COMPARISON OF PHENANTHRIDINE WITH OTHER AZA-AROMATIC HETEROCYCLES

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I. Introduction

Six-membered nitrogen heterocycles having a formal set of conjugated double bonds occupy a position of prime importance in organic chemistry. Not only do these heterocycles undergo a variety of reactions, but also these systems exhibit a broad spectrum of physiological properties. As they are isosteric with the corresponding aromatic carbocycles, these pyridinoid hydrocarbons may be designated as aza-aromatic heterocycles to stress their similarity to benzenoid hydrocarbons in both reactivity and structure. It is to be expected, however, that the cyclic nitrogen atom will endow aza-aromatic systems with distinguishing properties. These include basicity and a more pronounced proneness to attack by basic reagents. Moreover, the diminished symmetry of the pyridinoid ring allows the existence of more isomers; for example, there are three monosubstituted pyridines. The voluminous literature on aza-aromatic heterocycles attests to the chemical versatility of these systems.

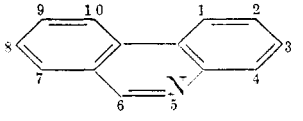
Although there are several monographs that consider in detail the known chemistry of individual heterocycles (89, 272), there exists no comprehensive correlation of the chemistry of aza-aromatic heterocycles as a whole. It is the purpose of this review to compare the analogous chemistry of these aza-aromatic heterocycles and their characteristic derivatives in terms of our present experimental and theoretical knowledge. Modern concepts of molecular structure will be invoked in synthesizing a rational view of aza-aromatic character. The discussion will be largely limited to the monoaza-aromatic heterocycles: pyridine, quinoline, isoquinoline, acridine, and phenanthridine. The behavior to be expected of polyaza-aromatic systems such as quinoxaline and triazine usually involves a reasonable extrapolation of the chemistry of the monoaza-aromatic systems. Five- and seven-membered nitrogen heterocycles such as pyrrole and azepine will not be considered.

Phenanthridine, a nitrogen isoster of phenanthrene, is taken as the focal point of these considerations. There are several valid reasons for this. First, there has recently been a revival of interest in the fundamental chemistry of the phenanthridine system. Despite the large number of phenanthridine derivatives prepared by the cyclization of biphenyl derivatives (249), little progress previously had been made in the substitutional chemistry of this nucleus. In fact, the nitration of phenanthridine, first reported in 1932 (196), gave rise to mononitrophenanthridines which were not identified until 1952 (57). In addition, the direct bromination of phenanthridine has been accomplished only recently (111). By consideration of the known behavior of other heterocycles, the remaining gaps in the knowledge of phenanthridine chemistry will become more apparent.

Second, the discovery of the trypanocidal potency of certain phenanthridine derivatives (197) and their general bacteriostatic properties (8) has given the phenanthridine system a new-found physiological importance. Third, since its molecular asymmetry presents nine nonequivalent positions for substitution, phenanthridine may subject any theory of substitution to a more rigorous test. Factors determining the preferred site of substitution may be more carefully evaluated with such a complex system.

In addition to the discussion of phenanthridine in relation to other aza-aromatic heterocycles, there is included in tables 5 to 11 a compilation of the known phenanthridine derivatives. This list of compounds is intended to supplement that given in a previous review (249). This latter article contains an adequate survey of phenanthridine chemistry up to 1950, but generally lists only those phenanthridines prepared by the cyclization of 2-acylaminobiphenyls. A more detailed and interpretative discussion, but lacking a tabulation of compounds, has also appeared (263). The present list attempts to cover the literature from 1884 through 1955, although some more recent articles are included.

The numbering systems of the nitrogen heterocycles appearing in this review are in accord with usages of *Chemical Abstracts*. Both the *Ring Index* (207) and *Chemical Abstracts* (since 1937) advocate the numbering system for phenanthridine shown in formula I. The system employed previous to 1937 and still favored by foreign journals is given in formula II. This system has the merit of paralleling that of phenanthrene. Nevertheless, for the sake of conforming to American usage, system I will be employed throughout this review.



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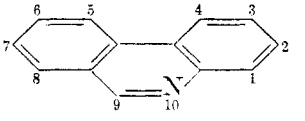


II

II. Aromaticity

The fact that chemical knowledge gathered from the study of aliphatic compounds failed to account for the behavior of aromatic systems has been termed historically the "benzene problem." Eminent chemists from almost the beginning of organic chemistry have been intrigued by the unusual stability of these systems and the preference for substitution rather than addition reactions. It

has been long recognized, moreover, that certain cyclic nitrogen compounds such as pyridine also possessed this aromatic character. Thus an analogous "pyridine problem" arose. Here, indeed, the experimental facts were even more puzzling. Not only did pyridine derivatives have unique properties such as basicity, but they underwent reactions with sodium amide and potassium hydroxide (61, 63) with a facility unknown to benzene.

Preëlectronic interpretations of the aromatic character of pyridine closely paralleled the explanations proposed for the behavior of benzene. Korner and Dewar (85) proposed a cyclic structure of alternate oscillating double bonds analogous to Kekulé's representation of benzene (144), and shortly afterwards Riedel (222) supported a Dewar structure containing a para bond between the nitrogen and the gamma carbon. This was followed by a centric structure advanced by Bamberger (20). However, perhaps the representation of pyridine most in accord with modern views was that based on Thiele's theory of partial valences (250). It would be overdemanding to expect that a fully satisfying solution to the problem of aromaticity would predate the knowledge of molecular structure and the nature of chemical bonding. Thus, the subsequent formulation of the electronic theory of valence (152, 171) coupled with newer experimental data gave a firm foundation to the more satisfying views which were to follow.

The discovery of the electron and the postulation of its role in chemical bonding laid the stage for a more intimate understanding of chemical behavior. The statement by de Broglie (41) that small particles such as electrons should exhibit wave properties was experimentally confirmed by Davisson and Germer (72), who showed that an electron beam could indeed be diffracted. Schrödinger (232) and Heisenberg (127) independently began to give mathematical expression to these wave properties of matter. Heisenberg's uncertainty principle postulated that both the energy and the position of an electron could not be determined exactly. The position of an electron in an atomic field was therefore expressed as a probability function, the results of which were expressed as electron density patterns. Application of these quantum-mechanical calculations to such simple systems as the hydrogen molecule permits the observed energy of the chemical bond to be duplicated to a high degree (134), but extension to larger molecules in a similar manner thus far is unfeasible owing to mathematical complexities. Consequently, the search has been undertaken to develop simplified, approximate methods for estimating molecular energies which would still yield useful information. In the study of aromatic systems factors to be unified and rationalized include: the inherent stability of such systems; the orientation of substituting species; the relative reactivities of related aromatic compounds. Quantum-mechanical calculations have made gratifying progress in attaining these goals, but certain facets of present theory are still quite unsatisfactory. Often the divergence of theoretical predictions and experimental results indicates the importance of certain factors neglected in the simplified treatment and stresses the fact that theory and experiment must keep close company if they are to be mutually helpful.

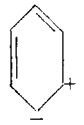
Two approximate methods of treating aromatic compounds such as benzene and pyridine are the valence-bond method and the molecular orbital method.

Both methods have commendable features, but they are different approaches to the same problem. Neither is intrinsically a more accurate description of the molecule, but in certain instances one method may prove more convenient than the other.

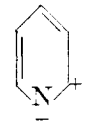
For the organic chemist the valence-bond method has the advantage of beginning with the classical, preëlectronic valence formulae and treating them according to wave-mechanical principles. In the approach of Hückel (133) and of Pauling and Wheland (209) a fair approximation of the molecular wave function (Ψ) for benzene was found to be a linear combination of the two Kekulé (ψ_{K_1}, ψ_{K_2}) and the three Dewar structures (ψ_{D_1}, ψ_{D_2}, ψ_{D_3}).

$$\Psi = C_1(\psi_{K_1} + \psi_{K_2}) + C_2(\psi_{D_1} + \psi_{D_2} + \psi_{D_3})$$

This set of valence-bond formulae is a complete but not a unique set, as others could be used. Solution of the wave equation tends to be more complicated, since one employs many-electron functions and takes account of electron spin. The result is a unique structure of lowered energy, difficult to express in common structural symbols, but one whose nature can be judged from coefficients (C_1 and C_2) of the contributing structures. There are other ionic structures which do not contribute significantly to the ground state of benzene (III) (and hence may be neglected), but are important in pyridine (IV).



III



IV

Invoking such ionic structures is useful in explaining the chemical reactivity of nitrogen heterocycles. In this regard, Daudel (71) has carried out a valence-bond treatment of pyridine.

The molecular orbital approximation assumes that the atoms composing the molecule of benzene are arranged as they are in the final molecule. The electrons constituting the skeletal framework of the molecule (σ-electrons) are then fed in. Owing to the geometry of these bonds, little interaction other than covalent-bond formation will take place. However, since the carbon atoms have formed a planar hexagon by assuming sp^2 hybridization, each carbon atom has a p orbital extending above and below the plane of the ring. Since these p orbitals overlap, they interact to form three pi orbitals of lower energy and three of higher. Hence the six remaining electrons upon being fed in will occupy the three lowest-lying molecular pi orbitals. The diminution of energy upon the overlapping of the p orbitals is explained by the delocalization of the p-electron in a pi orbital spread out above and below the ring (68). By the application of the so-called "π-electron approximation," the energy calculations consider only the stabilization obtained by the delocalization of six π-electrons in three molecular orbitals. Hence the wave function Ψ is considered to be:

$$\Psi = \sum_{n=1}^{6} C_n \psi_n$$

As in the wave-particle in a box, the energy of the electron is diminished by increasing the positional latitude of the particle. The results of molecular orbital calculations on such systems are considerably simpler, but they do not lead to any structural formulae. Instead a molecular diagram giving data on π-electron density, bond order, and free valence is indicated. The avoidance of classical molecular formulae is a merit of the method, as it obviates the often misunderstood notion of resonance hybrids. Nevertheless, the enlightened use of valence-bond structures is quite advantageous in certain qualitative considerations. Semiquantitative calculations, on the other hand, are more readily made by means of the molecular orbital method.

A close consideration of the treatment of the pyridine molecule by the method of molecular orbitals will be given below. The utility, scope, and limitations of such calculations are not often stressed. Consequently, it is important that organic chemists be aware of the approximations involved and the dependability of such calculations.

III. Theoretical Views of the Chemistry of Aza-aromatic Systems

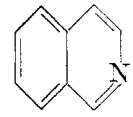
A. General Considerations

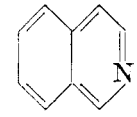
An adequate theoretical treatment of aza-aromatic heterocycles must rationalize not only the stability of the ring system but the different orientations of substitution encountered when cationic, anionic, and free-radical reagents are employed. Moreover, the basicity and dipole moments of these systems must be accounted for.

B. Bond Fixation

As a consequence of the electronic theory of valence it was realized that the basicity of these nitrogen compounds could be due to the unshared electron pair on the nitrogen and that the dipole moment was a manifestation of the electronegativity difference between carbon and nitrogen. Prior to quantum-mechanical treatment of these systems, previous attempts to rationalize reactivity have been based on the concept of "static bonds" in these heterocycles. For example, such proposed formulae for isoquinoline were

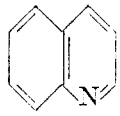

V


VI


VII

and by chemical reactivity V was adjudged a better representation of isoquinoline than VII, since certain anionic reagents added to the system in a 1,2 rather than a 2,3 manner. VI was considered less satisfactory than V, because according to the Fries rule, VI had only one fully aromatic ring. A classical application of the "static bond" concept is the work of Renshaw, Friedman, and Gajewski (221), who coupled the known aminoquinolines with diazonium compounds.

Assuming that coupling would occur ortho to the amino group only if a double bond intervened, or para if two double bonds were present, these workers found that the sites of reaction were in accord with Erlenmeyer's structure of quinoline (VIII).



VIII

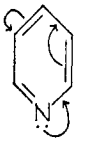
However, the fact that quinoline does indeed have resonance energy (69 kcal. per mole) means that other resonance structures make appreciable contributions to the resonance hybrid. Even if the Erlenmeyer structure were to be the largest single contributor of the linear combination function (i.e., that its ψ would have the largest coefficient), the delocalization or resonance energy would make the resulting unique structure of still lower energy.

Another related approach to the rationalization of the chemical behavior of nitrogen heterocycles has been forwarded by Bergstrom (31). Extending Franklin's ammonia system of compounds, Bergstrom considered the C=N linkage as an ammono aldehyde and hence viewed quinoline as a cyclic ammono aldehyde ether in this system of compounds. All the addition reactions to the azomethine linkage could be correlated with the behavior of aldehydes in similar cases. Derivatives substituted in the alpha position, such as amino, halo, hydroxyl, and methyl, could be compared with amides, acid halides, acids, and methyl ketones. Explanation of similar behavior of the gamma, but not the beta, position rested upon Fuson's principle of vinylogy (106) by which the gamma position would be a vinylogous alpha position. This implicitly assumes bond fixation to the positions represented by Erlenmeyer's formula (VIII).

These views give a fair understanding of chemical behavior but do not take cognizance of modern advances in molecular structure. Besides, the use of chemical reactivity to determine electronic configurations is quite unsatisfactory in aromatic systems, since the molecule will be perturbed by different reagents to varying degrees.

C. QUANTUM-MECHANICAL TREATMENT OF AZA-AROMATIC HETEROCYCLES

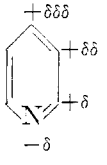
The modern concept of aromaticity as evolved from quantum-mechanical considerations is readily extrapolated to heterocycles such as pyridine, quinoline, and phenanthridine. Owing to the presence of the nitrogen, certain changes must be made in the treatment. The most apparent property distinguishing these compounds from carbocycles is basicity. This stems from the unshared pair of sp^2 hybridized electrons on the nitrogen. Since this orbital extends out from the nitrogen in the plane of the ring (sigma orbital), it cannot overlap with the π-electron cloud which has a node in the plane of the ring. This is theoretically significant, because electromeric interactions have been suggested (16) whereby this electron pair would enhance the electron density at the beta position (IX).



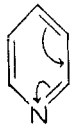
IX

However, the nonoverlapping or orthogonality of the sigma and pi orbitals mitigates against such interactions. Another consequence of this orthogonality is that fixation of a proton on the nitrogen will disturb the pi cloud only by increasing the effective electronegativity of the nitrogen atom. This point is made because the reduced reactivity of pyridine is often explained (198) in terms of the positive-pole pyridinium ion present in acid solution, analogous to the anilinium ion. Such a view neglects the difference in electronic shifts in forming these two cations. This electronic difference is reflected in the unlike behavior of aniline and its ion. On the other hand, pyridine appears to give the same orientation as its ion. The anilinium ion has a reduced reactivity, because fixation of a proton on the nitrogen changes hybridization from sp^2 to sp^3 and thus removes the nitrogen p orbital from overlapping with the pi cloud. Calculations suggest that the pyridinium ion (120) will have only a second-order diminution of charge density at the beta position compared with the unprotonated molecule.

A valence-bond view of pyridine and other pyridinoid systems should take account of two electronic effects caused by substituting the CH in benzene by N. First, by the inductive effect the electronegative nitrogen withdraws electrons



X



XI

toward itself by the sigma-bond framework in the order alpha > beta > gamma carbon (X). Second, the pi cloud at the alpha and gamma carbons will be further depleted of π-electrons (XI). It is clear that such heterocycles will have unequal charge distributions. The physical consequence will be the generation of a dipole moment, whereas chemically the pyridine molecule should be quite susceptible to anionic attack at the alpha and gamma positions.

The molecular orbital treatment of aza-aromatic heterocycles has been considered by many workers, including Coulson and Longuet-Higgins (177), Dewar (74), Wheland and Pauling (275), and the French school (217). Although the method involves fairly simple calculations and gives interesting results, some rather formidable assumptions make the results subject to certain reservations.

As a trial wave function for the energy calculations of the pyridine molecule the assumption is made that an approximate wave function (Ψ) is that obtained

by taking a linear combination of the nitrogen p orbital wave function and the five carbon 2 p orbital wave functions (π-electron approximation):

$$\Psi = C_1\psi_1 + C_2\psi_2 + C_3\psi_3 + C_4\psi_4 + C_5\psi_5 + C_6\psi_6$$

This wave function is substituted in the modified wave equation

$$E = \frac{\int \Psi \mathrm{H} \Psi \, \mathrm{d}\tau}{\int \Psi^2 \, \mathrm{d}\tau}$$

$$E = \frac{\int \left(\sum_{n=1}^{6} C_n \psi_n \right) \mathrm{H} \left(\sum_{n=1}^{6} C_n \psi_n \right) \mathrm{d}\tau}{\int \left(\sum_{n=1}^{6} C_n \psi_n \right)^2 \mathrm{d}\tau}$$

where E = energy of the system, H = Hamiltonian of the system, and $\mathrm{d}\tau$ = spatial increment. This expression is expanded and the integrals obtained are denoted thus:

$$\int \psi_\mathrm{N} \mathrm{H} \psi_\mathrm{M} \, \mathrm{d}\tau = \int \psi_\mathrm{M} \mathrm{H} \psi_\mathrm{N} \, \mathrm{d}\tau = \mathrm{H_{NM}} = \mathrm{H_{MN}}$$

$$\int \psi_\mathrm{N} \psi_\mathrm{M} \, \mathrm{d}\tau = \int \psi_\mathrm{M} \psi_\mathrm{N} \, \mathrm{d}\tau = S_\mathrm{NM} = S_\mathrm{MN}$$

The energy equation is then partially differentiated according to each coefficient to give six differential equations, $\partial E/\partial C_n$, $n = 1, 2, \cdots 6$. By the variation theorem (215) a minimization of energy can be obtained by setting each resulting equation equal to zero. The first of the resulting secular equations is

$$C_1(\mathrm{H_{11}} - ES_{11}) + C_2(\mathrm{H_{12}} - ES_{12}) + \cdots + C_6(\mathrm{H_{16}} - ES_{16}) = 0$$

Now, in order to simplify solution of these equations the following assumptions are imposed:

$\mathrm{H_{NN(N=3,4,5)}} = q$ = energy of a carbon 2 p electron localized on a carbon atom (coulomb integral of carbon)

$\mathrm{H_{NN(N=1)}} = q + x\beta$ = energy of electronegative nitrogen atom for its 2 p electron

$\mathrm{H_{NN(N=2,6)}} = q + y\beta$ = energy of 2 p electron of an alpha carbon atom made more electronegative by the adjacent nitrogen atom

$\mathrm{H_{N,N+1}} = \beta$ = resonance integral (nonadjacent = 0)

$S_\mathrm{NN} = 1$; for normalized wave function

$S_{\mathrm{NM(N\neq M)}} = 0$; neglect of overlap

Rewriting the equations and using these approximations, one obtains this determinant:

$$\begin{vmatrix} q - E + x\beta & \beta & 0 & 0 & 0 & \beta \\ \beta & q - E + y\beta & \beta & 0 & 0 & 0 \\ 0 & \beta & q - E & \beta & 0 & 0 \\ 0 & 0 & \beta & q - E & \beta & 0 \\ 0 & 0 & 0 & \beta & q - E & \beta \\ \beta & 0 & 0 & 0 & \beta & q - E + y\beta \end{vmatrix} = 0$$

Useful results can be obtained by solving this determinant for the six roots of E expressed in terms of q and β to give the energy levels for the π-electrons of pyridine. However, the two parameters x and y must be assigned values to account for the decreased energy of a coulomb integral of an electronegative atom (β has negative sign). Unfortunately, no perfectly reliable method is known to estimate these values. Therefore, the error introduced by this uncertainty overshadows the other assumptions of the method. Depending upon the values chosen, the calculated π-electron densities of pyridine vary a great deal. This is illustrated by the data given in table 1. The most promising approach to estimating x and y seems to be the calculation of the dipole moment of pyridine by the vector addition of the pi and sigma dipole contributions. With $x = 0.6$ Löwdin (178) obtained a calculated moment of 2.36 D for pyridine, whereas Orgel and coworkers (206) obtained a value of 2.15 D when x was taken as 1.0. In correlating Hammett sigma values with π-electron densities of heterocycles, Jaffe (138) adjusted the value of x to give the best fit of values and found $x = 0.59$ to give good agreement. However, the experimental value of 2.15 D for the dipole moment of pyridine was recently obtained by microwave spectroscopy (73) and this tends to support a value of $x = 1.0$.

The charge densities could be calculated by inserting the three lowest values of E in the secular equations and obtaining the coefficients of the molecular wave functions. Calculations are simplified, however, by using first-order perturbation theory (177). This is especially advantageous with molecules such as

TABLE 1

π-Electron densities of pyridine and values chosen for parameters x and y

Calculated π-Electron Densities in Pyridine				x	y	Reference
N	C_α	C_β	C_γ			
1.59	0.85	0.95	0.82	2.0	0.25	(177)
1.59	0.83	0.96	0.82	2.0	0.2	(275)
1.274	0.946	0.980	0.874	1.0	0.4	(45)
1.327	0.901	0.982	0.910	0.9	0.1	(216)
1.264	0.920	0.983	0.934	0.6	0.0	(226)
1.234	0.909	1.006	0.940	0.6	0.0	(120)
1.190	0.932	0.993	0.958	0.48	0.0	(120)

phenanthridine, where the molecule is treated as a perturbed phenanthrene. As the parent carbocycle has more symmetry, the calculations can be simplified by group theory (94). The error introduced by the use of perturbation methods is well within the uncertainty caused by the estimation of x.

Besides the charge densities of the different atoms in aza-aromatic heterocycles, free-valence and mobile-bond indices can also be calculated. Free valence indicates the bonding tendency of an atom and is roughly linearly related to the polarizability of the atom. Mobile-bond order measures the multiple-bond character of a chemical linkage (68).

The chemical interpretation of these results is summarized thus (177). The assumption is made that all chemical reagents attack the heterocyclic substrate in one of three manners: first, by electrophilic or cationic attack such as nitration; second, by nucleophilic or anionic attack such as amination with potassium amide; or third, by free-radical processes such as phenylation with benzoyl peroxide. Electrophilic reagents will attack the heterocycles at sites of high π-electron density and nucleophilic reagents will seek out positions of low π-electron density. It is believed that free-radical reagents prefer positions having a high free-valence index.

Some interesting conclusions were reached in a study of the charge densities of a series of nitrogen heterocycles. First, the effect of aza substitution on π-electron density diminishes with the distance between the site of substitution and a given atom. Second, the electronic effect of replacing an additional CH by N appears to be additive. Third, the greater the net charge at a position (either + or −), the more reactive it is to a charged reagent (− or +). Fourth, when there is little difference in the charge densities of positions, the polarizabilities of the positions become important.

Although this view of chemical reactivity is valuable, serious objections can be raised to the view that there is an undoubted correlation between calculated electron distribution and the observed chemical behavior. The nitration, bromination, and sulfonation of quinoline point up several weaknesses in this unified approach. For electrophilic attack the calculated charge densities favor $C_8 > C_6 > C_3$. Sulfonation does indeed occur at C_8, but a temperature factor is involved, as C_6 is attacked at higher temperatures (109). In addition, bromination occurs at C_3, although C_8 and C_6 seem more preferable from theory. If there is little difference in reactivity among the three positions, one would expect that the 8- and 6-isomers would also be found, but this is contrary to experiment (156). Finally, nitration occurs mainly at C_5 with less at C_8 (69). These difficulties in utilizing the charge densities of heterocycles to predict sites of substitution have been attributed to the importance of neglected factors.

From this stemmed the realization that changes in electronic configuration required to attain the transition state of the reaction might often be a predominant factor in determining the site of reaction (273). Another aspect, seriously ignored in the charge-density approach, is the specific nature of the reagent. The behavior of quinoline with the three different electrophilic reagents mentioned above illustrates the importance due to the reagent. Until Brown's work

(46, 47), which will be discussed shortly, there was little concern over whether different electrophilic species might vary in their electronic demands upon the aromatic system in the course of reaction. Thus, a complete theoretical treatment of these aza-aromatic heterocycles necessitates consideration of many other factors besides the ground-state charge distribution of the substrate heterocycle. The following discussion will highlight those factors which must be weighed in the synthesis of a satisfactory rationalization of aza-aromatic chemical behavior.

D. TRANSITION-STATE TREATMENT OF AROMATIC SUBSTITUTION

In the transition-state view of chemical reactivity one reflects upon the electronic alterations undergone in the course of reaction. The variation in the energy of a system is considered as the substituting reagent interacts with the aromatic substrate to form a new bond as the old bond of the displaced group is stretched until the group is expelled. It is felt that a high-energy intermediate may be formed, as XIII, with the two transition states (XII and XIV) involved in getting in and out of such a state. The transition state of higher energy will determine the rate of substitution as the reaction proceeds along the reaction coordinate x (figure 1). The energy of activation ($E^{\ddagger}$) is the difference between the energy of the rate-determining transition state (XII or XIV) and that of the ground state of the reagents. If different aromatic carbon atoms are present in a molecule, substitution should occur preferentially at that carbon atom having the lowest $E^{\ddagger}$. One could then make an accurate prediction of preference in aromatic substitution if there were some manner of assessing the energy of the transition state. Owing to the uncertainty in the exact configuration of this transition state, any semiquantitative calculations must be based upon an assumed model for this state.

In substitution reactions occurring at aromatic carbon atoms it is likely that the original sp^2 hybridization is transformed to approximately an sp^3 or tetrahedral configuration (see XIII in figure 1) in the course of reaction. Consequently, Wheland (273) sought to assess the loss of resonance energy of various aromatic

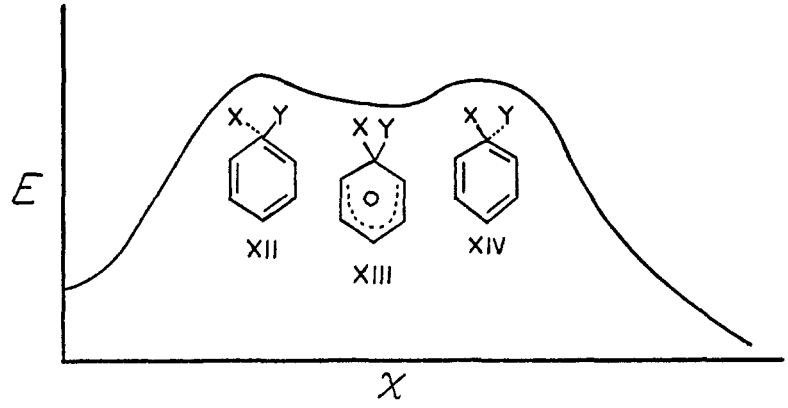
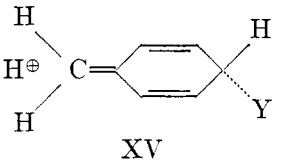


FIG. 1. Variation of the potential energy along the reaction coordinate r

systems by taking such a tetrahedral configuration for the transition-state model. The resonance energy of the tetrahedral model was calculated by the method of molecular orbitals. The resonance energy of the transition state, minus the resonance energy of the ground state obtained in a similar fashion, gave the loss in stabilization (W_B) in going to the transition state. The quantity W_B was taken as an index of $E^{\ddagger}$. Hence, the fact that naphthalene is attacked usually at the 1-position rather than at the 2-position is rationalized by the fact that $W_{B_1} < W_{B_2}$. The method can be applied to electrophilic, nucleophilic, and free-radical attack. Applied to pyridine, the method gave results in general accord with experiment.

Since the chemical reactivity of aza-aromatic systems can be interpreted either in terms of the ground-state electronic distribution of the heterocycle or the loss of resonance energy in attaining a tetrahedral transition stage, the choice between the two approaches will depend upon the position of the transition state along the reaction coordinate x in figure 1. Both views, however, express extremes of the actual case. As the electrophilic reagent is varied from nitric acid through bromine to sulfuric acid, one might expect a variation in the electronic perturbation of the substrate aromatic compound and hence a shift in the nature of the transition state. Recent studies by Brown and coworkers (46, 47) give experimental foundation for this view and show that the nature of the reagent is important. These workers computed the relative rates of electrophilic substitution of benzene and toluene. With a given reagent a high r(toluene)/r(benzene) was taken as evidence that the transition state in toluene received considerable hyperconjugative aid and hence that it resembled a tetrahedral configuration at the carbon atom attacked (XV).

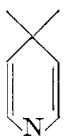


XV

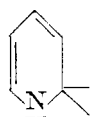
Conversely, a low ratio suggested that the transition state had been reached before a tetrahedral configuration had been attained. As it did not receive hyperconjugative aid, such a reagent was considered more reactive. In a parallel study the meta/para ratios for the attack of the same reagents on toluene were determined. A high value of meta/para suggested that the reagent under consideration had a lower selectivity than one yielding a low meta/para value. In such a manner it was observed that reagents having a high reactivity had a low selectivity (nitric acid), whereas those reagents exhibiting a lower reactivity had a higher selectivity (bromine). (Two exceptions, sulfonation and mercuration, are explicable in terms of proton elimination being the rate-determining step.) Electronically, this correlation may be interpreted thus: The less reactive and more selective electrophilic reagents seem to attain a transition state whose geometry is closely approximated by a tetrahedral configuration at the carbon atom under attack (XIII). Here the factor deciding the site of attack will be the loss of

resonance stabilization (i.e., the localization energy) caused by the removal of the p orbital of that carbon atom from the aromatic pi cloud. On the other hand, since the more reactive reagents attain a transition state which is shifted from the tetrahedral model toward the reactants, the site of attack on the aromatic system will depend less on the localization energies and more on the charge densities and autopolarizabilities of the aromatic ground state. Thus, more reactive electrophilic reagents have sufficiently strong cationic centers to polarize the aromatic pi cloud at longer distances and to cause interaction. These looser transition states may consist of a longer new bond or a nonlocalized pi complex.

This relationship between the selectivity and reactivity of chemical reagents seems to be one of wide utility. For example, it seems quite reasonable to extrapolate it to cover nucleophilic attack on aza-aromatic heterocycles as well. Both organolithium and organomagnesium reagents are able to alkylate nitrogen heterocycles such as pyridine and quinoline. Nevertheless, there is a distinct difference of behavior with pyridine. Organolithium reagents attack the alpha position readily (285), whereas allylmagnesium bromide attacks the gamma position with lessened facility (113). An explanation of this difference may be in the following considerations: n-Butyllithium is an extremely vigorous nucleophilic reagent, attacking the heterocycles from pyridine to phenanthridine readily even at low temperatures. Allylmagnesium bromide, on the other hand, is a selective nucleophile toward aza-aromatic heterocycles, since it yields only 9 per cent of product with pyridine and gives 81 per cent with acridine. If Brown's correlation on electrophilic attack is extended to nucleophilic attack, one sees that the extremely reactive n-butyllithium will attain a transition state shifted toward the ground state, where charge density and autopolarizability favor attack at the 2-position (225). With the less reactive allyl Grignard reagent the transition state should be close to tetrahedral. Invoking Hammond's thermic postulate (121), one can then say that since the latter transition state resembles the allyl-dihydro magnesium bromide product geometrically, it must also resemble the product in energy. Consequently, this product or the dihydro derivative obtained upon hydrolysis is a fair model for the transition state. Hence the respective localization energies for the alpha and gamma positions will become important. Since 1,4-dihydropyridines (XVI) seem to be more stable than 1,2-dihydro derivatives (34) (XVII), the activation (localization) energy may be



XVI



XVII

lower for an attack on the gamma position in pyridine by selective nucleophiles. Other examples of the preference of selective nucleophiles for attack of the gamma position will be mentioned later (Section V,G,4).

IV. Factors Affecting the Mode of Attack on Aza-aromatic Systems

A. SPECIES UNDERGOING ATTACK

The approximate calculations leading to π-electron densities and indices of free valence have already been discussed. It was further stated that the pyridinium ion, present in electrophilic processes, differed in degree and in kind from the "positive-pole" anilinium ion. It is conceded, however, that the charged nature of the pyridinium ion should somewhat hinder electrophilic attack by both the direct field effect and the decrease in the polarizability of the pi cloud. On the other hand, such complexes as the 1-methylpyridinium ion or 1-oxide greatly enhance the reactivity of the alpha and gamma positions toward nucleophilic attack. Here there is increased electronegativity of the hetero atom, further diminishing the electron densities of these positions. No information is available on the effect of quaternization on the facility of attack by free radicals. If the polarizability of the site attacked is a dominating factor, the lessened polarizability of the heterocycle complex should decrease its reactivity.

As detailed discussion will later show, there is often an increase in reactivity to a given reagent as one passes through the series: pyridine, quinoline, isoquinoline, phenanthridine, and acridine. This holds true for electrophilic, nucleophilic, and free-radical attack. In the light of previous comments on the relation between the reactivity of reagents and the nature of the transition state, no one explanation is complete. The possible contributing factors can be summarized. First, the alpha and gamma carbon atoms become more positive as this series is ascended, and the remaining carbon atoms tend toward greater polarizability. This is especially true of dibenzopyridines, where the perturbing nitrogen is more distant. Hence reactivity toward both nucleophilic and electrophilic reagents increases. Second, the localization energy required to remove a p orbital from conjugation with the pi cloud becomes progressively less in this series of heterocycles.

A point should be made concerning the term of "substrate" for the heterocycle. This is arbitrarily applied for convenience. Previously it was said that with a given substrate, a more reactive reagent shifted the transition state toward the ground state and away from a tetrahedral configuration (figure 1). Conversely, it is also true that with a given reagent a more reactive heterocycle will also shift the transition state to the left.

B. ATTACKING SPECIES

Brown's (46, 47) work has shown that the nature of the electrophilic species does indeed determine the electronic demands to be made by the reagent. The correlation is applicable to electrophilic attack on aza-aromatic heterocycles and can be extended to cover nucleophilic attack as well. It would be interesting to determine how the behavior of the fairly stable triphenylmethyl radical compared with the reactive phenyl radical in the reaction with pyridine.

It is well to remember that experimental conditions can alter the nature and reactivity of a species. For example, electrophilic chlorination may occur through

a number of species, Cl_2, $H_2OCl^{\oplus}$, HOCl, or $Cl^{\oplus}$, depending upon conditions. As these chlorinating species vary in reactivity, it might be expected that they will attack aza-aromatic systems with various behavior. Also, the species could be changed from electrophilic to free radical in character by the use of higher temperatures or different catalysts.

C. REVERSIBILITY

The reversible nature of some substitution reactions is important in that such reactions tend to obscure the first choice of an attacking species. As a reversal of a substitution reaction will pass through the same reaction configurations as did the forward process (microscopic reversibility), the activation energy of the reverse process will be the activation energy of the forward reaction plus its thermodynamic heat of reaction:

$$E^{\ddagger}_{\text{rev.}} = E^{\ddagger}_{\text{forward}} + \Delta H$$

Reversibility of highly exothermic processes such as nitration is therefore extremely rare. One reported case cites the formation of 4-nitroacenaphthene from 2-nitroacenaphthene (193). Much more common are reversible sulfonations and brominations (109).

Similar to the classical sulfonation of naphthalene, quinoline yields under moderate conditions 8-quinolinesulfonic acid. The reversible nature of this process is evident from the fact that both quinoline and 8-quinolinesulfonic acid yield 6-quinolinesulfonic acid when heated at 300°C. with fuming sulfuric acid (109). Evidently sulfonation and desulfonation occur easily at the 8-position. The activation energy for sulfonation at the 6-position being higher, a higher temperature is required. The desulfonation of the 6-position is so difficult that sulfonation at the 6-position is effectively irreversible. The fact that reversible substitution reactions may take place makes it difficult to correlate halogenation reactions carried out at high temperatures with calculated π-electron densities.

D. SUBSTITUENTS

The electronic behavior of substituents in determining orientation and activation in aromatic systems has been admirably unified by Ingold, Hughes, and others (137). It may be said for heterocyclic systems in general that the presence of strongly activating or deactivating substituents will largely determine the orientation of entering electrophilic groups. In the case of nucleophilic attack, however, these species are still directed to positions alpha or gamma to the nitrogen atom.

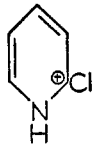
The steric effects of substituents are often important in determining the position attacked by electrophilic species. For example, the nitration of quinoline gives mostly 5-nitroquinoline and some 8-nitroquinoline (69). However, the nitration of 4-methylquinoline gives mostly the 8-isomer (141). Presumably the proximity of the 4-methyl group presents a steric barrier to the attack of the nitronium ion at the 5-position.

E. CATALYSTS

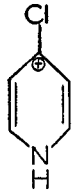
Effectively, a catalyst is an agent which by raising or lowering the activation energy for a reaction retards or accelerates the attack on the molecule. The significance of catalysis in studying the reactivity of aza-aromatic heterocycles is that such assistance can alter the orientation of the attacking species or reactivity of the molecule. This is illustrated by the following examples.

Wibaut's extensive work on the high-temperature halogenation of pyridine and quinoline (129, 277–279) reveals that as the catalyst is changed from iron(II) bromide to copper(I) bromide the orientation changes from predominantly beta to alpha. Presumably the catalyst alters the attacking species from an electrophilic to a free-radical agent (89).

The nucleophilic solvolysis of α- and γ-halo compounds has been found to proceed more readily under acidic than under basic conditions. Evidence adduced by Banks (22) indicates that the protonation of the nitrogen further activates the alpha and gamma positions (XVIII, XIX) to attack by the nucleophilic water molecule.



XVIII



XIX

As might be expected, hydrogenation catalysts show varying behavior. Raney nickel in alcohol preferentially reduces the pyridinoid ring (2), whereas colloidal platinum in acetic acid leads to a completely reduced product (235).

F. TEMPERATURE

The halogenation and nitration of pyridine show a sensitivity of orientation to temperature. At 300°C. with vapor-phase reactants the beta positions are favored. Around 500°C. much decomposition occurs, but attack occurs primarily at the alpha positions (129, 277). Again an explanation proposes a switch from electrophilic to radical attack (274).

The importance of temperature in cases of reversible reactions such as sulfonation has already been pointed out. However, the isomer distribution in such irreversible reactions as nitration is also somewhat sensitive to the reaction temperature. An elevation in temperature will make attack at less reactive positions significantly larger.

G. SOLVENT

The effect of solvent for the displacement reactions in aliphatic systems has been elegantly treated by Hughes and Ingold (134). From these conclusions one would expect some retardation of reaction rate in electrophilic or nucleophilic

reactions run in highly polar solvents. The high dielectric properties of such media should diminish the interaction of charged species.

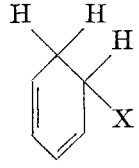
On the other hand, the electrophilic species generated by a given reagent may largely depend upon the solvent. For example, it is felt that electrophilic halogenation may be carried on by species such as HOX, $H_2OX^{\oplus}$, X_2, and $X^{\oplus}$. These species vary in reactivity and the existence of any one of them in a solvent system depends upon the solvating and dielectric properties of the medium. As it is felt that the reactivity of an electrophilic species determines the electronic demands which it will make on an aza-aromatic heterocycle, the solvent employed may influence orientation. An example of this is the nitration of quinoline. With mixed acid the products are 5- and 8-nitroquinolines. However, with lithium nitrate in acetic anhydride 3-nitroquinoline is formed in low yield (76). Previous workers reported that the 7-nitro isomer was formed (15). Acetyl nitrate is felt to be the active agent in the latter case.

V. Chemical Properties

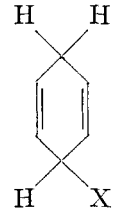
A. Substitution reactions

Substitution and addition reactions in aza-aromatic systems tend to overlap. It has been pointed out that a substitution reaction on an aromatic system consists in the formation of a new bond and rupture of the old bond. Such a process may occur concertedly, or there may be formed a tetrahedral intermediate of varying stability (figure 1). Substitution then occurs in two discrete steps. If the intermediate is sufficiently stable, it may be isolated. Subsequent elimination of the original group may then require a distinct chemical reaction. As this intermediate is often isolable in nucleophilic attack on nitrogen heterocycles, the net result is an addition reaction, but as recovery of the aromatic system can be effected, it will be considered as substitution.

Factors contributing to the superior stability of the tetrahedral adduct in aza-aromatic systems might be considered briefly. In the case of benzene the formation of a 1,2 adduct (XX) should require a localization energy of 1.528 β ($\beta \simeq 20$ kcal.), the difference between the resonance energy of benzene and that of the butadiene-type adduct. For a 1,4 intermediate (XXI), however, the conjugation of the formal double bonds is completely disrupted and the localization energy is 2.0 β.

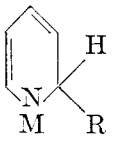


XX

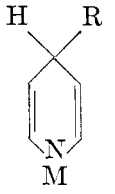


XXI

Addition of organometallic reagents ($R^{\ominus}M^{\oplus}$) to pyridine leads to 1,2 or 1,4 adducts similar to those depicted above for benzene (XXII, XXIII).

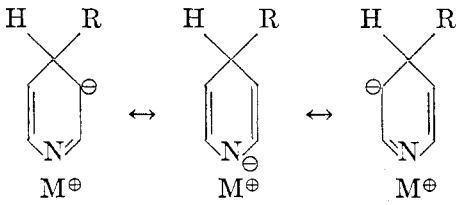


XXII



XXIII

The localization energies for the corresponding pyridine adducts should be less than those given for the benzene molecule. When M is added to the nitrogen, this hetero atom still possesses two electrons which can occupy a p orbital. The latter orbital can overlap with the residual pi cloud, somewhat analogous to pyrrole systems. The net result is a smaller loss in resonance energy. Moreover, owing to the highly polar N—M bond, the anion XXIV can contribute even greater stabilization to the adduct.



XXIV

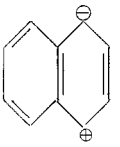
B. ELECTROPHILIC SUBSTITUTION

1. Nitration

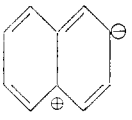
The species considered as the active agent in nitration is the nitronium ion, $NO_2^{\oplus}$ (110). Brown's study indicates that this is a very reactive electrophile of low selectivity. Although the transition state is not very close to the reactants because of the high activation energy of nitration, it seems to be sufficiently shifted from the tetrahedral model to depend more upon the charge density and polarizability of the ground state of the heterocycle.

In the series pyridine < quinoline < isoquinoline < acridine < phenanthridine, the ease of nitration increases significantly. Pyridine gives a 22 per cent yield of 3-nitropyridine when a solution of pyridine in 100 per cent sulfuric acid reacts with potassium nitrate and nitric acid at 300°C. (104, 146). This is contrasted with the quantitative yield of six mononitrophenanthridines obtained when phenanthridine nitrate is dissolved in concentrated sulfuric acid (196). The increasing reactivity of the benzo- and dibenzopyridines can be attributed to the decreasing effect of the hetero nitrogen atom on the more distant benzenoid ring. This leads to an increased polarizability at the carbon atom being nitrated. The isomers formed in the nitration of pyridine, isoquinoline, and acridine are generally in accord with predictions based on calculations of charge density (177). Phenanthridine and quinoline, on the other hand, do not give reasonable agreement. In quinoline it is felt that the more favorable polari-

zability of the "alpha" positions (C_5 and C_8) overrides the greater charge densities at C_6 and C_3. Dewar (75) suggests that quinoline be considered as a perturbed naphthalene molecule. A valence-bond approach rationalizes the greater polarizability of the "alpha" positions in naphthalene by pointing out that structure XXV has six other contributing structures, whereas structure XXVI has only five (217).

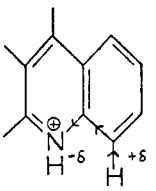


XXV



XXVI

As this enhanced polarizability facilitates nitration, the nitration of quinoline at the 5- and 8-positions is understandable. With the more reactive phenanthridine the tendency toward random substitution is seen in the formation of the 1-, 2-, 3-, 4-, 8-, and 10-nitrophenanthridines (57). The predominance of the 1- and 10-nitrophenanthridines again can be attributed to the greater polarizability of these "alpha" positions. The charge densities favor electrophilic substitution in this order (177): $C_4 > C_{10} > C_8 > C_2 > C_1$, and their failure with nitration has been attributed to their closeness (263). The extremely small amount of 4-nitrophenanthridine formed may be due to the diminished polarizability of the 4-position caused by the adjacent protonated nitrogen (XXVII). This is also reflected in the smaller amount of 8-nitroquinoline and 4-nitroacridine isolated from the nitration of quinoline and acridine, respectively (69, 164, 165).



XXVII

Nitration of these heterocycles with oxides of nitrogen (231) or a mixture of lithium nitrate and acetic anhydride (15) requires further study. Although the latter reagent was reported to give a low yield of 7-nitroquinoline, a recent communication by Dewar and Maitlis (76) claims that it is really 3-nitroquinoline. Certainly the latter isomer would seem more reasonable from charge density predictions.

A comprehensive review of the experimental results and theoretical implications of aza-aromatic nitration has been prepared by Schofield (229).

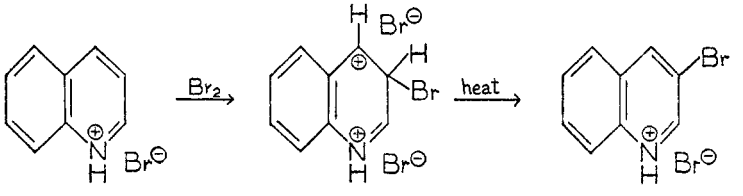
2. Halogenation

Halogenation of aromatic systems occurring under 300°C. and in the presence of Lewis acids is considered to occur by an electrophilic mechanism. The intimate

details of the process are not nearly as well known as they are in the case of nitration.

Comparative data on the bromination of these nitrogen bases are quite meager. If bromination accomplished by heating the perbromide hydrobromide is examined, it appears that the facility of bromination does not vary markedly. Pyridine gives only 37 per cent of 3-bromopyridine but also 26 per cent of 3,5-dibromopyridine (181); quinoline yields 62 per cent of the 3-isomer (156); and isoquinoline forms up to 74 per cent of 4-bromoisoquinoline (114). The lack of any sharp difference in reactivity may stem from the fact that in all cases attack is on the deactivated pyridinoid ring. Acridine and phenanthridine have no available positions beta to the nitrogen in the pyridinoid ring. The position assumed by the entering bromine atom might help to elucidate the factors determining the selectivity of bromination. Bromination of acridine with *N*-bromosuccinimide (228) led to small amounts of two isomeric bromoacridines. The unidentified products were thought to be the 2- and 4-isomers. The analogous reaction with phenanthridine gave a 40 per cent yield of 2-bromophenanthridine (111). Recently, 2-bromoacridine and 2,8-dibromoacridine have been obtained by heating acridine with bromine in glacial acetic acid (1).

The orientation in the bromination of quinoline and isoquinoline has long been considered anomalous. As was indicated previously, charge densities would favor attack in the order $C_8 > C_6 > C_3$ for quinoline and $C_5 > C_7 > C_8$ for isoquinoline (177). Preference for the deactivated pyridinoid ring over the benzenoid ring suggests that there are unusual features about halogenation which require further study. It is conceivable that bromine could react with the polar C_3—C_4 bond and thus halogenate the heterocycles by an addition-elimination process (XXVIII to XXX).



XXVIII XXIX XXX

The similar behavior of chlorination (19), iodination (245), and mercuration (253) may be explicable in a parallel fashion.

3. Sulfonation

The sulfonation of these nitrogen heterocycles results in various isomeric sulfonic acids depending upon the strength of oleum and the temperature employed. The reversible nature of sulfonation, previously mentioned, vitiates theoretical predictions of the most likely sites of substitution. Moreover, the reactive nature of the electrophilic sulfur(VI) oxide present in oleum tends to the formation of more isomers. Thus, the sulfonation of quinoline occurs mainly at C_8, but the C_5, C_6, and C_7 positions are also attacked (65, 101, 157). The

ease of sulfonation seems to increase in the following order: pyridine < quinoline < isoquinoline < phenanthridine (97, 100, 112). Attempts have been made to sulfonate acridine, but with limited success (162, 163).

There is evidence that the transition state of sulfonation has made much progress along reaction coordinate x in figure 1. Melander (185) has observed that tritium-substituted aromatic systems do show a kinetic isotope effect when sulfonated. This may be interpreted to mean that the step of proton rupture (XIV in figure 1) is rate-determining. Since the transition state is much removed from the ground state, localization energies may be a better criterion for predicting sites of attack than charge densities. Pyridine can be sulfonated at the only feasible position (C_3) under rather stringent conditions. If the lower localization energy of an "alpha" position is recalled, the major attack at C_8 in quinoline, at C_5 in isoquinoline, and probably C_4 in phenanthridine is understandable. The reversal of these sulfonations at more elevated temperatures demonstrates the ready accessibility of the transition state from both directions along the reaction coordinate x.

4. Mercuration

The mercuration of aza-aromatic heterocycles is usually carried out in two steps. First, the base and mercury(II) acetate are warmed to yield a complex of two molecules of base with one molecule of the mercury salt. This is probably a Werner-type complex. Upon heating the complex, the heterocycle is mercurated with the elimination of acetic acid (253).

Mercuration is in general a less reactive electrophilic process than nitration or sulfonation. In its reactivity and its orientation in heterocycles, it parallels the behavior of bromination. With pyridine, quinoline, and isoquinoline it attacks the same positions as does bromination. (In the case of quinoline it also attacks the 8-position.) The mercurations of acridine and phenanthridine have not been reported.

As was mentioned under the discussion of bromination, the mercuration may occur by means of an addition-elimination process.

5. Friedel–Crafts alkylation

The electrophilic alkylation of these heterocyclic bases has not been accomplished. As with nitrobenzene, the aza-aromatic heterocycles fail in this reaction because of complexation of the catalyst with the hetero nitrogen atom. It is quite possible, however, that alkylation of dibenzopyridine systems could be realized under forcing conditions.

C. NUCLEOPHILIC SUBSTITUTION

1. Alkylation

An alkylation procedure of limited utility is the Ladenburg synthesis of alkylpyridines (159). Heating alkyl halide salts of pyridine at 290–300°C. leads to a

mixture of 2- and 4-alkylpyridines. Although the mechanism has not been studied, orientation suggests that it proceeds by a nucleophilic or, more likely, a free-radical process.

Reaction of these heterocycles with Grignard reagents ordinarily has been carried out under "forcing" conditions such as the use of dioxane (29) or an autoclave (32). This illustrates the lowered nucleophilicity of ordinary Grignard reagents. It is significant that allylmagnesium bromide reacts readily with phenanthridine, acridine, and quinoxaline in ether solution. The allyl anion is stabilized by resonance; hence this Grignard reagent should have an enhanced polar character (XXXI).

$$\underset{\text{XXXI}}{\text{BrMgCH}_2\text{CH=CH}_2} \rightleftarrows \overset{\ominus}{\text{C}}\text{H}_2\text{CH=CH}_2 + \overset{\oplus}{\text{M}}\text{gBr}$$
$$\updownarrow$$
$$\text{CH}_2\text{=CH}\overset{\ominus}{\text{C}}\text{H}_2$$

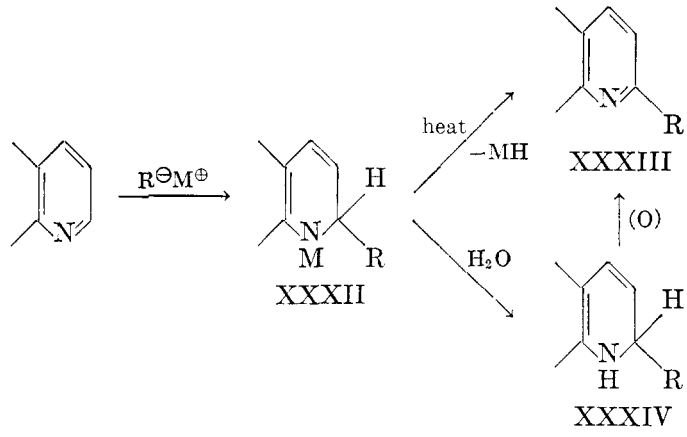
With a series of aza-aromatic heterocycles and anils, allylmagnesium bromide gave the following reactivity series: pyridine < quinoline ≃ isoquinoline < phenanthridine ≃ benzalaniline ≃ acridine < quinoxaline < benzophenone anil (112, 113). The selective character of allylmagnesium bromide versus that of *n*-butyllithium in the reaction with pyridine has been discussed previously (Section III,D).

The reaction of Grignard reagents occurs mainly at the alpha positions in quinoline, quinoxaline, isoquinoline, and phenanthridine. In pyridine and acridine the gamma position is attacked. Some of the earlier work has been discredited. Although Bergmann and Rosenthal (29) reported that benzylmagnesium chloride and pyridine gave a small yield of 2-benzylpyridine, repetition of this work by Veer and St. Goldschmidt (255) led to the conclusion that the 4-isomer was formed instead. Parallel studies using allylmagnesium bromide (113) support the work of the latter authors. Likewise, Bergstrom and McAllister (32) reported the preparation of 2-ethylpyridine from ethylmagnesium bromide and pyridine in an autoclave. Recently, 2-ethylpyridine was prepared unambigously (119) and shown to differ from the product of Bergstrom and McAllister. Repetition of the autoclave reaction gave only bipyridines (116).

The most elegant alkylation procedure involves the use of alkyllithium compounds (285). Applicable also to arylation, the reaction proceeds easily at room temperature. The heterocycles pyridine, quinoline, isoquinoline, acridine, and phenanthridine react extremely readily with *n*-butyllithium. The attack occurs predominantly at the alpha position except in acridine, where only the gamma position is available.

The reaction mechanism of lithium and Grignard reagents seems to involve the nucleophilic attack of the alkyl anion on the heterocycle (or heterocycle complexed with the reagent (224)) at the positions of lowered charge density. The isolable adduct (XXXII) formed may split out the metallic hydride thermally (XXXIII), or the dihydro compound obtained upon hydrolysis may be

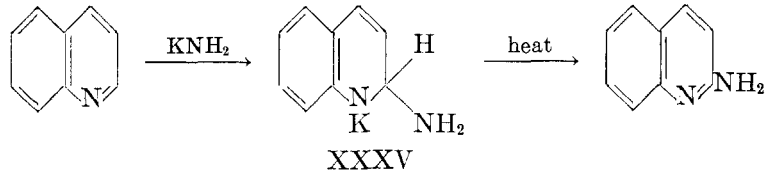
oxidized (XXXIV):



The factors determining the attack of allylmagnesium bromide at the gamma position of pyridine have been discussed previously (Section III,D). The Grignard reactions carried out under autoclave conditions, however, may well involve free-radical processes.

2. Amination

Aza-aromatic bases react readily with potassium amide to yield amino derivatives with the evolution of hydrogen (161). With pyridine and quinoline both the alpha and gamma derivatives are formed. There seems to be no marked difference in yield among pyridine (82–90 per cent), quinoline (63 per cent), isoquinoline (83 per cent), phenanthridine (90 per cent), and acridine (72 per cent). Data indicate that this process is a nucleophilic attack of the amide anion on the positions of lowest charge density with the expulsion of the hydride ion. The process is thus quite analogous to nucleophilic alkylation.



Bergstrom (30) has obtained experimental evidence for the intermediate adduct (XXXV).

The amide ion is a reactive nucleophile, but less reactive than the hydride or alkyl anion.

3. Hydride-ion reduction

The behavior of a series of aza-aromatic heterocycles towards lithium aluminum hydride has been studied recently by Bohlmann (37). Although no quantitative data were presented, facility of reaction increased in the order pyridine <

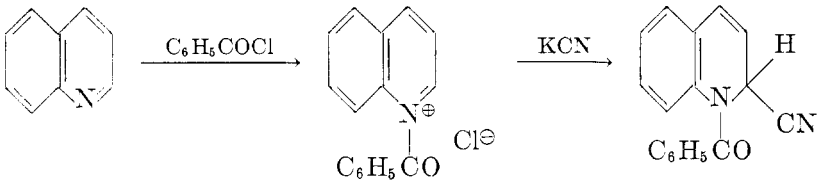
quinoline < quinoxaline < acridine. Interestingly enough, piperidine was formed in 10 per cent yield from pyridine, together with an unstable product behaving like 1,2-dihydropyridine. The product from quinoline was possibly a mixture of 1,2- and 1,4-dihydroquinolines, as two distinct orange-red picrates were isolated. The behavior of phenanthridine with this reagent has been studied independently (284) and 5,6-dihydrophenanthridine was obtained in 74 per cent yield. These data also suggest a dependence of reactivity on the lowered charge density of the alpha and gamma positions, as reaction probably occurs through a nucleophilic attack of the hydride ion. The behavior of lithium aluminum hydride is quite analogous to that of *n*-butyllithium, although the latter seems to be more reactive.

4. Hydroxylation

The nucleophilic hydroxylation of these nitrogen bases by dry potassium hydroxide was discovered by Chichibabin (61). Recently, the reaction was extended to phenanthridine (112). Analogous to amination, hydroxylation occurs through a nucleophilic attack of the hydroxide ion at a position of lowered charge density. The large activation energy of the process is reflected in the high temperatures required (200–300°C.). Amination and hydroxylation probably have as their rate-determining step the expulsion of the hydride ion. The carbon–hydrogen bond energy is 87.3 kcal. per mole, whereas that of a carbon–nitrogen bond and a carbon–oxygen bond are 48.6 and 70.0 kcal. per mole, respectively (208). Judged by the time and temperature, the facility of hydroxylation increases thus: pyridine < quinoline < isoquinoline < phenanthridine. Reaction takes place uniformly at the alpha position.

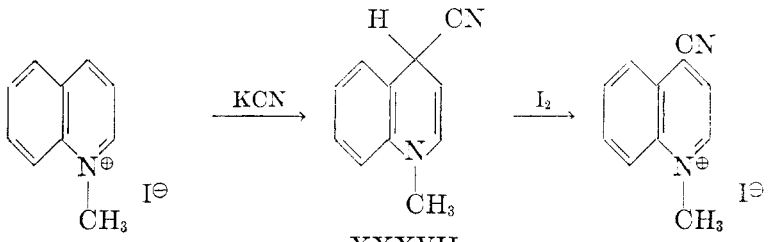
5. Cyanation

Various procedures lead to the nucleophilic attack of cyanide ion on these heterocycles. A general method developed by Reissert (220) has been applied to quinoline, isoquinoline, and phenanthridine (283), but failed with pyridine (219). The procedure involves the reaction of potassium cyanide with the benzoyl chloride complex (XXXVI) of the heterocycles in anhydrous solvents.



XXXVI

The reaction proceeds readily and the cyanide ion attacks the alpha position. This is to be contrasted with the Kaufmann reaction (143), in which treatment of quinoline methiodide with potassium cyanide leads to a dihydro intermediate (XXXVII) oxidizable by iodine to 4-cyanoquinoline methiodide.



XXXVII

Surely attack at either the alpha or the gamma position in quinoline is compatible with nucleophilic cyanation, but the switch in orientation must be considered. The fact that the benzoyl chloride complexes of heterocyclic bases may be used as benzoylating agents (180) suggests a loosely bound complex on the nitrogen (XXXVI). On the other hand, methiodides of heterocyclic bases are not methylating agents under ordinary circumstances. This points to a methyl group intimately bound to the nitrogen. Such a group could create a definite steric barrier to attack at the alpha position, whereas the benzoyl chloride complex might be loose enough to permit access to the alpha position.

Finally, acridine reacts readily with hydrocyanic acid in alcohol to give 9-cyanoacridine (166). Examination of the experimental conditions reveals that the cyanide ion, a rather unreactive nucleophile, requires activation of the heterocycle by quaternization of the nitrogen atom. With the more reactive acridine system such activation is unnecessary.

D. FREE-RADICAL SUBSTITUTION

Admittedly much less is known about the intricacies of free-radical attack (267). However, such processes seem to be involved in surface reactions (catalytic hydrogenation and metal reductions), in reactions at very high temperatures (vapor-phase bromination at 500°C.), and in reactions involving metals or radical sources (sodium metal or peroxides).

1. Phenylation

If the polarizability of a position is important, the alpha and the gamma positions should be preferred in radical processes (273). Experiment partially confirms this. When pyridine is phenylated by radicals from benzoyl peroxide or basic benzenediazonium salts (123), all three phenylpyridines are isolated but predominantly the alpha isomer. The reactivity of the phenyl radical may cause a tendency toward random substitution.

2. Methylation

Recently, Levy and Szwarc (170) carried out a quantitative study of the interaction between aromatic systems and methyl radicals obtained from the decomposition of acetyl peroxide. No attempt was made to determine the orientation of the methyl groups in the products. Instead, the aromatic systems were assigned relative reactivities towards methyl radicals with benzene taken as

TABLE 2

Relative reactivities of aromatic systems toward methyl radicals (benzene taken as 1)

Carbocycle	Reactivity Index	Heterocycle	Reactivity Index
Naphthalene	22	Pyridine	3
Phenanthrene	27	Quinoline	29
Chrysene	58	Isoquinoline	30
Pyrene	125	Acridine	430
Anthracene	820		

unity. The values given in table 2 were obtained. In general, the aza-aromatic heterocycle is slightly more reactive than its parent carbocycle, but acridine is anomalous in this respect. It was observed that there was a linear relation between the logarithm of the methyl affinities and the singlet-triplet excitation energies of the aromatic systems.

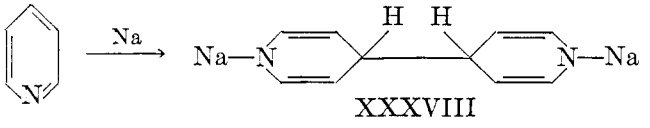
3. Reduction

This discussion embraces those reductions involving a metal coupled with an acid or a base. Modern opinion considers as fiction the importance of "nascent" hydrogen in such reductions. Burton and Ingold (51) have pictured such reductions as occurring on the metal surface as free-radical or nucleophilic transfer of electrons to the pi cloud of the electrophilic molecule. With nitrogen heterocycles the electron-receptive centers would be the alpha and gamma positions. The anion formed will accept protons from the solvent at the position of highest charge density. The pyridinoid ring, once partially disrupted in this manner, tends to becompletely reduced. For an explanation of such nonthermodynamic reductions, the discussion of Hammond (121) should be read.

Sodium and alcohol, and tin and hydrochloric acid, form piperidine, 1,2,3,4-tetrahydroquinoline, and 1,2,3,4-tetrahydroisoquinoline from the respective heterocycles (20, 152, 169). Acridine and phenanthridine are reduced to 9,10-dihydroacridan (118) and 5,6-dihydrophenanthridine (135), respectively.

4. Coupling

The use of active metals as reducing agents for these heterocycles has led frequently to bimolecular reduction. In the aldehyde analogy of Bergstrom this is equivalent to the pinacol reduction. The reaction occurs with pyridine (91), quinoline (271), acridine (227), and derivatives of isoquinoline (77), but it has not been reported for phenanthridine. At room temperature pyridine seems to couple mainly through the gamma positions (XXXVIII) and to a lesser extent through the alpha positions.

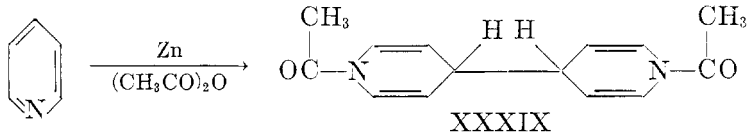


XXXVIII

Presumably such coupling occurs on the metal surface by free radical processes. At higher temperatures 2,3′, 3,3′, and 3,4′ coupling products are also formed,

besides polypyridines (236). The behavior of quinoline is different, as it forms mainly the 2,3′ coupling product (271). Acridine yields 9,9′-biacridine (227).

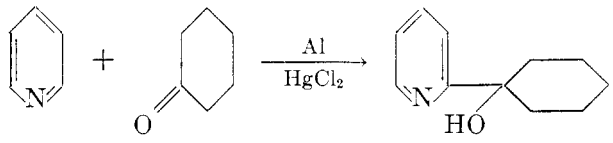
An interesting reaction discovered by Dimroth (84) and extended by Wibaut and Arens (273) is the reductive coupling of pyridine with zinc and acetic anhydride (XXXIX):



XXXIX

The conditions suggest that the acetylpyridinium ions are reduced on the zinc surface by a simultaneous two-electron transfer, analogous to the pinacol reduction.

Recent work (175) has led to a mixed pinacol reduction with pyridine and aliphatic ketones. The predominant product is the 2-isomer (XL), although the amount of the 4-isomer is sometimes significant (251).



XL

5. High-temperature reactions

Reactions occurring under stringent conditions of heat and pressure tend toward radical processes. It has been mentioned that vapor-phase bromination (129, 277–279) and coupling indicate that free-radical processes are operative.

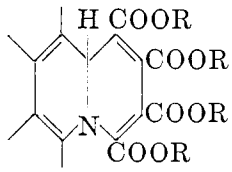
E. ADDITION REACTIONS

1. Hydrogenation

Catalytic hydrogenation of these nitrogen bases may occur selectively in the pyridinoid ring. For example, Raney nickel reduction of pyridine (3), quinoline (2), and isoquinoline (108) leads to piperidine, 1,2,3,4-tetrahydroquinoline, and 1,2,3,4-tetrahydroisoquinoline, respectively. Under these conditions acridine yields acridan (7) and phenanthridine forms 5,6-dihydrophenanthridine (135). With platinum and glacial acetic acid the aza-aromatic heterocycles tend to be completely reduced (235). The greater tendency of the pyridinoid ring to reduction may be attributed to its greater electrophilicity when adsorbed on the metal surface.

2. Reaction with dialkyl acetylenedicarboxylate

A rather peculiar reaction is undergone by dialkyl acetylenedicarboxylate and pyridine (79), quinoline (78), isoquinoline (80), or phenanthridine (82). Although several labile adducts have been isolated, the accepted structure of the stable adduct is XLI:



XLI

Like anthracene, acridine undergoes a normal Diels–Alder reaction because no alpha position is available (81). The mechanisms of these reactions are not clear, but it is possible that radical processes determine preference for the alpha and gamma positions.

3. Nitrogen complexes

Acceptance of the unshared sp^2 electrons on the hetero atom by an atom or cation tends to increase the effective electronegativity of the nitrogen. The resultant effect on the charge density has been considered previously (Section IV,A,E).

a. *N*-Oxides

The action of per acids on these nitrogen heterocycles leads to the formation of *N*-oxides. Careful studies on the ease of formation have not been made, but the action of hydrogen peroxide in acetic acid suggests that phenanthridine may be more difficult to oxidize than quinoline or pyridine (204). In the former case phenanthridone is formed as a by-product (189). This increased resistance may be due to the lower basicity of phenanthridine.

b. Quaternization

The reaction with alkyl halides or dialkyl sulfates occurs with a notable variation in facility. Methyl iodide reacts readily with pyridine, quinoline, and isoquinoline, but acridine and phenanthridine require heating in hot nitrobenzene or benzene for quaternization. As the calculated electron density on the nitrogen increases from pyridine to acridine, one would expect acridine to be more reactive than pyridine. Parallel studies with the quaternization of tertiary alkyl amines show that there is a marked dependence of activation energy on the basicity of the amine (92). The lowered reactivity of phenanthridine can be due to its weak basicity, but not that of acridine (table 3).

TABLE 3

pK_a values for heterocyclic bases at 20°C.

Base	pK_a IN H_2O	pK_a IN 50% ETHANOL
Pyridine	5.23	
Isoquinoline	5.14	
Quinoline	4.94	
Acridine	5.60	4.11
Phenanthridine		3.30

TABLE 4

pK_a values of diaza-aromatic heterocycles at 25°C.

Base	pK_a	Base	pK_a
Quinazoline	3.51	Pyrimidine	1.30
Phthalazine	3.47	Phenazine	1.23
Cinnoline	2.70	Quinoxaline	0.8
Pyridazine	2.33	Pyrazine	0.60

c. Salt formation

The unshared electron pair on the nitrogen can accept a wide variety of Lewis acids, ranging from protons to aluminum chloride. The basicity of these heterocycles toward protons has been of considerable theoretical and physiological interest. Expressed in terms of pK_a for the equilibrium,

$$B: + H^{\oplus} \rightleftarrows BH^{\oplus}$$

$$K_a = \frac{[B:]\,[H^{\oplus}]}{[BH^{\oplus}]}$$

the values are given in table 3 (6). The decrease in basicity in going from pyridine to phenanthridine is opposed to predictions based on charge densities (177). Dyatkina (86) suggests that a change in the carbon–nitrogen resonance integral may be the source of this discrepancy, and Brown and Dewar (45) feel that second-order terms involving the self-polarizability of the nitrogen atom may be important.

The pK_a values of certain diaza-aromatic heterocycles are presented in table 4 (6). Introduction of a second nitrogen atom greatly reduces the base strength.

F. RING STABILITY

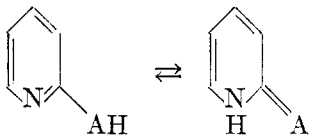
The thermal stability of these nitrogen heterocycles is reflected in their recovery from the pyrolytic products of soft coal. Both acridine and phenanthridine distil unchanged at around 350°C.

Oxidation of these bases with alkaline potassium permanganate indicates the superior stability of the pyridinoid ring. The resistance of pyridine to oxidation makes it a suitable solvent for oxidation reactions. With quinoline the benzenoid ring is preferentially destroyed, yielding 2,3-pyridinedicarboxylic acid. Isoquinoline is also attacked in the benzenoid ring, leading to 3,4-pyridinedicarboxylic acid. Degradation studies of substituted phenanthridines have yielded phthalic acid (263), but the products from phenanthridine itself have not been reported. The general preservation of the pyridinoid ring may be due to its diminished polarizability. The nature of the attack is somewhat dependent upon the oxidizing agent employed, however.

G. COMPARISON OF CHARACTERISTIC DERIVATIVES

The characteristic behavior of the alpha and gamma derivatives of these heterocycles is a direct consequence of the lowered π-electron density at these

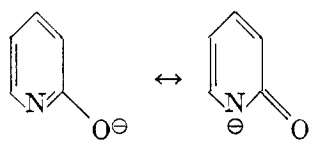
positions and hence warrants careful examination. Experimental evidence in the case of the amino, methyl, and hydroxyl derivatives has suggested the possibility of tautomerism (XLII, XLIII).



XLII XLIII

A = NH, O, CH_2.

Many researchers have attempted to determine chemically which tautomer is more descriptive of the real state of the molecule. Thus, workers have methylated 2-hydroxypyridine with dimethyl sulfate in basic solution and also with diazomethane. Since the first reagent gave *N*-methyl-2-pyridone and the second 2-methoxypyridine, it was felt that tautomer XLIII is more important in basic solution and that tautomer XLII predominates in neutral solution (186, 218). Such evidence is of no validity, since in basic solution one is probably dealing with the anion (XLIV):



XLIV

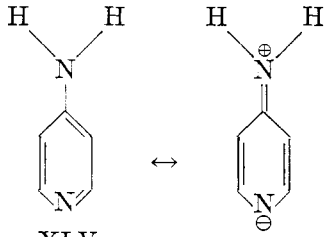
The point at which methylation will occur then depends upon how much the anion is deformed in the course of reaction. If little deformation is necessary, the site of highest charge density will be methylated. If much deformation is necessary, the site causing the lesser loss of delocalization energy will be attacked. These considerations stress the unreliability of using chemical methods only to study tautomeric systems.

1. Amino derivatives

The position of the possible tautomeric equilibrium between the α- or γ-amino tautomer and the imino form has been studied by both chemical and physical means. Besides alkylation experiments similar to those carried out with 2-hydroxypyridine, the behavior of these amines upon diazotization, hydrolysis, and attempted Schiff base formation has been adduced as proof for the existence of one or the other tautomer. All this chemical evidence is subject to objection, as a chemical reaction perturbs the system a great deal. If one tautomer reacts more readily, the existence of a mobile equilibrium will allow the more reactive form to be replenished at the expense of the less reactive one.

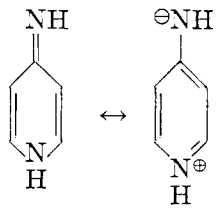
Even the physical methods of studying such tautomerism yield ambiguous results in certain instances. Leis and Curran (167) measured the dipole moment of 4-aminopyridine and compared it with that of aniline and pyridine. They ruled

out the imino form XLVI in favor of the amino form XLV, as they thought that the former could not account for the high dipole moment.



XLV

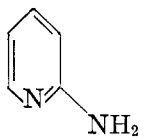
Angyal and Angyal (12) argued, however, that this conclusion did not follow of necessity, as the imino form could have significant dipolar character (XLVI).



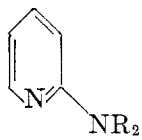
XLVI

That imines can have high dipole moments was demonstrated by the value obtained from 1,4-dihydro-4-imino-1-methylquinoline (5.1 D), as compared with that of 4-aminoquinoline (4.4 D).

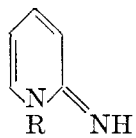
The observation of the shifts obtained in the ultraviolet spectra of aminopyridines, aminoquinolines, and aminoisoquinolines in acidic and basic solutions led Steck and Ewing (239) to state that the α- and γ-amino derivatives existed in the imino form. This conclusion was based upon the assumption that nuclear protonation should cause a bathochromic shift, whereas protonation of the amino group should cause a hypsochromic shift in the ultraviolet spectra. Since there was little appreciable bathochromic shift of the spectra of the amines in acid solution, it was concluded that the hetero nitrogen was largely saturated. The pitfalls of conclusions from spectral shifts are discussed in a careful fashion by Angyal and Angyal (12). A more reliable criterion is that of the similarity of the spectra of the amines to that of *N*-methylated derivatives. Such a comparison was carried out by Anderson and Seeger (10) with the 2- and 4-aminopyridines. The close similarity of the spectrum of 2-aminopyridine (XLVII) to that of 2-methylamino- and 2-dimethylaminopyridines (XLVIII) and its dissimilarity to that of *N*-methylpyridonimine (XLIX) indicate that 2-aminopyridine is in the amino form.



XLVII

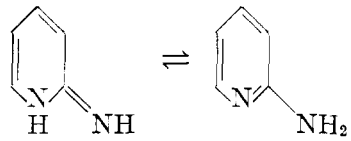


XLVIII



XLIX

Moreover, no evidence could be obtained for any tautomeric equilibrium. The same conclusions were reached with 4-aminopyridine. Angyal and Angyal (12) calculated that the equilibrium constant for the tautomeric system (L, LI)



L LI

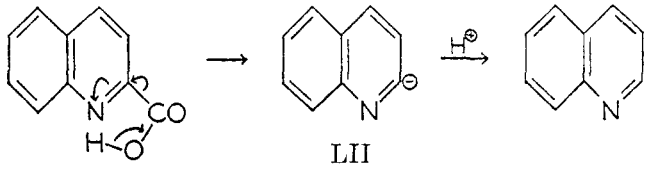
is

$$K_{taut} = \frac{[A]}{[I]} = \frac{K_a \text{ (amine)}}{K_a \text{ (imine)}} = 10^3$$

The loss in aromatic resonance energy in going from the amine to the imine was 4.5 kcal. per mole. K_a (imine) was estimated by using the K_a of *N*-methylpyridonimine. From examination of existing evidence these authors concluded that the amino form was also the more stable form for the corresponding amines of quinoline, isoquinoline, acridine, and phenanthridine.

2. Carboxylic acids

The characteristic tendency of α- and γ-carboxylic acids to undergo thermal decarboxylation has been compared with the instability of α-keto acids. The mechanistic studies of Hammick (44, 87) on the decarboxylation of 2-quinolinecarboxylic acid strongly support the following mechanism:



LII

That an intermediate anion (LII) is involved is indicated by the products isolated when carbonyl compounds, quinoline, or *m*-dinitrobenzene is present during decarboxylation. The long lifetime of this anion is due to the stabilizing effect of the diminished charge density at the alpha position. The stabilization is probably not through resonance delocalization, as the anion is in an sp^2 orbital which is orthogonal to the pi cloud. More likely, it is a direct inductive effect along the sigma bonds toward the nitrogen.

Careful studies on the ease of decarboxylation of α- and γ-carboxylic acids have not been carried out. However, 2,3-pyridinedicarboxylic acid decomposes around 230°C. into nicotinic acid; 2-quinolinecarboxylic acid undergoes decarboxylation above its melting point (158°C.); and 1-isoquinolinecarboxylic acid decomposes at 161°C. Simply heating 6-phenanthridinecarboxylic acid to 150°C. brings about smooth conversion to phenanthridine (223). γ-Carboxylic

acids usually require a higher temperature for decarboxylation. 9-Acridinecarboxylic acid yields acridine when heated at 295°C. for a short time (166).

3. Dihydro derivatives

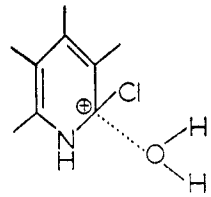
Reduction of heterocyclic bases or the addition of organometallic reagents to the pyridinoid ring leads to dihydro derivatives. As one passes up the series pyridine < quinoline ≃ isoquinoline < acridine ≃ phenanthridine, the stability of the dihydro derivative shows a definite increase. With pyridine it appears that 1,4-dihydro derivatives may be more stable chemically than 1,2-dihydro compounds. The former are the products isolated from the Hantzsch pyridine synthesis (34) and react sluggishly with silver nitrate (202). 1,2-Dihydropyridines are obtained from the alkylation of pyridine with alkyllithium compounds (285) and react readily with silver nitrate (202).

These dihydropyridines together with those of quinoline and isoquinoline are readily oxidized in air and are difficult to isolate in pure condition. On the other hand, acridine (118) and phenanthridine (135) can be converted to fairly stable dihydro products. The increase in the stability of dihydro derivatives of polycyclic systems may be attributed to the decrease in the localization energies of the C=N bond in the parent heterocycle.

4. Halogen derivatives

Halogens situated alpha and gamma to the hetero nitrogen are prone to nucleophilic displacement by such reagents as water, alcohols, phenols, sulfides, and amines (49). Although Chapman and his group (35, 59) have compared halonitrobenzenes with halopyridines by kinetic studies, only qualitative comparisons have been made among halo derivatives of aza-aromatic heterocycles. Bradlow and Vanderwerf (39) studied the hydrolysis of various halopyridines and haloquinolines by heating them with dilute hydrochloric acid. α-Fluoropyridine underwent hydrolysis, whereas the corresponding chloro and bromo derivatives did not. Since 2-chloroquinoline could also be hydrolyzed, it was more reactive than the corresponding pyridine compound. The enhanced reactivity of γ-halopyridines over that of α-halopyridines was attributed to the stability of the tetrahedral transition state (compare Section III,D). By Waters' quinoid hypothesis (268) such a para structure (gamma position) would be more stable than the ortho form (alpha position).

Comparison of the halo derivatives of pyridine, quinoline, isoquinoline, phenanthridine, and acridine shows that the ease of solvolysis increases in the same order. Strikingly enough, 9-chloroacridines and 6-chlorophenanthridines are so prone to solvolysis under neutral or acidic conditions that attempted recrystallization from ethanol leads to extensive conversion to acridones and phenanthridones, respectively. Halo derivatives of diaza- and triaza-aromatic heterocycles show an even greater reactivity. The presence of additional hetero nitrogens further decreases the electron density at the alpha positions (177). Since water and ethanol are nucleophiles of moderate reactivity, it is reasonable to represent the transition state as close to the tetrahedral model (LIII).



LIII

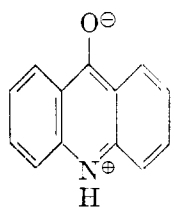
The increased reactivity of halophenanthridines and haloacridines can then be related to the lower localization energies of the alpha and gamma carbon atoms, respectively.

5. Hydroxyl derivatives

The nature of the tautomeric equilibrium for hydroxyl compounds has been given careful study by many workers. 2-Hydroxypyridine can undergo *O*- or *N*-methylation depending upon the conditions. Ultraviolet absorption studies of 2-hydroxypyridine in acidic and basic solutions have been compared with those of *N*-methylpyridone and 2-methoxypyridine, respectively. The resemblance of spectral curves seems to indicate that in neutral or acid solution 2-hydroxypyridine is predominantly in the pyridone form. Similar data were obtained from 4-hydroxypyridine (238).

The 2- and 4-hydroxyquinolines do not show appreciable spectral shifts in solutions of any pH. It was concluded from this that the quinolone tautomer is the more stable form (93). As with the amine-imine tautomeric system, more satisfactory evidence lies in the spectral similarities of carbostyril and *N*-methylquinolone (172).

The infrared spectra of acridone and phenanthridone have pronounced carbonyl bands at 6.1 μ and imino bands at 3.1 μ. These compounds therefore seem to be cyclic amides. Moreover, only *N*-methylation has been accomplished. Albert has explained the extreme stability of acridone in terms of "dipolar resonance" contribution (5) (LIV):

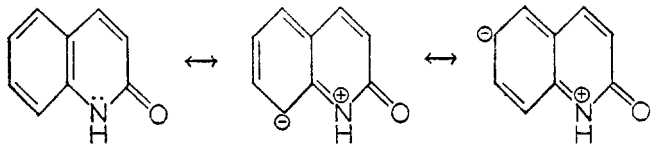


LIV

A molecular orbital approach would simply take cognizance of the pi-pi interactions possible between the oxygen and C_9 and the nitrogen and the aromatic pi cloud. Thus, it seems that the ketonic tautomer becomes progressively more stable as one goes from pyridones to acridone (16).

The substitutional chemistry of these derivatives is interesting, since they are prone to electrophilic attack in the benzenoid ring ortho and para to the NH

group. This is in accord with a neutral group having unshared electrons adjacent to the benzene ring (137) (LV).

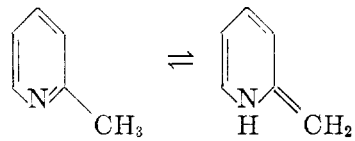


LV

Thus, carbostyril is nitrated in the 6- and 8-positions (105); acridone is sulfonated (122) and nitrated in the 2- and 4-positions (162, 163); and phenanthridone is nitrated in the 2- and 4-positions (57, 203) and brominated, chlorinated, and iodinated in the 2-position (112, 199).

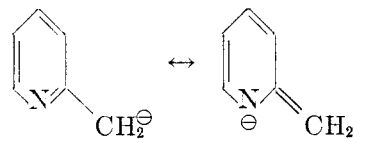
6. Methyl derivatives

Derivatives having methyl groups alpha and gamma to the nitrogen may be considered as methyl ketone ethers in the ammonia analogy of Bergstrom (31). The chemical reactions of such methyl derivatives include halogenation, oxidation, alkylation, and condensation with carbonyl and nitroso reagents (89). The lability of the hydrogen atoms has been explained in terms of a possible tautomeric equilibrium (LVI, LVII).

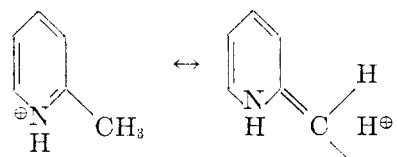


LVI LVII

However, infrared data do not support the presence of much of the imino form (58). Either the anion (LVIII) or the cation (LIX), formed by the abstraction or addition of a proton, respectively, is stabilized by resonance. This stabilization of the charged species should increase both the acidity of the methyl hydrogens and the basicity of the hetero nitrogen.



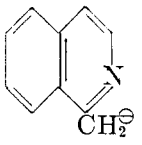
LVIII



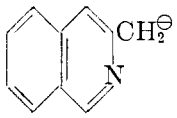
LIX

Hence the behavior of the α- and γ-methyl derivatives is markedly dependent upon the basicity or acidity of the system. As stressed previously, the subsequent chemical reactions will not depend so much upon which tautomer predominates, as upon the electronic demands of the reagent used. Chemical behavior tends to support this interpretation.

In rationalizing the superior reactivity of 1-methylisoquinoline over that of 3-methylisoquinoline Gensler (108) points out that the anion (LX) formed in base-catalyzed condensations has a greater stability due to resonance delocalization than anion LXI.



LX

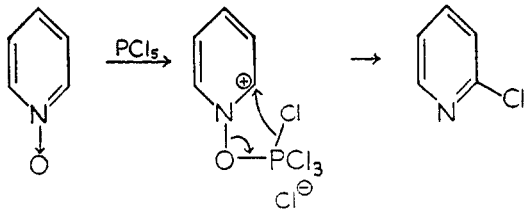


LXI

Consequently, if the base-catalyzed condensations of these methyl compounds with aldehydes depend on the presence of the anion, Gensler's argument could be extended to aza-aromatic heterocycles in general. If one counts the resonance structures stabilizing the anion and assumes that the larger the number, the more stable the anion, one obtains a series of methyl anions of increasing stability. Thus, as one passes up the series 2- and 4-methylpyridines < 2-methylquinoline $\simeq$ 4-methylquinoline < 1-methylisoquinoline < 6-methylphenanthridine $\simeq$ 9-methylacridine, the anion should become increasingly more stable. One would expect both the acidity of the methyl hydrogens and the ease of base-catalyzed condensation to increase in this order.

7. *N-Oxides*

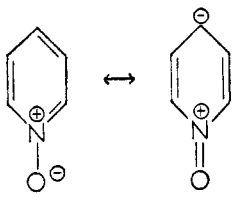
The enhanced reactivity of the alpha and gamma positions in *N*-complexes has already been discussed. The characteristic reaction of *N*-oxides will be considered here. Interactions with such nucleophilic reagents as phosphorus(V) chloride (LXII), potassium cyanide, and Grignard reagents lead to removal of the oxygen and attack at the alpha or gamma position (90).



LXII

Of great theoretical interest has been the behavior of pyridine-1-oxide with nitric acid. Contrary to expectations this reaction leads to an excellent yield of 4-nitropyridine-1-oxide (204). Both the facility and orientation of this nitration are surprising, as the orientation would suggest a nucleophilic attack by nitric

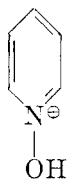
acid. However, a valence-bond description of pyridine-1-oxide shows that the unshared electron pairs on the oxygen can overlap with the pi cloud (LXIII, LXIV).



LXIII LXIV

Dipole-moment data are in accord with such charge separation (174). Nitration can thus occur electrophilically at the 4-position, which has an enhanced charge density and polarizability.

Recently Mosher and Welch (200) have attempted the sulfonation and bromination of pyridine-1-oxide. Sulfonation occurred at the 3-position and no bromination could be effected. In fuming sulfuric acid the oxygen is probably extensively protonated (LXV),



LXV

and thus the activating influence of the oxygen is diminished. Consequently, orientation would again resemble that of pyridine. Recently, the mercuration of pyridine-1-oxide at the 4-position was reported (254).

The behavior of acridine-10-oxide and phenanthridine-5-oxide toward nucleophilic reagents parallels that of other oxides. Attack occurs at the free gamma or alpha position, respectively.

VI. Tables of Phenanthridine Derivatives

Tables 5 to 11 attempt to include those phenanthridine derivatives reported from 1884 to 1955, with the exception of those previously compiled by Theobald and Schofield (249). It was considered undesirable to list every characterized phenanthridine derivative however, as a multitude of quaternary alkyl halide salts and urethans have been reported. Instead, only the basic derivative is listed and the quaternary salts obtained from it can be found by referring to the accompanying references. If the fundamental system has been characterized only as a quaternary salt derivative, this fact is indicated after the melting point. For example, 8-amino-6-*p*-dimethylaminostyrylphenanthridine has been isolated and analyzed only as its 8-acetylamino 5-methiodide; hence this quaternary salt has been listed as 8-amino-6-*p*-dimethylaminostyrylphenanthridine, m.p. 270–271°C. (8-acetylamino CH_3I).

TABLE 5

Monosubstituted phenanthridine derivatives

Substituent*	Melting Point	References
	°C.	
Phenanthridine	105–106	(205, 247, 248)
1-Amino	115.5–117	(57)
2-Amino	152–153	(57)
3-Amino	144–145	(57)
6-Amino	195.5	(196)
7-Amino	208–210	(57)
8-Amino	203–204	(13, 57)
9-Amino	194–195	(13, 57)
10-Amino	143.5–144.5	(57)
6-*p*-Aminobenzyl	115–120 (CH_3Cl)	(56)
6-*o*-Aminophenyl	168.5	(195)
6-*m*-Aminophenyl	159–161	(195)
6-*p*-Aminophenyl	197–199	(195)
6-[5′,6′-Benzo-2′-(*o*-chlorophenyl)-4′-quinolyl]	260	(182)
6-Benzoyl	152	(223)
6-Benzyl	111–112	(13, 67)
6-Benzylamino	147–148 (sulfonyl)	(99)
6-Benzylaminomethyl	201–203 (HCl)	(99)
2-Bromo	162–163	(111)
6-(5′-Bromo-2′-methoxyphenyl)	148	(182)
6-Phenanthridinebutyric acid	158	(223)
6-Phenanthridine-α-carbethoxyacrylic acid	91 (ethyl ester)	(223)
6-Phenanthridinecarboxaldehyde	141–141.5	(54, 223)
6-Phenanthridinecarboxylic acid	155 (d.)	(223, 256)
6-*o*-Carboxyphenyl	268–270	(147)
6-Chloromethyl	129–131	(99)
6-*o*-Chlorophenyl	125	(182)
6-*m*-Chlorophenyl	137–138	(182)
6-*p*-Chlorophenyl	157.5	(182)
6-Cyanomethyl	105–108	(99)
6-*p*-Cyanostyryl	200–201	(96)
6-Cyclohexenyl	205	(70)
6-(3′,5′-Diaminophenyl)	241 (CH_3Cl)	(258)
6-Diethylaminomethyl	72.5–73	(169)
6-(2′-Diethylaminoethylamino)	238–243 (2HCl)	(256)
6-(4′-Diethylamino-1′-methylbutylamino)	192–193 (dipicrate)	(257)
6-(1′,6′-Dihydro-1′-methyl-6′-oxo-3′-pyridyl)	211–212	(212)
6-(2′,2′-Dihydroxyisopropyl)	129.5	(256)
6-(2′-Diisobutylaminoethylamino)	142–144 (2HCl)	(256)
6-(2′,5′-Dimethoxyphenyl)	163	(182)
6-(3′,4′-Dimethoxyphenyl)	169	(182)
6-Dimethylamino	61.5	(197)
6-(2′-Dimethylaminoethoxymethyl)	190–191 (2HCl)	(99)
6-(2′-Dimethylaminoethyl)	152–154 (HCl)	(99)
6-(2′-Dimethylaminoethylamino)	251–254 (2HCl)	(99)
6-(2′-Dimethylaminoethylaminomethyl)	240 (3HCl)	(99)
6-(*N*,*N*-2′-Dimethylaminoethylbenzylamino)	350–356 (2HCl)	(99)
6-Dimethylaminomethyl	86–87	(169)
6-*p*-Dimethylaminostyryl	236.5–237.5 (CH_3I)	(211)
6-Diphenacylmethyl	157	(223)
2-Ethoxy	95–97	(188)
6-Ethoxy	60	(182)
6-(4′-Ethoxy-3′-methoxyphenyl)	118–120	(182)
6-*p*-Ethoxyphenyl	149–150	(182)
1-Ethyl	233 (picrate)	(151)
2-Ethyl	62–63.5	(151)
3-Ethyl	216 (picrate)	(151)
4-Ethyl	231 (picrate)	(151)
6-Heptyl	50	(70)

TABLE 5—*Concluded*

Substituent*	Melting Point	References
	°C.	
3-Hydroxy	245	(13)
4-Hydroxy	186–188	(33)
8-Hydroxy	281–282	(13)
9-Hydroxy	271–272	(13, 88)
6-(1′-Hydroxy-2′-nitroethyl)	132	(223)
6-*m*-Hydroxyphenyl	225–226	(182)
6-*p*-Hydroxyphenyl	237	(182)
6-*p*-Isopropoxyphenyl	118–119	(182)
6-(4′-Isopropoxy-3′-methoxyphenyl)	137–139	(182)
6-Isopropylaminomethyl	209–210 (2HCl)	(99)
3-Methoxy	57–58	(13)
4-Methoxy	140–142	(33)
8-Methoxy	90	(13)
6-*p*-Methoxybenzyl	125–127	(67)
6-*o*-Methoxyphenyl	127	(182)
6-*m*-Methoxyphenyl	128–129	(182)
6-*p*-Methoxyphenyl	147.5–148	(70, 182)
6-(3′-Methoxy-4′-propoxyphenyl)	128–129	(182)
2-Methyl	89–89.5	(13, 145)
3-Methyl	81	(13, 223)
4-Methyl	95	(145)
6-Methyl	85	(13, 211)
8-Methyl	87.5–88	(13)
6-Methylamino	187	(197)
6-(3′,4′-Methylenedioxyphenyl)	113	(182)
6-(4′-Methyl-1′-piperazylmethyl)	222–223	(9)
6-Methylthio	70–71	(210)
6-*p*-Methylsulfonylphenyl	238	(70)
6-[2′-(4″-Morpholinyl)ethylamino]	258–260 (2HCl)	(99)
6-[2′-(4″-Morpholinyl)ethylaminoethyl]	201–203 (2HCl)	(99)
6-(4′-Morpholinylmethyl)	95	(99, 182)
6-(1′-Naphthyl)	123.5	(214)
1-Nitro	160.5–161.5	(57)
2-Nitro	266–267	(13, 57, 223)
3-Nitro	196–197	(13, 57)
4-Nitro	191–192	(57)
8-Nitro	180	(13, 223)
9-Nitro	194	(13)
10-Nitro	166–166.5	(57)
6-*p*-Nitrobenzyl	168–169	(56)
6-(5′-Nitro-2′-furyl)	187	(182)
6-Nonyl	47.5–48	(70)
6-Phenoxymethyl	142	(223)
6-(2′-Phenyl-4′-quinolyl)	183–184	(182)
6-(1′-Piperidylethylamino)	265–270 (2HCl)	(256)
6-(1′-Piperidylethyl)	173–176 (2HCl)	(99)
6-(1′-Piperidylmethyl)	98–99	(169, 197)
6-*p*-Propoxyphenyl	116–117	(182)
6-(2′-Pyridyl)	133	(70)
6-(4′-Pyridyl)	160	(182)
6-Phenanthridinepyruvic acid	183–184 (ethyl ester)	(168)
6-(2′-Thienyl)	215 (picrate)	(53)
6-*m*-Tolyl	98–99	(182)
6-*p*-Tolyl	108	(115, 182)
6-Tribromomethyl	181–182	(43)
6-(2′,4′,6′-Trinitroanilino)		(194)
6-Phenanthridinevaleric acid	108–115	(223)

* In a few instances the complete name of the compound is given.

TABLE 6

Disubstituted phenanthridine derivatives

Substituent*	Melting Point	References
	°C.	
3-Alloxy-6-methyl	68–69	(190)
8-Amino-6-*p*-aminobenzoyl	217 (CH_3Br)	(55)
8-Amino-6-*p*-aminobenzyl	205 (CH_3Cl)	(56)
2-Amino-6-*m*-aminophenyl	201	(182)
2-Amino-6-*p*-aminophenyl	233	(197)
3-Amino-6-*p*-aminophenyl	257 (CH_3Cl)	(56)
8-Amino-6-*o*-aminophenyl	158 (CH_3Cl)	(260)
8-Amino-6-*m*-aminophenyl	240 (CH_3I)	(258)
8-Amino-6-*p*-aminophenyl	208–210	(24, 182)
9-Amino-6-*p*-aminophenyl	>300 (CH_3Cl)	(56)
2-Aminophenanthridine-6-carboxaldehyde	215	(54)
3-Aminophenanthridine-6-carboxaldehyde	198–199 (urethan)	(54)
7-Aminophenanthridine-6-carboxaldehyde	221–223 (urethan)	(57)
8-Aminophenanthridine-6-carboxaldehyde	234–235	(54)
9-Aminophenanthridine-6-carboxaldehyde	201–203 (urethan)	(57)
2-Aminophenanthridine-6-carboxylic acid	190	(57)
3-Aminophenanthridine-6-carboxylic acid	183	(57)
7-Aminophenanthridine-6-carboxylic acid	105–110 (urethan)	(57)
8-Aminophenanthridine-6-carboxylic acid	202	(57)
9-Aminophenanthridine-6-carboxylic acid	235	(57)
2-Amino-6-*p*-dimethylaminostyryl	267.5–268.5 (2-acetylamino CH_3I)	(211)
8-Amino-6-*p*-dimethylaminostyryl	270–271 (8-acetylamino CH_3I)	(211)
2-Amino-6-methyl	152	(196)
3-Amino-6-methyl	174–175	(56)
4-Amino-6-methyl	111–112	(240)
6-Amino-2-methyl	170–171	(131)
6-Amino-4-methyl	116–117	(131)
7-Amino-6-methyl	134.5	(56)
8-Amino-6-methyl	232.5–233.5	(211)
9-Amino-6-methyl	196.5	(56)
8-Amino-6-*p*-nitrobenzoyl	280	(55)
8-Amino-6-*p*-nitrobenzyl	246–247	(56)
3-Amino-6-*p*-nitrophenyl	259	(56)
7-Amino-6-*p*-nitrophenyl	180	(56)
8-Amino-6-*o*-nitrophenyl	230	(260)
8-Amino-6-*p*-nitrophenyl	279	(260)
9-Amino-6-*p*-nitrophenyl	260	(56)
10-Amino-6-*p*-nitrophenyl	221–222	(95)
2-Amino-6-phenyl	248	(182)
8-Amino-6-phenyl	168	(182)
10-Amino-6-phenyl	192–193	(95)
2-Amino-6-(2′-phenyl-4′-quinolyl)	228 ($2CH_3I$)	(182)
2-Amino-6-(3′-pyridyl)	165–166	(212)
8-Amino-6-(3′-pyridyl)	227–229	(212)
6-*m*-Aminophenyl-8-hydroxy	275–277 (CH_3Cl)	(67)
6-*m*-Aminophenyl-8-methoxy	236–238 (CH_3Cl)	(67)
6-*m*-Aminophenyl-2-nitro	185 (urethan)	(261)
6-*m*-Aminophenyl-8-propoxy	206 (CH_3Cl)	(67)
6-*p*-Aminobenzyl-8-hydroxy	252 (CH_3Cl)	(67)
6-*p*-Aminobenzyl-8-methoxy	241 (CH_3Cl)	(67)
6-*p*-Aminophenyl-8-benzyloxy	184 (CH_3Cl)	(67)
6-*p*-Aminophenyl-8-butoxy	190 (CH_3Cl)	(67)
6-*p*-Aminophenyl-8-ethoxy	225–226 (CH_3Cl)	(67)
6-*p*-Aminophenyl-3-hydroxy	297–298 (CH_3Cl)	(67)
6-*p*-Aminophenyl-8-hydroxy	269–271 (CH_3Cl)	(67)
6-*p*-Aminophenyl-8-isopropoxy	174–175 (CH_3Cl)	(67)
6-*p*-Aminophenyl-3-methoxy	235 (CH_3Cl)	(67)
6-*p*-Aminophenyl-8-methoxy	253 (CH_3Cl)	(67)
6-*p*-Aminophenyl-2-nitro	297	(261, 262)
6-*p*-Aminophenyl-8-propoxy	215 (CH_3Cl)	(67)
8-Benzyloxy-6-methyl	208–209	(67)
8-Benzyloxy-6-*p*-nitrophenyl	180	(67)
2-Bromo-6-*p*-bromophenyl	234–235	(24)

TABLE 6—*Concluded*

Substituent*	Melting Point	References
	°C.	
2-Bromo-6-(2′-diethylaminoethylamino)	— (2HCl)	(257)
2-Bromo-6-(4′-diethylamino-1′-methylbutylamino)	217–218 (dipicrate)	(257)
2-Bromo-6-methyl	128–129	(24)
8-Butoxy-6-*p*-nitrophenyl	173	(67)
6-Chloro-2-ethoxy	160–162	(188)
6-Chloro-8-methoxy	107	(257)
4-Chloro-6-methyl	113–114	(240)
x-Chloro-6-methyl	91.5–92.5	(182)
6-Chloro-2-nitro	253–254	(203)
6-Chloro-3-nitro	209	(13)
6-Chloro-4-nitro	178–179	(203)
6-Chloro-8-nitro	207–208	(13, 203)
2-Chloro-6-phenyl	141–142	(182)
8-Chloro-6-phenyl	120	(182)
6-*p*-Chlorophenyl-8-hydroxy	244 (CH_3Cl)	(67)
6-*p*-Chlorophenyl-8-methoxy	157–158	(67)
6-*p*-Chlorophenyl-8-nitro	291	(70)
2-Cyano-6-*p*-cyanophenyl	340	(24)
8-Cyano-6-*p*-cyanophenyl	322–323	(24)
2-Cyano-6-methyl	202–203.5	(24)
6-(3′,5′-Diaminophenyl)-8-methoxy	232 (CH_3Cl)	(67)
6-(2′-Diethylaminoethylamino)-3-methoxy	207 (dipicrate)	(257)
4-(2′-Diethylaminoethylamino)-6-methyl	56–57	(240)
6-(1′,6′-Dihydro-1′-methyl-6′-oxo-3′-pyridyl)-2-nitro	304–305	(212)
6-(1′,6′-Dihydro-1′-methyl-6′-oxo-3′-pyridyl)-8-nitro	339–340	(213)
1,4-Dimethyl	76.5	(145)
2,4-Dimethyl	84.5	(145)
3,6-Dimethyl	104.5–105.5	(211)
6,9-Dimethyl	214 (picrate)	(38)
x,*y*-Dimethyl	241 (picrate)	(130)
2-Dimethylamino-6-methyl	146	(197)
6-(3′,5′-Dinitrophenyl)-8-methoxy	252–253	(67)
8-Ethoxy-6-*p*-nitrophenyl	233	(67)
8-Hydroxy-6-*p*-hydroxyphenyl	264 (CH_3Cl)	(67)
8-Hydroxy-3-iodo	235	(13)
3-Hydroxy-6-methyl	325–327	(190)
7-Hydroxy-6-methyl	>300 (HCl)	(56)
8-Hydroxy-6-methyl	298–300	(67)
8-Hydroxy-6-*m*-nitrophenyl	250	(67)
3-Hydroxy-6-*p*-nitrophenyl	330 (CH_3Cl)	(67)
7-Hydroxy-6-*p*-nitrophenyl	262–263	(56)
8-Hydroxy-6-*p*-nitrophenyl	275	(67)
9-Hydroxy-6-*p*-nitrophenyl	280–282	(56)
8-Hydroxy-6-phenyl	263 (CH_3Cl)	(67)
8-Isopropoxy-6-*p*-nitrophenyl	159–160	(67)
8-Methoxy-6-*p*-methoxyphenyl	94	(67)
3-Methoxy-6-methyl	72–73.5	(190)
8-Methoxy-6-methyl	57	(67)
8-Methoxy-6-*p*-nitrobenzyl	142	(67)
3-Methoxy-6-*p*-nitrophenyl	199	(67)
8-Methoxy-6-*m*-nitrophenyl	183–184	(67)
8-Methoxy-6-*p*-nitrophenyl	233–234	(67)
8-Methoxy-6-phenyl	216–217 (CH_3Cl)	(67)
6-*p*-Methoxyphenyl-8-nitro	232–233	(70)
3-Methyl-6-*p*-dimethylaminostyryl	240–240.5 (CH_3Cl)	(211)
6-Methyl-2-nitro	201	(223)
6-Methyl-4-nitro	167–167.5	(240)
6-Methyl-8-nitro	242–243	(203)
8,9-Methylenedioxy	181	(149)
6-*p*-Methylsulfonylphenyl-8-nitro	292	(70)
2-Nitrophenanthridine-6-carboxaldehyde	241–242	(54)
4-Nitrophenanthridine-6-carboxaldehyde	203–204	(57)
2-Nitrophenanthridine-6-carboxylic acid	265–266	(57)
4-Nitrophenanthridine-6-carboxylic acid	170	(57, 240)
2-Nitro-6-phenyl	228–229	(182)
2-Nitro-6-(2′-phenyl-4′-quinolyl)	>295	(182)
8-Nitro-6-(2′-phenyl-4′-quinolyl)	282	(182)
6-*m*-Nitrophenyl-8-propoxy	146	(67)
6-*p*-Nitrophenyl-8-propoxy	169	(67)

* In a few instances the complete name of the compound is given.

TABLE 7

Tri- and polysubstituted phenanthridine derivatives

Substituent*	Melting Point	References
	°C.	
4-Allyl-3-hydroxy-6-methyl	102–103	(190)
8-Amino-6-*p*-aminophenyl-2-bromo	265	(258)
3-Amino-6-*p*-aminophenyl-8-methoxy	>300 (6-acetylamino CH_3Cl)	(261)
6-Amino-2,4-dimethyl	142–143	(131)
6-Amino-3,8-dinitro	321–322	(4)
8-Amino-3-nitro-6-phenyl	227.5	(261)
6-*m*-Aminophenyl-3,8-diamino	221 (CH_3Cl)	(265)
6-*p*-Aminophenyl-3,8-diamino	246	(264)
6-*p*-Aminophenyl-3,8-dichloro	216 (CH_3Cl)	(173)
6-*p*-Aminophenyl-1,10-dimethyl	134	(223)
6-*p*-Aminophenyl-8-methoxy-3-nitro	221–223 (6-acetylamino)	(261)
6-Benzoyl-3,8-diamino	244	(55)
6-Benzyl-3,8-diamino	259 (bisurethan)	(264)
4-Carbomethoxy-8,9-methylenedioxy	149–151	(150)
2-Chloro-6-*p*-chlorophenyl-8-nitro	315	(70)
6-Chloro-3,8-dinitro	225	(4)
6-Cyclohexyl-3,8-diamino	233–234 (bisurethan)	(264)
3,8-Diaminophenanthridine-6-carboxaldehyde	270–275 (bisurethan)	(54)
3,8-Diamino-6-(5′,6′-dihydro-3′-pyranyl)	215–216 (bisurethan)	(264)
3,8-Diamino-6-*p*-methoxyphenyl	190–192 (bisurethan)	(264)
2,8-Diamino-6-methyl		(64)
3,8-Diamino-6-methyl	265.5	(260)
3,8-Diamino-6-(5′-nitro-2′-furyl)	286–288 (bisurethan)	(264)
3,8-Diamino-6-*m*-nitrophenyl	208.5–210.5 (bisurethan)	(265)
3,8-Diamino-6-*p*-nitrophenyl	247 (bisurethan)	(264)
2,8-Diamino-6-phenyl	194	(258)
3,8-Diamino-6-phenyl	198	(258)
3,8-Diamino-6-(3′-pyridyl)	262–264	(213)
3,8-Diamino-6-(2′-thienyl)	229–230 (bisurethan)	(264)
3,8-Dibromo-6-*p*-nitrophenyl	255	(173)
3,8-Dichloro-6-*p*-nitrophenyl	250	(173)
2,8-Dichloro-6-phenyl	193	(102)
3,8-Dicyano-6-phenyl	302	(173)
3,8-Bis(diethylamino)-6-phenyl	255 ($2CH_3I$)	(265)
6-(1′,6′-Dihydro-1′-methyl-6′-oxo-3′-pyridyl)-3,8-dinitro	>360	(213)
6-(2′,2′-Dihydroxyisopropyl)-2,3,8,9-tetramethoxy	214	(223)
1,10-Dimethyl-6-*p*-nitrophenyl	148	(223)
1,10-Dimethyl-6-phenyl	177 (picrate)	(223)
3,8-Dimethyl-6-phenyl	260–262 (CH_3I)	(264)
3,8-Dinitro-6-*m*-nitrophenyl	305–306	(265)
3,8-Dinitro-6-*p*-nitrophenyl	356–358	(265)
3,8-Dinitro-6-(3′-pyridyl)	293–294	(213)
4-Ethyl-8,9-methylenedioxy	142–143	(150)
6-Ethyl-2,3,8,9-tetramethoxy	202	(223)
2,3,8,9-Tetramethoxy	185	(223)
2,3,8,9-Tetramethoxyphenanthridine-6-carboxylic acid	240	(223)
2,3,8,9-Tetramethoxy-6-(4′-chlorobutyl)	223	(244)
3,6,8-Triamino	200	(4)
2,6,8-Trimethyl	123	(102)

*In a few instances the complete name of the compound is given.

VII. Physical Properties

A. Molecular Dimensions

As aza-aromatic heterocycles are derived formally from the parent carbocycles by substituting N for CH, the similarity in bond lengths and bond angles is not surprising. The regular hexagonal configuration of benzene is confirmed by studies

TABLE 8

5,6-Dihydrophenanthridine derivatives

Substituent*	Melting Point	References
	°C.	
5,6-Dihydrophenanthridine	123–125	(284)
8-Acetoxy-5,6-dimethyl	110–111	(55)
5-Acetyl-6-methyl-2-nitro	204	(223)
5-Acetyl-2-nitro	181	(223)
5-Acetyl-8-nitro	176	(223)
8-Amino-6-*p*-aminobenzoyl-5-methyl	174–175 (8-urethan)	(55)
2-Amino-6-*p*-aminophenyl-5-methyl	165–170 (bisurethan)	(55)
8-Amino-5,6-dimethyl	172–173 (8-acetylamino)	(55)
5-Benzoyl-6-cyano	140.5–141.5	(283)
6-Benzoyl-3,8-diamino-5-methyl	193–195 (bisurethan)	(55)
6-Benzyl-5-methyl	175–177 (HCl)	(55)
5-Cinnamalacetyl-6-cyano	229–230	(283)
5-Cinnamalcrotyl-6-cyano	234–236	(283)
5-Cinnamoyl-6-cyano	198–199	(283)
6-Cyano-5-methyl	120	(252)
5-(2′-Cyanoethyl)	150–152	(25)
3,8-Diamino-5,6-dimethyl	169–171 (bisurethan)	(55)
3,8-Diamino-6-butoxy-5-methyl-6-phenyl	215–220	(23)
3,8-Diamino-5-methyl-6-phenyl	184–186 (3,8-diacetylamino)	(55)
5-(2′-Diethylaminoethyl)	158–159 (dipicrate)	(135)
5-(2′-Dimethylaminoethyl)	183–184 (dipicrate)	(135)
6,6-Diphenyl	147.5–148	(115)
5-Ethyl	210 (picrate)	(117)
5-Ethyl-6-methyl	148–149	(98)
5-Formyl-9-hydroxy-5,6-dihydrophenanthridine-8,10-dicarboxylic acid	140–141 (diethyl ester)	(88)
9-Hydroxy-5,6-dihydrophenanthridine-8,10-dicarboxylic acid		(88)
8-Hydroxy-6-methyl	182	(55)
8-Methoxy-6-*p*-methoxyphenyl-5-methyl	94	(55)
6-*p*-Methoxybenzyl-5-methyl	168 (HCl)	(55)
5-Methyl	108	(142)
6-Methyl	89	(25, 223)
6-Methyl-5-(2′-diethylaminoethyl)	186–187 (HCl)	(98)
5-Methyl-6-phenyl	102–103	(55)
5-[2′-(4″-Morpholinyl)ethyl]	189–191 (HCl)	(135)
5-Methyl-6-(1′-nitroethyl)	112.5–113.5	(169)
5-Methyl-6-(1′-nitropropyl)	102–103.5	(169)
6-Phenyl-6-*p*-tolyl	143.5–144	(115)
5-(1′-Piperidylethyl)	236–238 (2HCl)	(135)

* In a few instances the complete name of the compound is given.

of the vibration-rotation spectrum (11). Electron-diffraction measurements of bond lengths in benzene gave 1.39 ± 0.02 Å. for C—C and 1.08 ± 0.04 Å. for C—H. Parallel measurements on the pyridine molecule showed the same dimensions for the C—C and C—H bond lengths within experimental error, and gave a value of 1.37 ± 0.03 Å. for the C—N bond length (230). In the light of a recent measurement of the dipole moment of pyridine by microwave spectroscopy, however, De More, Wilcox, and Goldstein (73) suggested the following parameters: C—N = 1.35–1.36 Å.; C—C = 1.39 Å.; C—H = 1.08 Å.; and the angle CNC = 114–117°. Such a narrowed molecule is in better agreement with the data obtained.

TABLE 9

Other hydrogenated phenanthridine derivatives

Substituent	Melting Point	References
	°C.	
Tetrahydro:		
7,8,9,10-Tetrahydro	64	(131, 145)
Tetrahydro	210–212 (picrate)	(40)
6-Amino-7,8,9,10-tetrahydro	165	(131)
6-Amino-2,4-dimethyl-7,8,9,10-tetrahydro	136–137	(131)
6-Amino-2-methyl-7,8,9,10-tetrahydro	169–170	(131)
6-Amino-4-methyl-7,8,9,10-tetrahydro	121–122	(131)
8,9-Dimethoxy-2,3-dimethyl-6-phenyl-1,1a,4,5a-tetrahydro	178–180	(242)
6,9-Dimethyl-7,8,9,10-tetrahydro	78	(38)
2,3-Dimethyl-8,9-methylenedioxy-1,1a,4,5a-tetrahydro	157–158.5	(242)
7-Hydroxy-6-methyl-7,8,9,10-tetrahydro	167	(237)
7-Oxo-6-methyl-7,8,9,10-tetrahydro	118	(237)
Hexahydro:		
5,6,6a,7,8,10a-Hexahydro	104	(40)
2,3-Dimethoxy-8,9-dimethyl-5,6,6a,7,10,10a-hexahydro	240 (HCl)	(243)
9-Methoxy-1,1a,4,5,5a,6-hexahydro	240–242 (HCl)	(280)
9-Methoxy-5-methyl-1,1a,4,5,5a,6-hexahydro	211.5–213	(280)
5-Methyl-8,9-methylenedioxy-1,1a,4,5,5a,6-hexahydro	239–243 (HCl)	(183)
8,9-Methylenedioxy-1,1a,4,5,5a,6-hexahydro	280–282	(183)
Octahydro:		
1,2,3,4,7,8,9,10-Octahydro	37–38	(62)
5,6,6a,7,8,9,10,10a-Octahydro	72	(40)
Octahydro	74	(154)
2,3-Dihydroxy-9-methoxy-1,1a,2,3,4,5,5a,6-octahydro	212–213	(280)
2,3-Dihydroxy-9-methoxy-5-methyl-1,1a,2,3,4,5,5a,6-octahydro	223–225 (HCl)	(280)
8,9-Dimethyl-5,6,6a,7,8,9,10,10a-octahydro	180–181 (HCl)	(243)
6-Methyl-1,2,3,4,7,8,9,10-octahydro	68	(62)
6-Methyl-1,1a,2,3,4,5,5a,6-octahydro	57–58	(98)

The dimensions of other aza-aromatic heterocycles are probably quite similar to those of the parent carbocycles. One may expect a short carbon–nitrogen bond throughout this series of heterocycles, owing to the polar nature of the bond. As in the case of carbocycles, the C—C and C—N bond lengths in these heterocycles should be related to their multiplicity. In the sense of Pauling (208) bond multiplicity is a measure of the "double-bond character" of a carbon–carbon bond. A high bond multiplicity for a carbon–carbon bond means that it is represented more frequently as C=C in the valence-bond structures of the resonance hybrid. Such a bond will be shorter and will tend to resemble an olefinic bond in chemical behavior. Double-bond reactions such as oxidation by osmium tetroxide, ozonization, and argentation (complexation with silver ion) seem to occur at bonds of high multiplicity (16, 148).

B. MOLAR REFRACTION

The polarizability of a molecule depends upon the displacement of electrons by an electric field and is measured by the molar refraction. Early attempts to set up a system of atomic refraction constants and thus to calculate the molar refraction of a compound *a priori* failed with unsaturated systems. Conjugated

TABLE 10

6(5H)-Phenanthridinone derivatives

Substituent*	Melting Point	References
	°C.	
6(5*H*)-Phenanthridinone	293	(52, 247)
1-Amino	319–323	(57)
2-Amino	285 (urethan)	(57)
3-Amino	250 (urethan)	(57)
7-Amino	295 (urethan)	(57)
8-Amino	319–320	(231a)
9-Amino	280 (urethan)	(57)
10-Amino	330–334	(57)
5-Benzyl-2-ethoxy	156–157	(188)
5-Benzyl-1(or 3)-methoxy	152–154	(188)
5-Benzyl-8,9-methylenedioxy	159–161.5	(191)
N,N'-Bis[6(5*H*)-phenanthridinone]	>310	(256)
2-Bromo	323–324	(199, 257)
2-Bromo-5-ethyl	116	(117)
2-Bromo-5-methyl	188–189	(125)
5-Carballoxy	93–94	(155)
5-Carbethoxy	143–144	(155)
5-Carbisopropoxy	123	(155)
5-Carbobenzoxy	134	(155)
5-Carbocyclohexoxy	151	(155)
5-Carbomethoxy	127	(155)
5-Carbopropoxy	76	(155)
5-(2'-carboxyethyl)	162–163	(83)
6(5*H*)-Phenanthridinone-1-carboxylic acid	285	(153)
6(5*H*)-Phenanthridinone-4(or 7)-carboxylic acid	299	(66)
2-Chloro-5-methyl	192	(125)
5-(2'-Cyanoethyl)	169–170.5	(25)
5-(2'-Diethylaminoethyl)	193–195 (HCl)	(99)
2,3-Dimethoxy-8,9-dimethyl-6a,7,8,10a-tetrahydro	220	(243)
2,4(or 7,9)-Dimethyl	258	(60)
2,5-Dimethyl	139	(125)
4,5-Dimethyl	141–142	(125)
8,9-Dimethyl-6a,7,8,9,10,10a-hexahydro	220	(243)
8,9-Dimethyl-6a,7,8,9,10,10a-hexahydro-6-thio	160	(243)
2,4-Dimethyl-7,8,9,10-tetrahydro	123	(234)
1,3-Dinitro-5-methyl	281	(126)
5-Ethyl-2-methoxy	138	(117)
5-Ethyl-4-methoxy	117	(117)
5-Ethyl-2-methyl	97	(117)
Hexahydro	176–178	(4)
4-Methyl	240	(184)
5-Methyl-6(5*H*)-phenanthridinone-9-carboxylic acid	162–163 (methyl ester)	(83)
5-Methyl-8,9-methylenedioxy	238	(103, 149)
5-Methyl-2-nitro	249	(126)
5-Methyl-4-nitro	92–93	(126)
2-Methyl-7,8,9,10-tetrahydro	108	(234)
5-Methyl-6-thio	70	(210)
1-Nitro	325–327	(57)
2-Nitro	380–384	(57, 203, 257)
3-Nitro	349	(57)
4-Nitro	265–267	(57, 203, 240)
8-Nitro	329	(13, 57, 203)
10-Nitro	316–318	(57)
5-Phenyl	118–119	(257)
7,8,9,10-Tetrahydro	272	(36, 131, 282)
6a,7,8,10a-Tetrahydro	194–195	(40)
6a,7,8,10a-Tetrahydro-6(5*H*)-phenanthridinone-7-carboxylic acid	216	(40)
6-Thio	281–283	(210, 248)
2,4,5-Trimethyl	194	(60)

* In a few instances the complete name of the compound is given.

TABLE 11

Miscellaneous di- and triphenanthridinyl derivatives

Derivative	Melting Point	References
	°C.	
3-Azo-8-hydroxyphenanthridine	295	(13)
1,2-Di(2′-amino-6′-phenanthridinyl)ethene	>340 (bisurethan)	(54)
1,2-Di(3′-amino-6′-phenanthridinyl)ethene	310 (bisurethan)	(54)
1,2-Di(8′-amino-6′-phenanthridinyl)ethene	278 (bisurethan)	(54)
1,2-Di(9′-amino-6′-phenanthridinyl)ethene	295–300 (bisurethan)	(57)
1,2-Di(2′-nitro-6′-phenanthridinyl)ethene	>360	(54)
1,2-Di(4′-nitro-6′-phenanthridinyl)ethene	>360	(57)
1,4-Di(6′-phenanthridinyl)butane	214	(223)
1,2-Di(6′-phenanthridinyl)ethane	280–282	(99)
1,2-Di(6′-phenanthridinyl)ethanol	191–192	(54)
1,2-Di(6′-phenanthridinyl)ethene	304–305	(54)
N,*N*-Di(6′-phenanthridinyl)amine	160–161 (sulfonyl)	(99)
N,*N*-Di(6′-phenanthridinyl)isopropylamine	203–205	(99)
1,2,3-Tri(6′-phenanthridinyl)propane	264–266	(54)

TABLE 12

Molar refractions of aza-aromatic heterocycles and their exaltations from calculated values

Heterocycle	Molar Refraction (Found)	Molar Refraction (Calculated)	Difference
Pyridine	24.02	25.16	−1.14
Isoquinoline	41.41	40.49	0.92
Quinoline	41.83	40.49	1.34
Acridine	62.34	55.83	6.51

molecules gave experimental values higher than calculations would predict. In the modern view of conjugation these exaltations are understandable, as they imply a greater electronic polarizability. The delocalization of π-electrons in conjugated systems not only lowers the energy of the ground state of the molecule, but decreases the energy of the lower-lying levels of the excited states even more. The net result is a decrease in electronic excitation energy and an increase in polarizability as the conjugated system is extended (compare Section E). This explains why deviations (exaltations) from values obtained by atomic and group refraction constants become more pronounced as one goes to polycyclic systems. This is shown by the aza-aromatic heterocycles in table 12 (14, 48). Instead of the use of empirical refraction constants a modern treatment of condensed aromatic systems has taken account of the high mobility of the π-electrons and the planarity of the ring system. With these calculations the discrepancy between experimental and predicted molar refractions is significantly smaller (table 13) (233). Referring to the aromatic systems in table 13, one can see that the molar refraction, and hence the mean polarizability, of a given heterocycle is less than that of the parent carbocycle. The polarizability of aromatic systems is markedly anisotropic; the electron cloud is more polarizable in the plane of the ring and less so perpendicular to the plane of the ring. In comparison with the parent carbocycle, the main reduction in polarizability of the nitrogen heterocycle occurs in the direction normal to the molecular plane (160). Previous

TABLE 13

Molar refractions of condensed aromatic systems and their exaltations from calculated values (π-electron treatment)

Compound	Molar Refraction (Found)	Molar Refraction (Calculated)	Difference
Benzene	26.2	26.2	0.0
Naphthalene	44.1	43.5	0.6
Anthracene	65.4	62.0	3.4
Phenanthrene	62.3	62.0	0.3
Pyrene	74.0	70.8	3.2
Isoquinoline	41.6	41.5	0.1
Quinoline	41.8	41.5	0.3
Acridine	64.3	60.2	4.1

TABLE 14

Dipole moments of aza-aromatic heterocycles (benzene solution)

Heterocycle	μ (in Debye Units)	Heterocycle	μ (in Debye Units)
Pyridine	2.21	Phenanthridine	1.50
Quinoline	2.14	Acridine	1.95
Isoquinoline	2.53		

workers had concluded that the main reduction in polarizability in going from benzene to pyridine occurred along the dipolar axis (241).

C. DIPOLE MOMENTS

The significance of dipole data in determining charge distribution in pyridine has been pointed out. The experimental determination of the dipole moment of pyridine has given values ranging from 2.2 D to 2.3 D. The dipole moment of pyridine vapor by microwave spectroscopy is 2.15 $\pm$ 0.05 D (73). Middleton and Partington (187) have demonstrated that the solvent employed affects the value obtained from determinations run in solution. A carbon disulfide solution yields a value of 2.10 D, whereas a carbon tetrachloride solution gives 2.33 D for the dipole moment of pyridine.

Comparative dipole-moment data for aza-aromatic heterocycles are given in table 14 for determinations run in benzene (28, 107).

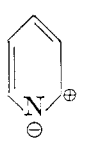
D. INFRARED SPECTRA

Absorption of photons having a wavelength between 2 μ and 15 μ leads to vibrational excitations in a molecule. These may be stretching or deformation vibrations. Pyridines and quinolines exhibit the following stretching vibrational bands: CH near 3.3 μ; C=C and C=N in the region 6.0–6.3 μ and 6.5 μ. Ring vibrations and CH deformation give bands in the regions 8.4 μ, 9–10 μ, and 11–16 μ. Although the ring vibrations of pyridine closely parallel those of benzene, hydrogen-deformation vibrations are quite different and are shifted to lower frequencies. The C=C and C=N stretching bands are also slightly lower than those of benzene. In quinoline and isoquinoline the region between 6.3 and 6.7 μ has a more complex band structure (26).

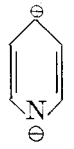
E. ULTRAVIOLET SPECTRA

Electromagnetic radiation having a wavelength between 2000 and 7500 Å. embraces the visible and ultraviolet regions. Absorption by a molecule of photons possessing energy in this range may cause promotion of its electrons to higher electronic states. With conjugated molecules not only is the ground-state energy lowered, owing to resonance, but the energy levels of the excited states are sharply lowered. Because of this, the greater the length of a conjugated system the smaller will be the energy difference between the ground state and the lowest-lying excited state. Thus naphthalene shows a bathochromic shift from the maximum in absorption of benzene, as less energetic (longer wavelength) photons are absorbed. As one passes through the series benzene, naphthalene, anthracene, phenanthrene, naphthacene, pentacene, and hexacene, this shift actually brings the absorption into the visible region and a colored molecule results.

From studies made by Mulliken (201) it can be concluded that the greater the increase of polarity of the molecule in the excited state, the greater is the intensity of absorption. As polar forms such as LXVI and LXVII are more im-



LXVI



LXVII

portant in describing the excited states of pyridine, it is clear why pyridine has an ϵ_{max} of 2000 at 2500 Å., while benzene has an ϵ_{max} of 250 at 2600 Å. In addition, Maccoll (172) has pointed out that in the series benzene, pyridine, pyrimidine, pyridazine, and *s*-tetrazine the maximum in absorption undergoes a bathochromic shift, the shift being most marked when hetero nitrogens are adjacent.

In examining the ultraviolet spectra of pyridine, quinoline, isoquinoline, quinazoline, phenanthridine, 5,6-benzoquinoline, and other heterocycles, Badger, Pearce, and Pettit (17) drew these general conclusions. First, there is a considerable loss in fine structure in aza-aromatic heterocycles, but the maxima are not significantly shifted. The absorption shoulders of the nitrogen heterocycles begin, however, at slightly longer wavelengths. Second, the group III maxima between 2500 and 3500 Å. show a uniformly greater intensity in the nitrogen heterocycles.

F. THERMOCHEMICAL DATA

The calculation of resonance energies from the observed heats of combustion or hydrogenation of aromatic compounds and the use of bond energies is a well-known procedure (208). The values obtained for certain carbocycles and heterocycles are given in table 15 (217). The values given show that the resonance energy of a given heterocycle is approximately the same as that of the parent carbocycle. From this it may be judged that isoquinoline and phenanthridine should have resonance energies of around 75 and 120 kcal. per mole, respectively. The large resonance energies of pyridine, quinoline, and acridine indicate that

TABLE 15

Empirical resonance energies of aromatic systems

Compound	Resonance Energy	Compound	Resonance Energy
	kcal./mole		*kcal./mole*
Benzene	41	Pyridine	43
Naphthalene	77	Quinoline	75
Anthracene	116	Acridine	106
Phenanthrene	130	Phenazine	105
Pyrene	152		

no single "static bond" structure can describe the heterocyclic molecule adequately.

VIII. Physiological Properties

Aza-aromatic heterocycles and their derivatives have received much attention from the biological chemist because of their pronounced physiological properties. The alkaloids studied by early workers with natural products were found to contain such ring systems as the pyridine, quinoline, and isoquinoline nuclei. Moreover, the dietary factors nicotinic acid and pyridoxine are now known to be pyridine derivatives. With the advent of chemotherapy many research workers sought to modify the structures of known alkaloids, in order to obtain physiologically active agents which were less toxic. As a natural extension many basic derivatives of aza-aromatic heterocycles were screened for biological activity and with considerable success. The vast amount of research carried out in this quest for chemotherapeutic agents is adequately covered in several reviews (50, 136, 140, 246). Summarily, it might be stated that pyridine derivatives such as cetylpyridinium chloride and 5-amino-2-butoxypyridine are employed as antiseptics; isoquinoline systems are present in narcotics (heroin) and in antispasmodics (papaverine); quinoline and acridine derivatives (Atabrine, Plasmochin) are satisfactory antimalarial agents; and phenanthridine compounds are effective against sleeping sickness in cattle.

In view of the diversified physiological activity of aza-aromatic heterocycles no comprehensive correlation of activity and chemical constitution is to be expected. Recently, however, Albert, Rubbo, and Burvill (8) have made an extensive study of the antibacterial activity of aza-aromatic systems and have proposed that the bacteriostatic action of these bases depends upon ionization and molecular shape. Acridines which were more than 50 per cent ionized (as cations) at 37°C. were found to exert a strong bacteriostatic action. Certain acridines, however, possessed the required degree of cationic ionization but were only feebly antibacterial. These latter compounds all involved "dimensional factors." For example, 9-amino-1,2,3,4-tetrahydroacridine is shown by Hirschfelder models to be nonplanar. Proceeding from Ehrlich's principle (136) that "*Corpora non agunt nisi fixata,*" the authors proposed that the acridine cations are attracted to the anions of nucleoproteins and lie flat on the bacterial surface. The stability of this union is enhanced by the van der Waals forces arising from

the large aromatic pi cloud. If the molecule has too small a planar area (pyridines and quinolines) or if it is less planar due to hydrogenation (9-amino-1,2,3,4-tetrahydroacridine), van der Waals forces cannot maintain the drug–protein union. Bulky side chains can inhibit this planar union also. As support for this hypothesis, inactive 2-methylquinolines could be changed into effective bacteriostats by condensing them with benzaldehyde. Presumably the planar styryl side chain enhances the flat area of the molecule and thus increases the secondary forces of attraction. From related experiments the authors concluded that the critical area of the molecular plane should be between 28 and 38 $\mathring{A}.^2$

IX. References

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