

HETERO-SYNTHESSES WITH ISOCYANIDES

By

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It is with great pleasure, the author proudly dedicates this dissertation to his parents and brother whose unselfish sacrifices, experience, and encouragement helped make this goal a reality.

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TABLE OF CONTENTS

	Page
ACKNOWLEDGEMENTS.....	iv
LIST OF TABLES.....	ix
ABSTRACT.....	x
CHAPTER I Reactions of <u>t</u> -Butyl Isonitrile.....	1
Introduction.....	1
Discussion.....	7
Conclusions with Comments for Further Research.....	42
II Evidence for the Structure and Conformation Conjugated Diimines.....	52
Introduction.....	52
Discussion.....	53
Conclusion.....	92
III 4,5-Dihydro-1H-1,4-benzodiazepines (118)...	99
Introduction.....	99
Discussion.....	107
Conclusion.....	123
IV 5-Imino-2-oxo-1,2,3-oxathiazolidines (160).	128
Introduction.....	128
Discussion.....	130
Conclusion.....	140
V Experimental.....	142
<u>t</u> -Butyl Isonitrile (5).....	143
<p>Nitrobenzylidene-<u>t</u>-butylamine (18a).....</p> Reaction of <u>p</u> -Nitrobenzylidene- <u>t</u> -butylamine (18a) with <u>t</u> -Butyl Isonitrile.....	143
α-Cyano-4-Nitrophenylglyoxylidenedi- <u>t</u> -butyl- amine (20a).....	146
1- <u>t</u> -Butyl-5-cyano-4-(4-nitrophenyl)imidazole (21a).....	146

Table of Contents (continued)

	Page
α -(N- <u>t</u> -Butylacetamido)- β - <u>t</u> -butylamino-4-nitrocinnamionitrile (26a).....	147
General Procedure for the Preparation of <u>p</u> -Nitrobenzylidene-2,6-dialkylaniline...	148
Reaction of <u>p</u> -Nitrobenzylidene-2,6-dimethylaniline (18b) with <u>t</u> -Butyl Isonitrile.....	148
α -Cyano-4-nitrophenylglyoxylidene- α -(<u>t</u> -butylamine)- β -(2,6-dimethylaniline) (20b).....	150
1-(2,6-Dimethylphenyl)-4-cyano-5-(4-nitrophenyl)imidazole (22b).....	151
The Attempted 1,4-Cycloaddition of α -Cyano-4-nitrophenylglyoxylidene- α -(<u>t</u> -butylamine)- β -(2,6-dimethylaniline) (20b) with <u>p</u> -Benzoquinone.....	152
The Attempted 1,4-Cycloaddition of α -Cyano-4-nitrophenylglyoxylidene- α -(<u>t</u> -butylamine)- β -(2,6-dimethylaniline) (20b) with Ketene Diethylacetal. The Preparation of 4- <u>t</u> -Butyl-3-cyano-4,5-dihydro-9-methyl-2-(4-nitrophenyl)-1H-1,4-benzodiazepine (35).....	152
4- <u>t</u> -Butyl-4,5-dihydro-9-methyl-2-(4-nitrophenyl)-3H-1,4-benzodiazepin-3-one (39).....	153
<u>p</u> -Nitrobenzylidenemethylamine (18c).....	153
Reaction of <u>p</u> -Nitrobenzylidenemethylamine (18c) with <u>t</u> -Butyl Isonitrile.....	153
α -Cyano-4-nitrophenylglyoxylidene- α -(<u>t</u> -butylamine)- β -(methylamine) (20c).....	154
4-Cyano-1-methyl-5-(4-nitrophenyl)imidazole (22c) and 1- <u>t</u> -butyl-5-cyano-4-(4-nitrophenyl)imidazole (21a).....	155
4-Cyano-1,2-dimethyl-5-(4-nitrophenyl)imidazole (27c).....	156
<u>p</u> -Nitrobenzylidenebenzylamine (18d).....	157
Reaction of <u>p</u> -Nitrobenzylidenebenzylamine (18d) with <u>t</u> -Butyl Isonitrile.....	157
<u>p</u> -Nitrophenylglyoxal Hydrate (22).....	159
<u>p</u> -Nitrophenylglyoxylidene- α - <u>t</u> -butylamine (23).....	159
<u>p</u> -Nitrophenylglyoxylidenedi- <u>t</u> -butylamine (24a).....	160
α , β -Di- <u>t</u> -butylamino-4-nitrocinnamionitrile (19a).....	161
Phenylglyoxal Hydrate (63).....	162
Phenylglyoxylidene- α - <u>t</u> -butylamine ⁴⁰ (64).....	162
Phenylglyoxylidene- α , β -di- <u>t</u> -butylamine (65).....	162

Table of Contents (continued)

	Page
α -Cyano-phenylglyoxylidenedi- <u>t</u> -butyl-amine (68).....	162
4-Nitrophenylglyoxylidene-bis(2,6-dimethylaniline) (144).....	163
α -Cyano-4-nitrophenylglyoxylidene- α,β -bis(2,6-dimethylaniline) (107).....	164
Benzylidene-di- <u>t</u> -butylamine (93).....	165
4,5-Diphenylglyoxalone.....	166
4,4'-Dinitrobenzil.....	166
4,4'-Dinitrobenzylidenedi- <u>t</u> -butylamine (94).....	166
Benzophenone- <u>t</u> -butylimine (84).....	167
<u>p</u> -Nitroacetophenone- <u>t</u> -butylimine.....	167
Phenanthrenequinone-di- <u>t</u> -butylimine (95)...	168
Glyoxylidenedi- <u>t</u> -butylamine (82).....	169
Reaction of Glyoxylidenedi- <u>t</u> -butylamine with Acetone Cyanohydrin.....	169
α -Cyanoglyoxylidenedi- <u>t</u> -butylamine (87)...	170
1,2-Di- <u>t</u> -butylamino-1,2-dicyanoethylene...	171
α,β -Dicyanoglyoxylidenedi- <u>t</u> -butylamine....	172
Glyoxylidenedi- <u>o</u> -toluidine (148).....	172
2,3-Di- <u>o</u> -toluidinoacrylonitrile (149).....	173
α -Cyanoglyoxylidenedi- <u>o</u> -toluidine (109)...	174
α,β -Dicyanoglyoxylidenedi- <u>o</u> -toluidine (109)	174
Benzylideneaniline.....	175
2-Anilino-2-phenylacetone nitrile (110).....	176
N-Phenylbenzimidyl Cyanide (111).....	176
N- <u>t</u> -Butyl-N'- <u>o</u> -tolylethylenediamine (165).	177
Glyoxylidene- <u>t</u> -butylamine- <u>o</u> -toluidine (166).....	178
N- <u>t</u> -Butyl-2-chloro-2-phenylacetamide (172)	178
N- <u>t</u> -Butyl-2-(N'- <u>o</u> -tolyl)-2-phenylacetamide (173).....	179
1-N- <u>t</u> -butyl-2-(N'- <u>o</u> -tolyl)-2-phenylethylenediamine (174).....	180
Reaction of 1-N- <u>t</u> -Butyl-2-(N'- <u>o</u> -tolyl)-2-phenylethylenediamine (174) with Activated Manganese Dioxide.....	181
General Procedure for Preparation of 1H-1,4-Benzodiazepines.....	181
2-Chloroacetamides.....	182
2-Chloroacet- <u>o</u> -toluidide.....	182
General Procedure for Preparation of 2-Aminoacetamides.....	184
General Procedure for Preparation of 5-Imino-2-oxo-1,2,3-oxathiazolidines (195)	184
Reaction of α -Cyano-4-nitrophenylglyoxylidenedi- <u>t</u> -butylamine (20a) with <u>m</u> -Chloroperbenzoic Acid.....	185

Table of Contents (continued)

	Page
APPENDIX.....	189
BIBLIOGRAPHY AND NOTES.....	217
BIOGRAPHICAL SKETCH.....	227

LIST OF TABLES

Table		Page
I	Preliminary Reactions.....	8
II	Variations on Experiment F.....	9
III	Chemical Shifts of H-4 and H-6.....	41
IV	NMR Spectra of the Diimines.....	95
V	Optimization Reaction for <u>35</u>	109
VI	Reaction Parameters for the Preparation of 1H-1,4-Benzodiazepines.....	125
VII	Spectral Properties of 2-Aminoacetamides.....	133
VIII	Spectral Properties of 5-Imino-2-oxo-1,2,3- oxathiazolidines.....	135
IX	Physical Parameters for Several <i>p</i> -Nitrobenzyl- dene-2,6-dialkylanilines.....	149
X	Physical Parameters for 2-Chloroacetamides.....	183
XI	Physical Parameters for 2-Aminoacetamides.....	186
XII	Physical Parameters for 5-Imino-1,2,3-oxathiazo- lidines.....	187

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As part of the continued study of the reactions of t-butyl isonitrile, it was found that two equivalents of t-butyl isonitrile added in the presence of an acid catalyst to p-nitrobenzylidenealkyl- or arylamines which lacked aryl electrons available for cyclization. The product was assigned the structure of an α,β -diamino-p-nitrocinnamitrile derivative based on spectral evidence and analytical data as well as an independent synthesis. The α,β -diamino-p-nitrocinnamitrile derivatives were found to be useful precursors to diimines, and heterocyclic rings difficultly obtained by other synthetic methods.

In order to unequivocally determine the structures of the diimines prepared from the α,β -diamino-p-nitrocinnamitrile derivatives, other diimines were prepared by alternative routes. Each of these compounds displayed a temperature dependent nmr spectrum which was explained in terms of an equilibrium of two conformations. The "normal" nmr pattern was explained in terms of a completely planar

Z-s-trans-E conformer and the "abnormal" nmr pattern was explained in terms of a planar E-s-trans-E diimine system with a skew aryl group on the β -imine carbon atom. Other spectral properties of these diimines were also discussed.

Since the diimines displayed anomalous spectral properties, further chemical support was sought. It was thought that a Diels-Alder adduct of one of the diimines might clarify some of the problems. All attempts to react α -cyano-4-nitrophenylglyoxylidene- α -(t-butylamine)- β -(2,6-dimethylaniline) with various dienophiles met with failure. However, α -cyano-4-nitrophenylglyoxylidene- α -(t-butylamine)- β -(2,6-dimethylaniline) did cyclize in base to yield 4-t-butyl-3-cyano-4,5-dihydro-9-methyl-2-(4-nitrophenyl)-1H-1,4-benzodiazepine. This compound was transformed further with sodium hypochlorite to 4-t-butyl-4,5-dihydro-9-methyl-2-(4-nitrophenyl)-3H-1,4-benzodiazepin-3-one. The potential biological utility of the benzodiazepines made it important to determine the generality of the base catalyzed cyclizations. For this purpose, a series of unsymmetrically N-substituted diimines were needed. It was thought that they could be prepared from α -aminoimidoyl chlorides. A series of aryl and aliphatic substituted 2-aminoacetamides were prepared and reacted with thionyl chloride followed by base to give not the desired imidoyl chloride, but instead 5-imino-2-oxo-1,2,3-oxathiazolidines in good yield. This structure was assigned on the basis of analytical, chemical, and spectral data. Further reactions of the novel ring system were discussed.

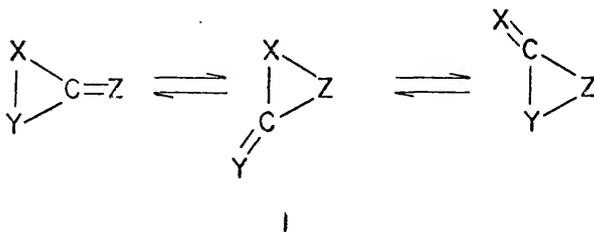
CHAPTER I

Reactions of t-Butyl Isonitrile

Introduction

Compounds of the general structure (1) have the potential for facile molecular reorganization,¹⁻⁴ Scheme I.

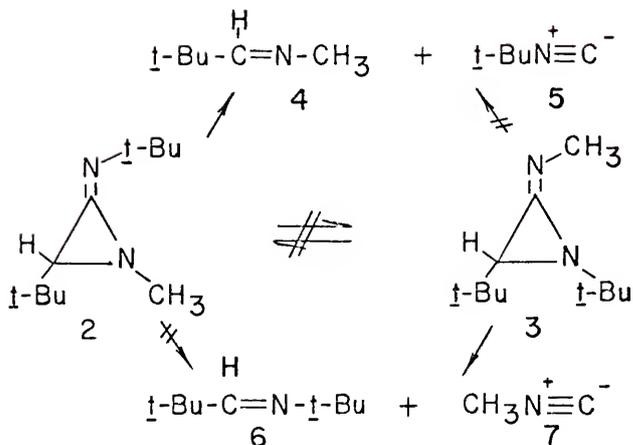
Scheme I



Recently the iminoaziridines (2 and 3) were prepared by Quast and Schmitt from the corresponding 2-bromoamidine in high yield.⁵ At room temperature they isolated a 50:50 mixture of 2 and 3 and found that 2 started to decompose at 50°C to yield 4 and 5 (half life about 17 hours at 60°C) while 3 on the other hand only decomposes above 120°C into 6 and 7. All attempts to observe the isomerization (2↔3) either directly or by identification of the isomeric thermolysis products failed, Scheme II.

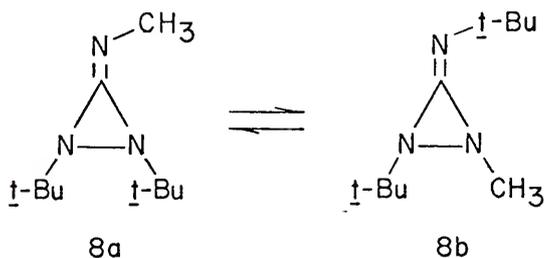
Scheme I type isomerizations were observed with imino-diaziridines. Quast and Schmitt found that when N,N'-di-t-

Scheme II



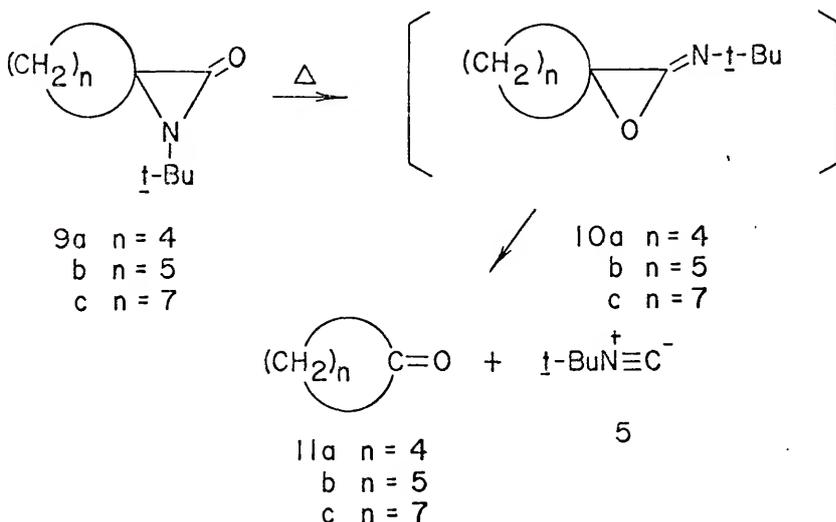
butyl-N"-methylguanidine was treated with *t*-butyl hypochlorite an 83% yield was obtained of a mixture of the isomeric imino-diaziridines (8a) and (8b) in a ratio of 3:2.⁶ Whereas, 8a and 8b remained unchanged at -20°C, at 60-90°C either 8a or 8b led to an equilibrium mixture of the two with less than 2% thermal decomposition, Scheme III. This represented the first

Scheme III



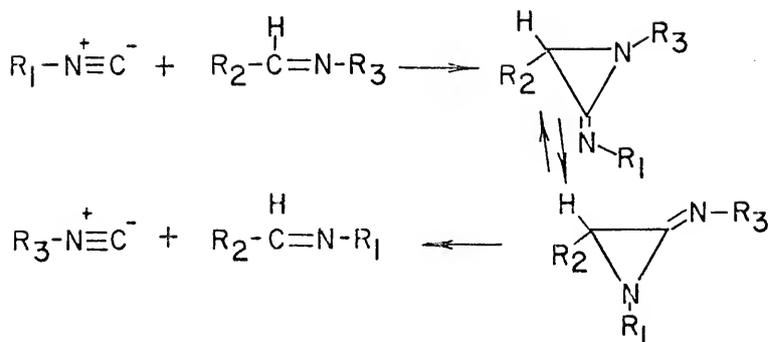
reversible isomerization of a hetero analog of methylene-cyclopropane. In 1964, Sheehan and Lengyel reported the thermal decomposition of the spiro- α -lactam (9b).⁷ This compound decomposed quantitatively within 10 minutes at 75°C to give cyclohexanone and t-butyl isonitrile as major products, Scheme IV.

Scheme IV



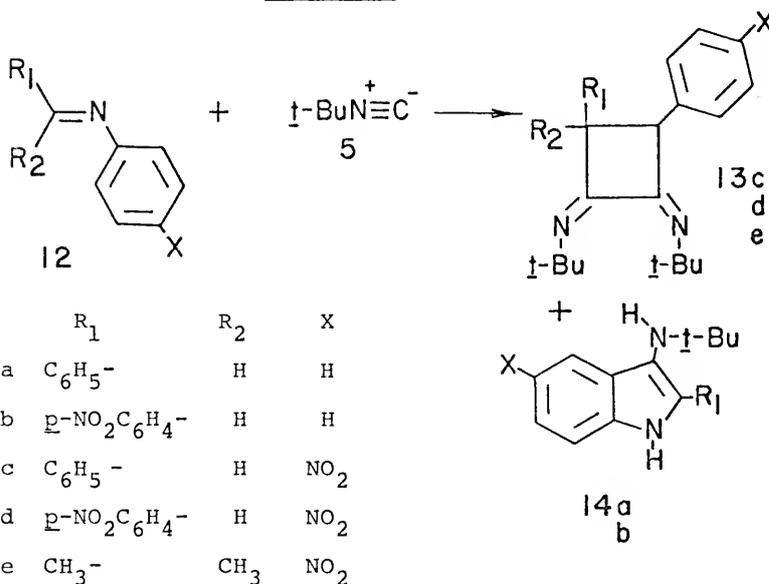
The results of the thermolyses of 2, 3 and 9 suggested that heteromethylenecyclopropanes (1) might be generated by the reverse of this dissociation if suitable acceptors and conditions were chosen. With this in mind, the isomerization sequence depicted in Scheme V was attempted under various conditions.^{8,9} Although these attempts did not produce additional examples of the isomerization illustrated in Scheme V, a number of new and potentially useful reactions

Scheme V



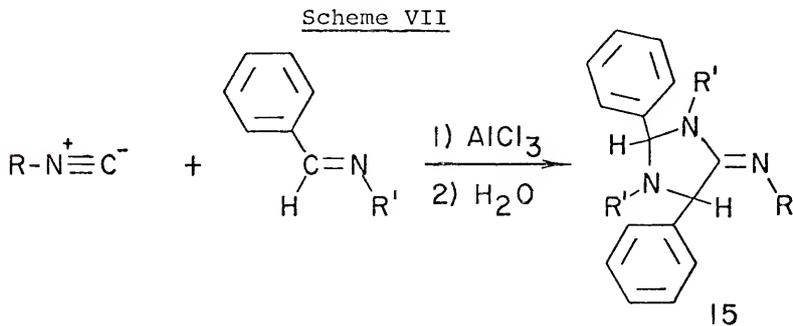
between imines and isonitriles were discovered. It was found, for example, that benzylidene-N-arylamines reacted with *t*-butyl isonitrile to afford a 1:1 adduct (3-*t*-butyl-amino-2-phenylindole) and/or a 1:2 adduct [2,3-bis(*t*-butyl-amino)azetidene],^{8,9} Scheme VI. Other systems have formed

Scheme VI



similar 1:2 adducts with isonitriles. At about the same time, other workers observed that 1,1-ditrifluoromethyl-2,2-dicyanoethylene reacts with two equivalents of *t*-butyl isonitrile to yield the 1,2-diiminocyclobutane derivative¹⁰ and a variety of aldehydes and ketones react with isonitriles in a ratio of 1:2 to form 2,3-diiminooxetanes.¹¹

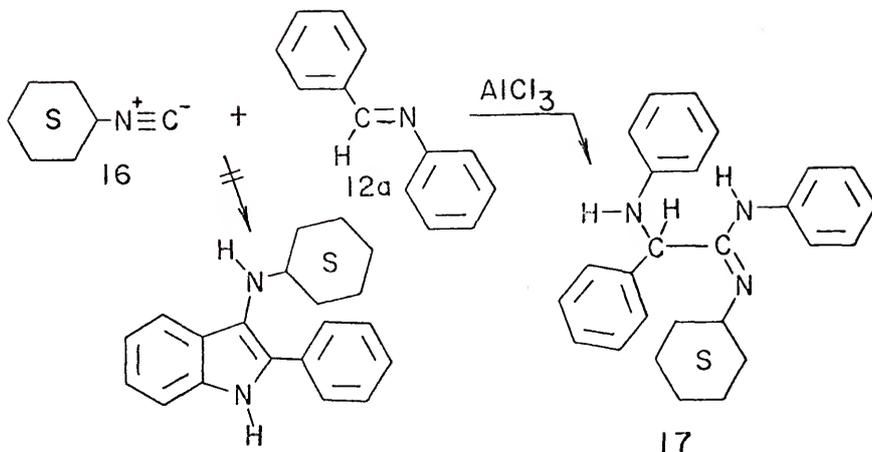
In spite of these publications,¹² a coherent picture of predictive value had not emerged at the inception of this work. Thus Saegusa *et al.*¹³ found that alkyl isonitriles reacted with two equivalents of benzylidene-*N*-alkylamines in the presence of AlCl₃, SnCl₄ or BF₃ etherate to produce an imidazolidine derivative, Scheme VII. However, when cyclohexyl isonitrile was allowed to react with *N*-arylimine (12a)



- a R=C₆H₁₁, R'=CH₃
 b R=C₆H₁₁, R'=C₂H₅
 c R=*t*-Bu, R'=CH₃

in the presence of AlCl₃ they obtained an acyclic product, *N,N'*-diphenyl-1-phenyl-2-cyclohexylimino-ethylenediamine (17), instead of the indole (14a) obtained by Deyrup *et al.*,^{8,9} Scheme VIII.

Scheme VIII



Further work in these laboratories also had revealed the complexity of isonitrile-imine chemistry. Yun⁹ reacted t-butyl isonitrile with p-nitrobenzylidenealkylamines in a variety of solvents. Instead of the imidazolidine derivatives¹³ she obtained α,β -diamine-p-nitrocinnamionitriles.⁹ However, her results varied rather drastically with a change in solvent. As a result products were obtained for which no structure had been assigned.

The purpose of this research was to react t-butyl isonitrile with p-nitrobenzylidenealkyl- and arylamines in a specific set of reaction conditions in order to obtain definitive results. The cyclic and acyclic products were isolated and identified. The interesting chemical aspects of these products were also surveyed.

Discussion

At the inception of this research no trend could be discerned among the maze of reactions between t-butyl isonitrile and imines, except in the case of the work cited earlier (ref. 8). Some of the reactions were conducted in carbon tetrachloride in sealed tubes, while others were conducted in chloroform or methylene chloride, with or without hydrogen chloride and at or above room temperature. Every alteration of the reaction conditions produced a different set of adducts. Even a given set of reaction conditions gave irreproducible results. Many of the structures could only be tentatively assigned, if at all. In order to obtain a coherent set of results of predictive value, a set of reaction conditions had to be established which would give consistent results. Initial efforts concentrated on three imines, which lacked N-aryl electrons available for cyclization (Scheme VI).

Yun had determined that the sealed tube reaction between p-nitrobenzylidene-t-butylamine (18a) and t-butyl isonitrile in carbon tetrachloride gave α,β -di-t-butylamino-4-nitrocinnamionitrile (18a) in a 7% yield.⁹ Since the yield was not satisfactory, this system was examined first.

Hydrogen chloride and possibly water were believed necessary for the reaction between the imine and t-butyl isonitrile. Thus a preliminary series of reactions was conducted whereby 1.5 mmol of p-nitrobenzylidene-t-butylamine (18a) were reacted with 4.5 mmol of t-butyl isonitrile in 50 ml of wet solvent¹⁴ which had been saturated with

hydrogen chloride vapor. Each system was refluxed for 24 hours, washed with 10% sodium carbonate, dried, and the solvent removed by evaporation. The resulting oil was examined by nmr spectroscopy. Table I lists the details and results of these reactions.

These results show that the reaction conducted in chlorobenzene (reaction F) gave the highest estimated yield of 19a. However one question was still left unanswered: was water also necessary? Three more preliminary experiments were conducted in the same way as described for Table I except that these reactions were conducted in a nitrogen atmosphere and the moisture content was varied. Table II lists the variations and results of these experiments as determined by nmr spectroscopy.

The results indicated that the moisture content of these reactions was important. Experiment F-1 indicated that

Table II

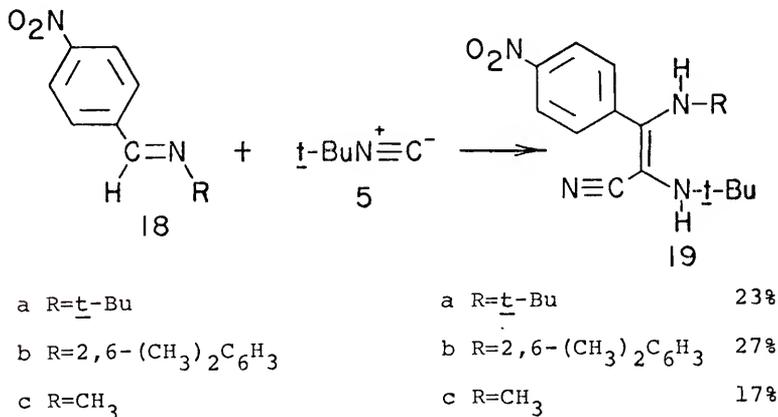
Variations on Experiment F

Experiment No.	Variation	Results
F-1	The chlorobenzene was dried with anhydrous MgSO ₄ and saturated with dry vapor.	Very low yield of <u>19a</u> . Almost no reaction.
F-2	Used the same conditions as described in Table I except that the t-butyl isonitrile was added in two equal portions in 12 hour intervals.	Same result as experiment F.
F-3	Added 4 ml of conc. hydrochloric acid, then saturated the solvent with HCl vapor.	Entirely different results.

moisture was necessary for the reaction, but experiment F-3 indicated that too much water was also detrimental to the success of the reaction. The solvent had to be wet, but not to the point of having droplets of water suspended in the system.

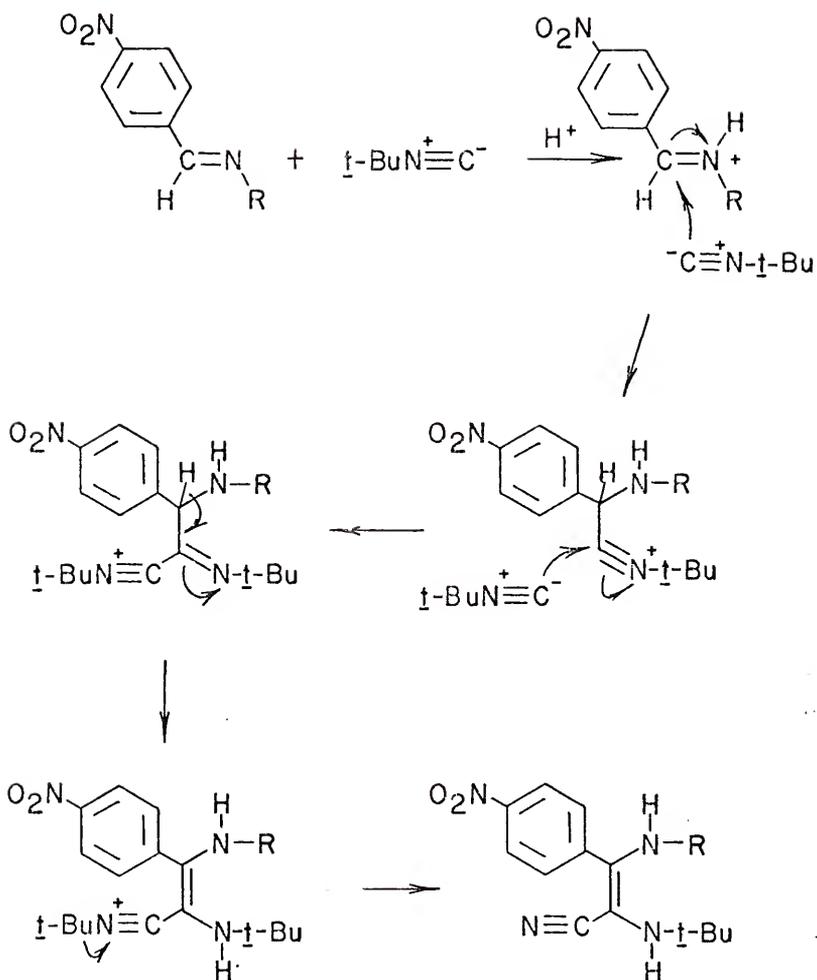
Similar preliminary reactions were conducted between *t*-butyl isonitrile and *p*-nitrobenzylidene-2,6-dimethylaniline (18b) and *p*-nitrobenzylidenemethylamine (18c) in order to find an appropriate solvent and reaction conditions to optimize the yields of 19b and 19c respectively. From these results preparative reactions were conducted in a wet solvent saturated with hydrogen chloride vapor. The major products¹⁵ and their yields are depicted in Scheme IX. A mechanism

Scheme IX



is proposed to account for the major product of these reactions in Scheme X.

Scheme X



The nmr spectra of 19 show characteristic similarities. When the β -nitrogen is bonded to an alkyl group the t-butyl group bonded to the α -nitrogen appears at 1.20 δ , but at about 1.37 δ when the β -nitrogen is attached to an aryl group. The α -N-H group appears at 1.80-2.00 δ . The β -N-H group, which appeared as a quartet in the case of 19c, appears at about 6.00 δ when R=alkyl and at about 7.00 δ when R=aryl, and the p-nitrophenyl group appears as an AB quartet with $J_{AB}=8.5$ Hz, $|1-3| = |2-4| = 41$ Hz,¹⁶ and $\Delta\nu_{AB}=40.1$ Hz.¹⁶

The infrared spectra of 19 shows an N-H band at 3.09 μ , and a nitrile band at 4.60 μ . The mass spectra exhibit molecular ions consistent with the expected molecular weights.

Compound 19a had been prepared before as an orange solid.⁹ This modification was also obtained in the present work and the spectral results were identical to those previously reported.⁹ However, a yellow modification was obtained which had nmr and mass spectra which were identical to the orange modification. The melting point was considerably higher and the infrared spectrum was slightly different in the "finger print" region. Whether the two modifications were due to two geometrical isomers or to two crystalline modifications could not be determined unequivocally without further physical data, i.e. x-ray analysis. It was found, however, that the modifications were interconvertible simply by seeding a solution of 19a with a crystal of the desired modification. The yellow modification was easier to isolate.

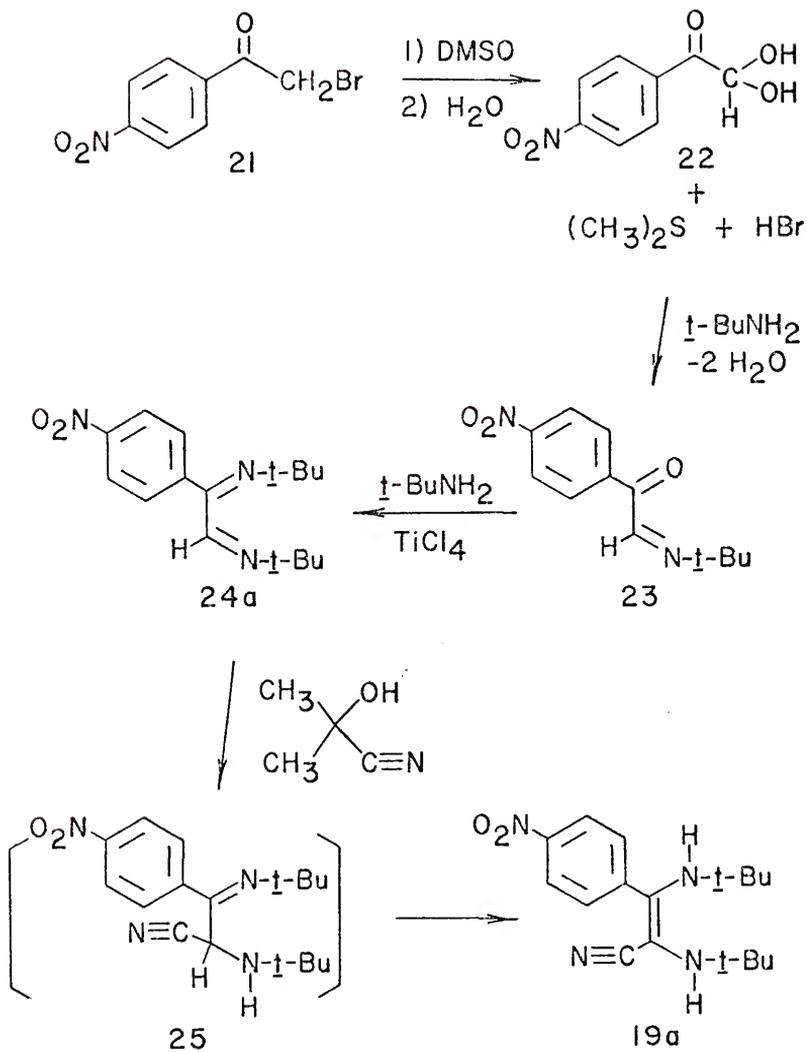
The structure of 19a was also established by preparing it by an alternative route. Kornblum *et al.* had shown that dimethylsulfoxide oxidized *p*-nitrophenacylbromide (21) to *p*-nitrophenylglyoxal hydrate (22).¹⁷ It was found that the crude hydrate (22) would react with *t*-butylamine under mild conditions to give an α -mono-imine (23). In order to force the β -carbonyl to react more stringent conditions were required. When 23 was reacted with *t*-butylamine and titanium (IV) chloride,¹⁸ the diimine 24a was obtained.

It has been shown that imines react with hydrogen cyanide.¹⁹ The aldimine, since it is a derivative of an aldehydic carbonyl, was expected to be more reactive towards addition reactions than the ketimine. Thus the diimine (24a) reacted with one equivalent of acetone cyanohydrin to yield 19a in good yield, Scheme XI. Apparently tautomerism of 25 is faster than the reaction with a second equivalent of acetone cyanohydrin since no diaddition products were observed. The material was obtained as the yellow modification.

A second product was isolated from the reaction of *p*-nitrobenzylidene-*t*-butylamine. This compound, 20a, was isolated in a low yield as white needles. This product is believed to have resulted from air oxidation of the crude solution of 19a during the purification procedure.²⁰ Its structure proved elusive because of its anomalous spectra. These spectral properties will be discussed in Chapter 2.

A third product was isolated in low yield from the same isonitrile reaction and was identified as an imidazole (21a

Scheme XI

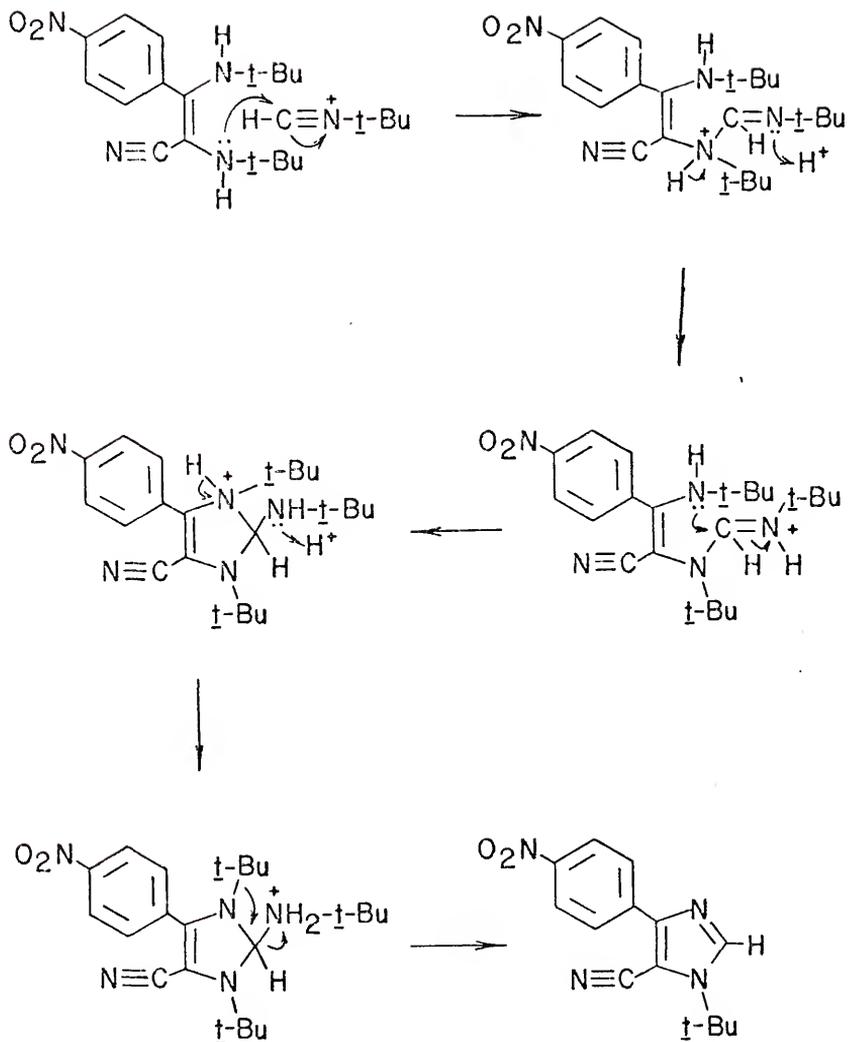


or 22a) from its nmr, ir, and mass spectra. Without further evidence, it was not possible to distinguish between alternative structures 1-t-butyl-5-cyano-4-(4-nitrophenyl)imidazole (21a) or 1-t-butyl-4-cyano-5-(4-nitrophenyl)imidazole (22a). Subsequent fortuitous results (to be discussed later) allowed assignment of structure 21a. The product is believed to have resulted from the condensation of 19a with a protonated molecule of t-butyl isonitrile with the subsequent loss of t-butylamine and a t-butyl group. However, it is also possible that t-butyl isonitrile which has hydrolyzed to N-t-butylformamide could also condense with 19a to give 21a with the loss of water, t-butylamine, and a t-butyl group, Scheme XII.

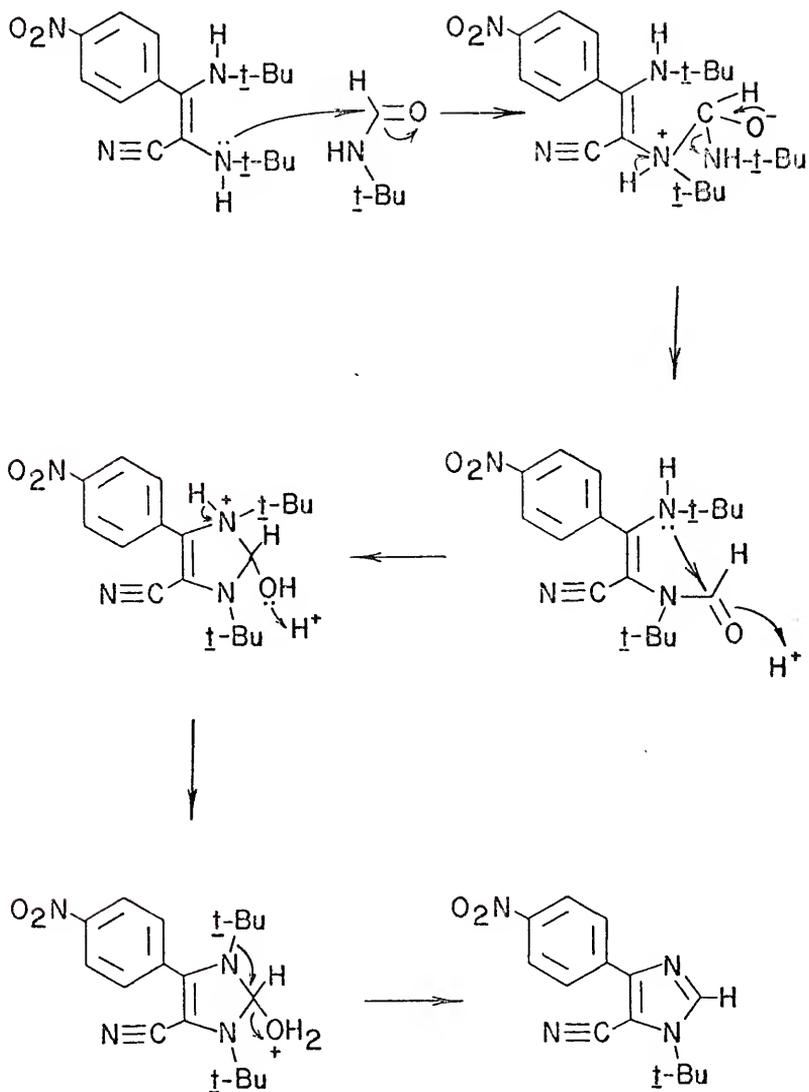
The minor products obtained from the reaction of 18a with t-butyl isonitrile stimulated ideas for further chemical reactions of 19. An attempt was made to convert 19a to 20a by oxidizing the former. After several unsatisfactory procedures were tried, it was found that 19a reacted spontaneously with sodium hypochlorite (Clorox) at room temperature to yield 20a in good yield. Similarly 19b and 19c reacted with Clorox to form 20b and 20c respectively in good yields, Scheme XIII. It seems probable that an intermediate N-Cl derivative undergoes base induced elimination to 20.²¹ However, the system can also be treated as an enamine allowing a different mechanism to be written²² (Scheme XIV).

It was thought that the diamines 19 might be precursors to the imidazoles. It has been shown that a convenient

Scheme XII



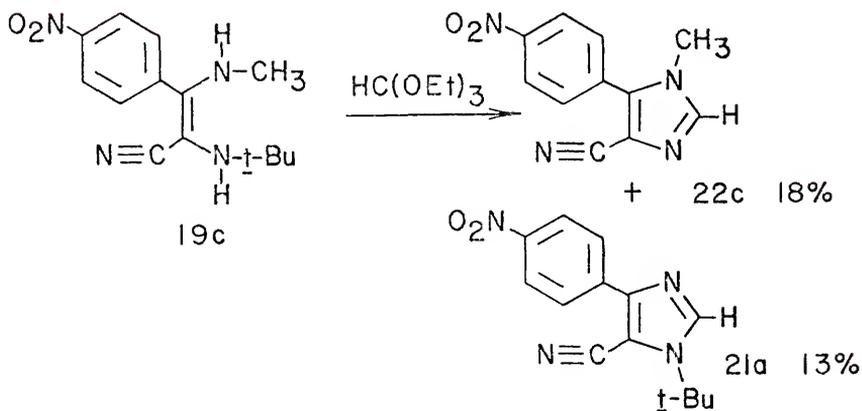
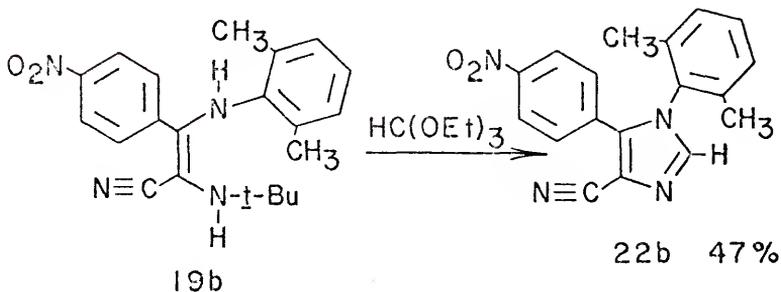
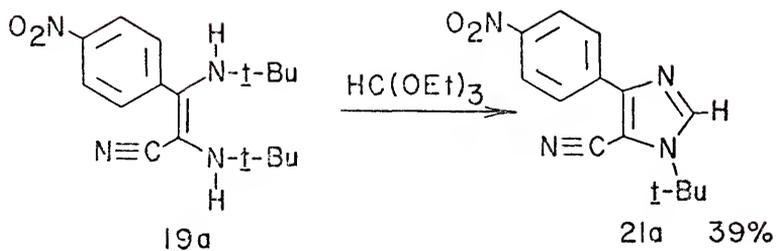
Scheme XIII (continued)



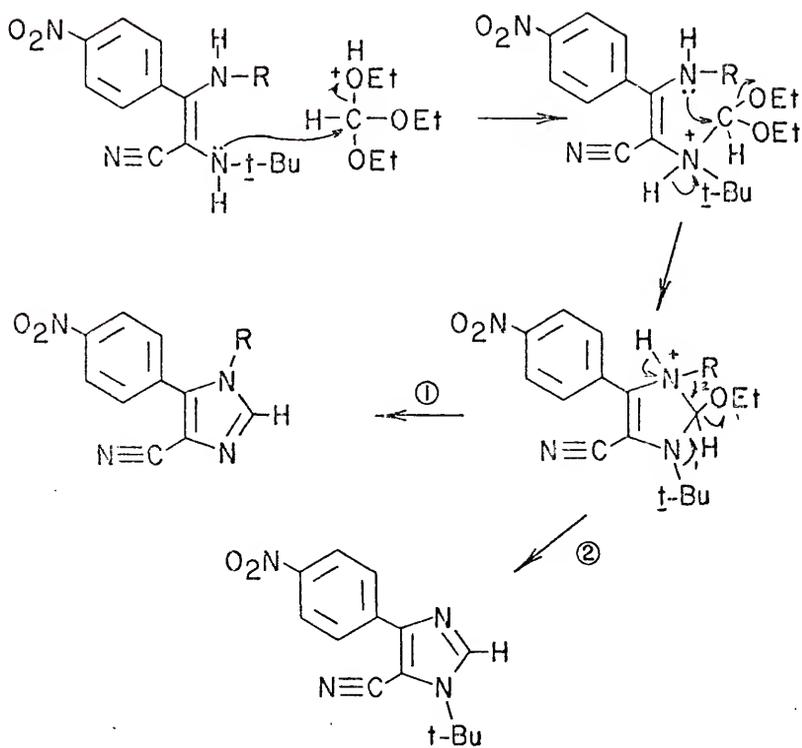
method for preparing benzimidazoles is realized by reacting o-phenylenediamine with triethylorthoformate.^{2,3} However, in order for the imidazole ring to become aromatic, either the R group or the t-butyl group would have to be expelled. Since an imidazole ring was obtained during the preparation of 19a it was hoped that the same imidazole could be obtained from the reaction of 19a with triethylorthoformate. This reaction did yield an imidazole whose spectral properties and melting point were identical to the compound obtained earlier. Since both nitrogen substituents were t-butyl groups, no unequivocal structure assignment could be made between 21a and 22a. However a reaction of 19c with triethylorthoformate would allow a distinction between 21a and 22a. If the methyl group were displaced during the reaction, the imidazole 21a would be obtained. It seemed just as likely that the t-butyl group would be lost and the methylimidazole (22c) would be obtained. Fortunately both imidazoles were isolated and 21a was identical to the imidazole obtained from 19a. The diamine 19b also yielded an imidazole, Scheme XV. A mechanism to account for these products is suggested in Scheme XVI.

The structures of 19 were supported by further chemical evidence. Acetylation of 19a and 19b in refluxing acetic anhydride in the presence of sodium acetate yielded monoacetylated products 26a and 26b respectively, Scheme XVII. Compound 26b had been prepared and identified earlier.⁹

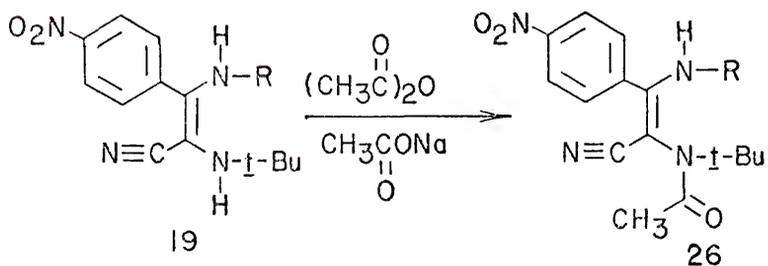
Scheme XV



Scheme XVI



Scheme XVII



a R=t-Bu

a R=t-Bu

66%

b R=2,6-(CH_3) $_2$ C_6H_3 b R=2,6-(CH_3) $_2$ C_6H_3

75%

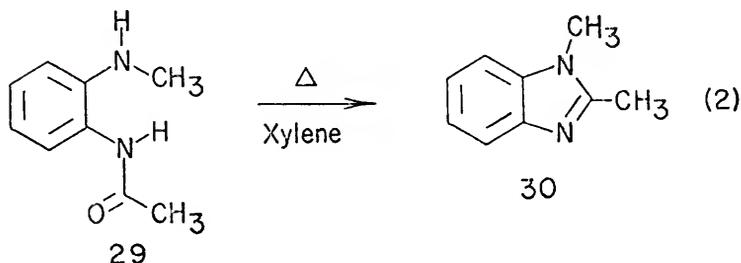
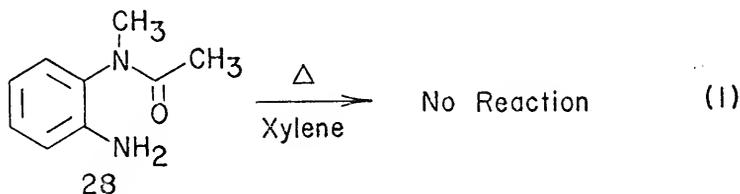
Structure 26b showed a carbonyl absorption in the infrared spectrum at 5.98μ indicative of an amide. In the nmr spectrum the t-butyl groups had shifted from 1.32δ in the starting material to about 1.67δ in 26b due to the electron withdrawing effect of the acetyl group. The nmr spectrum also indicated an N-H group at 6.42δ which is the β -N-H group in the starting material and a singlet at 2.37δ which was assigned to the acetyl-methyl group.⁹

Similarly, 26a showed a carbonyl absorption in the infrared spectrum at 5.98μ indicative of an amide. Again the nmr spectrum showed that a t-butyl group has shifted from 1.20δ in the starting material to 1.55δ in 26a. The nmr spectrum also shows a N-H peak at 5.10δ which is the β -N-H group in the starting material and a peak at 2.20δ which was assigned to the acetyl-methyl group. Neither 26a nor 26b gave a fragmentation pattern in the mass spectra which unequivocally determined the position of the acetyl group.

When 19c was refluxed in acetic anhydride with sodium acetate, 26c was not obtained, but instead an imidazole 27c was obtained, Scheme XVIII. The produce 27c may have formed from the initial formation of 26c followed by cyclization. The product gave a molecular ion m/e 242. The acetate derivative would have demanded m/e 316. The infrared spectrum indicated no N-H or carbonyl groups. The nmr spectrum showed two methyl groups. The one at 2.49δ is characteristic of a methyl group attached to a carbon atom in an aromatic ring. The other methyl group appeared at 3.60δ and is indicative

of a methyl group attached to a nitrogen in an imidazole ring (see the nmr spectrum data for 22c).

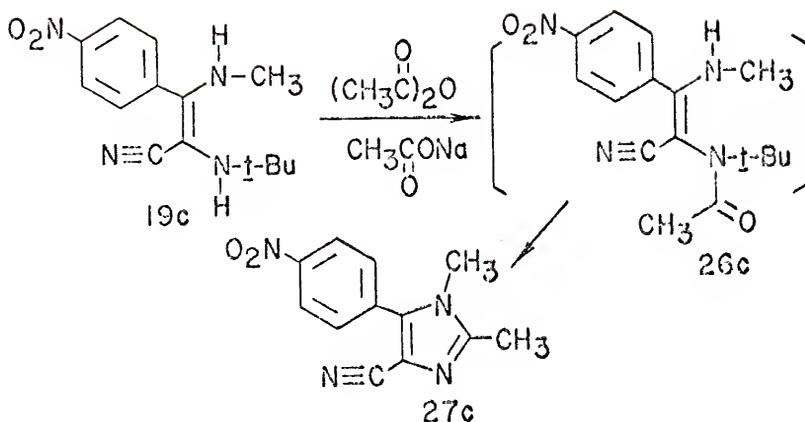
The fact that o-phenylenediamine reacts with carboxylic acids, acid anhydrides, esters, and amides to form benzimidazoles^{2,3} makes the formation of 27c somewhat expected. What is difficult to reationalize is why 26a and 26b did not cyclize to 27b respectively. Three possible explanations are available: (1) When the group attached to the β -nitrogen is bulky, for example a t-butyl group or 2,6-dimethylphenyl group, cyclization cannot take place because of steric interference. (2) Cyclization of 26a and 26b to 27a and 27b respectively could take place during longer reaction times or 26c would be isolated in shorter reaction



times. (3) The last explanation is based on an article by Roeder and Day.²⁴ They found that 28 would not cyclize to 30 in refluxing anhydrous xylene, but that 29 did cyclize very efficiently to 30. Obviously, steric problems cannot explain the difference. They indicated that a hydrogen has to come from each nitrogen to form the mole of water. More aptly put, the amide group must be able to enolize. If this is the case, cyclizations in the case of 26 to 27 may depend on the ease of the loss of the α -6-butyl group to form the acetamide moiety to allow enolization. In view of the cyclizations to imidazoles 21 and 22 it would appear that 26a would not cyclize to 27a because the α -t-butyl group is not lost at all, but 26b should cyclize to 27b because formation of 22b indicates a fairly facile loss of the α -t-butyl group. Similarly 26c would cyclize to 27c for these reasons. Of the three possible explanations it is believed that the third explanation may be the best and could be verified by refluxing both 26a and 26b for longer reaction times in an appropriate solvent.

Although Raman spectroscopy had confirmed the presence of the nitrile group in 20, confirmatory conclusive chemical evidence was desired. Usually nitriles will react in 75% sulfuric acid to yield acids,²⁵ but 20b completely disintegrated to a black tar in sulfuric acid.

Scheme XVIII

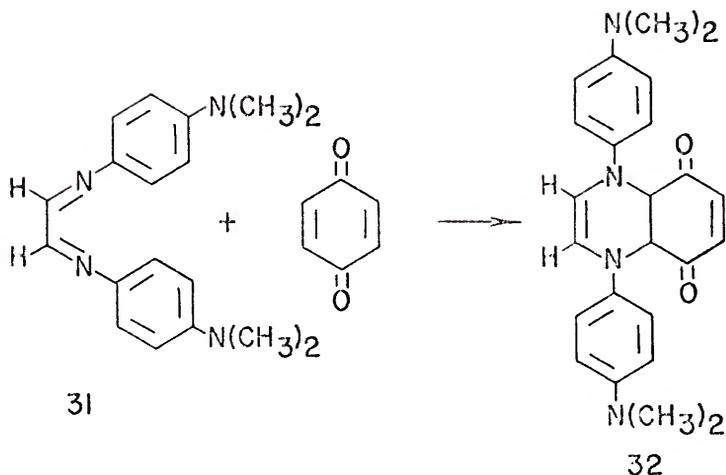


Other possible reactions were then looked at. Compounds 19, 21, and 22 all showed a nitrile absorption in the infrared and in each case a cinnamitrile linkage was present in the molecule. If by some method the double bond could be returned to the carbons to give the cinnamitrile linkage, then the nitrile band ought to be a strong band in the infrared spectrum again. A Diels-Alder reaction seemed like a good candidate to accomplish such a transformation.

Yun had attempted to react 20b with dimethyl acetylenedicarboxylate. However, no Diels-Alder adduct formed.⁹

Tomimatsu²⁶ had shown that di-(p-N,N-dimethylaminoanil)-glyoxal (31) reacted with p-benzoquinone to yield an adduct 32, Scheme XIX. When 20b was reacted with p-benzoquinone under similar conditions no reaction took place, Scheme XX.

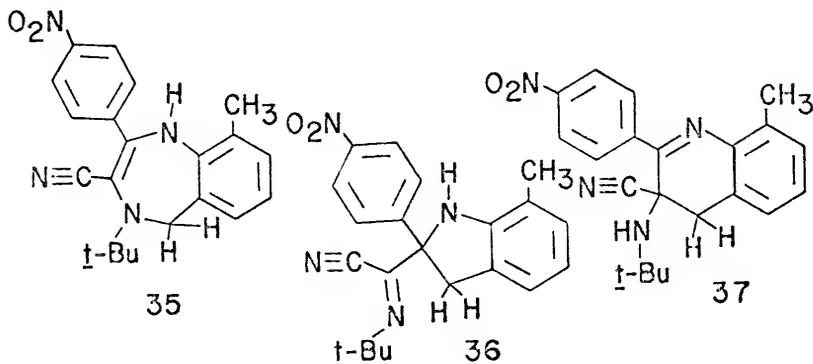
Scheme XIX



An alternative approach was then turned to which employed an electron rich dienophile to react with the electron deficient diazabutadiene.²⁷ Ketene diethylacetal was chosen for this purpose. Instead of a Diels-Alder adduct, an isomer of 20b was obtained. This isomer was assigned a 1H-1,4-benzodiazepine structure (35) Scheme XX. Subsequent experiments revealed that potassium-t-butoxide, which was present to stabilize the ketene diethylacetal, was necessary for cyclization.

Structure 35 was a novel and unexpected product and its structural assignment presented a few initial problems. The nmr spectrum indicated a t-butyl group at 1.19 δ , a methyl group at 2.12 δ , a CH₂ group at 4.22 δ , an N-H group at 5.72 δ , and aromatic protons due to a p-nitrophenyl group and the three protons on the other ring. The mass spectrum

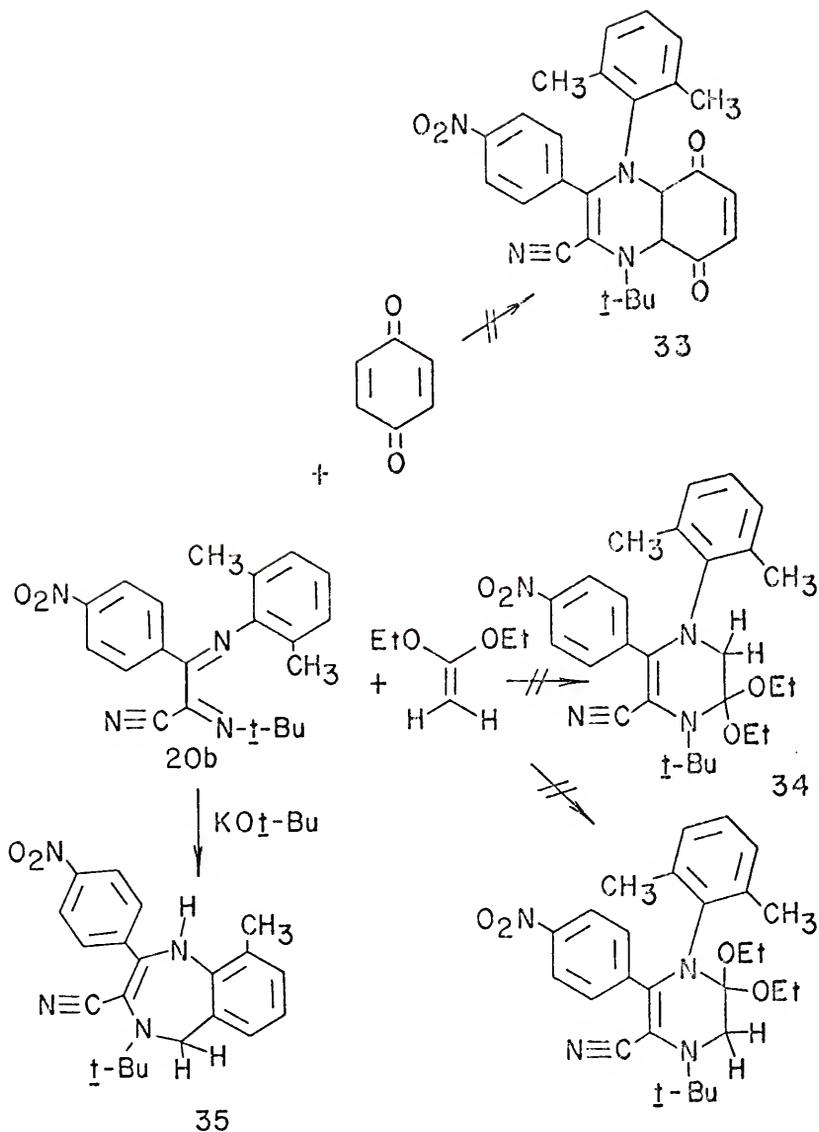
gave a molecular ion at m/e 362. Three structures would tentatively fit the data (35, 36, 37).



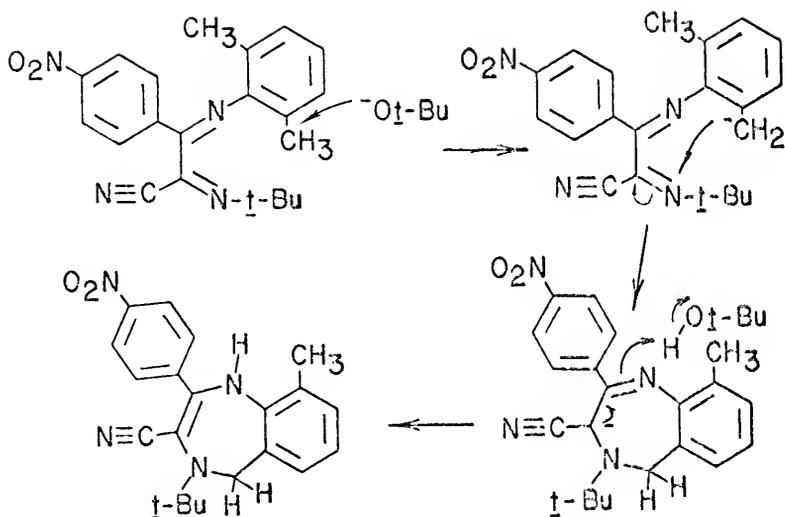
The infrared spectrum showed an N-H bond at 2.94μ , a strong nitrile band at 4.53μ , and no C=N band. The lack of a C=N band in the infrared spectrum rules out both 36 and 37. A mechanism to 35 is proposed in Scheme XXI.

Thus the hypothesis that if 20 could undergo some reaction that would return the cinnamitrile linkage to the molecule, then the nitrile band would reappear in the infrared spectrum was verified by this conversion. With the Raman spectra, the fact that 20 results from the oxidation of 19 which has a nitrile group, and this cyclization reaction which allowed the nitrile band to return in the infrared spectrum, it is certain that the nitrile group is still present in 20.

Scheme XX

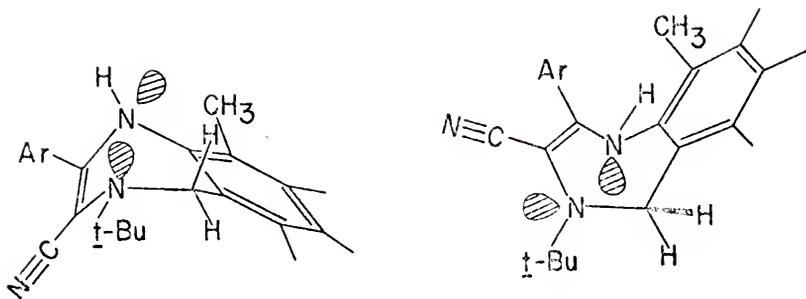


Scheme XXI



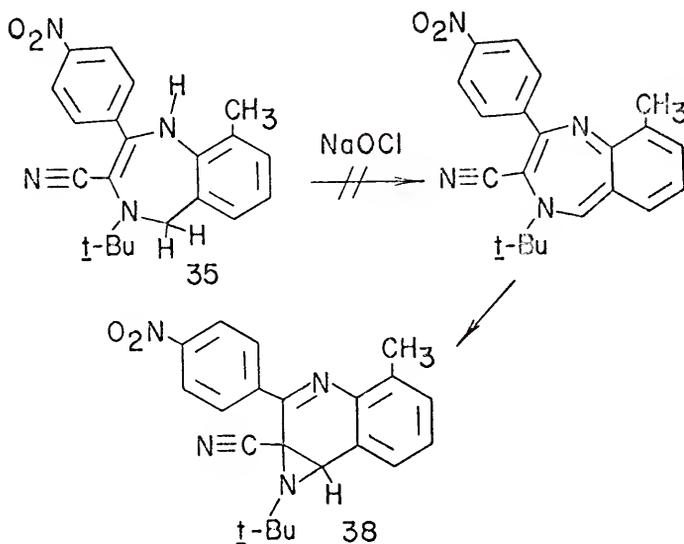
A reaction was conducted with 35 and Clorox in an attempt to constrict the seven-membered ring into a dihydroquinoline structure fused to an aziridine ring (38). Instead a new compound formed whose nmr spectrum showed a t-butyl group at 1.48 δ , a methyl group at 2.15 δ , an AB quartet for a CH_2 group at 4.20 δ , and seven aromatic protons. The infrared spectrum indicated no NH or nitrile groups, but did indicate a carbonyl bond at 6.08 μ . The compound was assigned structure 37 Scheme XXII. Thus the nitrile group had finally disappeared both physically and spectrally.

An explanation is in order for the reason that the CH_2 group in 35 is a singlet vs an AB quartet in 39. Inspection of molecular models indicates that there are two possible

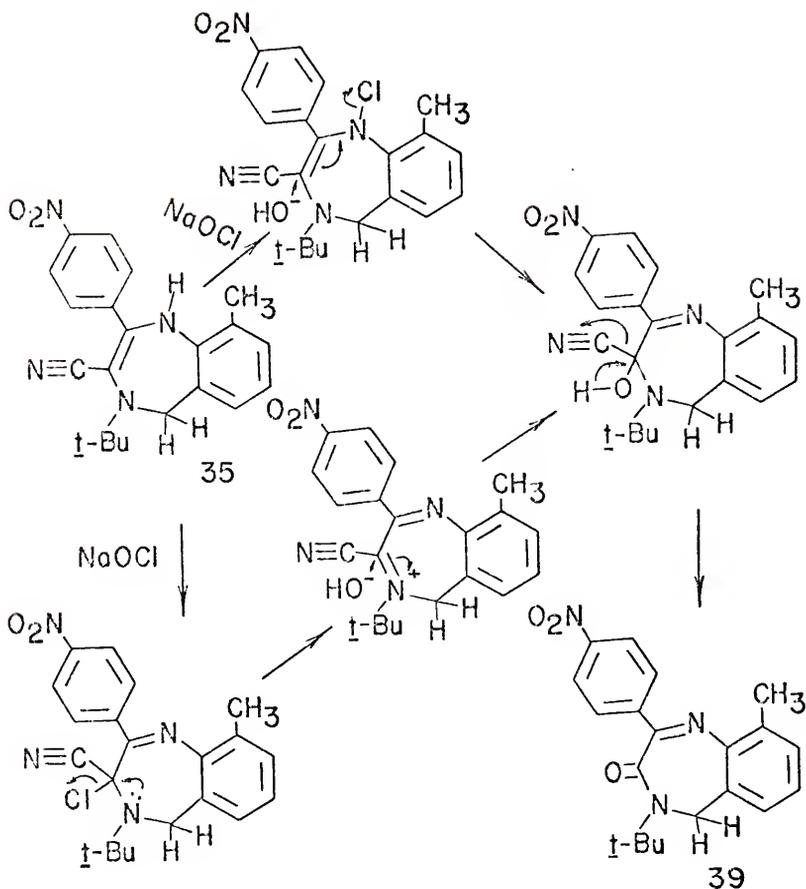


35

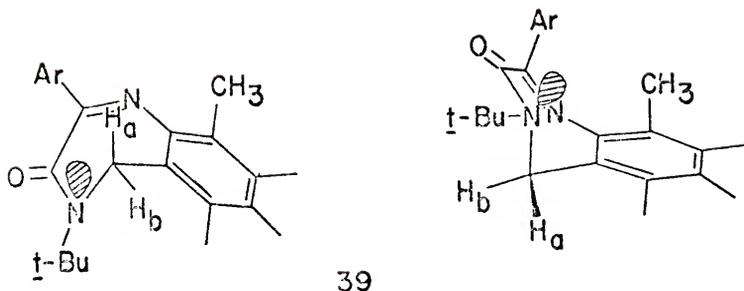
conformations of 35. Either conformation allows both protons to be in the same environment due to the fast inversion of nitrogen. This brings about a singlet in the nmr spectrum.



Scheme XXII



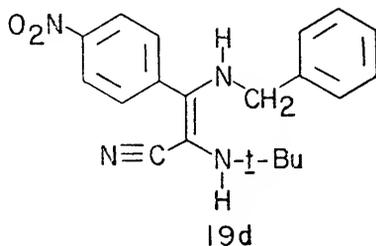
In structure 39, if one assumes that the nitrogen attached to the t-butyl group has considerable sp^2 character, and that the double bond in the 1-position is in the same plane as the carbonyl group, but not the benzene ring, there are again two possible conformers. In either conformation the CH_2 group is held rigid. This allows one proton to be shielded by the pair of electrons on the nitrogen and the other proton



would be in a different environment. The two protons would split each other to form a doublet of doublets.

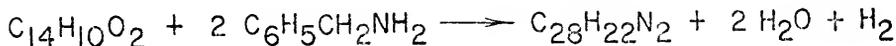
At this point it appeared that a set of reaction conditions had been realized which gave consistent results. When *t*-butyl isonitrile was reacted with *p*-nitrobenzylidenealkyl- or arylamine, a derivative of 19 was obtained as the major product. This would allow us not to be able to predict the results of a reaction before it was attempted in the laboratory. The theory was tested.

Based on our previous evidence, if *p*-nitrobenzylidenebenzylamine (18d) was reacted with *t*-butyl isonitrile the major product expected would be 19d. However, when the reaction



was attempted, the nmr spectrum of the crude reaction product indicated that 19d was present in a rather low yield as compared to previous examples, but there also appeared to be several other products present. Altogether four products were isolated, Scheme XXIII. Compound 40 was isolated and characterized earlier.²⁸

Japp and Davidson²⁹ found that when they reacted benzil with two equivalents of benzylamine in ether at room temperature they obtained a gummy substance which they believed to be the diimine (43). However, upon heating the mixture to 100°C they obtained a compound with the empirical formula $C_{28}H_{22}N_2$. They wrote, this material was "formed according to the equation,"

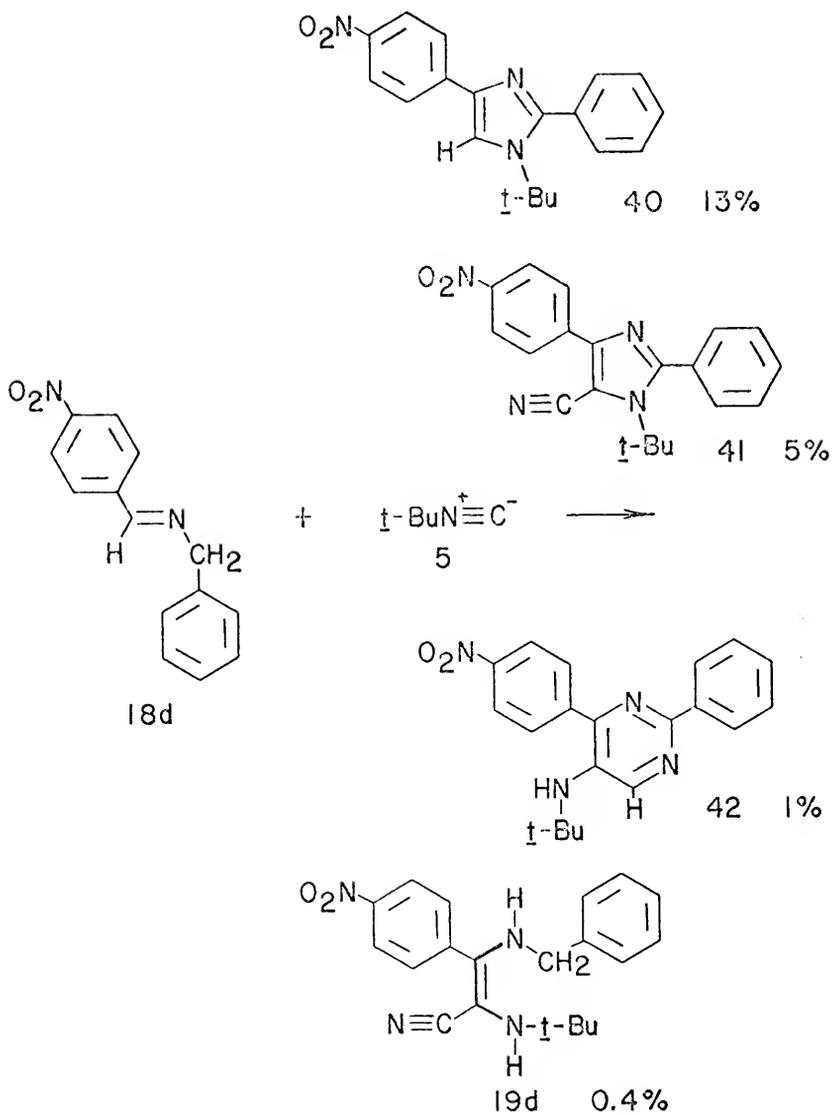


Compound $C_{28}H_{22}N_2$ (44a) was identified as the C-1 benzyl derivative of lophine (2,4,5-triphenylimidazole). They verified the structure by reacting lophine with benzylchloride to obtain 46. Similarly, ethylamine reacted with benzil to form similar products, Scheme XXIV.

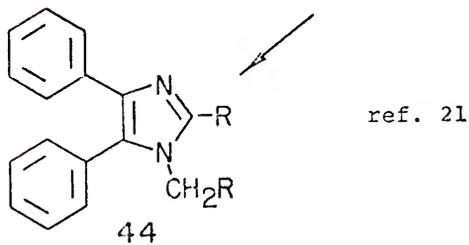
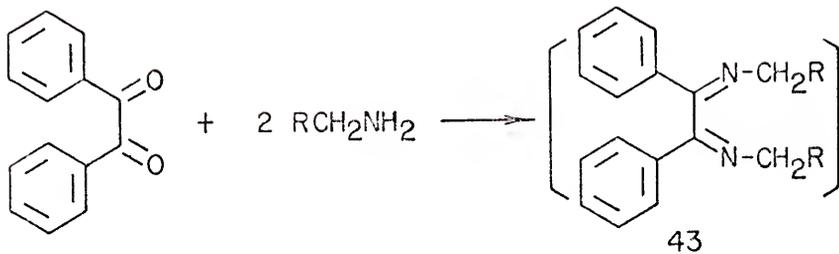
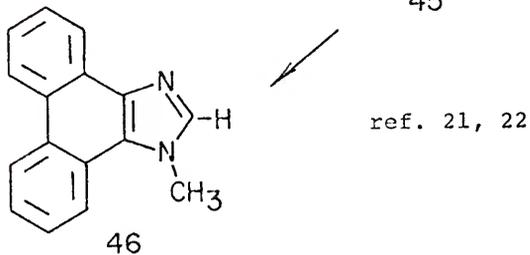
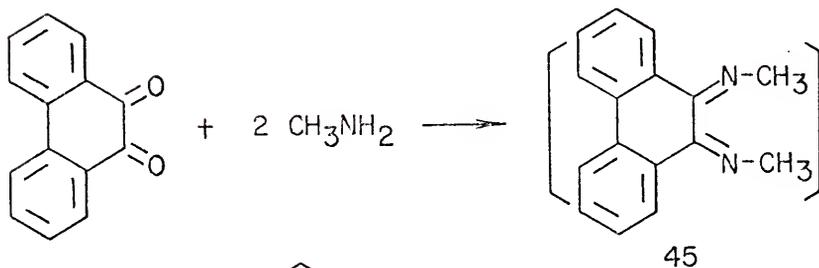
They also repeated some work by Zincke³⁰ who had reacted phenanthraquinone with methylamine, but were unable to identify the product obtained. Japp and Davidson proposed an imidazole derivative 46 for their product, Scheme XXIV.

Similarly, Hinsberg³¹ had reacted o-phenylenediamine with two equivalents of benzaldehyde and instead of the diimine (47) obtained a benzimidazole derivative 48, Scheme XXIV.

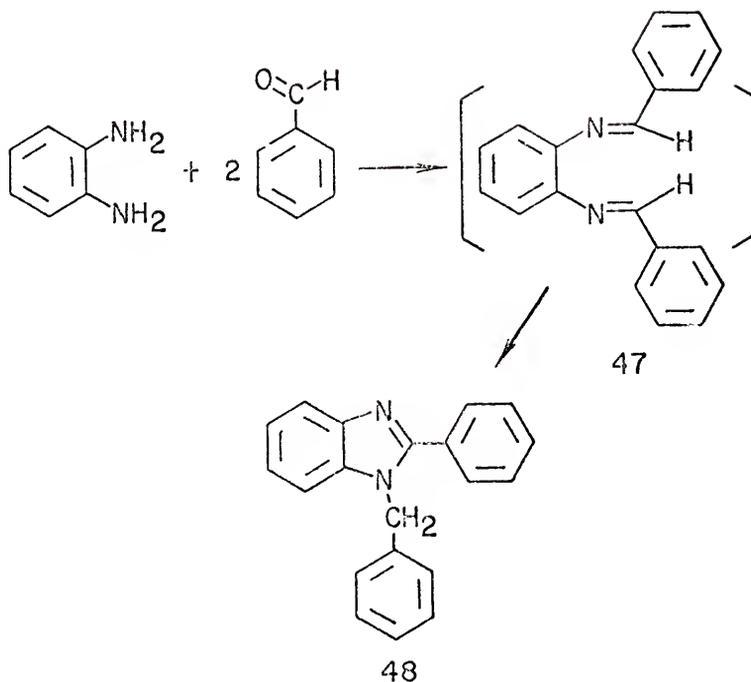
Scheme XXIII



Scheme XXIV

a $\text{R}=\text{C}_6\text{H}_5$ b $\text{R}=\text{CH}_3$ 

Scheme XXIV (continued)



Thus the transformations to bring about 40 and 41 via 19d are not without analogy. Unfortunately none of the references cited offer a proposed mechanism to account for their products.

In order to propose a mechanism to account for structures 40, 41, and 42 a problem is envisaged. The mechanism must account for the loss of both hydrogens from the benzyl-CH₂ group. This same problem, remember, was circumvented in references 21-23 by writing loss of hydrogen. The same solution could be used here; however loss of hydride ion and

a proton, or, assuming that oxygen inserted into a C-H bond, loss of water would also seem reasonable. It has not been substantiated, but it is believed that a large portion of the cyclizations took place on the alumina column. The basis for this is the estimated yield of 19d in the crude nmr spectrum was much higher than that actually isolated. Oxidation of 19d to 20d might be a facile process which could be followed by an equally easy rearrangement to 41 and 42. A mechanism is proposed to account for the products of the reaction in Scheme XXV.

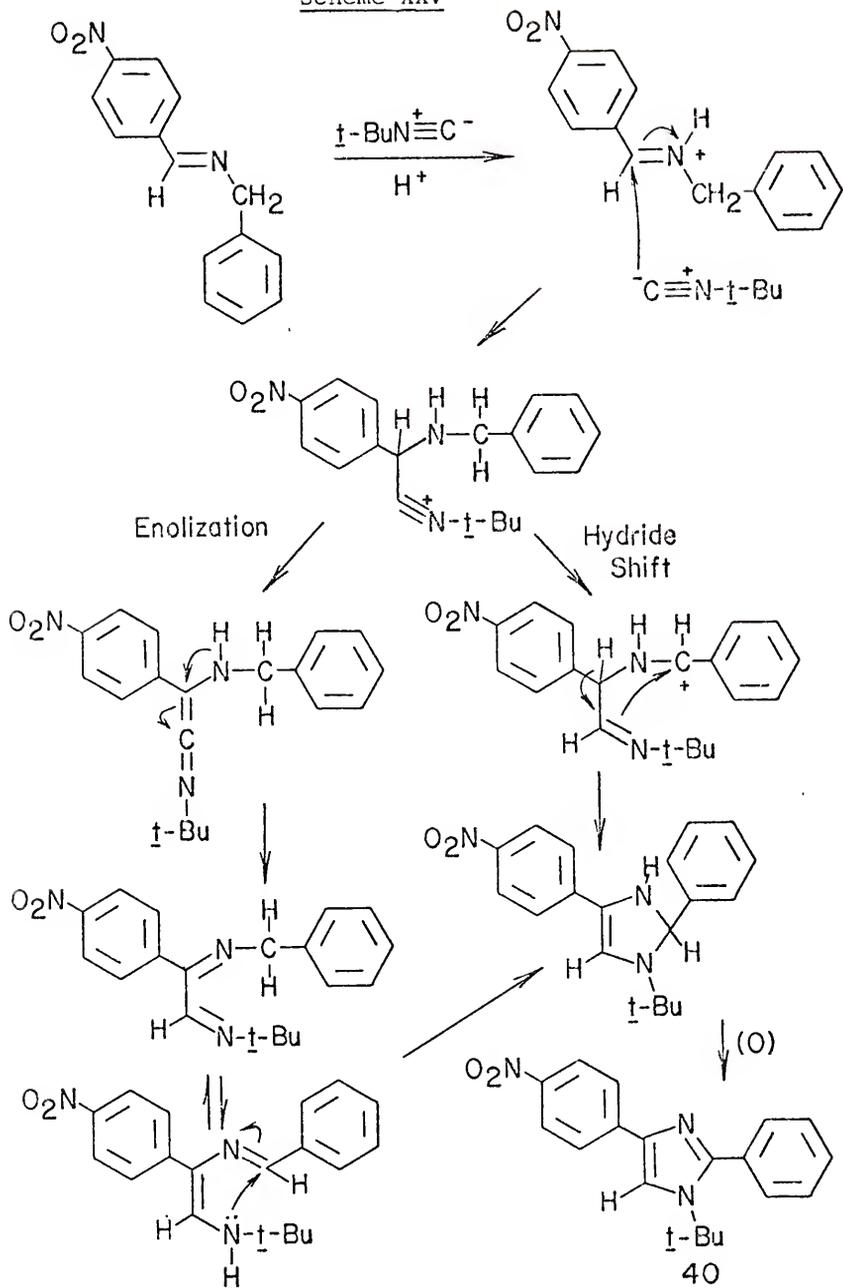
The structure of compound 40 was assigned from spectral evidence.²⁷ The nmr spectrum showed a t-butyl group at 1.48 δ , a phenyl group, a p-nitrophenyl group, and a single proton at 7.56 δ . The infrared spectrum showed no N-H, nitrile, or C=N bands. The mass spectrum indicated a molecular ion at m/e 321.³²

The nmr spectrum of 38 showed a t-butyl group at 1.65 δ , a phenyl group and a p-nitrophenyl group. The infrared spectrum showed no N-H or C=N bands, but did show a strong nitrile band at 4.51 μ . The mass spectrum of 41 showed a molecular ion at m/e 346. It was therefore the nitrile derivative of 40.

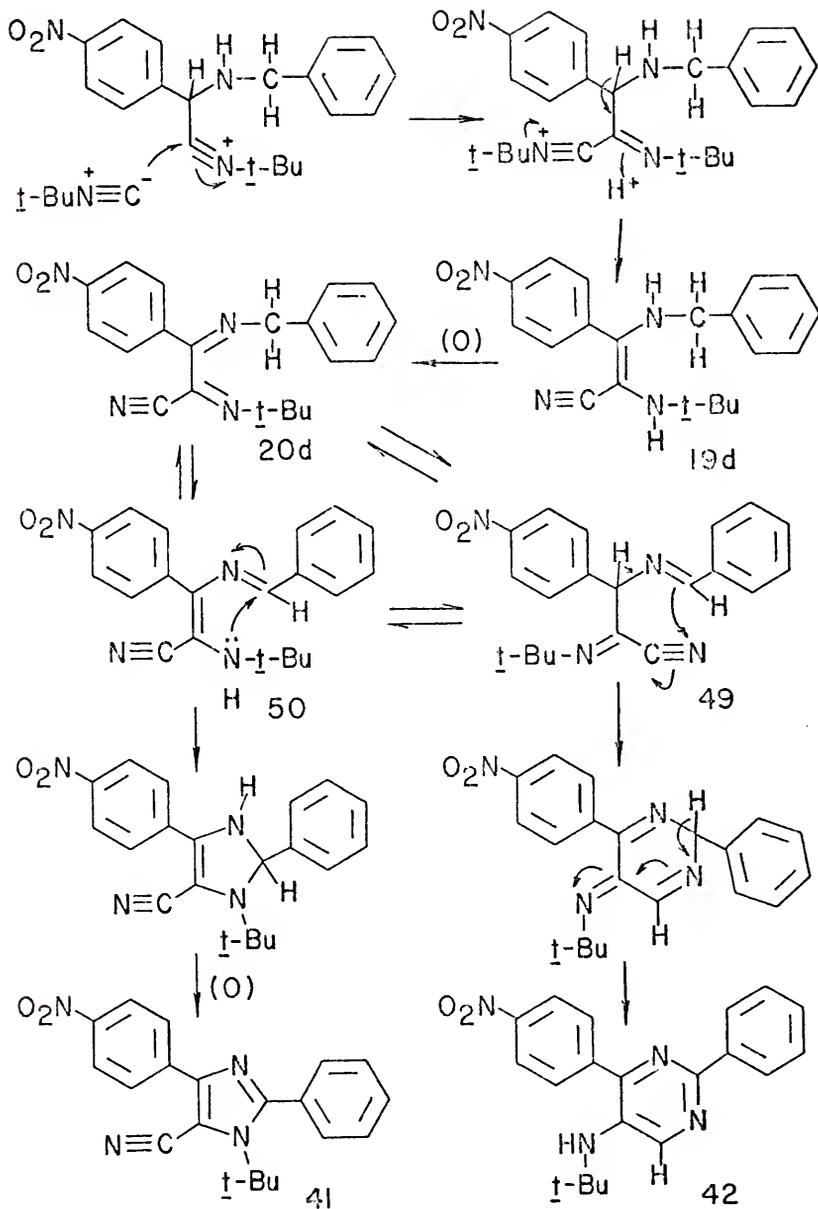
Compound 19d was identified with little trouble. Its spectral properties were very similar to 19c.

Compound 42 requires a bit more scrutinizing of the spectral data. The nmr spectrum indicates a t-butyl group at 1.45 δ , an N-H group at 5.05 δ , a phenyl group, a p-nitrophenyl

Scheme XXV



Scheme XXV (continued)

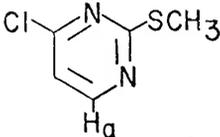
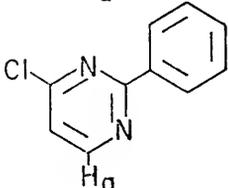
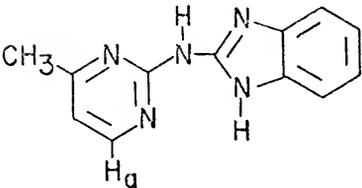
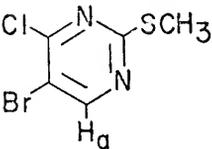
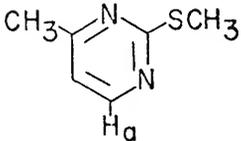


group, and a single proton at 8.41 δ . The mass spectrum gives a molecular ion at m/e 348. The infrared spectrum indicated an N-H band, but no nitrile band and no C=N band.

Based on the molecular weight of 348, four structures can be proposed: 20d, 42, 43, and 44. The nmr and ir spectra rule out 20d, because no benzyl-CH₂ group appears in the nmr spectrum and the infrared spectrum shows no C=N, and nitrile bands which are demanded for compound 20d. Even if one were to invoke the spectral anomaly of the other derivatives of 20, i.e. weak nitrile bands in the infrared spectrum, compound 20d lacks an N-H group. For the same reasons 43 can also be removed as a candidate. Compound 44 comes closer to meeting the spectral demands for this compound; however 44 also falls short. Compound 44 demands a nitrile band in the infrared spectrum which is not present in the spectral data. Also the imine-proton in 44 would not appear at 8.41 δ , but at 7.00-8.00 δ . Compound 42 does fit the spectral data. The compound would be expected to show no nitrile or C=N bands in the infrared spectrum. Furthermore the proton in the 4- or 6-position of a 2-phenylpyrimidine derivative should appear approximately in the vicinity of 8.41 δ . Table III lists a few pyrimidine derivatives with protons in the 4- or 6-position.

It should be reiterated at this point that the reaction of p-nitrobenzylidene-benzylamine with t-butyl isonitrile adds another example to the set of consistent results established in this research. This reaction helped to establish that 19 is the primary product of the reaction between p-nitrobenzy-

Table IIIChemical Shifts^a of H-4 and H-6

<u>Structure</u>	<u>δ_{Ha}</u>
	8.37
	8.95
	9.03
	8.53
	8.27

^aSadtler Index, Sadler Research Laboratories, 3316 Spring Garden Street, Philadelphia, Pa. 19104.

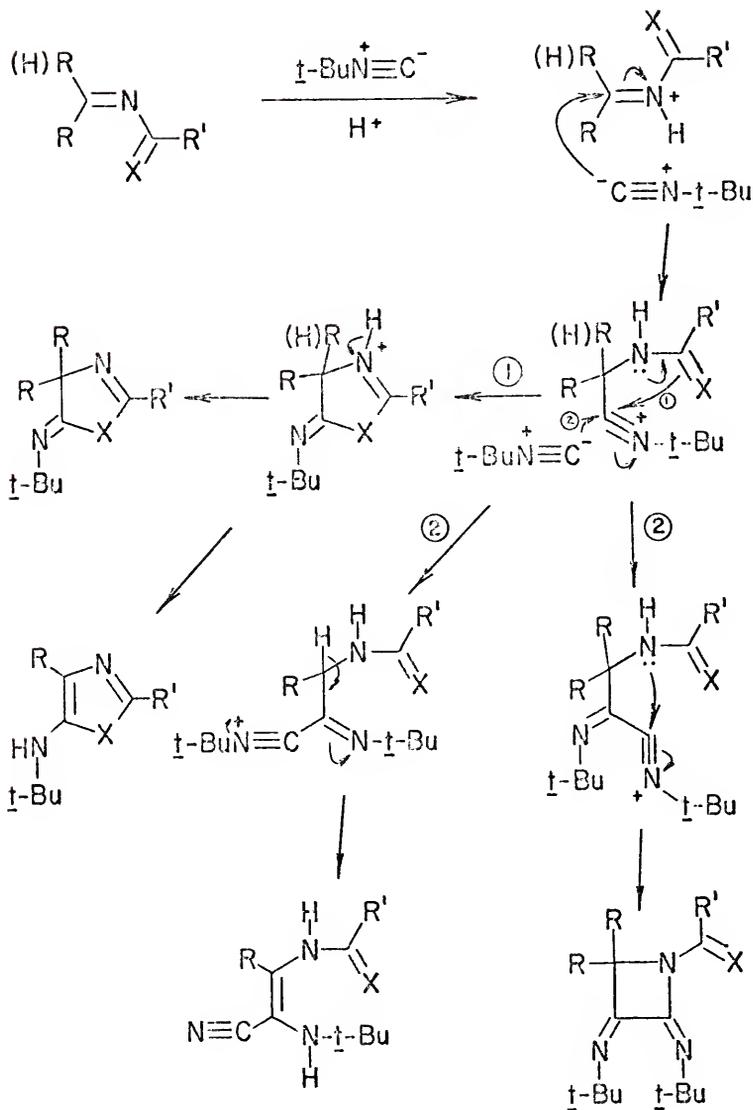
lidenealkyl- or arylamine and t-butyl isonitrile. However, the stability of 19 is also important. In the case of 19a oxidation to 20a takes place to some extent. However, in the case of 19d oxidation not only takes place but the system can cyclize. This is the extra variable which makes predicting the reaction a little more challenging.

Conclusions with Comments for Further Research

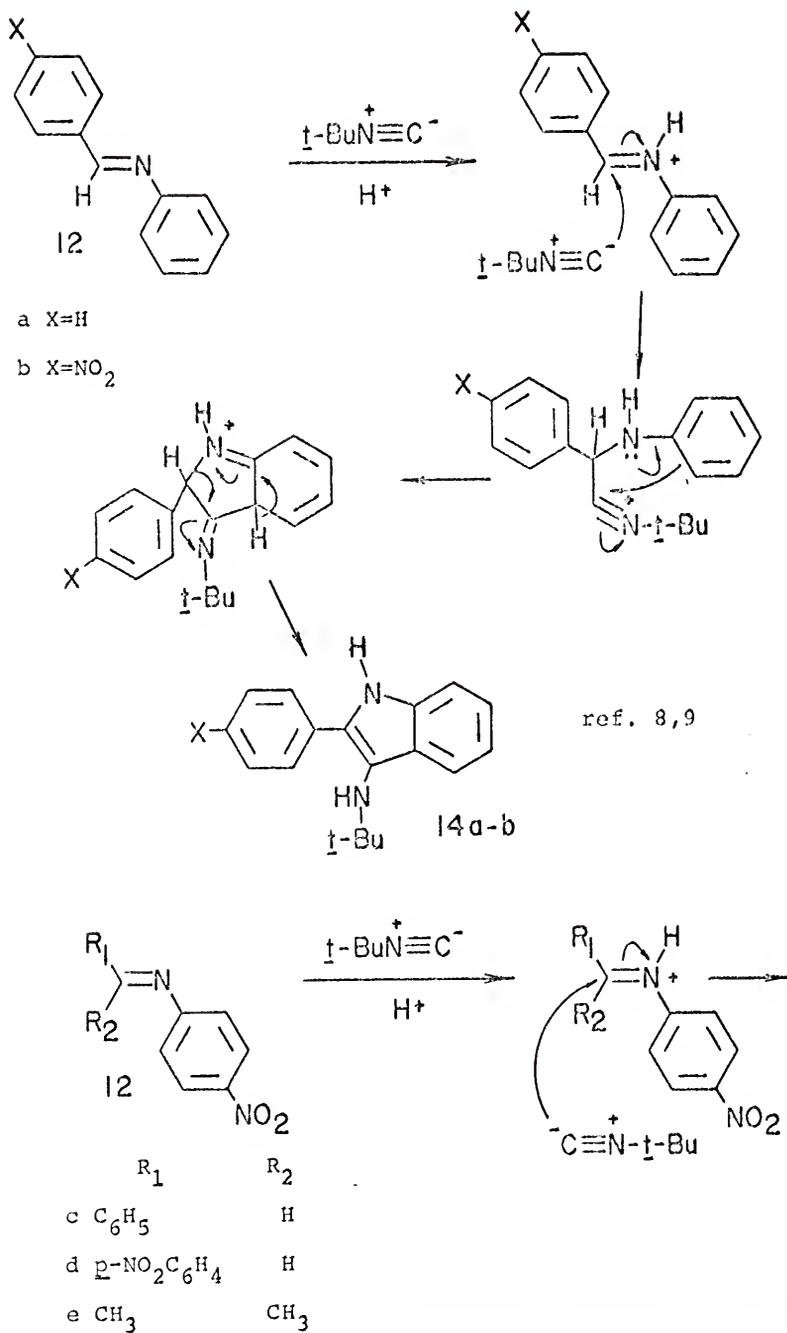
At the conclusion of this research a clear, concise pattern can be envisaged for the reactions of imines with t-butyl isonitrile. In the presence of an acid catalyst the imine is first protonated, providing a driving force for the attack of the first equivalent of t-butyl isonitrile. Depending on the group attached to the nitrogen, the system can either cyclize or can add a second equivalent of t-butyl isonitrile. This system can then cyclize, or enolize and lose a t-butyl group. Scheme XXVI and Scheme XXVII summarize in detail the reactions of imines with t-butyl isonitrile conducted in this laboratory. Reactions analogous to those discovered by Killion³³ (Scheme XXVI) were reported by Gambaryan et al.,³⁴ Scheme XXVIII.

This research also demonstrated the usefulness of the diamines 19 as precursors to imidazoles and other heterocyclic rings which would be difficult to obtain by other synthetic methods.

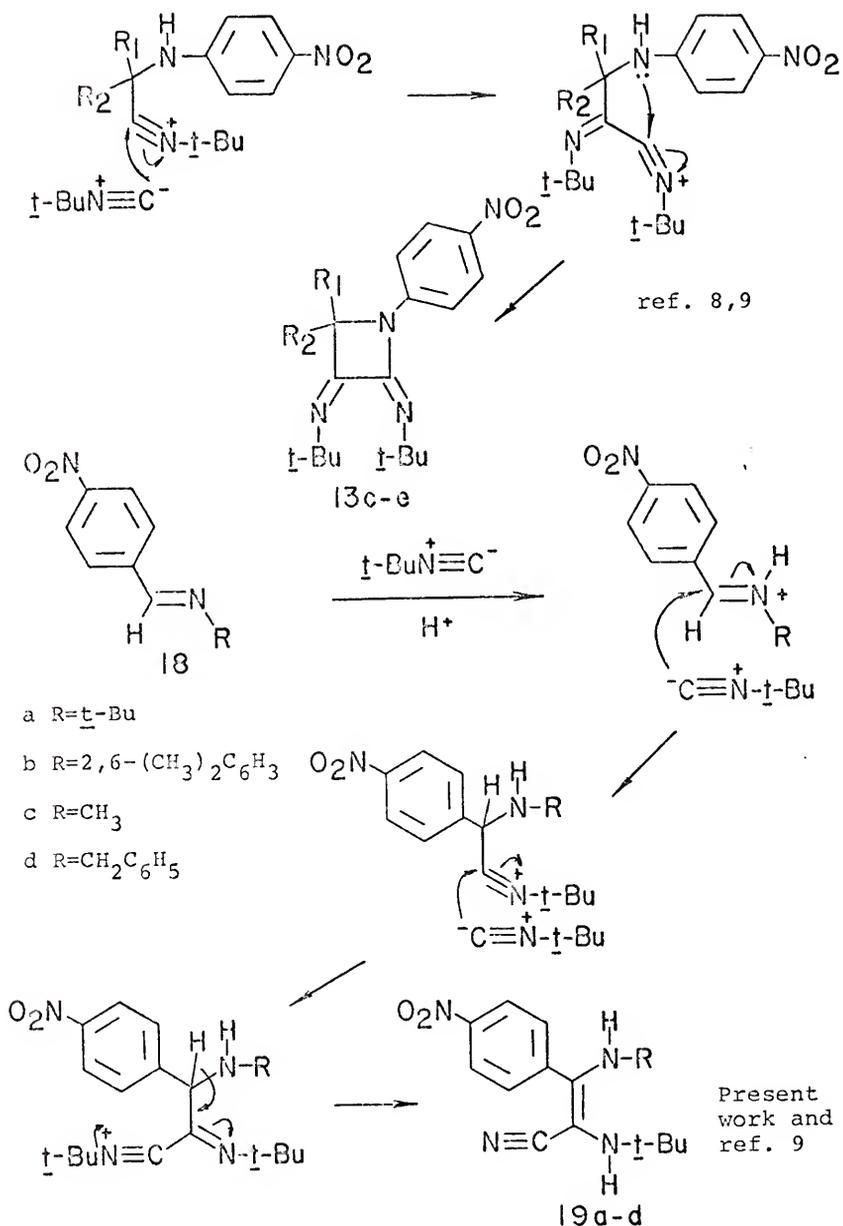
Scheme XXVI



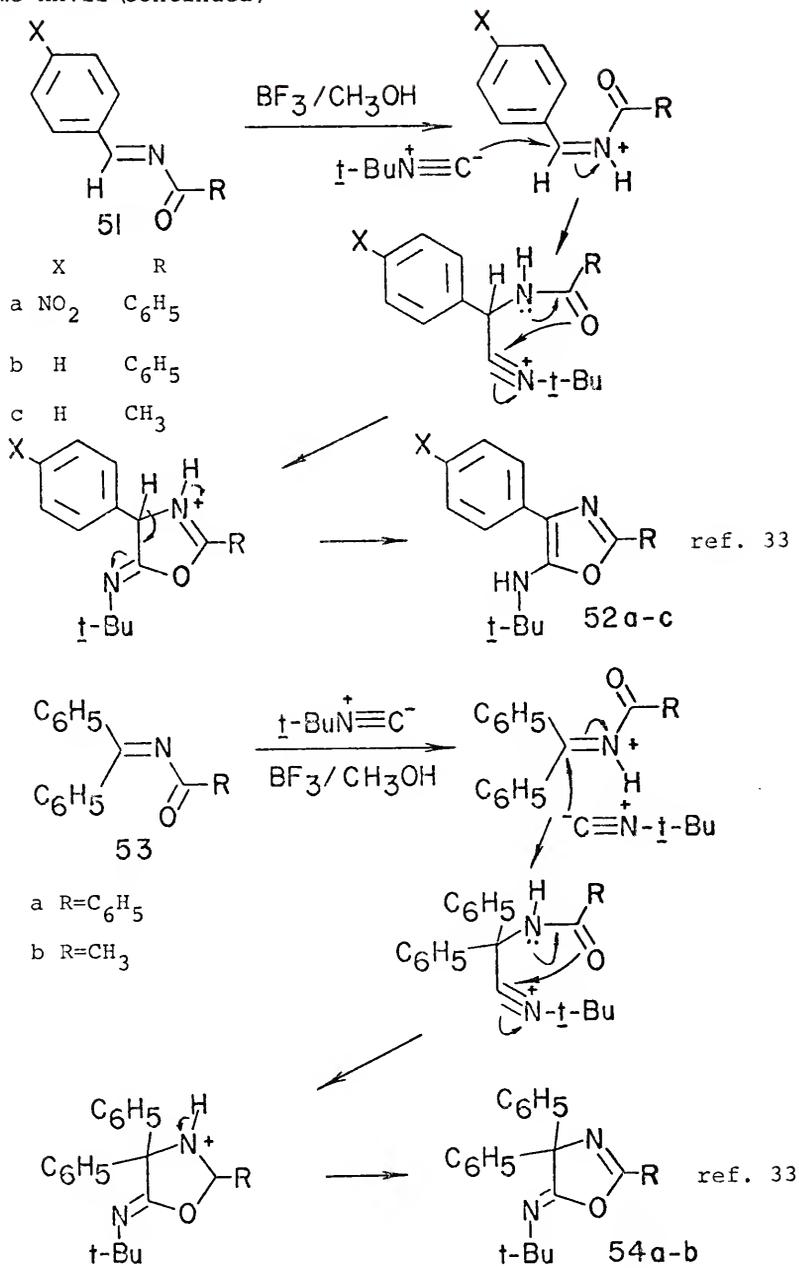
Scheme XXVII



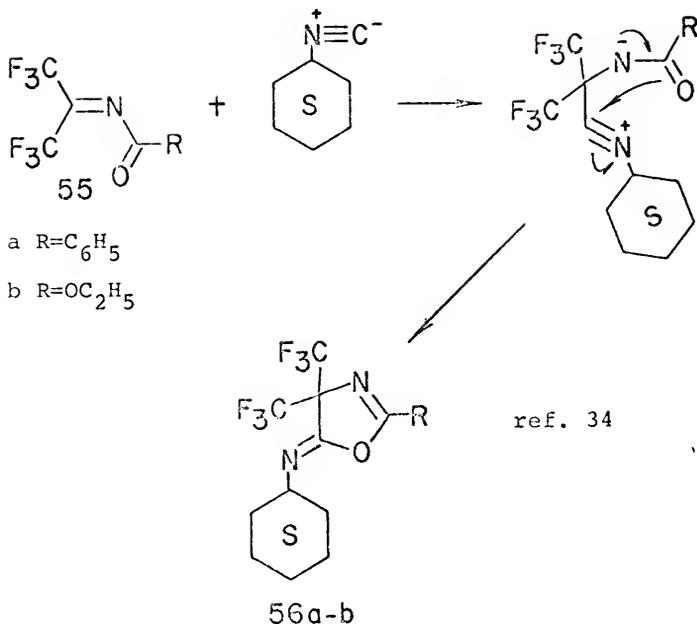
Scheme XXVII (continued)



Scheme XXVII (continued)



Scheme XXVIII

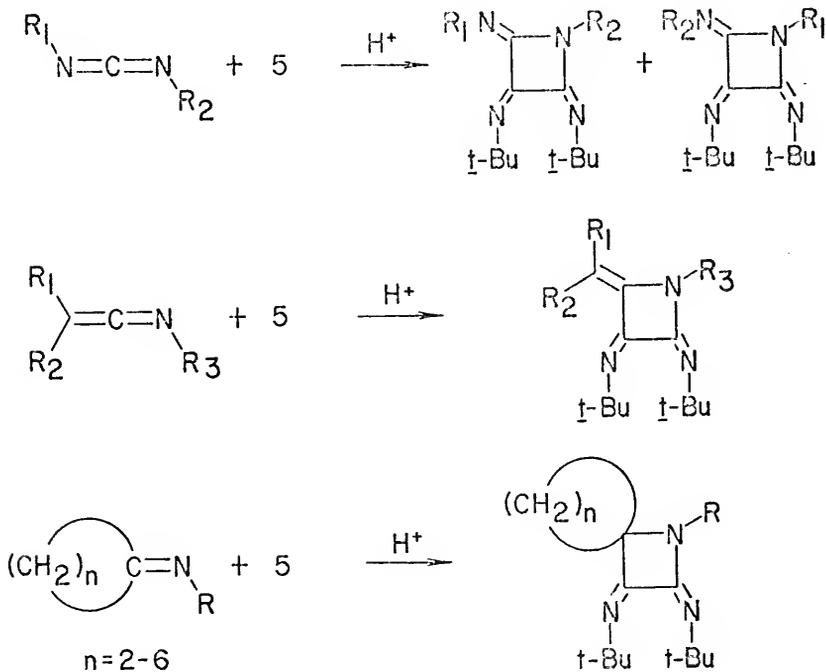


Recently Honzl and Krivinka³⁵ have reported novel results from the reaction of *t*-butyl isonitrile and hydrogen chloride. They isolated some *cis*- α,β -di-*t*-butylaminosuccinonitrile derivatives which resulted by a pathway similar to that proposed in this research for imines and *t*-butyl isonitrile in the presence of hydrogen chloride.

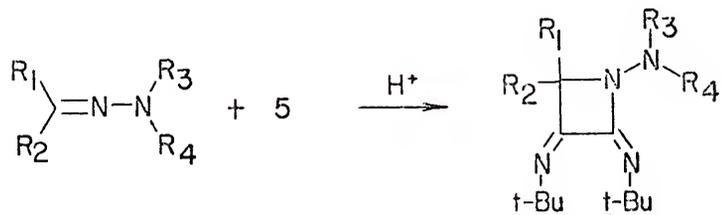
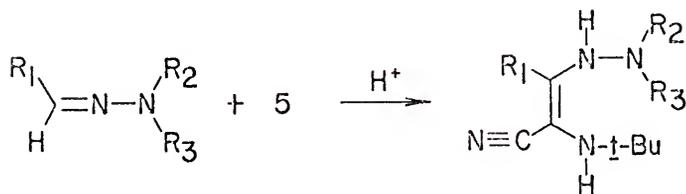
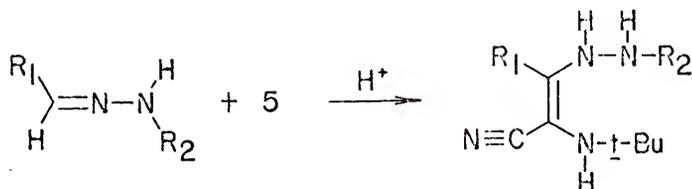
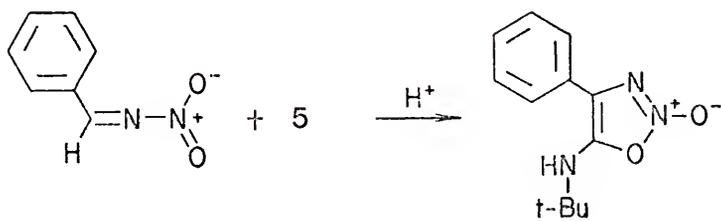
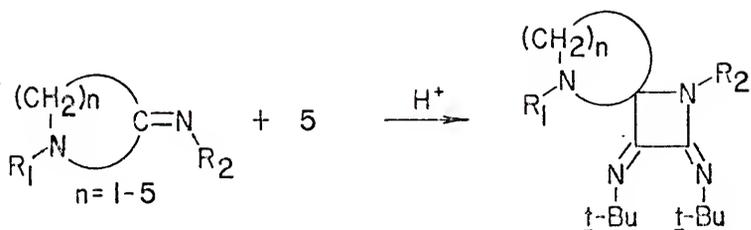
The reactions of imines with isocyanides produce some very interesting results. These results have stimulated ideas for further reactions to be attempted. Scheme XXIX lists a few proposed reactions along with the expected product or products based on the results shown in detail in Scheme XXVII.

Scheme XXIX is by no means a complete list of possibilities, but represents some chemistry which still has not been looked at. Also it is very doubtful that all the products represented in Scheme XXIX are stable. In fact many of these reactions may not even go in pathways analogous to those proposed. Whatever pathway these reactions would follow, it might lead to a very interesting product which might serve mankind in some beneficial way. This is the most anyone could hope for.

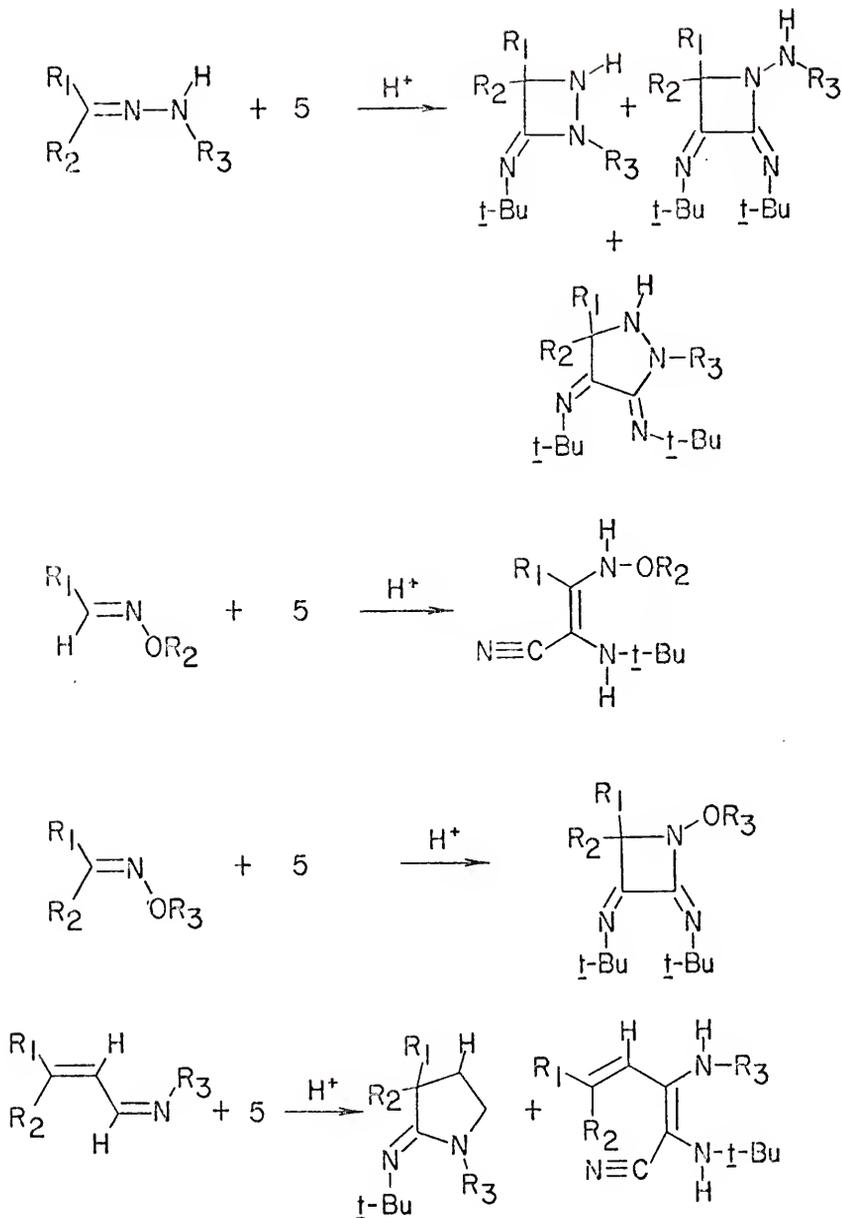
Scheme XXIX



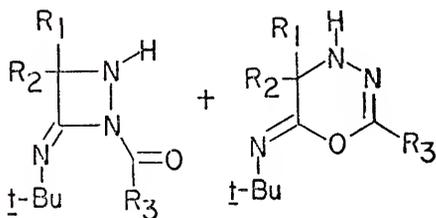
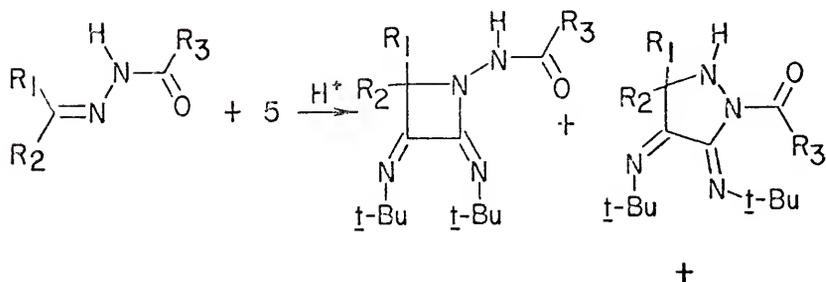
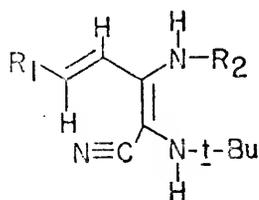
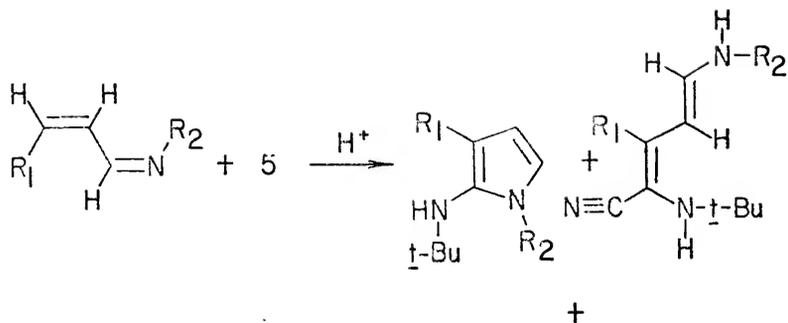
Scheme XXIX (continued)



Scheme XXIX (continued)



Scheme XXIX (continued)

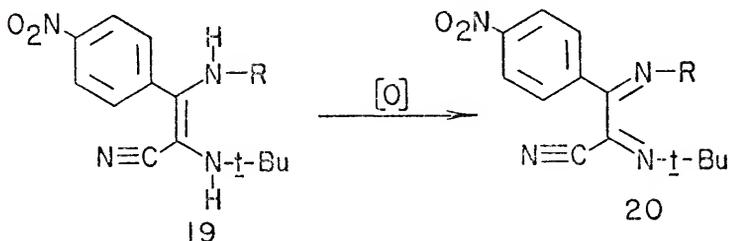


CHAPTER II

Evidence for the Structure and Conformation of Conjugated Diimines

Introduction

In Chapter I a series of compounds was described which had been isolated from the oxidation of 19 and which had abnormal spectral properties. A similar compound had previously been obtained by Yun,⁹ who prepared 20b from the reaction of



a R=t-Bu

b R=2,6-(CH₃)₂C₆H₃

c R=CH₃

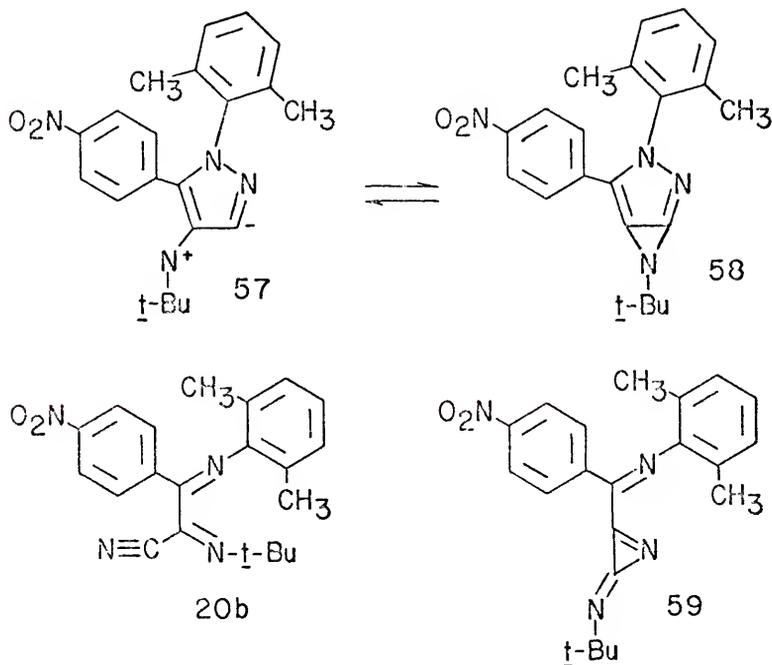
a R=t-Bu

b R=2,6-(CH₃)₂C₆H₃

c R=CH₃

19b with m-chloroperbenzoic acid. Although she proposed structure 20b for the major product, this structure was difficult to reconcile with its anomalous temperature dependent nmr spectra, the lack of a distinct nitrile band in its infrared spectrum, and the fact that it did not form a Diels-Alder adduct with dimethyl acetylenedicarboxylate. For this

reason she also considered three other structures for this compound: 57, 58, and 59.



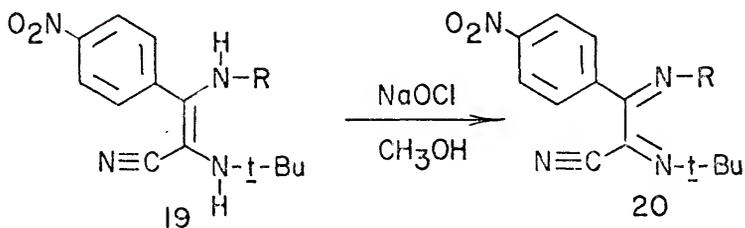
The problem was ultimately left unresolved.

It is the purpose of this chapter to explain the anomalous nmr spectra for the compounds resulting from the oxidation of 19, and to present further examples of compounds made by other synthetic routes which show similar nmr spectral results. The significance of the weak or absent nitrile bands in the infrared spectra will also be discussed.

Discussion

In Chapter I, it was shown that the oxidation of 19 a-c with sodium hypochlorite (Clorox) yielded 20 a-c. The fact

that the structures of 19 a-c were firmly established was



a R=t-Bu

b R=2,6-(CH₃)₂C₆H₃

c R=CH₃

a R=t-Bu

b R=2,6-(CH₃)₂C₆H₃

c R=CH₃

initially the most important piece of evidence for assigning the structure of 20 a-c as derivatives of α -cyano-4-nitrophenylglyoxylidenediamines. Mass spectral evidence indicated that 20 a-c had molecular weights two units less than their respective starting materials, 19 a-c. In each case the infrared spectrum showed a C=N- band and an extremely weak nitrile band. The weakness of the band allowed the (erroneous) conclusion that no nitrile group was present. The nmr spectra were equally unenlightening.

The nmr spectrum of 20a is shown in the Appendix NMR No. 2. The two peaks at 1.17 δ and 1.32 δ were assigned to the two t-butyl groups. The two peaks at 1.42 δ and 1.58 δ were initially left unassigned. The protons attributable to the p-nitrophenyl groups also seemed peculiar. A portion of the aryl hydrogen region seemed to be shielded much more than expected. The two blips at 7.81 δ also caused some consternation. The extra peaks could easily be attributed to impurities. Considerable (but unsuccessful) effort was expended in an attempt

to remove these extra peaks by chromatography or recrystallization from several different solvents.

The nmr spectrum of 20b posed similar problems. Yun alluded to this fact earlier.⁹ The nmr spectrum of 20b is shown in the Appendix NMR No. 5. The two peaks at 1.29 δ and 1.50 δ which were very broad were assigned by integration to the t-butyl group and the peak at 2.01 δ to the methyl groups. The aromatic protons appeared in a region from 6.75-8.32 δ . Again it is evident that a portion of the aromatic region attributed to the p-nitrophenyl group appears at a higher field than usual.

The nmr spectrum of 20c, which is reminiscent of 20a, is shown in the Appendix NMR No. 8. The t-butyl group appeared at 1.39 δ and the methyl group appeared at 3.35 δ . The peaks at 1.58 δ and 3.53 δ were initially left unassigned. The aromatic region showed the same peculiarities as 20a.

Since infrared spectroscopy is an absorption phenomenon whereby the resulting vibration causes a change in the dipole moment of the molecule,³⁶ and the Raman effect is a light scattering phenomenon whereby the intensity of the Raman shift depends on the polarizability of the molecule,³⁷ frequencies permitted in Raman spectroscopy may be forbidden in infrared spectroscopy and vice versa. With this in mind it was hoped that if the nitrile group was forbidden by infrared selection rules, it might be revealed by Raman spectroscopy. Compounds 20a and 20b were submitted to Raman spectroscopy.³⁸ The presence of the nitrile group was confirmed by this spectral

technique. Thus structures 57, 58, and 59, which were mentioned in the introduction to this chapter, were unequivocally ruled out.

Compound 20b was found by Yun to give a temperature dependent nmr spectrum.⁹ These results were repeated in the present research and are shown in the Appendix NMR No. 6. At 133.5°C the nmr spectrum resolved to a spectrum which indicated a t-butyl group at 1.34 δ , the methyl groups at 2.05 δ , a 3 proton singlet at 6.88 δ due to the 2,6-dimethylphenyl group, and a quartet due to a p-nitrophenyl group. In terms of the expected nmr spectrum of 20b, this spectrum was more appealing.

The question at this point was: does 20a also give a temperature dependent nmr spectrum? Thus 20a was heated in the nmr probe and the results are shown in the Appendix NMR No. 3. The peaks coalesced until at 128°C an nmr was obtained which seemed much more compatible with the nmr spectrum expected for 20a. It showed two peaks at 1.25 δ and 1.37 δ to account for the t-butyl groups and a quartet for the p-nitrophenyl group.

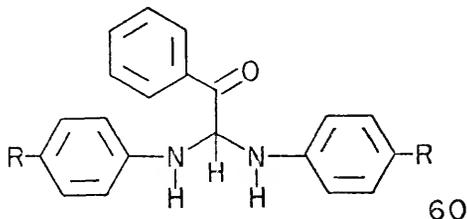
In summary, the evidence presented here: resolution of the nmr spectra, confirmation of the nitrile group by Raman spectroscopy, the correct molecular weight, and correct analysis, plus the chemical evidence presented in Chapter I, provides ample proof for the structures assigned to 20. However, the anomalous temperature dependent nmr spectra still required explanation in order to secure the structure. For this reason a series of model compounds were prepared in a manner similar to that shown in Scheme IX. For convenience the discussion will be recapitulated here.

Kornblum et al.¹⁷ had shown that phenacylbromide and 4'-substituted-phenacylbromides were oxidized by dimethylsulfoxide to the corresponding glyoxal hydrate. Schemes XI, XXX and XXXI give examples of this reaction.

p-Nitrophenylglyoxal hydrate (22) reacted with one equivalent of t-butylamine under mild conditions to give p-nitrophenylglyoxylidene- α -t-butylamine (23). The use of titanium (IV) chloride¹⁸ allowed the addition of a second equivalent of t-butylamine to give the diimine 24a, Scheme XXX.

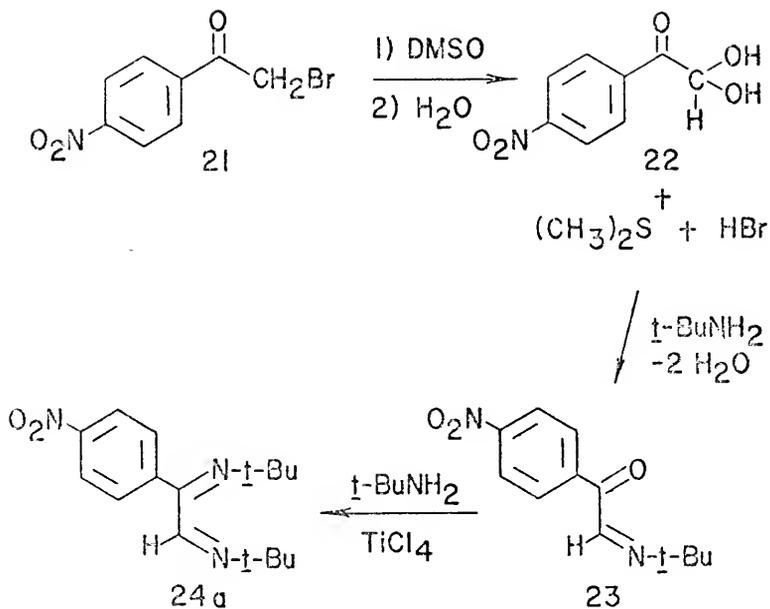
The nmr spectrum of 24a is shown in the Appendix NMR No. 10. Note that the nmr spectrum shows four t-butyl groups, two aldimine C-H groups, and two p-nitrophenyl groups. Each pair of t-butyl groups was in approximately 45:55 ratio.

Proctor and Rehman³³ had shown that phenylglyoxal reacted with aromatic amines to give derivatives of 23. However, they also isolated a second compound 60. It was necessary, therefore, to demonstrate that this nmr spectrum was not due to a mixture of 24a and 61. The infrared spectrum confirmed the

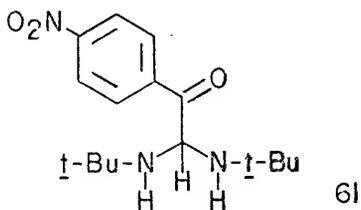


absence of an N-H group and also did not reveal a carbonyl group. The mass spectrum indicated a molecular ion at m/e 289 which corresponds to 24a and no peak was observed at

Scheme XXX



m/e 307 as would be expected for 61. The analysis for 24a checked for $\text{C}_{16}\text{H}_{23}\text{N}_3\text{O}_2$. Therefore, these data coupled with the fact that similar compounds give a temperature dependent nmr spectrum, indicate that the nmr spectrum of 24a is a mixture of isomers.



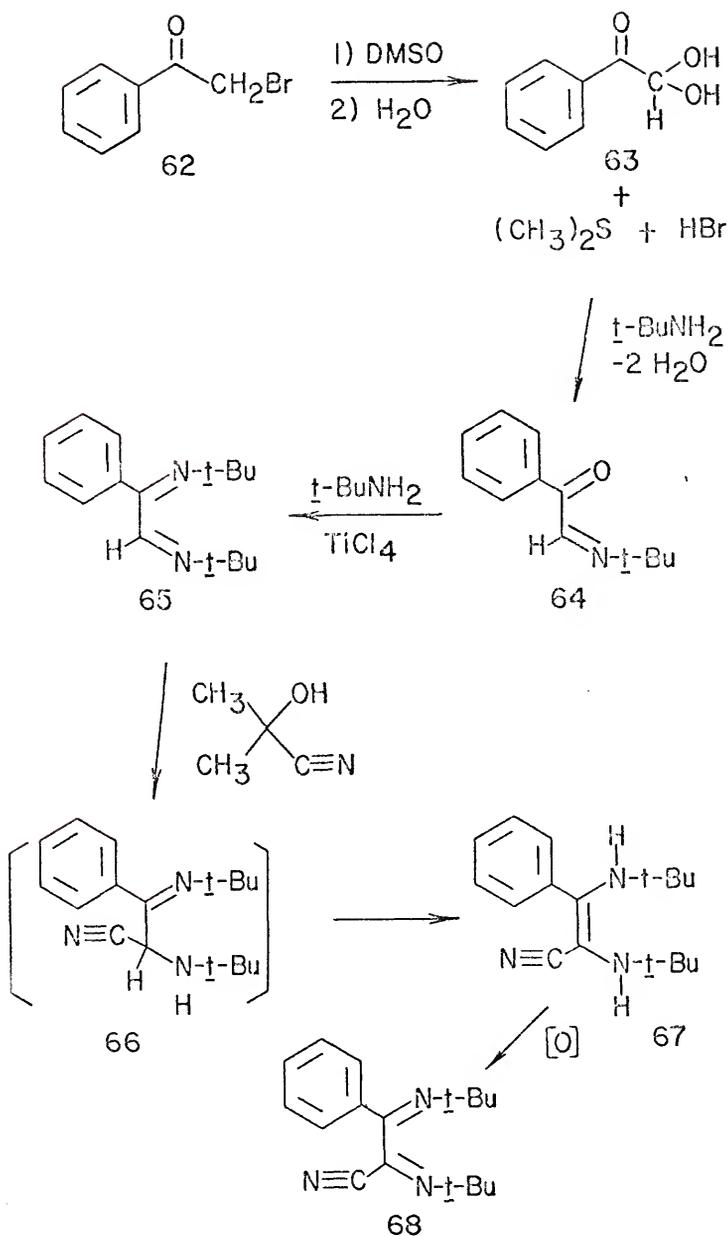
The phenyl analogue was also prepared in analogous manner.⁴⁰ Phenylglyoxal hydrate 63 was prepared¹⁷ and reacted with one equivalent of t-butylamine under mild conditions to give 64 which could not be purified further. Using titanium (IV) chloride¹⁸ a second equivalent of t-butylamine was added to form 65. Compound 65 was not purified further,⁴⁰ Scheme XXI.

The nmr spectrum of 65 is shown in the Appendix NMR No. 11. This nmr spectrum resembles 24a (Appendix NMR No. 10). Again the nmr spectrum shows four t-butyl groups, two aldimine C-H protons and two phenyl groups.

An opportunity was seen to obtain the phenyl derivatives of 19a via the synthetic methods shown in Scheme XI. Therefore 65 was reacted with one equivalent of acetone cyanohydrin to give 67. The addition of hydrogen cyanide probably formed 66 initially followed by enolization before the addition of a second equivalent of hydrogen cyanide. Compound 67 was isolated but lost during a second recrystallization. The compound autooxidized to 68.

The nmr spectrum of 68 was no surprise. It was expected to resemble the nmr spectrum of 20a and this is verified in the Appendix NMR No. 13. The two peaks at 1.15 δ and 1.30 δ were assigned to the two t-butyl groups. The two peaks at 1.40 δ and 1.56 δ were temporarily left unassigned, but were thought to be due to a second isomer of 68. The aromatic region indicated the phenyl group plus aromatic protons due to a minor isomer. It should be noted that the nitrile band in the infrared spectrum for this compound is also very weak in analogy to 20a.

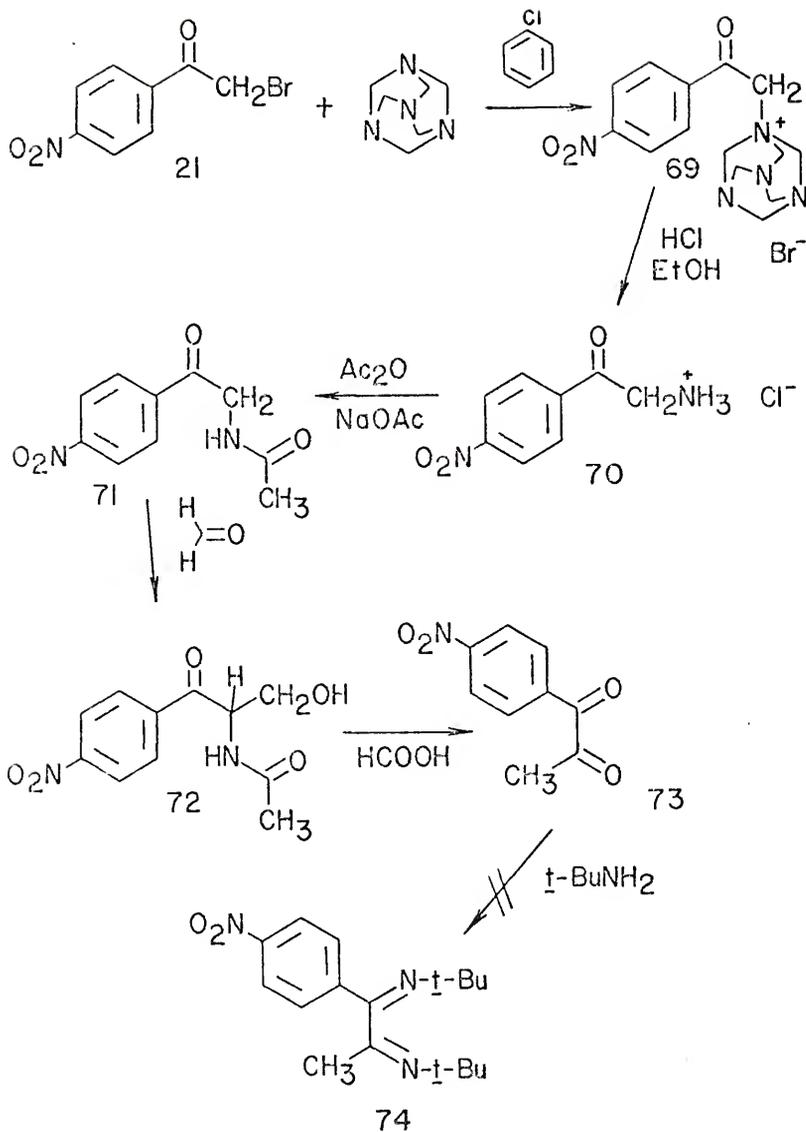
Scheme XXXI



One trend that was definitely revealed by the nmr spectra was that, as the group on the α -carbon increased from hydrogen to cyanide, the minor isomer decreased in concentration. It was thought that if the group at this position could be steadily increased the effect would be to completely eliminate the second isomer in the nmr spectra. For this reason p-nitrophenyl-1,2-propanedione⁴¹ (73) was prepared from p-nitro- α -acetamide- β -hydroxypropiofenone⁴² (72), Scheme XXXII. Unfortunately p-nitrophenyl-1,2-propanedione (73) failed to yield the diimine (74) either in mild reaction conditions or with titanium (IV) chloride.¹⁸ All that was obtained was tar.

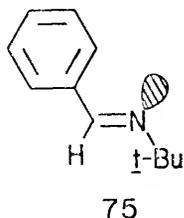
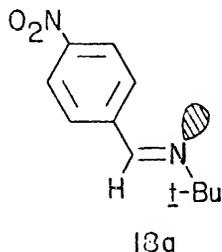
Once the structures of compounds 20 a-c, 24a, 65, and 68 were established as diimines, an explanation could be proposed for their anomalous nmr spectra. This explanation suggests that two conformations are populated at ambient temperatures and that at this temperature a barrier exists to their interconversion. Assignment of detailed structures to these conformations will be made on the basis of (1) the response of the relative proportions of the two conformations to changes in steric size of the various substituents and (2) an analysis of chemical shifts caused by anisotropic groups in these molecules in comparison to suitable model compounds.

Close inspection of the aromatic region in the nmr spectra of compounds 20 a-c, 24a, 65, and 68 (Appendix NMR No. 2, 5, 8, 10 and 11) reveals that each spectrum has two groups of peaks in the aromatic proton region. This is

Scheme XXXII^{41,42}

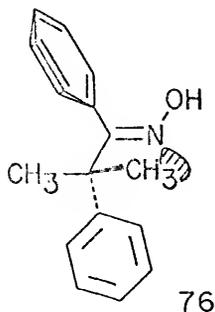
particularly noticeable in the p-nitrophenyl compounds, e.g. 20 a-c, and 24a. One group of protons ("normal") occurs at 7.83 δ and 8.22 δ . The other group ("abnormal") appears at 7.25 δ and 8.22 δ . The peaks at 7.83 δ and 7.25 δ correspond to the protons ortho to the imine group.

Two model compounds, p-nitrobenzylidene-t-butylamine (18a) and benzylidene-t-butylamine (75), are submitted in the Appendix NMR No. 14 and 16 respectively as evidence for a "normal" aromatic ring attached to an imine bond bearing



an N-t-butyl substituent. Note that in the nmr spectrum of 18a the protons ortho to the nitro group appear as a doublet at 8.20 δ and the protons ortho to the aldimine group appear as a doublet at 7.89 δ . Similarly, the nmr spectrum of 75 shows the protons in the 3,4 and 5-positions of the phenyl ring as a multiplet at 7.27-7.50 δ and the protons ortho to the aldimine group appear as a multiplet at 7.67-7.88 δ . These aromatic rings are expected to be in the same plane^{4,3} as the imine double bond in order to achieve maximum π overlap. The "normal" ortho protons thus lie in the deshielding area of the imine group.

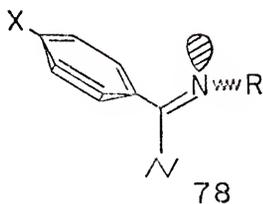
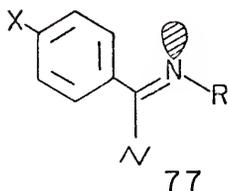
A model compound for an "abnormal" phenyl group is 2-methyl-2-phenylpropiophenone oxime, (76).⁴⁵ In the nmr spectrum the protons in the 3,4 and 5-positions of the phenyl group attached to the oxime bond appear as an upfield multiplet at 7.10-7.55 δ and the protons ortho to the oxime bond appear as a multiplet at 6.53-6.82 δ . In this case the protons ortho to the oxime bond are shielded by approximately 0.70-1.00 δ . It is proposed that the aromatic ring is twisted out



of plane due to non-bonded interactions and the ortho protons thus lie in the shielding cone of the C-N double bond.

From this evidence the orientation of the aryl group in both conformers of 20 a-c, 24a, 65, and 68 can now be proposed. In the cases where the aromatic ring appears "normal" in the nmr spectrum, the aromatic ring is coplanar with the attached imine group (partial structures 77). In the cases where the aromatic ring appears as "abnormal," the aromatic ring is skew to the plane of the imine groups (partial structure 78). Furthermore, in the case where the aromatic ring is coplanar with imine bond (partial structure 77), it may be assumed for steric reasons that the group attached to the imine nitrogen

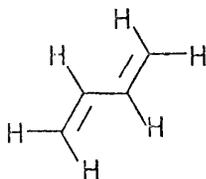
is E with respect to the aromatic ring,⁴⁶ c.f. 18d and 75.



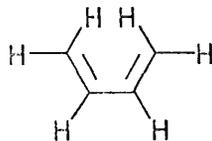
X=H R=t-Bu

X=NO₂, R=t-Bu, 2,6-(CH₃)₂C₆H₃, CH₃

The stereochemical nomenclature used in the rest of this chapter requires definition. The terms "s-cis" and "s-trans" have been proposed for the arrangement of groups around a single bond.⁴⁸ The two conformations of butadiene serve as examples of this terminology. The E-Z system is



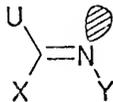
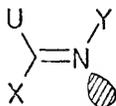
s-trans



s-cis

used to define the configuration about the C-N double bond.⁴⁹

The two substituents attached to the carbon linked by a

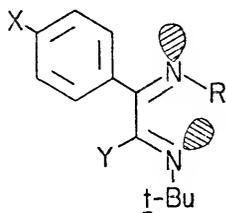


Sequence U>X

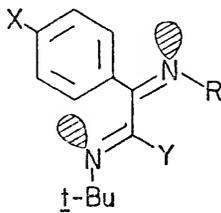
double bond nitrogen are arranged in the appropriate Cahn-Ingold-Prelog sequence.⁵⁰ Then, if the groups of higher sequence (U and Y above) are on the same side, the configuration is Z (from the German zusammen), if they are on opposite sides, E (from the German entgegen).

Returning now to the nmr spectra of 20 a-c and 68 the minor conformer has the planar moiety 77 and the major conformer has non-planar moiety 78. However, in 24a and 65 this is reversed, i.e. the major conformer has the planar moiety 77 and the minor conformer has the non-planar moiety 78. With this information a relationship can be invoked. The more deshielded alkyl groups are associated with the planar moiety 77 and vice versa the more shielded alkyl groups are associated with the non-planar moiety 78.

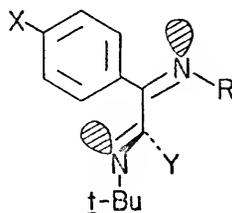
Three possible conformations (79c, 79t, and 79s) can be suggested for the conformer which contains the moiety 77. The conformation of the α -imine was suggested to be E in order to avoid steric interactions.



Z-s-cis-E
79c



Z-s-trans-E
79t

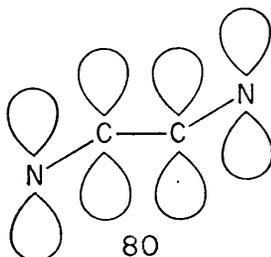


Z-skew-E
79s

X=H, R=t-Bu

X=NO₂, R=t-Bu, 2,6-(CH₃)₂C₆H₃, CH₃

Overlap between adjacent p-orbitals allows π bonding between the central carbon atoms (80). In such cases, the energy is lowest in the planar conformations *s-cis* (cisoid) and *s-trans* (transoid). However, the activation energy required for rotation about the central bond is generally not very high.⁵¹ Steric factors and other electronic factors⁵²

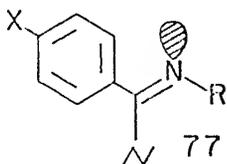


could swing the balance away from a planar minimum towards a variety of skew conformations.

Careful considerations of the nmr spectral data indicate that the diimine system does favor the planar conformation. This argument is supported by the observation that as Y increases in size from H to C≡N the concentration of the conformer 79 decreases. If the α -imine group of this conformer (79s) were skew, the size of Y would be expected to have little effect on the relative concentration of 79. The *Z-s-trans-E* (79t) would be most responsive to the size of Y and also would accommodate bulky R groups most easily. Therefore the *Z-s-trans-E* (79t) conformer is proposed to be the most favored conformer of 79.

Further evidence which is consistent with a planar diimine configuration for 79c or 79t is seen in the resonance

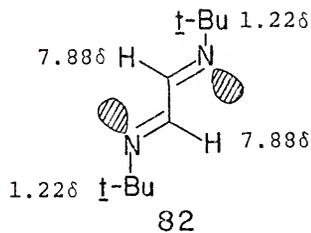
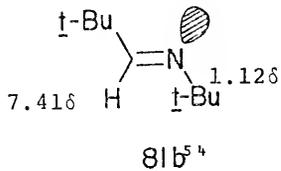
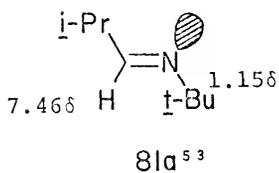
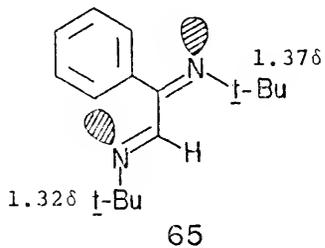
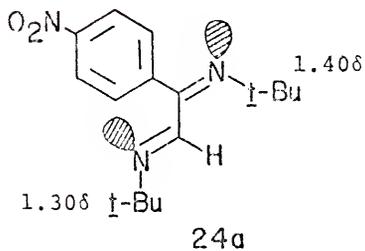
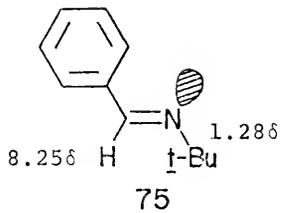
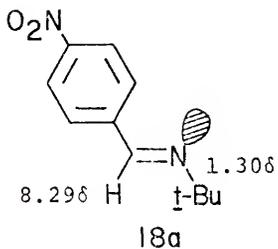
line for the aldimine proton in the case of 24a and 65. Comparison of the nmr resonance line of the aldimine proton in 24a and 65 with 18a and 75 respectively, reveals that the former pair is deshielded by 0.10 δ , Scheme XXXIII. Similarly the t-butyl group attached to the β -imine nitrogen in 24a and 65 is also shielded by 0.10 δ as compared to the t-butyl group in 18a and 75, respectively. Compounds 18a and 75 contain the planar moiety 77. Therefore the second imine group in



24a and 65 must cause the extra deshielding in the system.

Three more models, 81a,⁵³ 81b,⁵⁴ and 82,^{55,56} are presented in Scheme XXXIII which support the proposed planarity. The aldimine proton of an aliphatic t-butyl imine of known conformation, 81, has a resonance line in the nmr spectra at 7.41-7.46 δ . The conformation of 82 has recently been proposed to be E-s-trans-E with some E-s-cis-E^{55,56} although a non-planar species could explain their data.⁵² The aldimine proton of 82 has its resonance line in the nmr spectrum at 7.88 δ . These models establish that if the imine group in 79 were skew to the planar moiety 77 the aldimine proton would be expected to appear in the vicinity of 7.40-7.90 δ . The fact that the aldimine proton in 79 appears at 8.32-8.39 δ , gives support that the system is completely conjugated and therefore planar. Thus it is proposed that the deshielding

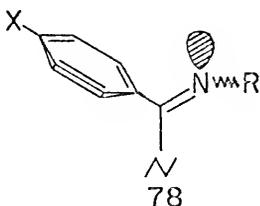
Scheme XXXIII



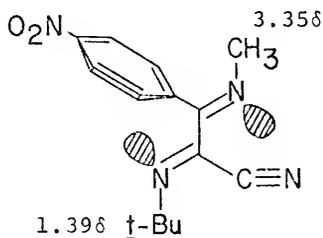
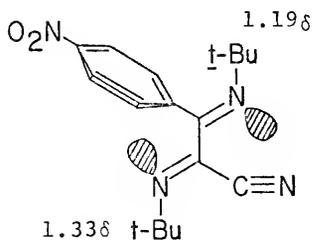
anisotropic effects caused by the completely planar conformation of 79 causes the deshielding of the aldimine proton.

In summary the favored conformation of 79 is completely planar because of (1) resonance arguments which invoke some double bond character to the central bond of a diimine system, (2) steric arguments which show a decrease in 79 with increase in the size of group Y, and (3) deshielding of the aldimine protons due to anisotropic effects of a completely planar system. Furthermore, based on non-bonded interactions, the most favored planar conformation of 79 is Z-s-trans-E (79t).

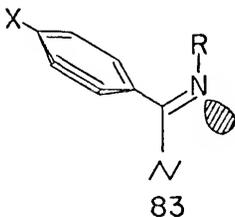
The discussion is now turned to the second conformer in the nmr spectra of 20 a-c, 24a, 65 and 68 which has the non-planar moiety 78. Comparison of the nmr spectrum of



20c with 20a discloses that the t-butyl group attached to

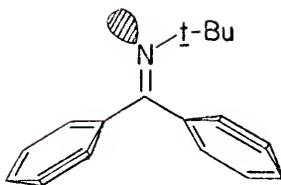


the β -imine nitrogen is the most shielded t-butyl group in the nmr spectrum of 20a (Appendix NMR No. 2). This would indicate that the t-butyl group attached to the β -imine nitrogen is in the shielding cone of the aryl group. Therefore the conformation of the β -imine is *Z* with respect to the aryl group, (83). This would also explain why the aryl group in the non-planar moiety 78 or 83 is skew. It is



physically impossible for the aryl group to remain in the same plane as the imine double bond when the *N*-substituent is *Z* with respect to the aryl group because of non-bonded interactions.

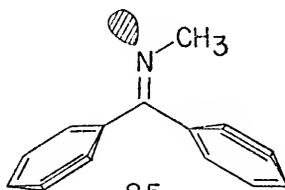
A model compound, the t-butyl imine of benzophenone (84),¹⁸ whose nmr spectrum is shown in the Appendix NMR No. 17, is presented for the chemical shift of a t-butyl imine group interacting with the shielding cone of a benzene ring. The chemical shift for the t-butyl group is 1.15 δ in 84 as compared to the chemical shift of 1.19 δ , 1.10 δ , 1.10 δ , and 1.16 δ for similar t-butyl groups in 20a, 24a, 65, and 68, respectively.



84

It has been shown that in benzophenone each phenyl group is twisted from coplanarity by 41° .⁴⁴ Therefore the t-butyl group would have to interact with the shielding cone of one of the benzene rings.

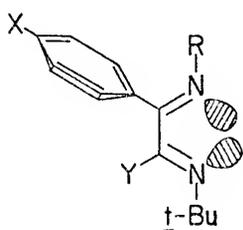
Similarly the methyl imine derivative of benzophenone (85)¹⁸ should serve as a model for the chemical shift in the nmr spectrum for a methyl imine interacting with the shielding cone of a benzene ring. The chemical shift of the methyl group in 85 was found to be 3.13δ in carbon tetrachloride. The corresponding methyl group in 20c appears at 3.35δ in deuteriochloroform. The difference could possibly be due to solvent effects.⁵⁷⁻⁵⁹



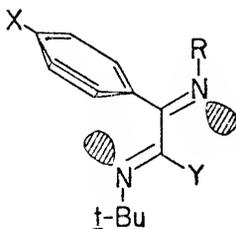
85

As in conformer 79, the β -imine of the conformer containing the non-planar moiety 93 is suggested to have the

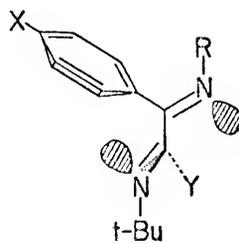
E conformation in order to avoid steric interactions of the t-butyl groups with the lone pair of electrons on the β -imine nitrogen or the π cloud of the aryl group. Thus three conformations (86c, 86t, and 86s) can be proposed for the conformer containing the non-planar moiety 83.



E-s-cis-E
86c



E-s-trans-E
86t

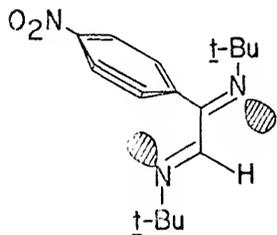


E-skew-E
86s

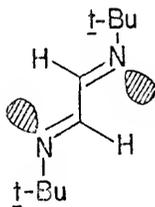
Of the three conformers of 86 the E-skew-E (86s) seems least likely due to lack of stabilization due to resonance. The E-s-cis-E conformer (86c) also seems unfavorable due to the severe electronic repulsions caused by the lone pair of electrons on each imine nitrogen. The E-s-trans-E conformer (86t) seems to be favored because it minimizes non-bonded interactions and is stabilized due to the planar configuration of the diimine system.

The aldimine proton in this conformer is 24a and 65 should show the nmr spectrum resonance line consistent with the resonance line of the alkimine proton in 82. As was mentioned earlier the conformation of this compound is proposed to be E-s-trans-E.^{55,56} The aldimine proton in this conformation in 24a gives an nmr resonance line at 7.93 δ and in 65 a

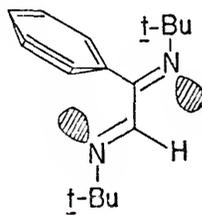
resonance line at 7.97δ which is in good correlation with the model. This also gives evidence that the aldimine proton is s-trans to the aryl group because if it were s-cis the



24a



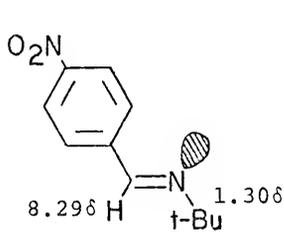
82



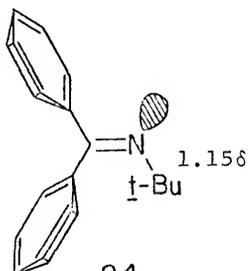
65

aldimine proton would be much closer to the shielding cone of the aryl group and would therefore be expected to be more shielded than the aldimine proton in 82.

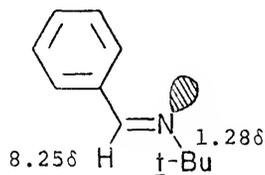
Further predictions for this system can be made and compared with observed data. If the t-butyl group in the planar diimine 82 is used as a standard, one would expect that the t-butyl group attached to the β -imine nitrogen in conformer 86 to be shielded by no more than $0.15\delta^{60}$ due to



18a



84

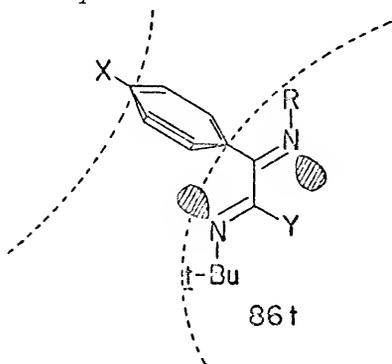


75

interaction with the shielding cone of the aryl group.

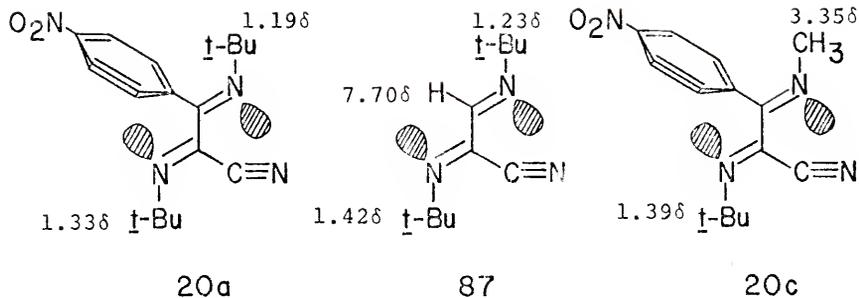
Inspection of the nmr spectra of 20a, 24a, 65, and 68 (Appendix NMR No. 2, 10, 11, and 13) confirms this result.

The shielding cone of the aryl group would be expected to shield the t-butyl group attached to the α -imine nitrogen when the diimine system is in the *s*-*trans* configuration.



However, this shielding would be expected to be weakened because the t-butyl group is much further away from the aryl groups and also because the t-butyl group is close to the periphery of the shielding cone. Inspection of the nmr spectra of 24a and 65 reveals that this prediction is also correct. The t-butyl group on the α -imine nitrogen appears at 1.15 δ and 1.13 δ in 24a and 65 respectively. Thus, compared to 82 the t-butyl group is shielded by less than 0.10 δ .

In order to discuss the t-butyl group attached to the α -imine nitrogen in 20a and 20c another model is needed. Compound 87 should serve as this model. In this model in the 3-position the t-butyl group on the imine nitrogen has a chemical shift in the nmr spectrum similar to that found in 82. However in the 2-position the imine is conjugated with



a nitrile group. Due to resonance and inductive effects this nitrile group deshields the t-butyl group by about 0.20 δ .

The t-butyl group attached to the α -imine nitrogen in 20a and 20c would be expected to appear around 1.42 δ if the aryl group were not present in the molecule. However the t-butyl group is interacting with the shielding cone of the aryl group. The aryl group shields this t-butyl group by about 0.10 δ or less, cf. 24a and 65. Therefore one would expect this t-butyl group in 20a and 20c to appear in the range 1.32-1.42 δ . Inspection of the nmr spectra of 20a and 20c reveals that the predictions are in good agreement with the results, i.e. the t-butyl group appears at 1.33 δ and 1.39 δ in 20a and 20c respectively.

Another trend which can be observed in the nmr spectra of 20 a-c is that as the substituent on the β -imine nitrogen is varied in size from methyl to t-butyl to 2,6-dimethylphenyl the concentration of 86t decreases while 79t increases. It is proposed that as the substituent on the β -imine increases in size the π cloud on the aryl group interacts with this

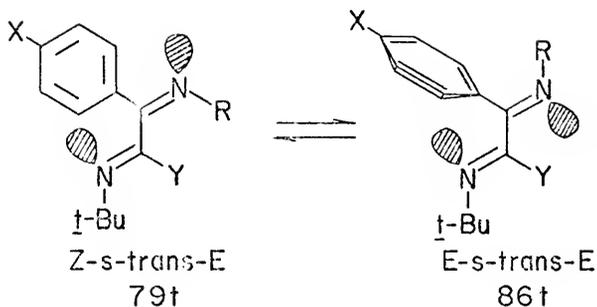
substituent to a greater and greater extent. When this interaction becomes too great isomerization of the β -imine nitrogen is favored to form conformer 79t in order to relieve this non-bonded interaction.

In summary the conformation of 86 is proposed to be E-s-trans-E with the aryl group skew to the plane of the diimine system because (1) the protons ortho to the diimine system in 86 are shielded because of their interaction with the shielding cone of the C-N double bond, (2) based on resonance argument the planar diimine system is of lower energy and therefore more stable, and (3) it eliminates non-bonded interaction more so than the s-cis conformation. Furthermore the conformation of the β -imine nitrogen is E in order to explain the forcing of the aryl groups out of plane and thus this twisting limits non-bonded interactions.

The overall equilibrium which is observed in the nmr spectra of 20 a-c, 24a, 65, and 68 is shown in Scheme XXXIV. The diimine system remains planar and the α -imine keeps an E conformation. However the β -imine nitrogen isomerizes from Z to E and with this isomerization forces the aryl group out of plane. When R becomes large the non-bonded interactions of R with the π cloud of the skew aryl group become too great, forcing the equilibrium back to 79t. When R is small the equilibrium favors 86t. However when Y is small 79t is favored but when Y is large 86t is favored.

Recently Kliegman and Barnes^{55, 56, 61, 62} have reported on the nmr and conformational studies of the diimines (88)

Scheme XXXIV



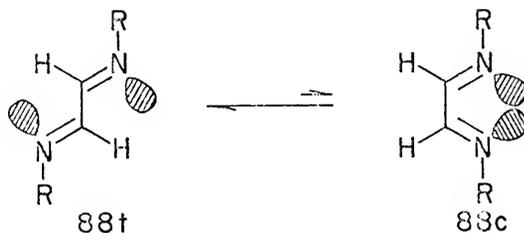
$\text{X}=\text{NO}_2$, $\text{Y}=\text{C}\equiv\text{N}$, $\text{R}=\text{t-Bu}$, $2,6-(\text{CH}_3)_2\text{C}_6\text{H}_3$, CH_3

$\text{X}=\text{H}$, $\text{Y}=\text{CN}$, $\text{R}=\text{t-Bu}$

$\text{X}=\text{NO}_2$, $\text{Y}=\text{H}$, $\text{R}=\text{t-Bu}$

$\text{X}=\text{H}$, $\text{Y}=\text{H}$, $\text{R}=\text{t-Bu}$

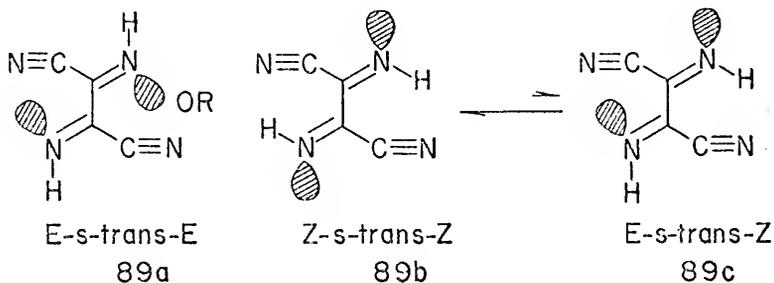
of glyoxal. They "established" that the most stable conformation of conjugated 1,2-diimines of glyoxal was E-s-trans-E (88t), with a small amount of the E-s-cis-E conformer (88c). This was accomplished by analysis of their nmr spectra and by titration with 0.1N HClO_4 in acetic acid.



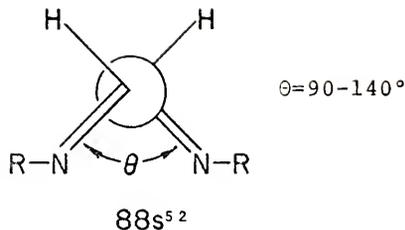
Their data do not "prove" that the most stable conformation of conjugated 1,2 diimines is E-s-trans-E. The

nmr spectral data argument for an E-s-trans-E conformation was based on comparison with aliphatic imines with presumably E conformations. Their nmr data can be said to be consistent with but not proof for an E-E conformation for the diimines. The conformation about the central C-C bond (s-trans, s-cis, or skew) cannot be determined from these data. All the chemical evidence established was that they could trap the E-s-cis-E conformer (88c) irrespective of its stability in solution.

Sheppard *et al.*⁶³ reported that diiminosuccinonitrile (89), on the basis of the proton nmr and dipole moment, was primarily transoid in structure. The major conformer was either 89a or 89b and the minor conformer was 89c.

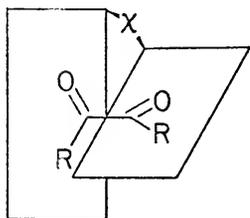


A dipole moment study was attempted on the conjugated 1,2-diimines of glyoxal.⁵² In general, the measurements were not very precise because of association in solution, thus making extrapolation to zero concentration difficult. Their results could be interpreted in terms of a mixture of 88t and 88c or as a non-planar conformer 88s. However, on the basis of the results on 1,2-diketones they preferred the



latter 88s. However, is this consistent with the results of 1,2-diketones?

It has been demonstrated that the effective (or average) conformations of benzil (90, $R=C_6H_5$), furil (90, $R=C_4H_3O$), and biacetyl (90, $R=CH_3$) in non-polar solvents are one in which the ketonic groups, with their appropriate bonds, are non-planar (as in 90) with azimuthal angles χ° ca. 97° , 118.5° , and 160° respectively.^{64, 65} The conformation of furfur-aldehyde was found to be s-trans (91). The skew structure

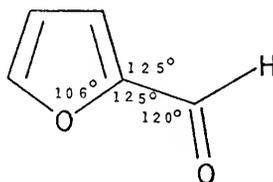


90^{64, 65}

benzil $R=C_6H_5$ $\chi=97^\circ$

furil $R=C_4H_3O$ $\chi=118.5^\circ$

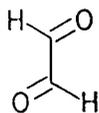
biacetyl $R=CH_3$ $\chi=160^\circ$



91⁶⁵

for the 1,2-diketones 90 was suggested to be caused by non-bonded interactions between the R group and the carbonyl oxygen. However the trend is evident. As R in 90 becomes

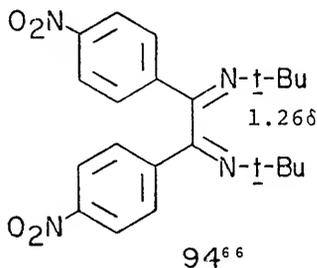
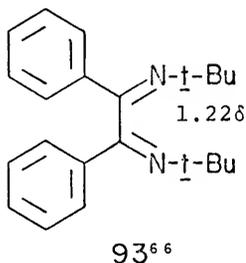
smaller the 1,2-diketone tends towards the s-trans conformation. Further extrapolation from this evidence, including the fact that the most stable conformation of 91 is s-trans, would suggest that glyoxal (92) ought to have an s-trans conformation, not the skew structure proposed by Kliegman and



92

Exner.⁵² Therefore one would expect that the most stable conformation of the conjugated 1,2-diimines of glyoxal to be planar based on the resonance arguments (80) and the evidence presented above. Furthermore the dipole moment measurements should be interpreted in terms of a mixture of 88c and 88t instead of 88s.

In the present work two more diimines, the di-*t*-butyl-imine derivative of benzil 93 and 4,4'-dinitrobenzil 94 were prepared. The nmr spectra of 93 and 94 are shown in the Appendix NMR Nos. 18 and 19 respectively.



Perusal of the nmr spectrum of 93 and 94 indicates that in each case only one *t*-butyl group and one aromatic multiplet is observed. Note that in 94 the *p*-nitrophenyl group is

exactly the same as that shown for p-nitrobenzylidene-t-butylamine (18a) (Appendix NMR No. 14). In fact the nmr spectra of 18a and 94 are identical if the aldimine proton is removed from that of 18a. The same statement can be made for 93 and 75.

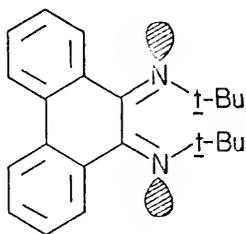
From the nmr spectra it is obvious that the aromatic rings are in the same plane as the imine group to which it is attached. Inspection of molecular models indicates that if both imines are in an *s*-trans configuration, it is impossible for both aryl groups to remain coplanar with the diimine system. Similarly if both imines are in the *s*-cis configuration, both aryl groups again cannot be coplanar with the diimine system.

The explanation is very simple. It has been shown that "the stable configuration of benzil in non-polar solvents is one in which the ketonic groups, with their appropriate bonds, are effectively situated in, or make rotational oscillations of low amplitude about, two planes which are roughly mutually perpendicular."^{64, 65} The same effect explains the nmr spectra for the benzilylidenedi-t-butylamines 93 and 94, Scheme XXXV. In other words, when Y is very large 79t is destabilized due to non-bonded interactions. Furthermore a twofold loss of overlap between the aryl and imine groups is not compensated for by the overlap of the planar diimine system in 86t.

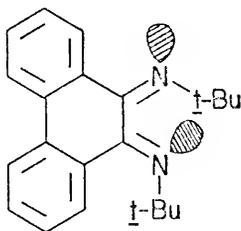
The discussion thus far has only indicated diimines in a *s*-trans configuration or in a skew configuration. It was interesting to determine if an *s*-cis diimine could be made.

For this purpose the di-t-butylimine derivative of phenanthrenequinone (95) seemed like a good possibility. The diimine would be held by the rigidity of the system in a *s-cis* configuration. Actually it really was expected that this system couldn't be synthesized because of the severe steric interactions.

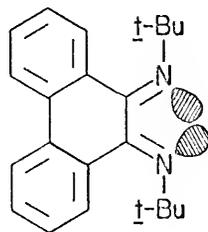
If compound 95 could be prepared it seemed likely that the system would exist in the *Z-s-cis-E* conformation. Inspection of molecular models would verify this. The *Z-s-cis-Z* conformer (95a) is physically impossible and the *E-s-cis-E* conformer (95c) which according to Kliegman and Barnes^{55,56,61,62} is the more stable conformation of some diimines, would also seem to suffer because of steric inter-



Z-Z
95a



Z-E
95b



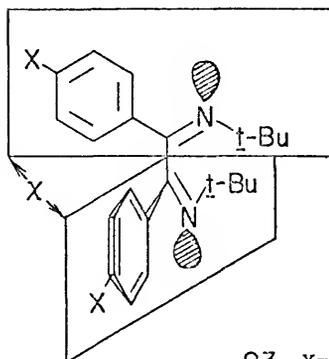
E-E
95c

actions of the t-butyl groups with the aromatic rings. Thus, the *Z-s-cis-E* topomer⁶⁷ (95b) seems to be most favored.

Phenanthrenequinone was reacted with two equivalents of t-butylamine in the presence of titanium (IV) chloride.¹⁸ The nmr spectrum (Appendix NMR No. 20) showed two t-butyl groups of equal intensity at 1.22 δ and 1.50 δ .⁶⁸ This result

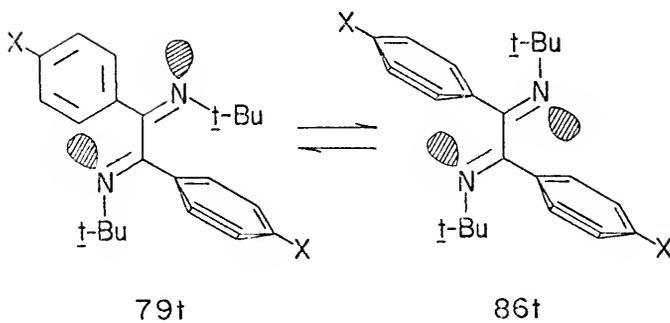
Scheme XXXV

Observed Conformation



93 X=H
 94 X=NO₂
 $\chi=97^\circ$

Conformations Not Observed



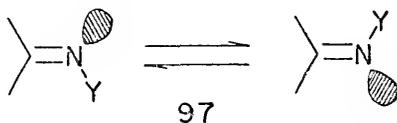
X=H

X=NO₂

thus verifies that the Z-s-cis-E conformation (95b) is the most favored in solution.

This system appears to have an interesting property. Since the imines are held s-cis and the t-butyl groups are held in the same plane topomerization becomes very difficult. In order for the imine nitrogen in the E conformation to invert the imine nitrogen in the Z conformation would also have to invert in a synchronous fashion producing a "windshield wiper effect." Another possibility would be that the imine nitrogen in the E conformation would have to wait for the imine nitrogen in the Z conformation to invert to the E conformation and then rapidly, by nmr time scale, invert to the Z conformation.

E-Z isomerization of N-alkyl or N-aryl imines usually takes place rapidly in solution, but some imines have been found to crystallize in one conformation.⁶⁹ However, oximes (97, Y=OH), oxime ethers (97, Y=OR), hydrazones, (97, Y=NR₂), azines (97, Y=N=CR₂), and N-haloimines (97, Y=F or Cl) have in some cases been found to be very resistant to isomerization in a variety of conditions.⁶⁹ Compound 95 may very well be unique, in that the N-alkylimines in solution do not invert because of the rigidity of the molecule and non-bonded interactions which exist in the system.

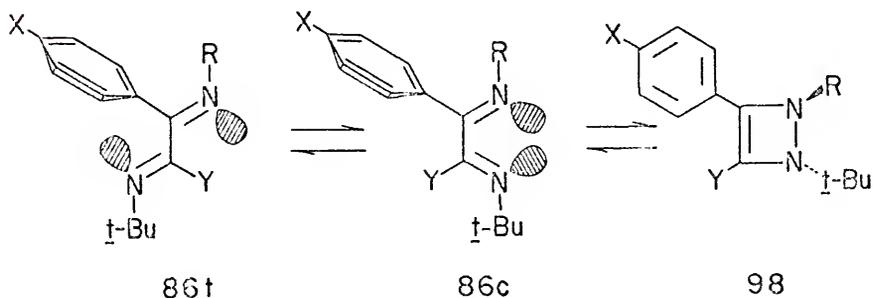


Y=OH, OR, NR₂, N=CR₂, F, and Cl

One other explanation for the abnormal nmr spectra in 20 a-c, 24a, 65 and 68 should be mentioned. It was thought that these diimines might be undergoing a thermally allowed conrotatory electrocyclic reaction,⁷⁰ to a Δ^3 -1,2-diazetene (98), Scheme XXXVI. The driving force for this cyclization would be the formation of a 6π electron aromatic system.

Effenberger and Maier⁷¹ supposedly prepared the

Scheme XXXVI

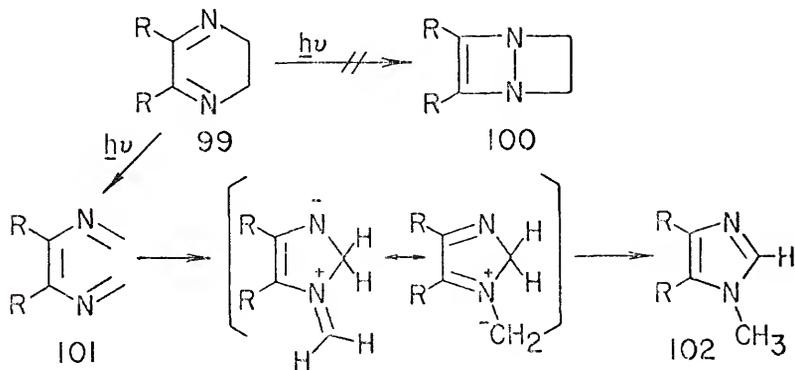


Δ^3 -1,2-diazetene system but only reported that "they did it." No evidence was reported to allow the reader a chance to evaluate the data himself. They did not appear to consider the thermally allowed conrotatory electrocyclic opening of this ring to a diimine system. Thus, this reference⁷¹ is open to question.

About this time Beak and Miesel⁷² examined the photolysis of 2,3-dihydropyrazine (99) systems. Based on previous work⁷³ they expected a photochemically allowed disrotatory electrocyclic reaction would take place to yield a bicyclo-[2.2.0] system (100). However, they obtained instead

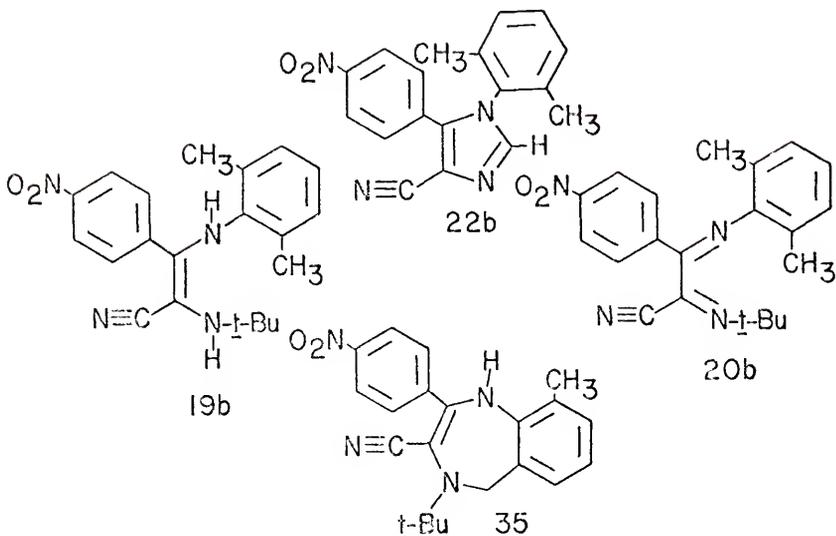
imidazole derivatives (102), Scheme XXXVII. This evidence seems to indicate that structures like 98 or 100 are dif-

Scheme XXXVII

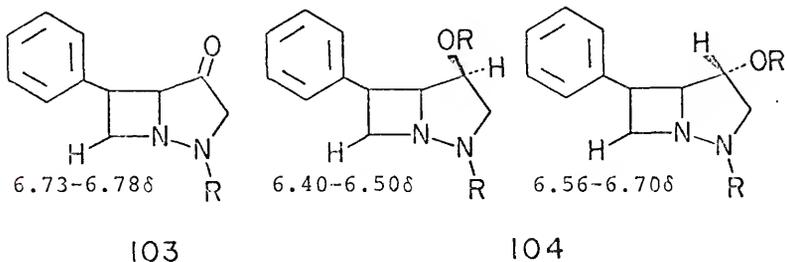


ficult to obtain.

It seems very improbable for several reasons that 98 would replace 79t in the nmr spectra of 20 a-c, 24a, 65, and 68. The reasons are: (1) As Y is increased in size in 98 there is no explanation why 86t would then be favored since steric interactions in 98 would also be minimal. (2) In 20c where the concentration of 86t decreases and the supposed 98 increases the nitrile band in the solution infrared spectrum should show a strong nitrile band due to the cinnamitrile linkage in 98 as was established by 19b, 22b, and 35. (It has been established that 20b shows a very weak nitrile bond.) (3) The nmr spectrum of 98 where Y=H would not be expected



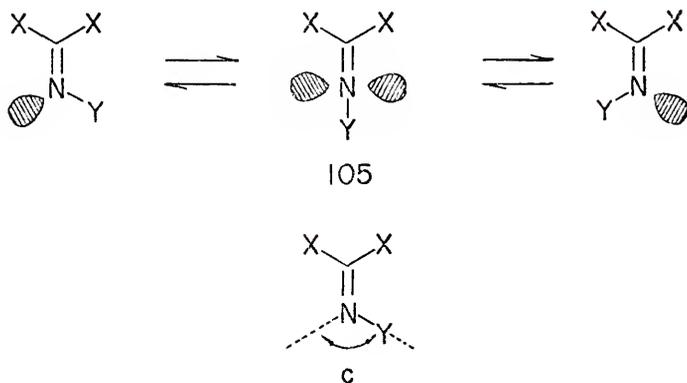
to appear at 8.32-8.93 δ based on the model compounds 103 and 104^{73f} unless there is a sizeable ring current.



Therefore it seems very unlikely that a Δ^3 -1,2-diazetidine (98) is being observed in the nmr spectrum of 20 a-c, 24a, 65 and 68 instead of 79t.

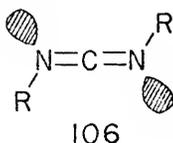
The mechanism by which the E-Z isomerization in imine nitrogens takes place in an inversion mechanism.⁵¹ The N-Y bond of 105 swings in the bond plane of the imine system from the Z into the identical E position ("in plane" isomerization, c).

The bond angle of (C-N-Y) increases to 180° in the transition state. The C=N is, to a first approximation, unaffected.⁵¹

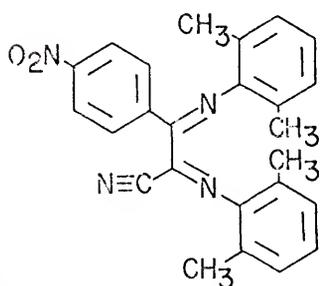


It has been shown that there is a similarity of the effect of the substituent Y on the E-Z isomerization in imines (105) and on the inversion at tricoordinated nitrogen (e.g. in aziridines).⁵¹ The isomerization rate increases very rapidly as the substituent Y is varied in the order: $RO^{\sim}R_2N < \text{halogen} < \text{alkyl} < \text{aryl} < \text{acyl}$. Substituents X on the imino carbon also increase the inversion rate in the following order: quinone ring < alkyl < acetyl < alkoxy carbonyl < aryl < methoxy < alkyl-thio < dialkylamino.⁵¹

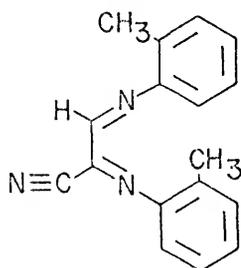
The fast inversion rate at nitrogen also explains why carbodiimides (106) do not form stable isomers. Inversion at the nitrogen is rapid by nmr time scale even at -100°C .⁵¹



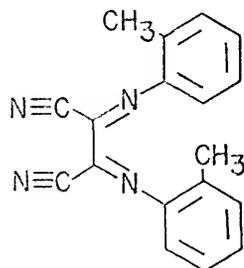
Finally, the variation of the nitrile band intensity in the infrared has still to be discussed. Throughout this chapter and Chapter I compounds 20 a-c and 68 have been indicated to show a very weak nitrile band in the infrared spectra. Other diimines, 107, 108, 109, and 89,⁶³ also show very weak nitrile bands in the infrared. The fact that 109 and 89 both show weak nitrile bands in the infrared



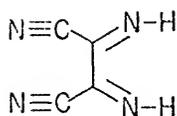
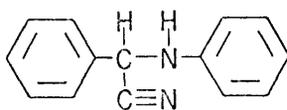
107



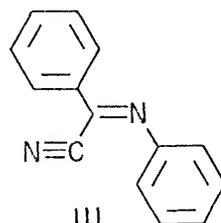
108



109

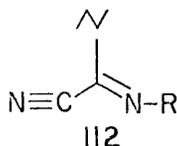
89⁶³

110



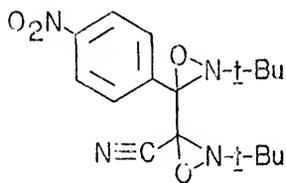
111

spectra indicate that the moiety 112 must be involved. To determine if conjugating the nitrile group with an imine

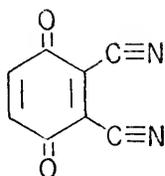
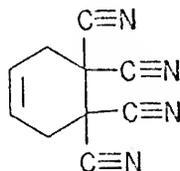


112

was the cause of weakening the intensity of the nitrile band in the infrared, compound 111 was prepared via the oxidation of 110. Compound 111 also had a very weak nitrile band but the intensity of the nitrile band in 110 was also greatly diminished. Compound 110 can be thought of as a glycinonitrile derivative. Inspection of the glycinonitrile derivatives listed in Sadtler Index⁷⁴ indicates that about one half of these compounds show very weak nitrile bands. Thus the moiety such as 112 was not the only cause of the weak nitrile bands. Three other compounds which show no appreciable nitrile bands in the infrared are 113, 114⁷⁵ and 115.⁷⁶ This definitely complicates the trend.



113

114⁷⁵115⁷⁶

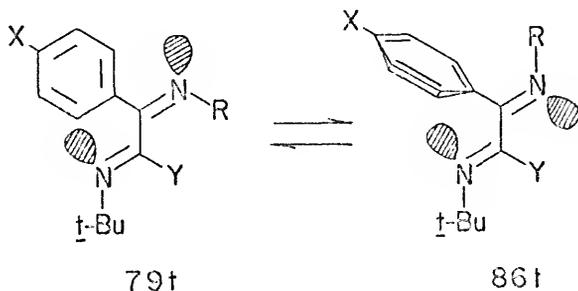
Other authors have been concerned with the variation of the intensity of the nitrile bands in the infrared. When the logarithm of the intensity of the nitrile bands of benzonitrile was plotted as a function of Hammett's σ factors a correlation was observed. As the electron-withdrawing power of the substituent increases the intensity of the nitrile band decreases.⁷⁷ Similarly it has been shown that the inductive

effect determines the intensity variations of the nitrile band in the methyl and halogen-substituted acetonitriles.^{7,8} Sandorfy et al.^{7,9} have suggested that two opposing effects take place on the dipole moment change during the vibrations of a nitrile group. The first effect is the charge separation during the stretching of the nitrile group in the sense ($C^+=N^-$). The second and opposing effect is that during the stretching of the $C\equiv N$ bond, the overlap of the nitrogen orbitals with the carbon orbitals becomes diminished. The nitrogen atom returns partially to the unhybridized state, the lone pair being pulled back to the nucleus and the bonding electrons toward the carbon atom. This process reduces the overall electric moment of the $(C\equiv N)$ group. There are thus two opposing effects on the dipole moment change during vibration, and their interplay will be strongly influenced by substituent effects. This explains the great variability of the intensity of this band.^{8,0}

Conclusion

The structure of 20 was proven to be derivatives of α -cyano-p-nitrophenylglyoxylidenedi-amine. The evidence was the resolution of the nmr spectra, confirmation of the nitrile group by Raman spectroscopy, the correct molecular weight, correct analysis, comparison to diimine prepared by other synthetic routes and the chemical evidence presented in Chapter I.

The anomalous nmr spectra of 20 a-c, 24a, 65 and 68 were explained by invoking an equilibrium between 79t (Z-s-trans-E conformer) and 86t (E-s-trans-E conformer). Conformer 79t was suggested based on the nmr spectrum



indicating a planar aromatic ring and an E conformation of the β -amine substituent with respect to the aryl group. The E conformation of the α -amine substituent with respect to the β -imine was suggested in order to relieve non-bonded interactions. Resonance arguments which invoke some double bond character to the central bond of the diimine system, steric arguments which indicate a decrease in 79t with an increase in the size of the Y group and the deshielding of the aldimine proton (Y-H) due to deshielding anisotropic effects of a completely conjugated system favor a completely planar configuration for 79.

Conformer 86t based on the nmr spectra was suggested to have an aromatic ring which was twisted with respect to the plane of the imine double bond. This skew aromatic ring was identified by its shielded protons ortho to the imine bond

caused by the interaction of these protons with the shielding cone of the imine double bond. The conformation of the β -imine substituent was suggested to be Z with respect to the aryl group in order to explain the cause of the non-planarity of the aromatic ring and the shielding of the β -imine substituent. The α -imine substituent was suggested to be E with respect to the β -imine in order to minimize non-bonded interactions. Due to resonance arguments the diimine system was proposed to be planar and therefore s-trans to eliminate non-bonded interactions.

Although model compounds allow for the prediction that 79 is a completely planar system with a Z-s-trans-E conformation and that 86 is a planar diimine system with a twisted aryl group with an E-s-trans-E conformation, there is no single piece of evidence which allows for the rigorous proof for the conformation of 86 or for that matter 79. The conformations of the model compounds are still in question,⁵² so even the foundations are weak. However, the evidence taken together lends merit to the assignments of the conformations of 86 and 79.

The nmr chemical shifts of all of the t-butyl groups and aldimine protons in compounds 20 a-c, 24a, 65, and 68 are presented for convenience in Table IV. Also the structures of other compounds discussed in this chapter along with the structures of the model compounds, their numbers, and the nmr chemical shifts for the imine substituents and aldimine protons are given in Scheme XXXVIII. This allows the reader a more concise view of the data.

Table IV
NMR Spectra of the Diimines

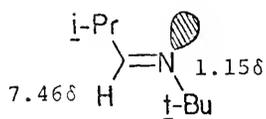
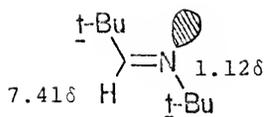
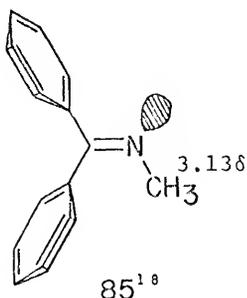
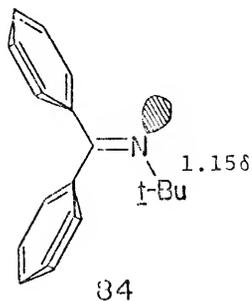
Compd. #	X=NO ₂		Compd. #	X=H		Y=H ppm(δ)	β-Me ppm(δ)	Y=H ppm(δ)
	α-t-Bu ppm(δ)	β-t-Bu ppm(δ)		α-t-Bu ppm(δ)	β-t-Bu ppm(δ)			
20a	1.33	1.19	20a	1.57	1.40	-	-	-
20b	1.29	-	20b	1.50	-	-	-	-
20c	1.39	-	20c	1.58	-	-	3.53	-
24a	1.15	1.10	24a	1.30	1.40	-	-	8.39
X=H								
65	1.13	1.10	65	1.32	1.37	-	-	8.32
68	1.31	1.16	68	1.55	1.40	-	-	-

Compd. #	R		Y
	X	t-Bu	
20a	NO ₂	t-Bu	C≡N
20b	NO ₂	2,6(CH ₃) ₂ C ₆ H ₃	C≡N
20c	NO ₂	CH ₃	C≡N
24a	NO ₂	t-Bu	H
65	H	t-Bu	H
68	H	t-Bu	C≡N

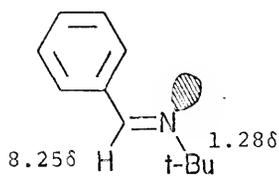
Chemical structure of a diimine with a para-substituted phenyl ring (X), an R group, and a tert-butyl group (t-Bu). The alpha and beta carbons are labeled.

Chemical structure of a diimine with a meta-substituted phenyl ring (X), an R group, and a tert-butyl group (t-Bu). The alpha and beta carbons are labeled.

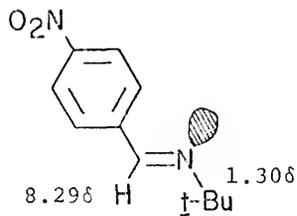
Scheme XXXVIII (continued)

81a⁵³81b⁵⁴85¹⁸

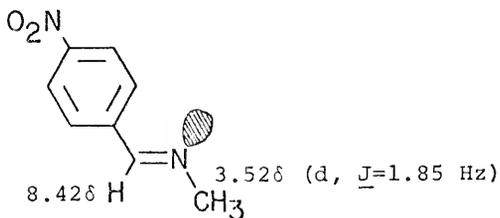
84



75



18a



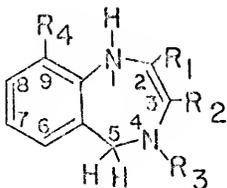
18c

The data and results presented here require a reexamination of the previous literature findings. At the same time further examples of diimine systems should be prepared to determine the limit for the substituent on the β -imine nitrogen before only 79t is observed. It would also be interesting to check the limit for the size of Y before 86t becomes unfavorable and the diimine system loses its coplanarity.

CHAPTER III

4,5-Dihydro-1H-1,4-benzodiazepines (118)

Introduction



118

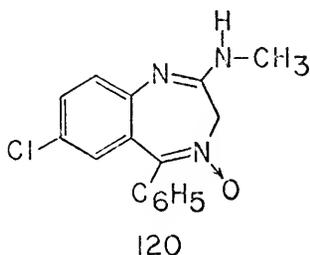
Benzodiazepines are bicyclic compounds having a benzene nucleus fused to a seven-membered ring containing two nitrogen atoms.⁸¹ Benzodiazepines are numbered as shown in formula 118, starting at the position adjacent to the carbocyclic ring, regardless of the positions of the nitrogen atoms.⁸² The latter are specified by prefixed numbers giving the lowest possible total; e.g., 118 is a 1,4-benzodiazepine. The term benzodiazepine implies a maximum degree of unsaturation, i.e., a total of three double bonds in the seven-membered ring. The position of the odd hydrogen atom (even if occupied by another mono- or divalent substituent) is indicated by the term 1H, 2H, 3H, etc. In dihydro- and tetrahydrobenzodiazepines the odd hydrogen is given the lowest possible number. This is, however, complicated by the fact that the first consideration is given to the

functional group which is expressed as a suffix to the name of the compound; e.g., 119 is a 4,5-dihydro-3H-1,4-benzodiazepin-3-one (indicated H assigned to the position of the

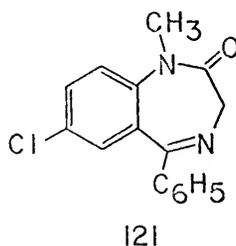


3-one group) but 118 is a 4,5-dihydro-1H-1,4-benzodiazepine (indicated H given the lowest possible numerical value in the absence of a substituent named as a suffix.)⁸¹

The discovery of Librium[®] (120), Valium[®] (121), Serax[®] (122), and Mogadon[®] (123) as psychosedative and tranquilizing agents resulted in an extensive investigation of the chemical and biological properties of these new compounds and their derivatives which belong to the class of the 1,4-benzodiazepines.^{81, 83} Among the large number of benzo-



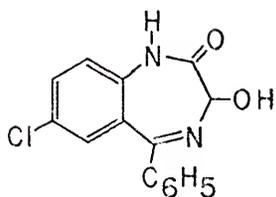
chlorodiazepoxide⁸⁴



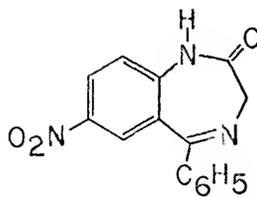
diazepam⁸⁴

diazepines that have been synthesized, only members of the 1,4-benzodiazepines group have shown sufficient pharmaco-

logical and clinical activity to warrant introduction as



122

oxazepam⁸⁴

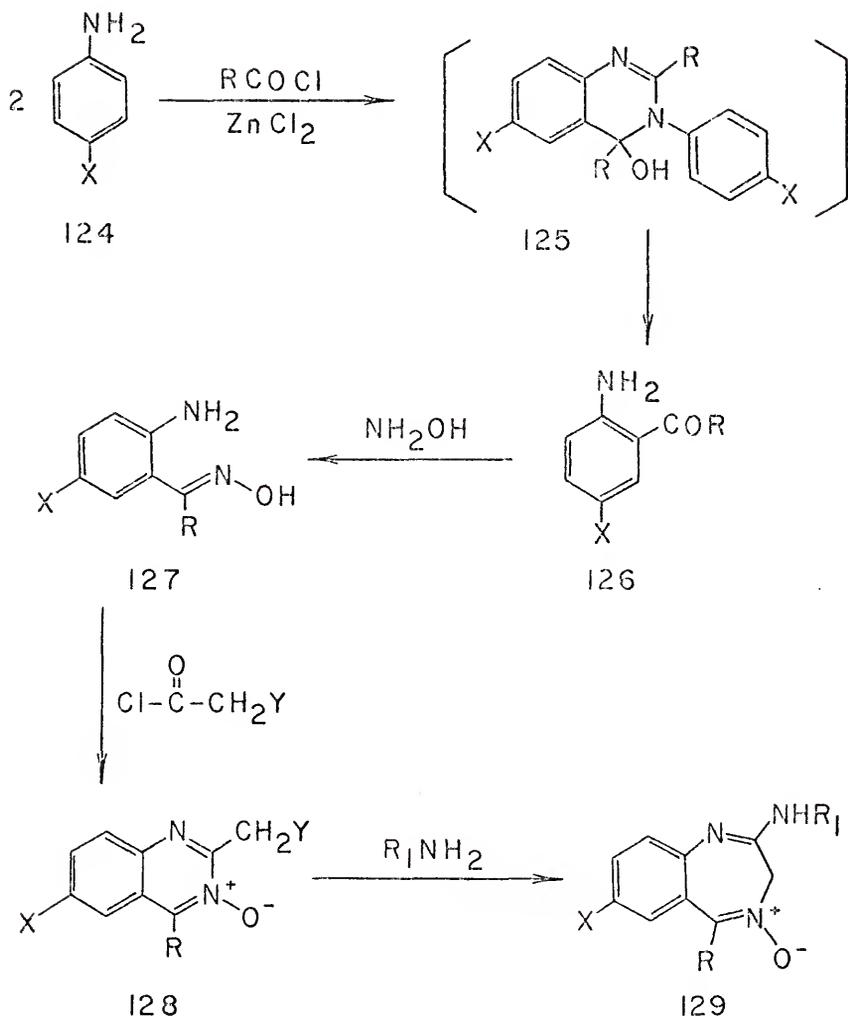
123

nitrazepam⁸⁴

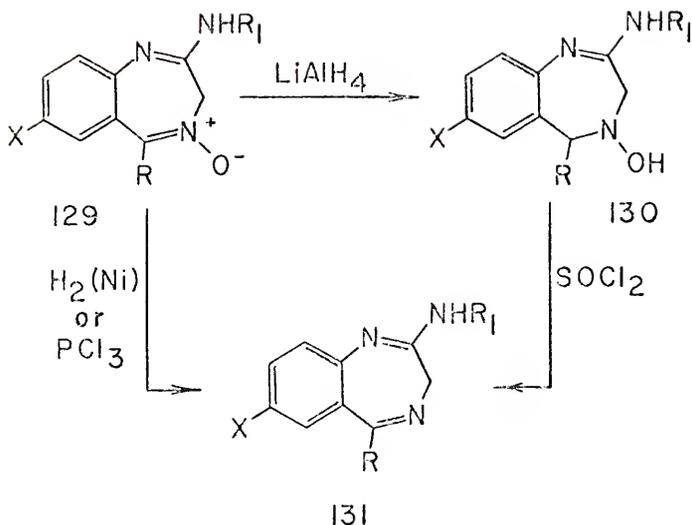
new drugs.⁸¹

The group of 1,4-benzodiazepines which have been most extensively explored are the 2-amino-1,4-benzodiazepine 4-oxides because of their pharmacological activity. The most widely used route to these compounds was the ring enlargement of quinazoline 3-oxides 128, when treated with ammonia or primary aliphatic amines, or hydrazine,^{81,85,86} Scheme XXXIX. Weakly basic aromatic amines (e.g., aniline) did not yield benzodiazepine 4-oxides (129), and only two secondary amines, dimethylamine and pyrrolidine, have been reported to cause ring enlargements to compounds of type 129, having a tertiary amino group in position 2. Compound 129 could be reductively deoxygenated,⁸¹ Scheme XL.

Scheme XXXIX



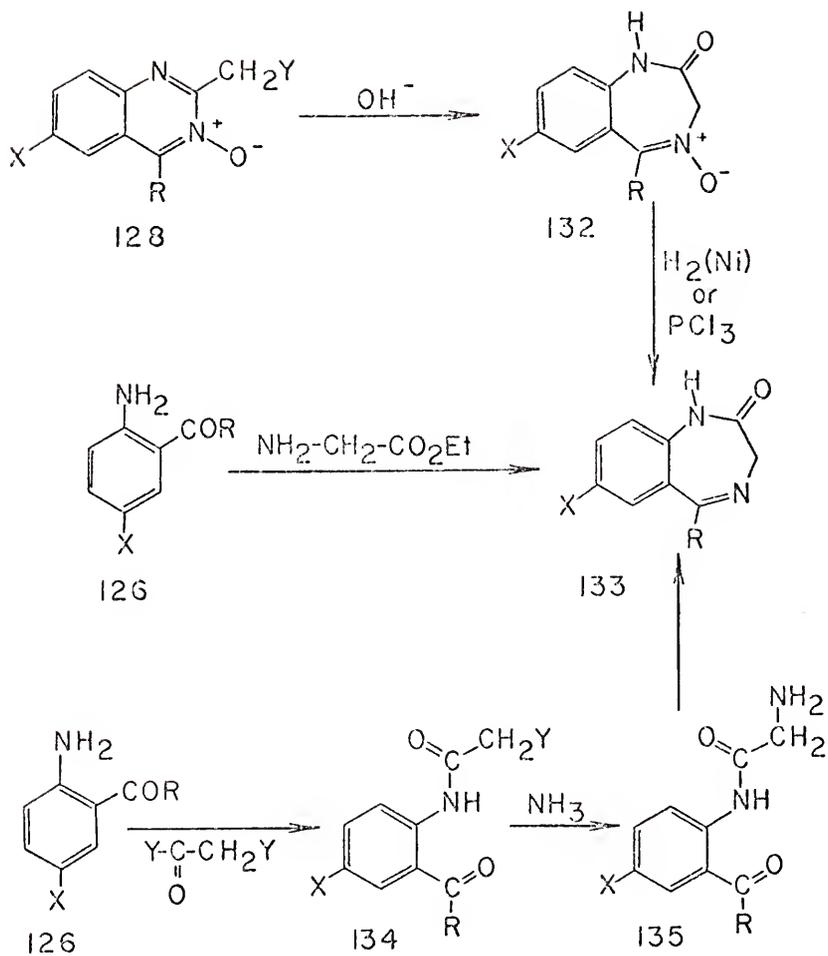
Scheme XL



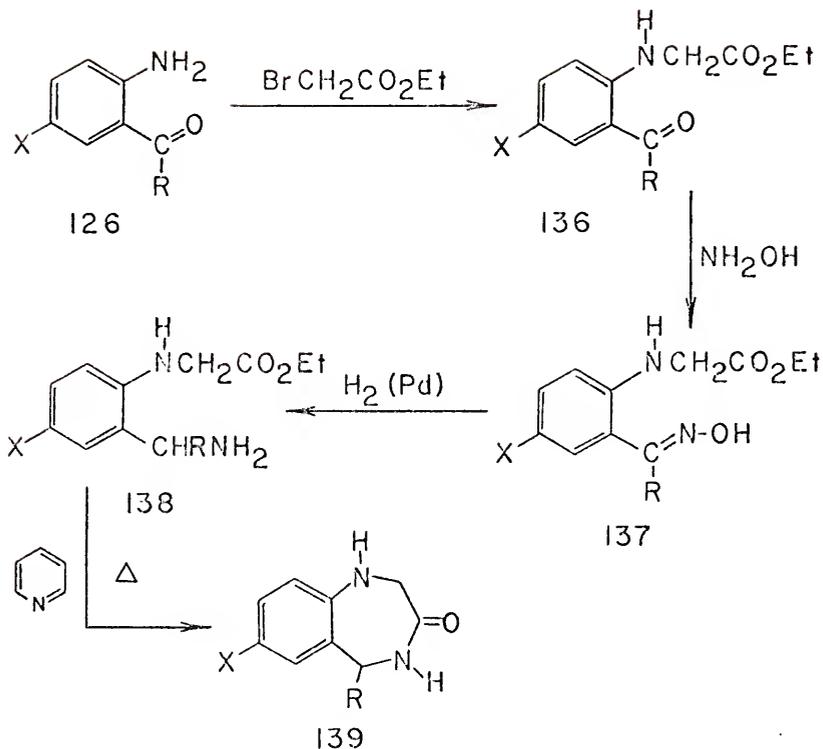
1,4-Benzodiazepin-2-one 4-oxides (132) have been obtained by ring enlargement of quinazoline 3-oxides (128) or treatment with aqueous sodium hydroxide. The N-oxide oxygen can be removed by catalytic hydrogenation over Raney nickel or with phosphorus trichloride. However, 1,4-benzodiazepin-2-ones (133) may be obtained directly from 2-aminobenzophenone (126) and glycine ester or an α -halo-acid halide,⁸¹ Scheme XLI.

3H-1,4-Benzodiazepin-3-one 139 is synthesized from 2-aminobenzophenone (126) as shown in Scheme XLII.⁸¹ Apparently this represents the only route to this compound.

Scheme XLI



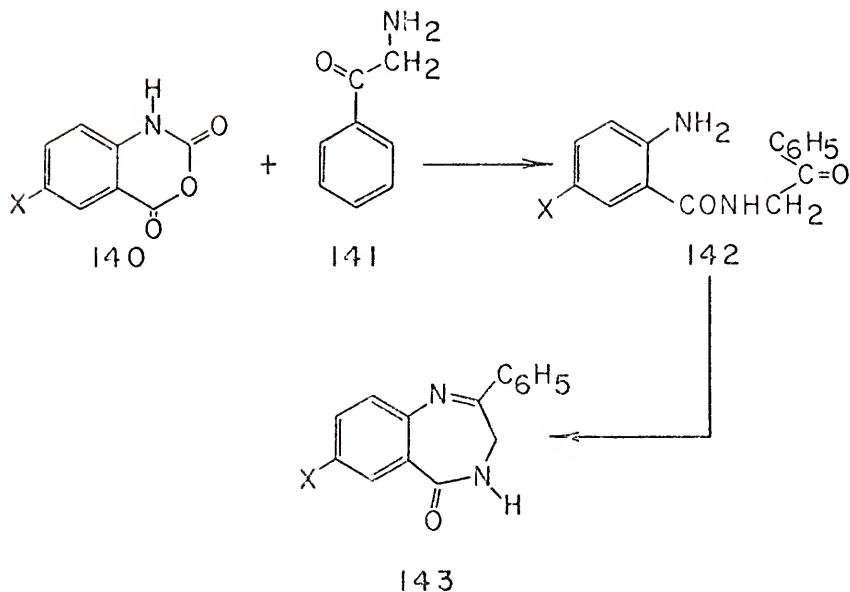
Scheme XLII



The 1,4-benzodiazepin-5-one 143 is prepared from the cyclization of 142, Scheme XLIII. Other cyclizations of a similar type also yield the 1,4-benzodiazepin-5-one (143).⁸¹

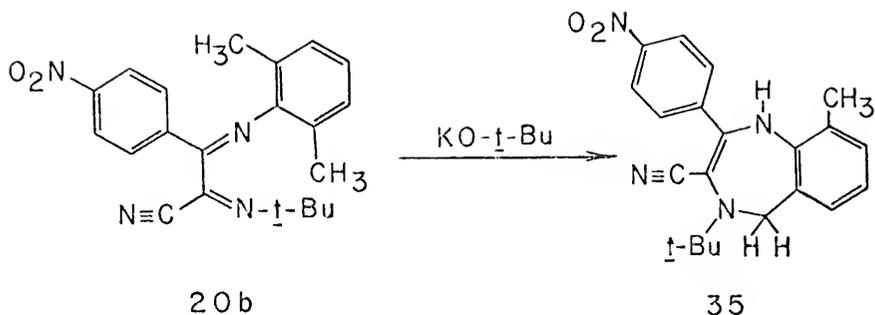
1,4-Benzodiazepines without functional groups on the 2-position have been made by the reduction of suitable benzodiazepinones. However, a number of direct syntheses have also been described.⁸¹

Scheme XLIII



The foregoing discussion was designed to indicate the types of reaction and the complexities involved in order to obtain 1,4-benzodiazepines. The discussion also implied the limitation of these reactions. For instance, since 1,4-benzodiazepines are generally prepared by reduction of the corresponding benzodiazepinone, substituents that are easily reduced (e.g., NO_2 , $-\text{C}=\text{O}$, $\text{C}\equiv\text{N}$, etc.) would not survive this reaction.

In Chapter I, a 4,5-dihydro-1H-1,4-benzodiazepine (35) ring was described which was obtained by the base catalyzed cyclization of 20b.



This appears to be the first example of a 4,5-dihydro-1H-1,4-benzodiazepine.

It is the intent of this work to optimize the conditions for the conversion of 20b to 35. Other diimines would then be prepared with the requisite *o*-tolyl or 2,6-dimethylphenyl group attached to one of the imine nitrogens. The generality and limitations of the reaction would then be determined. Since other 1,4-benzodiazepines display biological activity, the 1,4-benzodiazepines prepared in this research will be submitted to similar tests.

Discussion

The discovery of this cyclization was rather fortuitous. The Diels-Alder reaction of 20b with *p*-benzoquinone had failed. As a result ketene diethylacetal was used for the desired transformation to a Diels-Alder adduct. However, the desired reaction failed, but gave instead a base catalyzed cyclization to a 1,4-benzodiazepine (35) in a 53%

yield. The base was potassium t-butoxide used to stabilize the ketene diethylacetal.

In order to optimize the yield it was necessary to determine if the ketene diethylacetal was needed. The reaction was set up as before without the ketene diethylacetal, but with potassium t-butoxide and some t-butyl alcohol. The reaction worked but with an inferior yield. In order to see if the temperature was important a similar reaction was set up in refluxing benzene. The reaction failed indicating that the temperature of 160-170°C was important. Table V summarizes the reactions attempted and the results.

A different solvent was needed which had a boiling point between 160-170°C and was easily removed from the desired product. Diglyme (diethylene glycol dimethylether) seemed attractive since the boiling point was 161°C and the solvent which is very soluble in water thereby could be removed from the product. Table V summarizes the results of these reactions. Scheme XLIV recapitulates the mechanism proposed in Chapter I, Scheme XXI, for the conversion of 20b to 35.

The optimum conditions seemed to be refluxing 20b in diglyme with potassium t-butoxide for 10 hours. t-Butyl alcohol did not seem to be necessary.

In compound 20b there are three possible groups which may be varied: the p-nitrophenyl group, cyano group, and the t-butyl group. The 2,6-dimethylphenyl group cannot be altered except to remove one of the methyl groups (i.e., o-tolyl).

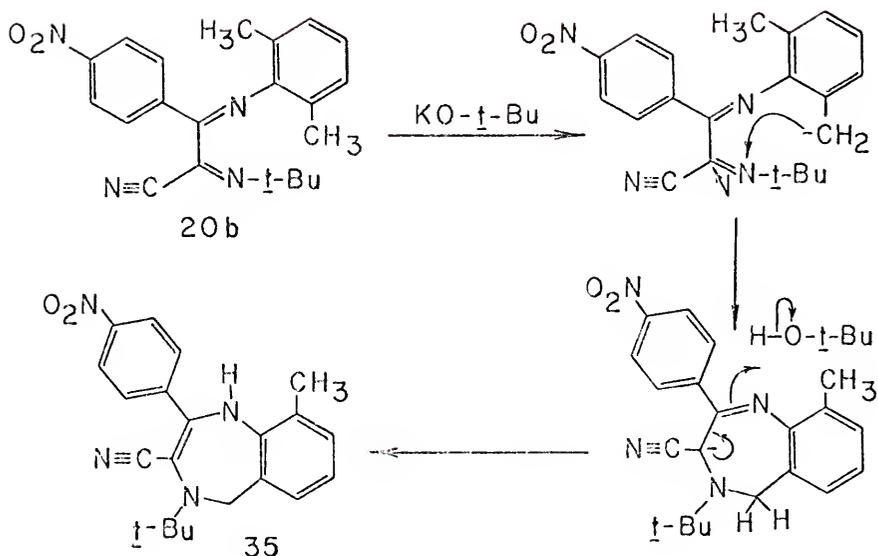
Table V

Optimization Reaction for 35

Reaction Number	Components besides <u>20b</u>	Solvent	Temp °C	Time hr	Yield %
1	Ketene diethylacetal and KO-t-Bu	C ₆ H ₆	160-170°	7 hr	53
2	KO-t-Bu/HO-t-Bu	C ₆ H ₆	160-170°	7 hr	35
3	KO-t-Bu/HO-t-Bu	C ₆ H ₆	81°	7 hr	No reaction
4	KO-t-Bu/HO-t-Bu	Diglyme ^a	161°	3 hr	Reaction only 50% complete by nmr spectrum
5	KO-t-Bu/HO-t-Bu	Diglyme	161°	7 hr	Reaction only 75% complete by nmr spectrum
6	KO-t-Bu/HO-t-Bu	Diglyme	161°	10 hr	62
7	KO-t-Bu	Diglyme	161°	10 hr	Results similar to reaction <u>6</u>

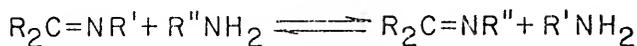
^aDiethylene glycol dimethylether

Scheme XLIV

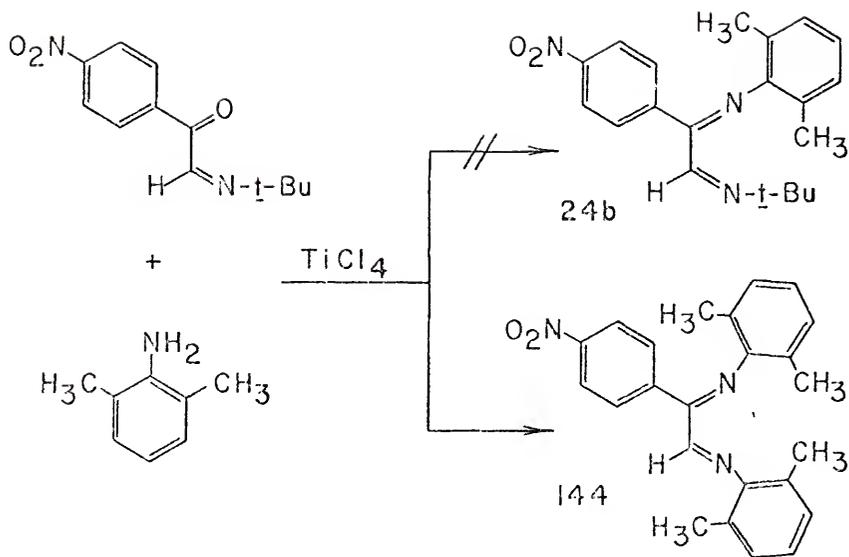


It seemed that the easiest diimine to prepare would be **24b**, Scheme XLV. Compound **23**, it was thought, ought to react with 2,6-dimethylaniline in the presence of titanium (IV) chloride¹⁸ to give **24b**. Unfortunately, the *t*-butylimine portion exchanged with 2,6-dimethylaniline to give **144** instead.

It has been shown in the literature that amino compounds will exchange with existing imine compounds to form a new imine compound.⁸⁷ The formation of the new imine bond depends on the equilibrium



Scheme XLV

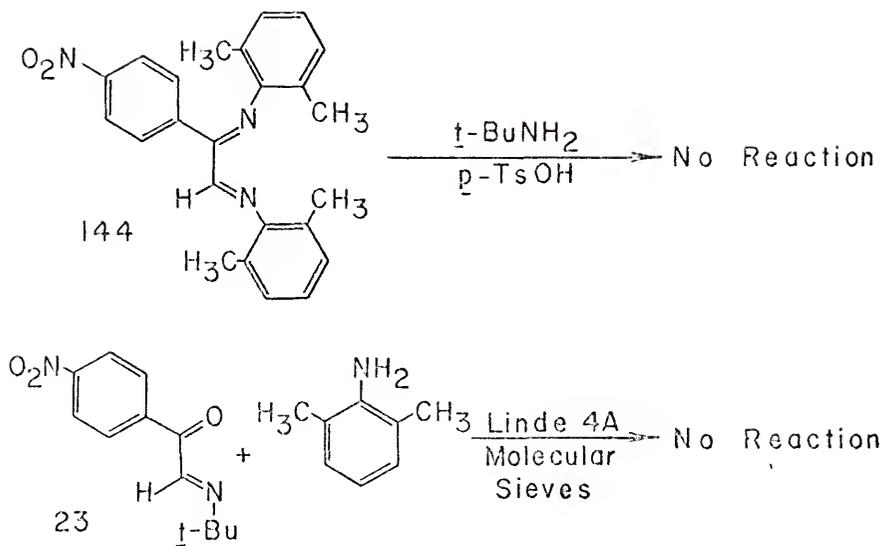


Thus, compound 144 was refluxed with *t*-butylamine in the presence of *p*-toluenesulfonic acid to form 24b. No reaction took place. Reaction of 23 with 2,6-xylylidine using Linde 4A molecular sieves as a dehydrating agent also failed to yield 144,⁸⁸ Scheme XLVI.

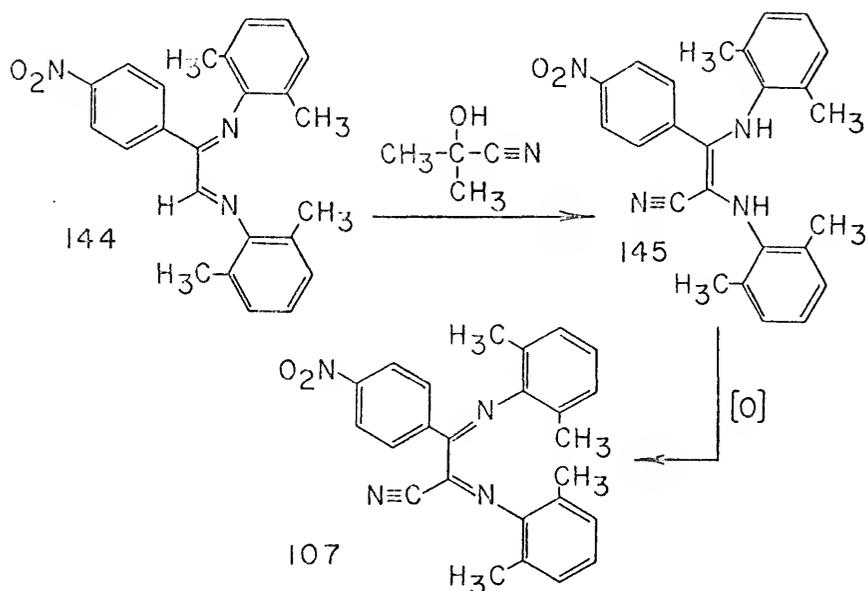
Compound 144 did however react with acetone cyanohydrin to yield 145 which oxidized during purification to 107, Scheme XLVII.

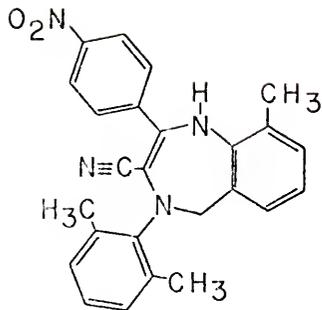
Compound 107 was reacted with potassium *t*-butoxide in diglyme for 10 hours. The nmr spectrum indicated that the desired product formed, 146 or its isomer 147, in low yield. Compound 144 was reacted under similar conditions and no reaction was obtained.

Scheme XLVI

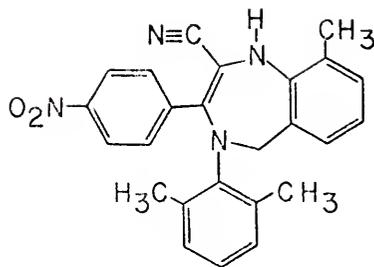


Scheme XLVII





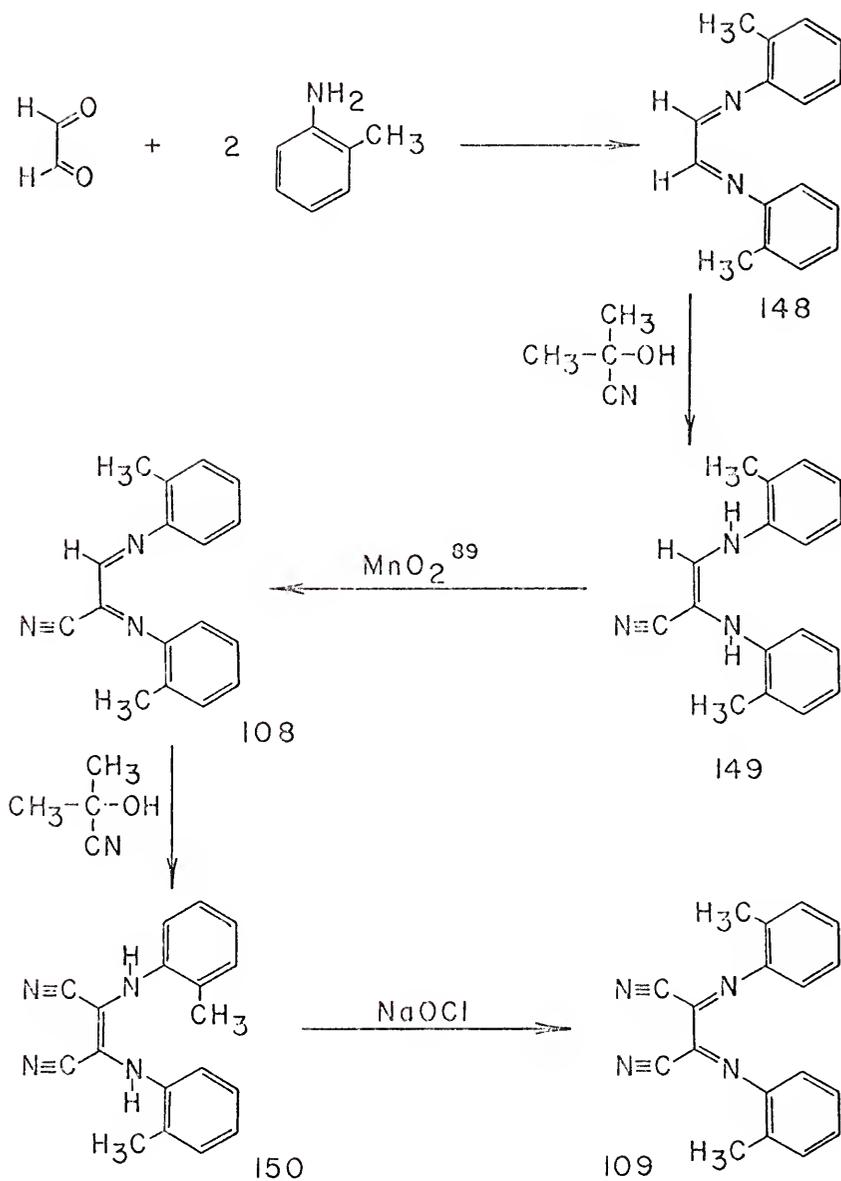
146

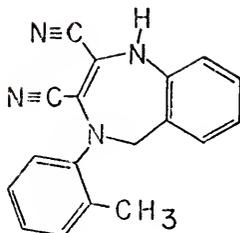


147

At this point *o*-toluidine was reacted with glyoxal to form the diimine 148. From this compound a series of compounds was prepared, 108 and 199, Scheme XLVIII. When compounds 148 and 108 were refluxed with potassium *t*-butoxide in diglyme only tar was obtained. Compound 109 seemed to react very rapidly in the refluxing medium and actually formed a large amount of tar in 5 minutes at reflux temperature. However, the nmr spectrum indicated that the desired product (151) may have formed in low yield. The reaction was repeated except the temperature was room temperature and the time was extended to 1 hour. The nmr spectrum of the reaction mixture indicated a cleaner reaction; however the yield appeared to be low for 151.

Scheme XLVIII



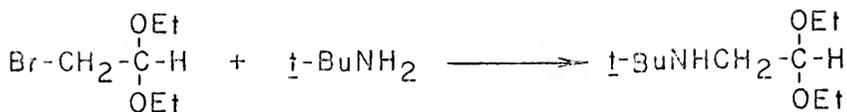


151

Thus far, the diimines that were prepared by alternative routes to 20b were substituted with the same group on both imine nitrogens. It appeared that the t-butyl group was important to some extent in order for the benzodiazepine to form. Diimines were needed with a t-butyl group on one imine nitrogen and a o-tolyl group on the other imine nitrogen. To this end other synthetic routes were investigated.

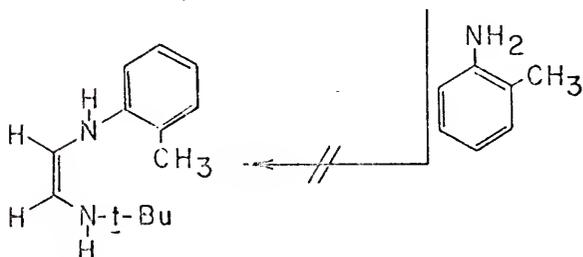
Using the method of Jones, et al.,⁹⁰ t-butylamine was reacted with α -bromoacetaldehyde diethylacetal (152) to give α -t-butylaminoacetaldehyde diethylacetal (153). Under a variety of conditions⁹¹ o-toluidine would not react with 153 to give 154, Scheme XLIX.

Scheme XLIX



152

153

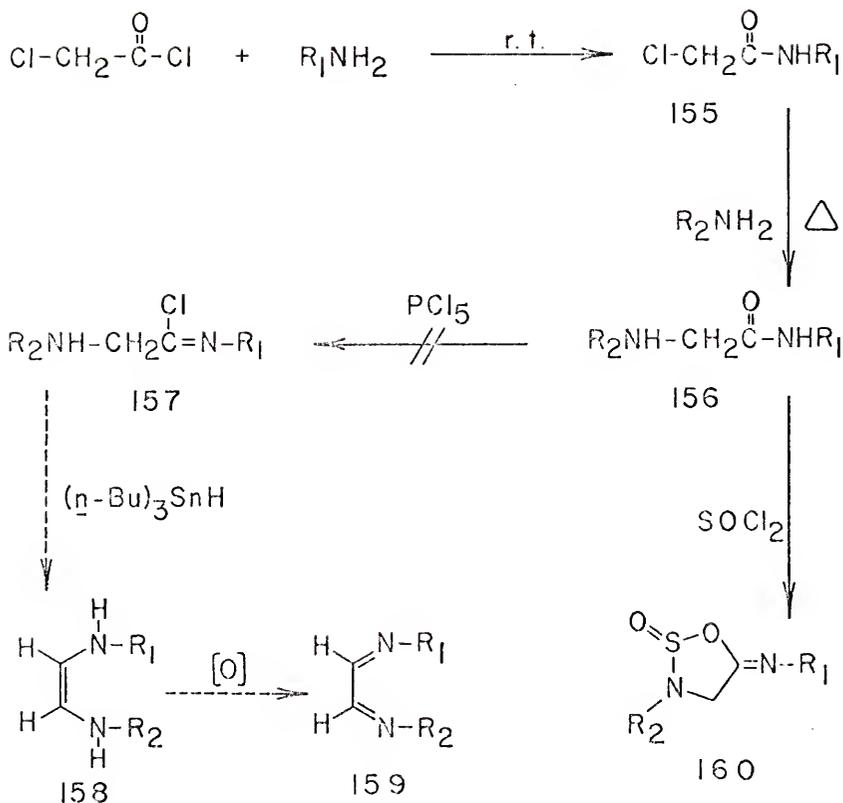


154

Other synthetic routes were proposed. It is known that amides react with phosphorus pentachloride, or phosgene, or thionyl chloride to form imidoyl chlorides (157).⁹² It was proposed to react the imidoyl chloride with a hydride (e.g., tri-*n*-butyl tin (IV) hydride) to produce a diamino ethylene compound (158). This could be oxidized to the diimine 159, Scheme L.

When 2-aminoacetamide (156) reacted with phosphorus pentachloride or thionyl chloride the desired product 157 did not form. With phosphorus pentachloride only a tar could be isolated,⁹² but with thionyl chloride a new product was isolated,⁹¹ a 5-imino-2-oxo-1,2,3-oxathiazolidine (160). Chapter IV covers the formation of the oxathiazolidines.

Scheme I

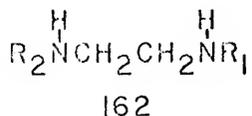


Until recently α -aminoketenimines 161 were unknown.⁹³ This class of compounds was thought to be of interest because of an expected facile rearrangement to an unsymmetrical diimine (159).



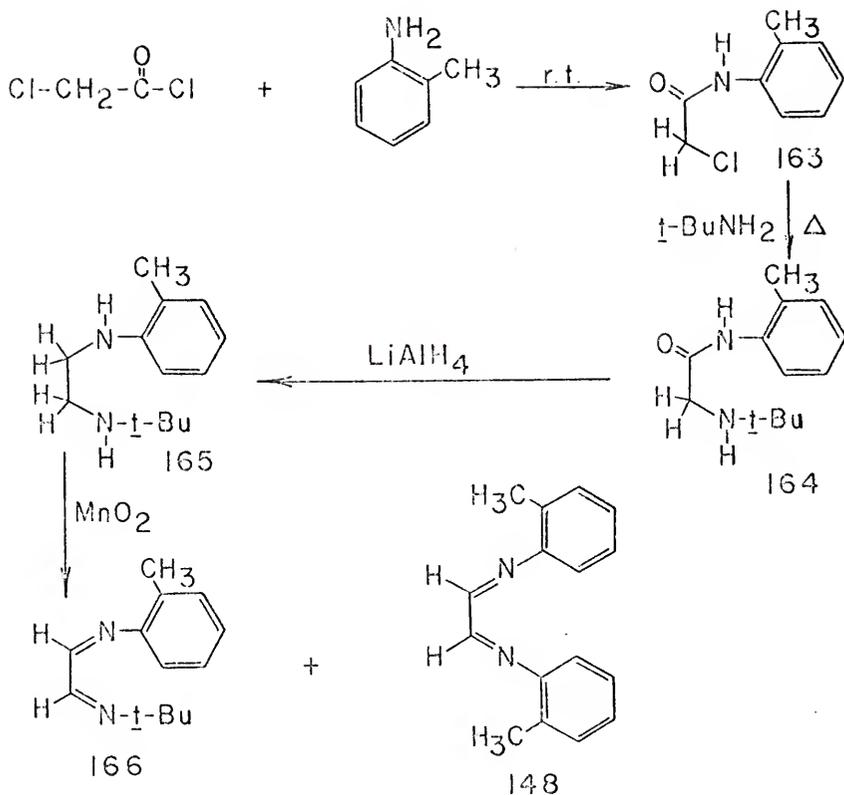
Stevens and Singhal⁹⁴ have shown that phosphorus pentoxide is an excellent dehydrating agent for the preparation of ketenimines. Applying their procedure to the present case using a 2-aminoacetamide and two and a half equivalents of phosphorus pentoxide yielded only tar and some starting material.⁹¹

Refusing to admit defeat, another idea was tried. If one could reduce the 2-aminoacetamide 156 to the ethylenediamine (162) then this compound might be oxidized to the unsymmetrical diimine (159).

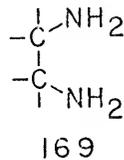
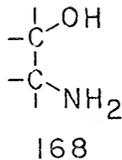
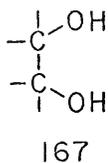


Specifically, α -chloroacetyl chloride was reacted with o-toluidine to product 2-chloroacet-o-toluidide (163). Compound 163 reacted with t-butylamine to give 2-t-butylaminoacet-o-toluidide (164). This compound was reduced with lithium aluminum hydride to give 165 which in turn was oxidized with manganese dioxide⁸⁹ to give the unsymmetrical diimine 166 in low yield, Scheme LI. Apparently, cleavage of the diamine to 148 is an important reaction with this

Scheme LI



oxidizing agent. Similar cleavage reactions have been shown to take place with lead tetraacetate and the following moieties:⁹⁵



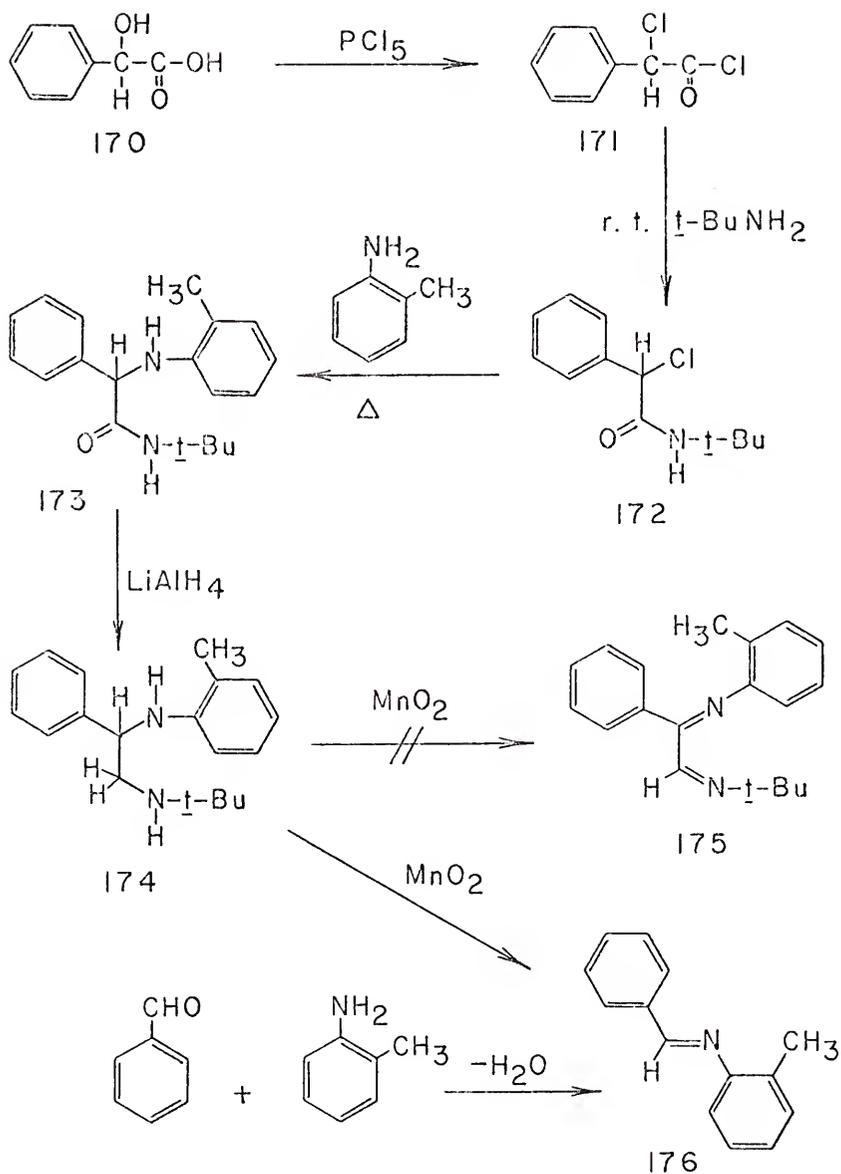
The simplest mechanism to account for the formation of 148 from 165 is proposed in Scheme LII. The mechanism is based on the mechanism proposed by Pratt and McGovern,⁸⁹ and literature references cited therein, for converting N-substituted benzylamines to N-substituted benzylidene amines with activated manganese dioxide.

Reaction of 166 with potassium t-butoxide in refluxing diglyme gave only tar. The results were similar to that of 148 conducted in similar reaction conditions.

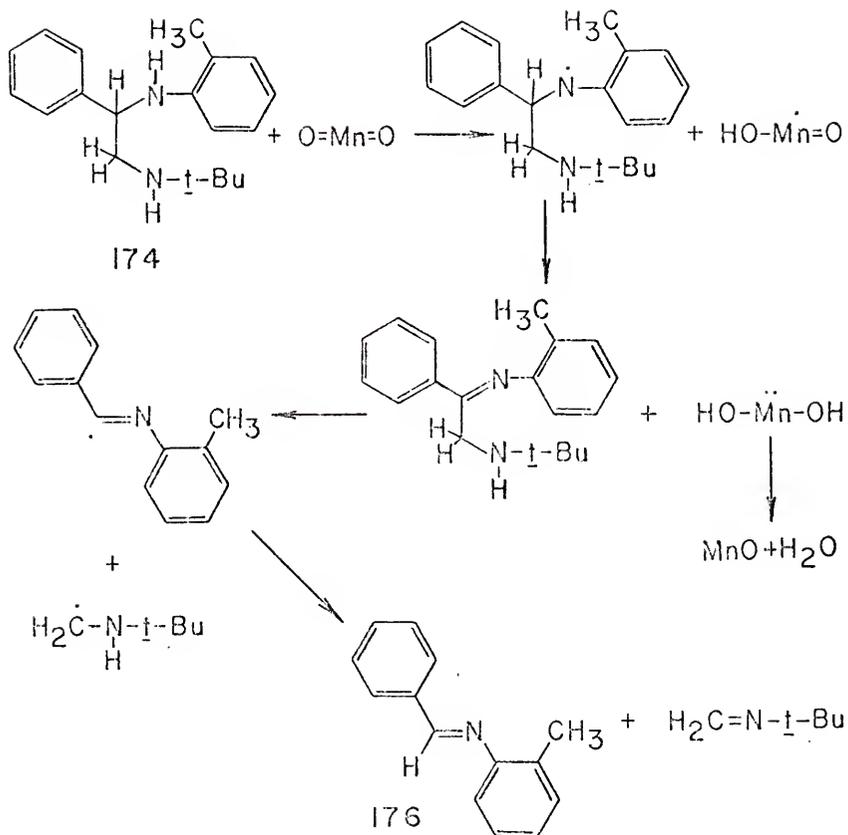
One further compound, phenylglyoxylidene- α -t-butylamine- β -(o-toluidine) (175) looked appealing as a precursor to a 1,4-benzodiazepine. The preparation of this product was similar to that by which 166 was obtained.

From D,L-mandelic acid (170) and phosphorus pentachloride was prepared 2-chlorophenylacetylchloride⁹⁶ (171). This compound was reacted with t-butylamine to give the amide 172 which is refluxed for 3 days with o-toluidine to give the 2-amino amide 173. Compound 173 was reduced during 638 hours to the diamine 174. However, oxidation with manganese dioxide⁸⁹ formed the cleavage product benzylidene-o-toluidine (176) in high yield. This product formed in preference to the desired product 175, Scheme LIII. The simplest mechanism which accounts for 176 from the oxidation of 174 is proposed in Scheme LIV.

Scheme LIII



Scheme LIV

Conclusion

Although the conditions were optimized for the conversion of 20b into 35, other available diimines failed to react efficiently in this reaction medium. Therefore, it can be said that this reaction is not general for all diimines bearing at least one o-tolyl or 2,6-dimethylphenyl sub-

stituent attached to an imine nitrogen. The results of these reactions are summarized in Table VI.

In the absence of recognizable products it is difficult to come to a firm conclusion on the roles played by the nitrogen substituent, the cyano group and the *p*-nitrophenyl group. The potential interest in these compounds warrants additional work to ascertain the scope and utility of these and related cyclizations. However, these facts must be examined in terms of the proposed mechanism.

In order to explain the formation of the 1,4-benzodiazepine 180 from the diimine 177, it has been suggested in Scheme LV, and similarly in Scheme XXI and XLIV, that the generated methylene carbanion must attack the imine nitrogen (e.g. path a, 178). This is very unusual, because it has been shown in the literature⁹⁷ that Grignard reagents and alkyllithium reagents attack the carbon atom of an imine system, Scheme LVI. One would have expected in view of these reactions, path b, 172, Scheme LV. However, no evidence for products indicative of path b, Scheme LV were observed.

It is clear that the negative charge of 180 must be stabilized and that the various substituents (nitrile, *p*-nitrophenyl, etc.) can contribute to this stabilization. It is also possible that the geometry required for the symmetry-allowed conrotatory electrocyclic reaction⁷⁰ (178→180) is particularly favorable.⁹⁸

Table VI

Reaction Parameters for the Preparation of 1H-1,4-Benzodiazepines



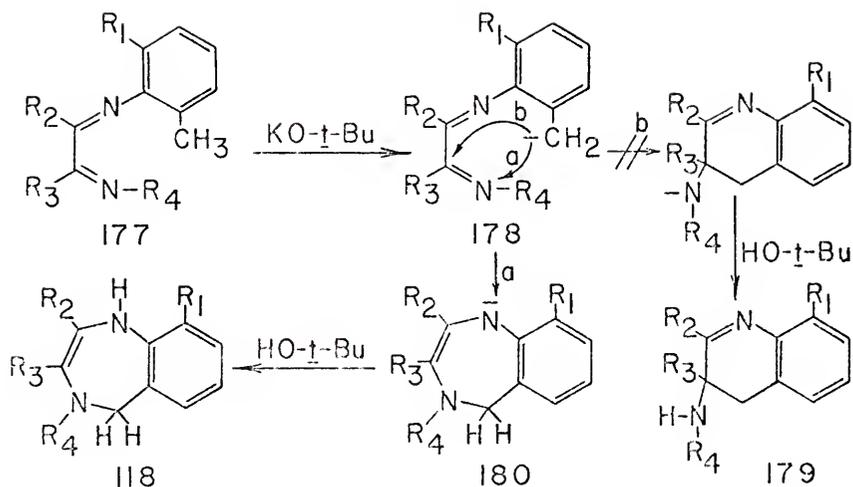
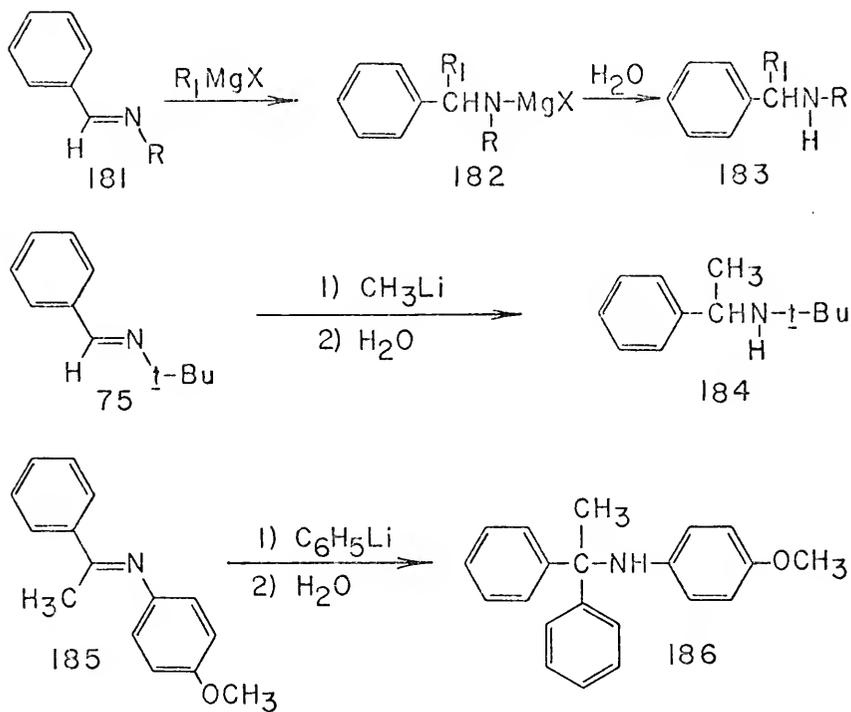
Starting Diimine No.	R ₁	R ₂	R ₃	R ₄	Time hr.	Product No.	Yield %
20b	CH ₃	<u>p</u> -NO ₂ C ₆ H ₄	CN	<u>t</u> -Bu	10	35	62
107	CH ₃	<u>p</u> -NO ₂ C ₆ H ₄	CN	2,6-(CH ₃) ₂ C ₆ H ₃	10	146	a
144	CH ₃	<u>p</u> -NO ₂ C ₆ H ₄	H	2,6-(CH ₃) ₂ C ₆ H ₃	10	-	No reaction
148	H	H	H	<u>o</u> -CH ₃ C ₆ H ₄	1	-	tar
166	H	H	H	<u>t</u> -Bu	7	-	tar
108	H	H	CN	<u>o</u> -CH ₃ C ₆ H ₄	1	-	Other products
109	H	CN	CN	<u>o</u> -CH ₃ C ₆ H ₄	1/12 (5 _a min) 1 _b	151	very low c

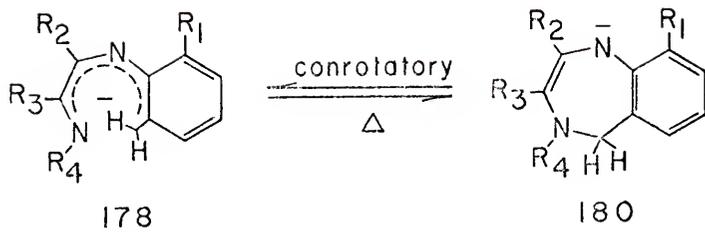
^aThe yield is low, but product appears to be present by its nmr spectrum.

^bThe reaction was conducted at room temperature.

^cThe nmr spectrum indicated that some product formed, but the yield is low.

Scheme LV

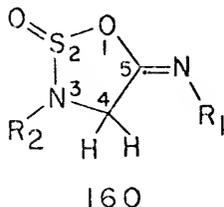
Scheme LVI⁹⁷



CHAPTER IV

5-Imino-2-oxo-1,2,3-oxathiazolidines (160)

Introduction

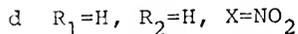
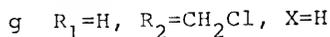
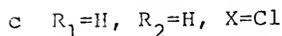
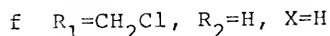
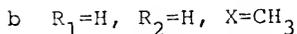
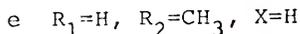
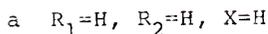
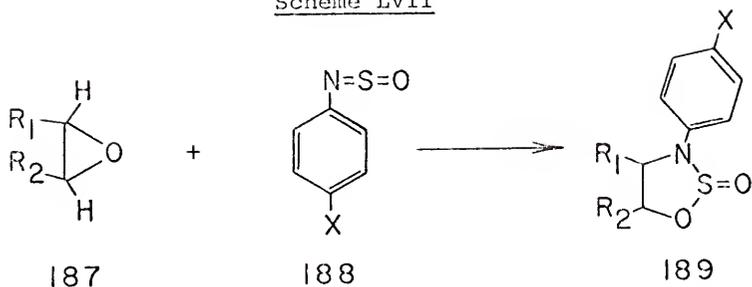


An oxathiazolidine is a five-membered heterocyclic ring containing a single oxygen, sulfur, and nitrogen atom. The numbering of the ring begins with the heteroatom of highest priority ($O > S > N$) and proceeds around the ring so as to give other hetero atoms or substituents the lowest numbers possible. Thus compound 160 is a 1,2,3-oxathiazolidine. The suffix -olidine implies a completely saturated system.⁹⁹

The earliest literature example¹⁰⁰ of the preparation of a 2-oxo-1,2,3-oxathiazolidine (189) was reported by Etlis, et al. (187) with thionylanilines (188) and a catalytic amount of tetraethylammonium bromide in sealed ampules at 95-100°C, Scheme LVII. A couple of isolated reports soon followed their example, but were not of a generalized nature.^{101,102}

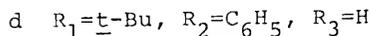
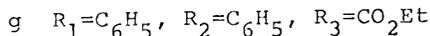
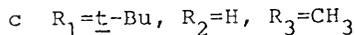
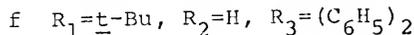
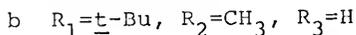
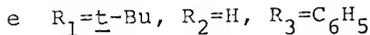
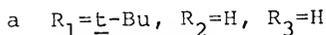
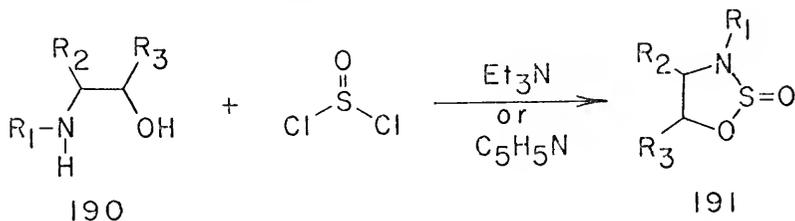
Recently Deyrup and Moyer¹⁰³ found that β -amino

Scheme LVII



alcohols (190) reacted with thionyl chloride in the presence of base to yield 2-oxo-1,2,3-oxathiazolidines (191), Scheme LVIII. They also revealed that 191 b-d were isolated as isomeric pairs. The asymmetric nature of the 2-oxo-1,2,3-oxathiazolidines was ascribed to the asymmetry at sulfur.

Scheme LVIII



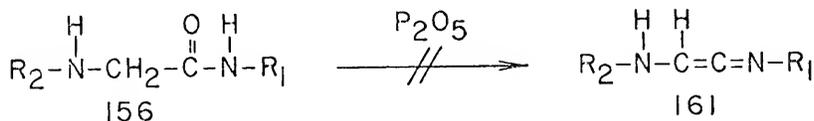
In this chapter another general procedure to 2-oxo-1,2,3-oxathiazolidines is described. Specifically the reaction of 2-aminoacetamides with thionyl chloride followed by the addition of pyridine leads to 5-imino-2-oxo-1,2,3-oxathiazolidines (160) in good to excellent yields. Evidence is presented towards the elucidation of the general structures of these compounds.

Discussion

A desire to prepare conjugated 1,2-diimines with a different substituent on each imine nitrogen 159 led to a consideration of α -diminoketenimines 161 as precursors. It was hoped that 161 could be prepared from 2-aminoacetamides



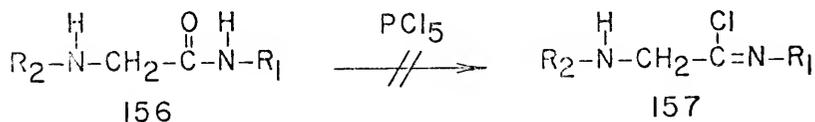
(156) and that tautomerism of 161 would lead to 159. A procedure similar to that described by Stevens and Singhal⁹⁴ using phosphorus pentoxide⁹¹ failed to yield tractable material.



A related route to the α -aminoketenimine (161) utilizes an imidoyl chloride (157) followed by dehydrochlorination with a tertiary amine. In a modification of the procedure described by Stevens and French¹⁰⁴ 2-aminoacetamide (156)



was reacted with phosphorus pentachloride. The resulting brown slurry was treated with excess triethylamine and after removing the solvents only an intractable tar was isolated. Since under the reaction conditions the hydro-



chloride salts might precipitate from solution and thus prevent the desired reaction, our attention then turned to thionyl chloride. This reagent is also known to produce imidoyl chlorides⁹² and the hydrochloride salts of the 2-amino group might remain in solution due to its polarity. In addition, the by-products of the reaction would be gases and would allow easier purification of the products.

The 2-aminoacetamides were dissolved in an excess of thionyl chloride and refluxed for two hours. After this period the excess thionyl chloride was removed in vacuo and the resulting oil slurried with dry benzene. To the slurry was added an excess of triethylamine and this was allowed to stir for two hours at room temperature. From the brown oil which resulted, a product was isolated in low yield which according to mass spectral analysis had the atoms of the starting 2-aminoacetamide and the element S=O, but the molecule was missing the original N-H protons. The

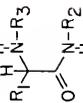
product was assigned the 5-imino-2-oxo-1,2,3-oxathiazolidine structure (160). This represents the first time that an imino group has been built into the 2-oxo-1,2,3-oxathiazolidine heterocyclic ring structure.¹⁰⁰⁻¹⁰³

A variety of 2-aminoacetamides were prepared and the experimental procedure was modified to obtain the 5-imino-2-oxo-1,2,3-oxathiazolidine in good to excellent yields.

The 2-aminoacetamides (194) were prepared from the corresponding 2-chloroacetamides (193) by refluxing 193 in benzene with an excess of the primary amine. Table XI in the Experimental Section summarizes the yields and physical properties of these 2-aminoacetamides (194). The spectral properties of the 2-aminoacetamides are listed in Table VII.

The conversion of the 2-aminoacetamides 194 to the 5-imino-2-oxo-1,2,3-oxathiazolidine 195, Scheme LIX was best accomplished by their reaction with thionyl chloride in dry benzene. After two hours of reflux the excess thionyl chloride was removed in vacuo and the resulting oil was dissolved in dry benzene to which dry pyridine was added as a proton acceptor instead of triethylamine. Triethylamine tended to cause formation of a copious amount of tar which made isolation of the product very difficult. Pyridine allowed for a much cleaner reaction and substantially improved the yields. The products of these reactions are listed along with their physical properties in Table XII in the Experimental Section. Table VIII lists the spectral properties of the products.

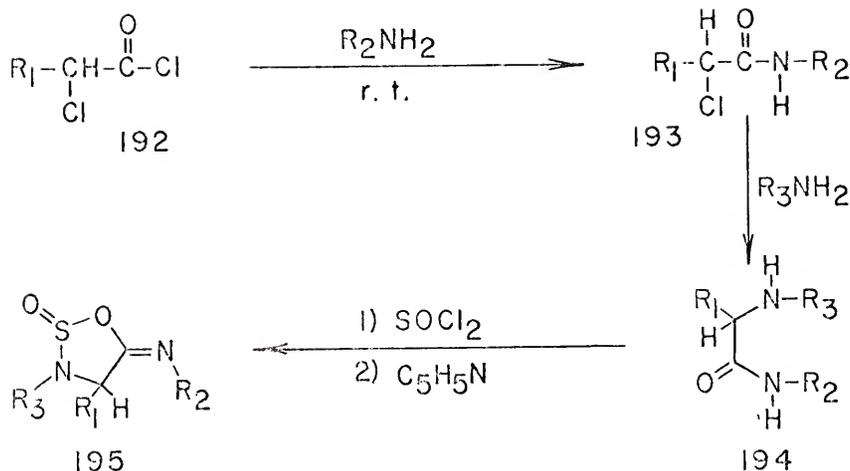
Table VII
Spectral Properties of 2-Aminoacetamides



Compd No	R ₁	R ₂	R ₃	IR (μ)		NMR data δ ppm ^a		R ₂	R ₃	NH	O C-NH
				N-H	C=O	R ₁	R ₂				
194 a	H	O-C ₆ H ₄ CH ₃	t-Bu	3.10	5.92	3.20 (s)	2.20 (s), 6.89-8.30 (m)	2.20 (s), 6.89-8.30 (m)	1.05 (s)	1.68 (s)	9.63 (s)
b	H	O-C ₆ H ₄ CH ₃	C ₆ H ₅	3.05	6.02	3.90 (s)	2.01 (s), 6.59-8.08 (m)	2.01 (s), 6.59-8.08 (m)	6.59-8.08 (m)	3.37 (s)	8.50 (s)
c	H	t-Bu	C ₆ H ₅	3.03	6.04	3.63 (s)	1.32 (s)	1.32 (s)	6.49-7.24 (m)	4.62 (s)	in [6.49-7.34 (m)]
d	H	i-Pr	t-Bu	3.07	6.05	3.05 (s)	3.98 (d, J=7.5 Hz), 1.18 (s)	3.98 (d, J=7.5 Hz), 1.18 (s)	1.06 (s)	1.95 (s)	7.37 (d, 7.5 Hz)
e	H	CH ₂ C ₆ H ₅	t-Bu	3.05	6.03	3.16 (s)	4.38 (d, J=6.5 Hz), 7.22 (s)	4.38 (d, J=6.5 Hz), 7.22 (s)	1.00 (s)	1.57 (s)	7.91 (t, 6.5 Hz)
f	C ₆ H ₅	C ₆ H ₅	t-Bu	3.10	5.96	6.96-7.73 (m), 4.37 (s)	6.96-7.73 (m)	6.96-7.73 (m)	1.14 (s)	1.61 (s)	9.93 (s)

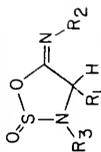
^aRelative to tetramethylsilane (TMS) in deuteriochloroform (CDCl₃).

Scheme LIX



A reaction was conducted to determine if the 2-oxo-1,2,3-oxathiazolidine had formed during the initial two-hour reflux and that a base such as pyridine was therefore not needed. After the two-hour reflux with thionyl chloride, water was added to the reaction instead of pyridine. Only the starting 2-aminoacetamide was isolated. The 5-imino-2-oxo-1,2,3-oxathiazolidine seems to be inert to water, aqueous base, or aqueous acid at room temperature. It appears that an intermediate such as 196 or 197 is formed initially, Scheme LX. The tertiary amine allows the cyclization to be completed by removing the hydrogen chloride. A mechanism for the formation of 195 from 194 is proposed in Scheme LX. The lack of formation of the imidoyl chloride 157 can be explained by invoking an intermediate such as 196.

Table VIII
Spectral Properties of 5-Imino-2-oxo-1,2,3-oxathiazolidines



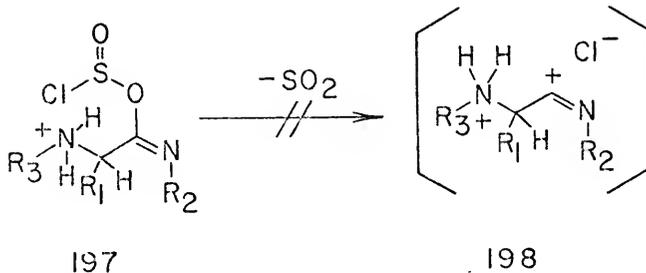
Compd No	R ₁	R ₂	R ₃	IR C=N (μ)	R ₁ ^b	H	NMR Data δ ppm ^a			R ₃
							(J _{AB} Hz, Δν _{AB} ^c Hz)	R (J _{AB} Hz, Δν _{AB} ^c Hz)	R (J _{AB} Hz, Δν _{AB} ^c Hz)	
195 a	H	<u>o</u> -C ₆ H ₄ CH ₃	<u>t</u> -Bu	5.81	4.09	(15.9, 19.2)	7.23 (s) and 2.27 (s)	7.23 (s) and 2.27 (s)	1.40 (s)	
b	H	<u>o</u> -C ₆ H ₄ CH ₃	C ₆ H ₅	5.83	4.49	(15.7, 12.8)	6.90-7.60 (m) and 2.30 (s)	6.90-7.60 (m) and 2.30 (s)	6.90-7.60 (m)	
c	H	<u>t</u> -Bu	C ₆ H ₅	5.81	4.30	(15.5, 15.2)	1.65 (s)	1.65 (s)	6.90-7.54 (m)	
d	H	<u>i</u> -Pr	<u>t</u> -Bu	5.83	3.93	(16.0, 22.0)	1.11-1.50 (m)	1.11-1.50 (m)	1.37 (s)	
e	H	CH ₂ -C ₆ H ₅	<u>t</u> -Bu	5.85	3.98	(16.0, 15.2)	4.70 (15.3, 36.7) and 7.29 (s)	4.70 (15.3, 36.7) and 7.29 (s)	1.35 (s)	
f-1	C ₆ H ₅	C ₆ H ₅	<u>t</u> -Bu	5.87	7.20- 7.90	(m), 5.11 (s)	7.20-7.90 (m)	7.20-7.90 (m)	1.36 (s)	
f-2	C ₆ H ₅	C ₆ H ₅	<u>t</u> -Bu	5.81	7.25- 7.55	(m), 5.25 (s)	7.25-7.55 (m)	7.25-7.55 (m)	1.30 (s)	

^aRelative to tetramethylsilane (TMS) in deuteriochloroform (CDCl₃)

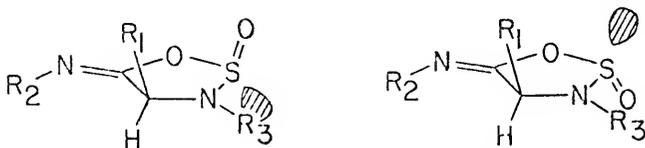
^bWhen R₁=H the values listed are for the center of the AB quartet.

^cSee reference 16.

However, the positive charge on the amine nitrogen in 197 may not allow the formation of 198 which would also hinder the formation of 157.



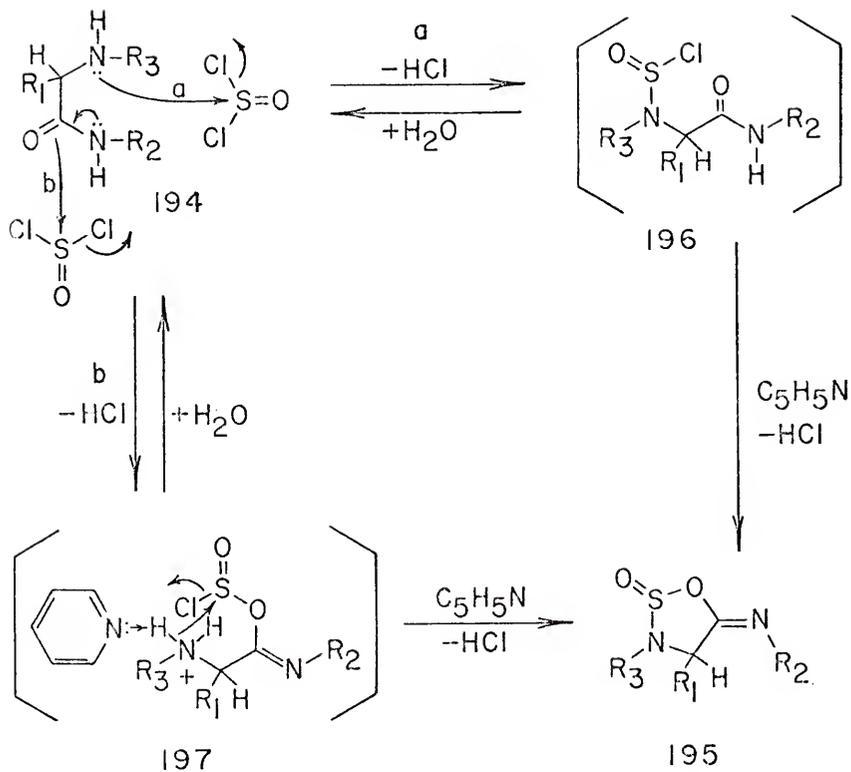
An examination of Table VIII reveals that 2-aminoacetamides 194 a-c yielded 5-imino-2-oxo-1,2,3-oxathiazolidines in which the geminal protons in the 4-position were non-equivalent as depicted by the AB nmr spectra, Table VIII. It is also noted that a d,l mixture of 2-aminoacetamide 194f yielded a pair of isomers. Existence of isomeric pairs requires that these heterocyclic compounds possess a non-carbon dissymmetric center. The asymmetric nature of the 2-oxo-1,2,3-oxathiazolidines has been ascribed to the asymmetry at the sulfur atom.¹⁰³ Additional isomerism



195

attributable to asymmetry at either nitrogen was not observed.

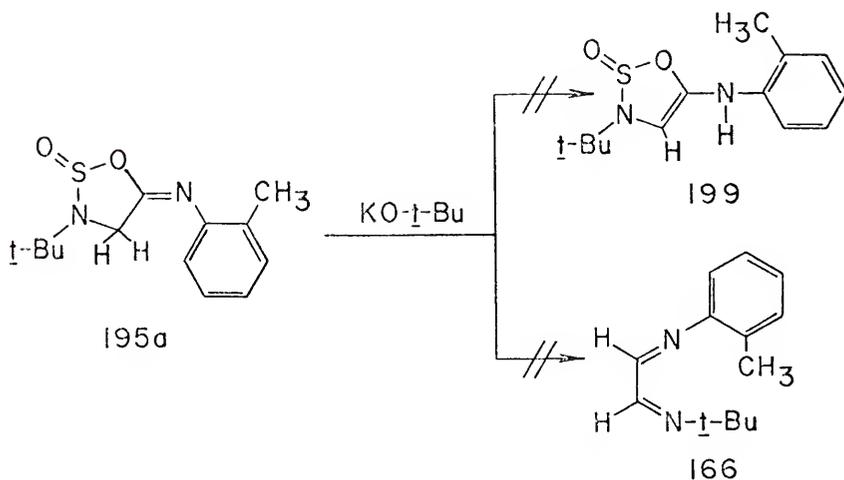
Scheme LX



Attempts to unequivocally assign a cis or trans structure to the isomers of 195f were unsuccessful. One would have expected that protons cis to the sulfoxide group to be deshielded by its acetylenic like anisotropy.¹⁰³ However inspection of molecular models indicate that it is possible for the proton in question to be also affected by the phenyl groups. Since the orientation of the phenyl groups is not known, it is difficult to determine whether they would effectively shield or deshield the proton. The C-N double bond would also affect the proton and the pair of electrons on the sulfur atom would possibly shield the proton to some extent. A solution to the dilemma could not be reached since it is difficult to ascertain which effects were more important.

In order to determine if it was possible to obtain the

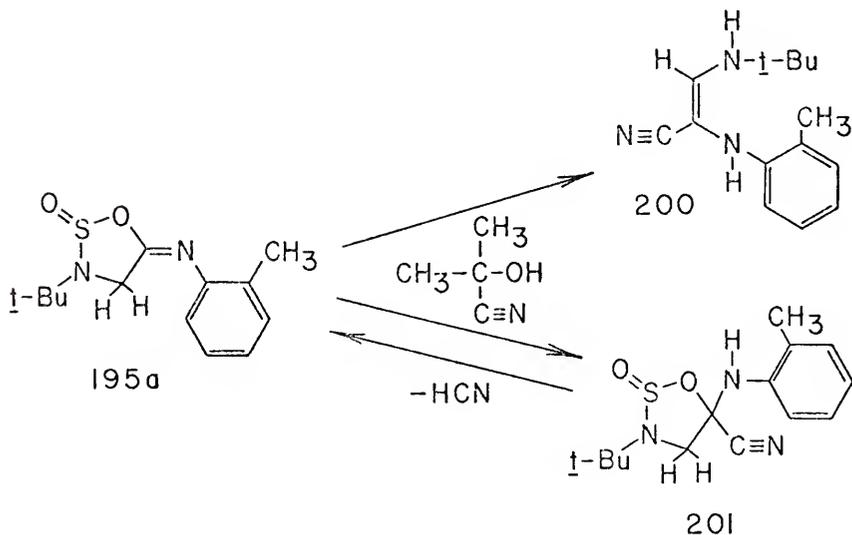
Scheme LXI



diimine 159 from the 5-imino-2-oxo-1,2,3-oxathiazolidine 195, compound 195a was refluxed with a catalytic amount of potassium *t*-butoxide in benzene. Neither the diimine 166 nor the enolized product 199 formed, Scheme LXI. The starting material hydrolyzed and all that was identified was *o*-toluidine.

One additional reaction was attempted. Acetone cyanohydrin and 195a were refluxed together in an attempt to prepare the acrylonitrile derivative 200. Instead of forming 200, it was also possible to form 201 by the addition of hydrogen cyanide across the C-N double bond¹⁹ in 195a. A new product formed, possibly 201 but it decomposed with the loss of hydrogen cyanide back to 195a, Scheme LXII, during the attempts to purify the product.

Scheme LXII

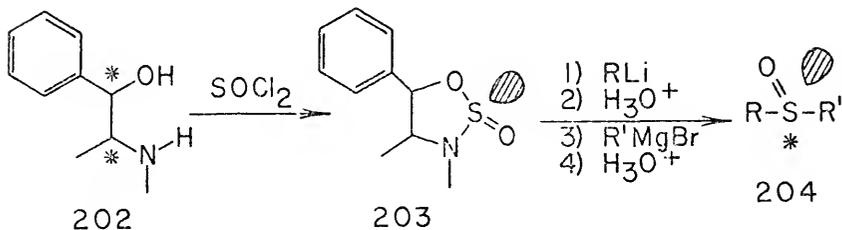


Conclusion

Initial attempts to prepare conjugated 1,2-diimines (159) via α -aminoketenimines (161) were unsuccessful. Similarly, attempts to prepare an α -amino imidoyl chloride (157) were also unsuccessful. During an attempt to prepare 157 from an 2-aminoacetamide (156) and thionyl chloride followed by a tertiary amine a new compound was isolated. This compound was identified as 5-imino-2-oxo-1,2,3-oxathiazolidine (160) or (195). The identification resulted from the analyses of the mass spectral data, indicating the elements of the original 2-aminoacetamide plus S=O but minus two protons, the infrared spectra, indicating a O=C=N moiety but no N-H group, and the nmr spectrum which indicated a ring system with geminal protons in different environments.

The number of useful reactions of 2-oxo-1,2,3-oxathiazolidines besides hydrolysis back to starting material is limited. Wudl and Lee¹⁰⁵ have demonstrated that either enantiomer of any open-chain chiral sulfoxide could be prepared via the route shown in Scheme LXIII.

Scheme LXIII¹⁰⁵



Further examples of 2-oxo-1,2,3-oxathiazolidenes are currently being developed in our research laboratories. General reactions of 2-oxo-1,2,3-oxathiazolidines are also being investigated.

CHAPTER V

Experimental

Melting points and boiling points are uncorrected. Melting points were determined in a Thomas-Hoover Unimelt capillary melting point apparatus. Boiling points were either determined by distillation or by a capillary technique.¹⁰⁶

Infrared spectra were recorded on a Perkin-Elmer 137 spectrophotometer. All nmr spectra were recorded on a Varian A-60-A spectrometer. Chemical shifts of nmr spectra run in organic solvents are reported in ppm (δ) downfield from internal tetramethylsilane. Visible and uv spectra were recorded on a Perkin-Elmer LR-1 laser-excited Raman spectrometer. Molecular weights were determined from mass spectral data and are in agreement with the proposed empirical formula in all cases. Mass spectra were recorded on a Hitachi Perkin-Elmer RMU-6E mass spectrometer. Microanalyses were obtained from Galbraith Laboratories, Inc., Knoxville, Tennessee and from Atlantic Microlab, Inc., Atlanta, Georgia.

Separations by column chromatography were conducted using Fisher Adsorption Alumina (A-540, 80-200 mesh). Deactivated alumina were prepared by adding the desired amount of water (by weight percent) to the alumina and shaking until no lumps were visible. Solvent evaporations were

carried out using a Buchler rotary evaporator in vacuo (water aspirator) or by using a Buchi Rotaryvapor-R in vacuo (pumps).

t-Butyl Isonitrile (5)

t-Butyl isonitrile was prepared from N-t-butylformamide using the procedure of Ugi and co-workers¹⁰⁷ with a few minor changes. Since the boiling point of t-butyl isonitrile is 92-93°C (750 mm Hg),¹⁰⁸ n-pentane was substituted for petroleum ether. During the work-up procedure, instead of extracting the water layer with three 60 ml portions of n-pentane, the water layer was extracted with two 60 ml portions of n-pentane and a 60 ml portion of p-xylene. The dried organic layer was distilled at atmospheric pressure through a 45 cm vacuum-jacketed glass helices packed column. Yields of 74-75% were obtained.

p-Nitrobenzylidene-t-butylamine (18a)

p-Nitrobenzylidene-t-butylamine was prepared according to method B as described by Moffett and Hoehn.¹⁰⁹ Cordes and Jencks were the first to apply this method to the preparation of the title compound.¹¹⁰

Reaction of p-Nitrobenzylidene-t-butylamine (18a) with t-Butyl Isonitrile

Into a 500 ml separatory funnel were placed 300 ml of chlorobenzene and 50 ml of water. The separatory funnel was vigorously shaken and the two layers were allowed to separate until the organic layer had no visible water droplets sus-

pended. The water layer was discarded and the wet chlorobenzene was placed in a 500 ml round-bottomed flask equipped with a magnetic stirrer. The chlorobenzene was then saturated with hydrogen chloride vapor produced by the interaction of ammonium chloride and concentrated sulfuric acid.

With stirring p-nitrobenzylidene-t-butylamine (10.0 g, 48.5 mmol) was added along with t-butyl isonitrile (12.4 g, 116 mmol). The flask was equipped with a reflux condenser. The yellow slurry was flushed with nitrogen and then was refluxed in a nitrogen atmosphere for 12 hours. At reflux temperature the suspended solid appeared to dissolve and the solution turned dark red.

After 12 hours of reflux the solution was extracted with two 50 ml portions of 10% sodium carbonate and once with a 100 ml portion of water. The organic layer was dried with anhydrous magnesium sulfate, filtered and evaporated to a red-brown oil.

The oil was separated on a column of 5% deactivated alumina (2.5 cm x 51 cm) which was packed in 20-40 petroleum ether. The first fraction to be eluted using 20-40 petroleum ether and 25:75 mixture of benzene and 20-40 petroleum ether was α -cyano-4-nitrophenylglyoxylidenedi-t-butylamine (20a) which was obtained as a red oil. Crystallization from 20-40 petroleum ether and 60:40 mixture of ethanol and water yielded white needles (0.914 g, 6%): mp 112-113°C; ir (KBr) μ 3.36 (C-H), 4.49 (2227 cm^{-1}) very weak (C=N), 6.04 (1656 cm^{-1}) (C=N), 6.49 (NO_2), 7.44 (NO_2); nmr (mixture of isomers 80:20)

(CCl₄)_δ (major isomer): 1.17 (s, 9), 1.32 (s, 9), 7.25 (d, 2, \underline{J} =8.5 Hz), 8.22 (d, 2, \underline{J} =8.5 Hz); (minor isomer): 1.42 (s), 1.58 (s), 7.83 (d, \underline{J} =8.5 Hz), 8.72 (d, \underline{J} =8.5 Hz)
 NMR No. 2; Raman (ethanol) cm⁻¹ 2230 weak (C≡N), 1600 (C=N);
 uv max (ethanol) nm 345 (ε 249), 267 (ε 9700), 214 (ε 19200).

Anal. Calcd for C₁₇H₂₂N₄O₂: C, 64.94; H, 7.05; N, 17.82.
 Found: C, 64.69; H, 7.28; N, 17.69.

The second fraction to be eluted using 20:75 and 50:50 mixtures of benzene and 20-40 petroleum ether was α,β-di-t-butylamino-4-nitrocinnamionitrile (19a) which was obtained as a dark red oil. Crystallization from a 50:50 mixture of benzene and 20-40 petroleum ether yielded two crystalline modifications (3.40 g, 23%).

Modification A was obtained as orange needles mp 88-89°C.¹¹¹ This modification was obtained and characterized earlier by Yun.⁹ The ir, nmr and mass spectra were identical to those previously reported. Raman (ethanol) cm⁻¹ 2200 (C≡N); uv max (ethanol) nm 345 (ε 1830), 267 (ε 22000), 214 (ε 10600).

Modification B was obtained as yellow needles mp 117.5-118.5°C; ir (KBr)μ 2.94 (N-H) 3.28 C-H), 4.48 (C≡N), 6.47 (NO₂), 7.32 (NO₂); nmr spectrum was identical to that of modification A. See Appendix NMR No. 1.

Elution of the column with chloroform yielded a third fraction, 1-t-butyl-5-cyano-4-(4-nitrophenyl)imidazole (21a) as a dark oil. The oil yielded pale yellow plates from

absolute ethanol (0.34 g, 3%): mp 186-187°C; ir (KBr) μ 3.17 (C-H), 3.35 (C-H), 4.50 (C \equiv N); nmr (CDCl₃) δ 1.80 (s, 9); 7.78 (s, 1), 8.25 (s, 4).

Anal. Calcd for C₁₄H₁₄N₄O₂: C, 62.21; H, 5.22; N, 20.73.

Found: C, 62.32; H, 5.27; N, 20.82.

α -Cyano-4-Nitrophenylglyoxylidenedi-*t*-butylamine (20a)

Into a 25 ml round-bottomed flask equipped with a magnetic stirrer was placed α,β -di-*t*-butylamine-4-nitrocinnamonnitrile (19a) (0.100 g, 0.31 mmol) in 10 ml of absolute methanol. To this was stirring at room temperature was slowly added 4 ml of 5% sodium hypochlorite solution (Clorox). Immediately the solution changed from orange to colorless.

The solution was poured into 50 ml of water and extracted with chloroform. The chloroform layer was dried with anhydrous magnesium sulfate and filtered. Evaporation of the chloroform yielded a yellow oil which upon crystallization from 20-40 petroleum ether or a 50:50 mixture of ethanol and water yielded white needles (0.062 g, 62%): mp 112-113°C. The ir and nmr spectra and mp were identical to α -cyano-4-nitrophenylglyoxylidenedi-*t*-butylamine (20a).

1-*t*-Butyl-5-cyano-4-(4-nitrophenyl)imidazole (21a)

Into a 50 ml round-bottomed flask equipped with a magnetic stirrer, and a reflux condenser was placed α,β -di-*t*-butylamino-4-nitrocinnamonnitrile (19a) (100 g, 0.31 mmol) in 15 ml of triethylorthoformate. The reaction mixture was refluxed under a nitrogen atmosphere for 30 hours.

Excess triethylorthoformate was removed by evaporation and the resulting oil was crystallized from absolute ethanol to yield pale yellow plates (0.0326 g, 39%): mp 186-187. The ir and nmr spectra, and mp were identical to 1-t-butyl-5-cyano-4-(4-nitrophenyl)imidazole (21a).

α -(N-t-Butylacetamido)- β -t-butylamino-4-nitrocinnamionitrile (26a)

Into a 25 ml round-bottomed flask equipped with a magnetic stirrer and reflux condenser was placed α,β -di-t-butylamino-4-nitrocinnamionitrile (26a) (0.300 g, 0.93 mmol) in a mixture of anhydrous sodium acetate (0.33 g, 4 mmol) and 20 ml of acetic anhydride. The mixture was refluxed in a nitrogen atmosphere for 2 hours. The material was then poured into water and extracted with chloroform. The chloroform layer was then extracted with 50 ml of 5% sodium hydroxide solution, and again with water. The chloroform layer was dried with anhydrous magnesium sulfate, filtered, and evaporated to a brown oil.

The oil dissolved in benzene was percolated through a short column of 5% deactivated alumina packed in benzene to yield a yellow oil.

Crystallization from a mixture of benzene and 20-40 petroleum ether yielded bright yellow needles (0.236 g, 66%): mp 157-158°C ir (KBr) μ 3.00 (N-H), 3.38 (C-H), 4.55 (C=N), 5.98 (C=O); nmr (CDCl₃) δ 1.12 (s, 9), 1.56 (s, 9), 2.19 (s, 3) 5.09 (s, 1), 7.56 (d, 2, \underline{J} =8.5 Hz), 8.31 (d, 2, \underline{J} =8.5 Hz).

Anal. Calcd for $C_{19}H_{26}N_4O_3$: C, 63.67; H, 7.31; N, 15.63.

Found: C, 63.59; H, 7.40; N, 15.52.

General Procedure for the Preparation of *p*-Nitrobenzylidene-2,6-dialkylaniline

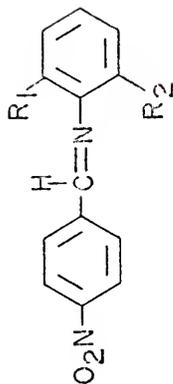
Into a 250 ml round-bottomed flask equipped with a heating mantle, magnetic stirrer, Dean-Stark trap, and a reflux condenser was placed *p*-nitrobenzaldehyde (10.0 g, 0.0662 m), 2,6-dialkylaniline¹¹² (0.0662 m), and a few crystals of *p*-toluenesulfonic acid in 100 ml of toluene. The reaction was refluxed from 8-10 hours. About 1 ml of water was usually collected. The solvent was removed by evaporation and the product was crystallized from absolute ethanol. Physical parameters of these reactions are listed in Table IX along with the physical properties of the *p*-nitrobenzylidene-2,6-dialkylanilines.

Reaction of *p*-Nitrobenzylidene-2,6-dimethylaniline (18b) with *t*-Butylisonitrile

Into a 1000 ml separatory funnel was placed 500 ml of benzene and 50 ml of water. The separatory funnel was shaken vigorously and the two layers were allowed to separate. The water layer was discarded and the wet benzene was transferred to a 1000 ml round-bottomed flask equipped with a magnetic stirrer. Then wet benzene was then saturated with hydrogen chloride vapor produced by the action of sulfuric acid on ammonium chloride.

The benzene was then decanted into another 1000 ml round-bottomed flask equipped with a magnetic stirrer which contained *p*-nitrobenzylidene-2,6-dimethylaniline (18b) (13.0 g,

Table IX

Physical Parameters for Several *p*-Nitrobenzylidene-2,6-dialkylanilines

Compd No	R ₁	R ₂	Time hr	Yield %	mp °C	Calc %		Found %			
						C	H	C	H		
18b ^a	CH ₃	CH ₃	10	99	98-99	70.85	5.55	71.00	5.64	11.02	11.02
18e	C ₂ H ₅	C ₂ H ₅	10	97	95-97	72.32	6.43	72.29	6.48	9.92	9.99
18f	CH ₃	C ₂ H ₅	8	97	91-93	71.62	6.01	71.60	6.03	10.44	10.53
18g	<i>i</i> Pr	<i>i</i> Pr	8	89	145-146.5	73.52	7.14	73.30	7.23	9.02	9.06

^aCompound (18b) was first prepared by Yun⁹

0.051 m). Into the stirred yellow slurry was then added t-butyl isonitrile (10.8 g, 0.13 m). The system was flushed with nitrogen and stirred in a nitrogen atmosphere at room temperature for 24 hours.

The resulting brown solution was extracted with 100 ml of 10% sodium carbonate and 100 ml of water. The organic layer was dried with anhydrous magnesium sulfate and filtered to yield a dark red solution. Evaporation of the solvent yielded a dark oil.

The oil was separated on a column of 5% deactivated alumina (2.5 cm x 25 cm) packed in 40-40 petroleum ether. The sample was placed on the column in benzene. Eluting the column with 25:75 and 50:50 mixtures of benzene and 20-40 petroleum ether yielded only one fraction which was obtained as a dark red oil. This compound was identified as α -(t-butylamino)- β -(2,6-dimethylanilino)-4-nitrocinnamionitrile (19b) and was crystallized from a 50:50 mixture of benzene and 20-40 petroleum ether or absolute ethanol yielding red orange granular crystals (5.01 g, 27%): mp 161-162°C. The mp, ir, and nmr are identical to that previously reported for this compound.⁹ See Appendix NMR No. 4. Additional data: Raman (CHCl_3) cm^{-1} 2180 ($\text{C}\equiv\text{N}$); uv max (ethanol) nm 367 (ϵ 2900), 274 (ϵ 23200).

α -Cyano-4-nitrophenylglyoxylicidene- α -(t-butylamine)- β -(2,6-dimethylaniline) (20b)

Into a 500 ml round-bottomed flask equipped with a magnetic stirrer was placed (19b) (1.9 g, 5.2 mmol) in

200 ml of methanol. To the dark red solution was added with stirring 75 ml of 5% sodium hypochlorite (Clorox) at room temperature. Immediately the solution turned yellow. After about 10 minutes of stirring the solution was poured into 150 ml of water and extracted with chloroform. The chloroform layer was dried with anhydrous magnesium sulfate and filtered. Evaporation of the solvent yielded an orange oil. Crystallization from absolute ethanol yielded orange granular crystals (1.61 g, 84%); mp 104-105.5°C; Appendix NMR No. 5. The mp, ir spectrum and nmr spectrum are identical to that previously reported.^{9,113} Additional data: Raman (CHCl_3) cm^{-1} 2240 (C≡N), 1650 (C=N); uv max (ethanol) nm 343 (ϵ 1200), 273 (ϵ 16400); visible max (ethanol) nm 385 (ϵ 718).

1-(2,6-Dimethylphenyl)-4-cyano-5-(4-nitrophenyl)imidazole (22b)

α -(t-Butylamino)- β -(2,6-dimethylanilio)-4-nitrocinnamonnitrile (19b) (0.600 g, 0.82 mmol) was dissolved in 30 ml of triethylorthoformate in a 50 ml round-bottomed flask equipped with a magnetic stirrer, heating mantle, and reflux condenser. The system was flushed with nitrogen and refluxed in a nitrogen atmosphere for 72 hours. Excess triethylorthoformate was removed by evaporation and the resulting brownish oil was crystallized from absolute ethanol to give grayish-purple needles (0.247 g, 47%): mp 189-190°C; ir (KBr) ν 4.46 (C≡N), 6.24 (C=C); nmr (CDCl_3) δ , 1.97 (s, 6), 7.16 (m, 3), 7.32 (d, 2, \underline{J} =9 Hz), 7.50 (s, 1), 8.09 (d, 2, \underline{J} =9 Hz).

Anal. Calcd for $C_{18}H_{14}N_4O_2$: C, 67.92; H, 4.43; N, 17.60.

Found: C, 68.08; H, 4.43; N, 17.51.

The Attempted 1,4-Cycloaddition of α -Cyano-4-nitrophenyl-glyoxylidene- α -(*t*-butylamine)- β -(2,6-dimethylaniline) (20b) with *p*-Benzoquinone

The procedure of Tomimatsu²⁶ was used in the reaction of (20b) (0.30 g, 0.82 mmol), *p*-benzoquinone (0.20 g, 1.85 mmol), and 10 ml of dry benzene in a sealed tube. The sealed tube was heated to 160-170°C for 7 hours. Upon cooling green needles of quinhydrone were obtained mp 167°C.¹¹⁴

Only starting material (20b) was isolated as determined by nmr spectroscopy.

The Attempted 1,4-Cycloaddition of α -Cyano-4-nitrophenyl-glyoxylidene- α -(*t*-butylamine)- β -(2,6-dimethylaniline) (20b) with Ketene Diethylacetal. The Preparation of 4-*t*-Butyl-3-cyano-4,5-dihydro-9-methyl-2-(4-nitrophenyl)-1*H*-1,4-benzodiazepine (35)

Into a sealed tube was placed (20b) (0.30 g, 0.82 mmol) and 0.2 ml of potassium *t*-butoxide stabilized ketene diethylacetal¹¹⁵ in 10 ml of dry benzene. The sealed tube was heated in an oil bath at 160-170°C for 7 hours. A darker red solution resulted.

Evaporation of the solvent gave an oil. Crystallization of the oil from 50:50 mixture of benzene and 20-40 petroleum ether yielded orange needles (0.16 g, 53%): mp 200-201°C; ir (KBr) μ 2.94 (N-H), 3.37 (C-H), 4.53 (C=N), 6.55 (NO₂), 7.44 (NO₂); nmr (CDCl₃) δ 1.19 (s, 9), 2.12 (s, 3), 4.22 (s, 2), 5.72 (broad s, 1), 6.70-7.10 (m, 3), 7.23 (d, 2, $J=8.5$ Hz), 8.23 (d, 2, $J=8.5$ Hz).

Anal. Calcd for $C_{21}H_{22}N_4O_2$: C, 69.59; H, 6.12; N, 15.46.

Found: C, 69.80; H, 6.23; N, 15.62.

4-t-Butyl-4,5-dihydro-9-methyl-2-(4-nitrophenyl)-3H-1,4-benzodiazepin-3-one (39)

Into a 25 ml round-bottomed flask equipped with a magnetic stirrer was placed (35) (0.157 g, 0.43 mmol) in 18 ml of methanol. With stirring at room temperature 6 ml of 5% sodium hypochlorite (Clorox) was added slowly. The solution changed from orange to yellow. The solution was stirred for 1/2 hour. The solution was poured into 50 ml of water and extracted with 100 ml of chloroform. The organic layer was dried with anhydrous magnesium sulfate, filtered and the solvent was evaporated yielding a yellow oil. Crystallization from 95% ethanol yielded yellow needles (0.106 g, 70%): mp 138.5-139.5°C; ir (KBr) μ 3.40 (C-H), 6.08 (C=O), 6.58 (NO₂), 7.44 (NO₂); nmr (CDCl₃) δ 1.48 (s, 9), 2.51 (s, 3), 4.20 (ABq, 2, $J=15.5$ Hz, $\Delta\nu=26.2$ Hz),¹⁶ 7.07-7.33 (m, 3), 8.23 (s, 4).

Anal. Calcd for $C_{20}H_{21}N_3O_3$: C, 68.36; H, 6.02; N, 11.96.

Found: C, 68.19; H, 6.20; N, 11.87.

p-Nitrobenzylidenemethylamine (18c)

p-Nitrobenzylidenemethylamine was prepared by the method of Buraway and Critchley.¹¹⁷

Reaction of p-Nitrobenzylidenemethylamine (18c) with t-Butyl Isonitrile

Into a separatory funnel was placed 500 ml of chlorobenzene with 50 ml of water. The mixture was shaken vigor-

ously and allowed to separate again. The wet chlorobenzene was then saturated with hydrogen chloride vapor produced by the action of concentrated sulfuric acid on ammonium chloride. This solvent was then poured over p-nitrobenzylidene-methylamine (5.0 g, 0.03 m) in a 1000 ml round-bottomed flask equipped with a magnetic stirrer, and reflux condenser. To this chalky white slurry was added t-butyl isonitrile (7.47 g, 0.09 m). The system was flushed with nitrogen and the slurry was refluxed in a nitrogen atmosphere for 4 hours. The very dark solution was washed with 50 ml of 10% sodium carbonate and with 100 ml of water. The resulting solution was dried and evaporated to a dark oil. The residue was chromatographed on a 5% deactivated alumina column (2.5 cm x 35 cm) packed in 20-40 petroleum ether. An amber colored oil was eluted from the column with benzene, and a 50:50 mixture of benzene and chloroform. The oil was identified as α -(t-butylamino)- β -(methylamino)-4-nitrocinnamionitrile⁹ (19c). Crystallization from a 50:50 mixture of benzene and 20-40 petroleum ether yielded yellow needles (1.42 g, 17%): mp 156-158°C.¹¹⁸ All spectral data were identical to those previously reported.⁹ See Appendix NMR No. 7.

α -Cyano-4-nitrophenylglyoxylidene- α -(t-butylamine)- β -(methylamine) (20c)

Into a 200 ml round-bottomed flask equipped with a magnetic stirrer was placed (19c) (0.40 g, 1.5 mmol) in 100 ml of methanol. To this was slowly added 5% sodium hypochlorite solution (Clorox). Immediately the solution

became colorless. The solution was poured into water and extracted with chloroform. The chloroform layer was dried with anhydrous magnesium sulfate, filtered, and evaporated to a yellow oil which quickly solidified. Recrystallization from 65-110 petroleum ether yielded white needles (0.203 g, 51%): mp 107-109°C, ir (KBr) μ 3.38 (C-H), 4.51 very weak (C \equiv N), 6.09 (C=N), 6.59 (NO₂), 7.44 (NO₂); nmr (mixture of isomers 92:8) (CCl₄) δ (major isomer): 1.39 (s, 9), 3.35 (s, 3), 7.27 (d, 2, $J=8.5$ Hz), 8.23 (d, 2, $J=8.5$ Hz); (minor isomer): 1.58 (s), 3.53 (s), 7.80 (d, $J=8.5$ Hz), 8.23 (d, $J=8.5$ Hz), see Appendix NMR No. 8.

4-Cyano-1-methyl-5-(4-nitrophenyl)imidazole (22c) and 1-t-Butyl-5-cyano-4-(4-nitrophenyl)imidazole (21a)

Into a 100 ml round-bottomed flask equipped with a condenser and a magnetic stirrer was placed (19c) (0.60 g, 2.2 mmol) in 50 ml of triethylorthoformate. The yellow solution was flushed with nitrogen and refluxed under nitrogen for 64 hours. Removal of the solvent gave an amber colored oil which was chromatographed over a 5% deactivated alumina column (1.5 cm x 35 cm) packed in a 50:50 mixture of benzene and 20-40 petroleum ether.

The first fraction to be eluted from the column with a 50:50 mixture of benzene and 20-40 petroleum ether and benzene was 1-t-butyl-5-cyano-4-(4-nitrophenyl)imidazole (21a) (0.095 g, 13%). All physical data were identical to previously reported data. See pages 145 - 147.

The second fraction to be eluted from the column with chloroform was 4-cyano-1-methyl-5-(4-nitrophenyl)imidazole (22c) (0.091 g, 18%): mp 187-192°C; ir (KBr) μ 3.25 (C-H) 4.46 (C \equiv N), 6.62 (NO₂), 7.38 (NO₂); nmr (CDCl₃) δ , 3.75 (s, 3), 7.63 (s, 1), 7.70 (d, 2, \underline{J} =8.5 Hz), 8.40 (d, 2, \underline{J} =8.5 Hz).¹¹⁹

4-Cyano-1,2-dimethyl-5-(4-nitrophenyl)imidazole (27c)

Into a 100 ml round-bottomed flask equipped with a magnetic stirrer, and reflux condenser was placed (19c) (0.3 g, 1.1 mmol), anhydrous sodium acetate (0.33 g, 4.4 mmol) and 40 ml of acetic anhydride. The red-orange solution was refluxed for 2 hours to yield a brownish-yellow solution. Most of the acetic anhydride was evaporated to yield a brownish-yellow solid. The solid was dissolved in chloroform and washed with 20 ml of 10% sodium hydroxide and 50 ml of water. The organic layer was dried with anhydrous magnesium sulfate, filtered, and the solvent evaporated. The residue was chromatographed on a 5% deactivated alumina column (1.5 cm x 35 cm) packed in benzene. The only fraction isolated was eluted from the column as a yellow oil in 25:75 and 50:50 mixtures of chloroform and benzene. Crystallization from 95% ethanol yielded yellow needles (0.122 g, 46%): mp 145-146°C; ir (KBr) μ 4.45 (C \equiv N), 6.60 (NO₂), 7.42 (NO₂); nmr (CDCl₃) δ 2.49 (s, 3), 3.60 (s, 3), 7.65 (d, 2, \underline{J} =8.5 Hz), 8.37 (d, 2, \underline{J} =8.5 Hz).

Anal. Calcd for C₁₂H₁₀N₄O₂: C, 59.50; H, 4.16; N, 23.13.

Found: C, 59.36; H, 4.40; N, 22.96.

p-Nitrobenzylidenebenzylamine (18d)

p-Nitrobenzylidenebenzylamine was prepared according to the method of Ingold and Piggott.¹²⁰

Reaction of p-Nitrobenzylidenebenzylamine (18d) with t-Butyl Isonitrile

Into a 500 ml separatory funnel was placed 250 ml of chlorobenzene with 50 ml of water. The separatory funnel was shaken vigorously and the two layers were allowed to separate completely. The water was discarded and the chlorobenzene was placed into a 300 ml round-bottomed flask equipped with a magnetic stirrer. The wet chlorobenzene was then saturated with hydrogen chloride vapor generated by the action of concentrated sulfuric acid on ammonium chloride.

Into a 500 ml round-bottomed flask equipped with a magnetic stirrer, and reflux condenser was placed p-nitrobenzylidenebenzylamine (5.0 g, 21 mmol). To this was added the chlorobenzene prepared as described and t-butyl isonitrile (5.2 g, 63 mmol). The white slurry was flushed with nitrogen and refluxed in a nitrogen atmosphere for 4 hours. The dark red mixture was cooled and extracted with 50 ml of 10% sodium carbonate and 100 ml of water. The organic layer was dried with anhydrous magnesium sulfate, filtered, and evaporated to a dark red oil. The residue was chromatographed in 5% deactivated alumina column (2.5 cm x 35 cm) packed in a 50:50 mixture of benzene and 20-40 petroleum ether. The first fraction to be eluted from the column in benzene as a yellow-brown oil was a mixture of products.

Crystallization from a 50:50 mixture of benzene and 20-40 petroleum ether yielded amber colored needles of 1-t-butyl-4-(4-nitrophenyl)-2-phenylimidazole²⁸ (40) (0.85 g, 13%): mp 182-183°C; ir (KBr) μ 3.37 (C-H), 6.25 (C=C), 6.67 (NO₂), 7.51 (NO₂); nmr (CDCl₃) δ 1.48 (s, 9), 7.41 (s, 5), 7.56 (s, 1), 7.88 (d, 2, \underline{J} =9 Hz), 8.17 (d, 2, \underline{J} =9 Hz).³²

Anal.¹²¹ Calcd for C₁₉H₁₉N₃O₂: C, 71.01; H, 5.96;
N, 13.07.

Found: C, 70.97; H, 5.95;
N, 13.16.

After the removal of (40) from the first fraction the yellow brown oil was rechromatographed on an activated alumina column (1.5 cm and 35 cm) packed in benzene. The first fraction eluted from this column with a 50:50 mixture of benzene and 20-40 petroleum ether was a yellow oil. The structure is proposed to be 5-t-butylamino-4-(4-nitrophenyl)-2-phenylpyrimidine (42). Crystallization from 65-110 petroleum ether yielded bright yellow needles (0.054 g, 1%): mp 150-151°C; ir (KBr) μ 2.90 (N-H), 3.37 (C-H), 6.24 (C=C), 6.59 (NO₂), 7.48 (NO₂); nmr (CCl₄) δ 1.45 (s, 9), 5.05 (Broad s, 1), 7.30-7.70 (m, 5), 7.96 (d, 2, \underline{J} =9.5 Hz), 8.16 (d, 2, \underline{J} =9.5 Hz), 8.41 (s, 1).¹¹⁹

The second fraction eluted from this column by benzene as an almost colorless oil which solidified was 1-t-butyl-5-cyano-4-(4-nitrophenyl)-2-phenylimidazole (41). Recrystallization from absolute ethanol yielded white needles (0.335 g, 5%): mp 185-186°C; ir (KBr) μ 3.37 (C-H), 4.51 (C=N), 6.24

(C=C), 6.49 (NO₂), 7.45 (NO₂); nmr (CDCl₃) δ 1.67 (s, 9), 7.40 (s, 5), 8.19 (s, 4).

Anal. Calcd for C₂₀H₁₈N₄O₂: C, 69.35; H, 5.24; N, 16.17.

Found: C, 69.44; H, 5.20; N, 16.16.

Third fraction to be eluted from the column with chloroform as a yellow oil was α -t-butylamino- β -benzylamino-4-nitrocinnamionitrile (19d). Crystallization from absolute ethanol yielded yellow needles (0.030 g, 0.4%): mp 115-116°C; ir (KBr) μ 3.04 (N-H), 3.41 (C-H), 4.61 (C \equiv N), 6.31 (NO₂), 7.42 (NO₂); nmr (CDCl₃) δ 1.21 (s, 9), 1.70 (broad s, 1), 4.00 (d, 2, $J=7$ Hz), 6.17 (very broad pk, 1), 6.85-7.32 (m, 5), 7.49 (d, 2, $J=8.7$ Hz), 8.20 (d, 2, $J=8.7$),¹¹⁹ Appendix NMR No. 9.

p-Nitrophenylglyoxal Hydrate (22)

p-Nitrophenylglyoxal hydrate was prepared from 2-bromo-4'-nitroacetophenone and dimethylsulfoxide according to the procedure of Kornblum et al.¹⁷ The material was used in the crude form.

p-Nitrophenylglyoxylidene- α -t-butylamine (23)

Into a 250 ml round-bottomed flask equipped with a magnetic stirrer, Dean-Stark trap, and a reflux condenser was placed crude p-nitrophenylglyoxal hydrate¹²² in 100 ml of benzene with a catalytic amount of p-toluenesulfonic acid. To this was added t-butylamine (6.57 g, 9.4 ml, 0.09 m). The Dean-Stark trap was filled with benzene and the system was flushed with nitrogen. The dark brown solution was

refluxed in a nitrogen atmosphere for 2 1/2 hours during which time 1/2 ml of water was collected. The brown solution was filtered to remove any impurities and the filtrate was evaporated to a dark brown oil. Crystallization from 2-propanol yielded pale yellow needles (5.8 g, 43%)¹²³: mp 74-75°C; ir (KBr) μ 3.25 and 3.45 (C-H), 6.02 (C=O), 6.10 (C=N), 6.60 (NO₂), 7.47 (NO₂); nmr (CDCl₃) δ 1.32 (s, 9), 8.00 (s, 1), 8.20 (d, 2, \underline{J} =9.5 Hz), 8.40 (d, 2, \underline{J} =9.5 Hz).

Anal. Calcd for C₁₂H₁₄N₂O₃: C, 61.53; H, 6.02; N, 11.96.

Found: C, 61.77; H, 6.10; N, 11.98.

p-Nitrophenylglyoxylidenedi-t-butylamine (24a)

Into a 300 ml round-bottomed flask equipped with a magnetic stirrer, condenser, gas inlet and outlet tubes for nitrogen, thermometer, and a dropping funnel was placed p-nitrophenylglyoxylidene- α -t-butylamine (23) (5.86 g, 0.025 m) and t-butylamine (18.25 g, 26.22 ml, 0.25 m) in 125 ml of benzene. The solution was cooled to 0-5°C in an ice bath and nitrogen was purged through the system. Titanium (IV) chloride¹⁸ (TiCl₄) (4.33 g, 2.5 ml, 0.22 m) dissolved in 50 ml of benzene was added dropwise during a 40 minute interval. The reaction mixture was stirred at room temperature for 4 days. The resulting mixture was cautiously poured into water to remove unreacted titanium (IV) chloride. The titanium dioxide was removed. The organic layer was separated from the water layer, dried with anhydrous magnesium sulfate, filtered, and evaporated to a yellow oil (7.23 g,

100%): bp 95°C (.05 mm Hg); 106 ir (neat) μ 3.40 (C-H), 6.10 (C=N), 6.60 (NO₂), 7.42 (NO₂); nmr (mixture of isomers 58:42) (CDCl₃) δ (major isomer): 1.30 (s, 9), 1.39 (s, 9), 7.87 (d, 2, \underline{J} =9 Hz), 8.14 (d, 2, \underline{J} =9 Hz), 8.38 (s, 1); (minor isomer): 1.10 (s, 9), 1.12 (s, 9), 7.24 (d, 2, \underline{J} =8.5 Hz), 7.92 (s, 1), 8.15 (d, 2, \underline{J} =8.5 Hz), Appendix NMR No. 10.

Anal. Calcd for C₁₆H₂₃N₃O₂: C, 66.41; H, 8.01; N, 14.52.

Found: C, 66.22; H, 8.04; N, 14.38.

α,β -Di-*t*-butylamino-4-nitrocinnamionitrile (19a)

A technique of Betts and Davey for converting ketones¹²⁴ into cyanohydrins was applied to the addition of hydrogen cyanide to a diimine. Into a 50 ml round-bottomed flask equipped with a magnetic stirrer, and reflux condenser was placed *p*-nitrophenylglyoxylidene- α,β -di-*t*-butylamine (24a) (0.71 g, 2.45 mmol) in 25 ml of methanol. To this was added 1 ml of acetone cyanohydrin and 1 ml of 10% potassium cyanide solution. The system was flushed with nitrogen and refluxed in a nitrogen atmosphere for 2 hours. The dark red brown solution was poured into 50 ml of water and extracted with chloroform several times. The chloroform layer was dried with anhydrous magnesium sulfate, filtered and evaporated to a red brown oil. The residue was chromatographed on a 5% deactivated alumina column (2.5 cm x 35 cm) packed in 20-40 petroleum ether. A single fraction was eluted using mixtures of 50:50 benzene and 20-40 petroleum ether and then adding more 20-40 petroleum ether. The yellow needles which

were obtained were identified as α, β -t-butylamino-4-nitrocinnamionitrile (19a) (0.50 g, 65%) mp 117.5-118.5°C.

Phenylglyoxal Hydrate (63)

Phenylglyoxal hydrate was prepared⁴⁰ according to the procedure described by Kornblum et al.¹⁷ from 2-bromoacetophenone and dimethylsulfoxide. The product was used in the crude form.

Phenylglyoxylidene- α -t-butylamine⁴⁰ (64)

The procedure was identical to that described for the preparation of p-nitrophenylglyoxylidene- α -t-butylamine (23) (p. 159) except that phenylglyoxylidene- α -t-butylamine (64) did not lend itself to facile purification so it was used crude for the next step. A partially purified sample gave the following nmr (CDCl_3) δ 1.30 (s, 9); 7.20-8.32 (m, 6).

Phenylglyoxylidene- α, β -di-t-butylamine (65)

Phenylglyoxylidene- α, β -di-t-butylamine was prepared in the same way as p-nitrophenylglyoxylidene- α, β -di-t-butylamine (24a) (p. 160) from the crude phenylglyoxylidene- α -t-butylamine (64). This material was only partially purified: nmr (mixture of isomers 52:48) (CDCl_3) δ (major isomer): 1.31 (s, 9), 1.37 (s, 9), 7.17-7.87 (m), 8.32 (s, 1); (minor isomer): 1.10 (s, 9), 1.12 (s, 9), 6.90-7.50 (m), 7.95 (s, 1), Appendix NMR No. 11.

α -Cyano-phenylglyoxylidenedi-t-butylamine (68)

α, β -Di-t-butylaminocinnamionitrile (67) was prepared

from crude phenylglyoxylidenedi-t-butylamine⁴⁰ (65) (4.81 g, 0.0197 m) with 8 ml of acetone cyanohydrin and 8 ml of 10% potassium cyanide by the same method as that described for α,β -di-t-butylamino-4-nitrocinnamionitrile (19a) (p. 161). The product oxidized in air after column chromatography and yielded α -cyanophenylglyoxylidenedi-t-butylamine (68). The yellow oil after air oxidation was crystallized from 65-110 petroleum ether to yield white needles (1.15 g, 22%)¹²⁵: mp 80-82°C; ir (KBr) μ 3.40 (C-H), 4.52 very weak (C \equiv N), 6.07 (C=N), 6.24 (C=C); nmr (mixture of isomers 75:25) (CDCl₃) δ (major isomer) 1.15 (s, 9), 1.30 (s, 9), 6.87-7.77 (m, 5); (minor isomer): 1.40 (s), 1.56 (s), 6.87-7.77 (m), Appendix NMR No. 12.

Anal. Calcd for C₁₇H₂₃N₃: C, 75.80; H, 8.61; N, 15.60.

Found: C, 75.90; H, 8.67; N, 15.57.

4-Nitrophenylglyoxylidene-bis(2,6-dimethylaniline) (144)

Into a 300 ml round-bottomed flask equipped with a magnetic stirrer, a nitrogen gas inlet and outlet tube, dropping funnel, condenser, and thermometer was placed 4-nitrophenylglyoxylidene- α -t-butylamine (23) (5.86 g, 0.025 m) and 2,6-xylidene (30.25 g, 30.7 ml, 0.25 m) in 160 ml of benzene. The solution was cooled to 0-5°C in an ice bath and nitrogen was purged through the system. Titanium (IV) chloride¹⁸ (TiCl₄) (3.46 g, 2.0 ml, 0.018 m) dissolved in 50 ml of benzene was added dropwise over 40 minutes. The reaction mixture was stirred at room temperature

for 4 days. The resulting mixture was cautiously poured into water to remove unreacted titanium (IV) chloride. The titanium dioxide was removed and the organic layer was separated from the water layer. The organic layer was then washed with three 100 ml aliquots of 10% sulfuric acid to remove unreacted 2,6-xylylene. The organic layer was dried with anhydrous magnesium sulfate, filtered and evaporated to a red orange oil. The material contained no t-butyl group (nmr spectrum of crude sample) and the material could not be purified further. Crude nmr (mixture of isomers) (CDCl_3) δ 2.00, 2.05, 2.11, and 2.19 (4s, 12), 6.80-7.10 (m, 6), 7.25-8.38 (m, 5).

α -Cyano-4-nitrophenylglyoxylidene- α,β -bis(2,6-dimethylaniline) (107)

Into a 100 ml round-bottomed flask equipped with a magnetic stirrer, heating mantle, and reflux condenser was placed crude 4-nitrophenylglyoxylidene-bis(2,6-dimethylaniline) (144) (2.65 g, 0.007 m) in 60 ml of methanol. To this was added acetone cyanohydrin (2.8 g, 0.033 m) and 2 ml of 10% potassium cyanide solution. The black solution was flushed with nitrogen and refluxed in a nitrogen atmosphere for 1 hour. The solution was poured into water and extracted with chloroform. The red chloroform solution was dried with anhydrous magnesium sulfate, filtered, and evaporated to a red oil. An nmr spectrum of this oil indicated that α,β -bis-(2,6-dimethylanilino)-4-nitrocinnamitrile (145) was present along with a small amount of the title compound. The

material was then placed on a 5% deactivated alumina column (2.5 cm x 35 cm) packed in 20-40 petroleum ether. When 20-40 petroleum ether, 25:75, and 50:50 mixtures of benzene and 20-40 petroleum ether were used as eluents only one fraction was obtained as a red oil. Crystallization from absolute ethanol yielded yellow needles of the oxidized material (α -cyano-4-nitrophenylglyoxylidene- α,β -bis(2,6-dimethylaniline))¹²⁶ (107) (0.75 g, 26%): mp 143.5-145°C; ir (KBr) μ 3.45 (C-H), 4.50 weak (C \equiv N), 6.10 (C=N), 6.25 (C=C); nmr (CDCl₃) δ 2.08 and 2.14 (2s, 12), 6.47 and 7.10 (2s, 6), 7.42 (d, 2, $J=9$ Hz), 8.13 (d, 2, $J=9$ Hz).

Anal. Calcd for C₂₅H₂₂N₄O₂: C, 73.15; H, 5.40; N, 13.65.

Found: C, 73.09; H, 5.50; N, 13.60.

Benzilylidene-di-*t*-butylamine (93)

Into a 2000 ml round-bottomed flask equipped with a magnetic stirrer, nitrogen gas inlet and outlet tubes, a condenser, thermometer, and dropping funnel was placed benzil (21.0 g, 0.10 m) and *t*-butylamine (73 g, 105 ml, 1.0 m) in 700 ml of benzene. The solution was cooled to 0-5°C with an ice bath and the system was purged with nitrogen. Titanium (IV) chloride¹⁸ (TiCl₄) (24.46 g, 14.14 ml, 0.12 m) dissolved in 100 ml of benzene was added dropwise over an interval of 75 minutes. The reaction mixture was stirred at room temperature for 1 day. The dark maroon solution was cautiously poured into water to remove unreacted titanium (IV) chloride (TiCl₄). The titanium dioxide was removed and the organic layer was separated from the water

layer. The organic layer was dried with anhydrous magnesium sulfate, filtered, and evaporated to a yellow oil. Crystallization from absolute ethanol yielded white granular crystals (28.83 g, 90%): mp 115-117°C; ir (KBr) μ 3.40 (C-H), 6.12 (C=N); nmr (CDCl₃) δ 1.22 (s, 18), 7.12-7.86 (m, 10).

Anal. Calcd for C₂₂H₂₈N₂: C, 82.45; H, 8.81; N, 8.74.

Found: C, 82.47; H, 8.91; N, 8.79.

4,5-Diphenylglyoxalone

4,5-Diphenylglyoxalone was prepared by the procedure described by either Chattaway and Coulson¹²⁷ or Corson and Freeborn.¹²⁸

4,4'-Dinitrobenzil

4,4'-Dinitrobenzil was prepared from 4,5-diphenylglyoxalone according to the procedure described by Chattaway and Coulson¹²⁷ with one change: the reaction time was extended from 3 days to 6 days.

4,4'-Dinitrobenzilylidenedi-t-butylamine (94)

Into a 1000 ml round-bottomed flask equipped with a magnetic stirrer, nitrogen gas inlet and outlet tubes, and condenser, a dropping funnel, and a thermometer was placed 4,4'-dinitrobenzil (3.00 g, 0.01 m) and t-butylamine (7.3 g, 10.5 ml, 0.1 m) in 500 ml of methylene chloride. The mixture was stirred for 1 hour to obtain an amber solution. The solution was cooled to 0-5°C with an ice bath. Titanium (IV) chloride (TiCl₄) (3.06 g, 1.77 ml, 0.016 m) dissolved in 50

ml of methylene chloride was added dropwise during a 30 minute interval. The reaction mixture was stirred at room temperature for 4 hours. The reaction was cautiously poured into water to remove excess titanium (IV) chloride. The titanium dioxide was removed and the organic layer separated from the water layer. The organic layer was dried with anhydrous magnesium sulfate, filtered, and evaporated to a yellow oil. Crystallization from absolute ethanol yielded dark yellow needles (3.17 g, 77%): mp 157-158°C; ir (KBr) μ 3.40 (C-H), 6.12 (C=N), 6.24 (C=C), 6.60 (NO₂), 7.45 (NO₂); nmr (CDCl₃) δ 1.26 (s, 18), 7.90 (d, 4, \underline{J} =8.5 Hz), 8.20 (d, 4, \underline{J} =8.5 Hz).

Anal. Calcd for C₂₂H₂₆N₄O₄: C, 64.38; H, 6.38; N, 13.65.

Found: C, 64.41; H, 6.46; N, 13.59.

Benzophenone-t-butylimine (84)

The title compound was prepared by the procedure of Morretti and Torre.¹⁸

p-Nitroacetophenone-t-butylimine

Into a 500 ml round-bottomed flask equipped with a magnetic stirrer, nitrogen gas inlet and outlet tubes, a dropping funnel, a thermometer, and condenser was placed p-nitroacetophenone (4.96 g, 0.03 m) and t-butylamine (21.9 g, 31.5 ml, 0.3 m) in 210 ml of benzene. The solution was cooled to 0-5°C in a ice bath and nitrogen was purged through the system. Titanium (IV) chloride¹⁸ (TiCl₄) (3.46 g, 2.0 ml, 0.018 m) dissolved in 50 ml of benzene was added

dropwise during a 40 minute interval. The reaction was allowed to stir at room temperature for 2 hours. The reaction was cautiously poured into water to remove excess titanium (IV) chloride (TiCl_4). The titanium dioxide was removed and the organic layer was separated from the water layer. The organic layer was dried with anhydrous magnesium sulfate, filtered, and evaporated to a yellow oil. The yellow oil does solidify and melts below room temperature, but could not be purified further.¹²⁹ An nmr spectrum of the oil was run: nmr (CDCl_3) δ 1.39 (s, 9), 2.36 (s, 3), 7.86 (d, 2, $J=8.5$ Hz), 8.10 (d, 2, $J=8.5$ Hz).

Phenanthrenequinonedit-*t*-butylimine (95)

Into a three-necked 300 ml round-bottomed flask equipped with a magnetic stirrer, nitrogen gas inlet and outlet tubes, a condenser, a dropping funnel, and a thermometer was placed phenanthrenequinone (4.164 g, 0.02 m) and *t*-butylamine (29.2 g, 42 ml, 0.4 m) in 150 ml of methylene chloride. The system was purged with nitrogen and cooled to 0-5°C in an ice bath. To this dark brown solution was added titanium (IV) chloride¹⁸ (TiCl_4) (4.74 g, 2.7 ml, 0.025) dissolved in 50 ml of methylene chloride at such a rate to keep the temperature below 5°C, about 30 minutes. The mixture turned yellow with solid suspended. The reaction was stirred at room temperature for 4 days. The resulting dark brown slurry was cautiously poured into water to remove excess titanium (IV) chloride. The titanium dioxide was removed and the organic layer was

separated from the water layer. The organic layer was dried with anhydrous magnesium sulfate, filtered, and evaporated to a yellow solid. The product was crystallized from absolute ethanol and recrystallized from 65-110 petroleum ether to yield white needles (5.43 g, 85%): mp 122-124°C; ir (KBr) μ 3.44 (C-H), 6.12 (C=N), 6.27 (C=C); nmr (CDCl₃) δ 1.22 (s, 9), 1.50 (s, 9), 7.10-7.95 (m, 8).

Anal. Calcd for C₂₂H₂₆N₂: C, 82.97; H, 8.23; N, 8.80.

Found: C, 82.96; H, 8.30; N, 8.71.

Glyoxylidenedi-t-butylamine (82)

Glyoxylidenedi-t-butylamine was prepared by the method described by Kliegman and Barnes⁵⁶ from 40% glyoxal in water and t-butylamine.

Reaction of Glyoxylidenedi-t-butylamine with Acetone Cyanohydrin

Into a 500 ml round-bottomed flask equipped with a magnetic stirrer was placed crude glyoxylidenedi-t-butylamine (6.2 g, 0.037 m) in 250 ml of methanol. To this was added acetone cyanohydrin (7.86 g, 5.6 ml, 0.0925 m) and 5.6 ml of 10% potassium cyanide solution. The reaction was stirred at room temperature for 6 hours.¹³⁰ The resulting slurry was evaporated to about 20 ml, dissolved in chloroform, extracted with water, dried with anhydrous magnesium sulfate, filtered and evaporated to a semisolid.

The semisolid contained two isolatable products by fractional crystallization. Crystallization from a 75:25 mixture of benzene and 65-110 petroleum ether yielded white granular crystals of α,β -di-t-butylaminosuccinonitrile (1.52 g, 18.5%): mp 168-169 (dec) $^{\circ}$ C; ir (KBr) μ 3.02 (N-H), 3.40 (C-H), 4.49 (C \equiv N); nmr (CDCl₃) δ 1.18 (s) t-butyl.¹³¹

Anal. Calcd for C₁₂H₂₂N₄: C, 64.83; H, 9.97; N, 25.20.

Found: C, 64.92; H, 10.00; N, 25.04.

The resulting mother liquor was crystallized from 65-110 petroleum ether to yield white needles of 2,3-di-t-butylaminoacrylonitrile (3.33 g, 46%): mp 64-69 $^{\circ}$ C; ir (KBr) μ 3.06 (N-H), 3.40 (C-H), 4.60 (C \equiv N), 6.12 broad ((C=N) and C=C)); nmr (CDCl₃) δ 1.13 (s, 9), 1.20 (s, 9), 1.77 broad (s, 1), 5.27 broad (d, 1, J=13 Hz), 6.79 (d, 1, J=13 Hz).

Anal. Calcd for C₁₁H₂₁N₃: C, 67.65; H, 10.84; N, 21.51.

Found: C, 67.73; H, 10.92; N, 21.43.

α -Cyanoglyoxylidenedi-t-butylamine (87)

Into a 500 ml round-bottomed flask equipped with a magnetic stirrer was placed 2,3-di-t-butylaminoacrylonitrile (15.12 g, 0.077 m) in 200 ml of methanol. To this was added 225 ml of 5% sodium hypochlorite solution (Clorox). The solution became almost colorless and warm after the addition. The solution was stirred for 5 minutes at room temperature and poured into about 200 ml of water and extracted with chloroform. The chloroform layer was separated

from the water layer, dried with anhydrous magnesium sulfate, filtered, and evaporated to a yellow oil. The resulting yellow oil was distilled to yield α -cyanoglyoxylidenedi-t-butylamine (87) (10.31 g, 69%): bp 48°C (0.35 mm Hg); ir (neat) μ 3.42 (C-H), 4.52 (C \equiv N), 6.10 and 6.21 (C=N); nmr (CDCl₃) δ 1.28 (s, 9), 1.49 (s, 9), 7.80 (s, 1).

Anal. Calcd for C₁₁H₁₉N₃: C, 68.35; H, 9.91; N, 21.74.

Found: C, 68.33; H, 9.97; N, 21.89.

1,2-Di-t-butylamino-1,2-dicyanoethylene

Into a 500 ml round-bottomed flask equipped with a magnetic stirrer was placed crude α -cyanoglyoxylidenedi-t-butylamine (0.082 m) in 250 ml of methanol. To the solution was added 7.5 ml of 10% potassium cyanide and acetone cyanohydrin (10.46 g, 7.5 ml, 0.123 m). The resulting yellow solution was stirred for 1 hour. The resulting solution was poured into 500 ml of water and extracted with chloroform to yield an amber colored solution. The organic layer was separated from the water layer, dried with anhydrous magnesium sulfate, filtered, and evaporated to a brown oil. Crystallization from 20-40 petroleum ether followed by a recrystallization from 70% ethanol-water mixture yielded cream colored needles of 1,2-di-t-butylamino-1,2-dicyanoethylene (10.27 g, 57%¹³²): mp 63-65°C (lit. 77°C³⁵); ir (KBr) μ 3.04 (N-H), 3.42 (C-H), 4.52 and 4.57 (C \equiv N), 6.42 (C=C); nmr (CDCl₃) δ 1.31 (s, 18), 3.53 (s, 2).

Anal. Calcd for C₁₂H₂₀N₄: C, 65.42; H, 9.15; N, 25.43.

Found: C, 65.26; H, 9.20; N, 25.30.

α, β -Dicyanoglyoxylidenedi-t-butylamine

Into a 250 ml round-bottomed flask equipped with a magnetic stirrer was placed 1,2-di-t-butylamino-1,2-dicyanoethylene (3.00 g, 0.013 m) in 130 ml of methanol. To the yellowish solution was slowly added 41 ml of 5% sodium hypochlorite solution (Clorox). The solution became colorless immediately but was stirred for 5 minutes at room temperature. The solution was poured into water and extracted with chloroform to yield a pale yellow solution. The organic layer was separated for the water layer, dried with anhydrous magnesium sulfate, filtered, and evaporated to a white solid. Crystallization from 20-40 petroleum ether or absolute ethanol yielded colorless gem like crystals of α, β -dicyanoglyoxylidenedi-t-butylamine (1.63 g, 55%): mp 84.5-86.5°C; ir (KBr) μ 3.42 (C-H), 4.50 (C \equiv N), 6.15 (C=N); nmr (CDCl₃) δ 1.51 (s, 18).

Anal. Calcd for C₁₂H₁₈N₄: C, 66.02; H, 8.31; N, 25.66.

Found: C, 66.00; H, 8.36; N, 25.72.

Glyoxylidenedi-o-toluidine (148)

Into a 300 ml three-necked round-bottomed flask equipped with a ice bath, paddle stirrer, and a dropping funnel was placed 40% glyoxal solution in water (91.4 g, 72.5 ml, 0.63 m). To this was added dropwise with stirring at 0°C o-toluidine (53.6 g, 0.5 m). The reaction mixture completely solidified as a yellow solid in the flask. The solid was removed by dissolving it in diethyl ether and

separating it from the water layer. The ethereal solution was dried with anhydrous magnesium sulfate, filtered, and evaporated to a yellow solid. Recrystallization from 2-propanol yielded yellow plates (49.07 g, 83%): mp 125.5-127.5°C (lit. 122-124°C⁶³ and 126.5-127.5°C¹³³); ir (KBr) μ 3.42 broad (C-H), 6.24 (C=N); nmr (CDCl₃) δ 1.49 (s, 6), 6.80-7.30 (m, 8), 8.26 (s, 2).

Anal. Calcd for C₁₆H₁₆N₂: C, 81.32; H, 6.82; N, 11.85.

Found: C, 81.15; H, 6.94; N, 11.77.

2,3-Di-*o*-toluidinoacrylonitrile (149)

Into a 500 ml round-bottomed flask equipped with a magnetic stirrer, and reflux condenser was placed glyoxyli-denedi-*o*-toluidine (148) (8.75 g, 0.037 m) in 300 ml of methanol. To this was added acetone cyanohydrin (7.86 g, 5.6 ml, 0.0925 m) and 5.6 ml of 10% potassium cyanide solution. The system was flushed with nitrogen and refluxed for 1 hour in a nitrogen atmosphere. The solution was evaporated to half its original volume, dissolved in chloroform and extracted with water. The chloroform layer was separated from the water layer, dried with anhydrous magnesium sulfate, filtered, and evaporated to a white solid. Recrystallization from absolute ethanol yielded white needles (9.0 g, 92%): mp 136-138°C; ir (KBr) μ 3.00 (N-H), 3.30 and 3.50 (C-H), 4.60 (C=N), 6.10 (C=C); nmr (CDCl₃) δ 2.00 (s, 3), 2.20 (s, 3), 4.55 broad (s, 1), 6.45-7.42 (m, 10).

Anal. Calcd for C₁₇H₁₇N₃: C, 77.54; H, 6.51; N, 15.96.

Found: C, 77.32; H, 6.61; N, 16.10.

α -Cyanoglyoxylidenedi-o-toluidine (109)

The procedure was adapted from the procedure described by Pratt and McGovern⁸⁹ for converting N-substituted benzylamines into N-substituted benzylidene amines with activated manganese dioxide. Into a 250 ml round-bottomed flask equipped with a magnetic stirrer, Dean-Stark trap, and a reflux condenser was placed activated manganese dioxide⁸⁹ (6.96 g, 0.08 m) in 150 ml of benzene. The mixture was refluxed for 12 hours during which time 0.4 ml of water was collected. The reaction mixture was cooled and 2,3-di-o-toluidinoacrylonitrile (149) (2.63 g, 0.01 m) was added. The reaction mixture was refluxed for 12 hours during which time 0.2 ml of water was collected. The hot solution was filtered through a Celite 545 bed to remove the manganese dioxide. The manganese dioxide was washed several times with methylene chloride. The resulting black solution was evaporated to a black oil. Several recrystallizations alternating between 2-propanol and 65-110 petroleum ether yielded yellow-orange needles (2.18 g, 83%): mp 100-102°C; ir (KBr) μ 3.30 and 3.40 (C-H), 4.50 very weak (C \equiv N), 6.12 (C=N); nmr (CDCl₃) δ 2.30 (s, 3), 2.47 (s, 3), 6.82-7.39 (m, 8), 8.30 (s, 1).

Anal. Calcd for C₁₇H₁₅N₃: C, 78.13; H, 5.79; N, 16.08.

Found: C, 78.25; H, 5.83; N, 16.07.

 α , β -Dicyanoglyoxylidenedi-o-toluidine (109)

Into a 250 ml round-bottomed flask equipped with a magnetic stirrer, and reflux condenser was placed α -cyano-

glyoxylidenedi-o-toluidine (108) (2.61 g, 0.01 m) in 150 ml of methanol. To this was added acetone cyanohydrin (2.55 g, 0.03 m) and potassium cyanide (0.255 g, 3.9 mmol). The system was flushed with nitrogen and refluxed in a nitrogen atmosphere for 1 hour. The resulting brown solution was poured into water and extracted with chloroform. The dark red chloroform solution was dried with anhydrous magnesium sulfate, filtered, and evaporated to a dark red oil. The expected product, 1,2-dicyano-1,2-di-o-toluidinoethylene (150), could not be isolated easily due to autooxidation by air. The oil was then placed in a 500 ml round-bottomed flask equipped with a magnetic stirrer in 200 ml of methanol. To this was added 45 ml of 5% sodium hypochlorite (Clorox). Immediately a yellow solid formed. After 5-10 minutes of stirring at room temperature the slurry was poured into water and extracted with chloroform. The resulting red solution was dried with anhydrous magnesium sulfate, filtered and evaporated to a red oil. Crystallization from absolute ethanol yielded yellow needles (1.26 g, 44%): mp 195-196°C; ir (KBr) μ 3.30 and 3.45 (C-H), 4.50 very weak (C≡N); nmr (CDCl₃) δ 2.43 (s, 6), 7.18-7.62 (m, 8).

Anal. Calcd for C₁₈H₁₄N₄: C, 75.51; H, 4.93; N, 19.57.

Found: C, 75.42; H, 4.96; N, 19.54.

Benzylideneaniline

Benzylideneaniline was prepared according to the procedure of Bigelow and Eatough.¹³⁴

2-Anilino-2-phenylacetonitrile (110)

Into a 500 ml round-bottomed flask equipped with a magnetic stirrer was placed benzyldeneaniline (18.12 g, 0.1 m) in 250 ml of methanol. Acetone cyanohydrin (25.53 g, 18.24 ml, 0.3 m) was added to this solution along with 18.24 ml of 10% potassium cyanide solution. The yellow solution was allowed to stir for 1/2 hour at room temperature. The resulting solution was poured into water and extracted with methylene chloride. The methylene chloride layer was separated from the water layer, dried with anhydrous magnesium sulfate, filtered, and evaporated to a yellow solid. The crude solid was recrystallized from 2-propanol to yield white needles¹³⁵ (19.7 g, 95%): mp 82.5-84.5°C (lit.¹³⁶ 85°C); ir (KBr) μ 3.06 (N-H), 3.37 (C-H), 4.50 (C \equiv N), 6.28 (C=C); nmr (CDCl₃) δ 3.90 broad (s, 1), 5.30 (s, 1), 6.50-7.67 (m, 10).

N-Phenylbenzimidyl Cyanide (111)

Into a 500 ml round-bottomed flask equipped with a magnetic stirrer was placed 2-anilino-2-phenylacetonitrile (110) (10.42 g, 0.05 m) in 250 ml of methanol. To this pale yellow solution was added 223.5 ml of 5% sodium hypochlorite solution (Clorox). Immediately the solution turned dark yellow with dark yellow oil precipitating from solution. The mixture was stirred for 5 minutes at room temperature and the mixture was poured into water and extracted with chloroform. The amber colored chloroform layer was separated from the water layer, dried with anhydrous

magnesium sulfate, filtered, and evaporated to a brown oil. The oil was redissolved in carbon tetrachloride and any insolubles were removed by filtration. The resulting red-brown solution was evaporated to a red-brown oil and crystallized from methanol to yield yellow plates¹³⁵ (8.74 g, 85%): mp 68-71°C (lit. 72°C¹³⁷ and 68-71°C¹³⁸); ir (KBr) μ 3.40 broad (C-H), 4.51 weak (C \equiv N), nmr (CDCl₃) δ 6.80-7.62 and 7.90-8.20 (m, 10).

N-t-Butyl-N'-o-tolyethylenediamine (165)

Into a 2000 ml round-bottomed flask equipped with a paddle stirrer, dropping funnel, condenser, and drying tube was placed powdered lithium aluminium hydride (11.4 g, 0.3 m) in 750 ml of tetrahydrofuran. During an interval of 1 1/2 hours, 2-t-butylaminoacet-o-toluidide (164) (22.03 g, 0.1 m) dissolved in 750 ml of tetrahydrofuran was added dropwise. The reaction was refluxed for 7 hours. The work-up procedure was identical to that described by Micovic and Mihailovic.¹³⁹ After removing the lithium and aluminium salts, the solvent was removed by evaporation. The resulting yellow oil was distilled to yield N-t-butyl-N'-o-tolylethylenediamine (165) (18.96 g, 92%): bp 101-103°C (0.3 mm Hg); ir (neat) μ 2.97 (N-H), 3.40 (C-H), 6.22 (C=C); nmr (CDCl₃) δ 1.00 broad (s, 1), 1.02 (s, 9), 2.07 (s, 3), 2.60-3.23 (m, 4), 4.10 broad (s, 1), 6.40-7.23 (m, 4).

Anal. Calcd for C₁₃H₂₂N₂: C, 75.68; H, 10.75; N, 13.58.

Found: C, 75.68; H, 10.81; N, 13.52.

Glyoxylidene-t-butylamine-o-toluidine (166)

Into a 2000 ml round-bottomed flask equipped with a heavy-duty magnetic stirrer, Dean-Stark trap, and a condenser was placed activated manganese dioxide⁸⁹ (69.55 g, 0.8 m) and a few crystals of p-toluenesulfonic acid in 946 ml of benzene. The mixture was refluxed for 12 hours during which time 4.8 ml of water was collected. The mixture was cooled and N-t-butyl-N'-o-tolylethylenediamine (165) (10.31 g, 0.05 m) dissolved in 100 ml of benzene was added. The reaction was refluxed for 24 hours during which time 1.2 ml of water was collected. The hot slurry was filtered through a Celite 545 bed and washed with a copious amount of chloroform. The solvent was removed by evaporation to yield a red oil. The yield of the desired product was low due to a substantial amount of C-C cleavage to yield glyoxylidenedi-o-toluidine (148).¹⁴⁰ The red oil was chromatographed on a 5% deactivated alumina column (1.5 cm x 35 cm) packed in 20-40 petroleum ether. The desired product was eluted from the column in 20-40 petroleum ether and a 25:75 mixture of benzene and 20-40 petroleum ether. The material still contained some glyoxylidenedi-o-toluidine. The red oil could not be purified further. Crude nmr (CDCl₃) δ 1.22 (s, 9), 2.31 (s, 3), 6.50-7.25 (m, 4), 8.02 (s, 2).

N-t-Butyl-2-chloro-2-phenylacetamide (172)

Into a three-necked 500 ml round-bottomed flask equipped with a magnetic stirrer, ice bath, dropping funnel, and drying tube was placed t-butylamine (9.13 g, 13.11 ml,

0.125 m) in 250 ml of benzene with 10 ml of dry pyridine. 2-Chloro-2-phenylacetylchloride⁹⁶ (171) (23.63 g, 0.125 m) dissolved in 50 ml of benzene was added dropwise to the chilled solution. After the addition the reaction was stirred at room temperature for the balance of 2 hours, the resulting solution was extracted with 50 ml of water. The organic layer was dried with anhydrous magnesium sulfate, filtered, and evaporated to a yellowish brown solid. The solid was recrystallized from 80% methanol in water to yield white needles (16.66 g, 59%): mp 127-128°C; ir (KBr) μ 3.06 (N-H), 3.28 and 3.38 (C-H), 6.03 (C=O), 14.13 (C-Cl); nmr (CDCl₃) δ 1.35 (s, 9), 5.26 (s, 1), 6.58 broad (s, 1), 7.18-7.50 (m, 5).

Anal. Calcd for C₁₂H₁₆ClNO: C, 63.85; H, 7.15; N, 6.20.

Found: C, 63.82; H, 7.22; N, 6.23.

N-t-Butyl-2-(N'-o-tolyl)-2-phenylacetamide (173)

Into a 250 ml round-bottomed flask equipped with a heating mantle, magnetic stirrer, and a reflux condenser was placed N-t-butyl-2-chloro-2-phenylacetamide (172) (11.29 g, 0.05 m) in 100 ml of benzene along with o-toluidine (53.58 g, 53.6 ml, 0.5 m). The system was flushed with nitrogen and refluxed in a nitrogen atmosphere for 3 days. The reaction mixture was cooled, extracted with 50 ml of water, 200 ml of 10% hydrochloric acid,¹⁴¹ 100 ml of 10% sodium hydroxide, and 50 ml of water. The organic layer was dried with anhydrous magnesium sulfate, filtered, and evaporated to a brownish solid. Recrystallization from

2-propanol yielded white needles (12.80 g, 86%): mp 135-136°C; ir (KBr) μ 2.98 and 3.08 (N-H), 3.30 and 3.40 (C-H), 6.05 (C=O); nmr (CDCl₃) δ 1.29 (s, 9), 2.20 (s, 3), 4.50-4.75 (m, 2), 6.15-7.60 (m, 10).

Anal. Calcd for C₁₉H₂₄N₂O: C, 76.99; H, 8.16; N, 9.45.

Found: C, 76.77; H, 8.28; N, 9.32.

1-N-t-butyl-2-(N'-o-tolyl)-2-phenylethylenediamine (174)

N-t-Butyl-2-(N'-o-tolyl)-2-phenylacetamide (173) (10.08 g, 0.34 m) dissolved in 255 ml of tetrahydrofuran was added dropwise over an interval of 1 hour to lithium aluminium hydride (7.00 g, 0.184 m) slurried in 300 ml of dry tetrahydrofuran in a 1000 ml round-bottomed flask equipped with a magnetic stirrer, a dropping funnel, a condenser, and a drying tube. The reaction mixture was refluxed for 638 hours.¹⁴² The work-up procedure was identical to that described by Micovic and Mihailovic.¹³⁹ The resulting solution after work-up was evaporated to a yellow oil. The resulting viscous yellow oil could not be separated from the starting material by the usual methods. The oil was then refluxed in 300 ml of 20% sulfuric acid for 4 hours to remove any residual amide present. The resulting turquoise colored solution was rendered basic with 10% sodium hydroxide and extracted with chloroform. The organic layer was dried with anhydrous magnesium sulfate, filtered, and evaporated to a yellow oil. A short path distillation yielded pure diamine (4.62 g, 48%): bp 142°C (0.25 mm Hg); ir (neat) μ 3.04 (N-H), 3.43 (C-H), 6.24 (C=C); nmr (CDCl₃) δ

1.78 broad (s, 1), 1.99 (s, 9), 2.22 (s, 3), 2.43-3.13 (m, 2), 4.03-4.37 broad (m, 1), 5.12 broad (s, 1), 6.13-7.42 (m, 9).

Anal. Calcd for $C_{19}H_{26}N_2$: C, 80.80; H, 9.28; N, 9.92.

Found: C, 80.55; H, 9.40; N, 9.79.

Reaction of 1-N-t-Butyl-2-(N'-o-tolyl)-2-phenylethylenediamine (174) with Activated Manganese Dioxide

Into a 300 ml round-bottomed flask equipped with a magnetic stirrer, a reflux condenser, and a Dean-Stark trap was placed activated manganese dioxide⁸⁹ (9.13 g, 0.105 m) in 150 ml of benzene. The mixture was refluxed for 12 hours during which time 0.6 ml of water was collected. The mixture was cooled and 1-N-t-butyl-2-(N'-o-tolyl)-2-phenylethylenediamine (174) (1.85 g, 6.56 mmol) was added. The reaction was refluxed for 24 hours. The hot solution was filtered through a Celite 545 bed and washed several times with chloroform. The solvents was removed by evaporation to yield a brown oil. The product was not the expected phenylglyoxylidene- α -t-butylamine- β -o-toluidine (175) but benzylidene-o-toluidine (176) as identified by its nmr spectrum.¹⁴³

General Procedure for Preparation of 1H-1,4-Benzodiazepines

Into a 25 ml round-bottomed flask equipped with a magnetic stirrer, and a reflux condenser was placed the diimine (0.300 g) in 10 ml of dry diglyme with catalytic amount of potassium t-butoxide. The system was flushed with nitrogen and refluxed in a nitrogen atmosphere for 1-10 hours.

The dark brown solution was poured into 50 ml of water and extracted with chloroform. The organic layer was dried with anhydrous magnesium sulfate, filtered, and evaporated to a brown oil. Product formation was determined by nmr. See Table VI for reaction parameters, and other pertinent data.

2-Chloroacetamides

All of the 2-chloroacetamides were prepared by standard procedures involving the reaction of α -chloroacetyl chloride with primary amines. In Table X the 2-chloroacetamides prepared are listed along with yields and their physical properties. Details for a typical preparation will illustrate the techniques involved.

2-Chloroacet-o-toluidide

Into a 500 ml three-necked round-bottomed flask equipped with a magnetic stirrer, a dropping funnel, and a drying tube was placed o-toluidine (13.4 g, 0.125 m) and dry pyridine (9.8 g, 10 ml, 0.125 m) in 250 ml of benzene. With stirring α -chloroacetyl chloride (Eastman) (14.1 g, 9.96 ml, 0.125 m) dissolved in 50 ml of benzene was added dropwise. After the addition the reaction mixture was allowed to stir the balance of the 2 hours at room temperature. The benzene was evaporated and the resulting oil dissolved in chloroform and washed with 50 ml of water, 50 ml of 5% sodium bicarbonate, and 50 ml of 5% hydrochloric acid. The organic layer was dried with anhydrous magnesium

Table X

Physical Parameters for 2-Chloroacetamides

Compound	Yield %	Mp °C	Recrystallization Solvent	IR (μ) N-H C=O
2-Chloroacet- <u>o</u> -toluidide	94	107-108 ^b	C ₆ H ₆ -65-110 Pet ether	3.14 6.05
N- <u>t</u> -Butyl-2-chloroacetamide	53	80-82 ^c	Sub. 85° (760 mm Hg) and 65-110 Pet ether	3.08 6.05
N- <u>iso</u> -Propyl-2-chloroacetamide	91	58-60 ^d	65-110 Pet ether	3.10 6.07
N-Benzyl-2-chloroacetamide	94	92-93 ^e	C ₆ H ₆ -65-110 Pet ether	3.10 6.10
2-Chlorophenylacetanilide ^a	93	145.5-147.5 ^f	C ₆ H ₆	3.09 6.00

^a 2-Chlorophenylacetyl chloride was prepared from d,l-mandelic acid by the procedure described by C.A. Bischoff and P. Walden, Ann., 279, 122 (1894).

^b E. Abderhalden, E. von Ehrenweil, S. Schwab, and O. Yumstein, Fermentforschung, 13, 408 (1932) rpt mp 111-112°C, D. Beke, K. Lampert, and L. Gyernek, Acta. Chim. Acad. Sci. Hung., 5, 143 (1954) rpt mp 112°C. A. Borovansky, A. Sekera, and C. Vrba, J. Am. Pharm. Assoc., 48, 402 (1959), rpt mp 108-109°C. K.N. Gaiind, B.D. Miglani and K.C. Gupta, Ind. J. Pharm., 24, 254 (1962) rpt mp 97-98°C.

^c J. Speziale and P.C. Hamm, J. Am. Chem. Soc., 78, 2557 (1956) rpt mp 82-83°C.

^d J. Speziale and P.C. Hamm, J. Am. Chem. Soc., 78, 2557 (1956) rpt mp 62-62.5°C.

^e E.K. Harvill, R.M. Herbst, and E.G. Schreiner, J. Org. Chem., 17, 1602 (1952) rpt mp 93-94.5°C.

^f J.M. Sandri and E.K. Fields US Patent 3,280,032, C.A., 66, p 4733w (1967) rpt mp 146-148°C.

sulfate, filtered, and evaporated to a yellowish white solid. Recrystallization from a 50:50 mixture of benzene and 65-110 petroleum ether yielded white needles (21.65 g, 94%): mp 107-108°C.

General Procedure for Preparation of 2-Aminoacetamides

Into a 250 ml round-bottomed flask equipped with a magnetic stirrer, heating mantle, and a reflux condenser was placed the 2-chloroacetamide (0.05 m) in 100 ml of benzene along with the primary amine (0.5 m). The reaction was refluxed for 14-60 hours (see Table XI) under a nitrogen atmosphere. After this time the 2-aminoacetamide was extracted into 10% hydrochloric acid to separate it from neutral or acidic by-products and then the acid layer was made basic with 15% sodium hydroxide solution and extracted with methylene chloride. The organic layer was dried with anhydrous magnesium sulfate, filtered, and evaporated. The residue was either crystallized or distilled. The reactions and reaction products are summarized in Table XI.

General Procedure for Preparation of 5-Imino-2-oxo-1,2,3-oxathiazolidines (195)

Into a 200 ml round-bottomed flask equipped with a heating mantle, a magnetic stirrer, a reflux condenser, and a drying tube was placed the 2-aminoacetamide (0.01 m) in 100 ml of benzene¹⁴⁵ with thionyl chloride (33.1 g, 20 ml, 0.278 m). The solution was refluxed for 2 hours, cooled, and evaporated to about 10-15 ml to remove excess thionyl chloride. To the residue was added 100 ml of ben-

zene and to this with stirring 25 ml of dry pyridine was slowly added. The resulting mixture was stirred to room temperature for 2 hours. The mixture was then extracted with 50 ml of water, 100 ml of 10% hydrochloric acid, 50 ml of 10% sodium hydroxide, and the 50 ml of water. The organic layer was dried with anhydrous magnesium sulfate, filtered, and evaporated to an oil. The resulting oil was crystallized from an appropriate solvent. Physical parameters of these reactions are listed in Table XII.

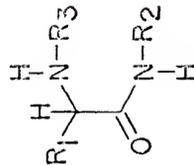
The isomers of compound 195f were separated by fractional crystallization since column chromatography over 5% deactivated alumina failed to yield separation. It was found that some isomer 195 f-1 could be removed very efficiently from isomer 195 f-2 by recrystallization from methanol.

Reaction of α -Cyano-4-nitrophenylglyoxylidenedi-t-butylamine (20a) with m-Chloroperbenzoic Acid

A modification of the procedure described by Emons¹⁴⁶ was used in the oxidation of α -cyano-4-nitrophenylglyoxylidenedi-t-butylamine (20a). Into a 200 ml round-bottomed flask equipped with a magnetic stirrer, and a dropping funnel was placed α -cyano-4-nitrophenylglyoxylidenedi-t-butylamine (20a) (0.628 g, 0.002 m) in 50 ml of methylene chloride. The reaction was cooled to 0-5°C in an ice bath. m-Chloroperbenzoic acid [1.73 g, (80% purity), 0.008 m] dissolved in 50 ml of methylene chloride was added dropwise to the solution over a 30 minute interval. The resulting

Table XI

Physical Parameters for 2-Aminoacetamides



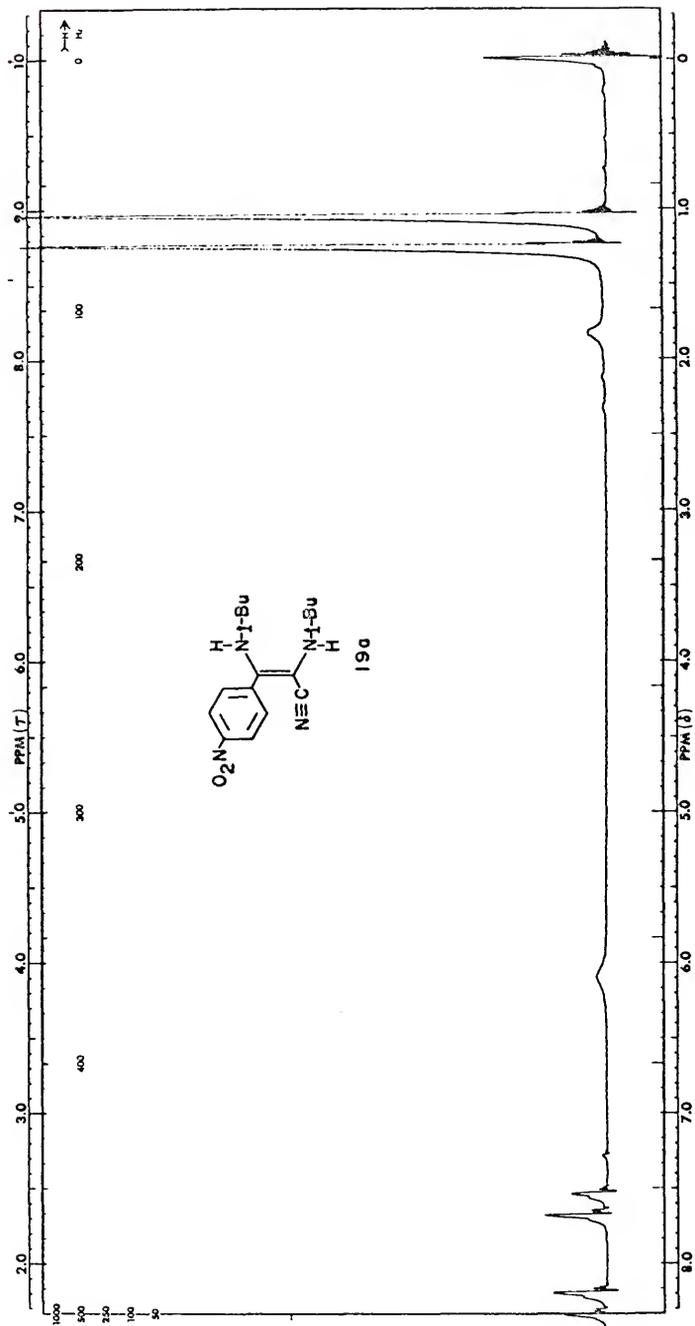
Compd NO	R ₁	R ₃	R ₂	Time hr	Yield %	Bp (mm Hg) Mp°C	Recrystallization Solvent	Found %	
								C	H
194 a	H	<u>t</u> -Bu	<u>o</u> -C ₆ H ₄ CH ₃	22	95	77-79	65-110 Pet ether	70.76	9.26
b	H	C ₆ H ₅	<u>o</u> -C ₆ H ₄ CH ₃	22	89	159.5-161	abs EtOH	74.82	6.77
c	H	C ₆ H ₅	<u>t</u> -Bu	14	51	72-74	C ₆ H ₆ -65-110 Pet ether	69.77	8.89
d	H	<u>t</u> -Bu	<u>i</u> -Pr	21	86	72 (.23)	-	62.65	11.66
e	H	<u>t</u> -Bu	CH ₂ C ₆ H ₅	21	96	36.5-37.5	65-110 Pet ether	70.79	9.20
f	C ₆ H ₅	<u>t</u> -Bu	C ₆ H ₅	60	58	123.5-125.5	MeOH	76.61	7.87
								Calcd %	
	C	H	N					C	H
194 a	70.87	9.15	12.72					70.76	9.26
b	74.97	6.71	11.66					74.82	6.77
c	69.87	8.80	13.58					69.77	8.89
d	62.75	11.70	16.26					62.65	11.66
e	70.87	9.15	12.72					70.79	9.20
f	76.56	7.85	9.92					76.61	7.87

solution was stirred for 2 days at room temperature. The solution was extracted with two 50 ml aliquots of 10% sodium carbonate. The organic layer was separated from the water layer, dried with anhydrous magnesium sulfate, filtered, and evaporated to a yellow oil. The residue was chromatographed on 5% deactivated alumina column (1.5 cm x 35 cm) packed in 20-40 petroleum ether, using 25:75 mixture of benzene and 20-40 petroleum ether. A single fraction was isolated which was crystallized from 65-110 petroleum ether to yield white needles of (113), (0.260 g, 37%): mp 96.5-98.5; ir (KBr) μ 3.25 and 3.40 (C-H), No (C=N), 6.23 (C=C), 6.58 (NO₂), 7.44 (NO₂); nmr (CDCl₃) δ 0.98 (s, 9), 1.2, (s, 9), 1.31 (s, ?), 7.68 (d, 2, \underline{J} =8.5 Hz), 8.25 (d, 2, \underline{J} =8.5 Hz).

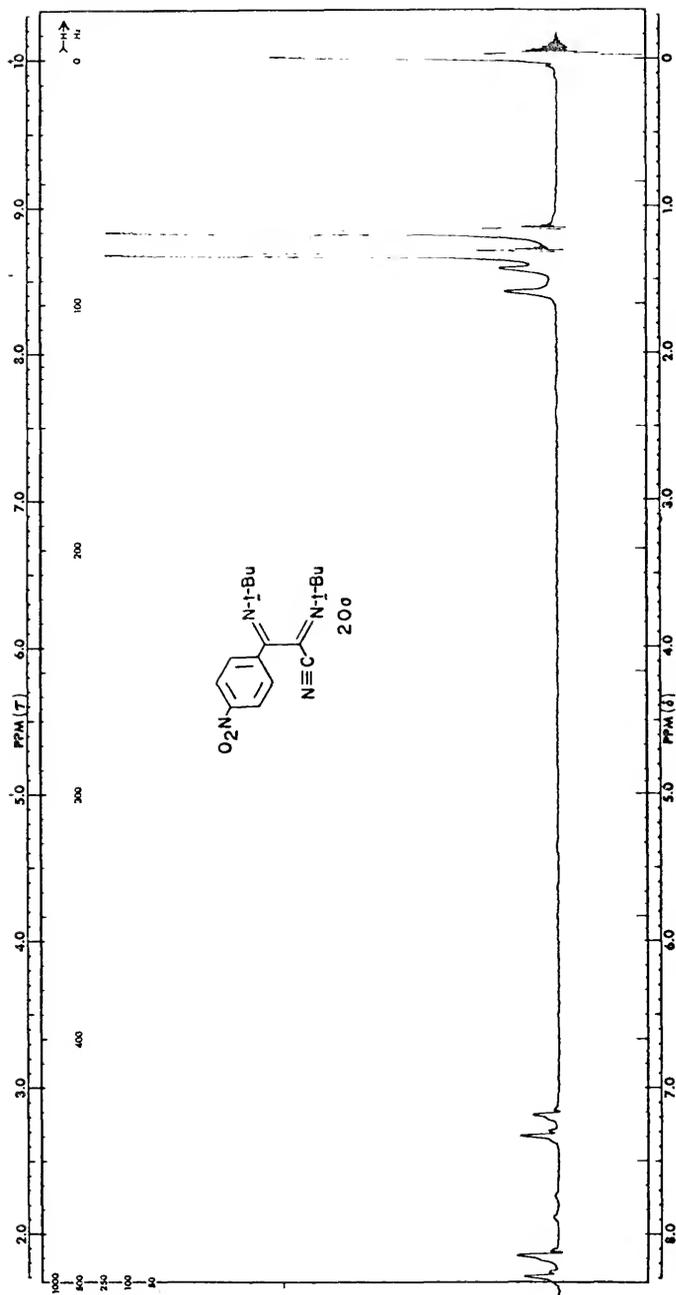
Anal. Calcd for C₁₇H₂₂N₄O₄: C, 58.95; H, 6.40; N, 16.17.

Found: C, 58.89; H, 6.60; N, 16.27.

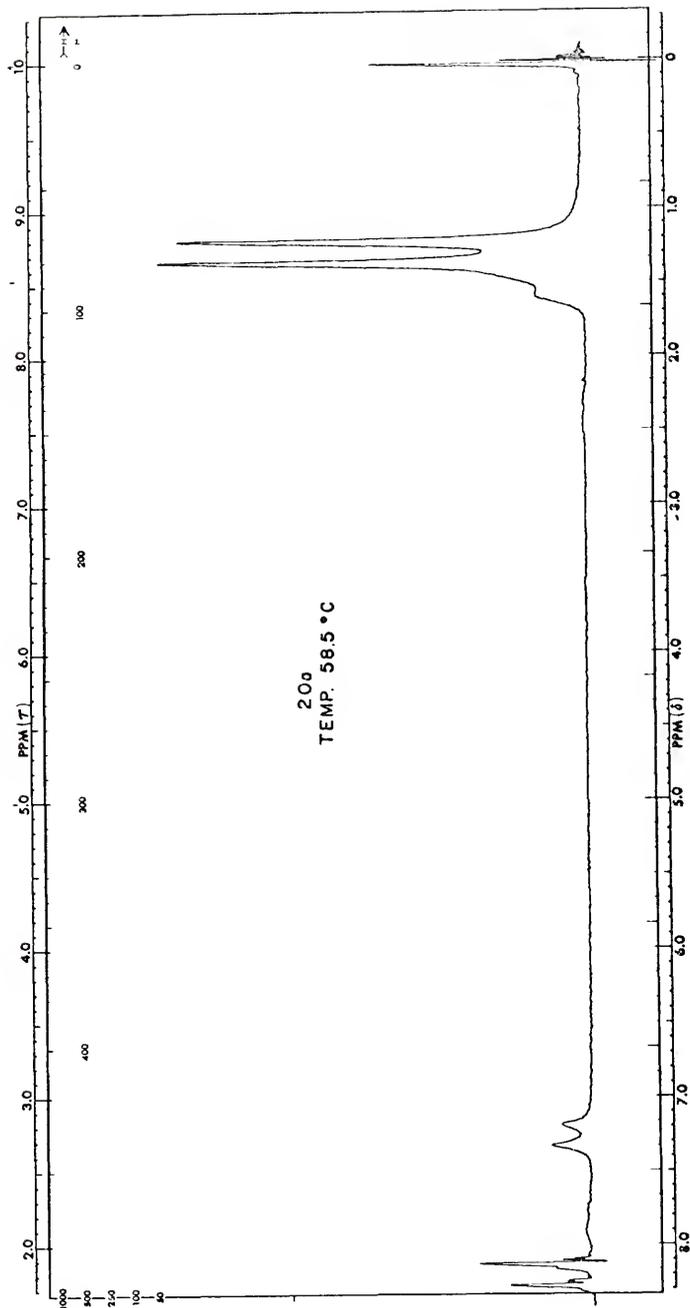
APPENDIX



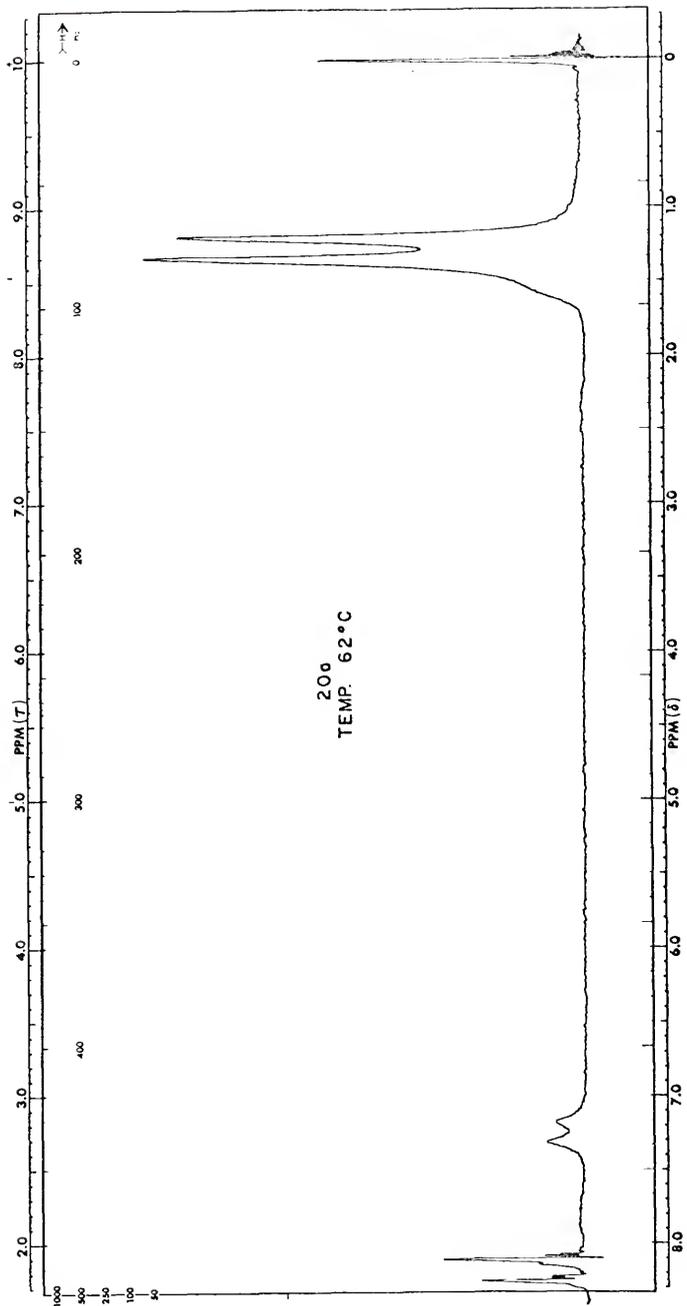
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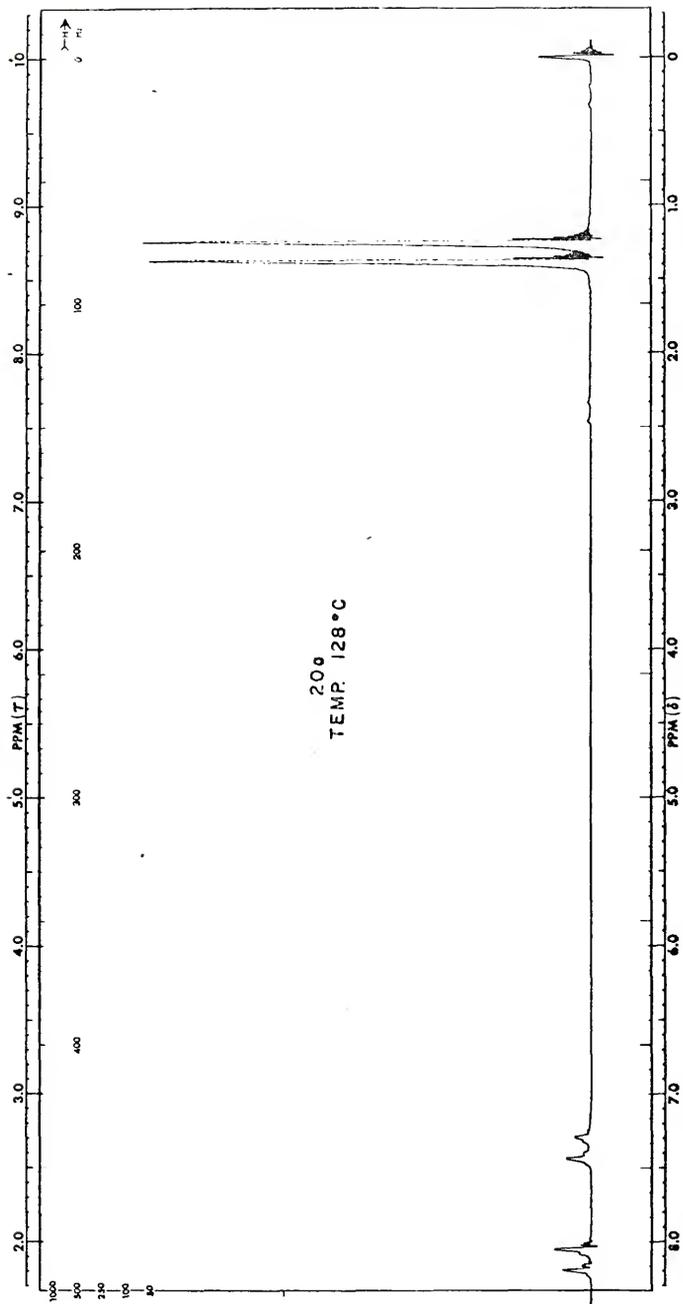
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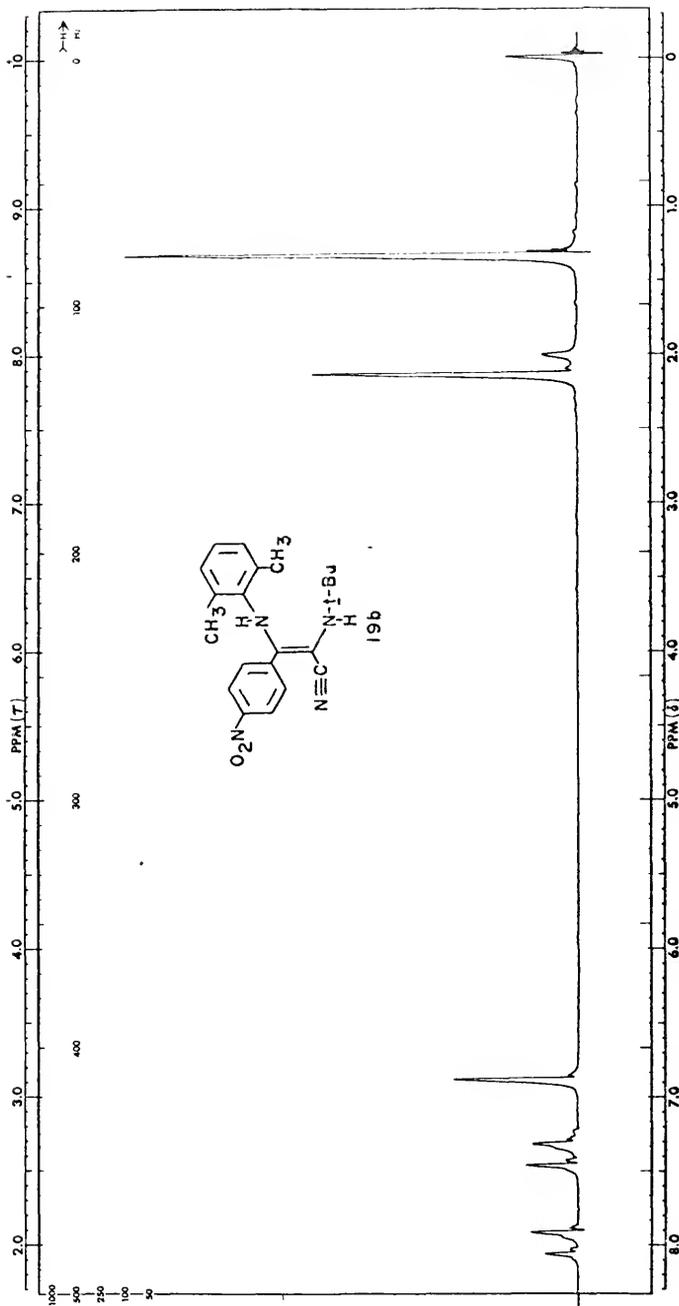
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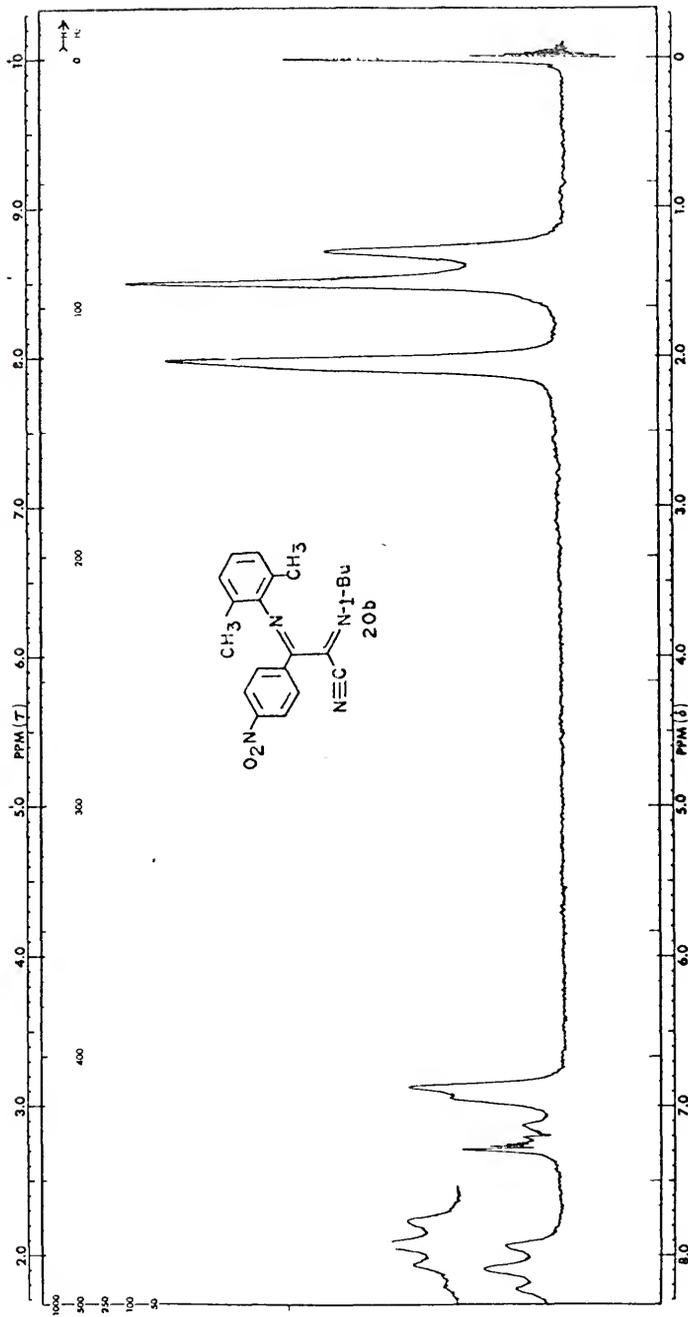
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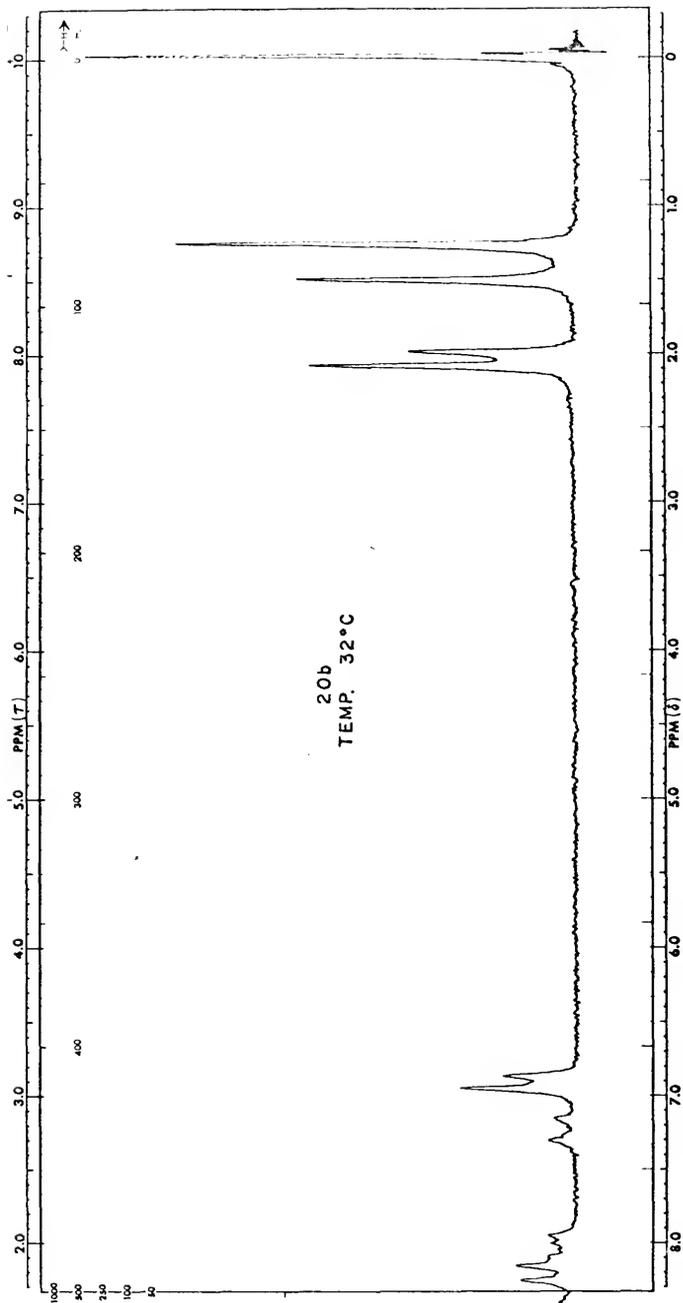
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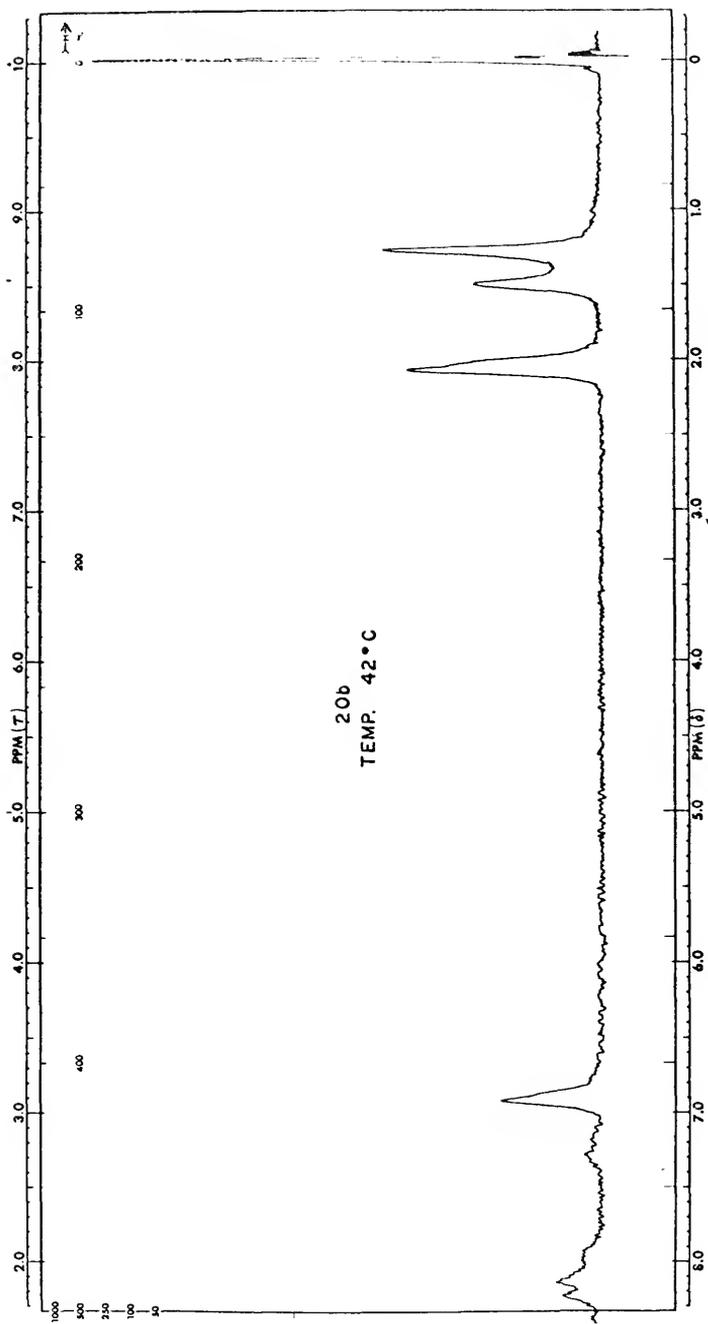
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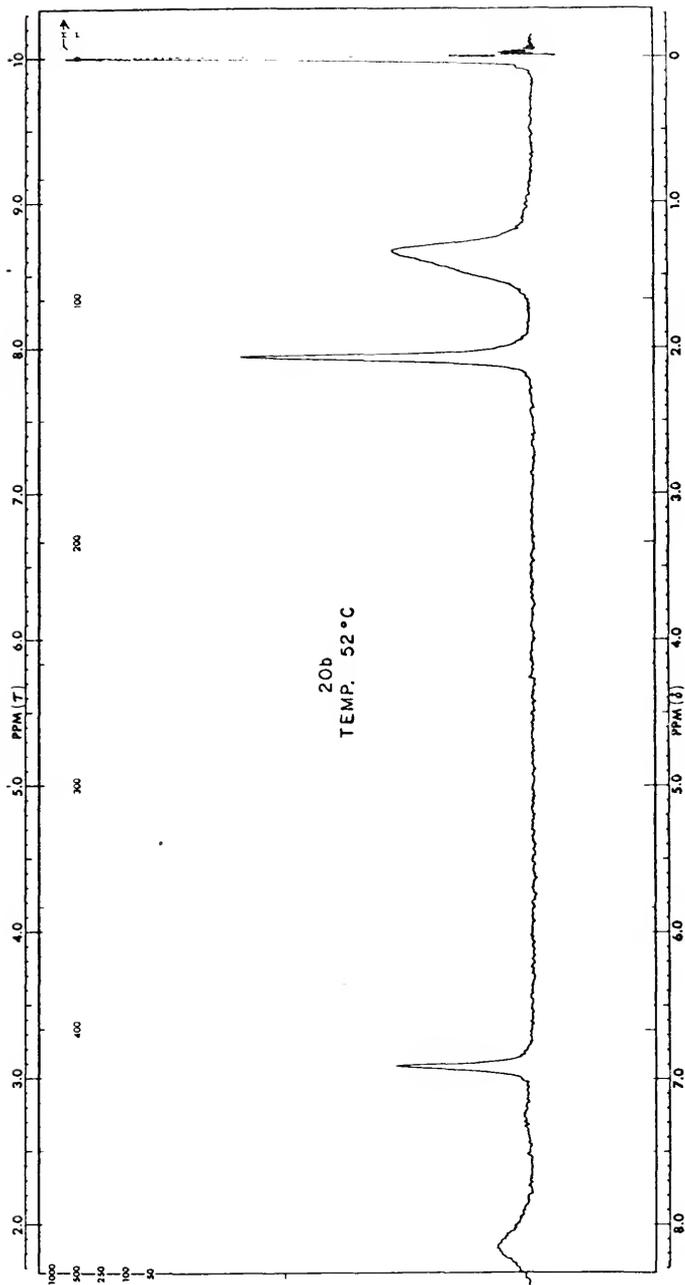
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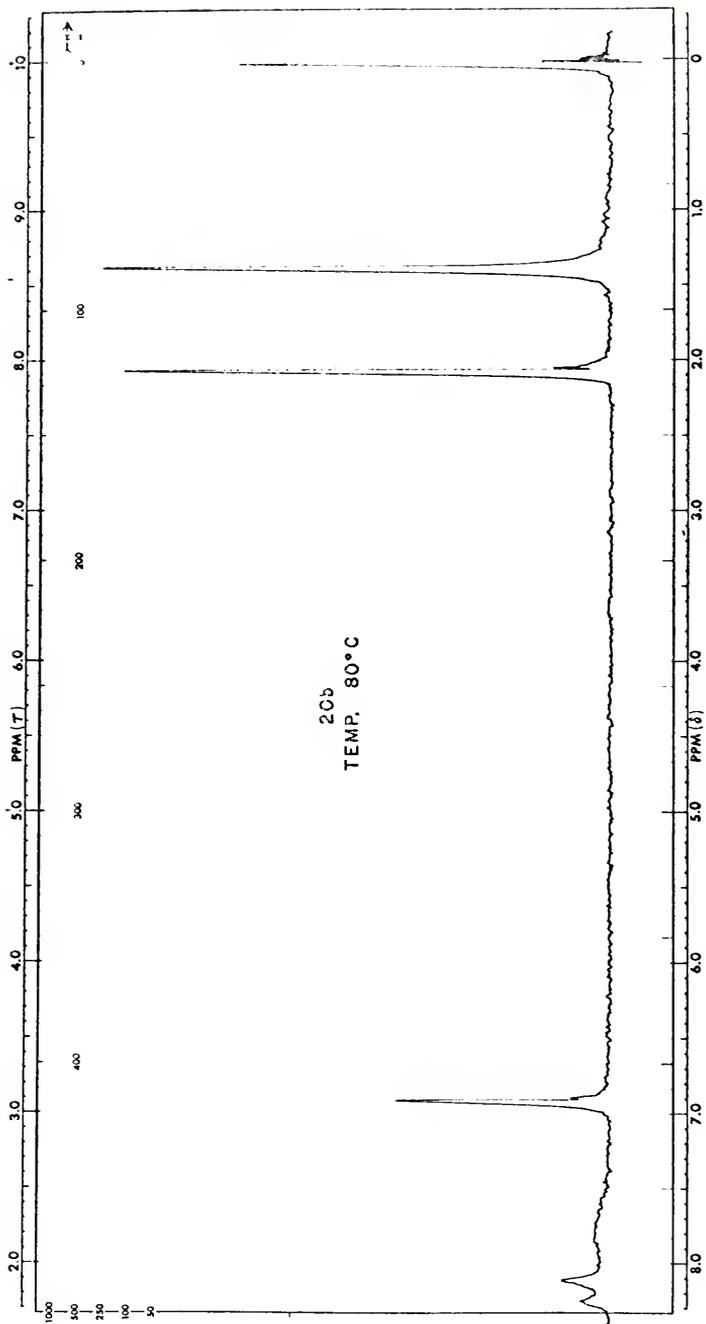
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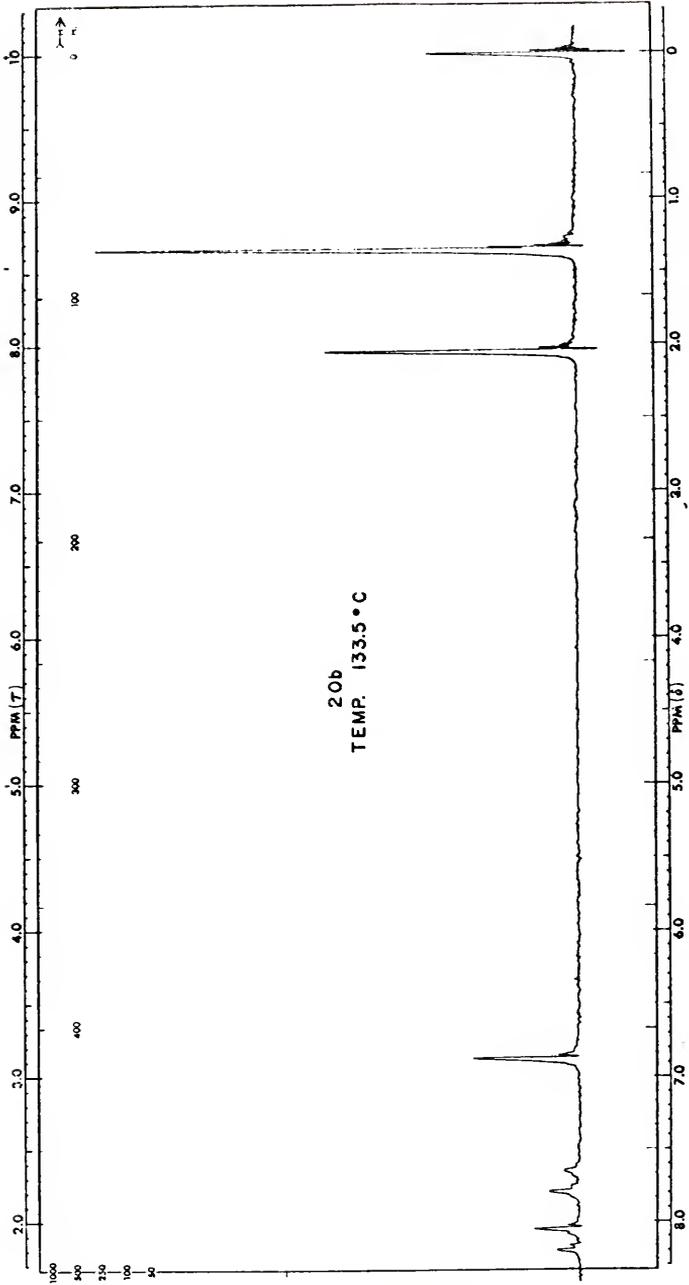
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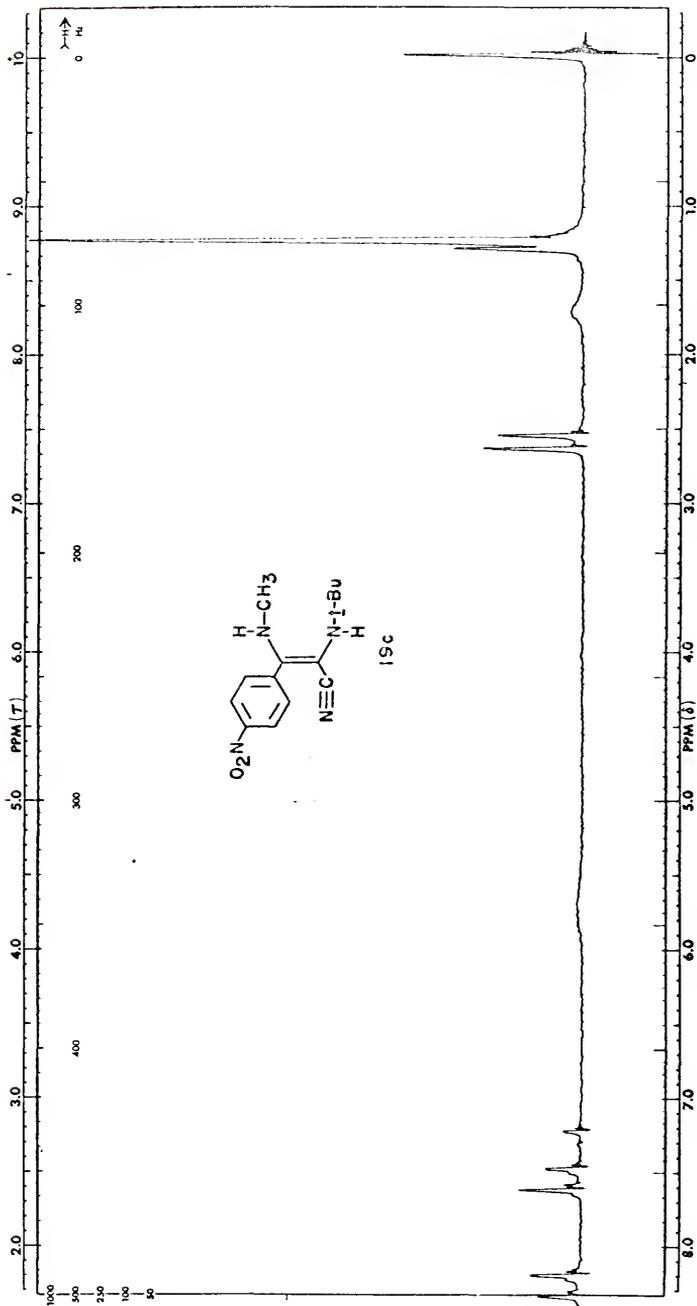
NMR NO. 6C



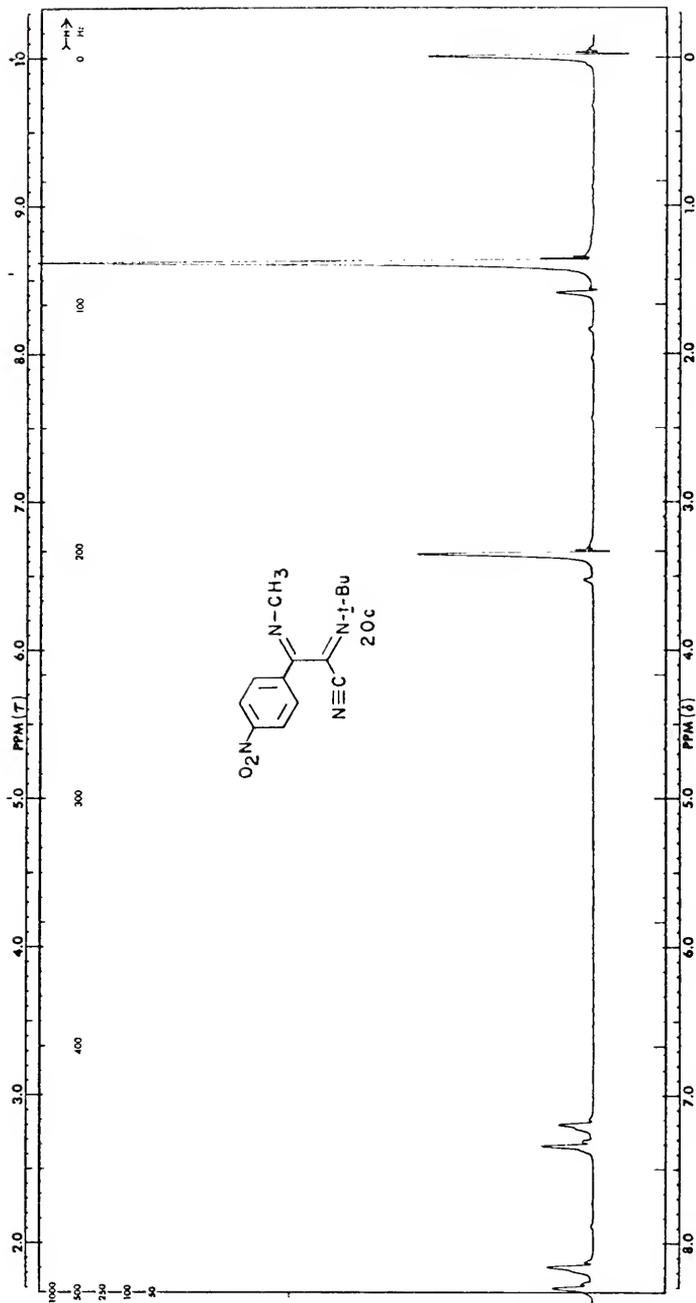
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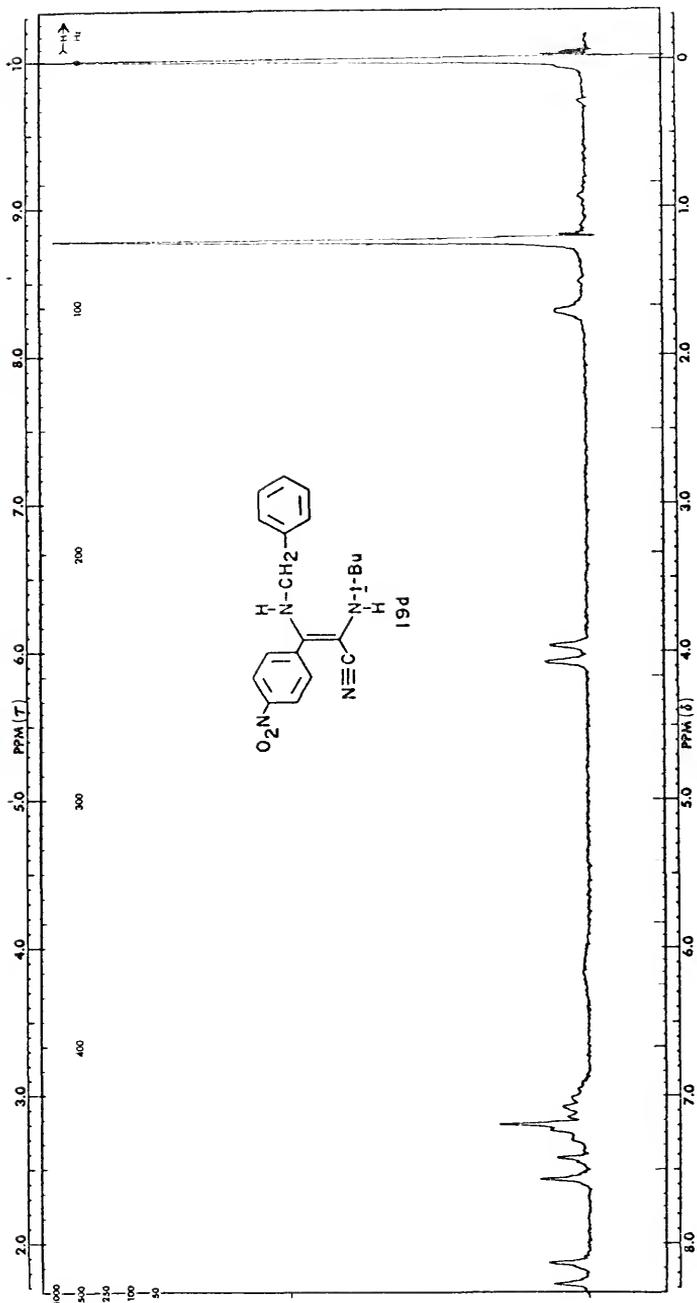
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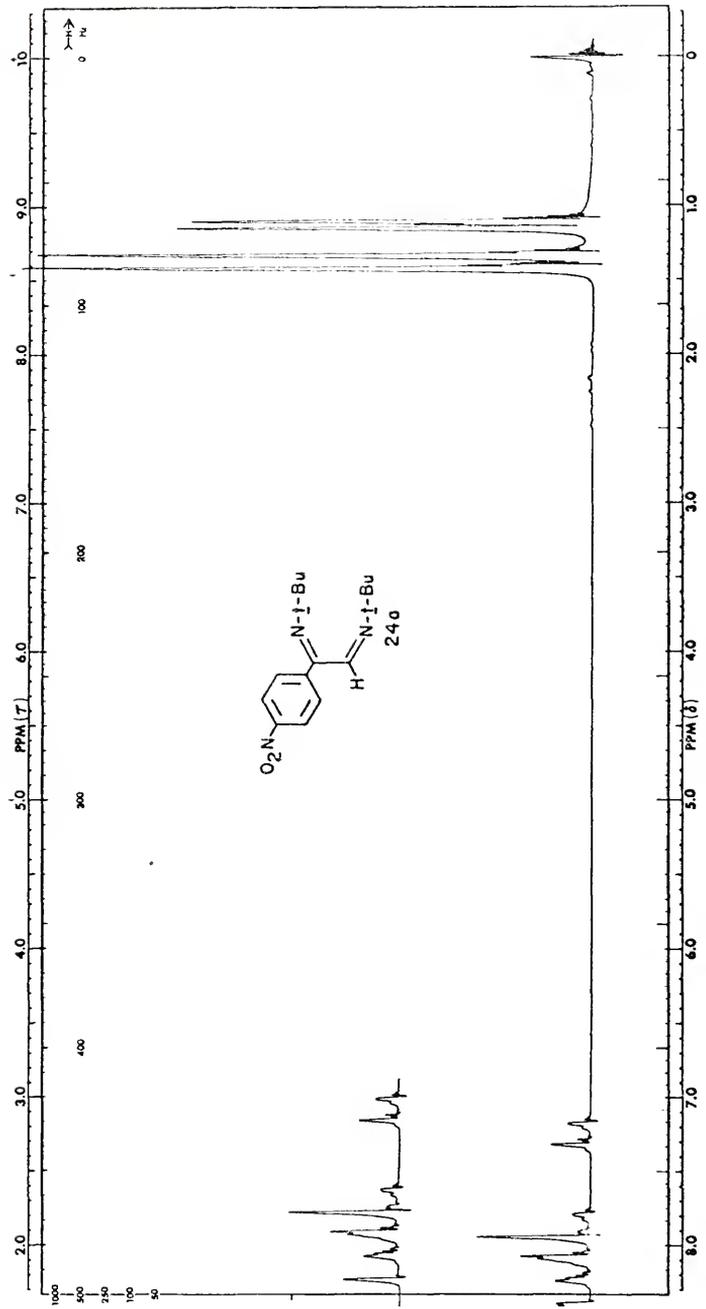
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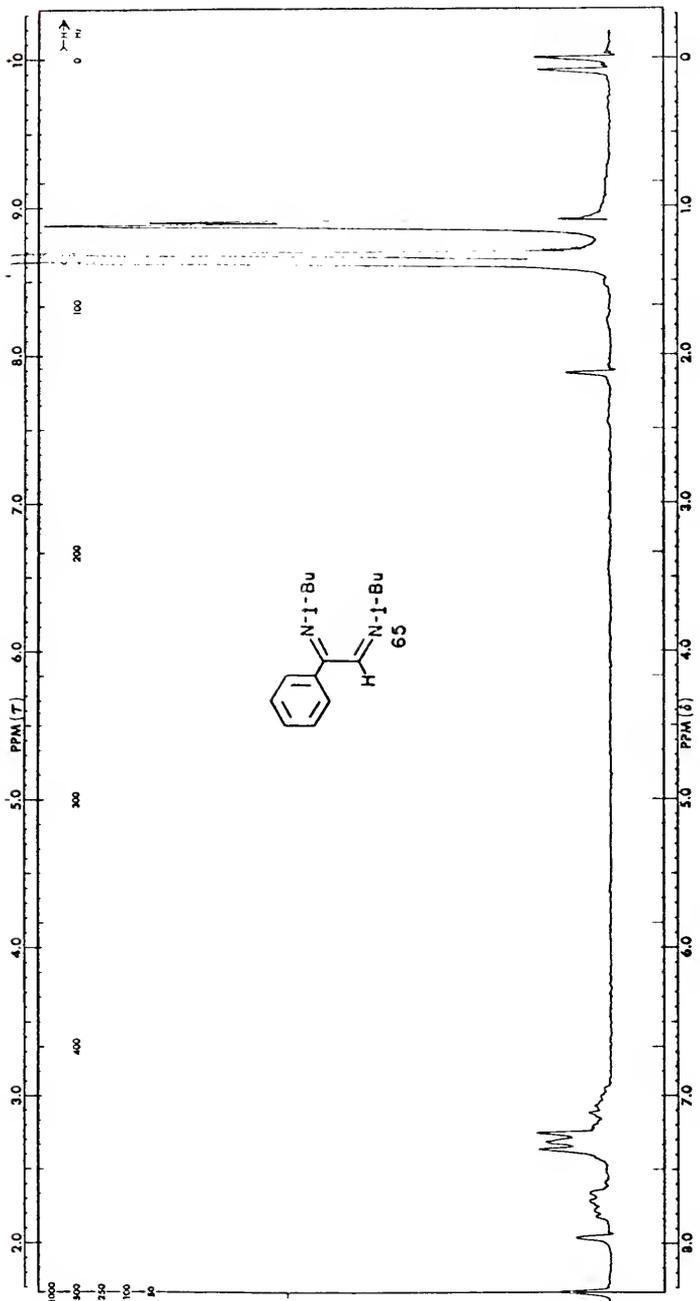
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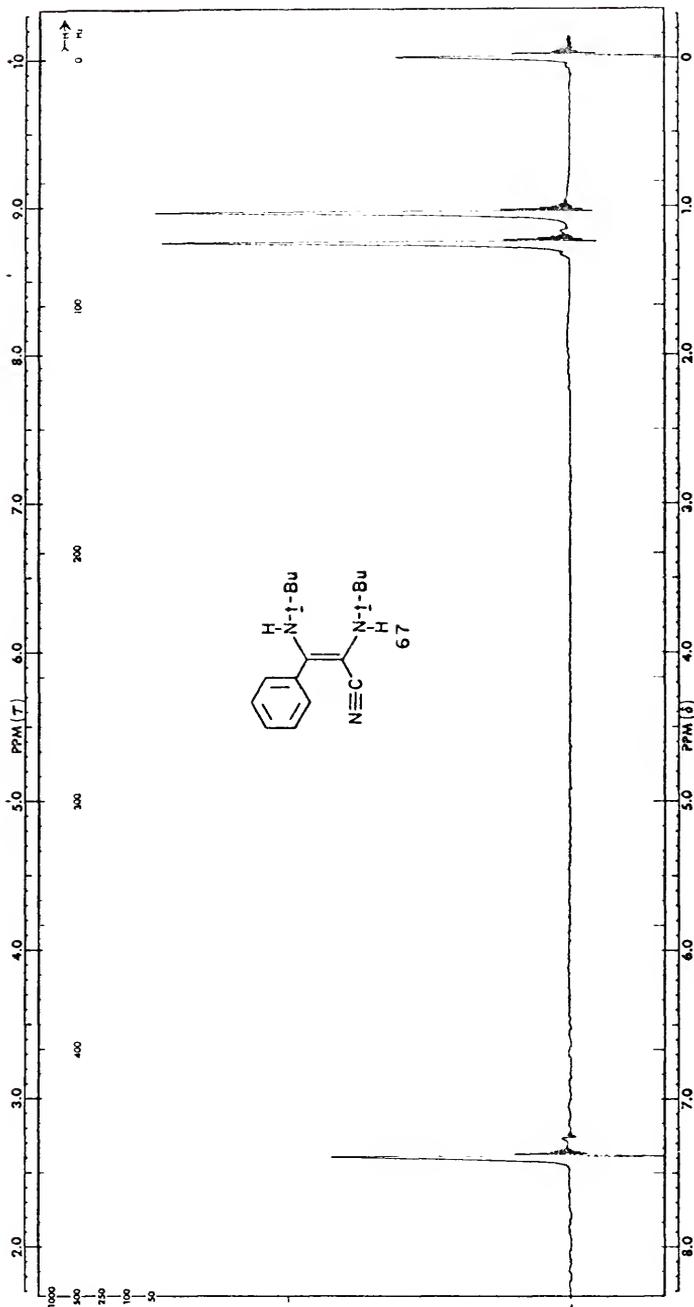
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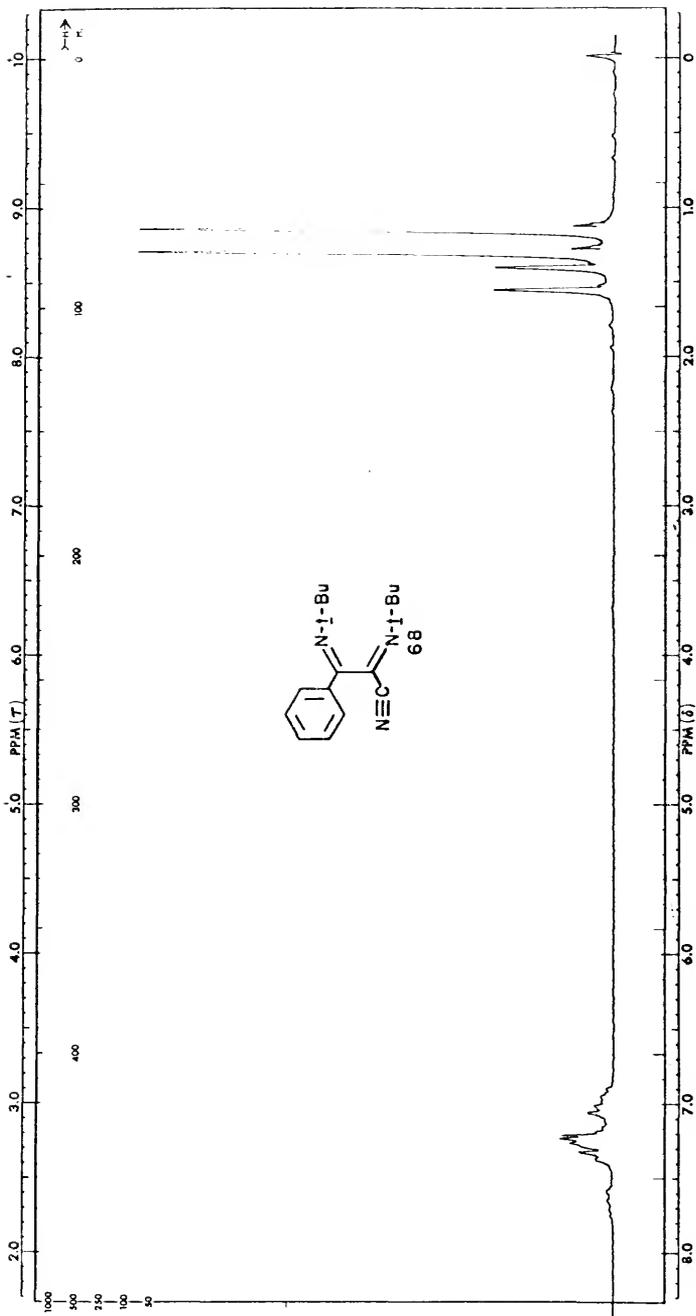
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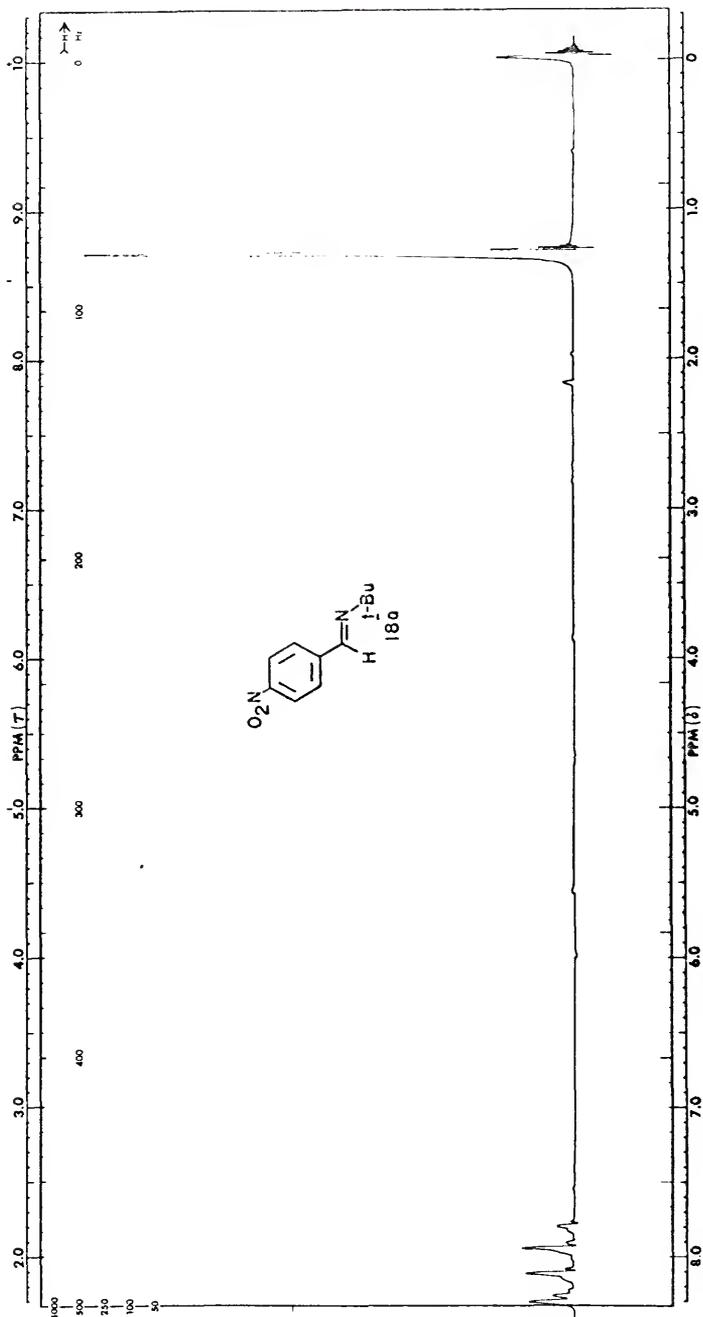
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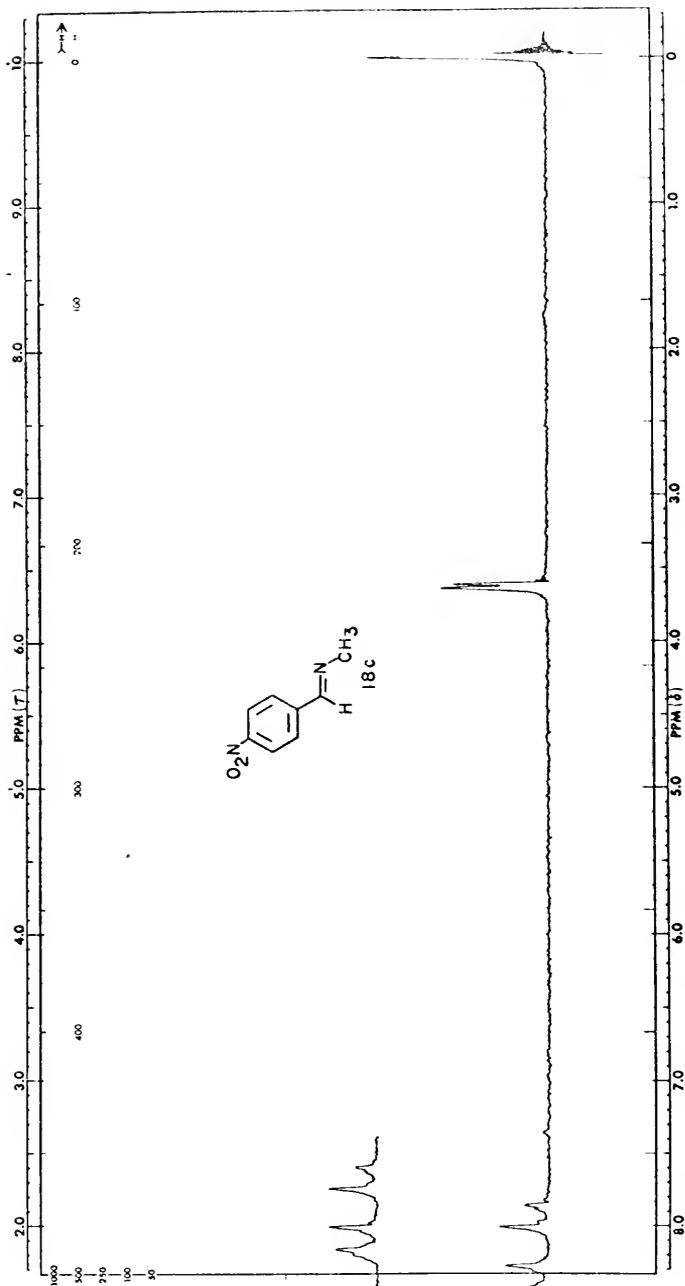
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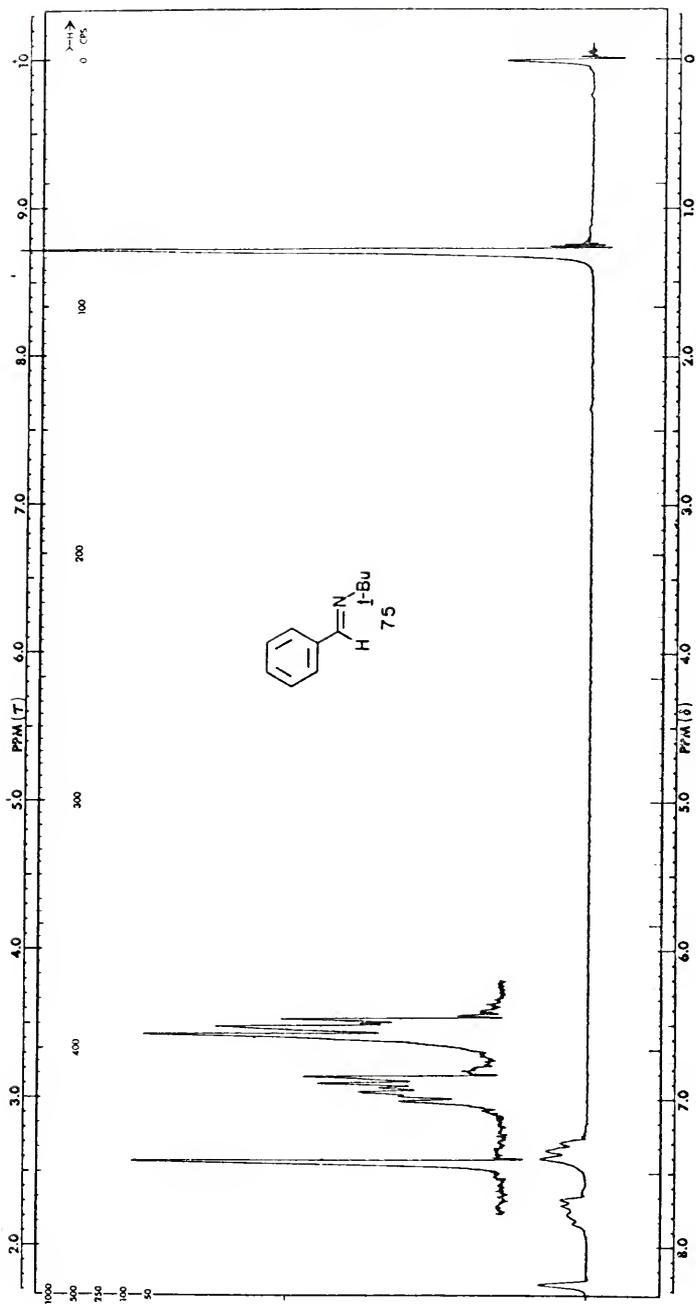
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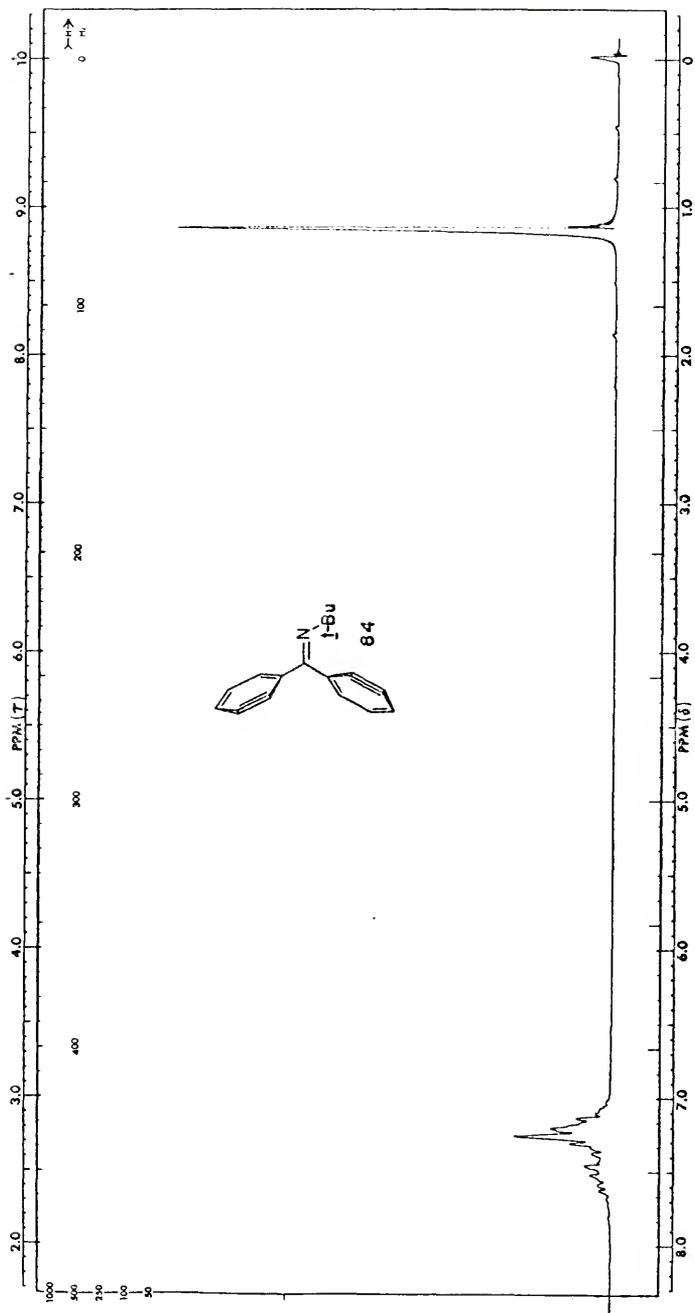
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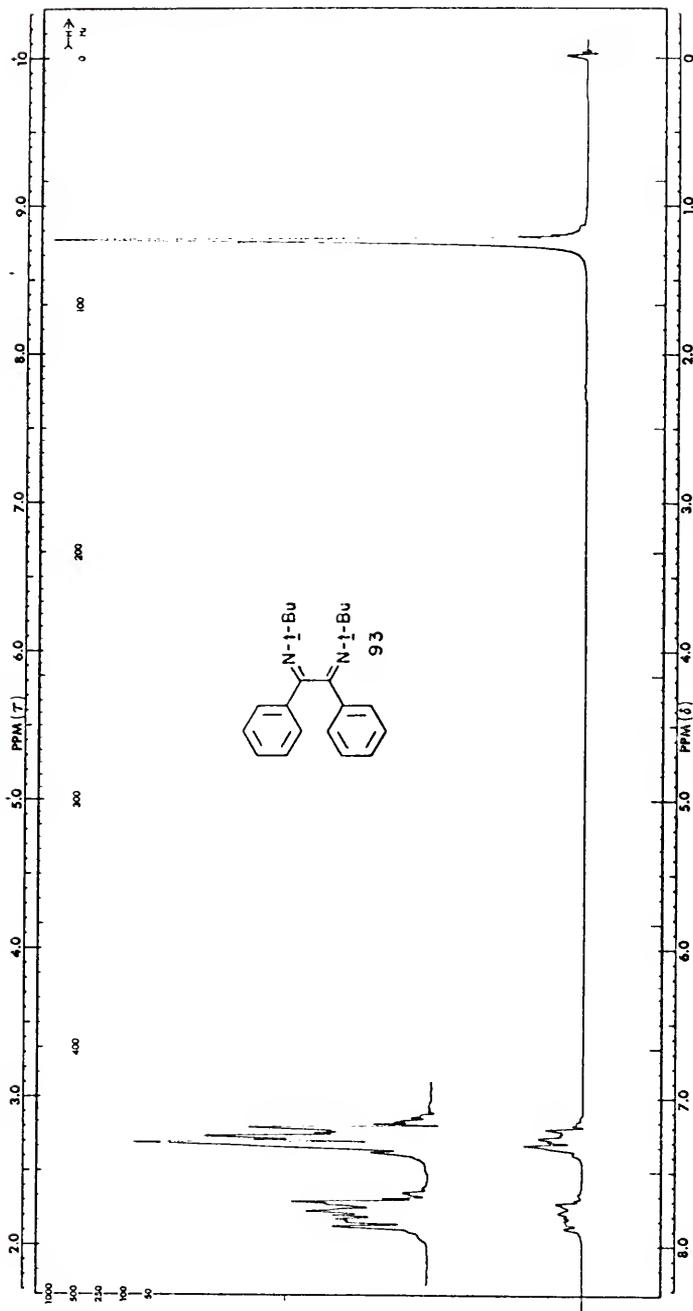
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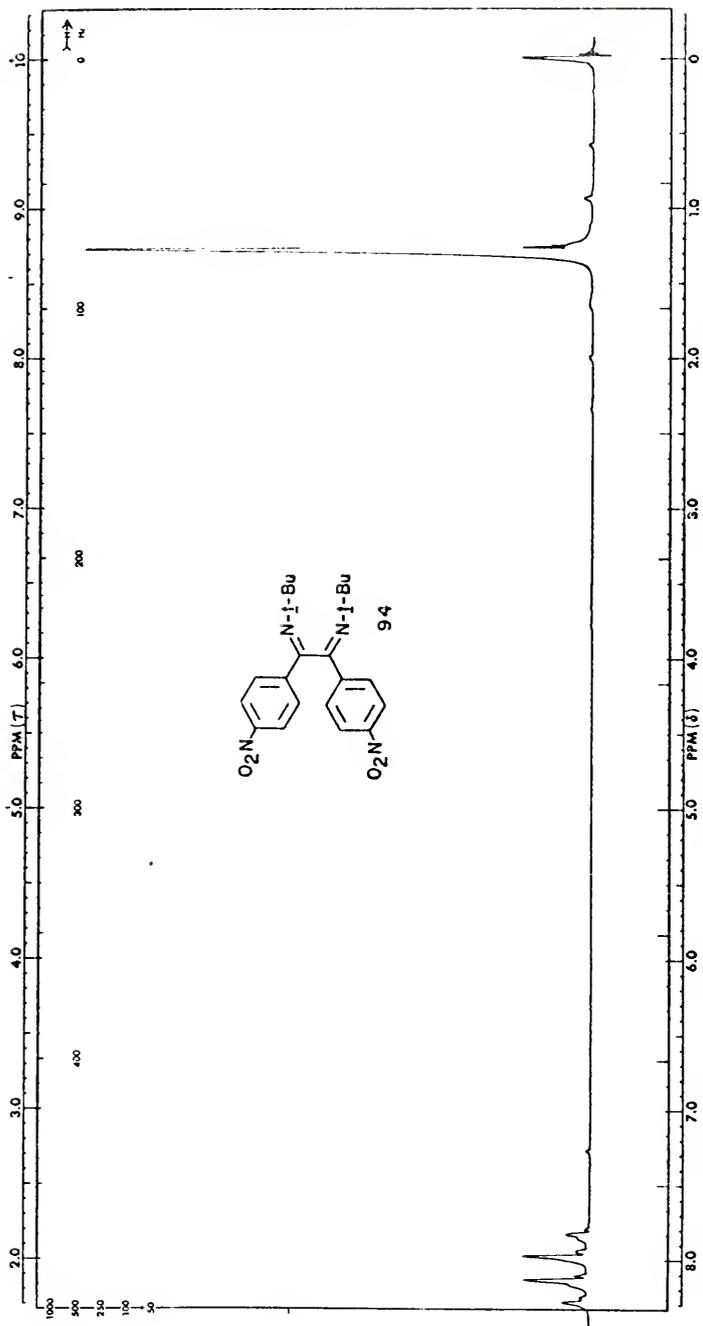
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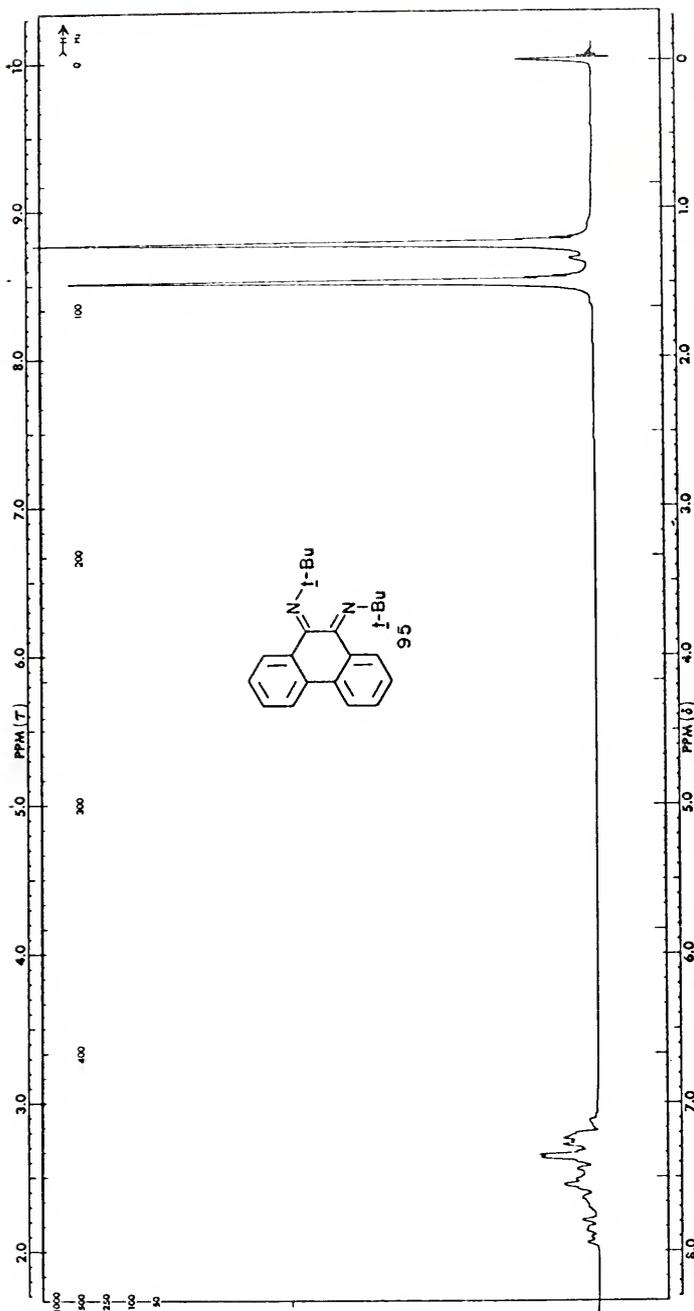
NMR NO. 17



NMR No. 18



NMR NO. 19



NMR No. 20

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16. Values for $\Delta\nu_{AB}$ were calculated from the following equation:

$$|1-3| = |2-4| = (\Delta\nu^2 + J_{AB}^2)^{\frac{1}{2}}$$

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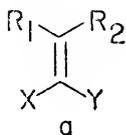
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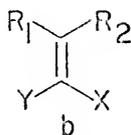
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67.



96



- When $R_1=R_2$ in 96, a and b are then chemically identical. Structures a and b are "degenerate isomers" for which the term "topomers" has been proposed.⁵¹ The process of interconversion would then be called "topomerization."
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113. The structure for this compound was not determined previously. In fact the proposed structure was ruled out since it did not fit all spectral data.⁹
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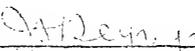
121. Analysis was obtained by M.M. Vestling.
122. This is the crude oil obtained from the reaction of 2-bromo-4'-nitroacetophenone (13.91 g, 0.057 m) in 100 ml of dimethylsulfoxide.
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140. This was determined by comparing the isolated material with an authentic sample.
141. The desired product does not seem to dissolve in 10% hydrochloric acid.
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BIOGRAPHICAL SKETCH

The author was born in St. Louis, Missouri on February 1, 1944. Soon after World War II his family moved to Parkersburg, West Virginia, where his father was employed by the O Ames Company. Jim grew up there and graduated from Parkersburg High School in 1962. In September, 1963, he enrolled at Marshall University in Huntington, West Virginia. After four years he graduated with honors with a B.S. degree in chemistry. In September, 1967, he entered Graduate School at the University of Florida in Gainesville. He worked in the Department of Chemistry as a Teaching Assistant while pursuing the degree of Doctor of Philosophy. For him the degree represents five years of hard work and the experience will long be remembered.

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.



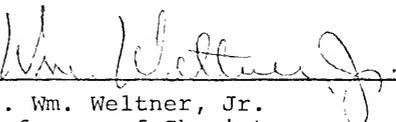
Dr. J.A. Deyrup, Chairman
Assoc. Professor of Chemistry

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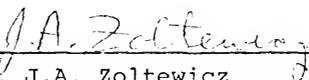
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I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

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Asst. Professor of Biochemistry

This dissertation was submitted to the Department of Chemistry in the College of Arts and Sciences and to the Graduate Council, and was accepted as partial fulfillment of the requirements for the degree of Doctor of Philosophy.

December, 1972

Dean, Graduate School



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