of same alkyl and aryl N_4-oxides were reported[21] and show a considerable shielding of C_3(-10.4 ppm) and C_5(-15.8 ppm) and slight deshielding of C_6(+3.0 ppm). This parallels the observations made for N_1- and N_2-oxides. That is to say, the shielding of a carbon atom between the two ring nitrogens is less than the shielding observed for ortho/para carbons adjacent to only one azine nitrogen and that positions meta to N-oxide are deshielded by 2-3 ppm (Scheme I). The only exception to this is C_6 carbon in N_2-oxide (13) which is shielded by about 5 ppm. This may be attributed to "through" nitrogen shielding also operative for proton chemical shifts (i.e. H_3 in pyridazine N-oxide and H_6 in 1,2,4-triazine 2-oxide).[14]

Similar effects are operative in the N-oxides of 3-amino-1,2,4-triazine. This suggests that substituent effects are additive. Table II contains the calculated and experimentally observed ^{13}C chemical shifts of several methyl, phenyl, amino-1,2,4-triazines and 1,2,4-triazine N-oxides. The predicted values are in good agreement (1-2 ppm) with the observed shifts. The SCS used for methyl groups are those reported by Braun and Frey[16], and for the 3-amino group they are: +5.2 ppm for ipso carbon (C_3); +0.2 ppm for meta carbon (C_5); -10.2 ppm for para carbon (C_6). $\Delta^{13}C$ values reported in Table II are probably even smaller if one takes into account solvent shifts, concentration effects and variance of

other experimental conditions described in literature. $\Delta^{13}C$ for C_3 of compounds with adjacent amino and N-oxide groups are probably also subjected to strong hydrogen bonding (i.e. compound 14) and C_3 of 3-amino-5,6-dimethyl-1,2,4-triazine 4-oxide (28) is probably influenced by intramolecular H-bonding as well as by steric effects. For the same reason, chemical shifts of 5,6-diphenyl derivatives 20 and 27 were not calculated.

Scheme I. Comparison of $\Delta^{13}C$ chemical shift changes[a] for the various ring positions of some 1,2,4-triazine N-oxides with pyrimidine N-oxide.



Position				
ortho (1,3-diaza)	-12 (C_2)	-	-14.5(C_3)	-10.4 (C_3)
ortho	-15 (C_6)	-21.1 (C_6)	-	-15.8 (C_5)
para	-14 (C_4)	-	-17.1 (C_5)	-
meta	+ 2 (C_5)	+ 3.1 (C_5)	-	+ 3.0 (C_6)
meta (through N)	-	+ 0.4 (C_3)	- 4.8 (C_6)[b]	-

a. $\Delta^{13}C(ppm) = \delta^{13}C$ parent N-oxide - $\delta^{13}C$ parent heterocycle

b. This value is -7.8 in ref. 14.

Table III gives the summation of predicted ^{13}C chemical shifts of three isomeric 1,2,4-triazine di-N-oxides (29-31) and the three possible 3-amino-1,2,4-triazine dioxides (4,32,33). From this data it is evident that compound 4 has to be the 2,4-dioxide. Differences between observed and predicted values are given in parentheses.

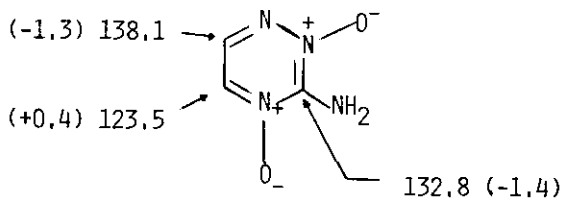


Table II. Calculated and Experimentally Observed ^{13}C Chemical Shifts for Some Selected 1,2,4-Triazines and Their N-Oxides (ppm).

Cmpd. No.	Molecular Formula	Chemical Shifts[a] C_3	C_5	C_6	Other	$\Delta^{13}C$ (ppm)[b] C_3	C_5	C_6	Other
11	$C_4H_5N_3O$	157.4 (158.7)	163.6 (166.1)	129.8 (129.1)	22.2 (21.3)	-1.3	+2.5	+0.7	+0.9
12	$C_5H_7N_3O$	155.9 (155.9)	162.6 (164.0)	137.6 (139.6)	22.0(5-Me) (22.0)	0	-1.4	-2.0	0
					13.0(6-Me) (13.0)				0
15	$C_4H_6N_4$	162.2 (162.7)	160.7 (159.6)	140.7 (140.8)	-	-0.5	-1.1	-0.1	-
16	$C_4H_6N_4$	161.0 (162.0)	149.8 (147.8)	149.1 (150.2)	-	-1.0	+2.0	-1.1	-
17	$C_5H_8N_4$	159.9 (162.1)	160.7 (158.9)	149.2 (147.1)	-	-2.2	+1.8	+2.1	-
18	$C_9H_8N_4$	162.7 (163.0)	155.7 (154.8)	136.6 (137.2)		-0.3	+0.9	-0.6	
19	$C_9H_8N_4$	161.3 (161.2)	146.8 (147.8)	147.6 (147.2)		-0.1	-1.0	+0.4	
21	$C_3H_4N_4O$	163.7 (165.0)	153.9 (155.9)	119.5 (120.7)		-1.3	-2.0	+0.1	
22	$C_4H_6N_4O$	163.1 (166.0)	162.7 (164.3)	119.4 (119.4)	21.3 (20.8)	-2.9[c]	-1.6	0	+0.5
23	$C_5H_8N_4O$	162.5 (164.3)	162.0 (162.1)	126.0 (127.6)	21.5(5-Me) (21.7)	-1.8	-0.1	-1.7	-0.2
					11.4(6-Me) (11.9)				-0.5
24	$C_3H_4N_4O$	148.8 (151.6)	132.7 (132.4)	135.8 (134.9)		+2.8[c]	+0.3	+0.9	
25	$C_5H_8N_4O$	147.6 (148.9)	141.8 (140.2)	142.3 (144.2)	-	-1.3	+1.6	-1.9	-
26	$C_9H_8N_4O$	148.5 (150.3)	137.7 (141.2)	132.4 (133.6)		-1.8	-3.4[d]	-1.2	
27	$C_5H_8N_4O$	151.7 (154.4)	143.1 (143.0)	150.1 (148.7)	-	-3.7[c,d]	+0.1	+1.4	-

a. Observed ^{13}C chemical shifts are given in parentheses. b. $\Delta^{13}C$ is to be interpreted here as the difference between calculated and reported chemical shifts. c. May be due to hydrogen bonding. d. Steric effects.

Table III. Predicted ^{13}C Chemical Shifts for 1,2,4-Triazine Di-N-Oxides and 3-Amino-1,2,4-triazine Dioxides (in ppm).

Compound	C_3	C_5	C_6
1,2-dioxide (29)	144.0[a] (143.9)[b]	135.6 (135.6)	124.9 (124.4)
1,4-dioxide (30)	148.1	136.9	132.7
2,4-dioxide (31)	133.1	116.7	149.0
3-amino-1,2-dioxide (32)	150.5[a] (152.0)[b]	138.8 (136.5)	115.9 (113.8)
3-amino-1,4-dioxide (33)	154.6	140.1	123.7
3-amino-2,4-dioxide (4)	134.4	123.1	139.4

a. Calculations based on 1-oxide. b. Based on 2-oxide.

Another unusual feature of compounds reported thus far is that many ^{13}C absorptions showed coupling to nitrogen. Fully proton-decoupled ^{13}C spectra had peaks which appeared as narrow triplets which we ascribed to ^{14}N -^{13}C spin-spin interactions. Usually ^{14}N nucleus is effectively decoupled. Because of the high symmetry of the bonding arrangement, the quadrupolar relaxation mechanism is very effective and thus ^{14}N -^{13}C coupling constants cannot be observed directly from the ^{13}C spectra. Furthermore, no such spin-spin coupling was ever reported for any other azine system. We believe that because 1,2,4-triazines are very electron deficient, the electric field gradients at ring nitrogens are very small and make it possible for J ^{14}N -^{13}C to be observed. This is especially true for the two adjacent nitrogens (N_1-N_2) and for carbon atoms when the nearest proton is in excess of 2.0Å away[22] (i.e. compound 16-Table IV) and which have no alternative dipolar relaxation mechanisms. Table IV shows some typical ^{14}N -^{13}C coupling constants for a few 1,2,4-triazines and respective N-oxides. No attempt was made to determine their sign, but we assumed that they are positive since ^{14}N nucleus has a positive gyromagnetic ratio.

Finally, we sought evidence which would establish the structure of compound 5. It is clear that 5 could conceivably exist as 2,5- or 4,5-dihydro tautomer. ^{13}C chemical shifts alone would be of little help since $\Delta^{13}C$ induced by hydrogen at N_2 and/or N_4 would be insignificant. However, use of deuterium isotope effects on ^{13}C nuclear shielding unambiguously identifies 5 as the 2,5-dihydro compound.

Table IV. ^{14}N - ^{13}C Spin-spin Coupling Constants for Same 1,2,4-Triazines and Their N-Oxides (in Hz).

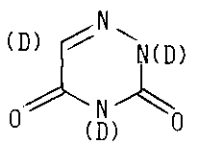
Compound	$J_{^{14}N - ^{13}C}$	
3-amino (14)	9.1 N(1)-C(6)	8.6 N(4)-C(5)
3-amino-5-methyl (15)	9.4 N(1)-C(6)	
3-amino-6-methyl (16)	16.5 N(1)-C(6)	
3-amino-5-phenyl (18)	6.2 N(1)-C(6)	
3-amino 1-oxide (21)	6.9 N(1)-C(6)	9.4 N(4)-C(5)
3-amino-5-methyl 1-oxide (22)	7.1 N(1)-C(6)	
3-amino-2-oxide (24)	7.9 N(1)-C(6)	8.7 N(4)-C(5)
3,5-dioxo (35)	8.3 N(1)-C(6)	
3-amino 5-oxo (34)	8.5 N(1)-C(6)	
1,2,3-triazole (7)	9.0 N(1)-C(2)	

The ^{13}C spectrum of 5 shows three different ring carbon singlets in the aromatic region at 155.9, 165.0 and 138.5 ppm, ascribable to C_3, C_5 and C_6, respectively, by the analogy with 3-amino-5-oxo-1,2,4-triazine (34) and 3,5-dioxo compound 35 (Table V). There are three exchangable protons which could be replaced by deuterium atoms and if the exchange is slow enough on the nmr time scale this should yield doublets or multiplets for $-NH_2$ group (isotopic triplets due to $-NH_2$, -NHD and $-ND_2$ forms). Since H/D exchange for phenols and amides is much slower than for the amino groups,[23] presence of deuterium at N_4 is expected to show a "doublet" for the carbonyl carbon (C_5). On the other hand, if deuterium exchanges at N_2-hydroxy site, C_5 would not be affected. Addition of three equivalents of deterium oxide did not show isotopic doublets for any of the three carbons, thus verifying the structure of 5 as depicted by us as the correct one. Appearance of C_3 as a singlet indicates a complete and rapid exchange of amino protons so that no partly deuterated intermediates are observed. Contrary to this, all three protons in compound 35 exchanged, including the one at position six. This, in turn, caused C_6 signal to appear as a narrow triplet (JC_6D = 7.8 Hz) and C_5 and C_3 as "doublets"; $^2\Delta C_3(D)$ = -0.08 ppm, $^2\Delta C_5(D)$ = -0.035 ppm.

Table V. ^{13}C Chemical Shifts of Same Dihydro-1,2,4-Triazines and Reference Compounds.

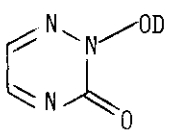
Cmpd No.	Substituent(s)	Chemical Shifts[a,b] C_3	C_5	C_6
35	3,5-dioxo	149.0 149.5[c]	157.3 158.1	135.4 137.1
34	3-amino-5-oxo	156.1	163.4	139.0
5	N_2-hydroxy-3-amino 5-oxo	155.9[d]	165.0	138.5
36	N_2-hydroxy-3-oxo	151.6[d]	132.3	134.7

a. All spectra were obtained on 1.5 molar solution in d_6-DMSO unless indicated otherwise (d_6-DMSO = 39.5 ppm served as double reference). b. δ (ppm) downfield from TMS. c. Data from ref. 24. d. Recorded in 50:50 mixture of d_6-DMSO/HMPA and with coaxial nmr tube containing TMS as external standard.

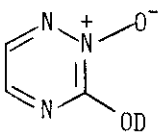


35a

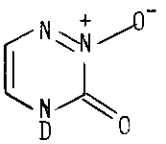
N_2-hydroxy-2,3-dihydro-1,2,4-triazin-3-one (36a) is also a correct representation for the compound we prepared earlier.[10] Upon the addition of D_2O no H/D isotope shifts were observed and therefore established 36a as the predominant tautomer ($K_T > 10^2$). If 36b and 36c were present, C_3 in 36b and C_3 and C_5 in 36c would have appeared as isotopic doublets.



36a



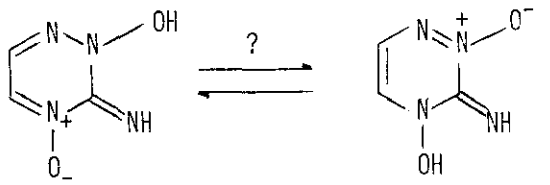
36b



36c

It is also important to point out that structure of 4 may not be best represented as a doubly charged di-N-oxide. We feel that structure 37 may be more appropriate. Due to insufficient quantities and low solubility of 4, we have not yet been able to determine whether tautomers 37a and/or 37b play an important role in stabilizing this highly charged molecule. However, it does seem

logical that in view of high π-deficiency of 1,2,4-triazine mono-N-oxides[9] it would be very difficult for a ring to carry an additional charge.



37a 37b

One way to answer this is to examine ^{15}N chemical shifts and compare them with those of mono-N-oxides which we reported in another communication.[25] Further studies are in progress.

EXPERIMENTAL

Starting Materials. All amines and amino-N-oxides were available from a previous study.[20] 5-Methyl-(11) and 5,6-dimethyl-1,2,4-triazine 1-oxide (12) were prepared by a procedure described elsewhere.[26] m-Chloroperbenzoic acid was used as the oxidant instead of perbenzoic acid to yield 11, mp 65-67°C (lit.[26] mp 65-67°C) and 12, mp 84-86°C (lit.[26] mp 84-85.5°C). Parent 1-oxide (9) was prepared from 3-methoxy compound (^{13}C nmr in d_6-DMSO: C_3, 167.2; C_5, 156.3; C_6, 125.7; OCH_3, 55.7 ppm) which was converted to 3-hydrazino derivative and oxidized with activated MnO_2 to yield a white solid, mp 63-64°C (lit.[26] mp 61.5-64°C).

^{13}C NMR Measurements. ^{13}C spectra of compounds 9, 11, 12, 13 and 28 were obtained as 1M solutions in $CDCl_3$ also used for field frequency locking (δ = 77.0 ppm) and TMS as a double reference internal standard. All other spectra were recorded as 1.2-1.5M solutions in d_6-DMSO (δ = 39.5 ppm) with solvent peak as reference. The spectra were recorded on a WP 200-SY Bruker spectrometer operating at the frequency of 200.130 MHz for proton and 50.327 MHz for ^{13}C nuclei, respectively, and operating in a Fourier transform mode. The spectrometer was equipped with Winchester 24 MFD data system and a PTS 160 frequency synthesizer. Standard spectral parameters for the proton-noise decoupled spectra were: data set = 3500; pulse width 10 μs (30° flip angle); interpulse delay 1-4s, typically 2.0 seconds; sweep width = 10 KHz; line broadening = 0.3 Hz; acquisition time = 0.5407 seconds; data size = 16K (8K real). Expanded spectra with smaller spectral widths (2.5 KHz; 0.31 Hz resolution) were used for evaluation of spin-spin coupling constants.

^{14}N-^{13}C coupling constants were observed only in DMSO solution at the settings indicated above.

H/D Isotope Exchange Studies. In a typical experiment, 150 mg (1.0 mmol) of a sample was dissolved in 2.0 ml of d_6-DMSO. The amount of deterium oxide added to observe isotopic doublets was equal to the number of equivalents of exchangable protons plus one equivalence as excess of deuterium source. Sample was left standing overnight, dried over several pellets of nonindicating Drierite and recorded. To ensure that exchange did take place, samples of 34 and 36 were heated and periodically run over a time span of three weeks.

3-Amino-1,2,4-triazine 2,4-Dioxide (4). Suspension of 3 (1.12 g; 10 mmol) in polyphosphoric acid (17 g) is heated slowly until the amine dissolves and then cooled to room temperature before the addition of hydrogen peroxide (1.3 ml = 2.0 g of 90%). Peroxide was added dropwise over a period of 4 h and temperature maintained at 24°C by external cooling (water bath). Thick, sticky slurry was stirred constantly with the glass rod to prevent excessive frothing. Reaction mixture was left standing at room temperature for 48 h, 50 ml of water added (caution), neutralized with solid Na_2CO_3, and extracted successively with acetonitrile/methanol mixture (4 x 150 ml). Evaporation of the solvent yielded a bright yellow solid (460 mg, 35.9% yield) which was recrystallized from 50:50 ethanol/dioxane (mp > 300°C). Anal. Calcd. for $C_3H_4N_4O_2$: C, 28.12; H, 3.15; N, 43.74. Found: C, 28.08; H, 2.99; N, 43.85.

Oxidation of 3 with Peracetic Acid. A solution of 2.0 g (18 mmol) of 3 was dissolved in 50 ml of hot glacial acetic acid, yellow solution brought to room temperature and to it added 4.0 ml of 27% hydrogen peroxide in several portions over a period of 5 h. This mixture was warmed to 60°C, kept there until bright yellow solution turned deep wine-red (1 h), and concentrated in vacuo (below 45°C) to one third of the original volume. Remaining solution was diluted with same volume of water and concentrated to a brown residue which was recrystallized from minimum volume of acetone-alcohol mixture to yield 5 (mp > 300°C), 511 mg, 22.2% yield. Anal. Calcd. for $C_3H_4N_4O_2$: C, 28.12; H, 3.15; N, 43.74. Found: C, 28.25; H, 3.18; N, 43.56.

The same product was obtained in 18% yield by careful hydrolysis of 3 with 0.2M NaOH. 3-Amino-1,2,4-triazine 2-oxide (3) was heated gently in the presence of NaOH for 15 min, cooled and neutralized with glacial acetic acid to give a white solid which was identical in all respects with compound 5 isolated from the

previous procedure.

Alkaline Hydrolysis of 3. Formation of 1,2,3-triazole (7). 3.0 g (26.8 mmol) of 3 was placed in 50 ml round bottom flask containing 20 ml of water and 4 g of NaOH. Whole mixture was heated on a steam bath for 2 h during which time vigorous exothermic reaction ensued with liberation of ammonia (wet lithmus paper turned basic). After this time, the reaction mixture was cooled and neutralized with glacial acetic acid (~4 ml). Refrigeration of this solution at 4°C for 5 h yielded reddish-brown solid which on recrystallization from acetone/water gave white crystals (mp 204-206°C) identified as 1,2,3-triazole (7) ($\delta^{13}C$ = 130.6 ppm in d_6-DMSO) by comparison with an authentic sample.[27] Mother liquor also contained some N-acetyl-2,3-dihydro-2-imidazolone (8) which was not isolated ($\delta^{13}C$ in d_6-DMSO: 160.9, 156.5, 152.8 and 172.8, 22.6 ppm - acetyl).

3-Amino-2,5-dihydro-1,2,4-triazin-5-one(34). 10 g of 3 was suspended in 100 ml of glacial acetic acid and treated slowly with 20 ml of 30% H_2O_2. The reaction is exothermic and refluxes spontaneously. When all of the starting material is consumed (30 min) the yellow solution is cooled with running water. The white powdery solid which precipitates out is filtered, rinsed with 30 ml of cold water and dried to afford pure 34 (mp > 300°C); ^1H in d_6-DMSO: δ 7.49, H_6; δ5.22, NH_2-broad, exchange in D_2O; in quantitative yield and was identical with an authentic sample prepared by literature method.[28]

3,5-Dioxo-2,3,4,5-tetrahydro-1,2,4-triazine (35). This compound was prepared by a literature procedure[29]; mp 267-268°C (lit.[29] mp 268-270°C).

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Received, 13th March, 1985