THE CHEMISTRY OF QUINOLIZINES

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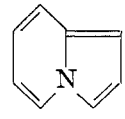
I. INTRODUCTION

The chemical literature abounds in the number of publications on the quinolizines, yet the chemistry of this group of heterocycles suffers from dearth of information in many directions and from the conspicuous absence of a comprehensive survey of the field. The only extensive account relating to them is to be found in a part of the chapter entitled "Bicyclic systems with a nitrogen atom common to both rings" in Volume 3 of *Heterocyclic Compounds*, edited by Elderfield (52). This can hardly be claimed to be exhaustive compared to the excellent review available on the indolizines (I) (12).

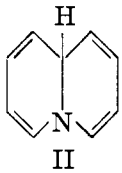


I

Indolizine

The present paper is therefore an effort to provide a truly comprehensive account of the large amount of work that has appeared in the past and in recent times concerning the synthetic quinolizine derivatives and those natural products containing the quinolizine nucleus.

The quinolizines contain a bicyclic naphthalenic ring system with a tertiary nitrogen atom in one of the bridgehead positions (II). They have alternatively

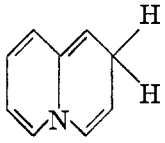


II

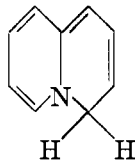
Quinolizine

been called pyridocolines and are referred to in *Chemical Abstracts* by either name.

Of the three tautomeric structures possible for the parent compound quinolizine (II, III, and IV), formula II is more widely used.



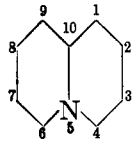
III



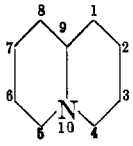
IV

Quinolizine

Two systems of numbering the quinolizine nucleus have been followed. The procedure adopted by *Chemical Abstracts* is indicated in formula V, while Japanese publications (132) on these compounds have preferred the order shown in formula VI.



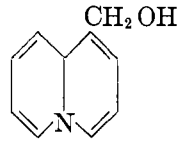
V



VI

The corresponding fully hydrogenated derivative has been designated variously as quinolizidine, octahydroquinolizine, octahydropyridocoline, piperidocoline, norlupinane, and 1-azabicyclo[0.4.4]decane.

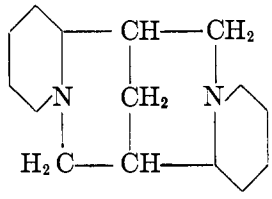
Interest in this class of compounds stems from their occurrence in numerous natural alkaloids. Alkaloids like lupinine (VII) possess the simple bicyclic quinolizine nucleus, while polycyclic ring structures incorporating the same nucleus are found in other bases of the lupin group (sparteine (VIII), matrine



VII

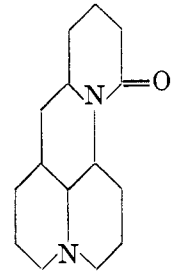
Lupinine

(IX)), the canadine alkaloids (berberine (X)), and the Ipecacuanha alkaloids (emetine (XI)) (67). Also, the basic quinolizine ring system is a structural feature present in many of the compounds exhibiting high curariform activity (40).



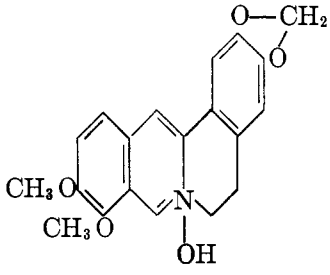
VIII

Sparteine



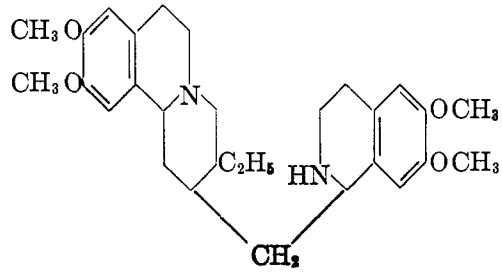
IX

Matrine



X

Berberine

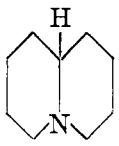


XI

Emetine

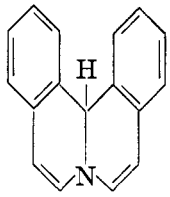
Since a very large number of the publications in the field relate to synthesis, this phase will be discussed first, followed by an account of the chemical behavior and physical properties of the quinolizines. Many of the interesting properties of the quinolizine ring system have been studied only with the saturated bicyclic quinolizine derivatives (XII) or those in which it is fused to two benzene rings (XIII). This will be reflected in the section dealing with the reactions and properties of the ring system.

The name "quinolizine" for the aromatic ring structure and the name "octahydroquinolizine" for the perhydro derivative will be used throughout. The numbering of the ring system will be in accordance with the practice of *Chemical Abstracts* as indicated in formula V.



XII

Norlupinane



XIII

II. METHODS OF SYNTHESIS OF QUINOLIZINES

A. Intramolecular alkylation of an amino group to form azabicycloalkanes

Almost all the methods adopted for the synthesis of the bicyclic quinolizines lead to the corresponding fully hydrogenated compounds. Norlupinane A, obtained from the natural alkaloid lupinine by oxidation and decarboxylation (33), is the simplest octahydroquinolizine (XII). One of the earliest methods adopted for the preparation of this compound was the intramolecular alkylation of an amino group to form 1-azabicyclo[0.4.4]decane. The method in general as adopted by Prelog and Bozicevic (94) may be outlined as follows:

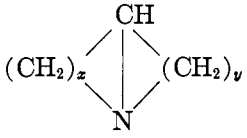
$C_2H_5O(CH_2)_xBr$ is condensed with ethyl malonate to give $C_2H_5O(CH_2)_x$-$CH(COOC_2H_5)_2$. The latter by interaction with $C_2H_5O(CH_2)_yBr$ yields

$$C_2H_5O(CH_2)_xC(CH_2)_yOC_2H_5$$
$$\|$$
$$(COOC_2H_5)_2$$

On hydrolysis and decarboxylation this compound gives $C_2H_5O(CH_2)_xCH$-$(COOH)(CH_2)_yOC_2H_5$ which, by the Curtius-Schmidt reaction, followed by treatment with hydrogen bromide, yields

$$Br(CH_2)_xCH(CH_2)_yBr$$
$$|$$
$$NH_2$$

The latter by the action of alkali gives



When $x = y = 4$, the product is octahydroquinolizine.

Apart from the recent synthesis of octahydroquinolizine itself (145), not many quinolizine derivatives have been made by this method. This was the first unequivocal synthesis of the base octahydroquinolizine, for an earlier attempted synthesis by Clemo and Ramage (33), involving a Clemmensen reduction of 1-ketoöctahydroquinolizine, led to the isomer 1-azabicyclo[0.3.5]-decane. The latter was also synthesized unambiguously following the above-mentioned procedure (99).

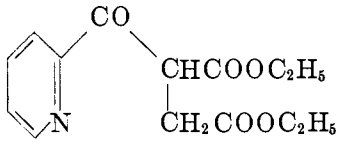
Although this particular method has not been much utilized for the synthesis

of the quinolizines, it has been well exploited for the preparation of other ring homologs (98, 100) and of the members of the quinuclidine group (95, 96, 97).

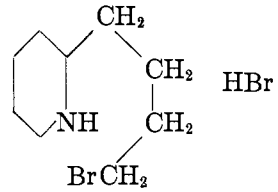
B. Intramolecular alkylation of bromoalkylpiperidine derivatives

A highly useful variation of the method described above which has been widely studied is the cyclization of piperidine derivatives as halides. Several methods are available for the preparation of the bromoalkylpiperidines.

The synthesis of octahydroquinolizine by Clemo, Ramage, and Raper (35) is illustrative. Condensation of ethyl picolinate with ethyl succinate gave the keto ester (XIV). From this by hydrolysis, decarboxylation, and reësterification the pyridylbutyric ester was obtained. The latter on reduction with sodium and alcohol gave the 2-piperidyl-ω-butanol. The corresponding bromobutylpiperidine hydrobromide (XV) was obtained by the action of hydrogen bromide.



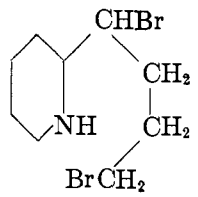
XIV



XV

On treatment with alkali XV gave octahydroquinolizine.

Winterfeld and Holschneider (150) obtained the same compound by an essentially similar method, utilizing the action of sodium ethoxide on XVI, followed



XVI

by reduction of the 1-bromoöctahydroquinolizine with palladized calcium carbonate.

The higher homolog, lupinane or 1-methyloctahydroquinolizine, has also been synthesized by similar methods (152).

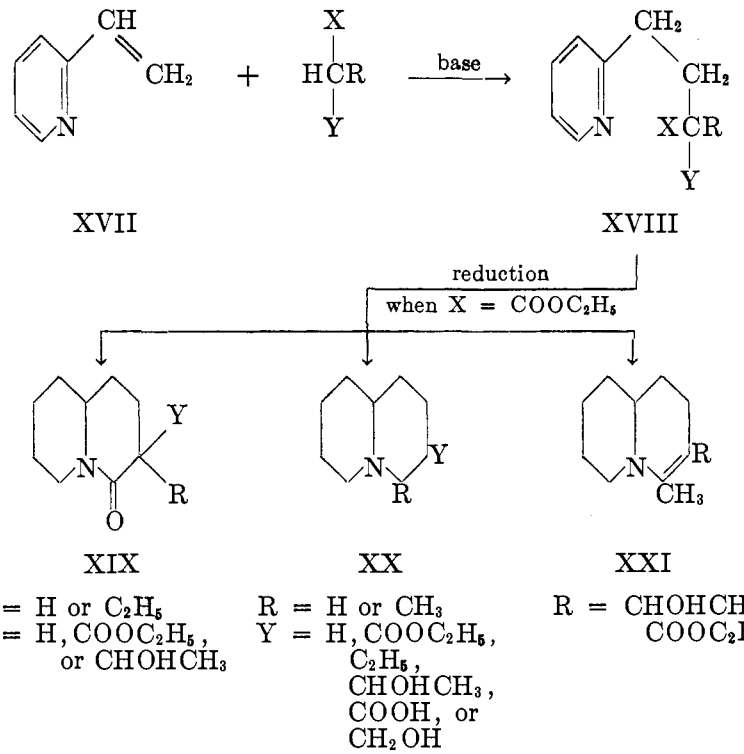
Closely related methods have been employed in the syntheses of *dl*-bromolupinane, *dl*-lupinine or 1-hydroxymethyloctahydroquinolizine, and allolupinine, the structural isomer of 1-hydroxymethyloctahydroquinolizine (31, 148, 151).

C. Cyclization of piperidine derivatives as amides

This method consists in general of intramolecular cyclodehydration of appropriately substituted pyridyl or piperidyl derivatives. The cyclodehydration may be effected by heat or hydrogenation. The latter is a process that has the advan-

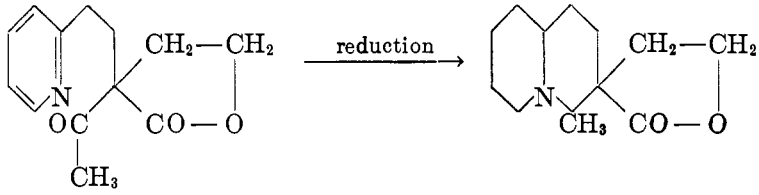
tage of being simpler and of more general applicability than many others available for the synthesis of quinolizines.

A two-step synthesis for a variety of octahydroquinolizine derivatives, based on this procedure, has been devised by Boekelheide and Rothchild (10, 11). The general method involves the addition of active methylene compounds to 2-vinylpyridine, followed by reductive cyclization of the addition products to the octahydroquinolizine derivatives. Diethyl malonate, diethyl ethylmalonate, ethyl acetoacetate, ethyl benzoylacetate, and acetylacetone have been added to 2-vinylpyridine. The products were cyclized under different conditions with various catalysts such as Raney nickel, platinum oxide, and copper chromite. The general scheme can be outlined as follows:

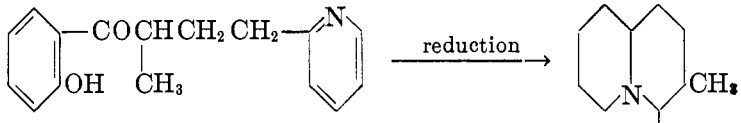


Such of those quinolizine derivatives as incorporate a lactone ring would resemble derivatives of erythroidine and hence might reasonably be expected to exhibit curariform activity. With this end in view, a few quinolizine derivatives of this type have also been synthesized by the method of reductive cyclization (4).

α-Aceto-γ-butyrolactone adds to 2-vinylpyridine to form XXII, which on reduction furnishes the quinolizine derivative XXIII. Likewise, the addition product (XXIV) of 4-hydroxy-3-methylcoumarin with 2-vinylpyridine was successfully reduced to 4-(*o*-hydroxyphenyl)-3-methyloctahydroquinolizine (XXV).

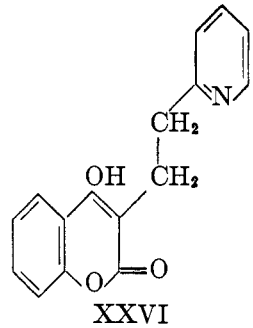


XXII XXIII



XXIV XXV

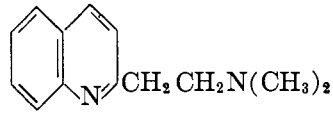
However, although 4-hydroxycoumarin added to 2-vinylpyridine in good yield to form XXVI,



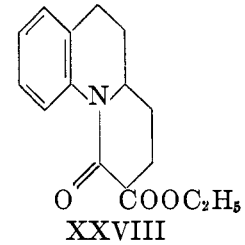
XXVI

the latter failed to undergo reductive cyclization to the corresponding quinolizine.

Reductive cyclizations of this type have also been extended to the quinoline series. Since 2-vinylquinoline was difficult to obtain in the laboratory, the Mannich base (XXVII) prepared from quinaldine was alkylated with diethyl malonate, ethyl acetoacetate, and ethyl benzoylacetate to furnish the appropriate derivatives required for reductive cyclization. The addition product with ethyl malonate gave on reduction the quinolizine derivative XXVIII (9).

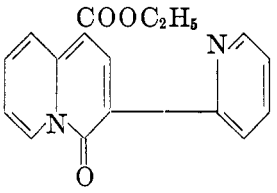


XXVII

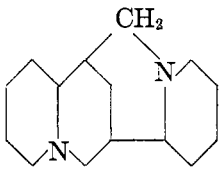


XXVIII

The method of reductive cyclization has also rendered possible a very elegant total synthesis of the alkaloids sparteine and isosparteine by a two-step procedure (76, 77). Ethyl 2-pyridylacetate and ethyl orthoformate condensed in the presence of acetic anhydride to form 1-carbethoxy-4-keto-3-(α-pyridyl)quinolizine (XXIX). This compound on hydrogenation over copper chromite at 250°C. at a pressure of 300–350 atm. yielded the two bases sparteine and isosparteine (XXX).

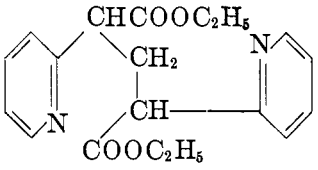


XXIX



XXX

A similar condensation of ethyl 2-pyridylacetate with formaldehyde or methylene iodide resulted in the formation of diethyl 2,4-di(2′-pyridyl)glutarate (XXXI).



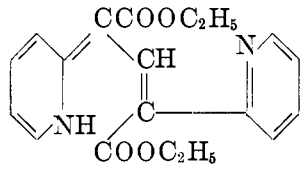
XXXI

This on hydrogenation in a like manner gave the same bases.

The reductive cyclization of oximino diesters occurs in the same manner, with the oximino nitrogen as the incipient bridgehead of the final quinolizine derivative (79). Since the formation involves only two steps and the yields average between 50 and 60 per cent, this is another attractive procedure for the preparation of quinolizine derivatives. Leonard and Goode (78) have synthesized octahydroquinolizine by the reductive cyclization of the oxime derived from diethyl δ-ketoazelate, $C_2H_5OOC(CH_2)_2CH_2COCH_2(CH_2)_2COOC_2H_5$.

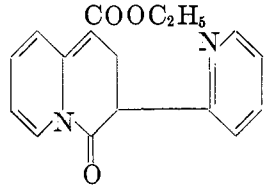
Whereas reductive cyclization results in the formation of the saturated quinolizine derivatives, cyclodehydration effected under the action of heat yields the aromatic quinolizines directly. This procedure has therefore been widely employed in the synthesis of several bicyclic and polycyclic quinolizines.

The earliest attempt towards the synthesis of sparteine (30) utilized this procedure. Ethyl 2-pyridylacetate condensed with ethyl orthoformate in the presence of acetic anhydride to yield 1-carbethoxy-4-keto-3-(2′-pyridyl)quinolizine (XXIX). The analogous reaction of ethyl 2-quinolylacetate with the same reagents resulted in the formation of the corresponding benzoquinolizine carboxylate (32). It was proposed by Clemo and coworkers that XXIX was formed by ring-closure of the tautomeric form of the bismethenyl compound (XXXII).



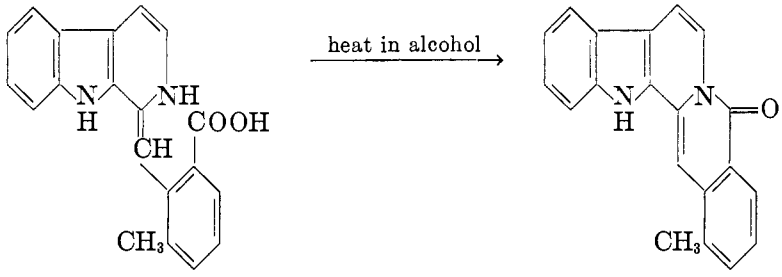
XXXII

In several such instances ring-closure to the quinolizine derivative has been observed even while distilling the intermediate compounds. Cyclization occurs when diethyl di(2-pyridyl)glutarate, obtained by the condensation of ethyl-2-pyridylacetate and methylene iodide, is reduced and the product is distilled (36). Even the preparation of the diethyl dipyridylglutarate is accompanied by the formation of 1-carbethoxy-4-keto-3-(2-pyridyl)-2,3-dihydroquinolizine (XXXIII).



XXXIII

Such facile ring-closure between the carbethoxy group and the —NH— group has been explained on the basis of the familiar α-methylpyridine–α-pyridonemethine equilibrium (77, 157). The easy interconvertibility of dehydroketoyobyrine and the product of its hydrolysis, even on attempted recrystallization from alcohol, is illustrative of this mechanism (157).

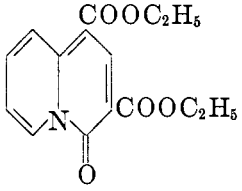


XXXIV XXXV

Simultaneous loss of hydrogen has also been observed in these ring-closures leading to the formation of the quinolizine derivatives. Thus while Clemo, Raper, and Short (36) report the formation of the 2,3-dihydro derivative (XXXIII), Leonard and Beyler (77) describe a compound of the completely aromatic type resulting from simultaneous loss of hydrogen (XXIX). The homologous methyl ester of XXIX has also been isolated from the methylene iodide and formaldehyde condensations with methyl 2-pyridylacetate (108).

The successful utilization of the intermediates derived from ethyl 2-pyridyl-

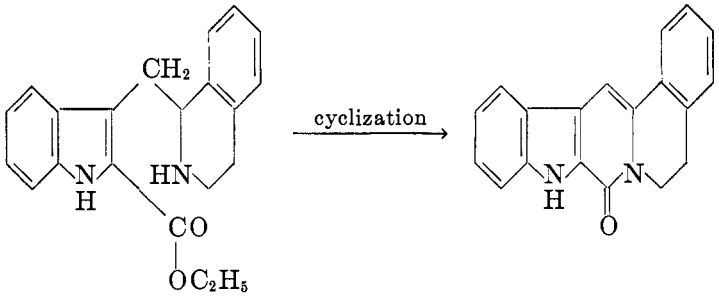
acetate in the formation of these quinolizine derivatives led to the idea of employing ethyl 2-pyridylacetate itself as a 1,3-diketone capable of undergoing cyclic condensation with suitable enol ethers. When ethyl 2-pyridylacetate was heated with diethyl ethoxymethylenemalonate, 1,3-dicarbethoxy-4-ketoquinolizine was obtained as the sole product (XXXVI). Hydrolysis and decarboxyla-



XXXVI

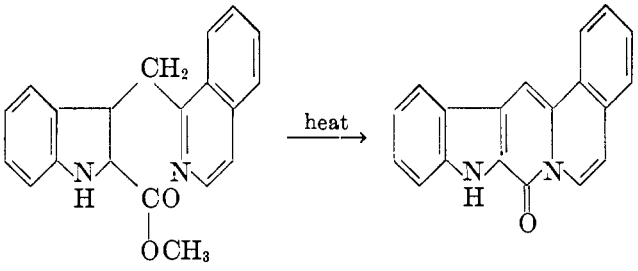
tion of XXXVI gave the simple quinolizine derivative, 4-ketoquinolizine. The octahydro derivative of the latter is obtained directly by the cyclodehydration of γ-(α-piperidyl)butyric acid (35, 109).

Extension of this procedure in the synthesis of a few indoloquinolizines has also been successfully carried out. In an attempt to prepare potential curariform compounds, Boekelheide and Ainsworth have reported the cyclization of XXXVII to the corresponding indoloquinolizone (XXXVIII).



XXXVII XXXVIII

Likewise, 1-(2′-carbomethoxyskatyl)isoquinoline (XXXIX) undergoes cyclodehydration to 1,2-benzo-7,8-(2′,3′-indolo)quinolizone (XL) (5, 6). Intramo-



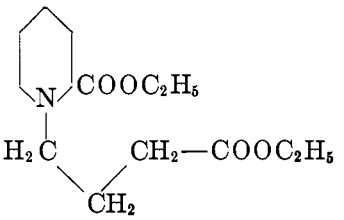
XXXIX XL

lecular cyclodehydration is thus a method of general applicability for several types of quinolizine derivatives.

This short account of the cylodehydration also shows the great versatility of ethyl 2-pyridylacetate as an intermediate in the synthesis of the aromatic quinolizine derivatives. Despite the easy accessibility of this reagent (155), only a limited study of its use has been made. In a like manner to the employment of ethyl ethoxymethylenemalonate with ethyl 2-pyridylacetate, ethyl ethoxymethylenecyanoacetate, ethyl ethoxymethyleneacetoacetate, ethyl ethoxymethyleneoxaloacetate, methoxymethyl cyanoacetate, and methoxymethyl malonate offer equally good possibilities. These reagents provide varying substituents in one half of the quinolizine molecule. Substituents in the pyridylacetate molecule (like alkoxy or acyl groups) would offer variation in the other half of the ring system.

D. Dieckmann ring-closure

This method of obtaining quinolizine derivatives has been exploited chiefly by Clemo and coworkers. One of the earliest attempts towards the synthesis of the alkaloid lupinine (33) involves the application of the Dieckmann ring-closure to ethyl γ-2-carbethoxypiperidinobutyrate (XLI).



XLI

The product, 1-ketoöctahydroquinolizine, was found to undergo contraction of the ketonic ring when subjected to Clemmensen reduction. This was established by an unambiguous synthesis of the resulting compound, 1-azabicyclo[0.3.5]-decane (99). The 2-keto and 3-keto bases were also synthesized by similar ring-closures (28, 29).

Among the other ketoquinolizines which have been made by this method are methyl 9-ketoöctahydroquinolizine-1-carboxylate (34), 2-carbethoxy-1-keto-octahydroquinolizine (27), 1-keto-2-methyloctahydroquinolizine (27), 1-keto-8-methyloctahydroquinolizine (25), 2-keto-1-methyloctahydroquinolizine (31), 1-keto-5,6-benzo-1,2,3,4,7,8-hexahydroquinolizine (26), and 1-keto-7,8-benzo-1,2,3,4,6,9-hexahydroquinolizine (37).

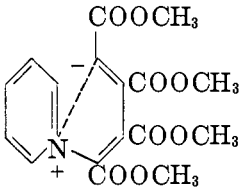
The Dieckmann ring-closure method has the advantage of using easily accessible intermediates and producing directly the various possible keto derivatives of octahydroquinolizine.

E. Diene synthesis

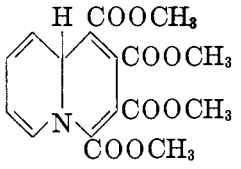
Apart from the intramolecular cyclodehydration procedure discussed earlier, the diene synthesis is the one other method leading directly to the formation of the aromatic quinolizine derivatives.

In the course of an investigation of the addition of acetylenedicarboxylic acid and its esters to aromatic ring systems (42), Diels and Alder discovered that the addition took place across the —C=N— of an aromatic nucleus. Further investigations revealed that similar addition products were obtainable with pyridine, quinoline, isoquinoline, α-picoline, stilbazole, and phenanthridine, all of which could be converted to quinolizine derivatives.

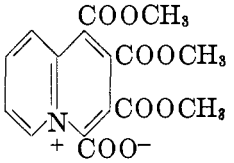
The reaction of acetylenedicarboxylic ester with pyridine was not simple. A variety of products was obtained, depending on the nature of the solvent employed. In acetic acid solution, only hexamethyl trimellitate is formed by the trimerization of the acetylenic ester. In ethereal solution, however, a mixture of three substances is formed (46). Diels and Alder refer to these as the red substance (XLII), the yellow substance (XLIII), and Kashimoto's compound



XLII



XLIII

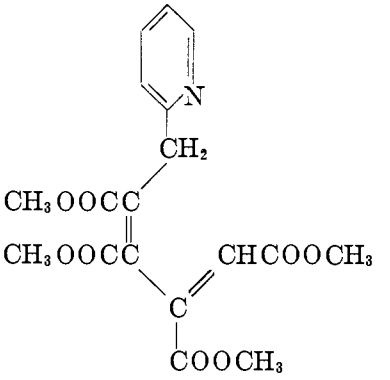


XLIV

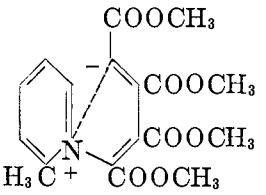
(XLIV). The yellow substance and Kashimoto's compound are quinolizine derivatives. The red substance is converted to the yellow one on crystallization from solvents; it can also be transformed into Kashimoto's compound by the action of mercuric acetate and acetic acid.

The proof of these structures is based mainly on the nature of the products obtained on oxidation. With hydrogen peroxide, α-picolinic acid *N*-oxide was formed, indicating that one point of attachment of the acetylenedicarboxylic ester was the α-position of the pyridine ring (44). The yellow substance was also progressively decarboxylated and hydrogenated to give octahydroquinolizine.

The reaction of α-picoline with dimethyl acetylenedicarboxylate in ethereal solution at 0°C. likewise gave two products (49). A red stable adduct (XLV) and a yellow labile product (XLVI) analogous to the compounds from pyridine were obtained.

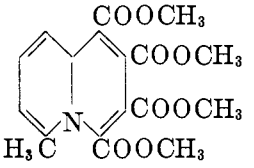


XLV



XLVI

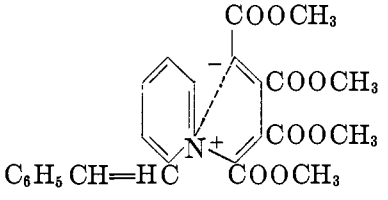
The labile adduct is converted to the quinolizine derivative (XLVII) by heat



XLVII

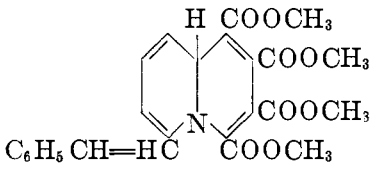
or acetic acid.

Similarly, the reaction of stilbazole with acetylenedicarboxylic ester gave an orange labile adduct (XLVIII). This, however, on heating in phenol or in xylene gives two different quinolizine derivatives.

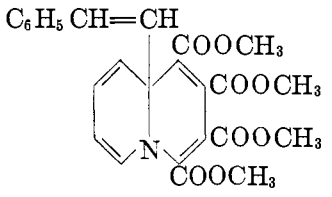


XLVIII

heat in phenol or xylene



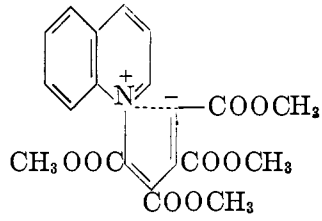
XLIX



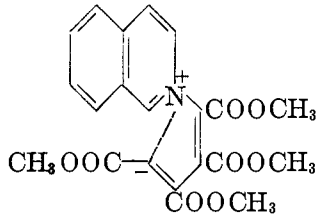
L

The reaction of dimethyl acetylenedicarboxylate with quinoline, isoquinoline,

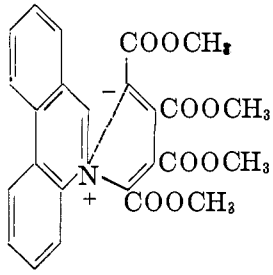
and phenanthridine (45, 46, 47, 50) gave the respective labile adducts LI, LII,



LI

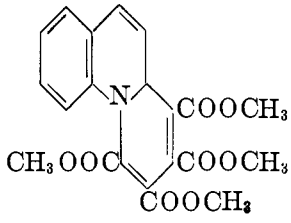


LII

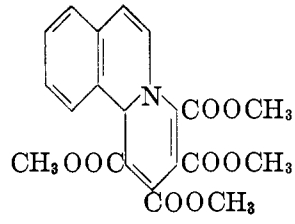


LIII

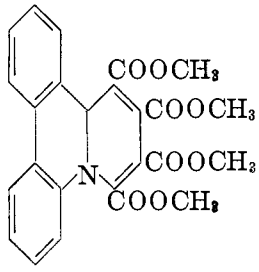
and LIII. These labile adducts on heating yielded the stable quinolizine derivatives LIV, LV, and LVI.



LIV



LV



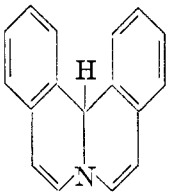
LVI

The application of the diene synthesis to the preparation of quinolizines is limited to the few compounds listed above. The literature contains no other reference. The reason for this may be sought in the great instability of the addi-

tion products and their facile conversion to indolizine compounds on attempted transformation to useful quinolizine derivatives.

F. Application of the Bischler–Napieralski reaction to N-substituted pyridones and other cyclic amides

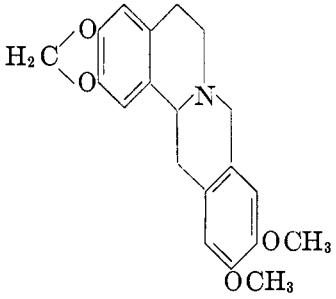
The several methods of synthesis discussed in the preceding sections relate mainly to the formation of bicyclic quinolizine derivatives. Polycyclic structures incorporating this ring system have all been made almost exclusively by the Bischler–Napieralski reaction. Since a great number of alkaloids carry the quinolizine skeleton to which two other benzene rings are fused (XIII), attempts



XIII

towards their synthesis have led to an extensive application of this reaction.

The earliest reference to the employment of this reaction for the synthesis of quinolizine derivatives is the synthesis of oxyberberine and related compounds by Haworth and Perkin (62). In their method, the formyl derivative of bromoveratrylnorhydrohydrastinine was treated with phosphorus oxychloride; the product was reduced by zinc and sulfuric acid to yield tetrahydro-ψ-berberine (LVII).

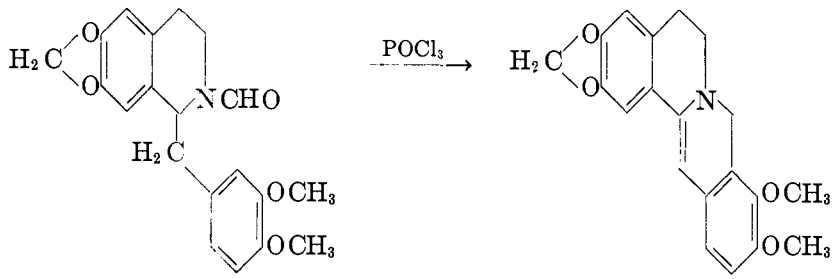


LVII

Tetrahydro-ψ-berberine

Similar treatment of the formyl derivative of veratrylnorhydrohydrastinine gave dihydro-ψ-berberine (LIX) in excellent yield.

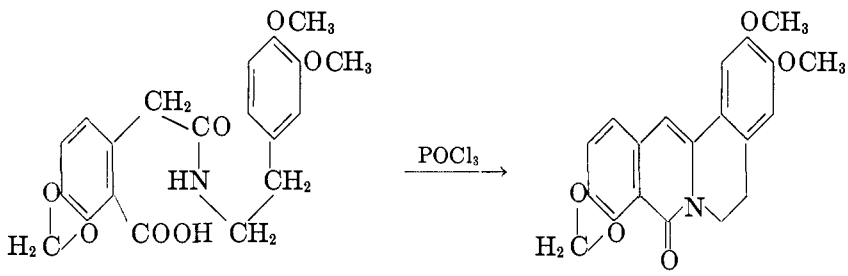
Subsequently several such cyclizations of *N*-formyl derivatives of 1-benzyltetrahydroisoquinolines have been carried out, resulting in the formation of a host of other compounds possessing the structural features of protoberberine (19, 20, 21, 24, 41, 65, 73, 74).



LVIII LIX

Dihydro-ψ-berberine

A useful variant of this procedure is the cyclization of the methyl ester of *N*-(β-veratrylethyl)-3,4-methylenedioxyhomophthalamic acid (LX) to oxyepi-



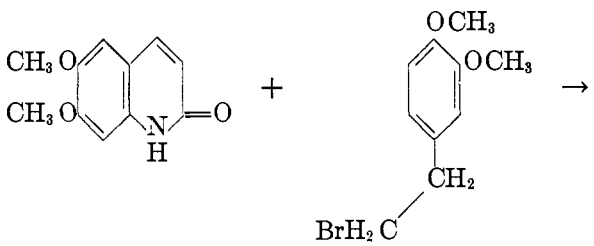
LX LXI

Oxyepiberberine

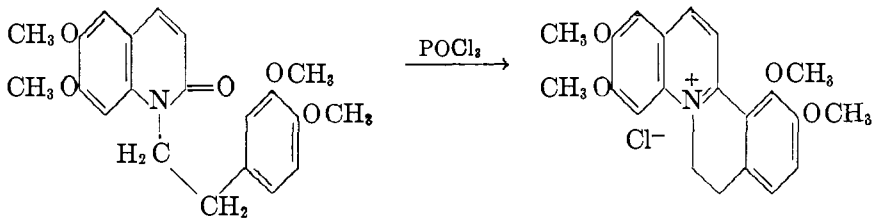
berberine (LXI). This modification also has found extensive application (22, 23, 38, 51, 61, 64, 68, 115).

In the preparation of the cyclic amides for these ring-closures, an ingenious modification was effected by Sugasawa and Kakemi (118, 119, 122). *N*-Alkylated quinolones or isoquinolones were prepared by the action of β-arylethyl halides on the potassium derivatives of substituted carbostyrils and isocarbostyrils. These were cyclized to the quinolizinium compounds under the action of phosphorus oxychloride.

A further improvement in the preparation of these pyridones was devised by the same workers. This consisted in the oxidation by alkaline ferricyanide of the

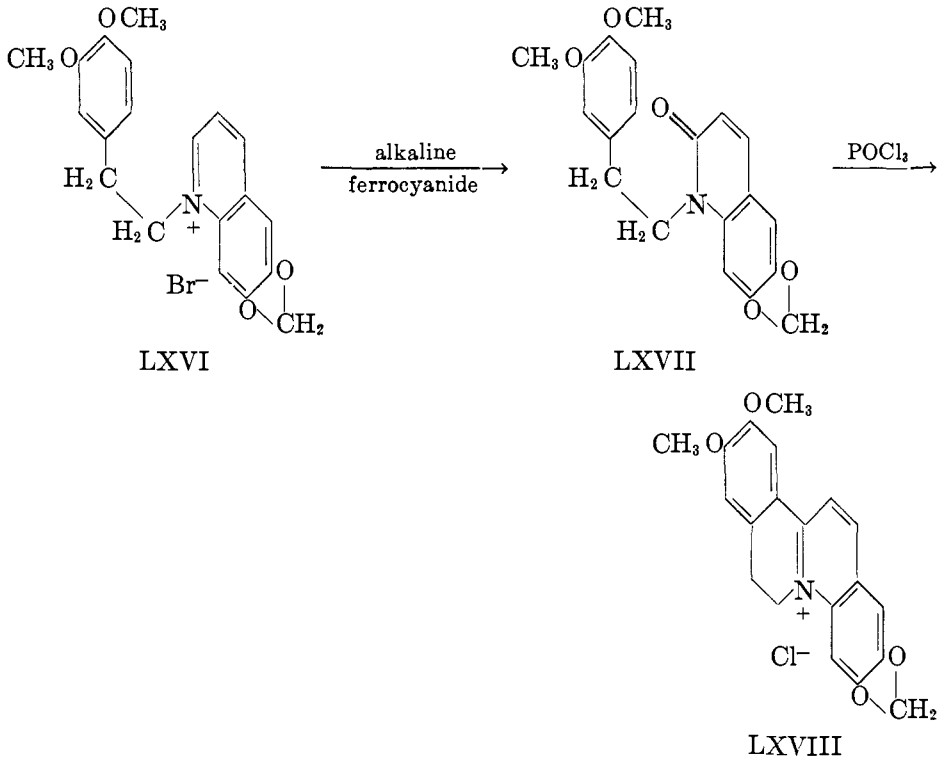


LXII LXIII



LXIV LXV

quaternary salts formed between variously substituted quinolines and isoquinolines and similarly substituted β-arylethyl halides. This facile formation of cyclic amides and their ready conversion to the quinolizinium compounds has opened up vast possibilities for the easy synthesis of polycyclic quinolizines. The following synthesis would be illustrative of this procedure:



LXVI LXVII LXVIII

A large number of benzo- and dibenzoquinolizines have been synthesized, chiefly by Sugasawa and coworkers, employing this procedure (1, 116, 120, 121, 123, 125, 126, 127, 131, 132, 133, 136, 140). Naphthoquinolizines (58), pyrrolidyl-, thiazolyl-, and quinolylbenzoquinolizines (137, 138), and analogs of emetine (87, 88, 128) are among the numerous other compounds made by this procedure.

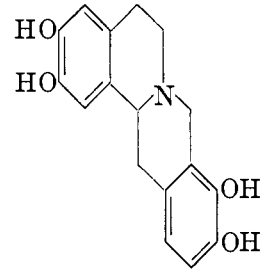
In a few other instances, the cyclic amides required for similar ring-closure

have been made by the condensation of suitable β-arylethylamines with corresponding lactones, acid anhydrides, or α-pyrones (117, 129, 130, 139, 143, 146).

From the numerous quinolizine derivatives reported, it is apparent that this method is of much practical importance in the preparation of various polycyclic quinolizines. The yields are remarkably high. A striking feature is the excellent yield even in those instances where ring-closure takes place on an unsubstituted benzene ring. This is in marked contrast to the poor yields in analogous isoquinoline-forming cyclizations and has been attributed to the tendency of the pyridone ring to pass to a completely aromatic structure (1, 58, 116).

G. Application of the Pictet–Spengler reaction

Apart from its applicability in the synthesis of isoquinolines, this reaction has found wide use in the synthesis of the quinolizine ring system also. Derivatives of protoberberine and of paraberine have been made essentially by the application of this reaction. The earliest reported synthesis by this method was that of tetrahydro-ψ-berberine from 1-veratrylnorhydrohydrastinine (91, 92). Owing to doubtful claims made by Pictet and Gams that the product of this reaction was tetrahydroberberine, the synthesis was later repeated by Haworth, Perkin, and Rankin (66). Their findings—that the product was actually tetrahydro-ψ-berberine—were also confirmed by Späth and Kruta (111). These authors also synthesized the corresponding compounds in which the alkoxyl groups were replaced by hydroxyl.



LXIX

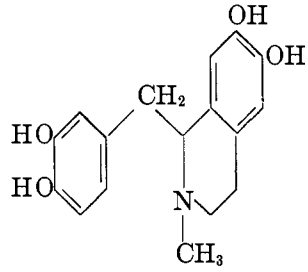
Synthesis of compound LXIX under biological conditions was achieved by Schöpf (105).

Among other compounds made by this reaction are the following: corydaline (112), 7-demethylo-ψ-corydaline (63), norcoralydine and coralydine (41, 59, 60, 90, 93), 2,3-12,13-bismethylenedioxyberbine (113, 114), tetrahydro-ψ-berberine (14), derivatives of paraberine (18, 70, 124, 125), and a few other derivatives of protoberberine (13, 15, 126).

H. Other methods of synthesis

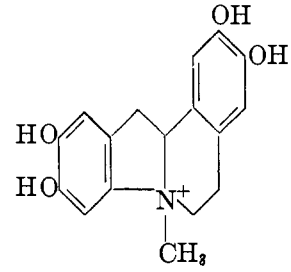
Besides the several methods detailed above for the synthesis of the quinolizine ring system, a few others of less general applicability are found in the literature. Intramolecular cyclodehydrogenation is one such. In the course of an attempt to

oxidize laudanosoline (LXX) with chloranil, Robinson and Sugasawa (103) iso-



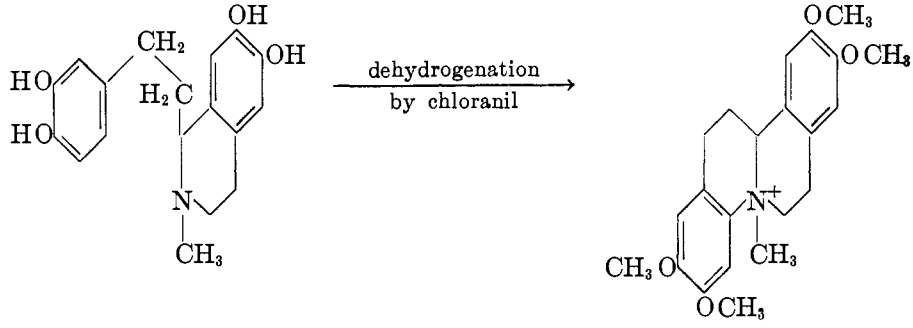
LXX

Laudanosoline



LXXI

lated a tetrahydroxydibenzotetrahydroquinolizinium salt (LXXI), the constitution of which was established by Hofmann and Emde degradations. Subsequently, *dl*-homolaudanosoline (LXXII) was oxidized in the same manner (141, 142) to yield the corresponding quinolizinium salt (LXXIII).

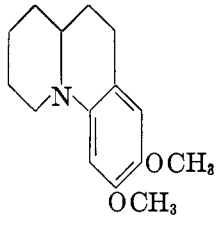


LXXII

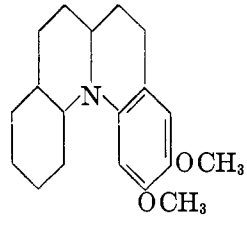
dl-Homolaudanosoline

LXXIII

4′,5′-Dimethoxy-1,2,6,7,8,9-hexahydro-1′,2′,3′,4-benzoquinolizine (LXXIV) and 4′,5′-dimethoxy-1,2,6,7,8,9,3″,4″,5″,6″-decahydro-1′,2′,3,4,6,7,1″,-2″-dibenzoquinolizine (LXXV) have also been synthesized by similar dehydrogenation with chloranil (134, 135).



LXXIV

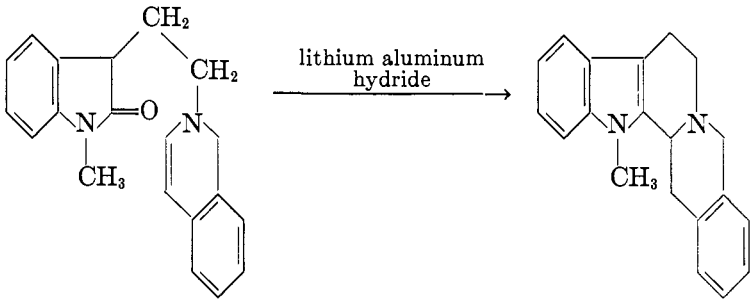


LXXV

The literature also contains references to expansion of the indolizine ring sys-

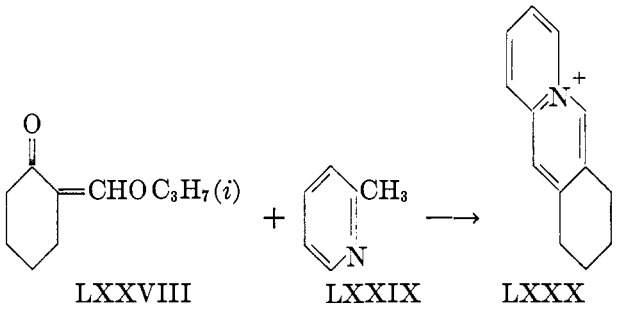
tem to that of the quinolizine (85) and contraction of the higher ring homolog to the quinolizine derivative (82).

Reduction with lithium aluminum hydride of suitably substituted oxindoles has also led to the quinolizine derivative of the yohimbine type (69).

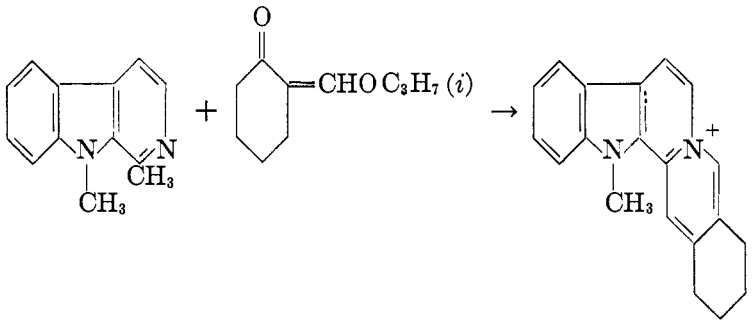


LXXVI LXXVII

Indoloquinolizines analogous to the alkaloid semperverine have been synthesized by the condensation of the lithium derivative of *N*-methylharman with 2-(isopropoxymethylene)cyclohexanone (156).



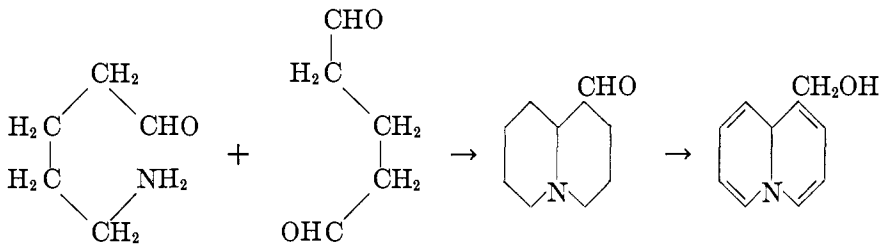
LXXVIII LXXIX LXXX



LXXXI LXXVIII LXXXII

Lupinine and sparteine have also been synthesized successfully under biological conditions (3, 104). Condensation of δ-aminovaleraldehyde (LXXXIII) with

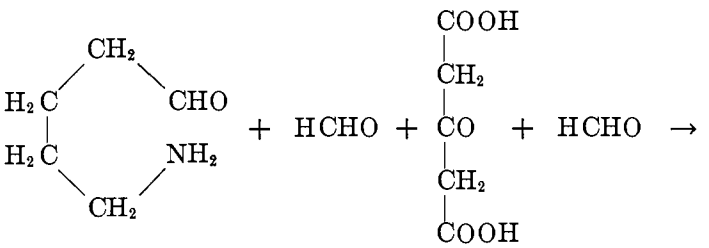
glutaraldehyde (LXXXIV) led to the lupin nucleus,



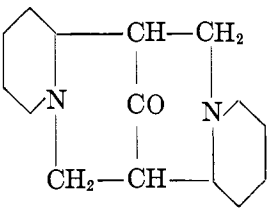
LXXXIII LXXXIV LXXXV VII

Lupinine

while reaction between δ-aminovaleraldehyde and acetonedicarboxylic acid (LXXXVI) in the presence of formaldehyde resulted in the formation of ketosparteine.



LXXXIII LXXXVI



LXXXVII

Ketosparteine

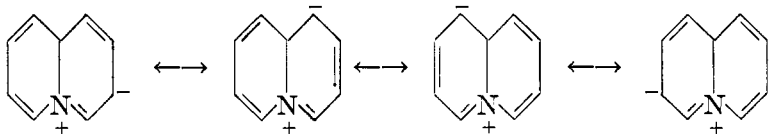
III. REACTIONS AND PROPERTIES OF QUINOLIZINES

A. Quinolizine and derivatives

A surprising feature in the chemistry of the quinolizines is the fact that the parent compound quinolizine itself is unknown. No synthesis, isolation, or charterization of this substance has been reported in the literature. Although the formation of quinolizine has been observed in the stepwise decarboxylation of the adduct from methyl acetylenedicarboxylate and pyridine, the product could only have been a mixture of indolizine and quinolizine, for hydrogenation gave only a mixture of the two octahydro bases (46). The recent attempt to prepare quinolizine (8) by the lithium aluminum hydride reduction of 4-ketoquinolizine

was also unsuccessful. This observation is unusual in view of the fact that 4-keto-quinolizine shows the characteristic infrared absorption for a nitrogen-disubstituted amide (8).

Quinolizine should be an interesting compound. Elderfield (52) has pointed out that it can exist in three tautomeric forms (II, III, IV; see page 1020). It is not known if these three different structures are characterizable as three different compounds. Of these, one contains a highly reactive methylene group. Only one of the three is a symmetrical molecule; the other two should be optically active, since they lack symmetry. In addition to the three tautomeric structures, quinolizine can be represented as a resonance hybrid of the following ionic structures:

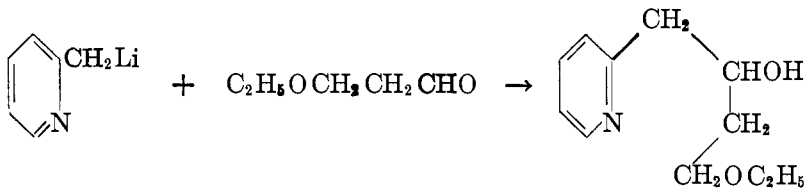


LXXXVIII LXXXIX XC XCI

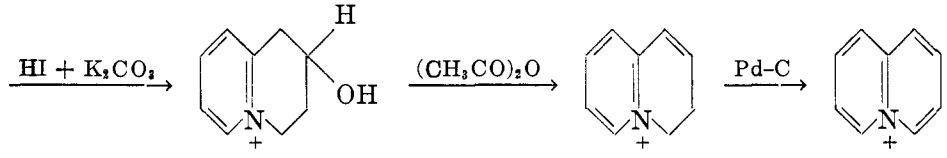
A scrutiny of these formulas shows the greater electron availability at the 1-, 3-, 7-, and 9-positions relative to the others; hence these should be the positions accessible for attack by electrophilic reagents. Little is known regarding the reactivity of quinolizine towards nitration, sulfonation, halogenation, or application of reactions like the Friedel–Crafts. (Although cytisine has been nitrated successfully and the nitro derivative reduced to the amino derivative, which was then diazotized, it is not known which position the nitro group enters.)

Since the azomethine linkage, —C=N—, is absent in ordinary quinolizine, deactivation of the ring by electron withdrawal is not possible in this instance. Quinolizine differs from the other heterocyclic compounds like pyridine, quinoline, or isoquinoline in this respect.

That quinolizine is not a completely aromatic structure has been commented upon by Elderfield (52). It could become so by the formation of the dehydroquinolizinium cation. Although such a cationic structure has been known for long in several polycyclic quinolizines, the simple dehydroquinolizinium cation was unknown until very recently. Boekelheide and Gall have now reported the synthesis of dehydroquinolizinium iodide (7) by the following method:



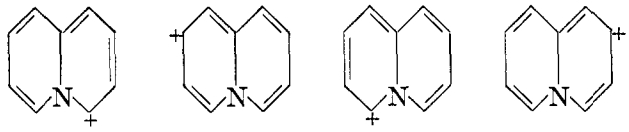
XCII XCIII XCIV



I⁻ I⁻ I⁻

XCV XCVI XCVII

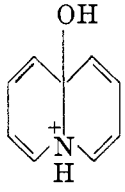
The formation of the dehydroquinolizinium cation should result in a general deactivation of the ring. With a formal positive charge on the ring nitrogen this cation can be likened to the quaternary salts of pyridine or quinoline. The corresponding resonance structures can be represented as follows:



XCVIII XCIX C CI

Thus in the dehydroquinolizinium cation, the 2-, 4-, 6-, and 8-positions will be highly reactive towards nucleophilic reagents and unreactive towards electrophilic attack.

The formation of the dehydroquinolizinium cation has also been observed by Diels and Alder (44) in the oxidation of methyl quinolizinetetracarboxylate with dilute nitric acid. In this oxidation, the hydroxy compound (CII) appears to be the intermediate stage.

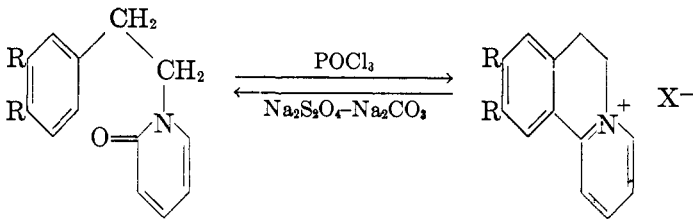


X⁻

CII

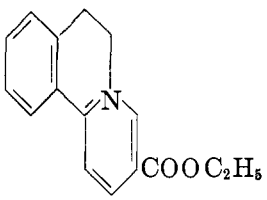
An interesting observation concerning these quinolizinium compounds has been made by Sugasawa, Akahoshi, and Suzuki (116). It relates to their behavior under the action of basic reagents. On treatment with sodium hydroxide, sodium carbonate, sodium bicarbonate, ammonium hydroxide, sodium carbonate and sodium thiosulfate, and sodium bicarbonate and sodium thiosulfate, these dehydroquinolizinium cations revert to the cyclic amides (CIII, CIV).

This facile ring-fission proceeds in good yields in aqueous solutions at room temperature. The transformation appears to be a base-induced reaction. With aqueous sodium hydroxide the change is almost instantaneous, while with



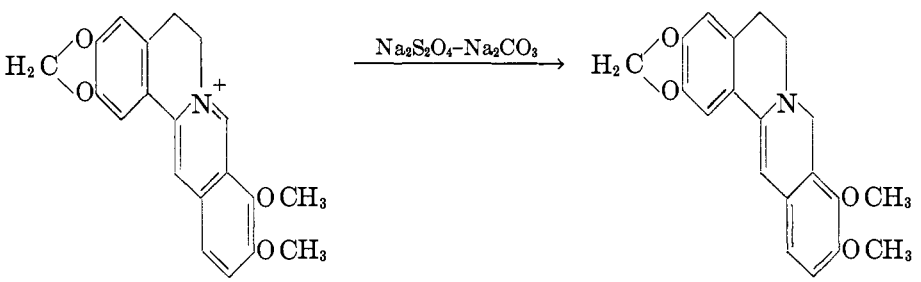
CIII CIV

weaker basic reagents such as sodium carbonate, sodium bicarbonate, and ammonia it is sluggish. But the addition of sodium dithionite greatly accelerates the rate. Methylenedioxy groups in the benzene nucleus stabilize the ring against such cleavage both in the mono- and the dibenzoquinolizinium series, while the



CV

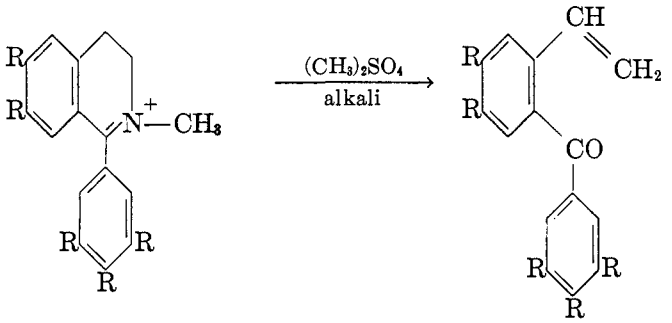
carbethoxy group in the quinolizine part (CV) greatly diminishes the stability of the ring. However, the similarly constituted berberinium salt (CVI) undergoes smooth partial hydrogenation by means of sodium dithionite–sodium carbonate, giving a dihydro derivative (CVII).



CVI CVII

Hence the ring-scission under basic conditions seems to be associated with the dehydroquinolizinium cation of the type of CIV and is comparable to the transformations described by Gensler and Samour (57) and by King, Jurd, and King (71). In the latter instances compounds of a vinylbenzophenone type are produced when 3,4-dihydroisoquinoline metho salts are treated with dimethyl sulfate and alkali or methyl iodide and alkali (CVIII, CIX).

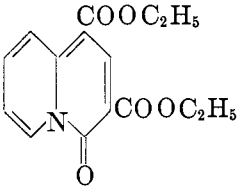
4-Ketoquinolizine is the one monosubstituted quinolizine reported so far. Monosubstituted quinolizines, other than those in which the substituent is attached to the bridgehead carbon atom, should exhibit optical activity, for such substitution renders the molecule unsymmetrical (with the bridgehead carbon



CVIII CIX

atom made asymmetric). These possibilities have not been verified. No alkyl, aryl, or acyl derivative of quinolizine has so far been reported in the literature.[1]

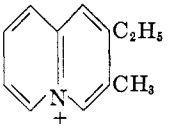
4-Ketoquinolizine is an interesting compound. It has been obtained by the hydrolysis and decarboxylation of the corresponding dicarbethoxy derivative



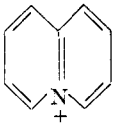
XXXVI

(XXXVI) and by the dehydrogenation of 4-ketoöctahydroquinolizine (109). This is the only instance available in the literature describing the dehydrogenation of an octahydroquinolizine derivative. It would be profitable to study whether the dehydrogenation of octahydroquinolizine furnishes only one or more products. 4-Ketoquinolizine is a highly deliquescent yellow solid melting at 72°C. It forms an unstable and deliquescent picrate and hydrochloride. Its infra-

[1] *Note added in proof:* However, recently Richards and Stevens (102a) have reported the preparation of ethylmethyldehydroquinolizinium picrate

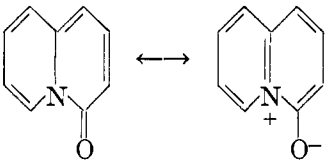


by the condensation of picolyllithium with ethoxymethylene diethyl ketone. This synthesis closely resembles that of the dehydroquinolizinium ion



reported by Boekelheide and Gall (7). The ultraviolet absorption spectra of the two compounds exhibit marked similarity.

red spectrum shows absorption at 6.0 μ characteristic of a di-*N*-substituted amide. However, it is completely unreactive towards lithium aluminum hydride. Also, it does not react with *n*-butylmagnesium bromide, although with this reagent it forms colored complexes from which it is recovered unchanged on hydrolysis. An attempt at hydrogenolysis of the corresponding thio derivative also ended in failure. That 4-ketoquinolizine is a resonance hybrid of the following structures (CX, CXI) is indicated by the close resemblance between the ultraviolet absorption spectrum of this compound and that of its hydrochloride.



CX CXI

4-Ketoquinolizine

In the course of the preparation of 4-ketoquinolizine, much information regarding the relative stability of the quinolizinecarboxylic esters has accrued from a study of the hydrolysis of 1,3-dicarbethoxy-4-ketoquinolizine and 3-carbethoxy-1-carbomethoxy-4-ketoquinolizine. The latter have been prepared by the condensation of ethyl 2-pyridylacetate and methyl 2-pyridylacetate, respectively, with ethyl ethoxymethylenemalonate (8). They are crystalline solids. On boiling with hydrochloric acid, they are hydrolyzed and decarboxylated to form 4-ketoquinolizine. Shorter reaction periods result in the formation of 1-carbomethoxy-3-carboxy-4-ketoquinolizine and 1-carbomethoxy-4-ketoquinolizine, indicating thereby that the 3-carbethoxy group is more readily hydrolyzed and decarboxylated. Similar stepwise decarboxylation has been observed in the case of the quinolizine-1,2,3,4-tetracarboxylate obtained by the diene synthesis. However, in this instance little is known regarding the relative lability of the different ester groups. Complete decarboxylation eventually leads to a mixture of bases, which on hydrogenation provides octahydroquinolizine and octahydroindolizine derivatives.

Since most of the methods of synthesis of the quinolizine derivatives lead to the saturated compounds, few other unsaturated compounds have been studied. Even in these cases little else is known beyond their preparation.

B. Octahydroquinolizine and its alkyl and aryl derivatives

In contrast to the meagre information available concerning the reactions and properties of the aromatic quinolizine derivatives, the study of the perhydro derivatives has attracted greater attention, owing to the variety of the methods available for their preparation.

Octahydroquinolizine itself has been made in a number of ways. There has been a wide discrepancy in the description of this compound, particularly owing to the unexpected ring-contraction undergone by 1-ketoöctahydroquinolizine during Clemmensen reduction (28). Subsequently, the same compound has been

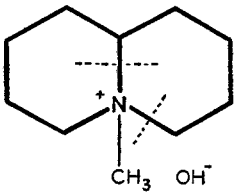
TABLE 1

Characteristics of octahydroquinolizine

Boiling Point	Melting Point of Picrate	Reference	Boiling Point	Melting Point of Picrate	Reference
°C.	°C.		°C.	°C.	
166–167	203	(43)	72/16 mm.	—	(35)
38–40/1 mm.	194	(28)	77–78/18 mm.	—	(44)
43/0.5 mm.	213	(33)	78/18 mm.	198–199	(11)
75/14 mm.			165–169/748 mm.	198–199	(78)
92–93/14.5 mm.	193	(150)	84–85/34 mm.	194	(145)

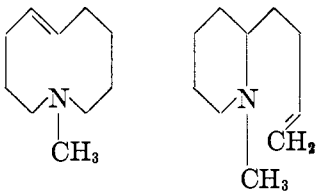
prepared by the reduction of 2-ketoöctahydroquinolizine by the Clemmensen procedure, by the Wolff–Kishner reduction of 1-ketoöctahydroquinolizine, and by the method of reductive cyclization. The characteristics of this base are recorded in table 1.

No attempt to dehydrogenate octahydroquinolizine has been reported nor has any other reaction of this base been studied. With a view to establishing its identity as distinct from the product of Clemmensen reduction of 1-ketoöctahydroquinolizine, the behavior of octahydroquinolizine under Hofmann degradation conditions has been investigated. Since the ring can cleave at two points (CXII)



CXII

it should be possible to isolate two products, CXIII and CXIV.



CXIII CXIV

Actually, Clemo, Ramage, and Raper isolated two bases as their picrolonates. The formation of 2-*n*-butyl-1-methylpiperidine was established by synthesis, while the other compound was assumed to be 1-methylcycloazadecane (35).

Degradation by the use of cyanogen bromide has also been tried with octahydroquinolizine (43) and has been found to yield 2-*n*-butylpiperidine.

A few alkyl and aryl derivatives of octahydroquinolizine have been reported. All these bases are, like the parent base, liquids yielding crystalline picrates.

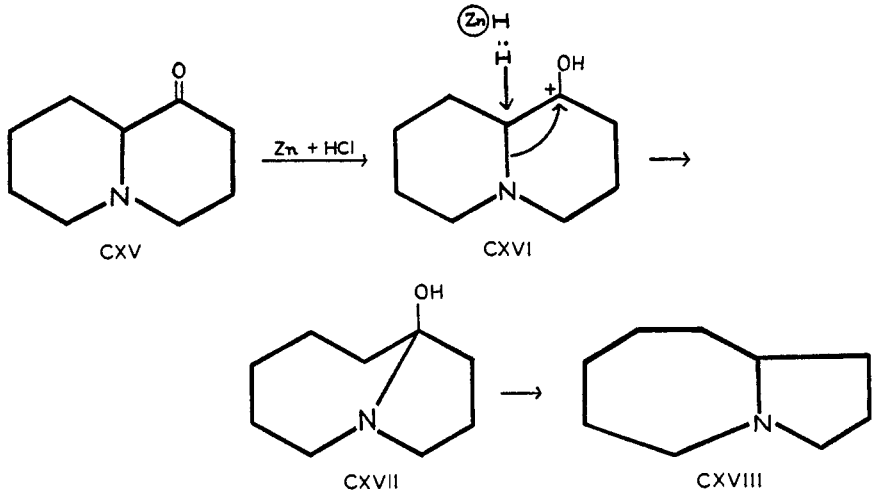
Their boiling points and the melting points of their picrates are recorded in table 2.

Apart from the description of the preparation of these compounds, no other property has been studied. In all cases no attempts have been made even to isolate the pure diastereoisomers. This is attributable to the fact that these compounds were made only incidental to other investigations.

C. Ketoöctahydroquinolizines

The unusual ring-contraction undergone by 1-ketoöctahydroquinolizine under Clemmensen reduction conditions stimulated interest in the study of other ketooctahydroquinolizines.

1-Ketoöctahydroquinolizine has been obtained by the Dieckmann condensation of 2-carbethoxypiperidine *N*-butyrate. This has formed the subject of much investigation by Leonard and coworkers. On reduction by the Clemmensen procedure, it yields 1-azabicyclo[0.3.5]decane. It has been established that this phenomenon is common to all α-amino ketones, because 3-ketoöctahydroquinolizine and 1-keto-6,7-benzo-1,2,3,4,8,9-hexahydroquinolizine undergo such rearrangements under analogous conditions (26, 29). The mechanism of this change has been studied in detail by Leonard and Wildmann (81). These authors have postulated that the initial step involves the formation of a carbonium ion on the carbonyl carbon, followed by the migration of the R_2N— group to this geometrically fixed, adjacent carbonium ion. This is succeeded by a simultaneous or subsequent attack of hydrogen at the newly formed carbonium ion of the α-carbon atom. Reduction from this stage to the last step does not appear to be unusual (2).



Although 3-ketoöctahydroquinolizine was originally supposed to undergo normal reduction (29), it was also later shown to conform to the behavior of the other cyclic α-amino ketones (80).

All the ketoöctahydroquinolizines are liquids, forming crystalline derivatives. Of these the 4-keto base is more widely known, since several intramolecular

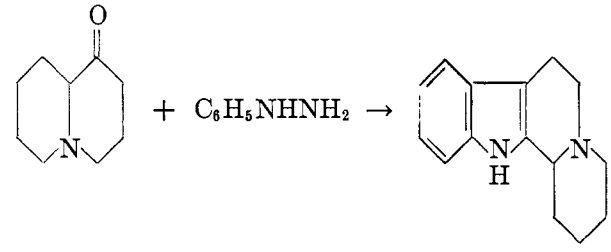
TABLE 2

Derivatives of octahydroquinolizine

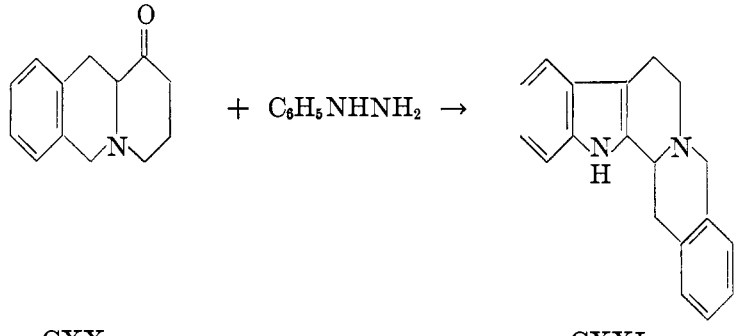
Octahydroquinolizine Derivative	Boiling Point	Melting Point of Picrate	Reference
	°C.	°C.	
1-Methyl	76–77/11.5 mm.	163	(152)
2-Methyl	47–48/1 mm.	150	(27)
2-Methyl	58/1 mm.	158	(25)
3-Methyl	80–87/10 mm.	155–157	
	104–108/20 mm.		(11)
4-Methyl	79/13 mm.	191–195	(11)
4-Phenyl	87–89/0.5 mm.	213–214	(4)

cyclodehydration methods lead to the formation of this compound. Clemo, Ramage, and Raper originally regarded this as a non-basic oil. Subsequently it has been reported to yield a crystalline hydrochloride (11, 35, 85). Although it is analogous to a di-*N*-substituted amide, it is completely unaffected by lithium aluminum hydride. In this respect it resembles the corresponding unsaturated derivative 4-ketoquinolizine (11). However, it has been reduced to the deoxy base by catalytic hydrogenation using copper chromite. The 1-, 2-, and 3-ketoöctahydroquinolizines are all reduced smoothly to octahydroquinolizine by the Wolff–Kishner procedure.

1-Ketoöctahydroquinolizines react with phenylhydrazine to form the corresponding indoloquinolizines (37, 102).



CXV CXIX



CXX CXXI

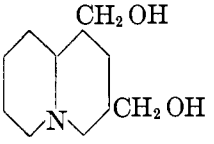
This fact has been utilized in the synthesis of the yohimbine type of compounds.

The action of Grignard reagents on these keto compounds has hardly been investigated in any detail. Although methylmagnesium iodide reacted with 2-ketoöctahydroquinolizine, the yield of 2-hydroxy-2-methyloctahydroquinolizine was extremely small (27). More detailed investigations have been carried out on the action of various Grignard reagents on the alkaloid lupanine (149). Winterfeld and Hoffmann originally concluded that the alcohols obtained by the action of butylmagnesium bromide, phenylmagnesium bromide, and ethyl- and methylmagnesium iodides were too unstable to be isolated (154). In each case they were able to isolate only the corresponding alkyldehydrosparteine. Subsequently, Petkov, by extracting the reaction mixture with anhydrous ether at −80°C., was able to obtain ethyllupinol, butyllupinol, and heptyllupinol by the action of ethyl-, butyl-, and heptylmagnesium bromide, respectively, on lupanine. Heptyllupinol was obtained only in small yield and was not purified (89).

Among the other ketoöctahydroquinolizines known are 1-ketododecahydro-6,7-benzoquinolizine, 1-keto-6,7-benzo-1,2,3,4,8,9-hexahydroquinolizine, 1-keto-8-methyloctahydroquinolizine, 1-keto-2-methyloctahydroquinolizine, and 2-keto-1-methyloctahydroquinolizine (25, 26, 27, 31).

D. Octahydroquinolizinecarboxylic acid esters

The preparation of the carbalkoxy derivatives of octahydroquinolizines by the reductive cyclization of vinylpyridine adducts and by the reduction of the corresponding quinolizine esters has already been referred to in detail (Section II,C). These esters, like the corresponding unsaturated compounds, are readily hydrolyzed and decarboxylated on heating with acids (8, 11). They readily form hydrazides on treatment with hydrazine. Reduction by lithium aluminum hydride yields the respective carbinols (CXXII) (56).



CXXII

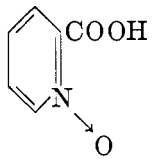
The recent synthesis of tetrahydrodeoxycytisine (56) utilizes the action of lithium aluminum hydride on 1,3-dicarbethoxy-4-ketoöctahydroquinolizine to produce the dicarbinol. The latter by treatment with hydrobromic acid is converted to the corresponding dibromide, which on heating with ammonia gives a mixture of the two racemates of tetrahydrodeoxycytisine. In this instance the 4-keto group of the 1,3-dicarbethoxy-4-ketoquinolizine has been found to be reducible by the action of lithium aluminum hydride—an observation in striking contrast to the behavior of 4-ketoquinolizine on treatment with the same reagent (8).

E. Oxidation of quinolizine derivatives

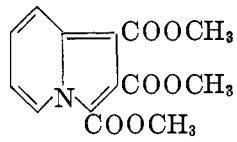
The information available as to oxidative studies on the quinolizines is very meagre. Work in some detail has been published concerning the action of oxi-

dizing agents like hydrogen peroxide, chromic acid, and dilute nitric acid on the different quinolizine derivatives obtained by the diene synthesis. In all cases analogous products have been obtained (44).

Oxidations with hydrogen peroxide invariably lead to the pyridinecarboxylic acid *N*-oxides (see formula CXXIII), while treatment with dilute nitric acid or chromic acid results in the formation of the corresponding lower ring homolog (CXXIV).



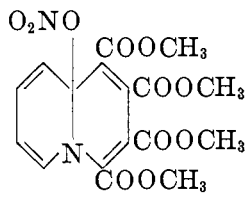
CXXIII



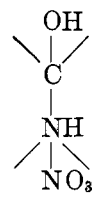
CXXIV

Methyl indolizinetricarboxylate

With concentrated nitric acid, the ester nitrate CXXV is obtained. Warm water transforms CXXV into the hydroxy nitrate (CXXVI), which upon treatment with dilute nitric acid yields methyl indolizinetricarboxylate (CXXIV).



CXXV



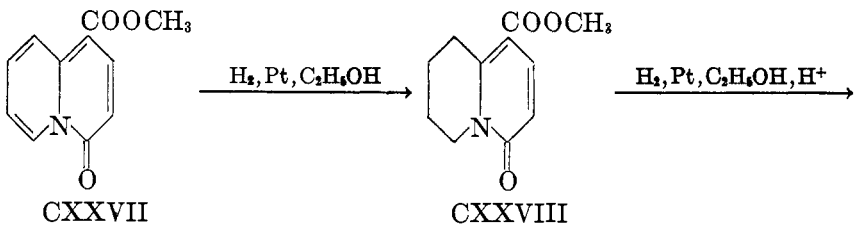
CXXVI

In the same manner, the other diene adducts with α-picoline, stilbazole, quinoline, and isoquinoline yield the respective indolizine derivatives with dilute nitric acid; with hydrogen peroxide they yield 2-picoline-6-carboxylic acid *N*-oxide, quinoline-2-carboxylic acid *N*-oxide, and isoquinaldic acid *N*-oxide, respectively (45, 47, 48, 49).

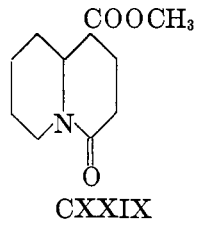
F. Reduction of quinolizine derivatives

The reduction of quinolizine-1,2,3,4-tetracarboxylate with platinum oxide in acetic acid has been reported to give a tetrahydro derivative (46), while the completely decarboxylated base on hydrogenation under similar conditions yields the octahydro base. This preferential reduction of one of the rings alone is not surprising in view of the later observation on the reduction of 1-carbomethoxy-4-ketoquinolizine (8). The reduction of this compound stopped at the tetrahydro stage in acid solution and proceeded further only in a neutral medium.

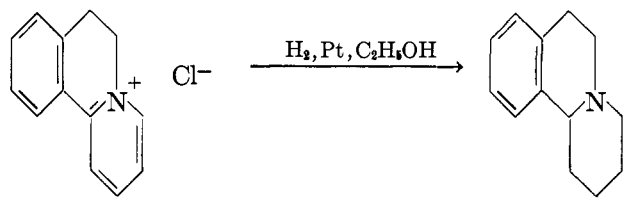
The quinolizine ring is easily reduced by catalytic hydrogenation. The simple dehydroquinolizinium iodide is converted smoothly into the octahydro base by hydrogenation with platinum oxide in alcohol at room temperature and at atmospheric pressure (116). Several other benzoquinolizinium compounds have also been similarly reduced with equal facility (58).



CXXVII CXXVIII

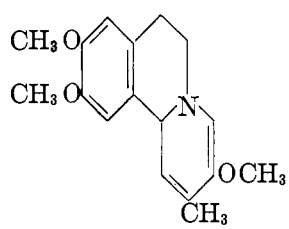


CXXIX



CXXX CXXXI

However, partial hydrogenation of the quinolizine nucleus has presented considerable difficulties. With the ultimate aim of synthesizing the alkaloid rotundin from *Stephania rotunda* (72), Sugasawa, Akahoshi, and Suzuki (116) at-

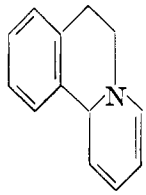


CXXXII
Rotundin

tempted the selective reduction of the 5,10-double bond in CXXX. The use of platinum as catalyst or reduction by zinc amalgam always yielded only the hexahydro derivative (CXXXI). Titanium trichloride in hydrochloric acid failed to effect any reduction.

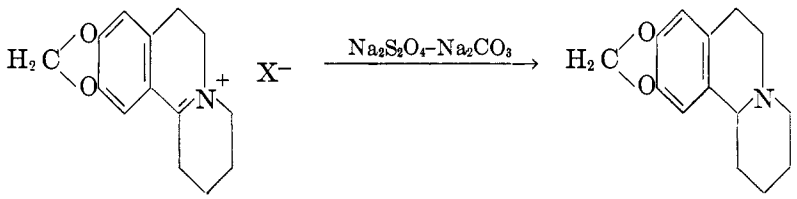
When sodium dithionite in aqueous sodium carbonate solution was tried, it was observed that ring-cleavage took place, resulting in the formation of the original *N*-phenethyl-2-pyridone. This has already been referred to in detail (Section III,A).

Ultimately it was found that the use of lithium aluminum hydride was successful in selectively reducing the 5,10-double bond alone. The resulting compound (CXXXIII) was very sensitive to oxidation and reduced Fehling's and



CXXXIII

silver nitrate solutions in the cold (116). Subsequent investigations showed that the similar compound CVI underwent smooth selective hydrogenation, giving a dihydro derivative (CVII) (see page 1042). Likewise, 4′,5′-methylenedioxy-3,4,6,7,8,9 - hexahydro - 5,10 - dehydro(2′,1′,1,2-benzo)quinolizinium salt (CXXXIV) underwent partial saturation with the same reagents to yield CXXXV.

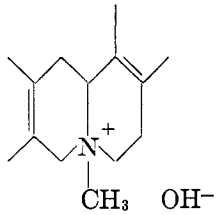


CXXXIV CXXXV

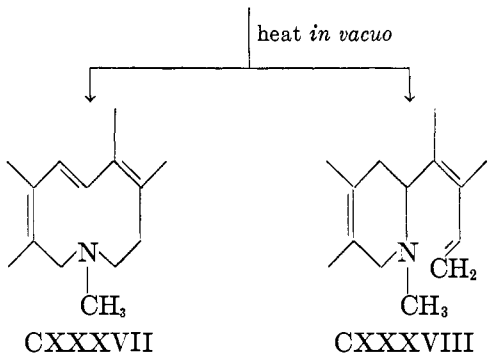
G. Ring-cleavage of quinolizine derivatives

The facile ring-scission suffered by the dehydroquinolizinium cations under the action of alkaline reagents has already been discussed (Section III,A). That the octahydroquinolizine ring system can cleave at two points under Hofmann degradation conditions has also been referred to in the discussion on octahydroquinolizine. However, a third possibility also arises in the case of unsymmetrically substituted octahydroquinolizine derivatives, since the products due to ring-scission at the 4,5-bond and the 5,6-bond would be different. This possibility has been encountered in the case of the alkaloid lupinine and of methyl lupinate methiodide. The latter yielded 1-methylazacyclodecane and another base which was different from 2-*n*-butyl-1-methylpiperidine and the monocyclic derivative. Exhaustive methylation of lupinine was complicated, since the intermediate products were mixtures of structural isomers formed by the breaking of more than one of the three —N— linkages at one operation (147).

The polycyclic quinolizine alkaloid berberine (CXXXVI) also opens in two ways when the methohydroxide of its tetrahydro derivative is dried in a vacuum.

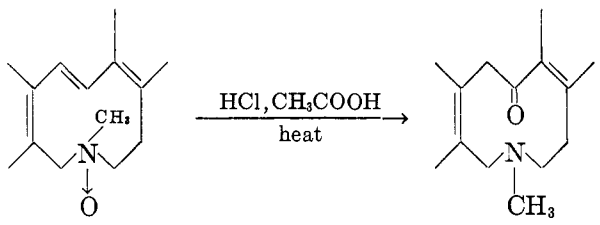


CXXXVI
Berberine



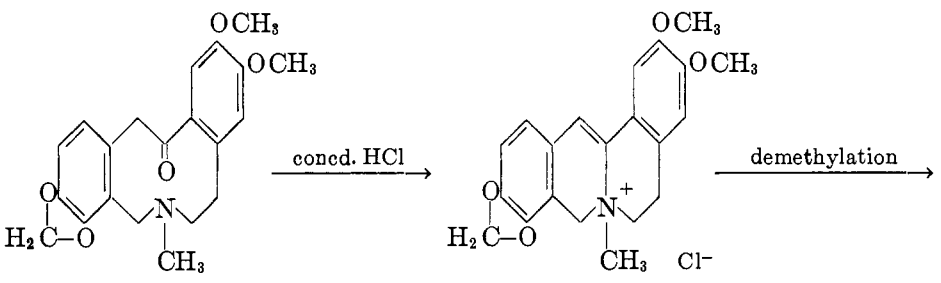
CXXXVII CXXXVIII

The anhydro base containing the ten-membered ring is characteristic of the alkaloids of the cryptopine group. They can be converted to the latter type by forming the amine oxide (CXXXIX) and heating it with hydrochloric acid in acetic acid.



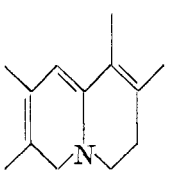
CXXXIX CXL

The cryptopine type of alkaloid can also be converted to one of the berberine type. When cryptopine (CXLI) is treated with concentrated hydrochloric acid it forms isocryptopine chloride (CXLII), which on de-*N*-methylation yields dihydroepiberberine (CXLIII).



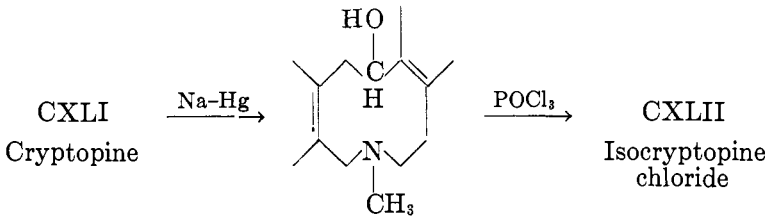
CXLI CXLII

Cryptopine Isocryptopine chloride



CXLIII

The same change can also be carried out by reducing cryptopine (CXLI) with sodium amalgam to the carbinol (CXLIV) and treating the latter with acetyl or phosphoryl chloride to obtain CXLII.

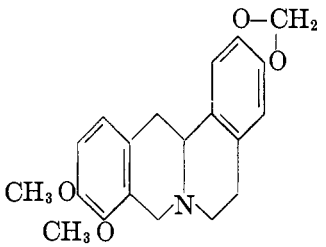


CXLIV

This facile interconvertibility between the two ring systems is found to be a common feature of the various alkaloids of the protoberberine series.

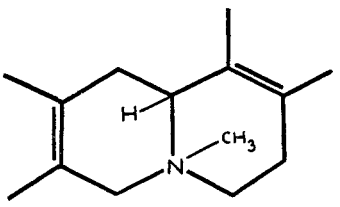
IV. STEREOCHEMISTRY OF QUINOLIZINES

The stereochemistry of the octahydroquinolizine derivatives presents an interesting study, since it is very closely analogous to the *cis*- and *trans*-decalin system. Octahydroquinolizine itself will not be resolvable since the molecule is symmetrical. It has been reported to form only one methiodide, whereas alkaloids like sparteine and matrine form two monomethiodides. Others containing a reduced quinolizine ring fused to two benzene rings also form such stereoisomeric quaternary salts. Thus canadine (CXLV)

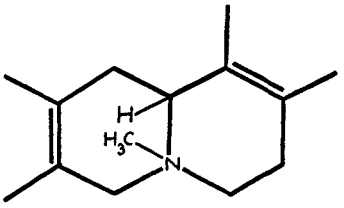


CXLV
Canadine

forms two methiodides (CXLVI and CXLVII). These salts are regarded as



CXLVI

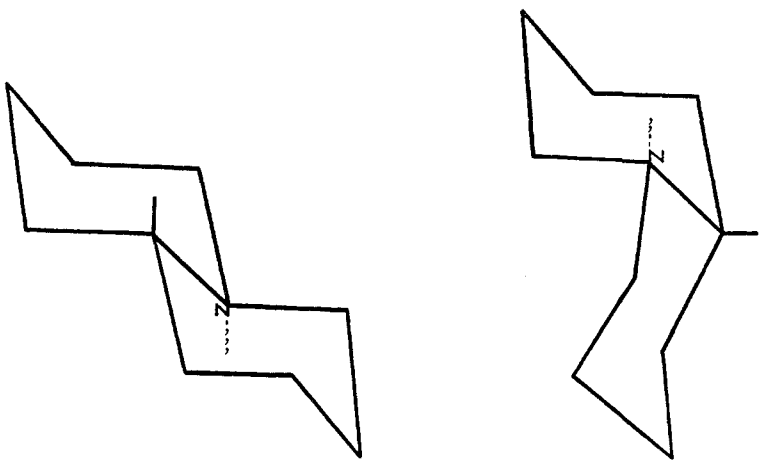


CXLVII

diastereoisomeric forms. Tetrahydroberberine similarly forms pairs of metho salts, but other salts of the tertiary bases (hydrochloride, etc.) do not occur in such stereoisomeric forms, probably because their interconversion is too facile.

Monosubstitution products of octahydroquinolizine must all be resolvable, since they destroy the symmetry of the molecule. However, those in which the angular hydrogen is substituted can exist in only one form, which will not be resolvable. These compounds must also exist in diastereoisomeric pairs. This can be illustrated by reference to the five different monosubstitution products possible: namely, those in which the hydrogen atoms from positions 1, 2, 3, 4, and 10 are replaced. Of these the 1,2,3,4 substitution products should exist in diastereoisomeric pairs, both forms being resolvable.

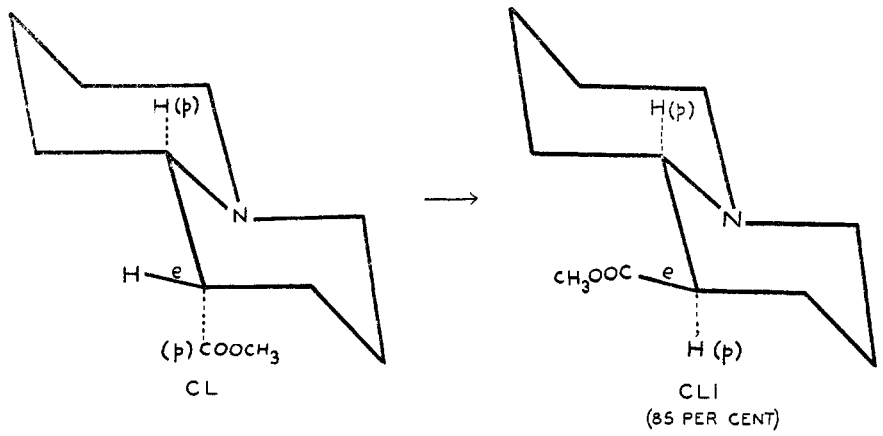
The recent concepts of the polar and equatorial bonds which have enormously clarified the relative stability and ease of formation of several cyclohexane derivatives have also been extended to the derivatives of octahydroquinolizine (39, 75). The octahydroquinolizine ring system, as mentioned earlier, can be sterically compared to the decalins. Since the stable form of the decalins is a chair-chair conformation, the octahydroquinolizine ring can also be expected to assume the same conformation. Of the two chair-chair conformations (*cis* and *trans*), one is analogous to *trans*-decalin less one tertiary hydrogen atom (CXLVIII). The other corresponds to *cis*-decalin less one hydrogen atom. However, the hydrogen removed from *trans*-decalin to form the analogous quinolizine derivative is polar to both rings, whereas that removed from *cis*-decalin to form CXLIX is polar to one ring and equatorial to the other. Therefore, the *trans*



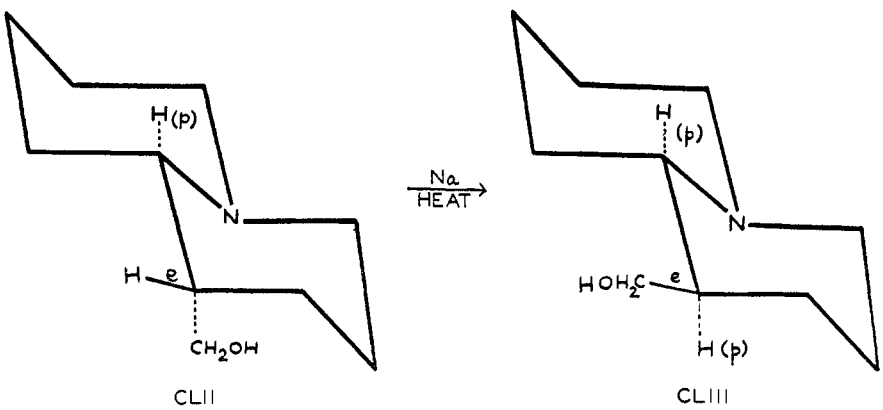
CXLVIII CXLIX

conformation of octahydroquinolizine may be expected to be more stable than the *cis*, inasmuch as *trans*-decalin is more stable than *cis*-decalin.

Such considerations have been applied to deduce the plausible conformation of the alkaloid lupinine (39, 75). The latter has been found to be the less stable of the two 1-hydroxymethyloctahydroquinolizines. Equilibration of methyl lupininate with sodium methoxide gives a mixture containing 85 per cent of the epi ester, while esterification of lupininic acid by treatment with phosphorus pentachloride followed by methanol yields a mixture containing the same proportion of the epi ester (107) (CL, CLI).



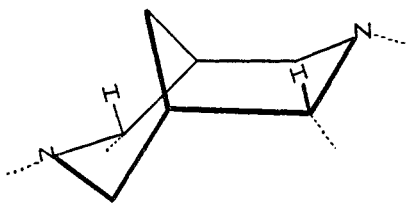
Similarly, equilibration of *l*-lupinine by heating with sodium yields the more stable epimer. This, it is suggested, would correspond to a shift from the 1,10 polar equatorial conformation (CLII) to the preferred 1,10 diequatorial conformation (CLIII).



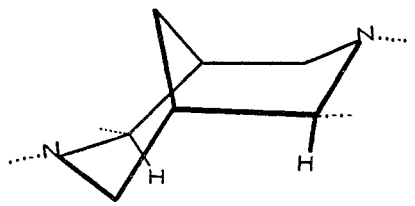
This assignment is also in accord with the isolation of only one of the diastereoisomeric racemates of 1-carbethoxy-4-ketoöctahydroquinolizine in the recent synthesis of lupinine (8). Since this involves the catalytic hydrogenation over platinum in neutral medium to establish the asymmetric centers at C_1 and C_{10}, it is reasonable to assume that the product contains the hydrogen atoms in these positions in a *cis* relationship to each other. Lupinine therefore has the polar hydroxymethyl group in the *trans* chair-chair conformation to the octahydroquinolizine nucleus. Independent support for this configuration has also been derived from the infrared absorption spectrum of lupinine (84). In dilute solution in chloroform, lupinine shows a broad band at 3400 cm.$^{-1}$, indicating that the hydroxyl group is hydrogen-bonded. In dilute solution this is likely to be an intramolecular OH$\cdots$N bond, which is possible only when the hydroxymethyl group is polar.

Similar deductions have also been made in the case of the C_{15} lupin alkaloids (sparteine, lupanine, anagyrine, and thermopsine) on the basis of stereospecific hydrogenation reactions and certain conversions of the oxygenated derivatives of sparteine (83).

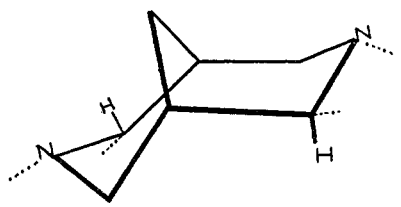
The stereochemistry of sparteine in particular has been discussed in great detail by Leonard and Beyler (77). In the sparteine ring system there are four asymmetric carbon atoms, C_6, C_7, C_9, C_{11}. But the configurations at C_7 and C_9 are interdependent because the C_8 methylene bridge can span the distance between C_7 and C_9 only in a *cis* manner. The three racemic pairs of sparteine can therefore be classified into three types. With respect to the methylene bridge at C_8, one of these can have both the hydrogens at C_6 and C_{11} *cis*, another the hydrogens on C_6 and C_{11} *trans*, and the third with the hydrogen on C_6 *cis* and the hydrogen on C_{11} *trans* (structures CLIV, CLV, and CLVI).



CLIV



CLV



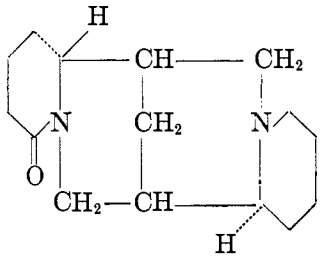
CLVI

Leonard and Beyler have proposed the structure CLVI for sparteine, because this alone exhibits configurational differences between rings B and C. Stereochemical differences have actually been observed in three instances: (*1*) The catalytic reduction of dioxosparteine, which has two structurally equivalent carbonyl groups at C_{10} and C_{17}, produced *dl*-oxosparteine. Only one of the carbonyl groups could be reduced under such conditions (53). (*2*) Aphyllidine, which has a 5,6-double bond and a carbonyl group at C_{10}, could be reduced to *d*-sparteine by low-pressure hydrogenation, whereas oxosparteine with no double bond and a carbonyl group at C_{17} could not be reduced (55). (*3*) Aphylline, which has a sparteine structure with a carbonyl group at C_{10}, was readily hydrolyzed to the amino acid, while oxosparteine with a carbonyl group at C_{17} required drastic treatment to effect ring-cleavage (86, 110). Thus the stereochemistry of sparteine can be represented by the partial diagram shown in structure CLVI.

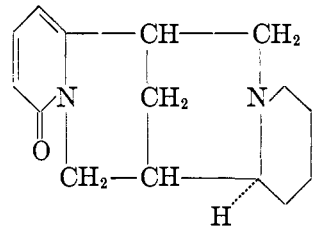
The steric interrelationships between sparteine and the other alkaloids of the lupin family have been established from stereospecific hydrogenation reactions and other conversions of the oxygenated derivatives of sparteine.

By x-ray determination, α-isosparteine is found to have the *cis-cis* structure (CLIV). Hence β-isosparteine must have the *trans-trans* structure shown in formula CLV.

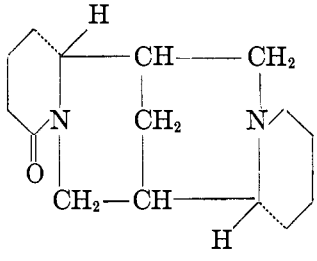
The structures of the other bases, lupanine, anagyrine, isolupanine, and thermopsine, as derived from that of sparteine, can be indicated as follows:



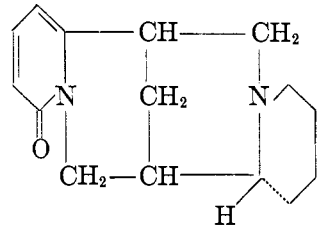
CLVII
Lupanine



CLVIII
Anagyrine



CLIX
Isolupanine



CLX
Thermopsine

Thus, although the stereochemistry of the derivatives of octahydroquinolizine has been well investigated, quinolizine or its derivatives have not been studied from the viewpoint of stereochemical possibilities. The possibility of optical activity in quinolizine itself, since it has two unsymmetrical prototropic structures, has been mentioned before. No attempt has so far been made to resolve any quinolizine derivative.

V. ABSORPTION SPECTRA OF QUINOLIZINES

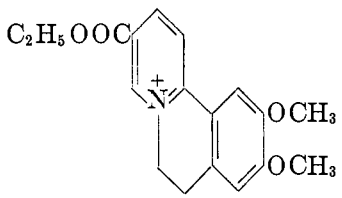
As is the case with several other properties of the quinolizine derivatives, data on the absorption spectra of these compounds are scanty. No systematic study of either the ultraviolet absorption characteristics or the infrared absorption measurements has been made.

The close similarity in the ultraviolet absorption spectra of 4-ketoquinolizine and its hydrochloride has already been mentioned (Section III,A). They show identical maxima at 230 mμ ($\log \epsilon = 4.1$) and 390 mμ ($\log \epsilon = 4.1$), suggesting that 4-ketoquinolizine has considerable resonance contribution from the ionic structure (CXI on page 1044).

The ultraviolet absorption due to the simple dehydroquinolizinium ion has

recently been reported by Boekelheide and Gall (7). The aqueous solution of this compound shows absorption maxima at the following wave lengths: 226 (log ϵ = 4.25), 272 (log ϵ = 3.42), 283 (log ϵ = 3.47), 310 (log ϵ = 4.03), 316.5 (log ϵ = 3.98), and 323.5 mμ (log ϵ = 4.23). It has also been observed that *N*-methylisoquinolinium iodide shows absorption in the same general regions but "lacks the fine structure of the more symmetrical dehydroquinolizinium ion."

The benzoquinolizinium cation of the type shown in formula CLXI shows



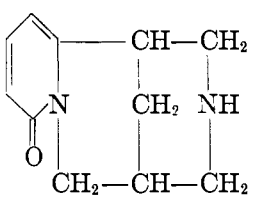
CLXI

three absorption maxima at 270 mμ (log ϵ = 3.76), 305 mμ (log ϵ = 3.98), and 390 mμ (log ϵ = 4.23) (146).

Several other benzo-, dibenzo-, and naphthoquinolizinium cations show characteristic maxima between the wave lengths 280 and 320 mμ, but no generalizations can be made for lack of systematic investigations in this direction (144).

Infrared absorption studies have also been made in the case of a few quinolizine derivatives, especially in the alkaloids of the lupin series (84). The spectrum of lupinine shows the presence of an associated hydroxyl group (hydroxyl absorption band at 3400 cm.$^{-1}$), indicating thereby that there is an intramolecular OH···N bond. This observation has served to confirm the conclusion that the hydroxymethyl group in lupinine occupies a polar position.

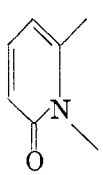
In the imino absorption region, cytisine (CLXII), which has a secondary nitrogen atom, shows characteristic absorption at 3280 cm.$^{-1}$



CLXII

Cytisine

In the carbonyl region, the alkaloids cytisine, anagyrine, thermopsine, and *N*-methylcytisine, which contain the following partial structure



absorb at 1653–1652 cm.$^{-1}$ They also show another absorption between 1570 cm.$^{-1}$ and 1566 cm.$^{-1}$, which Marion, Jones, and Ramsay assign to the α-pyridone ring.

VI. BIOLOGICAL ACTIVITY OF QUINOLIZINES

The pharmacological properties of alkaloids bearing the quinolizine nucleus have been well summarized in earlier accounts (67).

The knowledge of the chemical structure of emetine and its pharmacological properties stimulated interest in the synthesis of other related quinolizine compounds. However, none of these has been found to have amoebicidal activities comparable to that of the natural base (17). Likewise, the occurrence of the quinolizine nucleus in compounds possessing curariform activity (40) led to the preparation of a number of quinolizine derivatives incorporating the structural features of the natural bases like erythroidine. The results indicated that simple quinolizine derivatives, either as tertiary or as quaternary amine salts, do not possess any curariform activity (4, 11).

VII. USES OF QUINOLIZINES

The study of the quinolizines has been exclusively of academic interest and hardly any use has been made of them either in medicine or in other fields of commercial interest. Nevertheless, the three alkaloids emetine, sparteine, and thermopsine form an exceptional group, since they find some use in medicinal applications.

Emetine, the principal alkaloid from ipecac, has been variously used as an expectorant, as an amoebicide, and in the treatment of the liver fluke *Fasciola hepatica*. It has also been recommended occasionally for schistosomiasis when antimonial chemotherapeutic agents are too toxic (17). Nevertheless, the great toxicity of this alkaloid has considerably limited its use even in these cases.

Thermopsine, from *Thermopsis lancelolata*, is considered to be even more effective than emetine as an expectorant in tuberculosis.

Sparteine has been made use of in medicine as a diuretic and a cardiovascular active drug (17).

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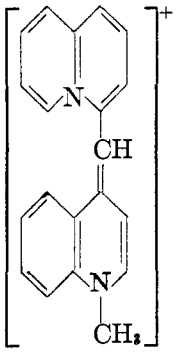
IX. ADDENDUM

It was indicated under Section II,C that the incorporation of substituents in the pyridylacetate molecule would offer variations in one half of the quinolizine nucleus. Boekelheide and Gall (7a) have now reported the preparation of 1,3-dicarbethoxy-6-methyl-4-ketoquinolizine by the interaction of ethyl 6-methyl-2-pyridylacetate and diethyl ethoxymethylenemalonate. Contrary to the behavior of the corresponding lower homolog, the carbethoxy groups in the quinolizine compound obtained in this case could not be hydrolyzed at all under acid conditions. However, under the conditions of basic hydrolysis, the ester groups could be removed in good yield.

Another interesting observation relates to the formation of the 4-thio derivative. Although the simple 4-ketoquinolizine readily forms the corresponding thio compound, the 6-methyl homolog failed to give such a derivative even under a variety of conditions, using many different preparations of phosphorus sulfides.

Incidental to these findings, it has been observed that 4-thioquinolizine reacts with methyl iodide to form 4-methylmercaptodehydroquinolizinium iodide. The latter on reaction with lepidine methiodide gives in good yield a red-purple dye of the following structure:



The synthesis of another benzoquinolizine derivative by the alkylation of di-

ethyl malonate has also been reported recently. In the course of the preparation of 1-vinylisoquinoline, Boekelheide and Sieg (11a) have investigated the alkylation of diethyl malonate with 1-(β-dimethylaminoethyl)isoquinoline methiodide. The product has tentatively been assigned the following structure: