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The Chemistry of the Benzo(a)quinolizine Ring System

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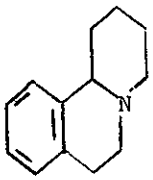
The synthesis and reactions of the benzo(a)quinolizine ring system have been reviewed. This ring system appears in a number of natural products and compounds of medicinal interest.

INTRODUCTION:

The benzo(a)quinolizine ring system (1) appears in a wide variety of alkaloids such as emetine (2), ankorine (3) and tubulosine (4).

The appearance of this system in a number of natural products aroused the first interest in its synthesis. Subsequently, it has been found that certain benzo(a)quinolizines possess medicinal activities. For example, Brossi[1] has found reserpine-like activity in several benzo(a)quinolizines. This reserpine-like activity is typified by the commercial drugs quantril (5) and tetrabenazine (5a). A number of groups have reported that emetine has antineoplastic activity and this activity is also demonstrated by various benzo(a)quinolizines.[2]

This review will cover the preparation and reactions of the benzo(a)quinolizines. Much of this work has been centered on their use as intermediates in



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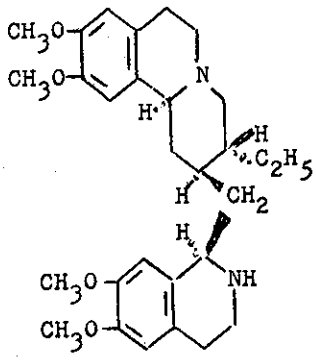

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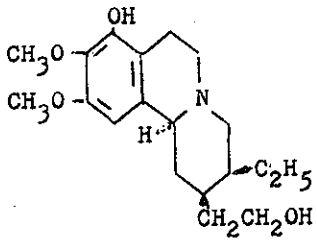

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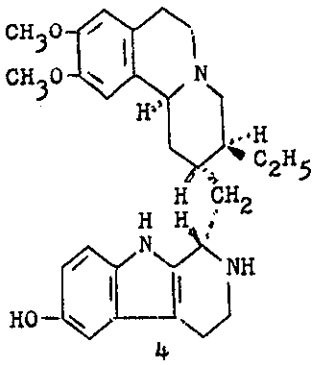

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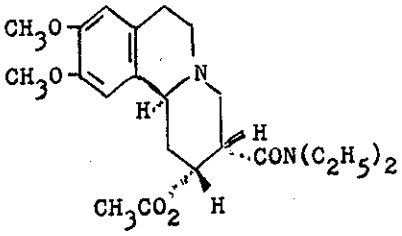

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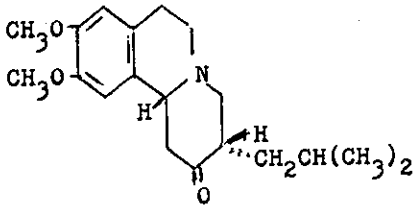

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the course of the synthesis of these natural products.

SYNTHESIS:

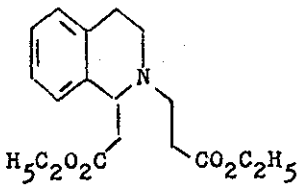
The useful syntheses of the benzo(a)quinolizine ring system fall into three major categories. These categories are (1) Dieckmann condensation of diesters of the type 6; (2) cyclization of piperidine derivatives of the type 7; and (3) reaction of 3,4-dihydroisoquinolines with α,β-unsaturated ketones 8. The major points of some of the more commonly used routes in each category will be discussed.

Cyclization of Diesters 6:

This approach to the synthesis of the tricyclic ring system was successfully employed by Openshaw and Battersby[3,4] to prepare ketone 9. The reaction of 3,4-dimethoxyphenethylamine with an excess of diethyl malonate followed by cyclization with phosphoric oxide and reduction gave 10, which was condensed with ethyl α-formylbutyrate and hydrogenated to give the diester 11. The diester (11) was then cyclized to 9 using sodium ethoxide in toluene.

Additional applications of this basic procedure have appeared in works by Brossi,[1] Mizukami,[5] and Buzas.[6] A modification of this procedure was introduced by Schneider.[7] Ring closure of 12 with metallic sodium in benzene led to the benzo(a)quinolizine 13. Reduction of the ketone carbonyl in 13 afforded the ester 14.

A second modification was introduced by Kawanishi.[8] This method involved the preparation of the diester prior to synthesis of the isoquinoline system. The diester 15 was prepared in several steps from 3-(3,4-dimethoxyphenethylamino)propionitrile (16). Reaction of the diester (15) with phosphorous oxychloride followed by catalytic reduction gave tetrahydroisoquinoline derivative 17. Cyclization of 17 by sodium hydride gave 18 which was hydrolyzed and decarboxylated to give the 1-substituted benzo(a)quinolizin-2-ones 19.



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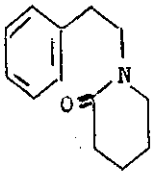

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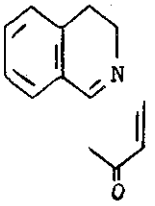

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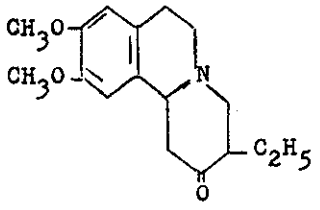

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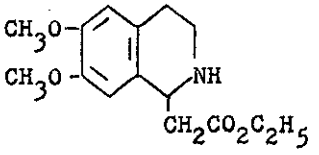

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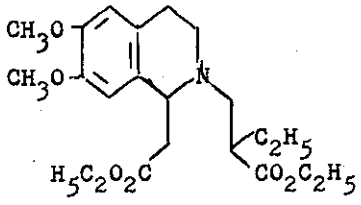

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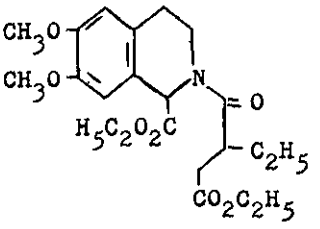

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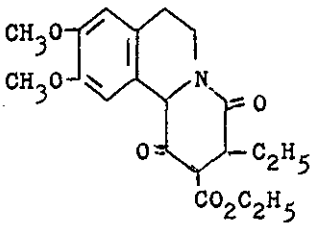

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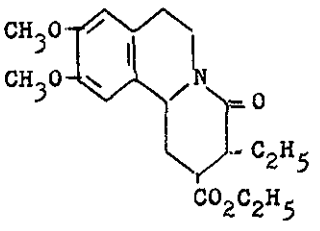

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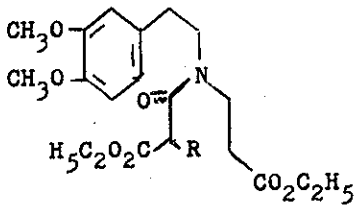

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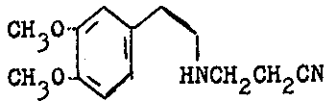

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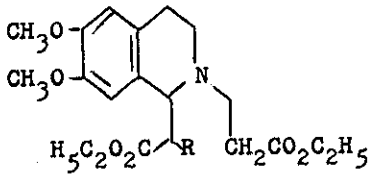

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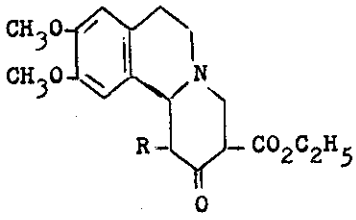

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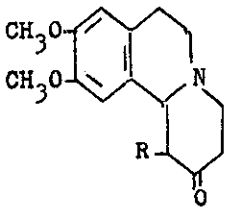

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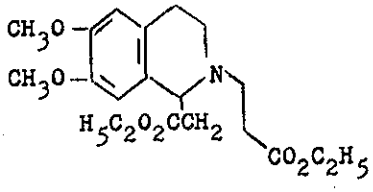

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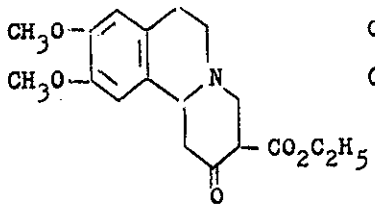

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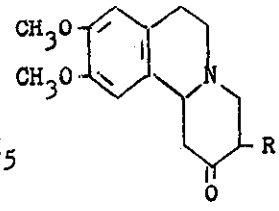

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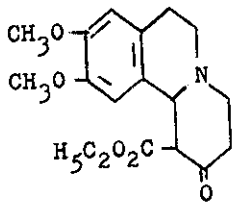
Since in most naturally occurring compounds the benzo(a)quinolizine system bears a substituent in the 3-position this either has to be allowed for in the initial starting materials or added after cyclization of the third ring. In most cases, the former method had been used, however, Brossi,[1] in the course of preparing a large number of 3-substituted benzo(a)quinolizin-2-ones, devised a method for inserting the 3-substituent after cyclization. Dieckmann condensation of the diester 20 gave the 3-carbethoxy substituted benzo(a)quinolizine 21. The highly acidic hydrogen at the 3-position was removed with base and the appropriate substituent was introduced via its chloride or bromide. Hydrolysis of the ester followed by decarboxylation gave the 3-substituted benzo(a)quinolizine-2-ones 22.

Two products are possible from the Dieckmann cyclizations. In the early work by Brossi[1] and Mizukami[5] cyclizations of the diester 20 gave only the 3-carbethoxy ketone 21. In later work, however, Buzas[6] found that both products are formed to varying degrees. The relative yields vary with the metal used for the cyclization and the best yield of the less common isomer 23 was obtained using sodium hydride in benzene.

A scheme which utilizes a slightly different condensation has been worked out by Van Binst.[9] 1-Ethoxycarbonylmethyl-3,4-dihydroisoquinoline is reduced catalytically followed by reduction with lithium aluminum hydride and alkylation with ethyl bromoacetate to give 23a. The alcohol 23a is then converted via the chloride to the nitrile which with sodium ethoxide in toluene leads to 23b. Treatment with hot aqueous hydrochloric acid gave the ketone 23c which was transformed to the 3-ethyl compound via a Wittig reaction.

Ring Closure of Piperidone Derivatives 7:

The first total synthesis of emetine[10] utilized an approach of this type. Condensation of diethyl glutaconate with ethyl cyanoacetate in the presence of



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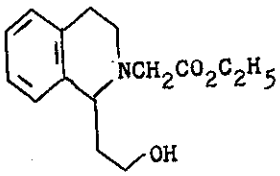
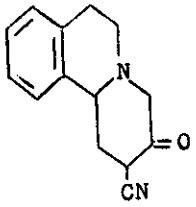
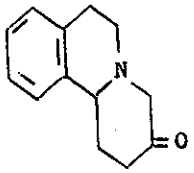


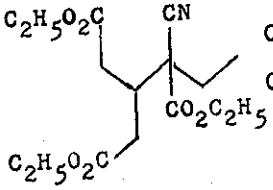
23a



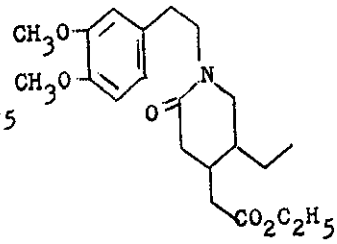
23b



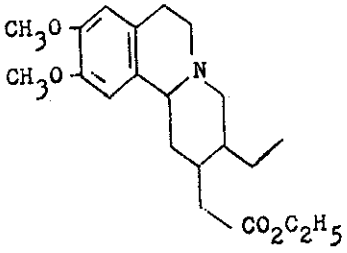
23c



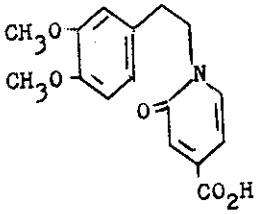
23d



23e



23f



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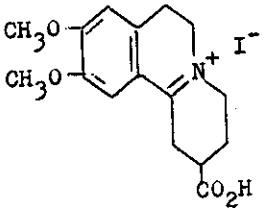

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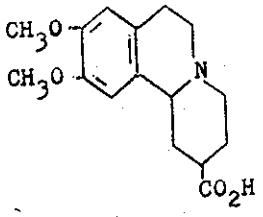

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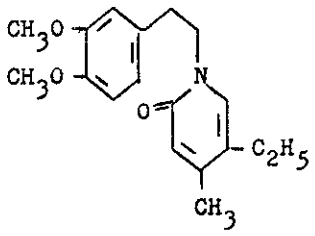
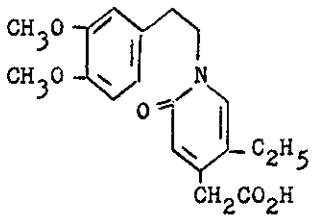
sodium ethoxide followed by alkylation with ethyl iodide gave 23d. Careful saponification and decarboxylation followed by reaction with homoveratrylamine and reduction gave 23e. Cyclization of 23e with phosphorous oxychloride followed by reduction gives 23f.

Most of the early work in this area is typified by the synthesis of the acid 24 by Pailer.[11] This compound was a key intermediate in several early syntheses of 3-bisnoremetine. Pailer's synthesis involved condensation of β-(3,4-dimethoxyphenyl)ethyl bromide with ethyl isonicotinate to give a quaternary salt which was oxidized in alkaline solution, using potassium ferricyanide, to give the pyridone 25. Esterification with diazomethane and then catalytic reduction gave a piperidone derivative which was cyclized with phosphorous oxychloride to give the benzo(a)quinolizine derivative 26. This salt was treated with aqueous silver chloride and catalytically reduced to 24. This synthesis was adequate for preparation of the 3-bisnoremetines, however, it needed modification to be useful in the preparation of emetine and other natural products carrying substituents in the 3-position.

Using a similar procedure, Barash and his coworkers[12] produced separable stereoisomers of emetine. Condensation of an appropriately substituted pyridone, prepared in several steps from β-collidine, with β-(3,4-dimethoxyphenyl)ethyl iodide gave the N-substituted pyridone 26a. Treatment of 26a with ethyl oxylate, followed by dilute acid and then oxidation with alkaline hydrogen peroxide gave 27 which on catalytic reduction gave two stereoisomeric piperidines. Esterification of the piperidines followed by cyclization with phosphorous oxychloride gave the two diastereomeric esters 28. Reduction of these salts (28) over platinum gave, in each case, only one isomer (29). This benzo(a)quinolizine derivative (29) could be condensed with β-(3,4-dimethoxyphenyl)ethylamine and cyclized to give both (±)-emetine and (±)-isoemetine.



26a



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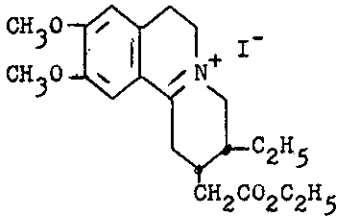

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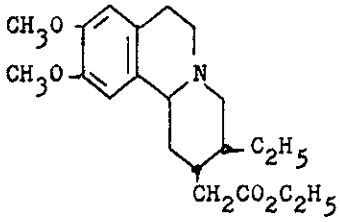

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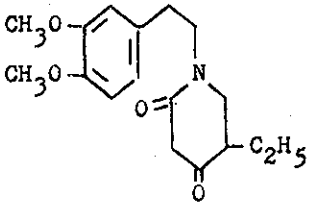

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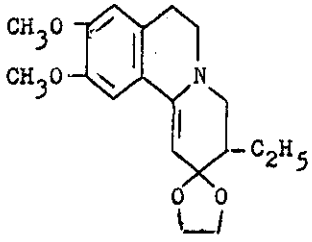

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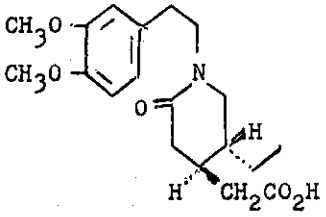

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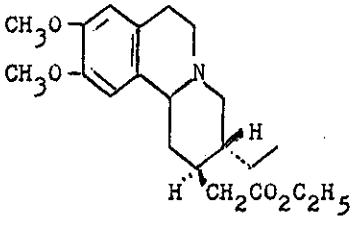
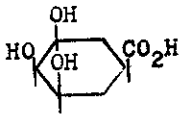


31b

A modification of this procedure was reported by Sugasawa[13,14] and subsequently used by Osbond[15] in the preparation of some benzo(a)quinolizines for studies of medicinal activity. This modification begins with the synthesis of the N-substituted piperidone 30 as described by Ban.[16] Condensation of 30 with ethylene glycol gave a dioxolan which was cyclized using phosphorous pentoxide and sea sand in boiling pyridine to give the benzo(a)quinolizine derivative 31. Catalytic reduction of 31 followed by acid hydrolysis gave the ketone 9.

A second approach, utilizing the lactam 30 produced by Ban, was developed by Battersby and Turner.[17,18] The ketonic carbonyl of 30 was reduced with sodium borohydride. Acylation of the alcohol and subsequent base catalyzed elimination followed by a Michael addition using diethyl malonate, hydrolysis and decarboxylation gave 31a. Esterification of 31a and then phosphorous oxychloride induced ring closure and catalytic reduction gave 31b.

A third ingenious variation on this approach to the benzo(a)quinolizines is that originated by Burgstahler and Bithos.[19,20] Their synthesis begins with the conversion of the all cis hexahydrogallic acid (32) to the triacetate which was treated with thionyl chloride and the acid chloride reacted with 1-diazopropane to give a diazoketone. This diazoketone was decomposed in 1,2-dimethoxyethane with silver oxide, in the presence of β-(3,4-dimethoxyphenyl)ethylamine to give an amide, via the Wolf rearrangement. Selective hydrolysis of the acetates gave the triol amide 33 which was reacted with periodic acid to give primarily the lactam 34 but also a small amount of the hydroxy lactam aldehyde 35. On treatment with dilute phosphoric acid the mixture of cleavage products (34 and 35) underwent ring closure to the benzo(a)quinolizine 36. Oxidation of the aldehyde group with silver oxide followed by esterification gave the lactam ester 37. Reduction of 37 with lithium borohydride, followed by tosylation and reductive removal of both the toxylate and lactam gave the substituted benzo(a)-quinolizine 38.



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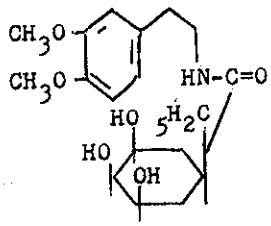

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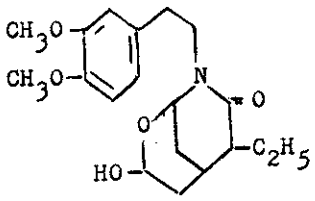

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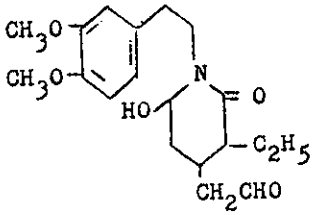

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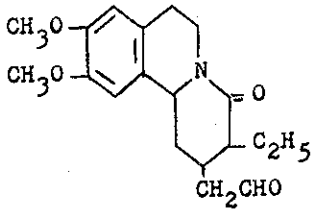

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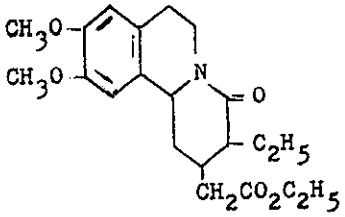

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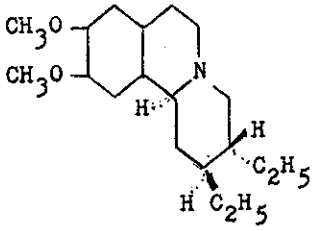

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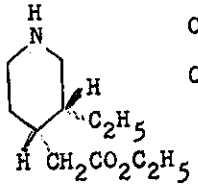

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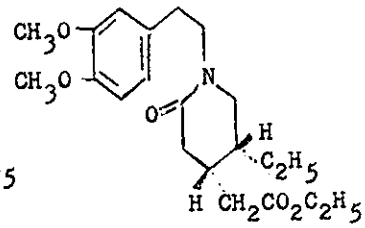

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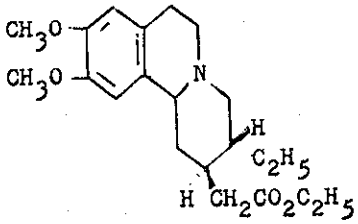


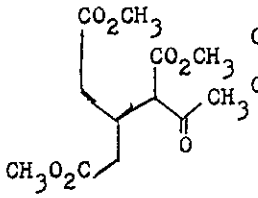
38c

Another approach utilizing the N-substituted piperidones was devised by Fujii and Yoshifuji.[21] They produced (+)-38a of known stereochemistry from cinchonine. Reaction of (+)-38a with 3,4-dimethoxyphenacyl bromide followed by treatment with sodium borohydride, oxidation with mercuric acetate and then hydrogenolysis gave 38b from which (-)-38b could be isolated. This cis acid can be isomerized to the trans acid by refluxing in hydrochloric acid. Esterification, cyclization with phosphorus oxychloride and catalytic reduction gave 38c. This type of approach has also been used by van Tamelen.[22,23] A Mannich reaction between 38d, formaldehyde and β-(3,4-dimethoxyphenyl) ethylamine followed by cyclization and reduction gives 38e. Hydrolysis, decarboxylation and reesterification then gives 38f which is converted to 38g by a Mozingo reductive sequence. Gootjes[24] has prepared N-substituted piperidones for cyclization to benzo(a)-quinolizines using 3-substituted valerolactones. The lactones are cleaved to bromoesters and these esters are reacted with β-(3,4-dimethoxyphenyl)ethylamine in refluxing xylene to give the N-substituted piperidones 38h in good yield. Cyclization and reduction gives the benzo(a)quinolizines 38i.

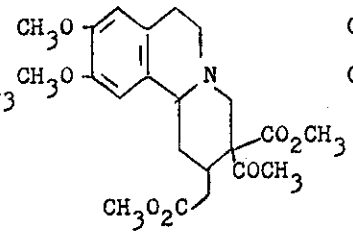
Reactions of 3,4-Dihydroisoquinolines with Unsaturated Ketones 8:

By far the most widely used method for preparation of the 3-substituted benzo(a)quinolizin-2-ones (39) is the reaction of appropriately substituted 3,4-dihydroisoquinolines (40) with derivatives of methyl vinyl ketone (41).

This approach to the synthesis of benzo(a)quinolizin-2-ones was initiated by the work of Brossi,[25] who found that the first Hoffmann elimination product of 9, 42, could be reconverted to 9 by treatment at room temperature with 48% hydrobromic acid. It was found that in acetic acid the compound 42 could be cleaved to the products 43 and 44. These findings led Brossi[25] to attempt the reverse reaction. When an alkaline ethanol-water solution of 6,7-dimethoxy-3, 4-dihydroisoquinoline and 3-methylene-pentan-2-one (44) was left standing at room temperature this solution deposited the ketone 9 in 14% yield.



38d



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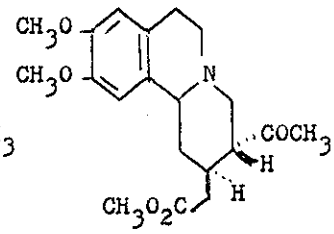
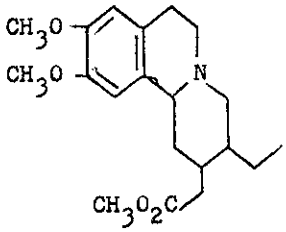


38f



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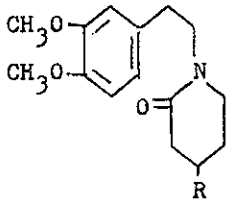
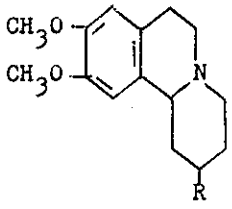
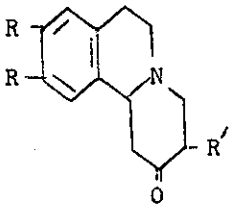


38h



38i



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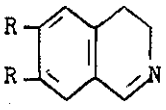

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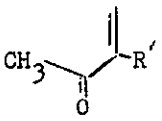

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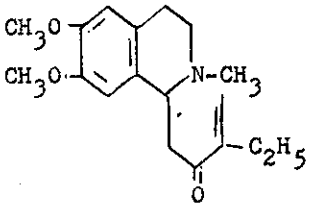

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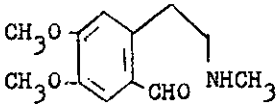

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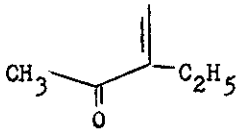


44

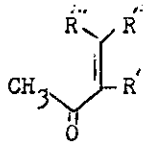
The successful preparation of 9 by Brossi led Szántay and Beke[26] to further investigate the reaction. They found that a two step process led to isolation of the product in better yield. Substituted 3,4-dihydroisoquinolines (40) could be reacted with appropriately substituted α,β -unsaturated ketones 45 to give iminium salts which without purification were dissolved in water and treated with base to effect cyclization in good overall yield.

Possibly the simplest preparation of the 3-substituted benzo(a)quinolizin-2-ones, however, not giving the best yield, was derived by Lenard and Bite.[27] In this 'one-pot' preparation the 3-ethyl compound 9 is prepared in 43% yield by reaction of ethyl α-ethylacetoacetate, formaldehyde and 3,4-dihydro-6,7-dimethoxyisoquinoline.

The course of the reaction between α,β-unsaturated ketones and isoquinoline derivatives was also examined by Openshaw and Whittaker.[28] They found that heating 1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline hydrochloride with formaldehyde and methyl n-propyl ketone yielded approximately equal amounts of the two Mannich products 46 and 47.

The base 46 could be oxidized with mercuric acetate in aqueous acetic acid and then demercurated with hydrogen sulfide to give the ketone 9, while the other isomer 47, under the same conditions, gave no product. Substituting ethyl α-ethylacetoacetate for the methyl n-propyl ketone precluded the formation of the unwanted isomer 47 and increased the overall yield of the ketone 9 to 54%. At the same time they also considered the reaction of 6,7-dimethoxy-3,4-dihydroisoquinoline with Mannich base cations of the type 48. Via an amine interchange these reactions also led clearly to the expected benzo(a)quinolizin-2-one (9) in a yield of 75%.

Mechanistic studies of the reactions of α,β-unsaturated ketones with 3,4-dihydroisoquinolines have ellucidated the reaction pathway.[29,30] The rate con-



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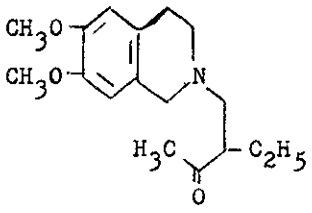

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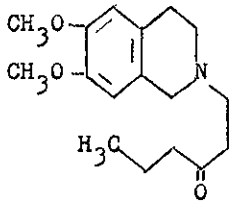

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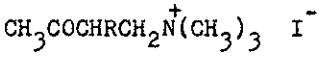

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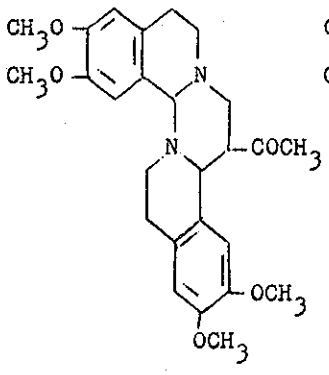

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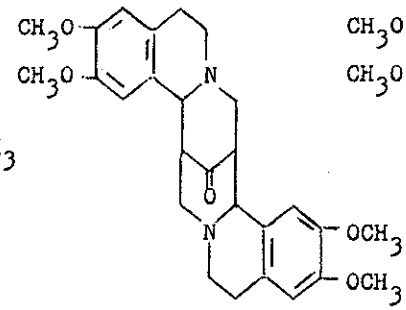

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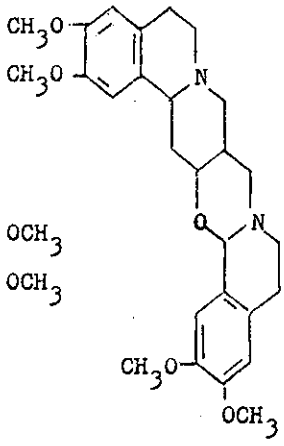

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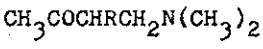

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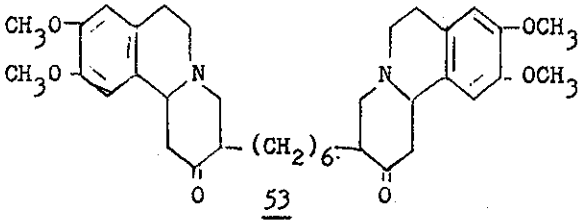


53

stants revealed that the reaction proceeds with good speed in acidic media, in neutral aqueous ethanol the overall rate was very slow, while in basic media problems involving side reactions arose. Side reactions are known to occur in this type of benzo(a)quinolizin-2-one preparation. Most of these reactions can be attributed to pH effects. In the absence of catalytic amounts of acid or base the product 49 is observed from the reaction of two molecules of 6,7-dimethoxy-3,4-dihydroisoquinoline with one molecule of methyl vinyl ketone.[31-34] Novel systems of the structures 50 and 51 have also been formed. System 50 is formed by the action of a diMannich base on 6,7-dimethoxy-3,4-dihydroisoquinoline at high pH, and system 51 is formed from the same isoquinoline and the Mannich base in the absence of catalytic amounts of acid or base.[32-34]

Whittaker,[32] by spectroscopically following the reaction between the 3,4-dihydro-6,7-dimethoxyisoquinoline and Mannich base 52, found that the low yield of products reported in earlier works was caused by low concentrations of the two reactive species. This problem was overcome by running the reactions in aqueous solution. Not only did this solve the proton transfer problem but since the benzo(a)quinolizin-2-ones are water insoluble they crystallized from solution upon formation and caused the reactions to proceed to completion. Using this procedure, yields of 90% or better are typical.

Substituents can also be introduced into the 1-position of the ring system by appropriate variation of the Mannich base.[35,36] In a similar manner dimers of the type 53 have been synthesized by reaction of appropriate Mannich bases with 6,7-dimethoxy-3,4-dihydroisoquinoline.[2]

Miscellaneous Preparations:

Several preparations of benzo(a)quinolizines have appeared in the literature which do not fit into the three categories described, but are of interest.

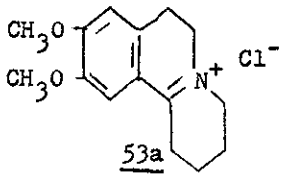
Pyman,[37] in an early preparation, cyclizes 1-δ-chlorobutyl-6,7-dimethoxy-3,4-dihydroisoquinoline to 53a by heating. Catalytic reduction of 53a gives 53b.

Benzo(a)quinolizines bearing substituents in the 2-position can be prepared by the method of Schoepf and Klug.[38] This method utilizes the reaction of the Grignard reagent prepared from vinyl bromide with 1-methyl-1,2,3,4-tetrahydroisoquinolines which have ketonic substituents on the methyl group, to give carbinols of the type 54. These carbinols are treated with excess thionyl chloride to give the unsaturated halides which in the presence of base cyclize to the 1,2-dehydrobenzo(a)quinolizines 55. Catalytic hydrogenation of these compounds yield the saturated 2-substituted benzo(a)quinolizines 56. Substitution of bromobutene for the vinyl bromide gives the 3-ethyl substituted analog.

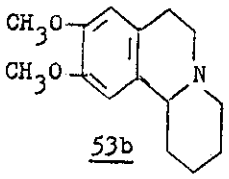
Schneider and coworkers[39] have reported a sequence for introducing substituents into the 4-position of the benzo(a)quinolizines. Appropriately substituted 3,4-dihydroisoquinolines are reacted with acetone derivatives to give 1-substituted 1,2,3,4-tetrahydroisoquinolines 57 which are then reacted with aldehydes in buffered aqueous media to give the substituted benzo(a)quinolizines 58.

Another approach to the benzo(a)quinolizines is that taken by von Strandtmann and coworkers[40] who reacted 3,4-dihydroisoquinolines with β-diketones. For example, heating equimolar amounts of 6,7-dimethoxy-3,4-dihydroisoquinoline and the diketone 59 gives the benzo(a)quinolizine 60 in 65% yield.

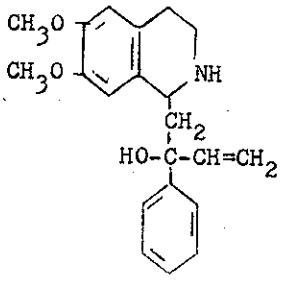
Popp and coworkers[41,42] have utilized Reissert compound intermediates to enter the benzo(a)quinolizine system. Reaction of isoquinoline, potassium cyanide and 4-chlorobutanoyl chloride gives the Reissert compound 61. Treatment of this intermediate with sodium hydride in dimethyl formamide gives the benzo-(a)quinolizine 62 which on reduction with lithium aluminum hydride gives 63. Catalytic hydrogenation of 63 gives the parent benzo(a)quinolizidine 64.



53a



53b



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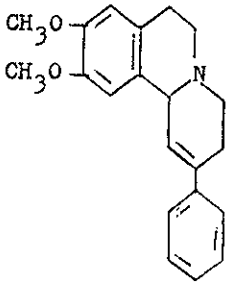

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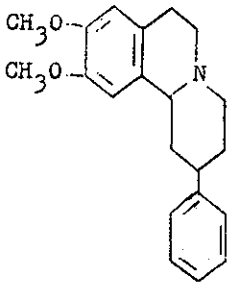

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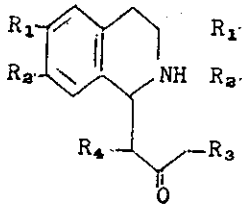

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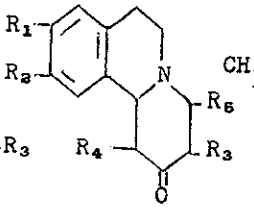

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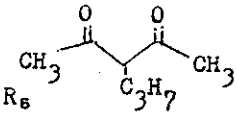

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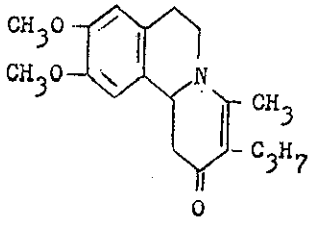

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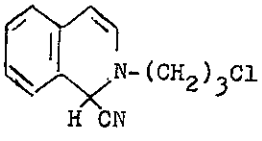

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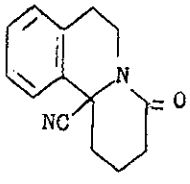

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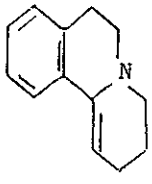

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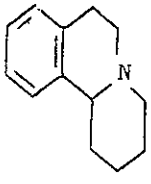


64

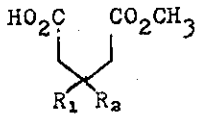
Gootjes[43,44] has used the reaction of β-phenylethylamines and 3-substituted glutaric acids to produce 2-substituted benzo(a)quinolizines. Reaction of β-(3,4-dimethoxyphenylethylamine with a half ester of the type 64a gives a half amide-half acid. Esterification with diazomethane followed by treatment with phosphorous oxychloride yields 64b. Catalytic reduction and cyclization gives 64c which on reduction with lithium aluminum hydride yields the benzo(a)quinolizine 64d. Gootjes[45] also uses a similar route to prepare 1- and 3-substituted benzo(a)quinolizines.

In recent work Kametani, et al.[46] prepared benzo(a)quinolizines by reacting 1-methyl-3,4-dihydroisoquinolines with diethyl α,γ-diethoxycarbonylglutaconate to give the compounds 65 which are reduced with sodium borohydride to give the benzo(a)quinolizines 66. Alternatively, silica gel chromatography of 65 gave the further unsaturated lactam 67.

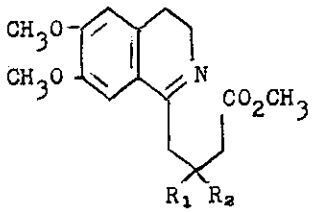
In further work[47] Kametani's group has found that heating 1-methyl-3,4-dihydroisoquinolines with crotonic anhydride in pyridine gives several products, one of which is the benzo(a)quinolizine 68. They also found that heating the same isoquinoline with glutaconic anhydride gave 69 as the sole product in 56% yield.

Brossi [48] prepares 53b by reacting N-acetyl-β-(3,4-dimethoxyphenyl)ethylamine with 4-carbomethoxybutyrl chloride, under Friedel-Crafts conditions. A combined hydrolysis and cyclization gives 69a. Catalytic reduction of 69a and thermal cyclization followed by lithium aluminum hydride reduction yields 53b.

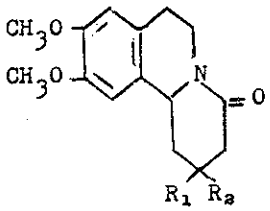
Reaction[48a] of the addition product of isoquinoline and phenylisocyanate with dimethyl acetylenedicarboxylate gave a mixture that include the diadduct[48b] 69b. Other similar adducts have been obtained.[92a, 92b]



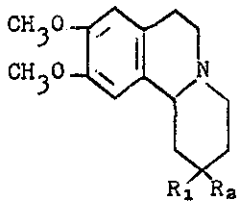
64a



64b



64c



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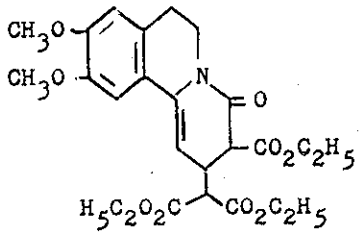
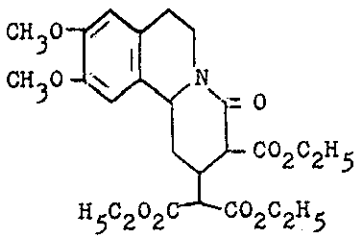


65



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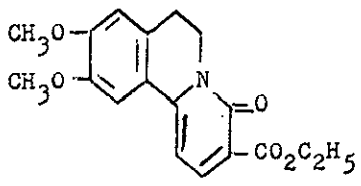

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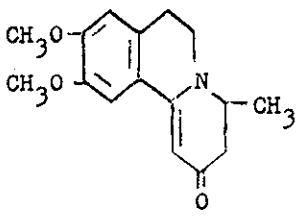

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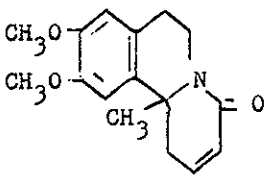

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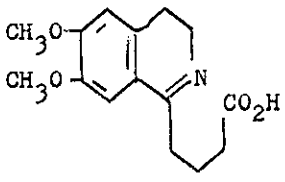
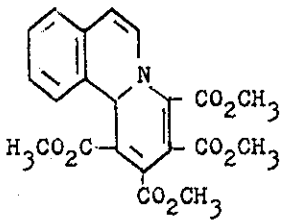
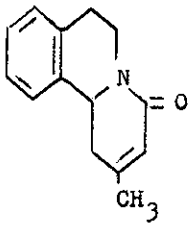


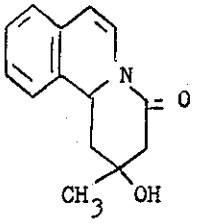
69a



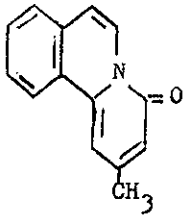
69b



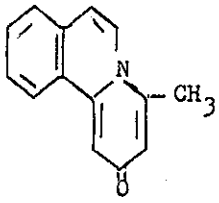
69c



69d



69e



69f

Treatment[48c] of 1-acetonyl-2-acetyl-1,2-dihydroisoquinoline with potassium hydroxide gave 69c and 69d. The latter can be converted to the former with potassium hydroxide. Oxidation of 69c with chloranil gave 69e which was not identical with 69f which was one of the products[48d] obtained from the reaction of isoquinoline-N-oxide with diketene. Catalytic hydrogenation of 69f gave the dihydro derivative (60, C_3H_7 = H).

Sterochemistry:

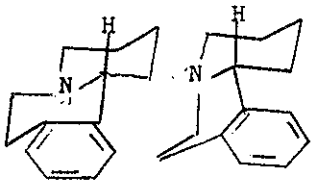
The general structures of the benzo(a)quinolizine alkaloids were, for the most part, worked out by exhaustive degradative procedures. These procedures in combination with early syntheses completely ellucidated the overall structure of the system but did little or nothing to establish the absolute configuration

at the asymmetric centers. The elucidation of the stereochemistry of the four asymmetric centers in the alkaloid emetine was the work of several groups and appears in works by Ban,[49] Battersby,[50,51] Brossi[52] and van Tamelen.[53] The stereospecific syntheses carried out by these groups are covered in detail in the review by Szántay.[54]

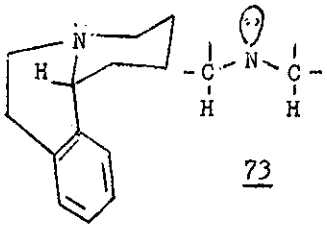
Of a more general nature is the determination of the stereochemistry of the B/C ring junction in the benzo(a)quinolizines. Works by Bohlmann[55] and Brossi[56] deal with assigning conformational structures to the benzo(a)quinolizines via infrared and NMR spectra respectively.

One trans fused (70) and two cis fused (71, 72) conformations are possible when both rings are in the preferred chair conformation. Only in the trans fused case, 70, can the lone pair of electrons on the nitrogen assume a trans-diaxial position relative to the two α-hydrogens (73). It is this conformation that gives rise to the infrared absorptions, in the 2700-2800 cm^{-1} range, known as Bohlmann bands. These bands are present in the spectrum whenever the lone pair on the nitrogen is unbound. When the nitrogen electron pair becomes involved in a bonding situation as in an N-oxide or amide the Bohlmann bands disappear. When observable, these bands are indicative of the trans fused quinolizine system.

Also arising from the three conformations are distinctive NMR absorptions for the angular proton at position 11b. By studying models it is found that in structure 70 the angular hydrogen is trans-diaxial to the lone pair of electrons. In one cis conformer, 71, the angular hydrogen is psuedo equatorial to ring B and axial to ring C; while in the other conformer, 72, it is psuedo axial to ring B and equatorial to ring C. These subtle differences give rise to unique NMR spectra. In the trans fused system (70) the angular proton is always observed at a field higher than 6.2 ppm τ, but additionally, the splitting



70 71



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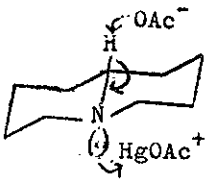
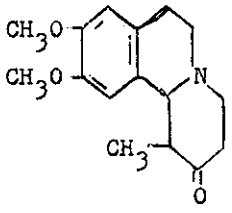
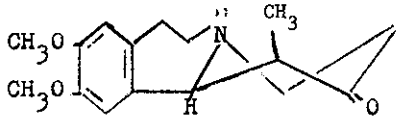


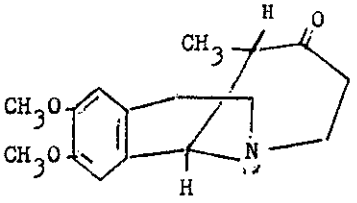
73a

72



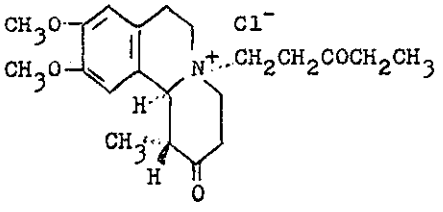


trans



cis

74



75

patterns may be used to differentiate between the two cis forms. The angular proton in the conformer 71 is gauche (ae) to one adjacent methylene proton and trans-diaxial (aa) to the other. The NMR signal of this proton is a quartet with small ae (J=5Hz) and large aa (J=11Hz) splittings in a ratio of approximately 1:1:1:1. In the other cis conformer, 72, the angular proton is gauche to both adjacent methylene protons and the approximately equal coupling constants give a 1:2:1 triplet.

Gootjes[57] has found that the cis and trans fused benzo(a)quinolizines can be differentiated by the rates at which they are oxidized by mercuric acetate. The trans fused isomers react at rates typically one to two orders of magnitude faster than the identical cis fused compounds. This is attributable to the facile trans periplanar elimination made possible by the trans-diaxial orientation of the lone pair of electrons on the nitrogen and the proton at C-11 in the trans fused system 73a.

The normal preparation of benzo(a)quinolizin-2-ones, utilizing 3,4-dihydroisoquinolines and α,β-unsaturated ketones, yields the thermodynamically more stable trans fused system. However, in recent work by Buzas[36] it has been shown, that at least in some cases, the less stable cis junction conformer is formed first and then converted to the more stable trans isomer by heating. In the preparation of ketone 74 the original compound formed was the cis isomer which was converted, by heating, to the trans form. The trans conformer could be isolated in good yield in the normal reaction sequence. The cis fused isomer could be obtained by reacting the dihydroisoquinoline with a twofold excess of ethyl vinyl ketone and isolating the salt 75. Decomposition of the salt 75 in cold alkaline solution gives the free cis ketone.

Reactions:

The reactions of the benzo(a)quinolizines will be discussed according to

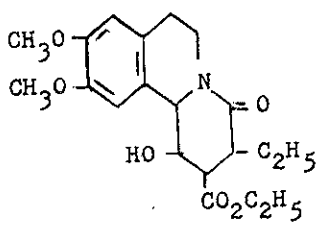
the site of the reaction and categorized further by reaction type. In general, only reactions taking place on the benzo(a)quinolizine framework will be discussed in detail. Reactions on pendant groups normally occur as would be expected and will only be outlined.

As a result of the synthetic methods used to prepare the benzo(a)quinolizines carbonyl groupings generally appear in two locations, positions 2 and 4 in the ring system. Carbonyls in the 4-position are amides and are typically only reduced by lithium aluminum hydride to give the totally reduced systems.[7]

In one instance,[7] a carbonyl group appearing in the 1-position (13) is removed through a reductive sequence. The ketone is reduced catalytically to the alcohol 76 which is converted to its mesyl derivative, and the methane sulfonate group is displaced by the anion of benzyl mercaptan to give 77. The thiol ether 77 is desulfured over Raney nickel to give 14.

Papers by Brossi[58] and Sugimoto[59] deal extensively with the products of the reduction of the 2-ones. Both authors determine the ratio of axial alcohol to equatorial alcohol under various reductive conditions. Sugimoto's work deals with the reduction of 78, while Brossi looks at reductions of 79. The two compounds give essentially the same product ratios under similar conditions. The ratios vary from 95% equatorial-2% axial using catalytic hydrogenation over platinum oxide in acetic acid to 41% axial-52% equatorial using aluminum isopropoxide in benzene. Brossi[58] reacts the alcohols produced with phosphorus pentachloride to get the secondary halides 80. Osbond[15] has shown that the 2-ol 81 with mercuric acetate gives 82.

In seeming contradiction to the findings above is the reduction of 83 to 84. This reduction is one step in the preparation of the anti-hypertensive agent quantril (5) and is reported by Szántay[60] to give the axial alcohol in 90% yield. This apparent deviation from thermodynamic control is explained by the tauto-



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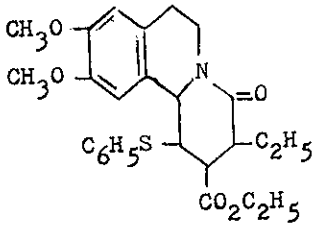

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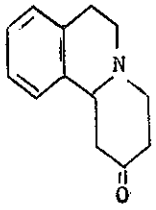

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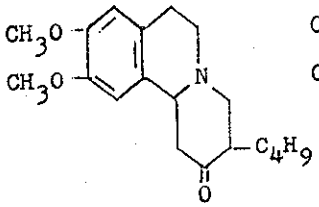

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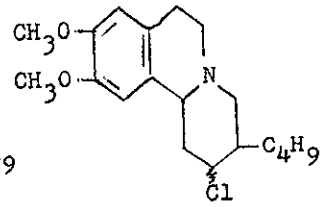

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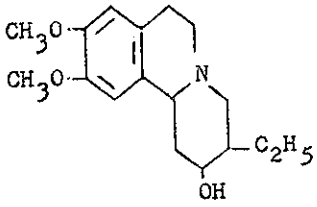

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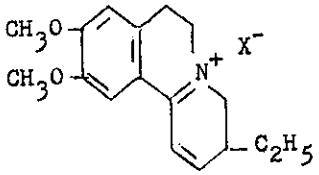

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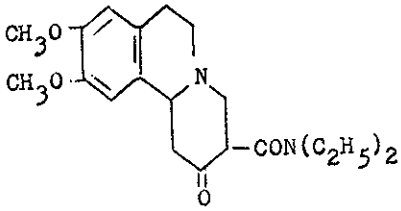

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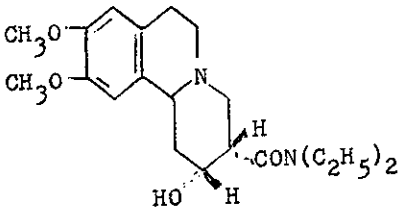

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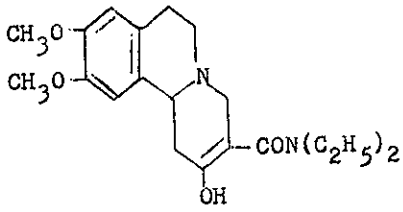


85

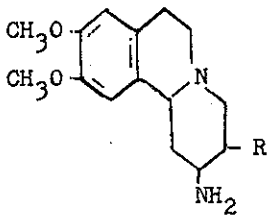
merism of the ketone 83. Infrared and NMR spectra studies show that equilibrium between 83 and 85 is found to lie in favor of 85 (85%). Chemisorption of 85 on the catalyst surface from the unhindered side gives rise to the product with the hydroxyl group in the axial position.

We[2] have carried out reductive aminations on the 2-ones using sodium cyanoborohydride and ammonium acetate to give the primary amines 86 in good yields. Previously[61] these compounds had been available by two other routes. Dissolving metal reduction of the oxime gives the equatorial amine 87. Tosylation of the equatorial alcohol gives 88 which with azide ion gives 89 which upon catalytic hydrogenation yields the axial amine. Bite[62,63] has reacted the amines with a wide variety of aldehydes to give Schiff bases.

Ketals (90) of the benzo(a)quinolizines are known to form readily as long as R_1 and R_2 are hydrogen. Szántay[64] has found only one case, that of R_2 = phenyl, in which ketal formation occurs in the presence of an α-substituent. Szántay attributes the lack of ketal formation in the α-substituted compounds to a positive inductive effect exerted by the α-substituent. The effect, operating across space, diminishes the influence of the charged nitrogen, which is necessary for ketal formation. Mizukami[5] has prepared the dimethyl ketal of 22 (R=Me). Methanol is eliminated from this ketal to give the vinyl ether 91 by heating at 220Å in a sealed tube with aluminum t-butoxide.

The cyanohydrin of 9 has been prepared by two methods.[2,65] Reaction of the ketone 9 with the anion of 2-benzoyl-1,2-dihydroisoquinaldonitrile in dimethylformamide gives the cyanohydrin which is also obtained by reaction of the hydrochloride salt of 9 with aqueous sodium cyanide.

Condensation of the ketone 9 with lithium acetylide has been carried out by Brossi and coworkers.[66] The two epimeric alcohols formed were separated by paper chromatography and on catalytic reduction the products (92) gave 93.



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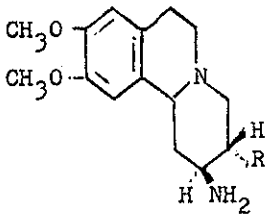

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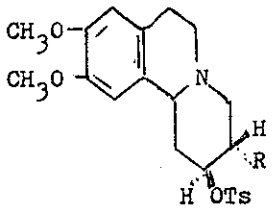

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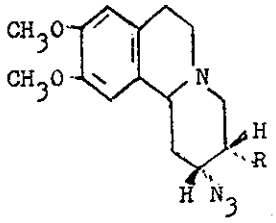

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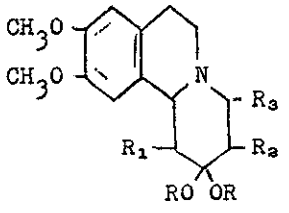

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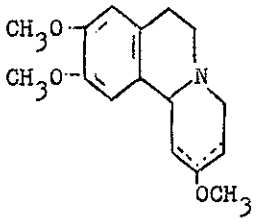

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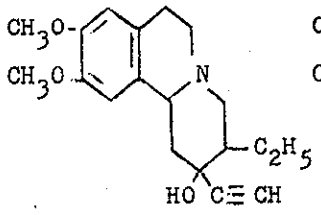

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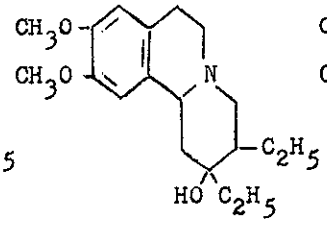

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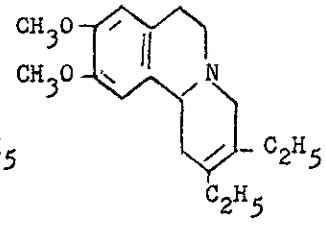

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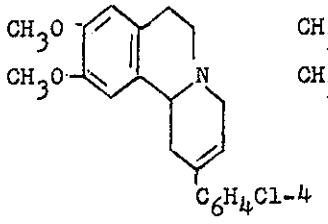

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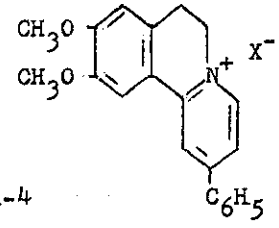

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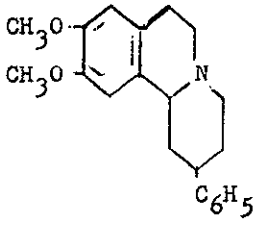


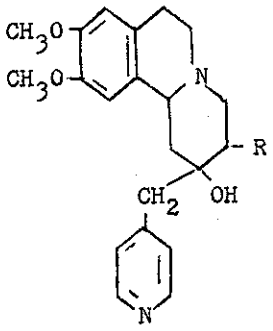
97

Several types of Grignard reactions have been run on the ketone 9. Brossi[66-68] condensed 9 with ethyl magnesium iodide to obtain the two epimers of the carbinol 93 which on dehydration in concentrated sulfuric acid gave 94. Both epimers of the alcohol are produced in the reaction of the ketone 22 (R=H) with p-chlorophenyl magnesium bromide. Dehydration of these alcohols using concentrated sulfuric acid gives 95 while dehydration with phosphorous oxychloride in pyridine or oxidation with mercuric acetate gives 96. Catalytic hydrogenation converts 95 and 96 to 97.

Kumar, et al.[69] have reacted several ketones 22 (R=Et, ^{i}Bu) with the lithium salts of 2-picoline, 4-picoline and 1-methylisoquinolines to give emetine analogs such as 98. Reaction[70] of the ketone 9 with the anion of trimethyl sulfoxonium iodide gives the spiro epoxide 99. Reaction[2] of the anion of tosylmethyl isocyanide with 9 gives the nitrile 100.

The ketone 22 (R=H) has been condensed[2] with the anion of 2-benzoyl-1,2-isoquinaldonitrile to give 101 which can be hydrolyzed with base to the corresponding carbinol. This reaction can be contrasted to the reaction of 22 (R=Me, Et) with this anion to give cyanohydrins.[65]

Ethyl cyanoacetate and malonitrile have been used by a number of groups[71-77] to add two carbon fragments to the carbonyl group. Battersby[4] condensed the ketone 9 with malonitrile to obtain the dicyano compound 102. Brossi[72] reports conversion of 102 to the acid 103 (R=COOH) using 20% HCl. The acid can also be converted to the amide 103 ($R=CONH_2$), chloride 103 (R=COCl), and primary alcohol 103 ($R=CH_2OH$). Szántay[76] has carried out a number of reactions on the dinitrile 102 in the preparation of dimethoxydespyrrolocorynantheidine. Reduction of 102 with sodium borohydride gives the saturated dinitrile which can be hydrolyzed with sodium methoxide in methanol to the enamine 104. The enamine 104 with methanolic HCl gives the half ester which with HCl gas in dry methanol gives the



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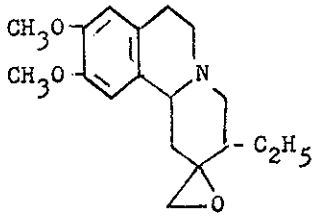

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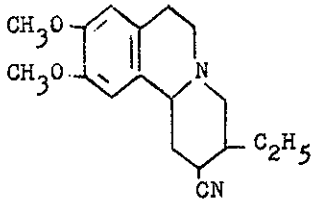

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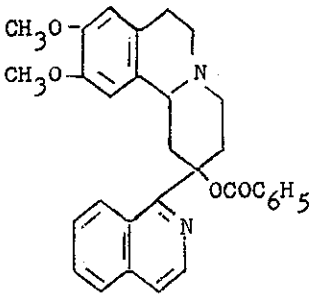

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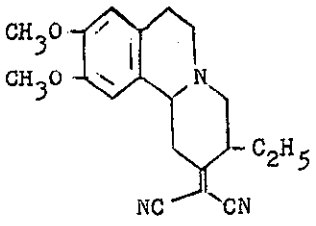

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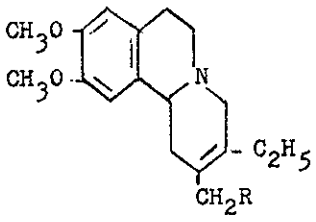

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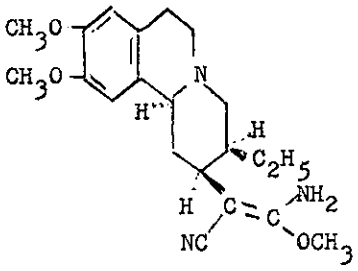


104

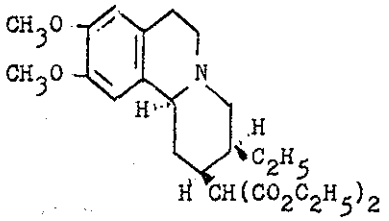
diester 105. Reduction of the diester with lithium aluminum hydride at -70° gives the α-formyl ester 106. The α-formyl ester (106) treated with HCl gas in methanol at -10° gives the vinyl ether 107.

Battersby[4] first reported the addition of ethyl cyanoacetate to the ketone 9 to give 108. Brossi[71] isolated 108 as a crystalline compound and reduced it catalytically to the saturated ester which with HCl gave the acid 109, which was esterified in ethanol.

Szántay[78] has found that mild oxidation causes rotation about the double bond in compounds 102 and 108. Oxidation of 108 with mercuric acetate gives the diene 110. Oxidation of 108 which is entirely one geometric isomer, E or Z, yields a mixture of the two dienes. The barrier to rotation ($\Delta G^{\ddagger}$) is found to be approximately 24 kcal/mole, and an ionic mechanism is believed to be involved. However, in compound 111 rotation takes place following bond migration and no rotation about the double bond is thought to occur.

Benzo(a)quinolizines are known to undergo Wittig reactions with difficulty. Openshaw[79] has been able to obtain the Wittig product 112 (R=Me) from 9 and methoxycarbonylmethylenetriphenylphosphorane only by using severe conditions, refluxing xylene or at 150° in the absence of solvent. This compound can be reduced catalytically to the saturated ester or hydrolyzed to the acid 112, (R=H). Whittaker[80] has also reported reaction of 9 with 6,7-dimethoxy-3,4-dihydroisoquinolin-1-ylmethylenetriphenylphosphorane to give 113.

Addition of phosphonates is carried out on the benzo(a)quinolizines easily at room temperature. Openshaw[81] reports condensation of 9 with methyldiethylphosphonoacetate to give 112 (R=Me) in low yield. Szántay[82-85] reports condensation of 9 with triethylphosphonoacetate, under different conditions, obtaining a 60% yield of 112, (R=Et). Catalytic reduction of 112 gives the saturated ester which can be reduced with diisobutyl aluminum hydride at -60° to give the aldehyde protoemetine, 114.



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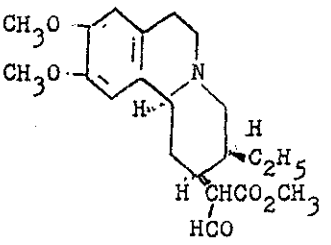

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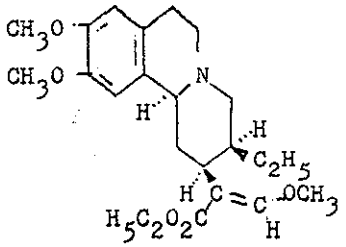

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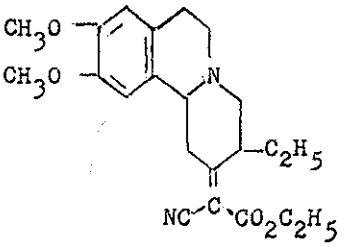

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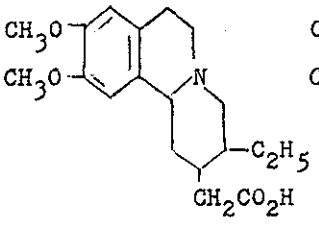

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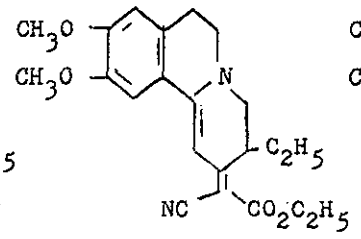

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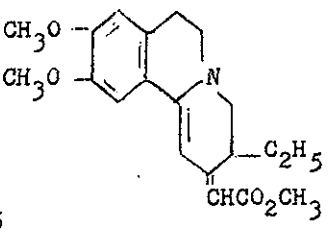

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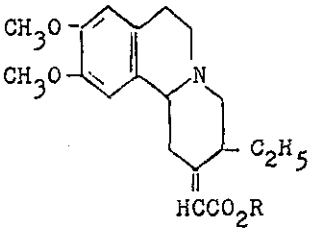

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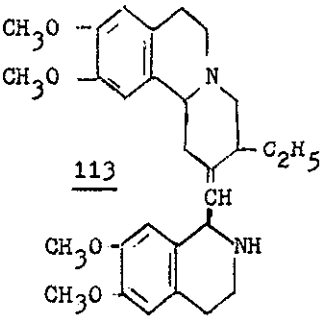

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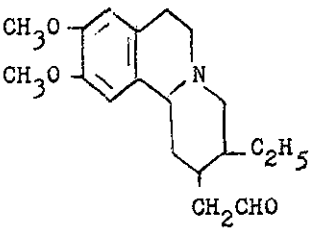


114

Buzas[86] reports condensation of the novel phosphonate 115 with 9 to give 116 in 92% yield.

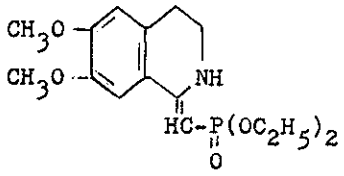
Oximes of the benzo(a)quinolizines form easily, in good yields. Buzas[35] has found that the ratio of syn to anti isomers varies with the method of preparation. The configuration of the isomers can be determined by NMR, since the OH proton on the syn isomer lies close enough to the proton at C-11 to cause mutual splitting. Also, in a mixture, the OH proton of the syn isomer absorbs at slightly higher δ value than the anti proton.

Bite[62] and Buzas[87] have investigated formation of oximino ethers from the oximes of benzo(a)quinolizines (117). Reaction of the oxime with sodium hydride or sodium ethoxide followed by alkylation gives the oximino ethers. Alternatively, substituted hydroxylamines are reacted directly with the ketones.

Bite[88] has reduced the oximes to amines using lithium aluminum hydride. These amines, in the presence of base form amides with acid chlorides. Reaction of the oxime directly with an acid chloride gives compounds of the type 118.

Havera[89,90] and coworkers have reacted the ketone 22 (R=H) with a number of amines to form Schiff bases. Reduction of the imines gives secondary amines 118a which can be acylated by reaction with anhydrides.

Schmidt and Beckmann rearrangements of the benzo(a)quinolizin-2-ones give the lactams in good yields. Buzas[91] has found that the Beckmann rearrangement proceeds as expected from the tosylates of the oximes. The Schmidt reaction gives the product derived from the migration of the most highly substituted carbon. The lactams produced are smoothly reduced to the azepines with lithium aluminum hydride in THF. Whittaker[92] has found the major product formed in the reaction of 9 with HN_3 to be 119. Reduction of the methiodide of 119 using sodium amalgam gives 120 via the enamine. Oxidation of 119 with mercuric acetate gives 121 and 122.



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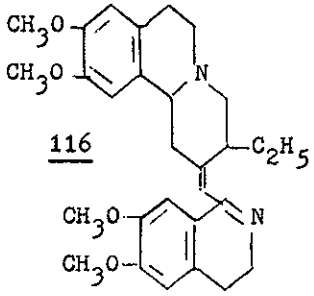

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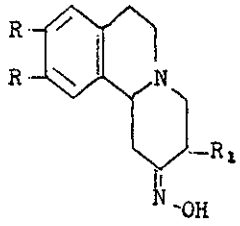

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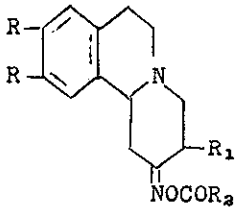

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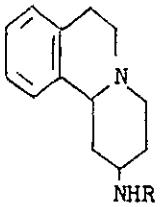

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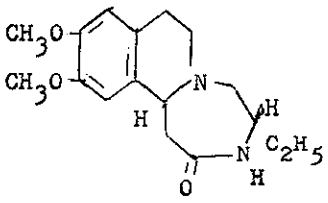

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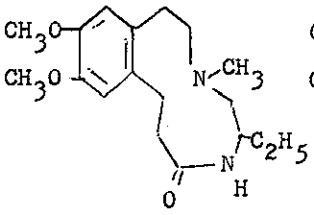

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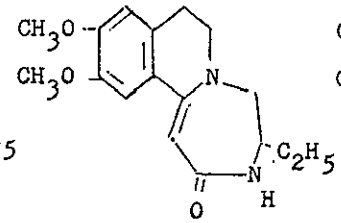

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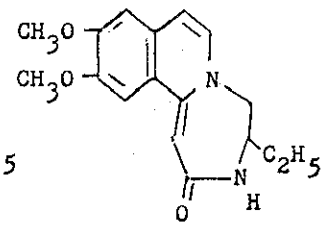

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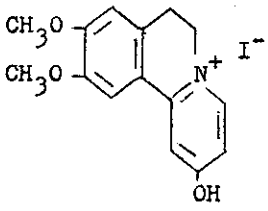

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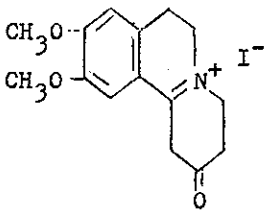

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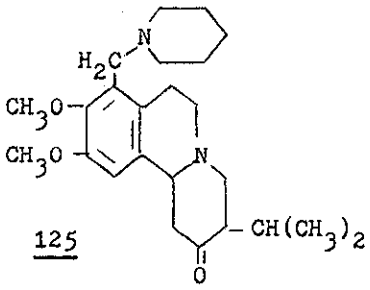

125

As has been previously shown mercuric acetate will oxidize the benzo(a)-quinolizines to varying degrees of unsaturation depending on the conditions used. The aromatized system (123) is accessible through pyrolysis of the iodide salt 124.[15] However, oxidation using mercuric acetate under mild conditions[81] gives only oxidation of the carbon-nitrogen bond to compounds of the type 124. These compounds are easily reduced back to the saturated systems. The salts of the type 123 as well as 124 are smoothly reduced by hydrogen over a platinum catalyst.[67]

Bite[62] has investigated the Mannich reaction on benzo(a)quinolizines. The Mannich reaction works only with piperidine and reacts in the 8-position to give the product 125.

Brossi[58] has found that 48% hydrogen bromide will cleave the 9 and 10 methoxy groups on benzo(a)quinolizines. Diazomethane will react with the diphenol produced to regenerate the methyl ethers.

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