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SYNTHETIC AND NITROGEN-15 NMR STUDIES  
OF SOME HETEROAROMATIC SYSTEMS

PART 1: SYNTHESSES AND REACTIONS OF TRI-,  
TETRA-, AND PENTAAZAINDENES.

PART 2: NITROGEN-15 NMR:  
A. GROUND STATE CONTRIBUTIONS OF  
SOME POLYAZAINDENES.  
B. CHEMICAL SHIFT CONTRIBUTIONS OF  
SOME SUBSTITUTED POLYAZABENZENES  
AND THEIR N-OXIDES.

BY ROGER MARTIN SHEETS

a dissertation submitted in partial fulfillment of the  
requirements for the degree of

DOCTOR OF PHILOSOPHY  
in

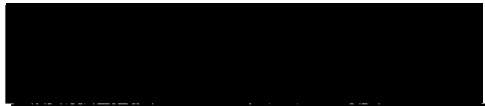
ENVIRONMENTAL SCIENCE AND RESOURCES / CHEMISTRY

Portland State University


1986

TO THE OFFICE OF GRADUATE STUDIES AND RESEARCH:


The members of the Committee approve the dissertation of  
Roger Martin Sheets presented April 24, 1986.

  
William W. Paudler, Chairperson


  
Larry I. Crawshaw


  
Gary L. Gerd


  
Alfred S. Levinson

  
Makoto Takeo

APPROVED:

  
David W. McClure, Head, Department of Chemistry

  
Pavel K. Smejtek, Coordinator, Environmental  
Sciences and Resources Ph.D. Program

  
Bernard Ross, Dean of Graduate Studies and Research

AN ABSTRACT OF THE DISSERTATION OF Roger Martin Sheets for the  
Doctor of Philosophy in Environmental Sciences and Resources:  
Chemistry presented April 24, 1986.

Title: Synthetic and Nitrogen-15 NMR Studies of Some  
Heteroaromatic Systems.


Part 1: Syntheses and Reactions of Tri-, Tetra-,  
and Pentaazaindenes.


Part 2: Nitrogen-15 NMR.

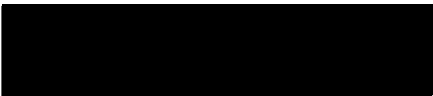
A. Ground State Contributions of Some  
Polyazaindenes.

B. Chemical Shift Contributions of Some  
substituted Polyazabenzenes and Their  
N-Oxides.


APPROVED BY MEMBERS OF THE DISSERTATION COMMITTEE:

  
William W. Paudler, Chairperson

  
Larry I. Crawshaw

  
Gary L. Gayd

  
Alfred S. Levinson

  
Makoto Takeo

Beginning in the mid-1960's synthetic nucleoside derivatives of polyazaindolizines and polyazaindenes were studied for their anticancer activities. The most promising nucleosides for anticancer activity were pyrrolo-, imidazo-, and 5-triazolo- pyrimidines and triazines.

Syntheses of 1,2,4-triazolo[3,4c]-1,2,4-triazine-7-oxide, 1,2,4-triazolo[3,4c]pyrazine-7-oxide and 1,2,4-triazolo[2,3c]pyrazine-7-oxide were achieved by the cyclization of the appropriate 3-hydrazinoazine N-oxide with diethoxymethyl acetate. When different one carbon cyclization agents react with the 3-hydrazinoazine-1-oxides they did not produce the expected polyazaindene-7-oxides. The reaction of formic acid with 3-hydrazino-1,2,4-triazine-1-oxide or 3-hydrazinopyrazine-1-oxide produced the 3-formylhydrazino derivatives. Similarly, the reactions of the 3-hydrazino -pyrazine-1-oxide and -triazine-1-oxide with benzaldehyde, acetic anhydride, or phenylisothiocyanate produced the 3-benzylideno, 3-acetyl, and 3-(4-phenylthiosemicarbizide) derivatives, respectively.

The direct N-oxidation of imidazo[1,2a]pyrazine with meta-chloroperbenzoic acid produced the imidazo[3,4c]-pyrazine-7-oxide.

Proton nuclear magnetic resonance analyses of the polyazaindenes N-oxides has produced a set of shielding and deshielding parameters for ring protons. The mass spectral information obtained for the polyazaindene N-oxides suggests

that the five membered ring of polyazaindene N-oxide has a decreased reactivity to electrophilic reagents when compared to the parent compound.

The nitrogen-15 nuclear magnetic resonance spectra obtained for selected polyazaindenes were used to predict the percentage of contribution between two ground state resonance contributing structures.

The nitrogen-15 nuclear magnetic resonance spectra of several substituted pyridine, pyrazine, pyrimidine and 1,2,4-triazine derivatives and their N-oxides were correlated with substituent contributions and ground state contributing structures. From this data, correlations between the nitrogen-15 chemical shifts and aromatic electron deficiency have been established.

#### ACKNOWLEDGEMENTS

The author extends gratitude to Dr. William W. Paudler, for his patience, guidance, and assistance. Additional appreciation is given to Dr. Harry L. Blewitt for counsel and support during the long years, you were the first and I am the last. Additional appreciation is given to Dr. Gary L. Gard for his unblinding faith in the "Human Spirit". A special thanks to Dennis Grahn for bringing me back.

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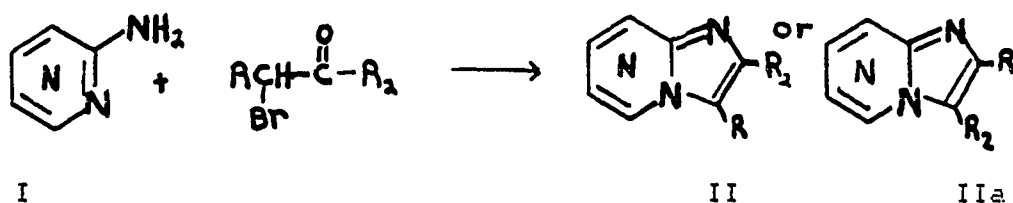
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## PART :

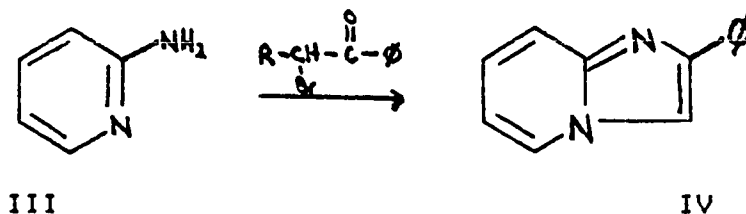
### I. HISTORY OF THE POLYAZAINDENES

#### A. Syntheses from Aminoazines.

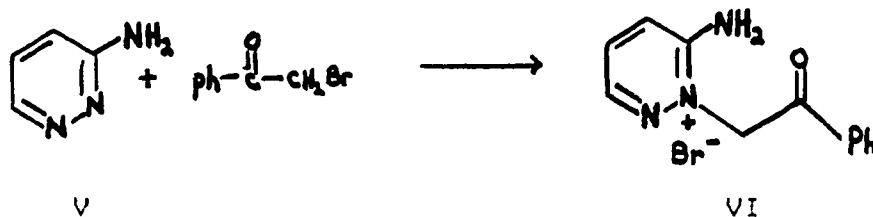
The condensation of aminoazines with alpha-bromocarbonyl compounds can, in principle, produce two different products. However, only one of the possible compounds is obtained, unless a Dimroth rearrangement occurs. The initial step in this process involves attack at



the alpha-carbon of the halocarbonyl compound by the ring nitrogen of the aminoazine(I). This cyclization explains the substitution positions for imidazo[1,2a]pyridine (1).



Yoneda and coworkers prepared 3-amino-1-phenacylpyridazinium bromide (VI) by the condensation of aminopyridazine (V)

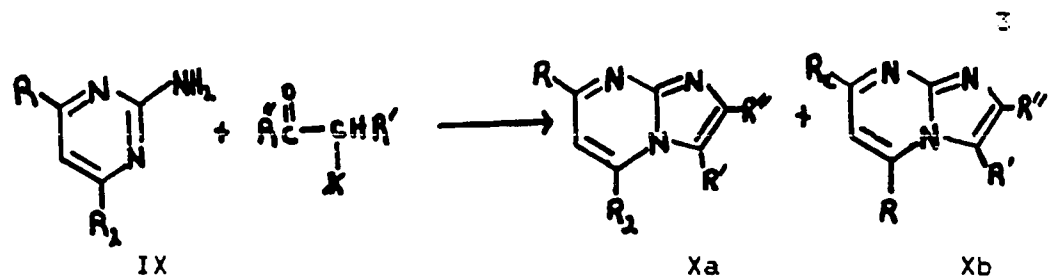


and phenacyl bromide (2). If both positions ortho to the amino-substituent are nitrogens, then the possibility of the formation of isomeric products exists. The direction of this type of cyclization is controlled by the size of the substituents (R-3 and R-4) and suggests that steric consideration contribute largely to the success of the cyclization process (3). The condensation yields may be increased by causing the reaction to occur in refluxing methanol, ethanol (3) or dimethylformamide in the presence of sodium bicarbonate (4). The reasons for the success these conditions do not appear to be clear.

The reaction of aminopyrazine (VII) with alpha-halo-carbonyl compounds results in relatively low yields of the imidazo[1,2a]pyrazines (VIII) (3). The use of alpha-ketoaldehydes in an acidic mixture (or formaldehyde and sodium cyanide) give better yields of the 3-substituted imidazo[1,2a]pyrazines (VIII) (5,6).

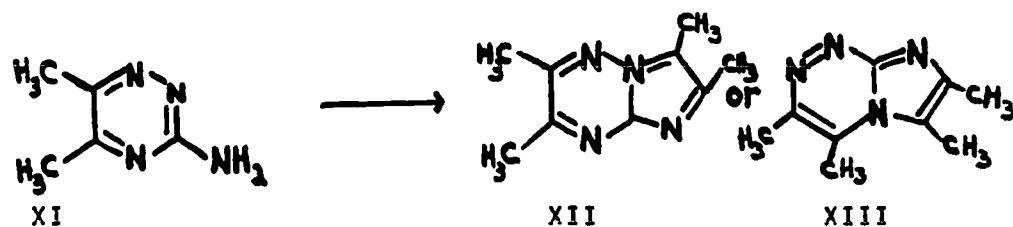


The condensation of 2-aminopyrimidines (IX) with alpha-halocarbonyl compounds gives very good yields (60%-90%) of substituted imidazo[1,2a]pyrimidines (7). The direction of cyclization in 2-aminopyrimidines is controlled by the steric (7a,8) and electronic (4) effects of the substituents.



The reaction of 3-amino-1,2,4-triazine (XI) with  $\alpha$ -halocarbonyl compounds can produce two different imidazo-1,2,4-triazines (XII, XIII) (9).

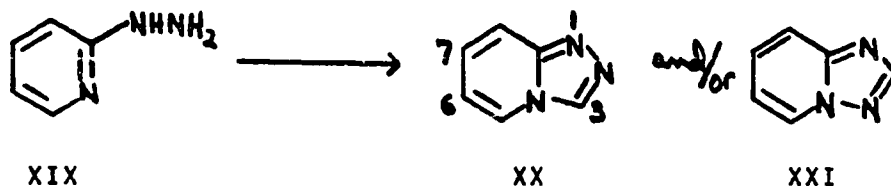
In deciding between assignments XII or XIII, Barton and Paudler obtained the proton NMR spectrum of the product produced by the reaction of 3-amino-5,6-dimethyl-1,2,4-triazine (XI) with 3-bromo-2-butanone to produce 2,3,7,8-tetramethyl-*as*-triazine (XII) or 2,3,5,6-tetramethyl-*as*-triazine (XIII) (11). The proton NMR spectrum showed no



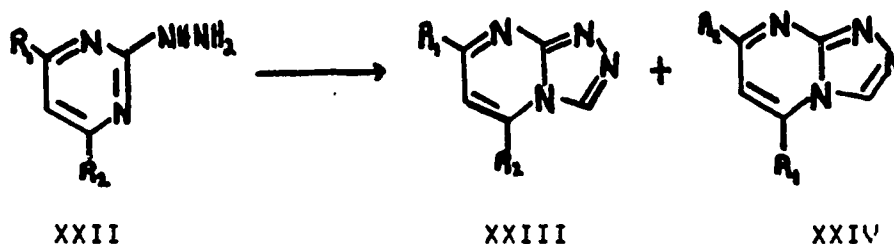
abnormal deshielding of the methyl groups. An observation which indicates that compound XIII rather than compound XII is formed since the peri-situated 3- and 5-methyl groups in XII would sterically interact causing a deshielding of both of the methyl groups (11). Similar cyclization of substituted 2-amino-s-triazine with 3-bromo-2-butanone by Fusco and Rossi (9) and Loev and Goodman (10) confirm this interpretation

## B. Syntheses from Hydrazinoazines.

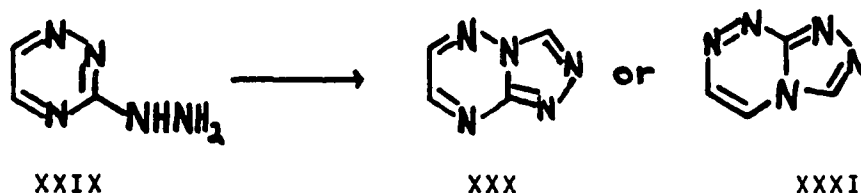
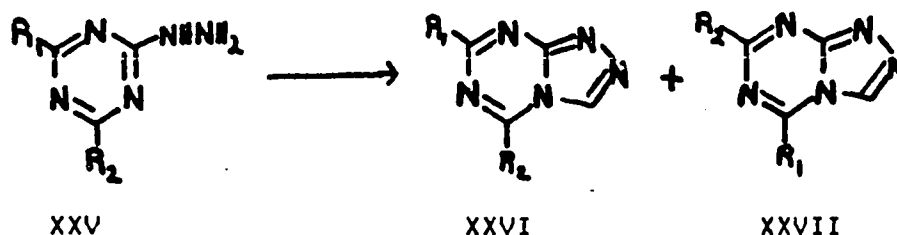
Cyclization of hydrazinoazine (XIX) with an activated one carbon cyclizing agents (i.e. ethyl orthoformate, ethyl formate, diethoxymethyl acetate) is a direct and simple method for the synthesis of triazoloazines (XX). However, the product produced in this reaction can rearrange to produce compound XXI via a Dimroth rearrangement. This type of rearrangement is known to involve the breaking of the 4-5 bond in structure XX (see Dimroth rearrangement).



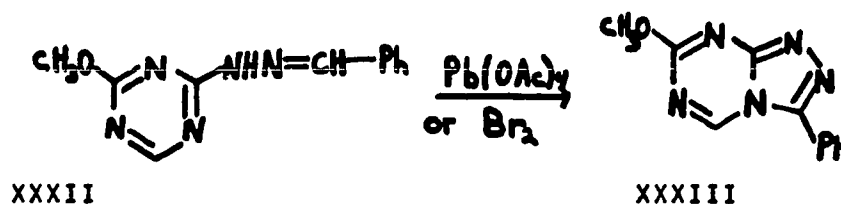
The cyclization of 2-hydrazinopyrimidine (XXII), 2-hydrazino-1,3,5-triazine (XXV) and 3-hydrazino-1,2,4-triazine (XXIX) with one carbon cyclization agents can produce two different products. The orientation of cyclization is influenced by the substituent and the reaction conditions. For example, the reaction of 3-hydrazino-5-hydroxy-6-methyl-1,2,4-triazine with formic acid produces compound XXX. When





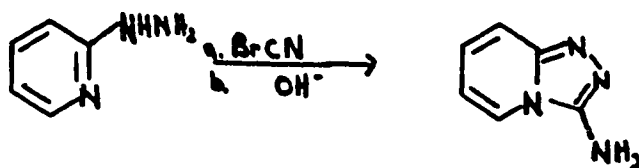


XXIX is reacted under neutral conditions, compound XXXI is produced(12). Cyclization of 2-benzylidenehydrazino-4-methoxy-1,3,5-triazine (XXXII) is controlled by the steric and electronic effects of the methoxyl substituent and the major product is 7-methoxy-3-phenyl-1,2,4-triazolo[4,3a]-1,3,5-triazine (13).



Substitution at position 3, in the pi-excessive ring of the triazoloazines, is controlled by the type of cyclization agent. For example, formic acid and acetic anhydride produce the hydrogen- and methyl- derivatives, respectively. Other reagents that produce 3-hydrogen substitution are ethyl orthoformate, ethyl orthoacetate, or

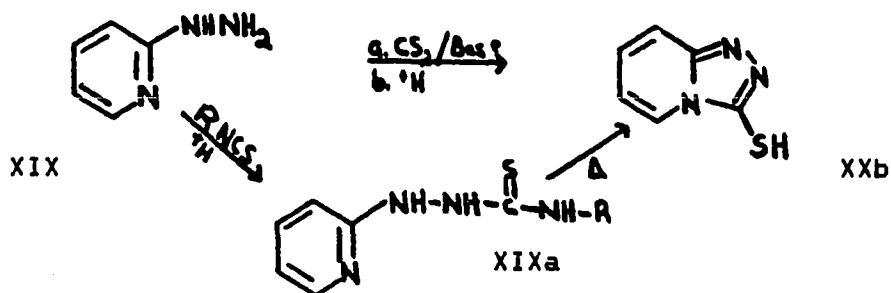
diethoxymethyl acetate. These compounds react under very mild conditions and thereby prevent the Dimroth rearrangement. However, these reagents can be used for the cyclization of hydrazinopyrazines (15) and hydrazinopyridazines (16). Condensation with cyanogen halides



XIX

XXa

at low temperature can produce the 3-amino-triazoloazines (XXa) (14,16,17). Similarly, the reaction of carbon disulfide, or the thermal decomposition of phenylisothiocyanate derivatives (XIXa) produce the 3-mercapto compounds (XXb) (18-21,22a).



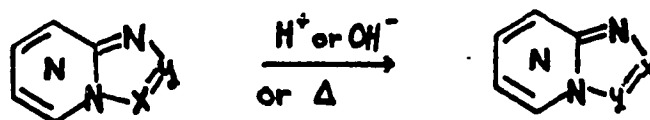
XIX

XIXa

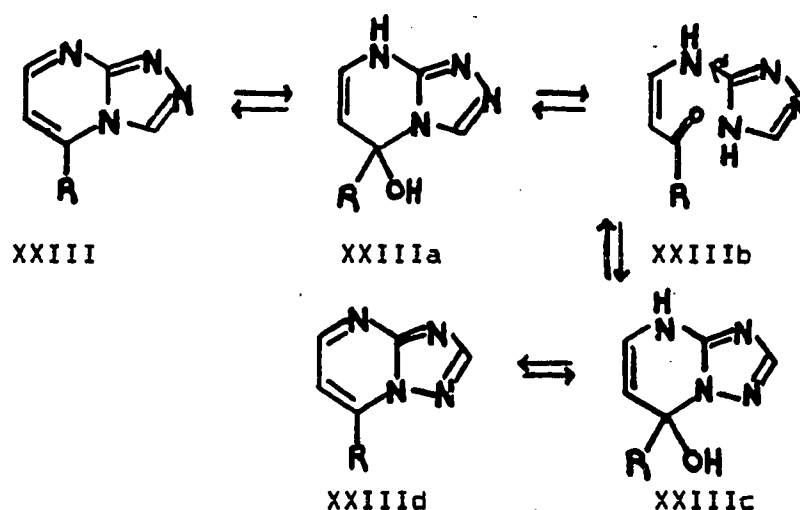
XXb

### C. Dimroth Rearrangement

The Dimroth rearrangement is a general reaction which, when applied to appropriate polyazaindene rings, produces "different" azaindenes. This type of rearrangement can be base, acid, or thermally induced.



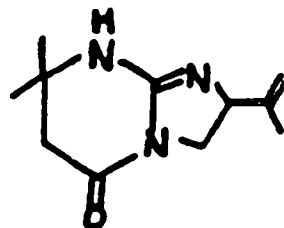
The generally accepted mechanism of the acid or basic catalyzed rearrangement involves the equilibrium-controlled



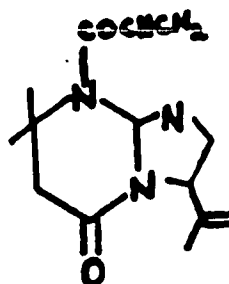
covalent hydration at C-5. This is followed by tautomeric ring opening of the azine ring to a carbonyl intermediate (XXIIIb). Rotation of the 8-9 bond followed by cyclization produces the new polyazaindene structure (XXIIId) (7a,22).

#### D. Biological and Medicinal Properties.

Only few polyazaindenes occur in nature. Alchornine, and alchornidine, which were isolated from *Alchornea javanensis* are based on the hexahydroimidazo-[1,2a]pyrimidine structure (23). The degradation of



alchronine



alchornidine

saxitoxin, a shellfish toxin isolated from Saxidomus giganteus, produced a tetrahydropyrrolopyrimidine (24).

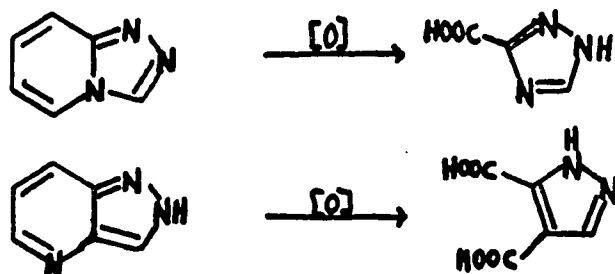
Based on the structural similarities with purine, many polyazaindene derivatives have been converted to their nucleoside counterparts. These derivatives held the potential of having biological activity due to their similarity with naturally occurring nucleosides. The anticancer activity of these nucleosides has been studied. Among the carbohydrate-base combinations that have been closely examined are the pyrazolo[2,3a]pyrimidine (26), 1,2,4-triazolo-[2,3a]- and -[4,3a]pyrimidine (28) and 1,2,4-triazolo[2,3a]-1,3,5-triazine (27).

Table 1 gives the parent name and current uses of several polyazaindenes. These applications include both medicinal and industrial uses.

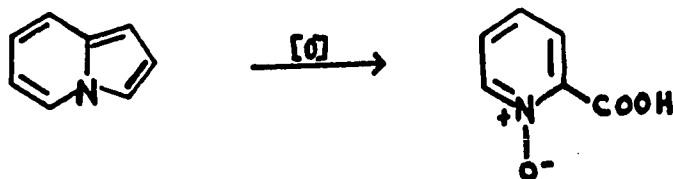
## II. HISTORY OF POLYAZAINDENE N-OXIDES

### Syntheses of Polyazaindene Pi-deficient N-oxides.

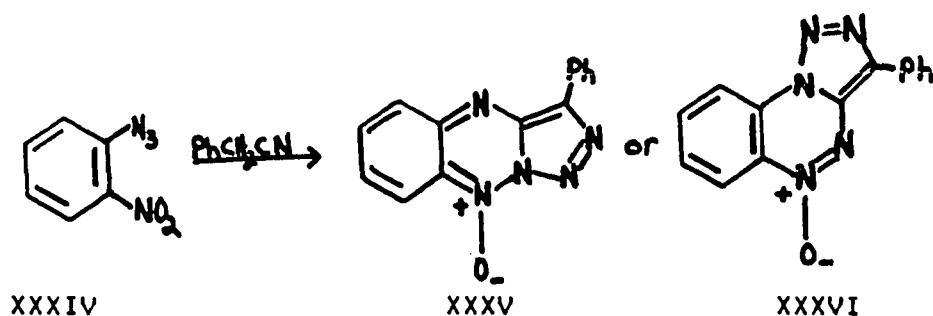
Oxidation of polyazaindenes with potassium permanganate at room temperature yields substituted azoles (29).



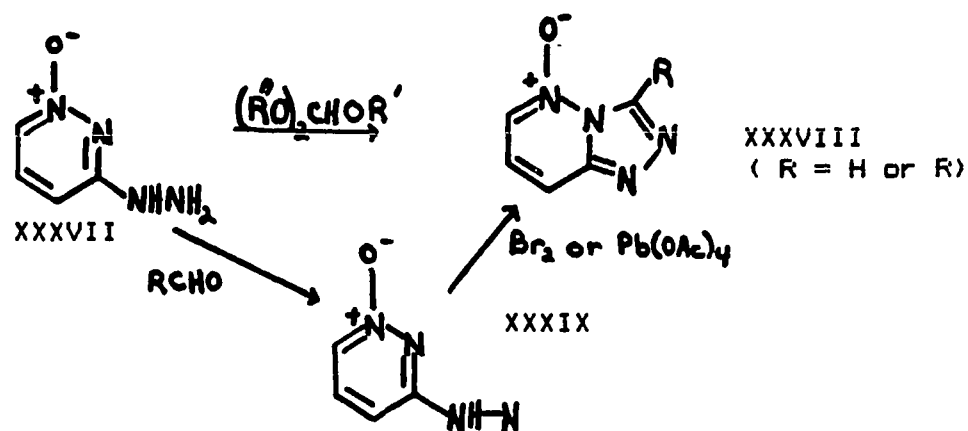
The oxidation of indolizines (pyrrolo[1,2-a]pyridines) destroys the ring system and leads to alpha-picolinic acid N-oxide (30).



In 1957, Lieber and coworkers found that ortho-nitrophenyl azides(XXXIV) reacted with phenyl acetonitrile in the presence of sodium methoxide to produce 1,2,3-triazolo[5,1c]1,2,4-triazine-5-oxide(XXXV) (31). Tennant repeated the reaction of 2-azidonitrobenzene with phenyl acetonitrile and concluded that the true product was the alternate structure XXXVI (32).

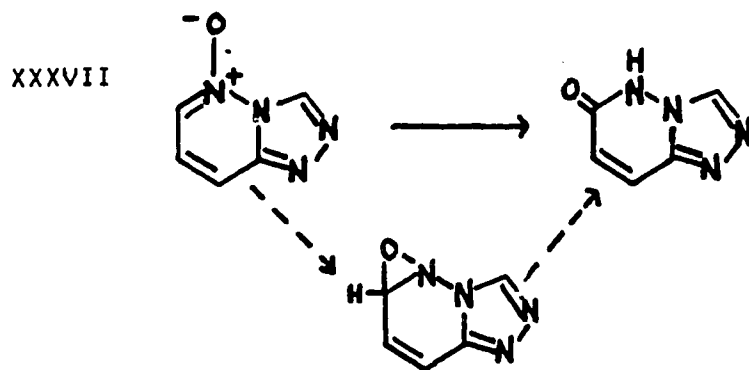


In 1968, the first parent polyazaindene N-oxide was synthesized by Tisler and coworkers (33). The reaction of 3-hydrazinopyridazine-1-oxide (XXXVII) with diethoxymethyl acetate gave the 1,2,4-triazolo[4,3b]pyridazine-5-oxide (XXXVIII) (33). Tisler also reacted the 3-hydrazinopyridazine-1-oxide (XXXVII) with different alkyl and aryl aldehydes to produce the corresponding alkyl- and arylidenes (XXXIX). These alkylidenes (XXXIX) and arylidenes (XXXIX) can be oxidized with lead tetraacetate or bromine to



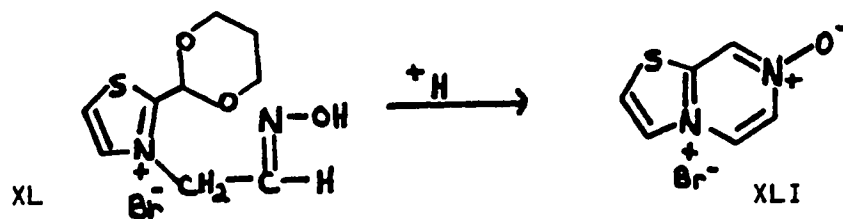
produce the 3-substituted triazolopyridazine N-oxides. Another synthesis of 3-substituted triazolopyridazines involved the direct cyclization of XXXVII with cyanogen bromide in the presence of triethylamine (XXXVIII, R = NH<sub>2</sub>)

(33). Tisler and coworkers showed that ultraviolet irradiation or sunlight smoothly transformed the triazolopyridazine-N-oxides (XXXVIII) into the corresponding 6-hydroxy-s-triazolo[3,4b]pyridazines. This rearrangement is



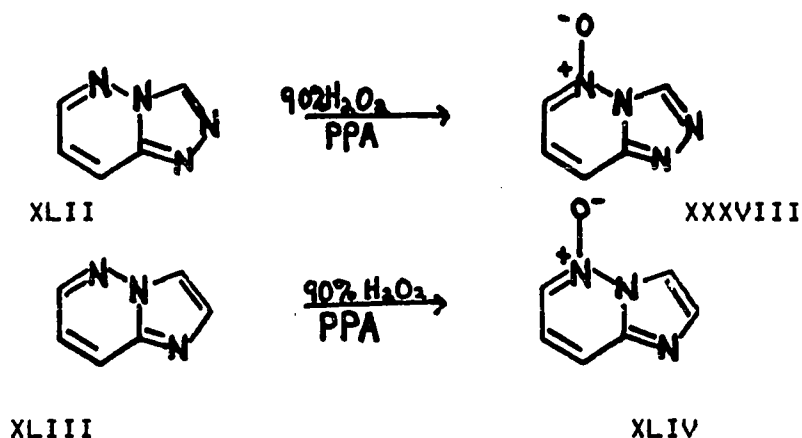
postulated to proceed through an oxaziridine intermediate (33).

In 1969, Glover and coworkers cyclized 1-(2-oximinoethyl)-2-(1,3-dioxolan-2-yl)thiazolium(XL) with sulfuric acid to produce thiazolo[2,3c]pyrazinium bromide-7-oxide(XLI) (34).

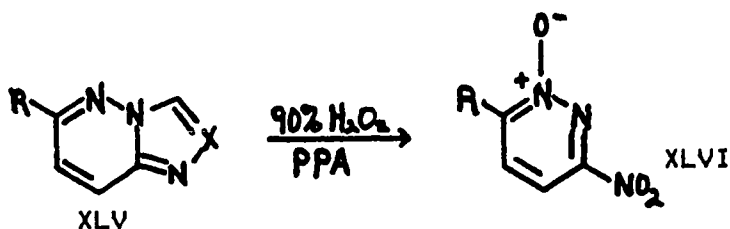


In 1970, Tisler and coworkers were able to oxidize the parent 1,2,4-triazolo[4,3b]pyridazine (XLII) with 90% hydrogen peroxide in polyphosphoric acid to produce XXXVIII

(35). This oxidation was also successful in converting imidazo[1,2b]pyridazine(XLIII) to the corresponding N-oxide(XLIX). Tisler and coworkers suggested that the role of the polyphosphoric acid might involve the uptake of water, rather than act as a proton donor or a Lewis acid.

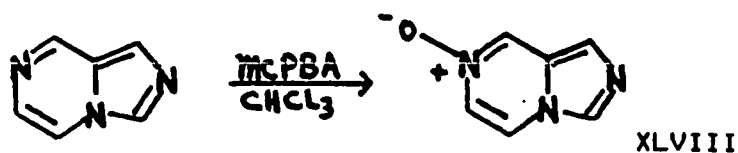


The same workers demonstrated that several 6-substituted polyazaindenes (XLV), when oxidized with 90% hydrogen peroxide in polyphosphoric acid produce the 6-substituted-3-nitro-pyridazine-1-oxides (XLVI) (35).



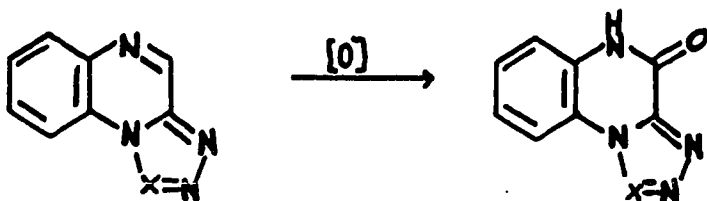
In 1973, Abushanab and coworkers reported the successful oxidation of imidazo[1,5a]pyrazine(XLVII) with meta-chloroperbenzoic acid in chloroform to give the imidazo[1,5c]pyrazine-7-oxide(XLVIII) (36).





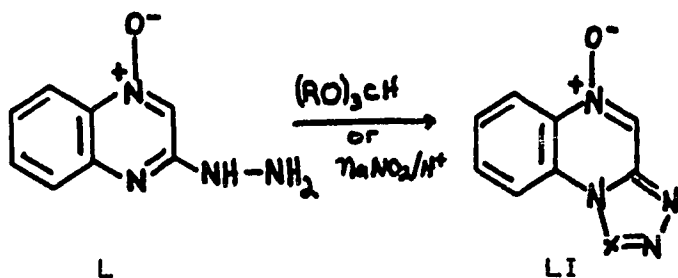
XLVII

Attempts by Koshel and coworkers to prepare the N-oxides of 1,2,4-, and 1,2,3,4-azoloquinoxalines (XLIX) with hydrogen peroxide in acetic acid, alkaline potassium permanganate, or acidic chromic anhydride resulted in an unusual oxidation of C-4 rather than N-oxidation. (37) Successful syntheses of these heteroaromatic N-oxides were achieved by Cue and coworkers using the N-oxide

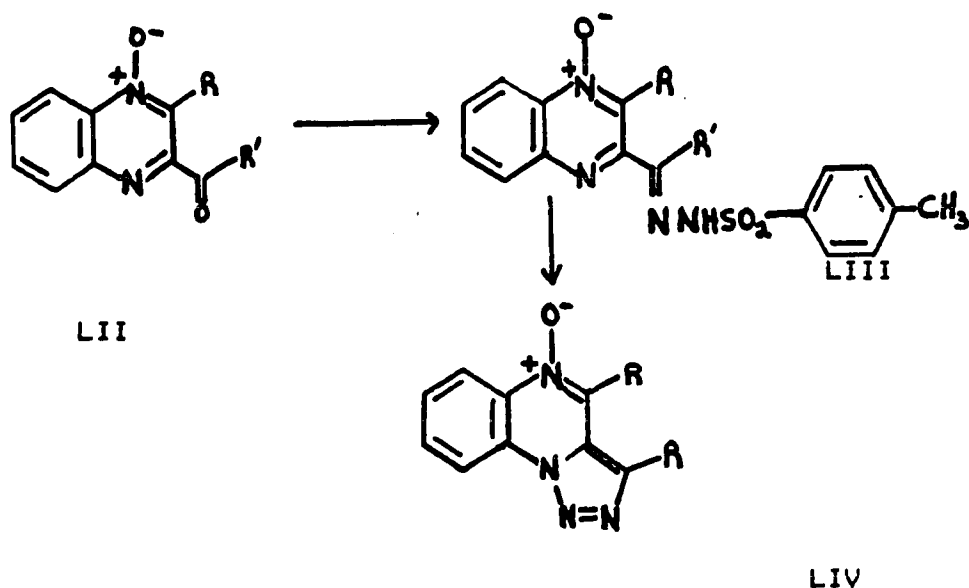


XLIX

precursors (38). Cue and coworkers cyclized 3-hydrazinoquinoxaline-1-oxide (L) with ethyl orthoformate to yield 1,2,4-triazolo[4,3-c]quinoxaline-5-oxide (LI, x=CH). The 3-hydrazino compound (L) was converted to the tetraazolo[1,5-a]quinoxaline-5-oxide (LI, x=N) by a diazotiza-



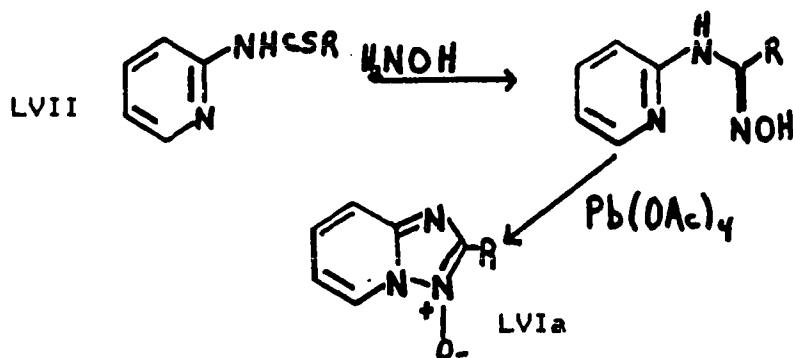
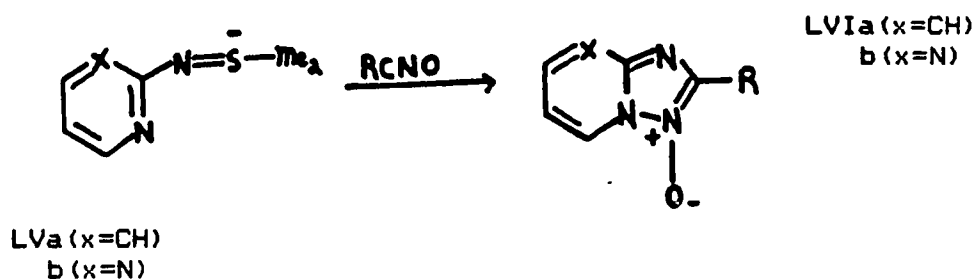
tion reaction in aqueous acetic acid (38). Cue and coworkers also synthesized the 1,2,3-triazolo[1,5a]quinoxaline-5-oxide by the treatment of **LII** with *p*-toluenesulfonylhydrazine in methanol to yield the tosylhydrazone (**LIII**). The reaction of **LIII** with sodium methylate in methanol gave 1,2,3-triazolo[1,5a]quinoxaline (**LIV**) (38).



#### Syntheses of Polyazaindene Pi-excessive N-oxides.

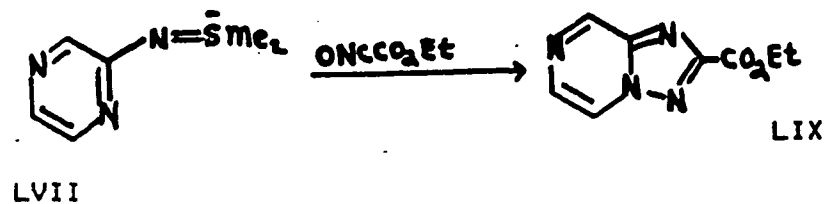
Rees and coworkers in 1974 were first to prepare *pi*-excessive polyazaindene N-oxides (39). They found that pyrido- and pyrimidino-SS-dimethylsulphimides (LV) react with *p*-toluonitrile to give the 2-*p*-tolyl-1,2,4-triazolo[1,5a]pyridine-3-oxide (LVia) and the 2-*p*-tolyl-1,2,4-triazolo[1,5a]pyrimidine-3-oxide (LVib), respectively (39). Rees and coworkers synthesized the 2-*p*-tolyl-1,2,4-triazolo-

[1,5a]pyridine (LVIIa) via a different method as an independent structure proof (39). This is shown in scheme 1.

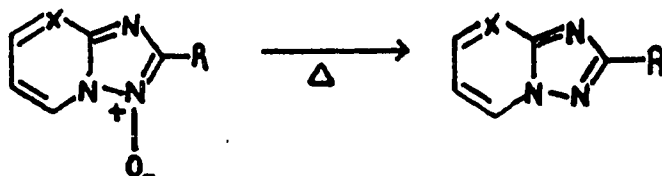


Scheme 1

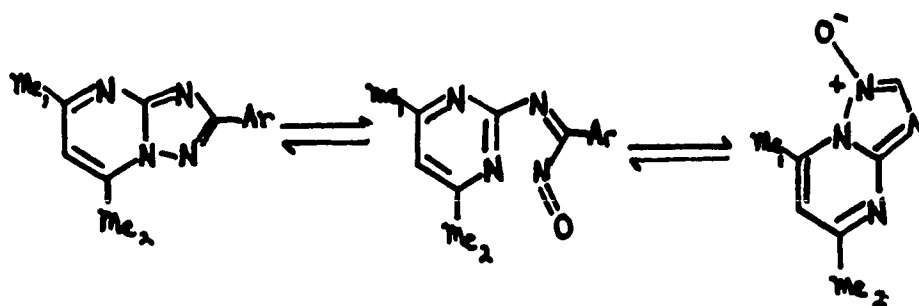
Later, Rees expanded the reactions of the sulphemides to pyrazin-2-ylsulphemide (LVII) to produce 1,2,4-triazolo-[1,5a]pyrazine-3-oxide (LIX) (40). The thermal stability of



peri-substituted triazolopyridine-3-oxides was greatly reduced relative to the parent N-oxides. Thus, when the triazolopyridine-3-oxides were heated under reflux in toluene, deoxygenation occurred after 7 to 8 hours (scheme 2) (39,40). Temperature dependence was noted in the thermal treatment of 5,7-dimethyl-1,2,4-triazolo[1,5a]pyrimidine-3-oxide. In this case the compound rearranges to "shift" methyl groups (scheme 3) (40).

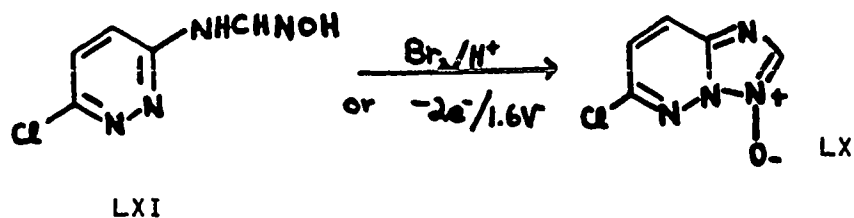


Scheme 2

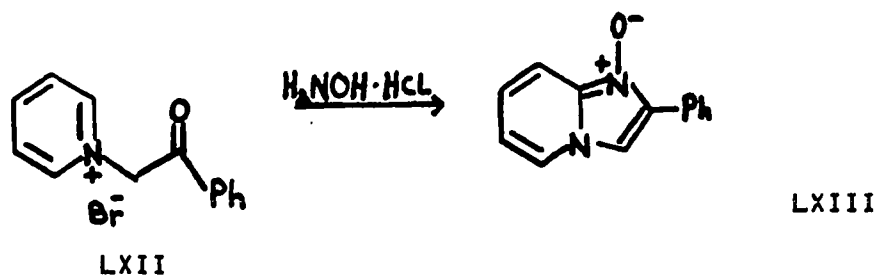


Scheme 3

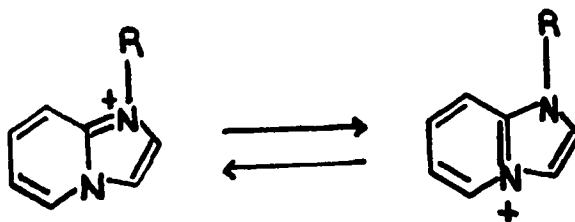
Tisler and coworkers found that when 6-chloro-3-hydroxyiminomethyleneaminopyridazine(LXI) reacted with bromine in acetic acid buffered solution 6-chloro-1,2,4-triazolo[1,5b]pyridazine-3-oxide(LX) was produced in high yield (71%) (41). The oxidation of LXI was also accomplished using an electrochemical method (42).



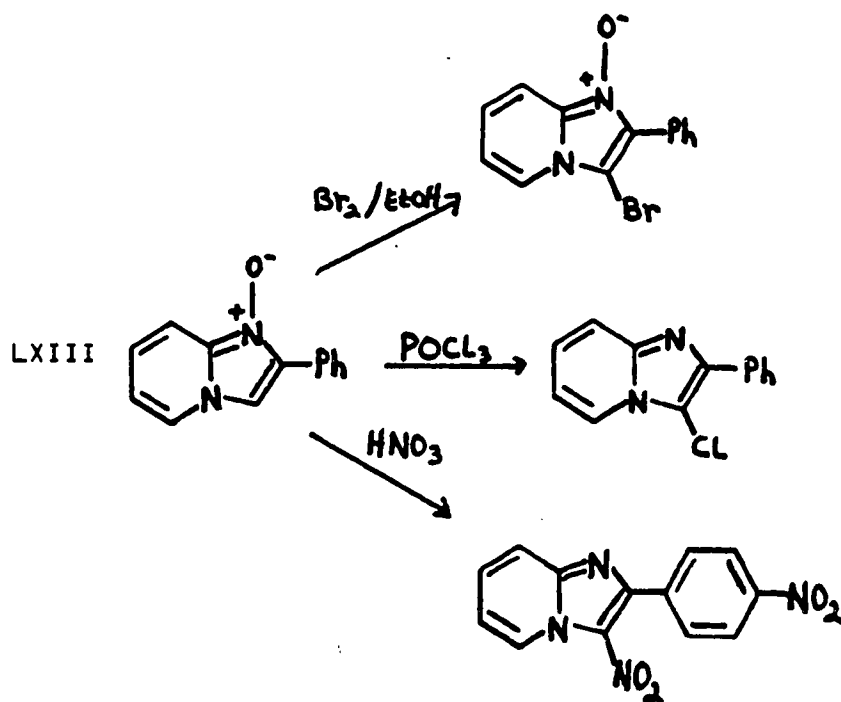
In 1978, Faudler and Hand produced 2-phenylimidazo[1,2-a]pyridine-1-oxide (LXIII) from 2-bromo-1-phenacylpyridinium bromide (LXII) and hydroxylamine hydrochloride (43). They noted that the ground state resonance contributing structure was not altered greatly by the presence of the N-oxide function (see scheme 4).



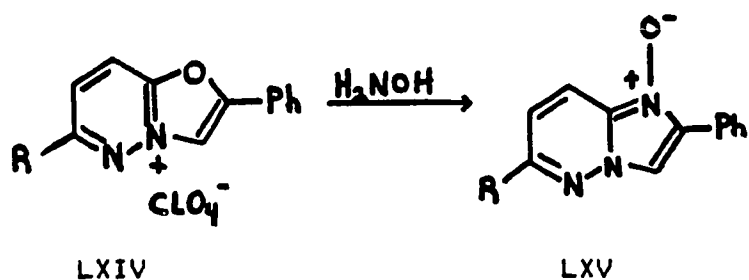
The presence of the N-oxide function does not alter the reactivity of the imidazo[1,2-a]pyridine system (see scheme 5) (43).



Scheme 4



Miyasaka and coworkers prepared imidazo-[1,2b]pyridazine-1-oxide (LXV) by reacting oxazolo[3,2b]-pyridazinium perchlorates (LXIV) with hydroxylamine (44).

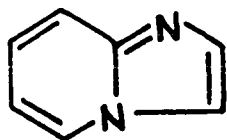


Miyasaka and coworkers examined the electrophilic substitution reactions of LXV and noted that these substitution reactions at position 3 were also not effected by the N-oxide group (45).

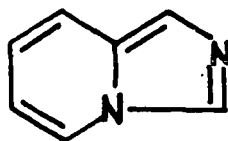
## III. DISCUSSION

Paudler and coworkers have made numerous contributions to the field of polyazaindene chemistry. The ring systems that have been studied to date include imidazo[1,2-a]pyridine (LXVI), imidazo[1,5-a]pyridine (LXVII), pyrazolo[1,2-a]pyridine (LXVIII), pyrrolo[1,2-a]pyrazine (LXIX), imidazo[1,2-a]pyrazine (LXX), imidazo[1,2-a]pyrimidine (LXXI), imidazo[1,5-a]pyrimidine (LXXII),  $\underline{s}$ -triazolo[1,2]pyridine (LXXIII),  $\underline{s}$ -triazolo[4,3-a]pyrimidine (LXXIV),  $\underline{s}$ -triazolo[1,5-a]pyrimidine (LXXV), imidazo[1,2-b]- $\underline{as}$ -triazine (LXXVI), and imidazo[2,1-c]- $\underline{as}$ -triazine (LXXVII).

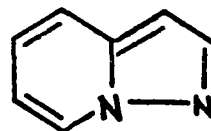
The chemistry of these polyazaindene systems has



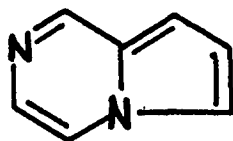
LXVI



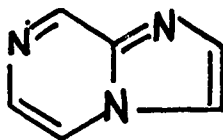
LXVII



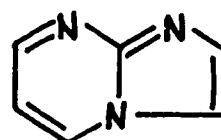
LXVIII



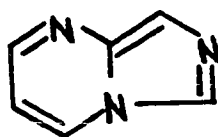
LXIX



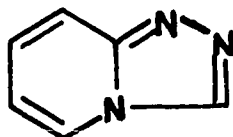
LXX



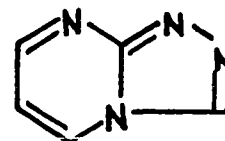
LXXI



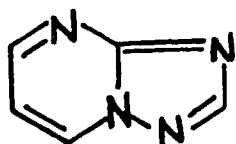
LXXII



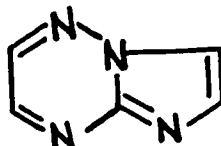
LXXIII



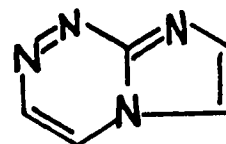
LXXIV



LXXV



LXXVI



LXXVII

been studied in detail. These studies include: syntheses, electrophilic reactions, protonation and methylation reactions, hydrogen-deuterium exchange, nuclear magnetic resonance, mass spectral work, and correlation of molecular orbital calculations with the experimental results.

The present research was begun for the purpose of gaining a basic understanding of the chemistry of the poorly understood polyazaindene N-oxide series.

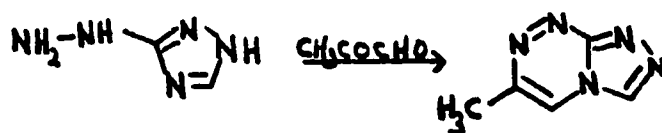
This investigation consists of the following research areas: (a) synthesis of the parent s-triazolo[3,4c]-as-triazine-7-oxide, s-triazolo[3,4c]pyrazine-7-oxide and s-triazolo[3,2c]pyrazine-7-oxide (b) reactions of 3-hydrazino-as-triazine-1-oxide and 3-hydrazinopyrazine-1-oxide with different cyclization reagents (c) reaction of s-triazolo[3,4c]-as-triazine-7-oxide and s-triazolo[3,4c]pyrazine-7-oxide (d) synthesis and reactions of imidazo[1,2c]pyrazine-7-oxide, (e) spectral information (NMR and Mass Spectra) of s-triazolo[3,4c]-as-triazine-7-oxide, s-triazolo[3,4c]pyrazine-7-oxide, s-triazolo[3,2c]pyrazine-7-oxide and imidazo[2,1c]pyrazine-7-oxide.



A second important purpose deals with the possible biological activity in these systems. Testing and evaluation will be done in subsequent studies by other workers. What follows represents efforts to accomplish these above goals.

Syntheses and Structure Determination of the Parent s-Triazolo[3,4c]-as-triazine-7-oxide(LXXIX) and s-Triazolo[3,4c]pyrazine-7-oxide(LXXXI).

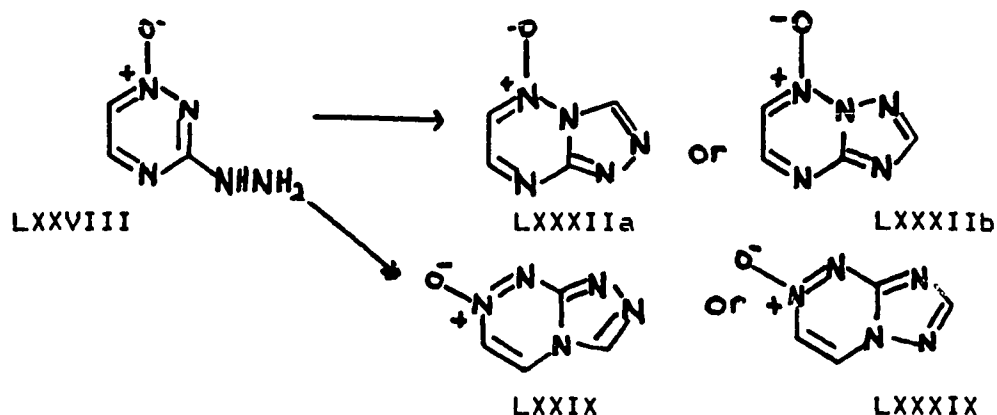
Synthesis of the s-triazolo[3,4c]-as-triazine-7-oxide(LXXIX) was done by thermal cyclization of 3-hydrazino-as-triazine-1-oxide(LXXVIII) with diethoxymethyl acetate. The effect of the N-oxide upon cyclization was not known prior to this work. Cyclization of 3-hydrazino-as-triazines is always to the N-2 nitrogen. The only known synthesis for s-triazolo[3,4c]-as-triazine (LXXXIII) is cyclization of a substituted azole ring to form the azine ring (46).



LXXXIII

Several possibilities exist for preparing the cyclized product of 3-hydrazino-as-triazine-1-oxide(LXXVIII). Cyclization of LXXVIII could occur at either N-2 or N-4 producing two different isomers. The potential

exists that either of these compounds may undergo Dimroth



rearrangement of give  $\alpha$ -triazolo[3,2c]- $\alpha$ -triazine-7-oxide (LXXXIX) or  $\alpha$ -triazolo[2,3b]- $\alpha$ -triazine-7-oxide (LXXXII). The only known cyclization of a 3-substituted- $\alpha$ -triazine into the 4-position is that found for 2-methyl-3-azido- $\alpha$ -triazine (LXXXV) (47). In all other reported cases cyclization has occurred at the N-2 position.

The reaction of diethoxymethyl acetate with 3-hydrazino- $\alpha$ -triazine-1-oxide (LXXVIII) produces only one product in high yield. The elemental and mass spectral analysis showed the molecular formula to be C<sub>4</sub>H<sub>3</sub>N<sub>5</sub>O. The mass spectrum shows a parent peak of 137 m/e and the facile loss of 16 mass units, the N-oxide oxygen. This result points to the probable presence of the N-oxide (51).

Comparison of the proton NMR spectrum with known structures was successful in determining the structure of this compound. Table 2 gives the proton NMR data of several polyazaindenes and their N-oxides, while table 3 gives the

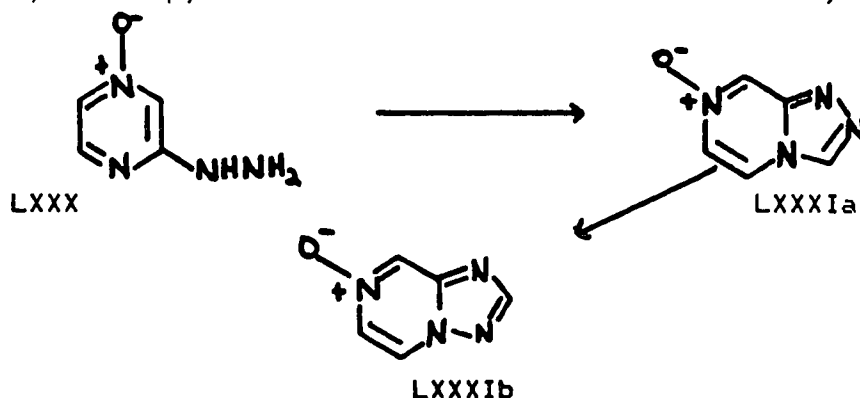
differences in the resonance positions for the s-triazolo- and imidazo-compounds.

The normal deshielding of peri-hydrogens relative to the N-oxides is approximately 0.5 ppm. This deshielding was first noted in the 1,8-naphthridine-1-oxide by Paudler and coworkers (48), and later by Tisler and coworkers (35). The effect on the chemical shift of the non-peri hydrogen by the N-oxide is very small (<0.1 ppm) and can occur in either direction. This latter small proton chemical shift is observed in the cyclization of the 3-hydrazino-as-triazine-1-oxide (LXXVIII) (51). Consequently, cyclization in the reaction of 3-hydrazino-as-triazine-1-oxide with diethoxymethyl acetate occurred at the N-4 nitrogen (51).

Table 3 lists H-NMR chemical shifts of non-rearranged polyazaindene versus the Dimroth rearranged polyazaindene. The rearranged product has a typical proton chemical shift upfield by approximately of 0.5 to 1.2 ppm for the azole hydrogen. In general the non-rearranged polyazaindenes have typical azole proton chemical shifts of 9.25 ppm while the Dimroth rearranged product have a typical azole proton chemical shifts of 8.2 to 8.75 ppm. By comparison, the cyclized product from the reaction of 3-hydrazino-as-triazine-1-oxide(LXXVIII) with diethoxymethyl acetate, has a azole proton chemical shift of 9.28 ppm. This clearly establishes that the Dimroth rearrangement did not occur.

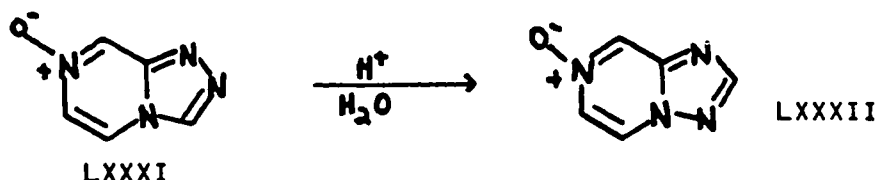
Final structure elucidation of the s-triazolo[3,4c]-

as-triazine-7-oxide(LXXIX) was accomplished by the preparation of a second polyazaindene N-oxide. The reaction of 3-hydrazinopyrazine-1-oxide(LXXX) with diethoxymethyl



acetate can produce either the s-triazolo[3,4c]pyrazine-7-oxide(LXXXIa) or the s-triazolo[1,5c]pyrazine-7-oxide(LXXXIb) by the Dimroth rearrangement. The product obtained has the correct empirical formula,  $\begin{matrix} \text{C} & \text{H} & \text{N} & \text{O} \\ 5 & 4 & 4 & \end{matrix}$  based on elemental analyses. The mass spectrum as anticipated for a N-oxide shows a M-16 ion (the loss of oxygen). The mass spectrum has a base peak due to the parent ion. The proton nuclear magnetic resonance spectrum contains a singlet at 9.21 ppm and an ABX pattern at 7.79 ppm, 8.74 ppm and 9.14 ppm. The proton chemical shift of the singlet is in agreement with s-triazolo[3,4c]pyrazine-7-oxide(LXXXIa), rather than the s-triazolo[1,5c]pyrazine-7-oxide(LXXXIb). These chemical shifts are in agreement with the structure assigned to the product formed by the cyclization of 3-hydrazino-as-triazine-1-oxide(LXXVIII) with diethoxymethyl acetate (51).

Additional information was obtained when the s-triazolo[3,4c]pyrazine-7-oxide(LXXXIa) was treated with aqueous hydrochloric acid. On treatment with 1 normal hydrochloric acid in ethanol, the triazolopyrazine-N-oxide



undergoes the Dimroth rearrangement to the s-triazolo[3,2c]pyrazine-7-oxide(LXXXIb). The proton NMR spectrum of this compound contains a singlet at 8.62 ppm and exhibited an ABX pattern at 9.06 ppm, 8.03 ppm and 9.11 ppm (51). Hence these H-3 proton shifts are in excellent agreement with the predicted resonance position (see table 2).

#### Other Reactions of 3-Hydrazino-as-Triazine-1-oxide and Pyrazine-1-oxide.

The reaction of 3-hydrazino-as-triazine-1-oxide(LXXVIII) with formic acid yields 3-formylhydrazino-as-triazine-1-oxide(LXXXVIa). This cyclization may be hindered by the protonation of the N-4 nitrogen in an acidic reaction medium. Similar results are obtained with formic acid and 3-hydrazinopyrazine-1-oxide(LXXX). However, the cyclization can be completed by heating with 3-formylhydrazinopyrazine-1-oxide(LXXXVIb). The product obtained has an identical retention time when applied to a thin layer chromatographic

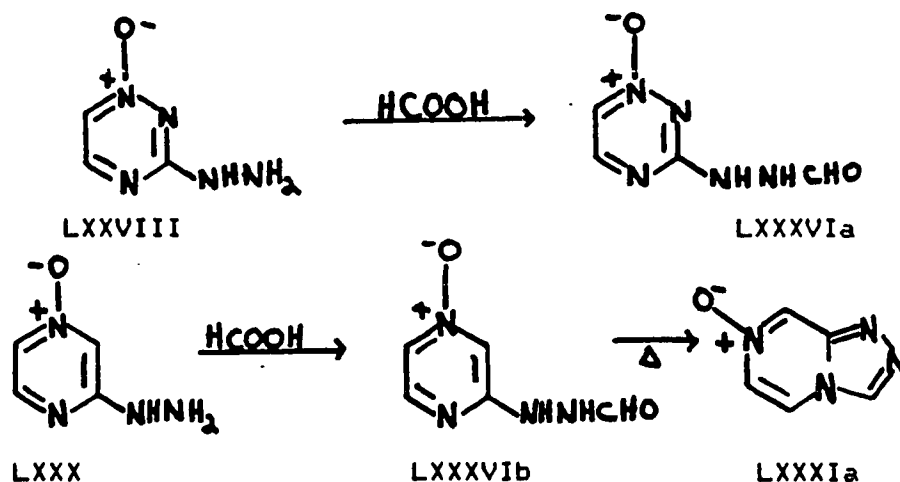
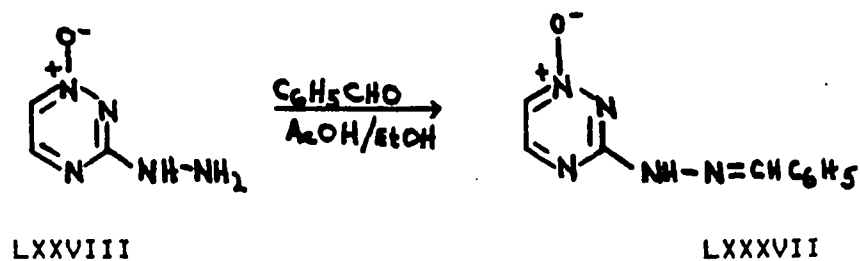


plate as a known sample of  $\alpha$ -triazolo[3,4c]pyrazine-7-oxide(LXXXI).

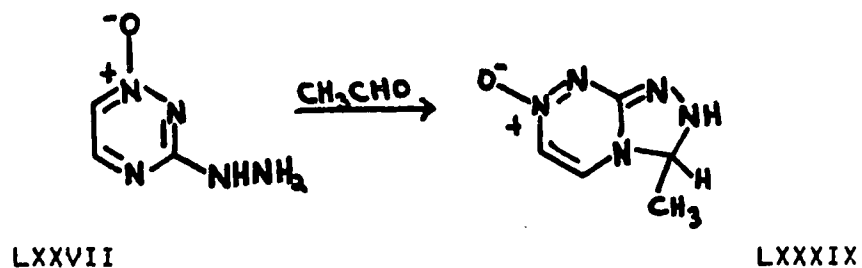
The reaction of 3-hydrazino- $\alpha$ -triazine-1-oxide(LXXVIII) with benzaldehyde in acetic acid affords 3-benzylidenohydrazino- $\alpha$ -triazine-1-oxide(LXXXVII). This benzylidene product was treated with lead tetraacetate in an unsuccessful attempt to complete the cyclization. It returned the benzylidino compound unchanged! A similar, attempted cyclization of the 3-benzylideno compound with



bromine in acetic acid and sodium acetate also failed. The reaction of 3-hydrazinopyrazine-1-oxide(LXXX) with

benzaldehyde produces 3-benzylidenohydrazinopyrazine-1-oxide(LXXXVIII). Cyclization to the corresponding bicyclic compound was not achieved by using lead tetraacetate or bromine in acetic acid.

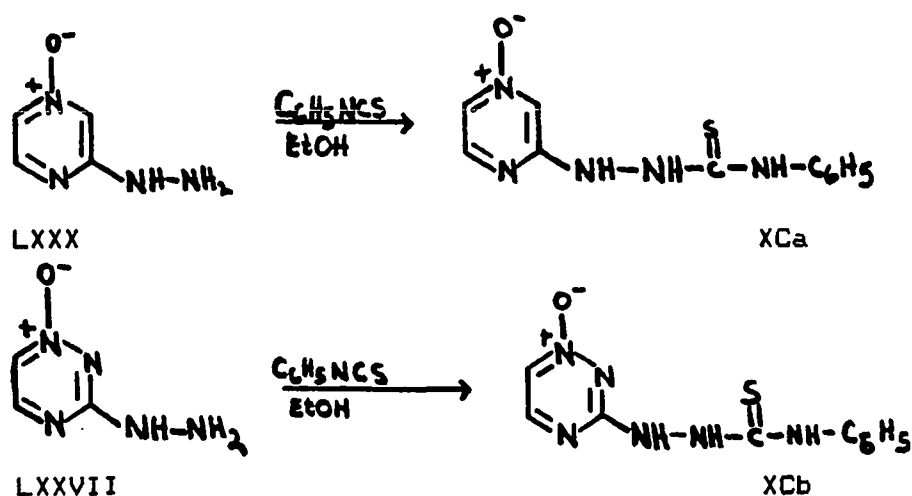
The reaction of 3-hydrazino-as-triazine-1-oxide(LXXVIII) with acetaldehyde did not produce the expected methylideno compound but instead produces the 2,3-dihydro-3-methyl-s-triazolo[3,4c]-as-triazine-7-oxide (LXXXIX). There are two features of the NMR spectrum that show this cyclization occurs without aromatization. The first is the proton chemical shifts of 3-benzylideno-(LXXXVIII), 3-formyl-(LXXXVIb) pyrazine-1-oxide, 3-benzylideno-(LXXXVII) and 3-formyl-(LXXXVIa) -as-triazine-1-oxide (see table 4). The proton resonance positions of the formyl and benzylideno protons are about 8.50 ppm, whereas the proton chemical shift of the product formed from acetaldehyde with 3-hydrazino-as-triazine-1-oxide (LXXVIII) is at 7.60 ppm. This indicates that the chemical environment



is different for the normally observed proton chemical shifts for the derivatives of 3-hydrazino-as-triazine-1-oxide. The second is the proton resonance positions of the

ring protons and the differences between these chemical shifts are given below (see table 4). With the 3-hydrazino-as-triazine-1-oxide derivatives there is a difference in the proton chemical shifts of 0.5 ppm for the aromatic protons, (H-5) - (H-6). The chemical shifts for H-5 and H-6 of the methyleno compound are 7.63 and 8.30, respectively. The difference, (H-5) - (H-6), is -0.67 ppm, which is greater than expected, represents an upfield shift (increased shielding). This shielding effect is due to the change or loss of the azine ring aromaticity. These results rule out that the compound is the methyleno derivative.

The reaction of 3-hydrazino-pyrazine-1-oxide(LXXX) and as-triazine-1-oxide(LXXVII) with phenyl isothiocyanate produces the expected 3-(4-phenylthiosemicarbizide)-pyrazine-1-oxide(XCa) and as-triazine-1-oxide(XCb). This is



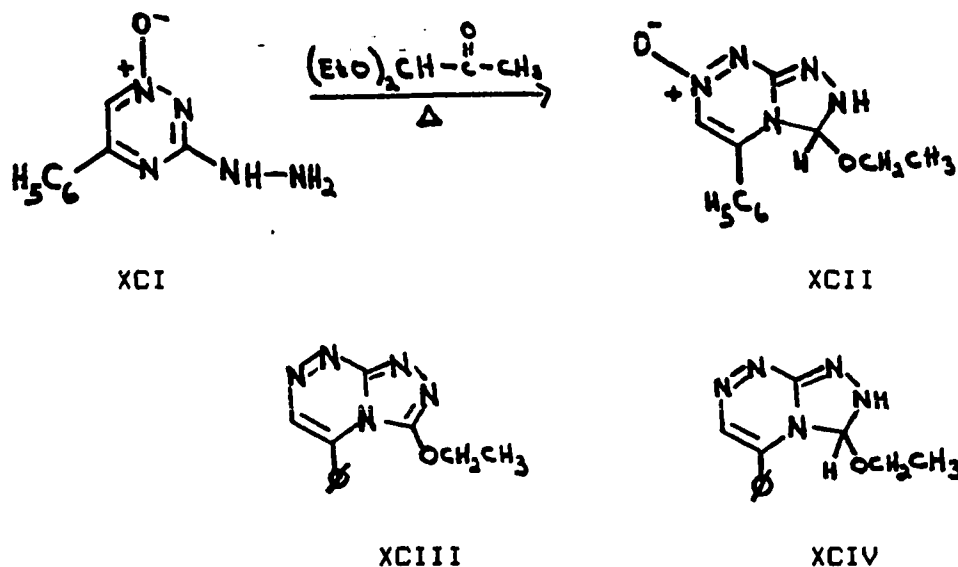
shown in Table 4. The thermal decomposition of these compounds did not produce either of the expected cyclized



products. These reactions need to be examined further!

The reaction of cyanogen bromide or carbon disulfide in the presence of base with 3-hydrazino-pyrazine-1-oxide(LXXX) or as-triazine-1-oxide(LXXVIII) failed to produce the 3-amino or the 3-mercapto derivatives, respectively.

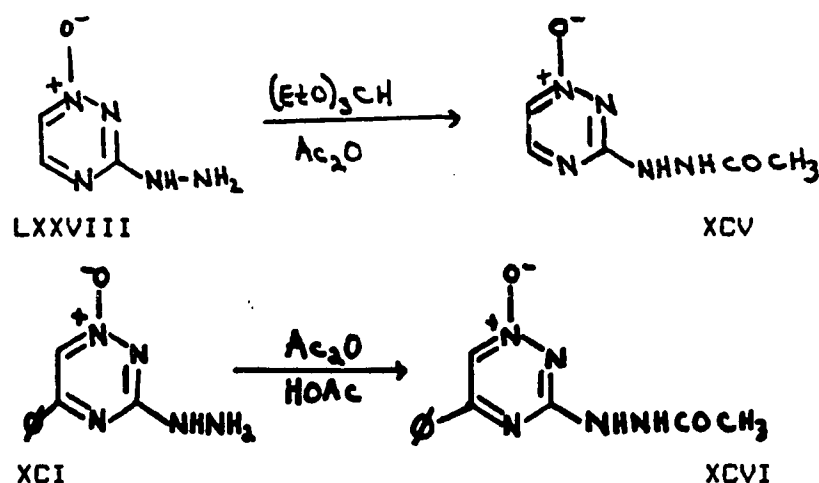
The reaction of the 3-hydrazino-5-phenyl-as-triazine-1-oxide(XCI) with diethoxymethyl acetate produces 2,3-dihydro-3-ethoxy-5-phenyl-s-triazolo[3,4c]-as-triazine-7-oxide(XCII); cyclization without aromatization in this case



may be a result that the N-oxide group can not participate in the removal of the ethoxy group without opening the triazole ring. Attempts to aromatize the azole ring with 10% palladium on carbon were successful but at the expense of the N-oxide. The loss of the N-oxide is the result of the failed aromatization allowing deoxygenation by the 10%

palladium on carbon. The resulting products are 3-ethoxy-5-phenyl-s-triazolo[3,4c]-as-triazine(XCIII) and 2,3-dihydro-3-ethoxy-5-phenyl-s-triazolo[3,4c]-as-triazine (XCIV).

The formation of the 3-acetylhydrazino-as-triazine-1-oxide(XCV) and 3-acetylhydrazino-5-phenyl-as-triazine-1-



oxide(XCVI) occurs via the reaction of acetic anhydride in triethyl orthoformate with 3-hydrazino-as-triazine-1-oxide or in acetic acid with the 5-phenyl derivative, respectively. Further attempts to cyclize the acetyl derivative failed causing decomposition.

#### REACTIONS OF S-TRIAZOLO[3,4C]PYRAZINE-7-OXIDE AND S-TRIAZOLO[3,4C]-AS-TRIAZINE-7-OXIDE.

A variety of reactions was studied using triazolopyrazine-N-oxide and triazolotriazine-N-oxide. Unfortunately, the expected product was not obtained. A few of the reactions will be mentioned and all will be listed in the experimental section.

The deuterium exchange of the H-3 proton has been well documented by Faudler's research group (49). The attempted exchange of the triazolopyrazine-N-oxide and the triazolotriazine-N-oxide results in the uniform disappearance of all chemical shifts in the proton NMR spectrum. The disappearance of the proton chemical shifts can be explained in two ways. The first way suggests that all protons are exchanging at an equal rate. Secondly, the bicyclic compounds may be decomposing.

The latter process is correct since the bicyclic compounds could not be isolated from the reaction vessel after the "exchange" experiment.

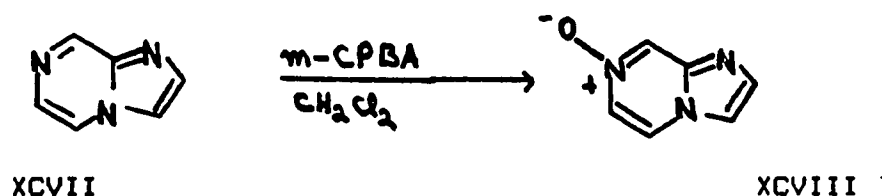
All attempts to study the reaction of triazolopyrazine N-oxide or triazolotriazine N-oxide with electrophilic reagents failed and resulted in product decomposition. The most probable cause for the decomposition was that most electrophilic agents were generated in water or water was employed during the reaction workup. This water usage, under basic conditions, may start the Dimroth rearrangement which may lead to sample decomposition in either products or reactants. It has been observed that the addition of base to hydrazino compounds produced a red color when the pH of the system exceeded 6. Attempts to recover any organic material from the basic solution failed. Spectral evidence showed the loss of bicyclic system ( NMR and mass spectrum ) and

replacement with some type of amino or imino compound (infrared spectrum).

Attempts to deoxygenate the s-triazolo[3,4c]-as-triazine-7-oxide(LXXIX) with triethyl phosphite or many other deoxygenation reagent (see experimental section) failed to produce the non-oxide derivative. One possible explanation is that a very strong N-O bond (a large amount of backbonding) exists in these compounds.

#### SYNTHESIS OF IMIDAZO[2,1c]PYRAZINE-7-OXIDE(XCVIII).

The direct oxidation of the imidazo[2,1c]pyrazine with meta-chloroperbenzoic acid in chloroform is successful. This type of reaction is unusual because most attempts to oxidize the bicyclic rings of 'indolazine-like' or 'indene-like' structures result in the cleavage of the azole ring (29). Only two other cases of this direct type of oxidation have been reported (see Historical Section).



#### REACTIONS OF IMIDAZO[2,1c]PYRAZINE-7-OXIDE.

As with s-triazolo[3,4]-pyrazine-7-oxide(LXXXI) and -as-triazine-7-oxide(LXXIX), the attempted electrophilic substitution of imidazo[2,1c]pyrazine-7-oxide(XCVII) resulted in sample decomposition. This behavior is

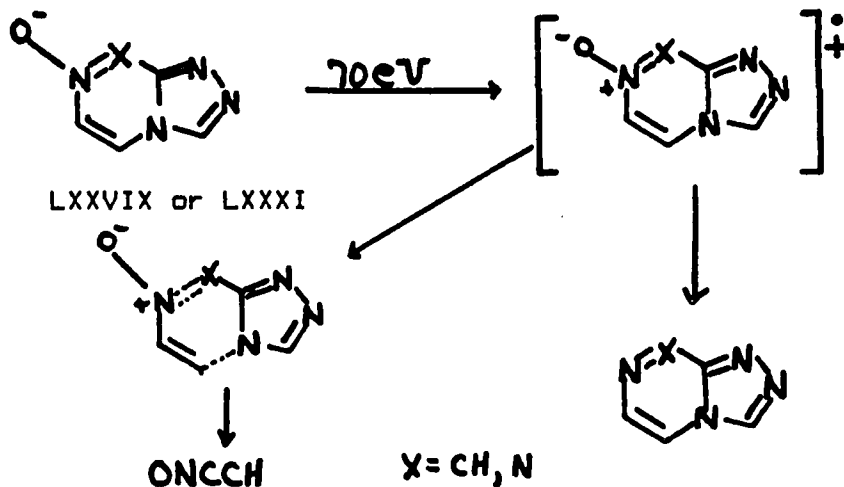
consistent with the three other polyazaindene-N-oxides discussed earlier and suggests that the N-O bond facilitates the decomposition of the polyazaindene N-oxides.

Attempts to deoxygenate the imidazo[2,1c]pyrazine-7-oxide were unsuccessful and resulted in the decomposition of the bicyclic ring system.

**NUCLEAR MAGNETIC RESONANCE AND MASS SPECTRA INFORMATION ON S-TRIAZOLO[3,4c]-AS-TRIAZINE-7-OXIDE, S-TRIAZOLO[3,4c]PYRAZINE-7-OXIDE, AND IMIDAZO[2,1c]PYRAZINE-7-OXIDE.**

**MASS SPECTRAL INFORMATION.**

The mass spectra of all polyazaindene have one fragmentation pattern in common, the base peak (100%) is the molecular ion peak ( $M^+$ ). The large  $M^+$  peak may well reflect the stability caused by the aromatic properties of the bicyclic ring system. In the case of the parent systems of triazolopyrazine and triazolotriazine, the base peaks are at 136 amu and 137 amu, respectively. This is followed by



the loss of 16 amu which is the cleavage of the N-O bond. Neither the triazolopyrazine N-oxide nor the triazolotriazine N-oxide have a large M-16 peak (12.7% and 20.9%, respectively).

The major pathway for cleavage of triazolo- pyrazine- N-oxide and triazine N-oxide is through the azine ring. Both the triazolopyrazine and triazolotriazine N-oxides have a M-55 loss. This loss represents the cleavage of the 7-8 bond ( alpha to the N-O bond ) and the splitting of the 4-5 bond ( gamma to the N-O bond which is alpha to the bridging nitrogen at position 4 ). This results in the loss of the HCCNO fragment which "leaves" only the azolo ring system.

The remaining fragments are caused by the decomposition of the azole ring system and are not identified.

#### NUCLEAR MAGNETIC RESONANCE SPECTRAL INFORMATION

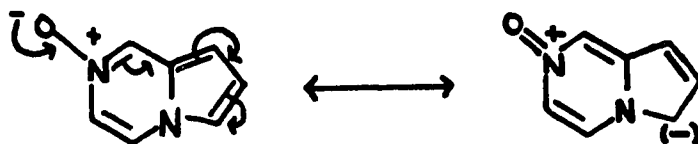
The proton nuclear magnetic resonance spectra of seven polyazaindenes N-oxides have been determined by this study and compared in part with the results obtained by other workers. These proton NMR data are compiled in table 4.

An interesting change that occurs between the parent compound versus the N-oxide is the characteristic shielding effect of the N-oxide on the ortho protons. This effect has been examined and described by Paudler and coworkers for a number of 6-membered heteroaromatic compounds (50). The typical shielding of 0.23- 0.50 ppm for the H-8 proton is

also seen in the polyazaindene structures. A similar shielding effect ( 0.04 to 0.65 ppm ) is found for the H-6 proton. These shielding effects are within the range of shifts proposed by Paudler and coworkers for the six membered heteroaromatic systems (50). These chemical shift differences suggest that these compounds have similar degrees of N-oxide backbonding.

The proton meta in these N-oxides is deshielded by 0.5 to 0.76 ppm. This shift is not seen in the proton chemical shifts in azines, but is observed in Carbon-13 chemical shift values (50). This deshielding effect observed here may be in part due to electronegative induction from the bridging ortho nitrogen.

The proton NMR chemical shifts of the azole ring of the polyazaindenes shows a small deshielding effect for the N-oxidation of the azine ring. The H-2 chemical shift differences are larger than the H-3 shifts (H-2, 0.12 to 0.25 ppm; H-3, 0.00 to 0.15 ppm). This is unexpected since a reasonable resonance form can be drawn that places a negative charge on the carbon at position 3 (H-3 is the

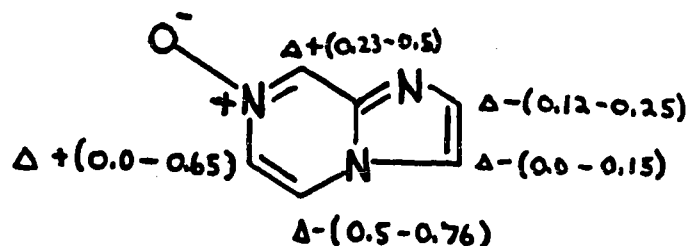


position that is substituted by electrophilic reagent in the polyazaindene series). The deshielding effect observed here

does not cause failure of the electrophilic substitution but indicates a decreased reactivity.

The H-2 proton resonance position deshielding effect may be due to a long range inductive effect caused by the N-oxide function.

This study has produced shielding and deshielding parameters for polyazaindene system after N-oxidation. These shifts are tabulated in table 4 and are as follows:





## IV. EXPERIMENTAL

Melting points were taken with a Thomas Hoover capillary apparatus and are uncorrected. H-NMR spectra were recorded with a Varian HA-100 spectrometer. Mass spectra were obtained with a Hitachi Perkin-Elmer RMU-6M instrument equipped with a solid-sample injector and employing an ionizing voltage of 70 eV. Elemental analyses were determined by The Analytical Services Laboratory of the University of Alabama, Chemistry Department.

Reactions of 3-Hydrazino-1,2,4-triazine-1-oxide.

3-Formalhydrazino-1,2,4-triazine-1-oxide

A solution of 0.202g (0.0016 mol.) 3-hydrazino-1,2,4-triazine-1-oxide in formic acid was heated for two hours on a steam bath. The yellow solution was allowed to cool to room temperature and the excess formic acid was removed under vacuum to dryness. The remaining dark yellow oil was dissolved in water and the solution was neutralized with sodium carbonate. The water solution was then continuously extracted with methylene chloride for 72 hours to yield a light yellow solid (m.p. 176-178 C, 82% yield)

Anal. CHN: found C 30.95% ; H 3.37%; N 46.7% ;

calculated for C<sub>4</sub>H<sub>5</sub>N<sub>5</sub>O : C 30.98%; H 3.22%; N 45.15%.

Mass spectral data: parent ,m/e 155 ; m/e 127 (-28) loss of CO; m/e 112 (-44) loss of HNCHO ; m/e 97 (-59) loss of NH-NH-CHO.

H-NMR : 8.78 ppm(doublet), 8.47 ppm(singlet), 8.27 ppm(doublet).

Attempted Reaction of 3-hydrazino-as-triazine-1-oxide with Formamidine Acetate.

Formamidine acetate 0.163g (0.00157 mol) was added to 0.200g (0.00157 mol) of 3-hydrazino-as-triazine-1-oxide in 25 mL of distilled water. The resulting solution was refluxed over a steam bath for 48 hours. The remaining water was removed under vacuum and the remaining yellow solid was collected by vacuum filtration. This material was placed in a sublimation apparatus at 60 C / 0.5mm Hg. The sublimate when analyzed by mass spectroscopy and NMR proved to be the starting material with trace amounts of 3-formylhydrazino-1,2,4-triazine-1-oxide.

Synthesis of 1,2,4-Triazolo[3,4c]-1,2,4-triazine-7-oxide.

To 0.7 mL (0.004mol) of diethoxymethyl acetate was added 0.200g (0.00157 mol) of 3-hydrazino-1,2,4-triazine-1-oxide. This solution was heated on a steam bath for 10 minutes and cooled to room temperature. The crystals which separated were collected by vacuum filtration and washed with absolute ethanol and air dried (yield 193mg, 90%, m.p. 190-191 C (decomp)).

Anal. found: carbon 35.02 %; hydrogen 2.31% ;nitrogen 50.33%: calculated for C<sub>4</sub> H<sub>3</sub> N<sub>5</sub> O: carbon 35.03%; hydrogen 2.18%; nitrogen 51.09%.

Mass spectral data: m/e-137 M<sup>+</sup>;m/e-121 (-16) loss of oxygen.

H-NMR.Spectral data : 8.1 ppm.(doublet), 9.1 ppm.

(doublet), 9.2 ppm. (singlet).

Synthesis of 3-Benzylidenehydrazino-1,2,4-triazine-1-oxide.

3-Hydrazino-as-triazine-1-oxide, 0.127g (0.001 mol), was suspended in 30 mL of absolute ethanol. To this suspension was added 5 mL acetic acid. The resulting clear solution was then heated on a steam bath. To the hot solution was added 0.120g (0.001 mol) of benzylaldehyde in 5 mL of ethanol. The solution was lightly refluxed over a steam bath for 10 minutes, and evaporated to dryness under vacuum. The light yellow solid was collected by vacuum filtration ( m.p. 209-210 C, yield 65%).

Anal. : CHN: found ;carbon 56.02; hydrogen 4.26; nitrogen 32.78 ; calculated calculated for C<sub>10</sub> H<sub>9</sub> N<sub>5</sub> O: carbon 55.81; hydrogen 4.18; nitrogen 32.56.

Mass Spectral data: m/e-215 (M+), m/e-138 (M-77) loss of phenyl, m/e-112 (M-130) loss of phenylcyanide.

H-NMR Spectrum: 8.27 ppm (doublet), 8.53 ppm (broad singlet), 8.80 ppm (doublet), 8.00 and 7.75 ppm (phenyl).

Attempted Reaction of 3-Benzylidenehydrazino-1,2,4-triazine-1-oxide with Lead Tetraacetate.

3-Benzylidenehydrazino-1,2,4-triazine-1-oxide, 0.450g (0.002 mol), was placed in 35 mL of glacial acetic acid. To this suspension was added 0.886g ( 0.002 mol) lead tetraacetate and placed in the dark for 30 minutes. To the suspension 80 mL of water was added and the pH was adjusted

to 7 using sodium bicarbonate. The solution was placed in the dark for 4 hours and the black precipitate was removed by vacuum filtration. The remaining yellow solution was extracted with 4X50 mL portions of chloroform. The chloroform extract was washed with 50 mL of a saturated solution of sodium carbonate and then dried over anhydrous sodium carbonate. The chloroform solution was reduced in volume under vacuum and the precipitate that formed was collected by vacuum filtration. Mass Spectral and H-NMR data showed only the presence of starting material.

MS: m/e-215; m/e-112.

Attempted Reaction of 3-Benzylidenehydrazine-1,2,4-triazine-1-oxide with Bromine in Acetic Acid.

3-Benzylidenehydrazine-1,2,4-triazine-1-oxide, 0.200g (0.0009 mol), was suspended in 3 mL of glacial acetic acid. To this suspension 0.8 mL (0.015 mol) bromine in glacial acetic acid was added over a 30 minute time period. The suspension was filtered by vacuum filtration and the precipitate was analyzed by mass spectrum and showed only starting material, 0.174g (88%) recovered.

Synthesis of 2,3-Dihydro-3-methyl-s-triazolo[3,4c]-1,2,4-triazine-1-oxide.

3-Hydrazino-1,2,4-triazine-1-oxide, 0.127g (0.001 mol), was suspended in 30 mL of absolute ethanol and 5 mL of acetic acid. This solution was heated over a steam bath until it turned clear. To this hot solution was added 0.1g (0.0022

mol) acetaldehyde in 5 mL absolute ethanol which was refluxed over a steam bath for 15 minutes. The light yellow solution was evaporated to dryness under vacuum and the yellow solid was collected by vacuum filtration. The yellow solid was recrystallized from 50% chloroform/ 50% hexane mixture to yield a very light yellow solid that darkened with exposure to air. The yellow solid was dissolved in absolute ethanol and applied to a thick layer Tlc plate of silica grade 3 (neutral) and eluted with 94% ethyl acetate, 5% ethanol (absolute), and 1% ammonium hydroxide. Two products were collected from the plate, #1 the 3rd up the plate yielded 0.03g which was 2,3-dihydro-3-methyl-5-triazolo[3,4-c]-as-triazine-7-oxide. Melting point 133-134 C.

Anal. CHN : found; carbon 39.13% , hydrogen 4.67% ,  
nitrogen 43.06%; calculated for C<sub>5</sub>H<sub>9</sub>N<sub>5</sub>O: carbon 39.21 % ,  
hydrogen 4.57% , nitrogen 45.75%.

Mass Spectral data: m/e-153 (M+), m/e-138 (-15) loss of methyl, m/e-112 (-41) loss of acetonitrile.

H-NMR Spectral data: 2.06 ppm (doublet), 7.60 ppm (singlet), 7.63 ppm (doublet), 8.28 ppm (doublet), 9.75 ppm (broad singlet).

The second compound identified (the 5th up the plate) was 3-(1-methylidene-2-vinyl-hydrazino)-1,2,4-triazine-1-oxide (yield 10 mgs.).

CHN : found; carbon 46.77%, hydrogen 5.06%, nitrogen  
40.61%; calculated for C<sub>7</sub>H<sub>9</sub>N<sub>5</sub>O: carbon 46.93% , hydrogen

5.03%, nitrogen 39.10%.

H-NMR Spectrum; 6.22 ppm (multiplet), 1.87 ppm (doublet), 7.63 ppm (doublet), 7.83 ppm (doublet), 8.28 ppm (doublet).

Attempted Reaction of 2,3-Dihydro-3-methyl-s-triazolo[3,4c]-as-triazine-7-oxide with Lead Tetraacetate.

To 0.300g ( 0.00196 mol) of 2,3-Dihydro-3-methyl-s-triazolo[3,4c]-as-triazine-7-oxide suspended in 30 mL of glacial acetic acid was added 0.886g (0.002 mol) of lead tetraacetate with stirring. This suspension was placed in the dark for 30 minutes then the dark precipitate was filtered by vacuum filtration. The light yellow solution was extracted with 4-50 mL portions of chloroform. The chloroform extract was washed with saturated sodium carbonate solution and dried over anhydrous sodium carbonate. The solution was evaporated to dryness under vacuum. Mass Spectral information showed only starting material. m/e-153 and m/e-138.

Attempted Reaction of 2,3-Dihydro-3-methyl-s-triazolo[3,4c]-as-triazine-7-oxide with Bromine in Glacial Acetic Acid.

To 0.154g (0.001 mol) of 2,3-dihydro-3-methyl-s-triazolo[3,4c]-as-triazine-7-oxide suspended in 5 mL of glacial acetic acid was added dropwise 0.8 mL (0.015 mol) bromine in 8 mL of glacial acetic acid over a 30 minute time period. The suspension was stirred for 1.5 hours then evaporated to dryness under vacuum. The yellow solid was

collected and mass spectral analysis showed recovered starting material (92% recovery).

Synthesis of 3-(4-Phenyl-thiosemicarbazine)-1,2,4-triazine-1-oxide.

To a suspension of 0.200g (0.00157 mol) 3-hydrazino-1,2,4-triazine-1-oxide in 12 mL of chloroform was added 0.4 mL (0.0033 mol ) phenyl isothiocyanate. This suspension was refluxed over a steam bath of 30 minutes. Analysis by thin layer chromatography utilizing ultraviolet light detection showed the major component of this solution was the 3-hydrazino-as-triazine-1-oxide. An additional 0.5 mL of phenyl isothiocyanate was added and the solution was refluxed for 3 hours. The solution was evaporated to dryness under vacuum and the white solid was collected by vacuum filtration (0.291g ,77% yield: melting point 171-172 C).

Anal. CHN: found; carbon 45.90%, hydrogen 3.55%, nitrogen 31.63% :calculated for  $\begin{matrix} C & H & N & OS \\ 10 & 10 & 6 \end{matrix}$ ; carbon 45.97%, hydrogen 3.83%, nitrogen 32.18%.

Mass Spectral data; m/e-261 (M+), m/e-135 (-127) loss of 3-hydrazino-1,2,4-triazine-1-oxide, m/e-127 (-135) loss of phenyl isothiocyanate relative to the parent ion (M+).

<sup>1</sup>H-NMR Spectral data; 8.29 ppm (doublet), 8.63 ppm (phenyl), 8.79 ppm (doublet), 10.21 ppm (broad singlet contains 3 protons).

Attempted Reaction of 3-(4-Phenyl thiosemicarbazine)-1,2,4-triazine-1-oxide with Heat.

A suspension of 0.147g (0.00055 mol) of 3-(4-phenyl-thiosemicarbazine)-1,2,4-triazine-1-oxide was heated to a reflux in 25 mL of toluene for 30 minutes in the dark. The solution was cooled to room temperature and the suspension was filtered by vacuum filtration. 0.100g of a yellow solid was collected. NMR and mass spectral analysis showed only starting material. The toluene solution was evaporated to dryness under vacuum and showed by mass spectral analysis only decomposed material ( no mass units above 112 amu ).

Attempted Reaction of 3-Hydrazino-1,2,4-triazine-1-oxide with Carbon Disulfide in Base.

To a hot refluxing suspension of 0.200g (0.00157 mol) 3-hydrazino-1,2,4-triazine-1-oxide in 15 mL of absolute ethanol and 3 mL of base ( triethylamine or 0.1N NaOH ) was added 2 mL of carbon disulfide. The solution at this point was blood red in color. The solution was refluxed for 30 minutes allowed to cool to room temperature. The solution was evaporated to dryness under vacuum. The resulting dark brown solid did not have a melting point( >350 C). Mass spectral analysis did not produce a fragmentation pattern. H-NMR spectral analysis produced no peak in the spectrum. Infrared spectrum did not show an aromatic ring system.



Attempted Reaction of 3-Hydrazino-1,2,4-triazine-1-oxide with Cyanogen Bromide.

To a suspension of 0.200g (0.00157 mol) of 3-hydrazino-1,2,4-triazine-1-oxide in 10 mL of absolute ethanol was added 0.17g (0.0016 mol) cyanogen bromide. This solution was heated over a steam bath for 1 hour and to this solution was added 1 mL triethylamine. The solid suspended in the solution was collected by vacuum filtration. Mass Spectral analysis showed only the starting 3-hydrazino-1,2,4-triazine-1-oxide present. Retention times of thin layer chromatography analysis with an authentic sample of 3-hydrazino-as-triazine-1-oxide was identical to the solid collected by filtration.

Synthesis of 2,3-Dihydro-3-ethoxy-5-phenyl-1,2,4-triazolo-[3,4-c]-1,2,4-triazine-7-oxide.

To 0.4 mL of diethoxymethyl acetate was added 0.080g (0.00039 mol) of 3-hydrazino-5-phenyl-1,2,4-triazine-1-oxide. This solution was heated over a steam bath for 10 minutes. During this time a light yellow crystal formed in the reaction vessel. This crystal was collected by vacuum filtration then air dried (0.100g (0.00038 mol), yield 97%).

Anal. CHN.: found; carbon 55.75%, hydrogen 5.13%, nitrogen 26.83%; calculated for  $\text{C}_{12}\text{H}_{13}\text{N}_5\text{O}_2$ ; carbon 55.59%, hydrogen 5.02%, nitrogen 27.02%.

Mass Spectral data; m/e-259 (M<sup>+</sup>), m/e-215 (-44) loss of acetaldehyde fragment.

H-NMR Spectral data: 10.37 ppm(singlet), 8.88 ppm(singlet), 8.46 ppm(phenyl), 7.89 ppm(phenyl), 7.35 ppm(singlet), 4.53 ppm(quartet), 1.66 ppm(triplet).

Reaction of 2,3-Dihydro-3-ethoxy-5-phenyl-1,2,4-triazolo-[3,4c]-1,2,4-triazine-7-oxide with 10% Palladium (Pd) on Carbon.

To 30 mL of p-xylene with 0.100g of 10% Pd on carbon was added 0.100g (0.00034 mol) of 2,3-dihydro-3-ethoxy-5-phenyl-1,2,4-triazolo[3,4c]-1,2,4-triazine-7-oxide. This suspension was refluxed for 22 hours then allowed to cool to room temperature. The solution was filtered by vacuum filtration and the black carbon was air dried (0.102g recovered). To the p-xylene solution small quantities of n-hexane was added until a precipitate formed (solid A, 0.023g) and was collected by vacuum filtration. Additional hexane was added to the p-xylene solution and another precipitate formed which was collected by vacuum filtration (solid B, 0.01g). The p-xylene solution was evaporated to dryness under vacuum to yield a brown solid. This solid material did not have a mass spectral fragmentation pattern or produce a H-NMR spectrum.

Solid A was redissolved in chloroform and recrystallized by slow evaporation under nitrogen, yield 20 mgs. Thin layer chromatographic analysis showed only one compound present. Mass spectral analysis identified this compound to be 2,3-dihydro-3-ethoxy-5-phenyl-1,2,4-

triazolo[3,4c]-1,2,4-triazine.

Solid B mass spectrum showed a molecular weight of 243. This compound was identified as 3-ethoxy-5-phenyl-1,2,4-triazolo[3,4c]-1,2,4-triazine.

Synthesis of 3-Acetylhydrazino-5-phenyl-1,2,4-triazine-1-oxide.

A solution of 1.0 mL of ethyl orthoformate and 0.56 mL of acetic anhydride was freshly prepared. Of this solution 0.4 mL was added to 0.080g (0.00039 mol) of 3-hydrazino-5-phenyl-1,2,4-triazine-1-oxide and heated over a steam bath for 1 minute. The precipitate was collected by vacuum filtration and washed with methylene chloride and hexane (0.095g, 100% yield; m.p. 242-243 C). Mass Spectra showed a molecular weight m/e of 245, and m-28 m/e-217.

Anal. CHN: found ; carbon 53.66%, hydrogen 4.51% , nitrogen 29.01%; calculated for  $\begin{matrix} C & H & N & O \\ 11 & 11 & 5 & 2 \end{matrix}$  ;carbon 53.87%, hydrogen 4.489% , nitrogen 28.57%.

Mass Spectral data: m/e-245 (M+), m/e-217 (M-28, loss of nitrogen)

H-NMR Spectral data: 10.33 ppm(singlet), 10.01 ppm(singlet), 8.97 ppm(singlet), 8.53 ppm(phenyl), 7.97 ppm(phenyl).

ATTEMPTED REACTIONS OF 1,2,4-TRIAZOLO[3,4c]-1,2,4-TRIAZINE-7-OXIDE

Attempted Deuterium Exchange with 1,2,4-triazolo[3,4c]-1,2,4-triazine-7-oxide with Sodium Methyate.

To a solution of 0.04g (0.0003 mol) 1,2,4-triazolo-[3,4c]-1,2,4-triazine-7-oxide in 0.4 mL dimethyl sulfoxide with one drop of deuterium oxide was added a trace amount of sodium methyate. This solution was placed in a NMR tube and the spectrum was taken every five minutes for one hour. All NMR signals disappeared at a progressive rate. The sample was extracted with ether and the remaining solid was applied to a thin layer chromatography plate and eluted with ethyl acetate-90% / ethanol-10%. The retention times of the appearing spots were unique when compared with the starting material.

Attempted Deuterium Exchange of 1,2,4-Triazolo[3,4c]-1,2,4-triazine-7-oxide with Trifluoroacetic Acid.

To a solution of 0.032g (0.00023 mol) 1,2,4-triazolo-[3,4c]-1,2,4-triazine-7-oxide in 0.4 mL dimethyl sulfoxide with one drop of deuterium oxide was added 2 drops trifluoroacetic acid. This solution was placed in a NMR tube and the spectrum was taken every 5 minutes for one hour. All NMR signals disappeared at an equally progressive rate. The sample was extracted with ether to remove the dimethyl sulfoxide which left a brown solid. This solid was dissolved in 90% ethyl acetate / 10% ethanol and applied to a thin

layer chromatography plate and eluted with the same solvent. The retention times of the spots that appeared, when compared with the authentic sample, were distinctly unique.

Attempted Deoxygenation of 1,2,4-Triazolo[3,4c]-1,2,4-triazine-7-oxide with Triethyl Phosphite.

1,2,4-Triazolo[3,4c]-1,2,4-triazine-7-oxide, 0.160g (0.0017 mol), was heated to reflux with 5 mL triethyl phosphite under nitrogen for 3 hours. The triethyl phosphite was removed under vacuum leaving a light yellow solid. The yellow solid was dissolved in 90% ethyl acetate /10% ethanol and applied to a thin layer chromatography(TLC) plate and eluted with the same solvent. The retention time of the detected spot was identical to the starting material. H-NMR spectral analysis was identical to the starting material.

Attempted Reaction of 1,2,4-Triazolo[3,4c]-1,2,4-triazine-7-oxide with Acetic Anhydride.

5-Triazolo[3,4c]-as-triazine-7-oxide 0.100g, (0.0007 mol), in 1 mL (0.01 mol) of acetic anhydride was heated over a steam bath of 1 hour. The solid material in the reaction vessel was filtered under vacuum and air dried. The solid material was applied and elute on a TLC plate and the detected spots were identical to the starting material.

Attempted Reaction of 1,2,4-Triazolo[3,4c]-1,2,4-triazine-7-oxide with Acetic Anhydride in Acetic Acid.

1,2,4-Triazolo[3,4c]-1,2,4-triazine-7-oxide, 0.070g (0.0005 mol), was dissolved in 5 mL of hot acetic acid,

0.8 mL of acetic anhydride was added and then the solution was heated over a steam bath for 45 minutes. At this time the solution was evaporated to dryness under vacuum to yield an oily brown solid. TLC, H-NMR and mass spectral analyses showed starting material and acetic acid.

Attempted Reaction of 1,2,4-Triazolo[3,4b]-1,2,4-triazine-7-oxide with Phosphorous Oxychloride.

Phosphorous oxychloride, 0.9 mL (0.0096 mol), was added to 0.050g (.00036 mol) of 1,2,4-triazolo[3,4c]-1,2,4-triazine-7-oxide then heated over a steam bath for 30 minutes. The solution was evaporated to dryness under vacuum to yield a yellow solid, H-NMR and mass spectral analyses showed only starting material.

Attempted Reaction of 1,2,4-Triazolo[3,4c]-1,2,4-triazine-7-oxide with Phosphorous Trichloride.

To 2 mL of phosphorous trichloride was added 0.126g (0.0009 mol) of 1,2,4-triazolo[3,4c]-1,2,4-triazine-7-oxide. This mixture was heated over a steam bath for 24 hours. The phosphorous trichloride was removed by reduced pressure leaving a needle like crystal. H-NMR spectrum showed only the starting material which was confirmed by the melting point of 191-194 C.

Attempted Bromination of 1,2,4-Triazolo[3,4c]-1,2,4-triazine-7-oxide with N-Bromosuccinimide(NBS).

1,2,4-Triazolo[3,4c]-1,2,4-triazine-7-oxide, 0.130g (0.00095 mol), was dissolved in hot acetic acid. To this

solution 1.68g (0.0094 mol) of NBS was added as a slurry in 13 mL of acetic acid. This solution was heated over a steam bath for 1 hour and was then allowed to cool to room temperature. The solution was evaporated to dryness under vacuum to yield a yellow solid. Thin layer chromatographic analysis detected three spots, the first was 1,2,4-triazolo[3,4c]1,2,4-triazine-7-oxide, the second was succinimide and the third was NBS.

Attempted Rearrangement of 1,2,4-Triazolo[3,4c]-1,2,4-triazine-7-oxide with Ultra Violet Light

1,2,4-Triazolo[3,4c]-1,2,4-triazine-7-oxide, 0.060g (0.00044 mol), was dissolved in 125 mL of dioxane and irradiated with 600 watts of 254 nm ultra violet light for 16 hours. At 2,4,6,8,10,12, and 16 hours thin layer chromatography was performed and the results showed the loss of starting material with replacement with numerous new compounds. The solution was evaporated to dryness under vacuum to yield a brown oil. Mass Spectrum and H-NMR spectrum analyses showed the loss of aromatic protons and a general decomposition of the sample into unknown fragments.

# REACTIONS OF 3-HYDRAZINOPYRAZINE-1-OXIDE.

## Preparation of 3-Hydrazinopyrazine-1-oxide

3-Chloropyrazine-1-oxide, 0.615g (0.0047 mol), was dissolved in 10 mL of freshly distilled dry tetrahydrofuran. To this solution with stirring was added 0.3 mL (0.0094 mol) of 95+ % hydrazine. Immediately upon addition anhydrous methanol was added to dissolve the hydrazine. This solution was allowed to stand at room temperature for 48 hours in the dark. A white precipitate was formed and was collected by vacuum filtration and washed with methylene chloride ( 86.8% yield, m.p. 200-200.5 C (decomp)).

Anal. CHN: found; carbon 37.94%, hydrogen 4.53%, nitrogen 43.87%; calculated for C<sub>4</sub>H<sub>6</sub>N<sub>4</sub>O; carbon 38.11%, hydrogen 4.76%, nitrogen 44.43%.

H-NMR Spectral data: 8.01 ppm(doublet), 7.58 ppm(doublet of doublets), 7.83 ppm(singlet)

## Synthesis of 1,2,4-Triazolo[3,4-c]pyrazine-7-oxide.

3-Hydrazinopyrazine-1-oxide, 100g (0.0008 mol), was added to 0.5 mL of diethoxymethyl acetate. The solution immediately turned yellow and produced heat. The solution was warmed over a steam bath for 3 minutes and then cooled to room temperature. The solution was evaporated under vacuum to yield a dark brown oil. The oil was recrystallized from absolute ethanol and Norite to yield a white solid



(0.036g, 36% yield, m.p. 204-205 C (decomposition)).

Anal. CHN: found; carbon 44.26%, hydrogen 2.61%, nitrogen 41.16% : calculated for  $\text{C}_5\text{H}_4\text{N}_4\text{O}$ ; carbon 44.14%, hydrogen 2.94%, nitrogen 41.16%.

Mass Spectral data : m/e-136 (M+), m/e-135 (M-1), m/e-120 (M-16).

H-NMR Spectral data: 9.21 ppm(singlet), 9.14 ppm (singlet), 8.74 ppm(doublet), 7.79 ppm(doublet of doublets).

#### Synthesis of 3-Benzylidenehydrazinopyrazine-1-oxide

To a stirring solution of 0.510g (0.0047 mol) of 3-hydrazinopyrazine-1-oxide in 50 mL of ethanol and 12 mL of acetic acid at 80 C was added 0.5 mL of benzaldehyde. This solution was heated over a steam bath for 25 minutes and was evaporated under vacuum to yield a yellow solid. The product was washed with ethanol and chloroform and recrystallized from benzene( m.p. 194 C (decomposition), 0.196g, 56% yield).

H-NMR Spectral data: 8.96 ppm(multiplet), 8.74 ppm (multiplet), 8.53 ppm(multiplet)

#### Synthesis of 3-(4-phenyl-thiosemicarbizide)pyrazine-1-oxide.

3-Hydrazinopyrazine-1-oxide, 0.200g (0.0016 mol), was suspended in 12 mL of chloroform and heated to 80 C. To this hot solution 0.4 mL of phenyl isothiocyanate was added and maintained at 80 C for 4 hours. The solution was allowed

to cool to room temperature and the white crystals were collected by vacuum filtration( m.p. 153-154 C, yield 0.300g, 73%).

The Following Reactions Were Attempted With 3-Hydrazinopyrazine-1-oxide.

Reactants	Time/Degree C.	Results
formic acid	0-2.5hrs/80 C	3-formyl
acetaldehyde/acetic acid	1 hr./ 80 C	decomposition
BrCN/MeOH +triethylamine	1 hr./ r.t.	decomposition
BrCN/acetic acid	1 hr./ 80 C	starting material
carbon disulfide + the following bases		
sodium hydroxide	1.5 hrs./r.t.	total decomp.
pyridine	1 hr./ 60 C	total decomp.
triethyl amine	1 hr./ r.t.	total decomp.

Reactions Attempted with 3-Hydrazinopyrazine-1-oxide Derivatives.

Reactants	Conditions/Time+Temp.	Results
benzylidene	bromine/acetic acid 1 hr./ r.t.	starting material
phenyl thio semicarbize	heat- 5 hrs./ 140 C	starting material

Reactions of 1,2,4-Triazol[3,4c]pyrazine-7-oxide.

Dimroth Rearrangement of 1,2,4-triazol[3,4c]pyrazine-7-oxide with Dilute Acid.

1,2,4-Triazol[3,4c]pyrazine-7-oxide, 0.300 (0.0022 mol), was dissolved in 0.4 mL of perdeutero-dimethyl sulfoxide. To this solution 50 microliters of trifluoroacetic acid was added. The sample was placed in a NMR spectrometer and the resulting spectra were taken every 15 minutes over a six hour period. H-NMR spectral analysis showed a new singlet at 8.62 ppm. After several hours of observation H-8 now is spilt into two new peaks at 9.14 and 9.06 with a ratio of 60 to 40. The later new shift of 9.06 was due to the 1,2,4-triazol[3,2c]pyrazine-7-oxide.

NMR : 9.11(doublet), 9.06(singlet), 8.62 (singlet), 8.03(doublet of doublets)

Reactions Attempted with 1,2,4-Triazol[3,4c]pyrazine-7-oxide

Reactants	Time/ Degree C	Results
acetic anhydride	1 hr./ 80 C	starting material
bromine/acetic acid/water	24 hrs./r.t.	total decomp.
nitric acid/sulfuric acid	1 hr. /r.t.	total decomp.
sodium nitrite/37% HCl	1.5 hrs./r.t.	total decomp.
bromine/ ethanol	1.5 hrs./r.t.	starting material

# SYNTHESIS AND REACTIONS OF IMIDAZO[2,1-c]PYRAZINE-7-OXIDE.

## Synthesis of Imidazo[2,1-c]pyrazine-7-oxide

Imidazo[1,2-a]pyrazine, 1.01g (0.00848 mol), was dissolved in 22 mL of chloroform at 60 C. To this solution 2.9g (0.017 mol) of meta-chloroperbenzoic acid in 40 mL chloroform was added dropwise over a ten minute period. The solution was maintained at 60 C for 20 minutes and then the solution was evaporated to yield a light yellow solid. This solid was added to 25 mL of saturated sodium carbonate solution and was continually extracted with chloroform for 64 hours. The extract was dried over sodium carbonate and evaporated to dryness under vacuum to yield a light yellow solid. This solid was recrystallized for absolute ethanol to give white needles( m.p. 167 C (decomp), 0.3g 26.2% yield).

H-NMR Spectral data : 8.83(singlet), 8.81(doublet), 8.05(singlet), 7.78(doublet of doublets), 7.76(singlet).

## Reactions of Imidazo[1,2-c]pyrazine-7-oxide.

Reactants	Time/ Degree C	Results
Phosphorous oxychloride	0.5 hrs./ r.t.	decomposition
bromine/water-ethanol	1 hr. / 80 C	starting material
nitric and sulfuric acid	1 hr. /80 C	decomposition
sodium nitrite/HCl	1.5 hrs/ 80 C	decomposition
bromine/acetic acid	1.5 hrs./ 80 C	starting material

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TABLE I

Application of Several Fused Polyazaindenes.

Parent compound	Application
1,2,4-triazolo[4,3a]pyridine	Photography
1,2,3-triazolo[4,5b]pyridine	Pesticide
1,2,3-triazolo[4,5b]quinoline	Antiallergic
1,2,4-triazolo[4,3b]pyridazine	Vasodilator
1,2,4-triazolo[1,5a]pyrimidine	Photography
	Herbicide
	Emetic
1,2,4-triazolo[4,3a]pyrazine	Bronchodilator
1,2,4-triazolo[4,3a]quinoxaline	Rice growth control
imidazo[1,2a]pyrazine	Bioluminescent

TABLE II

PROTON NUCLEAR MAGNETIC RESONANCE CHEMICAL SHIFTS OF SOME  
POLYAZAINDENES AND THEIR N-OXIDES. (a)

COMPOUND	H-1	H-2	H-3	H-5	H-6	H-7	H-8
S-TRIAZOLO[1,2a]PYRIDINE (b)	---	---	9.16	8.47	6.92	7.32	7.80
S-TRIAZOLO[1,5a]PYRIDINE (b)	---	8.35	---	7.82	7.52	7.04	8.62
S-TRIAZOLO[4,3a]- PYRIMIDINE (c)	---	---	9.28	9.02	7.15	8.77	---
S-TRIAZOLO[1,5a]- PYRIMIDINE (c)	---	8.76	---	9.52	7.46	8.89	---
S-TRIAZOLO[3,4c]- PYRAZINE-7-OXIDE	---	---	9.21	8.74	7.79	---	9.14
S-TRIAZOLO[1,5c]- PYRAZINE-7-OXIDE	---	8.62	---	9.11	8.03	---	9.06
S-TRIAZOLO[1,5a]- PYRAZINE (d)	---	8.50	---	8.58	8.19	---	9.37
S-TRIAZOLO[3,4c]- 1,2,4-TRIAZINE-7-OXIDE	---	---	9.28	9.07	8.10	---	---
IMIDAZO[1,5a]PYRAZINE- 7-OXIDE (e)	7.63	---	8.25	7.97	7.38	---	8.56
IMIDAZO[1,5a]PYRAZINE (e)	7.83	---	8.28	7.58	7.91	---	9.03
S-TRIAZOLO[4,3b]- PYRIDAZINE-7-OXIDE (f)	---	---	9.74	---	8.35	8.35	8.04
S-TRIAZOLO[4,3b]- PYRIDAZINE (d)	---	---	9.15	---	8.40	7.17	8.20

TABLE II CONTINUED

COMPOUND	H-1	H-2	H-3	H-5	H-6	H-7	H-8
IMIDAZO[1,2b]- PYRIDAZINE-7-OXIDE(f)	---	7.66	8.20	---	7.82	7.00	7.58
IMIDAZO[1,2b]- PYRIDAZINE(d)	---	7.81	9.45	---	8.30	7.00	7.95

(a) all chemical shifts are recorded in parts per million and are down field from TMS.

(b)

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(e) see reference number 36.

(f) see reference number 33.

TABLE III

CHANGES IN CHEMICAL SHIFTS OF DIMROTH REARRANGED AND NON  
REARRANGED COMPOUNDS.

COMPOUND	(H-3),	(H-2)	H-5	H-6	H-7	H-8
TRIAZOLOPYRIDINE	9.16	8.35	8.47 7.82	6.92 7.52	7.32 7.04	7.80 7.62
TRIAZOLOPYRIMIDINE	9.28	8.76	9.02 9.00	7.15 7.19	8.77 8.77	--- ---
TRIAZOLOPYRAZINE 7-OXIDE	9.21	8.63	8.74 9.11	7.79 8.03	--- ---	9.14 9.06
TRIAZOLOPYRIDAZINE	9.15	8.35	--- ---	8.40 8.44	7.17 7.42	8.20 8.08
TRIAZOLO- <del>A</del> STRIAZINE	9.13	8.59	--- ---	8.61 Me (2.79)	8.45 8.67	--- ---
TRIAZOLOPYRAZINE	9.38	8.50	7.90 8.19	8.59 8.58	--- ---	9.40 9.37

TABLE IV

CHEMICAL SHIFTS OF 3-HYDRAZINO-AS-TRIAZINE-1-OXIDES.  
DIFFERENCES BETWEEN H-5 - H-6

-----  
COMPOUND

H-5 - H-6 = difference      OTHER PROTONS(ppm)  
-----

3-HYDRAZINE-AS-TRIAZINE-1-OXIDE

8.68 - 8.10 = 0.58

NONE

3-(4-PHENYL-THIOSEMICARBIZIDE )HYDRAZINO-AS-TRIAZINE-1-OXIDE

8.77 - 8.26 = 0.51

NONE

3-BENZYLIDENEHYDRAZINO-AS-TRIAZINE-1-OXIDE

8.80 - 8.28 = 0.52

benylideno proton 8.50

3-FORMYLHYDRAZINO-AS-TRIAZINE-1-OXIDE

8.88 - 8.32 = 0.56

formyl proton 8.50

3-METHYLIDENEHYDRAZINO-AS-TRIAZINE-1-OXIDE

(expected)

8.80 - 8.30 = 0.50

methylideno proton 8.50

(found)

7.60 - 8.30 = -0.70

methylideno proton 7.60  
-----

TABLE V

DIFFERENCES BETWEEN PARENT AND N-OXIDE PROTON CHEMICAL SHIFTS OF SOME POLYAZAINDENES.

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IMIDAZO[1,2a]PYRAZINE

<u>POSITION</u>	<u>PARENT</u>	<u>N-OXIDE</u>	<u>DIFFERENCE</u>
H-2	7.80	8.05	-0.25
H-3	7.80	7.76	+0.04
H-5	8.07	8.71	-0.65
H-6	7.82	7.78	+0.04
H-8	9.06	8.83	+0.23

TRIAZOLO[3,4c]1,2,4-TRIAZINE

	3-METHYL		
H-3	9.13	9.28	-0.15
H-5	8.80	9.07	-0.27
H-6	---	8.10	---

TRIAZOLO[3,4c]PYRAZINE

	8-CHLORO		
H-3	9.23	9.21	+0.02
H-5	7.90	8.74	-0.76
H-6	7.36	7.79	+0.43
H-8	---	9.14	---

TRIAZOLO[1,5a]PYRAZINE

H-2	8.50	8.62	-0.12
H-5	8.58	9.11	-0.53
H-6	8.19	8.03	+0.16
H-8	9.37	9.06	+0.31

IMIDAZO[1,5a]PYRAZINE

H-1	7.83	7.63	+0.20
H-3	8.28	8.25	+0.03
H-5	7.58	7.97	-0.41
H-6	7.91	7.38	+0.53
H-8	9.03	8.56	+0.47

---

TABLE V CONTINUED

-----  
s-TRIAZOLO[3,4b]PYRIDAZINE

<u>POSITION</u>	<u>PARENT</u>	<u>N-OXIDE</u>	<u>DIFFERENCE</u>
H-3	9.15	<u>9.74</u>	<u>-0.59</u>
H-6	8.40	8.35	+0.05
H-7	7.17	7.46	-0.29
H-8	8.20	8.04	+0.16

## IMIDAZO[1,2b]PYRIDAZINE

H-2	7.76	7.66	+0.10
H-3	7.99	<u>8.80</u>	<u>-0.81</u>
H-6	8.30	7.82	+0.48
H-7	7.00	7.00	0.00
H-8	7.95	7.58	+0.38

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PART 2



## I. HISTORY OF NITROGEN-15 NUCLEAR MAGNETIC RESONANCE (NMR).

Since Nitrogen-14 and Nitrogen-15 nuclei have non-zero spin quantum numbers they lend themselves to nuclear magnetic resonance spectroscopic studies. In 1957, Ray and Ogg examined the nitrogen-14 spectra of several compounds to aid in structure determination studies (1). Continued studies of nitrogen nuclear magnetic resonance spectra provided the necessary background information for others to expand its use (2-6).

Nitrogen-14 is present to the extent of 99.64%, with a spin quantum number of 1, and consequently a very large quadrupole moment. The spin-lattice relaxation time,  $T_1$  (see equation 2) , is large causing an increase in the  $T_2'$  term. Inclusion of the  $T_2'$  value into equation 1 increases the,  $I(H)$ , causing this line broadening. This line broadening in nitrogen-14 can be up to 1000 hz.

$$I(H) = T_2' / \pi \exp \left[ \frac{-(H-H_M) \exp 2}{(T_2' \exp 2) / \pi} \right] \quad \text{eq. 1}$$

$$1/T_2' = 1/T_1 + 1/T_2 \quad \text{eq. 2}$$

This line-broadening problem is not present in the nitrogen-15 isotope with the spin quantum number of 1/2. The biggest drawback in using the nitrogen-15 isotope is that it has a very low natural abundance and a rather low sensitivity.

Conversion from nitrogen-14 chemical shifts to nitrogen-15 chemical shifts can be done by multiplying by the ratio of the magnetogyric ratios with the nitrogen-14 chemical shifts ( see equation 3).

$$\text{N-15 chemical shifts} = (\gamma_{\text{N-15}} / \gamma_{\text{N-14}}) * \text{N-14 shifts} \quad \text{eq. 3}$$

The chemical shift of nitrogen nuclei can be expressed in terms of the semiempirical formula (equation 4) as developed for carbon-13 nuclear magnetic resonance spectroscopy. This qualitative treatment of the nitrogen chemical shift is hindered by the electrons which greatly

$$\sigma_{\text{total}} = \sigma_{\text{dloc}} + \sigma_{\text{ploc}} + \sigma_{\text{other}} \quad \text{eq. 4}$$

affect chemical shifts. The term  $\sigma_{\text{dloc}}$  is the local diamagnetic screening of the nucleus and comes from the magnetically induced local electron circulation about the nucleus (for example proton chemical shifts are dominated by this term, which is closely related to electron density). The local paramagnetic term,  $\sigma_{\text{ploc}}$ , is a measure of the spherical symmetry of electron distribution and is negative. The greater it becomes the more the electrons are in orbitals of nonzero angular momentum.

The  $\sigma_{\text{other}}$  term in equation 4 expresses the influences on the chemical shift by causes other than the nitrogen nucleus. The "other" sources include anisotropic

field and solvent effects, along with a number of other minor ones.

The major influences on the nitrogen chemical shifts arise from the diamagnetic and paramagnetic terms in equation 4. The "other" influences on the nitrogen chemical shifts are considered very small and are not treated in this qualitative analysis.

The paramagnetic term in equation 4 can be represented by three structurally related subterms. (see equation 5)

$$\sigma_{\text{ploc}} = 1/E * [1/(r \exp^3)] * \text{sumQ} \quad \text{eq. 5}$$

The E subterm from equation 5 is related to the electronic excitation energy between the ground-state and the weighted excited-states of nitrogen. This subterm is the measure of accessibility of low-lying excited states of the nucleus.

The subterm  $[1/r \exp^3]$  in equation 5 is the inverse cube of the non-s orbital radius. This subterm is a direct measure of the amount of "s" character in the nucleus.

The subterm (sumQ) in equation 5 is a measure of the charge-density and bond-order and is related to the hybridization of the nucleus.

Equation 5 allows some general deshielding components to be identified and they are the following:

1. a smaller transitional energy of the low-lying states is involved when deshielding occurs.
2. a smaller radius of orbitals with greater "s" character cause deshielding.
3. changes in bond length or changes in hybridization of the nucleus ( multiple bonding ) cause deshielding.

#### BONDING EFFECTS ON NITROGEN-15 CHEMICAL SHIFTS

Two types of nitrogen generally exist in different heteroaromatic systems. Type I is referred to as 'pyrrole-like'. These 'pyrrole-like' nitrogens have an unshared pair of electrons incorporated into the  $\pi$  system of the heteroaromatic system. These 'pyrrole-like' nitrogen chemical shifts are similar to those found in the nitrogen in anilines.



Type II nitrogen is labeled 'pyridine-like'. This type of nitrogen is  $sp^2$  hybridized and its geometry places its unshared pair of electrons orthogonal to the  $\pi$  system. The 'pyridine-like' nitrogens have an additional  $n - \pi^*$  transition which deshields them considerably more than the 'pyrrole-like' nitrogens.

Proton tautomerism is possible when both nitrogens are present in the same heteroaromatic system (as in imidazole above). This type of tautomerism causes, in many

instances, the observation of only one absorption peak in the nitrogen NMR spectrum. This tautomeric exchange averaging causes some line broadening and is most evident in the nitrogen-15 spectra.

#### A. Solvent Effects

Litchman and coworkers measured the effects of solvent dilution on ammonia nitrogen-15 chemical shifts (7,8) and proposed a linear combination of six interaction parameters, each of which makes a contribution to the nitrogen-15 chemical shifts at infinite dilution (9).

A-OH	hydrogen bonding between the N-15 lone pair and a solvent OH proton
A-NH	hydrogen bonding between the N-15 lone pair and a solvent NH proton
A-Me	interaction between the N-15 lone pair and a solvent methyl group
A-Et	interaction between the N-15 lone pair and a solvent ethyl group
Bo	hydrogen bonding between solvent oxygen lone pair and the N-15 protons
Bn	hydrogen bonding between solvent nitrogen lone pair and N-15 protons

On the basis of this model and a number of assumptions the infinite dilution shifts for ammonia in EtOH as a solvent are:

$$\text{shift EtOH} = 1/2 \text{ A-Et} + 1/2 \text{ A-OH} + \text{Bo} \quad \text{eq. 6}$$

Roberts and others have established various relationships for the nitrogen chemical shifts of pyridine in different solvents (10). The correlation with Kosower's  $Z$  values and N-15 chemical shifts affords a coefficient of correlation ( $r$ ) of 0.944 (10a) and a relationship between the  $n$  to  $\pi^*$  transitions and the nitrogen chemical shift seems indicated. Similar studies of solvent dependences were done on pyrroles, indoles, pyrazoles and imidazoles (11). The theoretical validity of these types of correlations were shown by Kato, Kato and Yonezawa (12).

Kolling used the Kamlet, Taft and Addoud method of computing the hydrogen-bonding and acceptor effects ( $\pi^*$  and  $\alpha$  terms) versus the nitrogen-15 chemical shifts and obtained a useful relationship (14). This correlation yielded a multiple linear regression equation of:

$$S = 5.92(\pi^* + 3.3\alpha) + 1.5 \quad \text{eq. 7}$$

correlation coefficient = 0.993

Kolling proposed that this equation is valid not only for the weaker hydrogen-bonding donors and acceptors but also for the non-hydrogen-bonding solvents. The dominant mechanism for the medium effects on chemical shifts is the probe-solvent dipolar interactions (14).

Many of these solvent dependent chemical shifts have been recorded and tabulated, and, in general, a typical shift of 10 to 20 ppm is common (13,15).

### B. Protonation of Nitrogen

In 1964, Herbison-Evans and Richards described the effects of protonation on pyridine (4) and reported a shielding of 120 ppm for the pyridinium ion relative to pyridine. This was rationalized as the result of removing the nonbonding electrons of the nitrogen by protonation and causing changes in the local paramagnetic term of the  $n \rightarrow \pi^*$  transition to the greater  $\sigma \rightarrow \pi^*$  transition.

Roberts and others have shown that the protonated shifts of azoles and azines are similar to those of the azines but the magnitude is not as great (10,11). These workers concluded that the solvent was not only changing the ion-pair distance but also the counterion influence on the nitrogen chemical shifts as well (10a).

Methylation of azine nitrogens has the same effect as protonation and the products show considerably less sensitivity to solvent influences. The nitrogen chemical shifts of methylated compounds are minimally influenced by changes in the counter anion (10a).

In general, protonation and methylation shields the nitrogens by about 100 ppm (13,15).

### C. N-Oxidation

N-oxidation produces shielding of the nitrogen chemical shift, but the magnitude of displacement is much smaller than the shift upon protonation (4,16). One possible

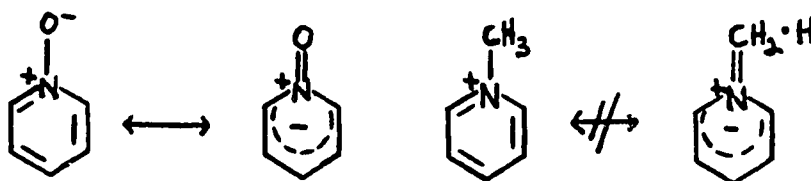
reason for this smaller effect is that, although the azinium ion stabilizes the non-bonding electrons, the two  $n \rightarrow \pi^*$  transitions in oxygen decrease the overall magnitude of the chemical shift contribution (4). An interesting trend can be seen for the number of  $n \rightarrow \pi^*$  transitions and the chemical shifts:

PYRIDINE	320 PPM DOWNFIELD	
PYRIDINE-N-OXIDE	280 PPM DOWNFIELD	2 (N TO $\pi^*$ )
N-HYDROXYPYRIDINE	230 PPM DOWNFIELD	1 (N TO $\pi^*$ )
PYRIDINIUM ION	200 PPM DOWNFIELD	0 (N TO $\pi^*$ )

The upfield shift of the pyridine-N-oxide nitrogen relative to the pyridine nitrogen is consistent with the removal of the lone pair of electrons (16a) which suggests that the smaller overall shift is due to the increased electronegativity of the oxygen (16a). Lichter also noted that the nitrogen chemical shift of pyridine-N-oxide, relative to that in the pyridinium ion is of 88.7 ppm (16a). This is more than twice the difference of the  $^2$  nucleus (39.6 ppm) between C-1 of the phenoxide ion and benzene (16a). This shift might well be a reflection of the higher  $\pi$  bond character in the N-O bond compared to the C-O bond (16a). Roberts and Yavari made a similar proposal to account for differences between the N-15 chemical shifts in pyridine-N-oxide and the pyridinium ion (16b). Roberts also reasoned that another fundamental difference between pyridine-N-oxide and the pyridinium ion nitrogen-15 chemical



shifts is that a resonance form for the pyridinium ion could not be drawn (16b).



#### LINEAR CORRELATIONS

Herbison-Evans and Richards have shown that there exists a relationship between the ultraviolet spectra and nitrogen-14 chemical shifts of a number of substituted pyridines (4). This crude correlation suggests contributions of the  $n$  to  $\pi^*$  transitions to the chemical shifts (4).

In 1972, Webb and coworkers plotted the nitrogen chemical shift versus the  $\pi$ -charge density and the mobile bond orders and obtained a linear correlation for the azoles and the benzazoles (17a). Earlier, Webb and coworkers used this type of correlations in the azine and the substituted pyridine series (17e). The INDO molecular orbital calculations were used to obtain the  $\pi$ -charge densities of several simple azines which were plotted against the nitrogen chemical shifts of these azines (17c). These plots gave a very good linear correlations but, were insensitive to any geometric changes (17d).

Stefaniak compared the chemical shifts of monoazines and azines versus their N-oxides and noted that the shifts,

within the two groups, are parallel to each other (18). A linear equation for the diazines and monoazines vs their N-oxides was calculated and is: (18)

for diazines:

$$y(\text{N-oxide}) = 0.3117 \times (\text{N}) + 62.0 \quad \text{eq. 8}$$

$$y(\text{N}) = 2.984 \times (\text{N-oxide}) - 182.9 \quad \text{eq. 9}$$

$$\text{correlation coefficient} = 0.9645$$

for monoazines:

$$y(\text{N-oxide}) = 0.7646 \times (\text{N}) + 37.48 \quad \text{eq.10}$$

$$y(\text{N}) = 1.2969 \times (\text{N-oxide}) - 47.93 \quad \text{eq.11}$$

$$\text{correlation coefficient} = 0.9956$$

Similar linear correlations exist between the N-oxides and the pi charge densities calculated by the Pariser-Parr-Pople method (18). The corresponding equations are:

for diazines:

$$y(\text{N-oxide}) = 353.4 \times (q) - 328.8 \quad \text{eq.12}$$

$$y(q) = 0.002642 \times (\text{N-oxide}) + 0.9434 \quad \text{eq.13}$$

$$\text{correlation coefficient} = 0.9663$$

for monoazines:

$$y(\text{N-oxide}) = 6071.5 \times (q) - 7029.5 \quad \text{eq.14}$$

$$y(q) = 0.00013878 \times (\text{N-oxide}) + 1.160 \quad \text{eq.15}$$

$$\text{correlation coefficient} = 0.9179$$

In 1980, von Philipsborn and coworkers reported the beta, gamma, and delta-substituent effects of the amino and alkyl groups of pyrimidines (19). A linear correlation was observed between the amino substituents on the ring nitrogen chemical shifts (N-15) in aminopyridines and the corresponding carbon-13 chemical shifts in aminobenzenes. Similarly, a relationship between the nitrogen-15 chemical

shifts of aminopyrimidines and the carbon-13 chemical shifts of aminopyridines exist (19).

for aminopyridine:

$$\text{difference of shift(N shift)} = 3.73 * \text{difference of shift} \\ \text{shift(C-13 Shift)} - 4.62 \quad \text{eq.16}$$

$$\text{correlation coefficient} = 0.9985$$

for aminopyrimidine:

$$\text{difference of shift(N shift)} = 2.78 * \text{difference of shift} \\ \text{(C-13 shift)} - 3.38 \quad \text{eq.17}$$

$$\text{correlation coefficient} = 0.9904$$

Webb, Witanowski and Stefaniak expanded Stefaniak's earlier work (18) to include several additional azine N-oxides (20). Webb's correlation of the nitrogen chemical shifts of azines and the average excitation energy calculated local paramagnetic term times the average excitation energy (20). The correlation coefficient was 0.9963.

The substituent correlations of pyridine were later expanded by von Philipsborn and coworkers to include most of the available substituents and a new correlation equation was derived (21). A similar substitution correlation was also derived for pyrimidines (21).

for pyridine:

$$\text{difference of shift(N-15 shift)} = 3.52 * \text{difference of} \\ \text{shift(C-13 shift)} - 1.87 \quad \text{eq.18}$$

$$\text{correlation coefficient} = 0.9654$$

for pyrimidine:

$$\begin{aligned} \text{difference of shift(N-15 shift)} &= 2.89 * \text{difference of} \\ &\quad \text{shift(C-13 shift)} - 0.47 \\ &\text{eq.19} \\ \text{correlation coefficient} &= 0.9789 \end{aligned}$$

The substituent effects of pyrazine were described in 1980 by Gunther and coworkers (22) in the same way as had been done by von Philipsborn and coworkers (21). A linear correlation with N-2 gave the following equation:

for pyrazine:

$$\begin{aligned} \text{difference of shift(N-15 shift)} &= 3.05 * \text{difference of} \\ &\quad \text{shift(C-13 shift)} - 9.68 \\ &\text{eq.20} \\ \text{correlation coefficient} &= 0.9744 \end{aligned}$$

Attempted correlations with N-4 did not yield satisfactory results.

In 1983, Yanez and coworkers described the linear correlation with charge density and the amino-substituted pyridines and pyrimidines (23) similar to the results of von Philipsborn and coworkers (19).

## II. NITROGEN-15 CHEMICAL SHIFTS

The chemical shift standard reference for nitrogen-14 and -15 is anhydrous ammonia at 25 C. The chemical shift behavior of ammonia as a liquid and a gas has been studied extensively, (7-9) and its resonance position is easily established and is readily reproduced.

An excellent secondary reference is nitromethane.

Although the nitrogen chemical shift of nitromethane is influenced by solvents, its strong resonance signal is easily detected. Another advantage is that the nitromethane nitrogen lies at the low-field end of the "normal" spectrum. The nitrogen nuclei of heteroaromatic compound absorb in this region. Nitromethane can be used as a combination of reference and lock signal (if the nitrogen isotope enriched nitromethane in perdeuterio nitromethane is used). This combination, when used as an external reference, is the one of choice.

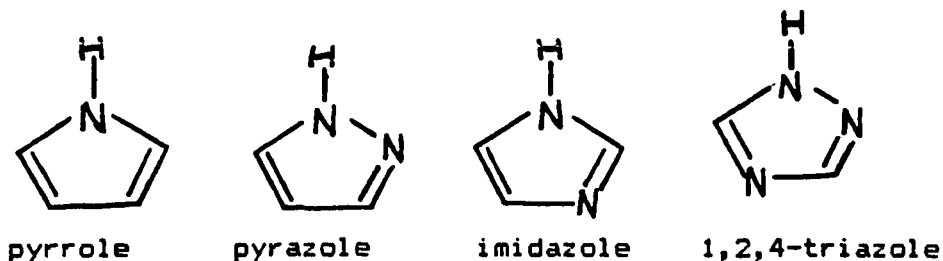
#### AZOLE CHEMICAL SHIFTS

The nitrogen-14 and -15 chemical shifts of some of the azoles are listed in table 2.

In the five membered heteroaromatics, both the 'pyrrole-like' and the 'pyridine-like' nitrogens can be present, and if they are a proton exchange can occur. The proton exchange phenomenon produces one spectral line in the NMR time scale, unless the resonance positions are widely separated (10c).

Pyrrole, the simplest of all the azoles, has a nitrogen-14 chemical shift of 148.8 ppm down field for ammonia (10c). Methylation of the pyrrole nitrogen results in a small shielding effect on the nitrogen of 5 to 8 ppm.

Furazone has nitrogens at positions 1 and 2 and both 'pyridine- and pyrrole-like' nitrogens present. The



resonance position of both nitrogens is 251 ppm (10c). Methylation produces two nitrogen chemical shifts of 206.2 ppm for the methylated nitrogen and 308 ppm for the non-methylated nitrogen (10c).

Imidazole nitrogens at positions 1 and 3, behaves similarly to those in pyrazole (10c,11b).

The 1,2,4-triazole, nitrogens at positions 1,2 and 4, produce only one chemical shift (245 ppm) in acetone. This is due to rapid proton exchange which averages these chemical shifts (10c). Methylation of 1,2,4-triazole produces 3 unique resonances of 228.2 (n-methyl), 261 (N-2) and 329 (N-4) (10c). These resonances are different than those reported in Table 2 for 1-methyl-1,2,4-triazole.

Additive chemical shift rules for 'pyrrole-like' nitrogens are reported by Webb and coworkers (14b,17a,24) and are dependent on several algebraic summations. Their contributions are as follows:

1.  $-50 + 1.5$  ppm for each pyridine like nitrogen in positions 2 or 5.
2.  $-30 + 4$  ppm for each pyridine like nitrogen at position 3
3.  $-12 + 2$  ppm additionally for each pyridine like

- nitrogen which is next to a nitrogen at position 2 or 5
4. +7 + 2.5 ppm additionally for each pyridine like nitrogen which is next to position 3 or 4.

The nitrogen chemical shifts in the oxazoles were found to be very similar to the chemical shifts found in the azole series. (24) The similarities between the adjacent nitrogen or oxygen on nitrogen-15 chemical shifts has been determined. (24)

The oxazoles, thiazoles, n-methylazoles and indolizines have been examined by Stefaniak in 1978 (25). The additive rules used by Webb and coworkers were extended for azoles to account for the introduction of sulfur (25).

#### B. CHEMICAL SHIFTS OF AZINES.

In 1964, Richards and coworkers reported the nitrogen-14 chemical shifts of pyridine and several substituted pyridines (4). They showed the existence of strong solvent effects in several 2-substituted pyridines and in the 2-,3- and 4-picoline-N-oxides (4).

In 1965, an attempt was made to correlate hyperconjugation, conjugation and charge-transfer interactions in substituted-pyridine and pyridine N-oxide (5). The authors found that any electron/bonding change with the lone pair of electrons leads to the reduction of the paramagnetic term in equations 4 and 5. This effect is seen by the greater shielding of pyridinium

ions and in pyridine-N-oxide. The 2-,3- and 4-amino pyridines have been studied (5). This study is important, because of the possible tautomeric and resonance forms that can exist in the 2 and 4 isomers where electron flow from the ortho and/or para substituted compounds (see example below for aminopyridine) (5). The resonance stabilization would result in the shielding of the ring nitrogen and deshielding of the amino nitrogen (5).

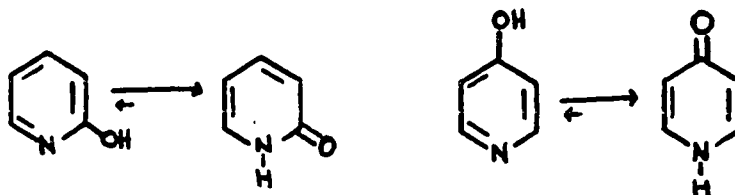


Substituent effects on pyridine were reported in more detail by Webb and coworkers (26). The substituent effects were divided into two groups; group I (i.e. nitro, cyano, formyl and acetyl) which represented the electron-withdrawing effect via an inductive and/or conjugative mechanism, and group II (i.e. hydroxy, methoxy, amino, and methyl groups) represented the electron releasing effect by resonance contributions or hyperconjugation. The electron withdrawing substituents shifted the nitrogen-14 resonances downfield relative to the resonance position of pyridine (17b). Webb and coworkers noted that in two compounds, the 2-nitro and the 2-acetylpyridine, showed a higher than expected chemical shift by 15-18 ppm. This interesting



effect was probably due to forced non-coplanarity of the ring and/or substituent dipole-dipole repulsions (17b).

For group II substituents, the amino and hydroxy groups can exist in a tautomeric forms (see below). Webb and coworkers determined that the pyridone form of the 2- and 4-hydroxy pyridine were favored by the higher chemical shifts observed (26). Similarly the 2- and 4- aminopyridine structures are favored by the lower chemical shifts (26). The substitution at the meta position produced the

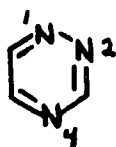


smallest resonance shifts, and substitution at the ortho position causes some steric effects (26). The para substitution showed good agreement with the conjugative and inductive effects expected by both groups (26). In 1974, Webb and coworkers reported the chemical shifts of several parent heterocycles (17c) which were correlated against the calculated paramagnetic terms in equation 5. Webb and coworkers in another article reported the chemical shifts of the azines (17a).

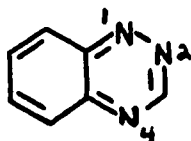
1,3,5-triazine	282 ppm
pyrimidine	298 ppm
pyridine	322 ppm
pyrazine	338 ppm
1,2,4,5-tetrazine	385 ppm
pyridazine	400 ppm

Stefaniak, in 1976, reported the chemical shifts of several azine-N-oxides and these are reported in table 3 (18). Stefaniak noted that a trend existed between the mono-N-oxides nitrogen chemical shift and the addition of conjugated aromatic rings (18). Stefaniak developed a additive scheme to calculate these trends (18).

Webb and coworkers, in 1978, reported the chemical shifts of 1,2,4-triazine and benzo-1,2,4-triazine (25). These chemical shifts were calculated by additive rules developed by Webb earlier (17). In general they found the following trends: (1) the (N-1)-(N-2) one bond interaction was predicted to have a large deshielding effect; (2) the (N-2)-(N-4) two bond interaction is predicted to cause a moderate shielding effect, (3) and the (N-1)-(N-4) three bond interaction was predicted to have a moderate deshielding effect. The actual and predicted nitrogen chemical shifts are shown below:



N-1	421.8 ppm
N-2	277.9 ppm
N-4	298.5 ppm



N-1	458.1 ppm
N-2	406.3 ppm
N-4	281.7 ppm

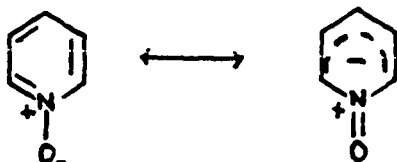
calculated values of 1,2,4-triazine

N-1	469 ± 8 ppm
N-2	428 ± 8 ppm
N-4	388 ± 8 ppm

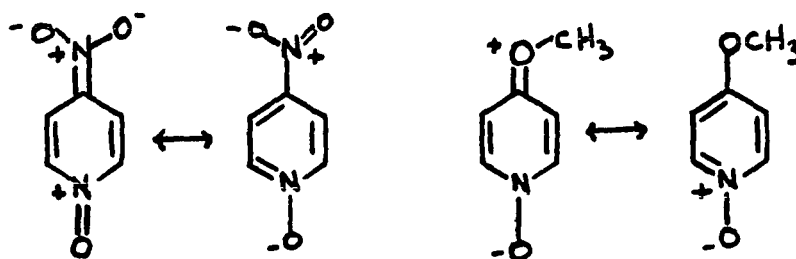
The 1,5-, 1,6-, 1,8-naphthyridines nitrogen-14 chemical shifts are very similar to those of quinoline and isoquinoline. In addition the nitrogen in the adjacent aromatic ring has little effect on either nitrogen-14 chemical shifts (26). In 1,8-naphthyridine, the peri-position nitrogen has very little effect on the adjacent nitrogen-14 chemical shift (26).

1,8-naphthyridine	293 ppm
1,6-naphthyridine	316 ppm
1,5-naphthyridine	308 ppm
quinoline	309 ppm
isoquinoline	312 ppm
quinazoline	290 ppm

Lichter and coworkers in 1978 examined the nitrogen-15 chemical shifts of alkylpyridines and picolinium, lutidinium ions as well as the picoline N-oxides (15a). They noted that ortho and/or para substitution induced small upfield shifts while the meta substitution produces essentially no change in the nitrogen-15 chemical shift relative to pyridine (15a). The authors noted that the pyridine-N-oxide nitrogen resonance is upfield relative to pyridine and was consistent with the loss of the lone pair of electrons on nitrogen. The magnitude of this loss for pyridine-N-oxide was less than that found for the pyridinium ion. This result was thought to be a reflection of higher pi bond character in the N-O bond (see below). Roberts confirmed these results (15b).



Roberts and coworkers found that the small nitrogen-15 chemical shifts observed in pyridine are very sensitive to the type and the position of the substituents (15b). For example, chemical shift changes of 4-methoxypyridine-N-oxide was 33 ppm higher field than that of 4-nitropyridine-N-oxide (15b). This result was attributable to the highly electronegative effect of the 4-nitro group and the very strong electron releasing effect of the 4-methoxy group influencing the resonance structures of pyridine-N-oxide (15b). These effects are illustrated below:

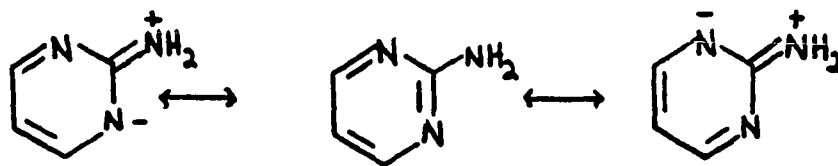


Several azine-N-oxides nitrogen chemical shifts were calculated by additive rules developed earlier by Webb (20). It is of interest that the calculated nitrogen-15 chemical shifts of several azine-N-oxides agreed closely with their experimental values (20).

The substituent effect on pyridine, pyrimidine and pyrazine have been reported (21-22). The linear correlation

have been discussed earlier in this text, the chemical shifts of these substituted compounds are described in the following paragraph.

Von Philipsborn and coworkers predicted the nitrogen-15 chemical shifts of the amino substituents on pyrimidine and pyridine (19). The ring nitrogen of pyridine, pyrimidine and pyridazine (relative to the ortho amino group) experiences substantial shielding (19). The shielding shifts in general (parent azine minus substituted azine) for the ortho, meta, and para positions were -50.8, -0.9 and -40.7 ppm respectively (19). A similar trend can be seen for the amino pyrimidines, however, the magnitude of the nitrogen-15 chemical shift was approximately half of what was expected. Von Philipsborn and coworkers suggested that a more effective conjugation was present in the pyrimidine system (19), see conjugated resonance form following:



#### NITROGEN CHEMICAL SHIFTS OF POLYAZAINDENES

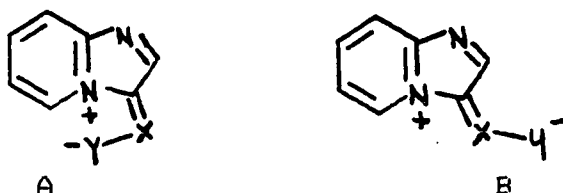
The polyazaindenes systems have only recently been examined by nitrogen-15 NMR. Webb and coworkers in 1979 examined seven polyazaindene systems (17d). The chemical shift assignments were determined by the AEE calculation. (See table 4 for the chemical shifts.)

One of the major purposes of this work was to examine the polyazaindene systems. Correlation of the ground-state resonance contributing structure was calculated. The results of this study follows (page 91-95). In addition substitution parameter for pyridine, pyrimidine, pyrazine and 1,2,4-triazine has been studied. The pyrazine- and 1,2,4-triazine- N-oxides contribution to the nitrogen-15 chemical shifts is preposed. The results of this study follows (page 95-99).

## III. DISCUSSION

A. N-15 Chemical Shifts of a Number of Polyazaindenes:  
Correlation with Charge Separated Resonance Contributing Structures

Studies by the Faudler research group have focused on the existence of several different ground-state resonance forms in these systems (27,28). In 1977, Faudler and coworkers proposed structures A and B, based on the low-

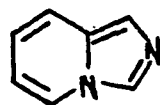
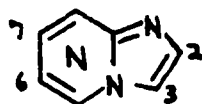


frequency proton nuclear magnetic resonance spectrum and on the infrared carbonyl absorption in the compounds bearing an aldehyde or dichloroacetyl groups (27). In 1980 this research group again examined the imidazo[1,2a]pyridine structures (A and B) by nuclear magnetic resonance spectroscopy (28). This time the uniform field theories of Buckingham's were employed to show that the same charge separated structural effects are indeed valid (28).

Table 5 shows the N-15 chemical shifts obtained in this study, as well as those reported in ref 17d. Among all of the polyazaindenes the bridgehead-atom, N-4, is always the most shielded nitrogen, except in some instances where it is directly bonded to another nitrogen atom(8,9,11). The contribution of the resonance contributing structures such



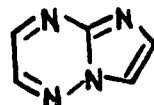
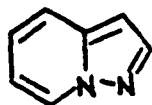




I: N-X = nil  
 IV: N-X = N-7  
 V: N-X = N-8  
 VI: N-X = N-2

II

and (2) Polyazaindenes with N-4 chemical shifts in the range 221-318 ppm.



III: N-X = N-2  
 VII: N-X = N-1, N-2  
 X: N-X = nil  
 IX: N-X = N-1, N-8  
 XI: N-X = N-1

VIII

Clearly, N-4 in those polyazaindenes with an N-N bond involving the bridge nitrogen is invariably more deshielded than the nitrogens in those compounds without this structural feature.

If one considers these polyazaindenes as arising from the modification of a given pi-deficient ring system by fusion to a 5-membered ring, the change in the chemical shift between the monocyclic nitrogen and the chemical shift of this now bridge-nitrogen in the polyazaindene will reflect the contribution of resonance contributing structures involving a positive charge on N-4. A plot of the difference in nitrogen-15 chemical shift between the

bridgehead-nitrogen of the corresponding polyazaindene and the nitrogen-15 chemical shift of the 'parent' 6-membered ring heterocycle against the nitrogen-15 chemical shifts of the bridgehead nitrogen should be linear. The slope of this line will reflect the shielding caused by the 5-membered ring. Among all of these compounds, the only ones which do not fulfill this linearity requirement are those where the nitrogen is ortho or para to the bridge nitrogen in the 6-member ring (IX and VIII) ( see figure 1). The remaining nine polyazaindenes fall on the correlation line with Equation 21 (see figure 1).

#### Equation 21

$$\begin{aligned} &[\text{N-15 chemical shift (N-4 of polyazaindene)} \\ &- \text{N-15 chemical shift (parent 6-membered heterocycle)}] \\ &= 0.93[\text{N-15 chemical shift (N-4 of polyazaindene)}] + \\ &203 \end{aligned}$$

When the chemical shift difference between the N-methyl pyridinium ion and pyridine ( $\delta = 123$  ppm) and the N-methylpyridinium ion chemical shift (N-15 chemical shift = 179 ppm) is added to the graph shown in Fig. 1, they also fall on the correlation line. Thus, the relative contribution of resonance contributing structures such as C and D is given by this correlation. In other words, compounds 5,6,2 and 1, exist to an extent greater than 70% in the resonance forms C and D, respectively. Those polyazaindenes where the bridgehead nitrogens are directly bonded to another nitrogen (either at position 3 or 5)

(compounds 9, 10, 11, 7, 3 and 8) exist largely (greater than 70%) in the non-charge separated forms (such as in general structure E). Two polyazaindenes, 1,4,7-triaza derivative 4, and, the 1,4,5,8-tetraaza derivative 8, do not fall on the correlation line, nevertheless compound 4 can be judged as existing largely in the charge separated form (C), while the latter does not.

**B. Nitrogen-15 Chemical Shifts of Some Pyrazines, 1,2,4-Triazines and Their N-Oxides; Correlation with Carbon 13 Chemical shifts and Substitution Parameters.**

The existence of the linear relationships found by W. Stadeli and W. von Philipsborn and others suggests that a similar pattern should exist among the various parent heterocyclic systems and the des-monoaza analogs. In other words, the pyrazine nitrogen chemical shift should be related to the carbon-13 chemical shift of the gamma-carbon in pyridine. The pyridazine nitrogen chemical shift value should be related to the carbon-13 value for the alpha-carbon of pyridine and the pyrimidine nitrogen chemical shift should be related to the carbon-13 value of the beta-carbon of pyridine.

Figure 2 depicts the graph obtained when these considerations are applied to seven different nitrogens in 5 different heteroaromatic ring systems. The equation for this graph is:

## Equation 22

$$\text{Nitrogen-15 Chemical Shift} = 4.00 * \text{Carbon-13 Chemical Shift} - 200$$

Clearly the correlation coefficient of  $r=0.991$  is excellent.

Table 8 compares the delta-chemical shifts(substituted - parent) for pyridine (15a), pyrimidine (29), pyrazine (22) long with pyrazine and 1,2,4-triazine obtained in this study.

Comparison of one substituents effect among the four different ring systems is not consistent. For example, a 2-methoxy group causes shielding differences of -41, -49, -63, and -60, respectively, in the series: pyrimidine to pyridine to pyrazine to 1,2,4-triazine. Similar effects are noted for all of the other substituents, except for the fluoro instance (whether this is real or reflects some solvent-hydrogen bonding problem is a mute question for these analyses).


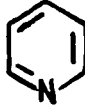
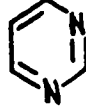

Linear correlation of delta-nitrogen-15 chemical shift verse delta-carbon-13 chemical shift of the ortho substituted benzene in pyridine, pyrimidine and pyrazine follow the general equation of:

## equation 23

$$[\text{Nitrogen-15 chemical shift}(\text{substituted heteroaromatic} - \text{parent})] = [ \text{Carbon-13 chemical shift}(\text{ ortho-carbon substituted benzene} - \text{benzene}) ] + C$$

These equations are tabulated in table 9.

The Paudler research group has recently proposed a set of  $\pi$ -deficiency parameters ( $\pi$ -delta) for a number of heteroaromatic compounds (30). These values, obtained from the carbon-13 chemical shift data, are:

				
$\pi$ -delta	0.992	0.886	0.772	0.638
intercept	-14.13	-4.70	+1.76	[+11.65 $\pm$ 0.5]est.

Thus, there is a gratifying interrelationship between the  $\pi$ -delta values of these heteroaromatic compounds (the smaller this value, the more  $\pi$ -deficient is the ring system) and the nitrogen-15 chemical shifts (increasing intercept value correspond to increasing  $\pi$ -deficiency). A linear correlation gives the following equation:

#### Equation 24

$$\text{Nitrogen-15 Intercept} = -72.03(\pi\text{-delta value}) + 57.93$$

The correlation coefficient is 0.992 which is clearly excellent. When equation 24 used the intercepts of previously reported correlation the resulting correlation coefficient is lower ( $r = 0.918$ ). This difference is not clearly understood.

#### Pyrazine and 1,2,4-Triazine N-Oxides

These N-oxides represent unique examples among this type of heterocyclic N-oxide because, backdonation of the

lone-pair electrons of the N-oxide oxygen leads to charge density increases on the ortho and para nitrogens with respect to the N-oxide function shown by the following:

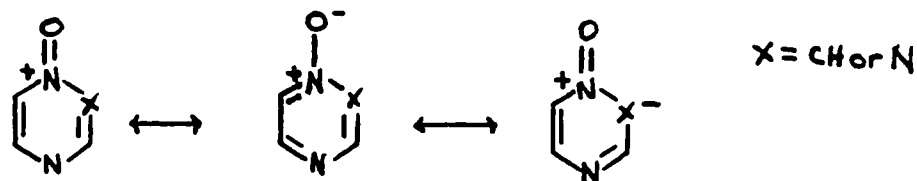


Table 10 gives the chemical shift differences experienced by the various nitrogens in some of the substituted pyrazines and 1,2,4-triazines when compared to their non-oxidized analogs.

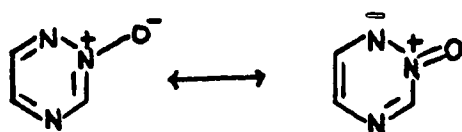
Clearly, N-oxidation does not only cause shielding of the oxidized nitrogen (difference = 25-30 ppm) in pyrazines but also causes shielding ( difference = 18-30 ppm) of the non-oxidized nitrogen as well. The 3-methoxy- and the 3-amino- pyrazine-1-oxides attenuate this effect due to their electron donating properties. Thus, the major ground state contributing structure for pyrazine-N-oxide is the following:



The 1,2,4-triazine-1-oxide chemical shift change for N-1 is -71 and -87 ppm for the 3-methoxy and 3-amino derivatives respectively. The shielding effect, as mentioned by Webb (20) for the parent compound, is clearly much larger than that observed in pyrazine-N-oxide. The N-4 shielding

effect (-27 ppm and -21 ppm, respectively) is the same order of magnitude as that observed for the pyrazine-1-oxide. The shielding (-39 ppm and -46 ppm, respectively experienced by N-2) is quite extensive and bespeaks a considerable contribution to the ground state structure.

In the 1,2,4-triazine-2-oxides, chemical shift changes for N-2 is -75 ppm and -69 ppm for the 3-amino and 3-bromo derivatives, respectively. An amazingly large and equal shielding is observed for the N-1 (-76 ppm and -73 ppm, respectively) in these compounds. Thus, it appears that a similar degree of backbonding exists in the 1- as well as the 2- oxides and, that in the former case charge dispersal occurs by N-2 and N-4, while in the latter case it is mainly "carried" by N-2 (N-4 cannot be involved by resonance). Therefore, the major resonance contributing structure must be the charge separated species.



## IV. EXPERIMENTAL

The N-15 spectra were obtained on a Nicolet NT-200 instrument operating at 20.27 MHz. Samples were placed in 20 mm o.d. tubes. A typical sweep window of 2 KHz. using 8 K words of memory was used to obtain the free induction decay data. N-15 decoupling was carried out with an inverse gated technique to suppress the NOE.

A co-axial 5 mm tube of 99% enriched nitromethane in deuterionitromethane served as a combination lock and reference capillary, 0.05 M tris(acetylacetonate)chromium, Cr(acac)<sub>3</sub>, was used to shorten the T-1 values. Normal operating conditions employed a 90 degree flip angle and a pulse delay of 8 seconds.

Melting points were obtained on a Thomas Hoover capillary melting point apparatus and were not corrected.

These procedures were modified by the author and the physical properties are identical to the known samples

#### 1. SYNTHESSES OF SEVERAL POLYAZAINDENDS FOR NITROGEN-15 SPECTROSCOPY

##### Imidazo[1,2-a]pyridine

A solution of 39.4g (0.20 mol) alpha-bromoacetaldehyde diethyl acetal in 80 mL of dioxane and 20 mL of water was warmed for 3 minutes. To this solution 5 drops of concentrated HCL was added, and the solution was refluxed until it turned clear (30 minutes). The solution was allowed to cool to room temperature and 19.2g (0.20 mol) of 2-aminopyridine was added along with 17.0g(0.20 mol) of sodium bicarbonate. This solution was refluxed for 22 hours. The reaction mixture was made basic with 1N sodium hydroxide and then extracted continuously with chloroform for 8 hours. The chloroform extract was dried over anhydrous sodium carbonate and reduced under vacuum to yield a dark oil. The oil was vacuum distilled at 0.05 mmHg(b.p. 109-113 C, yield 88.3%).



### Synthesis of Imidazo[1,2-a]pyrazine.

To a solution of 20 mL dioxane, 20 mL of water and 9.9g (0.05 mol) alpha-bromoacetaldehyde diethyl acetal (97%) was added 5 drops of concentrated hydrochloric acid. The solution was refluxed for 30 minutes until a clear solution was obtained. This solution was allowed to cool to room temperature and then 4.7g (0.05 mol) of 2-aminopyrazine was added. The solution was refluxed for 15 minutes and to the hot solution was added 5.3g (0.062 mol) of anhydrous sodium bicarbonate. This solution was refluxed for 15 hours and then was continuously extracted with methylene chloride for 72 hours. The extract was dried over sodium carbonate and reduced under vacuum to yield a dark solid compound. This solid was sublimed at 22 C/ 0.05mm Hg (m.p. 83-84 C , 42% yield).

### Synthesis of Imidazo[1,2-a]pyrimidine.

The imidazo[1,2-a]pyrimidine was prepared by condensing alpha-bromoacetaldehyde diethyl acetate with 2-amino pyrimidine by the procedure used for the synthesis of imidazo[1,2-a]pyridine. The imidazo[1,2-a]pyrimidine was purified by column chromatography on grade 3 neutral Woelm alumina using 50% petroleum ether / 50% ethyl acetate. The eluent was evaporated to dryness under vacuum to yield a white solid (m.p. 215-217 C, 58% yield).

### Synthesis of Imidazo[[1,2b]-1,2,4-triazine.

The imidazo[1,2b]-1,2,4-triazine was prepared by condensation of alpha-bromoacetaldehyde diethyl acetal with 3-amino-1,2,4-triazine by the procedure used for the preparation of imidazo[1,2a]pyridine. Purification of the imidazo[1,2b]-1,2,4-triazine was by sublimation at 25 C / 0.05 mmHg vacuum to yield a light yellow solid ( 36% yield, m.p. 110-111 C).

### Synthesis of Imidazo[1,5a]pyrazine.

A mixture of 6.0g (0.057 mol) 2-aminomethylpyridine and 12 mL of formic acid were refluxed for 3 hours. Fractional distillation yielded 5.3g (0.038 mol, yield 86%) of 2-formamidomethylpyridine.

The 2-formamidomethylpyridine was added to 12 mL of phosphorous oxychloride in 30 mL of benzene and refluxed for 3.5 hours. The excess phosphorous oxychloride and benzene were removed under vacuum distillation. To the remaining residue, 50 mL of ice water basified with 15N ammonium hydroxide was added and extracted with 4X50 mL portions of chloroform. The chloroform extract was reduced under vacuum and the resulting oil was vacuum distilled. Imidazo[1,5a]pyridine was collected at 95-100 C / 0.06 mm ( m.p. 56-58 C, 62% yield).

Synthesis of 1,2,4-triazolo[4,3a]pyridine.

A solution of 5.0g (0.045 mol) 2-hydrazinopyridine in 20 mL of formic acid was refluxed for 6 hours. The solution was reduced under vacuum and the dark oil was applied to a grade 3 alumina (neutral) column and eluted with 50% benzene / 50% diethyl ether mixture to yield 1.3g (0.011 mol, yield 24.3%) of 1,2,4-triazolo[4,3a]pyridine.

Synthesis of 1,2,4-triazolo[1,5a]pyridine.

A solution of 2.0g (0.0168 mol) 1,2,4-triazolo[4,3a]pyridine in 50 mL 50% sodium hydroxide solution was refluxed for 48 hours. This solution was continuously extracted with methylene chloride for 105 hours and then evaporated under vacuum to yield a dark oil. The oil was dissolved in diethyl ether and slowly concentrated under a gentle stream of nitrogen to yield a white solid. The white solid was recrystallized in petroleum ether to yield 1.05g (52.5% yield) of 1,2,4-triazolo[1,5a]pyridine.

Synthesis of 1,2,4-Triazolo[1,5a]pyrimidine.

A solution of 20g (0.24 mol) of 3-amino-1,2,4-triazole and 80g (0.36 mol) of 1,1,3,3-tetraethoxypropane in glacial acetic acid was warmed to 120 C for 12 hours. The solution was evaporated to dryness under vacuum and the solid residue was sublimed at 130 C / 0.05 mm Hg. The yield was 13g (44.7%), and the melting point was 140-142 C.

## 2. SYNTHESSES OF SUBSTITUTED PYRAZINES AND TRIAZINES AND THEIR N-OXIDES.

### Syntheses of Substituted Pyrazine N-Oxides.

#### Synthesis of 2- and 3-Methyl Pyrazine-1-oxides.

To a room temperature solution of 24 mL (0.31 mol) 30% hydrogen peroxide in 36 mL of acetic acid was added 13.8g (0.146 mol) of 2-methyl pyrazine. This solution was heated in a 80 degree oil bath for 17 hours. The resulting solution was evaporated to 1/3 volume under vacuum which was then made basic with solid sodium carbonate and 100 mL water. The basic solution was extracted with 4X50 mL portions of methylene chloride. The extract was dried over sodium carbonate (anhydrous) then evaporated to dryness under vacuum. The remaining solid material was applied to a 250g alumina grade III column and eluted with 50% ether / 50% benzene to obtain 2.0g (12.5%) of 2-methyl pyrazine-1-oxide and 2.0g (12.5%) of 3-methylpyrazine-1-oxide.

#### Synthesis of 2-Chloro Pyrazine-1-oxide.

To a stirring solution of 11.4g (0.1 mol) of 2-chloro pyrazine in 100 mL of concentrated sulfuric acid at 10 degrees was carefully added 30g (0.11 mol) of potassium persulfate. The reaction mixture was allowed to stir at room temperature for 24 hours. The solution was then carefully poured over 300g of ice and water. The aqueous solution was then extracted with 4X100 mL portion of methylene chloride. The methylene chloride extract was washed with a

saturated solution of sodium carbonate and water. This mixture was then dried over anhydrous sodium carbonate. The extract was evaporated to dryness under vacuum and the remaining solid material was sublimed at 75 C / 0.04 mm Hg to yield 2.8g (21.5%) of 2-chloropyrazine-1-oxide.

#### Synthesis of 3-Chloropyrazine-1-oxide.

To a solution of 48 mL (0.62 mol) 30% hydrogen peroxide in 72 mL of acetic acid was added 27.6g (0.2115 mol) of 2-chloropyrazine. The solution was then heated in a oil bath to 80 C for 17 hours. The solution was then reduced to 1/3 volume and neutralized with a saturated solution of sodium carbonate. The basic solution was extracted with 4X50 mL portions of methylene chloride and the extract was dried over anhydrous sodium carbonate. The dried extract was evaporated to a white solid under vacuum. The solid material was sublimed to yield 13.8g (50%) of 3-chloropyrazine-1-oxide.

#### Synthesis of 3-Methoxy Pyrazine-1-oxide.

To a solution of 7.0g (0.304 mol) sodium metal in 200 mL of anhydrous methanol was added dropwise 3.84g (0.0294 mol) of 3-chloro pyrazine-1-oxide in 150 mL of anhydrous methanol. This solution was allowed to stir for 48 hours and then the excess methanol was removed under vacuum to leave a yellow oil. This oil was added to 100 mL of saturated sodium carbonate solution and extracted with 5X100 mL

portions of methylene chloride. The extract was dried over sodium carbonate (anhydrous) then evaporated under vacuum to yield a yellow solid. A yield of 2.95g (79.6%) of 3-methoxy-pyrazine-1-oxide was obtained.

#### Synthesis of 3-Amino Pyrazine-1-oxide.

3-chloro pyrazine-1-oxide, 2g (0.0153 mol), was placed in 100 mL of methanolic ammonia and heated to 95 C for 6 hours. The tube was allowed to cool and the solid precipitate was collected by vacuum filtration. The solid material was sublimed at 80 C / 0.03 mm Hg to yield 1.6g (94.2%) of 3-amino pyrazine-1-oxide.

#### Syntheses of Substituted 1,2,4-Triazine-1 and 2-oxides.

##### Synthesis of 3-Methoxy-1,2,4-Triazine-1-oxide.

Meta-chloroperbenzoic acid, 7.0g (0.034 mol) in 60 mL of acetonitrile was added dropwise to 3.65g (0.033 mol) 3-methoxy-1,2,4-triazine in 120 mL of acetonitrile warmed to 60 C. After addition the solution was maintained at 65 C for 16 hours. The acetonitrile was removed under vacuum to yield a yellow solid. To this, 40 mL of saturated sodium carbonate solution was added followed by extraction with 5X 100 mL portions of chloroform. The chloroform extract was dried over anhydrous sodium carbonate which was then evaporated under vacuum to yield a light yellow solid. The solid was sublimed at 50 C / 0.05 mm Hg to yield 2.79g (66%) of 3-methoxy-1,2,4-triazine-1-oxide.

Synthesis of 3-Amino-1,2,4-Triazine-1-Oxide.

To 40 mL of cold methanolic ammonia was added 2.54g (0.20 mol) of 3-methoxy-1,2,4-triazine-1-oxide. This solution was placed in a sealed tube and heated in an oil bath at 100 C for 6 hours. The tube was allowed to cool to room temperature and a solid precipitate was collected by vacuum filtration. A yield of 1.95g (87%) of 3-amino-1,2,4-triazine-1-oxide was obtained.

Synthesis of 3-Amino-1,2,4-Triazine-2-Oxide.

To a solution of 7.0g (0.034 mol) 85% meta-chloroperbenzoic acid in 60 mL of acetonitrile was added dropwise to 2.85g of 3-amino-1,2,4-triazine in 120 mL of acetonitrile. The resulting solution was placed in an 80 C oil bath for 5 hours. This solution was allowed to cool to room temperature and was evaporated to dryness under vacuum. The solid material was triturated with 100 mL of ether and 100 mL of benzene. The yellow powder was sublimed to yield 2.9g (87%) 3-amino-1,2,4-triazine-2-oxide.

Synthesis of 3-Bromo-1,2,4-Triazine-2-oxide.

To a solution of 1.12g (0.01 mol) 3-amino-1,2,4-triazine-2-oxide in 100 mL of 2N hydrobromic acid at 0 C was added dropwise to a solution of 4.14g (0.06 mol) in 20 mL water. After addition the dark brown solution was maintained at 0 C for 2 hours and was then extracted with 5X100 mL

portions of methylene chloride. The methylene chloride extract was washed with 50 mL of a saturated solution of sodium carbonate then dried over anhydrous sodium carbonate. The methylene chloride extract was evaporated to dryness under vacuum to yield a white solid which was sublimed. A yield of 0.96g (55%) of 3-bromo-1,2,4-triazine-2-oxide was obtained.

#### Syntheses of Some Substituted Pyrazines.

##### Synthesis of 2-Aminopyrazine.

To 50 mL of methanolic ammonia was added 1g (0.0087 mol) of 2-chloropyrazine and the solution was heated in a sealed tube for 6 hours. After heating the tube was allowed to cool to room temperature and the solution was evaporated to dryness under vacuum to yield a white solid. This solid was sublimed at 70 C / 0.05 mm Hg to yield 0.73g (89%) of 2-aminopyrazine.

##### Synthesis of 2-Methoxypyrazine.

To a solution of 10g (0.43 mol) sodium metal in 200 mL of anhydrous methanol was added dropwise with stirring 5g (0.043 mol) of 2-chloropyrazine in 100 mL of anhydrous methanol. The resulting solution was stirred at room temperature for 48 hours. The solution was fractionally distilled to remove the methanol and the resulting residue was added to 100 mL water. The water solution was extracted with methylene chloride and the methylene chloride extract



was dried over anhydrous sodium carbonate. The dried extract was evaporated to dryness under vacuum to yield 3.2g (67.6%) of 2-methoxy pyrazine.

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TABLE I  
COMPARISON OF NITROGEN-14 TO NITROGEN-15

	N-14	N-15
SPIN QUANTUM NUMBER	1	1/2
NATURAL ABUNDANCE	99.63%	0.37%
SENSITIVITY RELATIVE TO PROTON-1	0.00101	0.00194
SENSITIVITY RELATIVE TO CARBON-13 AT NATURAL ABUNDANCE	17.22	0.0214
NMR FREQUENCY AT 4.7 TESLA	14.452	20.272

TABLE II

## NITROGEN-14,-15 CHEMICAL SHIFTS FOR SOME AZOLES

COMPOUND	SOLVENT	SHIFT (A)	REF
PYRROLE	DMSO	N-1 155.6	B
N-METHYL PYRROLE	NEAT	N-1 147	A
	METHANOL	145	A
	DMSO	150	B
	DMSO	149.9	C
INDOLE	NEAT	N-1 130	A
N-METHYL INDOLE	DMSO	N-1 126.6	C
PYRAZOLE	CDCL <sub>3</sub>	N-1,2 248.0	B
N-METHYL PYRAZOLE	METHANOL	N-1 200	A
		(NMe)	
	CDCL <sub>3</sub>	N-2 300	B
		N-1 200.9	
		(NMe)	
		N-2 306.5	
ISOXAZOLE	NEAT	380	A
ISOTHIAZOLE	NEAT	298	A
IMIDAZOLE	DMSO	212.6	B
N-METHYLIMIDAZOLE	NEAT	N-1 157 (Me)	A
		N-3 255	
	DMSO	N-1 162.6 (Me)	B
		N-3 260.7	
	DMSO	N-1 161.5 (Me)	C
		N-3 262.1	
OXAZOLE	METHANOL 4/1 V/V	253	A
THIAZOLE	NEAT	322	A
1,2,3-TRIAZOLE	DMSO	N-1,3 311.2	B
		N-2 304.3	
	CDCL <sub>3</sub>	N-1,3 301.2	B
		N-2 318.3	

TABLE II CONTINUED

COMPOUND	SOLVENT	SHIFT (D)	REF.
1-METHYL-1,2,3- TRIAZOLE	NEAT	N-1 236	A
		N-2 368	
		N-3 350	
	DMSO (E)	N-1 237.2	B
		N-2 363.9	
		N-3 349.5	
	DMSO	N-1 236.9	C
		N-2 364.9	
		N-3 351.8	
2-METHYL-1,2,3- TRIAZOLE	NEAT	N-1,3 327	A
		N-2 248	
	DMSO	N-1,3 326.2	C
		N-2 245.2	
THIA-2,3-DIAZOLE	ACETONE	N-2 436	A
		N-3 410	
OXA-2,5-DIAZOLE	NEAT	N-2,5 347	A
	ACETONE	N-2,5 346	A
THIA-2,5-DIAZOLE	NEAT	N-2,5 345	A
	ETHER	N-2,5 346	A
1,2,4-TRIAZOLE	DMSO	N-1,2 252.8	B
		N-4 245.5	
1-METHYL-1,2,4 TRIAZOLE	NEAT	N-1 185	A
		N-2 295	
		N-4 249	
	DMSO	N-1 208.9	B
		N-2 298.0	
		N-4 252.1	
	DMSO	N-1 208.9	C
		N-2 298.3	
		N-3 252.8	
4-METHYL-1,2,4- TRIAZOLE	METHANOL	N-1,2 298	A
		N-4 158	
	DMSO	N-1,2 319.9	B
		N-4 163.5	
	DMSO	N-1,2 320.4	C
		N-4 162.4	

TABLE II CONTINUED

COMPOUND	SOLVENT	SHIFT	REF.
1,2,4-OXADIAZOLE	ETHER 1/1 V/V	N-2 360 N-4 240	A
1,2,4-THIADIAZOLE	ETHER 1/3 V/V	N-2 274 N-4 310	A
OXA-3,4-DIAZOLE	NEAT	N-3,4 298	A
THIA-3,4-DIAZOLE	ETHER 1/1 V/V	N-3,4 370	A

(a). See Ref. 25

(b). Nitrogen-15 data from: D.S. Wofford, D.M. Forkey and J.G. Russell, J. Org. Chem. 1982, 47, 5132.

(c). Nitrogen-15 data from: L. Stefaniak, J.D. Roberts, M. M. Witanowski and G.A. Webb, Org. Magn. Reson. 1984, 22, 215.

(d). All shifts have been corrected to anhydrous ammonia and are recorded in parts per million (ppm).

(e). DMSO is dimethyl sulfoxide.



TABLE III

NITROGEN-14,-15 CHEMICAL SHIFT DATA FOR AZINE-N-OXIDES(d)

COMPOUND	SOLVENT	CHEMICAL SHIFTS(a)
PYRIDINE-N-OXIDE	ACETONE	294
QUINOLINE-N-OXIDE	ACETONE	315
ISOQUINOLINE-N-OXIDE	ACETONE	290
PYRIDAZINE-N-OXIDE	ACETONE	325 N-1 N-2 NOT REPORTED
	CHLOROFORM(b)	N-1 325.5 N-2 347.4
PYRIMIDINE-N-OXIDE	ACETONE	289
PYRAZINE-N-OXIDE	ACETONE	N-1 312 N-4 NOT REPORTED
	CHLOROFORM(b)	N-1 304.5 N-4 309.8
CINNOLINE-1-OXIDE	ACETONE	N-1 321 N-2 NOT REPORTED
CINNOLINE-2-OXIDE	ACETONE	N-1 NOT REPORTED N-2 327
QUINAZOLINE-3-OXIDE	ACETONE	N-3 288 N-1 NOT REPORTED
	DMSO(b)	N-1 290.7 N-3 290.7
QUINAXOLINE-N-OXIDE	ACETONE	N-1 303 N-4 NOT REPORTED
	DMSO(b)	N-1 299.5(c) N-4 303.4(c)

(a) all shifts have been corrected to anhydrous ammonia and are recorded in parts per million(ppm).

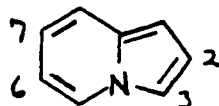
(b) see reference number 19 for data.

(c) arbitrary assignment, see reference number 19.

(d) see reference number 18.

TABLE IV

NITROGEN-15 CHEMICAL SHIFTS OF SOME POLYAZAINDENES (a)

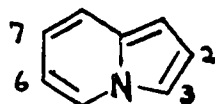


COMPOUND	N-1	N-2	N-3	N-4
PYRAZOLO[2,3a]PYRIDINE	---	---	305	239
IMIDAZO[1,5a]PYRIDINE	---	244	---	193
IMIDAZO[1,2a]PYRIDINE	248	---	---	202
1,2,3-TRIAZOLO[1,5a]- PYRIDINE	---	339	411	260
1,2,4-TRIAZOLO[2,3a]- PYRIDINE	230	---	286	239
1,2,4-TRIAZOLO[4,3a]- PYRIDINE	319	262	---	194
1,2,3,4-TETRAZOLO[1,5a] PYRIDINE	314	366	306	247

(a) reference number 17d

TABLE V

NITROGEN-15 CHEMICAL SHIFTS OF SOME POLYAZAINDENES



NITROGEN-15 CHEMICAL SHIFTS (AMMONIA=0)


COMPOUND #	N-1	N-2	N-3	N-4	N-5	N-6	N-7	N-8
1a	249	---	---	202	---	---	---	---
2	---	242	---	193	---	---	---	---
10	---	---	305	238	---	---	---	---
4	240	---	---	195	---	---	292	---
5	229	---	---	180	---	---	---	271
6	319	262	---	194	---	---	---	---
7	---	339	411	260	---	---	---	---
8	413	366	306	247	---	---	---	---
9	249	---	---	318	414	---	---	269
11	218	---	266	221	---	---	---	269
11	230	---	286	239	---	---	---	---

(a) our data is in DMSO with nitromethane(shift=380.23(ppm)) external standard

(b) nitrogen chemical shifts of six-membered heteroaromatic compounds employed in Figure 1: pyridine, 302; pyrimidine, 298; pyridazine, 400; pyrazine, 338; 1,2,4-triazine, N-1=420, N-2=382, N-4=318 in chloroform, and all others are in DMSO

TABLE VI

NITROGEN-15 CHEMICAL SHIFT DATA OF SOME PYRAZINES AND THEIR N-OXIDES (c)

SUBSTITUENT		N-15 SHIFTS (ppm) (b)	
		N-1	N-4
H		332 d	332 d
2-methyl		324 (331.3) a	326 (333) a
2-methoxy		269 (278.5) a	335 (341.5) a
2-amino		265 (273.5) a	326 (334.2) a
2-chloro		316 (323.0) a	336 (342.8) a
2-carboxylic acid		325 (332.8) a	327 (334.8) a
2-amido		314 (322.7) a	328 (335.9) a
3-methyl, 1-oxide		297	302
2-methyl, 1-oxide		296	298
3-chloro, 1-oxide		307	287
2-chloro, 1-oxide		287	306
3-methoxy, 1-oxide		305	248
3-amino, 1-oxide		301	247
1-oxide		309	304

(a). number in parathenses see reference 19.

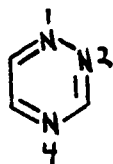
(b). chemical shifts are given with respect to ammonia at 0 ppm, nitromethane=380.23 ppm, all compounds were run DMSO at 1 molar concentration.

(c). These compounds were prepared in accordance with the procedures in: S.A. Krueger and W.W. Paudler, J. Org. Chem. 1972, 37, 4188.

(d). nitrogen-14 data from 17e

TABLE VII

NITROGEN-15 CHEMICAL SHIFT DATA OF SOME 1,2,4-TRIAZINES AND THEIR N-OXIDES.



SUBSTITUENT	N-15 SHIFT(a)		
	N-1	N-2	N-4
H(B)	420.0	382.0	318.0
3-amino	415.7	319.0	250.0
3-methoxy	416.0	322.0	253.6
3-methylthio	412.0	351.0	282.0
3-amino,1-oxide	328.9	273.0	228.9
3-methoxy,1-oxide	330.0	282.9	232.0
3-amino,2-oxide	341.0	242.0	277.0
3-bromo,2-oxide	351.4	309.0	305.8
H, 1-oxide(e)	337		

(a) see footnote b in table 6

(b) nitrogen-14 data given are slightly different: N-1=422  
N-2=278, and N-4=298

(c) the compounds were prepared by procedures given in:  
B.T. Keen, R.J. Radel and W.W. Paudler, *J. Org. Chem.*  
1977, 42, 3498.

(d) the deshielding of N-4 with respect to the non-oxidized  
3-amino compound may will reflect the inductive  
electron-withdrawing effect of the N-oxide  
counteracting the shielding effect of the 3-amino group.

TABLE VIII

NITROGEN-15 CHEMICAL SHIFT DIFFERENCES (ppm) BETWEEN PARENT HETEROCYCLIC COMPOUNDS (R=H) AND SUBSTITUTED HETEROCYCLIC ANALOGS.<sup>a</sup>



R	N-1, N-3	N-1	N-1	N-4	N-1	N-2	N-4	C-13 ORTHO (SUBSD. - BENZENE)
amino	-49	-51.5	-67	-6	-4.3	-63	-68	-13.3
methoxy	-41	-49.2	-63	+3	-4.0	-60	-64.4	-14.4
fluoro	-47	-41.6	-91.9c-29.2c	---	---	---	---	-12.9
chloro	-6	-7.5	-16	+4	---	---	---	+0.4
cyano	+19	-0.9	-46.5c-44.5c	---	---	---	---	+3.6
methyl- thio	-15	-24	-63.7c-47.8c-8.0	-31	-36.0			
methyl- carb- oxylate	+13	+11.8	-47.8c-45.0c	---	---	---	---	+2.1
methyl	---	-0.4	-8	-6	---	---	---	+0.7

(a) Negative numbers indicate shielding with respect to the parent compound; underlined numbers refer to nitrogens ortho to the substituted carbon.

(b) Data from: G.C. Levy and G.L. Nelson, "Carbon-13 Nuclear Magnetic Resonance For Organic Chemists.", Wiley Interscience, New York, NY, 1972, p.81 and references cited therein. See text comment in connection with these data.

(c) see reference 22.

TABLE IX

DIFFERENCE NITROGEN-15 SHIFT = SLOPE \* (DIFFERENCE CARBON-13  
SHIFT - INTERCEPT)

COMPOUND	SLOPE	INTERCEPT
PYRAZINE	3.66(3.05)a	-14.13(-9.86)a
PYRIDINE	3.14(3.52)b	-4.70 (-1.87)b
PYRIMIDINE	3.52(2.89)b	+1.76 (-0.49)b
1,2,4-TRIAZINE	-----	[+11.65±0.5]est.

(a) see reference 22

(b) see reference 21

TABLE X

NITROGEN-15 CHEMICAL SHIFT DIFFERENCE (ppm) BETWEEN SOME  
SUBSTITUTED HETEROCYCLIC COMPOUNDS AND THEIR N-OXIDES

## A. SUBSTITUTED PYRAZINE N-OXIDE

R	NITROGEN SHIFT DIFFERENCE (ppm)		
	N-1	N-2	N-4
H	-28(a)		-23(a)
3-methyl	-27		-24
2-methyl	-28		-28
3-chloro	-29		-29
2-chloro	-29		-30
3-methoxy	-30		-21
3-amino	-25		-18

## B. SUBSTITUTED 1,2,4-TRIAZINE 1-OXIDE

R			
H	-78(a)	unpublished	unpublished
3-methoxy	-71	-39	-27
3-amino	-87	-46	-21

## C. SUBSTITUTED 1,2,4-TRIAZINE 2-OXIDE

R			
3-amino	-75	-76	+27
3-bromo	-69	-73	-13

(a) see reference 20



Figure 1

Plot of Structures A minus Parent 6-Numbered ring (B)  
vs. Bridge Nitrogen Chemical Shift of A

