ate, water, 1.5 *N* hydrochloric acid, and again with water. The chloroform solution was dried and concentrated to 21.9 g of an oil which, when treated with ether, yielded 5 g (14%) of pale yellow prisms. Recrystallizations from methylene chloride-hexane gave colorless prisms: mp 164–166°; mass spectrum *m/e* (rel intensity) 357 (5), 315 (12), 273 (42), 242 (50), 231 (100), 230 (69), 105 (50).

Anal. Calcd for $C_{18}H_{16}ClN_3O_3$: C, 60.42; H, 4.51; N, 11.74. Found: C, 60.37; H, 4.60; N, 11.62.

2′-Benzoyl-4′-chloro-*N*-(2,2-diacetylhydrazono)methylacetanilide (24).—A solution of 800 mg (2 mmol) of **23**, 7 ml of acetic anhydride, and 10 ml of pyridine was stirred overnight at room temperature. The reaction mixture was poured over ice and extracted with chloroform. The organic extract was washed with water, dried, and concentrated *in vacuo*. The residue was washed with chloroform leaving 250 mg (44%) of the dimeric orange product from **5** (*vide supra*). The chloroform wash was treated with hexane and yielded 125 mg (14%) of colorless prisms: mp 134–136°; mass spectrum *m/e* (rel intensity) 399 (3), 357 (14), 315 (7), 298 (20), 273 (34), 242 (43), 231 (100), 230 (50), 105 (24).

Anal. Calcd for $C_{20}H_{18}ClN_3O_4$: C, 60.08; H, 4.54; N, 10.51. Found: C, 59.83; H, 4.58; N, 10.50.

5-Chloro-2-(1,2,2-triacetyl-1-hydrazinylmethyleneamino)benzophenone (25).—A mixture of 50 g (0.18 mol) of **5**, 100 ml of pyridine, and 200 ml of acetic anhydride was stirred at room temperature for 41 hr. The volatile materials were removed *in vacuo* leaving an oil which was partitioned between chloroform and water. The organic phase was washed with water, 5% sodium bicarbonate, water, 1.5 *N* hydrochloric acid, and again with water. The chloroform was removed *in vacuo* yielding an oily residue which was crystallized from ethanol to give 37.3 g (51.8%) of colorless crystals, mp 101–104°. Recrystallizations from ethanol gave colorless blocks: mp 105–107°; ir (KBr) 1730, 1672, 1647 cm^{-1}; mass spectrum *m/e* (rel intensity) 399 (18), 357 (22), 315 (29), 298 (57), 273 (76), 242 (86), 231 (100), 230 (80), 105 (55).

Anal. Calcd for $C_{20}H_{18}ClN_3O_4$: C, 60.08; H, 4.54; N, 10.51. Found: C, 60.13; H, 4.46; N, 10.52.

3-Acetamido-6-chloro-3,4-dihydro-4-hydroxy-4-phenylquinazoline (26).—A solution of 10% potassium hydroxide in methanol was added dropwise to a solution of 8 g (20 mmol) of **25** and 20 ml of methanol at 45°.

When the solution had maintained a pH of 10, it was allowed to stand for 30 min and was then diluted with 300 ml of water. The precipitate was removed by filtration, washed with water, and dried at 65–70° *in vacuo* (5 g, 79.3%). Recrystallizations from THF-ether gave colorless prisms: mp 160–162°; ir (KBr) 3240, 1670, 1610 cm^{-1}; nmr (DMSO) 1.60 (s, 3, $NCOCH_3$); mass spectrum *m/e* (rel intensity) 315 (2), 297 (35), 282 (36), 254 (70), 240 (33), 239 (55), 220 (100), 205 (44).

Anal. Calcd for $C_{16}H_{14}ClN_3O$: C, 60.86; H, 4.47; N, 13.31. Found: C, 60.75; H, 4.46; N, 13.19.

Registry No.—**2**, 10352-28-0; **5**, 27610-14-6; **6**, 27537-87-7; **6** HCl, 27537-88-8; **13** HCl, 27537-89-9; **14**, 27537-90-2; **16**, 17433-16-8; **17**, 27537-92-4; **19**, 27537-93-5; **20**, 27537-94-6; **21**, 27537-95-7; **23**, 27537-96-8; **24**, 27537-97-9; **25**, 27537-98-0; **26**, 27537-99-1.

Acknowledgment.—The authors are indebted to the following members of the Physical Chemistry Department under the direction of Dr. P. Bommer: Dr. W. Benz, Dr. V. Toome, Mr. S. Traiman, and Dr. T. Williams and their staffs for the spectral data and to Dr. F. Scheidl and his staff for the microanalyses. We also wish to thank Professor G. Büchi for valuable discussions.

1,2,4-Triazines. IV. Synthesis and Characterization of 1,2,4-Triazine *N*-Oxides

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The N-oxidation of 1,2,4-triazines affords the 1-oxides when C_3 is either unsubstituted or is substituted by a methoxyl group. It has been shown that N-oxidation of 3-amino-1,2,4-triazines affords the 2-oxides as major products. This is in contrast to some of the reported data which suggested that oxidation of 3-amino-5,6-diphenyl-1,2,4-triazine yields the 1-oxide.

Recent developments of new syntheses of 1,2,4-triazines[1-3] have made this ring system readily available and permit its study in some detail.

We now wish to describe the preparation and structure elucidation of some 1,2,4-triazine *N*-oxides.

Several papers[4-7] have dealt with the N-oxidation of some 3-amino- and 3-methoxy-1,2,4-triazines with alkyl and aryl substituents in the 5 and 5,6 positions of the 1,2,4-triazine ring. The only all-alkyl or all-aryl substituted 1,2,4-triazine that has been N-oxidized is the 3,5,6-triphenyl compound,[8] where the 1-oxide is formed as the major product (33%) and the 2-oxide as the minor one (8%).

The N-oxidation of 1,2,4-triazines can, *a priori*, occur at either N-1, N-2, or N-4. In order to establish the position of N-oxidation one can, in theory, determine the dipole moments of these substances and thus elucidate their structures, or one can examine the differences in proton chemical shifts between the N-oxidized compounds and the appropriate bases themselves.

The oxidation with perbenzoic acid of compounds **1a–d** (see Scheme I) afforded mono-*N*-oxides in 15–40% yields after chromatography on neutral grade III alumina.

The mass spectra of these compounds clearly indicate the presence of an *N*-oxide function by the appearance of a P − 16 peak. In addition to this fragmentation process, all compounds (including those with no substituents at C-3) having a methyl or a phenyl group substituted at C-6 give rise to a P − 17 peak which is more abundant than the P − 16 ion. This observation suggests that we are dealing with the 1- rather than the 2-

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[1] W. W. Paudler and J. M. Barton, *J. Org. Chem.*, **31**, 1720 (1966).

[2] W. W. Paudler and R. E. Herbener, *J. Heterocycl. Chem.*, **4**, 224 (1967).

[3] W. W. Paudler and T. K. Chen, *ibid.*, **7**, 767 (1970).

[4] T. Sasaki and K. Minamoto, *Chem. Pharm. Bull.*, **12**, 1329 (1964).

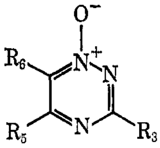
[5] T. Sasaki and K. Minamoto, *ibid.*, **13**, 1168 (1965).

[6] T. Sasaki and K. Minamoto, *J. Org. Chem.*, **31**, 3914 (1966).

[7] T. Sasaki and K. Minamoto, *ibid.*, **31**, 3917 (1966); *Chem. Abstr.*, **67**, 3102 (1967).

[8] C. M. Atkinson, D. A. Ibbitson, F. J. Rice, and J. P. B. Sandall, *J. Chem. Soc.*, 4209 (1964).

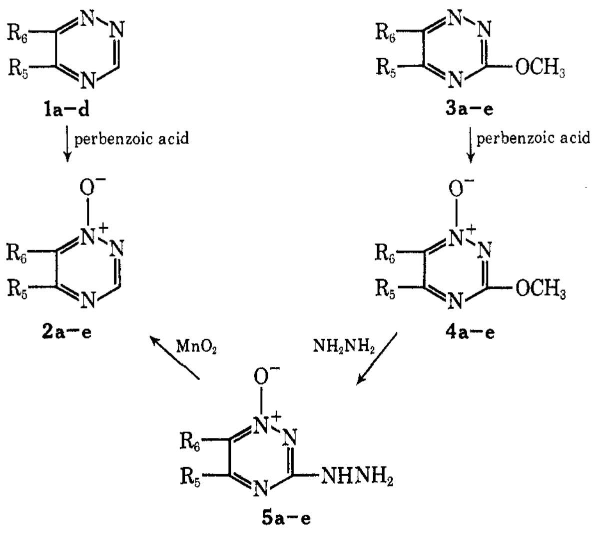
TABLE I
ANALYTICAL DATA FOR SOME 1,2,4-TRIAZINE 1-OXIDES



Pmr Data													
Chemical shifts, τ[a]						Coupling constants, cps		Calcd, %			Found, %[b]		
R_3	R_5	R_6	R_3	R_5	R_6	$J_{R_3R_6}$	$J_{R_5R_6}$	C	H	N	C	H	N
H	H	H	1.0	1.43	1.95[c]	1.8	3.3	37.11	3.09	43.30	37.41	3.20	43.52
OCH_3	H	H	5.94	1.63	2.17		3.3	37.80	3.94	33.07	37.87	3.89	33.04
H	CH_3	H	1.15	7.50	2.05	1.5		43.24	4.50	37.84	43.70	4.50	37.99
H	C_6H_5	H	1.0	1.97 (m) 2.44 (m)	1.52	1.5		62.43	4.05	24.28	62.19	4.05	23.67
H	CH_3	CH_3	1.26	7.40	7.51			48.00	5.60	33.60	48.17	5.12	33.85
H	C_6H_5	C_6H_5	1.02	2.68 (*ca.*)	2.68 (*ca.*)			72.79	4.42	16.87	72.85	4.67	17.08
OCH_3	CH_3	H	5.95	7.55	2.25			42.55	4.96	29.79	43.23	4.90	29.79
OCH_3	C_6H_5	H	5.85	1.97 (m) 2.43 (m)	1.70			59.11	4.43	20.69	58.81	4.60	20.57
OCH_3	CH_3	CH_3	5.99	7.48	7.60			46.40	5.80	27.10	47.04	5.87	26.48
OCH_3	C_6H_5	C_6H_5	5.86	2.68 (*ca.*)	2.68 (*ca.*)			68.82	4.66	15.05	68.87	4.18	14.96

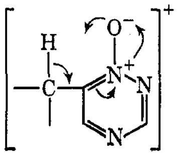
[a] All pmr spectra were obtained as 1% w/v solutions in $CDCl_3$. A Varian HA-100 spectrometer was used. The chemical shifts of the nonoxidized 1,2,4-triazines are reported in ref 3. [b] The mass spectrometric molecular weights of all compounds were obtained with a Hitachi Perkin-Elmer RMU-6E instrument and were found to be in agreement with the theoretical values. Elemental analyses were done by Mrs. P. Jones of this department. [c] The chemical shifts for H-3, H-5, and H-6 in 1,2,4-triazine are 0.12, 1.16, and 0.52, respectively, in $CDCl_3$.

SCHEME I



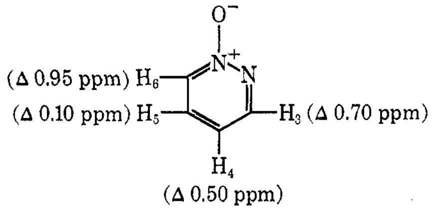
a, $R_5 = R_6 = CH_3$
b, $R_5 = R_6 = C_6H_5$
c, $R_5 = CH_3$; $R_6 = H$
d, $R_5 = C_6H_5$; $R_6 = H$
e, $R_5 = R_6 = H$

or 4-oxides since one can envision a McLafferty-type rearrangement to be operating which involves the following process.[9]

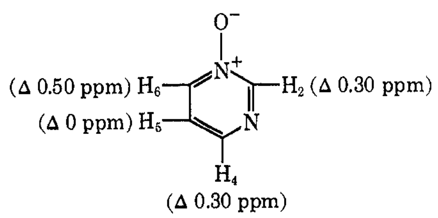


This implication is further supported by an analysis of the pmr spectra (see Table I) of pyrimidine and pyridazine *N*-oxides and a comparison of the proton chemical shift changes that occur in these compounds when they are transformed from their nonoxidized to their N-oxidized forms.

Thus H-3, H-4, H-5, and H-6 in pyridazine 1-oxide experience shielding (Δ) with respect to the corresponding proton chemical shifts in pyridazine itself,[10] by the following amounts.



Similarly, the various protons in pyrimidine *N*-oxides[10,11] are affected as follows.



A comparison of the chemical shift changes of the corresponding protons in the various 3-unsubstituted 1,2,4-triazines, with their counterparts in the *N*-oxides,

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[9] T. Sasaki, K. Minamoto, M. Nishikawa, and T. Shima [*Tetrahedron*, **25**, 1021 (1969)] describe the mass spectra of various 3-amino- and 3-alkoxy-1,2,4-triazine 1- and 2-oxides and identify the abundant P − 17 fragment as arising from a McLafferty rearrangement involving the protons on the 3 substituent of the 2-oxide. Our results show that a C-6 substituent can also account for this OH loss in the 1-oxides. Detailed studies of these processes are in progress.

[10] E. Ochiai, "Aromatic Amine Oxides," Elsevier, Amsterdam, Netherlands, 1967, p 101 ff.

[11] W. W. Paudler and S. A. Humphrey, *J. Org. Chem.*, submitted for publication.

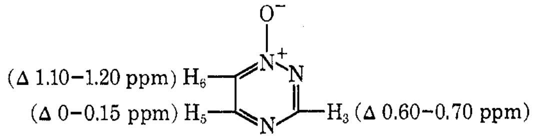
shows that H-3 is shielded by 0.6–0.7 ppm, H-5 by 0.15 ppm, and H-6 by 1.1–1.2 ppm.

If we are dealing with 2-oxides, we should expect, by analogy with H-3 in pyrimidine *N*-oxide, that H-3 be more shielded by about 0.3 ppm in the 1,2,4-triazine *N*-oxide. A similar effect would be anticipated if the 1,2,4-triazines had been oxidized at N-4. An analogous argument can be made for the chemical shift changes experienced by H-5 and H-6 of the 1,2,4-triazines upon N-oxidation.

On the other hand, if we assume that N-oxidation has occurred at N-1, then the similarity in the chemical shift changes at H-3 in 1,2,4-triazine upon oxidation at N-1 and at H-3 in the pyridazine 1-oxide are rather striking. The proton ortho to the *N*-oxide linkage, H-6, is also shielded (1.1–1.2 ppm) to the large extent observed for H-6 (0.95 ppm) in pyridazine 1-oxide.

The rather small change of the chemical shift of H-5 (0.15 ppm) in the 1,2,4-triazine 1-oxides as compared to the corresponding 1,2,4-triazines is also in accord with the small changes observed in the chemical shifts of H-5 in pyridazine (0.1 ppm) and in pyrimidine (0 ppm) upon oxidation at N-1.

Thus the following "composite" picture of the chemical shift changes of the various protons of different 1,2,4-triazines upon oxidation at N-1 can be drawn.



These data clearly establish that we are indeed dealing with 1,2,4-triazine 1-oxides.

Unfortunately, when an attempt was made to N-oxidize 1,2,4-triazine itself, no *N*-oxide could be isolated. This is perhaps not surprising since we have already shown[3] that the 5 position in 1,2,4-triazines is readily involved in covalent hydration in acidic media.

The oxidation of 3-methoxy-1,2,4-triazines (**3a–e**) also afforded the *N*-oxides in satisfactory yields. Since H-3 is no longer available for purposes of pmr analyses in order to establish the site of oxidation, it was necessary to convert those compounds where both C-5 and C-6 are substituted (**4a** and **4b**) into their 3-hydrazino derivatives and oxidize the latter compounds with MnO_2, by the procedure previously described,[3] to the 3-unsubstituted *N*-oxides. When this was done, the resulting compounds proved to be identical with the *N*-oxides obtained from the direct oxidation of the 3-unsubstituted compounds (**1a** and **1b**). Thus N-oxidation of 3-methoxy-5,6-diphenyl- and 3-methoxy-5,6-dimethyl-1,2,4-triazine also occurs at N-1. The 3-methoxy-5,6-diphenyl 1-oxide is identical with the compound described as the 2-oxide by Sasaki and Minamoto.[4]

An analysis of the pmr spectra of compounds **4c**, **4d**, and **4e**, in a manner analogous to that described for the 3-unsubstituted 1,2,4-triazines (**1a–d**) allows one to establish that these compounds also are 1-oxides.

Finally, the elusive parent 1,2,4-triazine 1-oxide itself was obtained by means of oxidation of the 3-hydrazino-1,2,4-triazine 1-oxide (**5e**). The pmr spectrum of this compound (see Table I) is in agreement with its assigned structure.

It has been well established[12,13] that the proton on a carbon atom adjacent to the *N*-oxide linkage is subject to base-catalyzed H → D exchange. When the 5-methyl-1,2,4-triazine 1-oxide was treated with dilute sodium deuterioxide in D_2O, the H-6 proton singlet disappears and the H-3 doublet becomes a singlet. Thus, this chemical evidence further confirms our structure assignments.

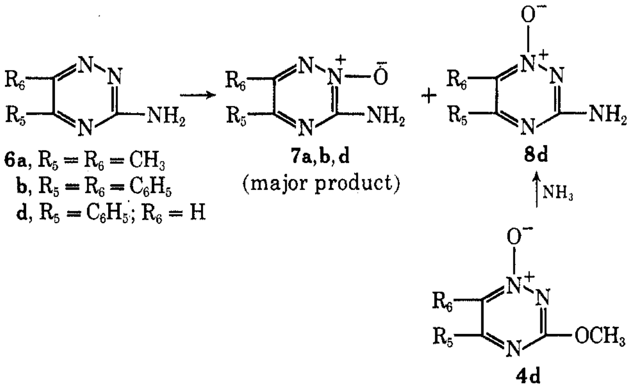
Sasaki and Minamoto[4] have described the N-oxidation of 3-amino-5,6-diphenyl-1,2,4-triazine and have concluded on the basis of dipole moment measurements in dioxane that N-oxidation occurs at N-1.

Since dipole moments determined in dioxane are notoriously inaccurate and the theoretical difference between the 1- and 2-oxides is only 0.22 D, it is not established whether this compound is the 1- or 2-oxide.

The same workers[4] converted their 3-methoxy-5,6-diphenyl-1,2,4-triazine *N*-oxide, now shown to be the 1-oxide (*vide supra*), to a 3-amino *N*-oxide which is different from that obtained by direct oxidation of 3-amino-5,6-diphenyl-1,2,4-triazine.

In order to bring all of this evidence into accord, we must conclude that the assignments made by Sasaki and Minamoto are in error and that, in fact, the oxidation of 3-amino-5,6-diphenyl-1,2,4-triazine affords the 2-oxide, in analogy with the results obtained by them upon oxidation of the 3-amino-5,6-dimethyl-1,2,4-triazine, and that the *N*-oxide obtained by treatment of the 3-methoxy-5,6-diphenyl-1,2,4-triazine *N*-oxide with ammonia is the 1-oxide. This interpretation also brings into harmony the observation of these workers, that the major product of oxidation of 3-amino-5-phenyl-1,2,4-triazine is the 2-oxide. In fact, when we treat the 3-methoxy-5-phenyl-1,2,4-triazine 1-oxide with ammonia, the resulting amino *N*-oxide is identical with the minor *N*-oxide obtained from the oxidation of 3-amino-5-phenyl-1,2,4-triazine as described by Sasaki and Minamoto.[4] These transformations are delineated in Scheme II. Finally, it should be mentioned that the oxidation of 3-aminobenzo-1,2,4-triazine also yields the 2-oxide as the major product.[14] Thus, it appears that a 3-amino substituent facilitates oxidation at N-2 while oxidation at N-1 occurs when C-3 is either unsubstituted or is substituted by a methoxy or phenoxy group.

SCHEME II



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[12] J. A. Zoltewics and G. M. Kaurrman, *J. Org. Chem.*, **34**, 1405 (1969).

[13] W. W. Paudler and S. A. Humphrey, *ibid.*, **35**, 3467 (1970).

[14] J. C. Mason and G. Tennant, *J. Chem. Soc. B*, 911 (1970).

TABLE II

EXPERIMENTAL VARIABLES FOR THE SYNTHESES OF VARIOUS TRIAZINE 1-OXIDES

Compd no.[a]	Procedure[b]	Reaction time, days	Reaction temp, °C	% yield	Mp, °C
2e	B	Step 1, 2 hr			
		Step 2, 4.5 hr	28	12[c]	61.5–64
4e	A	4	45	15	70.5–72
2c	A	4.5	28	27	65–67
	B	Step 1, 1 hr	28	11	
		Step 2, 6 hr			
2d	A	2	28	26	137.5–139.5
	B	Step 1, 6 hr	28	18[c]	
		Step 2, 6 hr			
2a	A	3.5	28	30	84–85.5
	B	Step 1, 3 hr	85	20[c]	
		Step 2, 4 hr	28		
2b	A	3	28	17	170–172
	B	Step 1, 12 hr	28	25[c]	
		Step 2, 4 hr			
4c	A	2.5	28	26	120–121.5
4d	A	3.5	28	39	127–128.5
4a	A	4	28	45	56–57.2
4b	A	3.5	28		
		0.5	45	23	156–158[d]

[a] See Schemes I and II for identification. [b] See Experimental Section for details. [c] Overall yield. [d] Lit.[6] 157.5–158.5.

Experimental Section

3-Methoxy-5-phenyl-1,2,4-triazine 1-Oxide (4d). General Procedure A.—To 1.094 g (0.00585 mol) of **3d** dissolved in 20 ml of chloroform was added 4 ml (0.00616 mol) of perbenzoic acid solution (0.00154 mol/ml). After standing at room temperature for 84 hr, the chloroform solution was washed with 40–50 ml of concentrated aqueous sodium carbonate. The aqueous layer was then extracted with chloroform (four 30-ml portions), and the concentrated chloroform extract was chromatographed on neutral alumina (grade III). The main fraction, when eluted with benzene, yielded a white solid. Sublimation at 100° (0.3 mm) afforded 0.46 g (38.7%) of **4d** (mp 127–128.5°).

1,2,4-Triazine 1-Oxide. General Procedure B. Step 1.—To 0.2 g of 3-methoxy-*as*-triazine 1-oxide in 4 ml of tetrahydrofuran was added 0.1 g of 95% hydrazine. Enough absolute methanol was added to dissolve all of the hydrazine. A yellow precipitate began to form within minutes. This solid was collected after 2 hr (0.185 g of shiny yellow crystals, mp 194° dec).

Step 2.—The hydrazine compound was then dissolved in a mixture of 200 ml of tetrahydrofuran and 15 ml of absolute methanol. To this solution was then added 5 g of activated MnO_2 and the slurry was stirred for 4.5 hr and filtered. Evaporation of the filtrate to dryness yielded a yellow oil which was sublimed at 40° (0.2 mm) to afford 18 mg of a 1,2,4-triazine 1-oxide (mp 61.5–64°).

Table II lists various triazine 1-oxides obtained by procedures A and B.

3-Amino-5-phenyl-1,2,4-triazine 1-Oxide.—3-Methoxy-5-phenyl-1,2,4-triazine 1-oxide (0.2 g) dissolved in 3 ml of 5% alcoholic ammonia was heated in a sealed tube on a steam bath for 8.5 hr. The cooled reaction mixture was filtered to yield 0.1 g of yellow needles (mp 228.5–230.5°, from ethyl alcohol).[7] An additional 0.5 g of product was obtained when the filtrate was concentrated further. This compound does not give a color test with aqueous $FeCl_3$ solution even after being warmed on a steam bath for 5 min.

Registry No.—**2a**, 27531-58-4; **2b**, 27531-59-5; **2c**, 27531-60-8; **2d**, 27513-61-9; **2e**, 27531-62-0; **4a**, 27531-63-1; **4b**, 27531-64-2; **4c**, 27531-65-3; **4d**, 27531-66-4; **4e**, 27531-67-5.

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