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REVIEW ON REACTIONS OF ACETYLACETALDEHYDE WITH AROMATIC AND BIOGENIC AMINES AND INDOLES – SYNTHESIS OF HETEROCYCLES *VIA* HYDROXYMETHYLENE KETONES

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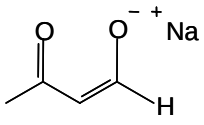
Abstract - In 1960 Teuber *et al.* started with the study of the reactions of several derivatives of acetylacetaldehyde with aromatic and biogenic amines (dopamine and tryptamine), as well as indole compounds. Teuber´s scientific work resulted in a series of heterocyclic skeletons that are related to alkaloids such as strychnine, yohimbine, ajmalicine and emetine as well as to some analogues of *bis*-indole alkaloids. We review Teuber´s research results as well as reactions from other authors working in this field obtained within the last 40 years (1960 –2000).

CONTENTS

I. INTRODUCTION

In 1888 Claisen[1] discovered the sodium salt (**1**) of acetylacetaldehyde (**2**). Due to the low stability[2] of the *β*-dicarbonyl form of **2,** more stable derivatives have been prepared, such as 4,4-dimethoxy-2-butanone (**3**) and 4-methoxy-3-buten-2-one (**4**). These derivatives allow the synthesis of many heterocyclic systems.[3]



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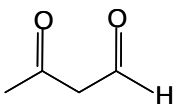

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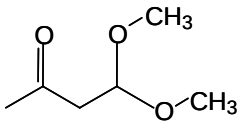

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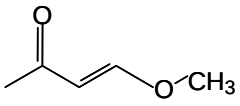

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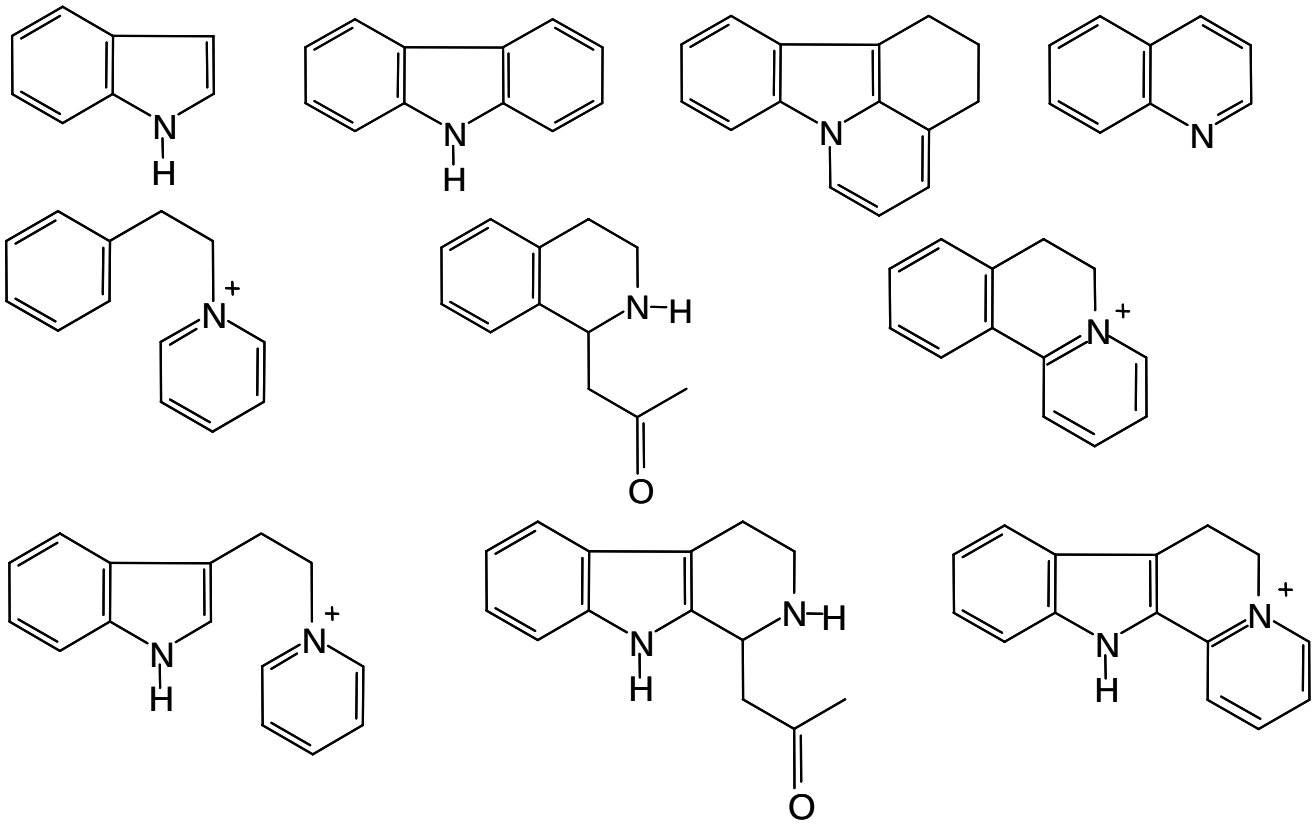
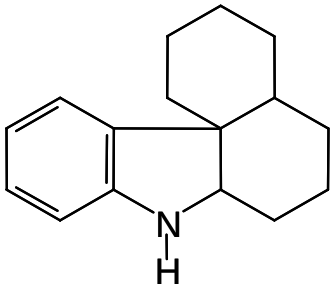
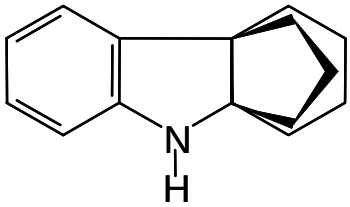
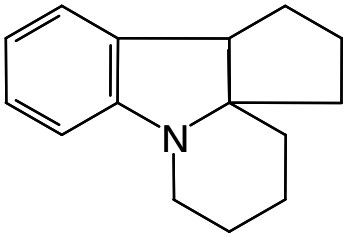
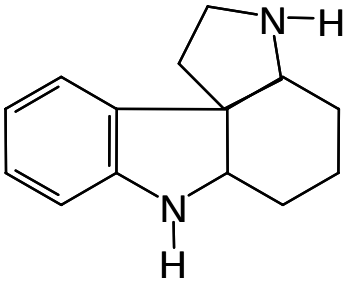
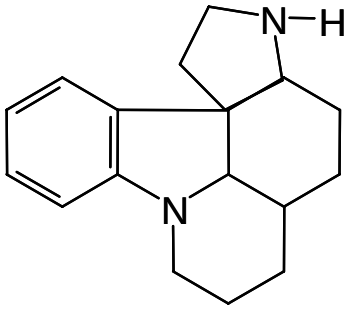
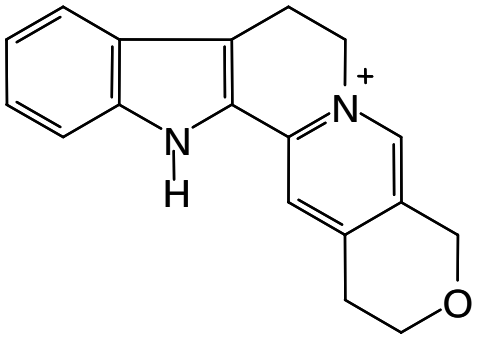
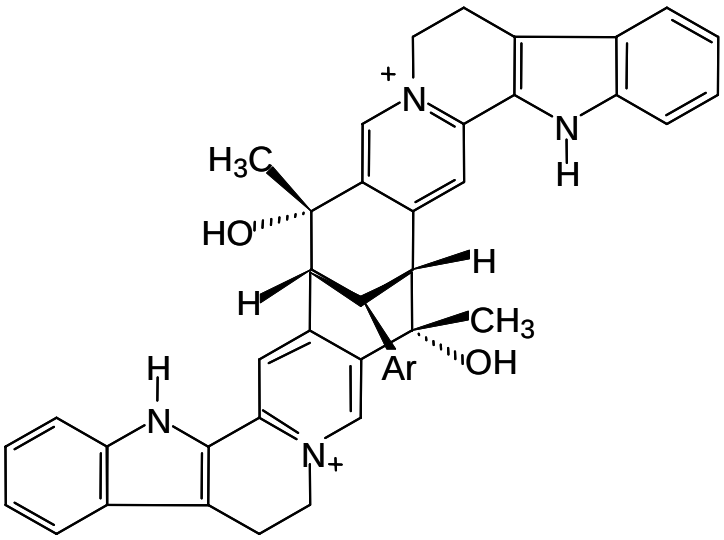
Franke *et al*. reviewed the earlier use of acetylacetaldehyde derivatives in synthesis of heterocycles.[4] It is relevant to mention the use of the silanized enol ether form of 4-methoxy-3-buten-2-one (**4**) in Diels-Alder reactions[5] as well as the use of its potassium enolate in synthesis of γ-pyrones.[6]

Teuber *et al*. started in 1960 with the study of the reactions of several derivatives of **2** with aromatic and biogenic amines (dopamine and tryptamine) as well as indole derivatives. Teuber tried to find model eactions to explain the biosynthesis of indole and isoquinoline alkaloids.[7,8]

Even though studies on the biosynthesis of the afore mentioned alkaloids exclude[9-11] the participation of **2**, Teuber´s scientific work resulted in a series of heterocyclic systems[12] (see Scheme I, below) that are related to alkaloids such as strychnine, yohimbine, ajmalicine and emetine, among others.[13]

Scheme I



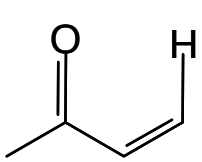
We review Teuber´s research results as well as reactions from other authors related with this subject obtained within the period 1960-2000 and confine mainly to the structure formulas of these reactions.

II. REACTIONS WITH ACETYLACETALDEHYDE DERIVATIVES

The dimethyl acetal (**3**) and enol ether (**4**) used in the following reactions gave rise to the same products.

A. KETOVINYLATIONS

Ketovinylation is named the coupling of a 3-buten-2-one-4-yl group (**5**) into a molecule of an organic compound. This reaction has already received much attention when performed with *β*-chlorovinyl methyl ketone (**6**).[14-16] The reaction with **3** and **4**, however, is more versatile and better suited for model reactions of biological interest.



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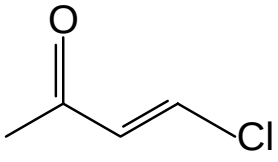

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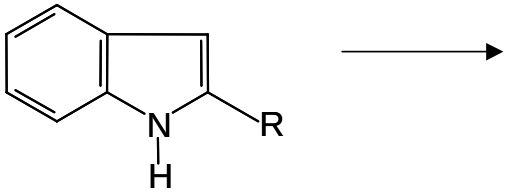
1. *C*- and *N*-ketovinylation of the indole ring system



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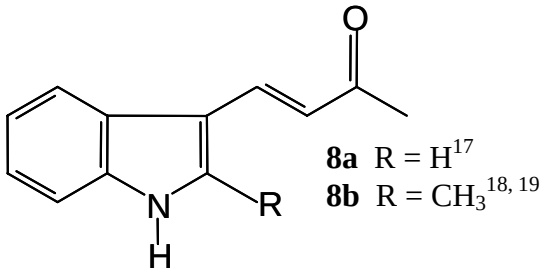
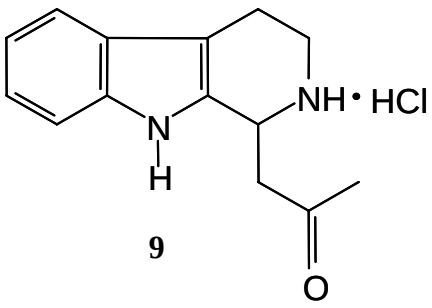


8a R = H[17]
8b R = CH_3[18, 19]

Noland[20] obtained **8b** by means of **6**, Teuber[18,19] by means of **3** and **4.**

A ketovinyl group can be created by ring opening. Ring opening[21] of tetrahydro-*β*-carboline (**9**) generates compound (**10**).



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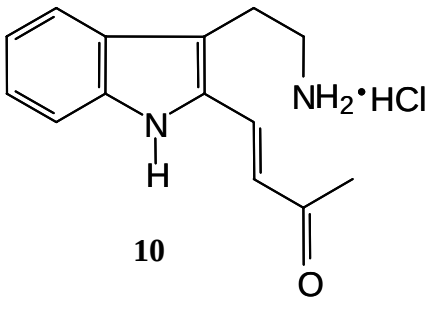
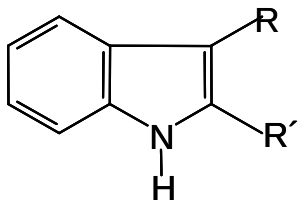


10

In the case of *β*-substitution of the indole ring system, the ketovinylation occurs on nitrogen, when the starting compound is stirred with conc. hydrochloric acid and 4,4-dimethoxy-2-butanone (**3**).



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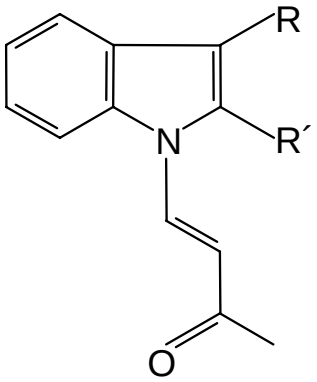
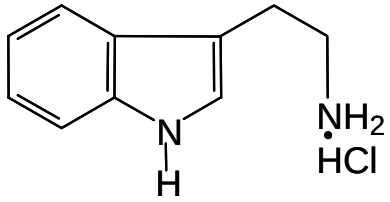


12a R = CH_3, R´ = H[18]
12b R = CH_3, R´= CH_3[18,22,23]
12c R = CH_2CN, R´= CH_3[23,24]
12d R = CH_2COOH, R´= CH_3[23,24]
12e R = CH_2 $COOCH_3$, R´= CH_3[23,24]
12f R = CH_2CONH_2, R´= CH_3[23,24]



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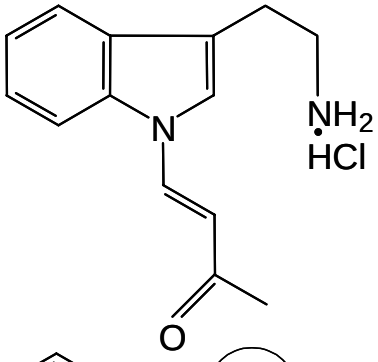
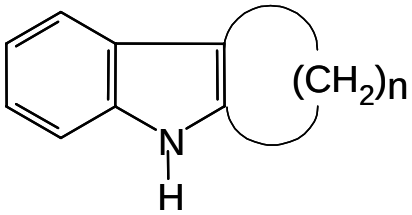


14[17,21,25]



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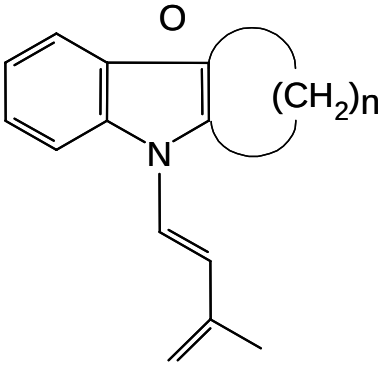
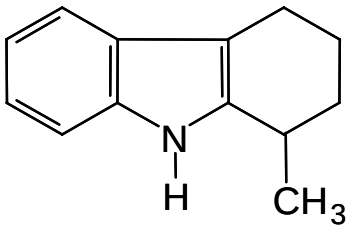


16a n = 3[26,27]
16b n = 4[17,18,22,26,28]
16c n = 5[17,18,22,26,28]
16d n = 6[17,18,22,26,28]



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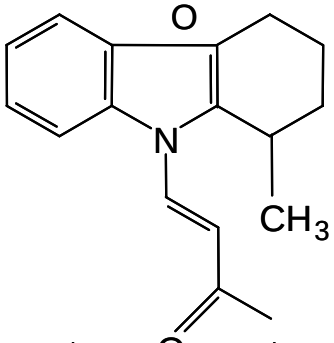
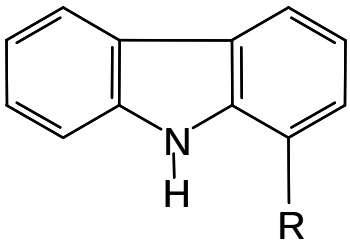


18[17,18]



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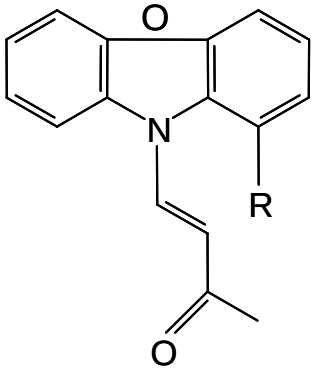
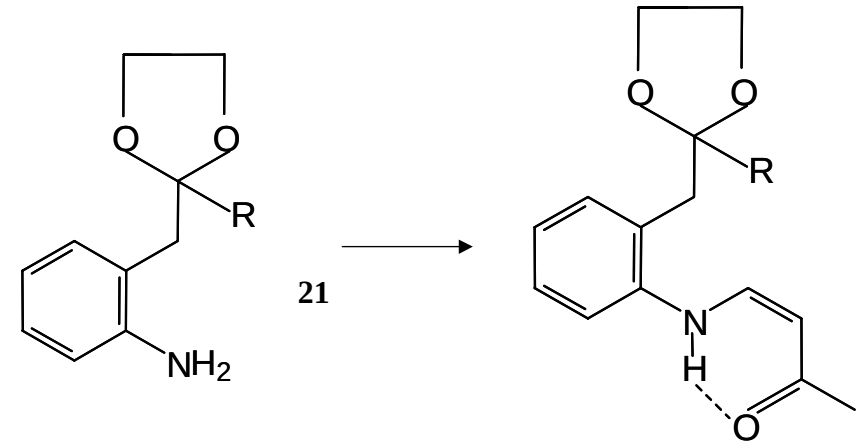


20a R = H[18]
20b R = OH[18]

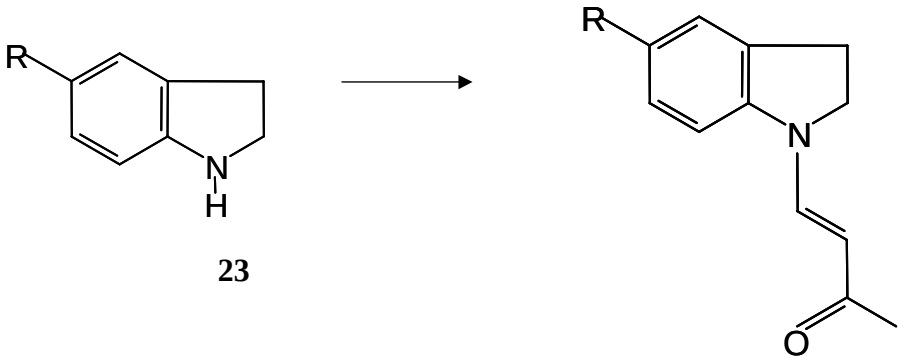
Regarding the formation of *N*-indolobutenone from unsubstituted indole, see reference 4 (p. 83).

2. *N*-ketovinylation of aromatic and biogenic amines



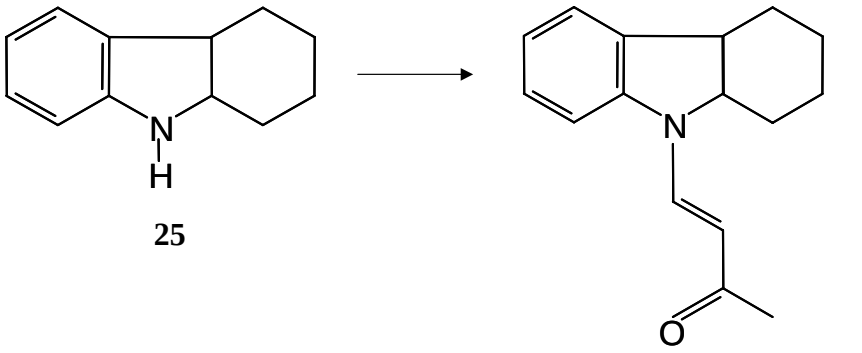
21

22a R = CH_3[19,29]
22b R = CH_2CH_3[19,29]
22c R = $CH(CH_3)_2$[19,29]
22d R = $(CH_2)_3CH_3$[19,29]



23

24a R = H[18]
24b R = $COCH_3$[18]



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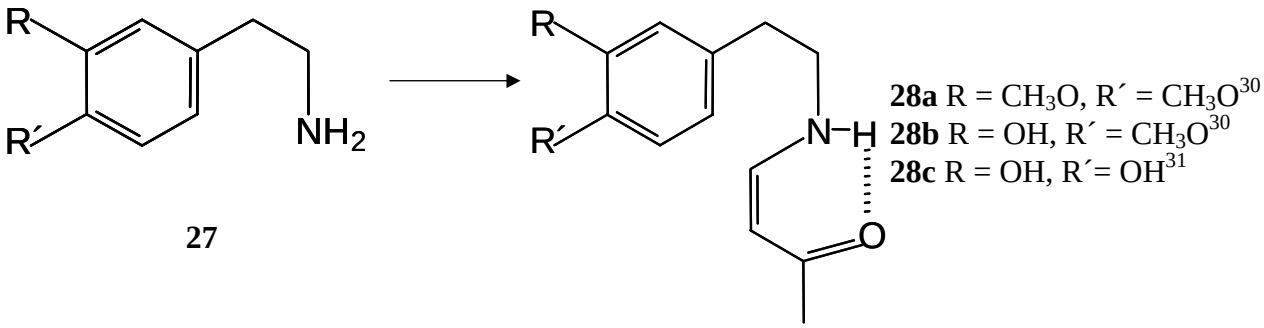
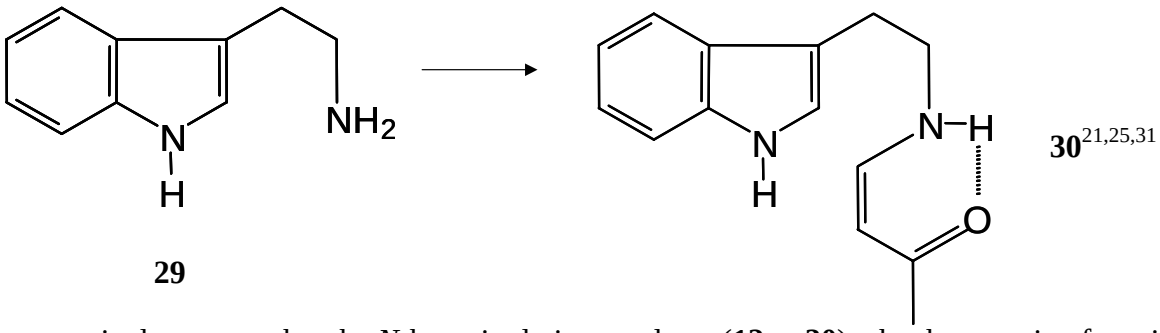
26[18]



27

28a R = CH_3O, R´ = CH_3O[30]
28b R = OH, R´ = CH_3O[30]
28c R = OH, R´= OH[31]



29 **30**[21,25,31]

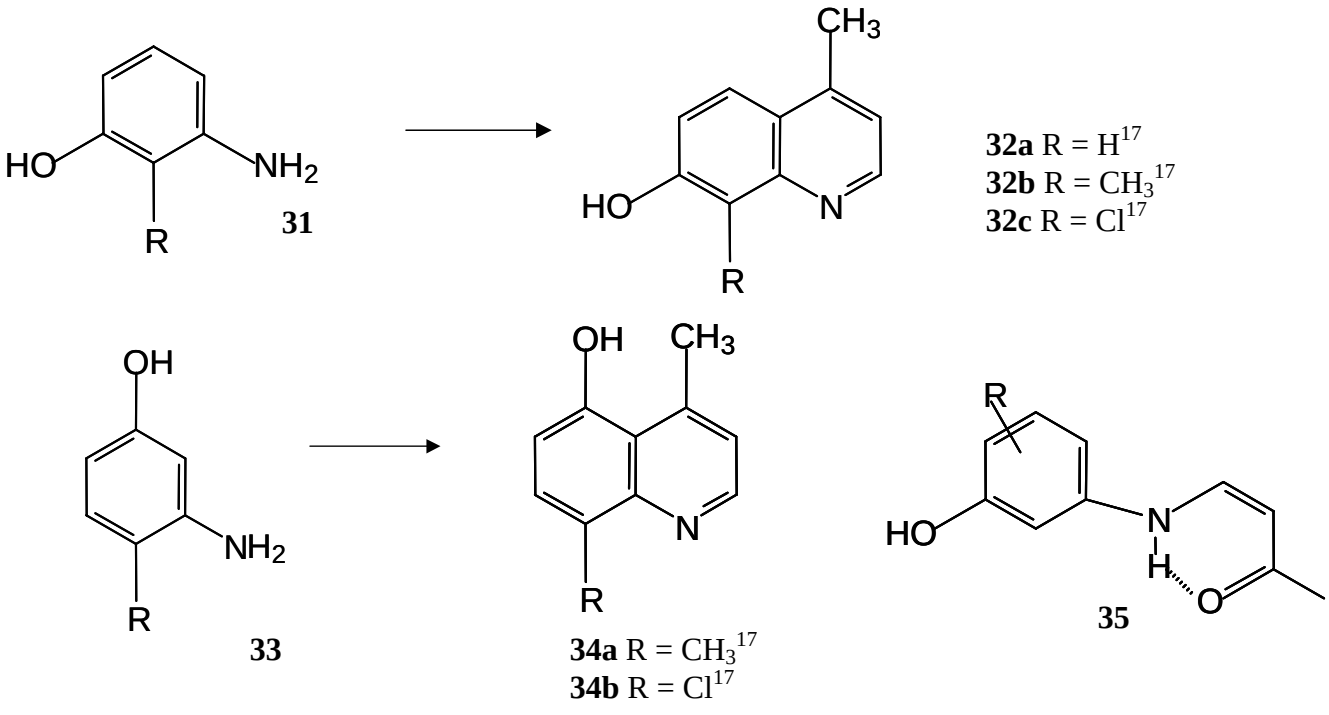
The spectroscopic data prove that the *N*-ketovinylation products (**12** to **30**) take the enamine form instead of an imine.[32,33]

The ketovinylated indole compounds (**8** to **20**) have a *trans* double bond, while the aromatic amine derivatives (**22**) and those of biogenic amines (**28**, **30**) have a *cis* double bond, since in the last two families of compounds the NH can form a hydrogen bond to the carbonyl oxygen.[34] In indoline derivatives (**24**, **26**) the lack of the hydrogen-bond-donating NH favors a *trans* double bond.

B. FORMATION OF HETEROCYCLES

1. Quinolines

meta-Hydroxy-substituted anilines yield compounds (**32** and **34**), *via* an anilinobutenone intermediate[17] of the general formula (**35**), without adding a strong acid.



31

32a R = H[17]
32b R = CH_3[17]
32c R = Cl[17]

33

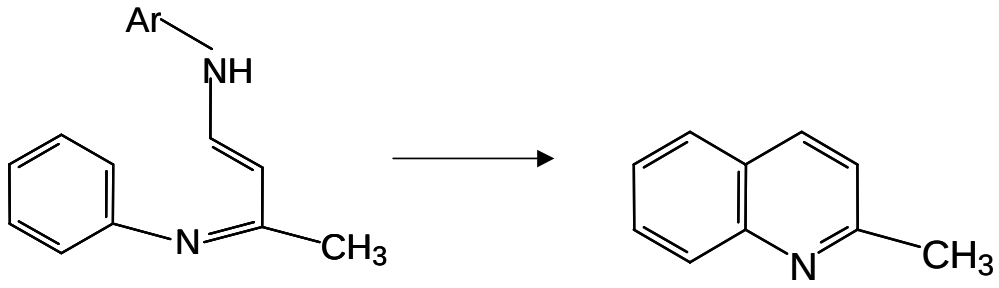
34a R = CH_3[17]
34b R = Cl[17]

35

When starting from unsubstituted aniline and from acetylacetaldehyde derivatives the process stops at the

anilinobutenone stage, without cyclization.[35] Thus, cyclization of anilinobutenones requires an electron-donating *meta* substituent and a free position *ortho* to the amino group. Anilinobutenones derived from *m*-aminophenol ethers cyclize only in the presence of strong acids.[36]

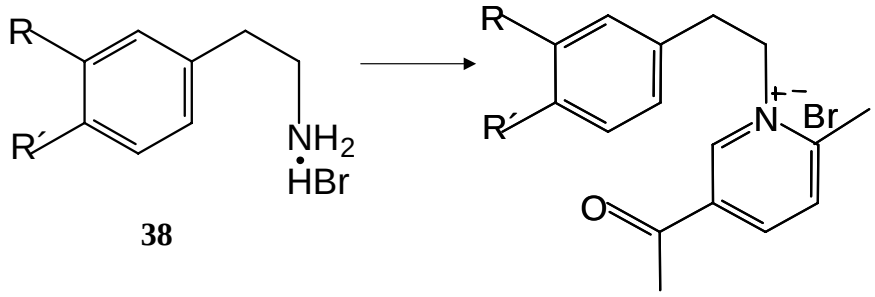
According to Franke *et al.*,[3] the reaction of *β*-chlorovinyl methyl ketone (**6**) with aniline is very interesting. When using a 1:1 molar ratio they obtain the corresponding anilinobutenone (**35**), but when using a 1:2 molar ratio the dianiline derivative (**36**) is formed, which in turn cyclizes to yield the quinoline (**37**) by adding sulfuric acid.



36 **37**

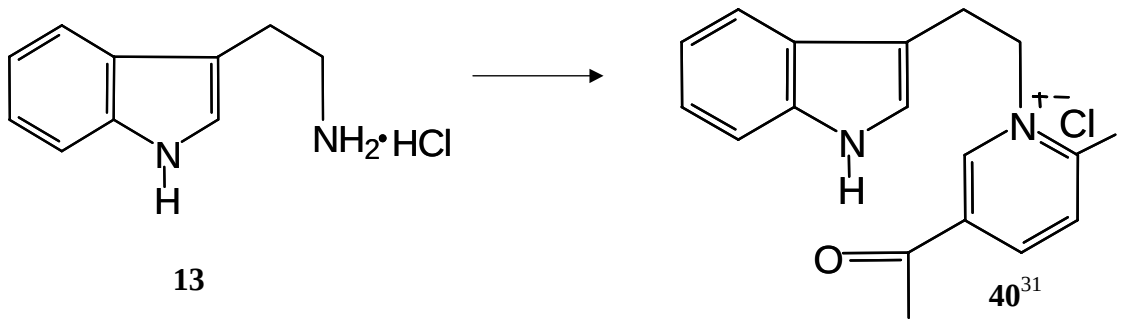
2. Pyridinium salts

In these reactions two molecules of acetylacetaldehyde are involved.



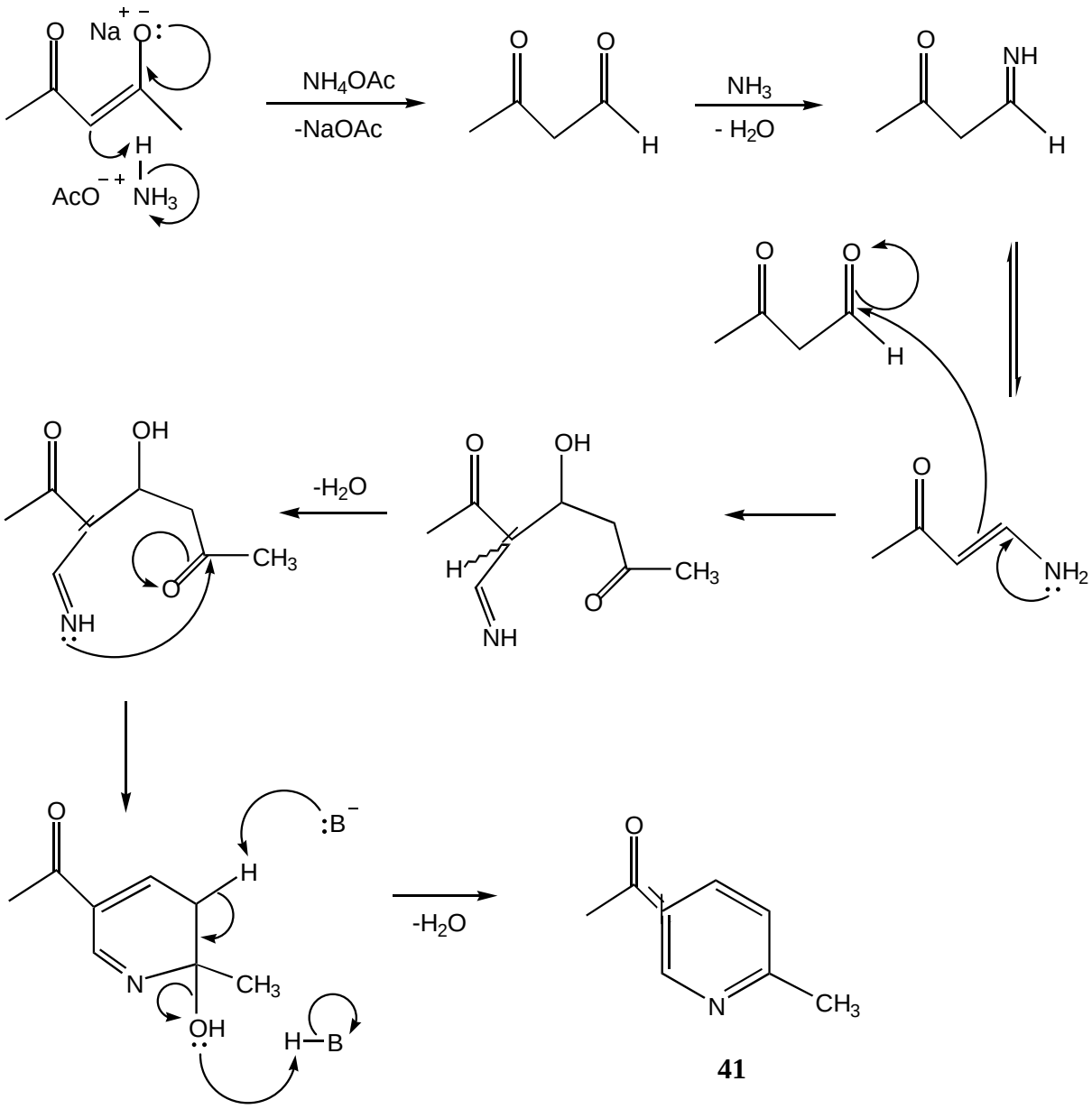
38

39a R = H, R´= H[17,37]
39b R = CH_3O, R´ = CH_3O[17,37,38]
39c R = OH, R´= CH_3O[30]
39d R = OH, R´= OH[31,38-40]



13 **40**[31]

The pyridinium salts (**39** and **40**) result from the corresponding biogenic amines. Their formation follows the mechanism proposed[41] by Benary and Psille for the formation of 2-methyl-5-acetylpyridine (**41**). Here the carbanion of the primarily formed aminobutenone attacks the aldehyde carbonyl of the second acetylacetaldehyde as the key step for the following water elimination and ring closure.



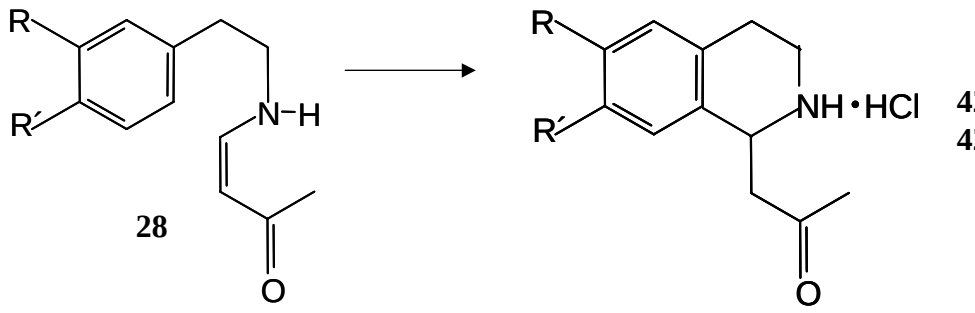
41

It has been possible to isolate the corresponding intermediate enamines (**28**, **30**) to later generate the pyridinium salts.

38a and **b** yield the corresponding pyridinium salts (**39a** and **b**) and do not cyclize to yield benzo-quinolizines.[42] However, their analogues (**38c** and **d**) besides the formation of a pyridinium salt (**39c** and **d**) also do cyclize to yield benzoquinolizines, although through a different mechanism and yielding a 3,4-substitution pattern (instead 2,5-) on the resulting pyridine ring (see below).

Tryptamine hydrochloride (**13**) yields both a pyridinium salt (**40**) and the corresponding indoloquinolizine.

3. Tetrahydroisoquinolines



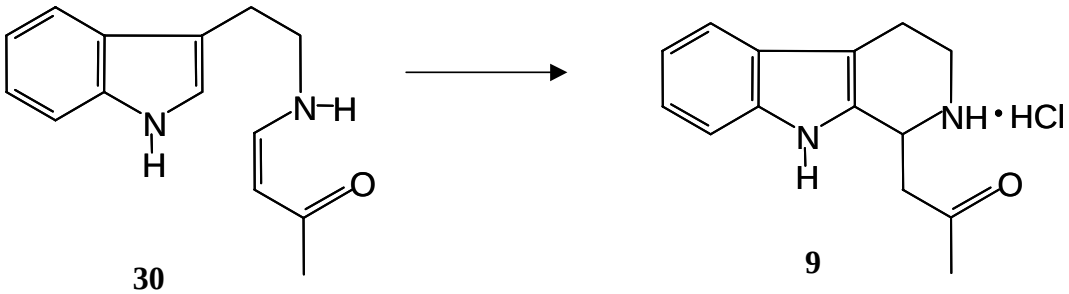
28

42a R = OH, R´ = CH_3O[30]
42b R = OH, R´ = OH[31]

Compounds (**42**) can be obtained directly from the corresponding aminobutenones. If R and R' are hydrogen atoms or methoxy groups the aminobutenone (**28**) does not undergo a Pictet-Spengler cyclization to yield the corresponding tetrahydroisoquinoline (**42**), because none of the groups present in the molecule can induce charge on the aromatic ring to localize electron in the necessary position to achieve reaction.

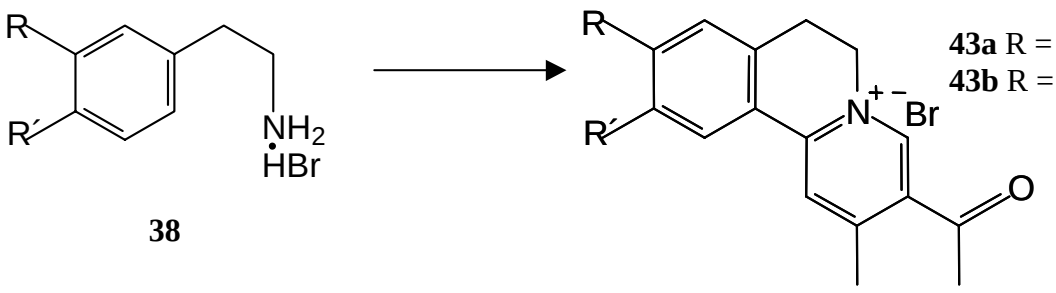
4. Tetrahydro-*β*-carbolines

Tetrahydro-*β*-carboline (**9**) is isolated as a by-product of the different reactions of tryptamine hydrochloride with acetylacetaldehyde derivatives.[17,21,38,43-45] It is obtained in high yield[21] from aminobutenone (**30**).



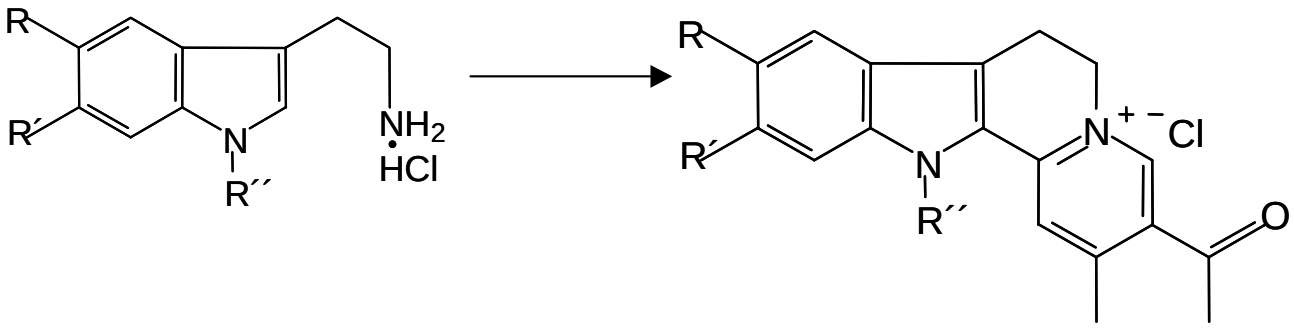
30 **9**

5. Benzoquinolizinium and indoloquinolizinium salts



38

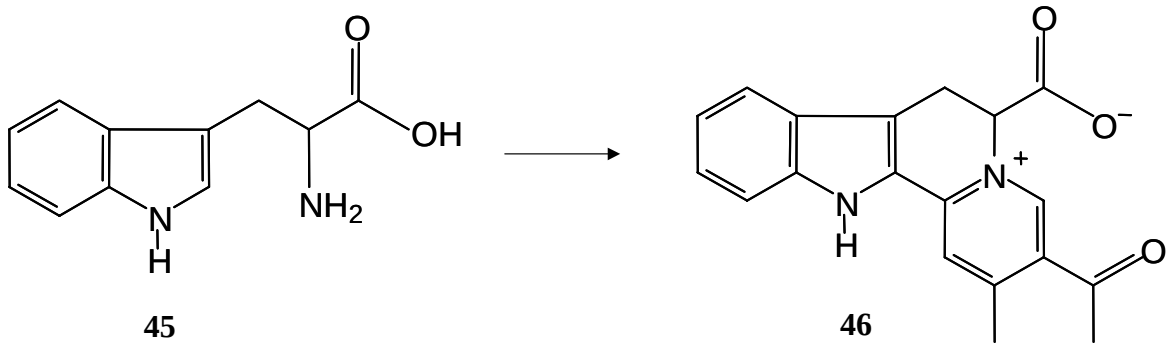
43a R = OH, R´ = CH_3O[30]
43b R = OH, R´ = OH[31,38, 40]



44a R = H, R´ = H, R´´ = H [17,43-46]
44b R = H, R´ = H, R´´ = CH_3 [43,44]
44c R = H, R´ = CH_3O, R´´ = H [43,44]
44d R = CH_2CH_3, R´ = H, R´´ = H [44]

The biogenic amines generate their quinolizinium salts (**43**, **44**) *via* their aminobutenones (**28**, **30**). These undergo Pictet-Spengler cyclization[47] to generate the tetrahydroisoquinolines (**42**) or the tetraydro-β-carboline (**9**), respectively, before forming their quinolizinium salts.

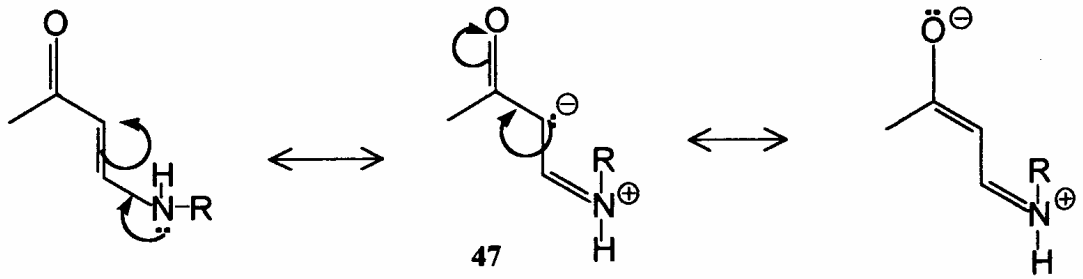
The aminoacid tryptophane (**45**) behaves as its amine and generates[48] the indoloquinolizinium salt (**46**).



45 **46**

The 3,4-substitution pattern observed on the pyridinium ring of the quinolizinium salts excludes the initial formation of a pyridinium salt (with a 2,5-substitution pattern) before the cyclization that yields ring B of the benzoquinolizinium system or ring C of the indoloquinolizinium system.

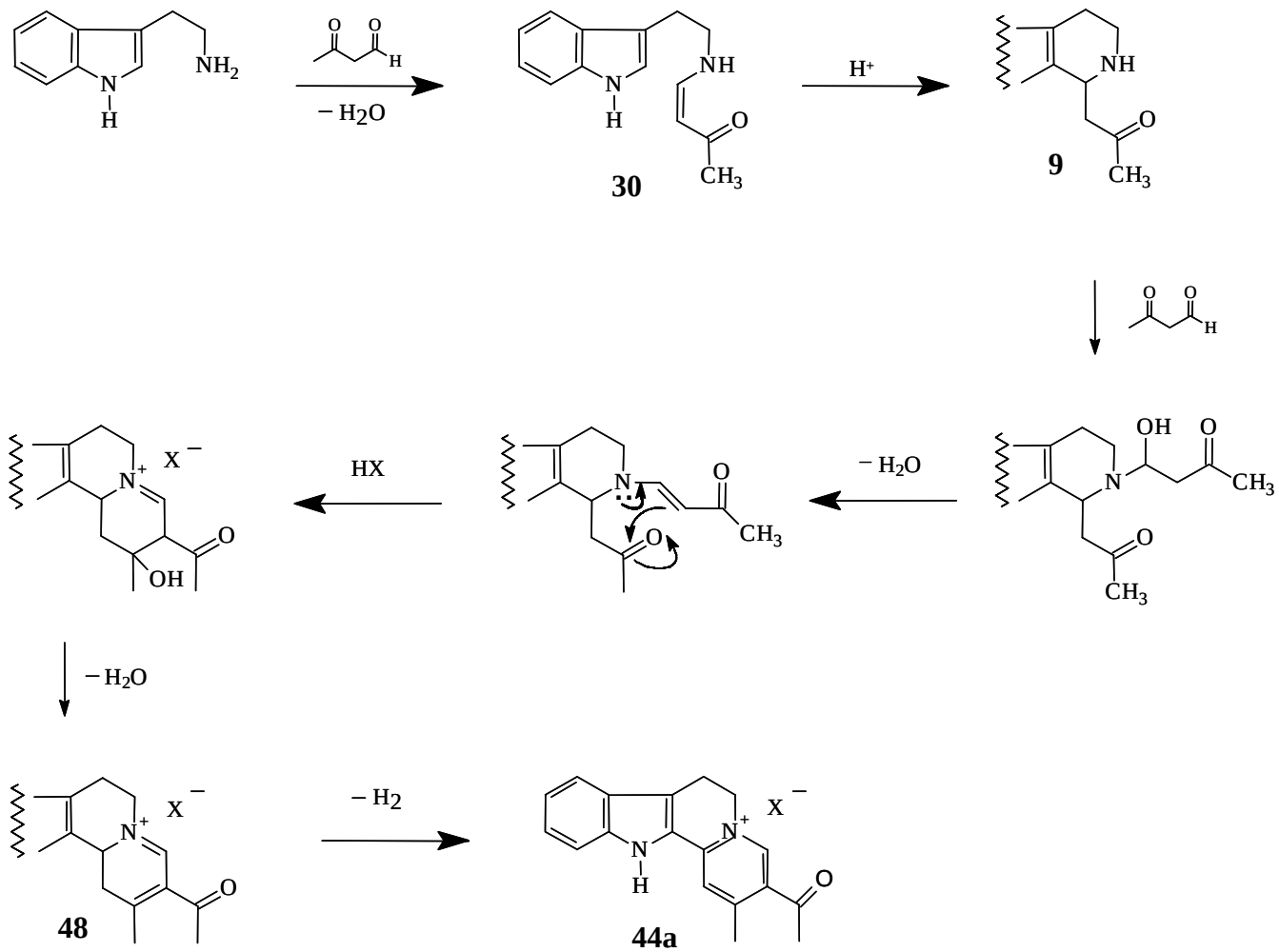
One can explain the different substitution patterns of the pyridinium and quinolizinium salts on a mechanistic basis. In both cases an aminobutenone is formed that yields a carbanion like **47**, stabilized by extended conjugation.



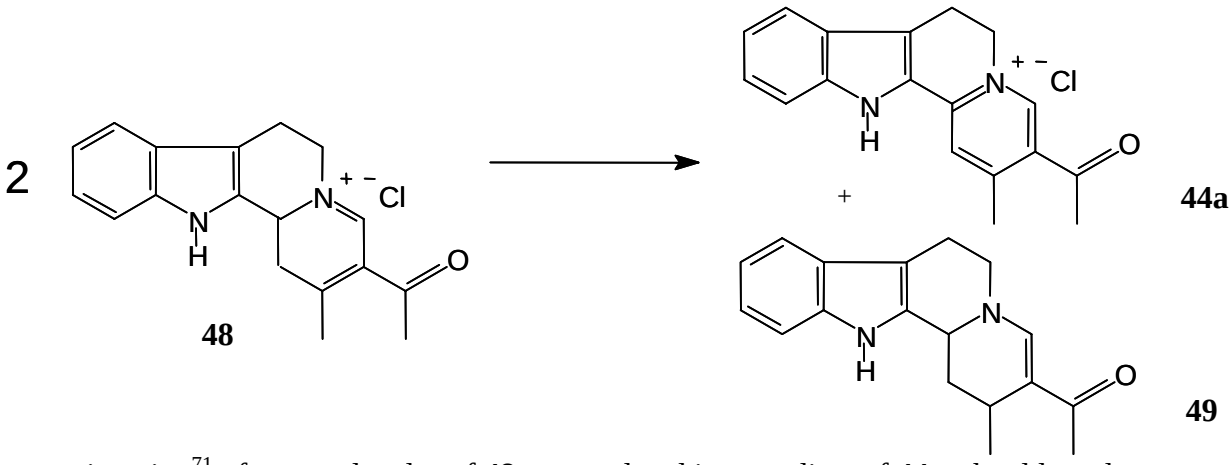
47

This carbanion, instead of the lone pair on nitrogen, attacks the most reactive carbonyl group in the second acetylacetaldehyde molecule participating in the reaction; that is the aldehyde group. This results in a 2,5-substitution pattern on the pyridinium salts (see above).

Both, tetrahydroisoquinolines and tetrahydro-*β*-carbolines - generated through a Pictet-Spengler reaction on the corresponding aminobutenones - fail to form a sufficiently stabilized carbanion. In these cases the lone pair on nitrogen attacks the aldehyde carbonyl group on the second molecule of acetylacetaldehyde giving rise to the 3,4-substitution pattern on the pyridine ring formed. The formation of indolo-quinolizinium salt (**44a**) illustrates this.

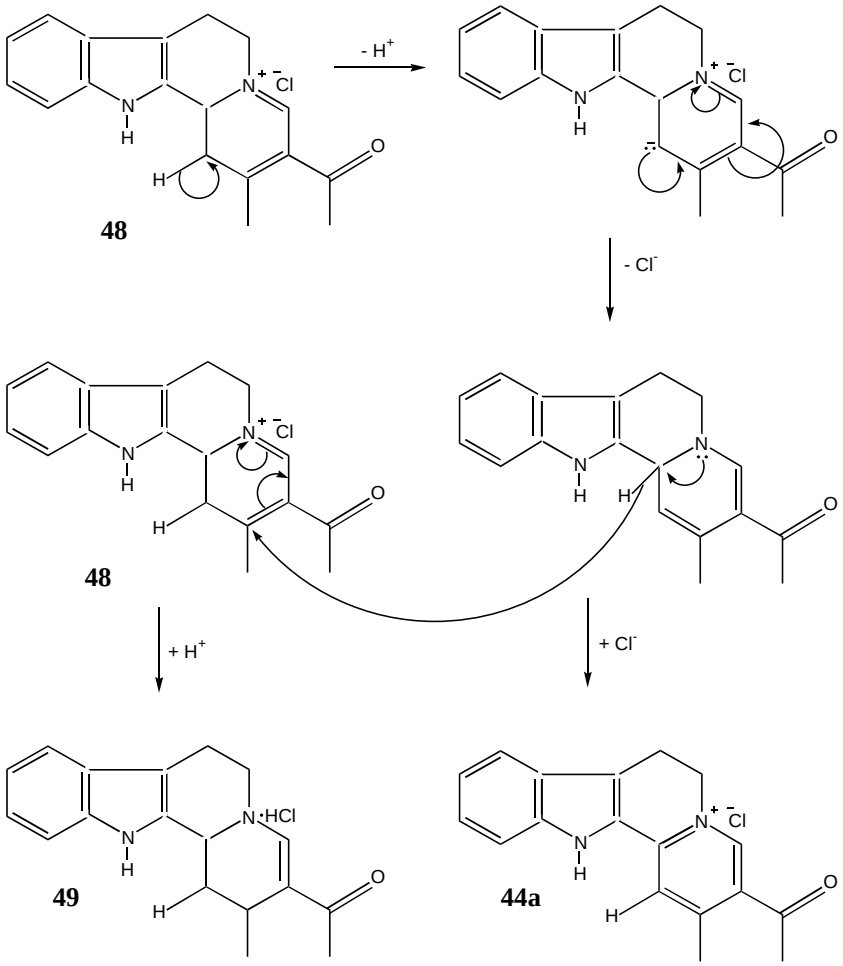


We emphasize that the formation of pyridinium salts from one amine molecule and two molecules of acetylacetaldehyde eliminates three molecules of water, while the formation of the quinolizinium salts requires the elimination of an additional hydrogen molecule. For this reason, we postulate a final disproportionation[71] step in the formation of the quinolizinium salts. Actually **44a** was isolated with a 38% yield and, in the same run, tetrahydropyridine (**49**) was isolated with a 12% yield.



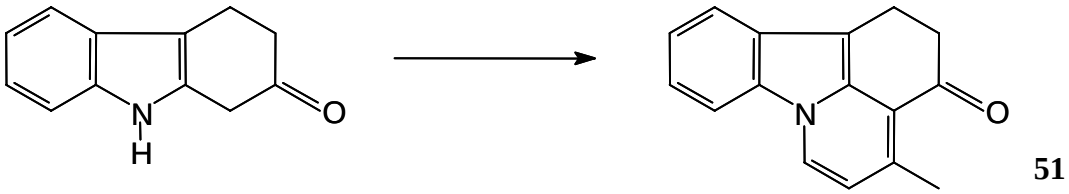
A disproportionation[71] of two molecules of **48**, a postulated intermediate of **44a**, should produce equimolar quantities of the indoloquinolizinium salt and its analogue (**49**) with a tetrahydropyridine ring. Since the yield is not 1:1 (38% and 12% respectively), we assume that compound (**49**) undergoes further decomposition. The addition of a strong oxidizer (*o*-chloranil) to the reaction mixture of tryptamine hydrochloride with acetylacetaldehyde, increases the yield of **44a** from 38% to 69%, and it is no more possible to isolate compound (**49**).

Our postulated mechanism implies the formal transfer of a hydrogen molecule between two molecules of **48** as shown:



6. Other heterocycles

The tetracyclic compound (**51**) forms in the reaction of 2-ketotetrahydrocarbazole (**50**), with several derivatives of acetylacetaldehyde.[17,18,72-74]

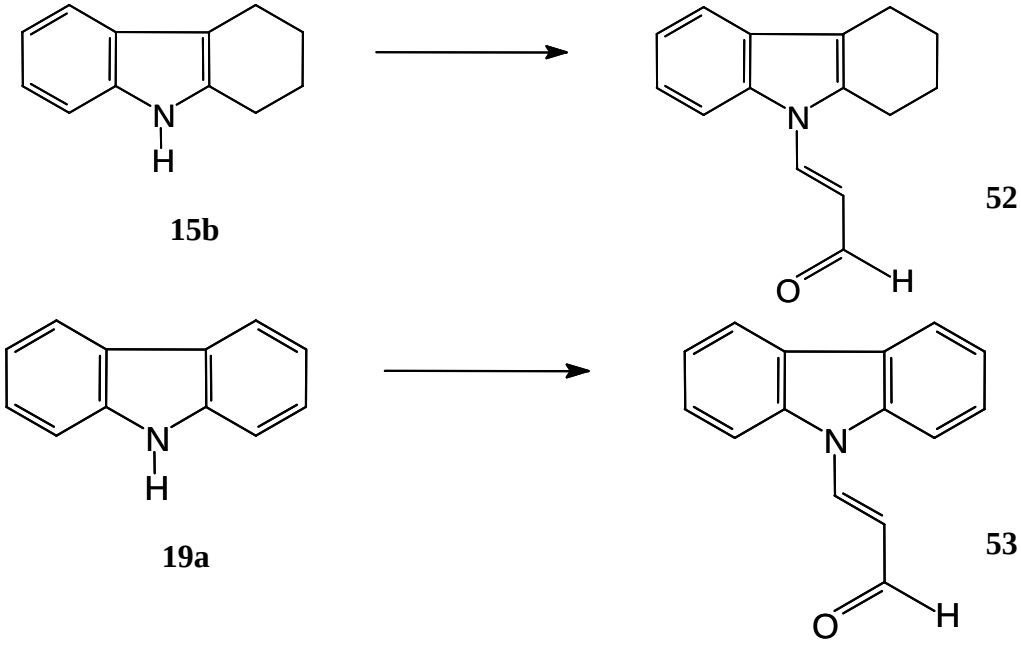


50 **51**

III. REACTIONS WITH OTHER β-DICARBONYL COMPOUNDS

1. With malonic dialdehyde derivatives

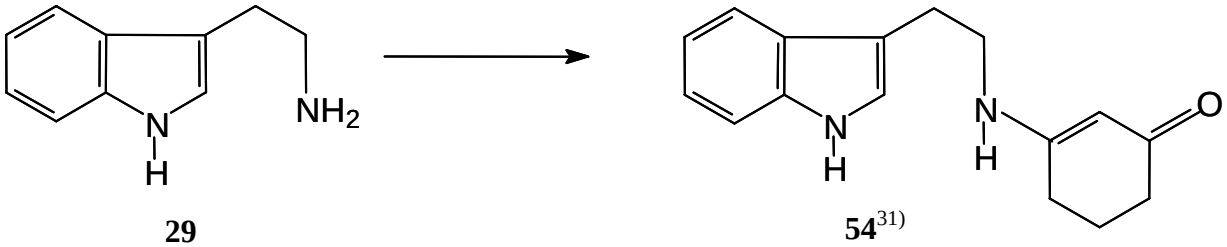
Similar to acetylacetaldehyde the malonic dialdehyde, in form of its triethyl acetal enol ether,[18] reacts with α, β-substituted indole compounds.



15b **52**

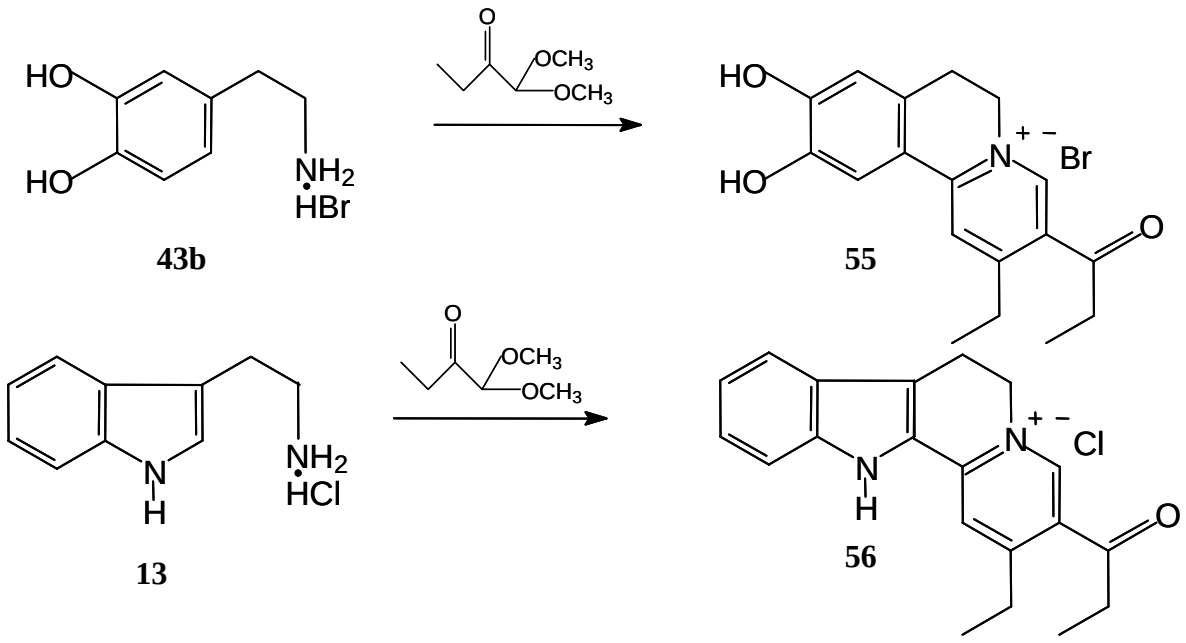
19a **53**

2. With dihydroresorcinol



29 **54**[31)]

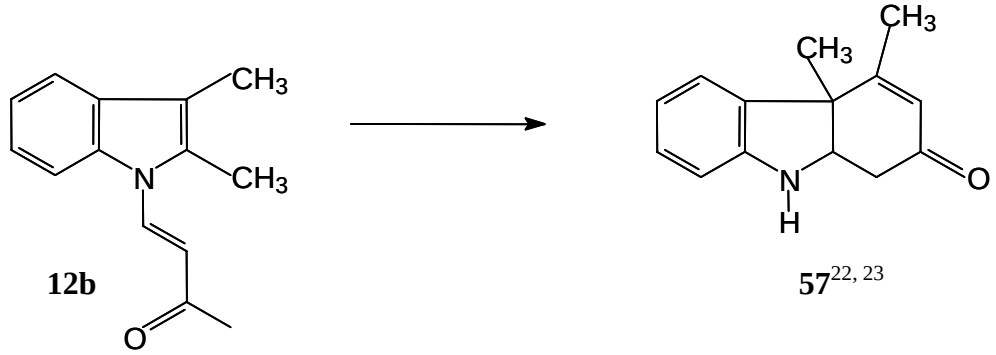
3. With 1,1-dimethoxypentan-3-one



The formation of compounds (**55**) and (**56**) demonstrates the general applicability of the reactions between *β*-dicarbonyl compounds and biogenic amines, providing a useful reaction for the syntheses of benzoquinolizines and indoloquinolizines as possible intermediates in the synthesis of isoquinoline and indole alkaloids and their analogues.

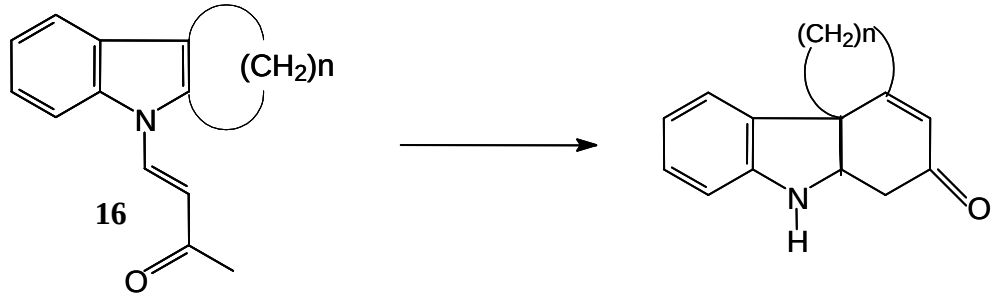
IV. FURTHER TRANSFORMATIONS OF THE OBTAINED HETEROCYCLES

A. REARRANGEMENT AFTER *N*-KETOVINYLATION ON THE INDOLE SYSTEM



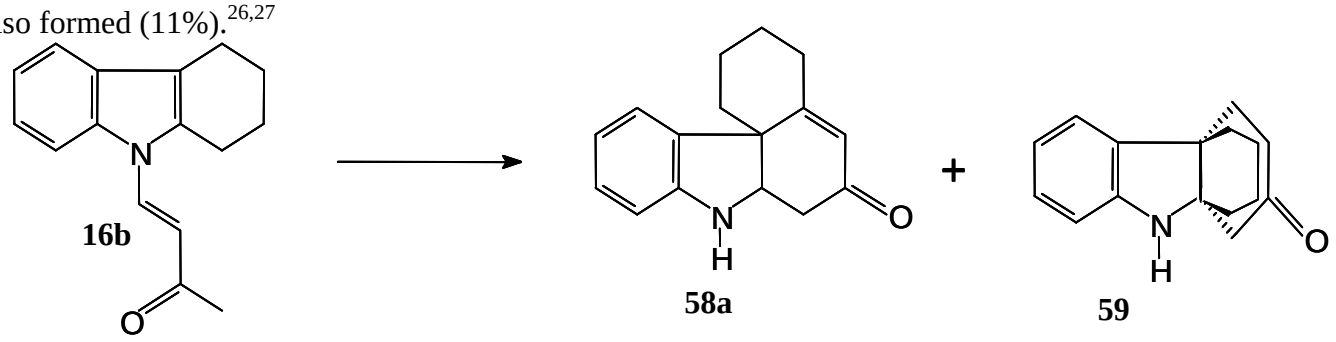
57[22, 23]

The rearrangement is also possible if there is a ring attached to the indole nucleus.[22,23,26-28,49]

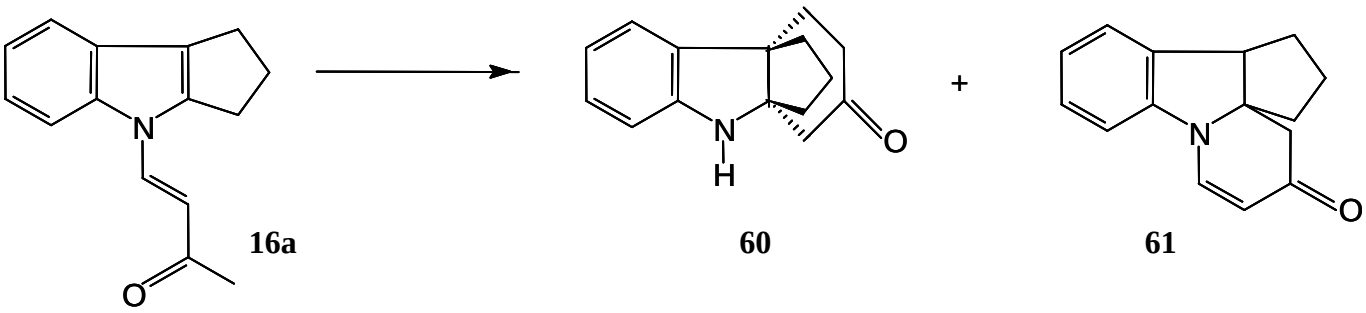


58a n = 4
58b n = 5
58c n = 6

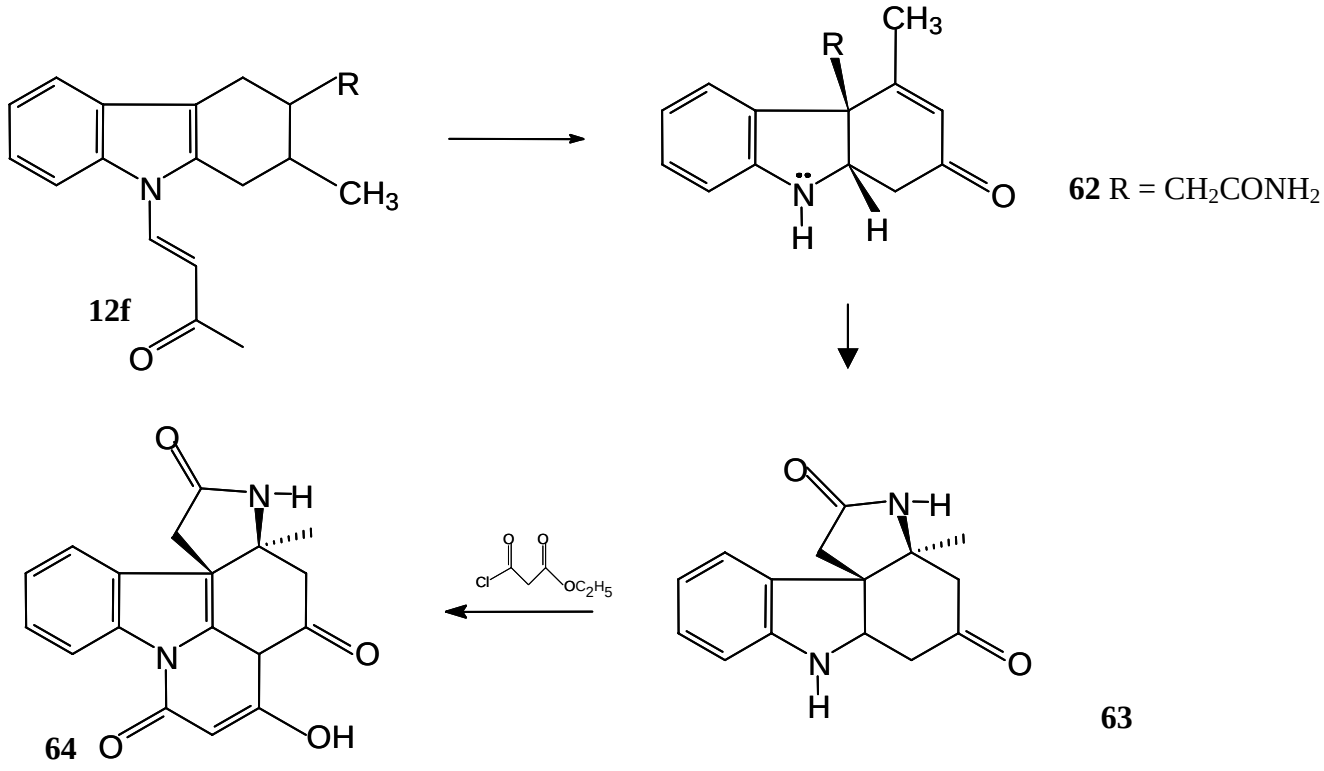
In the case of tetrahydrocarbazole (**16b**), besides the rearrangement product (71%), a propellane (**59**) is also formed (11%).[26,27]



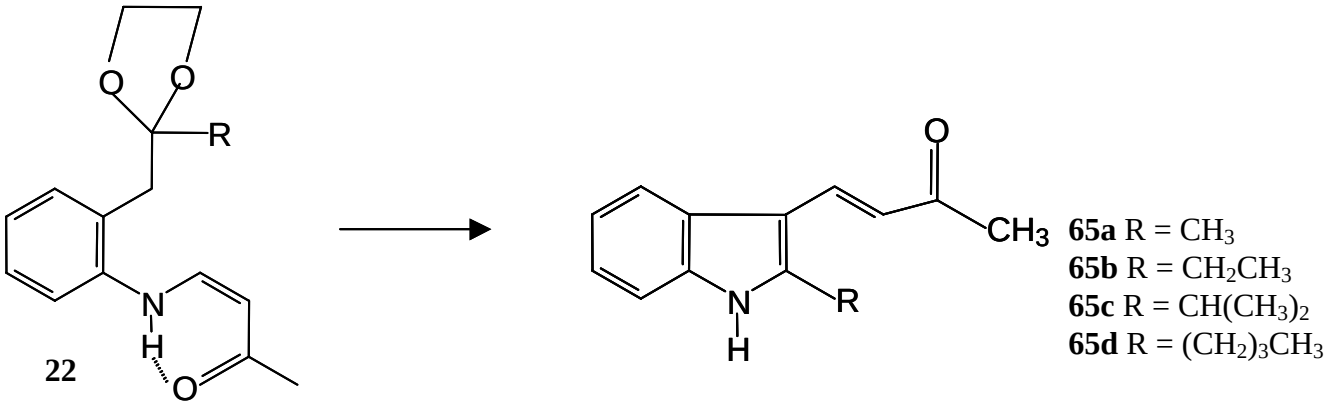
With cyclopentindole only the propellane (**60**) and a cyclization product (**61**) are isolated (low yield).[26,27]



Starting from the rearranged product (**62**) the synthesized pentacycle (**64**) can be an intermediate in the synthesis of indole alkaloids related to strychnine.[23,24]

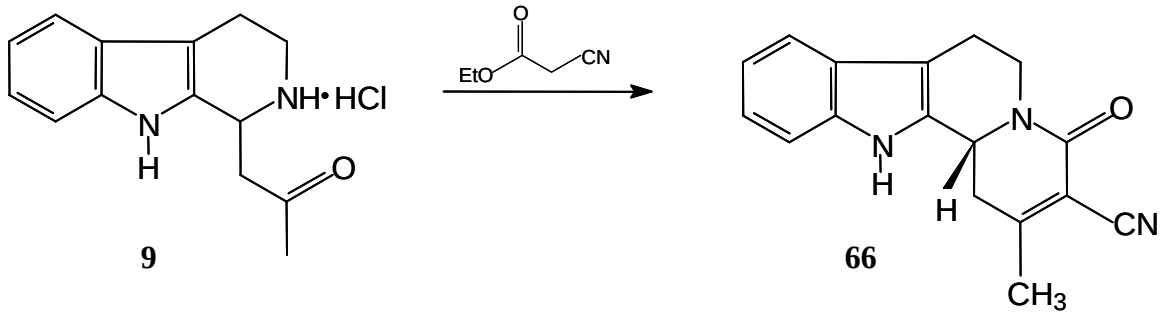


B. INDOLE FORMATION AFTER *N*-KETOVINYLATION OF AROMATIC AMINES[19,29]

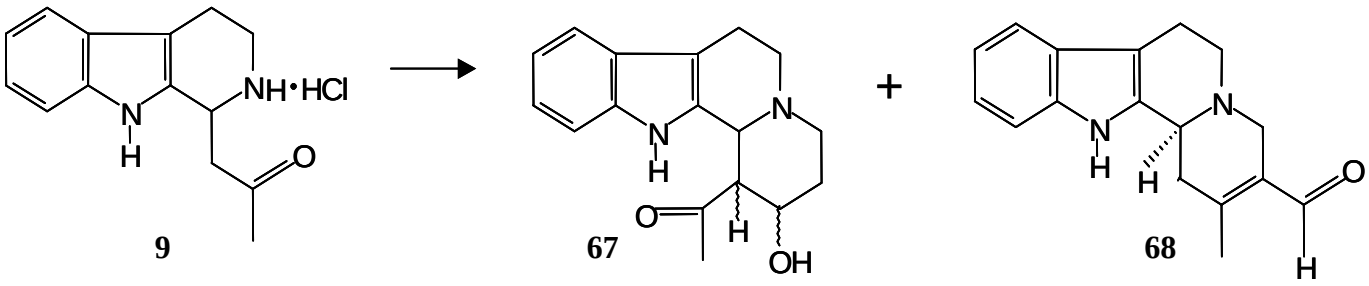


C. TRANSFORMATIONS OF TETRAHYDRO-*β*-CARBOLINES

The tetrahydro-*β*-carboline (**9**) also can be reacted with another molecule of acetylacetaldehyde to form indoloquinolizine (**44a**) (see above) but also with other *β*-dicarbonyl compounds to form quinolizidines. With carbethoxyacetonitrile the tetracyclic compound (**66**) (*cis*-quinolizidine) is formed.[21,50]

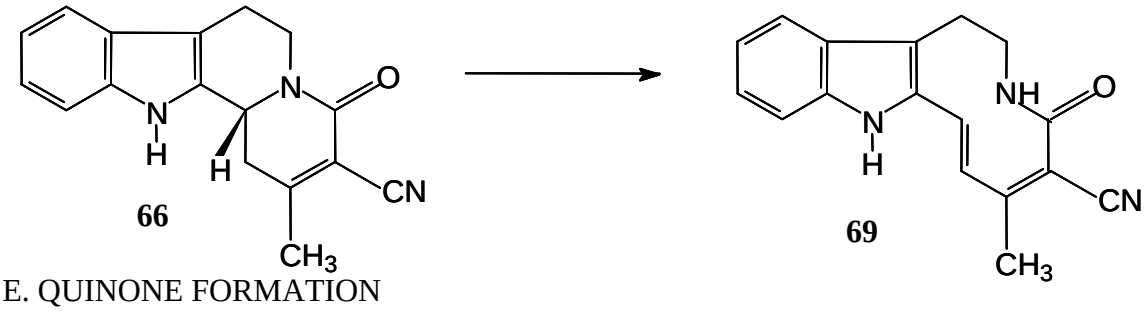


Laronze *et al.* studied the reaction of compound (**9**) with acrolein and obtained a mixture of ketols with the general structure (**67**) (19%) and the aldehyde (**68**) (18%) with *trans* configurated quinolizidine system.[51]



D. RING OPENING IN TRICYCLIC AND TETRACYCLIC SYSTEMS

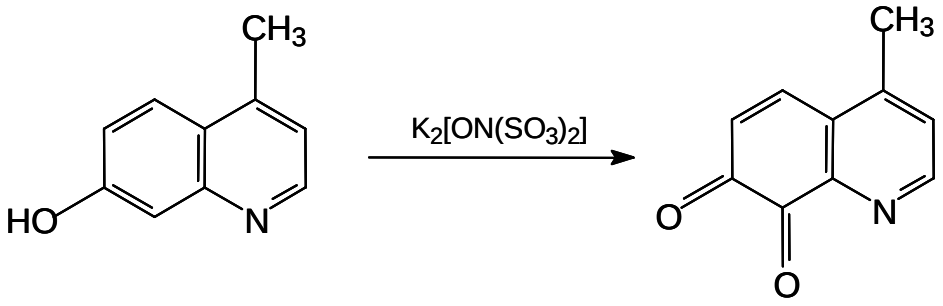
Similar to the ring opening of **9** to **10**, a *retro*-Pictet-Spengler reaction[21,50] can be also observed with the tetracyclic system (**66**).



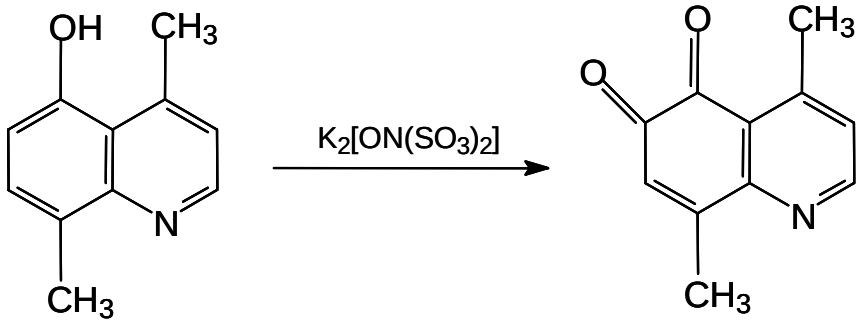
66 **69**

E. QUINONE FORMATION

5- And 7-hydroxyquinolines prepared by the afore mentioned method[17] allow the preparation of the corresponding *o*-quinones by Fremy-salt oxidation.



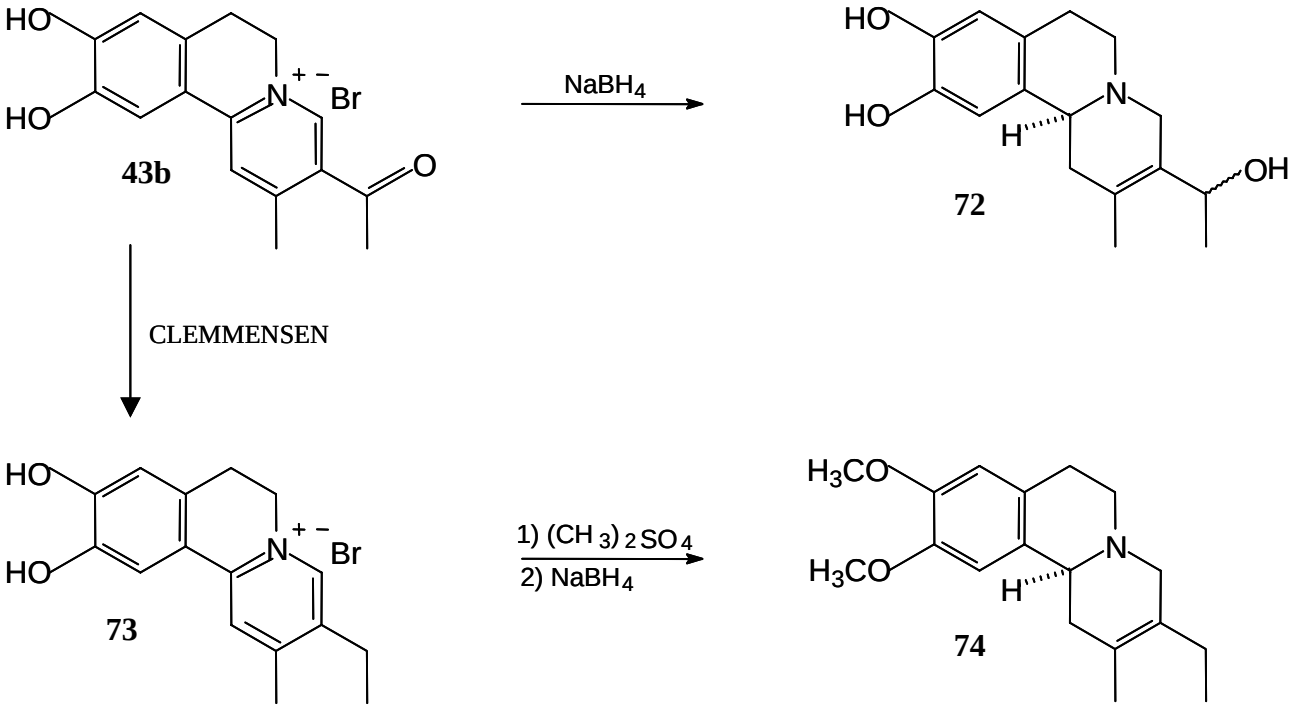
32a **70**



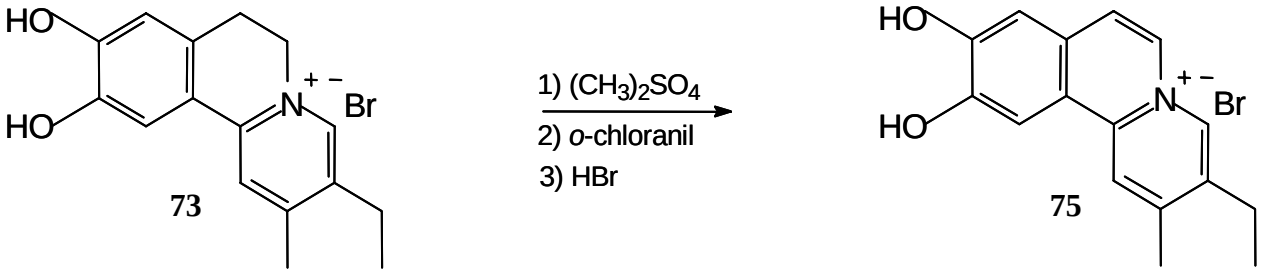
34a **71**

F. TRANSFORMATIONS OF BENZOQUINOLIZINIUM SALTS

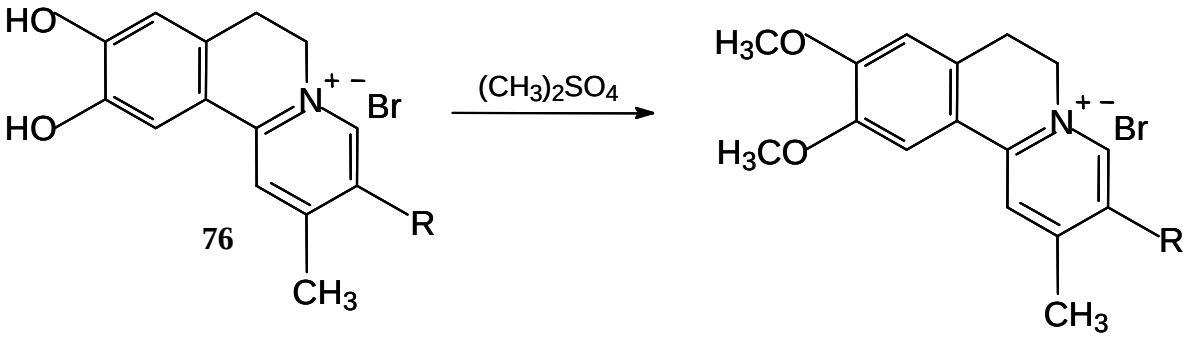
1. Reductions[40,52]



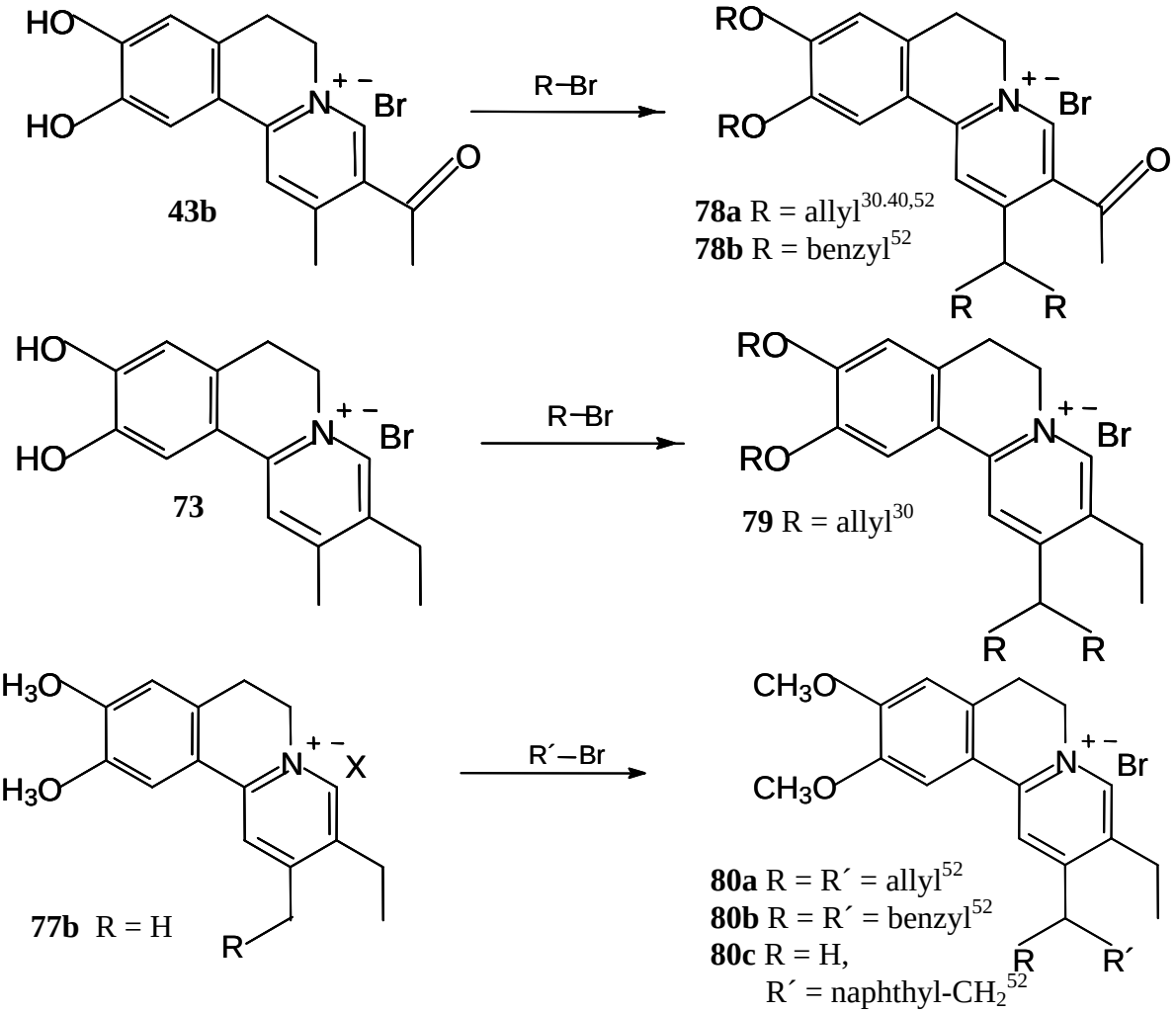
2. Oxidations[40,52]



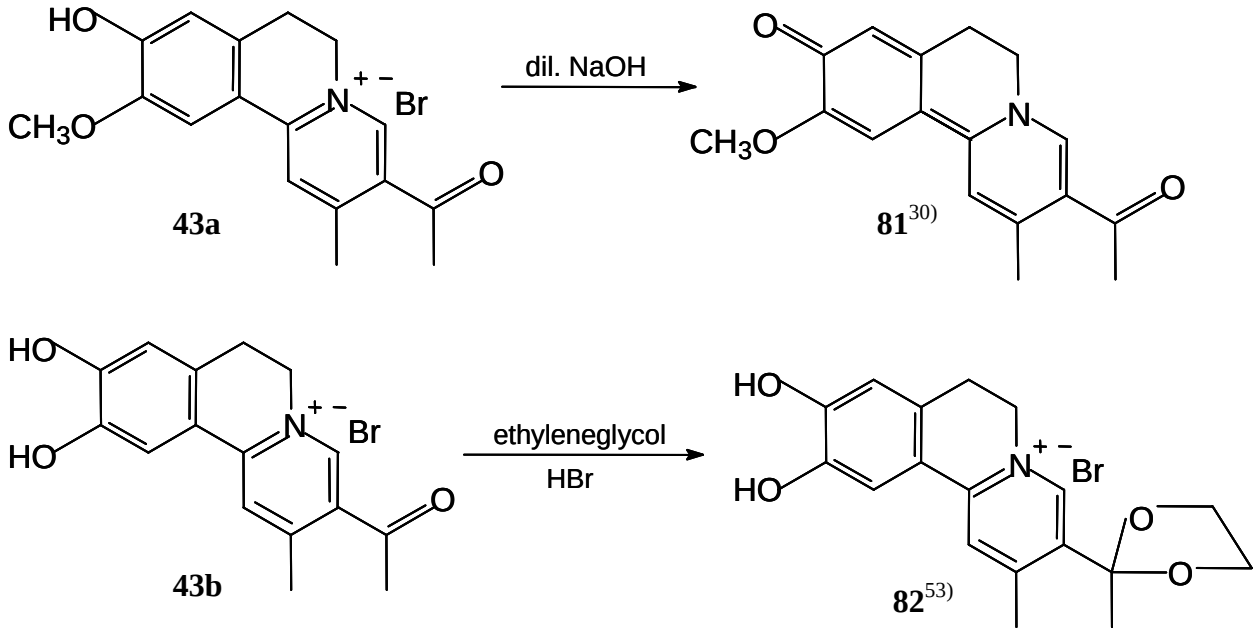
3. Alkylations



77a R = $COCH_3$[40,52]
77b R = CH_2CH_3[40,52]

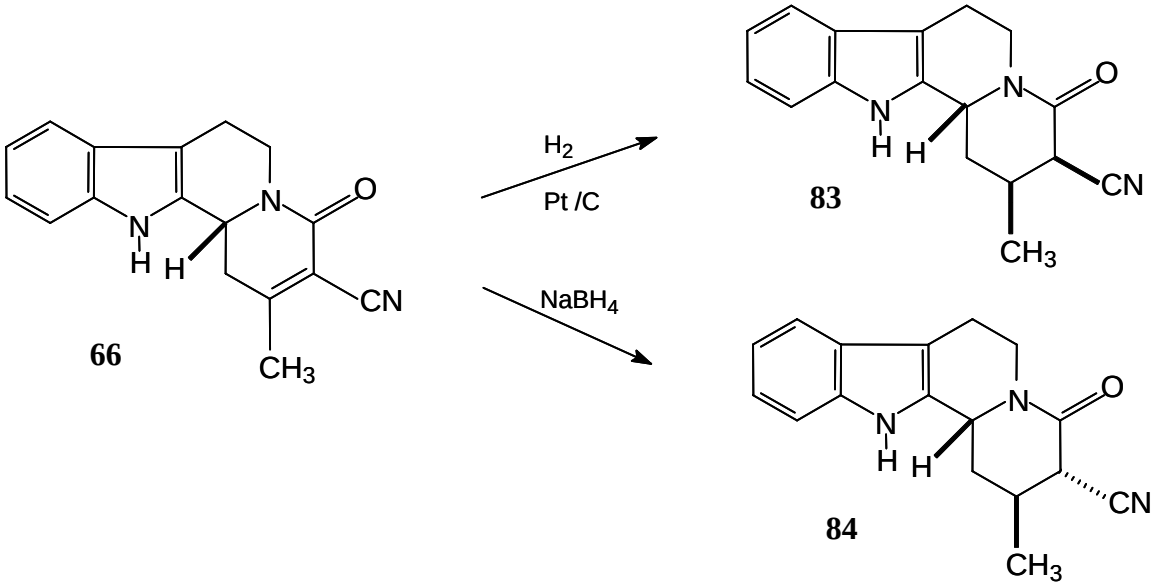


4. Miscellaneous transformations



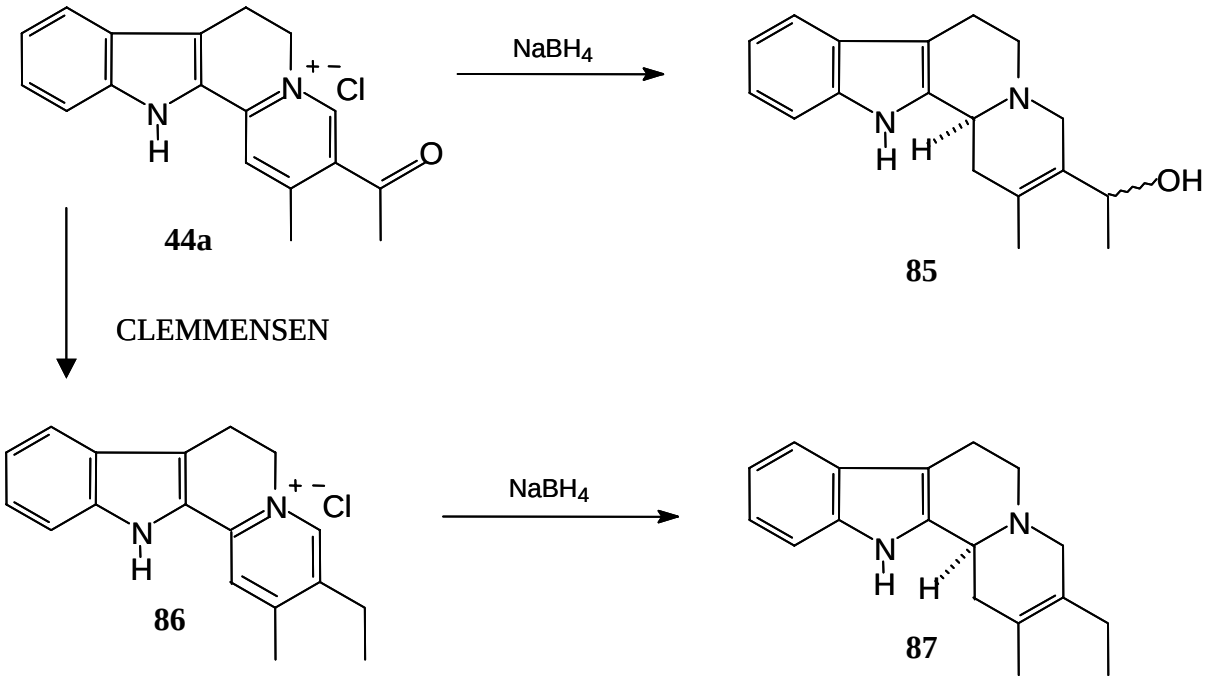
G. TRANSFORMATIONS OF INDOLOQUINOLIZINIUM SALTS

1. Reductions



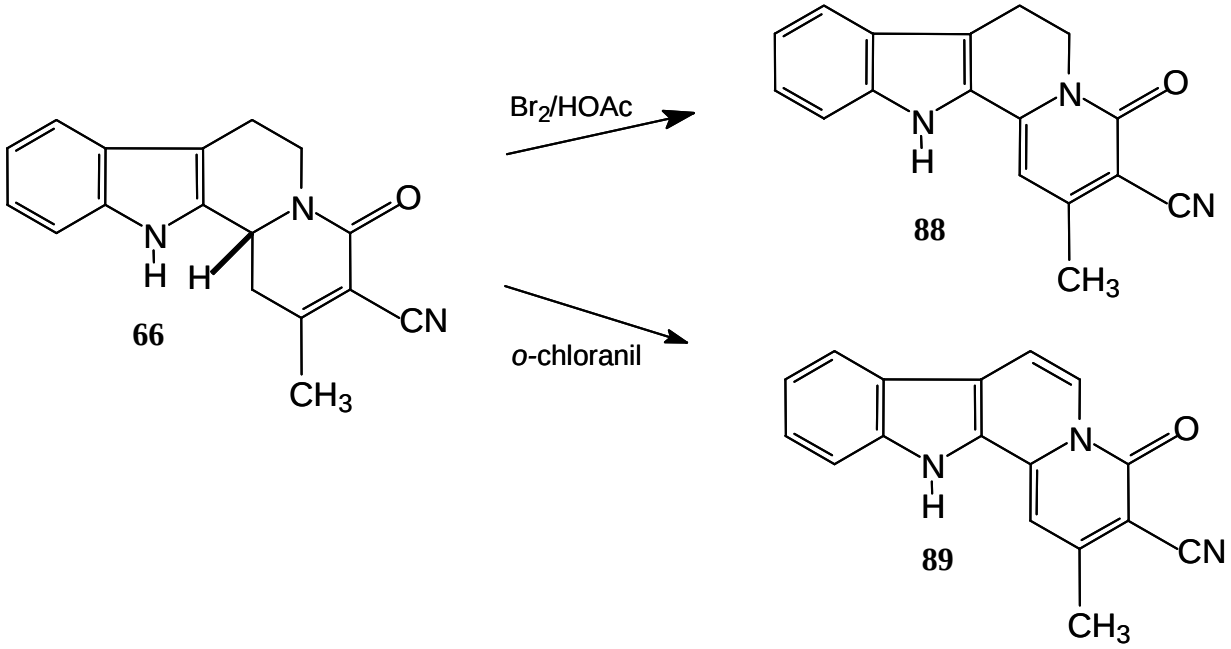
Both **83** and **84** are isolated as diastereomeric pairs.[50]

Contrary to the ring closure to **66** with *cis*-quinolizidine structure being formed, the boranate reduction of the indoloquinolizines derived from tryptamine and acetylacetaldehyde leads to a *trans*-quinolizidine structure.[45]

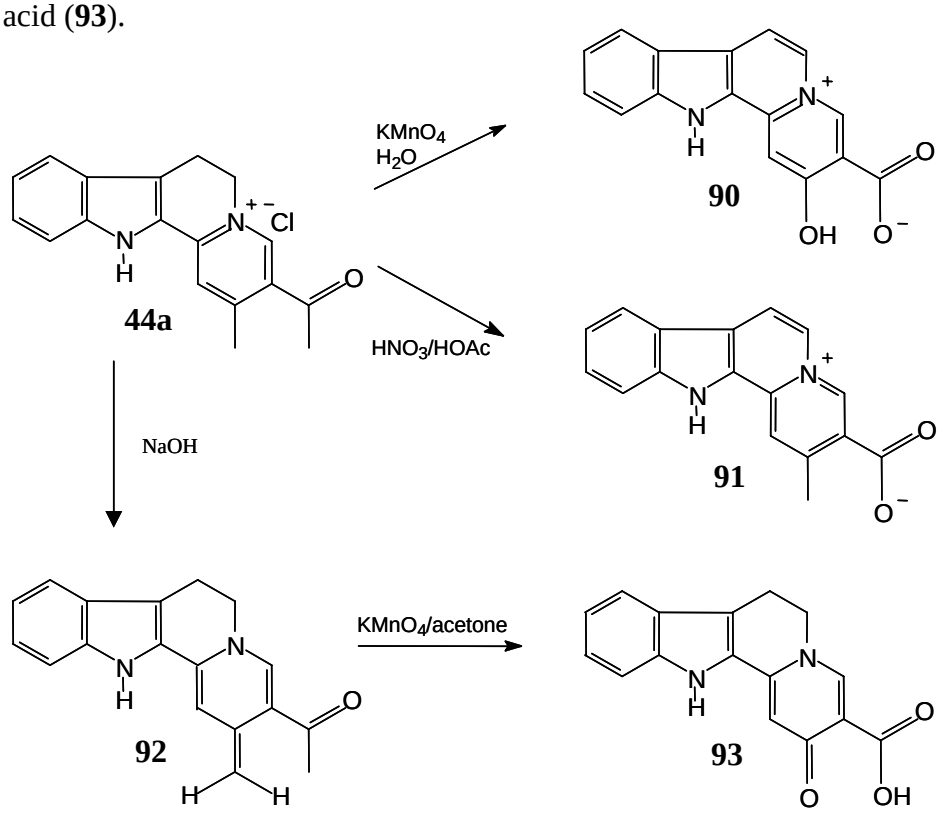


2. Oxidations and synthesis of flavoserpentine

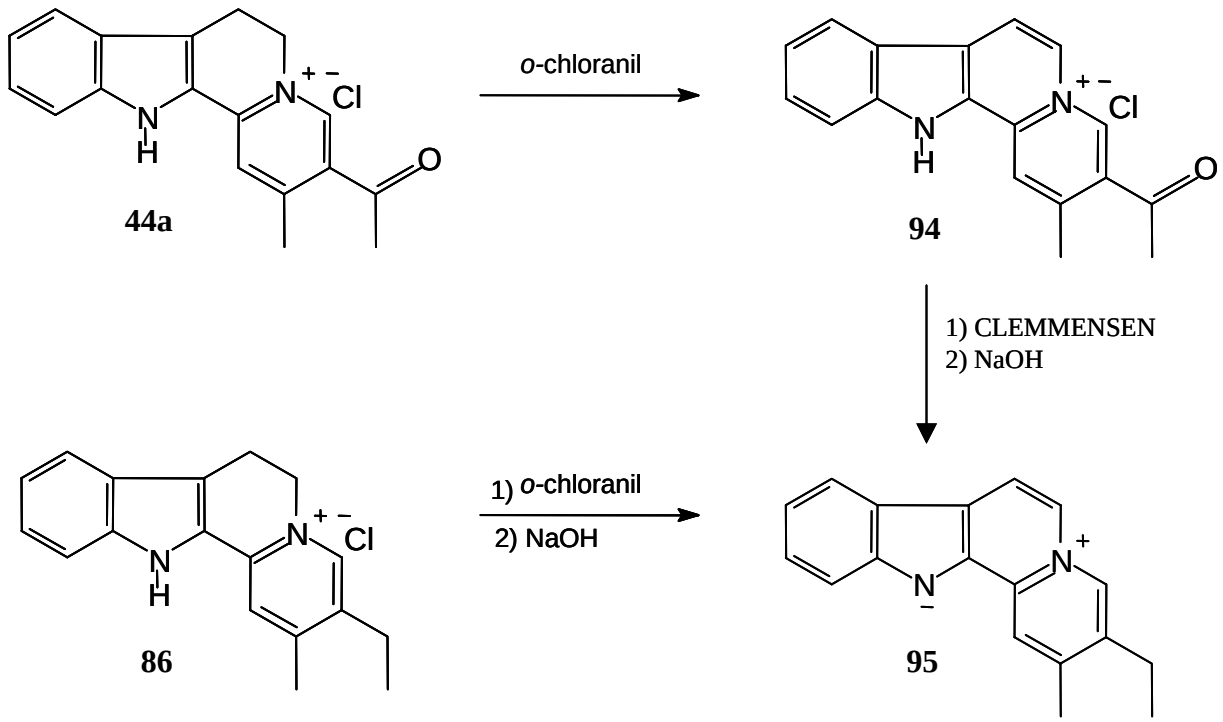
The tetrahydroindoloquinolizine (**66**) can stepwise be dehydrogenated by bromine or *o*-chloranil.[50]



On oxidation of **44a** in acidic solution with permanganate[43] or nitric acid[45] the acetyl side chain is degradated to carboxyl group yielding the zwitterionic compounds (**90** and **91**). If otherwise one oxidizes the corresponding base of **44a** with its pyridone-methide structure[45] (**92**) one obtains the non zwitterionic carboxy acid (**93**).



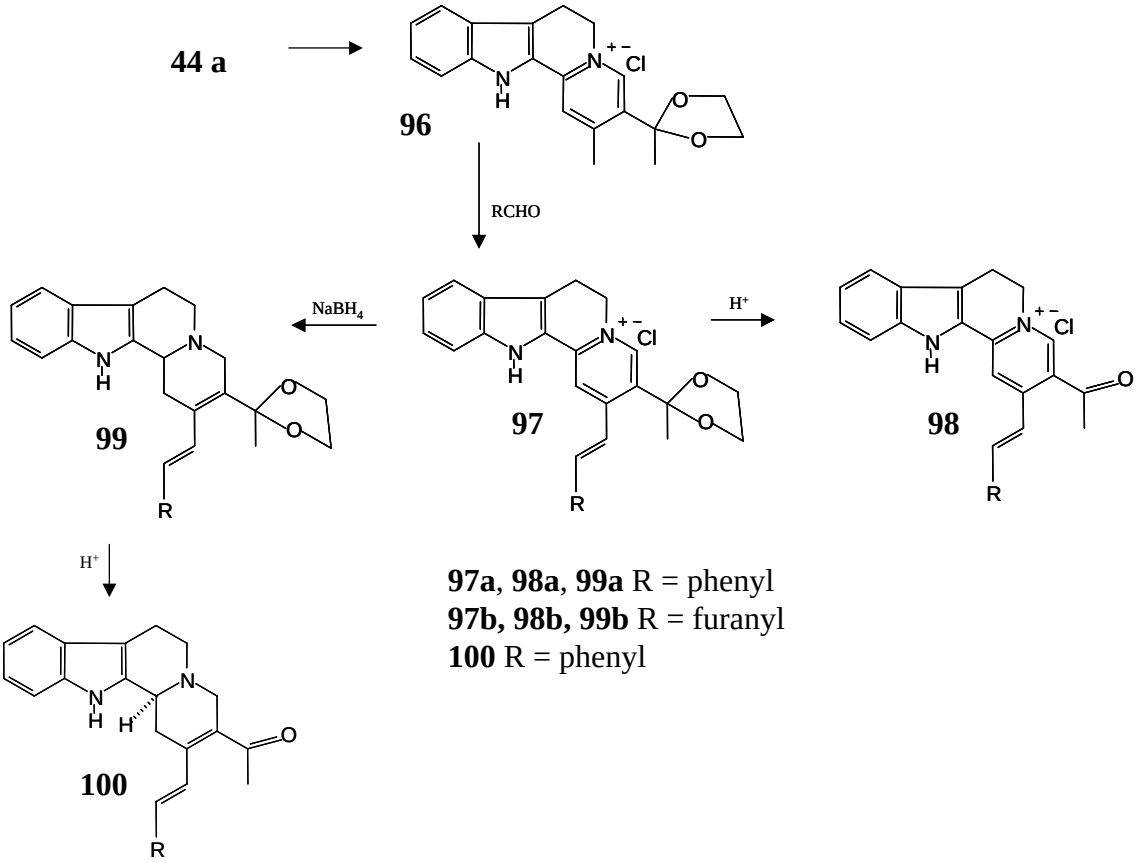
By combined dehydrogenation and Clemmensen reduction of the acetyl side chain the alkaloid flavoserpentine (**95**) is formed[45] from **44a**.



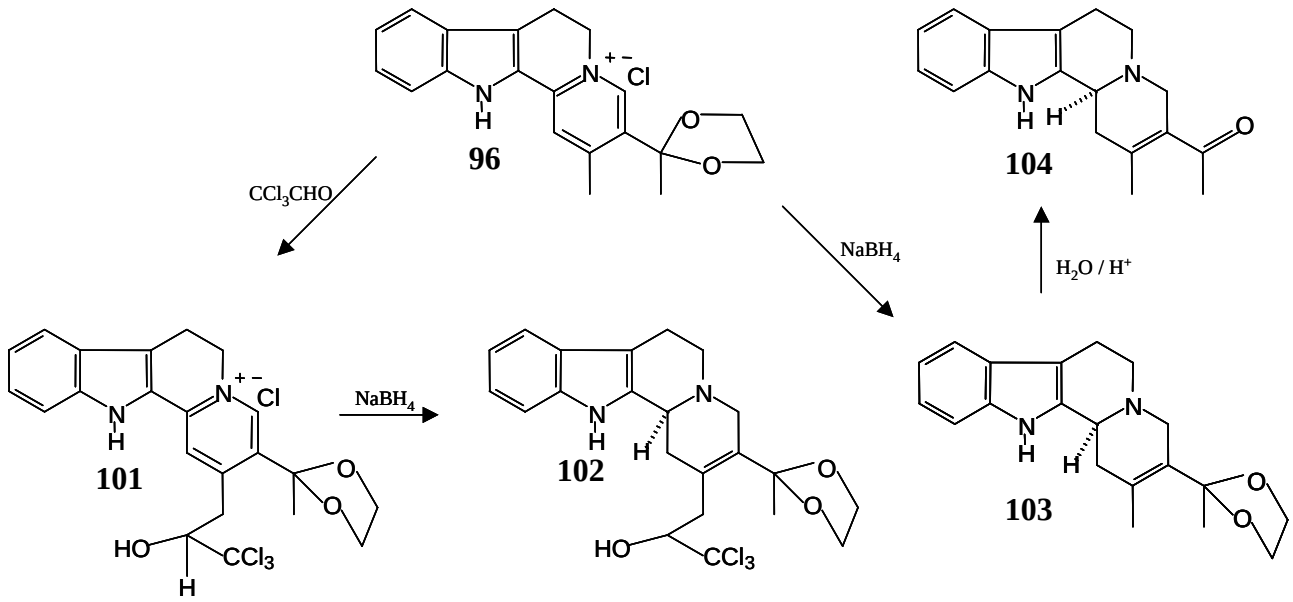
The intermediate (**94**) forms a flavoserpentine analogous zwitterion with sodium hydroxide.[45]

3. Transformations of ketals of indoloquinolizines

When the carbonyl group of **44a** is protected, like in ketal (**96**), it is possible to generate a carbanion in the methyl group that attacks aldehydes (benzaldehyde, furfural, chloral) reminding of an aldol reaction.[53]

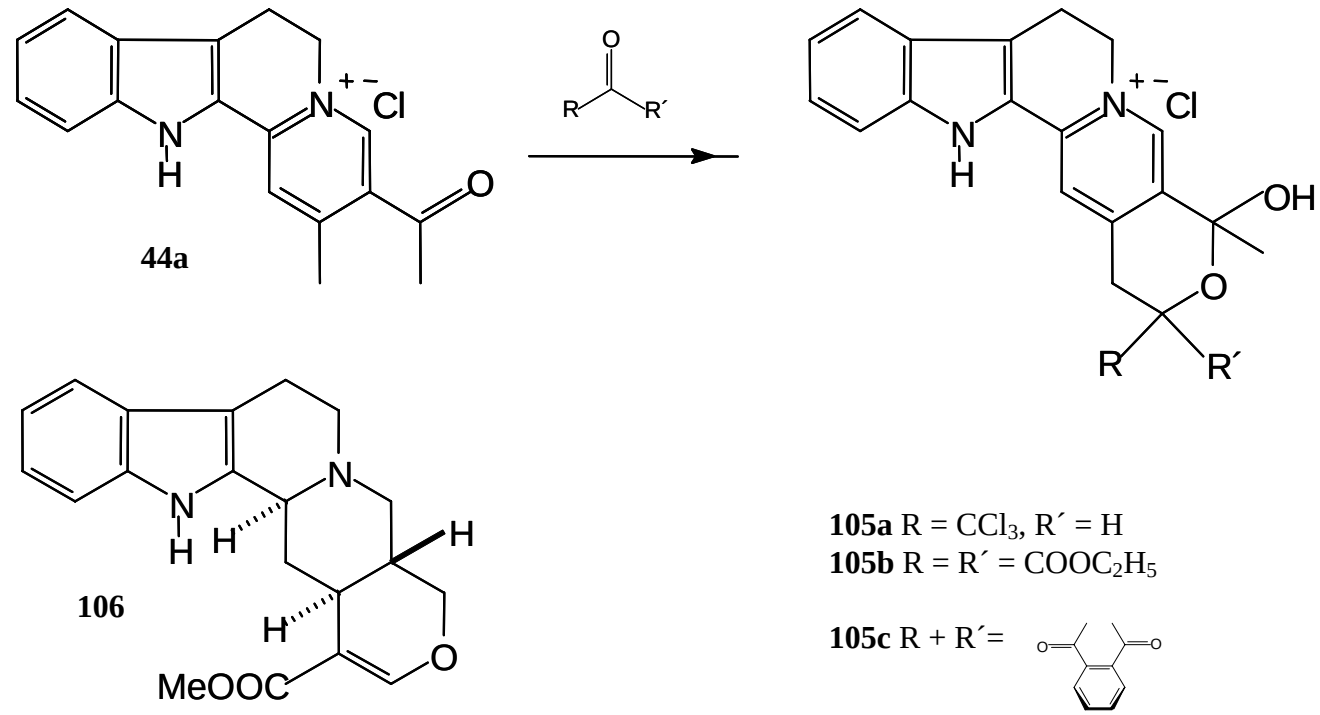


97a, **98a**, **99a** R = phenyl
97b, 98b, 99b R = furanyl
100 R = phenyl



4. Alkylations. Analogues of heteroyohimbane alkaloids

Reaction of **44a** with chloral, mesoxalic acid diethyl ester or ninhydrine leads, however, to a pentacyclic system (**105**) with a halfacetal structure[53] reminding of heteroyohimbane alkaloids, *e.g.*, ajmalicine (**106**).



105a R = CCl_3, R´ = H
105b R = R´ = $COOC_2H_5$

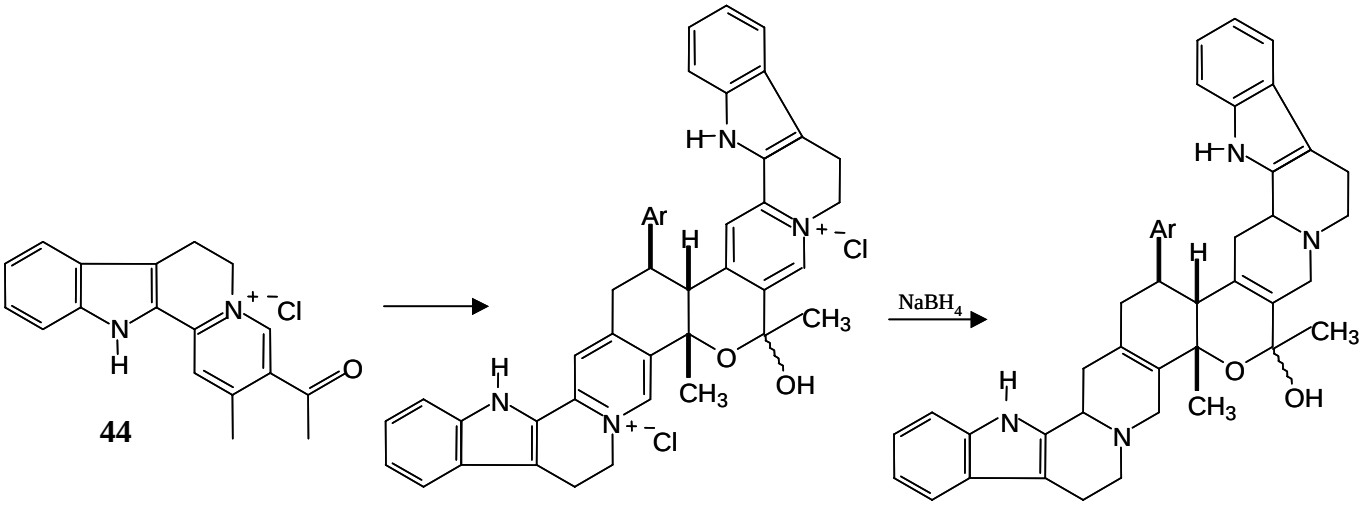
105c R + R´=

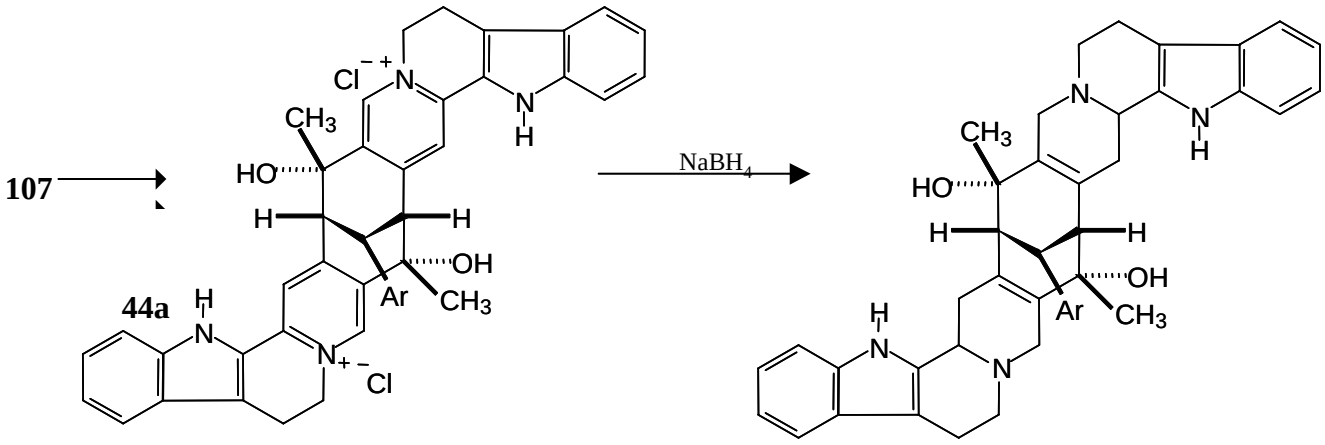
5. Dimerizations. Analogues of *bis*-indole alkaloids

The indoloquinolizine (**44a**) reacts in a remarkably different way with aromatic aldehydes when the carbonyl group is free and not protected by ketalization. The aldehyde then reacts with the ring-attached methyl group of two quinolizinium units forming a dimer (**107**) which is stabilized by intramolecular aldol and halfacetal ring closure.[54-56]

Is this dimer (**107**) heated for some time in methanol in the presence of piperidine, also the second carbonyl group reacts aldol like, giving up its halfacetal binding and the symmetrical ring of **109** with a bicyclo-nonadiene system is formed.

Boranate reduction of **107** and **109** reduced their pyridine rings (**108**, **110**).





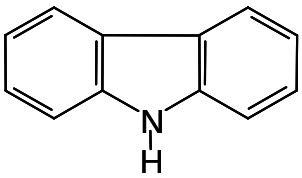
V. POSSIBLE PHARMACOLOGICAL EFFECTS OF THE SYNTHESIZED COMPOUNDS

Quite a number of compounds of this review can be considered as synthetic precursors of isoquinoline and indole alkaloids.[7,8]

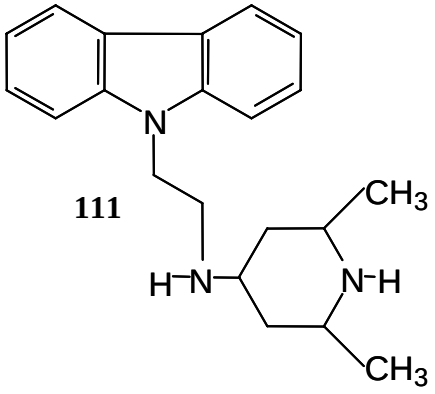
Well-known indole alkaloids show biological activity. Several therapeutic agents of current use proceed from natural products of this series or from some of their semisynthetic or synthetic counterparts.[57] Some possess structural analogies to various neuromediators. Therefore, they may act as agonists or antagonists of these mediators on some of their receptors. This type of mechanism can explain the use of various indole alkaloids as antiarrythmic, antihypertensive or adrenergic blocking agents and for the improvement of cerebral circulation.[75] Other indole and related alkaloids show antimitotic and cytotoxic activities and find uses as anticancer and antimalarial agents.[58]

In this respect, the pharmacological properties of many of these compounds remain unknown. In the following sections we emphasize those which, by virtue of their structural relationship to known compounds, most likely possess pharmacological activity.

Compounds (**16**, **18**, **20**, **52** and **53**) present skeletons related to carbazole (**19a**). Many carbazole derivatives show antimicrobial properties, antitumor and antiviral activity as well as cardiovascular and central nervous system activity.[59] Rincazole (**111**) is an interesting example, as a novel neuroleptic and antipyretic agent.[60]

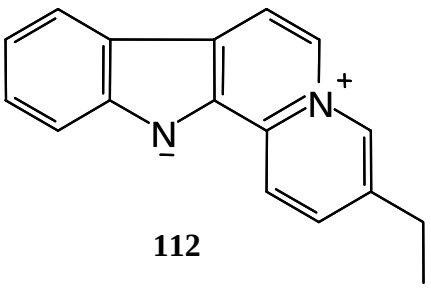


19a



111

Indoloquinolizines (**44**, **46**, **56**, **86**, **95-97**, **98**, **101**, **105**) are specially interesting. These compounds could have antitumor activity in their form of the zwitterions, reminding of the activity found by Beljanski[61-63] for flavopereirine (**112**) and sempervirine (**113**).



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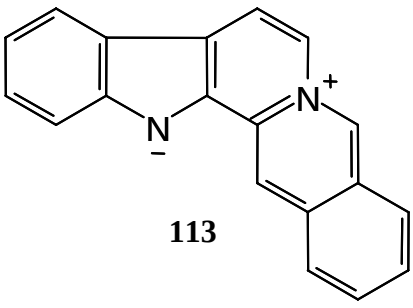
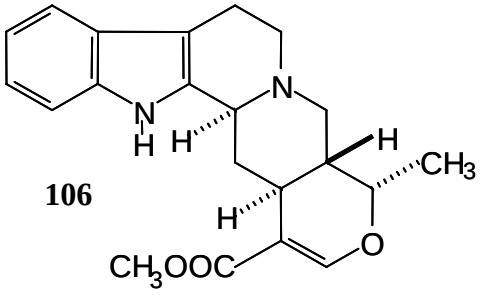
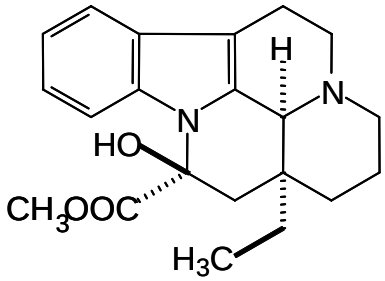


113

Compounds (**105**) can be considered ajmalicine (**106**) analogues und may act as cerebral blood-flow-increasing drugs, like vincamine (**114)**.[64]

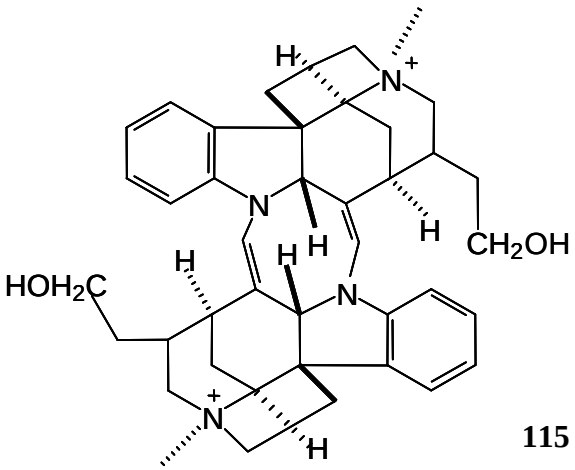


106

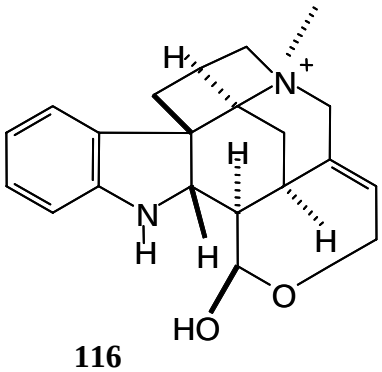


114

Dimeric compounds (**107**-**110**) could act as muscle relaxant.[65-67] The development of this type of drug is based on the discovery of the alkaloids contained in *Calabash curare,*[68] *e.g.*, C-Toxiferine (**115**), derived by dimerization of the Wieland-Gumlich aldehyde (**116**).



115



116

Usually, we can believe that a compound can act as a muscle relaxant if it shows the following structural features: a) ammonium, e.g., quaternary nitrogen.

b) *bis*-, rather than monoquaternary structures.

c) a distance between the two quaternary nitrogens of about 1.1 nm, roughly corresponding to 10 carbon atoms.[69]

The indoloquinolizine dimers (**109**) fulfill approximately the previously mentioned requirements, because of the bicyclononadiene system separating the two essential quaternary nitrogens.[70]

In the case of these dimers one also has to think of a possibility of antitumor properties in view of the activity of the *bis*-indole alkaloids vinblastine and vincristine.[65, 66]

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