

AN ABSTRACT OF THE THESIS OF

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(Name) (Degree) (Major) Chemistry

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Title A MEDICINAL CHEMICAL STUDY OF MANNICH BASES

DERIVED FROM SELECTED 2-PHENYLINDOLIZINES

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In a search for new therapeutic agents, a series of Mannich bases derived from the following 2-phenylindolizines were prepared: 2-phenylindolizine, 1,2-diphenylindolizine, 3-methyl-2-phenylindolizine, 3-ethyl-2-phenylindolizine, and 1-(2-hydroxyethyl)-2-phenylindolizine.

The investigation was based on the speculation that indolizine analogs of physiologically active indoles might be useful medicinally. A certain group of indoles, all of which have pronounced activity on the central nervous system, have in their structure a characteristic grouping, >N-C=C-C-C-N< , representing a spatial arrangement which might be a contributing factor in determining their activities. Examples of indoles with this intramolecular spread are bufotenine, psilocin, reserpine and lysergic acid diethylamide (LSD). Since Mannich bases substituted at the C-1 position of the indolizine ring possess the same intramolecular spread as the foregoing indoles, it was reasoned that such compounds might also exert activity on the

central nervous system. In a broader approach to the problem of finding new physiologically active compounds, three classes of Mannich bases were prepared based on the point of attachment of the dialkylaminomethyl group to the indolizine nucleus as follows: substitution at the C-1 position, substitution at the C-3 position and substitution at both the C-1 and C-3 positions.

The indolizines were prepared by the Chichibabin synthesis, which involves the heating of 1-phenacyl-2-picolinium bromides in aqueous sodium bicarbonate solution. In general, the Mannich reaction was carried out by pre-mixing the formaldehyde with the secondary amine and allowing to stand for periods varying from 15 minutes to one hour. This mixture was then added to the dioxane solution of the indolizine and the resulting reaction mixture allowed to stand at room temperature for 24 to 48 hours. In some cases the product crystallized on evaporation of the solvent accompanied by scratching with a glass stirring rod. In cases where no crystallization occurred on evaporation, the oily residue was washed, dried and taken up in a minimum of alcohol or acetone and allowed to stand in the refrigerator for periods ranging from five days to three weeks, whereupon crystallization occurred in several instances.

One of the compounds prepared, 1-diethylaminomethyl-3-methyl-2-phenylindolizine, exerted a depressant action on the central nervous system when injected intraperitoneally in mice as a

suspension in gum acacia. The approximate LD₅₀ for this compound was found to be in the range of 70 to 100 milligrams per kilogram of body weight.

The new compounds that were prepared in this study are:

1-dimethylaminomethyl-3-methyl-2-phenylindolizine, 1-diethylaminomethyl-3-methyl-2-phenylindolizine, 3-methyl-2-phenyl-1-pyrrolidinomethylindolizine, 3-methyl-2-phenyl-1-piperidinomethylindolizine, 3-methyl-1-morpholinomethyl-2-phenylindolizine, 3-methyl-1-methylphenylaminomethyl-2-phenylindolizine, 1-dimethylaminomethyl-3-ethyl-2-phenylindolizine, 1-diethylaminomethyl-3-ethyl-2-phenylindolizine, 3-ethyl-2-phenyl-1-pyrrolidinomethylindolizine, 3-ethyl-2-phenyl-1-piperidinomethylindolizine, 3-ethyl-1-morpholinomethyl-2-phenylindolizine, 3-ethyl-1-(4-methylpiperazinomethyl)-2-phenylindolizine, 1-(2-hydroxyethyl)-2-phenylindolizine, 1-(2-hydroxyethyl)-2-phenyl-3-pyrrolidinomethylindolizine, 3-dimethylaminomethyl-1,2-diphenylindolizine, 3-diethylaminomethyl-1,2-diphenylindolizine, 3-diisopropylaminomethyl-1,2-diphenylindolizine, 1,2-diphenyl-3-pyrrolidinomethylindolizine, 1,2-diphenyl-3-piperidinomethylindolizine, 1,2-diphenyl-3-morpholinomethylindolizine, 1,2-diphenyl-3-methylphenylaminomethylindolizine, 1,2-diphenyl-3-(4-methylpiperazinomethyl)indolizine, 1,3-bis(dimethylaminomethyl)-2-phenylindolizine, 1,3-bis(pyrrolidinomethyl)-2-phenylindolizine, 1,3-bis(piperidinomethyl)-2-phenylindolizine,

1,3-bis(morpholinomethyl)-2-phenylindolizine, bis(3-ethyl-2-phenyl-1-indoliziny)l)methane and bis(3-methyl-2-phenyl-1-indoliziny)l)methane.

A MEDICINAL CHEMICAL STUDY OF MANNICH BASES
DERIVED FROM SELECTED 2-PHENYLINDOLIZINES

by

WILLIAM BROOMFIELD HARRELL, JR.

A THESIS

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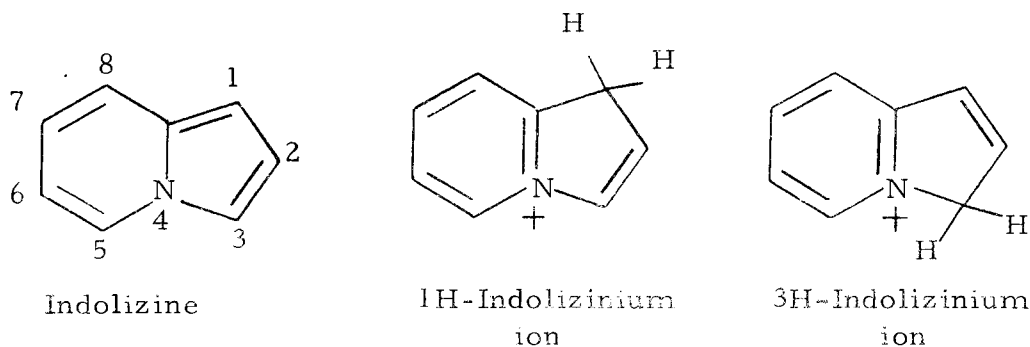
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A MEDICINAL CHEMICAL STUDY OF MANNICH BASES DERIVED FROM SELECTED 2-PHENYLINDOLIZINES

INTRODUCTION

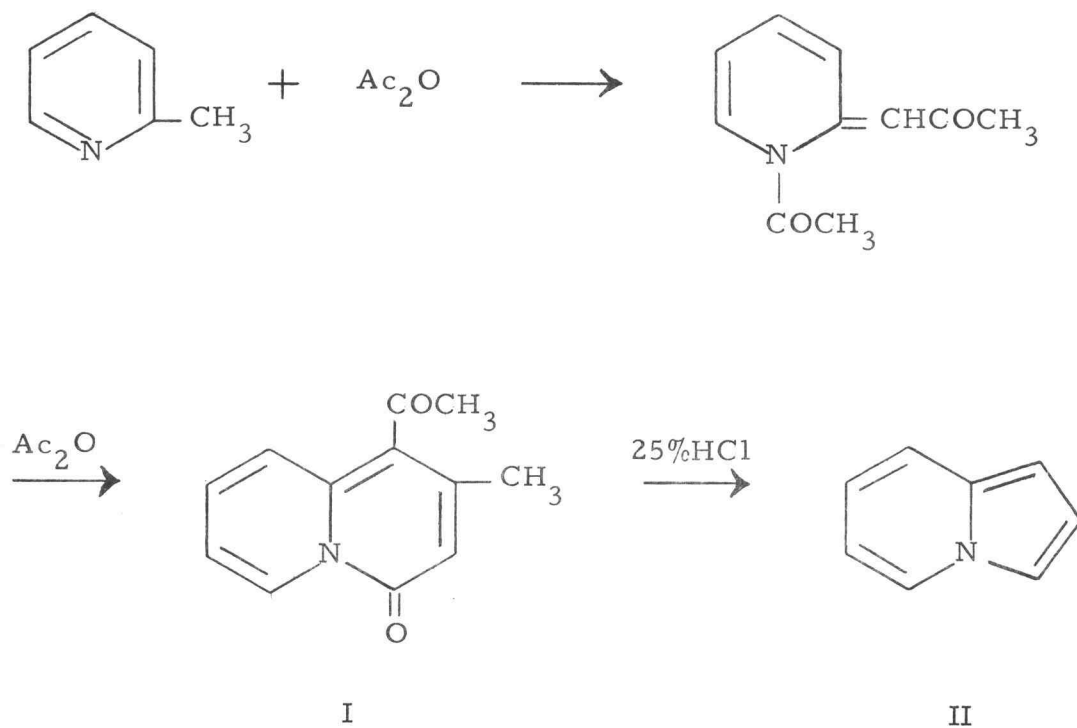
History and Development of Indolizines

The heterocyclic compound indolizine is found in the scientific literature under a variety of names. The name most commonly employed prior to 1957 (39) was pyrrocoline. However, other names used to designate this compound and its derivatives include pyrimidole, pyrrodine, 8-pyrrolopyridine, and pyrrolo(1,2-a)pyridine (74, p. 239). Moreover, several different numbering systems have been utilized in naming the various derivatives of this compound, thus resulting in considerable confusion in making literature searches and comparisons. The name indolizine is the currently accepted nomenclature by Chemical Abstracts and the numbering system employed by that publication as well as the structures of the two cationic forms of the compound are shown below. It should be noted that the numbering follows that of aromatic ring systems and not the usual heterocyclic numbering system which normally gives the hetero atom number one.

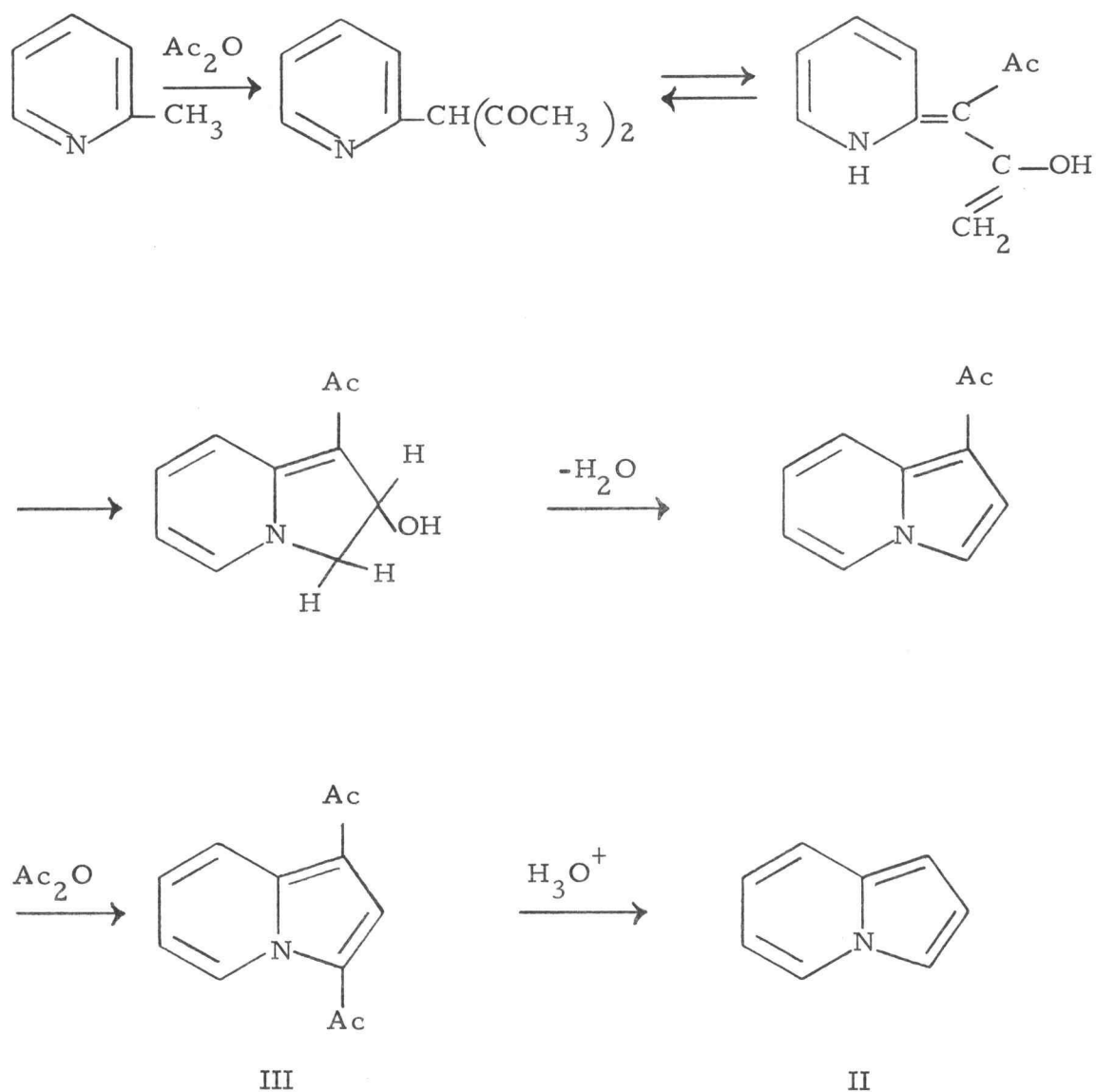


The above numbering system along with the name indolizine will be used throughout the work recorded here.

Scholtz reported the first synthesis of indolizine in 1912 (84). He reacted acetic anhydride with α -picoline and obtained a crystalline product with the empirical formula $C_{12}H_{11}O_2N$ which he called "picolide." Scholtz was able to show the presence of a carbonyl group by preparing the oxime, the semicarbazone and the phenylhydrazone of this compound. Upon treatment of picolide with hydrochloric acid it was hydrolyzed to indolizine with two molecules of acetic acid being produced as by-products. Although he correctly identified the hydrolysis product as indolizine, the structure incorrectly postulated for picolide was that of 1-acetyl-2-methyl-4-ketopyridocoline (I) and the path of the reaction was proposed as follows (85):



Chichibabin & Stepanow (41) conducted a study of the reaction of α -picoline with acetic anhydride as carried out by Scholtz. They postulated that the indolizine nucleus was present in picolide as well as its hydrolysis product and proposed the following course for the reaction and gave the structure of picolide as (III):



The structure of II was confirmed by Diels, et al. (48).

These workers reduced indolizine to the octahydro-derivative and proved that the reduced compound was identical with a known compound, the alkaloid δ -conic^oine.

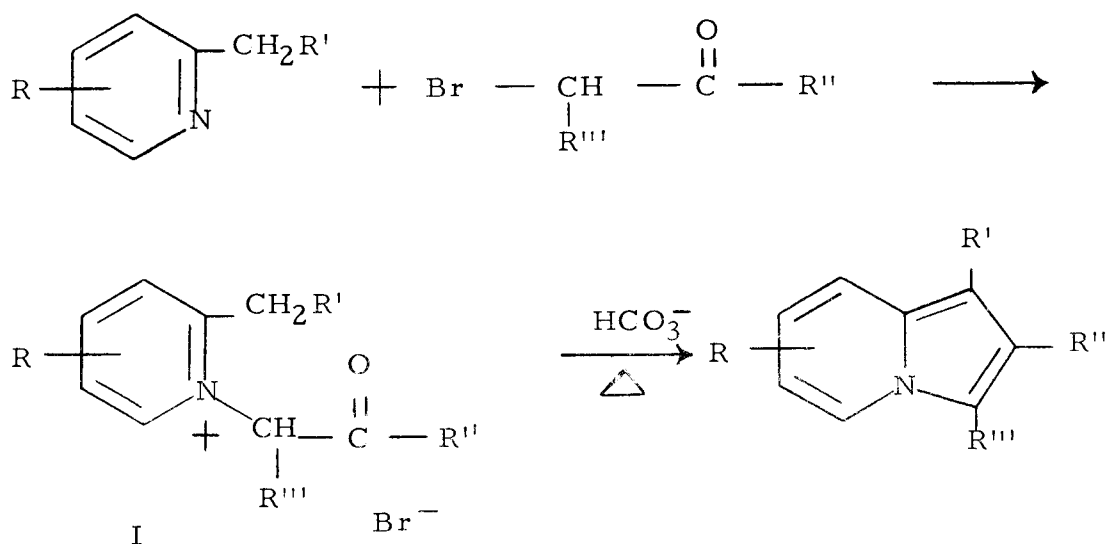
Methods of Synthesis

Although the Scholtz synthesis represents a convenient route to unsubstituted indolizine with readily available starting materials, the method is handicapped by its lack of versatility and its relatively low yields. The reaction is limited to the use of acetic and propionic anhydrides, since attempts to employ other anhydrides have proven unsuccessful (85). Moreover, with few exceptions, the reaction seems to be limited to α -picoline and other 2-methyl pyridines such as 2,4-lutidine and 2-methyl-5-phenylpyridine (16).

Indolizines have been prepared by several different synthetic approaches (16; 74, p. 240-251). A brief survey of the more widely employed syntheses is presented here.

The Chichibabin Synthesis

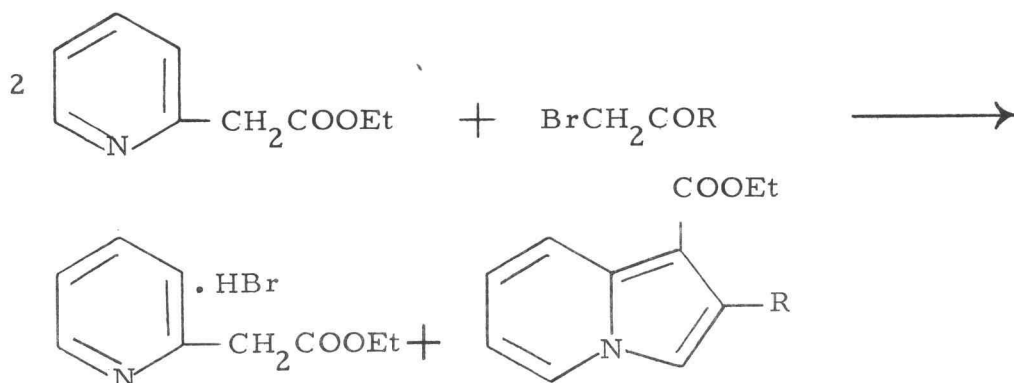
This method involves the condensation of α -halogenated ketones with α -picoline or substituted α -picolines (41). The synthesis proceeds via an intermediate pyridinium salt (I).



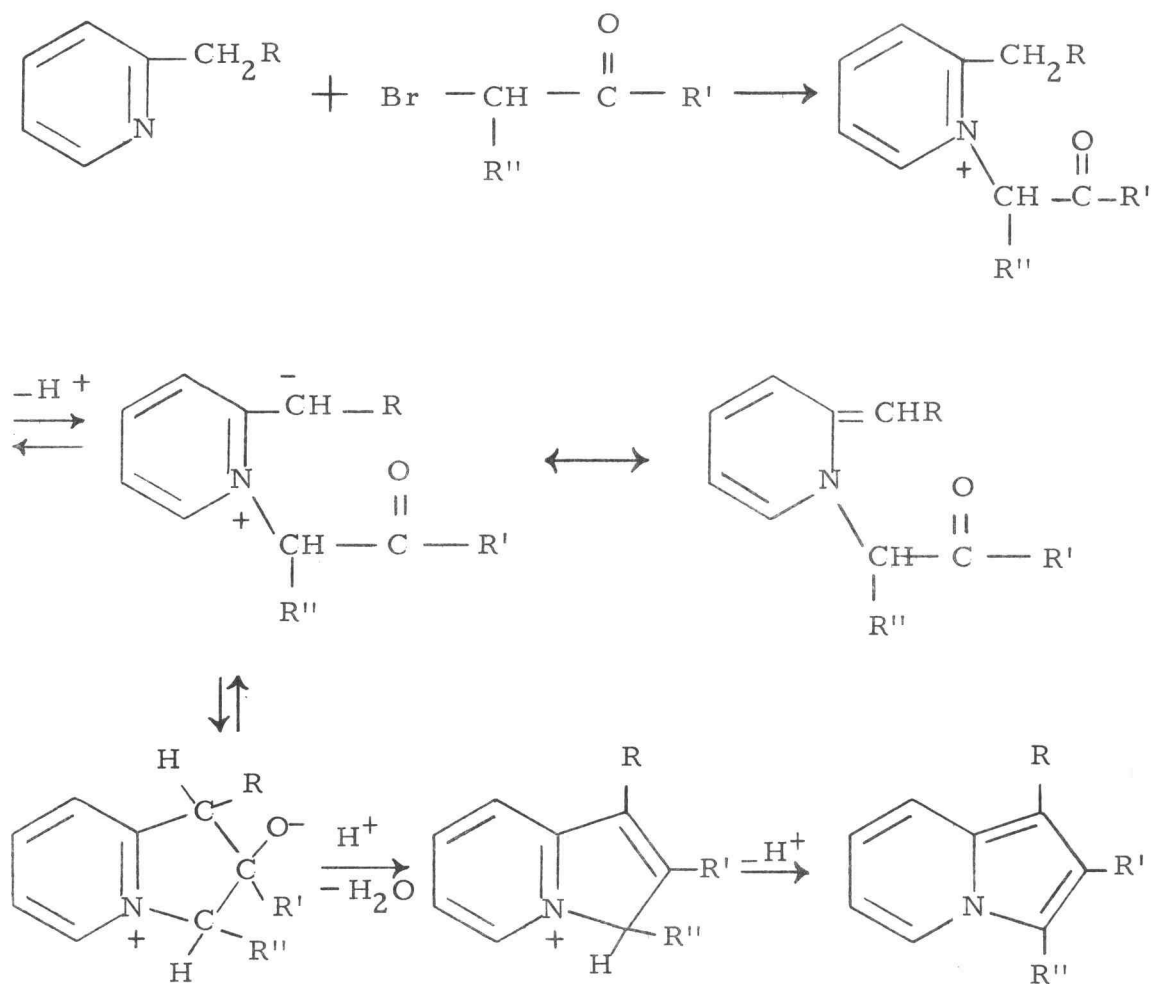
This method is by far the most widely employed route to substituted indolizines. Unfortunately, the method is of little value in the preparation of indolizine itself, because the reaction of α -picoline with α -bromoacetaldehyde proceeds in very low yield (40). The versatility of the Chichibabin reaction becomes apparent when one realizes the large number of compounds that can be prepared by selecting starting material with the appropriate groupings. Another advantage of this synthesis lies in the stability of the intermediate quaternary salt (I). Since in many instances the corresponding indolizine will be unstable, the pyridinium salt can be prepared and stored in quantity. The indolizine can then be freshly prepared in small amounts as the occasions for their need arise (59).

A modification of the Chichibabin synthesis has been reported by Wibberley and his co-workers (22, 23, 60). They discovered that by using activating groups on the 2-pyridyl methylene, the

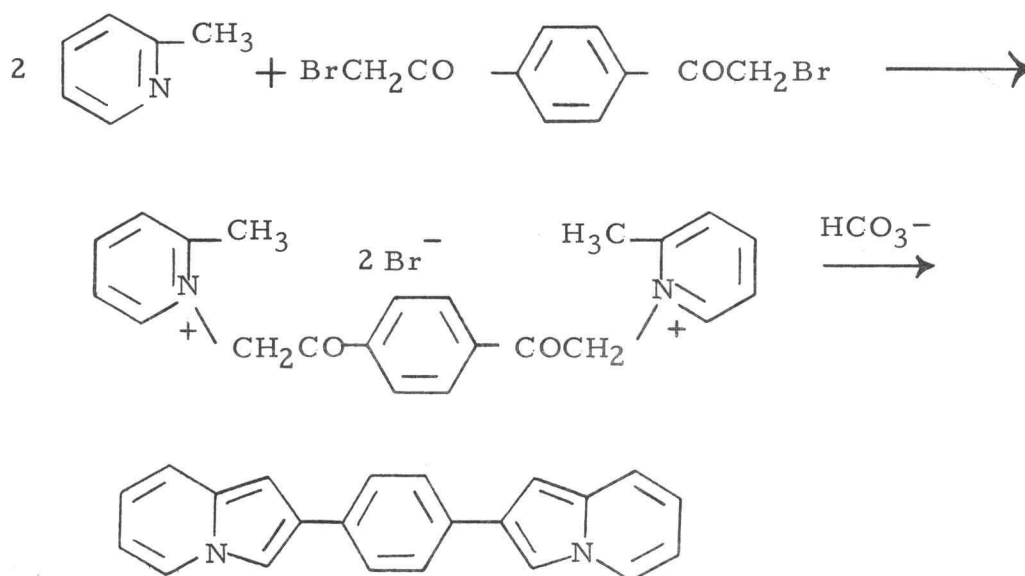
synthesis of indolizine derivatives could be accomplished in one step, thus by-passing the quaternary stage. A series of substituted indolizines were prepared by this method with ethyl 2-pyridylacetate, α -(2-pyridyl)acetonitrile and α -picolyl phenyl ketone being employed as starting pyridines. The reaction utilizes two moles of the pyridine derivative and one mole of the α -haloketone. One mole of the pyridine derivative serves as a base to remove hydrogen bromide and effect ring closure of the intermediate quaternary salt. The reaction is obviously limited to the preparation of indolizines with a substituent at the C-1 position.



These workers also proposed the following mechanism for the Chichibabin synthesis and postulated an intramolecular aldol-type reaction in the ring closure step:

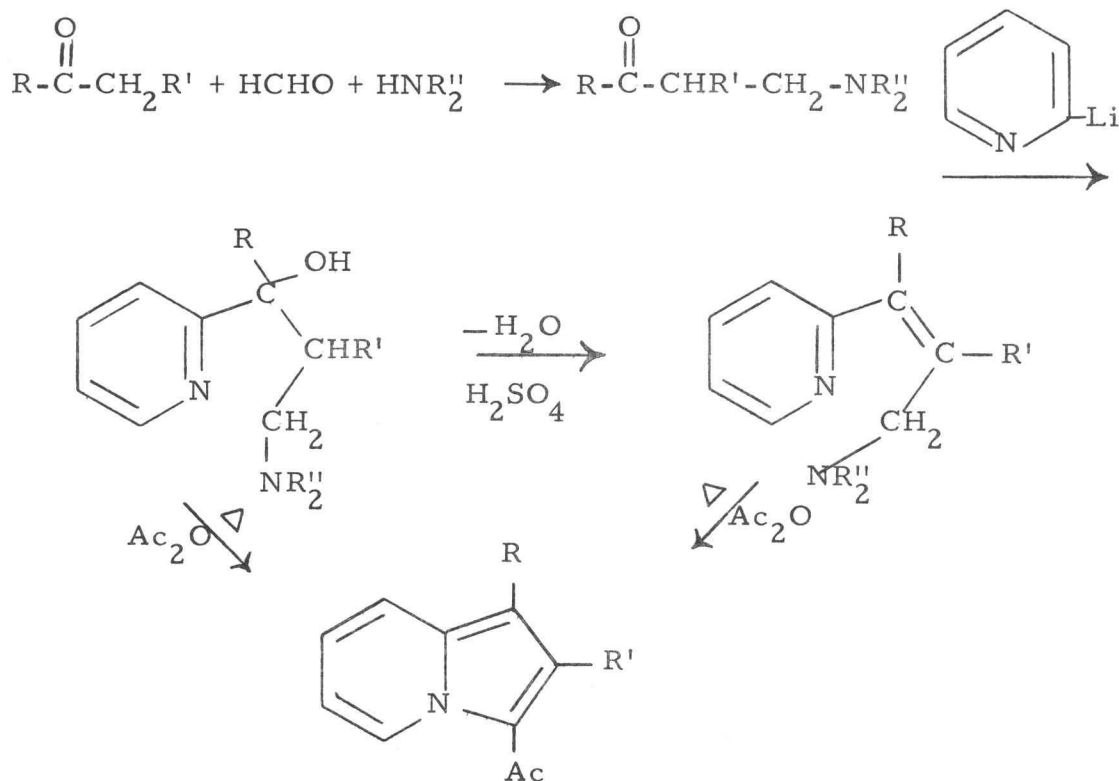


A good example of the versatility of the Chichibabin synthesis is the recent preparation of 1,4-bis(2-indolizinyl)benzene (32). α , α' -Dibromo-1,4-diacetylbenzene was reacted with α -picoline and the resulting bis-picolinium salt heated with aqueous sodium bicarbonate.



The Barrett Synthesis

A very useful route to indolizines which offers certain advantages over the Chichibabin synthesis was developed by Barrett (4, 5, 6). It is perhaps the best route to monosubstituted indolizines with alkyl or aryl groups at the C-1 position. In addition, it is the only practical route to 1:2-cycloalkanoindolizines. In the Barrett synthesis β -(dialkylamino)ketones are reacted with 2-pyridyl lithium and the resulting carbinol is refluxed with acetic anhydride to form the indolizine. The carbinol can be dehydrated to a substituted allylamine which will also produce the indolizine upon refluxing with acetic anhydride. The ketones employed in the sequence are made by the Mannich reaction.

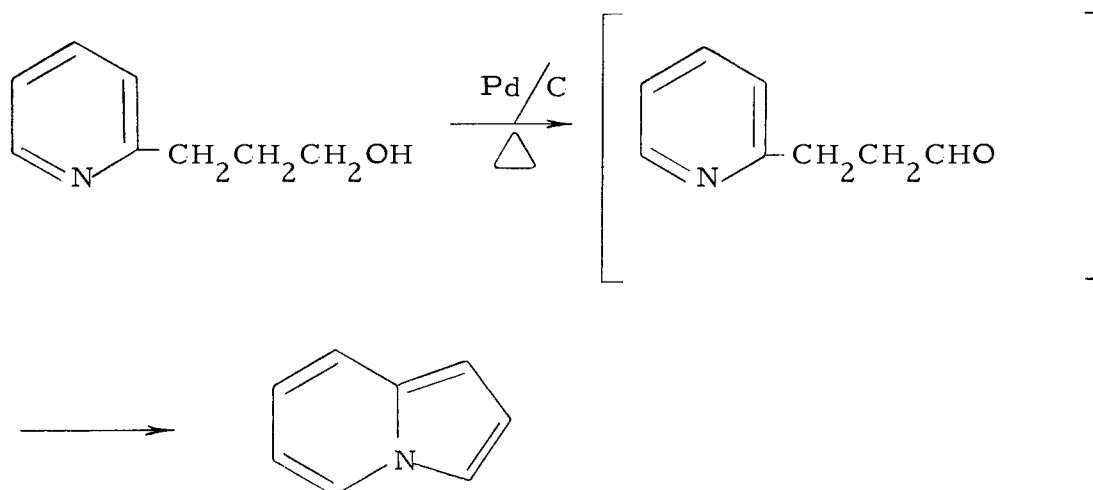


By starting with a cyclic ketone one obtains a 1:2-cycloalkano-indolizine as the product. This type of compound is not possible by the Chichibabin synthesis. The main disadvantages are associated with cis-trans isomerism of the allylamine and some undesirable side reactions. Small amounts of bis(indolizin-3-yl)methanes are formed which result from condensation with traces of formaldehyde liberated during the cyclization of the carbinols (74, p. 244).

The Boekelheide Synthesis

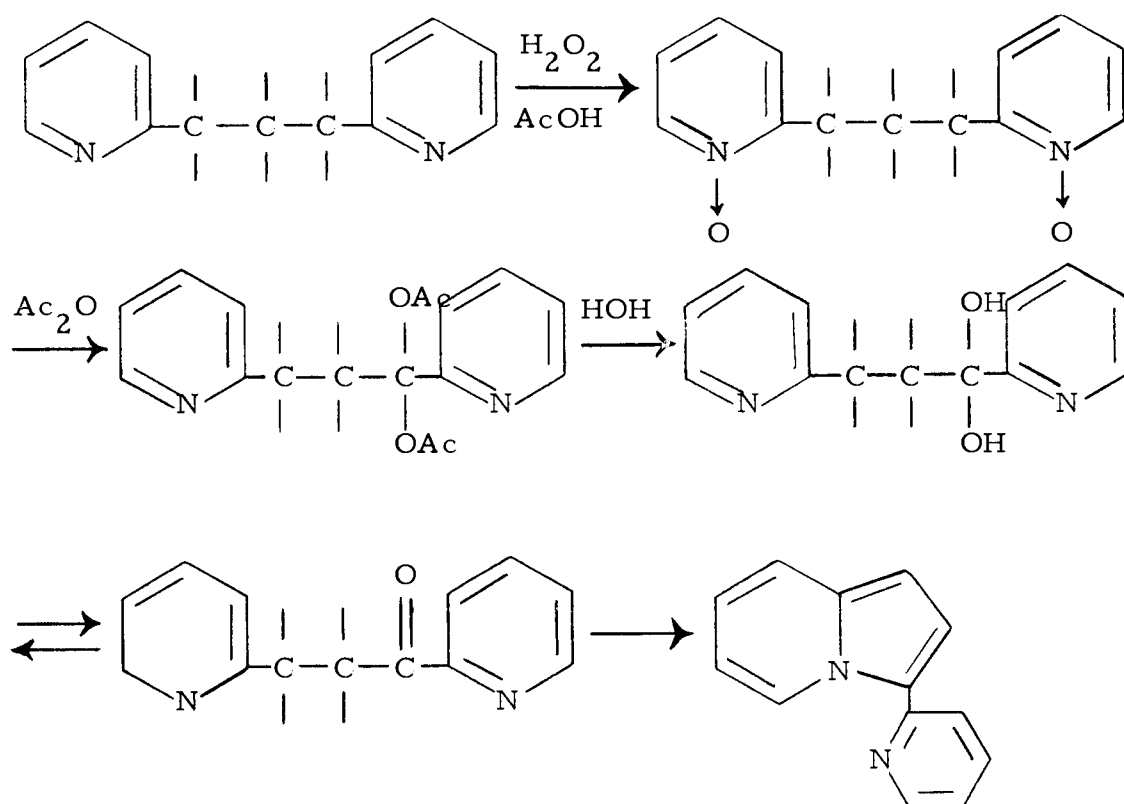
A quite interesting route to indolizines was introduced by Boekelheide and Windgassin (14). They prepared unsubstituted

indolizine by heating 3-(2-pyridyl)-1-propanol with palladium on charcoal, a dehydrogenating catalyst. This is an excellent method for preparing unsubstituted indolizine. However, the cost of starting materials would make this method less attractive for preparing substituted indolizines. They proposed that the reaction mechanism involved the intermediate 3-(2-pyridyl)propionaldehyde. However, this compound was not isolated during the course of the reaction.



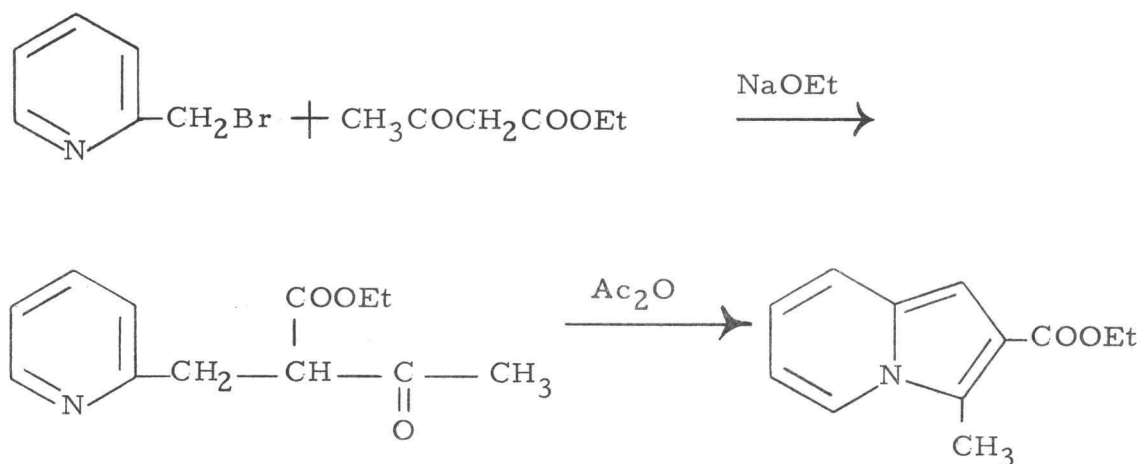
Evidence to support the existence of a carbonyl intermediate in this synthesis was provided by Michalski, Wojaczynski and Zajac (72, 73). Starting with 1,3-di(2-pyridyl)propane, they prepared the N, N'-dioxide by treating with hydrogen peroxide in acetic acid. This compound was then converted to 3-(2-pyridyl)-indolizine by refluxing with acetic anhydride. Upon work-up of the reaction residue they isolated 18% 1,3-di(2-pyridyl)-1-propanone. These workers proposed that the ketone resulted from the

decomposition of still another intermediate, 1, 3-di(2-pyridyl)-1, 1-propanediol diacetate, proceeding via the unstable gem-diol.



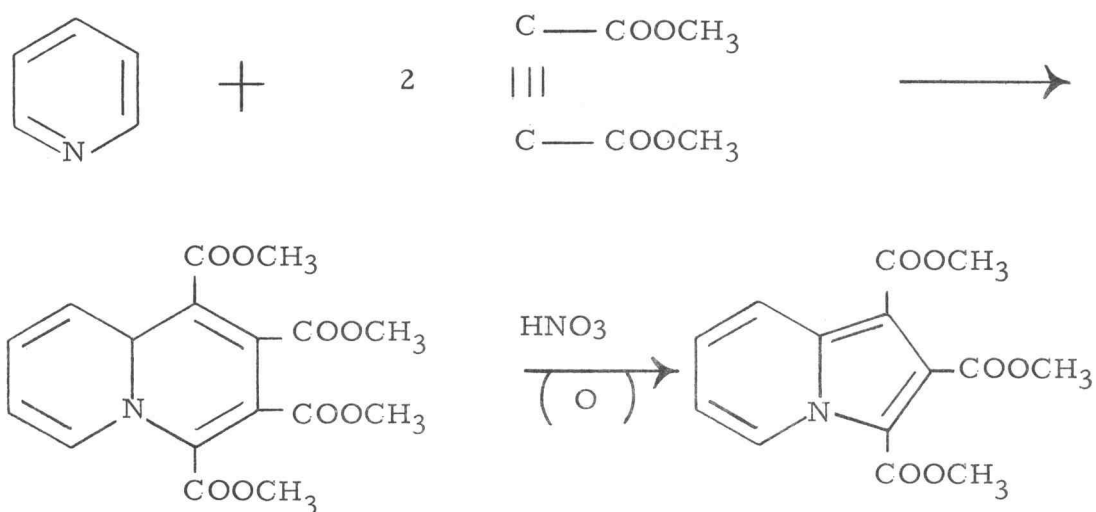
Following the suggested mechanism of a carbonyl intermediate, Hurst, Melton and Wibberley (60) very recently prepared a series of β -(2-pyridyl) carbonyl compounds by reacting 2-bromomethylpyridine with ethyl acetoacetate, ethyl malonate and several other active methylene compounds in the presence of sodium ethoxide. The corresponding indolizines were obtained by refluxing the β -(2-pyridyl) carbonyl compound with acetic anhydride. An intramolecular nucleophilic attack by nitrogen was proposed for the cyclization step. These authors were in general agreement with Michalski, Wojacznski and Zajac and noted that the two cyclizations strongly resembled

each other. The reaction sequence with acetoacetic ester is as follows:



The Diels-Alder Synthesis

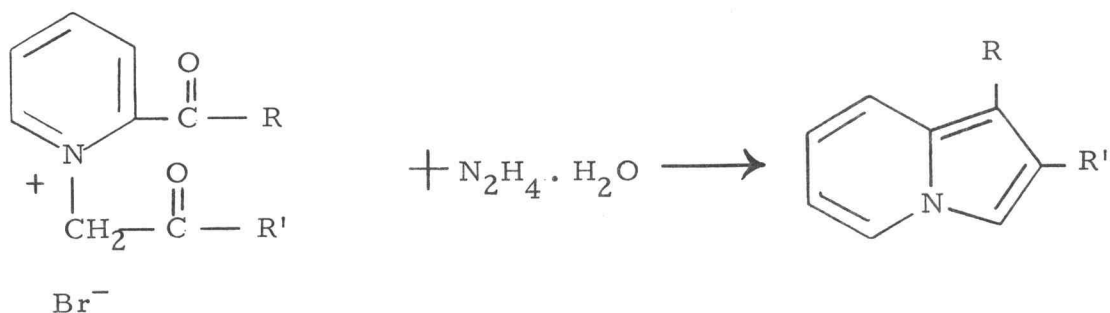
In this synthetic approach to indolizines, pyridine is reacted with dimethyl acetylenedicarboxylate and the resulting pyridocoline is converted to an indolizine by treatment with nitric acid or other suitable oxidizing agent (47, 49, 50, 51).



Although it provides a relatively convenient route to carboxy-indolizines, this method is limited by its obvious lack of versatility.

The Kroehnke and Weis Synthesis

This is the most recently reported method of synthesis for indolizines (65). The reaction is carried out by treating 1-phenacyl-2-acylpyridinium bromides with hydrazine hydrate. In some cases the reactants are simply combined at room temperature without solvent while mild refluxing with a suitable solvent is employed in others.



The reaction generally proceeds with yields in excess of 85% when R' is aryl. The yields are considerably lower when R' is methyl. In general the reaction proceeds in good yield whether the substituent R is methyl or phenyl. No compounds prepared by this method have been reported in which R or R' has been H. Also there has been no report of compounds with a substituent at C-3.

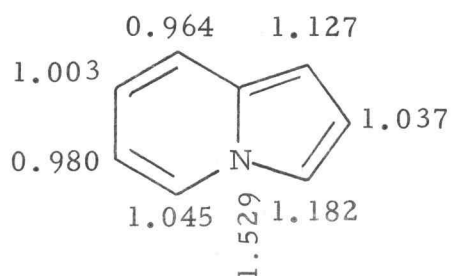
Chemical and Physical Properties of Indolizines

Unsubstituted indolizine and its simple alkyl derivatives are generally low melting solids or high boiling liquids (16; 74, p. 251). They are steam distillable and decompose on exposure to air and light. However, indolizines with an aryl group in the C-2 or C-5 positions are generally quite stable and non-volatile in steam. Many of these compounds are fluorescent when exposed to ultra-violet light. Indolizines give the characteristic color reactions of

indoles and pyrroles. These include the Angeli test for indoles, which is characterized by the formation of a colored melt with oxalic acid, and the Baeyer test for pyrroles, manifested by a color with a pine splinter in the presence of hydrochloric acid (74, p. 252). Those indolizines with an unsubstituted C-1 or C-3 position give a positive color test with Ehrlich's reagent (59), which is based on the formation of p-dimethylaminophenyl-bis(indoliziny)methanes.

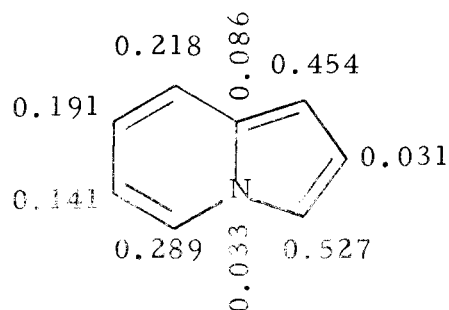
Most of the experimental evidence indicates that substitution on the indolizine nucleus is mainly a result of electrophilic attack (74, p. 254-263). Attempts to react a nucleophile with indolizines resulted in failure (16). The evidence further indicates that electrophilic substitution occurs preferentially at the C-3 position except when this position is blocked, in which case substitution takes place at C-1 (74, p. 253-254).

The π -electron densities and bond orders for indolizines were calculated by Longuet-Higgins and Coulson (69). They found that with the exception of the bridgehead nitrogen, the π -electron density was highest at the C-3 position with C-1 being next in the order of decreasing electron density.



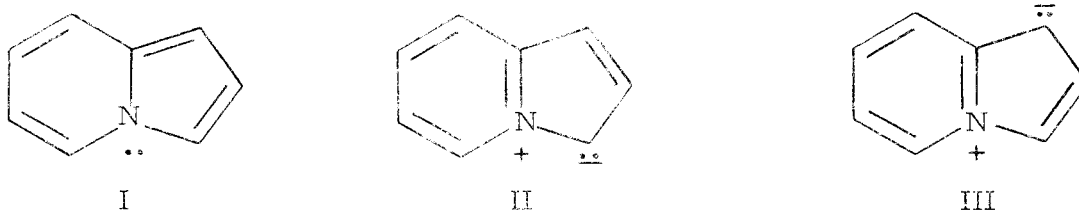
On the basis of their findings, these workers predicted that the order of reactivity toward electrophiles will be $3 > 1 > 5 > 2 > 7 > 6 > 8$. Experimental evidence has confirmed these predictions with respect to the C-3 and C-1 positions. However there has not been sufficient evidence to evaluate the relative reactivity of the remaining positions (74, p. 254).

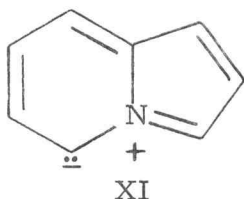
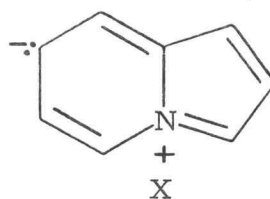
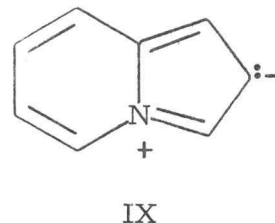
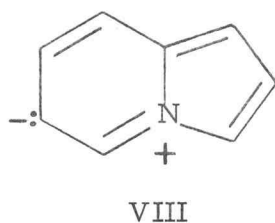
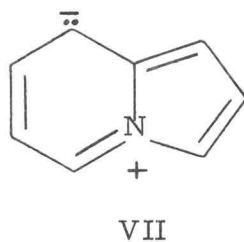
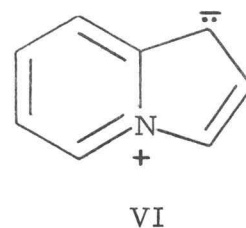
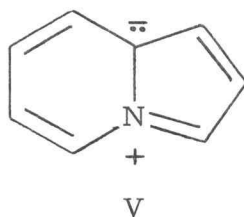
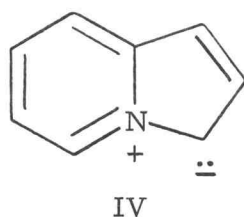
Fukui, et al. (56), employing the Linear Combination of Atomic Orbitals (L.C.A.O.) method, calculated the electron density of the highest occupied orbital in the ground state of indolizine. These electrons, as distinguished from other π -electrons, were called frontier electrons and were assumed to play a decisive role in determining the nucleophilic character of the compound. The values calculated for indolizine are shown in the following diagram:



The relative reactivities of the various positions toward electrophiles were therefore predicted to be $3 > 1 > 5 > 8 > 7 > 6 > 2$. Clearly these predictions are in general agreement with those of Longuet-Higgins and Coulson (69), especially with respect to the C-3 and C-1 positions. The inverted order of the C-2 and C-8 positions is the most notable disagreement.

Borrows and Holland (16) explained the chemical reactivity of the C-1 and C-3 positions by examining the contributing forms to the resonance hybrid of indolizine.





They noted that while a form can be written which places the negative charge on each of the carbons in the ring system, only four such forms (II, III, IV and VI) will permit Kekulé-type resonance of the six-membered ring. They reason that these four forms should make a much greater contribution to the resonance hybrid and inasmuch as two forms place the electron pair at C-1 while the other two place the negative charge at C-3, the reactivity of these two positions is explained.

Fraser, et al. (54, 55) studied the nuclear magnetic resonance spectra of the perchlorates of indolizine and several substituted

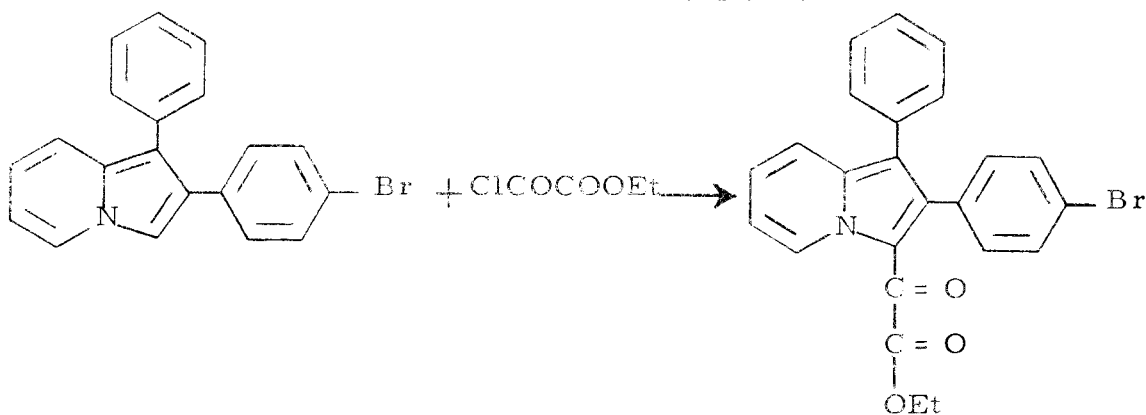
indolizines. They found no characteristic broad band or triplet which would indicate protonation at the nitrogen. They immediately concluded that protonation occurred at C-1 or C-3 since these are the only positions which would permit an aromatic pyridine structure. The n.m.r. spectra of all compounds investigated clearly indicated that protonation occurred almost exclusively at C-3 except when this position was blocked. In those compounds with a substituent at C-3 protonation occurred at both C-1 and C-3. Another study of n.m.r. spectra, which included several mono- and disubstituted indolizines as well as a deuterated compound, indolizine-1,3-d₂, was conducted by Black, et al. (9). Their findings were in general agreement with the foregoing. They further noted that the ratio of C-3:C-1 protonation was influenced by the nature of the substituents on the indolizine nucleus. The results of these two n.m.r. studies are compatible with the predictions of reactivity in terms of π -electron densities by Longuet-Higgins and Coulson (69).

The ultraviolet spectra of indolizines have been studied by numerous investigators (3, 4, 6, 16, 21, 59, 63, 83). In a recent publication (3) sixteen indolizines were studied and found to exhibit characteristic absorptions in three regions: 225-240 m μ , 270-310 m μ and 330-360 m μ . The introduction of a phenyl substituent at C-2 resulted in the expected bathochromic shift (63).

Even though indolizines are weak bases, they form salts readily with mineral acids and complexes with picric acid (74, p. 252).

Treatment with methyl iodide results in the formation of the indolizinium iodide together with nuclear methylation occurring at C-3 or C-1 (16). Indeed this property can be made use of as a synthetic tool for the introduction of alkyl groups at C-3 or C-1. Treatment of 2-methylindolizine with methyl iodide resulted in the formation of 2,3-dimethylindolizine and with a two molar excess of methyl iodide the product obtained was 1,2,3-trimethylindolizine (82).

Acylation occurs quite readily on indolizines (16). Treatment with acetic anhydride in the presence of sodium acetate readily yields the 3-acetyl derivative or the 1-acetyl compound in cases where the C-3 position is blocked. Under vigorous conditions the 1,3-diacetylindolizine can be prepared (18). The 1-or 3-benzoyl derivative can be prepared through the use of benzoyl chloride in the cold (19). Treatment of 1,2-diarylindolizines with ethoxalyl chloride, ClCOCOOEt , affords the 3-ethylglyoxyl derivative (92).



Introduction of alkyl groups is perhaps best accomplished by selecting the appropriate starting materials in carrying out the indolizine synthesis by one of the methods mentioned earlier in this work. As mentioned earlier, direct methylation or ethylation at the C-1 or C-3 position can also be accomplished by the action of methyl or ethyl iodide (16). Reduction of acyl groups to alkyl and aralkyl substituents by the Wolff-Kishner reaction and by lithium aluminum hydride has been reported (20, 82). Lithium aluminum hydride gives a much better yield in these reactions. The complete elimination of oxygen by this reagent is comparable to the analogous situation with acylindoles (74, p. 255). The Clemmenson reduction causes deacylation of indolizines in most cases, however limited success has been achieved with this reaction (20). Catalytic hydrogenation of acylindolizines to the corresponding alkyl derivative has been unsuccessful (20).

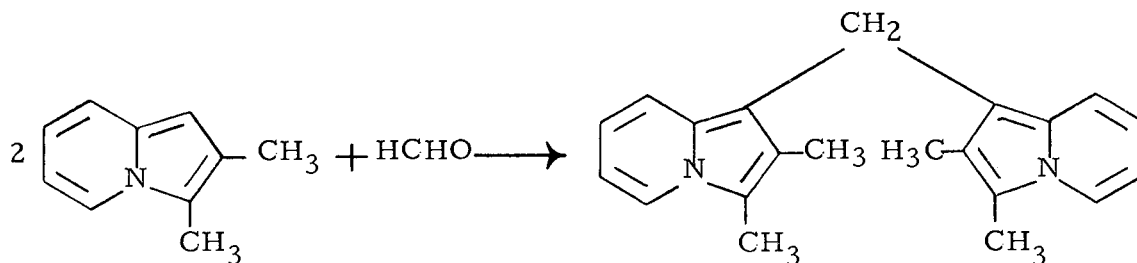
Nitration is readily accomplished on the indolizine nucleus by heating with nitric acid in the presence of sulfuric acid (19). This reaction is unique in that nitration occurs first at C-1 and is followed by attack at C-3. No explanation has been given for this apparent anomaly. Nitration of 2-phenylindolizine produces mainly the p-nitrophenyl derivative (19). The introduction of a nitro group at C-1 has recently been accomplished by subjecting 2-nitromethylpyridine to the Chichibabin synthesis (60).

Nitrosation of indolizine at C-1 or C-3 is readily accomplished by the action of nitrous acid (18). The nitroso group can also be introduced by employing ω -isonitrosophenacyl chloride in the Chichibabin reaction (18).

Attempts to halogenate indolizines have generally resulted in unstable products of indefinite composition (16; 74, p. 259). However, direct iodination of 2-phenylindolizine produced 1,3-diiodo-2-phenylindolizine (15) and Sholtz (85) reported the preparation of the 1,3-diiodo derivative of unsubstituted indolizine.

There are only two references cited in the literature concerning the use of the Mannich reaction on indolizines. Rossiter and Saxton (82) prepared 1-dimethylaminomethyl-2,3-dimethylindolizine by treating 2,3-dimethylindolizine with formaldehyde and dimethylamine. Carbon and Brehm (39) following the method of Rossiter and Saxton, reported the synthesis of 3-acetyl-1-dimethylamino methylindolizine. To date no other Mannich bases derived from indolizines have been reported.

Indolizines will react with aldehydes and ketones to produce bis(indoliziny)methanes. This is a significant side reaction in preparing Mannich bases with indolizine (82) which could predominate if conditions are not properly controlled.



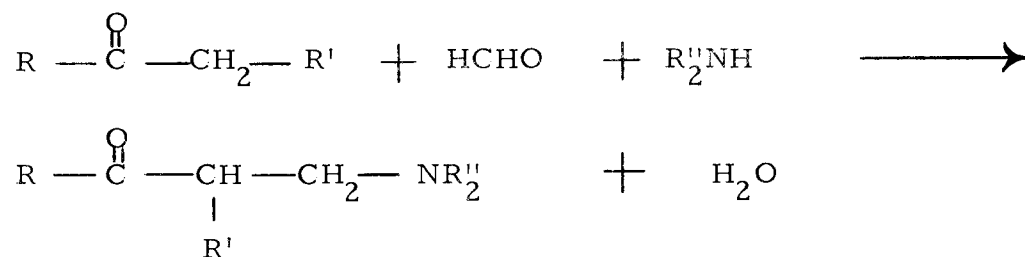
Compounds of this type have also been prepared from acetone (23), acetoacetic ester (85) and benzaldehyde (52, p. 417).

Discussion of the Mannich Reaction

An excellent review of the Mannich reaction has been presented by Blicke (10). Subsequently, several other reviews have been published on this subject (57, 61, 71, 76, 77, 81).

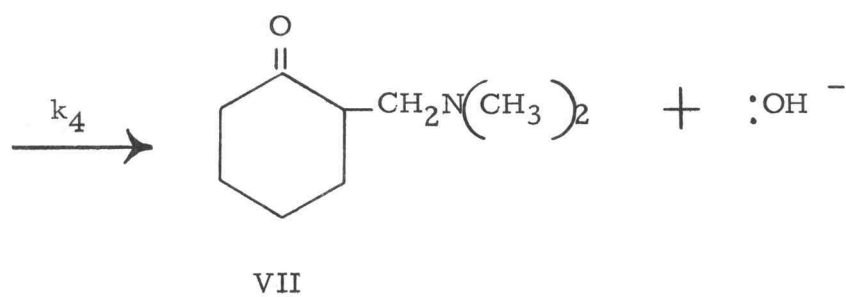
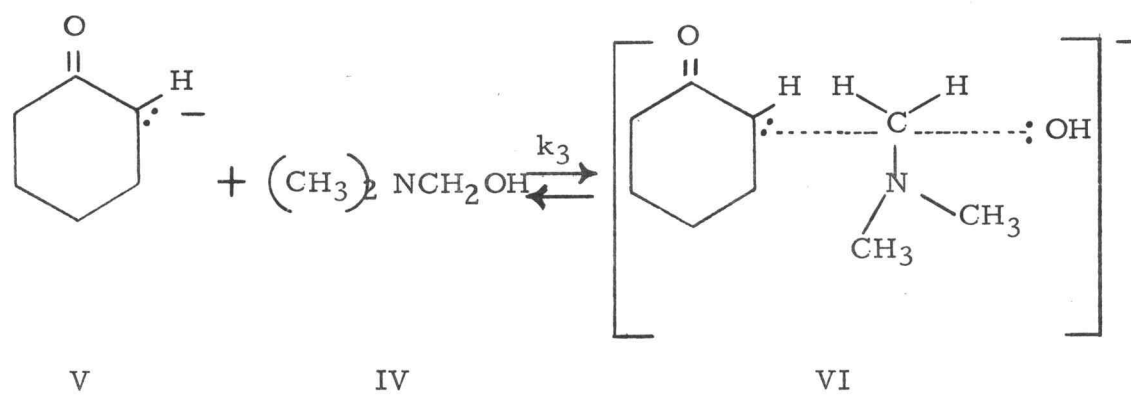
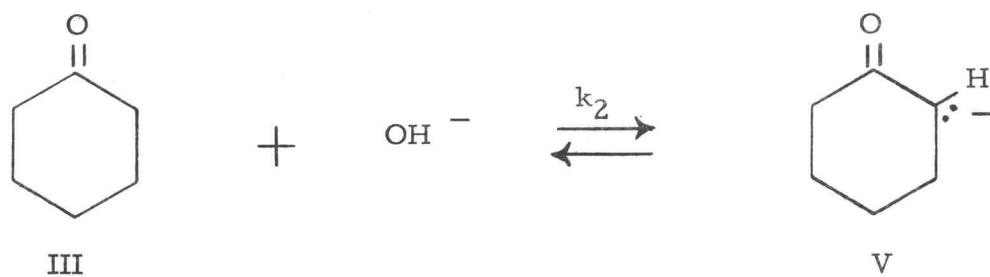
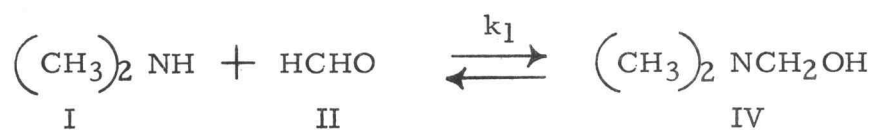
Essentially, the Mannich reaction (70) consists of the condensation of compounds containing one or more active hydrogens with formaldehyde and an amine. A wide variety of compounds with active hydrogens may be employed in this reaction. They include aldehydes, ketones, acids, esters, phenols, acetylenes and α -picolines (10). The amine employed is usually a secondary amine; however many such reactions have been carried out using primary amines or ammonia. Although formaldehyde or paraformaldehyde

is employed in the vast majority of Mannich reactions, other compounds such as acetaldehyde, benzaldehyde and anisaldehyde have served as the aldehyde component (10). The essential feature of this reaction is the replacement of the active hydrogen with an aminomethyl group, as illustrated below with ketones.



Although numerous mechanisms have been proposed for the Mannich reaction (1, 11, 45, 46, 53, 66, 90), none has been universally accepted. A recently advanced mechanism for this reaction was that proposed by Cummings and Shelton (46). They presented kinetic data to support two plausible mechanisms for the Mannich reaction; one that is base-catalyzed and pH dependent and another that is acid-catalyzed but independent of pH at low pH values. These mechanisms as applied to the reaction of cyclohexanone with formaldehyde and dimethylamine, are presented in the discussion which follows.

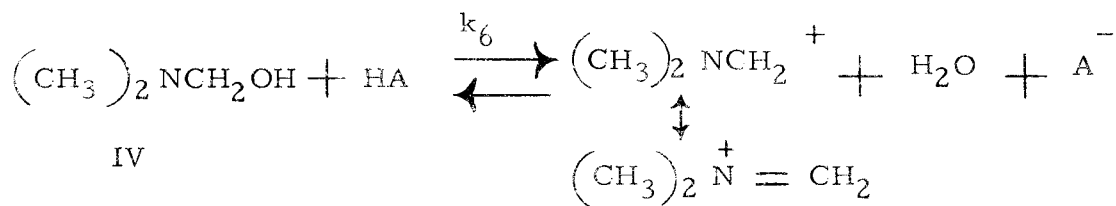
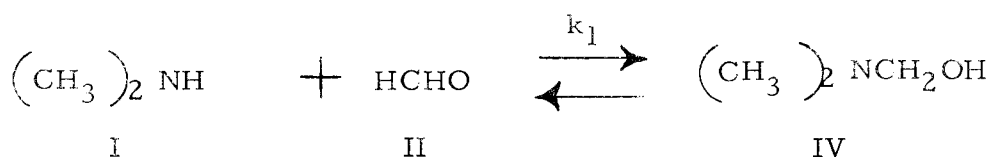
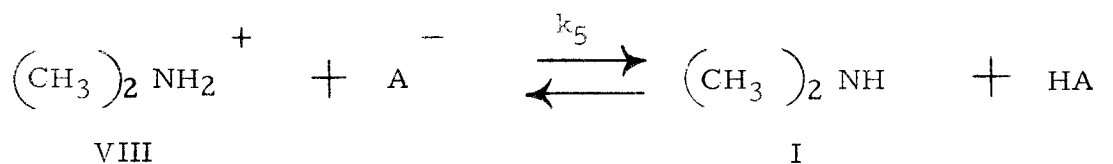
In the base-catalyzed process Cummings and Shelton propose an intermediate carbanion which reacts by a rate-determining $\text{S}_{\text{N}}2$ mechanism with the aminomethylol formed from the amine and formaldehyde.

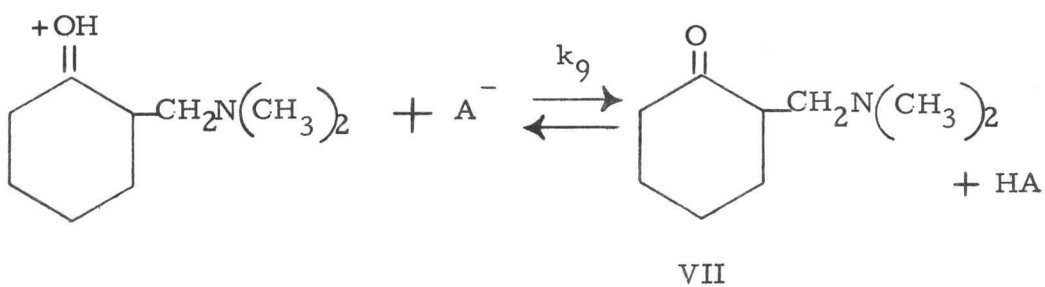
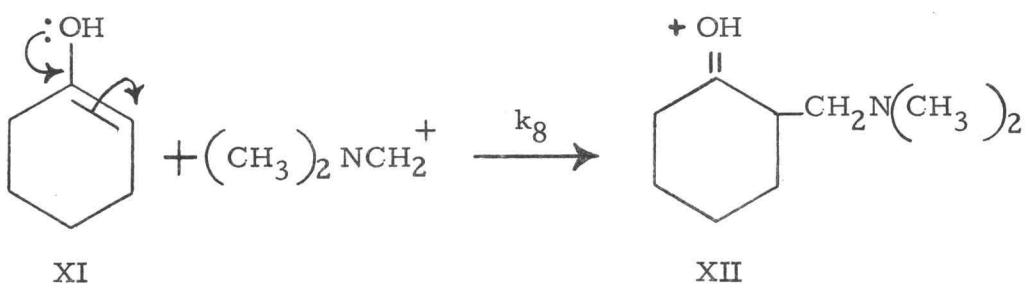
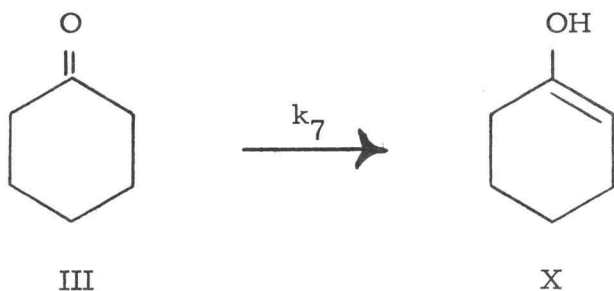


The reaction exhibits third order kinetics and the rate is proportional to the base concentration. The rate equation is:

$$\begin{aligned}
 \frac{dx}{dt} &= k_4 \text{ (VI)} \\
 &= k_4 k_3 \text{ (IV) (V)} \\
 &= k_4 k_3 k_2 k_1 \text{ (I) (II) (III) (OH}^- \text{)} \\
 &= k(\text{CH}_3\text{NHCH}_3) (\text{HCHO}) (\text{C}_6\text{H}_{10}\text{O}) (\text{OH}^-)
 \end{aligned}$$

In acid solution the amine is recognized as being in equilibrium with the salt form. As in the base-catalyzed mechanism, the free amine is the reactive species. According to Cummings and Shelton a resonance-stabilized carbonium ion is formed by the action of acid on the aminomethylol. The active hydrogen compound reacting in the enol form, combines with the carbonium ion by an $\text{S}_{\text{N}}1$ mechanism which is essentially irreversible and rate-controlling.

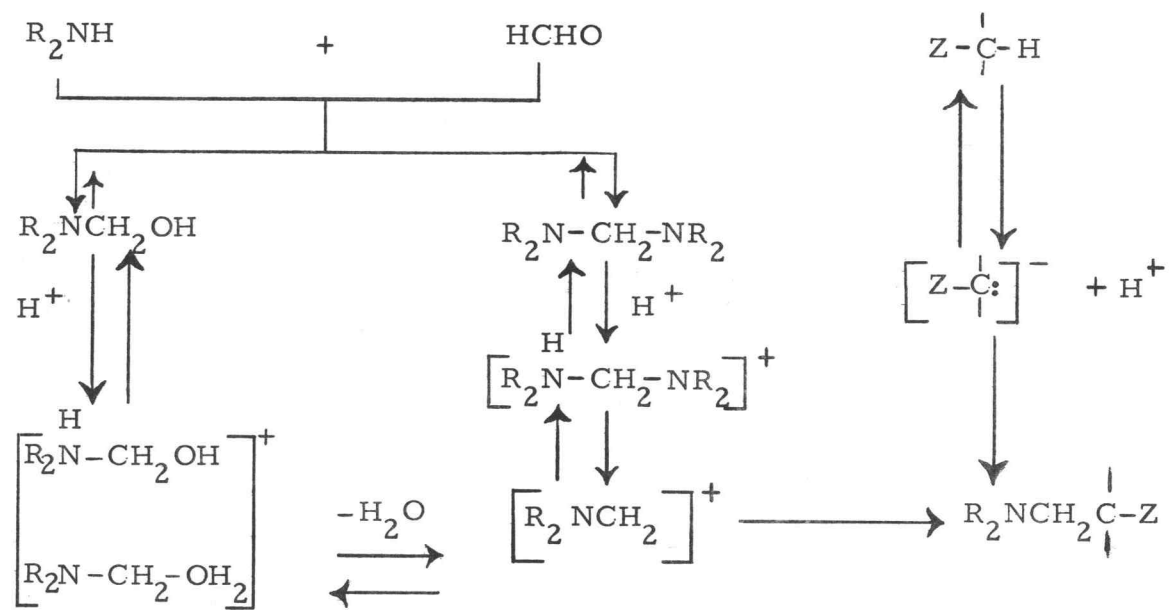




$$\text{Rate} = \frac{dx}{dt} = k_8 k_7 k_6 k_1 k_5 (\text{CH}_3\text{NHCH}_3)(\text{HCHO})(\text{C}_6\text{H}_{10}\text{O})$$

$$= k (\text{CH}_3\text{NHCH}_3)(\text{HCHO})(\text{C}_6\text{H}_{10}\text{O})$$

Both of the above mechanisms follow third order reaction kinetics at high and low pH values respectively. There is a deviation from third order kinetics in the region between pH 5 and pH 9, which led Cummings and Shelton to postulate that the mechanisms are in fact different in acidic and basic media and that both of the foregoing mechanisms are in operation in this transitional range. Third order reaction kinetics for the Mannich reaction was also observed by Alexander and Underhill (1). The findings in both of these investigations tend to disprove a mechanism presented by Lieberman and Wagner (66) who proposed the reaction of a carbonium ion with a carbanion as the rate-controlling step in the Mannich reaction. Lieberman and Wagner proposed a dual catalyzed reaction in an amphoteric system which involves the intermediate formation of an aminomethylol or a methylene-bis-amine or both. The active hydrogen compound, $Z-\overset{\overset{|}{\text{C}}}{\underset{\underset{|}{\text{H}}}{\text{C}}}-\text{H}$, is converted to a carbanion by the base present in the system.



PURPOSE OF THE INVESTIGATION

The purpose of this investigation was to prepare certain Mannich bases derived from 2-phenylindolizines, heretofore unprepared, to be tested for physiological activity. It was hoped that ultimately this project would lead to the development of new therapeutic agents.

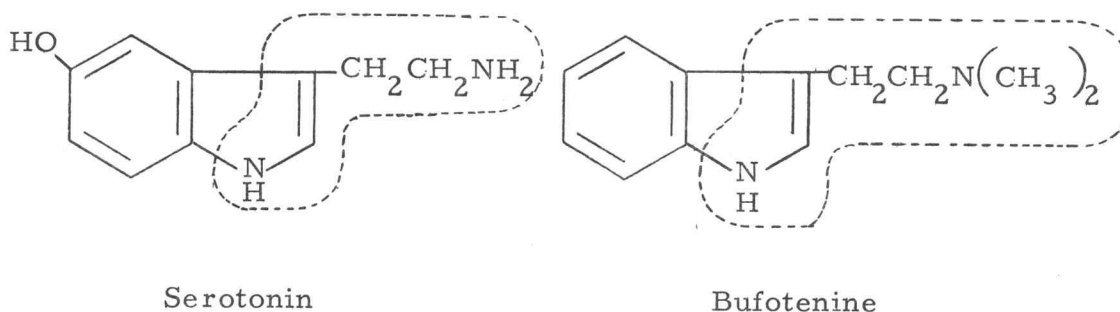
Many physiologically active compounds have the indole nucleus in their structure. The similarity between the indole and indolizine nuclei has prompted speculation that indolizine analogs of biologically important indoles could conceivably have potent physiological activity (37, 39, 91). It is this concept, coupled with the observation that very little work has been reported in this area, that encouraged the consideration of the indolizine nucleus for the present investigation.

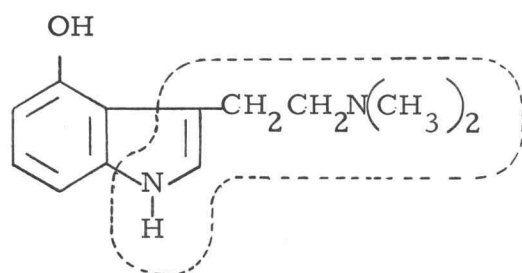
Reports on the biological activity of indolizines are very scarce in the literature. On subcutaneous injection 1-acetyl-3-amino-2-methylindolizine was shown to cause convulsions in frogs, mice, and rabbits (58). β -(1-Indoliziny)- α -aminopropionic acid, the indolizine analog of the amino acid tryptophane, has been prepared (39) and later shown to inhibit indole formation by an indole-accumulating mutant of Salmonella typhimurium (67). A series of arylindolizines were synthesized by Venturella for the purpose of

pharmacological testing (91, 92, 93), but to date no report on the pharmacology of these compounds has appeared in the literature. A summary of 2-phenylindolizines that have been reported in the literature is presented in Table I.

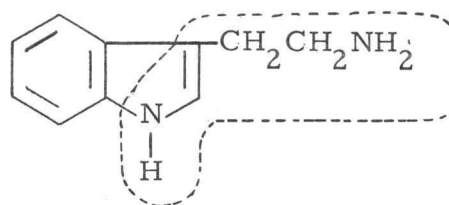
Having decided upon the indolizine structure, attention was then focused on the various possibilities of chemical modification which might logically be expected to produce physiologically active compounds.

Among the biologically active indoles, many are aminoalkyl derivatives such as serotonin, bufotenine, psilocin, tryptamine, reserpine and lysergic acid diethylamide (LSD); all of which are known to have pronounced activity on the central nervous system.

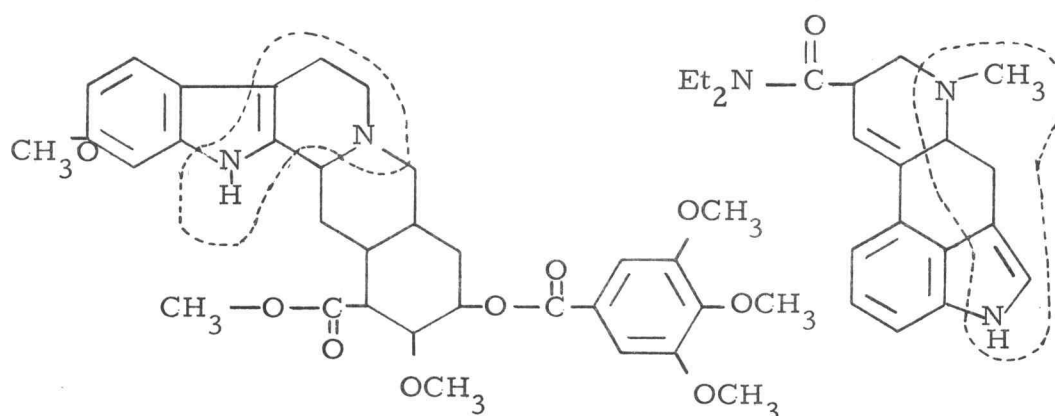




Psilocin



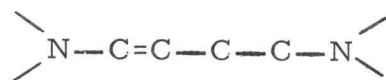
Tryptamine



Reserpine

LSD

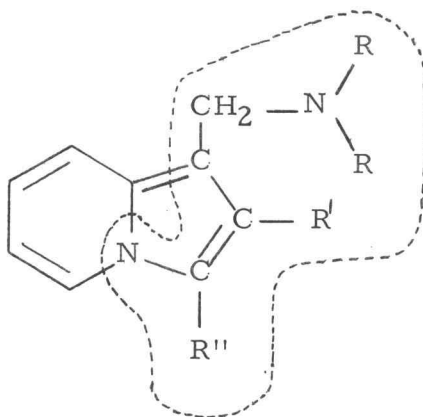
As shown in the above structures of these compounds the indole nitrogen and the extra-indole nitrogen are separated by four carbon atoms, a spatial arrangement which might be a contributing factor in determining their activities.



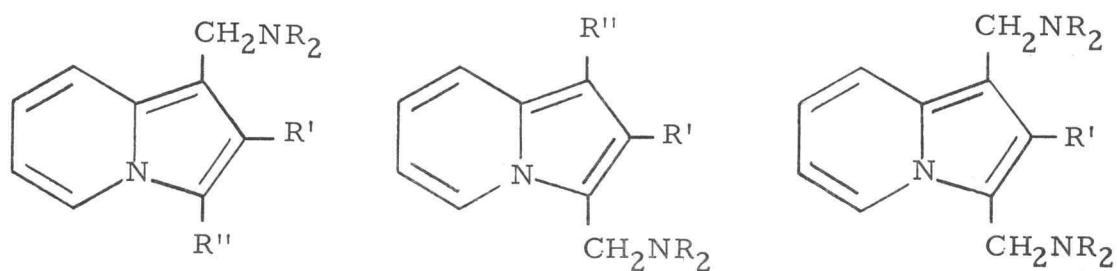
It has been shown that compounds which show similar intramolecular distances between functional groupings frequently have

similar or related activities (25, p. 56). These intramolecular distances have been studied with various series of drugs and suggested to be in correlation with the distances between the binding sites of the so-called biological receptors with which the drug combines in the living organism (8, 68). It was therefore speculated that certain aminoalkyl indolizines with the same carbon spread between the nitrogen atoms as the foregoing amino indoles might possess activity on the central nervous system.

The Mannich reaction was decided upon because the resulting dialkylaminomethyl substituent when introduced at the C-1 position would give the desired intramolecular spread ($\text{>N}-\text{C}=\text{C}-\text{C}-\text{C}-\text{N}<$).



In a broader approach to the problem of finding new physiologically active compounds it was decided to explore the Mannich reaction with several indolizines and prepare a series of Mannich bases of the following types:



The results of this investigation are reported in the experimental section.

Table I. 2-Phenylindolizines That Have Been Reported in the Literature

Empirical Formula	Indolizine	Properties	References
$C_{14}H_8N_4O_6$	1,3-Dinitro-2-(p-nitrophenyl)-	m. p. 232-3° (decompn.)	19
$C_{14}H_9BrN_2O$	2-(p-Bromophenyl)-3-nitroso-	m. p. 187-8° (decompn.)	26
$C_{14}H_9ClN_2O$	2-(p-Chlorophenyl)-3-nitroso-	m. p. 177° (decompn.)	26
$C_{14}H_9Cl_2N$	2-(3,4-Dichlorophenyl)-	m. p. 177°.	37
$C_{14}H_9FN_2O$	2-(p-Fluorophenyl)-3-nitroso-	m. p. 118°.	27
$C_{14}H_9I_2N$	1,3-Diiodo-2-phenyl-	HI salt, m. p. 203° (decompn.)	15
$C_{14}H_9N_3O_4$	1,3-Dinitro-2-phenyl-	m. p. 246-8°.	19
$C_{14}H_9N_3O_4$	1-Nitro-2-(p-nitrophenyl)-	m. p. 235-6° (decompn.)	19
$C_{14}H_9N_3O_4$	3-Nitro-2-(p-nitrophenyl)-	m. p. 211°.	19
$C_{14}H_{10}BrN$	2-(p-Bromophenyl)-	m. p. 260°.	26
$C_{14}H_{10}ClN$	2-(p-Chlorophenyl)-	m. p. 248°.	26
$C_{14}H_{10}FN$	2-(p-Fluorophenyl)-	m. p. 231°.	27
$C_{14}H_{10}IN$	2-(p-Iodophenyl)-	m. p. 278°.	37
$C_{14}H_{10}N_2O$	3-Nitroso-2-phenyl-	m. p. 97.5-8°.	18
$C_{14}H_{10}N_2O_2$	1-Nitro-2-phenyl-	m. p. 151-152°.	60
$C_{14}H_{10}N_2O_2$	2-(m-Nitrophenyl)-	m. p. 183°.	30
$C_{14}H_{10}N_2O_2$	2-(p-Nitrophenyl)-	m. p. 250-1° (decompn.)	19, 30
$C_{14}H_{11}N$	2-Phenyl-	m. p. 214-5°.	16, 17, 19 21, 40, 62
$C_{14}H_{11}NO$	1-Hydroxy-2-phenyl-	hydrochloride, m. p. > 360°.	60
$C_{14}H_{11}NO$	2-(p-Hydroxyphenyl)-	m. p. 243°.	35
$C_{14}H_{12}N_2$	1-Amino-2-phenyl-	m. p. 115-116°.	60
$C_{14}H_{12}N_2$	2-(m-Aminophenyl)-	m. p. 173°.	30

Table I. (continued)

Empirical Formula	Indolizine	Properties	References
$C_{14}H_{12}N_2$	2-(p-Aminophenyl)-	m. p. 204° .	30
$C_{15}H_{11}Cl_2N$	2-(3,4-Dichlorophenyl)-7-methyl-	m. p. 183° .	37
$C_{15}H_{12}BrN$	2-(p-Bromophenyl)-1-methyl-	m. p. $103-105^{\circ}$.	65
$C_{15}H_{12}BrNO$	2-(3-Bromo-4-methoxyphenyl)-	m. p. 225° .	37
$C_{15}H_{12}ClNS$	2-(3-Chloro-4-methylthiophenyl)-	m. p. 194° .	94
$C_{15}H_{12}ClN$	2-(p-Chlorophenyl)-5-methyl-	m. p. 111° .	37
$C_{15}H_{12}ClN$	2-(p-Chlorophenyl)-7-methyl-	m. p. 287° .	37
$C_{15}H_{12}FN$	2-(4-Fluoro-2-methylphenyl)-	m. p. 86° .	33
$C_{15}H_{12}FN$	2-(4-Fluoro-3-methylphenyl)-	m. p. 174° .	37
$C_{15}H_{12}FN$	2-(p-Fluorophenyl)-5-methyl-	m. p. 107° .	37
$C_{15}H_{12}FN$	2-(p-Fluorophenyl)-7-methyl-	m. p. 248° .	37
$C_{15}H_{12}FNO$	2-(3-Fluoro-4-methoxyphenyl)-	m. p. 197° .	34
$C_{15}H_{12}FNO$	2-(3-Fluoro-6-methoxyphenyl)-	m. p. 56° .	31
$C_{15}H_{12}N_2O_2$	1-Methyl-2-(m-nitrophenyl)-	m. p. $77-79^{\circ}$.	65
$C_{15}H_{12}N_2O_2$	1-Methyl-2-(p-nitrophenyl)-	m. p. $179-181^{\circ}$.	65
$C_{15}H_{12}N_2O_2$	5-Methyl-2-(m-nitrophenyl)-	m. p. 125° .	30
$C_{15}H_{12}N_2O_2$	5-Methyl-2-(p-nitrophenyl)-	m. p. 130° .	30
$C_{15}H_{12}N_2O_2$	7-Methyl-2-(m-nitrophenyl)-	m. p. 174° .	30
$C_{15}H_{12}N_2O_2$	7-Methyl-2-(p-nitrophenyl)-	m. p. 219° .	30
$C_{15}H_{13}N$	1-Methyl-2-Phenyl-	m. p. $81-83^{\circ}$; 95° .	63, 65
$C_{15}H_{13}N$	3-Methyl-2-phenyl-	m. p. $97-98^{\circ}$.	23
$C_{15}H_{13}N$	5-Methyl-2-phenyl-	m. p. $81-81.5^{\circ}$; $83-83.5^{\circ}$.	13, 95

Table I. (continued)

Empirical Formula	Indolizine	Properties	References
$C_{15}H_{13}N$	2-(p-Tolyl)-	m. p. 222°.	26
$C_{15}H_{13}NO$	2-(p-Methoxyphenyl)-	m. p. 180.5°; 205°.	37, 63
$C_{15}H_{13}NS$	2-(p-Methylthiophenyl)-	m. p. 255°.	37
$C_{15}H_{14}N_2$	2-(m-Aminophenyl)-7-methyl-	m. p. 176°.	30
$C_{16}H_{11}N_3O_5$	3-Acetyl-1-nitro-2-(p-nitrophenyl)-	m. p. 173.5°.	19
$C_{16}H_{12}INO$	3-Acetyl-1-iodo-2-phenyl-	m. p. 114-6°.	15
$C_{16}H_{12}N_2$	1-Cyano-3-methyl-2-phenyl-	m. p. 173-174°.	60
$C_{16}H_{12}N_2$	2-(p-Cyanophenyl)-3-methyl-	m. p. 181-3°.	86, 87, 88
$C_{16}H_{12}N_2O_2$	1-Acetyl-3-nitroso-2-phenyl-	HCl Salt, m. p. 99°.	18, 28
$C_{16}H_{12}N_2O_2$	3-Acetyl-1-nitroso-2-phenyl-	m. p. 154-154.5°.	18
$C_{16}H_{12}N_2O_3$	3-Acetyl-2-(p-nitrophenyl)-	m. p. 190.5-191°.	19
$C_{16}H_{12}N_2O_3$	3-Acetyl-1-nitro-2-phenyl-	m. p. 169°.	19
$C_{16}H_{13}NO$	2-(p-Acetylphenyl)-	m. p. 240-1° (decompn.)	17
$C_{16}H_{13}NO$	3-Acetyl-2-phenyl-	b. p. 0.05, 162-74°; m. p. 64.5°.	19
$C_{16}H_{13}NO$	5-Formylmethyl-2-phenyl	--	13
$C_{16}H_{13}NO_2$	3-Methyl-2-phenyl-1-indolizine- carboxylic acid	m. p. 172-174° (decompn.)	23
$C_{16}H_{14}ClNO$	2-(3-Chloro-4-ethoxyphenyl)-	m. p. 218°.	37
$C_{16}H_{14}FN$	2-(4-Fluoro-2-methylphenyl)- 5-methyl-	oil. picrate m. p. 155-6°.	33
$C_{16}H_{14}FN$	2-(4-Fluoro-2-methylphenyl)- 7-methyl-	m. p. 74°.	33
$C_{16}H_{14}FN$	2-(4-Fluoro-3-methylphenyl)- 7-methyl-	m. p. 174°.	37
$C_{16}H_{14}FNO$	2-(3-Fluoro-4-methoxyphenyl)- 7-methyl-	m. p. 209°.	34

Table I. (continued)

Empirical Formula	Indolizine	Properties	References
$C_{16}H_{14}FNO$	2-(3-Fluoro-6-methoxyphenyl)- 7-methyl-	m. p. 74° .	31
$C_{16}H_{14}N_2O$	1-Acetamido-2-phenyl-	m. p. $192-193^{\circ}$. (decompn.)	60
$C_{16}H_{15}N$	1,3-Dimethyl-2-phenyl-	m. p. 82° .	89
$C_{16}H_{15}N$	2-(2,4-Dimethylphenyl)-	m. p. 106° .	37
$C_{16}H_{15}N$	2-(2,5-Dimethylphenyl)-	m. p. 69° .	37
$C_{16}H_{15}N$	2-(3,4-Dimethylphenyl)-	m. p. 148° .	37
$C_{16}H_{15}N$	3-Ethyl-2-phenyl-	m. p. 94° .	20
$C_{16}H_{15}N$	6-Ethyl-2-phenyl-	m. p. $142-3^{\circ}$.	44
$C_{16}H_{15}N$	1-Methyl-2-(p-tolyl)-	m. p. 96° .	63
$C_{16}H_{15}NO$	2-(p-Ethoxyphenyl)-	m. p. 218° .	37
$C_{16}H_{15}NO$	2-(2-Methoxy-4-methylphenyl)-	m. p. 86° .	37
$C_{16}H_{15}NO$	2-(4-Methoxy-3-methylphenyl)-	m. p. 182° .	37
$C_{16}H_{15}NO$	2-(p-Methoxyphenyl)-1-methyl-	m. p. $95-97^{\circ}$.	63, 65
$C_{16}H_{15}NO$	2-(p-Methoxyphenyl)-7-methyl-	m. p. 239° .	37
$C_{16}H_{15}NO_2$	2-(2,4-Dimethoxyphenyl)-	m. p. 139° .	37
$C_{16}H_{15}NO_2$	2-(2,5-Dimethoxyphenyl)-	m. p. 94° .	37
$C_{16}H_{15}NO_2$	2-(3,4-Dimethoxyphenyl)-	m. p. 179° .	37
$C_{16}H_{16}N_2$	1-(2-Aminoethyl)-2-phenyl-	dipicrate, m. p. $135-136^{\circ}$.	2
$C_{17}H_{15}NO_2$	2-Phenyl-1-indolizinecarboxylic acid, ethyl ester	m. p. $106-107^{\circ}$.	23
$C_{17}H_{17}N$	2-(2,5-Dimethylphenyl)-7-methyl-	m. p. 134° .	37
$C_{17}H_{17}NO$	2-(4-Ethoxy-3-methylphenyl)-	m. p. 200° .	37
$C_{17}H_{17}NO$	2-(2-Methoxy-3,5-dimethylphenyl)-	m. p. 136° .	37

Table I. (continued)

Empirical Formula	Indolizine	Properties	References
$C_{17}H_{17}NO$	2-(4-Methoxy-2,5-dimethylphenyl)-	m. p. 124°.	37
$C_{18}H_{15}NO_2$	1,3-Diacetyl-2-phenyl-	m. p. 172.5-3°.	17
$C_{18}H_{16}N_2O_2$	3-Diacetylamino-2-phenyl-	m. p. 113-114°.	60
$C_{18}H_{17}NO_2$	3-Methyl-2-phenyl-1-indolizine- carboxylic acid, ethyl ester	m. p. 101-102°.	23
$C_{19}H_{21}NO$	2-(4-Methoxy-2-methyl-5-isopropyl- phenyl)-	m. p. 98°.	37
$C_{20}H_{13}BrClN$	2-(p-Bromophenyl)-1-(p-chlorophenyl)-	m. p. 178-180° (decompn.)	91
$C_{20}H_{13}ClN_2O_2$	1-(p-Chlorophenyl)-2-(p-nitrophenyl)-	m. p. 214-216°.	91
$C_{20}H_{14}BrN$	2-(p-Bromophenyl)-1-phenyl-	m. p. 138-139.5°; 143-145°.	65, 91
$C_{20}H_{14}ClN$	1-(p-Chlorophenyl)-2-phenyl-	m. p. 118°.	4
$C_{20}H_{14}ClNO$	1-(p-Chlorophenyl)-2-(p-hydroxy- phenyl)-	m. p. 130-131°.	92
$C_{20}H_{14}N_2O_2$	2-(m-Nitrophenyl)-1-phenyl-	m. p. 152-154°.	60
$C_{20}H_{14}N_2O_2$	2-(p-Nitrophenyl)-1-phenyl-	m. p. 158-160°; 166-167° (decompn.)	60, 91
$C_{20}H_{15}ClN_2$	2-(p-Aminophenyl)-1-(p-chlorophenyl)-	m. p. 165-167°.	91
$C_{20}H_{15}N$	2-(p-Biphenyl)-	m. p. 303-4° (decompn.)	28
$C_{20}H_{15}N$	1,2-Diphenyl-	m. p. 112°.	4
$C_{20}H_{15}N$	2,3-Diphenyl-	m. p. 94-5°.	44, 86, 87, 88
$C_{20}H_{15}NO$	2-(p-Hydroxyphenyl)-1-phenyl	m. p. 156-157°.	92
$C_{20}H_{15}NO$	2-(p-Phenoxyphenyl)-	m. p. 196°.	37
$C_{20}H_{15}NS$	2-(p-Phenylthiophenyl)-	m. p. 184°.	37
$C_{20}H_{16}N_2$	2-(p-Aminophenyl)-1-phenyl-	m. p. 153-154.5°.	91
$C_{20}H_{17}N_3O_2S$	2-(m-Sulfanilamidophenyl)-	m. p. 186°.	30

Table I. (continued)

Empirical Formula	Indolizine	Properties	References
$C_{20}H_{17}N_3O_2S$	2-(p-Sulfanilamidophenyl)-	m. p. 310° .	30
$C_{20}H_{18}N_2O_3$	3-Acetyl-1-diacetylamino-2-phenyl-	m. p. $162-163^{\circ}$.	60
$C_{20}H_{20}N_2O$	2-(p-Cyclohexylphenyl)-3-nitroso-	m. p. 188° .	38
$C_{20}H_{21}N$	2-(p-Cyclohexylphenyl)-	m. p. 208° .	38
$C_{21}H_{15}NO$	3-Benzoyl-2-phenyl	m. p. $137-8^{\circ}$.	17
$C_{21}H_{15}NO_2$	1-Benzoyloxy-2-phenyl-	m. p. $196-197^{\circ}$.	60
$C_{21}H_{16}ClNO$	1-(p-Chlorophenyl)-2-(p-methoxy-phenyl)-	m. p. $118.5-119.5^{\circ}$.	92
$C_{21}H_{17}N$	2-(4'-Methyl-4-biphenyl)-	m. p. 317° .	28
$C_{21}H_{17}N$	2-(p-Biphenyl)-7-methyl	m. p. $305-6^{\circ}$.	28
$C_{21}H_{17}N$	3-Benzyl-2-phenyl-	m. p. $100-1^{\circ}$.	20
$C_{21}H_{17}NO$	2-(4'-Methoxy-4-biphenyl)-	m. p. 310° .	36
$C_{21}H_{17}NO$	2-(p-Methoxyphenyl)-1-phenyl-	m. p. $97-98^{\circ}$.	92
$C_{21}H_{17}NS$	7-Methyl-2-(p-phenylthiophenyl)-	m. p. 191° .	37
$C_{21}H_{19}N_3O_2S$	7-Methyl-2-(m-sulfanilamidophenyl)-	m. p. 188° .	30
$C_{21}H_{20}N_2$	2-[3-(2',5'-Dimethyl-1-pyrryl)-phenyl]-7-methyl-	m. p. 171° .	29
$C_{21}H_{22}N_2O$	2-(p-Cyclohexylphenyl)-6-methyl-3-nitroso-	m. p. 190° .	38
$C_{21}H_{22}N_2O$	2-(p-Cyclohexylphenyl)-7-methyl-3-nitroso-	m. p. 196° .	38
$C_{21}H_{23}N$	2-(p-Cyclohexylphenyl)-6-methyl-	m. p. 207° .	38
$C_{21}H_{23}N$	2-(p-Cyclohexylphenyl)-7-methyl-	m. p. 226° .	38
$C_{22}H_{13}BrClNO_3$	2-(p-Bromophenyl)-1-(p-chlorophenyl)-3-indolizineglyoxylic acid	m. p. $174.5-175.5^{\circ}$.	92
$C_{22}H_{13}ClN_2O_5$	1-(p-Chlorophenyl)-2-(p-nitrophenyl)-3-indolizineglyoxylic acid	m. p. $193-195^{\circ}$.	92

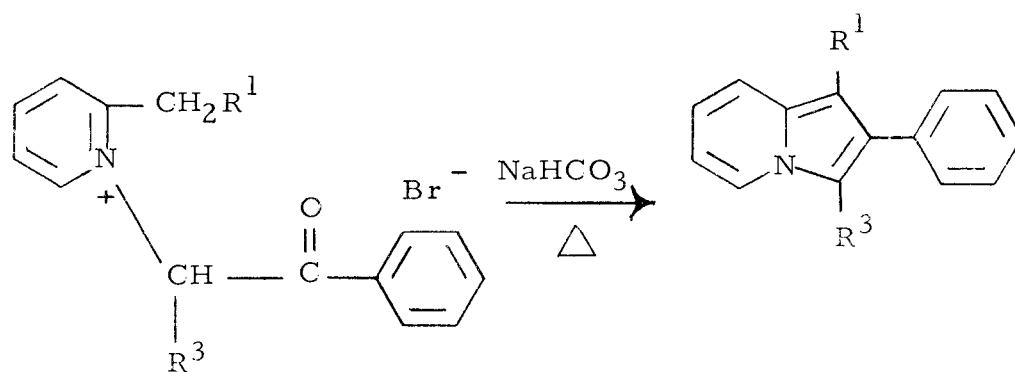
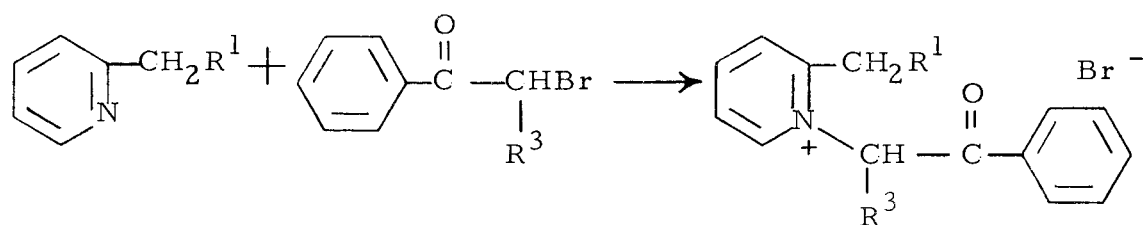
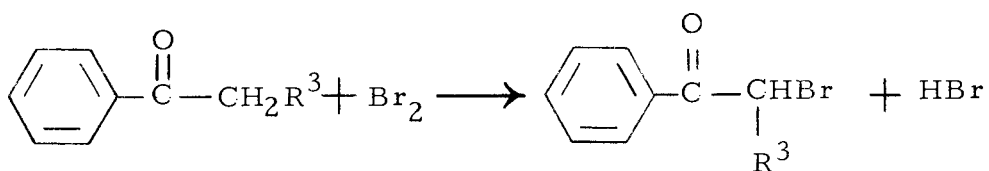
Table I. (continued)

Empirical Formula	Indolizine	Properties	References
$C_{22}H_{14}BrNO_3$	2-(p-Bromophenyl)-1-phenyl-3-indolizineglyoxylic acid	m. p. 179-180°.	92
$C_{22}H_{14}N_2O_5$	2-(p-Nitrophenyl)-1-phenyl-3-indolizineglyoxylic acid	m. p. 168-169°.	92
$C_{22}H_{16}ClNO$	3-Acetyl-1-(p-chlorophenyl)-2-phenyl-	m. p. 181-2°.	4, 5
$C_{22}H_{16}N_2$	1, 4-Bis(2-indoliziny)benzene	Subl. 410°.	32
$C_{22}H_{17}NO$	3-Acetyl-1, 2-diphenyl-	m. p. 175-6°.	4, 5
$C_{22}H_{18}N_2O_2$	1-(2-Nitro-1-phenylethyl)-2-phenyl-	m. p. 118-119°.	79
$C_{22}H_{19}NO$	7-Benzoyloxy-5-methyl-2-phenyl-	m. p. 152-153°.	2
$C_{22}H_{19}N_3O_3S$	2-[3-(4'-Acetamidobenzenesulfonylamido)phenyl]-	m. p. 230°.	30
$C_{22}H_{19}N_3O_3S$	2-[4-(4'-Acetamidobenzenesulfonylamido)phenyl]-	m. p. 283°.	30
$C_{22}H_{24}N_2O$	2-(p-Cyclohexylphenyl)-6-ethyl-4-nitroso-	m. p. 148°.	38
$C_{22}H_{25}N$	2-(p-Cyclohexylphenyl)-6-ethyl-	m. p. 159°.	38
$C_{23}H_{19}NO_2$	2, 3-Diphenyl-1-indolizinecarboxylic acid, ethyl ester	m. p. 151-152°.	23
$C_{23}H_{21}N_3O_3S$	2-[3-(4'-Acetamidobenzenesulfonylamido)phenyl]-7-methyl-	m. p. 263°.	30
$C_{24}H_{17}BrClNO_3$	2-(p-Bromophenyl)-1-(p-chlorophenyl)-3-indolizineglyoxylic acid, ethyl ester	m. p. 179.5-180°.	92
$C_{24}H_{17}ClN_2O_5$	1-(p-Chlorophenyl)-2-(p-nitrophenyl)-3-indolizineglyoxylic acid, ethyl ester	m. p. 215.5-216.5°.	92
$C_{24}H_{18}BrNO_3$	2-(p-Bromophenyl)-1-phenyl-3-indolizineglyoxylic acid, ethyl ester	m. p. 190-192°.	92
$C_{24}H_{18}N_2O_5$	2-(p-Nitrophenyl)-1-phenyl-3-indolizineglyoxylic acid, ethyl ester	m. p. 193-194°.	92

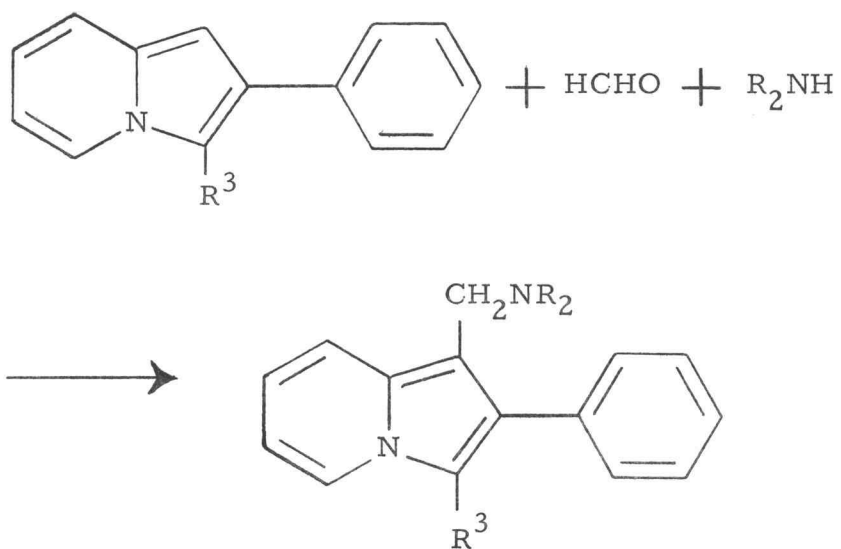
Table I. (continued)

Empirical Formula	Indolizine	Properties	References
$C_{24}H_{20}N_2$	1, 4-Bis(7-Methylindolizin-2-yl)benzene	m. p. 400°.	32
$C_{26}H_{18}ClN$	1-(p-Chlorophenyl)-2, 3-diphenyl-	m. p. 195-196°.	91
$C_{26}H_{19}N$	1, 2, 3-Triphenyl-	m. p. 196-197° (decompn.)	91
$C_{27}H_{22}BrClN_2O_2$	1-[2-(p-Bromophenyl)-1-(p-chloro-phenyl)-3-indoliziny]glyoxyloyl-piperidine	m. p. 178.5-179.5°.	92
$C_{27}H_{22}ClN_3O_4$	1-[1-(p-Chlorophenyl)-2-(p-nitro-phenyl)-3-indoliziny]glyoxy-loylpiperidine	m. p. 174-175.5°.	92
$C_{27}H_{23}BrN_2O_2$	1-[2-(p-Bromophenyl)-1-phenyl-3-indoliziny]glyoxyloylpiperidine	m. p. 189-190°.	92
$C_{27}H_{23}N_2O_4$	1-[2-(p-Nitrophenyl)-1-phenyl-3-indoliziny]glyoxyloylpiperidine	m. p. 186-187°.	92
$C_{28}H_{21}N$	5-(2, 2-diphenylvinyl)-2-phenyl-	m. p. 187.5-188.5°.	95
$C_{29}H_{20}Cl_2N_2$	Bis[1-(p-chlorophenyl)-3-indoliziny] methane	m. p. 255°.	4
$C_{41}H_{30}N_2$	Bis(1, 2-diphenyl-3-indoliziny) methane	m. p. 250°, (decompn.)	4

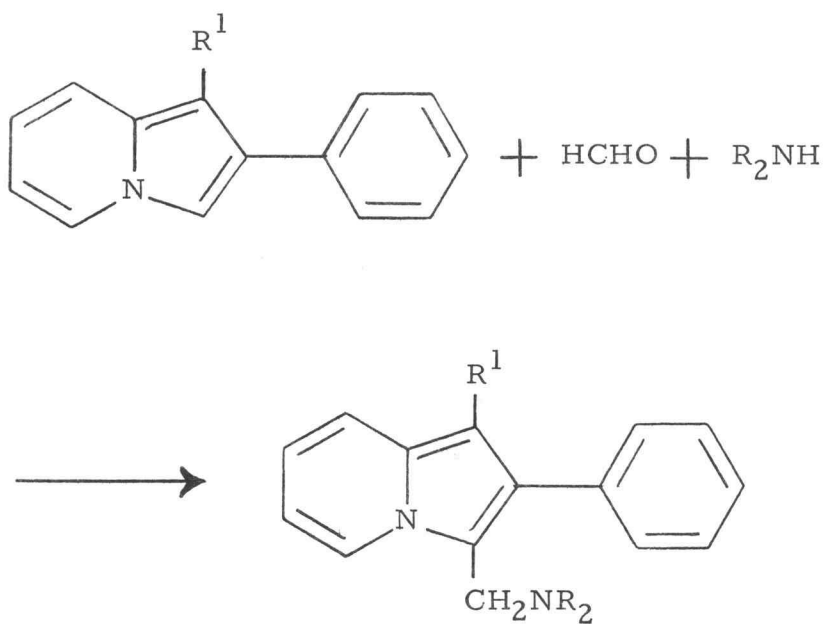
FLOW SHEET AND DISCUSSION

Flow SheetPreparation of indolizines

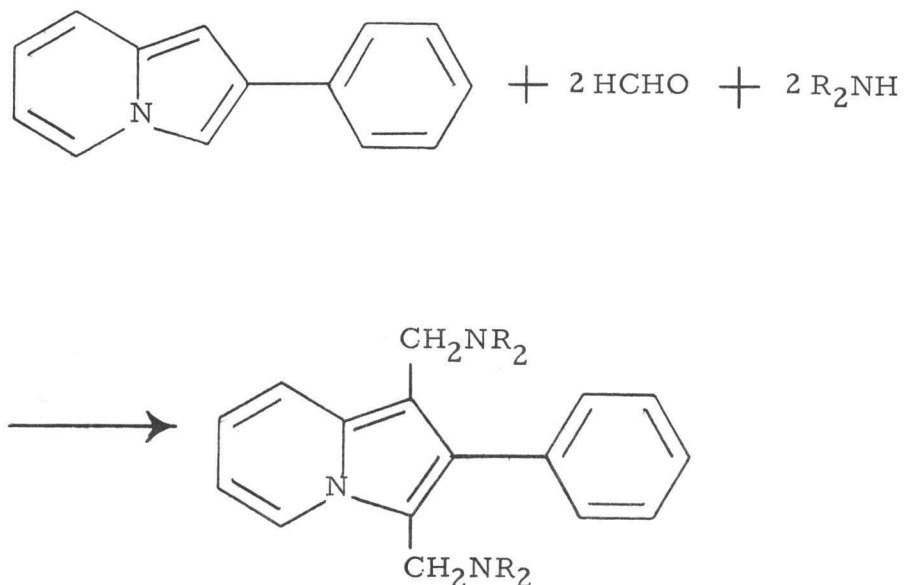
Preparation of Mannich bases at the C-1 position



Preparation of Mannich bases at the C-3 position



Preparation of Mannich bases at both the C-1 and C-3 positions



Discussion

All of the indolizines employed in this investigation have a phenyl substituent at the C-2 position. These compounds are in general quite stable to light, air and temperatures up to 150°. The Chichibabin synthesis (40) was employed in the preparation of these compounds. The phenacyl bromides required for the synthesis of the pyridinium salts were prepared by direct bromination of the corresponding phenone in anhydrous methanol.

The pyridinium compounds were best prepared by direct combination of the reactants at room temperature. These reactions tended to be exothermic and sometimes required an external ice

bath to control the reaction. When allowed to proceed without controlling the temperature, the yields were low; moreover unidentified, usually green by-products were formed, from which it was difficult to separate the desired product. The formation of 1-phenacyl-2-picolinium bromide proceeded with about 75 percent yield when the reactants were refluxed for 40 minutes in ethanol. However, the yield could be increased by about ten percent by allowing the reactants to stand without solvent in a water bath at room temperature. In the case of 1-phenacyl-2-(3-hydroxypropyl)-pyridinium bromide, no crystalline product could be isolated. The amber syrupy liquid which was produced in this reaction was heated with aqueous sodium bicarbonate without prior purification and gave a fair yield of the crystalline indolizine.

No significant problems were encountered in the ring closure step. The foaming which occasionally results from the effervescence of carbon dioxide was controlled by running the reaction in a large open beaker with adequate stirring. Periodic addition of water was necessary to maintain the proper volume. Better yields were obtained, especially with the low melting indolizines, by keeping the reaction mixture between 75° and 85°. The lower temperature also reduced the amount of foaming. Recrystallization of the indolizines could be accomplished readily from hot ethanol, dioxane:water, N,N-dimethyl formamide:water or cold acetone:water. Hot acetone

was avoided in order to forestall the possibility of condensation of the solvent with the indolizine.

In carrying out the Mannich reaction it was desirable to find a general method of preparation of these compounds which would be applicable to a variety of amines as well as a variety of indolizines. A considerable number of variations were explored before a satisfactory set of reaction conditions was obtained.

Rossiter and Saxton (82) ran the reaction of 2,3-dimethylindolizine, formaldehyde and dimethylamine using glacial acetic acid as the solvent. The initial product isolated from the reaction mixture was the undesired bis(indoliziny)lmethane in about 20 percent yield. The Mannich base was obtained as an unstable oil upon distillation of the residue under reduced pressure.

Following the method of Rossiter and Saxton, this investigator attempted to effect the reaction of 1,2-diphenylindolizine, formaldehyde and each of several amines: dimethylamine, diethylamine, diisopropylamine, pyrrolidine, piperidine and morpholine. In every case the major product was bis(1,2-diphenylindolizin-3-yl)methane. The remaining mother liquor was a dark green solution from which no further crystalline product could be obtained. Bis(1,2-diphenylindolizin-3-yl)methane was also obtained by running the reaction under the same conditions but in the absence of a secondary amine.

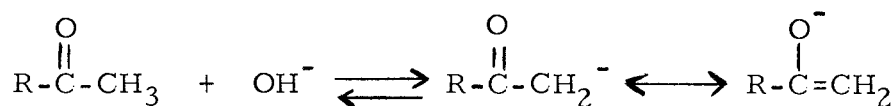
The same procedure as above was followed using

3-methyl-2-phenylindolizine and formaldehyde with each of the following amines: dimethylamine, piperidine, morpholine or pyrrolidine. On standing at room temperature the mixture assumed a deep maroon color in each case. When basified with sodium hydroxide each reaction mixture produced a red oil which was extracted with ether. Attempts to isolate a pure product by evaporation and recrystallization from several solvents as well as by distillation under reduced pressure were unsuccessful.

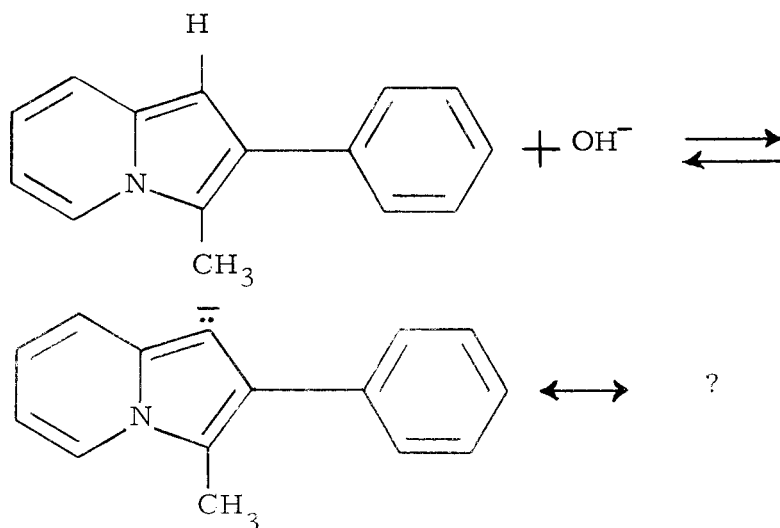
The use of amine salts was also attempted in carrying out the Mannich reaction with indolizines. Upon treatment of piperidine hydrochloride with 3-methyl-2-phenylindolizine and formaldehyde in ethanol an unstable bluish green material was obtained which could not be purified or characterized. Dimethylamine with 3-methyl-2-phenylindolizine and formaldehyde in acetic acid gave a purple dye from which no pure product could be obtained.

At this point it was considered advisable to examine more closely the mechanics of the Mannich reaction with the hope that a more favorable set of reaction conditions could be devised.

As mentioned earlier, Cummings and Shelton (46) proposed two mechanisms for the Mannich reaction. The base-catalyzed mechanism, when applied to ketones, involves the formation of an intermediate resonance stabilized carbanion.

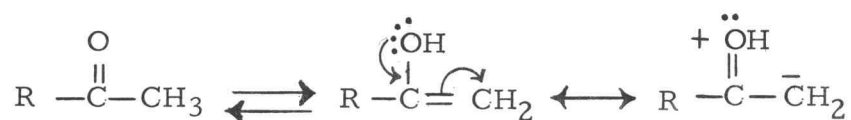


It occurred to the present investigator that ionization of this type is highly unlikely in the case of indolizines because the high electron density at positions C-1 and C-3 would tend to make the hydrogens attached to these positions less acidic than at any other position in the ring system. Furthermore, should such a carbanion exist, it would be highly unstable due to the fact that the electron pair cannot be delocalized.

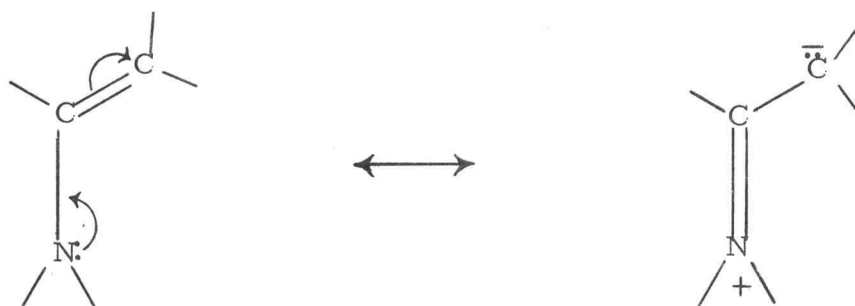


On the basis of these considerations the base-catalyzed mechanism of Cummings and Shelton was ruled out as having a major influence on the course of the Mannich reaction with indolizines.

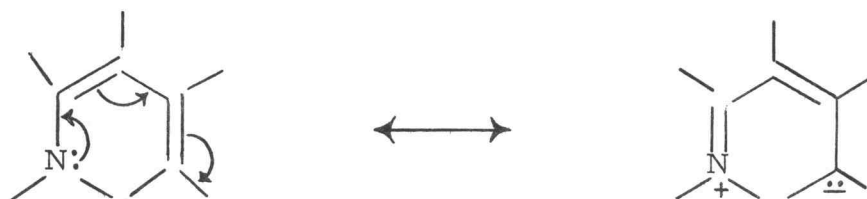
The acid-catalyzed mechanism proposes the enol form of the ketone as the reacting species.



An analogous situation exists with indolizines, since they can be regarded as being enamine in character (43).



Correspondingly, the nucleophilic character of position C-3 results from more extensive delocalization of the electron pair:



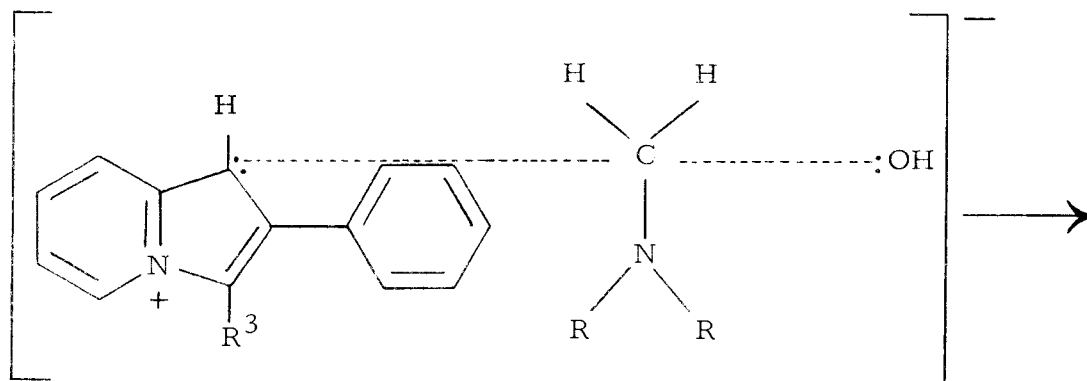
With the foregoing considerations, the conclusion was drawn that it was the enamine character of the indolizine that accounted for its participation in the Mannich reaction; thus one could not expect the rate of reaction to be increased by the addition of base to the reaction medium.

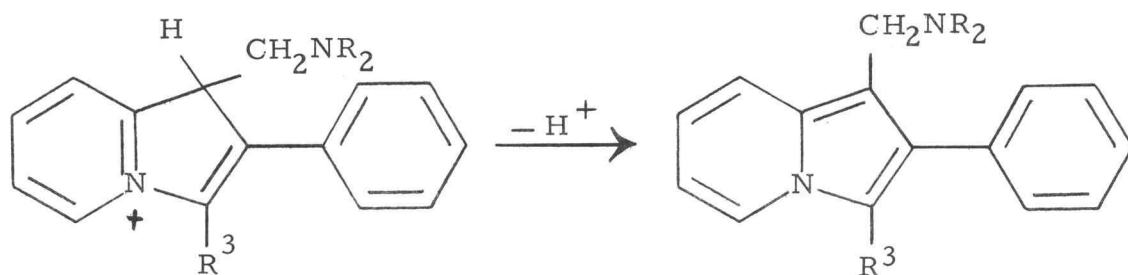
However, the problem still remained that acid conditions tended to favor condensation of the indolizine with the formaldehyde

resulting in the undesirable bis(indoliziny)lmethane. Moreover, when the amine salts were employed, also in acid media, highly colored dyes were obtained.

In order to avoid the foregoing unfavorable situations which tend to develop in acid media, attention was drawn to the possibility of running the reaction at a higher pH than that reported by Rossiter and Saxton (82).

It seemed entirely possible that the reaction mechanism could well involve an S_N2 final step as proposed by Cummings and Shelton for their base-catalyzed mechanism, with the only exception being that the nucleophile would be the aforementioned enamine instead of a carbanion. An S_N2 step would obviate the necessity for having a free carbonium ion, $R_2NCH_2^+$, functioning in an electrophilic capacity as indicated in their proposed acid-catalyzed mechanisms; thus permitting the reaction to be run at a higher pH.

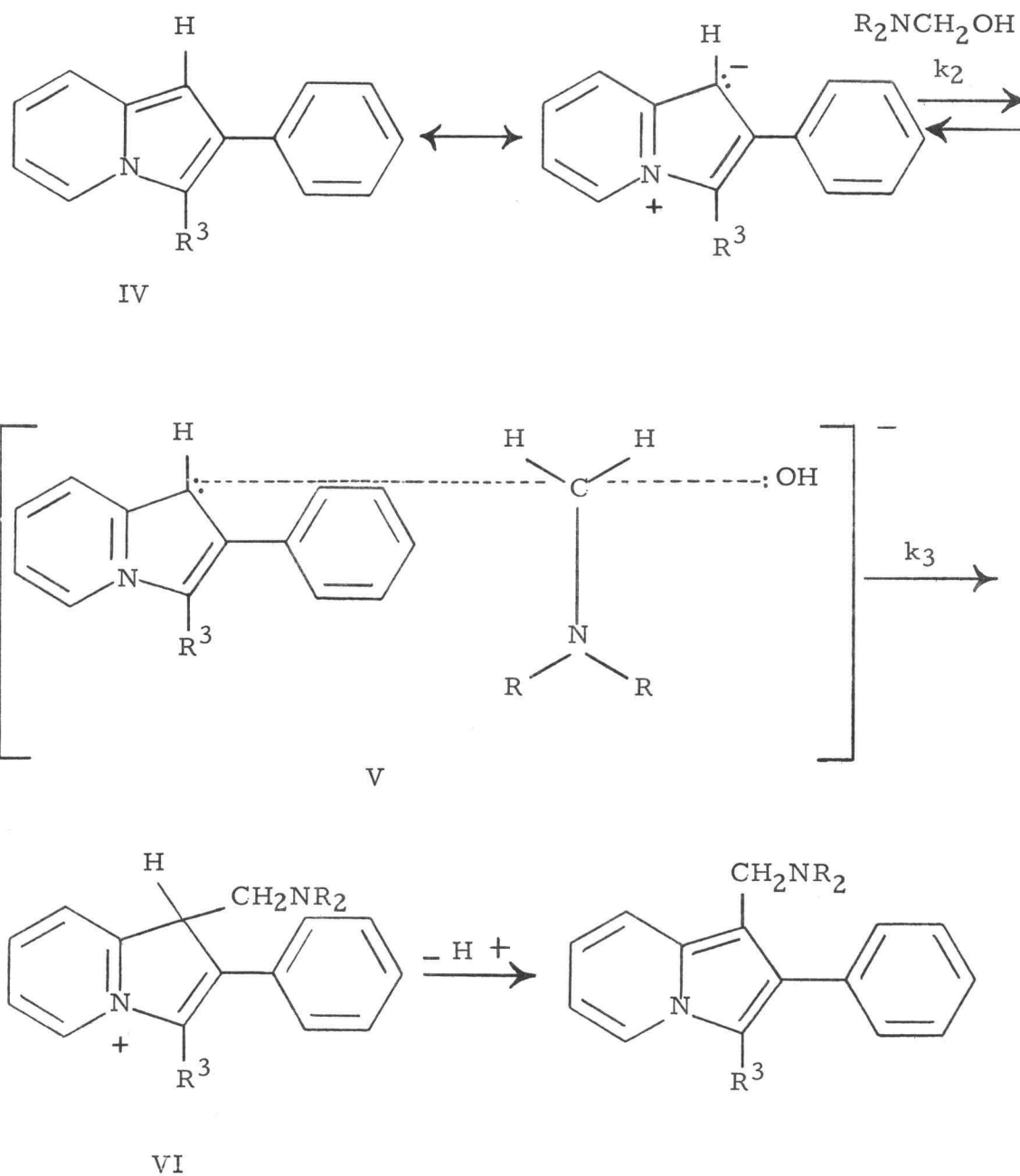




In essence then, the present investigator proposes that a third reaction mechanism might exist, especially in the case of indolizines, which is neither acid-catalyzed nor base-catalyzed. Such a mechanism would be consistent with the kinetic data presented by Cummings and Shelton and would embrace certain features of both the acid-catalyzed and the base-catalyzed mechanisms as set forth by them.

Theoretically, the mechanism proposed would be as follows:





The reaction would be expected to follow third order kinetics as reported (1, 46) and the rate equation would then be as follows:

$$\begin{aligned}
\frac{dx}{dt} &= k_3(V) \\
&= k_3 k_2 (V) \text{ (III)} \\
&= k_3 k_2 k_1 (I) \text{ (II) (IV)} \\
&= k(R_2NH) (HCHO) (\text{Indolizine})
\end{aligned}$$

Having decided to pursue the reaction according to the above mechanism, one final obstacle had to be removed. The free indolizines employed in this investigation are all quite insoluble in aqueous media. Since the use of aqueous formaldehyde was preferred and since dimethylamine was available only as the 25 percent aqueous solution, a non-acidic solvent had to be introduced which could permit the coexistence of all of the reactants in a homogeneous system. After trying several simple and mixed solvent systems two solvents proved to be adequate for the reaction. These two solvents were p-dioxane and N,N-dimethylformamide. p-Dioxane was preferred in most cases because its higher volatility facilitated its removal when the reactions were complete.

In general, the reactions were carried out by premixing the formaldehyde with the amine and allowing to stand for periods varying from 15 minutes to one hour. This mixture was then added to the dioxane solution of the indolizine and the resulting reaction mixture allowed to stand at room temperature for 24 to 48 hours.

Attempts to isolate the product by pouring the reaction mixture

into water invariably produced an oil which was difficult to crystallize. Evaporation of the solvent from the original reaction mixture also produced an oily residue in most cases, but occasionally a crystalline product could be obtained by this method.

Acidification of the reaction mixture or of the oily residue resulted in colored solutions of the salts which also could not be crystallized. Furthermore, basifying the acid solution followed by ether extraction resulted in recovery of the original oil upon evaporation of the ether.

Attempts to isolate the product by distillation of the oil under reduced pressure resulted in decomposition in every case.

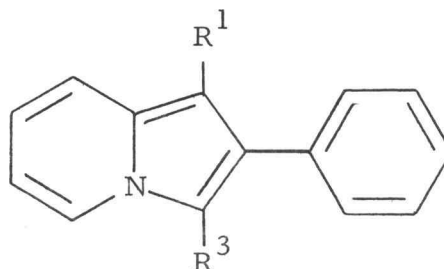
In many instances crystallization could be induced by vigorously scratching the inside of the vessel with a glass stirring rod during the evaporation phase. This technique was found to be of such value that it was included as a routine part of the work-up operation. In several instances where oils were obtained by simple evaporation, crystallization was induced by reconstituting with the solvent and repeating the evaporation while employing the scratching technique. In those cases where crystallization could not be induced by scratching during evaporation, the oily residue was washed, dried and taken up in a minimum of alcohol or acetone and allowed to stand in the refrigerator. Several crystalline products were obtained after standing for periods ranging from five

days to three weeks in the refrigerator.

All melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Elemental analyses were provided by Weiler and Strauss Microanalytical Laboratory, Oxford, England. The Mannich bases prepared in this investigation are presented in table II. The infrared spectra were taken on a Beckman Model IR-8 spectrophotometer, the use of which was provided through the courtesy of Dr. F. Thomas Bond of the Chemistry Department (O.S.U.). The infrared spectra of compounds prepared are reproduced in Appendix A. The ultraviolet spectra were recorded on a Beckman Model DB spectrophotometer and are reproduced in Appendix B.

Preliminary pharmacological screening was performed by Dr. Robert Brummett of the Pharmacology Department at the University of Oregon Medical School.

Table II. Table of Mannich bases prepared




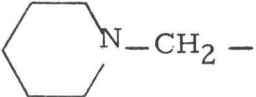
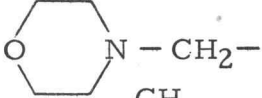
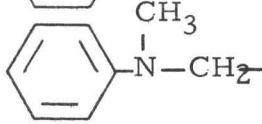
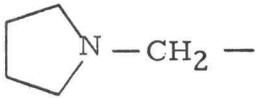
R^1	R^3	M. P.
$(CH_3)_2NCH_2-$	CH_3-	66-67°
$(C_2H_5)_2NCH_2-$	CH_3-	80-81°
	CH_3-	103.5-104.5°
	CH_3-	104.5-106.5°
	CH_3-	133-134°
	CH_3-	131-132°
$(CH_3)_2NCH_2-$	C_2H_5-	65.5-66°
$(C_2H_5)_2NCH_2-$	C_2H_5-	56-57°
	C_2H_5-	78-79°

Table II. Table of Mannich bases prepared (continued)

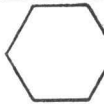
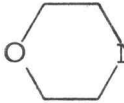
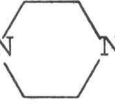

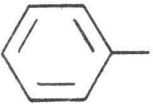

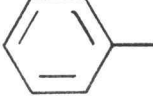
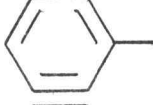

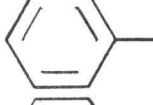


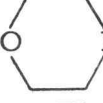


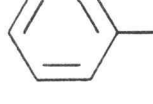

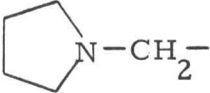
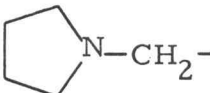
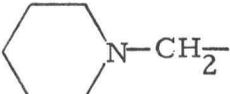
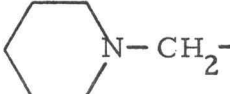
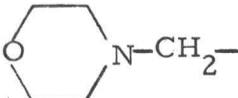
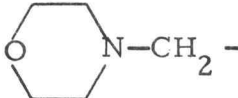
R^1	R^3	M. P.
 N-CH ₂ -	C ₂ H ₅ -	101-102°
 N-CH ₂ -	C ₂ H ₅ -	78-79°
CH ₃ -N  N-CH ₂ -	C ₂ H ₅ -	117-118°
HOCH ₂ CH ₂ -	 N-CH ₂ -	122-124°
	(CH ₃) ₂ NCH ₂ -	140-141°
	(C ₂ H ₅) ₂ NCH ₂ -	114.5-115.5°
	[(CH ₃) ₂ CH] ₂ NCH ₂ -	123-124°
	 N-CH ₂ -	143-144°
	 N-CH ₂ -	128-129°
	 N-CH ₂ -	141-142°
	 N(CH ₃)-CH ₂ -	162-163°
	CH ₃ -N  N-CH ₂ -	136-137°
(CH ₃) ₂ NCH ₂ -	(CH ₃) ₂ NCH ₂ -	68.5-69.5°

Table II. Table of Mannich bases prepared (continued)

R^1	R^3	M. P.
		106-107°
		98.5-99.5°
		156-157°

EXPERIMENTAL

Preparation of Phenacyl Bromides

Phenacyl Bromide

Thirty-six grams acetophenone (0.3 mole) and 125 ml. anhydrous methanol were placed in a 500 ml. 3-necked flask equipped with mechanical stirrer, dropping funnel and water-cooled condenser. The mixture was cooled by a surrounding ice-bath. Forty-eight grams bromine (0.3 mole) dissolved in 75 ml. anhydrous methanol was added dropwise to the well stirred mixture. The addition required about 1.5 hours. Stirring was continued for an additional one hour, during which time the reaction mixture became nearly colorless. The reaction mixture was poured over a mixture of ice and water with stirring. A white granular precipitate formed within ten minutes. The product was filtered at once with suction and washed thoroughly with distilled water. Recrystallization from ethanol yielded 51.0 Gm. (85.5%) crystalline product, m.p. 41-43°. The literature reported m.p. 50° (80). The product was not further purified, but the successful conversion to the known compound 2-phenylindolizine served as the basis for identification.

α -Methylphenacyl Bromide

One hundred grams propiophenone (0.74 mole) and 100 ml. anhydrous methanol were placed in a 1000 ml. three-necked flask equipped with dropping funnel, mechanical stirrer and water-cooled condenser. The stirred mixture was immersed in a water bath and the bath temperature was maintained at 80-90°. To the stirred mixture was added dropwise a solution of 119.2 Gm. bromine (0.74 mole) dissolved in 100 ml. anhydrous methanol. The bromine addition was carried out at such a rate as to maintain the reaction mixture in a nearly colorless state. Upon completion of the addition, the hot mixture was poured into 2500 ml. of ice-water and allowed to stand until the supernatant aqueous layer was nearly clear. The oily liquid was removed, dried over anhydrous magnesium sulfate and filtered. The yield was 140 Gm. (87%), b.p. 127-129°/13 mm. The literature reported b.p. 125-130°/10 mm. (64).

α -Ethylphenacyl Bromide

To a 1000 ml. three-necked flask equipped with dropping funnel, mechanical stirrer and water-cooled condenser was added 100 g butyrophenone (0.67 mole) and 100 ml. anhydrous methanol. The flask was immersed in a water bath and the bath temperature was maintained at 60-70°. To the stirred mixture was added

dropwise 107.2 Gm. bromine (0.67 mole) dissolved in 150 ml. ice-cold anhydrous methanol. The bromine solution was added at such a rate that the reaction mixture was maintained in a nearly colorless state. Stirring was continued for ten minutes after the reaction was complete. The reaction mixture was poured into 300 ml. of ice water and allowed to stand for one hour. The liquid product was removed, dried over anhydrous sodium sulfate and filtered. The yield of light amber liquid was 142 Gm. (92%), b.p. 140-145°/13 mm, density 1.35/25°. The literature reported b.p. 154-158°/20 mm, density 1.35/18° (42).

Preparation of Pyridinium Salts

1-Phenacyl-2-picolinium Bromide

Five grams phenacyl bromide (0.025 mole) was combined with 4.2 Gm. α -picoline (0.050 mole) and the mixture was carefully warmed to dissolve the salt. The reaction flask was immediately immersed in a water bath at room temperature and allowed to stand. The product which crystallized within 10 to 30 minutes, was filtered and washed with ether. The yield was 5.96 Gm. (84%), m.p. 216.5-218° (decompn.). The literature reported m.p. 215° (decompn.) (40, 65).

1-(α -Methylphenacyl)-2-picolinium Bromide

To 2.1 Gm. α -bromopropiophenone (0.01 mole) was added 1.8 Gm. α -picoline (0.02 mole) and the mixture allowed to stand at room temperature for 24 hours with occasional swirling of the flask. The resulting crystalline product was filtered and washed with cold ether. The yield was 2.3 Gm. (76.5%), m. p. 227-228°d. The product was recrystallized by dissolving in n-propyl alcohol and adding ether to the resulting solution. No physical properties could be located in the literature for this compound. The successful conversion to the known 3-methyl-2-phenylindolizine was used as the basis for identification.

1-(α -Ethylphenacyl)-2-picolinium Bromide

To 135 Gm. α -bromobutyrophenone (0.6 mole) was added 112 Gm. α -picoline (1.2 mole) in a 1000 ml. Erlenmeyer flask and the mixture allowed to stand for 24 hours at room temperature with occasional shaking. The partially crystallized product was filtered off and washed with ether. The product melted at 220-221°. The mother liquor was heated on a boiling water bath for three hours where upon an amber semi-solid mass formed on the bottom of the flask. The flask and its contents were cooled in the refrigerator and the supernatant liquid was decanted. The semi-solid residue was not

further purified, but was used together with the previously isolated crystalline product in the preparation of 3-ethyl-2-phenylindolizine. No physical constants could be located in the literature for this compound. The successful conversion to the known 3-ethyl-2-phenylindolizine was used as the basis for identification.

1-Phenacyl-2-benzylpyridinium Bromide

Fifty grams phenacyl bromide (0.225 mole) was combined with 50 Gm. 2-benzylpyridine (0.300 mole) in a 500 ml. Erlenmeyer flask without solvent. The mixture was warmed very slightly on a water bath to dissolve the phenacyl bromide and allowed to stand at room temperature for four hours. The crystalline product was filtered, washed with benzene and dried in air. The yield was 79.6 g (88%), m.p. 195-196° (decompn.). The literature reported m.p. 191-195° (75).

2-(3-Hydroxypropyl)-1-phenacylpyridinium Bromide

To 139 Gm. phenacyl bromide (0.7 mole) was added 100 Gm. 2-(3-hydroxypropyl)pyridine (0.74 mole) in a 1000 ml. Erlenmeyer flask without solvent. The mixture was warmed very slightly on a water bath to dissolve the phenacyl bromide and then allowed to stand at room temperature for 72 hours. The mixture was extracted with ether and the ether-insoluble resinous material which remained

was placed in the refrigerator to crystallize. No crystallization occurred after two days in the refrigerator. Attempts to isolate a crystalline product from either ethanol, acetone, dioxane or water were unsuccessful. The crude material was set aside to be used without further purification in the synthesis of 1-(2-hydroxyethyl)-2-phenylindolizine.

Preparation of Indolizines

2-Phenylindolizine

Thirty five grams 1-phenacyl-2-picolinium bromide (0.12 mole) was added to 2000 ml. of ten percent sodium bicarbonate solution in a 4000 ml. beaker equipped with a mechanical stirrer. The mixture was heated and the temperature maintained between 80° and 90° for two hours. Considerable foaming occurred during the reaction and this was controlled by supplementary manual stirring with a glass rod. Water was added at intervals to maintain the original volume of the reaction mixture. At the end of the reaction the mixture was filtered by suction while hot and the crystalline product washed with 500 ml. of hot distilled water. The product was partially dried by continued suction and then placed in a vacuum dessicator to complete the drying process. The yield was 22.9 Gm. (99%), m.p. 214-215°. The product was recrystallized

from hot N,N-dimethylformamide and exhibited the same melting behavior. The literature reported m.p. 214-215° (16, 19).

3-Methyl-2-phenylindolizine

Seven grams 1-(α -methylphenacyl)-2-picolinium bromide (0.023 mole) was added to 1000 ml. of ten percent sodium bicarbonate solution in a 4000 ml. beaker equipped with mechanical stirrer. The stirred mixture was heated on a hot plate and maintained at a temperature between 80° and 90° for three hours. The mixture was allowed to stand overnight and then filtered by suction. The crystalline product was thoroughly washed with hot water, air-dried and recrystallized from cold acetone:water. The yield was 4.3 Gm. (90.1%), m.p. 96-97°. The literature reported m.p. 97-98° (23).

1,2-Diphenylindolizine

Eighty-five grams 2-benzyl-1-phenacylpyridinium bromide (0.316 mole) was placed in a 4000 ml. beaker equipped with a mechanical stirrer. To this was added 3000 ml. of ten percent sodium bicarbonate solution. The stirred mixture was heated on a hot plate and the temperature maintained between 65° and 75° for two hours. There was no problem with foaming. The mixture was allowed to cool and was filtered by suction. The crystalline product was washed well with hot water followed by cold distilled water. The

product was recrystallized by dissolving in cold acetone, adding water to the saturation point and allowing to stand overnight. The yield was 51.3 Gm. (89%), m.p. 112-113°. The literature reported m.p. 112° (4).

1-(2-Hydroxyethyl)-2-phenylindolizine

The resinous ether-insoluble material obtained in the preparation of 2-(3-hydroxypropyl)-1-phenacylpyridinium bromide was placed in a 2000 ml. beaker equipped with a mechanical stirrer. To this was added 1000 ml. of ten percent sodium bicarbonate solution. The mixture was heated with constant stirring and the temperature maintained at 80-90° for two hours. The oily product which floated on the surface of the reaction mixture solidified on cooling. The solid product was pulverized with a mortar and pestle and extracted with cold 95 percent ethanol to remove most of the dark brown impurities. Immediate recrystallization from acetone: water yielded 44.8 Gm. (27% overall, based on phenacyl bromide), m.p. 101.5-102.5°. Analysis, calc. for C₁₆ H₁₅ NO: C, 80.98; H, 6.37; N, 5.90. Found, C, 81.10; H, 6.40; N, 5.81.

3-Ethyl-2-phenylindolizine

The semi-solid residue along with the crystalline material obtained in the preparation of 1-(α -ethylphenacyl)-2-picolinium

bromide were added to 3000 ml. of ten percent sodium bicarbonate solution in a 4000 ml. beaker equipped with mechanical stirrer. The mixture was heated with stirring on a hot plate and the reaction temperature maintained at 80° to 90° for three hours. The brown tarry material which formed during the reaction solidified on cooling. The solid material was collected and pulverized with a mortar and pestle. The powdered material was extracted with cold 95 percent ethanol to remove most of the dark color. Recrystallization from N,N-dimethylformamide:water yielded 59 Gm. of tan crystals (45% overall, based on α -bromobutyrophenone), m.p. 94-95°. The literature reported m.p. 94° (20).

Preparation of Mannich Bases

1-Dimethylaminomethyl-3-methyl-2-phenylindolizine

Ten milliliters of 25 percent aqueous dimethylamine (0.055 mole) and four milliliters of 37 percent aqueous formaldehyde (0.050 mole) were added to 20 ml. p-dioxane in a 125 ml. Erlenmeyer flask and the resulting solution was allowed to stand for 15 minutes. Two grams 3-methyl-2-phenylindolizine (0.01 mole) was then added and the flask was swirled to dissolve the indolizine. The reaction mixture was allowed to stand at room temperature for 24 hours. The amber-colored solution was transferred to an evaporating dish

and a steady stream of cold air was blown over the surface to evaporate the solvent. When the evaporation was about one-half complete, an oil separated which solidified when the evaporation was nearly complete. The crystalline residue was recrystallized from cold acetone:water and yielded 2.27 Gm. (86%), m.p. 66-67°.

Analysis, calc. for $C_{18}H_{20}N_2$: C, 81.78; H, 7.63; N, 10.60.

Found: C, 81.72; H, 7.71; N, 10.65.

1-Diethylaminomethyl-3-methyl-2-phenylindolizine

Ten milliliters of 37 percent aqueous formaldehyde (0.125 mole) was added to 9.15 Gm. diethylamine (0.125 mole) and the mixture allowed to stand in an ice bath for 15 minutes. The mixture was then poured into a solution containing five Gm. 3-methyl-2-phenylindolizine (0.025 mole) dissolved in 50 ml. dioxane. The reaction flask was stoppered and the clear reaction mixture allowed to stand for 24 hours at room temperature. At the end of this period the dioxane solution was transferred to an evaporating dish and the solvent was removed by evaporation under a stream of cold air. The oil which resulted slowly crystallized upon continued evaporation. The product was recrystallized from dioxane:water and yielded 6.5 Gm. (89%), m.p. 81-82°. Analysis, calc. for $C_{20}H_{24}N_2$: C, 82.15; H, 8.27; N, 9.58. Found: C, 82.36; H, 8.42; N, 9.34.

3-Methyl-2-phenyl-1-pyrrolidinomethylindolizine

Two milliliters of 37 percent aqueous formaldehyde (0.025 mole) and 1.78 Gm. pyrrolidine (0.025 mole) were combined and allowed to stand for 15 minutes in an ice bath. Ten milliliters of dioxane were added and the flask swirled to assure homogeneity. One gram of 3-methyl-2-phenylindolizine (0.005 mole) was added to the dioxane solution and was dissolved by swirling the flask. The clear reaction mixture was stoppered and allowed to stand at room temperature for 24 hours. The mixture was then poured into an evaporating dish and cold air was blown over the surface to evaporate the solvent. An oil was formed during the evaporation phase; however it slowly crystallized as evaporation was continued. The product was removed by filtration and recrystallized from dioxane:water. The yield was 1.3 Gm. (89%), m.p. 102-104°. Analysis, calc. for $C_{20}H_{22}N_2$: C, 82.72; H, 7.64; N, 9.65. Found: C, 82.45; H, 7.49; N, 9.40.

3-Methyl-2-phenyl-1-piperidinomethylindolizine

Six milliliters of 37 percent aqueous formaldehyde (0.075 mole), 6.3 Gm. piperidine (0.075 mole) and 35 ml. N,N-dimethylformamide (DMF) were combined and allowed to stand at room temperature for 15 minutes. Three grams of 3-methyl-2-phenylindolizine was

dissolved in the mixture, the flask was stoppered and the reaction allowed to proceed at room temperature for 36 hours. The clear reaction mixture was then transferred to an evaporating dish and a steady stream of cold air was blown across the surface to evaporate the solvent. The product began to crystallize when evaporation was about 25 percent complete. Evaporation was continued until about two-thirds of the solvent was removed. Crystallization of the product was completed by adding water dropwise with manual stirring until no further turbidity occurred. The product was removed by filtration, washed with 50 percent ethanol and recrystallized from dioxane:water. The yield was 3.85 Gm. (90.5%), m.p. 104.5-106.5°. Analysis, calc. for $C_{21}H_{24}N_2$: C, 82.85; H, 7.95; N, 9.20. Found: C, 82.79; H, 8.08; N, 9.05.

3-Methyl-1-morpholinomethyl-2-phenylindolizine

Two milliliters of 37 percent aqueous formaldehyde (0.025 mole) was combined with 2.2 Gm. morpholine (0.025 mole) and allowed to stand in an ice bath for 15 minutes. The mixture was poured into 10 ml. dioxane followed by the addition of one gram of 3-methyl-2-phenylindolizine (0.005 mole). The flask was swirled to dissolve the indolizine and then allowed to stand for 24 hours at room temperature. The reaction mixture was then transferred to an evaporating dish and the solvent was evaporated under a stream

of cold air. The crystalline residue was washed with 50 percent ethanol and recrystallized from dioxane:water. The yield was 1.2 Gm. (78%), m.p. 133-134°. Analysis, calc. for $C_{20}H_{22}N_2O$: C, 78.40; H, 7.24; N, 9.14. Found: C, 78.14; H, 7.31; N, 8.97.

3-Methyl-1-methylphenylaminomethyl-2-phenylindolizine

Four milliliters of 37 percent aqueous formaldehyde (0.050 mole) and 5.3 Gm. N-methylaniline (0.050 mole) were combined with 25 ml. dioxane and allowed to stand at room temperature for 15 minutes. Two grams of 3-methyl-2-phenylindolizine (0.01 mole) was added and the flask swirled until a clear solution resulted. The reaction was allowed to proceed by standing at room temperature for 24 hours. The mixture was then transferred to an evaporating dish, covered with a watch glass and allowed to stand overnight, whereupon crystallization occurred without the usual evaporation. The mixture was then placed in the refrigerator for three hours to achieve more complete crystallization. The product was removed by filtration, washed with dioxane:water (1:1) and dried by suction. The yield was 2.7 Gm. (82.8%). The product was recrystallized from acetone and gave m.p. 131-132°. Analysis, calc. for $C_{23}H_{22}N_2$: C, 84.63; H, 6.79; N, 8.58. Found: C, 84.60; H, 6.90; N, 8.47.

1-Dimethylaminomethyl-3-ethyl-2-phenylindolizine

Six milliliters of 37 percent aqueous formaldehyde (0.075 mole), 15 ml. of 25% aqueous dimethylamine (0.0825 mole) and 30 ml. p-dioxane were combined and allowed to stand at room temperature for 15 minutes. To the mixture 3.3 Gm. 3-ethyl-2-phenylindolizine (0.015 mole) was added and dissolved by swirling the flask. The reaction flask was stoppered and allowed to stand for 24 hours. The clear solution was then poured into an evaporating dish which was placed under a stream of cold air to evaporate the solvent. Crystallization was induced only as a result of vigorous scratching of the inside wall of the dish with a glass stirring rod during the evaporation phase. Previous attempts to get a crystalline product without vigorous scratching had been unsuccessful. The product was removed by filtration and recrystallized from acetone:water. The yield was 3.6 Gm. (87%), m.p. 65.5-66.0°. Analysis, calc. for $C_{19}H_{22}N_2$: C, 81.97; H, 7.97; N, 10.06. Found: C, 82.02; H, 8.02; N, 10.15.

1-Diethylaminomethyl-3-ethyl-2-phenylindolizine

Six milliliters of 37 percent aqueous formaldehyde (0.075 mole) and 5.49 Gm. diethylamine (0.075 mole) were combined with 30 ml. p-dioxane and put aside to stand at room temperature. After

15 minutes 3.3 Gm. 3-ethyl-2-phenylindolizine (0.015 mole) was dissolved in the mixture, the flask was stoppered and the reaction allowed to proceed at room temperature for 24 hours. At the end of the reaction period the clear dioxane solution was transferred to an evaporating dish and cold air was blown across the surface to evaporate the solvent. When the solvent was approximately one-half gone, crystallization was induced upon scratching the walls of the container with a glass stirring rod. The crystallized product was removed by filtration and recrystallized from ethanol. The yield was 3.7 Gm. (80%), m.p. 56-57°. Analysis, calc for $C_{21}H_{26}N_2$: C, 82.31; H, 8.55; N, 9.14. Found: C, 82.16; H, 8.65; N, 9.21.

3-Ethyl-2-phenyl-1-pyrrolidinomethylindolizine

To 30 ml. p-dioxane was added 5.34 Gm. pyrrolidine (0.075 mole) and six milliliters of 37 percent aqueous formaldehyde (0.075 mole) and the resulting solution allowed to stand at room temperature for 15 minutes. To this mixture 3.3 Gm. 3-ethyl-2-phenylindolizine (0.015 mole) was added and the flask was swirled until a clear solution was obtained. The reaction mixture was then set aside at room temperature for 24 hours. The clear solution containing the product was poured into an evaporating dish and cold air was blown across the surface to remove the solvent.

Crystallization of the product occurred upon scratching the walls of the container with a glass rod during the evaporation process. The product was removed by filtration, recrystallized from ethanol and yielded 3.5 Gm. (76%), m.p. 78-79°. Analysis, calc. for $C_{21}H_{24}N_2$: C, 82.85; H, 7.95; N, 9.20. Found: C, 82.89; H, 8.04; N, 9.13.

3-Ethyl-2-phenyl-1-piperidinomethylindolizine

To 30 ml. p-dioxane was added 6.3 Gm. piperidine (0.075 mole) and six milliliters of 37 percent aqueous formaldehyde (0.075 mole) and the resulting solution allowed to stand at room temperature for 15 minutes. 3-Ethyl-2-phenylindolizine, 3.3 Gm. (0.015 mole) was then added and dissolved by swirling the flask. The flask was stoppered and allowed to stand for 24 hours at room temperature. The mixture was poured into an evaporating dish and cold air was blown across the surface to evaporate the solvent. Crystallization of the product was induced by scratching the walls of the container with a glass stirring rod during the evaporation process. The crystalline product was collected on a sintered glass funnel with the aid of suction and recrystallized from ethanol. The yield was 3.8 Gm. (79%), m.p. 101-102°. Analysis, calc. for $C_{22}H_{26}N_2$: C, 82.97; H, 8.23; N, 8.80. Found: C, 83.07; H, 8.38; N, 8.80.

3-Ethyl-1-morpholinomethyl-2-phenylindolizine

Six milliliters of 37 percent aqueous formaldehyde (0.075 mole) and 6.6 Gm. morpholine (0.075 mole) were combined with 30 ml. p-dioxane and allowed to stand at room temperature for 15 minutes. 3-Ethyl-2-phenylindolizine, 3.3 Gm. (0.015 mole) was added and dissolved by swirling the flask. The reaction mixture was stoppered and allowed to stand at room temperature for 24 hours. The clear solution was transferred to an evaporating dish and a steady stream of cold air was blown across the surface to evaporate the solvent. Crystallization of the product occurred with vigorous scratching with a glass rod during the evaporation process. The product was removed by filtration and recrystallized from ethanol. The yield was 3.6 Gm. (75%), m.p. 78-79°. Analysis, calc. for $C_{21}H_{24}N_2O$: C, 78.72; H, 7.55; N, 8.74. Found: C, 78.88; H, 7.55; N, 8.81.

3-Ethyl-1-(4-methylpiperazinomethyl)-2-phenylindolizine

Six milliliters of 37 percent aqueous formaldehyde (0.075 mole) and 7.5 Gm. 1-methylpiperazine (0.075 mole) were combined with 30 ml. dioxane. Two drops of 50 percent aqueous sodium hydroxide was added and the mixture allowed to stand for 15 minutes at room temperature. To the mixture was added 3.3 Gm. 3-ethyl-2-

phenylindolizine (0.015 mole), the reaction flask swirled to obtain a clear solution and allowed to stand for 24 hours at room temperature. The mixture was poured into an evaporating dish and cold air was blown over the surface to evaporate the solvent. Crystallization was induced by vigorous scratching with a glass rod during the evaporation process. The crystalline product was removed by filtration and recrystallized from hot acetone:water. The yield was 3.8 Gm. (76%), m.p. 117-118°. Analysis, calc. for $C_{22}H_{27}N_3$: C, 79.24; H, 8.16; N, 12.60. Found: C, 79.05; H, 8.24; N, 11.96.

1-(2-Hydroxyethyl)-2-phenyl-3-pyrrolidinomethylindolizine

Six milliliters of 37 percent aqueous formaldehyde (0.075 mole) and 5.34 Gm. pyrrolidine (0.075 mole) were combined with 30 ml. dioxane and allowed to stand for 15 minutes at room temperature. 1-(2-Hydroxyethyl)-2-phenylindolizine, 3.57 Gm. (0.015 mole), was dissolved into the mixture which was then allowed to stand at room temperature for 24 hours. The reaction mixture was transferred to an evaporating dish and the solvent was removed by blowing cold air over the surface. Scratching with a glass rod during evaporation failed to induce crystallization and a residue consisting of a viscous oil was obtained. The oil was transferred to a 50 ml. Erlenmeyer flask with the aid of about three ml. ethanol and placed in the freezer compartment of the refrigerator. The product crystallized after one

week in the refrigerator. The crystals were removed by filtration, washed with 50 percent ethanol and recrystallized from hot N,N-dimethylformamide:water. The yield was 2.9 Gm. (62%), m.p. 122-124°. Analysis, calc. for $C_{21}H_{24}N_2O$: C, 78.72; H, 7.55; N, 8.74. Found: C, 78.65; H, 7.54; N, 8.72.

3-Dimethylaminomethyl-1,2-diphenylindolizine

Four milliliters of 37 percent aqueous formaldehyde (0.050 mole) and ten milliliters of 25 percent aqueous dimethylamine (0.055 mole) were combined with 30 ml. dioxane and allowed to stand for 15 minutes at room temperature. To this mixture was added 2.7 Gm. 1,2-diphenylindolizine (0.010 mole). After shaking to dissolve the indolizine the reaction was permitted to proceed at room temperature for 24 hours. The product was partially crystallized at the end of 24 hours. The mixture was poured into an evaporating dish and cold air was blown over the surface to remove the solvent and complete the crystallization of the product. The crystals were filtered by suction, washed with acetone:water (1:1) and dried in air. The yield was 3.1 Gm. (95%), m.p. 140-141°. The product was recrystallized from hot ethanol and showed no change in melting point. Analysis, calc. for $C_{23}H_{22}N_2$: C, 84.63; H, 6.79; N, 8.58. Found: C, 84.09; H, 7.45; N, 8.58.

3-Diethylaminomethyl-1,2-diphenylindolizine

Four milliliters of 37 percent aqueous formaldehyde (0.05 mole) and 3.66 Gm. diethylamine (0.05 mole) were combined with 20 ml. dioxane and allowed to stand at room temperature for 15 minutes. At that point 2.7 Gm. 1,2-diphenylindolizine (0.01 mole) was added and the resulting solution was allowed to stand at room temperature for 24 hours. The reaction mixture was transferred to an evaporating dish and the solvent was removed by evaporation under a steady stream of cold air. The crystalline product, which was present in great abundance, was removed by filtration and recrystallized from hot acetone:water. The yield was 3.1 Gm. (87.5%), m.p. 114.5-115.5°. Analysis, calc. for $C_{25}H_{26}N_2$: C, 84.71; H, 7.39; N, 7.90. Found: C, 84.32; H, 7.35; N, 7.82.

3-Diisopropylaminomethyl-1,2-diphenylindolizine

A solution was prepared by combining 5.1 Gm. diisopropylamine (0.05 mole) with four ml. 37 percent formaldehyde (0.05 mole) and 20 ml. dioxane and was allowed to stand at room temperature for 15 minutes. To this solution was added 2.7 Gm. 1,2-diphenylindolizine (0.01 mole). The flask was swirled to dissolve the indolizine and allowed to stand at room temperature for 24 hours. The reaction mixture was transferred to an evaporating dish and

cold air was blown across the surface to remove the solvent. No crystallization occurred during evaporation. The oily residue was taken up in ether, washed thoroughly with water and dried with anhydrous sodium sulfate. The ethereal solution was filtered, evaporated down to a thin syrupy liquid and placed in the freezer compartment of the refrigerator. Crystallization occurred after five days, perhaps aided by occasional scratching with a glass rod. The crystals were filtered off and recrystallized from hot acetone: water. The yield was 2.2 Gm. (58%), m.p. 123-124°. Analysis, calc. for $C_{27}H_{30}N_2$: C, 84.77; H, 7.90; N, 7.32. Found: C, 84.43; H, 7.85; N, 7.22.

1,2-Diphenyl-3-pyrrolidinomethylindolizine

A solution was prepared by combining 3.56 Gm. pyrrolidine (0.05 mole) with four ml. 37 percent aqueous formaldehyde (0.05 mole) and 20 ml. dioxane and was allowed to stand at room temperature for 24 hours. The mixture was then poured into an evaporating dish and a steady stream of cold air was blown over the surface to remove the solvent. The product crystallized out of solution during the evaporation. The crystalline material was removed by suction-filtration, washed with 50% aqueous acetone and recrystallized from hot acetone:water. The yield was 3.0 Gm. (85%), m.p. 143-144°. Analysis, calc. for $C_{25}H_{24}N_2$: C, 85.19; H, 6.86; N, 7.95.

Found: C, 85.81; H, 6.92; N, 6.81.

1,2-Diphenyl-3-piperidinomethylindolizine

Four milliliters of 37 percent aqueous formaldehyde (0.05 mole) and 4.2 Gm. piperidine (0.05 mole) were combined with 20 ml. dioxane and allowed to stand for 15 minutes. To the mixture was added 2.7 Gm. 1,2-diphenylindolizine which was dissolved by swirling the flask. The reaction mixture was set aside at room temperature for 24 hours and then transferred to an evaporating dish. Upon partial evaporation an oil separated at the bottom of the dish. Without further evaporation the two-phase liquid was transferred to an Erlenmeyer flask and placed in the freezer compartment of the refrigerator. Crystallization was noted after five days in the refrigerator. An excess of water was added to complete precipitation of the product. The mixture was returned to the refrigerator for an additional 24 hours. The crystalline product was removed by filtration and recrystallized from hot acetone:water. The yield was 3.3 Gm. (90%), m.p. 128-129°. Analysis, calc. for $C_{26}H_{26}N_2$: C, 85.21; H, 7.15; N, 7.64. Found: C, 85.18; H, 7.17; N, 7.55.

1,2-Diphenyl-3-morpholinomethylindolizine

To 20 ml. dioxane was added four ml. of 37 percent aqueous

formaldehyde (0.05 mole) and 4.4 Gm. morpholine (0.05 mole) and the mixture allowed to stand at room temperature for 15 minutes. 1,2-Diphenylindolizine, 2.7 Gm. (0.01 mole), was added and the resulting solution was allowed to stand at room temperature for 24 hours. The mixture was then transferred to an evaporating dish and cold air was blown across the surface to remove the solvent. Upon partial evaporation, an oil separated which was assumed to represent the product. After the oil formation was apparently complete, when about half of the solvent had been evaporated, the two-phased mixture was transferred to an Erlenmeyer flask and placed in the freezer compartment of the refrigerator. Crystallization of the oil occurred after six days and was perhaps prompted by occasional scratching with a glass stirring rod. The product was removed by suction-filtration and recrystallized from hot acetone: water. The yield was 2.9 Gm. (78.5%), m.p. 141-142°. Analysis, calc. for $C_{25}H_{24}N_2O$: C, 81.49; H, 6.57; N, 7.60. Found: C, 81.20; H, 6.54; N, 7.45.

1,2-Diphenyl-3-methylphenylaminomethylindolizine

N-Methylaniline, 8.01 Gm. (0.075 mole) and 37 percent aqueous formaldehyde, six ml. (0.075 mole), were mixed with 30 ml. dioxane and allowed to stand at room temperature for 15 minutes. 1,2-Diphenylindolizine, 4.05 Gm. (0.015 mole), was dissolved in

the mixture and the reaction was allowed to proceed for 36 hours at room temperature. During the course of the reaction, the crystalline product formed in abundance in the reaction flask. The flask was placed in the freezer compartment of the refrigerator for 12 additional hours to allow for complete crystallization. The cold mixture was filtered and washed with small amounts of cold ethanol. The product was recrystallized by dissolving in N,N-dimethylformamide, adding five percent water to the hot solution and allowing to cool. The yield was 4.95 Gm. (85%), m.p. 162-163°. Analysis, calc. for $C_{28}H_{24}N_2$: C, 86.56; H, 6.23; N, 7.21. Found: 85.80; H, 6.25; N, 7.98.

1,2-Diphenyl-3-(4-methylpiperazinomethyl)indolizine

Four ml. of 37 percent aqueous formaldehyde (0.05 mole) and five grams of 1-methylpiperazine (0.05 mole) were combined with 50 ml. dioxane. One-tenth ml. of 50 percent aqueous sodium hydroxide was added and the mixture was allowed to stand at room temperature for 15 minutes. To this mixture was added 2.7 Gm. 1,2-diphenylindolizine (0.01 mole) and the resulting solution was allowed to stand for 24 hours at room temperature. The mixture was poured into an evaporating dish and cold air was blown across the surface to evaporate the solvent. The sides of the dish were scratched vigorously with a glass rod during the evaporation. The

crystallization which occurred during the evaporation seemed to be a direct result of scratching. The crystalline product was removed by filtration and recrystallized from ethyl acetate. The yield was 3.2 Gm. (84%), m.p. 136-137°. Analysis, calc. for $C_{26}H_{27}N_3$: C, 81.85; H, 7.13; N, 11.01. Found: C, 82.00; H, 7.06; N, 10.70.

1,3-Bis(dimethylaminomethyl)-2-phenylindolizine

A mixture containing 20 ml. dimethylamine (0.11 mole), six ml. of 37 percent aqueous formaldehyde (0.075 mole) and 0.1 ml. of 50 percent sodium hydroxide was allowed to stand in an ice bath for 20 minutes. The mixture was added slowly with shaking to a flask containing two grams 2-phenylindolizine (0.01 mole) dissolved in 50 ml. N,N-dimethylformamide. The flask was stoppered and allowed to stand at room temperature for 72 hours. Water was added in excess very slowly to the reaction mixture and the product precipitated as a heavy oil. Excessive shaking was avoided during the addition of water to prevent the formation of an emulsion. After allowing to stand overnight, the aqueous layer was carefully decanted. The semi-solid residue was dissolved with heating in a minimum amount of hot ethanol. Water, equivalent to about ten percent of the volume of the alcoholic solution, was added while the solution was still hot. After allowing to cool to room temperature, the clear solution was placed in the freezing compartment of the refrigerator.

The product crystallized after two days in the refrigerator. The product was removed by filtration and washed with 50 percent ethanol. The yield was 2.7 Gm. (88%). Upon recrystallization from hot ethanol the compound gave m.p. 68.5-69.5°. Analysis, calc. for $C_{20}H_{25}N_3$: C, 78.14; H, 8.20; N, 13.67. Found: C, 78.05; H, 8.09; N, 13.86.

1,3-Bis(pyrrolidinomethyl)-2-phenylindolizine

A mixture containing ten ml. dioxane, 1.8 Gm. pyrrolidine (0.025 mole) and 1.8 ml. 37 percent aqueous formaldehyde (0.023 mole) was allowed to stand at room temperature for 15 minutes. To this mixture was added 0.97 Gm. 2-phenylindolizine (0.005 mole) and, after swirling occasionally for about one hour to dissolve the indolizine, the resulting solution was allowed to stand for 48 hours at room temperature. The mixture was poured into an evaporating dish and cold air was blown over the surface to remove the solvent. When evaporation was nearly complete the oily residue was washed with water and dried over anhydrous sodium sulfate. The sodium sulfate was removed by filtration, washed with five to seven ml. ether and the filtrate placed in the freezer compartment of the refrigerator. After three days the inside of the flask was scratched with a glass stirring rod and returned to the freezer. Crystals appeared within one hour. The mixture was allowed to remain in

the freezer for four hours longer to allow crystallization to be completed. The product was removed by suction, washed with cold ethanol and recrystallized from cold acetone:water. The yield was 1.2 Gm. (70%), m.p. 106-107°. Analysis, calc. for $C_{24}H_{29}N_3$: C, 80.18; H, 8.13; N, 11.69. Found: C, 80.24; H, 8.24; N, 11.68.

1,3-Bis(piperidinomethyl)-2-phenylindolizine

Six milliliters of 37 percent aqueous formaldehyde (0.075 mole) and 8.4 Gm. piperidine (0.10 mole) were combined with 75 ml. dioxane. One-tenth ml. of 50 percent sodium hydroxide was added and the mixture was allowed to stand for 15 minutes at room temperature. Two grams 2-phenylindolizine (0.01 mole) was dissolved in the mixture which was then allowed to stand at room temperature for 48 hours. The reaction mixture was transferred to an evaporating dish and cold air was blown across the surface. Evaporation was accompanied by vigorous scratching with a glass rod. The crystalline product which was obtained during the evaporation process was removed by filtration and washed with 50% ethanol. The yield was 3.3 Gm. (85%). On recrystallization from the ethanol the compound gave m.p. 98.5-99.5°. Analysis, calc. for $C_{26}H_{33}N_3$: C, 80.58; H, 8.58; N, 10.84. Found: C, 80.53; H, 8.57; N, 10.74.

1,3-Bis(morpholinomethyl)-2-phenylindolizine

Six milliliters of 37 percent aqueous formaldehyde (0.075 mole) and 8.7 Gm. morpholine (0.10 mole) were combined with 75 ml. dioxane. One-tenth ml. of 50 percent sodium hydroxide solution was added and the mixture was allowed to stand for 15 minutes at room temperature. Two grams 2-phenylindolizine (0.01 mole) was added and the flask swirled to achieve solution. The reaction mixture was allowed to stand at room temperature for 48 hours and then transferred to an evaporating dish. Evaporation was carried out by blowing cold air across the surface accompanied by vigorous scratching with a glass rod. The crystalline product obtained was removed by filtration and washed with 50 percent ethanol. The yield was 3.2 Gm. (81%). The product was recrystallized from ethanol and gave m.p. 156-157°. Analysis, calc. for $C_{24}H_{29}N_3O_2$: C, 73.63; H, 7.47; N, 10.73. Found: C, 73.75; H, 7.56; N, 10.84.

Preparation of Bis(indoliziny)methanesBis(3-ethyl-2-phenyl-1-indoliziny)methane

Three milliliters of 37 percent aqueous formaldehyde (0.037 mole) and one gram 3-ethyl-2-phenylindolizine (0.0045 mole) were dissolved in ten milliliters of glacial acetic acid and the mixture

was allowed to stand at room temperature for 48 hours. An equal volume of water was then added and the solution was made slightly basic with ammonium hydroxide. The gritty precipitate was filtered, washed with distilled water and air dried. The product was dissolved in a minimum amount of hot ethyl acetate and, after cooling, was placed in the freezer compartment of the refrigerator. Crystallization occurred after two days in the refrigerator. The yield was 0.71 Gm. (70%), m.p. 106-107°. Analysis, calc. for $C_{33}H_{30}N_2$: C, 87.19; H, 6.65; N, 6.16. Found: C, 87.29; H, 6.70; N, 6.20.

Bis(3-methyl-2-phenyl-1-indoliziny)l)methane

Ten milliliters of 37 percent aqueous formaldehyde (0.125 mole) and three grams 3-methyl-2-phenylindolizine (0.015 mole) were dissolved in 30 ml. dioxane and the mixture was allowed to stand at room temperature for 48 hours. Crystallization of the product commenced after the first 24 hours. At the end of the 48 hour period 20 ml. of water was added in five ml. portions over a two hour interval to complete crystallization. Rapid addition of the water tended to cause precipitation of an oil. The flask was allowed to stand an additional 24 hours in the refrigerator. The crystalline product was then filtered and washed with 50 percent ethanol. The yield was 2.7 Gm. (87%), m.p. 162-163° (decompn.). The product was recrystallized from hot acetone:water. Analysis,

calc. for $C_{31}H_{26}N_2$: C, 87.29; H, 6.14; N, 6.57. Found: C, 86.84; H, 6.12; N, 6.65.

PRELIMINARY PHARMACOLOGICAL INVESTIGATION

1-Diethylaminomethyl-3-methyl-2-phenylindolizine was administered intraperitoneally to mice as a suspension in gum acacia. The approximate LD_{50} was determined and found to be in the range of 70 to 100 milligrams per kilogram of body weight. In the lower dosage levels the drug caused the mice to become lethargic, but they did not sleep. They were easily aroused and the righting reflex was partially lost. There was no muscle relaxation. In the higher doses the animals went into convulsions. Death was caused by respiratory arrest. This compound is also being evaluated for anticonvulsant activity by the supramaximal electroshock method.

Three additional compounds have been submitted to the Walter Reed Army Medical Center in Washington, D. C., to be tested in their antimalarial screening program. The compounds that were sent are 1,2-diphenyl-3-piperidinomethylindolizine, 3-methyl-2-phenyl-1-piperidinomethylindolizine and 1,3-bis(piperidinomethyl)-2-phenylindolizine. They represent each of the three groups of Mannich bases prepared in this investigation.

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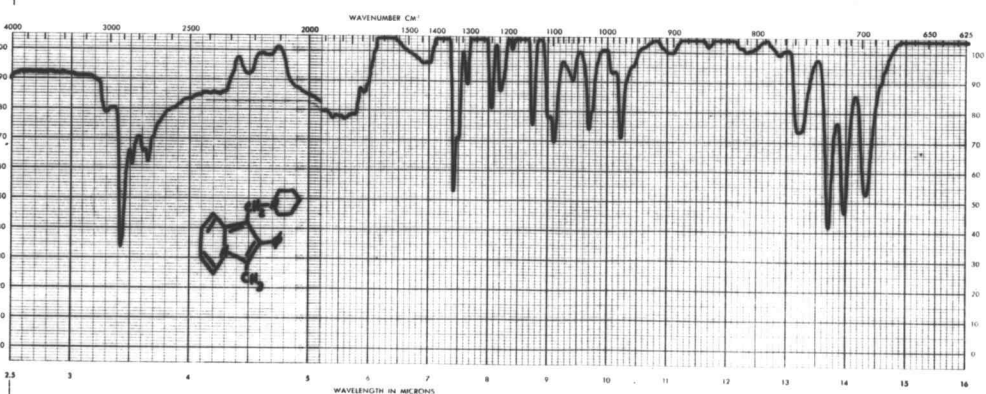
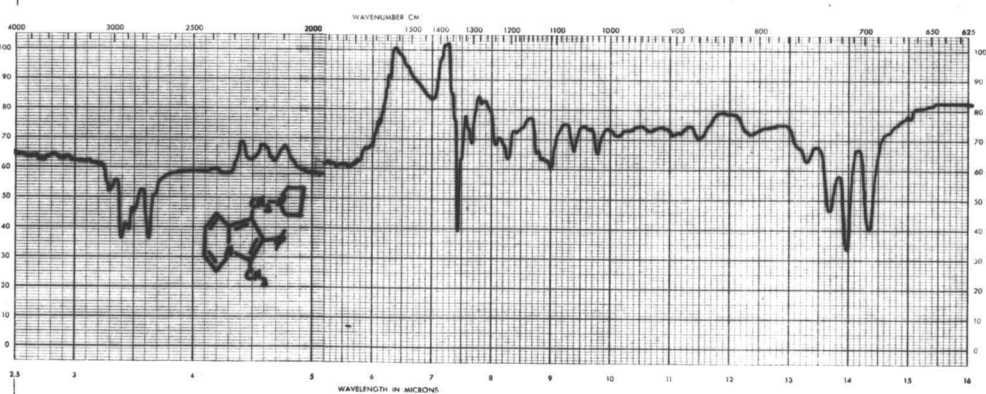
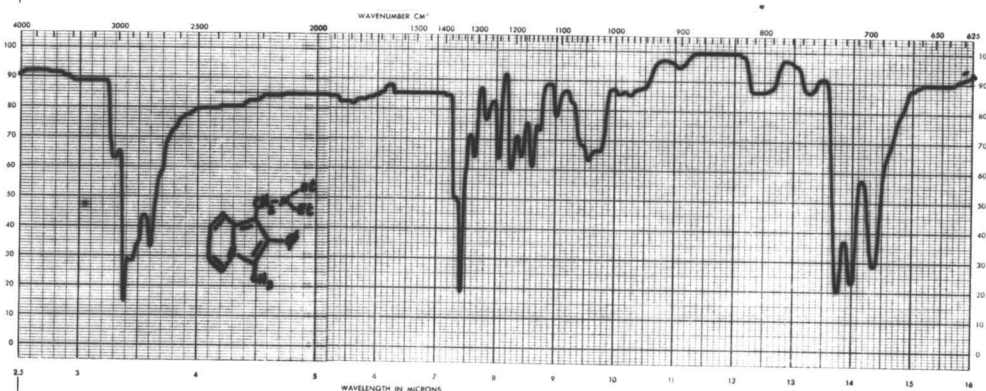
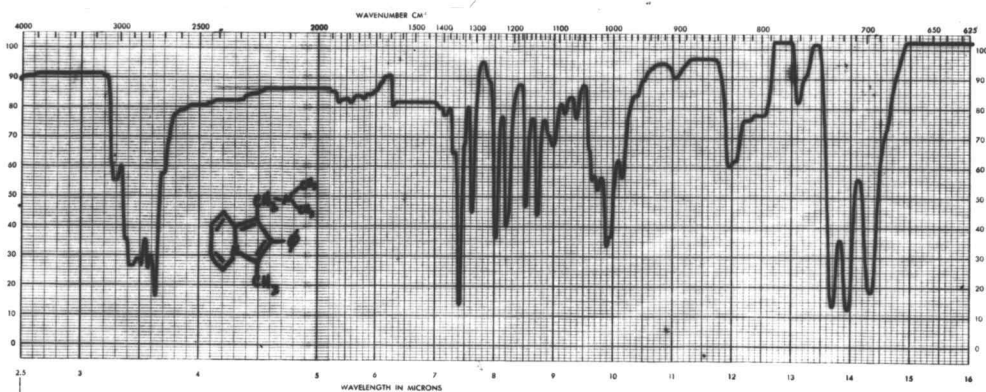
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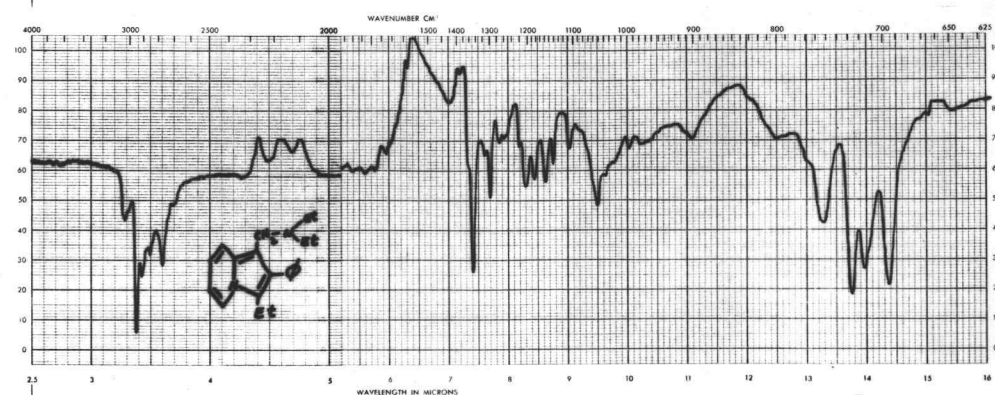
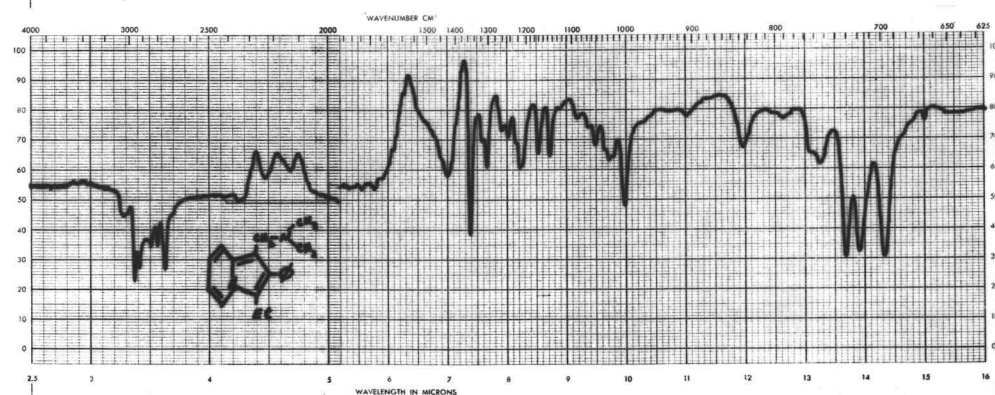
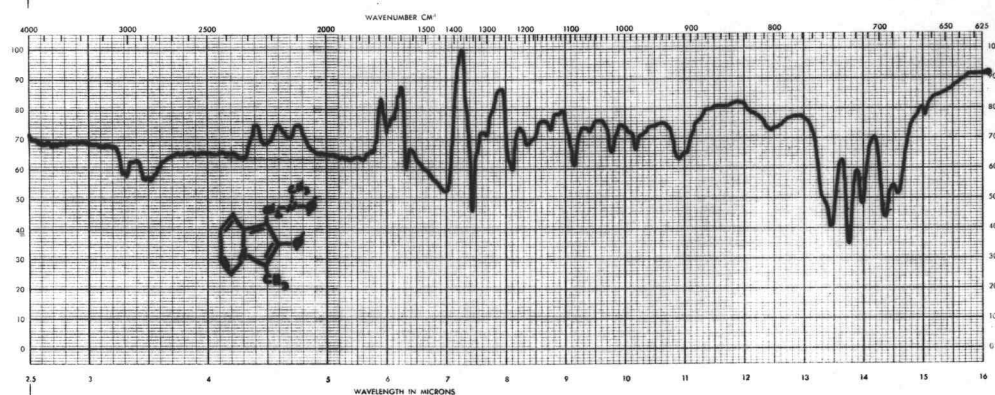
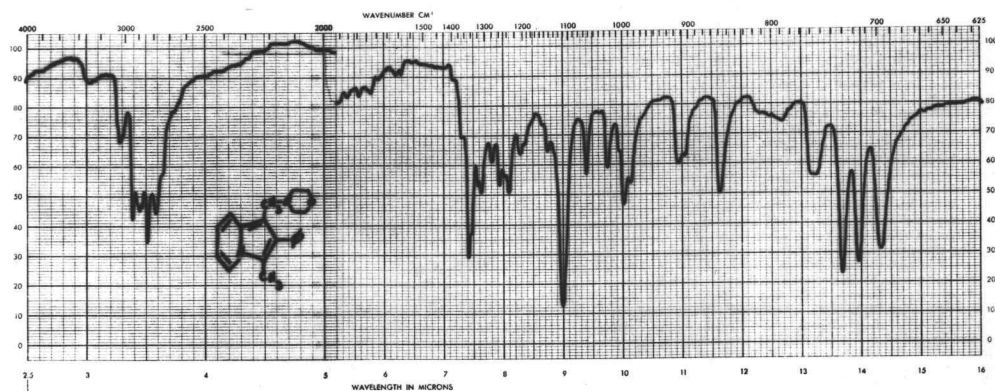
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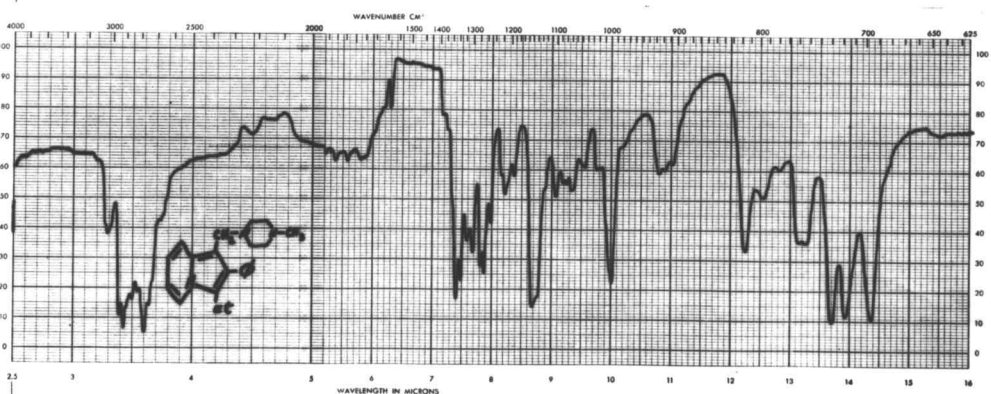
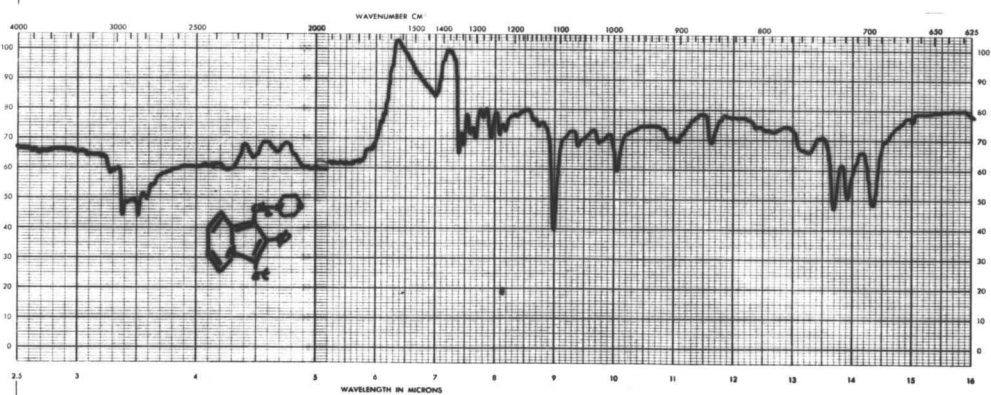
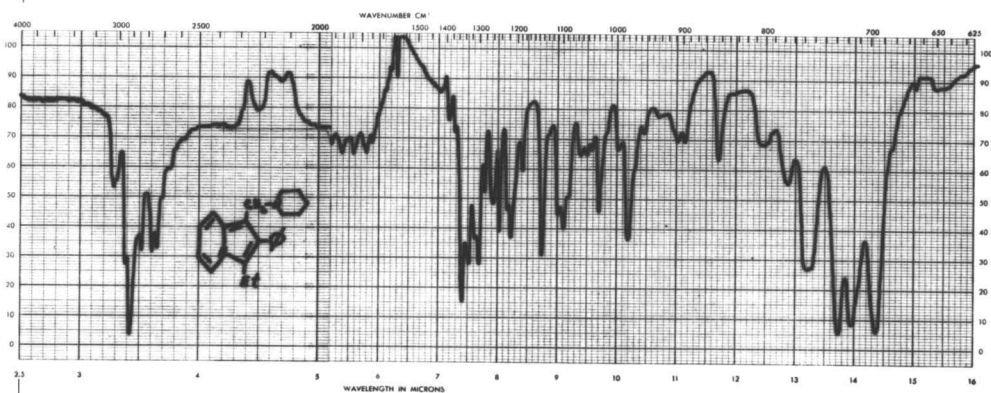
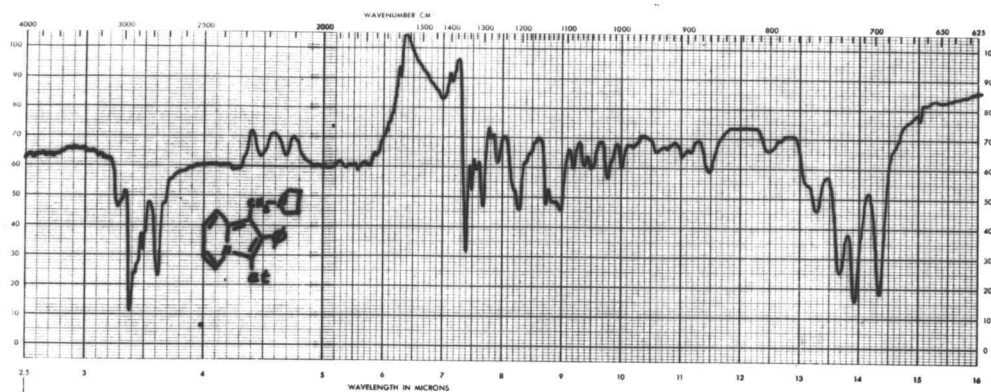
APPENDICES

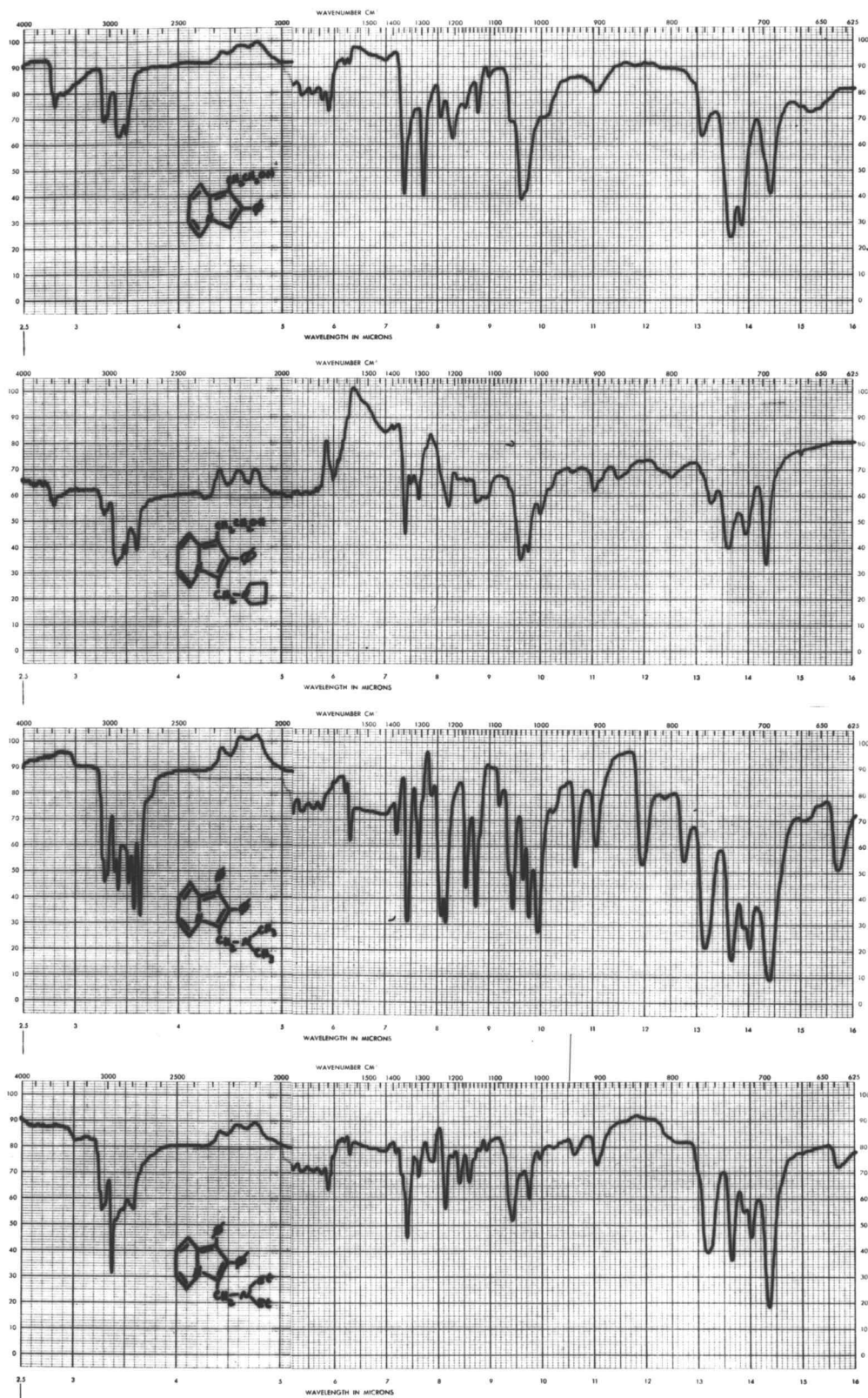
APPENDIX A

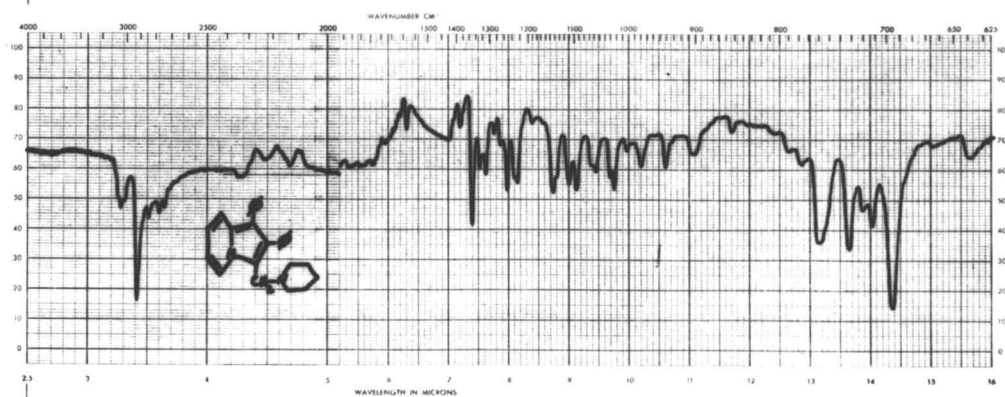
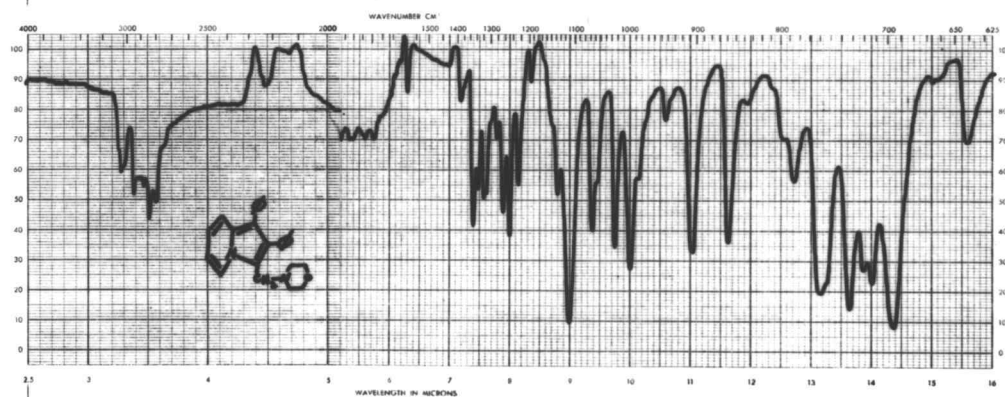
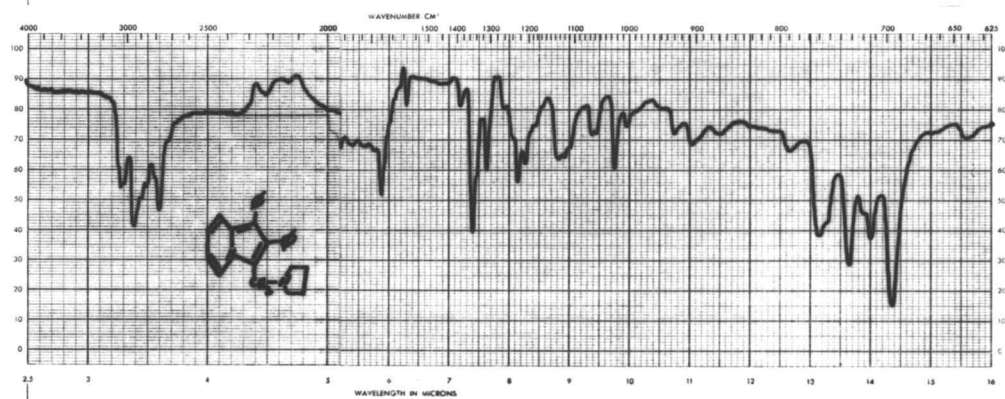
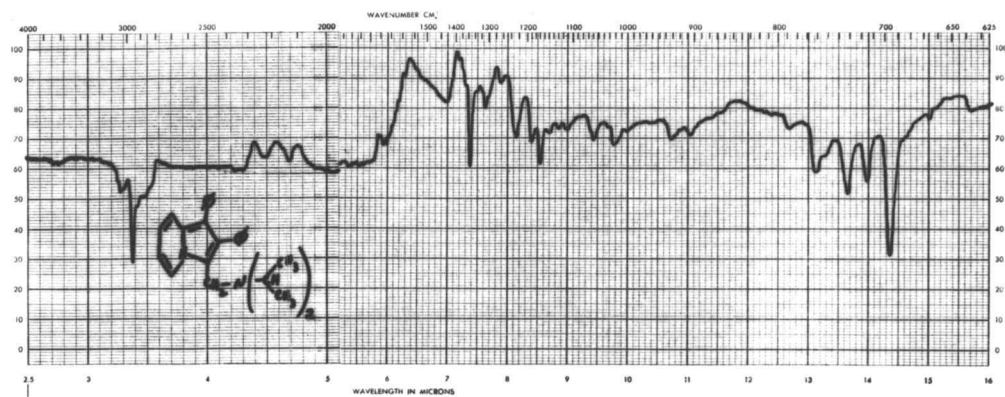
INFRARED SPECTRA OF COMPOUNDS SYNTHESIZED.
SODIUM CHLORIDE STANDARD CAVITY CELLS
WERE EMPLOYED AND THE SOLVENT WAS
CARBON DISULFIDE

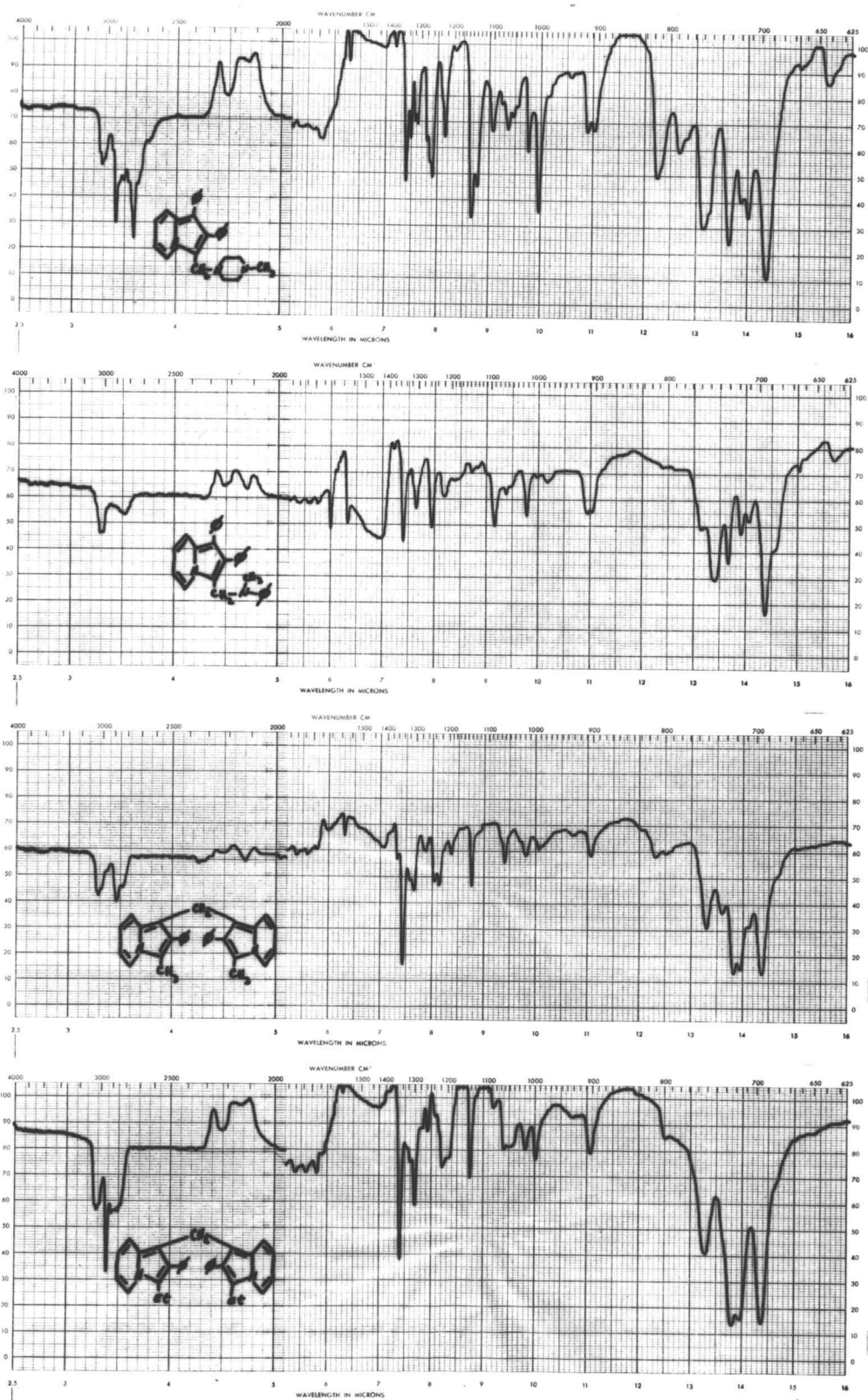


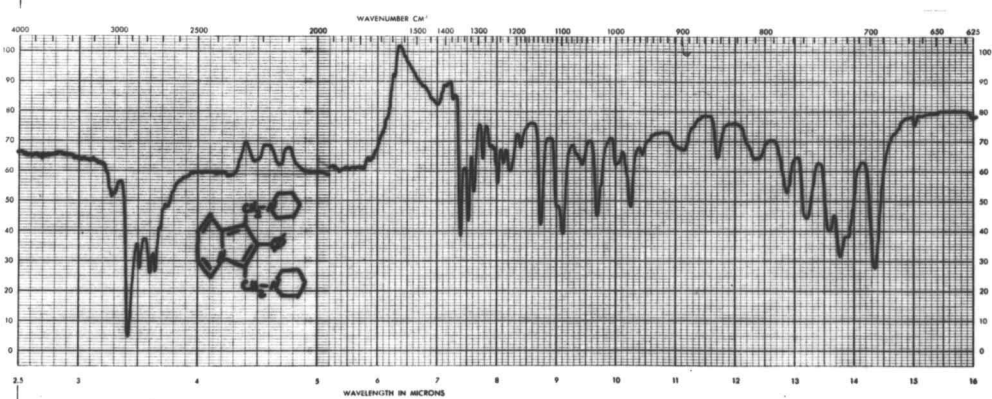
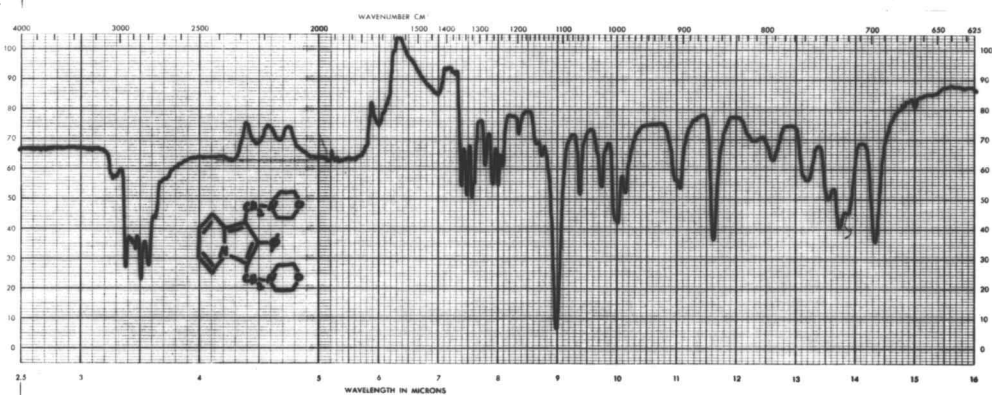
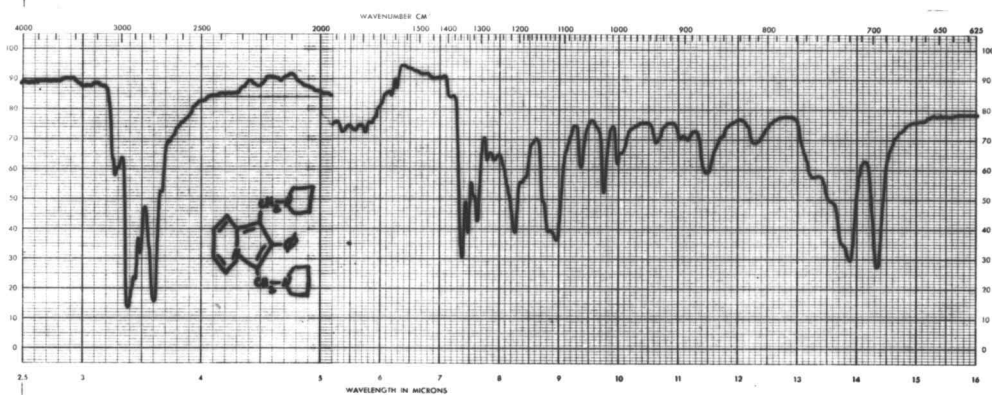
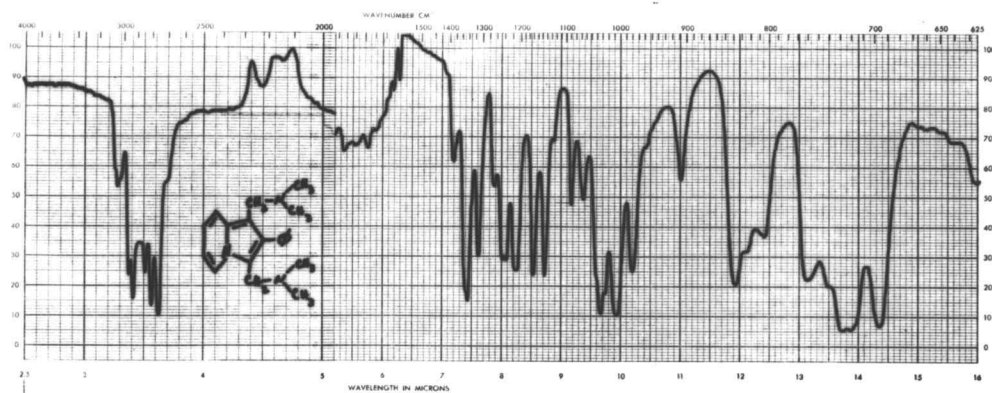












APPENDIX B

ULTRAVIOLET SPECTRA OF COMPOUNDS SYNTHESIZED.
ALL SPECTRA WERE TAKEN WITH ABSOLUTE
ETHANOL AS THE SOLVENT

