ADDITION OF STABILIZED CARBON NUCLEOPHILES TO N-ALKYLPYRIDINIUM SALTS. APPLICATIONS TO ALKALOID SYNTHESIS

M.-Lluïsa Bennasar, Rodolfo Lavilla, Mercedes Alvarez, and Joan Bosch*

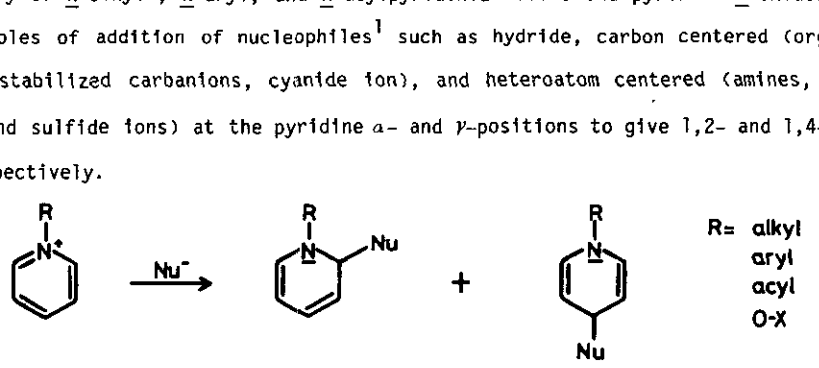
Laboratory of Organic Chemistry, Faculty of Pharmacy, University of Barcelona, 08028-Barcelona, Spain

Abstract - The application to alkaloid synthesis of the addition of stabilized carbon nucleophiles to N-alkylpyridinium salts is reviewed.

CONTENTS

1. INTRODUCTION

The chemistry of N-alkyl-, N-aryl, and N-acylpyridinium salts and pyridine N-oxides offers numerous examples of addition of nucleophiles[1] such as hydride, carbon centered (organometallic compounds, stabilized carbanions, cyanide ion), and heteroatom centered (amines, hydroxide, alkoxide, and sulfide ions) at the pyridine α- and γ-positions to give 1,2- and 1,4-dihydropyridines, respectively.



The regioselectivity of this kind of addition has received a variety of theoretical[2] and experimental[3] studies. According to theoretical considerations, addition at the pyridine α- or γ-positions can be expected depending on the hardness of the nucleophile:[4] hard nucleophiles preferentially attack at C-2 whereas soft ones react at C-4. On the other hand, the addition is considered to proceed both at the α- and γ-carbon centers under kinetic control

and at the γ-carbon under thermodynamic control.[3a,b] In the latter case, if the nucleophile is sufficiently stable, rapid addition and elimination leads to an equilibrium in which ultimately the thermodynamically more stable 1,4-dihydropyridine becomes the major product.

The stability of the resulting dihydropyridine adducts depends on several factors such as the type of nucleophile or the substituent at the pyridine nitrogen or at other ring positions. Thus, it is well known that an N- acyl group or an electron-withdrawing substituent at the pyridine β-position causes a stabilizing effect upon the dihydropyridine system.[5] On the other hand, the intramolecular dihydropyridine adducts are entropically less disfavoured than the intermolecular ones. Accordingly, the dihydropyridine adducts can be isolated in some cases but, in others, they spontaneously change or are directly converted to more stable products. These transformations can be classified in: i) conversion to the corresponding dihydropyridinium salt through acid treatment, ii) rearomatization of the adduct by oxidation or disproportionation, and iii) ring opening, especially in the case of 1,2-dihydropyridines.

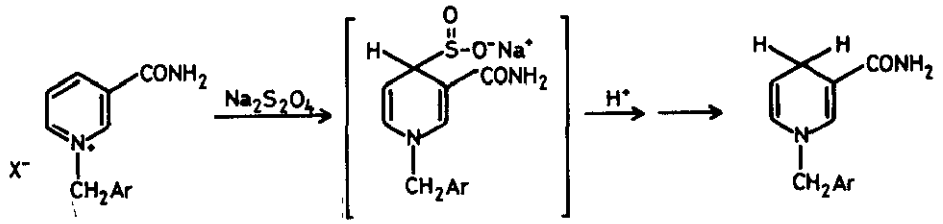
This review is centered on the application to alkaloid synthesis of the addition, in both the inter- and intramolecular modes, of stabilized carbon nucleophiles (enolate ions) to N-alkylpyridinium salts. This reaction, investigated long ago in the form of the base-catalyzed condensation of ketones and N-alkyl- and N-acylpyridinium salts,[6] possesses a particular synthetic interest since it constitutes an useful method of forming carbon-carbon bonds to give substituted dihydropyridines, which can be further elaborated into complex polycyclic alkaloid systems.[7]

2. INTERMOLECULAR ADDITIONS

We have classified these reactions in two groups, according to the treatment effected upon the initially formed dihydropyridine, which generally can not be isolated.

2.1. Addition followed by acid treatment

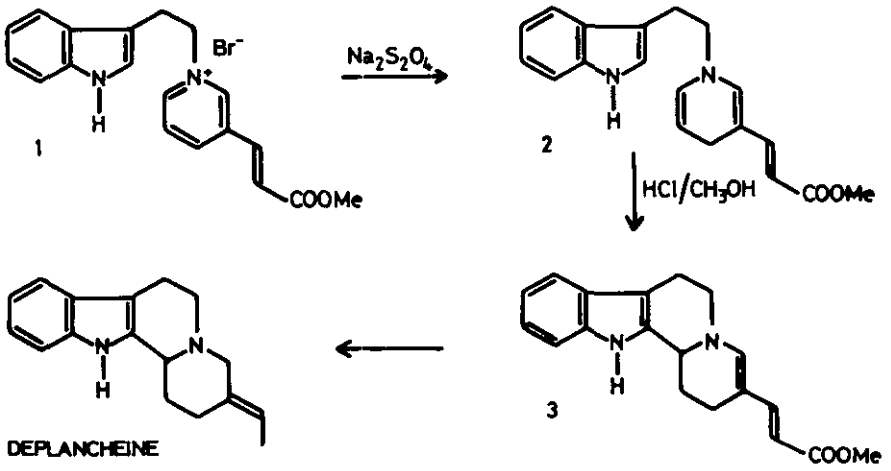
The sodium dithionite reduction of pyridinium salts bearing an electron-withdrawing substituent at the β-position affords 1,4-dihydropyridines.[8] The reaction proceeds via an intermediate sulfinate adduct, which is stable in alkaline solution but readily decomposes under neutral or



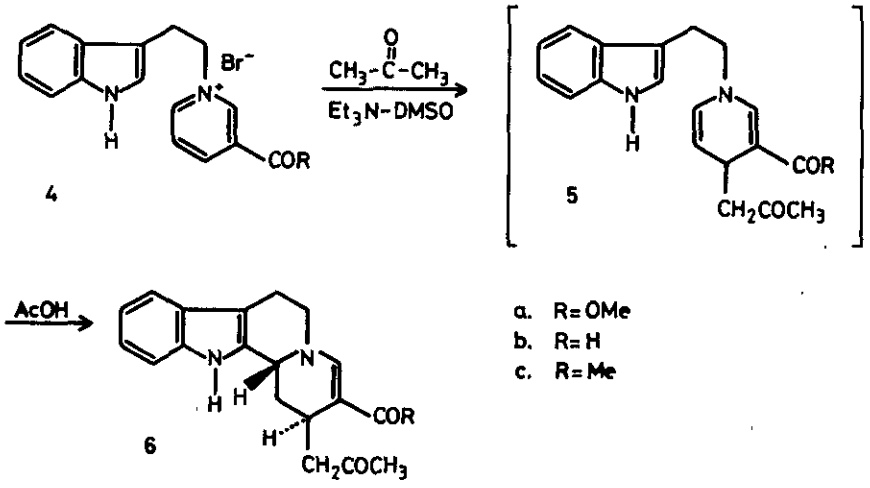
acidic conditions to give the reduced product.[9]

The regioselectivity of the process can be rationalized by considering the softness of dithionite anion as nucleophile and the reversible character of the first step of the reduction. The resulting 1,4-dihydropyridines are able to generate iminium salts in a regioselective manner since protonation occurs exclusively at the β-carbon of the unsubstituted enamine function rather than at the vinylogous amide moiety. Consequently, it is possible to effect regioselective cyclizations upon activated aromatic rings such as indole.[10]

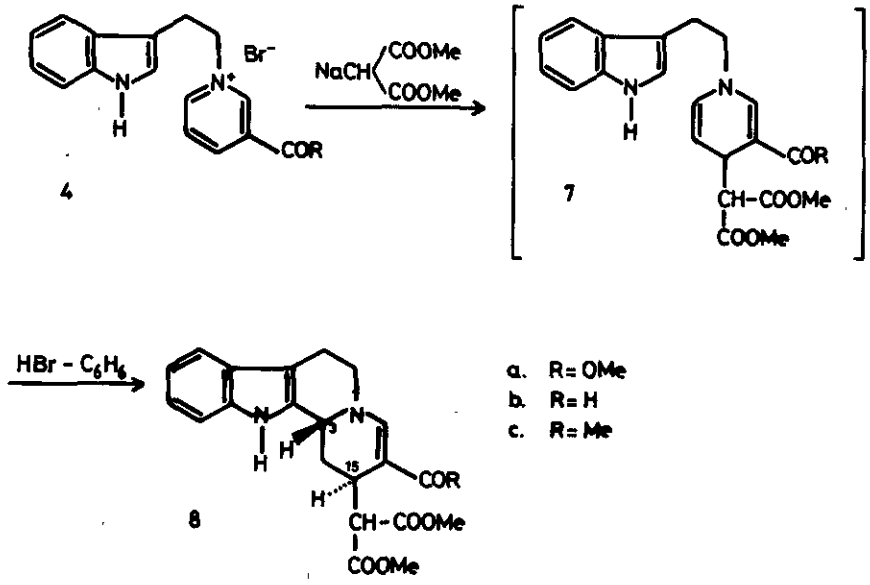
This methodology has been widely used in the synthesis of indolo[2,3-a]quinolizidine derivatives,[11] several vallesiachotamine models[12] and indole alkaloids of the gambirtannine type,[13] as well as in the total synthesis of the indole alkaloid deplancheine.[14] In the last case, the reduction of pyridinium salt **1** yielded the unstable enamine **2**, which was directly cyclized under acidic conditions to indoloquinolizidine **3**, a precursor of deplancheine.



The sodium dithionite reduction can be formally envisaged as a nucleophilic hydride attack at the γ-position of the pyridinium ring. Consequently, the use of a stabilized carbon nucleophile in the first step of the above nucleophilic addition-cyclization sequence should allow the introduction of functionalized carbon substituents at the 2-position of the indolo[2,3-a]quinolizidine ring system. This transformation has been satisfactorily accomplished by Wenkert since the base-induced condensation of pyridinium salts **4** with acetone, followed by acid treatment of the intermediate 1,4-dihydropyridines **5**, afforded the corresponding acetonyl derivatives **6a** (7%), **6b** (23%), and **6c** (10%), which can be considered as simplified analogues of vallesiachotamine.[15] In spite of the low yields, the above two-step sequence opened a new general scheme for the synthesis of the indoloquinolizidine skeleton, characteristic of many indole alkaloids.[16,17] When appropriate carbon nucleophiles were used, this methodology made possible the synthesis of

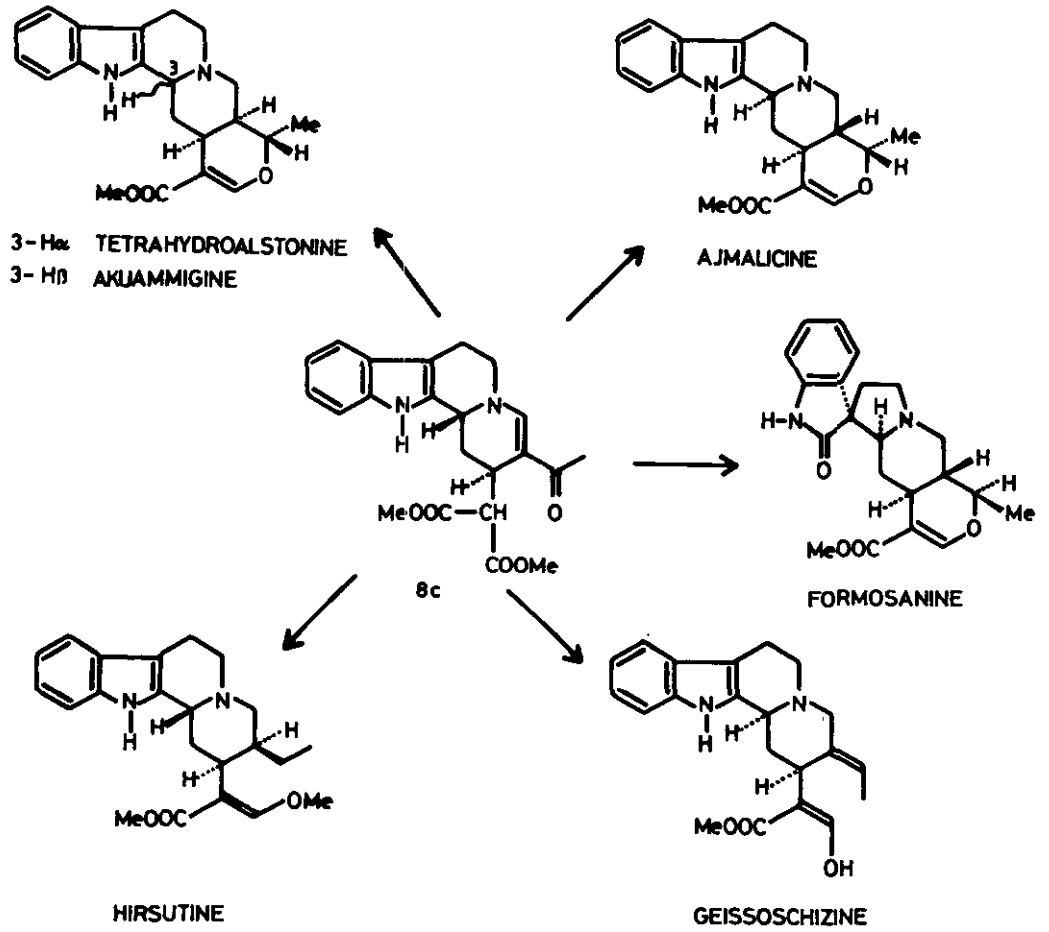


ajmalicinoid alkaloids after further elaboration of the γ-substituent. Thus, the addition of dimethyl sodiomalonate to pyridinium salts **4** followed by cyclization of the intermediate 1,4-dihydropyridines **7** with benzene saturated with hydrogen bromide gave the tetracyclic systems[18] **8a** (34%), **8b** (11%), and **8c** (29%).[19] The use of hydrogen chloride and/or other solvent systems (DME-benzene, $CHCl_3$-benzene) in the cyclization step did not affect appreciably the yield of tetracycle **8c**. In contrast, methanolic hydrogen chloride or glacial acetic acid were ineffective. In all cases the starting pyridinium salt is recovered in considerable extension,[18] not only as a consequence of the reversibility of the nucleophilic attack but also due to the tendence of the resulting dihydropyridines to undergo fragmentation into the starting pyridinium salts under acidic conditions.[20]



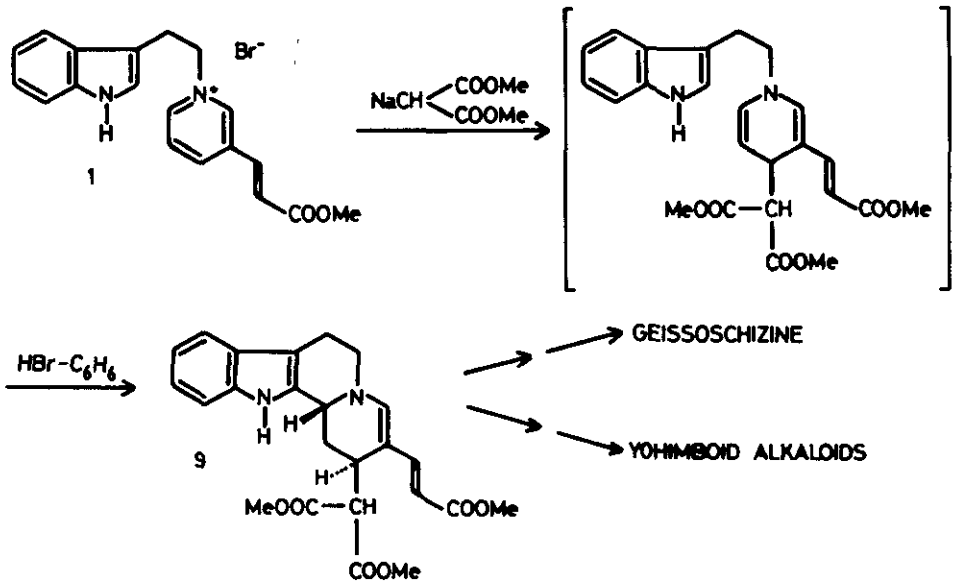
It is noteworthy that indolo[2,3-a]quinolizidines **6** and **8** (see also below) possess uniformly a 3-H/15-H trans-relationship. This stereochemical result is a consequence of the axial attack of the indole ring to the iminium double bond.

The tetracycle **8c** appeared to be a versatile intermediate since from which, short, highly specific syntheses of the racemates of the alkaloids akuammigine and tetrahydroalstonine, as well as formal total syntheses of the racemates of ajmalicine and the oxindole alkaloids formosanine and 7-isoformosanine have been reported.[18] The synthesis of (±)-hirsutine and (±)-geissoschizine from **8c** further illustrates the power of the new method for the construction of members of the corynanthoid alkaloids family.[21]



Similarly, when the same two-step reaction sequence, i.e., addition of the sodio salt of dimethyl malonate and subsequent acid-induced ring closure of the resultant γ-alkylated 1,4-dihydropyridine, was effected from pyridinium salt **1**, bearing a methoxycarbonylvinyl substituent at the β-position, tetracycle **9** was obtained in 18% yield.[22,23] Further elaboration of this intermediate resulted in formal total syntheses of (+)-yohimbine,[22,23] (-)-β-yohimbine,[22,23] (±)-alloyohim-

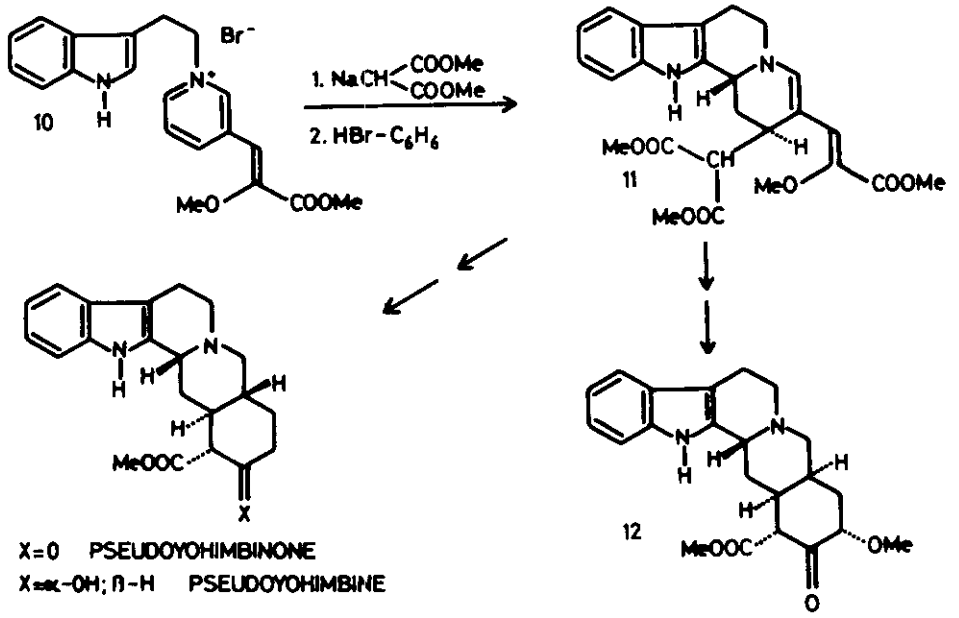
bine,[23] and (±)-α-yohimbine,[23] as well as in a new total synthesis of (±)-geissoschizine,[21] (±)-pseudoyohimbine, and (±)-pseudoyohimbone.[22,23]

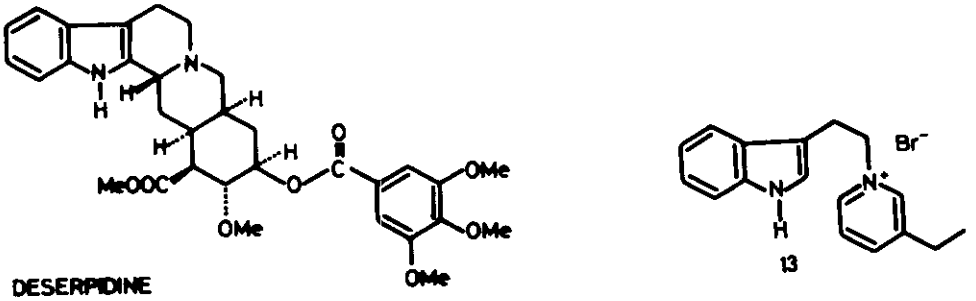


In order to control the regioselectivity of the Dieckmann condensation required for the construction of ring E in the above synthesis of pseudoyohimbine, a related sequence starting from pyridinium salt **10** was developed.[17] Tetracycle **11** is a precursor of pseudoyohimbinone and of pentacyclic ketone **12**.[17] The former had been transformed earlier into (±)-pseudoyohimbine[23] whereas the latter possesses the required relative configuration and appropriate E ring substituents for the synthesis of deserpidine.

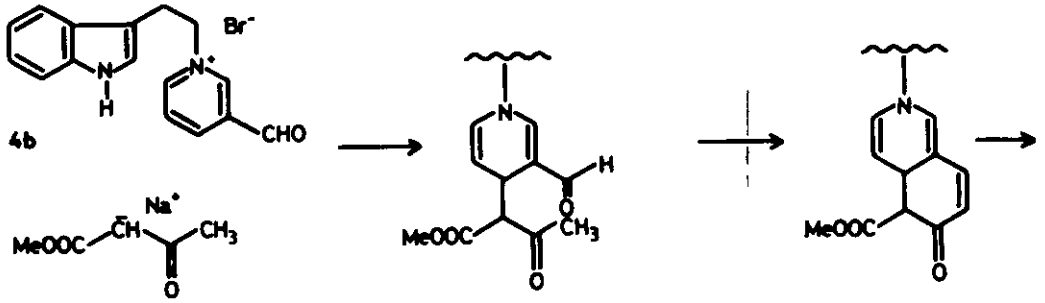
In contrast to the above results, no tractable products could be isolated from the reaction of pyridinium salt **13** with sodio malonic ester under a large variety of conditions.[18] The presence of an electron-withdrawing substituent (acyl or a vinylogue thereof) at the β-position of the pyridinium ring seems to be a necessary requisite for the success of the intermolecular addition-cyclization sequence. This substituent enhances the electrophilicity of the pyridine ring in the nucleophilic addition step, is the responsible of the regioselectivity in the cyclization process, and stabilizes both the dihydropyridine resulting from *Y*-addition and the enamine unit in the final cyclized product.

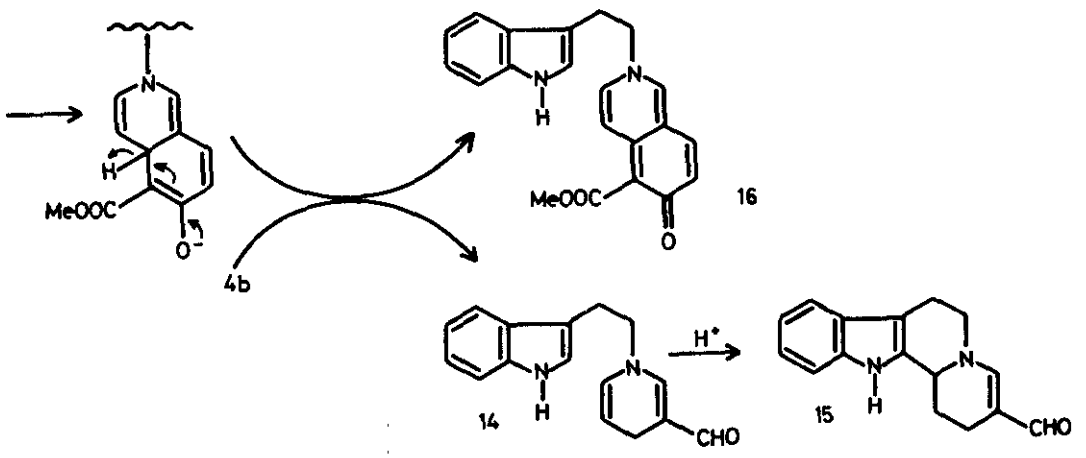
In order to evaluate if the nucleophile could be varied without affecting the overall scheme of alkaloid synthesis, the condensation of formylpyridinium salt **4b** with methyl sodioacetoacetate was investigated.[24] However, after the usual acid treatment, two unexpected products, **15** and **16**, were obtained. Their formation has been accounted for as illustrated in the Scheme and implies *an oxidation-reduction interference in the desired synthetic path.*



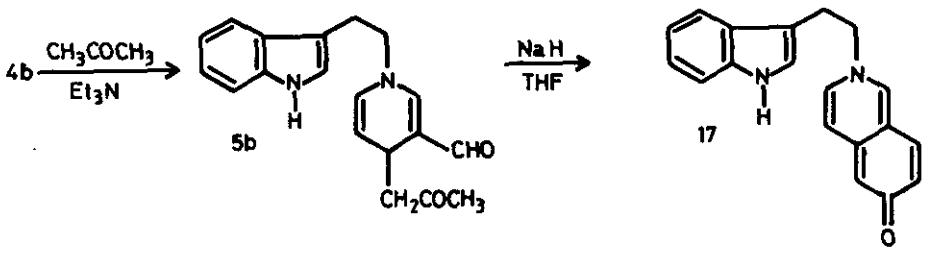


The vinylogous formamide **15** is the product resulting from 1,4-reduction of pyridinium salt **4b** and subsequent acid-induced cyclization of the resulting dihydronicotinaldehyde **14**, whereas keto ester **16** would be formed by γ-addition of the acetoacetic ester anion to **4b** followed by intramolecular aldol cyclization, dehydration, and dehydrogenation. In accordance with the above interpretation, when the acid treatment was suppressed the yield of **16** increased (29%) and dihydropyridine **14** was obtained as a minor by-product.

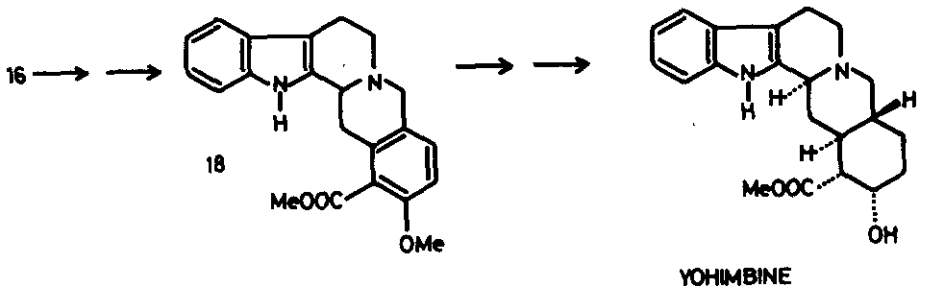




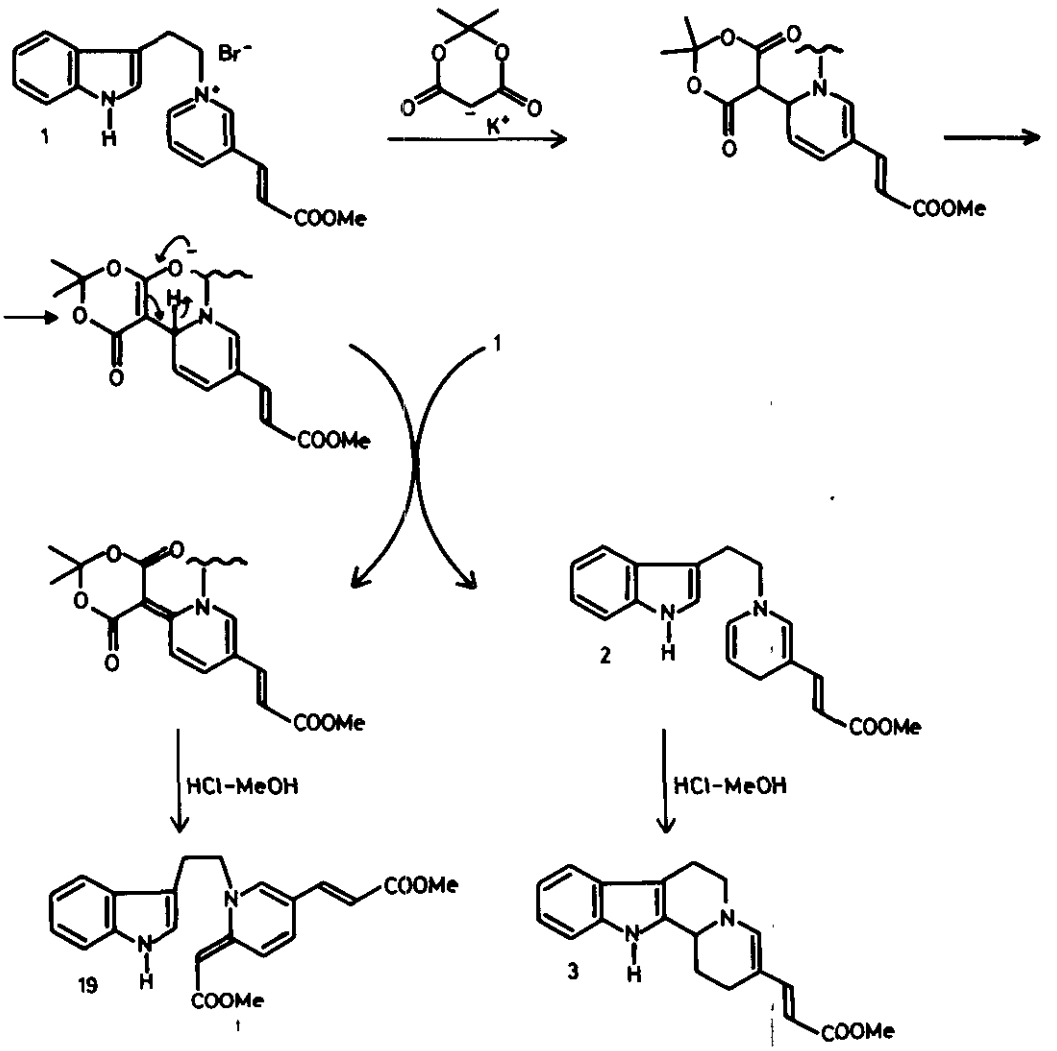
A similar process involving aldol condensation between a methyl ketone and a formyl group being part of a vinylogous amide moiety was produced[24] when 4-acetonyl-1,4-dihydropyridine **5b**[15] was treated with sodium hydride in tetrahydrofuran.



The unexpected keto ester **16** was synthetically useful since it could be elaborated[24] into O-methylhexadehydroyohimbine **18**, which represented a short, formal synthesis of (±)-yohimbine.[25]

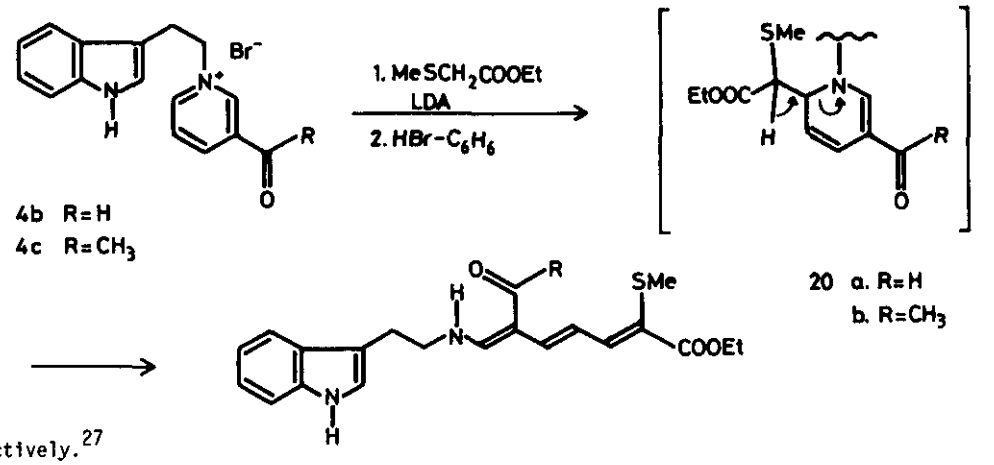


The replacement of the dimethyl malonate anion by the salt of Meldrum's acid produced a dramatic change in the global process.[26] Thus, reaction of the pyridinium salt **1** with the potassium salt of 2,2-dimethyl-4,6-dioxo-1,3-dioxane (Meldrum's acid) followed by the usual treatment with acid led to two isolable products. One of them was tetracycle **3** (7%), whose formation can be ra-



tionalized as above, by considering an hydride transfer to the γ-position of the pyridinium salt 1 and further acid-induced ring closure of the resulting 1,4-dihydropyridine. Interestingly, the major product (17%) was diester **19**. Its formation implies the trapping of the enolate at the α-position of the pyridine ring. This observation illustrates an example of interference in the thermodynamic process by a fast oxidation of the kinetic product.

A fact that also accounts for the low yields of the two-step alkaloid synthesis scheme developed by Wenkert is the existence of competitive, irreversible side reactions such as oxidation (see above)[24,26] or pyridine ring opening processes[27] that partly or fully block the equilibration of the kinetic α-addition product (a 1,2-dihydropyridine) to the thermodynamic γ-addition product (a 1,4-dihydropyridine). The opening of the pyridine ring was first observed in the reactions of β-acylpyridinium salts **4b** and **4c** with the lithio salt of ethyl (methylthio)acetate, followed by treatment with acid, in which vinylogous amides **20a** and **20b** were obtained in 43 and 35% yield,

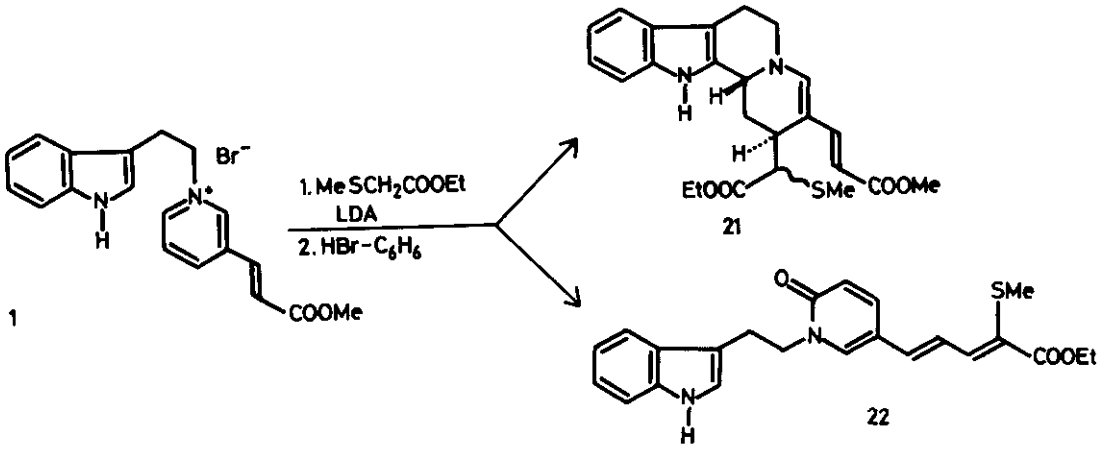


4b R=H
4c R=CH$_3$

20 a. R=H
b. R=CH$_3$

respectively.[27]

Exposure of salt **1** to the same nucleophile, and then to acid, led to a mixture of the desired γ-addition product **21** (21%) and 2-pyridone **22** (15%).[27] Formation of **22** again involves addition of the nucleophile at the α-carbon of the pyridine nucleus followed by ring opening. In this case the ester group of the acrylate moiety interacts with the tryptamine nitrogen atom in the resultant intermediate, with formation of the pyridone ring.[28]



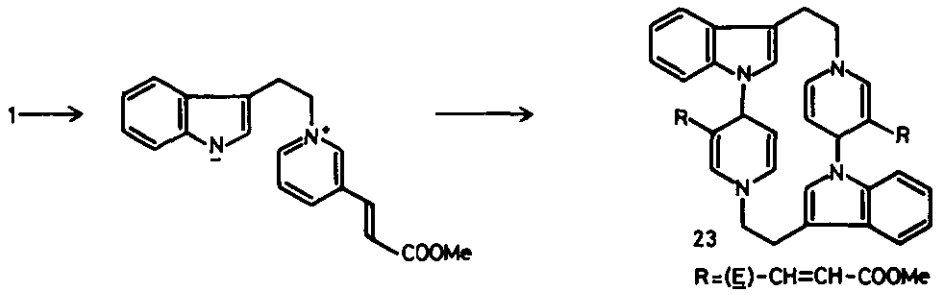
1

21

22

Recently, a new description of the mechanistic course of the carbanion addition to 3-acyl-pyridinium salts, probably involving a single electron-transfer from the nucleophile to the pyridine ring prior to carbon-carbon bond formation, has been postulated.[27] Consequently, the success of the above two-step sequence would be associated to the capacity of the nucleophile to stabilize not only the carbanion but also the radical created therefrom.

The first indication of the operation of an homolytic process came from the behavior of dimer **23** in dimethyl sulfoxide-chloroform solution. Formation of this material as an insoluble precipitate, which disappeared after longer reaction time , had been already observed in the reaction of dimethyl sodiomalonate with pyridinium salt **1**. However, it could be isolated in 90% yield on expo-

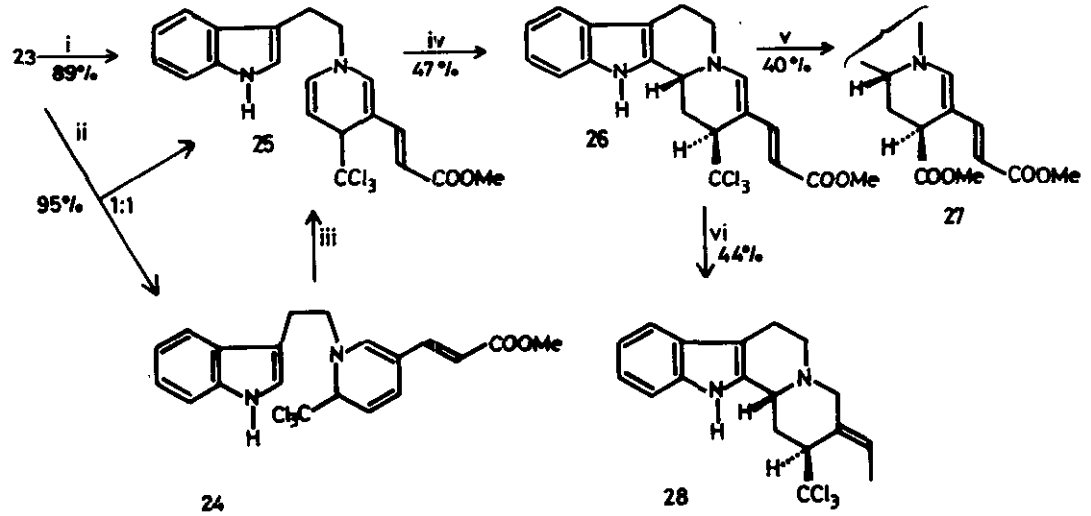


sure of salt **1** to sodium hydride in tetrahydrofuran.[27] In both cases its formation can be explained by considering the initial abstraction of the indole N-H proton by the malonate or the hydride acting as bases, and subsequent dimerization of the resulting zwitterion.

The following scheme summarizes the reactions of dimer **23** with chloroform under several reaction conditions. The 2-trichloromethyl-1,2-dihydropyridine **24** can be equilibrated to the most stable 1,4-isomer **25**,[29] whose cyclization produces tetracycle **26** in 47% yield.[27] Further elaboration of **26** for future use in alkaloid synthesis gave ester **27** and ethylidene derivative **28**.

It is worth mentioning that the overall yield of the above three-step conversion of salt **1** into tetracycle **26** is higher than the yields of the two-step addition-cyclization sequence in the malonic ester additions previously developed as a general method for the indole alkaloid synthesis.

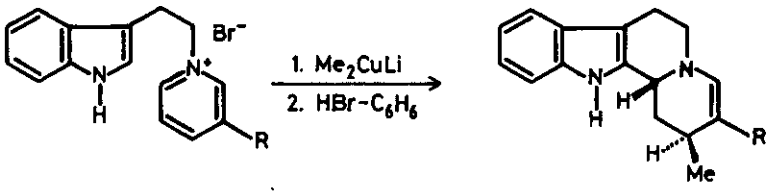
The above unusual results have been explained[27] on the basis of the homolysis of the bond between the indole nitrogen and the dihydropyridine γ-carbon of dimer **23** and subsequent interaction of



Reagents: (i) DMSO-$CHCl_3$, 0.5 h, reflux; (ii) DMSO-$CHCl_3$, 8 days, r.t.; (iii) DMSO-$CHCl_3$, 3 weeks, r.t.; (iv) $CHCl_3$ (HCl), 72 h, r.t.; (v) $AgNO_3$, CH_3OH, H_2O, r.t., 5 h; (vi) 4N HCl, 5 h, reflux; $NaBH_4$-CH_3OH.

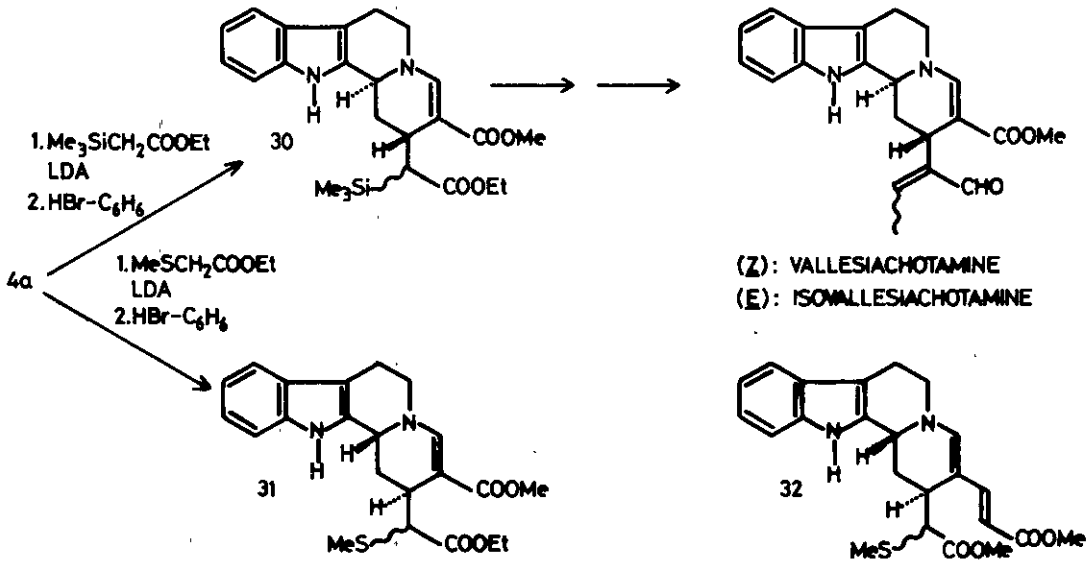
the resulting indolyl pyridyl radical pair with chloroform to give trichloromethyldihydropyridines **24** and **25**. In turn, the transformation of **24** into **25** has been visualized as a homolysis and restructuring of the resulting trichloromethyl pyridyl radical pair complex leading to the most stable product.[29]

In accordance with a homolytic mechanism, reaction of lithium dimethylcuprate[30] with pyridinium salts **1**, **4a**, and **4c**[31] and subsequent acid induced cyclization of the resultant 1,4-dihydropyridines produced tetracycles **29a-c** in yields higher than those obtained in malonic ester additions.[18,22,23]



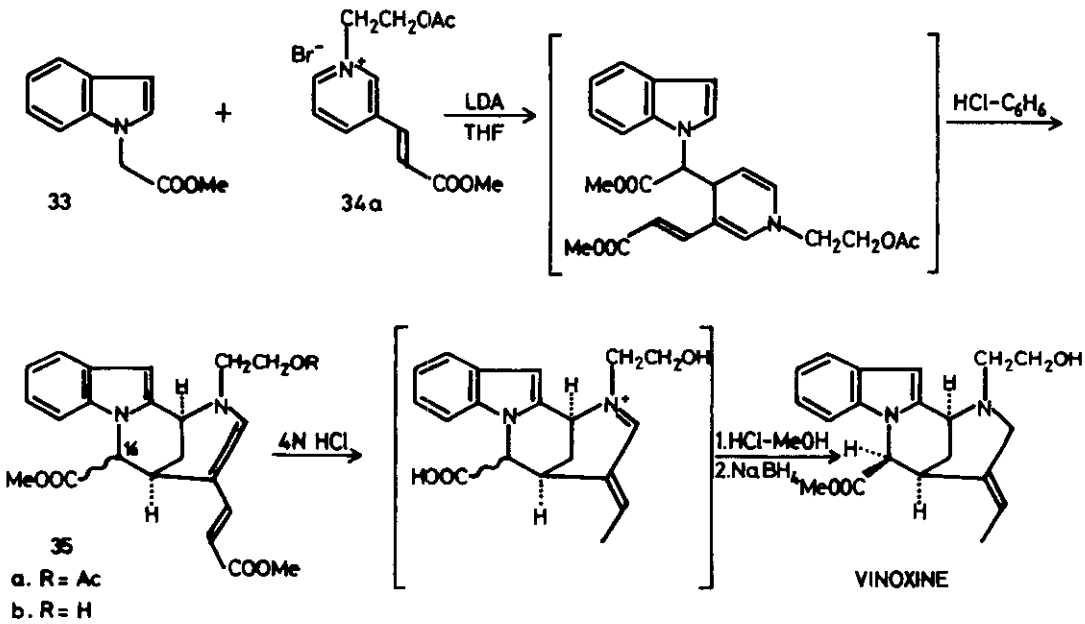
1.....R=(E)CH=CH-COOCH$_3$.....**29a (40%)**
4a.....R=COOCH$_3$.....**29b (53%)**
4c.....R=COCH$_3$.....**29c (43%)**

Similarly, the reactions of pyridinium salt **4a** with the lithio salts derived from ethyl (trimethylsilyl)acetate[31] or ethyl (methylthio)acetate,[27] followed by the usual acid treatment, afforded tetracycles **30** and **31**, respectively, in 47% and 64% yield, once again much higher than the yields obtained in the malonic ester additions. The former reaction constitutes the initial step in the total synthesis of the indole alkaloid vallesiachotamine.[32] Taking into account that radicals are

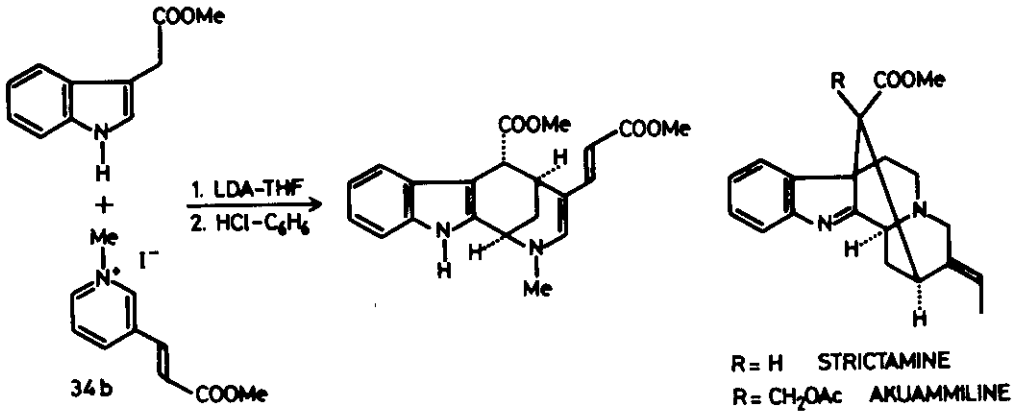


stabilized by the combined action of an electron-withdrawing and an electron-releasing substituent on the radical center (the captodative effect),[33] the above yields provide support to the proposed mechanistic description of the process.[27] However, a yield of only 28% has been reported for the formation of **32** by reaction of salt **1** with methyl (methylthio)lithioacetate and subsequent acid treatment.[27]

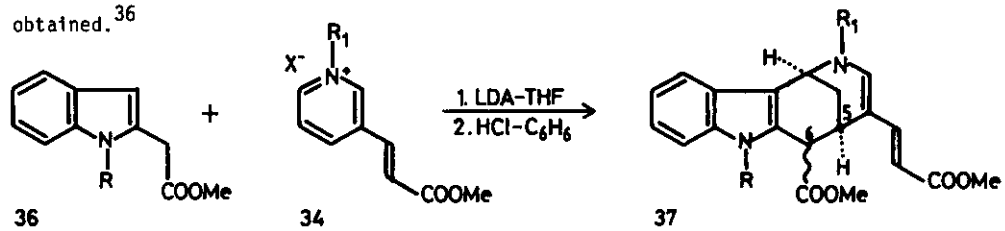
We have recently applied the same methodology, i.e., addition of a stabilized carbon nucleophile to an N-alkylpyridinium salt having an electron-withdrawing substituent at the 3-position followed by regiospecific cyclization of the intermediate 1,4-dihydropyridine, to the synthesis of the bridged indole alkaloid vinoxine.[34] Thus, interaction of ester **33** with pyridinium salt **34a** in the presence of LDA, followed by treatment with hydrogen chloride in benzene, afforded C-16 epimeric mixtures of tetracycles **35a** and **35b** in 30% overall yield. Further stereoselective elaboration of the E-ethylidene substituent of vinoxine and 16-epivinoxine was effected by taking advantage of the doubly vinylogous urethane moiety present in **35**.

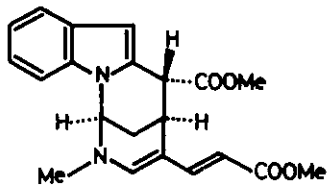


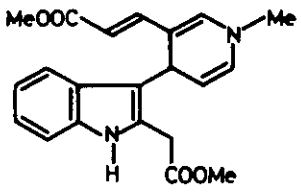
Following the same methodology from methyl 3-indoleacetate, we have recently obtained a bridged tetracyclic system[35] that possesses four of the five rings of pentacyclic alkaloids strictamine and akuammiline.



Similarly, exposure of pyridinium salts **34a** and **34b** to the lithium enolate of ester **36a** and subsequent acid-induced cyclization led to the bridged methanoazocino[4,3-b]indoles **37a** (70%) and **37b** (60%), respectively, as C-6 epimeric mixtures in which predominated (3:1) the 5-H/6-H trans-isomer. When the above two-step sequence was effected from ester **36b** and pyridinium salt **34b**, a mixture of the anticipated cyclized product **37c** (50%; only trace amounts of the 5-H/6-H cis-isomer) and the regioisomer **38** (<5%), in which cyclization had occurred upon the indole nitrogen, was obtained.[36]

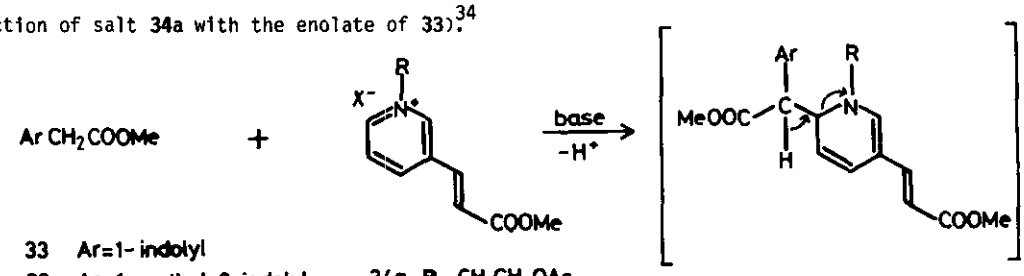






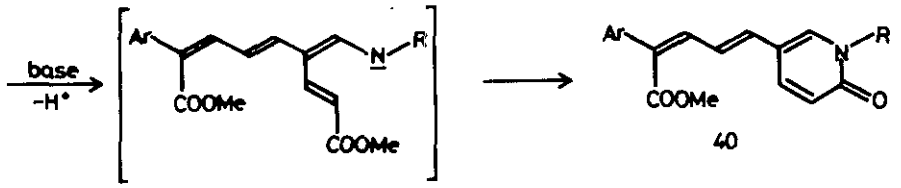
The modification of the reaction conditions in the first step produced a dramatic change in the product composition.[37] Thus, when reaction of pyridinium salt **34b** and ester **36b** was carried out in methanol solution in the presence of sodium methoxide as the base, 3-(1,4-dihydropyridyl)-in-

dole **39** was obtained in 60% yield. Its formation implies nucleophilic attack of the indole nucleus upon the γ-position of the pyridinium salt. In contrast, the use of tetrahydrofuran as the solvent led to a complex mixture, from which 2-pyridone **40a** was the only isolable product (<5% yield). The use of the same set of conditions (MeONa–THF) in the reaction of ester **36a** with salt **34b** also afforded a 2-pyridone system (**40b**), although in higher yield (60%). A related compound, **40c**, had been obtained[35] as a by-product in the first step of our synthesis of vinoxine (reaction of salt **34a** with the enolate of **33**).[34]



33 Ar=1-indolyl
36a Ar=1-methyl-2-indolyl
36b Ar=2-indolyl

34a R= CH_2CH_2OAc
34b R= CH_3

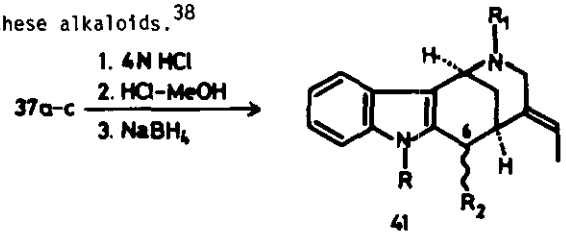


40

a. Ar=2-indolyl; R=CH_3
b. Ar=1-methyl-2-indolyl; R=CH_3
c. Ar=1-indolyl; R=CH_2CH_2OH

Pyridones **40** are related to that (**22**) reported by Wenkert,[27] and their formation involves again the attack of the nucleophile at the pyridine α-position, followed by ring scission and subsequent cyclization.[28]

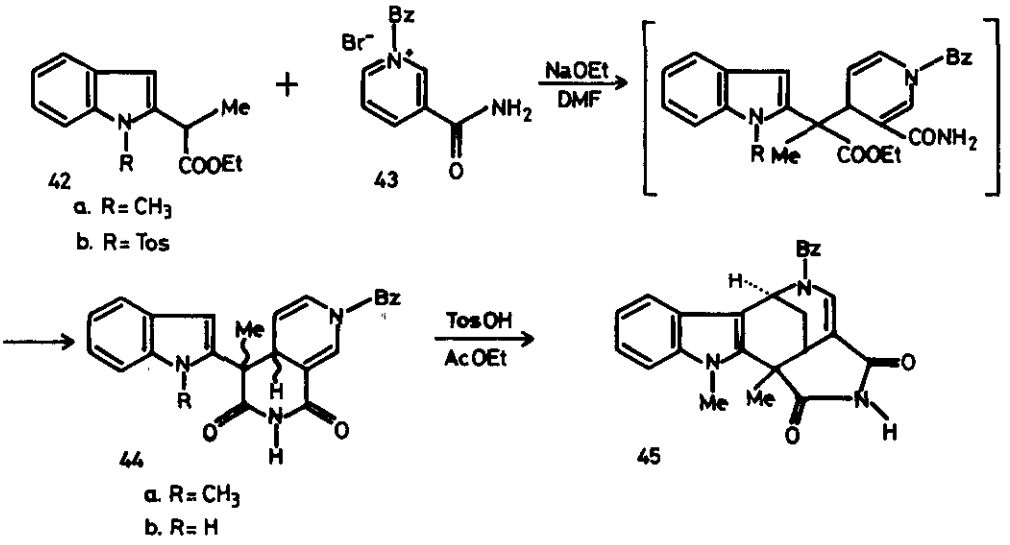
Tetracycles **37a–c** were further elaborated to the corresponding 4E-ethylidene derivatives **41**.[36] In the case of **37c** decarboxylation of the C-6 carboxy group occurred during the acid hydrolytic step and a mixture of the expected ester **41c** and **41d** (major component) was formed. Compounds **41** possess the ring skeleton of indole alkaloids uleine and dasycarpidone and incorporate four of the five rings as well as the characteristic C-16 and C-20 appendages of pentacyclic Strychnos indole alkaloids. The N-hydroxyethyl substituent of **41a** can allow further elaboration of ring E of these alkaloids.[38]



41

	R	R_1	R_2
a.	CH_3	CH_2CH_2OH	COOMe
b.	CH_3	CH_3	COOMe
c.	H	CH_3	COOMe
d.	H	CH_3	H

A compound related to tetracycles **37** has been prepared in the context of studies directed to the synthesis of ellipticine derivatives.[39] The synthesis is also based on the addition of an ester α-anion to a pyridinium salt, as illustrated in the following scheme. The initially formed 4-substituted-1,4-dihydropyridine was transformed (70%) in an esentially irreversible manner to 2,7-naphthyridine-1,3-dione **44a** by intramolecular nucleophilic attack of the amide nitrogen on the ester carbonyl group. Further acid cyclization upon the indole 3-position gave (78%) pentacycle **45**.



42 a. R = CH_3; b. R = Tos

43

44 a. R = CH_3; b. R = H

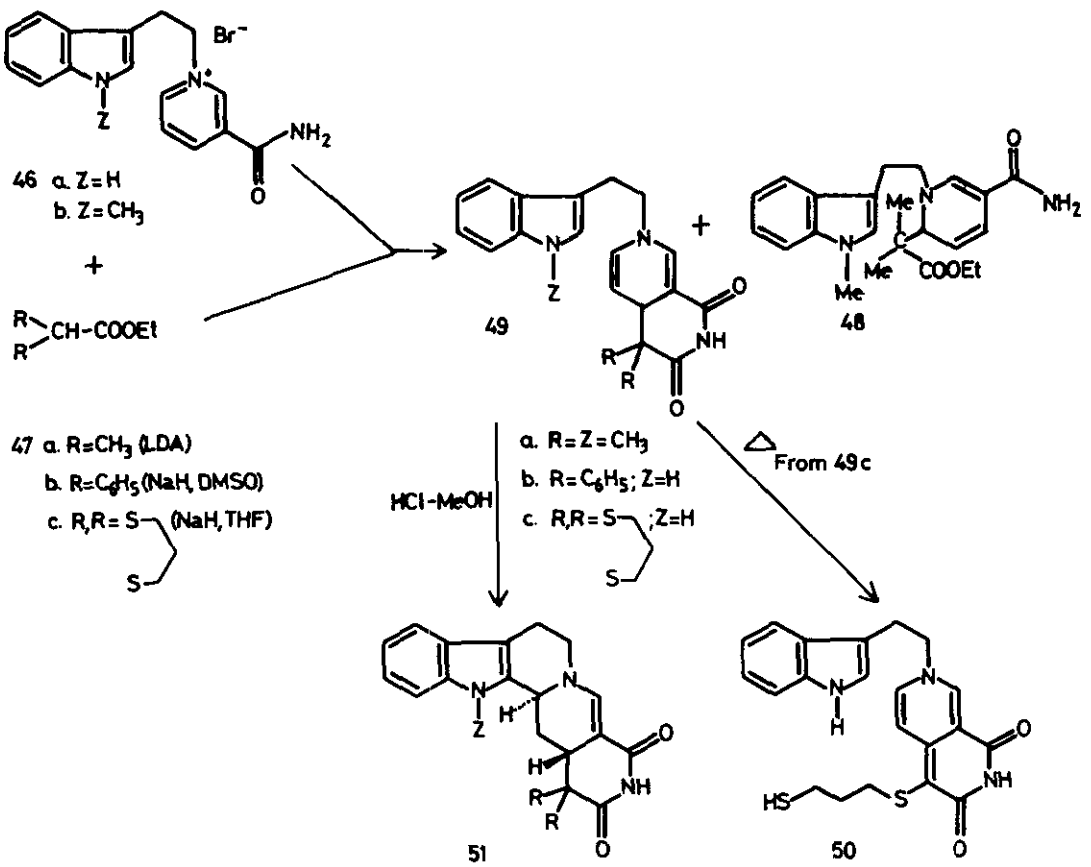
45

The straightforward construction of the above bridged systems clearly illustrates that the scope of the scheme of alkaloid synthesis developed by Wenkert can be extended to the synthesis of bridged polycyclic systems fused to the indole nucleus.

The intermolecular addition of ester α-anions to 1-(indolylethyl)-3-carbamoylpyridinium salts, followed by acid-catalyzed cyclization of the resultant (indolylethyl)naphthyridines, has been reported as a convenient route to synthesize pentacyclic naphthyridocarboline derivatives.[39] Thus, reaction of the anion derived from ester **47a** with salt **46b** led to a mixture of the α-adduct **48** and the naphthyridine derivative **49a**. Formation of the latter involves γ-addition to the pyridinium salt and subsequent cyclization of the intermediate adduct to the imide system **49**.

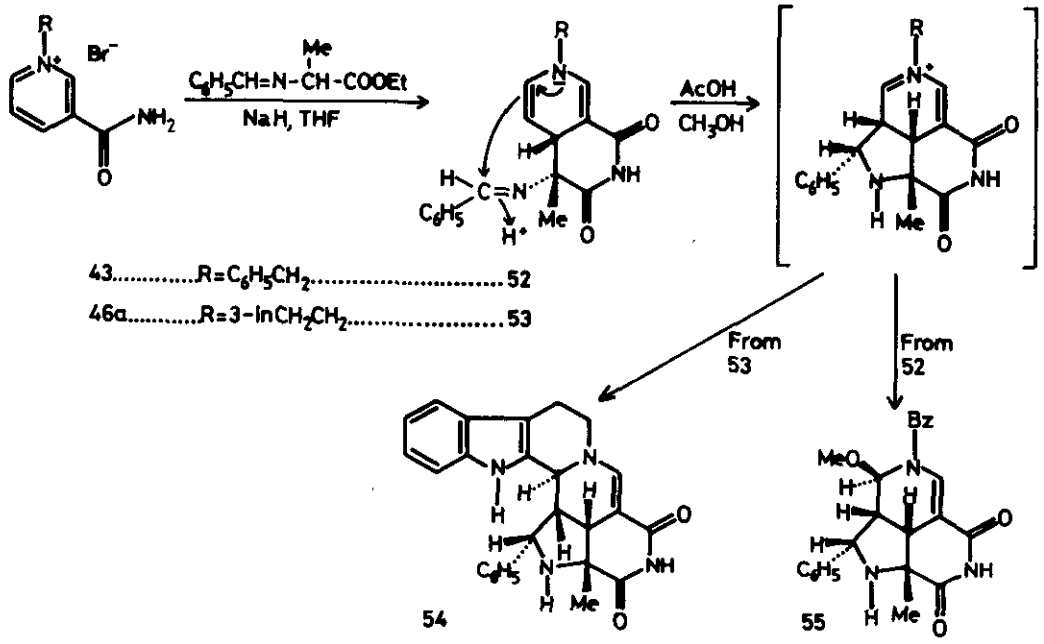
In contrast to the above result, addition of the anions of esters **47b** and **47c** to pyridinium salt **46a** led to naphthyridine-1,3-dione derivatives (**49b** and a mixture of **49c** and **50**, respectively) as the only isolable products (yield ca 50%). Compounds **49a-c** were cyclized in excellent yields (90%) to naphthyridocarbolines **51a-c**, respectively, by treatment with acid .[39]

The different regioselectivity in the addition of ester **47a**, as compared with **47b** or **47c**, is consistent with the different stabilization of the corresponding enolates. In the latter cases, the negative charge in the nucleophile is more stabilized and an equilibrium can be established



between the α-adduct and the thermodynamically favoured 1,4-dihydropyridine which, furthermore, undergoes irreversible cyclization to a stable imide system. The presumably greater stability of the radical formed by electron transfer from the enolates derived of **47b** and **47c** could also account for the exclusive observation of γ-attack to the pyridinium salt.

Similarly, the anion derived from the benzylidene derivative of alanine ethyl ester added to salts **43** and **46a** to form the anticipated naphthyridinediones **52** and **53**, respectively. Acid treatment of **53** gave hexacycle **54**, whose formation involves protonation of the benzylidene nitrogen, nucleophilic attack of the enamine moiety and, finally, electrophilic cyclization upon the indole nucleus.[39] A similar acid treatment from **52** afforded the polyheterocyclic compound **55**.[40]

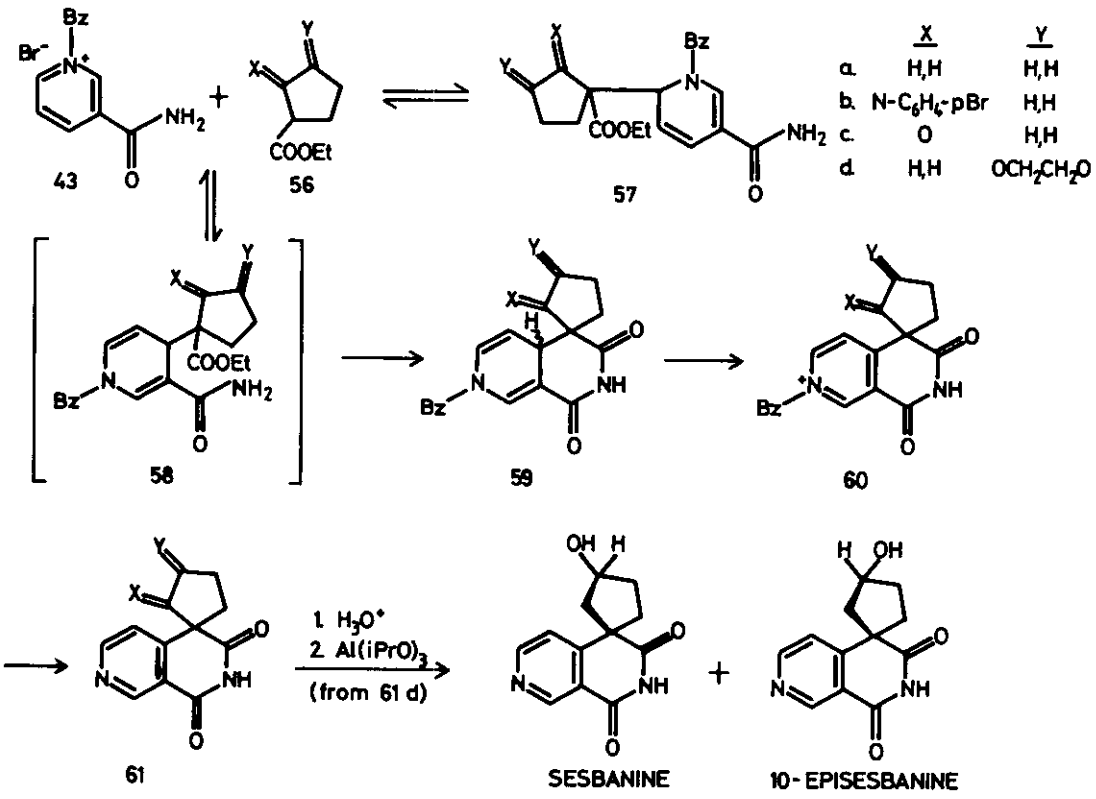


2.2. Addition followed by oxidation or reduction

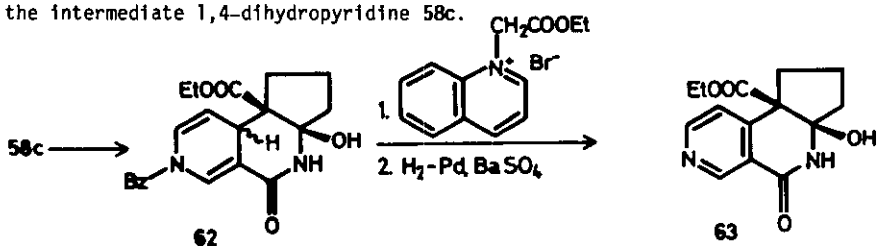
The dihydropyridines resulting from nucleophilic addition of carbanions to pyridinium salts can act as hydride donors either under the reaction conditions of the addition step or in a separate synthetic step.

Some examples of *in situ* oxidation of 1,2-[26] or 1,4-dihydropyridines,[24] in which the starting pyridinium salt acts as hydride acceptor, have been discussed above (see 2.1). In other cases, the dihydropyridine systems can be further oxidized by potent hydride acceptors such as *N*-benzyl- or *N*-(ethoxycarbonylmethyl)quinolinium salts to give stable pyridinium salts which can be subsequently elaborated to the desired products. This two-step operation (addition followed by oxidation) has been satisfactorily used in the context of the synthesis of sesbanine[40,41] and structural analogues possessing the unusual 2,7-naphthyridine-4-spirocyclopentane framework of this alkaloid.[40,42]

The strategy for the construction of the tricyclic ring system of sesbanine involves the reaction of an appropriately substituted cyclopentyl ester anion with *N*-benzylnicotinamide (**43**), followed by oxidation of the resultant 1,4-dihydropyridine and subsequent debenzylation. Thus, reaction of salt **43** with the enolate derived from **56a** (LDA) gave a mixture of 1,2-dihydropyridine **57a** (25%) and naphthyridine **59a** (51%), in which cyclization of the intermediate 1,4-adduct **58a** to an imide system had occurred.[40,42] Similarly, addition of the anion of **56d** (LDA) to **43** gave the 2,7-naphthyridine derivative **59d** (50%) along with the C-6 addition product **57d**.[40,41] In contrast, the



reaction of **43** with the more stable anions derived from **56b** (NaH, THF) or **56c** (potassium salt) led exclusively to the *γ*-addition products **59b** (97%) and **62** (67%), respectively.[40,42] The latter was formed by attack of the amide nitrogen to the keto group, instead of to the ester function, in the intermediate 1,4-dihydropyridine **58c**.

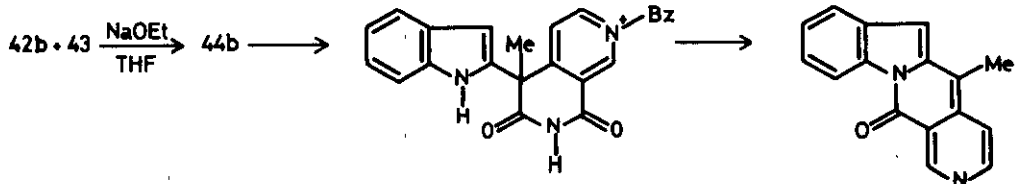


The different regioselectivity of the above additions is worthy of comment since, again, it increases with the stability of the nucleophile. When the reaction is carried out with relatively stable anions, the equilibrium is established between *α*- and *γ*-dihydropyridine adducts (**57** and **58**, respectively) to give the thermodynamic product, whereas with less stable anions mixtures of the kinetic *α*-adduct **57** and 1,4-dihydropyridines are formed.[40]

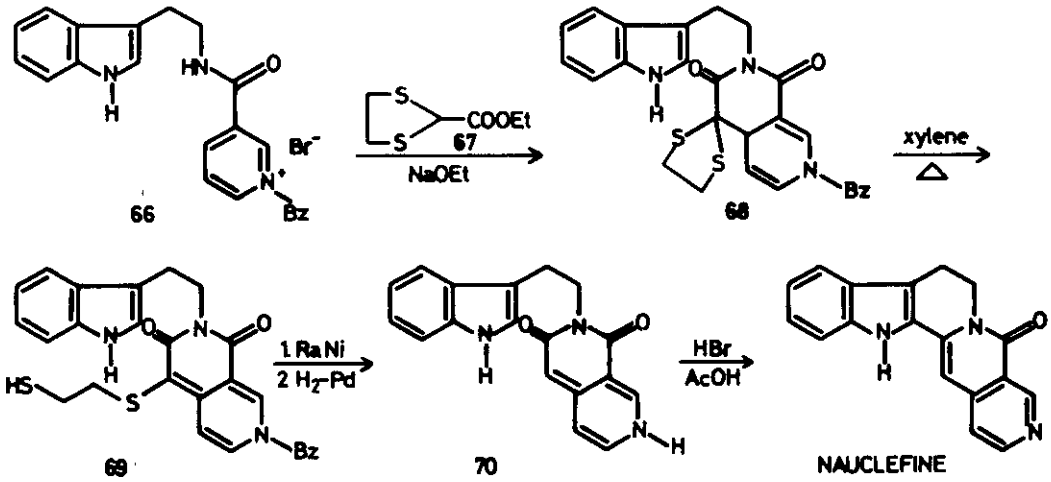
Oxidation of dihydropyridines **59a-b** and **62** was carried out by reaction with N-(ethoxycarbonylmethyl)quinolinium bromide to give in excellent yields the corresponding pyridinium salts, which were debenzylated to the pyridines **61a-b** and **63**, respectively, by hydrogenolysis over palladium

or by reaction with triphenylphosphine in DMF.[40] In the case of **59d**, N-benzylquinolinium bromide was used as oxidizing agent (67%), and the resulting pyridinium salt **60d** could be most conveniently (78%) debenzylated to **61d** by heating in vacuo. Deprotection of the carbonyl function of **61d** followed by stereoselective reduction gave a 6:1 mixture of (±)-sesbanine and its 10-epimer.[40,41]

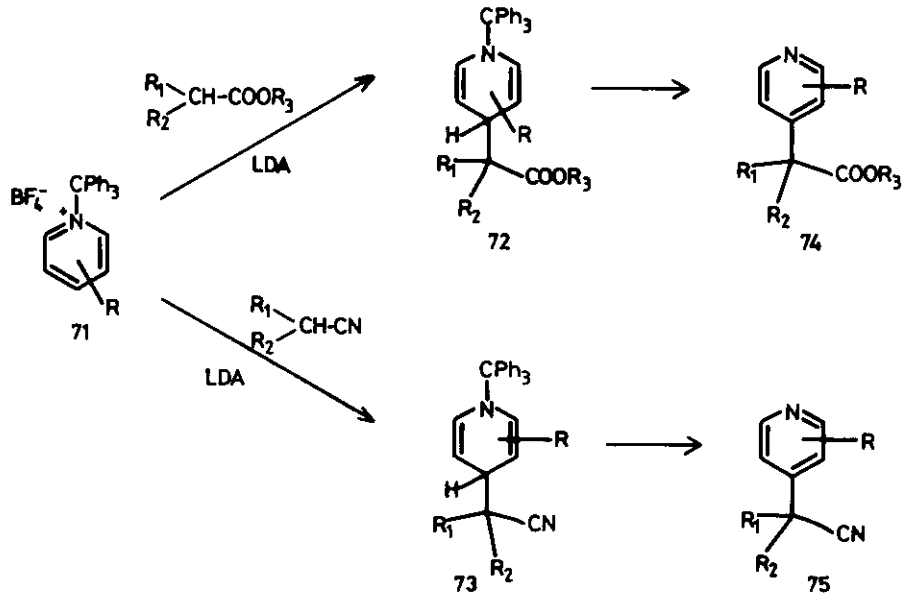
The following reaction sequence illustrates another example in which a 1,4-dihydropyridine is stabilized by oxidation. The unstable naphthyridinedione **44b**, prepared as the above derivative **44a**, was converted (95%) to pyridinium salt **64** by treatment with N-benzylacridinium bromide. Alcoholysis of **64** with potassium carbonate (DMSO-ROH) produced opening of the imide ring, followed by decarboxylation and intramolecular acylation of the indole nitrogen, to give tetracycle **65**.[39]



The synthesis of the indole alkaloid nauclefine illustrates an alternative fashion to transform the initially formed 1,4-dihydropyridine into a pyridine system by the way of a 1,4-dihydro-4-pyridylidene derivative. Reaction of N-benzylpyridinium salt **66** with the anion of ester **67** proceeded as expected to give dihydropyridine **68** which, upon heating, was converted to the dihydropyridylidene derivative **69** via a simple thiol elimination. Dihydropyridine **49c** showed a similar behavior, and protonation of the resulting dihydropyridylidene **50** produced a stable naphthyridinium ion. Desulfurization of **69** followed by removal of benzyl group gave the tautomeric pyridine derivative **70**, which was cyclized to nauclefine.[39]

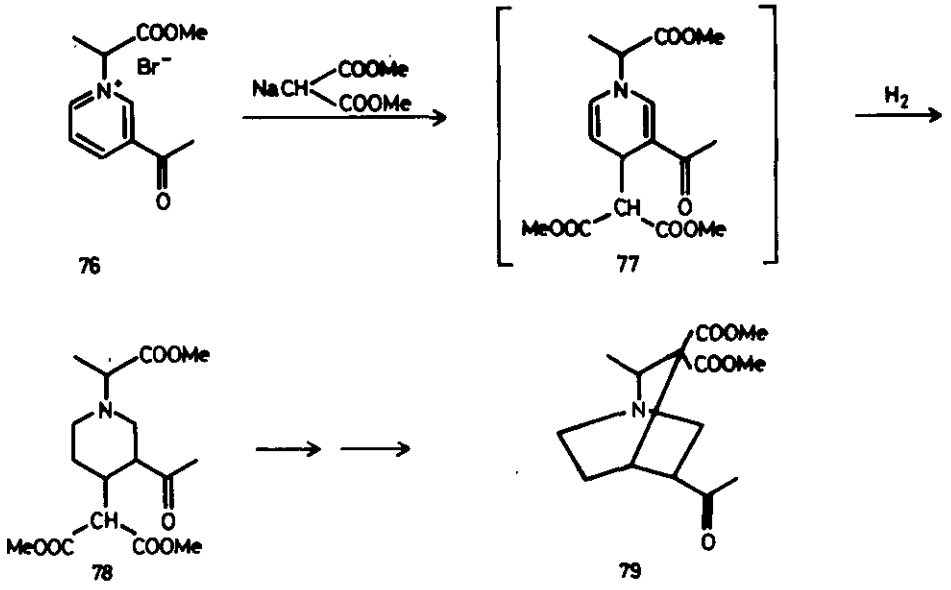


The oxidation of 1,4-dihydropyridines resulting from reaction between ester or nitrile α-anions and N-triphenylmethylpyridinium salts constitutes a convenient method for preparing regiospecifically α-(4-pyridyl)-esters or -nitriles, respectively.[43] Thus, addition of salts **71** to a tetrahydrofuran solution of the ester or nitrile lithium salts gave dihydropyridines **72** or **73**, respectively, which were not normally isolated, although in some cases isolation and characterization by ^{1}H-NMR spectroscopy was possible. Decomposition of these intermediate dihydropyridines to the corresponding pyridines **74** or **75** occurs either under the reaction conditions or in a separate step by air or dibenzoyl peroxide oxidation. The overall yield from the starting pyridines was of ca. 50%.



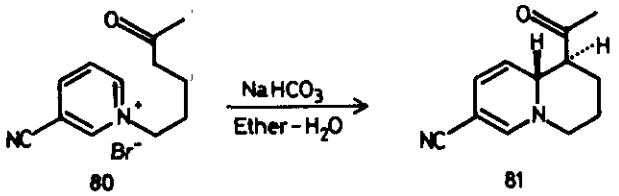
On the other hand, reduction of the dihydropyridine adducts formed by addition of carbon nucleophiles to N-alkylpyridinium salts could be a priori envisaged as an useful synthetic operation to stabilize those unstable systems and, simultaneously, to prepare 2-piperideines or piperidines. However, this two-step sequence (intermolecular addition followed by reduction) has received a few attention probably due to the reported discouraging results. On the contrary, it has been successfully used in the context of intramolecular additions (see below). Thus, attempts of hydrogenation of dihydropyridine adducts **7** over platinum or palladium led to products from which the malonate ester residue had been extruded.[18]

More recently, hydrogenation of 1,4-dihydropyridine **77** has been reported.[44] 3-Acetylpyridinium salt **76** was alkylated with dimethyl sodiomalonate and, without isolation, the labile dihydropyridine intermediate was hydrogenated to the piperidine **78**, although in very low yield (6%). This piperidine was further converted to the quinuclidine derivative **79**.

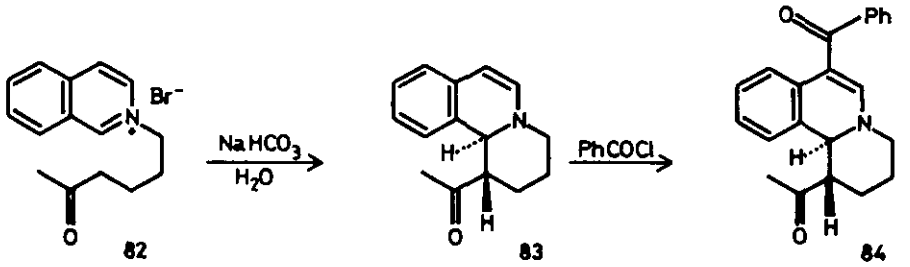


3. INTRAMOLECULAR ADDITIONS

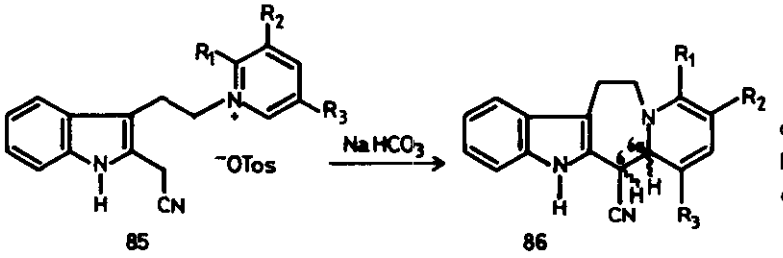
There are some important differences between the intra- and intermolecular modes of addition of stabilized carbon nucleophiles to N-alkylpyridinium salts. Firstly, inasmuch as the intramolecular dihydropyridine adducts are entropically less disfavoured than the intermolecular ones, they are generally obtained in higher yields and can be conveniently isolated and handled. Even in some cases the presence of an electron-withdrawing substituent at the β-position of the pyridinium salt is not a necessary requisite for the success of the addition. Secondly, given that the intramolecular addition involves a cyclization, the regioselectivity of the process (nucleophilic α- or γ-attack) is often governed by structural reasons. This fact is illustrated by the intramolecular condensation of N-(5-oxohexyl)pyridinium salt **80** under extremely mild conditions. The α-adduct **81** was obtained in 72% yield as a solid that could be chromatographed and crystallized.[45] As it could be expected,[20] the process is reversible and under acidic conditions (HCl, CF_3COOH) the dihydropyridine **81** was converted into the starting salt **80**.



The utility of this annulation procedure has been demonstrated by extending the reaction to the isoquinolinium salt **82**. The resultant unstable dihydroisoquinoline **83** was benzoylated to form the characterizable derivative **84**.[45] The absence of an electron-withdrawing substituent at the β-site of dihydropyridine ring could account for the instability of **83** as compared with **81** and **84**.

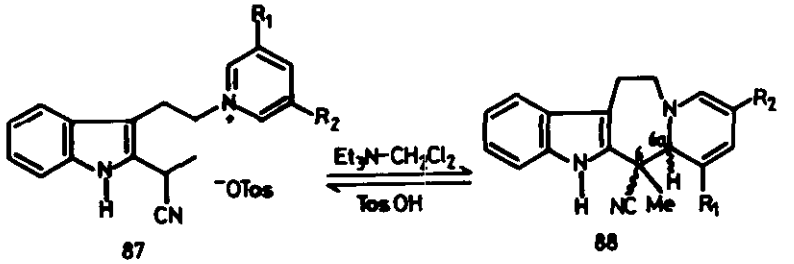


Cyclization of N-(2-cyanomethyltryptophyl)pyridinium salts **85** constitutes another interesting example of intramolecular addition of an enolate to the α-position of a pyridinium salt, favoured against the γ-attack by structural reasons.[46] Thus, salts **85** were rapidly transformed into dihydropyridines **86** when treated with $NaHCO_3$. Dihydropyridines **86a** (a single isomer having the 6-H/6a-H cis-relationship) and **86b** (an epimeric mixture in which predominated the cis-isomer) were obtained in 90% yield, again as stable crystalline substances, whereas dihydropyridines derived from **85c** were quite unstable and were not characterized.



	R_1	R_2	R_3
a.	H	CN	H
b.	H	COOMe	COOMe
c.	COOMe	H	COOMe

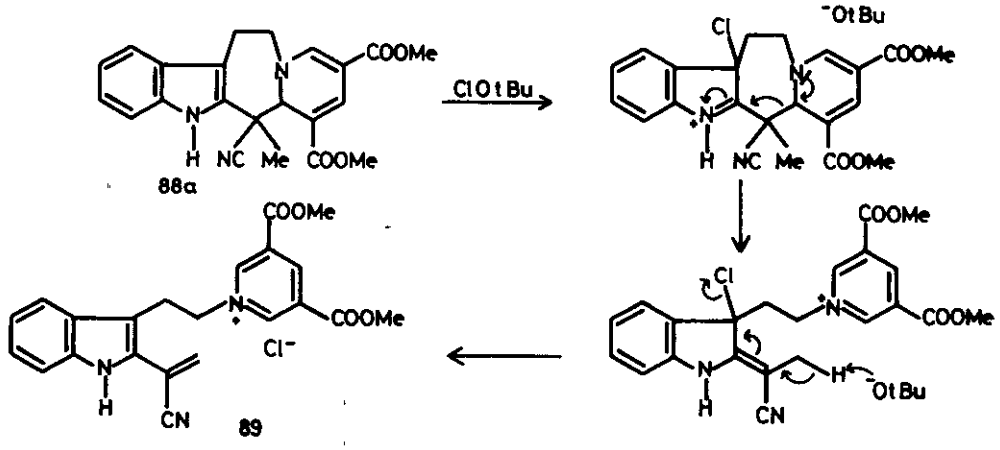
Similarly, in the context of studies on the synthesis and chemistry of a stabilized dehydrosecodine model system,[47] pyridinium salts **87a-c** were cyclized with triethylamine (or DBN in the case of **87b**) to afford in excellent yields mixtures of the epimeric α-adducts **88a-c**, respectively. In each case, the 6-Me/6a-H trans-epimer was formed as the major product. The separated epimers were stable in crystalline form but underwent epimerization in solution. All of these condensations could be reversed in the presence of strong acids.[20]



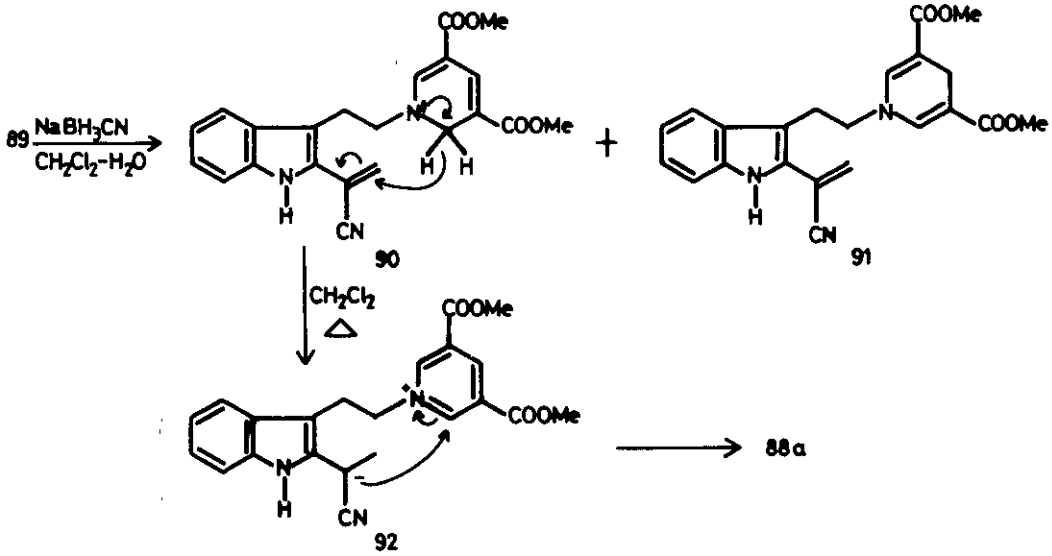
a. R_1=R_2= COOMe 79%
b. R_1=H; R_2=COOMe 98%
c. R_1=H; R_2= CN 50%

It is worth mentioning that dihydropyridines **86** and **88** incorporate the pyrido[1',2':1,2]azepino-[4,5-b]indole system present in the tetracyclic indole alkaloid ngouniensine.[48]

The bis(methoxycarbonyl)dihydropyridine **88a** was found to undergo an interesting oxidative fragmentation[47] with tert-butyl hypochlorite to give the (2-vinyltryptophyl)pyridinium salt **89** in 88% yield. The mechanism of this reaction is believed to involve initial chlorination at the 3-position of the indole nucleus followed by fragmentation of the seven-membered ring, as shown in the following Scheme. In contrast, dihydropyridine **88b**, which lacks the C-3 methoxycarbonyl substituent, undergoes chlorination at the dihydropyridine ring to give (95%) the corresponding 3-chloro-1,2-dihydropyridine.



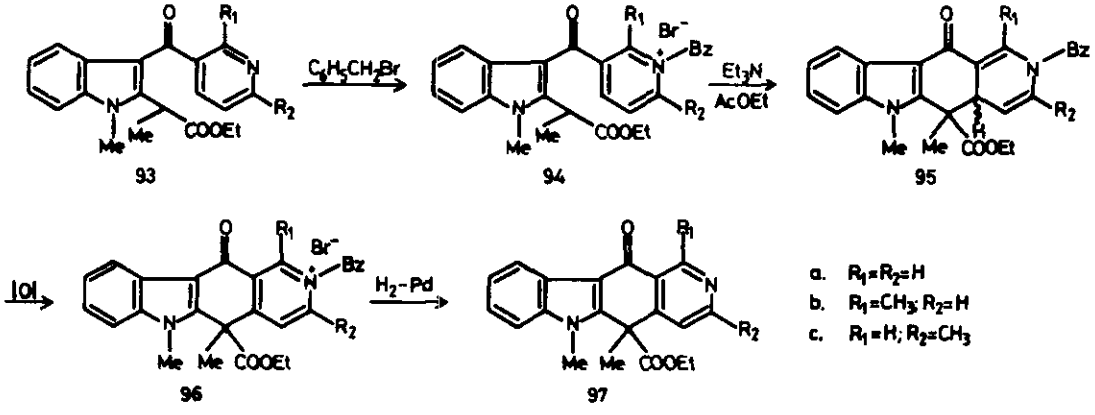
1,2-Dihydropyridine **90**, obtained together with the 1,4-isomer **91** by sodium cyanoborohydride reduction of pyridinium salt **89**, undergoes an intramolecular hydride transfer with oxidation of the dihydropyridine ring and reduction of the vinyl group. The resulting betaine intermediate **92** collapses (11% yield) to the previously isolated cyclic dihydropyridine epimers **88a**.[47] This cycli-



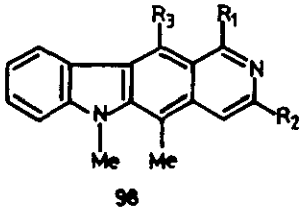
zation involves an intramolecular nucleophilic attack of a nitrile α-anion to the α-position of a pyridinium salt.

As in the intermolecular mode of addition, the intramolecular dihydropyridine adducts can be oxidized to the corresponding pyridinium salts and subsequently N-dealkylated to give pyridines. This methodology (intramolecular nucleophilic addition to the γ-position of an N-benzylpyridinium salt followed by oxidation of the resulting 1,4-dihydropyridine and subsequent debenzylation) has been successfully used by Pandit for the construction of the tetracyclic pyrido[4,3-b]carbazole skeleton of the indole alkaloids ellipticine and olivacine.[39,49-51]

Thus, quaternization of pyridyl ketone **93a** with benzyl bromide afforded pyridinium salt **94a**, which was directly used for the critical ring closure step. Cyclization of **94a** to dihydropyridine **95a** (mixture of epimers) proceeded smoothly upon reaction with triethylamine at room temperature (overall yield 81%).[39,49] Oxidation of **95a** with N-benzylacridinium bromide (90% yield) followed by reductive debenzylation (80% yield) gave pyridine **97a**.

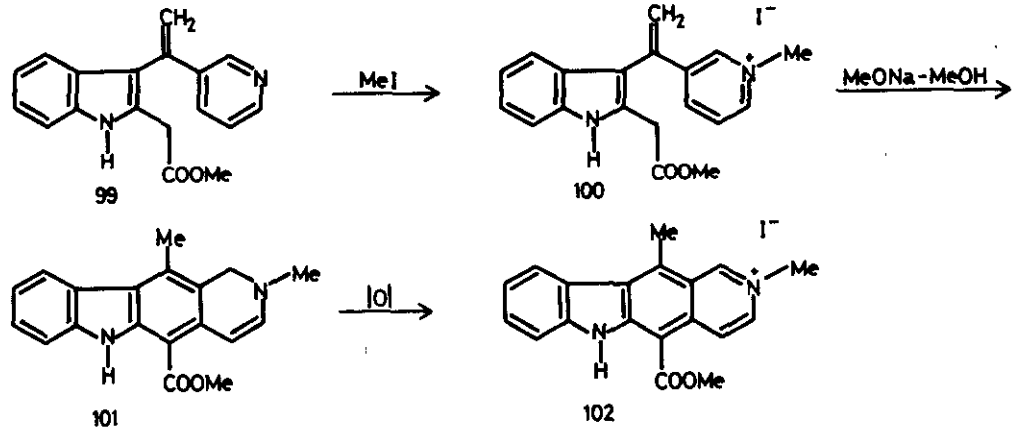


Similarly, starting from methylpyridyl ketones **93b**[39,50] and **93c**,[51] through a sequence of reactions consisting in quaternization, intramolecular nucleophilic addition, oxidation, and reductive debenzylation, pyridines **97b**[39,50] and **97c**,[51] respectively, were obtained. In the 2-methyl series the overall yield of the transformation **93**→**97** was 49% whereas in the 6-methyl series was 21%. Compounds **97** served as central intermediates for the synthesis of diverse ellipticine and olivacine analogues **98**.[39,49-51]

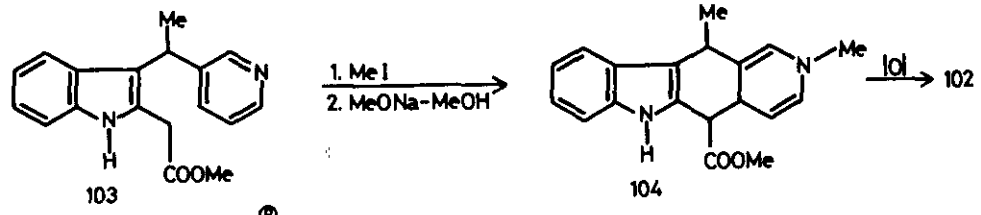


	R_1	R_2	R_3	
a	H	H	OH	ref. 39,49
b	H	H	Me	(or n-Bu, Bz, C_6H_5) ref. 39,50
c	Me	H	H	ref. 39,50
d	H	Me	Me	ref. 51
e	H	Me	H	ref. 51

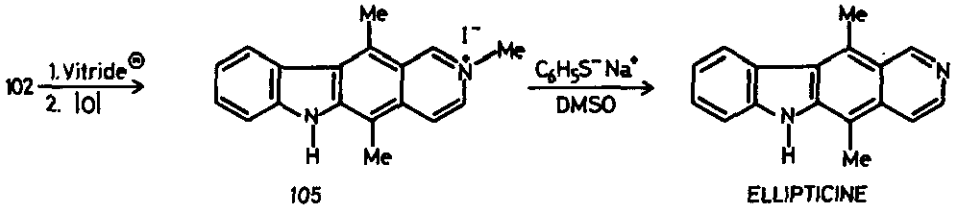
The above synthetic approach to the pyridocarbazole ring system is based on the intramolecular attack of an ester enolate to a pyridinium salt activated by an electron-withdrawing substituent. A closely related synthesis using an N-unsubstituted indole derivative and an unactivated N-methylpyridinium salt allowed the synthesis of ellipticine.[52] Thus, quaternization of indolyl pyridyl ethylene **99** to N-methylpyridinium salt **100** and immediate treatment with sodium methoxide in methanol produced the dihydropyridocarbazole derivative **101**, by isomerization of the initially formed 1,4-dihydropyridine. Oxidation of **101** by addition of N-methyl-3-ethoxycarbonylpyridinium iodide to the reaction mixture afforded the pyridinium salt **102**. The overall yield of the above *three-step sequence was 78%.*



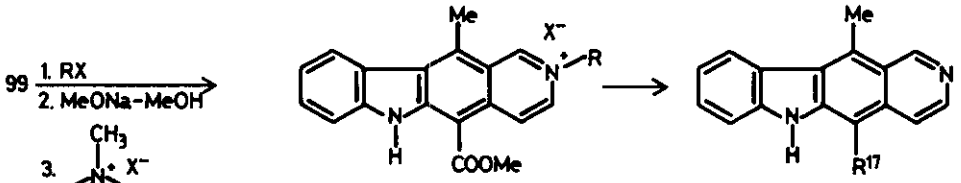
The same salt **102** was obtained in 57% overall yield through a similar synthetic sequence involving nucleophilic attack to a pyridinium salt bearing a 3-alkyl substituent.[52] In this case, no *isomerization of the first formed* 1,4-dihydropyridine **104** was observed.



Treatment of **102** with Vitride® brought about ester and pyridine reduction to give a dihydropyridine which was immediately reoxidized to **105**. Demethylation of salt **105** to ellipticine was satisfactorily accomplished (91%) by using *sodium thiophenoxide.*[52]



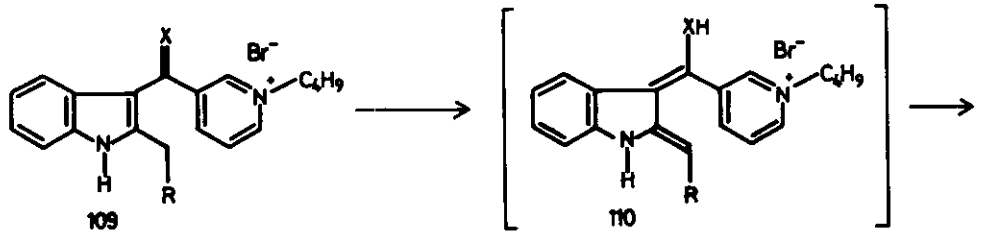
This synthetic entry to the pyridocarbazole ring system is quite general since starting from **99**, several ellipticine analogues **108**, oxidized at C-17, were obtained.[53] N-Benzylpyridinium salts **106** and **107** (80% overall yield) were prepared by a three-step reaction sequence similar to that employed for the preparation of the N-methyl derivative **102**. However, both demethylation of **102** with sodium thiophenoxide and debenzylation of **106** under a variety of experimental conditions were unsuccessful. The required N-dealkylation to **108a** could only be accomplished from the N-(p-nitrobenzyl)pyridinium salt **107**, either by reaction with p-nitrosodimethylaniline (47%) or by hydrogenolysis in the presence of palladium on charcoal (30%).

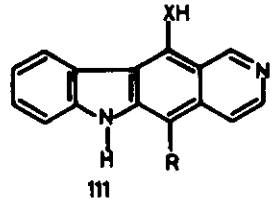


102 R= Me; X=I
106 R= $CH_2C_6H_5$; X=Br
107 R= $CH_2C_6H_5$ p-NO_2; X=Br

108 a. R= COOMe
b. R= CH_2OH
c. R= CHO
(17-oxoellipticine)

It is worth mentioning an efficient synthesis (72%) of ellipticine (**111a**) based on the thermolysis (350°C, 5 min) of pyridinium salt **109a**,[54] although the cyclization probably proceeds via an o-quinodimethane intermediate **110**. A similar result was obtained by heating (80°C) **109a** with sodium ethoxide in ethanol. Under these conditions cyclization probably involves nucleophilic attack of an indole α-anion to the pyridinium salt. However, when the related salt **109b** was pyrolyzed, only a trace of the pyrido[4,3-b]carbazole **111b** was isolated.[55] On the other hand, attempted photochemical or thermal cyclizations of 3-acylpyridinium salt **109c** were unsuccessful.[55]

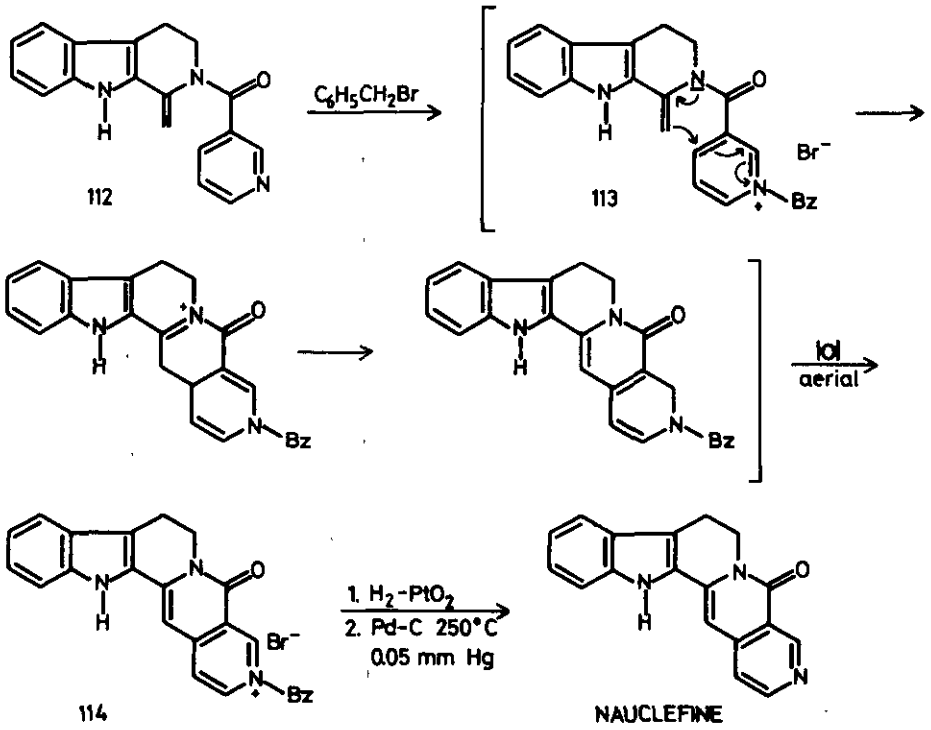




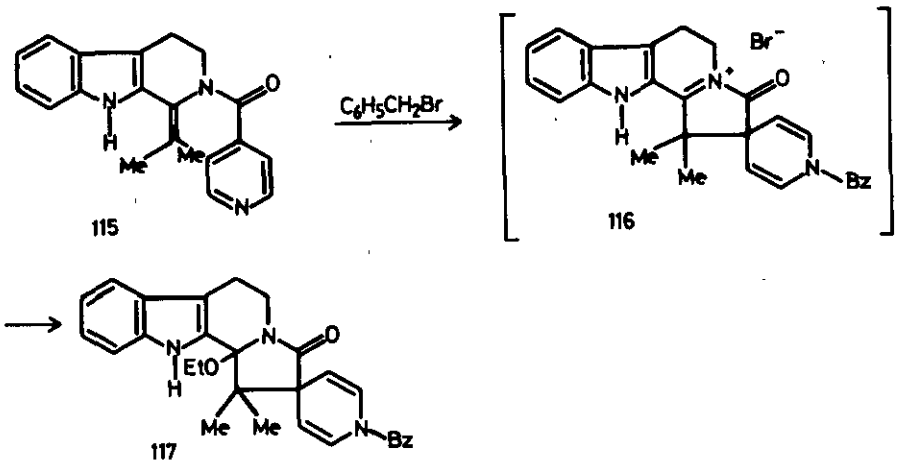
a. R=Me; X = CH_2
b. R=Et; X = CH_2
c. R=Me; X=O

The following synthesis of the indole alkaloid nauclefine offers an example of intramolecular nucleophilic attack of an enamide β-carbon to the γ-position of a 3-acyl-N-benzylpyridinium

salt.[56] Thus, when enamide **112** was treated with benzyl bromide the only product isolated was the the pentacyclic quaternary salt **114**. Its formation can be rationalized by considering that the initially formed pyridinium salt **113** undergoes regiospecific cyclization and that the resulting dihydropyridine (or tautomer) is rapidly oxidized by air. Pyridinium salt **114** was debenzylated to nauclefine by heating in toluene containing acetic acid and sodium acetate (55% overall yield from **112**)[56a] or, more efficiently, by hydrogenation followed by heating with palladium-charcoal (65% overall yield).[56b]

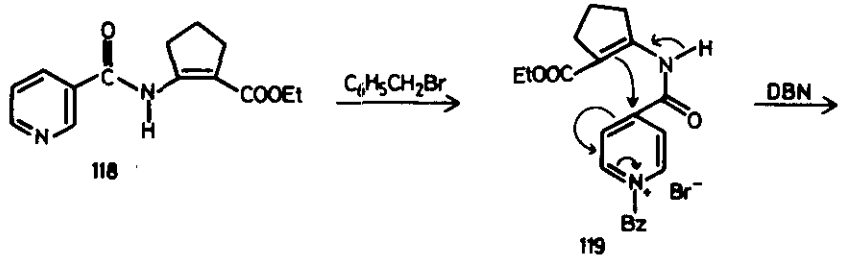


A related cyclization was observed when enamide **115** was treated with benzyl bromide.[56b] The nu-

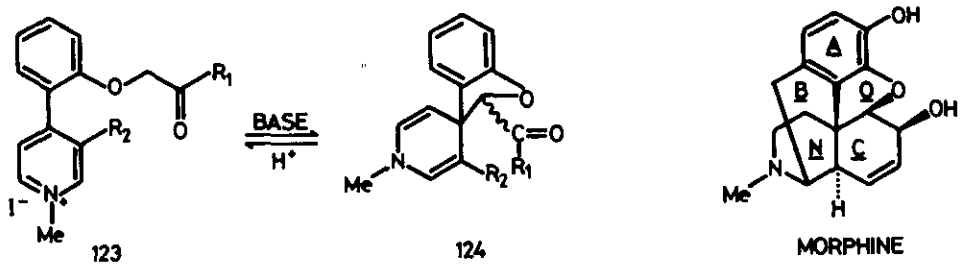


cleophilic β-carbon of the enamide moiety promotes again the cyclization by attack to the γ-position of the initially formed pyridinium salt. After column chromatography, the pentacyclic dihydropyridine **117**, which arises from the anticipated acyliminium salt **116** by attack of the solvent diethyl ether, was obtained (25%) as a crystalline solid. In this case, the quaternary spiro carbon prevents oxidation of the dihydropyridine ring.

A further example of intramolecular addition of an enamide carbon to a pyridinium salt followed by oxidation of the resulting dihydropyridine and subsequent debenzylation is depicted in the following Scheme. Treatment of N-benzylpyridinium salt **119** with DBN gave dihydropyridine **120** in 52% yield. In this case the oxidation was effected (91%) with N-(ethoxycarbonylmethyl)quinolinium bromide and the benzyl group was removed by hydrogenolysis (71%).[40]



The intramolecular addition of ketone and ester enolates to 4-arylpyridinium salts to produce spiro[benzofuran-3(2H),4'(1'H)-pyridines] has been employed as the key step in several synthetic approaches to simplified analogues of the morphine alkaloids.[57-61] Thus, pyridinium salts **123a** and **123b** were cleanly converted into the corresponding 1,4-dihydropyridines **124a** (92%)[57,58] and **124b** (80%)[60] by treatment with 4N sodium hydroxide in benzene-DMSO. The ester analogue **124c** was was prepared in 87% yield by treatment of **123c** with sodium ethoxide in ethanol.[57,58] Similarly, in order to explore the formation of C-3 substituted dihydropyridines, 4-(2-hydroxyphenyl)-1,3-dimethylpyridinium iodide was alkylated with chloroacetone and then treated with base (4N sodium hydroxide in benzene-hexane) to afford dihydropyridine **124d** (87% yield) as a 3:2 mixture of anti-syn isomers.[58] The spiro dihydropyridines **124** contain the tricyclic ANO ring system and the important quaternary carbon of the morphine molecule. As expected, the ring closure could be reverted by acid treatment, and dihydropyridines **124a** and **124c** were easily reconverted to the cor-



123 124

a. $R_1=CH_3$; $R_2=H$ c. $R_1=OCH_2CH_3$; $R_2=H$

b. $R_1=CH_2CH_2OCH_3$; $R_2=H$ d. $R_1=CH_3$; $R_2=CH_3$

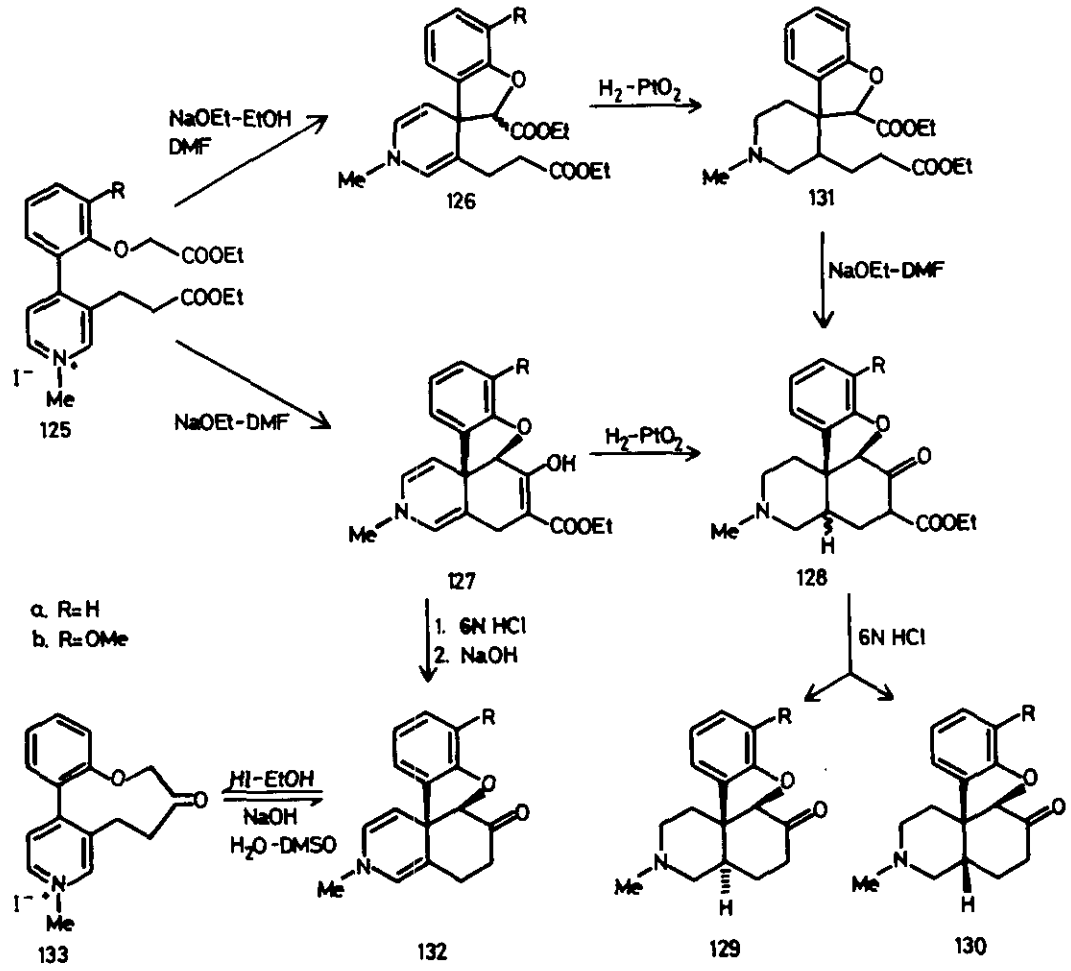
responding pyridinium salts with concentrated hydriodic acid or triethylammonium iodide in refluxing ethanol.

Two interesting features of the above ring closures are worthy of comment: the absence, again, of a stabilized electron-withdrawing group at the β-position of the dihydropyridine and the formation of a quaternary carbon center in the addition reaction.

The above methodology has been extended[59,60] to the preparation of partially reduced benzofuro-[3,2-e]isoquinoline derivatives, the tetracyclic skeleton of which corresponds to the ACNO ring system of morphine. In these cases, the starting pyridinium salt incorporates an ester-containing β-side chain that promotes a Dieckmann cyclization after the intramolecular addition step. Thus, treatment of pyridinium salt **125a** with sodium ethoxide in ethanol-DMF afforded (92%) dihydropyridine **126a** as 45:55 mixture of syn and anti epimers. However, the use of ethanol-free sodium ethoxide resulted in the formation of dihydrobenzofuroisoquinoline **127a** as the sole product (72%) by sequential closure of O and C rings.

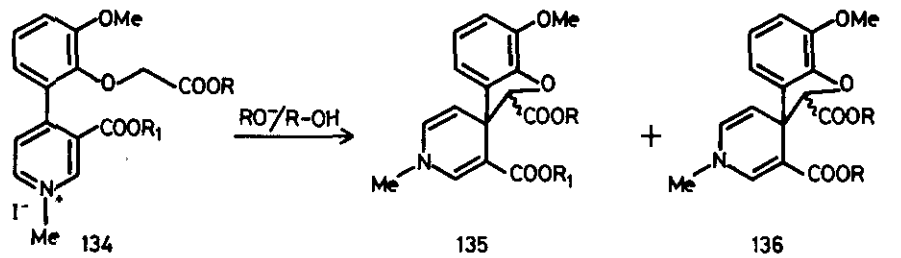
In contrast with the behavior of the intermolecular dihydropyridine adducts, catalytic hydrogenation of dihydropyridine **127a** gave in nearly quantitative yield a stereoisomeric mixture of the fused, polysubstituted piperidine **128a**. This hydrogenation is highly selective for the trans C/N ring junction characteristic of the morphine series, since subsequent acid hydrolysis of **128a** afforded (76%) a mixture of **129a** and **130a** in a ratio of 88:12. However, this ratio is reversed when catalytic hydrogenation (96%) is effected at the spirocyclic dihydropyridine stage (**126a**), prior to closure of the C ring by Dieckmann cyclization (64%). The isomeric mixture of piperidines **128a** obtained through this sequence was converted, as above, into **129a** and **130a**, but in a ratio of 29:71, respectively.[59,60]

Interestingly, 1,4-dihydropyridine **132a**, which was prepared from **127a**, undergoes elimination of the enol moiety with regeneration of a pyridinium species upon treatment with hydriodic acid. The resulting 3-oxacyclononanone derivative **133** was readily reconverted to **132a** with sodium hydroxide in aqueous DMSO.[59]



The synthesis of the benzofuroisoquinolines in the pharmacologically more interesting methoxy series was performed in a similar manner, from salt **125b**, through the three-step sequence **125b**——**127b** (69%)——**128b** (100%)——**129b**+**130b** (88:12 ratio; 68%).[60] *As in the above demethoxy series, the* Dieckmann cyclization of the initially formed dihydropyridine adduct is very slow in the presence of added ethanol and, under these conditions, spiro dihydropyridine **126b** is obtained in 63% yield as a mixture of epimers.

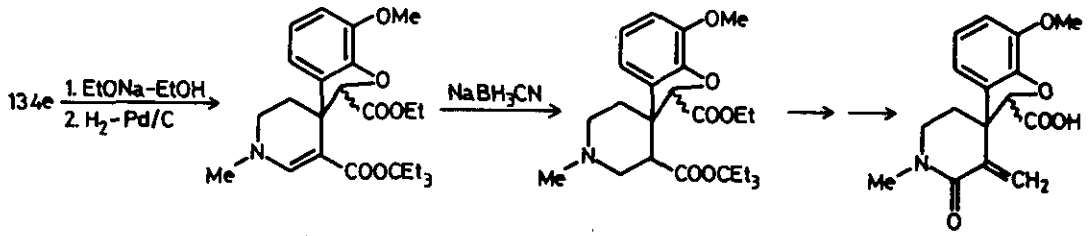
When the intramolecular ester enolate ring closure was effected from pyridinium salts **134**, having an alcoxycarbonyl substituent at the β-position, the expected tricyclic spiro[benzofuran-dihydropyridine] systems were obtained.[61] Thus, although treatment of **134a** with a variety of bases under *aprotic conditions* (LDA, LiTMP, KH, and t-BuOK in THF and DMF) afforded unrecognizable products, ring closure was satisfactorily accomplished with methoxide in methanol. However, under these conditions transesterification of the nicotinate ester was competitive and a 1:1 mixture of



134 135 136

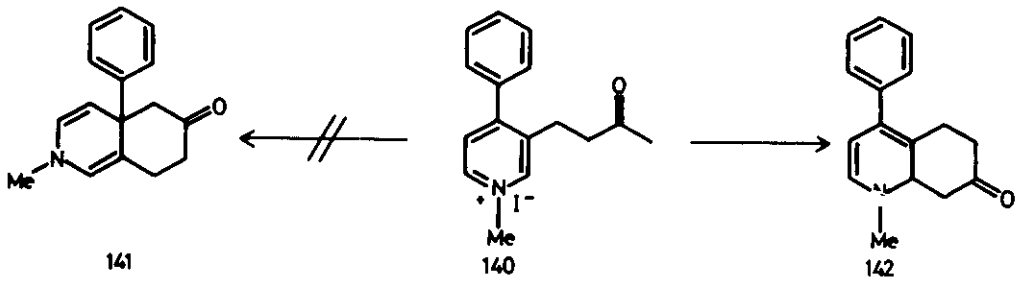
	R	R_1	135/136 ratio
a.	Me	t-Bu	1
b.	Et	t-Bu	2
c.	iBu	t-Bu	5
d.	Me	Et_3C	10
e.	Et	Et_3C	>20

esters **135a** and **136a** was formed. The use of other diester combinations (**134b-d**) afforded similar mixtures (see Scheme), whereas the bulkier 3-ethyl-3-pentyl ester (**134e**) prevented the transesterification and allowed the preparation of spiro dihydropyridine **135e** in 71% yield as a 10:1 mixture of diastereomers. The dihydropyridine double bonds could be reduced in two separate synthetic steps. Catalytic hydrogenation of **135e** brought about selective reduction of the unsubstituted enamine function to give (78%) tetrahydropyridine **137**. Subsequent sodium cyanoborohydride reduction of the vinylogous urethane double bond provided (96%) piperidine diester **138**, which was then converted to the α-methylene lactam **139**. This intermediate had been earlier[62] elaborated into an octahydro-1H-benzofuro[3,2-e]isoquinoline derivative containing four rings (ACNO) of the pentacyclic morphine skeleton. When the above three-step sequence **134e**——**138** was effected without purification of any intermediate, the overall yield was 75%.

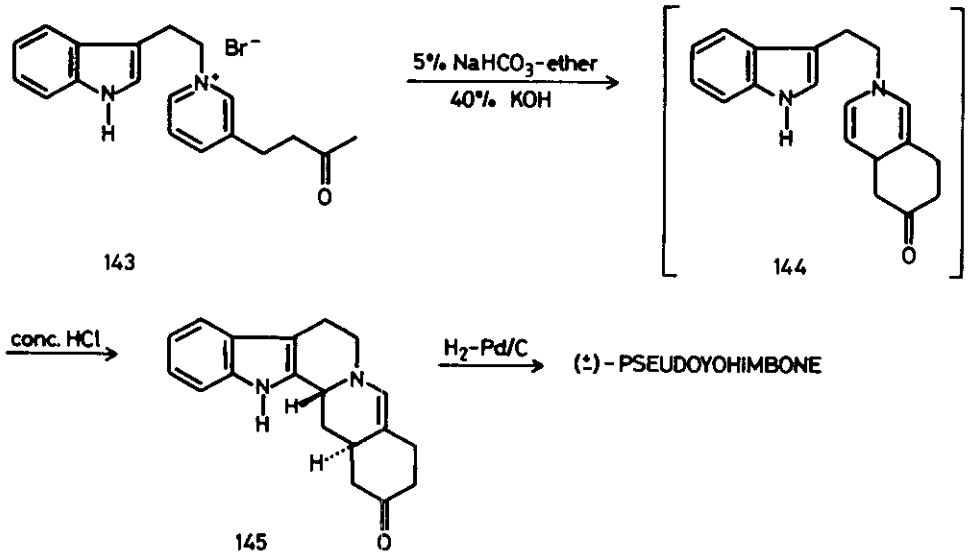


137 138 139

On the other hand, the applicability of the intramolecular pyridinium-enolate addition toward the formation of a related morphine fragment, the 4a-phenyldecahydroisoquinoline ring system **141**, has been investigated.[58] However, when pyridinium salt **140** was treated with 4N sodium hydroxide in DMSO, a single, unstable dihydropyridine, identified as the α-adduct **142**, was obtained in 97% yield.[58] This unusual regioselectivity has been explained by considering that, in this case, the α-adduct **142** is favoured by both steric and resonance factors. Thus, formation of **141** would require the generation of a quaternary carbon at the ring junction while the corresponding carbon



in **142** is tertiary. Furthermore, the diene system is conjugated with the benzene ring in the α-adduct **142**. In accordance with this interpretation pyridinium salt **143**, which bears as the above salt **140** a 3-oxobutyl side chain at the pyridine β-position but lacks the N-aryl substituent, was converted[18] in 14% yield into the pentacyclic ketone **145** by sequential treatment with base and acid, presumably by way of the N-adduct **144**. Hydrogenation of **145** yielded (±)-pseudoyohimbone.



In conclusion, the addition of stabilized carbon nucleophiles to N-alkylpyridinium salts, both in the inter- and the intramolecular modes, constitutes an useful procedure to obtain substituted 1,2- or 1,4-dihydropyridines, which have proved to be versatile synthons for alkaloid synthesis.

ACKNOWLEDGEMENT

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