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SOME ASPECTS OF AZEPINE CHEMISTRY AND THE EFFECT OF SUBSTITUENTS ON THE REACTIONS OF PHENYL NITRENE

by

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A dissertation submitted to the
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degree of Doctor of Philosophy,
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1970

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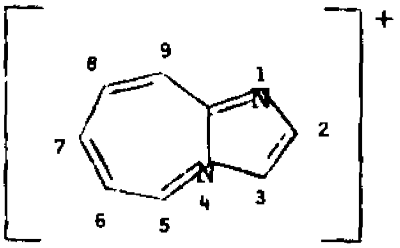
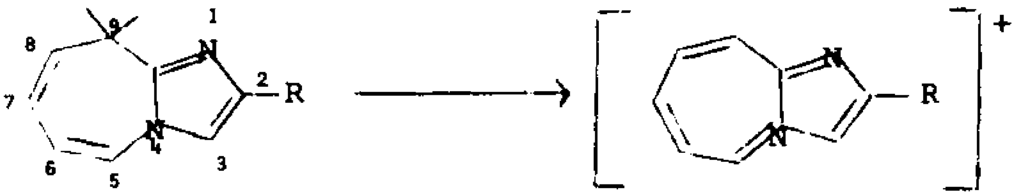
THESIS PART I

INTRODUCTION

While attempting to synthesize the imidazo[1,2-a]azepinium ion, I, a number of 2-substituted-9H-imidazo[1,2-a] azepines, II, were prepared[1]. Various homogeneous methods of two electron oxidation or in this case, hydride removal were tried on several of these in an attempt to remove a hydride ion from the 9 position (Equation 1). These methods include treatment of compounds IIb and IId with quinones such as dichlorodicyanobenzoquinone, DDQ, and tetrachlorobenzoquinone, chloranil, and the carbonium ion, triphenylmethyl carbonium ion, in the expectation that the theoretically interesting azepinium ion, I, would be generated.



I

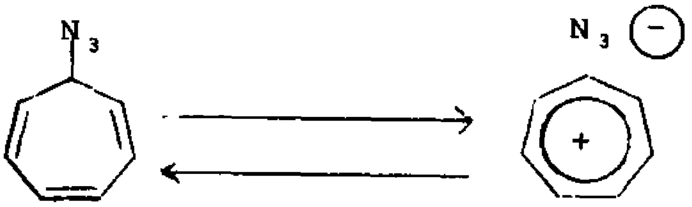


II R III

a) H
b) methyl
c) phenyl
d) p-bromophenyl
e) p-biphenyl

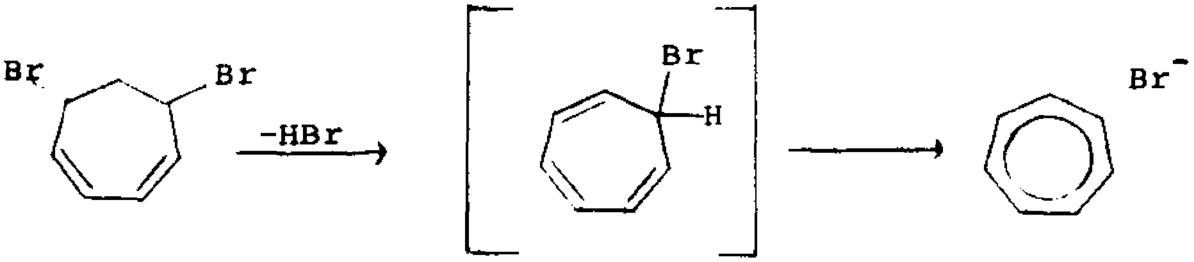
Equation 1

In order to circumvent the shortcomings of hydride removal after all trials had failed, the idea of employing a better leaving group than hydride was investigated. All that is necessary to achieve this desired ten π electron system, which is isoelectronic with azulene, from the imidazoazepines, II, is to remove the anionic species corresponding to a substituent in the 9 position. The ideal substituent would be one which could be induced to self-dissociate in a similar way to the way azidotropylidene, IV, dissociates depending on temperature and solvent to form tropylium azide ion pair, V,[2] (Equation 2) or similar to the way bromotropylidene, VII, immediately becomes tropylium bromide, VIII,[3] on formation (Equation 3). This would be tantamount to synthesizing



IV V

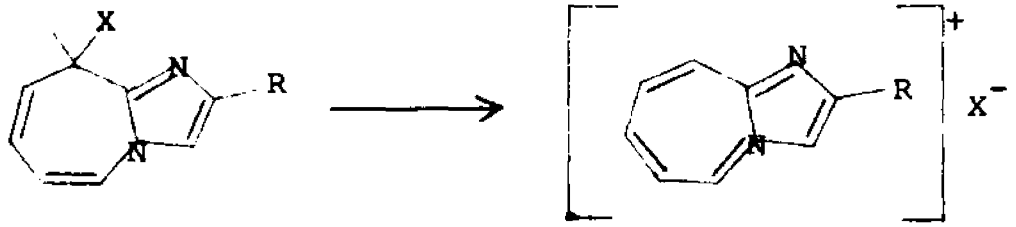
Equation 2



VI VII VIII

Equation 3

an imidazoazepine in the correct oxidation state (Equation 4).



IX X

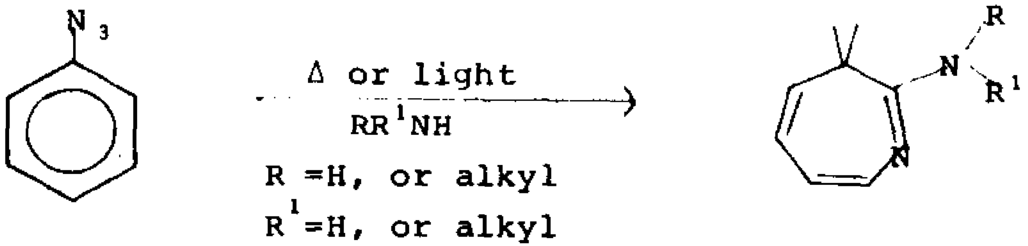
Equation 4

The most direct route to a 9H-imidazo[1,2-a]azepine appropriately substituted in the 9 position such as IX involves utilization of the 2-amino-3H-azepine similarly substituted in the 3 position[1] (Equation 5). However, the ring expansion reaction of phenyl azide, XII, in amine solvents[4,5]

XI IX

Equation 5

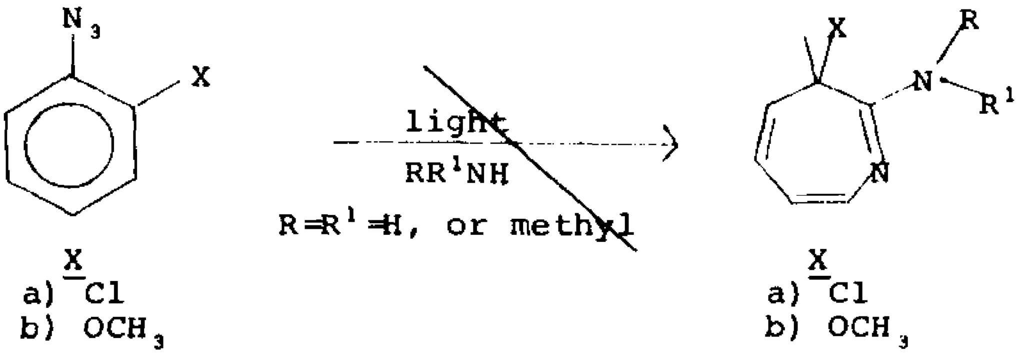
(Equation 6) to give 2-amino-3H-azepines, such as XIII, had



XII XIII

Equation 6

not been explored for substituted phenyl azides other than alkylphenyl azides[4]. Preliminary results for the photolytic decomposition of o-chlorophenyl azide, XIVa, and o-methoxyphenyl azide, XIVb, did not yield 3-substituted-2-amino-3H-azepine products, XV, (Equation 7).

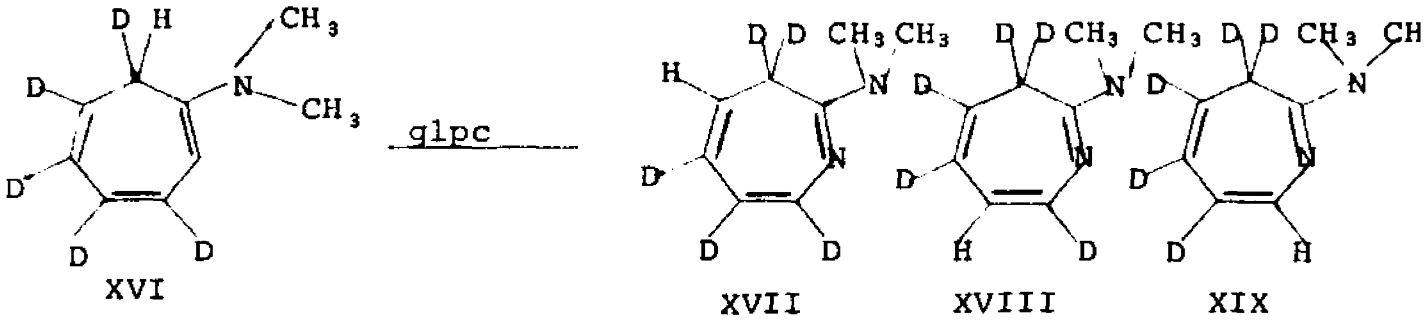


XIV

XV

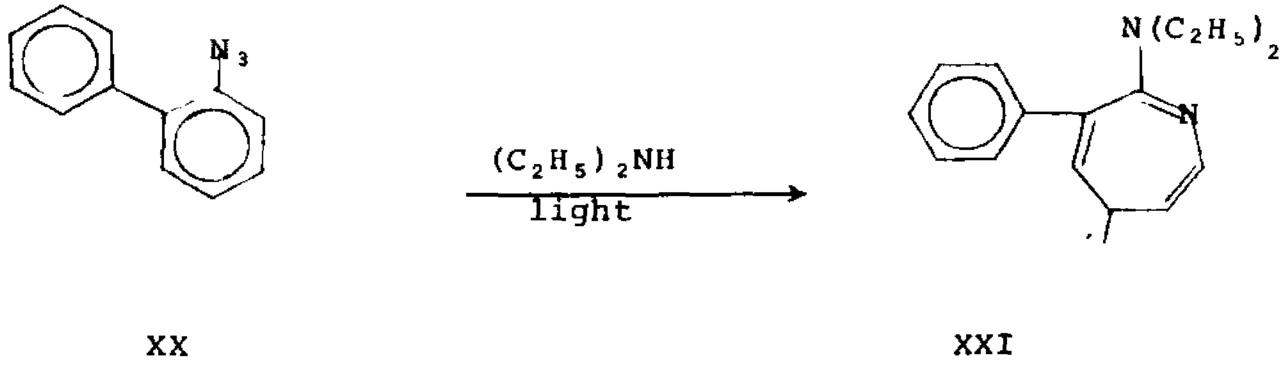
Equation 7

Whether the failure of XIVa and XIVb to undergo the ring expansion reaction was due to the substituent being ortho to the decomposing azido group or whether other than alkyl substituted phenyl azides in general do not give azepines prompted a study of the effect of p-substituents on azepine formation. Also, azepines derived from p-substituted phenyl azides might be just as satisfactory for the ultimate preparation of the azepinium ion, I, as compounds such as XV, in view of the findings of Odum and Seltzer[6] on the isomerization of a similar system. On thermal isomerization by glpc of 3,4,5,6,7-pentadeutero-2-dimethylamino-3H-azepine, XVI, the lone proton at the 3 position exchanges with deuterium mostly at the 6 position, XVII, but also at the 4, XVIII, and 7, XIX, positions (Equation 8). This suggests an



Equation 8

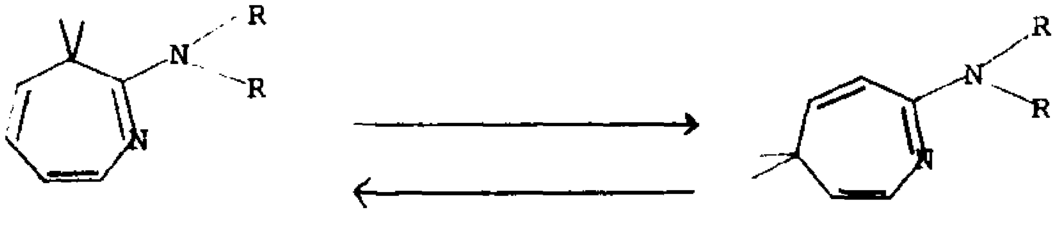
isomerization of the π system and the methylene group such that each of these positions has some allylic methylene character at least some of the time. Also, in the photolysis of 2-azidobiphenyl, XX, in diethylamine a small yield of 2-diethylamino-3-phenyl-5H-azepine, XXI, has been detected[7] (Equation 9), indicating a possible thermodynamic equilibrium



Equation 9

between the methylene group at the 3 position and at the

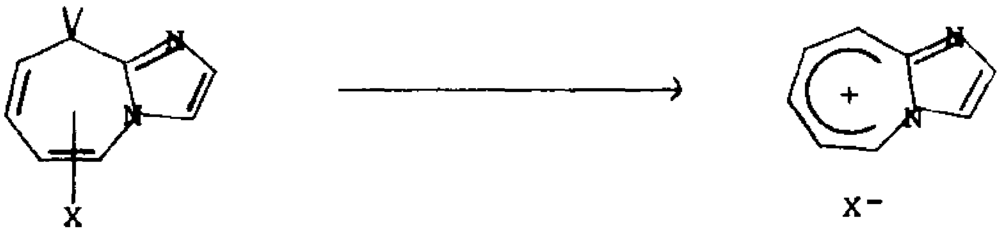
5 position (Equation 10) which without phenyl substitution



XIII XXII

Equation 10

normally lies entirely toward the 3 methylene. Thus, a 5,6, 7, or 8-substituted-9H-imidazo 1,2-a azepine, XXIII, might isomerize allowing the substituent to dissociate leaving an allylic π orbital conjugated with the rest of the π system (Equation 11).



XXIII XXIV

Equation 11

A number of p-substituted phenyl azides were photolyzed in dimethylamine and anhydrous, liquid ammonia. Those compounds-with resonance electron-donating substituents behaved similarly to phenyl azide while those with resonance electron-withdrawing substituents behaved differently. It was this different behavior of p-cyanophenyl azide which indicated possible chemical evidence of a singlet aryl nitrene. Since no cases of intermolecular reactions directly attributable to singlet aryl nitrenes had been reported previously, a more detailed investigation of these results was warranted.

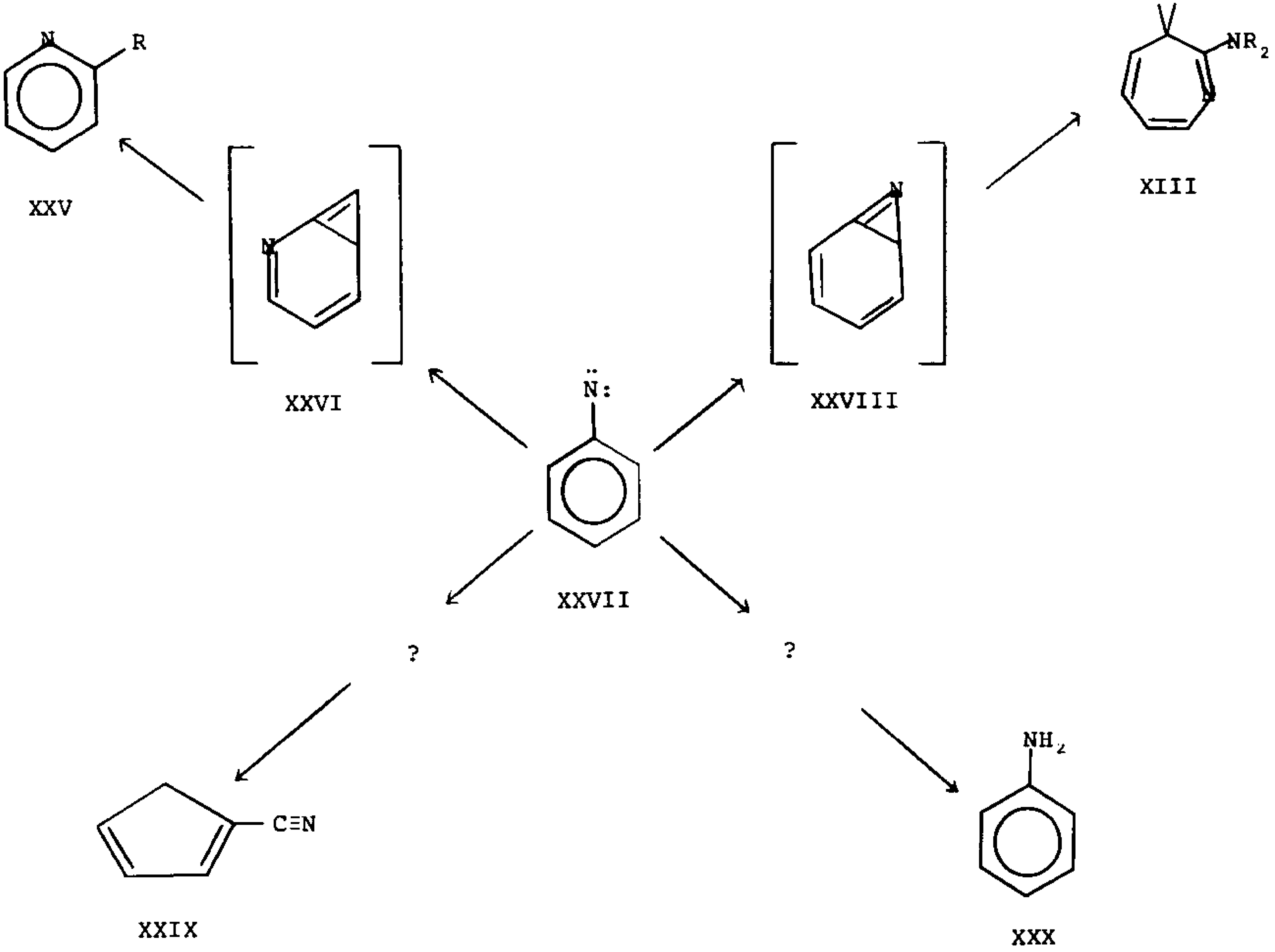
A CRITICAL REVIEW OF ARYL NITRENES

Aryl nitrenes are postulated as intermediates in a number of reactions[8], however, very little direct evidence of the spin states involved is available. Generally, deductions based on the nature of the final product formed are the only justifications for assigning singlet or triplet character to the intermediate nitrene. When these products are envisioned as in Scheme I to arise from isomeric intermediates, which is the case for most singlet aryl nitrenes to date, this assignment becomes even more speculative.

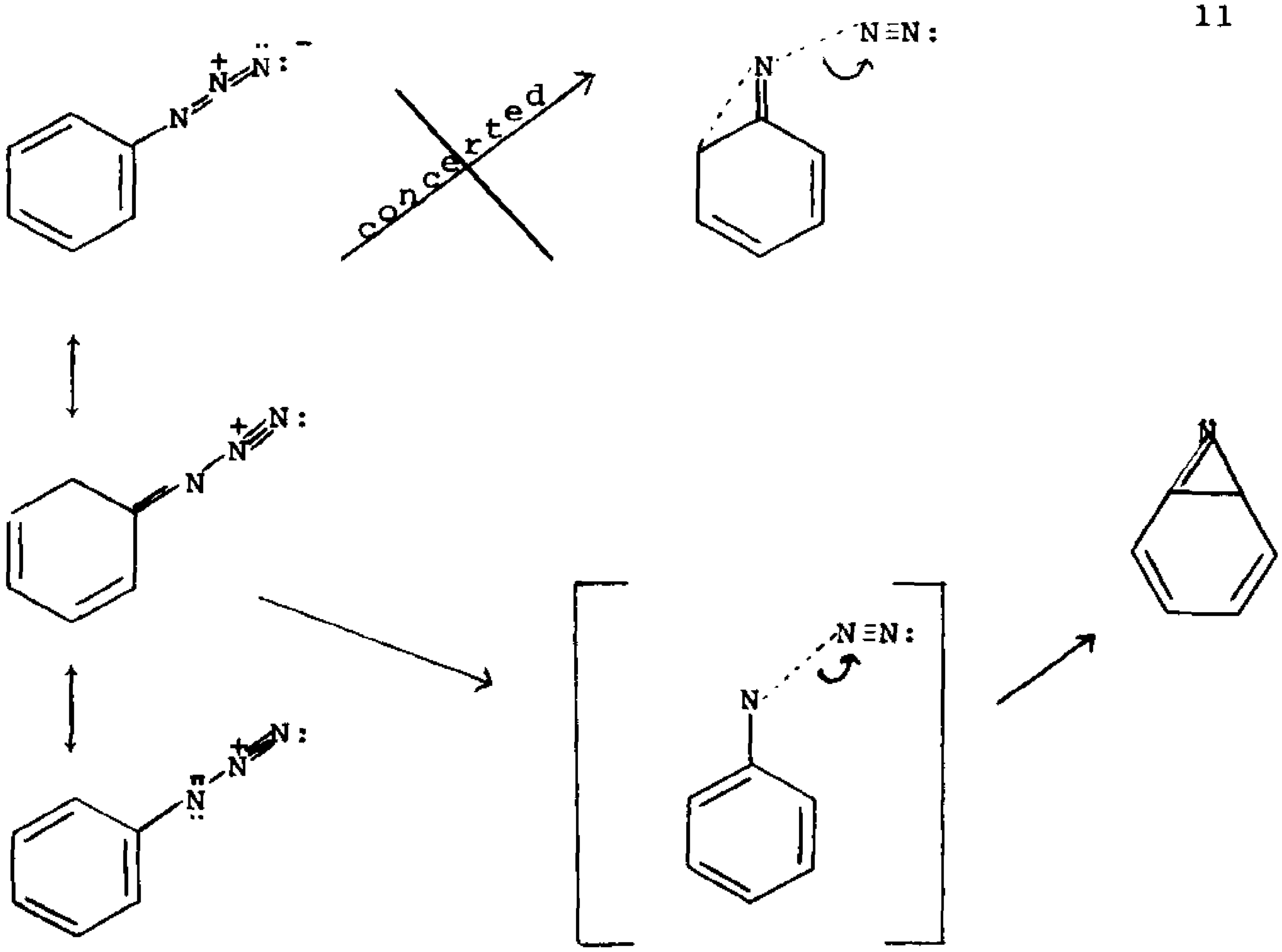
Kinetic Evidence for Aryl Nitrenes

The negligible variation in the rate of nitrogen evolution, when the kinetics of the decomposition of m-nitrophenyl, m-methoxyphenyl and m-methylphenyl azides in aniline solution were studied[9] showed that the loss of nitrogen is not concerted with formation of a carbon-nitrogen bond between the ortho carbon of the ring and the nitrogen of the azido group attached to the ring (Equation 12). The different m-substituents cause a large variation in electron density at the ortho position. This should greatly influence incipient bond formation if the carbon ortho to the azido group participates in the loss of nitrogen.

Though many different products, such as azepines, XIII, anilines, XXX, azo compounds, XXXI, hydrazo compounds, XXXII,

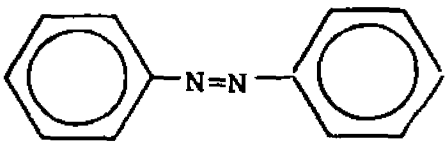


SCHEME I

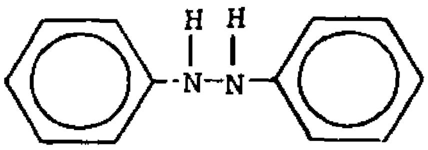


Equation 12

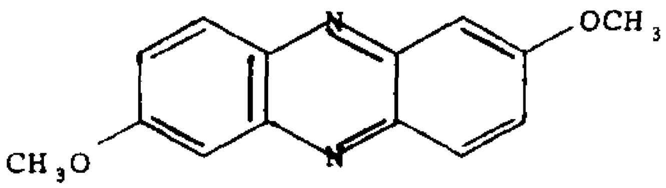
and phenazines, XXXIII, to name only a few, are formed depending on solvent, it has been demonstrated that the rate determining step for the thermal decomposition of phenyl azide



XXI



XXXII



XXXIII

and several m- and p-substituted phenyl azides is independent of solvent. In solvents such as tetralin[10], nitrobenzene[9,10], and aniline[9] the decomposition of phenyl azide is unimolecular and the rates are the same. Apparently the product forming step is not the rate determining step.

Smith and Hall[11] showed that there is an effect on the rate constant, eightfold from slowest to fastest, with p-substitution. All p-substituents increase the rate of nitrogen loss but there is no simple correlation with Hammett's substituent constants. There is a considerable variation in the enthalpies of activation with p-substitution but not with m-substitution. This variation is in the same qualitative order as the values of the Hammett $\Delta\sigma = \sigma_p - \sigma_m$ indicative of a mesomeric electronic interaction between the substituent and the azido group. The $\Delta\sigma$ corresponds to that portion of the substituent constant that is a measure of the resonance effect of a given substituent. While an azido group has a mildly electron-withdrawing inductive effect, its electron-donating conjugative effect is much greater than the halogens and more closely approximates an acylamino group[12], XXXIV. Thus, as in Figure 1, in the ground state resonance contributors placing increased π electron density into the benzene ring would be stabilized by the ability of the p-nitro group to help further delocalize this increased negative charge on the ring, XXXVI. On the other hand a p-methoxy group would

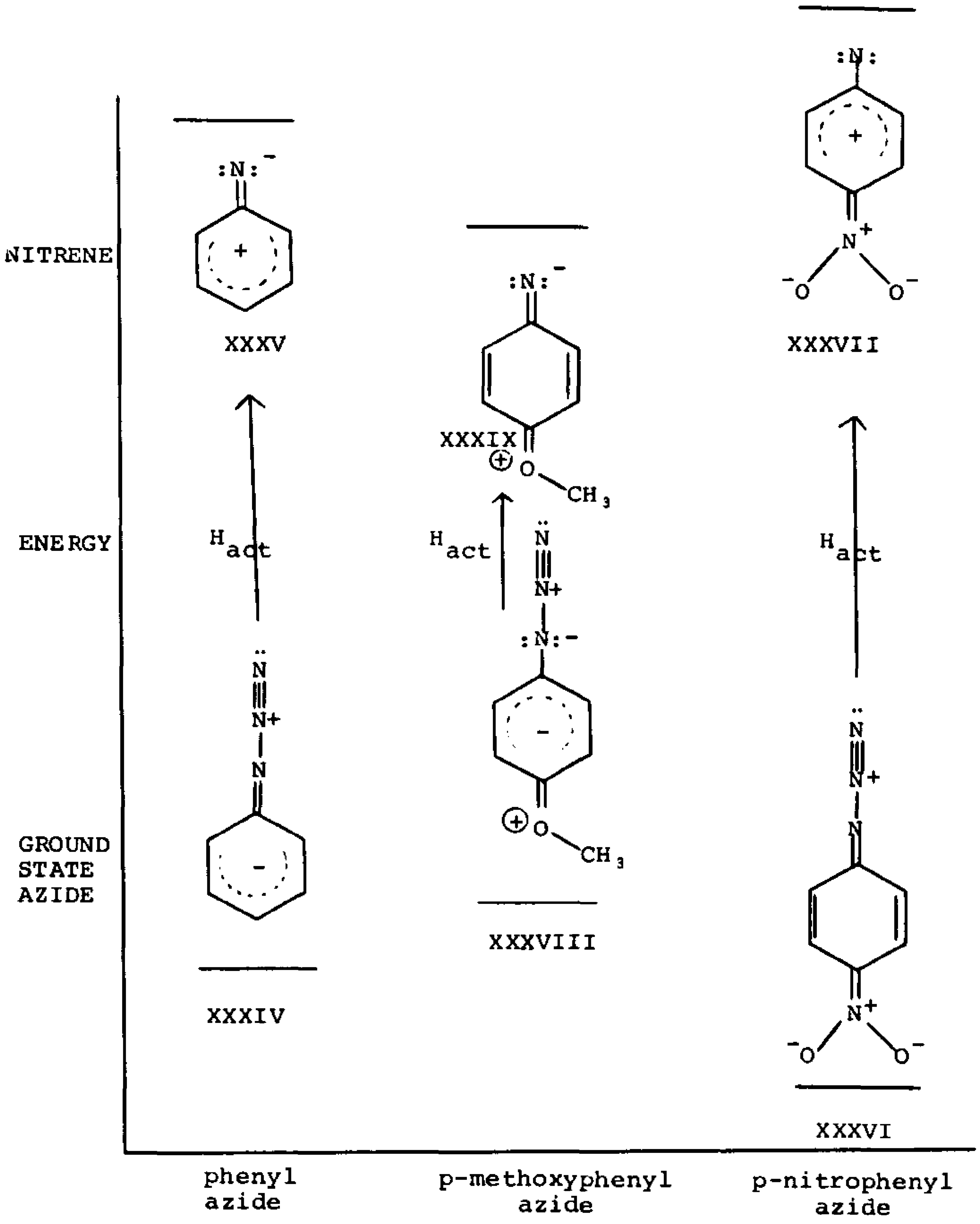
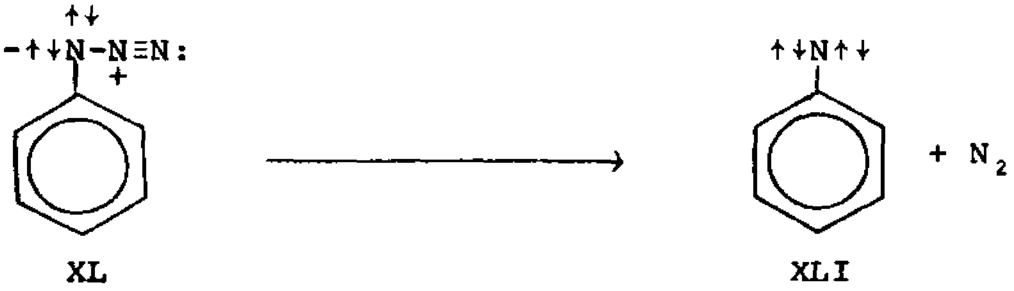

NITRENE
ENERGY
GROUND STATE AZIDE
XXXV
XXXIX
XXXVII
H act
XXXIV
XXXVIII
XXXVI
phenyl azide
p-methoxyphenyl azide
p-nitrophenyl azide

FIGURE 1

destabilize such contributors, XXXVIII, because of its ability to form resonance contributors also increasing the π electron density of the ring. Smith and Hall[11] suggested that the best estimate of the effect of substituents on the transition state was to consider the effects on the presumed initial product, aryl nitrene, XXXV. If we consider Wigner's principle of spin conservation the initially formed aryl nitrenes from the thermolysis of aryl azides, XL, should be in the signlet state, XLI (Equation 13). For the developing



Equation 13

singlet nitrene a polarity opposite to that of the ground state azide was proposed such that the π electron density of the ring would be reduced in the most important resonance contributors, XXXV. Such a case would then be stabilized by the π electron-donating p-methoxy group, XXXIX, and destabilized by the π electron-withdrawing p-nitro group, XXXVII, interactions. Table I contains values for the 2-azidobiphenyl series which are consistent with this explanation. The 2-

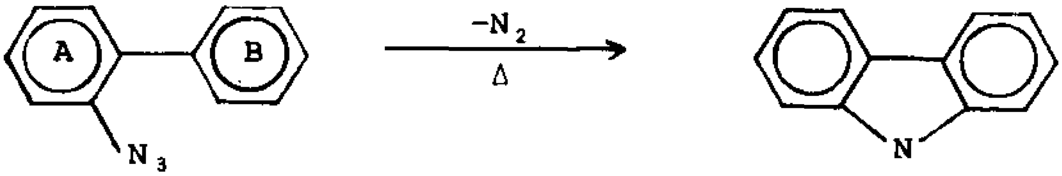
TABLE I

ENTHALPIES AND ENTROPIES OF ACTIVATION FOR THE DECOMPOSITION OF SOME 2-AZIDOBIPHENYLS[11]

2-Azidobiphenyl	ΔH_{act} kcal. mole^{-1}	ΔS_{act} cal. deg.$^{-1}$ mole^{-1} at 156°
unsubstituted	31.4 ± 0.5	-2.5 ± 1.1
5-methoxy-	25.5 ± 0.2	-12.3 ± 0.4
5-nitro-	41.6 ± 0.3	-1.0 ± 0.7
4-methoxy-	31.7 ± 0.2	-2.7 ± 0.4
4-nitro-	33.6 ± 1.1	2.4 ± 2.6
2',5'-dimethoxy	36.7 ± 0.3	9.0 ± 0.7

azidobiphenyl series is used as a model because of the high product yields and reliability of the data. Similarly to the simple phenyl azides m-substituents to the azido group in the biphenyl series have essentially no effect on the rate of nitrogen loss and p-substituents to the azido group vary the rate by a factor of 8.3 from slowest to fastest. Also, changes in the ring to which cyclization occurs as in the case of 2',5'-dimethoxy-2-azidobiphenyl have little effect on the rate indicating that the rate determining step is the same as in the simple phenyl azides.

In the case of carbazole formation from 2-azidobiphenyls[11] (Equation 14) electron-releasing substituents on the ring to which cyclization occurs, XXB, such as in 2',5'-dimethoxy-2-azidobiphenyl in Table I, increase the activation enthalpy of the azide decomposition. Electrophilic attack by the azido group on the other ring, XXB, prior to nitrogen loss or some other form of assistance in the nitrogen loss from the azide should show a lowering of the activation enthalpy.



XX XLII

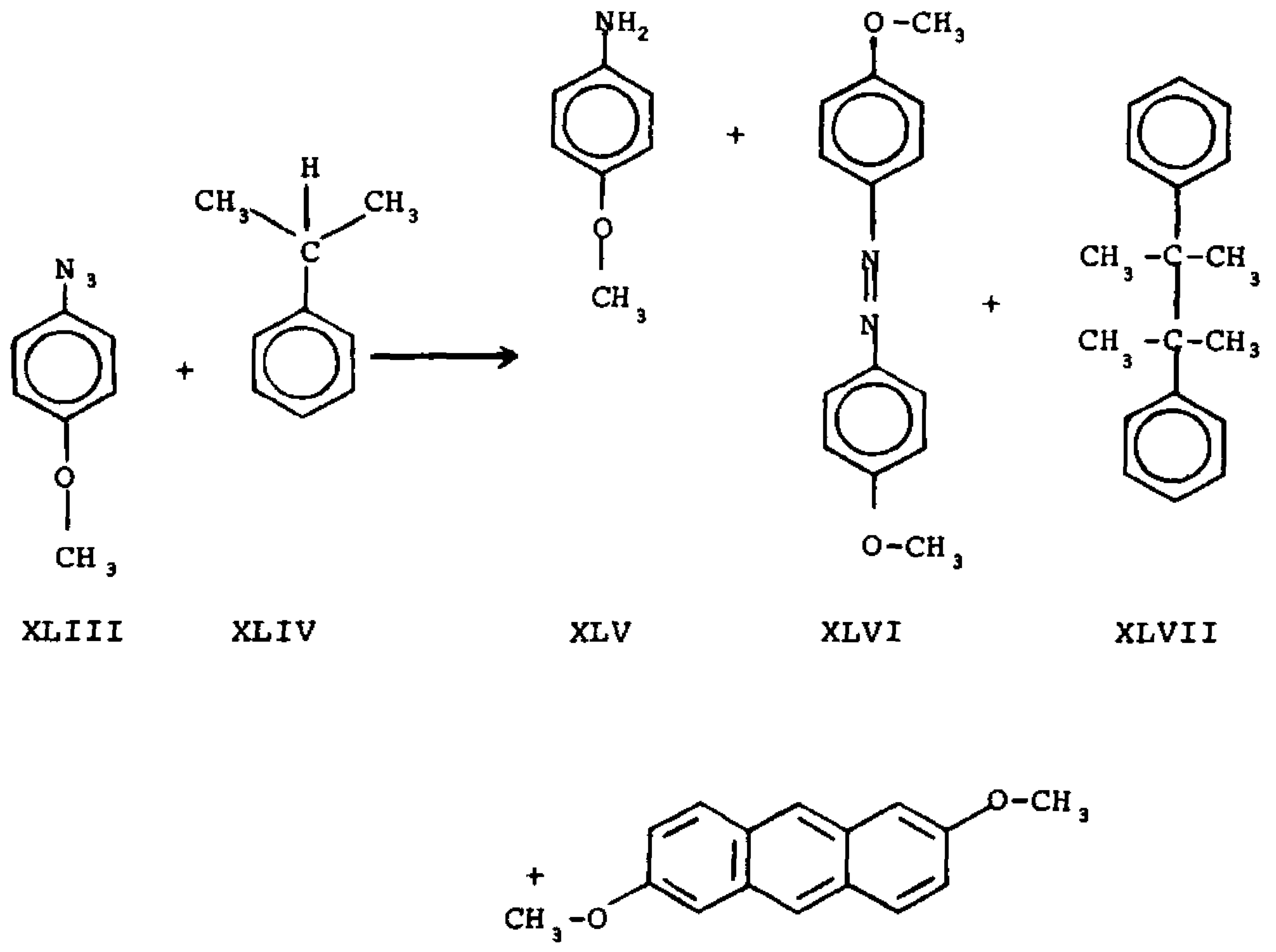
Equation 14

Also, a large decrease in entropy would be expected for this very ordered transition state instead of the significant increase observed. This is further evidence that a nitrene is generated before ring closure.

The rate constants for variously substituted phenyl azides do not vary as the enthalpies of activation since these are offset by a corresponding linear variation of the entropies of activation which results in an isokinetic temperature at about 250°[11].

Walker and Waters[13] also postulated the formation of aryl nitrenes based upon their observation of unimolecular decomposition of aryl azides in a variety of inert solvents. In addition to the expected major products, p-methoxyaniline, XLV, and 4,4'-dimethoxyazobenzene, XLVI, when p-methoxyphenyl azide, XLIII, was decomposed in boiling cumene, XLIV, some dicumyl, XLVII, and a small amount of 2,7-dimethoxyphenazine, XXXIII, was formed (Equation 15). The products, especially the dicumyl, XLVII, were explained by suggesting that aryl nitrenes behave as if they are biradical in nature or in other words, triplet nitrenes.

In summary the results of Smith and Hall for the 2-azidobiphenyl system in which carbazoles are formed, and m- and p-substituted phenyl azides in decalin where essentially anilines are formed, and Huisgen's work where azepines are formed, suggests that the rate determining step is the same



XLIII XLIV XLV XLVI XLVII

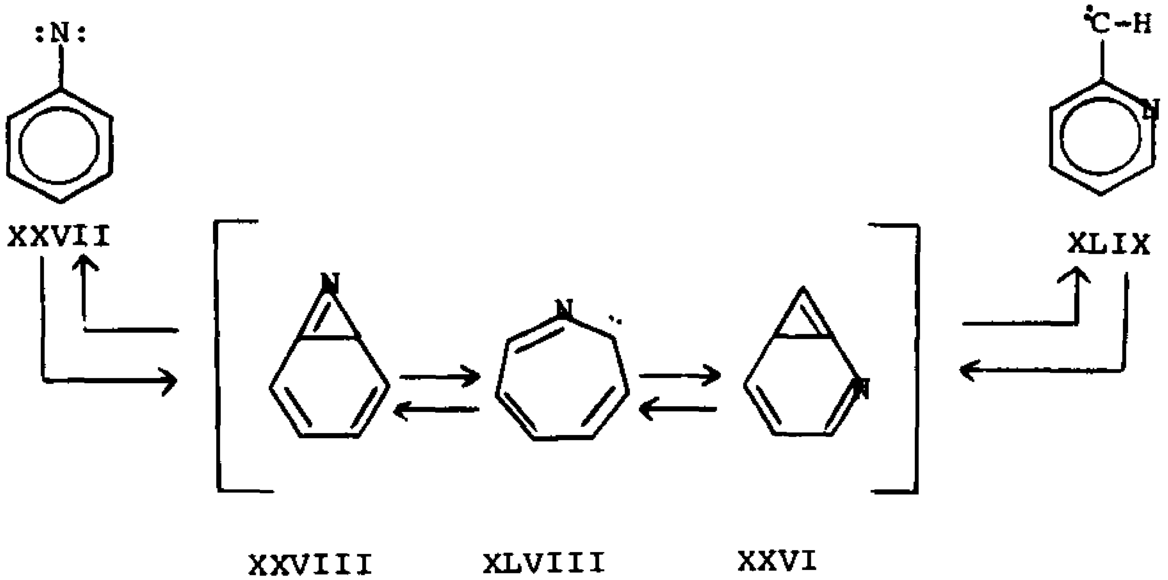
XXXIII

Equation 15

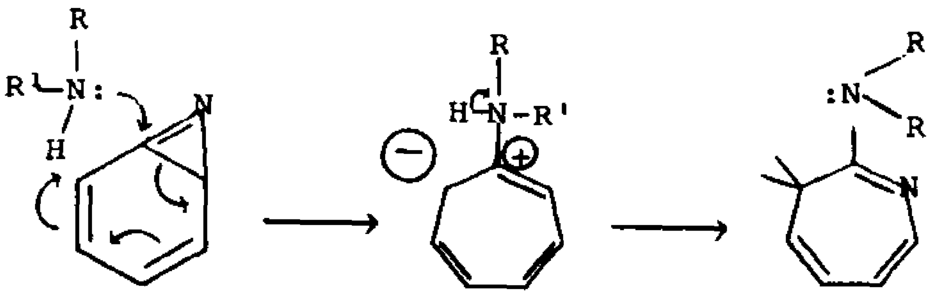
in all cases regardless of product. This step being the direct cleavage of the phenyl azide to a nitrene and nitrogen.

Related Intermediates to Nitrenes

No intermolecular reactions of aryl nitrenes has been demonstrated to be one of a singlet aryl nitrene. That is, of all the aryl nitrene reactions investigated no reactions analogous to those of singlet carbenes have been observed. Singlet carbenes are used as the model here because they are the most extensively studied spin paired, neutral, electron-deficient species known. The two major reactions which are considered characteristic of singlet carbenes are the insertion into carbon-hydrogen single bonds and the stereospecific addition of carbenes to olefinic double bonds. By insertion is meant the one step, three-centered, concerted mechanism whereby the carbene inserts itself into the carbon-hydrogen σ bond. Stereospecific addition to olefins is also a one step, concerted mechanism. Instead aryl nitrenes appear to be related to a multitude of other reactive intermediates on singlet surfaces which isomerize to stable compounds or react with other species in solution. The structures discussed most prominently in the literature,[8,14] are shown in Scheme II. There is no direct physical evidence to substantiate any of these structures and other forms are also possible. Their utility is demonstrated by the way they can account for almost all the products formed in a simple, reasonable sequence of chemical reactions. For example, the 2-amino-3H-azepines, XIII, are explained as arising from XXVIII[15] (Equation 16). The most striking argument invoking the relationship between these forms is the recently reported[14] thermal interconversion of 2-pyridyl carbene, XLIX, and phenyl nitrene, XXVII, (Scheme II). Crow



SCHEME II

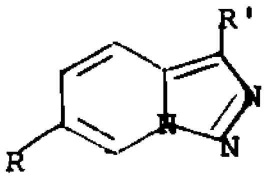


XXVIII

XIII

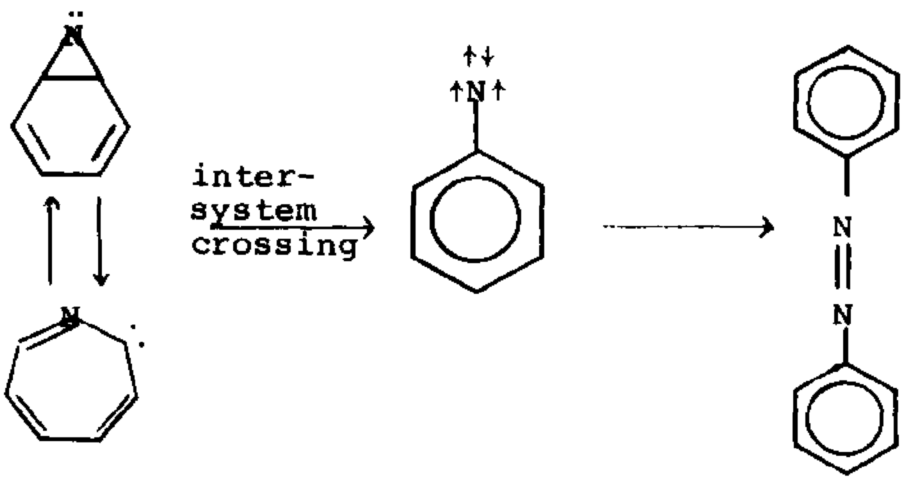
Equation 16

and Wentrup[14] approached the system from the 2-pyridyl carbene, XLIX, side by pyrolizing substituted and unsubstituted v-triazolo[1,5]pyridine, L, in the gas phase. The products in these decomposition reactions show a great similarity to the products in the pyrolysis of various phenyl azides. Also, the mass spectra, including metastables, of phenyl azide and v-triazolo[1,5-a]pyridine are identical. This suggests that the decomposition of these compounds, or at least the equivalent positively charged species generated in the mass spectrometer, give rise to an equilibrium mixture of common intermediates such as shown in Scheme II. They conclude that stabilization of the electron-deficient intermediates, either XXVIII or XLVIII or both, by participation of nucleophilic molecules leads to ring expansion products and in the absence of nucleophiles the intermediates eventually interconvert to the lowest energy species, the triplet nitrene, which dimerizes (Equation 17).



L

	R	R'
a)	CH_3	H
b)	H	CH_3
c)	CH_3	phenyl
d)	H	H



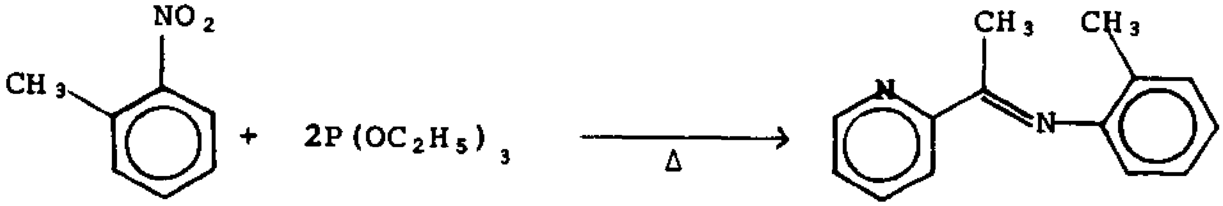
XLVIII

XXXI

Equation 17

In addition, coincidental formation of pyridines, LIII, in the deoxygenation of o-nitroalkylbenzenes, LII, by phosphites[16] (Equation 18), a reaction postulated to generate nitrenes[17], and in the gas phase pyrolysis of phenyl azides[18] suggested a mechanism involving some form of structural isomerism extruding carbon and inserting nitrogen and consistent with a path between XXVII and XLIX as in

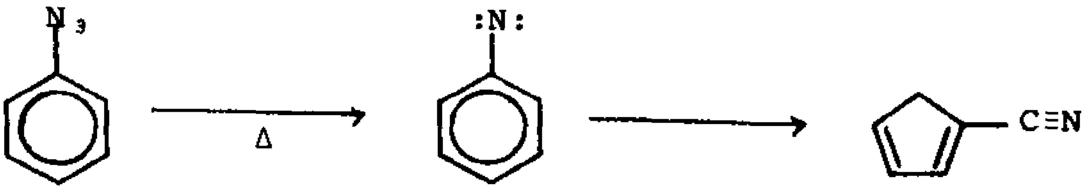
Scheme II.



LII LIII

Equation 18

The ring contraction of phenyl nitrenes to cyanocyclopentadienes (Equation 19) appears to arise from a hot singlet nitrene by a different pathway than the sequence in Scheme II since the yields of these products are greater[14] in the decomposition of phenyl azide, XII, than in the decomposition of v-triazolo[1,5-a]pyridine, L. This is consistent with the increase in cyanocyclopentadiene, XXIX, yield as the temperature of the reaction chamber is increased in the thermal decomposition of phenyl azide[19].

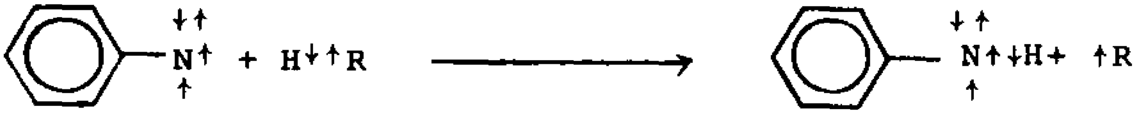


XII XXVII XXIX

Equation 19

Apparent Intermolecular Insertion-

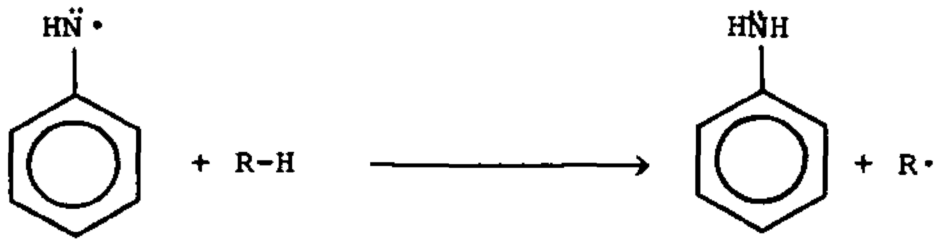
Unlike the behavior of other nitrenes such as carbethoxynitrenes[20], sulfonylnitrenes[21], and cyanonitrenes[22], which show substantial yields of carbene-like carbon-hydrogen insertion, aryl nitrenes give very poor yields of carbon-hydrogen insertion products. Evidence has been accumulating that even this insertion into hydrocarbons is actually due to a triplet aryl nitrene. Hall, Hill and Fargher[23] thermally decomposed phenyl azide in a variety of aliphatic hydrocarbons forming aniline, N-alkylanilines, azobenzene and polymer. The product yields varied erratically but the ratio of aniline to N-alkylaniline remained constant as the reactive hydrocarbon was diluted with inert solvents. From these results it was concluded that both the aniline and N-alkylaniline are formed from the same intermediate, a triplet nitrene, which abstracts a hydrogen generating two radicals (Equation 20). One of these is an anilino radical, LIV, and the other is an alkyl radical. The anilino radical,



LI LIV

Equation 20

LIV, can then abstract another hydrogen to give aniline (Equation 21), combine with an alkyl radical to give



LIV XXX

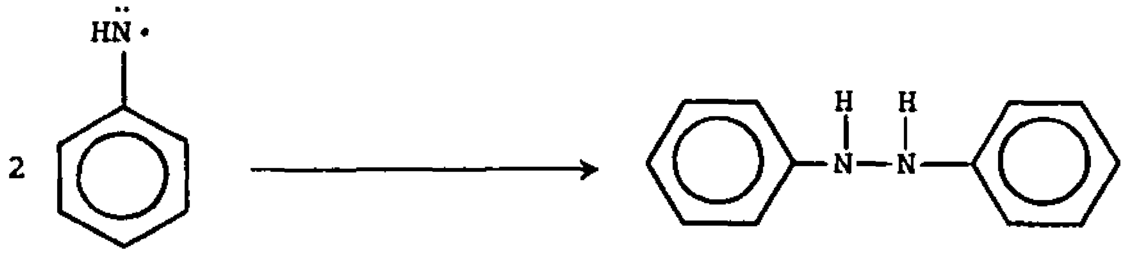
Equation 21

N-alkylaniline, LV, (Equation 22) or combine with another

LIV LV

Equation 22

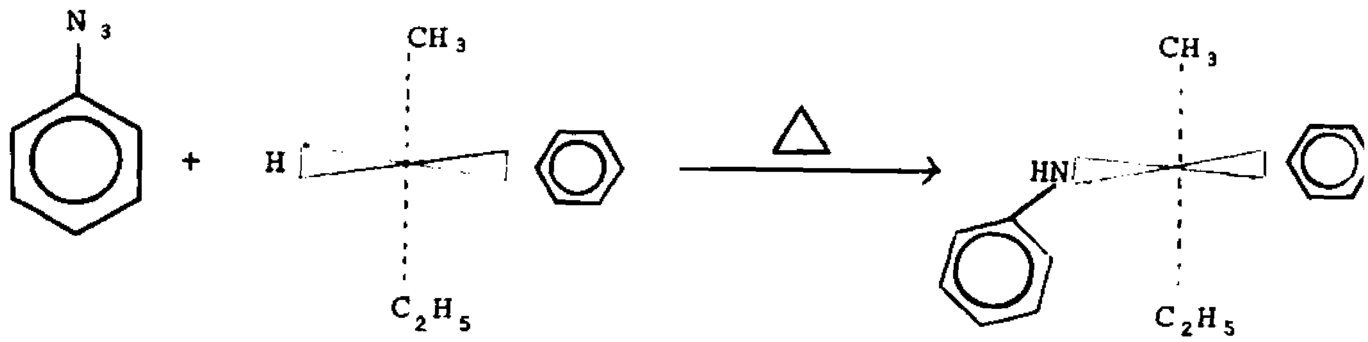
anilino radical to give hydrazobenzene, XXXII, (Equation 23).



LIV XXXII

Equation 23

That N-alkylanilines might be formed in greater yield than hydrazobenzene is not too surprising. Combination of an anilino radical with the alkyl radical generated on forming the anilino radical (Equation 20) can occur within the solvent cage before the two radicals have a chance to diffuse apart while combination of two anilino radicals would depend on the concentration of anilino radicals in the solution. Coupling of the two radicals within the solvent cage before they can diffuse away from each other must be a very fast reaction. Before these two radicals can combine though, one electron must invert its spin so that the two electrons in the new bond will be spin paired. The unshared pair of electrons on the nitrogen of a nitrene which are still present in the anilino radical can provide the necessary perturbing magnetic field which allows spin inversion to occur more rapidly than in cases where such unshared pairs are not present. This is a significant difference in a comparison of carbenes with nitrenes since carbenes do not possess similar electrons. When phenyl azide is decomposed in refluxing, optically active 2-phenylbutane[22], LVI, the 2-anilino-2-phenylbutane, LVII, isolated shows 40% retention of configuration (Equation 24). Based upon the carbene model this would be considered evidence for some singlet insertion occurring. However, it is also possible that the recombination of radicals generated on hydrogen



XII LVI LVII

Equation 24

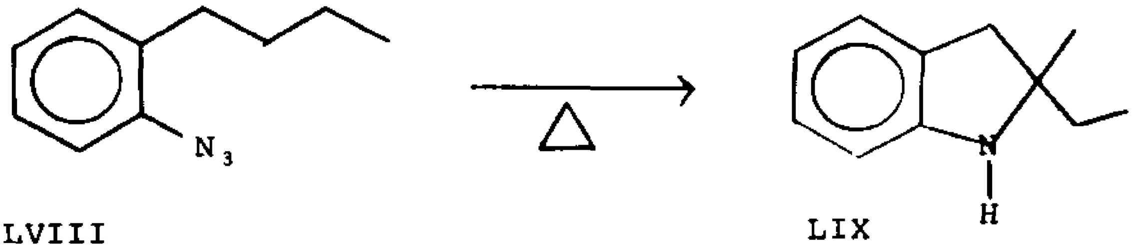
abstraction, including spin inversion, occurred before complete racemization of the alkyl radical could occur. Furthermore, when phenyl azide was decomposed in a mixture of 2-methylpropane and 2-methyl-2-deuteriopropane a deuterium isotope effect close to the observable theoretical maximum for a two step abstraction-recombination reaction was found[22]. A one step insertion reaction could not have yielded such an isotope effect.

In summary, the criteria for singlet and triplet nitrenes based upon carbene reactions may not be valid for aryl nitrenes since triplet nitrenes give apparent insertion products with retention of optical activity at an asymmetric carbon via a radical abstraction-recombination process.

Apparent Intramolecular Insertion

Previously, it had been acknowledged that hydrogen abstraction-recombination could explain the observed retention of optical activity in the formation of (-)2-ethyl-2-

methylindoline, LIX, by the thermal decomposition of (+)2-azido-1-(2-methylbutyl)benzene[24], LVIII, in an apparent intramolecular carbon-hydrogen insertion reaction (Equation 25). However, comparison of the liquid phase and vapor phase decompositions show that the product from the liquid phase reaction retained only 65% of the optical activity of the vapor phase product. This was taken as evidence in support of a one step, singlet insertion mechanism. The rationale for this is based on the greater probability of having reactions of a hot nitrene in the vapor phase. In the vapor phase the initially formed singlet nitrene would have very few ways to lose excess kinetic energy. This excess kinetic energy could then be used to overcome any activation energy barriers in the one step, insertion process. In addition, for an abstraction-recombination mechanism the vapor phase would offer fewer constraints than in solution on rotation about the carbon-carbon bonds connecting the optically active center to the rest of the molecule. This



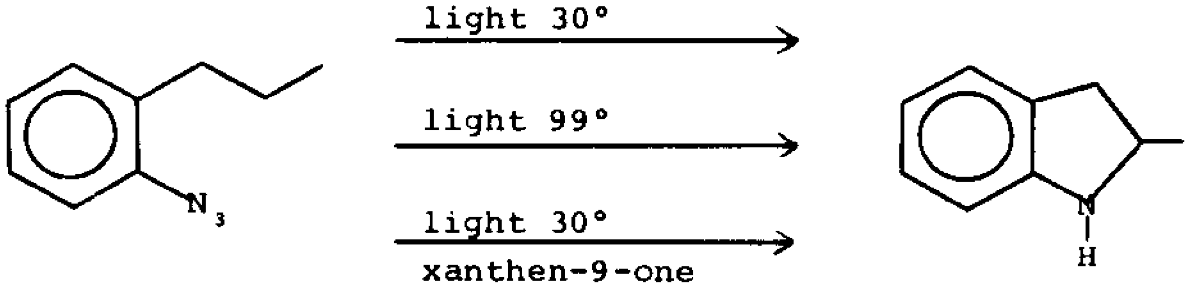
LVIII

LIX

Equation 25

should lead to greater racemization in the vapor phase than in the liquid phase which is opposite to what is observed. In solution singlet nitrene might be thermally deactivated by solvent collisions enhancing the effective competition of a nonstereospecific, two step, triplet, abstraction-recombination mechanism. The very high yields for this intramolecular apparent insertion, 50-60%, in comparison to the low, 5%, yield for intermolecular apparent insertion[25] can be consistent with either mechanism.

Very recently, Odum and Trattner[26] studied the decomposition of o-propylphenyl azide, LX, in octane (Equation 26).



LX

LXI

Equation 26

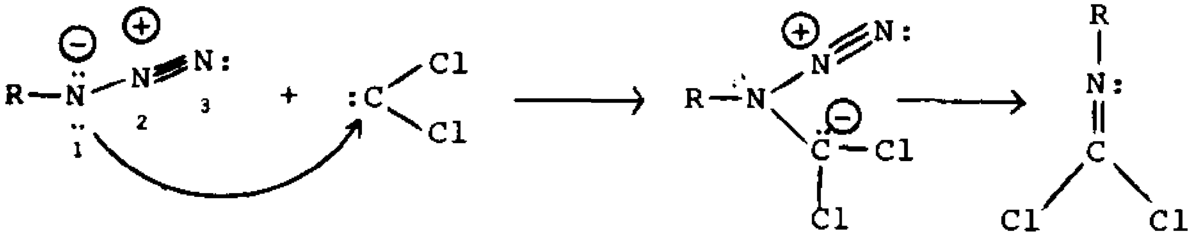
Direct photolysis at 30° resulted in no formation of 2-methylindoline, LXI, while at 99° the indoline, LXI, is formed. This is consistent with an energy of activation for the insertion of singlet aryl nitrene into a carbon-hydrogen bond. Also, photolysis in the presence of xanthen-

9-one as a triplet sensitizer at 30° resulted in formation of the indoline, LXI. Thus some triplet species can also lead to apparent insertion by a radical abstraction-recombination reaction.

At the present time the evidence is most consistent with a triplet aryl nitrene radical abstraction-recombination mechanism for apparent insertion in intermolecular reactions and a concerted, one step, insertion of singlet aryl nitrene in the intramolecular reactions with possibly some triplet abstraction-recombination also occurring.

Formation of Isocyanates

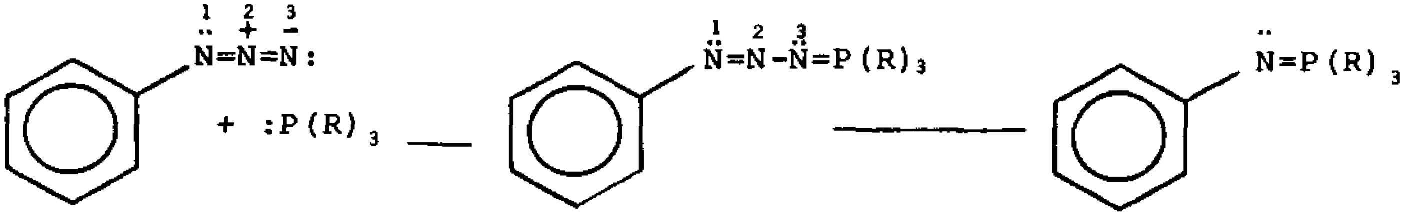
The recently reported reactions of aryl azides with carbon monoxide at elevated temperatures and pressures to give isocyanates[27,28] might involve the trapping of an initially formed aryl nitrene as anilines, azo compounds and other products common to those reactions involving aryl nitrenes are formed. However, the proposed mechanism for the reaction of dichlorocarbene with azides to give isocyanide dichlorides[29], LXII, offers an alternative explanation. This reaction which is carried out at 0°, well below the decomposition temperature of aryl azides, is postulated as involving electrophilic attack by the carbene at the nitrogen bonded to carbon with subsequent loss of nitrogen (Equation 27). Whether attack is at the nitrogen numbered 1 in structure



LXIII LXII

Equation 27

LXIII or at the terminal nitrogen, numbered 3, as in LXIV in the Staudinger reaction of aryl azides and phosphines[30] (Equation 28) is unimportant since in neither case is a free nitrene formed.

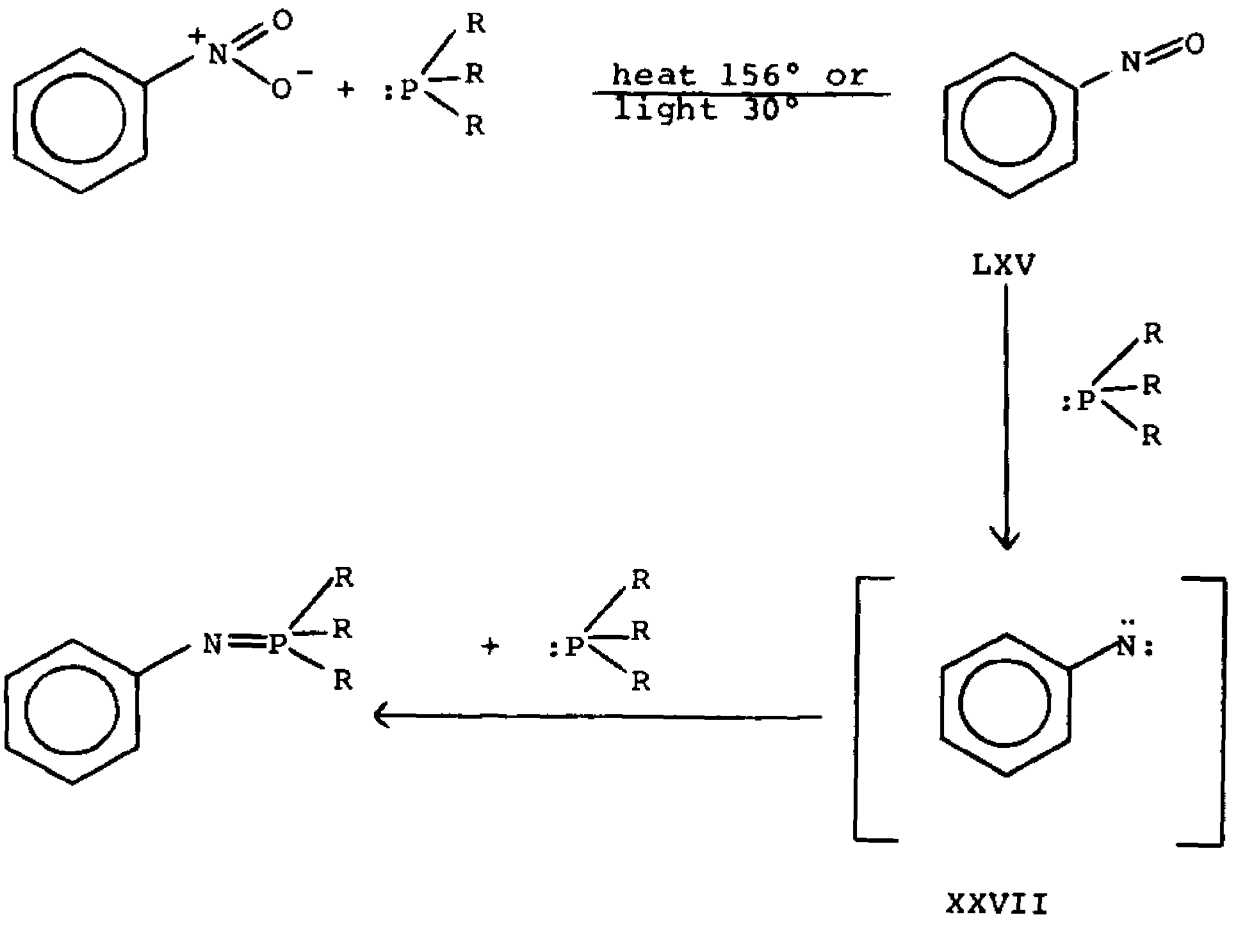


LXIV

Equation 28

Formation of Phosphorimidates

The thermal deoxygenation of nitro and nitroso substituted benzenes by tervalent phosphorus compounds (Scheme III) is a well documented reaction[31] for which strong evidence exists that it proceeds through an intermediate aryl nitrene.



SCHEME III

In particular the formation of phosphorimidates such as triethyl-N-p-dimethylaminophenylphosphorimidate[32], LXVI, appears to result from the direct trapping of nitrene intermediates. In this case increasing the ratio of triethyl phosphite to p-dimethylaminonitrosobenzene from 1:1 to 10:1 resulted in an increase of phosphorimidate yield from 13% to 63.5% with a corresponding decrease in yield of 4,4'-bisdimethylaminoazoxybenzene from 63.5% to 23%. The strongly electron-donating p-dimethylamino group is held responsible for stabilizing the intermediate nitrene thus increasing the chance of its capture by nucleophilic triethyl phosphite rather than its reacting with nitrosobenzene to give the azoxy compound. More recently, deoxygenation of substituted nitrobenzenes in refluxing triethyl phosphite[16,17] has resulted in the isolation of a number of phenyl ring substituted phosphorimidates in good yields. The substituents varied from strongly electron-donating ones, such as o- and p-methoxy, to strongly electron-withdrawing ones such as o- and p-carbomethoxy and o- and p-cyano. The unsubstituted nitro and nitroso compounds, nitrobenzene and nitrosobenzene, however, give negligible yields of triethyl N-phenylphosphorimidate while methyl substituents give yields of phosphorimidates from 42-79%. Formation of phosphorimidate is also apparently temperature dependent since higher yields are obtained in the thermal reaction at 156° than are formed in the photochemical reaction at 30°.

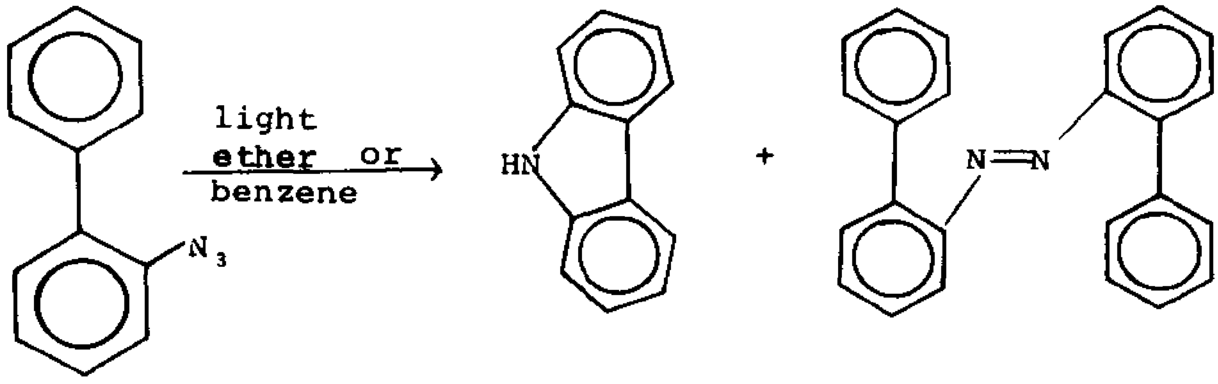
Sundberg assumes that the deoxygenation proceeds in two steps (Scheme III), the first being the removal of one oxygen by phosphite to give the nitrosobenzene, LXV, and the second, common to both procedures, the reaction with another molecule of phosphite to give the suspected nitrene, XXVII. The second reaction is known to proceed very rapidly at 0°. It is the first reaction which needs activation by photolysis or heating. It is possible that the intermediate which gives rise to the phosphorimidate might not be a nitrene, but if it is a nitrene there is no evidence establishing its multiplicity.

Rearrangement to Azepines

The formation of azepines via the proposed 7-azabicyclo-(4.1.0)hepta-2,4,6-triene intermediate, XXVIII, has been related to singlet phenyl nitrene[33]. By irradiating phenyl azide in diethylamine in the presence of a triplet sensitizer, p-dimethylaminobenzaldehyde, it was shown that the yield of azepine formed decreased markedly and the yield of aniline increased markedly compared to the unsensitized photolysis[5]. Also, the formation of azepine is not quenched by oxygen further indicating this is not a reaction of an excited triplet state. Therefore, a singlet state must be involved. Splitter and Calvin attribute aniline formation to the reduction of triplet phenyl nitrene after loss of nitrogen from triplet phenyl azide, although reduction of excited triplet azide is not ruled out.

OTHER INTRAMOLECULAR REACTIONS

There is considerably more evidence for singlet nitrenes participating in intramolecular reactions. One case is the previously mentioned results of Smolinsky and Feuer[24] for indoline formation from o-alkylphenyl azides where a higher percentage of retention of optical activity of apparent insertion product is found in the vapor phase decomposition than in solution. The work of Swenton[34] on the formation of carbazole from 2-azidobiphenyl is another, more definitive case. When 2-azidobiphenyl, LXVII, is photolyzed in ether or benzene, carbazole, LXVIII, is formed in 71% yield and azo-2-biphenyl, LXIX, is formed in 9% yield (Equation 29).

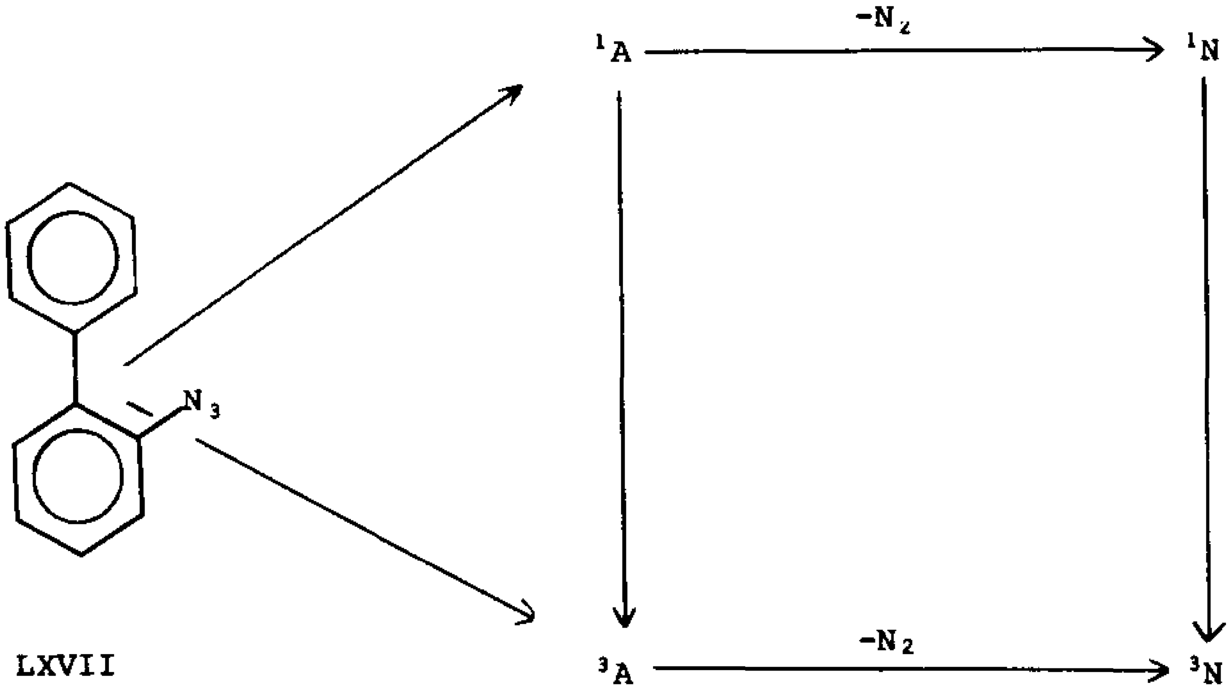


LXVII LXVIII LXIX

Equation 29

In the presence of a triplet photosensitizer the yield of carbazole drops to less than 8% and the yield of azo-2-biphenyl increases to 40-43%. In the direct photolysis of

2-azidobiphenyl in ether when piperylene, a triplet quencher, is added the carbazole yield increases from 71% to 87% and the azo-2-biphenyl yield decreases from 9% to 4%. Apparently the formation of carbazole, LXVIII, is associated with a singlet species or with a triplet species not quenched by piperylene and not the triplet species generated on photosensitization. Conversely, most of the azo-2-biphenyl, LXIX, formed is dependent upon the formation of a triplet species that is quenched by piperylene and is generated by sensitization. In Scheme IV the four species most probably involved in these reactions are presented. The excited singlet azide is represented by ^1A, the excited triplet azide by ^3A, the excited singlet nitrene by ^1N and the ground state triplet nitrene by ^3N. The excited singlet azide, ^1A, is formed first on direct photolysis and then it may undergo intersystem crossing to triplet azide, ^3A, or it may lose nitrogen forming singlet nitrene, ^1N. The triplet azide, ^3A, is formed first on transfer of triplet energy from a photosensitizer and then it can lose nitrogen to form triplet nitrene, ^3N. The singlet nitrene, ^1N, can also undergo intersystem crossing to form triplet nitrene, ^3N. The ground state of aryl nitrenes has been demonstrated to be the lowest triplet state by esr studies[35]. In bimolecular reactions in solution the assumption is made that ^3N is not in any excited state. Therefore the triplet nitrene, ^3N, is not quenched



LXVII

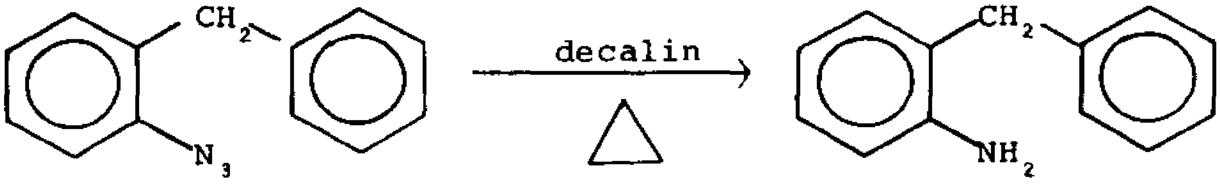
SCHEME IV

by piperylene since it is not possible to quench ground states. The triplet species which can be quenched by piperylene and which is formed first on photosensitization is the triplet azide, ^3A. This then is the triplet species referred to previously that most of the azo-2-biphenyl, LXIX, formed is dependent upon. However, three possibilities exist. The ^3A goes directly to azo-2-biphenyl, LXIX, or it first loses nitrogen forming ^3N which goes to the azo compound or both occur. If the azo compound, LXIX, arises entirely from ^3N then the quenching experiments show two things. The first is that ^3A is the major route by which ^3N is formed. The second is that some ^3N is formed from ^1N, unless a hundred-fold excess of piperylene does not completely quench ^3A. If the azo compound, LXIX, arises entirely from ^3A the quenching is incomplete in spite of a diffusion controlled rate in the presence of a hundred-fold excess of piperylene, the triplet energy of which is far below that of ^3A. Though ^3N cannot be quenched by piperylene it is possible that ^3N can react with piperylene analogously to triplet carbenes. It is difficult to rationalize the increase in carbazole yield with the trapping of ^3N by piperylene. The increase in carbazole is more consistent with the quenching of an excited triplet azide to give ground state azide which can then be reexcited to singlet azide.

It has been shown that carbazole formation in the photolysis of 2-azidobiphenyl is clearly a two step process involving the generation of an intermediate nitrene[36]. On photolysis of 2-azidobiphenyl in a glass matrix at 77°K a single product, identified spectroscopically as the aryl nitrene, is formed. This product, after standing long enough to decay to its ground state, which is the triplet state[34], is then irradiated at a wavelength corresponding to its maximum absorption frequency and it is thereby eventually converted to the product, carbazole, LXVIII. This formation of carbazole may occur in several ways. The irradiation of the ground state nitrene in the glass produces an excited triplet nitrene which may do two things. The excited triplet nitrene may dissipate energy into the matrix by a non-radiative process producing a vibrationally excited, ground state triplet nitrene. This hot nitrene could then undergo ring closure to carbazole. Such a mechanism is consistent with the very low quantum yield for the ring closure from the nitrene. The excited triplet nitrene may also undergo intersystem crossing to singlet nitrene which subsequently ring closes to carbazole. Intersystem crossing in this case is a transition of low probability which would also be consistent with the very low quantum yield for carbazole formation. The quantum yield for nitrene formation in the matrix and for carbazole formation in solution agree very well within experimental error indicating an identical first step and a separate intermediate at room temperature. The carbazole formed in Swenton's direct photolysis of 2-azidobiphenyl in ether solution must then be due to either ^1N or ^3N. If ^3N is the species that leads to carbazole then the yield of carbazole should not vary no matter how ^3N is formed in the direct photolysis reaction. When piperylene, the triplet quencher, is included in the direct photolysis any ^3A formed by intersystem crossing of the excited ^1A is quenched. The quenched ^3A, now returned to the ground state, may be reexcited to more ^1A. One of the pathways to ^3N, via ^3A, is eliminated and the pathway to ^1N is increased. Therefore the ratio of ^1N to ^3N formed in the presence of piperylene is shifted to favor more ^1N. Since the yield of carbazole also increases on inclusion of piperylene this strongly implies that most of the carbazole arises from ^1N.

The photosensitized reaction was run under conditions which excluded the formation of ^1A and therefore also ^1N. The formation of a very small amount of carbazole in the photosensitized reaction indicates that ^3N can also form some carbazole. The data from the direct and photosensitized reactions show that carbazole formation is primarily due to single nitrene and azo-2-biphenyl formation is due to triplet nitrene and/or triplet azide.

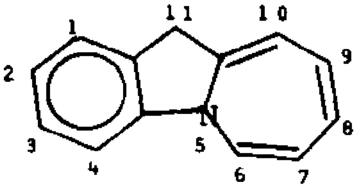
Not all intramolecular reactions give evidence for the intermediacy of singlet aryl nitrenes. For example, in the formation of azepino[2,1-a]-11H-indole, LXX, by the thermolysis of 2-azidodiphenylmethane[37], LXXI, an apparent nitrene insertion into a benzene ring occurs. This type of reaction is typical of singlet carbenes and of other singlet nitrenes such as cyanonitrene and carbethoxynitrene. On further consideration though, an entirely different interpretation is more consistent with the facts. At 160° in decalin the major product is 2-aminodiphenylmethane, LXXII, (Equation 30)



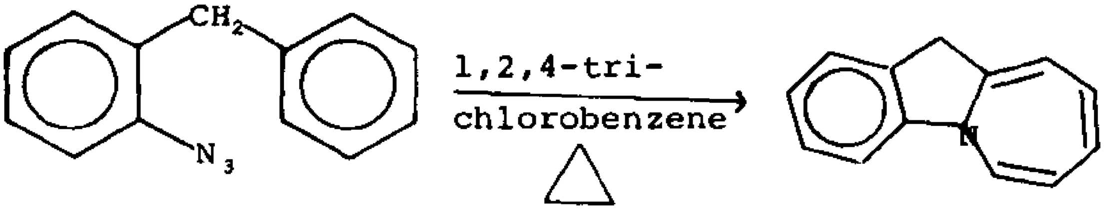
LXXI LXXII

Equation 30

which from previously mentioned examples appears to be a product of a triplet nitrene intermediate. In 1,2,4-trichlorobenzene at 160° however the nitrene appears to insert intramolecularly into the other phenyl ring to give the azepino[2,1-a]-11H-indole, LXX, (Equation 31). Krbcheck



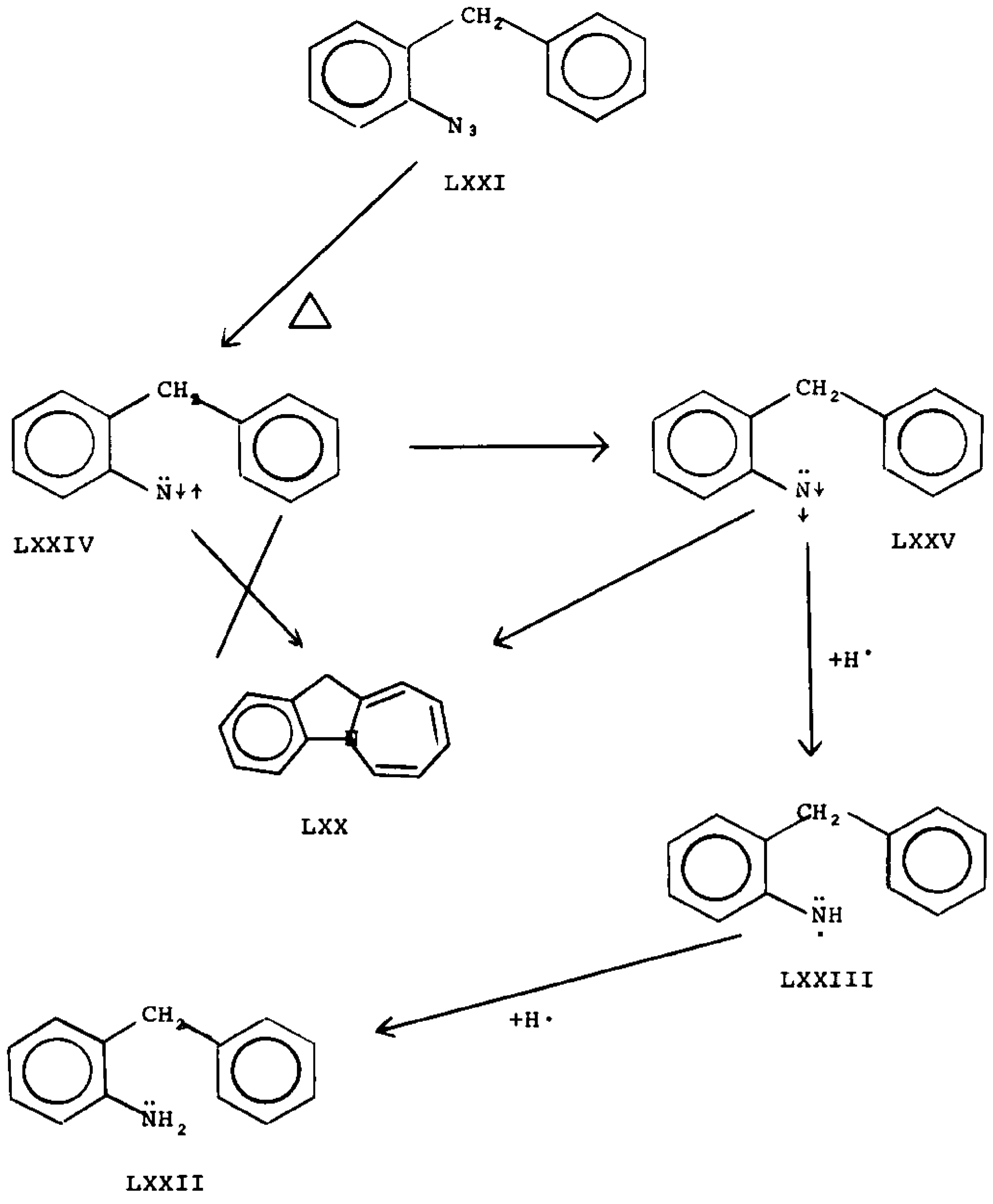
LXX



LXXI LXX

Equation 31

and Takimoto[37] suggest that this apparent insertion takes place only because 1,2,4-trichlorobenzene is a poorer hydrogen atom source than decalin. An outline of the possible species generated on thermal decomposition is in Scheme V. The first species formed on nitrogen loss is the singlet nitrene, LXXIV, due to spin conservation. This singlet may then decay to the lower energy, ground state triplet nitrene, LXXV, or it may react further. The formation of the 2-phenylanilino radical, LXXIII, precursor to 2-aminodiphenylmethane is a hydrogen abstraction reaction from the solvent. This is most probably a reaction of the triplet nitrene, LXXV. Triplet nitrene, LXXV, is only formed after the higher energy singlet nitrene, LXXIV, has had ample opportunity to react in some other way. Since azepine, LXX, formation only occurs when hydrogen abstraction is inhibited by a poor hydrogen donor solvent, 1,2,4-trichlorobenzene, it too must occur after the singlet nitrene has decayed to the triplet, LXXV.


CH$_2$
N$_3$
LXXI
△
CH$_2$
N
LXXIV
CH$_2$
N
LXXV
LXX
+H·
CH$_2$
NH
LXXIII
+H·
CH$_2$
NH$_2$
LXXII

SCHEME V

Also, halogenated solvents, such as 1,2,4-trichlorobenzene would be expected to enhance intersystem crossing of single nitrene, LXXIV, to triplet nitrene, LXXV, by a heavy atom effect. Thus it appears that the azepine results from addition to the π electron system of the adjacent ring by a triplet nitrene intermediate.

DISCUSSION OF RESULTS

Several ortho, meta and para substituted phenyl azides were prepared and photolyzed in anhydrous liquid ammonia and dimethylamine in an attempt to clarify the nature of the aryl nitrene intermediates involved and the effect of substituents on the azepine yielding ring expansion reaction.

Photolysis of o-Chlorophenyl and o-Methoxyphenyl Azides

When o-chlorophenyl azide was photolyzed in liquid ammonia no evidence of an azepine product was detected. Photolysis of o-methoxyphenyl azide similarly did not yield azepine. Various other o-substituents accelerate the decomposition of phenyl azide and lower the activation enthalpy of nitrogen loss in comparison with phenyl azide itself. Also, some o-substituents are incorporated in altered form into the products of phenyl azide decomposition[38]. Therefore it is unclear whether absence of azepines in the cases of o-chlorophenyl and o-methoxyphenyl azides is due to the substituents themselves or their being in the ortho position. Attention was therefore turned to the p-substituted phenyl azides where only the effects directly attributable to the nature of the substituent groups would be observed. m-Subsituted phenyl azides are not as satisfactory since two isomeric azepines would be expected to form. This would generate additional problems in separation and identification.

Photolysis of p-Methoxyphenyl Azide

When p-methoxyphenyl azide was photolyzed in dimethylamine only two products were detected along with some polymer. The minor product, present in 14% yield, had ir and nmr spectra as well as a glpc retention time identical to p-anisidine. The major product, a pale yellow oil present in 55% yield, had an elemental analysis consistent with 5-methoxy-2-dimethylamino-3H-azepine, LXXVI, and a comparison of its nmr spectrum with those of several azepines derived from various amines including dimethylamine[5,39] showed the expected similarities with a few interesting variations due to the 5-methoxy substituent. The chemical shifts for the protons at positions 3,6 and 7 of the azepine ring agree with the chemical shift ranges reported for the other azepines[5,39] as in Table II. The chemical shift for the proton at position 4 exhibits a very large upfield shift of more than one half of a τ unit or about 40Hz. The most plausible explanation for this is shown by analogy to the simplest vinyl ether. The cis β-proton in methyl vinyl ether occurs at 75 Hz above the corresponding value in ethylene[40]. In acrylonitrile where the anisotropy effect of the cyano group is expected to be equal to or larger than that for oxygen the calculated upfield anisotropy shift for the cis β-proton is only 11.5 Hz. Since the observed upfield shift in the ether is so large it is postulated that a more

TABLE II

CHEMICAL SHIFTS[a] OF VARIOUS AZEPINE PROTONS

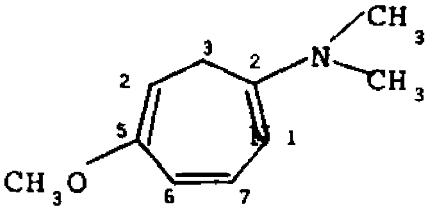
3H-Azepine	position of proton				
	3	4	5	6	7
2-Diethylamino[5]	7.47	5.02	3.80	4.40	2.98
2-Various amines[39]	7.49- 7.39	5.00- 4.87	3.80- 3.73	4.38- 4.28	3.04- 2.98
5-Methoxy-2-dimethylamino	7.47	5.67	-	4.38	2.93
5-Cyano-2-dibutylamino	7.23	4.37	-	4.30	2.83
5-Cyano-2-dimethylamino	7.37	4.33- 4.00[b]	-	4.33- 4.00[b]	2.80
5-Chloro-2-amino	7.43	4.73	-	4.23	3.13

a) All chemical shifts are in τ units.

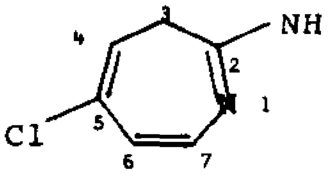
b) Uncertain assignment

c) Reference compound 2-amino-3H-azepine (see ref. 5).

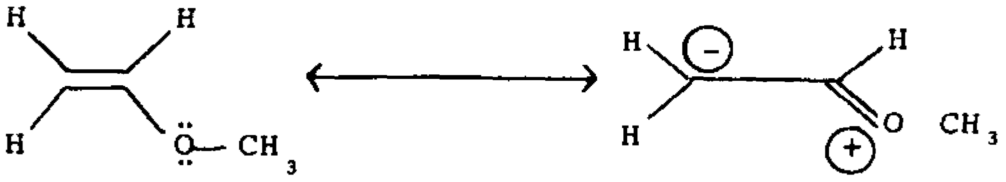
likely explanation involves lone-pair electrons on oxygen[34]. Conjugation of an unshared pair of electrons with the π system of the double bond, as shown in the mesomeric forms LXXVII and LXXVIII, brings about greater shielding of the β-protons and consequently an upfield shift. An inductive effect is ruled out for the β-protons since in methyl vinyl sulfide the β-protons are only 14-28 Hz above ethylene and according to the relative electronegativities of oxygen and sulfur any inductive effect should be in the opposite direction. Various substituents on the ethylene system may vary the magnitude of this upfield shift which is probably the case in the azepine system since it is not as large as



LXXVI



LXXIX



LXXVII

LXXVIII

in methyl vinyl ether.

The absence of a proton in the 5-position simplifies the spectrum at positions 4 and 6 by comparison to unsubstituted 2-dimethylamino-3H-azepine. The proton at position 4 appears as a triplet clearly coupled with the methylene protons at position 3 by a coupling constant of 7.5 Hz. The proton at position 6 appears as a doublet coupled with the vinyl proton at position 7 by a coupling constant of 8.5 Hz.

Photolysis of p-Chlorophenyl Azide

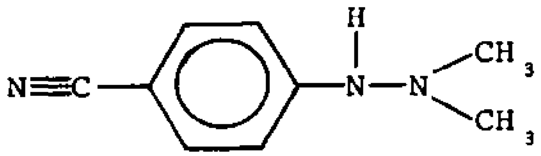
When p-chlorophenyl azide was photolyzed in liquid ammonia a compound melting at 112° was isolated in 7.3% yield. The nmr spectrum of this compound was with two exceptions similar to the spectrum of 2-amino-3H-azepine[5] as in Table II. The exceptions were the absence of the one proton pair of doublets corresponding to position 5, and the simplification of the peaks for positions 6 and 4. The one proton pair of doublets for the proton at position 6 is simplified to a single doublet and the one proton quartet for the proton at position 4 is simplified to a triplet. These changes are perfectly consistent with a chloro substituent at position 5 and elemental analysis also supports the 5-chloro-2-amino-3H-azepine structure, LXXIX. The chemical shifts of all protons agree with the corresponding values for unsubstituted 2-amino-3H-azepine. A comparison of the effect of the 5-

chloro substituent on the chemical shift of the proton at position 4 with the effect of a chlorine atom on the cis β-proton of the ethylene system shows that in vinyl chloride the cis β-proton is shifted about 0.1 τ units downfield with respect to ethylene while the 4 proton in the azepine is apparently not affected. The small effect of the chlorine at the β-position has been explained[41] as due to partial cancellation of the inductive effect by lone-pair conjugation.

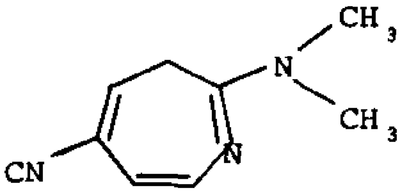
The relatively poor yield for this reaction may be accounted for by any of a number of possible explanations. A heavy atom effect caused by the chlorine atom in the molecule might enhance intersystem crossing of the photoexcited azide or of the proposed intermediate nitrene to their triplet states thus reducing the amount of 7-azabicyclo(4.1.0) hepta-2,4,6-triene intermediate leading to azepine thus increasing the yield of aniline and tars formed. Since yield data for aniline is lacking for this reaction this cannot be ascertained. Also optimum workup procedures were not established for this reaction so a significantly higher yield of LXXXIX may have been present but was not isolated.

Photolysis of p-Cyanophenyl Azide

Irradiation of p-cyanophenyl azide in dimethylamine gave only one major product in 72% yield. An ir spectrum of this product, a white, crystalline solid melting at 69.5-70.0° after recrystallization from methanol-water, had an intense absorption at 2220 cm^{-1} characteristic of nitrile, a strong singlet at 3250 cm^{-1}characteristic of one amino hydrogen and several peaks at 1525 cm^{-1} and 1606 cm^{-1} consistent with aromatic carbon-carbon stretching. The nmr spectrum was totally unlike that expected for an azepine and very greatly resembled the starting p-cyanophenyl azide and p-cyanoaniline. The six-proton singlet at 7.45 τ indicated that a dimethylamino group had been incorporated and a one proton broad singlet at 5.08 τ was attributed to the amino proton seen in the ir spectrum. The remainder of the spectrum consisted of two two-proton doublets in the aromatic region analogous to the pattern obtained from 1,4 disubstituted benzenes. The only structure to fit this assignment, 1,1-dimethyl-2-(4-cyanophenyl)hydrazine, LXXX, is also in agreement with the elemental analysis. The aromatic two-proton doublet centered at 3.15 τ was assigned to the protons ortho to the hydrazino group and the other doublet centered at 2.60 was assigned to the protons ortho to the cyano group. The coupling constant between these two doublets is 8.5 Hz which along with the chemical shifts agrees with those values reported for p-dimethylaminobenzonitrile[42]. Analysis of the reaction mixture by glpc detected p-cyanoaniline in 12% yield and another compound with a retention time on a very nonpolar glpc column only slightly longer than the hydrazine indicating that is it of comparable molecular weight with the hydrazine. Assuming a detector response equal to the hydrazine this compound was estimated to be formed in 11% yield. A nmr spectrum of a very crude sample of this compound showed a chemical shift and splitting pattern consistent with 5-cyano-2-dimethylamino-3H-azepine, LXXXI. The chemical shift data are included in Table II for comparison with other azepines.

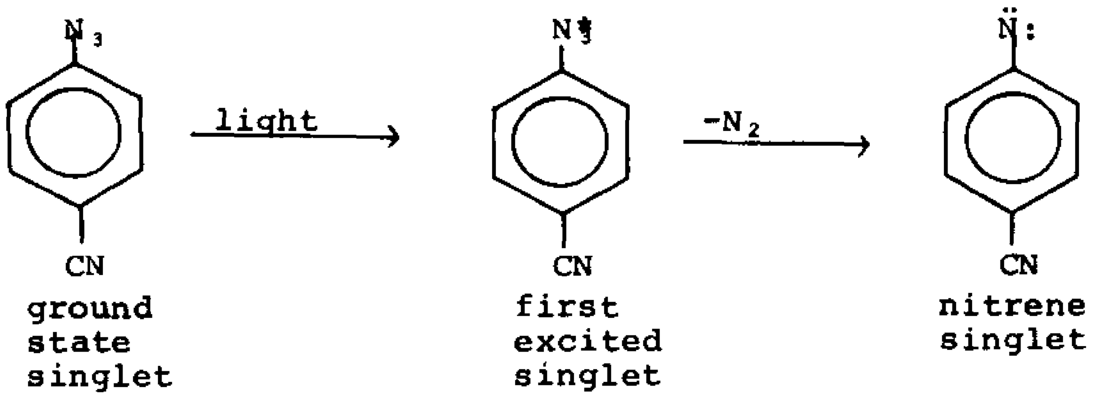


LXXX

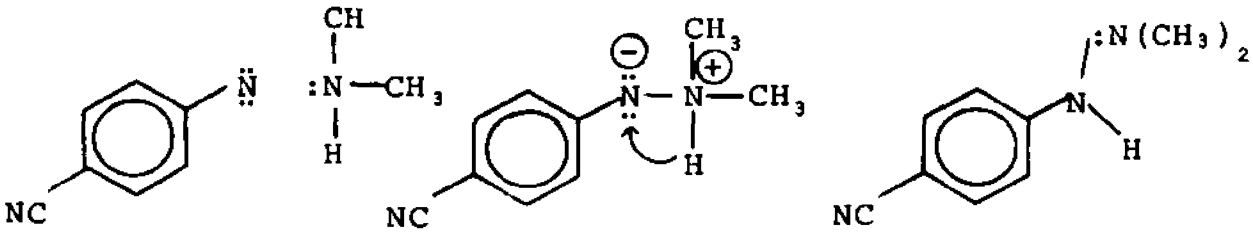


LXXXI

If one assumes spin conservation, the initial intermediate formed in the loss of nitrogen from the excited state p-cyanophenyl azide should be the singlet nitrene, LXXXII, (Equation 32). It is reasonable to expect that such an electron-deficient species would react with a strong base such as dimethylamine to give a hydrazine, LXXXIII) Equation 33).



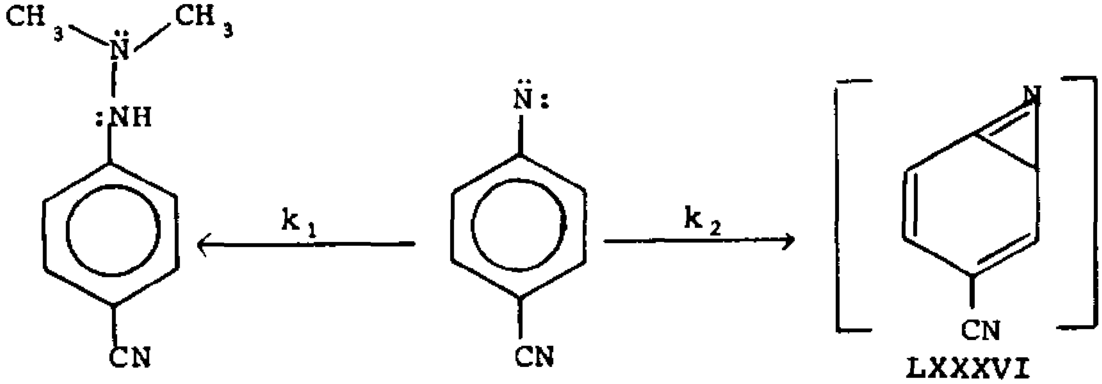
Equation 32



LXXXII LXXXIII

Equation 33

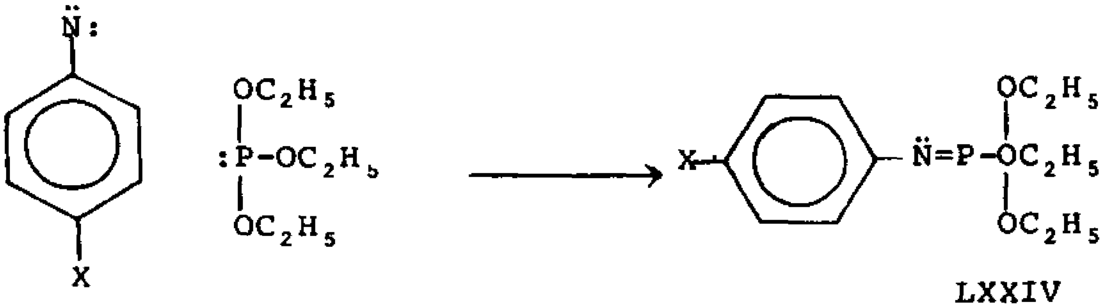
If we postulate that a free singlet phenyl nitrene rearranges as in Scheme II a p-cyano group could have two reinforcing effects due to its strong electron-withdrawing character. It could cause the nitrene to be more electrophilic than phenyl nitrene increasing its reactivity towards the basic solvent thus increasing k_1 in Equation 34, and it could decrease the electron density of the benzene ring inhibiting the rate for formation of the bicyclic intermediate, k_2 in Equation 34. Either one or both of these effects might be



LXXXVI

Equation 34

operative in the formation of hydrazine. Sundberg et al.[23] and Bunyan and Cadogan[25] use similar arguments to explain possible trapping of nitrenes by phosphite to give phosphorimidates, LXXXIV, (Equation 35). However, a major difference immediately becomes apparent since dimethylamine does not appear to trap aryl nitrenes substituted with electron-donors such as p-methoxy whereas phosphites do. Tervalent phosphorous compounds are not only highly nucleophilic, reacting rapidly with electron deficient centers, but they are also highly reactive toward nucleophiles. This amphoteric nature is due to the relatively high polarizability of phosphorus and the ability of phosphorus to expand its octet on reaction with nucleophiles[43]. The presence of π electron-donating substituents would increase any nucleophilic character of the singlet aryl nitrene such as that indicated by extended Huckel calculations which show extensive delocalization of the electron deficiency in phenyl nitrene and

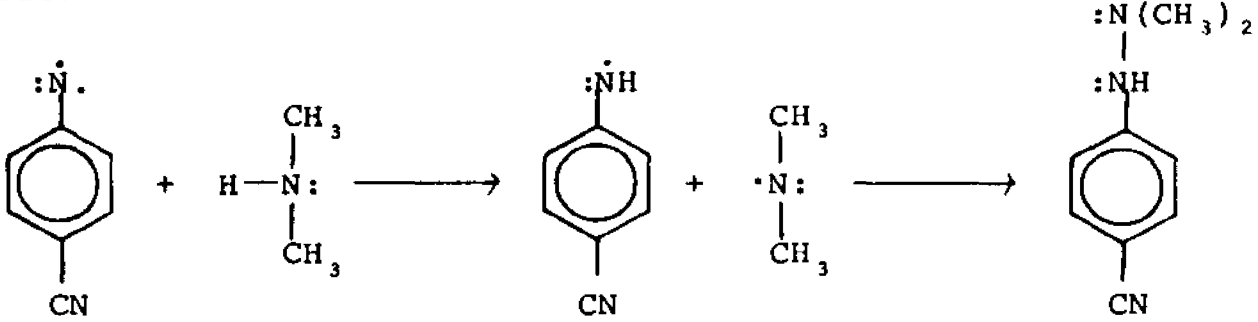

LXXIV

X = electron-withdrawing of electron-donating
substituent

Equation 35

an appreciable negative charge on nitrogen[44].

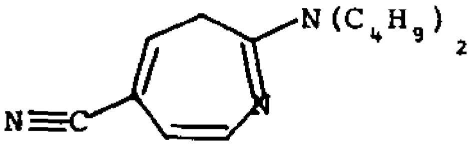
The possibility of an initially formed singlet p-cyanophenyl nitrene undergoing intersystem crossing to the ground state triplet nitrene which could yield hydrazine by a radical abstraction-recombination mechanism (Equation 36) analogous to Hall, Hill and Fargher's[23] could not be ruled out.



Equation 36

To test these hypotheses it was decided to photolyze p-cyanophenyl azide in the presence of an equimolecular amount of a triplet sensitizer. Lewis and Saunders[45] report a triplet energy for phenyl azide of about 75 kcal per mole in their studies of triplet energy transfer from various sensitizers to various azides in benzene solution. Using sensitizers of slightly below 75 kcal per mole almost diffusion controlled triplet energy transfer rates were observed. Xanthen-9-one has a triplet energy of 71-74 kcal per mole depending on solvent[46] and when the spectra of p-cyanophenyl azide and xanthen-9-one in dibutylamine were taken independently and compared the xanthen-9-one absorbed more than 99% of the light in the region 3300 Å to 3700 Å. This corresponds to 75% of all light emitted through a pyrex filter by the 3500Å internally phosphor-coated, mercury vapor lamps used for the photolyses. On photolysis in the presence of xanthen-9-one the p-cyanophenyl azide disappears rapidly and completely in an unusually clean reaction compared to the unsensitized run. The reaction mixture on analysis by glpc shows reversal of product yields with the steady formation of p-cyanoaniline as the major product in 91% yield and 1,1-dimethyl-2-(4-cyanophenyl)hydrazine as the minor product in 6% yield. Significantly, no loss of xanthen-9-one occurs until most of the azide is consumed indicating a transfer of energy from the excited xanthen-9-one to the azide before the xanthen-9-one can undergo further reaction. This evidence indicates quenching of the normal reactions of xanthen-9-one, namely hydrogen abstraction from the solvent by the n-π^* triplet resulting in reduction and pinacol formation[47]. Clearly in the sensitized experiment, triplet azide is formed on energy transfer and a triplet species, presumably triplet nitrene, is mostly reduced to the amine. It is also possible that the triplet azide is the species that abstracts hydrogen from the solvent then loses nitrogen giving rise to an anilino radical which further abstracts a hydrogen to yield aniline. These results are in agreement with the findings of Splitter and Calvin[26] for the sensitized photolysis of phenyl azide. The sensitizer used in those studies was p-dimethylaminobenzaldehyde which also sensitized p-cyanophenyl azide. By implication the large yield of hydrazine on photolysis in the absence of sensitizer is apparently due to the singlet nitrene. Two other possible explanations might be the solvent assisted loss of nitrogen from the photoexcited singlet state of the azide similar to a displacement of a molecule of nitrogen by solvent or the photodecomposition of a ground state complex between one molecule of p-cyanophenyl azide and one molecule of dimethylamine solvent losing nitrogen and forming hydrazine.

Since thermal decomposition of aryl azides in various solvents as discussed previously is a method for generating aryl nitrenes and since this process involves the ground electronic state of the azide it was of interest to see if a hydrazine product would be formed in the thermal decomposition of p-cyanophenyl azide in a secondary amine solvent. When p-cyanophenyl azide was decomposed in refluxing dibutylamine at 160° only one major product was formed in 66% yield. This product was a high boiling, yellow oil and its ir spectrum showed the characteristic nitrile absorption at 2220 cm^{-1} and two strong absorption peaks at 1510 cm^{-1} and 1570 cm^{-1} reported[39] as characteristic of the 2-amino-3H-azepines. Its nmr spectrum was also not consistent with a hydrazine structure. Instead it showed a pattern characteristic of and consistent with 5-cyano-2-dibutylamino-3H-azepine, LXXXV. The chemical shifts for the two proton doublets



LXXXV

at position 3, the one vinyl proton doublet at position 7 and the one vinyl proton doublet at position 6 were slightly downfield by comparison with other 2-aminoazepines as listed in Table II but their values were in line with those that might be expected for a 2-dibutylaminoazepine. The single proton triplet at position 4 showed a very great shift downfield and overlapped with the doublet for the proton at position 6. Referring again as in the case of the 5-methoxy and 5-chloro azepines to the appropriately substituted ethylene system as a model for the interaction of the cyano group at position 5 with the cis proton at position 4, the reason for the large downfield shift becomes clear. The α-proton in acrylonitrile lies at higher field than the β-protons even though the nitrile group is quite electronegative and should deshield the α-proton[48]. Due to the diamagnetic anisotropy of the nitrile group similar to that observed in acetylenic compounds the α-proton in acrylonitrile is effectively shielded. The diamagnetic anisotropy of the nitrile group also effects the cis β-proton and shields it by 0.3 τ units; however, the chemical shift of the cis β-proton is still 0.68 τ units downfield from ethylene. In 5-cyano-2-dibutylamino-3H-azepine the magnitude of the downfield shift of the proton at position 4 is only about 0.5 τ units but as in the 5-methoxyazepine this is probably due to the influence of the other substituents on this substituted ethylene system.

To rule out any possible solvent participation in the thermal decomposition of p-cyanophenyl azide in secondary amines the kinetics of the decomposition in dibutylamine, dipropylamine and decalin were measured and compared to values previously reported in the literature for decalin and other solvents. The rate of decomposition of p-cyanophenyl azide in amine solvents is of the same order of magnitude and in very close agreement with the rate of decomposition in other solvents. The data in Table III clearly demonstrates the absence of solvent effect for the thermal decomposition of p-cyanophenyl azide in secondary amines.

The minor yield of azepine product in the photolysis of p-cyanophenyl azide in dimethylamine and the isolation of

TABLE III

RATES OF DECOMPOSITION OF VARIOUS PHENYL AZIDES

Azide	Solvent	Temp.	$k \times 10^3$ min.	$k \times 10^5$ sec.	Reference
phenyl	decalin	141.3°	1.7	2.8	11
p-cyanophenyl	decalin	140°	2.0	3.3	this work
p-cyanophenyl	dibutylamine	138.7°	2.6	4.3	this work
p-methoxyphenyl	decalin	141.3°	8.4	14	11
p-methoxyphenyl	ethyl benzoate	139.3°	10.4	17.3	13
p-cyanophenyl	dipropylamine	110°	.34	.57	this work
p-methoxyphenyl	ethyl benzoate	111.3°	.36	.60	13
p-nitrophenyl	decalin	141.3°	3.9	6.5	11
p-nitrophenyl	dibutylamine	140°	22.0	36.7	this work

azepine as the major product in the thermolysis of p-cyanophenyl azide in dibutylamine indicated that there was possibly an energy of activation involved in the formation of the azepine via the bicyclic intermediate, LXXXVI, for a mechanism involving generation of an initial nitrene either photolytically or thermally. Since azepine is formed exclusively at 140° and the hydrazine almost exclusively at 6° then the ratio of products should change at various intermediate temperatures. The rate of thermal decomposition becomes too slow at these lower temperatures so photolysis at an intermediate temperature was tried. At 40° p-cyanophenyl azide was photolyzed in dibutylamine and on glpc analysis and subsequent isolation only the 5-cyano-2-dibutylamino-3H-azepine in 50% yield is formed along with a very low yield of p-cyanoaniline. The formation of azepine exclusively in dibutylamine might reflect a very low energy of activation for the bicyclic intermediate, LXXXVI, and one which might be solvent dependent so p-cyanophenyl azide was further photolyzed in dibutylamine at 0° (62% yield based on one run) and at -33° (yield undetermined). In both cases only 5-cyano-2-dibutylamino-3H-azepine along with minor yields of p-cyanoaniline was detected indicating that the nature of the secondary amine solvent is more important than temperature. The possibility of an energy barrier for azepine formation in dimethylamine still existed. A solution of p-cyanophenyl azide in dimethylamine was sealed in a Carius tube and heated to approximately 40° and photolyzed. The major product in this case was still the hydrazine, LXXX, and its ratio to the minor amount of azepine formed did not change with increase in temperature. p-Cyanophenyl azide was then thermally decomposed in dimethylamine in a high pressure, stainless steel bomb at 140-150°. The amount of p-cyanoaniline formed increased to 32% from the usual 10-15% found in the unsensitized photolysis reactions and the amount of hydrazine dropped to 7%. The minor amount of azepine was still produced in the same approximately 13% yield as in the photolysis reactions in dimethylamine. The hoped for increased activation energy for self-closure of the nitrene resulting in azepine formation as opposed to direct reaction of the nitrene to form hydrazine is apparently non-existent from these results. Instead, the difference between azepine formation and hydrazine formation appears to be directly related to the nature of the secondary amine solvent. The most obvious difference between dimethylamine and dibutylamine is that the concentration of nucleophilic amino nitrogen atoms is greater in dimethylamine than in dibutylamine. To test this p-cyanophenyl azide was photolyzed in dimethylamine diluted with pentane in 1:1 and 1:3 dimethylamine-pentane ratios. While the yield of hydrazine fell from 64% obtained in neat dimethylamine to 50% in 1:1 dimethylamine-pentane to

44% in 1:3 dimethylamine-pentane the results are in no way as dramatic as in the variation from dimethylamine to dibutylamine. The amino nitrogen concentration in dibutylamine would correspond most closely to the 1:1 dilution of dimethylamine in pentane unless there occurred a preferential solvation of azide by dimethylamine. The yields of p-cyanoaniline and azepine in all three dilutions remained constant and within experimental error.

Apparently the explanation involves some aspect of the steric differences between dimethylamine and dibutylamine. The much smaller size and less hindered amino nitrogen with its unshared pair of electrons of dimethylamine should allow for a tighter solvation shell around each p-cyanophenyl azide molecule in solution. This closer proximity of amino nitrogen might allow for solvent assisted displacement of nitrogen from the photo-excited state of the azide similar to other types of nucleophilic displacement. The amino nitrogen in dibutylamine might be sterically inhibited by the β-hydrogens from displaying this behavior in any observable amount. It is possible that this nitrogen displacement in dimethylamine might also take place in the ground state. In the case of the high temperature thermal decomposition of p-cyanophenyl azide in dimethylamine in a stainless steel bomb there might have been some surface reaction involving the metal vessel which would account for the results.

Thermal decomposition of the hydrazine may be ruled out since in another experiment the hydrazine was refluxed in dibutylamine at 160° for three and one half hours and on quantitative glpc analysis showed no decomposition.

Formation of a molecular complex between dimethylamine and p-cyanophenyl azide can also be evoked to explain the hydrazine formation. Again, the bulky dibutylamine might be sterically prevented from forming a complex with the azide. This intermediate complex might then undergo photodecomposition to give the hydrazine. There is evidence for a similar complex formation in the Staudinger reaction[30] of phenyl azides with tervalent phosphorus compounds and in the diazo transfer reaction[49] between azides and active methylene compounds.

If the transition state for hydrazine formation is visualized in terms of a critical minimum separation of reacting centers then the rate of nitrene rearrangement, on the assumption that a discrete nitrene is involved, would have to compete with the rate at which a favorable configuration between nitrene and amine is formed. This rate would depend on the distance between the amino nitrogen and the nitrene nitrogen. The bulky alkyl groups, more specifically the β-hydrogens, prevent the dibutylamino nitrogen from approaching as close as the relatively unhindered dimethylamino nitrogen. Thus in dibutylamine only azepine is formed.

Less electrophilic nitrenes than p-cyanophenyl nitrene might need even a closer approach than would be possible for dimethylamine before hydrazine formation could take place. Thus, hydrazine formation for the other substituted phenyl azides and phenyl azide itself are not observed. On dilution with an inert solvent, such as pentane, the dimethylamine nitrogens could still approach the necessary reaction configuration but would do so with lower frequency. The yield of hydrazine should decrease on increased dilution and this is observed. If fewer nitrenes are trapped at greater dilution then these nitrenes must react further to form more azepine, aniline or uncharacterizable polymeric products. Decreased dimethylamine concentration would tend to reduce apezine yield which might be sufficient to offset the expected increase. Aniline formation possibly is unrelated to singlet nitrene generated thus it would not be effected by pentane dilution. The material balance then indicates an increase in polymeric products.

The apparent trapping of the singlet p-cyanophenyl nitrene with dimethylamine suggested that other reactions characteristic of electron deficient species such as carbenes and other than aryl nitrenes might be observed for the first time for a singlet aryl nitrene. These included intermolecular insertion and stereospecific addition to olefinic double bonds. When p-cyanophenyl azide was photolyzed in cyclohexane however, only a high molecular weight polymeric material and a trace of p-cyanoaniline were detected. No apparent insertion products or other materials of comparable molecular weight were formed. Photolysis of p-cyanophenyl azide in cyclohexene gave four major products in significant yield; however, due to the well documented participation of intermediate triazolines in similar aryl azide-olefin reactions[50] conclusive evidence clarifying the nature of aryl nitrenes could not be obtained from this reaction so it was not investigated further.

Thermal decomposition of p-cyanophenyl azide in benzene in sealed tubes did not give any evidence of intermolecular insertion reaction either at a carbon-hydrogen bond to give N-phenyl amines or at a carbon-carbon bond to give 1H-azepines or aziridines.

Photolysis of p-Nitrophenyl Azide

Interestingly, the reaction of p-nitrophenyl azide might be expected to be analogous to the p-cyano compound, but this is not the case. Photolysis of p-nitrophenyl azide in dimethylamine produces p-nitroaniline in better than 90% yield and no other products of comparable molecular weight. This is not surprising as nitro groups are known to enhance intersystem crossing, as shown in the complete suppression of fluorescence of aromatic hydrocarbons on substitution of a nitro group, with concommittant phosphorescent quantum yield of the nitroaromatic approaching unity[51]. This explanation is further supported by the results of the photolysis of m-nitrophenyl azide in dimethylamine. In this case a 53% yield of m-nitroaniline was isolated and by qualitative glpc analysis only m-nitroaniline and unreacted m-nitrophenyl azide were detected. Apparently the effect of the nitro group is not specific to the para position.

There is a slight rate enhancement shown in Table III for the thermal decomposition of p-nitrophenyl azide in dibutylamine. In addition there is a peculiar absence of azepine, hydrazine or other products of comparable molecular weight in this reaction except for a small amount of p-nitroaniline. Smith and Hall[11] have also noted a peculiar behavior in the thermal decomposition of p-nitrophenyl azide. They observed more than stoichiometric quantities of nitrogen evolved in decalin at similar reaction temperatures. Apparently the decomposition of p-nitrophenyl azide is more complex than the other substituted phenyl azides and might proceed by entirely different mechanisms.

EXPERIMENTAL

Preparation of Substituted Phenyl Azides

The procedure given in "Organic Synthesis"[52] was used at one half molar scale without modification for all azides melting above room temperature. For lower melting azides including phenyl azide a modification in the isolation and purification of the product was made. This consisted of extracting the reaction mixture with either diethyl ether or methylene chloride several times to remove all of the azide and then washing the combined extracts with 2N NaOH until all phenol had been removed[5]. After drying ($MgSO_4$) the ether or methylene chloride solution was concentrated and vacuum distilled to yield the substituted phenyl azide.

The following azides were prepared: phenyl[5], bp48.5-50.0° (16 mm); $n^{25.2}D$ 1.5595; 79%; o-chlorophenyl[53], bp 46° (0.45 mm); $n^{20}D$ 1.5882; 83%; o-methoxyphenyl[54], bp 53-6° (0.45 mm); $n^{20}D$ 1.5701; 82%; o-azidobenzoic acid, mp 145-6° (recryst. from water); 62%; p-cyanophenyl[55], mp 65.5-66.0° (recryst. from EtOH); anal. calcd for $C_7H_4N_4$: C, 58.33; H, 2.80; N, 38-87; found: C, 58.54; H, 2.77; N, 38.78; 78%; p-chlorophenyl, bp 96° (20 mm); mp 19-20°; $n^{25}D$ 1.5814; 90%; p-bromophenyl, bp 118° (16 mm); 87%; m-nitrophenyl[56], mp 55.5-56.0° (recryst. from ligroin); 84%; p-methoxyphenyl[57], mp 35-36°; p-nitrophenyl (7), mp 63-64°;

Photolysis of p-Chlorophenyl Azide in Liquid Ammonia

A sample of 5.17g (0.034 moles) of p-chlorophenyl azide in 1 liter of anhydrous liquid ammonia was irradiated by three 275 watt sunlamps for 7.5 hours. The ammonia was evaporated and the residue was extracted with hot benzene. After evaporation of the benzene and cooling a crystalline solid was isolated, recrystallized from CCl_4 and sublimed to give 0.35 g (7.3%) of 5-chloro-2-amino-3H-azepine: mp 112°; nmr (CDCl and TMS) τ7.43 (doublet, 2H, J=7.0Hz, methylene), 4.73(triplet, 1H, J = 7.0Hz, vinyl), 4.47 (broad singlet, 2H, NH_2), 4.23 (doublet, 1H, J = 8.0Hz, vinyl), 3.13 (doublet, 1H, J = 8.0Hz, = CH-N).

anal. calcd for $C_6H_7ClN_2$: C, 50.54; H, 4.95; Cl, 24.86; N, 19.65; found: C, 50.56; H, 5.02; Cl, 24.66; N, 19.45.

Photolysis of p-Methoxyphenyl Azide in Dimethylamine

A solution of 5.85g (0.039 moles) of p-methoxyphenyl azide in 2 liters of anhydrous dimethylamine was irradiated by four 275 watt sunlamps for 6.5 hours. After evaporating the dimethylamine the residual oil was carefully fractionated to give a pale yellow oil (55% by glpc analysis with o-methoxyaniline as an internal standard): bp 60° (0.1 mm); $n^{25}D$ 1.5648; nmr ($CDCl_3$ and TMS) τ 7.47 (doublet, 2H, J = 7.5Hz, methylene), 7.08 (singlet, 6H, methyl), 6.53 (singlet, 3H, methyl), 5.67 (triplet, 1H, J = 7.5Hz, vinyl), 4.38 (doublet, 1H, J = 8.5Hz, vinyl), 2.93 (doublet, 1H, J = 8.5Hz, = CH-N). anal. calcd for $C_9H_{14}N_2O$: C, 65.03, H, 8.49; N, 16.85;

Found: C, 65.27; H, 8.29; N, 16.79.

Photolysis of p-Nitrophenyl Azide in Dimethylamine

A solution of 12.4g (0.075 moles) of p-nitrophenyl azide in 2 liters of dimethylamine was irradiated by four 275 watt sunlamps for 6 hours. The dimethylamine was evaporated and the semisolid residue dissolved in chloroform was extracted with 2N HCl. The chloroform layer after drying, filtering and removal of solvent yielded 2.66g of unreacted p-nitrophenyl azide: mp 62-4°; ir (KBr), 2120 cm^{-1} (azide). The aqueous acid layer was made basic with 10N NaOH and extracted with diethyl ether. The ether layer, after drying, filtering and evaporation yielded 5.98g (73%) p-nitroaniline: mp 141-3°; ir (KBr), identical to an authentic sample. Analysis of the reaction mixture after photolysis by glpc using trihexylamine as an internal standard showed 4-nitroaniline (89%) based on reacted azide.

Photolysis of m-Nitrophenyl Azide in Dimethylamine

A solution of 4.99g (0.03 moles) of m-nitrophenyl azide in 2 liters of dimethylamine was irradiated for 5 hours by four 275 watt sunlamps. After evaporation of the dimethylamine the residue which indicated only unreacted m-nitrophenyl azide and m-nitroaniline were present was dissolved in diethyl ether and extracted with 2N HCl. The ether layer, after drying, filtering and evaporating yielded 2.50_g (50%) of material identical to unreacted m-nitrophenyl azide: mp 48-50°; ir (KBr) 2120 cm^{-1} (azide). The aqueous acid layer was made basic with NaOH and extracted with diethyl ether. This ether layer, after drying, filtering and evaporating yielded 1.11g (53%) of m-nitroaniline: mp 96-8°; ir (KBr), identical to authentic m-nitroaniline.

Photolysis of p-Cyanophenyl Azide in Dimethylamine

A solution of 4.33_g (0.03 moles) of p-cyanophenyl azide in 2 liters of anhydrous dimethylamine is a vacuum jacketed pyrex flask was irradiated for 6 hours by four 275 watt sunlamps. After evaporating the dimethylamine the residue dissolved in methylene chloride was extracted with 2N HCl. The methylene chloride layer after drying ($CaCl_2$), filtering and evaporating yielded 2.55_g unreacted p-cyanophenyl azide: mp 65°. The aqueous acid layer was neutralized with 10N NaOH and extracted with methylene chloride. After drying ($CaCl_2$), filtering and evaporating the methylene chloride the dark colored residual oil was vacuum distilled giving a golden oil which crystallized on scratching. Recrystallization from methanol-water yielded white crystals of 1,1-dimethyl-2-(4-cyanophenyl)hydrazine: mp 69.5-70°; ir (KBr), 3260 cm^{-1} (sharp singlet, =N-H), 2220 cm^{-1} (strong singlet, cyano); nmr ($CDCl_3$

and TMS) τ 7.45 (singlet, 6H, methyl), 5.08 (broad singlet, 1H, = N-H), 3.15 (doublet, 2H, J=8.5 Hz, phenyl), 2.60 (doublet, 2H, J=8.5Hz, phenyl).

anal. calcd for C H N : C, 67.06; H, 6.88; N, 26.07;
found: C, 67.38; H, 6.97; N, 25.74.

Analysis of the photolysis reaction mixture by glpc using tributylamine as an internal standard showed 1,1-dimethyl-2-(4-cyanophenyl)hydrazine (64%), p-cyanoaniline (12%), 5-cyano-2-dimethylamino-3H-azepine (11%), estimated on the basis of the same detector response as used for the hydrazine and characterized by nmr spectrum (Table II).

Photolysis of p-Cyanophenyl Azide in Dimethylamine with Added Xanthen-9-one.

A solution of 1.44 g (0.01 moles) of p-cyanophenyl azide, 1.92 g (0.01 moles) of xanthen-9-one and 0.73 g tributylamine as an internal standard in 600 ml of dimethylamine was placed in a quartz reaction vessel and surrounded by a concentric pyrex filter. The irradiation was performed in a Rayonet reactor using mercury vapor lamps internally phosphor-coated with a maximum energy output at 3500 Å. After 1.5 hours of irradiation only remaining p-cyanophenyl azide (0%), p-cyanoaniline (91%) and 1,1-dimethyl-2-(4-cyanophenyl) hydrazine (7%) were detected by glpc.

Kinetics of Thermal Decomposition of p-Cyanophenyl Azide.

a) in decalin.

A solution of 0.869 g (6 mmoles) of p-cyanophenyl azide and 0.568 g tripentylamine as an internal standard in 20 ml of decalin was heated with stirring in an oil bath held at 140° for 6 hours. Aliquots were removed at various time intervals and analyzed by glpc. The log of remaining azide was plotted against time and half-life of 6 hours was determined corresponding to a rate: $k=2 \times 10^{-3}$ min^{-1} at 140°.

b) in dibutylamine.

Ten ml of 0.35M p-cyanophenyl azide with tributylamine as an internal standard in dibutylamine were placed under nitrogen in a jacketed vessel such that the chamber containing the solution was heated by the vapors of acetic anhydride refluxing at 138.7. Aliquots were taken at various time intervals and analyzed by glpc. From a plot of the log of the remaining azide against time a half-life of 270 minutes corresponding to a rate: $k=2.6 \times 10^{-3}$ $min.^{-1}$ 4.3×10^{-5} sec^{-1} at 138.7° was obtained.

c) in dipropylamine.

A 150 ml sample of 0.017M p-cyanophenyl azide in dipropylamine containing tributylamine as an internal standard was refluxed at 110°. Aliquots were taken at various time intervals and the log of unreacted azide was plotted against time.

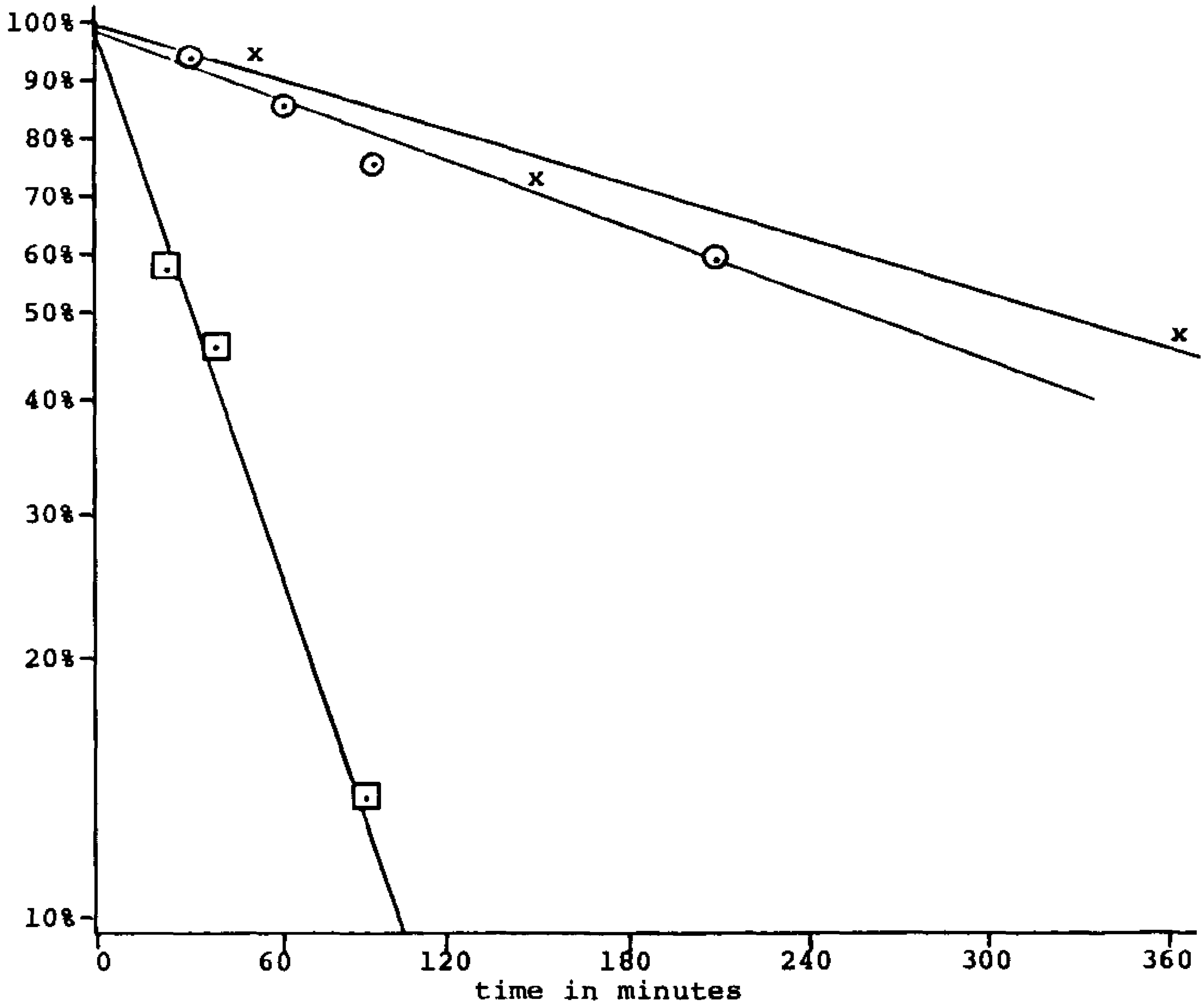
Figure 2

Kinetics of Decomposition of:

⊙ p-cyanophenyl azide in dibutylamine at 138.7°

x p-cyanophenyl azide in decalin at 140°

⊡ p-nitrophenyl azide in dibutylamine at 140°



Log % Azide Remaining vs. Time

A half-life of 34 hours corresponding to a rate: k=3.4 x 10^{-4} min^{-1} 0.57 x 10^{-5} sec^{-1} at 110° was determined.

Kinetics of the Thermal Decomposition of p-Nitrophenyl Azide.

a) in dibutylamine.

One ml of a 0.5M solution of p-nitrophenyl azide in dibutylamine containing trihexylamine as an internal standard was sealed under vacuum in each of 6 Carius tubes. The tubes were totally immersed in an oil bath at 140°. The tubes were removed, chilled, opened and analyzed by glpc at appropriate time intervals. The log of undecomposed azide was plotted against time and a half-life of 32 minutes corresponding to a rate: k=22 x 10^{-3} min^{-1} at 140° was determined.

Thermolysis of p-Cyanophenyl Azide in Dibutylamine.

A solution of 8.61 g (0.06 moles) of p-cyanophenyl azide in 70 ml of freshly distilled dibutylamine was refluxed at 160° for 3 hours. Distillation of the dibutylamine solvent at water aspirator pressure left a residual dark oil which on careful fractionation gave 5-cyano-2-dibutylamino-3H-azepine (66% by glpc analysis), a yellow oil: bp 106-114° (o.014 mm); ir (neat) 2220 cm^{-1} (nitrile), 1510 cm^{-1} and 1570 cm^{-1} (C=C and C=N stretching); nmr ($CDCl_3$ and TMS) τ 8.11-9.21 (multiplet, 14H, alkyl), 7.23 (doublet, 2H, J=7.5 Hz, methylene), 6.58 (triplet, 4H, J=7 Hz, -CH -N), 4.15-4.52 (multiplet, 2H, vinyl), 2.83 (doublet, 1H, J=7.5 Hz, =CH-N).

<u>anal.</u> calcd for $C_{15}H_{23}N_3$: C, 73.43; H, 9.45; N, 17.13
found: C, 73.52; H, 9.21; N, 17.41.

<u>Photolysis of p-Cyanophenyl Azide in Dibutylamine</u>

a) <u>at 40°</u>

A 30 ml sample of a 0.35M solution of p-cyanophenyl azide in dibutylamine with tributylamine as an internal standard was placed in a pyrex tube, preheated in a water bath and then irradiated for 5 hours in a Rayonet reactor equipped with internally phosphor-coated mercury vapor lamps with an energy maximum at 3500 Å. On glpc analysis 5-cyano-2-dibutylamino-3H-azepine identified by isolation from the reaction mixture was the only major product formed (50%) along with a minor yield of p-cyanoaniline.

b) <u>at 0°</u>

A 4 ml sample of a 0.16M solution of p-cyanophenyl azide dibutylamine with tributylamine as an internal standard was placed in a pyrex tube immersed in a recirculating water bath at 0°. The tube was irradiated for 3 hours by internally phosphor-coated mercury vapor lamps with an energy emission maximum at 3500 Å. 5-Cyano-2-dibutylamino-3H-azepine (62%) was detected along with a small amount of p-cyanoaniline.

c) <u>at -33°</u>

A 1.50 g (0.01 moles) sample of p-cyanophenyl azide and tributylamine as an internal standard were placed in the inner chamber of a pyrex, jacketed photolysis vessel with 500 ml of dibutylamine. The outer jacket was filled with refluxing anhydrous liquid ammonia. After 3 hours of irradiation by 3500 Å maximum emission phosphor-coated mercury vapor lamps the reaction solution showed the formation of 5-cyano-2-dibutylamino-3H-azepine by glpc analysis.

Thermolysis of p-Cyanophenyl Azide in Dimethylamine

A sample of 0.779 g (5.4 mmoles) of p-cyanophenyl azide, 0.149 g tributylamine as an internal standard and 25 ml of dimethylamine were placed in a high pressure bomb. The bomb was set in an oil bath in an oven at 140-150°. After approximately 3 hours the bomb reached 142° and was held at this temperature for 5 hours. The oven was then turned off and the bomb allowed to cool. After 2 hours the bomb had cooled to 60° and was left to stand overnight to reach room temperature. After opening the bomb the dimethylamine was evaporated and the residue dissolved in the methylene chloride.

Analysis by glpc showed 1.1% of the azide remained unreacted and the following yields of products: p-cyanoaniline (32%), 1,1-dimethyl-2-(4-cyanophenyl)hydrazine (7%) and 5-cyano-dimethylamino-3H-azepine (13%): nmr (CDCl and TMS) τ 4.00-4.50 (multiplet, vinyl).

Photolysis of p-Cyanophenyl Azide in Dimethylamine with Added Pentane

a) 1:1 dimethylamine-pentane

In the inner flask of a jacketed reaction vessel were placed 1.00 g (7 mmoles) of p-cyanophenyl azide, 0.238 g tributylamine as an internal standard, 250 ml of dimethylamine and 250 ml of pentane. The outer jacket of the reaction vessel was filled with refluxing dimethylamine and the apparatus was placed in a Rayonet reactor. The solution was stirred by a magnetic stirrer and irradiated by internally phosphor-coated mercury vapor lamps with an energy output maximum at 3500 Å for 4 hours. Aliquots were taken at various time intervals and glpc analysis showed: 1,1-dimethyl-2-(4-cyanophenyl)hydrazine (50%), p-cyanoaniline (14%) and 5-cyano-2-dimethylamino-3H-azepine (8%).

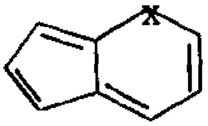
b) 1:3 dimethylamine-pentane

The same procedure as in (a) above was used for 1.04 g (7.2 mmoles) of p-cyanophenyl azide, 0.211 g of tributylamine, 125 ml of dimethylamine and 375 ml of pentane. Analysis by glpc showed: 1,1-dimethyl-2-(4-cyanophenyl)-hydrazine (44%), p-cyanoaniline (14%) and 5-cyano-2-dimethylamino-3H-azepine (13%).

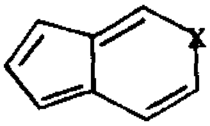
THESIS PART II

INTRODUCTION

In recent years considerable attention has been focused on a number of heterocyclic analogs of nonbenzenoid aromatic systems. Among those now known are many systems isoelectronic with azulene[58]. These can be divided into two structurally different classes, the pseudoazulenes and the heteroazulenes. The pseudoazulenes[59], LXXXVII and LXXXVIII,



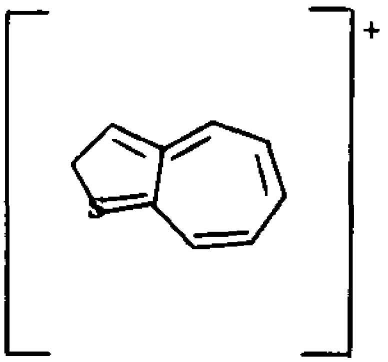
LXXXVII



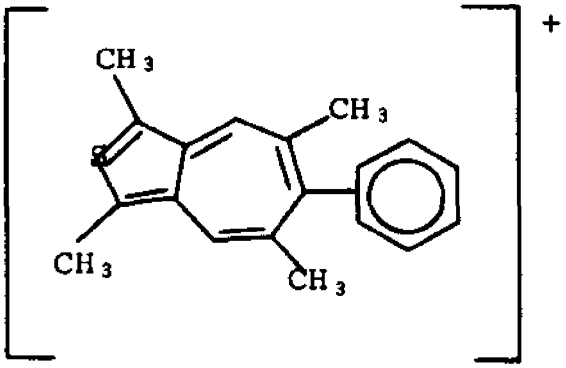
LXXXVIII

(X = O, S, or NR)

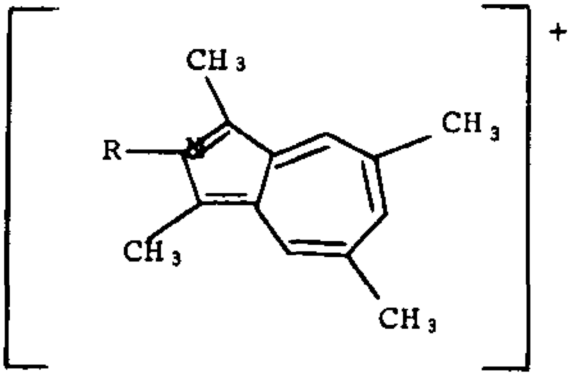
such as the cyclopentapyrans, the cyclopentapyridines and the cyclopentathiapyrans, resemble azulene very closely in many respects. This is especially demonstrated in their electronic spectra and reactivity toward electrophilic reagents. The heteroazulenes, represented chiefly by the 1-thiaazulenium cation[60], LXXXIX, the 2-thiaazulenium cation[61], XC, the 2-azoniaazulene salt[62], XCI, the 1-azaazulene[63], XCII, cannot be compared to azulene or to each other very readily since they show a great variety of stabilities, reactivities and other properties.



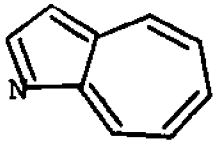
LXXXIX



XC



XCI



XCII

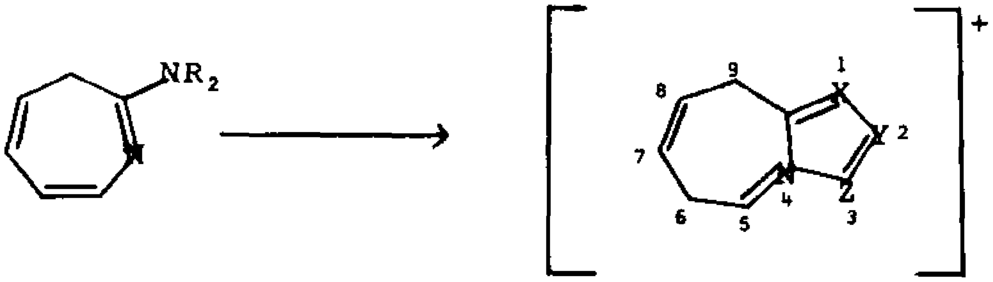
Aromatic Character

In heteroazulenes, such as LXXXIX-XCII, aromatic character cannot be investigated in terms of classical experimental criteria for aromaticity. These criteria were based upon chemical activity, such as unusual stability and the tendency to undergo ionic electrophilic substitution rather than ionic electrophilic addition. More applicable are the modern concepts of aromaticity that depend on cyclic, reasonably planar structures with a complement of π electrons defined by Huckel's rule (4n+2), which are delocalized.

This delocalization imparts a greater relative stability than an analog with localized bonds. Aromatic properties of heteroazulenic cations especially, are best described by physical quantities which depend on the extent of π electron delocalization. Since they do not lend themselves to the usual methods of quantitatively measuring resonance energies nor do they generally undergo electrophilic substitutions, inferences that they are aromatic must be made from absorption of uv and visible light at longer wavelengths in comparison to alkenes, the ability to be polarized, and the exhibition of anisotropy of their diamagnetic susceptibility. An nmr hydrogen resonance at low field indicative of a strong ring current of π electrons and the stability of the cation relative to attack by nucleophilic anions are also good experimental criteria for assigning aromatic character.

PROPOSED NEW HETEROAZULENES

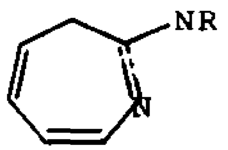
In all of the heteroazulenes mentioned previously, the hetero atom is in the five-membered ring and since no comparable system with the heteroatom in the seven-membered ring had been reported at the time this thesis was begun, it was felt that the synthesis of such a system would contribute valuable information toward a better understanding of the effect of heteroatoms on the aromaticity of non-alternant systems. The ready availability of 2-amino-3H-azepines, XCIII, by the photolysis of phenyl azides in anhydrous liquid amines[64] seemed like a very good starting point for the synthesis of such a heteroazulene system, XCIV, (Equation 37).



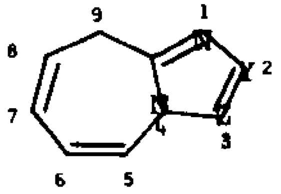
XCIII XCIV

Equation 37

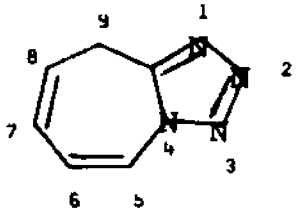
This system, XCIV, would have a nitrogen atom at the bridgehead, be isoelectronic with azulene and be cationic. Starting with 2-amino-3H-azepine, XCV, all that is needed is a method of constructing a two atom unsaturated bridge such as -Y=Z- in XCIV, between the 2-amino nitrogen and the axepine ring nitrogen. Oxidation of the resulting bicyclic compound, XCVI, could then lead to a ten π electron azaazulenium or azonia azulene ion, XCIV. Of the many conceivable five membered rings that might be constructed incorporating the amidine moiety, the two which offered the greatest promise were a tetrazole ring and an imidazole ring. These would give a 9H-tetrazolo[1,5-a]azepine system, XCVII, and a 9H-imidazo[1,2-a]azepine system, XCVIII, respectively.



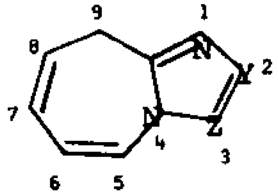
XCV



XCVI



XCVII



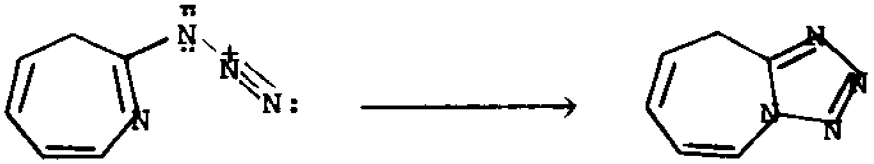
XCVIII

The Attempted Synthesis of 9H-Tetrazolo[1,5-a]azepine.

Three basically different approaches to the synthesis of the tetrazole structure were employed. The first approach involved the conversion of the 2-amino substituent into a group readily converted to or displaced by an azide group. The second approach was based on the ring expansion of pyridotetrazole and the third approach was an attempt to dehydrogenate pentamethylene tetrazole.

The Significance of a 2-Azido Substituent

If the 2-amino substituent on the 3H-azepine ring could be transformed into an azido group then spontaneous ring closure to a tetrazole might occur readily (Equation 38).



XCIX C

Equation 38

This is the essential step in the synthesis of a large number of 1,5-disubstituted tetrazoles[65]. Often it is unnecessary and frequently impossible to isolate the intermediate imide azide. Since 9H-tetrazolo[1,5-a]azepine, XCVIII, has never been synthesized before, the factors which influence the ring closure might prove to be very significant in this case.

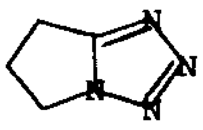
An equilibrium between tetrazoles and their isomeric azidoazomethine compounds (Equation 39) has been shown to exist for several different heterocyclic systems and has been postulated for a great many more[66-73]. In some cases factors exist which allow only the azido structure, CII, to be found and at the other extreme only the tetrazole structure is found. From studies of intermediate structures, where both forms are found simultaneously, a great deal has been learned about some of the apparent factors which influence this equilibrium.

CI CII

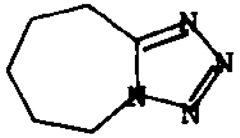
Equation 39

Tetrazole destabilization in bicyclic systems may occur for at least two probable reasons. These are the strain of ring-fusion and electron withdrawal[66].

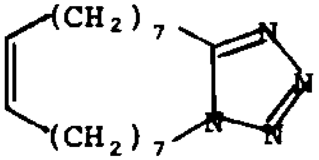
Electron-withdrawing substituents may be doubly effective by not only destabilizing the electron-attracting tetrazole ring but at the same time stabilizing the electron-donating azido group. Many saturated cyclic tetrazoles have been isolated with methylene bridges ranging from the trimethylene tetrazole[66], CIII, through pentamethylene tetrazole, CIV, (the saturated derivative of the proposed 9H-tetrazolo [1,5a]azepine) up to civetonetetrazole[65] which is a hexadecylmethylene bridged tetrazole with one degree of unsaturation, CV. Specifically in the case of trimethylene tetrazole, CIII, and its nitrogen analog, 5,6-dihydro-imidazo [1,2-e]tetrazole, CVI, the ir and uv spectra do not indicate the presence of any azide form but absorption bonds characteristic of tetrazoles are present. Ring fusion strain is apparently negligible, if present at all, since there is no change in the frequency or intensity of absorption brought about by steric distortion of the chromophoric system.



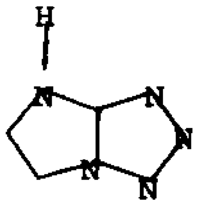
CIII



CIV

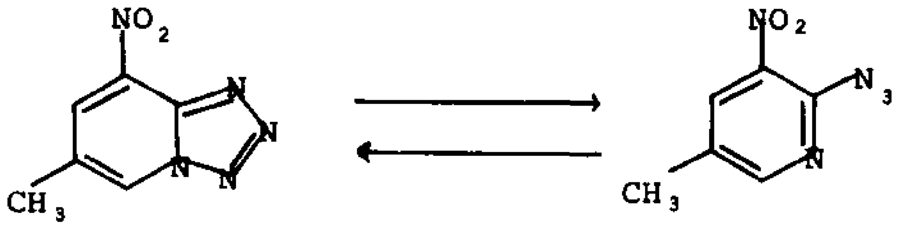


CV



CVI

The presence of an equilibrium in solution between pyridotetrazole, CVII, and 2-azidopyridine, CVIII, with electron withdrawing substituents in the pyridine ring (Equation 40) was established by the spectrophotomeric detection of both azido and tetrazolo groups[67]. With no substituents or with electron-donating substituents the azido form was not detected(66,71). Further highly significant data comes from the actual determination of equilibrium constants for several tetrazolo-azidopyrimidines for which the concentration of azide form vs tetrazole form were determined by nmr spectroscopy[68-70,72,73].



CVII CVIII

Equation 40

On the basis of this information the proposed 9H-tetrazolo[1,5-a]azepine, C, would be expected to exist primarily, if not entirely, in the tetrazole form because it should not be strained any more than the trimethylene tetrazole, CII, or the pyridotetrazole structures and because the unsaturated bridge should not be a strongly electron-withdrawing substituent by itself with the ability to destabilize the electron-attracting tetrazole form in favor of the electron-donating form.

Attempted Preparation of 2-Azido-3H-azepine

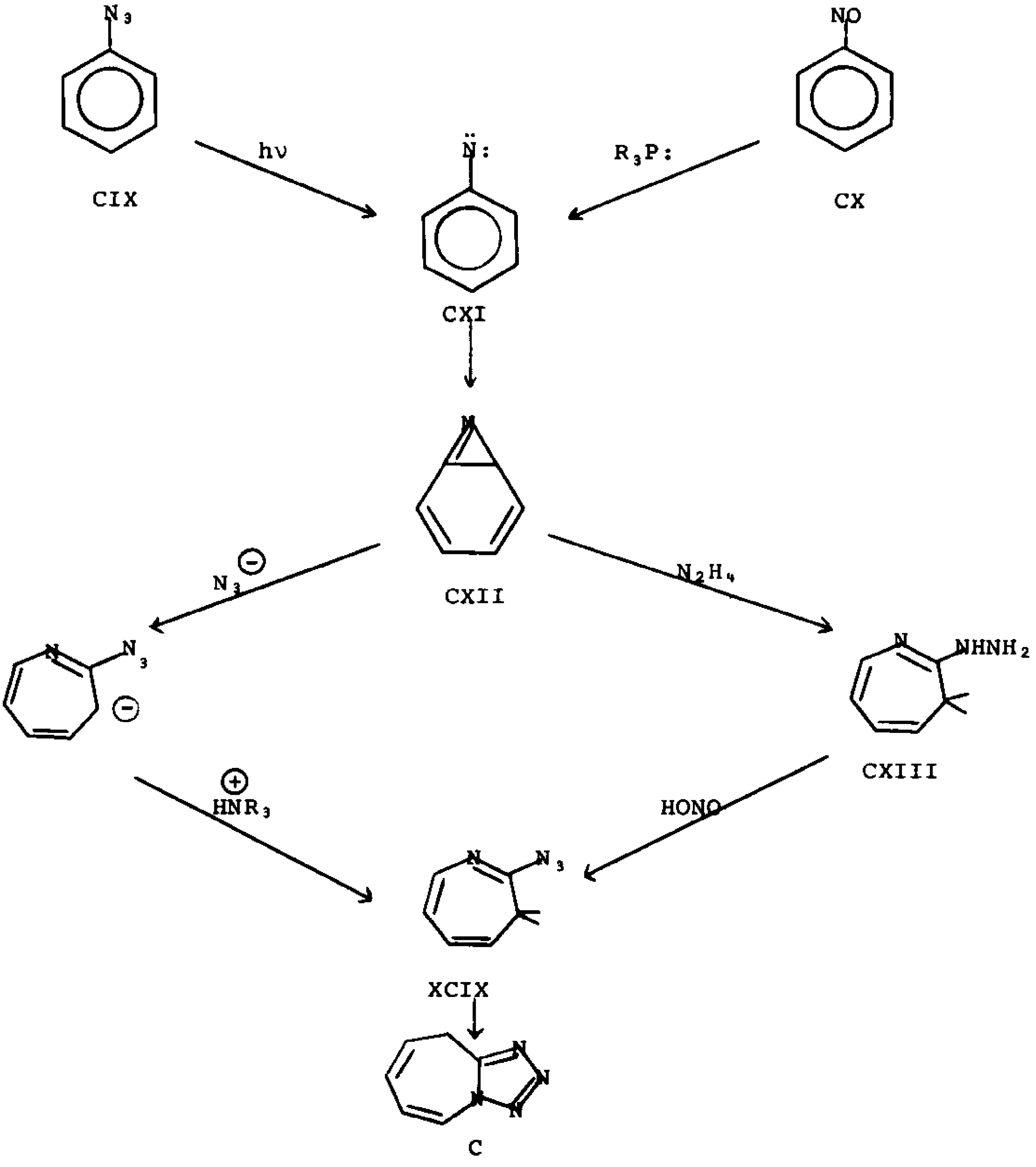
Four different synthetic approaches to the preparation of a 3H-azepine with a 2-azido substituent were investigated. One of these was based on carrying out the ring expansion of phenyl nitrene to 3H-azepine in the presence of nucleophilic azide ion (Scheme VI). Two other approaches involved the conversion of a 2-amino substituent into an azido substituent (Scheme VII). The fourth approach involved the displacement by azide of a 2-amino substituent or another group readily obtained from the 2-amino-3H-azepine (Scheme VIII).

Direct Attack on the Proposed Bicyclic Intermediate

The ring expansion reaction in the decomposition of phenyl azide in the presence of amines is well documented[64]. It was felt that other strong nucleophiles, such as hydrazine and azide ion might be able to trap the proposed bicyclic intermediate CXII as in Scheme VI to give a 2-hydrazino-3H-azepine, CXIII, or the 2-azido-3H-azepine, XCIX. The hydrazino compound should then be readily converted to XCIX by diazotization.

The photolysis of phenyl azide in a trimethylamine solution of hydrazine proved unsuccessful because of the great insolubility of hydrazine in the inert tertiary amine solvent.

Azide ion in the form of ammonium azide was prepared by passing ammonia through an ether solution of hydrazoic acid. Two different methods which have been used to give azepines[64], the photolysis of phenyl azide and the deoxygena-


N_3
CIX
hν
$\ddot{N}$:
R_3P:
NO
CX
CXI
N
CXII
$N_3^{\ominus}$
N_2H_4
N
N_3
⊖
N
NHNH$_2$
CXIII
$\overset{\oplus}{HNR_3}$
HONO
N
N_3
XCIX
N
N
N
N
C

SCHEME VI

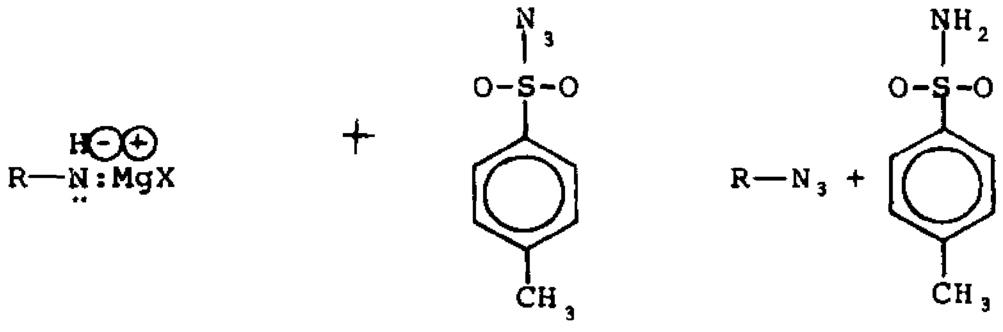
tion of nitrosobenzene with tributylphosphine, were carried out in the presence of ammonium azide. In both cases neither 2-azidoazepine nor tetrazole was detected.

The Raschig Hydrazine Synthesis

In the Raschig synthesis[74] chloramine undergoes nucleophilic attack by ammonia, primary and secondary amines to give hydrazines (Scheme VII). Therefore, 2-amino-3H-azepine, XLV, was treated with chloramine. This approach was unsuccessful since the desired 2-hydrazino-3H-azepine, CXIII, was not detected.

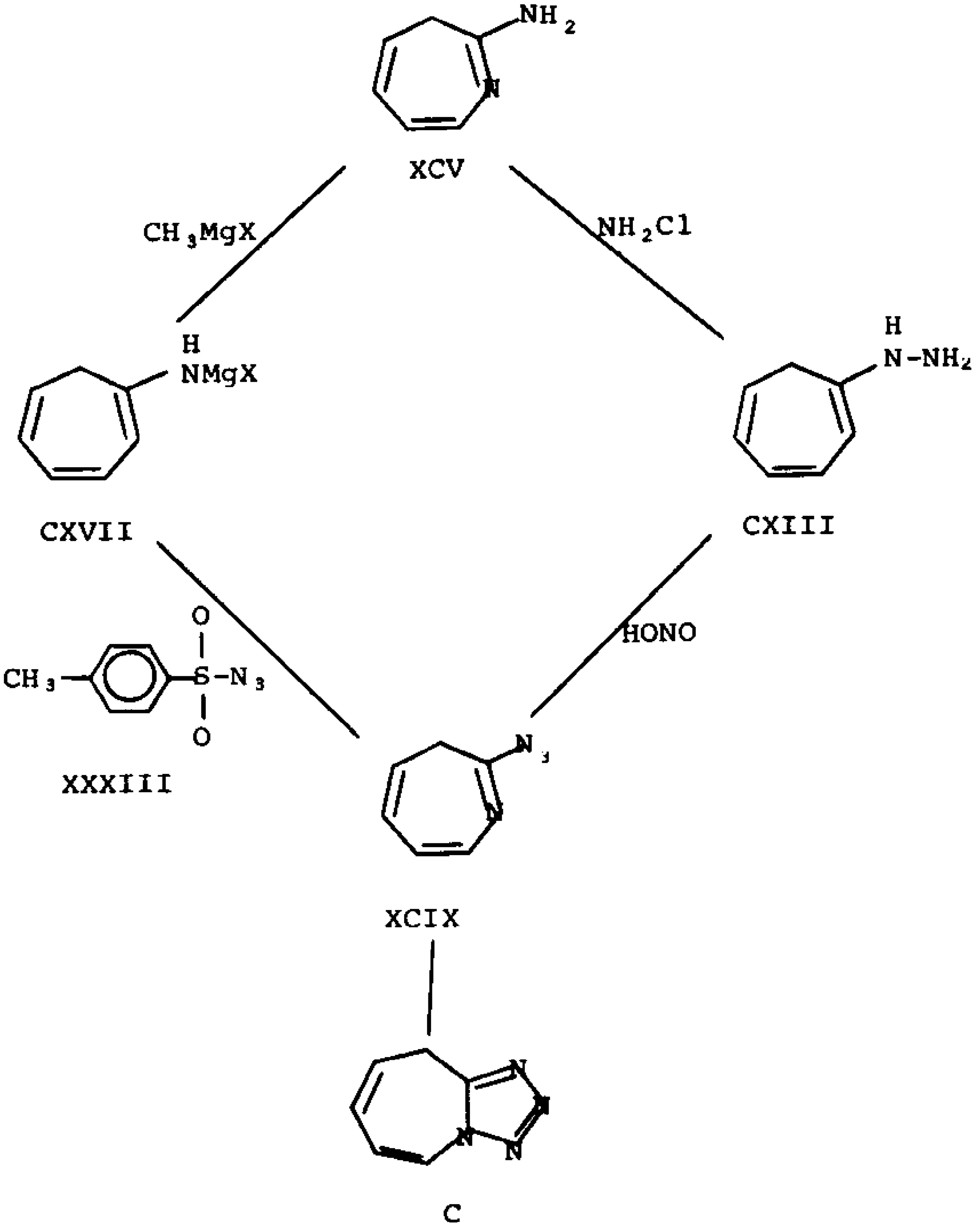
The Diazo Transfer Reaction

The diazo transfer reaction[75], in which active methylene compounds are converted to the corresponding diazoalkanes, has been extended recently to the transfer of two nitrogens to primary amines[76,77]. The corresponding amine anions, CXVIII, from the treatment of the amines with methyllithium or methylmagnesium chloride are treated with p-toluenesulfonyl azide, CXIX, and the corresponding azides, CXX, are formed in good yield (Equation 41). When 2-amino-3H-azepine



CXVIII CXIX CXX

Equation 41


NH$_2$
N
XCV
CH$_3$MgX
NH$_2$Cl
H
NMgX
H
N-NH$_2$
CXVII
CXIII
CH$_3$
O
S-N$_3$
O
XXXIII
HONO
N$_3$
N
XCIX
N
N
N
N
C

SCHEME VII

was treated with methylmagnesium chloride and then p-toluenesulfonyl azide under conditions reported to be successful with toluidine and p-chloroaniline[77] no 2-azido-3H-azepine or tetrazoloazepine was observed (Scheme VII). Prior to the publication of this most recent work of Anselme and Fischer[77] we had tried, to no avail, effecting the diazo transfer to 2-amino-3H-azepine with reagents other than p-toluenesulfonyl azide such as 2-azido-3-ethylbenzthiazolium fluoroborate, CXXI, and 2-azido-1-ethylpyridinium fluoroborate, CXXII. These compounds, CXXI and CXXII, are successful in transfer to active methylene compounds[78,79].

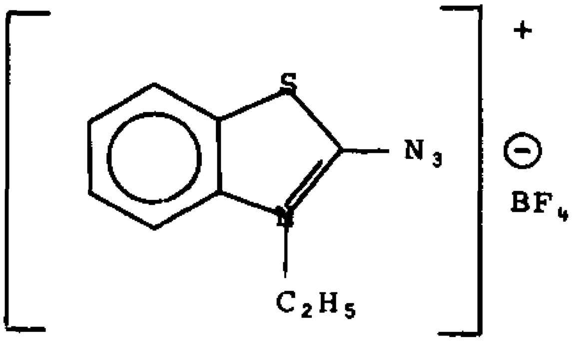
Displacements by Hydrazine and Azide.

Displacement of Ammonia.

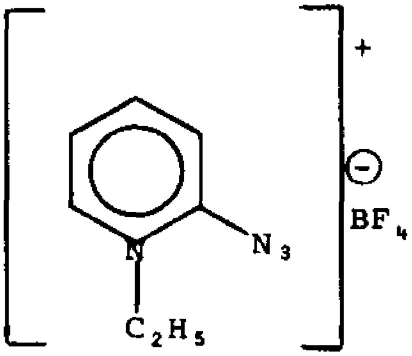
Scheme VIII summarizes the various types of displacement reactions tried. Perhaps the simplest among these is the direct exchange of hydrazine with ammonia in refluxing anhydrous hydrazine. This is a known displacement reaction of amidines[80] which was not successful in this case.

Displacement of an Ethoxy Group

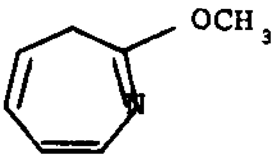
A variation on the displacement of an amino group is the displacement of a better leaving group such as an ethoxy group as ethanol or a chloro group as chloride. Both imidate esters, such as CXV and imidoyl chlorides, such as CXVI, appeared to be readily available from the lactam, 1,2-



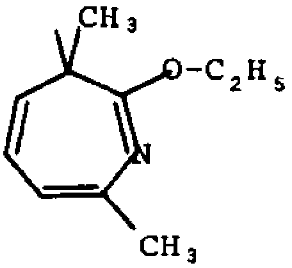
CXXI



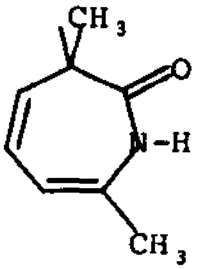
CXXII



CXXIII



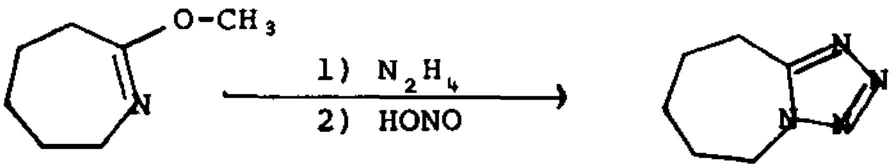
CXXIV



CXXV

dihydro-3H-azepin-2-one, CXIV, obtained on hydrolysis of 2-amino-3H-azepine, XCV, in refluxing water[5] (Scheme VIII). In fact, the imidate ester 2-methoxy-3H-azepine, CXXIII, is known[81] as is the ethyl imidate ester, CXXIV, prepared from the 3,7-dimethyl-1,2-dihydro-3H-azepin-2-one[82]. They were synthesized from the appropriate lactams by a known and general synthetic procedure[25]. In this process the lactam is treated with triethyloxonium fluoroborate to form the imidate ester. The 2-ethoxy-3H-azepine, CXV, was prepared in 52% yield by this method.

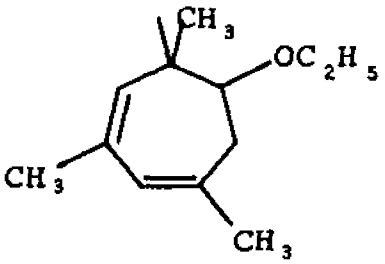
The imidate ester, CXV, was treated with anhydrous hydrazine and with hydrazine hydrate. In each case the reaction mixture was subsequently treated with nitrous acid in order to diazotize the expected intermediate amidrazone, CXIII, without prior isolation and so form the imidoyl azide. The 3,7-dimethyl-2-ethoxy-3H-azepine, CXXIV, was similarly treated. All of these attempts to prepare the tetrazole failed even though the procedure used was successfully applied in the model reaction, the known preparation of pentamethylene tetrazole, CIV, Metrazol, from O-methyl caprolactim[83], CXXVI, (Equation 42).



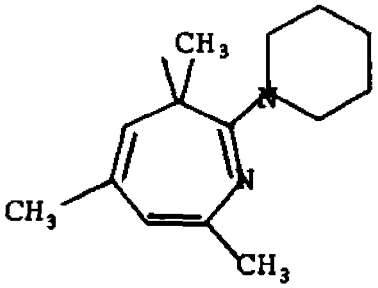
CXXVI CIV

Equation 42

The treatment of both the 2-ethoxyazepine, CXV, and its 3,7-dimethyl derivative, CXXIV, with sodium azide in glacial acetic acid gave only small yields of the lactams CXIV and CXXV and none of the tetrazoles. In both cases almost all of the imidate ester remained unreacted. Paquette[82] also met difficulty when attempting to displace the 2-ethoxy group of 2-ethoxy-3,5,7-trimethyl-3H-azepine, CXXVII. The only successful displacement of this type is the preparation of the 2-piperidino-3,5,7-trimethyl-3H-azepine, CXXVIII, by refluxing the imidate ester, CXXVII, in piperidine for five days[82].



CXXVII

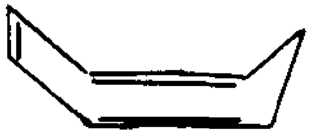


CXXVIII

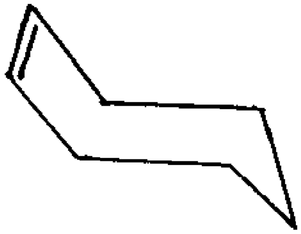
A final attempt was made to displace the 2-ethoxy group with hydrazoic acid at 80° in a sealed tube. After eight days no reaction had taken place except for the formation of a trace of the lactam, CXIV.

The difficulty encountered in displacing the ethoxy group, which is a known and well documented[84] reaction of imidate esters, stimulated the postulation of a possible stereochemical explanation. The analogy is made between the seven-membered cyclic systems containing only carbon and the systems containing one nitrogen since the stereochemistry of the all carbon system is known[85].

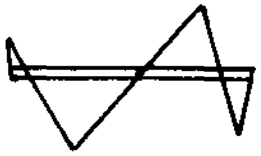
The cycloheptatriene, CXXIX, preferred conformation is boat shaped but at room temperature flipping is rapid, the barrier being only approximately 6 kcal/mole[85]. In the monounsaturated heptacyclic system, CXXX, there are two possible conformations of which the more rigid chair form, CXXXa, is more stable than the twisted, tubshaped form, CXXXb. Based on these models the conformations of 2-ethoxy-3H-azepine, CXVa, and O-methyl caprolactim, CXXVIa, are as in the boat cycloheptatriene and chair cycloheptene respectively. When Dreiding models of these molecules are constructed no significant steric hindrance about the imidate carbon in the triene is observed. In the case where methyl substituents are placed in the 3 and 7 positions of CXVa, significant steric hindrance is still not observed. This evidence is not conclusive but it does give strong indication that the difference in reactivity between O-methyl caprolactim and 2-ethoxy-3H-azepine is not dependent on steric factors.



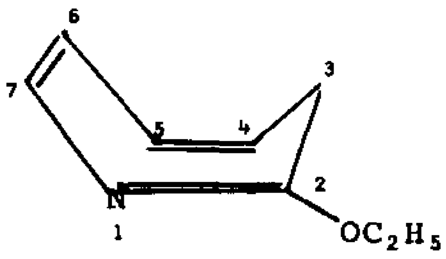
CXXIX



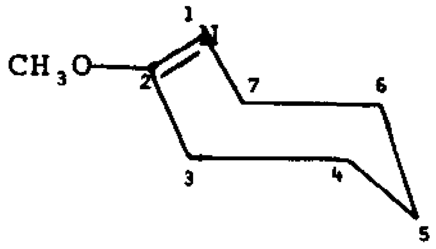
CXXa



CXXb



CXVa



CXXVIa

Paquette[82] also observed that the 2-ethoxyazepine, CXXVII, failed to undergo alkylation on nitrogen when treated with methyl iodide whereas 2-ethoxy pyridine and 2-ethoxy quinoline did undergo alkylation. He explained this as due to a reduced basicity of the azepine nitrogen with respect to the pyridine or quinoline nitrogen. If the ease of displacement of the 2-ethoxy group is a function of the basicity of the azepine nitrogen it is not obvious why there should be a difference between the basicity of the 2-ethoxy-3H-azepines and O-methyl caprolactim.

Displacement of a Chloro Group

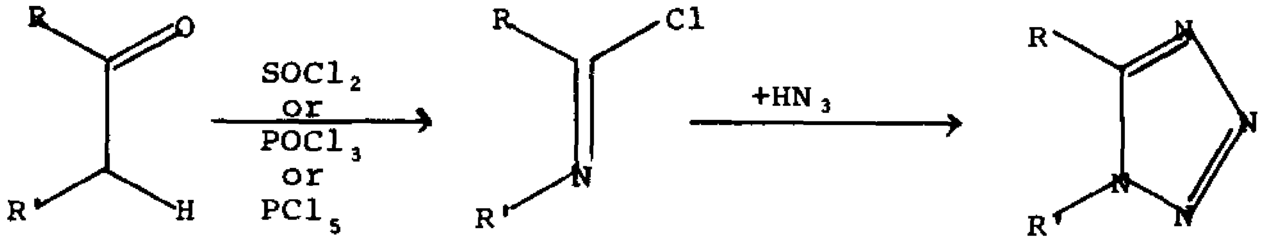
Another synthetic approach is the displacement of halide from the corresponding imidoyl chloride by hydrazine or azide. Paquette[82] attempted to prepare the imidoyl chloride, CXXXII, from the lactam, CXXXI, (Equation 43) and only succeeded in getting a very unstable material which quickly

CXXXI CXXXII

Equation 43

formed dark tarry products especially on the treatment with primary and secondary amines. According to the literature[86] this is not unusual as the imidoyl chlorides of aliphatic acid amides have been shown to be much too unstable to isolate.

The von Braun-Rudolf tetrazole synthesis[65,87] (Equation 44) does not require the isolation of the imidoyl chloride.



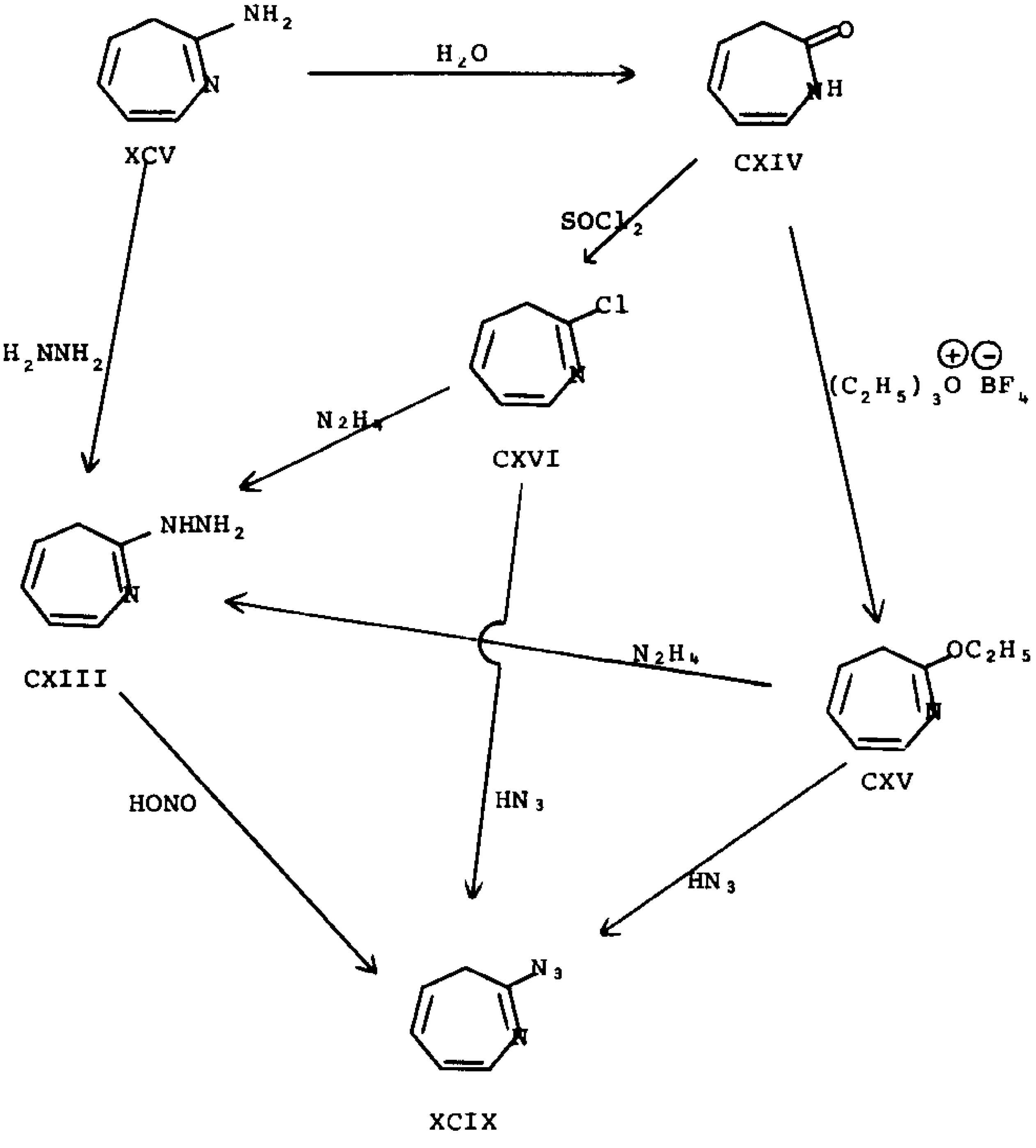
CXXXIII CXXXIV CXXXV

Equation 44

Numerous attempts to generate the 2-chloro-3H-azepine, CXVI, from the lactam, CXIII, (Scheme VIII) by such reagents as PCl_5, $POCl_3$, and $SOCl_2$, and then treat it with hydrazoic acid or sodium azide failed to yield any trace of the desired tetrazole.

Alternate Preparation of Lactam

The extensive investigation of proposed displacement reactions (Scheme VIII) required a substantial supply of the lactam, 1,2-dihydro-3H-azepine-2-one, CXIV. Though hydrolysis of 2-amino-3H-azepine, XCV, in boiling water proceeds in

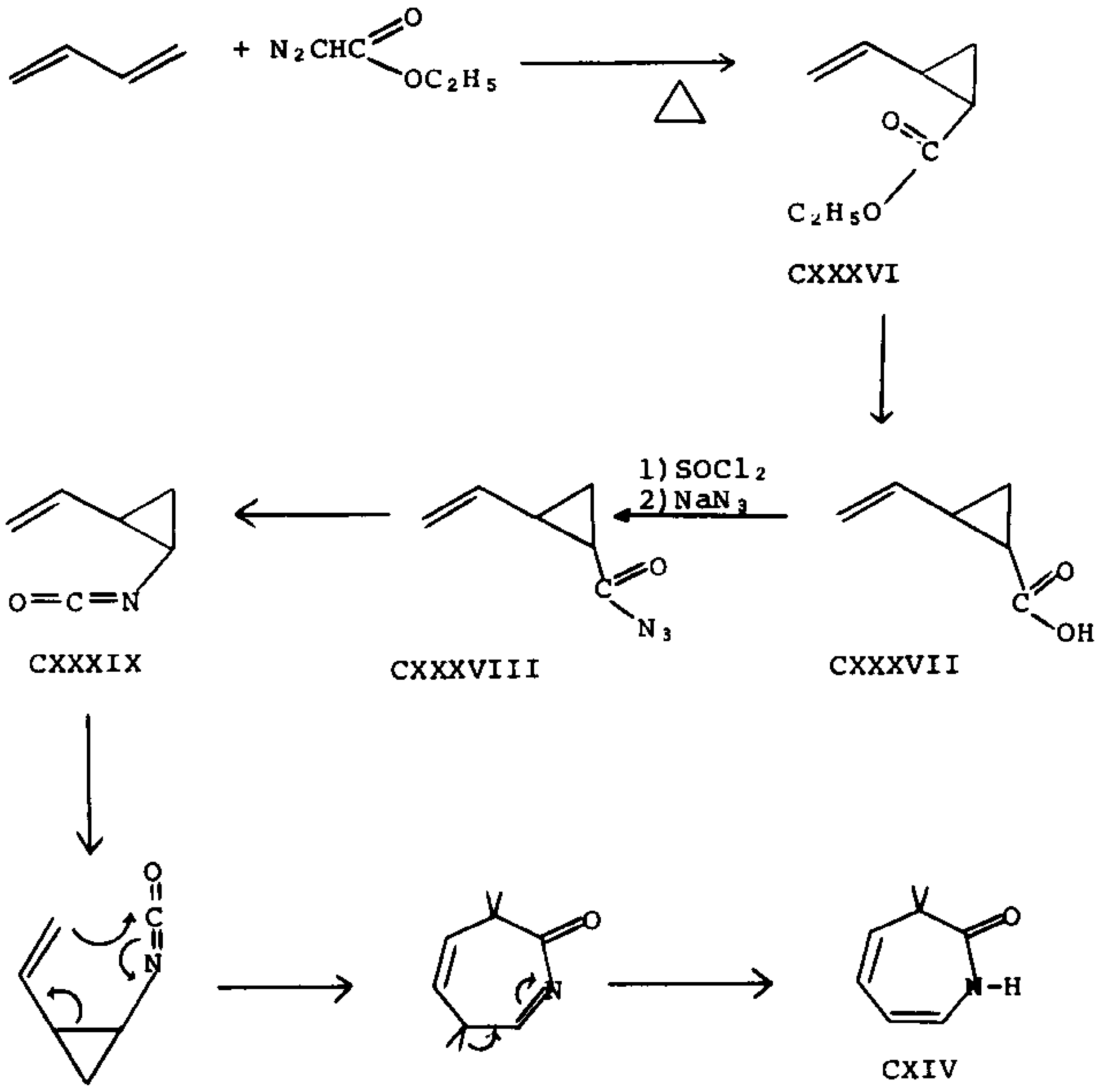

NH₂
N
XCV
H₂O
O
NH
CXIV
SOCl₂
H₂NNH₂
Cl
N
CXVI
(C₂H₅)₃O BF₄
N₂H₄
NHNH₂
N
CXIII
N₂H₄
OC₂H₅
N
CXV
HONO
HN₃
HN₃
N₃
N
XCIX

SCHEME VIII

essentially quantitative yield the supply of lactam is severely limited due to the low yield and length of isolation time in the preparation of the aminoazepine. Thus an alternate synthetic route to the lactam, CXIV, that would allow for the preparation of larger quantities more quickly, was sought. Interestingly, this lactam, CXIV, has also been synthesized from cis-2-vinylcyclopropyl isocyanate[81,88]. This method (Scheme IX) consists of the addition of carbethoxycarbene to butadiene, hydrolysis, conversion of the carboxylate group to isocyanate via a Curtius rearrangement of the azide and then a Cope type ring closure. The first step, the generation of carbethoxycarbene and its addition to butadiene, call for the use of a high pressure reaction bomb which does not allow for the use of this reaction on a large scale.

In order to run the reaction on a large scale in refluxing butadiene (bp 3.5°) at atmospheric pressure, a palladium π-allylic complex catalyst was employed to decompose the ethyl diazoacetate. This catalyst has been shown to decompose ethyl diazoacetate at 0°[89]. In butadiene the decomposition proceeded smoothly and rapidly yielding the desired ethyl 2-vinylcyclopropylcarboxylate (8%), diethyl fumarate (15%), and a substantial amount of dark brown polymer.

Another modification of the Vogel synthetic scheme



+ N_2CHC
O
OC_2H_5
Δ
O
C
C_2H_5O
CXXXVI
1) $SOCl_2$
2) NaN_3
O
C
OH
CXXXVII
O
C
N_3
CXXXVIII
O=C=N
CXXXIX
O
C
N
O
N
O
N-H
CXIV

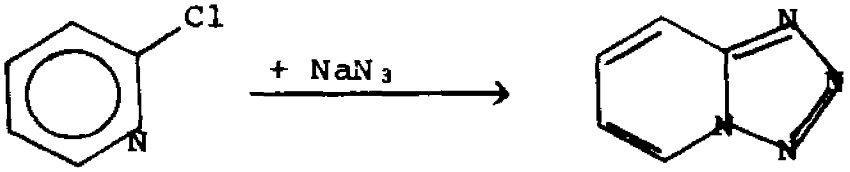
SCHEME IX

involves the photolysis of ethyl diazoacetate in butadiene, a reaction which surprisingly is not recorded in the literature but which should give the ethyl 2-vinylcyclopropylcarboxylate in fairly good yield. The pyrex reaction vessel filters out any light of shorter wavelength than 2800 Å meaning that 1,3-butadiene would not be affected since it does not absorb light of longer wavelength than 2170 Å. The ethyl diazoacetate, however, yields carbethoxycarbene with a quantum yield of 0.54 at 3130 Å and 0.31 at 3650 Å in heptane[90a] which should be analogous to the reaction in butadiene. Also, ethyl diazoacetate has previously been successfully decomposed with subsequent addition to carbon-carbon multiple bonds, for example, addition to 2-butyne occurs in 30% yield[91]. When ethyl diazoacetate was irradiated in butadiene the length of time required for significant reaction proved to be impractical on a preparative scale.

Since neither the catalytic decomposition nor the photolytic decomposition of ethyl diazoacetate in butadiene appeared to yield quantities of ethyl 2-vinylcyclopropylcarboxylate, which would have made the Vogel synthetic sequence[88] a more advantageous route to the 1,2-dihydro-3H-azepin-2-one than the hydrolysis of 2-amino-3H-azepine, they were not investigated further.

Attempted Ring Expansion of Tetrazolopyridine

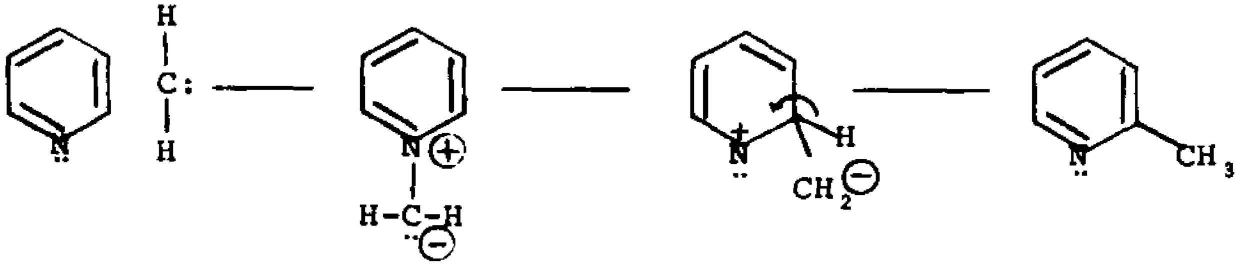
The ready availability of tetrazolopyridine by the von Braun-Rudolf synthesis[67,87] (Equation 45) presented the possibility of approaching the 9H-tetrazolo[1,5a]azepine system in an entirely different manner.



CXL CXLI

Equation 45

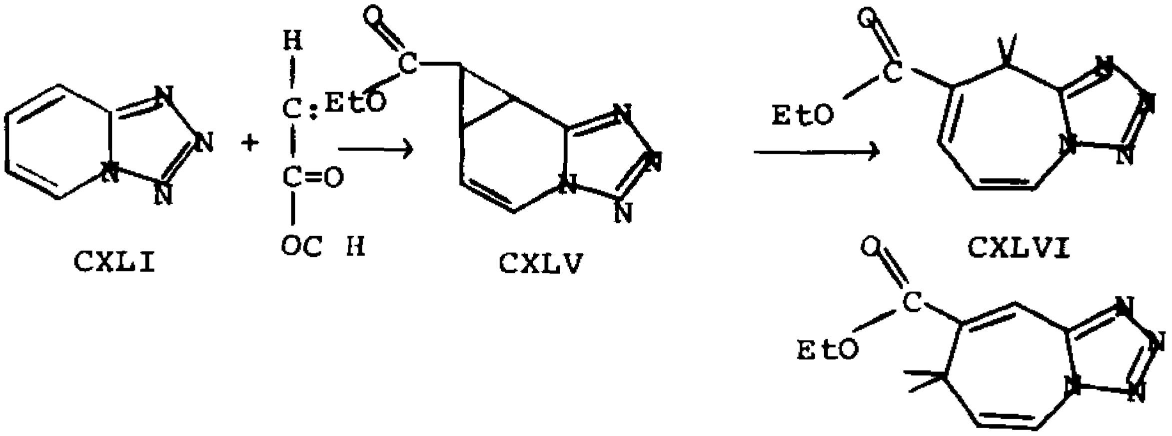
If the pyridine ring could be expanded by one carbon the tetrazoloazepine system would be formed. Some carbenes are known to expand benzene ring systems and some heterocyclic rings[90b]. An attempt to react pyridine with the photolytically derived carbene from diazomethane has yielded only 2-picoline[92]. This is explained by attack of the electron deficient carbene on the unshared electron pair of the pyridine nitrogen and subsequent rearrangement of the ylid formed (Equation 46). If the unshared pair of electrons on



CXLII CXLIII CXLIV

Equation 46

the pyridine nitrogen are unavailable as they are in tetrazolopyridine then perhaps a sufficiently energetic carbene will attack one of the double bonds and result in ring enlargement (Equation 47). The high melting point and relative insolubility in most common organic solvents of tetrazolopyridine limited the possible conditions for attempting this ring enlargement. The decomposition of ethyl diazoacetate in neat molten tetrazolopyridine was run but no ring expansion product was detected in the crude reaction mixture.

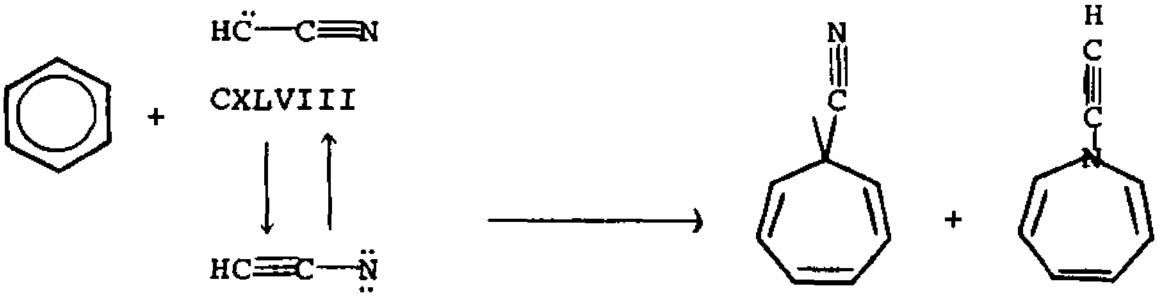


CXLI CXLV CXLVI CXLVII

Equation 47

Dewar and Pettit[93] reported the formation of cyanotropylidene, CL, when cyanodiazomethane was decomposed in benzene.

The intermediate carbene, CXLVIII, might also have reacted as a nitrene, CXLIX, and given an azepine product, CLI, which was lost in the workup and therefore not reported (Equation 48). This product, CLI, an acetylenic azepine, might prove an important starting point for other ring closure schemes. Attempts to generate the same carbene by alpha elimination of chloroacetonitrile with potassium t-butoxide did not give the carbene in either benzene or cyclohexane. Another approach to the desired azaazulenium



CXLVIII

CXLIX

CL

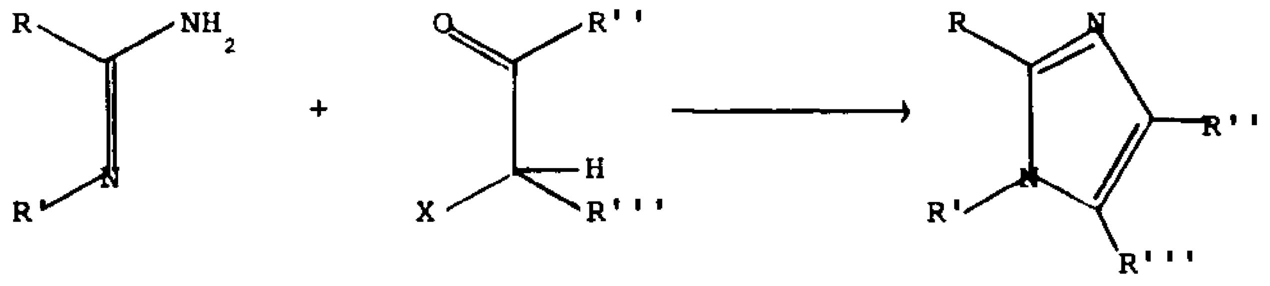
CLI

Equation 48

system was the dehydrogenation of pentamethylene tetrazole commercially available as the drug metrazol. Attempted homogeneous dehydrogenation with dichlorodicyanoquinone in glacial acetic acid containing perchloric acid did not yield the desired cationic product.

Preparation of 9H-imidazo[1,2-a]azepines

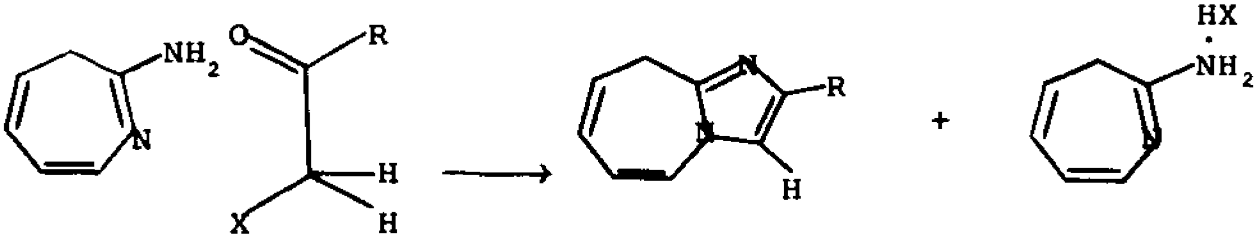
The reaction of α haloketones and amidines to give imidazoles is a very old and well documented one[94-98] (Equation 49). Using the amidine, 2-amino-3H-azepine, XCV, and various α haloketones, a number of 2-substituted-9H-



CLII CLIII CLIV

Equation 49

imidazo[1,2-a]azepines were synthesized (Table IV) (Equation 50). Since an equimolecular excess of amidine, CLII, was often used as a base to neutralize the hydrogen bromide or hydrogen chloride generated in the reaction (Equation 50), the yield data are based on the amount of α haloketone used.



XCV CLIII CLV CLVI

R=
a) H
b) methyl
c) phenyl
d) p-bromophenyl
e) p-biphenyl

X= Cl or Br

Equation 50

TABLE IV

PREPARATION OF 9H-IMIDAZO[1,2-a]AZEPINES

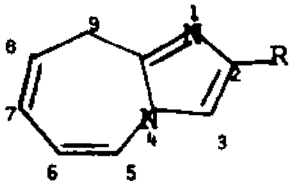
α Haloketone	Imidazole	Yield
bromoacetaldehyde	CLVa	27%
chloroacetaldehyde	CLVa	27%
chloroacetone	CLVb	18%
α bromoacetophenone	CLVc	20%
α,p'-dibromoacetophenone	CLVd	59%
α bromo-p-phenylacetophenone	CLVe	51%

TABLE V

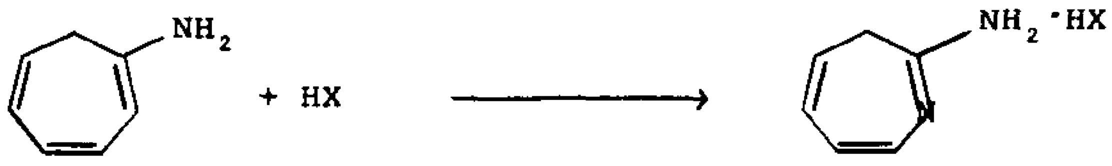
NMR DATA FOR 2-SUBSTITUTED-9H-IMIDAZO[1,2-a]AZEPINES

2-Substituent	position of proton				
	9	8 7 6	5	3	2
H	6.67	3.77-4.50	3.10	3.02	3.02
methyl	6.65	3.83-4.48	3.13	3.32	7.80 (methyl)
phenyl	6.55	3.75-4.49	3.10	2.80	-
p-bromophenyl	6.57	3.75-4.40	3.12	2.85	-
p-biphenyl	6.50	3.90-4.17	3.10	3.00	-

All chemical shifts are in τ units.



The preparation and characterization of the hydrochloride, CLVIa, and hydrobromide, CLVIb, salts of 2-amino-3H-azepine was of great help in isolating the desired imidazole products since in several cases these salts, CLVIa and CLVIb, were formed in greater yield than the imidazoles. Each salt was independently precipitated from an anhydrous ether solution of the amidine by bubbling the appropriate hydrogen halide through the solution (Equation 51).



XCV X= Cl or Br CLVI

Equation 51

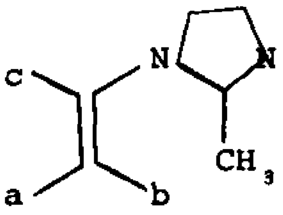
The hydrobromide, LXXb, is a white solid melting at 141°. It turns brown on exposure to light and air. The hydrochloride, CLVIa, is a white solid melting at 176° and is very stable to light and air. Both compounds are insoluble in methylene chloride but the hydrobromide, LXXb, shows significant solubility in chloroform while the hydrochloride, CLVIa, is insoluble. The nmr spectrum of the hydrochloride salt, CLVI, in dimethylformamide shows the characteristic two proton, 3H methylene, doublet at slightly lower field and a much closer overlap of the other protons also at lower field then in the free base. This is expected due to the deshielding of the positive charge of the amidinium ion.

A great variety of reaction conditions were investigated and many gave good yields for some of the imidazoles. The poor yields of the parent compound, 9H-imidazo[1,2-a]azepine, CLVa, (27%) and the 2-methyl compound, CLVb, (18%) are due to the great difficulty in isolating these high boiling, air and oxygen sensitive, viscous oils from the reaction mixture. In general imidazole formation appears faster and in higher yield when the α bromoketones are used. However, due to the greater insolubility of the hydrochloride, CLVIa, impurity, isolation and purification of the imidazole products is definitely easier and more complete when the α chloroketone is used. In almost all cases the imidazoles must be separated from the reaction mixture by extraction and then distillation. The high solubility of the azepine hydrobromide in the best extraction solvent, $CHCl_3$, allows the hydrobromide to be present in the distillation mixture. The presence of the hydrobromide salt, CLVIb, during distillation, reduces the yield greatly.

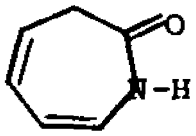
The nmr spectra are relatively easy to interpret due to the great similarities of the seven-membered ring protons to the nmr spectra of the 3H-azepines (Table II). In all of the 9H-imidazo[1,2-a]azepines (Table V) there is a two proton methylene doublet, a one proton vinyl doublet for the proton adjacent to the nitrogen of the seven-membered ring and three vinyl protons with very close chemical shifts. This closeness of chemical shifts results in a complex multiplet such that individual chemical shifts for each of these three protons cannot be assigned.

Using the model 1-vinyl-2-methylimidazole, CLVII,[99] which is analogous to part of the imidazoazepine ring system the vinyl proton at position c corresponds to the proton at position 5 of the imidazoazepines. The chemical shifts of these two protons are 3.14 τ for CLVII[99] and 3.10-3.12 τ for CLV (Table V). This corresponds to a very slight shift upfield from the chemical shift values of 2.98-3.04 τ for the equivalent proton at position 7 of the 2-amino-3H-azepines (Table II). The range of absorption for the protons at positions 6,7 and 8 of the imidazoazepines begins at approximately 3.75 τ and extends upfield to about 4.50 τ. The low field end of this range corresponds to the chemical shift value of 3.73-3.80 τ of the proton at position 5 of the aminoazepines which is the proton at lowest field of the three corresponding protons at positions 6,5 and 4 of the aminoazepines. The upper end of this range for these three imidazoazepine protons is at lower field by 0.4-0.5 τ units than the chemical shift for the proton at position 4 of the aminoazepines which is at the highest field of these three vinyl protons. This compression of the range of the vinyl proton absorption results in an even narrower range than the similar compression observed for the equivalent protons at positions 6,5 and 4 of the 1,2-dihydro-3H-azepin-2-one system[5](CXIV).

Interestingly, the methylene protons at position 9 of the imidazoazepines which correspond to the methylene protons at the 3 position of the aminoazepines and the lactam, CXIV, exhibit a very large downfield shift in comparison to the aminoazepine and lactam methylene protons. In the imidazoazepines the chemical shift for this doublet is at 6.50-6.67 τ while in the aminoazepines it is at 7.39-7.49 τ and in the lactam it is at 7.14 τ. The ring current of the imidazole ring may be responsible for this apparent deshielding of the methylene protons of the imidazoazepines compared to the equivalent protons of the aminoazepines or lactam.



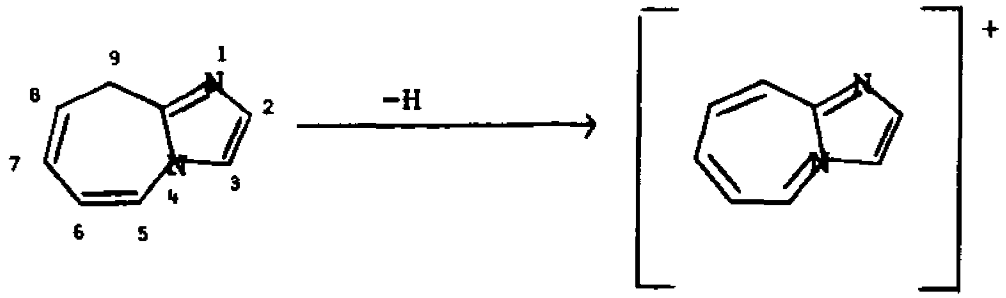
CLVII



CXIV

Attempted Oxidation of the 9H-Imidazo[1,2-a]azepine System

A number of factors were taken into account in the consideration of methods for the removal of a hydride from the 9 position of the imidazo[1,2-a]azepines, CLVa-e. Hydride removal as in Equation 52 should yield at least an allylic carbonium ion, CLX, but more probably greater conjugation leading to the more highly stabilized, tropylium-like, aromatic cation, CLVIIIa-b, should result. Also, the substrate CLV is a highly conjugated unsaturated system which in the case of the parent compound, CLVa, and the 2-methyl compound, CLVb, is sensitive to air oxidation and polymerization. Since the intention was to isolate the resulting cationic species, CLVIII, if possible, it was preferable to carry out the oxidation in the presence of a counterion of low nucleophilicity to reduce the chances of any further reactions of CLVIII, a possibly highly reactive species. If isolation of a salt of CLVIII is not possible it would be advantageous to try to follow its formation spectroscopically. This could be done more easily in a homogeneous system than in a heterogeneous system. Considering these criteria the recent literature was consulted for analogous, successful hydride abstractions. This study revealed two basic types of oxidizing agents to have the greatest promise. They are carbonium ions and quinones. In particular, the use of triphenylmethyl carbonium ion, CLX, was suggested by the success-

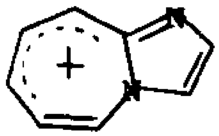


CLVa

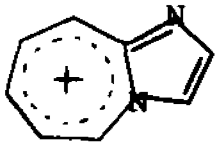
CLVIIIa

Equation 52

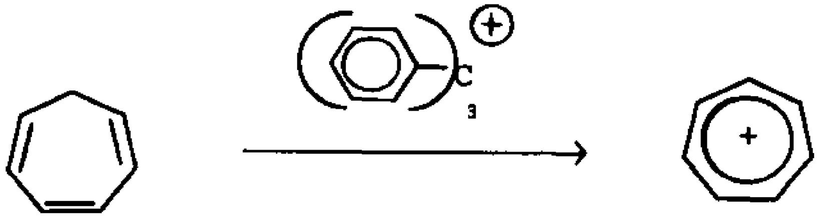
ful oxidation of tropylidene, CLXI, to tropylium ion, CLXII^{100}, (Equation 53) and the use of quinones, such as o-tetrachlorobenzoquinone, chloranil, and dichlorodicyanobenzoquinone, DDQ, CLXIII, was suggested by the oxidation of triphenylcyclopropene, CLXIV, to triphenylcyclopropenium ion, CLXV^{101}, (Equation 54) and the oxidation of 9,10-dihydroacridine, CLXVI, to the acridinium ion, CLXVII^{101}, (Equation 55).



CLIX



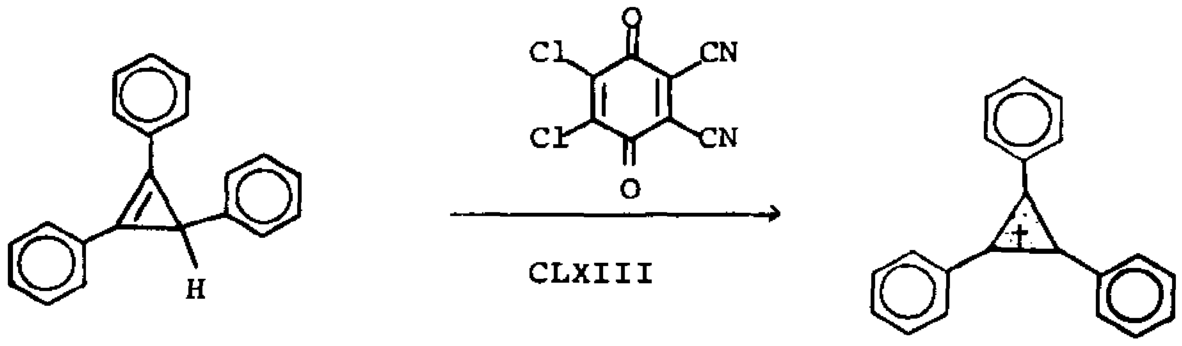
CLVIIIb



CLXI

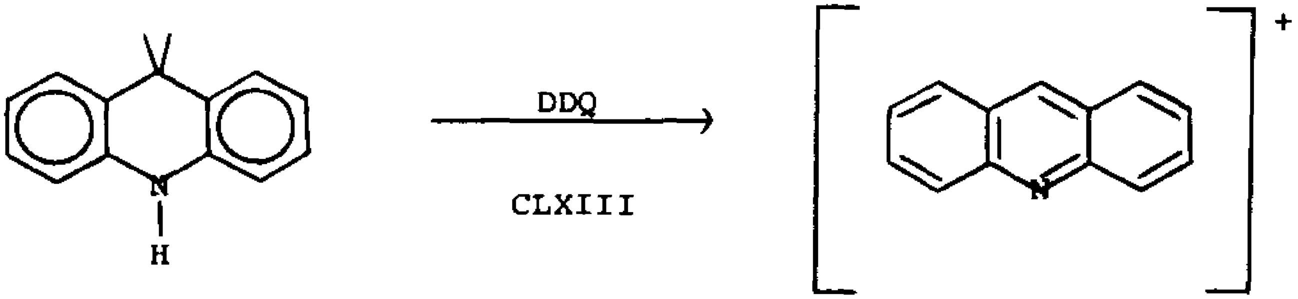
CLXII

Equation 53



CLXIV CLXV

Equation 54

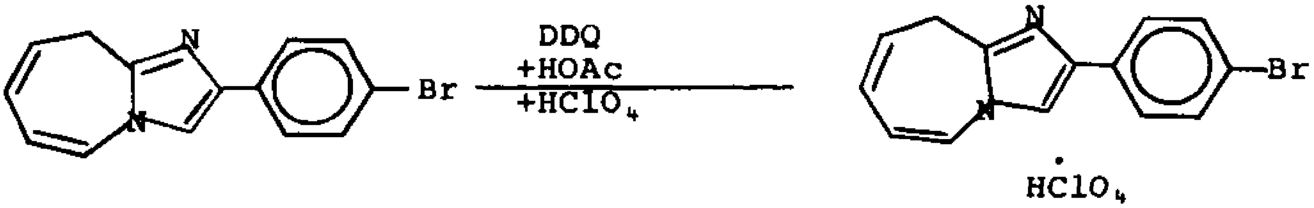


CLXVI CLXVII

Equation 55

Oxidations With DDQ

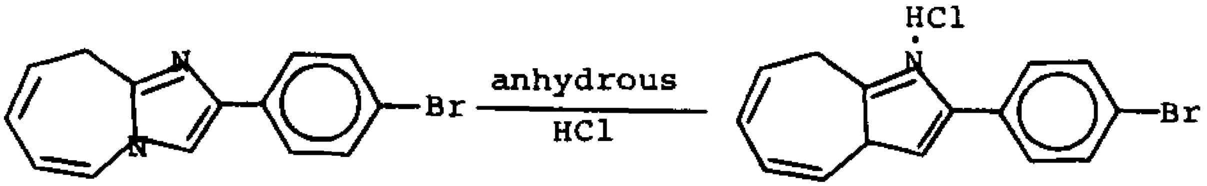
Because of the difficulty involved in preparing and keeping the liquid 9H-imidazo[1,2-a]azepines and because of the ease of preparation and stability of the solid 2-(p-bromophenyl) compound, CLVd, the latter was used in all preliminary attempts at hydride removal. When CLVd was treated with DDQ in glacial acetic acid-perchloric acid solution, a yellow precipitate formed. This precipitate, the perchlorate salt of the imidazole, CLXVIII, (Equation 56) was identical to that formed under the same conditions



CLVd

Equation 56

in the absence of DDQ. The ir spectrum of CLXVIII showed the characteristic perchlorate absorption at 1100 cm^{-1} and the remainder of the spectrum was identical to the spectrum of the hydrochloride salt of the imidazole, CLXIX, prepared by bubbling dry hydrogen chloride through a solution of the imidazole, CLVd, in methylene chloride and then evaporating the solvent (Equation 57). To avoid salt formation, the oxidation with DDQ was attempted in methylene chloride. Immediately on mixing separate pale yellow solutions of CLVd and DDQ an intense purple solution resulted and a very dark, almost black precipitate formed. The ir spectrum showed nitrile groups to be present (2220 cm^{-1}) indicating that the DDQ was involved in some way. Under conditions where reduction of oxidized form, CLVIII, would not be expected, the treatment of the very dark precipitate with perchloric acid yielded the perchlorate salt, CLXVIII. This indicated that oxidation had not occurred and that the dark precipitate was only a charge transfer complex of the imidazole, CLVd and DDQ.



CLVd CLXIX

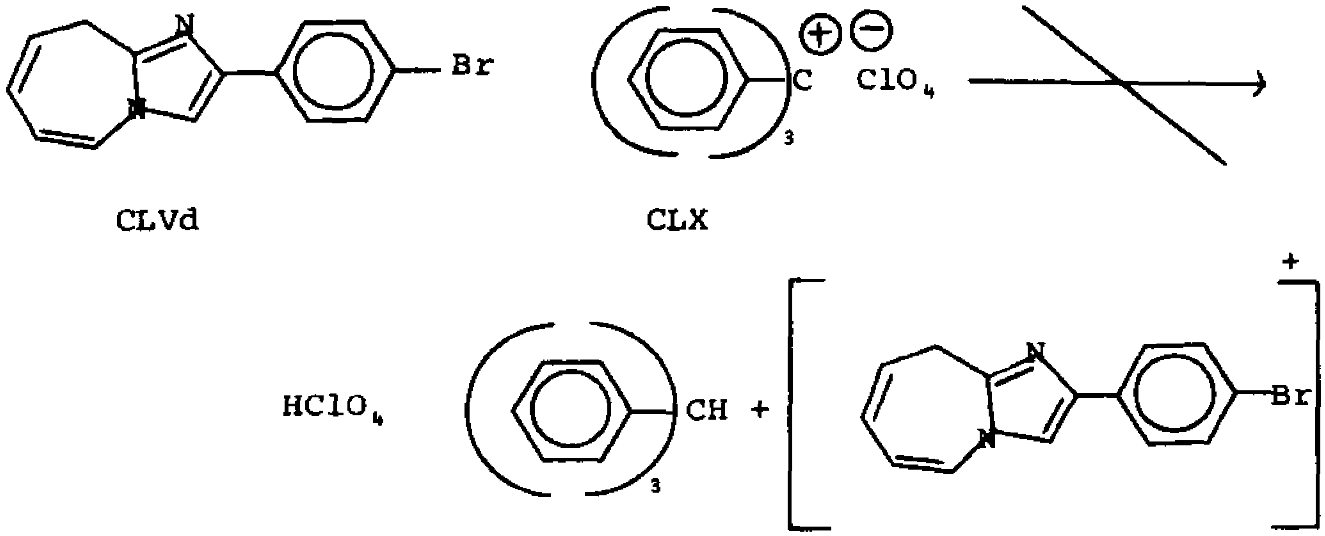
Equation 57

Oxidation by Chloranil

Attempted oxidation of CLVd by chloranil in methylene chloride gave no reaction other than formation of a minor amount of charge transfer complex which was detected by the visible color change of the solution. Evaporation of the solvent yielded unchanged starting compounds.

Oxidation by Triphenylmethyl Carbonium Ion

A bright yellow methylene chloride solution of triphenylmethyl perchlorate was added to a straw yellow solution of CLVd in methylene chloride. There was no change in color and no precipitate formed. After quenching with water, only triphenylcarbinol and no triphenylmethane was detected. If a hydride was transferred to the triphenylmethyl carbonium ion triphenylmethane would have been formed (Equation 58).

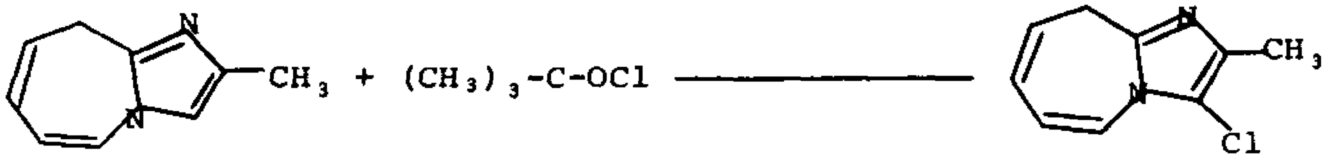


CLVd CLX

Equation 58

Oxidation by t-Butyl Hypochlorite

Treatment of 2-methyl-9H-imidazo[1,2-a]azepine, CLVb, with t-butyl hypochlorite resulted in substitution by chlorine in the imidazole ring in the 3 position (Equation 59).



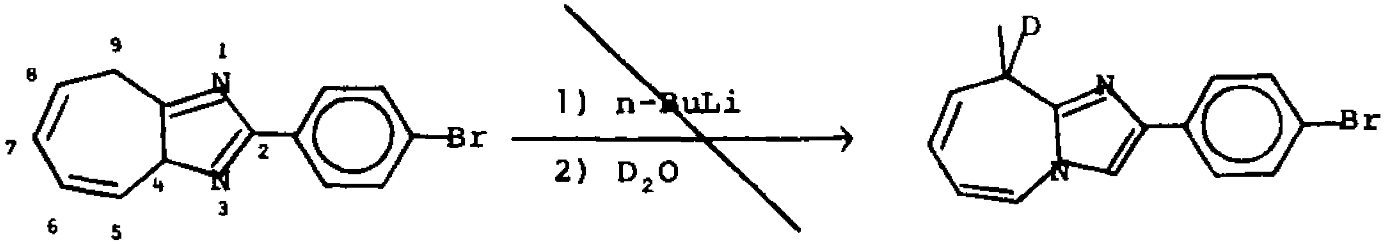
CLVb CLXX

Equation 59

This was confirmed by the disappearance of the singlet peak at 3.32 τ in the nmr spectrum which was assigned to the proton at position 3. The rest of the spectrum appeared to be unchanged.

Attempted Proton Removal

One approach to the chemistry of imidazoles is to consider one nitrogen to have properties similar to those of a pyridine nitrogen and the other nitrogen's properties similar to a pyrrole nitrogen. The nitrogen in the 1-position of the imidazoazepines would be the pyrido nitrogen and therefore would be a very basic site on the molecule. Attempts at removal of a hydride ion from the 9 position by an electrophilic species such as triphenylmethyl carbonium ion would then most probably result in quaternization of the nitrogen at position 1. If one proton at the 9 position was removed then it might be possible to preferentially remove the unshared electron pair of the resulting carbanion. Compound CLVd was treated with n-butyl lithium in anhydrous ether and then quenched with deuterium oxide (Equation 60).



CLVd

Equation 60

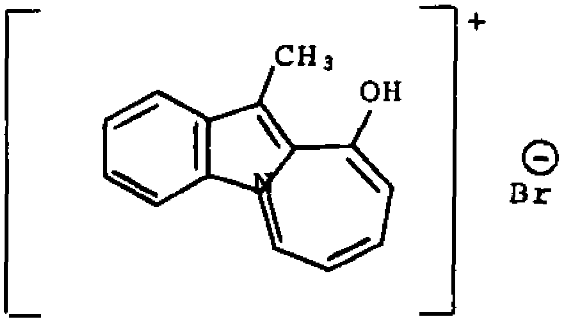
The nmr spectrum of the recovered material showed no incorporation of deuterium at the 9 position indicating that a carbanion had not been formed. On reflection, the weakly acidic nature of the proton at position 9 is probably due to the instability of the carbanion formed. This carbanion has two electrons in excess of the number of 6 necessary to impart unusual stability for a seven centered π system as prescribed by the Huckel 4n+2 rule. In fact, eight π electrons correspond to 4n electrons where n=2. This value is predicted to impart unusual instability to such a system.

A Different Approach

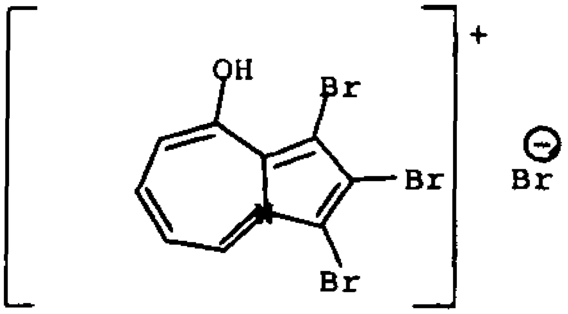
Since it did not appear to be possible to remove the hydride ion to give the desired imidazo[1,2-a]azepinium ion, plans were formulated to synthesize imidazoazepines in the correct oxidation state where perhaps a group other than hydride could be induced to undergo ionization to produce the desired ion. An example of an ionizable substituent might be a chloro group at the 9 position. Such a group might ionize analogously to the bromo substituent on bromotropylidene which yields tropylium bromide[3]. Further investigations in this direction were previously described in Part I of this thesis.

RECENT DEVELOPMENTS IN THE LITERATURE

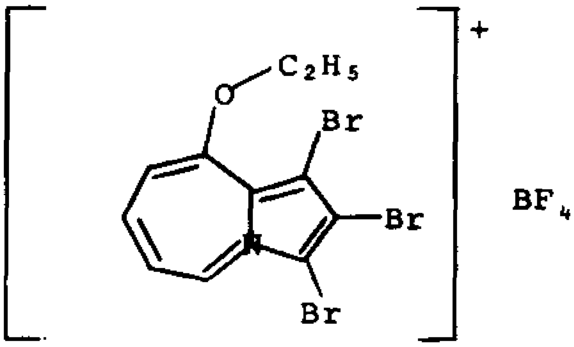
During the course of our investigations a system very closely related to our objective was successfully synthesized by Collington and Jones[102,103]. They prepared the azonia-azulenium salts, 1-methyl-2-hydroxyindolo[1,2-a]azepinium bromide, CLXXI, 1,2,3-tribromo-9-hydroxypyrrolo[1,2-a]azepinium bromide, CLXXII, and 1,2,3-tribromo-9-ethoxypyrrolo[1,2-a] azepinium fluoroborate, CLXXIII.



CLXXI

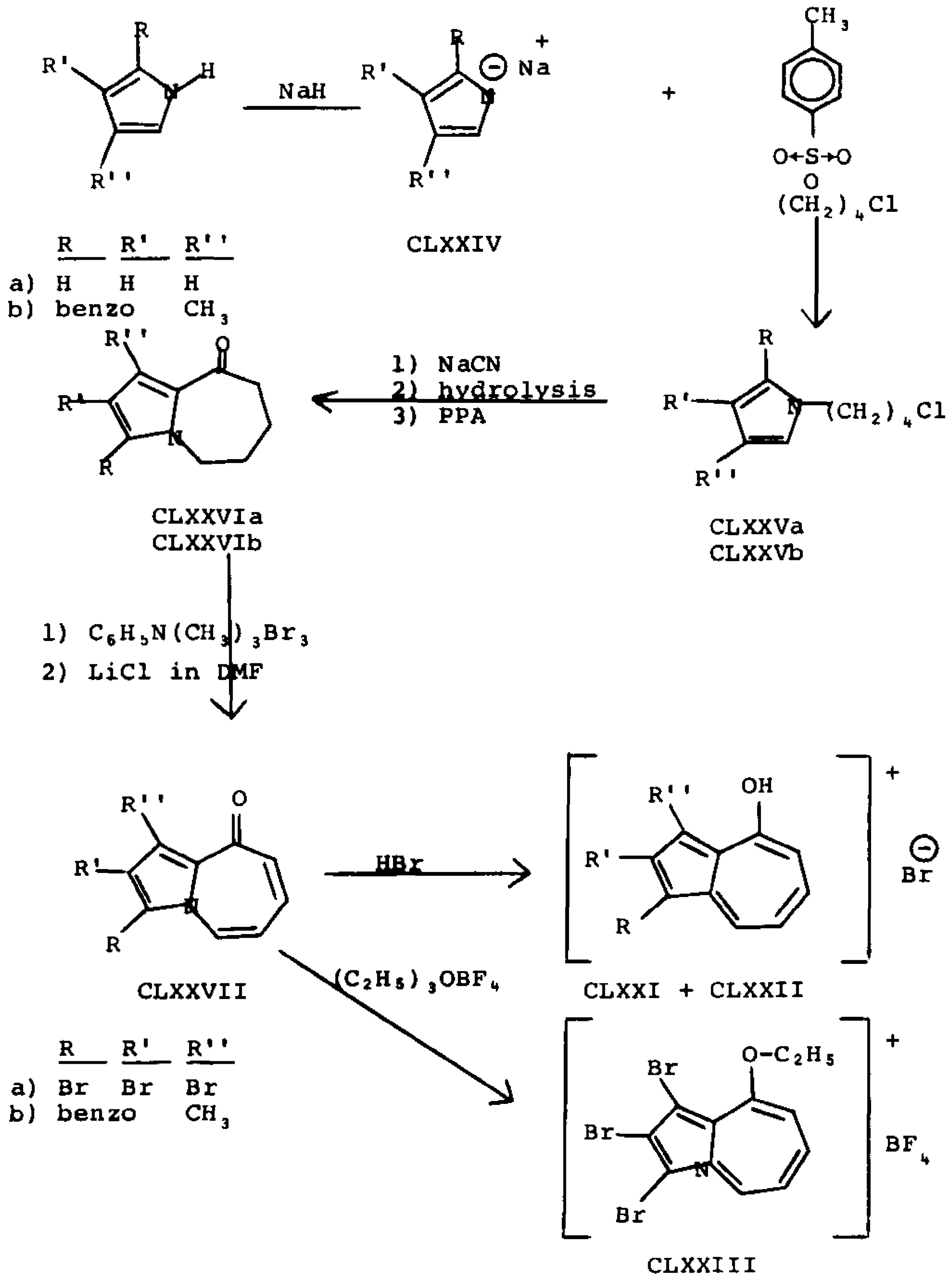


CLXXII



CLXXIII

The synthesis of these compounds as outlined in Scheme X begins with the reaction between the appropriate pyrrole anion, CLXXIV, and 4-tosyloxybutyl chloride which gives the N-chlorbutyl substituted pyrrole, CLXXV. Displacement of chloride with sodium cyanide and then hydrolysis of the nitrile formed gives a carboxylic acid which is cyclized by polyphosphoric acid to the tricyclic ketone, CLXXVI. The ketone, CLXXVIb, was dibrominated alpha to the carbonyl group by phenyltrimethylammonium tribromide and then it was dehydrobrominated to give the azepinone, CLXXVIIb. The ketone, CLXXVIa, was pentabrominated with bromine in carbon tetrachloride and then it was dehydrobrominated by lithium chloride in dimethylformamide to the azepinone, CLXXVIIa. A 79% yield of CLXXVIIa and an 82% yield of CLXXVIIb were obtained. Treatment of CLXXVIIa and b in chloroform with hydrogen bromide gave the crystalline salts CLXXI and CLXXII. Treatment of CLXXVIIa with triethyloxonium fluoroborate yielded the salt CLXXIII. The structures of CLXXVIIa and b in comparison to the imidazoazepines CLVa are in the correct oxidation state for the formation of the desired azonia azulenium salts. This is the major reason for the success of Gurnos and Jones and the failure of our method. It is also possible that if the five membered ring in our system had been a pyrrole or some other ring without the basic nitrogen of the imidazole at position 1 then our oxidation


R
R'
R''
H
N
NaH
Na
+
CH3
O←S→O
O
(CH2)4Cl
CLXXIV
R R' R''
a) H H H
b) benzo CH3
1) NaCN
2) hydrolysis
3) PPA
(CH2)4Cl
CLXXVIa
CLXXVIb
CLXXVa
CLXXVb
1) C6H5N(CH3)3Br3
2) LiCl in DMF
O
HBr
OH
Br
CLXXVII
(C2H5)3OBF4
CLXXI + CLXXII
R R' R''
a) Br Br Br
b) benzo CH3
O-C2H5
Br
Br
Br
BF4
CLXXIII

SCHEME X

attempts might have been successful.

The most striking property reported so far for these azonia azuleniums in the limited investigation of them is their blue color in solution which is similar to the blue color which gave azulene its name.

EXPERIMENTAL

Preparation of 2-Amino-3H-azepine[5]

A solution of 17.1 g of phenyl azide in 2 liters of liquid ammonia was irradiated for 6.5 hours in a vacuum jacketed Pyrex flask fitted with a dry-ice condenser by four 275 watt commercial sunlamps and a solution of 10.5 g phenyl azide in 1 liter of liquid ammonia was irradiated for 6.5 hours in a vacuum jacketed Pyrex flask fitted with a dry-ice condenser by three 275 watt commercial sunlamps. After combining and evaporating the ammonia solutions in a four liter Erlenmeyer flask in the hood, the residue was extracted with hot benzene and then the benzene extract was evaporated to dryness on a rotary evaporator. The solid, crystalline residue was washed with petroleum ether and 10.5 g (42%) of tan colored, crude product was collected on a Buchner funnel. Sublimation at 90-92° (0.2-0.5 mm) gave colorless crystals of 2-amino-3H-azepine: mp 90.5-91.0°.

Preparation of 2-Ethoxy-3H-azepine

Hydrolysis of 2-amino-3H-azepine to 1,2-dihydro-3H-azepine-2-one by refluxing an aqueous solution for five hours, the method of Doering and Odum[5], afforded enough lactam (mp 48-49°; 90% yield) for the preparation of the imidate ester, 2-ethoxy-3H-azepine, by Paquette's method[82].

In this method the lactam is treated with triethyloxonium fluoroborate in ether. The reaction mixture is neutralized with Na_2CO_3, extracted with chloroform and fractionated. The amount of lactam used was reduced to 0.1 moles which yielded 7.14 g (52%) of pale yellow oil: bp 24-26° (0.1 mm); $n^{25}D$ 1.5080;

anal. calcd for $C_8H_{11}N_1$: C, 70.45; H, 8.08; N, 10.21

found: C, 70.29; H, 8.30; N, 10.45

Treatment of 2-Ethoxy-3H-azepine with Hydrazoic Acid

A sample of 0.408 g (3 moles) of 2-ethoxy-3H-azepine and 4 ml of a 1.5M solution of hydrazoic acid[104] in diethyl ether was sealed under vacuum in a Carius tube. The tube was heated in an oil bath at 71-83° for eight days. After cooling, opening and evaporating the solvent and excess hydrazoic acid the residual oil showed only starting material and a trace of 1,2-dihydro-3H-azepine-2-one to be present on analysis by glpc.

Preparation of 2-Amino-3H-azepine Hydrobromide

Anhydrous hydrogen bromide was bubbled through a solution of 0.54 g (5 moles) of 2-amino-3H-azepine in anhydrous diethyl ether. A white precipitate weighing 0.94 g (99%) and melting at 141° was formed. This hydrobromide salt turned brown on standing.

Preparation of 2-Amino-3H-azepine Hydrochloride

Anhydrous hydrogen chloride was bubbled through a solution of 0.54 g (5 mmoles) of 2-amino-3H-azepine in anhydrous diethyl ether. A flocculent, white precipitate insoluble in methylene chloride and chloroform was formed: 0.71 g (99%), mp 176°; nmr (dimethylformamide) τ 6.63 (doublet, 2H, methylene), 3.07-4.43 (overlapping multiplets, 6H, vinyl).

Preparation of 9H-imidazo[1,2-a]azepine

To 100 ml of a 25% solution of aqueous K_2CO_3 was added 10.8 g (0.1 moles) of 2-amino-3H-azepine with stirring. The dropwise addition of 26.3 g (0.1 moles) of 30% aqueous chloroacetaldehyde resulted in a pale yellow oil separating from the clear solution. The aqueous phase was extracted with chloroform and the chloroform extracts were added to the yellow oil. After washing thoroughly with aqueous K_2CO_3 the chloroform was evaporated and the residual oil was distilled under reduced pressure. A clear, colorless liquid was collected: 3.56 g (27%); bp 90° (1 mm); mp 1-2°; nmr ($CDCl_3$ with TMS) τ 6.67 (doublet, 2H, J 6.0 Hz, methylene), 3.80-4.50 (multiplet, 3H, vinyl), 2.95-3.25 (multiplet, 3H=CH-N).

anal. calcd for $C_8H_8N_2$: C, 72.70; H, 6.10; N, 21.20
found: C, 71.77; H, 6.12; N, 21.51

Preparation of 2-Methyl-9H-imidazo[1,2-a]azepine

A 5.17 g (0.05 moles) sample of 90% 1-chloro-2-propanone was added dropwise with stirring to a solution of 10.8 g (0.1 moles) of 2-amino-3H-azepine in 30 ml of chloroform. An exothermic reaction occurred and the solution became dark red-brown. On chilling the reaction solution in the freezer for several days and then filtering, a first crop of 4.14 g of 2-amino-3H-azepine hydrochloride (mp 176-177°) was collected. The bulk of the chloroform was distilled at atmospheric pressure and an additional 0.94 g of crude 2-amino-3H-azepine hydrochloride was collected (mp 174-175°). The remaining solvent was removed and the residue was distilled under reduced pressure yielding a pale yellow, mobile liquid: 1.31 g (18%); bp 88° (0.8 mm); $n^{25}D$ 1.5683; nmr ($CDCl_3$ and TSM) τ 7.82 (doublet, 3H, J=1.5 Hz, methyl), 6.65 (doublet, 2H, J=6.0 Hz, methylene), 3.70-4.45 (multiplet, 3H, vinyl), 2.95-3.35 (multiplet, 2H, =CH-N).

Preparation of 2-(p-Bromophenyl)imidazo[1,2-a]azepine

To a solution of 5.64 g (0.02 moles) of p-bromophenacyl bromide in 30 ml of warm absolute ethanol was added a solution of 4.32 g (0.04 moles) of 2-amino-3H-azepine in 10 ml warm absolute ethanol. A rapid exothermic reaction occurred. After standing overnight, 2.46 g of a dark crystalline precipitate (mp 148-149°) was collected. After evaporating the solvent from the dark colored filtrate the residue was extracted with methylene chloride. The methylene chloride extracts were evaporated, yielding a crude solid which was recrystallized from aqueous ethanol to give 2.53 g of additional product (mp 148-149°). After combining both crops of product, additional recrystallization from acetone and then sublimation at 145° (0.05 mm) yielded 3.40 g (59%) of 2-(-bromophenyl)-9H-imidazo[1,2-a]azepine: mp 148.5-149.0°; nmr ($CDCl_3$ and TMS) τ 6.60 (doublet, 2H, J=6.0 Hz, methylene), 3.85-4.35 (multiplet, 3H, vinyl), 3.18 (doublet, 1H, J=8.0 Hz, =CH-N), 2.90 (singlet, 1H,=CH-N), 2.32-2.79 (2 overlapping quartets, 4H, aromatic).

<u>anal.</u> calcd for $C_{14}H_{12}N_2$: C, 80.73; H, 5.81; N, 13.46
found: C, 80.52; H,15.67; N, 13.32

Preparation of 2-Phenyl-9H-imidazo[1,2-a]azepine

A warm solution of 4.34 g (0.04 moles) of 2-amino-3H-azepine in 10 ml of absolute ethanol was combined with a warm solution of 3.10 g (0.02 moles) of phenacyl chloride in 10 ml of absolute ethanol. Since no immediate exothermic reaction occurred the mixture was warmed in a hot water bath for five minutes and then allowed to stand overnight. Evaporation of the alcohol on a rotary evaporator then sublimation of the residue at 85-90° (0.4 mm) yielded 2.28 g (55%) of 2-phenyl-9H-imidazo[1,2-a]azepine: mp 86-87°; nmr (CCl_4 and TMS) τ 6.65 (doublet, 2H, J=5.0 Hz, methylene), 3.84-4.55 (multiplet, 3H, vinyl), 3.10-3.45 (multiplet, 1H,

>CH-N), 2.10-3.05 (multiplets, 6H, aromatic and >CH-N).

anal. calcd for $C_{14}H_{12}N_2$: C, 80.73; H, 5.81; N, 13.46;
found: C, 80.52; H,15.67; N, 13.32.

Preparation of 2-(Biphenyl)-9H-imidazo[1,2-a]azepine

After several days an ethanolic solution of 1.38 g (5 mmoles) of p-phenylphenacyl bromide and 1.08 g (10 moles) of 2-amino-3H-azepine yielded 0.73 g (51%) of yellow, powdery crystals: mp 183-5°; nmr ($CDCl_3$ and TMS) τ 6.50 (doublet, 2H, J=5.0 Hz, methylene), 3.80-4.20 (multiplet, 3H, vinyl), 2.90-3.20 (multiplet, 1H,=CH-N), 2.00-2.80 (multiplets, 10H, aromatic and = CH-N).

Attempted Oxidations of 2-(p-Bromophenyl)-9H-imidazo[1,2-a] azepine

a) by chloranil

A clear yellow solution of 0.123 g (0.5 mmoles) of chloranil in methylene chloride was added to a colorless solution of 0.143 g (0.5 mmoles) of 2-(p-bromophenyl)-9H-imidazo[1,2-a]azepine in methylene chloride to give a deep red solution. After removal of the solvent the residue proved to be a physical mixture of the starting materials by infrared analysis.

b) by dichlorodicyanoquinone (DDQ)

A clear yellow solution of 0.114 g (0.5 mmoles) of DDQ in methylene chloride was added to a colorless solution of 0.149 g (0.5 mmoles) of 2-(p-bromophenyl)-9H-imidazo[1,2-a]azepine in methylene chloride and from the resulting intensely colored solution 0.187 g of finely divided, brown-black precipitate was collected: mp 145-7°; ir (KBr) 2220 cm^{-1} (nitrile). On treatment with 0.5N anhydrous perchloric acid in acetic acid the brown-black crystals yielded yellow crystals identical to the perchlorate salt of the imidazole.

A solution of 0.287 g (1 mmole) of 2-(p-bromophenyl)-9H-imidazo[1,2-a]azepine in glacial acetic acid was treated with 0.227 g (1 mmole) DDQ in glacial acetic acid-perchloric acid solution to yield a yellow crystalline precipitate: mp 220-3°; ir (KBr) 1100 cm^{-1} (perchlorate).

After dissolving 2-(p-bromophenyl)-9H-imidazo[1,2-a]-azepine in 0.5N anhydrous perchloric acid in glacial acetic acid and allowing to cool, yellow crystals were collected: mp 220-3°; ir (KBr) identical to spectrum above.

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BIOGRAPHICAL STATEMENT

Alan Aaronson was born in the City of New York on September 29, 1940. He received his elementary school education in the New York City Public School and the Pocantico Hills Central School Systems.

While attending Stuyvesant High School in New York City he decided to pursue Chemistry as his major in college.

Having graduated from Stuyvesant High School in 1957 he enrolled at the Queens College Branch of the City University on a New York State Regents Science Scholarship and graduated with a Bachelor of Science degree in 1961.

In the summer of 1961 Mr. Aaronson began working for the Revlon Research Center in New York as a New Products Development Chemist. He maintained this position for two years, during which time he took evening graduate courses in Chemistry at the Brooklyn College Branch of the City University.

It was in September 1963 that Mr. Aaronson returned to the City University as a full time graduate student on a teaching assistantship. In September 1964 he was matriculated into the Doctoral Program and his work on this thesis was begun in March 1965. He was a City University Dissertation Year Fellow during the academic year 1968-69.

He left the City University in October 1969 to accept a position as a research chemist at the Eastern Research Center of the Stauffer Chemical Company.

Mr. Aaronson was married in 1962 and has a 2-year old son.