SOME RECENT WORK ON SCHIFF BASES, IMINES AND IMINIUM SALTS IN SYNTHETIC HETEROCYCLIC CHEMISTRY - A REVIEW+

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Abstract -This review summarizes the versatile use of Schiff bases, imines and iminium salts for synthesizing a great variety of heterocyclic compounds. Addition reactions of Schiff bases with acid anhydrides, acid chlorides and esters have led to the synthesis of penicillins, β-lactams, pyrrolidinones and piperidinones. Condensations of homophthalic anhydrides with Schiff bases have been the key steps for synthesizing isoquinolinones, protoberberines, 8-oxoberbines, benzophenanthridines and indole alkaloids. Reactions of phthalide anions with iminium salts have been utilized for synthesizing protoberberines, phthalide isoquinolines and related alkaloids. Addition of lithium methyl methylthiomethylsulfoxide to Schiff bases and electroreductive addition of alkyl halides to iminium salts are also discussed.

+ Dedicated to Professor Tetsuji Kametani on the occasion of his 66th birthday (1st August, 1983) in appreciation of his continued active interest in Heterocyclic Chemistry.

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The use of ortho halogeno substituted Schiff bases for the synthesis of phenanthridines by photocyclization is discussed in addition to the use of photochemical method for the synthesis of benzoxazoles, benzothiazoles and benzimidazoles from appropriately ortho substituted Schiff bases. The mass spectral fragmentations and UV spectral data of several new Schiff bases are reported.

Contents:

INTRODUCTION

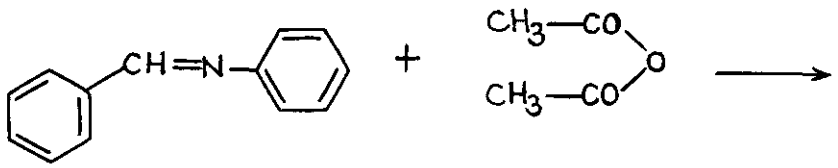
Imines play a significant role in the biosynthesis of α-amino acids and alkaloids. Pictet-Spengler reactions[1] and Pomeranz-Fritsch reactions[2] are prominent in synthetic isoquinoline chemistry. The past few years have witnessed intensifying new and imaginative approaches to the preparation of heterocyclic compounds by use of the imine moiety. Notable among these are 1) the addition reactions with acid chlorides, acid anhydrides (including homophthalic anhydrides), esters, aryloxyacetic acids, mercaptoacetic acid, nitrile oxide in the synthesis of β-lactams, synthetic penicillins, pyrrolidinones, piperidinones, aza analogues of tetrahydrocannabinols, dihydroisoquinolinones, tetrahydroisoquinolines, 8-oxoberbines, benzophenanthridines, thiazoloisoquinolines and oxadiazolines, 2) electroreductive addition of alkyl halides to iminium salts for the formation of alkaloids, 3) addition of anions of methyl methylthiomethylsulfoxide in the synthesis of protoberberines, 4) addition of phthalide anions for the synthesis of protoberberines and phthalide isoquinolines, 5) cyclization of

imine salts from α-amino acid decarbonylation to form berbines, 6) benzyne reactions of orthohalo anils in the synthesis of condensed polynuclear systems such as phenanthridines and benzophenanthridines, 7) cycloaddition reactions of azomethine ylides with alkenes to give pyrrolidines and 8) photochemical cyclizations in the synthesis of phenanthridines and azoles.

One of the earliest reviews on the chemistry of Schiff bases is by Layer in 1963[2a]. Complete references to the work of Kessar on orthohalo anils[3] as also its extensions by other workers are provided by Phillips and Castle[4] and Hearn and Swanson[4]. In Saul Patai's monumental work[5] "The Chemistry of Functional Groups" much of the recent imine chemistry is discussed. Our objective is mainly to highlight some subsequent major contributions.

1. Addition of Acid Anhydrides, Acid Chlorides and Esters to Schiff Bases

Schiff bases can readily be acylated with acid anhydrides and acid chlorides. Ekeley[6] reacted benzylideneaniline 1 with acetic anhydride and obtained a product which was assigned structure 2. This structure was later confirmed by Snyder[7] and Burgstahler[8]. The IR spectrum of the compound 2 in chloroform solution showed strong absorptions at 1745cm^{-1} (ester carbonyl) and 1671cm^{-1}



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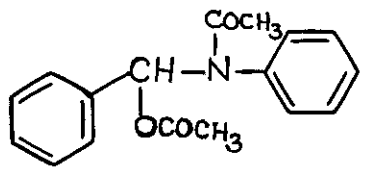
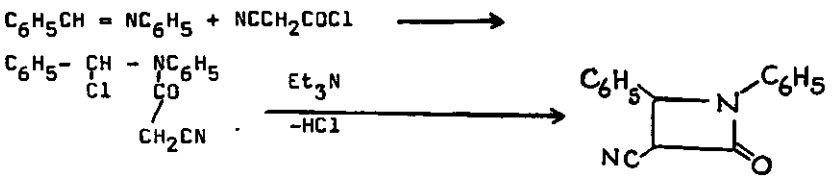


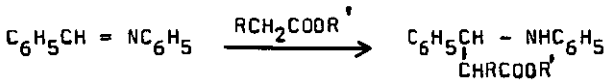
2

(disubstituted amide). Böhme[9] studied the reactions of Schiff bases with simple acid chloride (such as acetyl chloride and benzoyl chloride) and cyanoacetyl chloride. In the latter cases β-lactams were readily obtained as indicated below.

$$C_6H_5CH = NC_6H_5 \xrightarrow{RCOCl} C_6H_5\text{-}\underset{Cl}{CH}\text{-}\underset{C_6H_5}{NCOR}$$



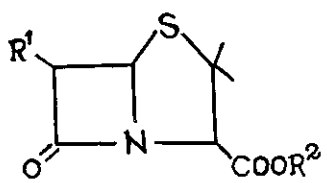
In the case of esters containing active methylene (or methine) group the reaction proceeds as shown:



1.1 Synthetic Penicillins - Acylation of 6-Aminopenicillanic Acid (6-APA)

The above acylation reactions have been well exploited in the syntheses of heterocycles. In 1967, Heuser[10] found it advantageous to isolate and purify 6-APA, the basic intermediate for the production of semisynthetic penicillins, as its Schiff bases. Later Heuser[11] reported that it was possible to acylate the Schiff bases directly to form the desired penicillin derivatives without the necessity of generating the free amino acid for use as starting material. Thus Heuser et al. directed their studies towards the acylation of the Schiff bases of 6-APA salts and esters. The synthesis of penicillin V (3d) and its methyl ester (3e) were investigated utilizing compounds 3a and 3b as substrate for acylation.

Upon addition of phenoxyacetyl chloride to a cold solution of 3a in $CDCl_3$, PMR and IR data showed the disappearance of the -CH=N- double bond without the formation of an aldehyde. Free 6-APA was not formed in the reaction under anhydrous conditions but was readily precipitated upon addition of water to the reaction mixture. After the addition of approximately one equivalent of acid chloride, the addition of a sodium 2-ethylhexanoate solution in anhydrous methyl isobutyl ketone did not produce the sodium salt of penicillin V (3d).



3a $R^1 = C_6H_5CH=N-$, $R^2 = (CH_3)_3CCH_2C(CH_3)_2NH_3^+$

3b $R^1 = C_6H_5CH=N-$, $R^2 = CH_3$

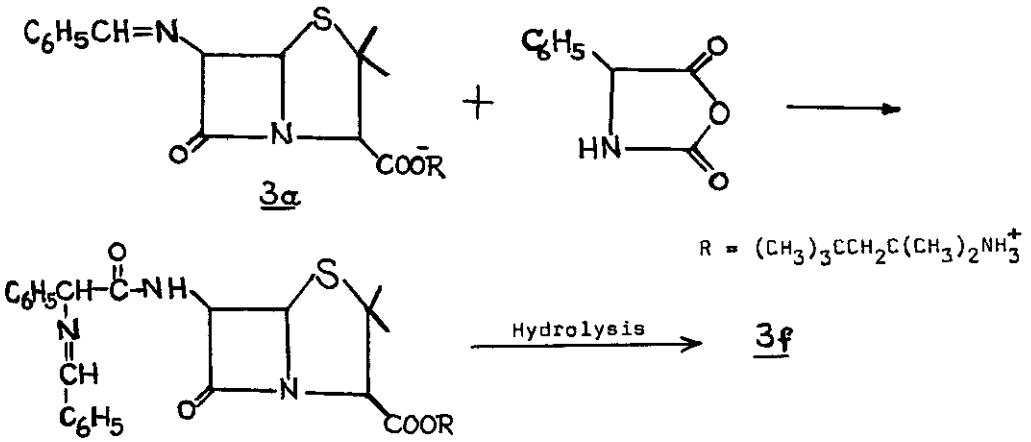
3c $R^1 = p\text{-}MeOC_6H_4CH=N-$, $R^2 = (CH_3)_3CCH_2C(CH_3)_2NH_3^+$

3d $R^1 = C_6H_5OCH_2CONH$, $R^2 = H$

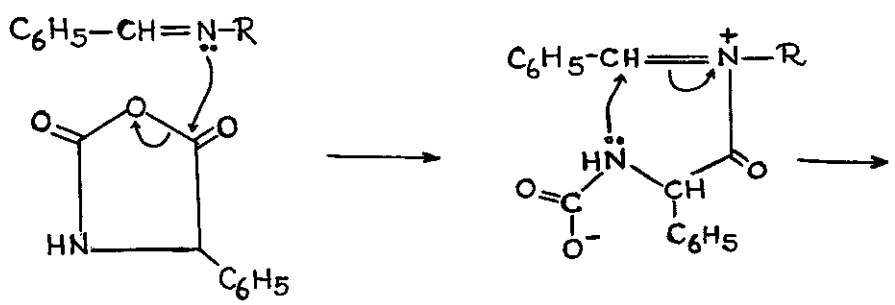
3e $R^1 = C_6H_5OCH_2CONH$, $R^2 = CH_3$

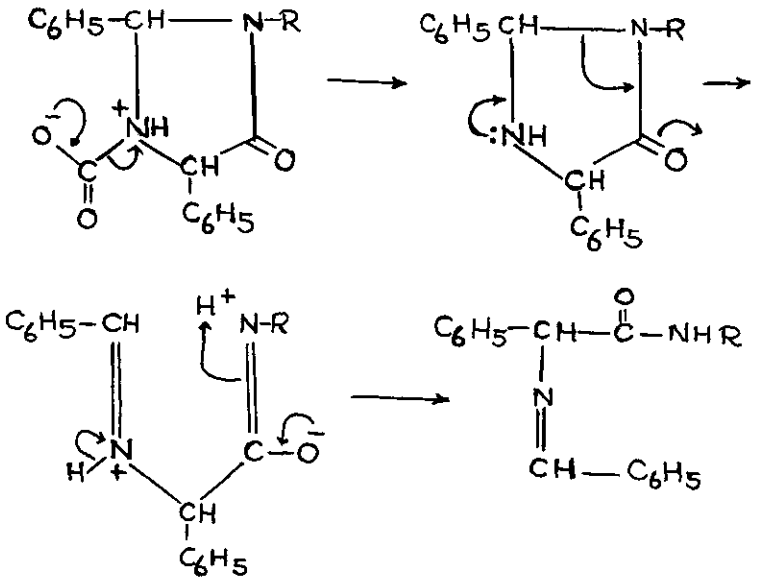
3f $R^1 = C_6H_5\underset{\underset{NH_2}{|}}{C}HCONH$, $R^2 = H$

However, after hydrolysis of the intermediate with water, sodium salt of penicillin V (3d) crystallized readily. N-Carboxy-D-phenylglycine anhydride (NCA) has been used to prepare ampicillins (3f) from 6-APA[12]. The benzylidene (3a) and anisylidene (3c) Schiff base salts of 6-APA both reacted with NCA, giving intermediate Schiff bases that could be hydrolysed to ampicillin (3f)[13]. The reactions involved are depicted below:



A probable mechanism for the addition of NCA to Schiff bases is shown below:



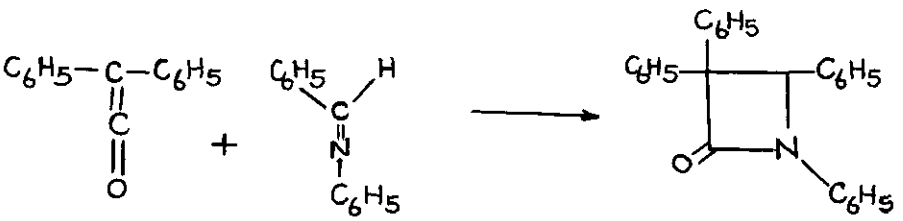


Thus, these procedures offer a general method for preparing semisynthetic penicillins from an intermediate Schiff base of 6-APA.

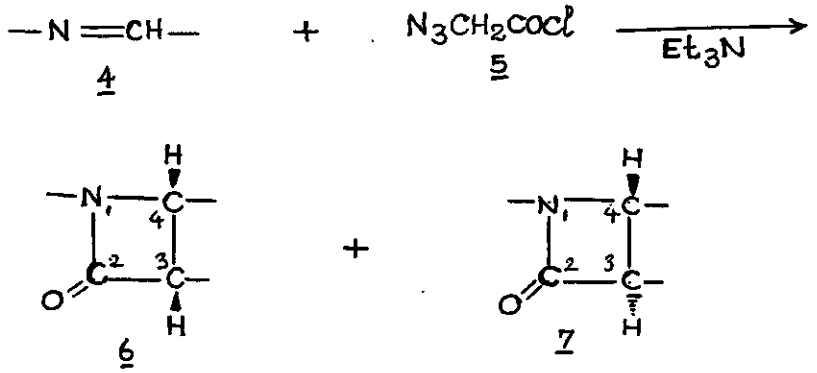
1.2 Synthesis of β-Lactams

β-Lactams as a class had been of limited interest until the discovery that penicillins possess this heterocyclic ring system as a key feature[14]. Further interest was aroused by the finding that the structure of the antibiotic cephalosporin C also contains the α-amino-β-lactam moiety[15]. Later it was reported[16] that the major alkaloid of Pachysandra terminalis is a steroidal alkaloid carrying a β-lactam ring. Thus it is apparent that β-lactams are not quite as uncommon in nature as was once considered.

In the course of his studies on the chemistry of ketenes, Staudinger[17] discovered that these compounds, in particular keto-ketenes, react with imines to produce β-lactams. The first known β-lactam, 1,3,3,4-tetraphenyl-2-azetidinone was prepared from diphenyl ketene and benzylideneaniline[18]. Bose[19] found that



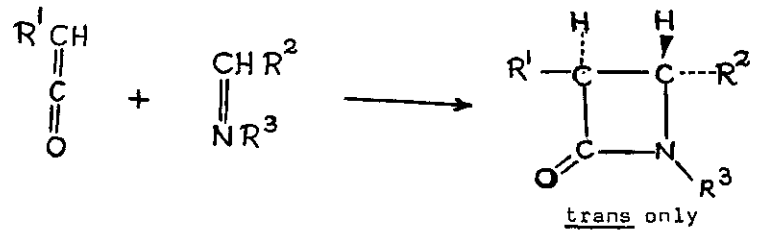
the reaction of Schiff base 4 with azidoacetyl chloride (5) in the presence of triethylamine in benzene afforded two diastereomeric α-azido-β-lactams 6 and 7. The stereochemistry of these isomers was deduced from the magnitude of the vicinal coupling constants of the protons at C-3 and C-4 (J=5.6Hz for cis and 2.0-2.8 for trans). The relative proportions of cis and trans isomers were found to depend on the sequence of addition of reactants[20]. When a methylene chloride solution of azidoacetyl chloride was added dropwise to a solution of benzylidene-aniline and triethylamine in the same solvent at or below room temperature the



product ratio was 3:1 of cis to trans. However, when triethylamine was added to a solution of the Schiff base and acid chloride, the relative proportion of cis and trans was reversed and was found to be about 1:3. This indicates that a certain degree of steric control can be exercised on the product of this reaction by changing the sequence of addition of reactants.

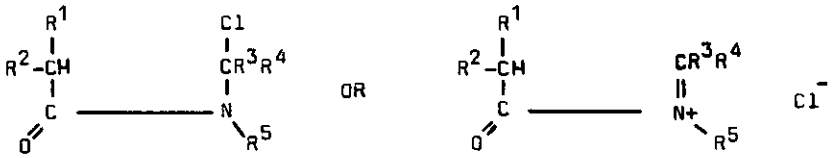
Mechanism for the formation of β-lactams

Initially, Sheehan and Ryan[21] have suggested the formation of a ketene from the acid chloride which reacts with the Schiff base to form the lactam.

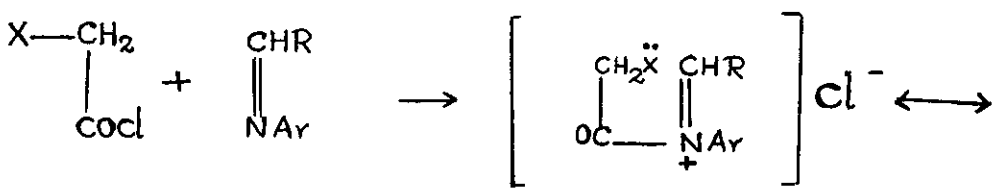


Later, Böhme et al.[9] suggested the formation of a salt to be the intermediate which undergoes dehydrohalogenation in the presence of triethylamine.

The addition of acid chlorides to Schiff bases is called the "Acid chloride-imine" reaction. In a series of publications[19,22] Bose and coworkers examined, in detail, both the mechanism and stereochemistry of "Acid chloride-imine" reactions. Contrary to the observations of Sheehan and Ryan[21], Bose and coworkers observed the formation of both trans and cis diastereomers in the "Acid chloride-imine" reactions. This suggests the possibility of the following intermediate:

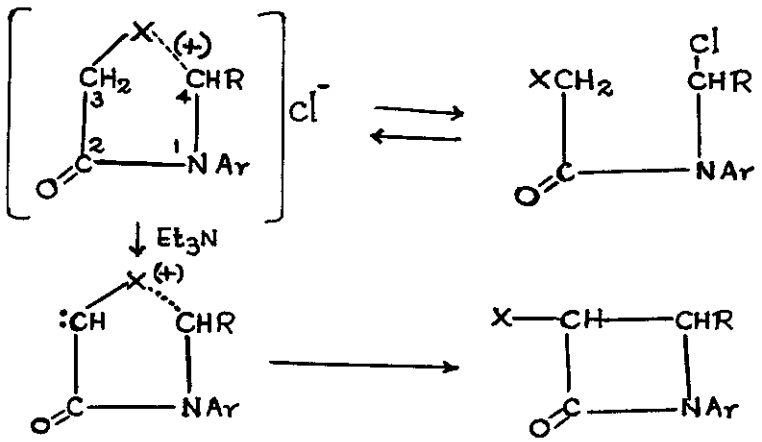


Acid chlorides possessing a N,O,S or Cl (with its lone pair of electrons) at the α-position form a five-membered intermediate where the lone pair of electrons on the substituent X partially neutralize the developed positive charge on the carbon next to the nitrogen. The five-membered intermediate possesses the right geometry wherein the prospective C-3 and C-4 of the β-lactam are close enough to form the bond (Scheme 1). Interestingly, if the heteroatom (N,O,S or Cl) is

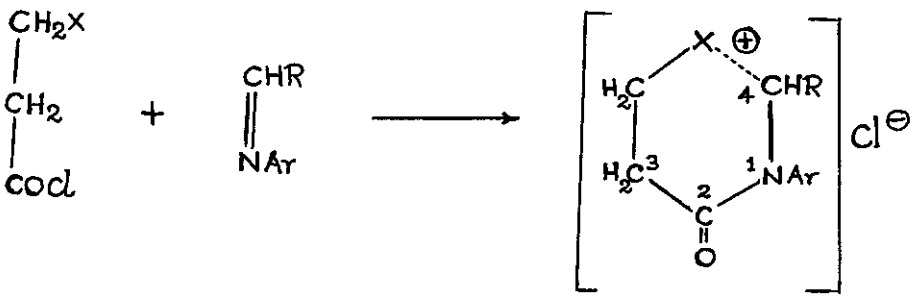


SCHEME 1 (cont. next page)

SCHEME 1 (Cont.)



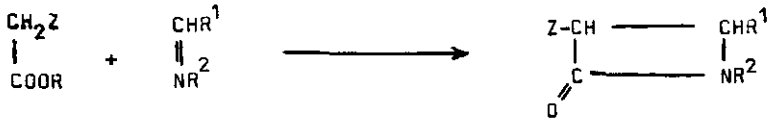
present at the β-position of the acid chloride only traces of trans β-lactam is produced. The possible 6-membered intermediate does not incorporate the right placement of the prospective C-3 and C-4 (Scheme 2).



Scheme 2

Traces of the observed β-lactam (trans) may have been formed via the ketene intermediate. These observations exemplify the multiplicity of the factors involved in determining the dominant mechanism.

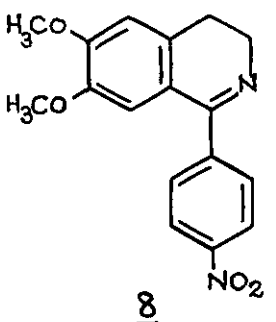
The synthesis of β-lactams could also be achieved with the use of mixed anhydrides in the place of acid chlorides[16]. Varieties of mixed anhydrides as indicated in Scheme 3 provided the β-lactams in good yield.



R	Z	R^1	R^2	Product
H	OPh	p-$MeOC_6H_4$	$CHPh_2$	Only cis
$COCF_3$	N_3	p-$MeOC_6H_4$	p-$HOOCC_6H_4$	Only trans
COOEt	N_3	Ph	Ph	cis and trans
COOiBu	N_3	Ph	Ph	cis and trans

Scheme 3

Imines in which C=N moiety is part of a ring system, eg. 3,4-dihydroisoquinoline 8, react with azidoacetyl chloride to give fused α-azido-β-lactam 9 in good yield. The β-lactam 9 could be catalytically reduced to aminolactam and subsequently acylated.



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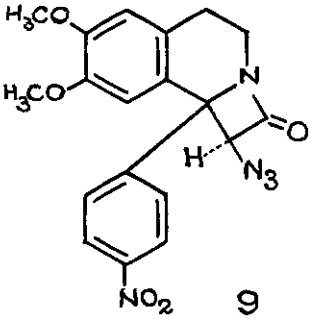

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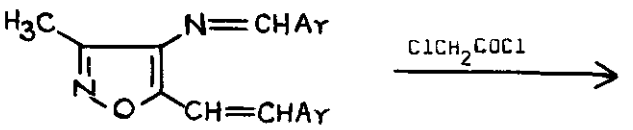
1.3 Attempted Addition of Chloroacetyl Chloride to Schiff Bases

In an attempt to synthesis β-lactams by the addition of chloroacetyl chloride to Schiff bases, Krishna Murthy et al.[23] reacted several 4-benzalamino-3-methyl-5-styrylisoxazoles (10) with chloroacetyl chloride. Unexpectedly in all cases studied the authors were able to isolate only the amide 11 and not the β-lactam 12.



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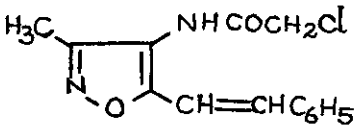

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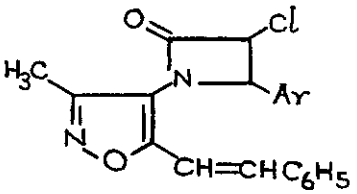

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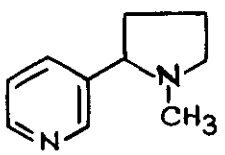
A plausible mechanism involving anchimeric assistance from the olefinic bond of the styryl moiety has been proposed. However, no mention of the possibility of the hydrolysis of the Schiff bases followed by acylation has been made.

1.4 Synthesis of Pyrrolidinones

In 1969, Neal Castagnoli Jr.[24] with his interest in examining structural parameters associated with peripheral and central nervous system activities of the tobacco alkaloid nicotine 13, led to a consideration of potentially versatile synthetic routes to substituted 2-arylpyrrolidinones. As a part of the



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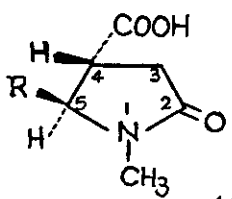
programme, he first studied the condensation of benzylidenemethylamine with succinic anhydride-an acylation reaction which has already been mentioned. Fractional crystallization of the reaction product yielded two diastereomeric pyrrolidinones 14 and 15; the trans isomer 14 being formed as the major product. The



(trans)

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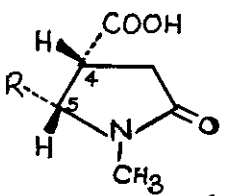

(Cis)

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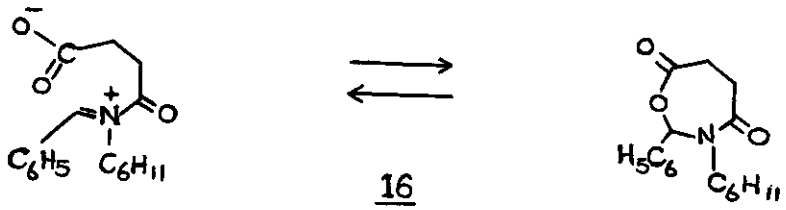
coupling constant $J_{4,5}$ (5Hz, trans isomer 14 and 9Hz, cis isomer 15) are in agreement with the values expected on the basis of dihedral angles H_{4-5} (14,120°; 15, 0°).

The intermediate 16 has been suggested for such reactions involving Schiff base and anhydride[24]. Evidence for such an intermediate had also been advanced[25].



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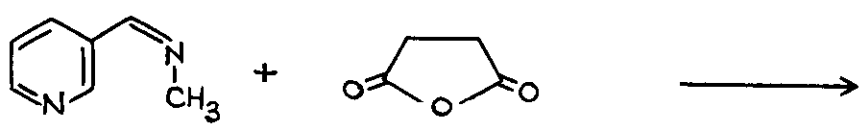
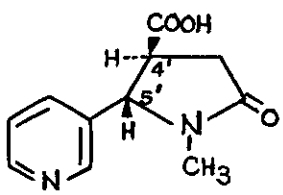
Electron donating substituents on the benzene ring which stabilize the positive charge on the nitrogen (structure 16) seem to favour the addition reaction.

On these lines, the condensation of N-3-pyridylidenemethylamine and succinic anhydride gave trans-1-methyl-5-(3-pyridyl)-2-pyrrolidinone[26] (17), the geometry being confirmed by a coupling constant of 5Hz for the C-5' methine doublet[24]. The pyrolidinone 17 has been further converted into 3'-methylnicotine 18.





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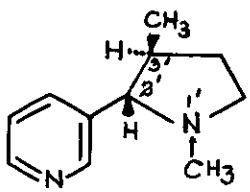

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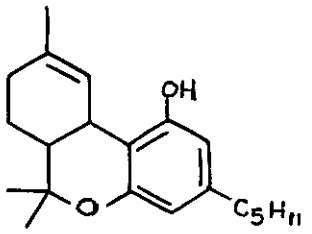
1.5 Synthesis of Piperidinones

Then Cushman and Castagnolli[27] turned their attention to an extension of this concept for the synthesis of piperidinones which they incorporated into interesting nitrogen analogues of the tetrahydrocannabinols (THC) 19 and 20. A number of THC

nitrogen analogues had been reported earlier, the synthesis of most of the analogues being based on the early work of Adams[28] and Todd[29]. These authors condensed ethyl 5-methylcyclohexanone-2-carboxylate (21) with olivetol (22) to give



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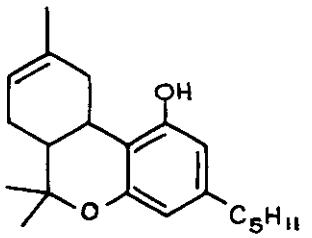

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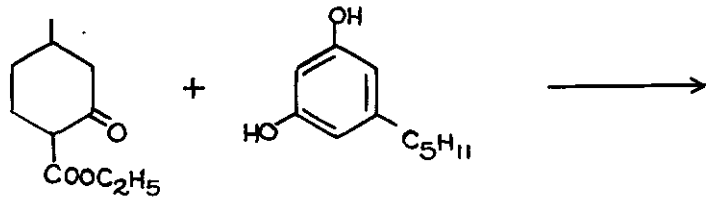
the benzopyrone (23). Treatment of (23) with methylmagnesium iodide yielded the unnatural and less physiologically active Δ^3-THC 24.



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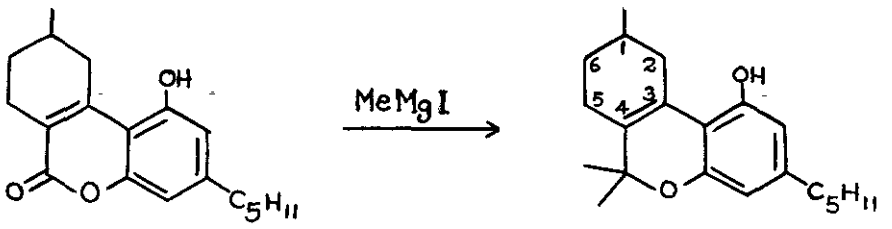
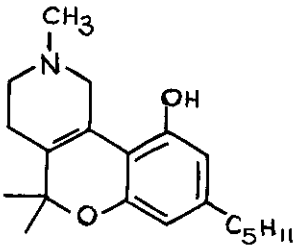


23 24

By condensation of appropriately substituted piperidinones with olivetol (22) under similar conditions, followed by reaction with methylmagnesium iodide aza analogues 25 and 26 have been prepared[30,31,32].



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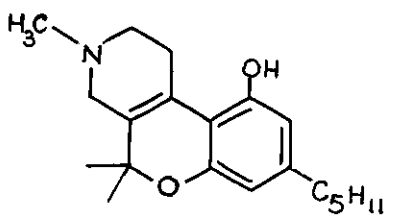
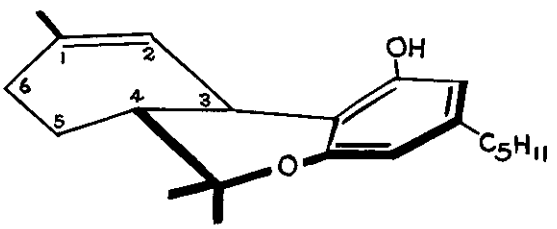


26

Since the unnatural Δ^3-isomer 24 is found to be less potent in animals and men than the trans isomers 19 and 20, any synthetic method devised to prepare nitrogen analogues of THC must provide integrity of the trans ring fusion and a 'natural' location of the olefinic double bond. Additionally such synthetic routes should be versatile with respect to structural modifications.



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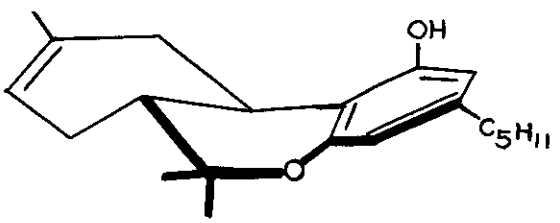
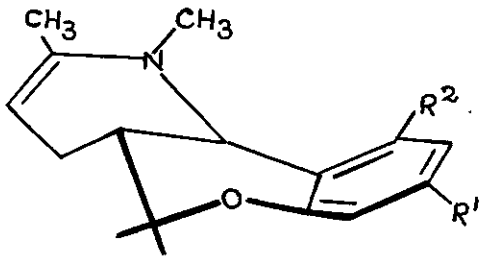


20

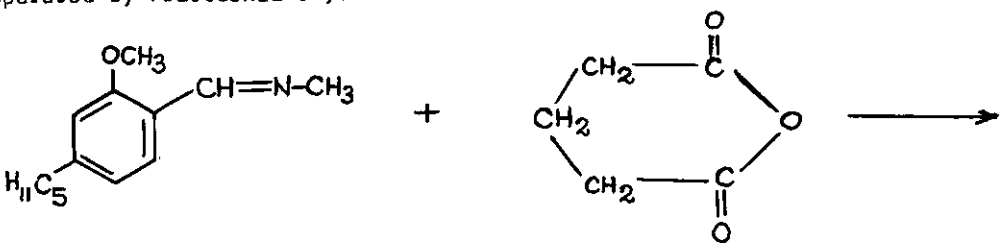
These objectives were achieved by Cushman and Castagnoli[27] in the synthesis of 27 and 28.

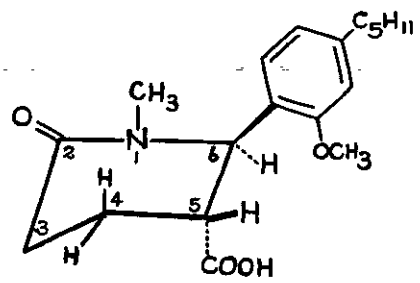


27 $R^1 = R^2 = H$

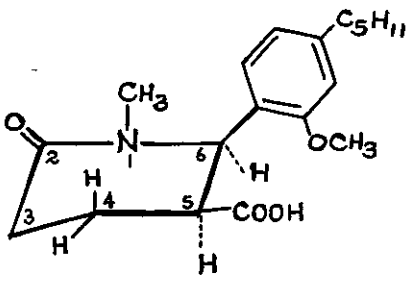
28 $R^1 = C_5H_{11}$, $R^2 = OH$

In the present review the scheme of synthesis of these two compounds is not discussed but only that of the key intermediate piperidinones which is relevant. Condensation of substituted o-anisylidene-methylamine with glutaric anhydride in refluxing xylene yielded a diastereomeric mixture of 29 and 30 which could be separated by fractional crystallization.





29

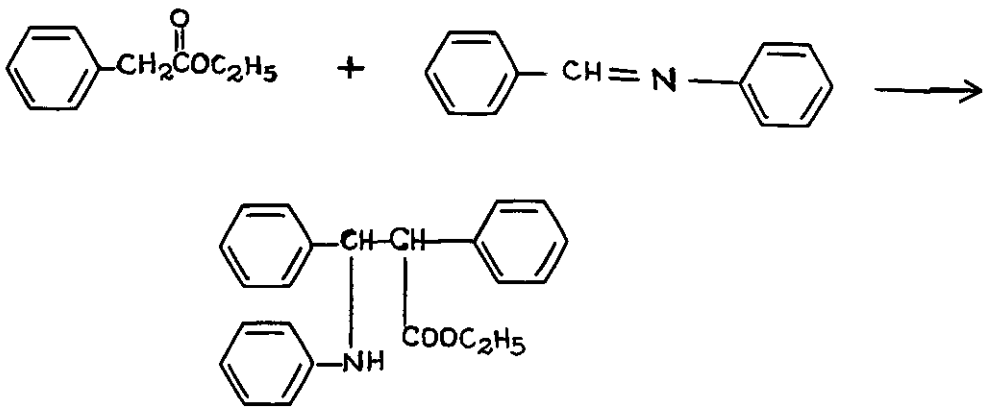


30

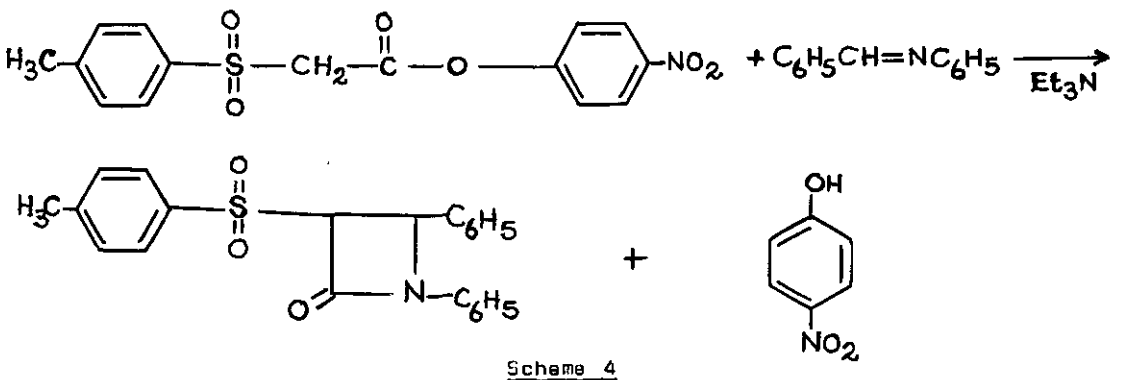
Again the major product was the trans isomer 29 whose configuration was indicated by a coupling constant of 2.5Hz between H_5 and H_6. The cis isomer (minor product) exhibited a coupling constant of 5Hz for the same protons. Additionally the methyl esters of 29 and 30 were prepared and their PMR spectra studied. A molecular model of the methyl ester of the cis acid 30 would indicate the ester methyl to lie in the shielding region of the aromatic ring. This is borne out by an upfield shift (δ 3.56) for this methyl group. The ester methyl of the trans compound shows an absorption slightly downfield at δ 8.75.

1.6 Reactions of Schiff Bases with Esters

Esters of phenylacetic acid react with benzylideneaniline to give the simple addition products as shown below[33]:



However, when a good leaving group is present in the alcoholic part of the ester, the adduct eliminates the alcohol (or phenol) to form the azetidinone ring (Scheme 4)[34].

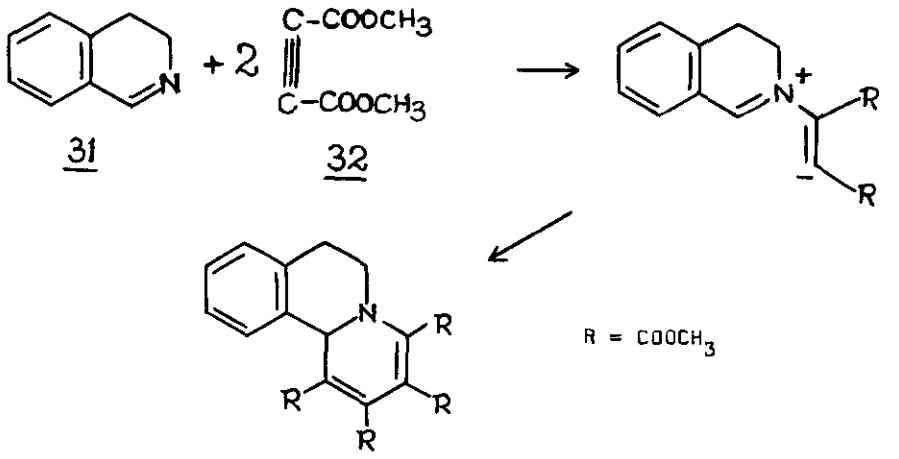


Scheme 4

This is a convenient method to synthesize azetidin-2-ones from imines and a carboxylic acid whose acid chloride is difficult to prepare.

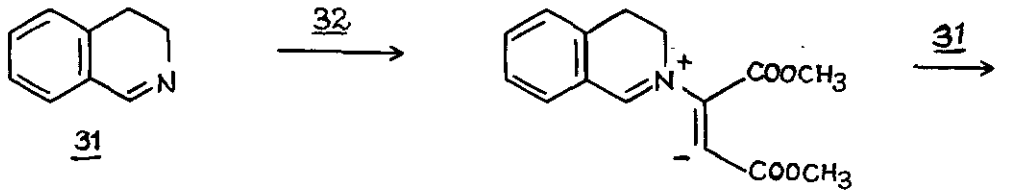
1.7 Reaction of 3,4-Dihydroisoquinoline with Acetylenedicarboxylic Ester

Huisgen and Herbig[35] studied the reaction of 3,4-dihydroisoquinoline(31) with acetylenedicarboxylic ester (32) and found that the product depended on the reaction condition. When equimolar quantities of 3,4-dihydroisoquinoline (31) and acetylenedicarboxylic ester (32) were mixed in dry ether, an exothermal reaction occurred with the formation of 33. A possible mechanism has also been suggested (Scheme 5).



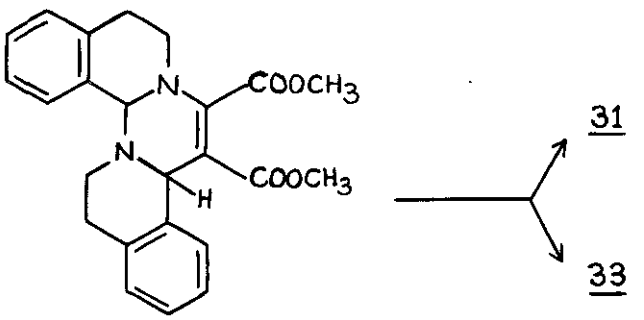
31 32 33

On the other hand when one equivalent of the acetylenedicarboxylic ester (32) in acrylonitrile was added dropwise over a long period to two equivalents of 3,4-dihydroisoquinoline (31) in the same solvent, a dimeric product (34) was



SCHEME 6 (Cont. next page)

SCHEME 6 (cont.)

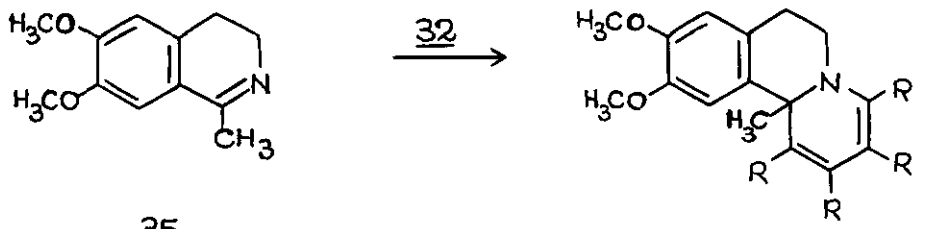


34

Scheme 6

obtained which is formed by the addition of a second molecule of dihydroisoquinoline (31) to the dipolar intermediate (Scheme 6). Additionally, when the dimeric product 34 was stirred with acetyl chloride or hydrochloric acid in benzene the tetra ester 33 and 3,4-dihydroisoquinoline were formed in good yield.

Nair[36] in a similar reaction, observed the formation of 1:2 adduct (36) when 1-methyl-6,7-dimethoxy-3,4-dihydroisoquinoline (35) was treated with acetylenedicarboxylic ester (32) in dry ether.

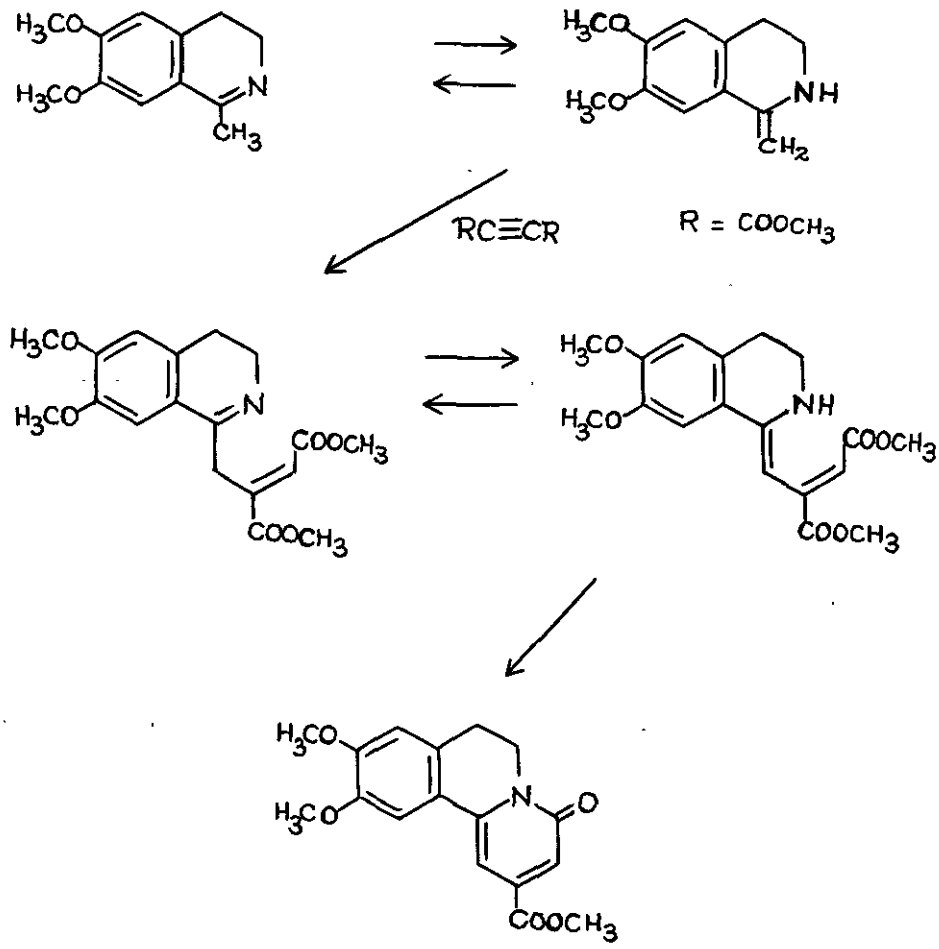


35

36

R = $COOCH_3$

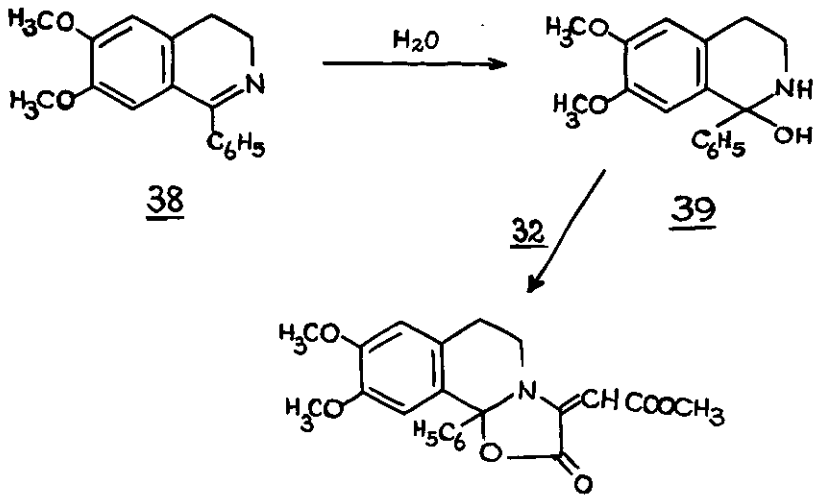
Interestingly, when methanol was used as solvent (in the place of dry ether) the product obtained was the lactam 37. This could only be formed by the enamine form of the dihydroisoquinoline (Scheme 7).



37

Scheme 7

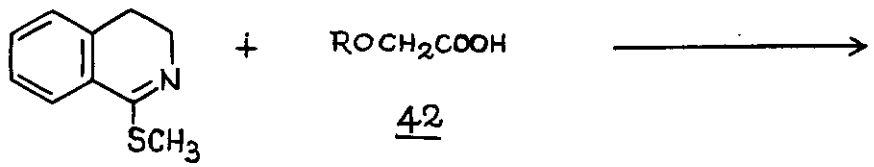
However, when 1-phenyl-6,7-dimethoxy-3,4-dihydroisoquinoline (38) and *dimethyl acetylenedicarboxylate* (32) were reacted in methanol under similar conditions an unexpected reaction took place with the formation of the lactone 40[37]. The authors explain the product as being formed after *a primary addition of water* across the ketimine followed by reaction with acetylenedicarboxylic ester. It is interesting to note that 1-methyl and 1-phenyl-substituted 3,4-dihydroisoquinolines react differently with dimethyl acetylenedicarboxylate under similar reaction conditions.



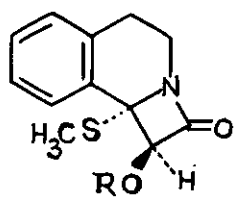
38 39 40

1.8 Addition of Aryloxyacetic Acids to Iminothioethers

1-Methylthio-3,4-dihydroisoquinoline 41 on annelation with aryloxyacetic acids 42 in the presence of $PDCl_3/Et_3N$ in CH_2Cl_2 afforded β-methylthio-β-lactams 43[38].



41 42



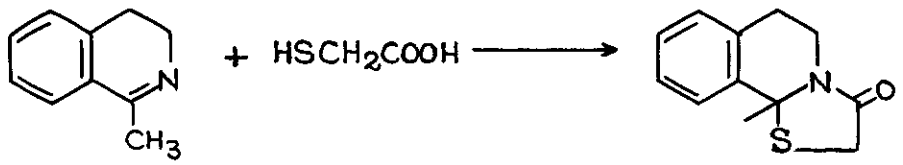
43

R = Phenyl,
R = 2,4-Dichlorophenyl,
R = β-Naphthyl

It should be mentioned here that the simple 3,4-dihydroisoquinoline did not undergo a similar reaction with phenoxyacetyl chloride.

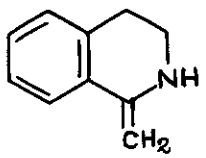
1.9 Addition of Mercaptoacetic Acid to 1-Methyl-3,4-dihydroisoquinoline

In a different kind of addition reaction, Nair et al.[39] had reported the formation of thiazoloisoquinoline (45) from the addition of 1-methyl-3,4-dihydroisoquinoline (44) with mercaptoacetic acid.



44 45

In this case, the authors could not distinguish between the cyclic ketimine and the corresponding enamine (46) as the reacting species since both forms could



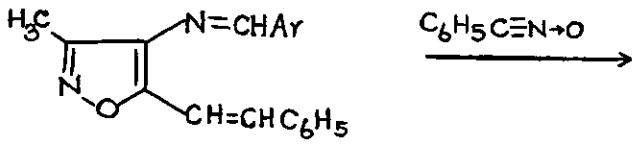
46

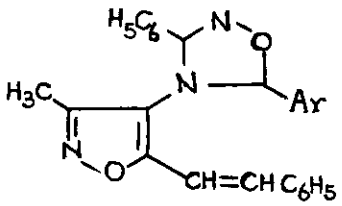
yield the same addition product. However, the reaction can easily be visualized as being trigerred by the addition of the nucleophilic thiol group to the protonated imine. The enamine form is less likely to be implicated.

1.10 Addition of Nitrile Oxide to Schiff Bases

Krishna Murthy et al.[40] studied the addition of benzonitrile oxide to a system containing both C=C and C=N bonds and observed the additions preferentially taking place at C=N bond. These authors studied the reactions of several Schiff bases derived from substituted anilines and found similar products in all cases (Scheme 8).

When the reaction was performed using two moles of benzonitrile oxide, the addition occurred only to the C=N bond indicating that the olefinic bond is inert even under these conditions. That the benzonitrile oxide addition has taken place to C=N in preference to C=C, is in keeping with the earlier observation[41]. The product in these reactions was always Δ^2-1,2,4-oxadiazolines which is in agreement with the findings of Clapp and Srivastava[42].





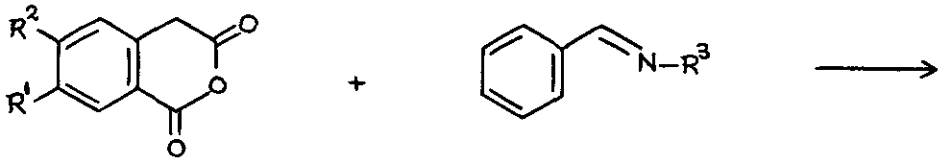
Ar = phenyl, p-methoxyphenyl, p-tolyl, p-chlorophenyl p-dimethylaminophenyl, m-methoxy- p-hydroxyphenyl, p-hydroxyphenyl and m-hydroxyphenyl

Scheme 8

2. Reactions of Schiff Bases with Homophthalic Anhydrides (1,3-Isochromanediones)

2.1 Synthesis of Isoquinolinones

In a preliminary report presented at the 5th International Congress of Heterocyclic Chemistry at Ljubljana in July 1975, Haimova et al. elaborated a novel and highly stereoselective synthesis of 3,4-dihydro-1(2H)-isoquinolinones from homophthalic anhydrides and azomethines. The details of this work were later published in 1977[43]. When homophthalic anhydrides 47 a-c were treated with Schiff bases 48a or 48b at room temperature (±)-trans-3-aryl-4-carboxy-3,4-dihydroisoquinolinones 49 a-d were obtained in 70% yield. In a typical experiment, to a mixture of 1 mmole of homophthalic anhydride and 1 mmole of azomethine, 2ml of dry dichloroethane was added. The mixture was refluxed for 10 min to achieve homogeniety and the resulting solution was allowed to stand at room temperature. The solid product was filtered off and the mother liquor worked up for more compound.



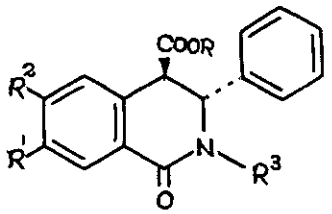
47a $R^1 = R^2 = H$

47b $R^1 = R^2 = OCH_3$

47c $R^1R^2 = OCH_2O$

48a $R^3 = H$

48b $R^3 = CH_3$



49a $R^1 = R^2 = R = H$, $R^3 = CH_3$

49b $R^1 = R^2 = OCH_3$, $R^3 = CH_3$ R = H

49c $R^1 = R^2 = OCH_2O$, $R^3 = CH_3$ R = H

49d $R^1 = R^2 = R^3 = R = H$

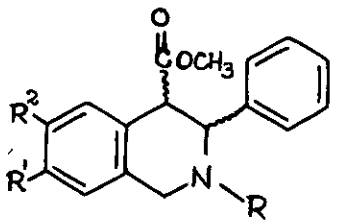
50a $R^1 = R^2 = H$, $R^3 = R = CH_3$

50b $R^1 = R^2 = OCH_3$, $R^3 = R = CH_3$

50c $R^1R^2 = OCH_2O$, $R^3 = R = CH_3$

50d $R^1 = R^2 = R^3 = H$, $R = CH_3$

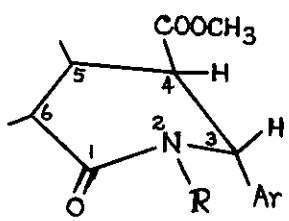
The relative configurations of 4-carboxy-3,4-dihydroisoquinolinones 49 a-d were established by chemical correlations with their respective methyl esters. The trans configurations of 4-methoxycarbonyl-3,4-dihydroisoquinolinones (50 a-d) were determined by direct comparison with authentic samples[44] as well as by comparing their PMR spectra. The diastereomeric isoquinolinones of the type 50 and their cis isomers were obtained without configurational changes *via* the oxidation of trans and cis tetrahydroisoquinolines of the type 51 with $KMnO_4$ in acetone[44]. It was found that the methyl protons of the methoxycarbonyl groups in compounds of the type 50 resonate in the trans isomers at lower fields than in the cis isomers probably because of the greater screening effect of the phenyl groups in the latter (trans-δ 3.68-3.78; cis-δ 3.37-3.48).



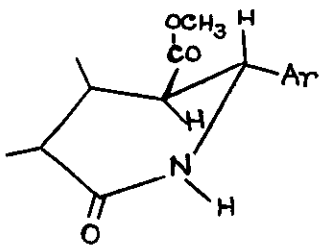
→ 50 a-d

51a $R^1 = R^2 = H$, $R = CH_3$
51b $R^1 = R^2 = OCH_3$, $R = CH_3$
51c $R^1R^2 = OCH_2O$, $R = CH_3$
51d $R^1 = R^2 = R = H$

The preferred conformation of all compounds of type 50 and some compounds of type 49 were established from their PMR spectra. Compounds 49 a-c and 50 a-c with alkyl or aryl substituted nitrogen have low vicinal coupling constants ($J_{3,4}$=1.15Hz). Compounds with unsubstituted nitrogen possess high spin-spin coupling constants ($J_{3,4}$=6.5-6.8Hz for trans 50 d). The tendency towards planarity arising from the conjugation between the amide function and phenyl group renders the conformers with C-3 carbon atoms out of the average plane of the ring most probable (51 and 52).



51



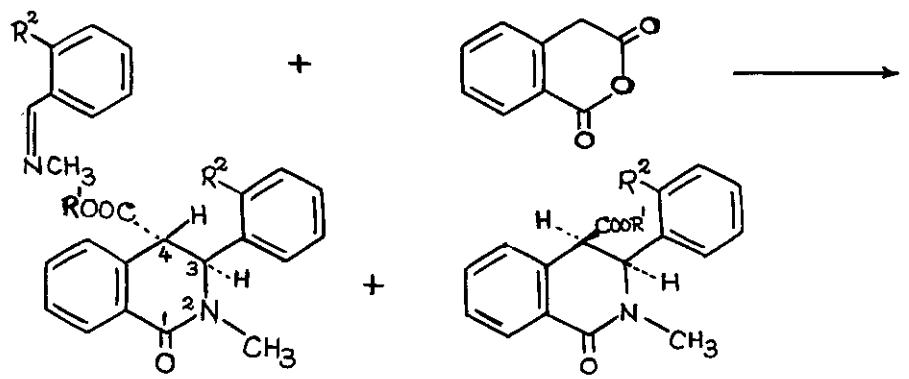
52

The low $J_{3,4}$ values observed for the N-substituted compounds are in agreement with conformation 51. The pseudo axial orientation of the substituents at C-3 and C-4 is more favourable because of the diminished repulsive interactions between the nitrogen substituent and the aryl group. The $J_{3,4}$ values for compounds unsubstituted at the nitrogen support conformation 52 with pseudo equatorial substituents at C-3 and C-4.

Independently, Cushman et al.[45] studied the condensation of a variety of aldimines and ketimines with homophthalic anhydride as a general method of synthesis of substituted 4-carboxy-3,4-dihydro-1(H)-isoquinolinones. Unlike in the

case of Haimova et al.[43] and in conformity with their earlier work[25], Cushman et al. obtained both diastereomers as reaction products. A typical experiment is detailed below:

Addition of homophthalic anhydride to a solution of o-methoxybenzylidene-methylamine in chloroform at room temperature resulted in a rapid exothermic reaction. The resulting mixture (1:2) of trans and cis- N-methyl-3-(o-methoxy-phenyl)-4-carboxy-3,4-dihydro-1(2H)-isoquinolinones 53a and 54a was isolated by filtration after 10 min in 96% yield and could be separated by fractional crystallization into minor ($J_{3,4}$=1Hz) and major ($J_{3,4}$=6Hz) diastereomers. On heating in refluxing acetic acid the mixture was converted completely into the minor diastereomer. Pure methyl esters 53b and 54b were prepared by treatment of the minor and major diastereomers 53a and 54a with diazomethane. Heating either compound at 165°C for 3 h in the absence of solvent yielded a 97:3 mixture of ester of minor and major diastereomer respectively as evidenced by integration of the methoxycarbonyl protons in the PMR spectra of the resulting mixture. The observed coupling constants for the trans ($J_{3,4}$=1Hz) and cis ($J_{3,4}$=6Hz) isomers 53a and 53b and 54a and 54b are in close agreement with those reported for related pyrrolidinones[24,25,26] and piperidones[27]. Similarly, the reaction of benzylidene-methylamine with homophthalic anhydride for 5 min in refluxing p-xylene afforded only the trans ($J_{3,4}$=1Hz) isomer 53c whereas isolation of the cis isomer 54c was favoured if the reaction was conducted at 7°C in benzene for 15 min. This study is indeed an excellent example of a reaction where the product formation is dependent on kinetic or thermodynamic control.



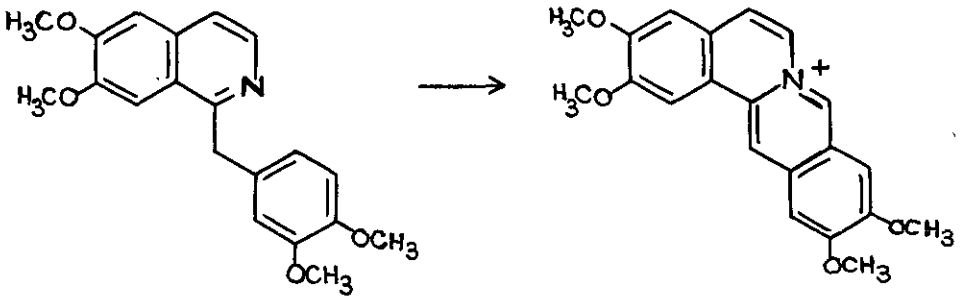
53a R^1 = H, R^2 = OCH_3
53b R^1 = CH_3, R^2 = OCH_3
53c R^1 = R^2 = H

54a R^1 = H, R^2 = OCH_3
54b R^1 = CH_3, R^2 = OCH_3
54c R^1 = R^2 = H

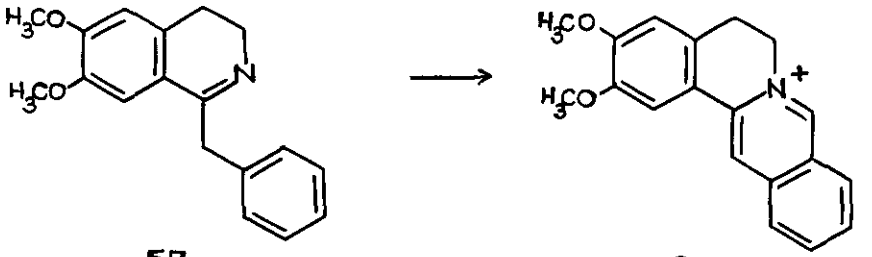
2.2 Synthesis of Protoberberines under Vilsmeier-Haack Condition

One of the earliest examples in the use of imines for the preparation of protoberberine derivatives is that of Professor Kametani in 1974[46]. Isoquinolines and 3,4-dihydroisoquinolines under Vilsmeier-Haack conditions yielded protoberberine derivatives whereas tetrahydroisoquinolines (which do not contain the imine moiety) do not react at all. Thus papaverine (55) yielded the protoberberine (56) when treated with dimethylformamide and phosphorous oxychloride. The 3,4-dihydroisoquinoline (57) under similar conditions gave 58.

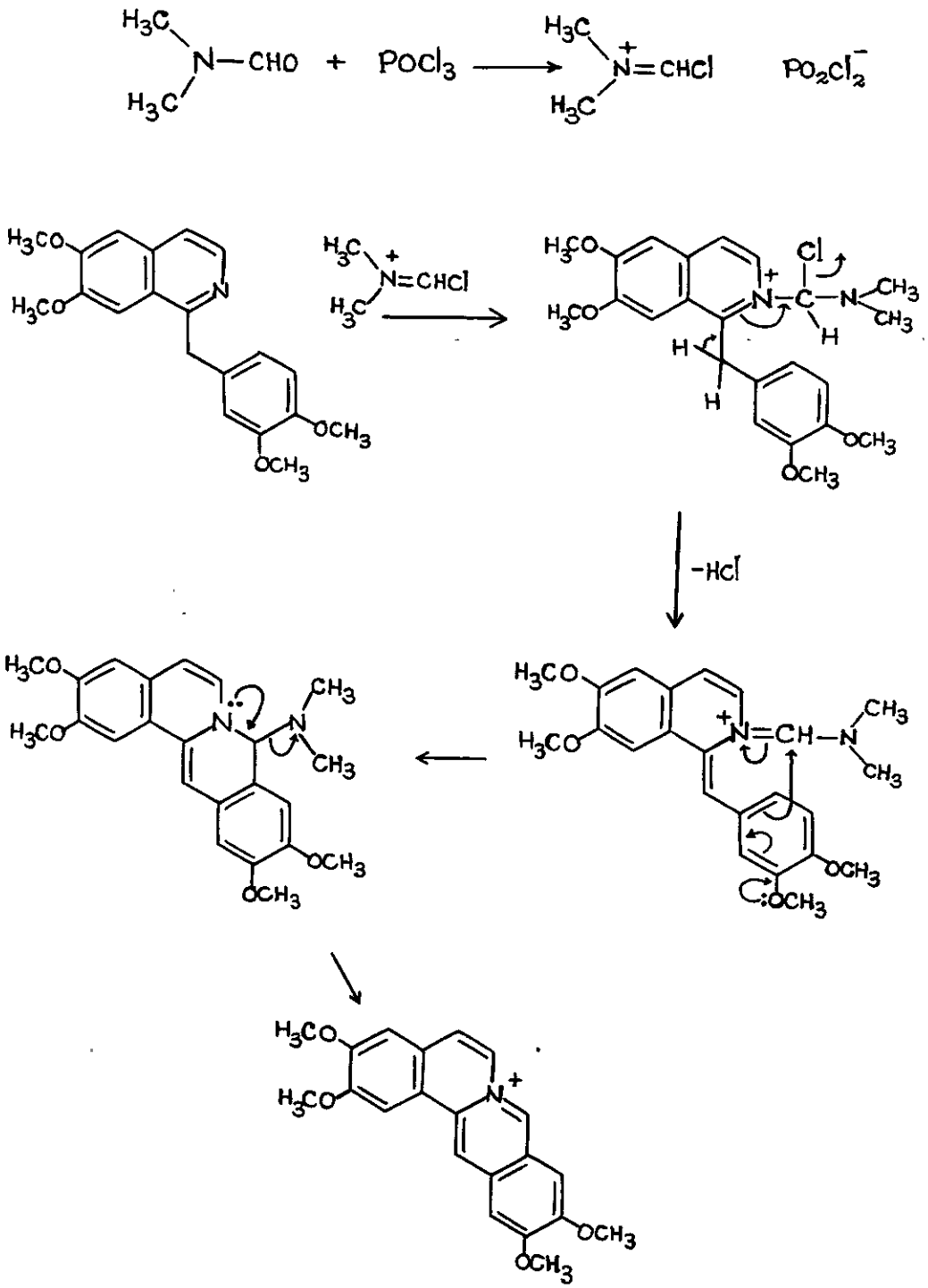
A probable mechanism for the formation of protoberberine is given in Scheme 9.



55 56



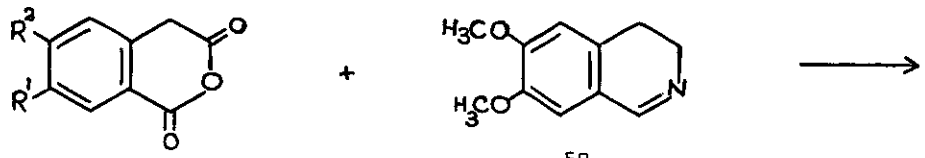
57 58



Scheme 9

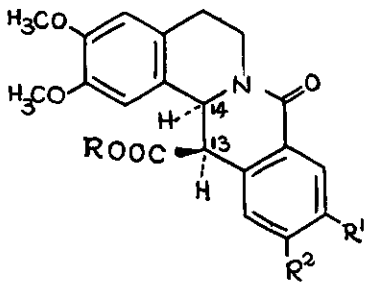
2.3 8-Oxoberbines - Haimova's Work

When cyclic imines such as 6,7-dimethoxy-3,4-dihydroisoquinoline 59 were condensed with homophthalic anhydrides 47b or 47c in dichloroethane solutions in the presence of triethylamine 13-carboxy-8-oxoberbines 60a and 60b were obtained[43].



47b
47c

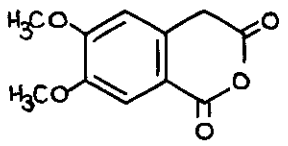
59



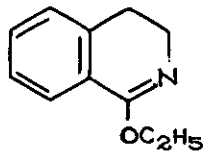
60a $R^1 = R^2 = OCH_3$, $R = H$
60b $R^1R^2 = OCH_2O$, $R = H$
61a $R^1 = R^2 = OCH_3$, $R = CH_3$
61b $R^1R^2 = OCH_2O$, $R = CH_3$

The 8-oxoberbines of the type 60 were analysed as their methyl esters 61. The PMR spectra of compounds 61a and 61b indicate that the protons at C-13 and C-14 are of cis configuration ($J_{13,14}$=4.5Hz), with the quinolizidine ring being trans fused. The correlation of PMR spectra with the relative configuration of 13-methyltetrahydroprotoberberines has been well established earlier[47].

As an interesting variation Haimova et al.[48] observed that lactim ether and imidoyl chlorides can be condensed with homophthalic anhydrides for the synthesis of 8-oxoberbines and related isoquinolines. Refluxing the homophthalic anhydride 47b with the lactim ether 62 in an inert solvent led to the formation of 8-oxoberbine 63.



47b



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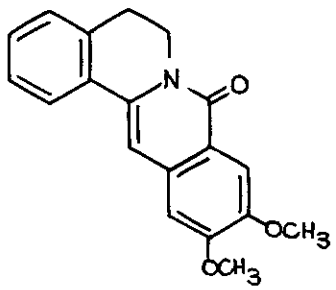
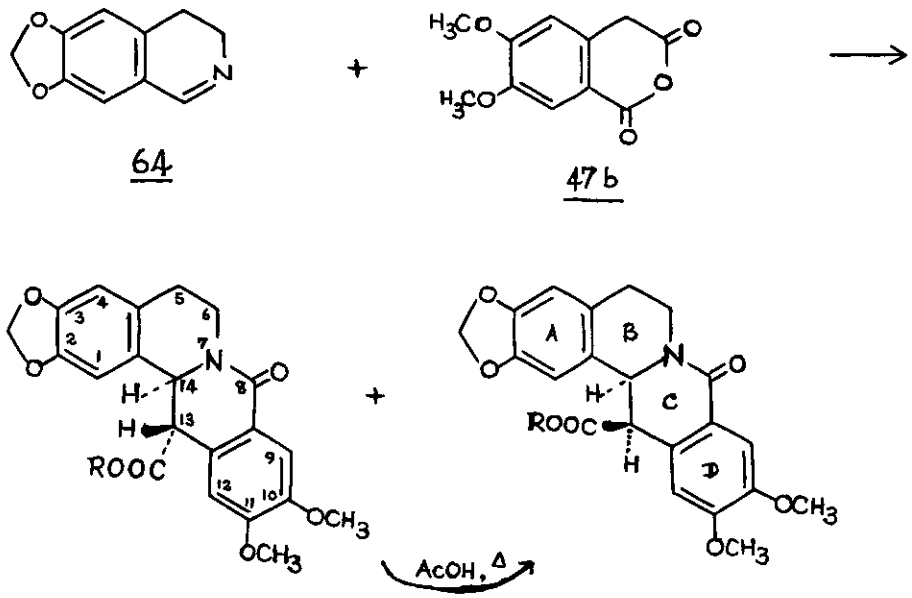


63

2.4 Synthesis of 2,3,10,11-Oxygenated 13-Methyltetrahydroprotoberberines - Cushman's Work

Condensation of norhydrastinine 64 with the homophthalic anhydride 47b in chloroform at room temperature proceeded exothermally to yield a mixture of trans and cis 2,3-methylenedioxy-8-oxo-10,11-dimethoxy-13-carboxytetrahydroprotoberberines 65 and 66 from which the major isomer ($J_{13,14}$=6Hz) crystallized in 90% yield[45,49,50]. Heating this product in refluxing acetic acid resulted in epimerization to the thermodynamically more stable diastereomer ($J_{13,14}$=4Hz). By analogy with related protoberberines, the PMR spectrum of the trans isomer (with the quinolizidine ring cis fused and hence thermodynamically less stable) is expected to display a larger coupling constant between protons H_{13} and H_{14} than the corresponding cis isomer[47,51-53](with the quinolizidine ring trans fused and hence thermodynamically more stable). The kinetic product was therefore assigned the trans relative configuration 65 while the thermodynamic product was assigned the cis configuration 66. The relative configurations have also been correlated with the PMR spectra of the methyl esters of 65 and 66. Examination of Dreiding models reveals that in contrast to the trans isomer 65a, the pseudoaxial methoxycarbonyl protons of the cis diastereomer 66a can rotate over the aromatic rings A and D. The appearance of the methoxycarbonyl proton signal in the PMR spectrum

of 66a at δ 3.40 which is 0.4 ppm upfield relative to that of the trans isomer 65a, provides further evidence in support of the relative configurations as assigned.



65 R = H (major)

65a R = CH_3

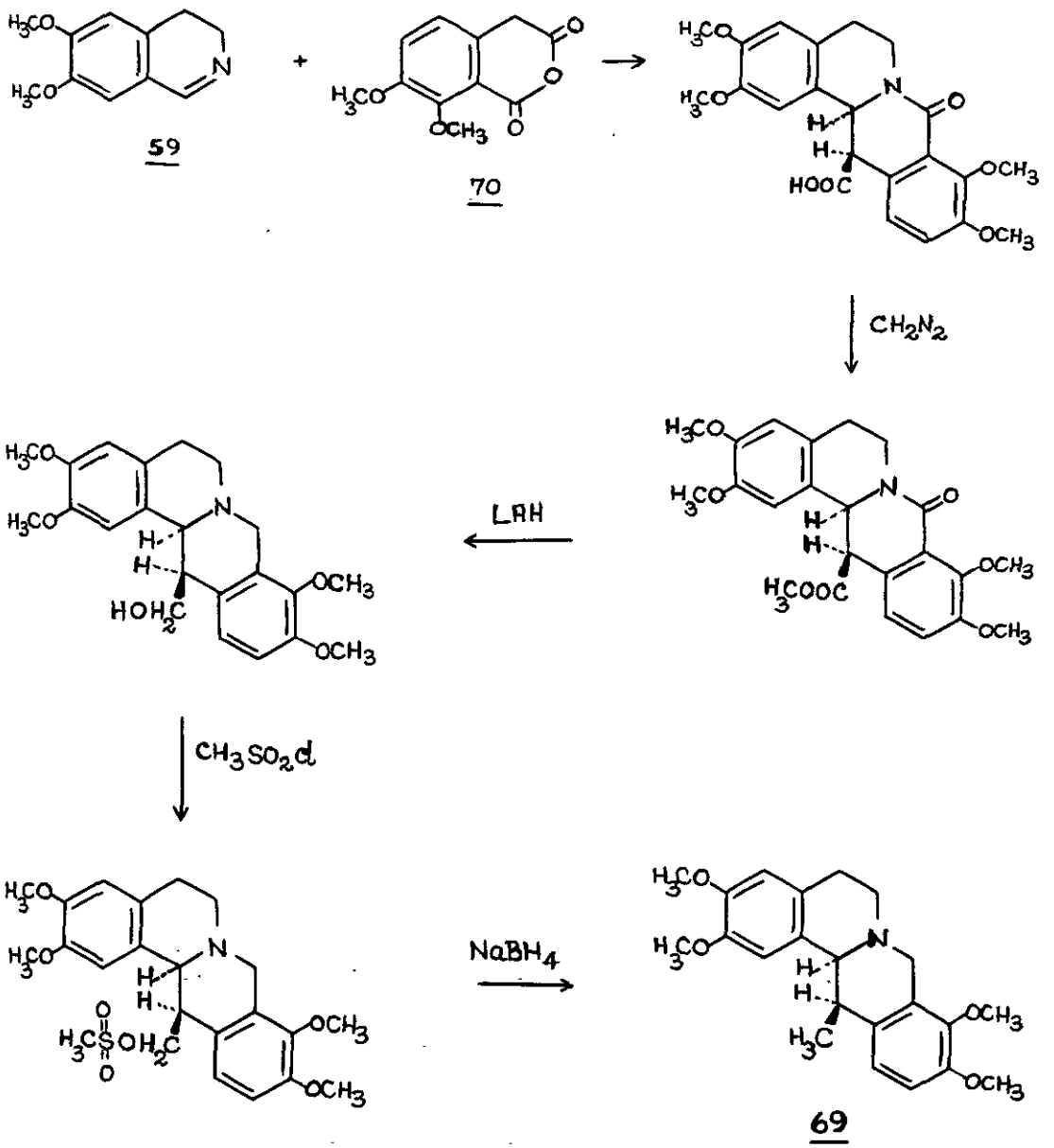
66 R = H (minor)

66a R = CH_3

2.5 Synthesis of 2,3,9,10-Oxygenated 13-Methyltetrahydroprotoberberines

The 9,10-dimethoxy substitution pattern of ring D of protoberberines presents a challenge since it is not readily accessible by Mannich cyclization of an appropriately substituted benzylisoquinoline. However, 3,4-oxygenated homophthalic anhydrides required for the preparation of 9,10-oxygenated 8-oxoberbines are easily accessible. Hence Cushman et al. utilized the general method of condensation of dihydroisoquinolines with dioxygenated homophthalic anhydrides for the syntheses of several 2,3,9,10-oxygenated 13-methyltetrahydroprotoberberines. Notable among these are the syntheses of optically active (+)-thalictricavine (67)[49] and (+)-thalictrifoline (68)[50]. Incidentally, Cushman's is the first synthesis of (+)-thalictrifoline, all previous attempts having failed[57].

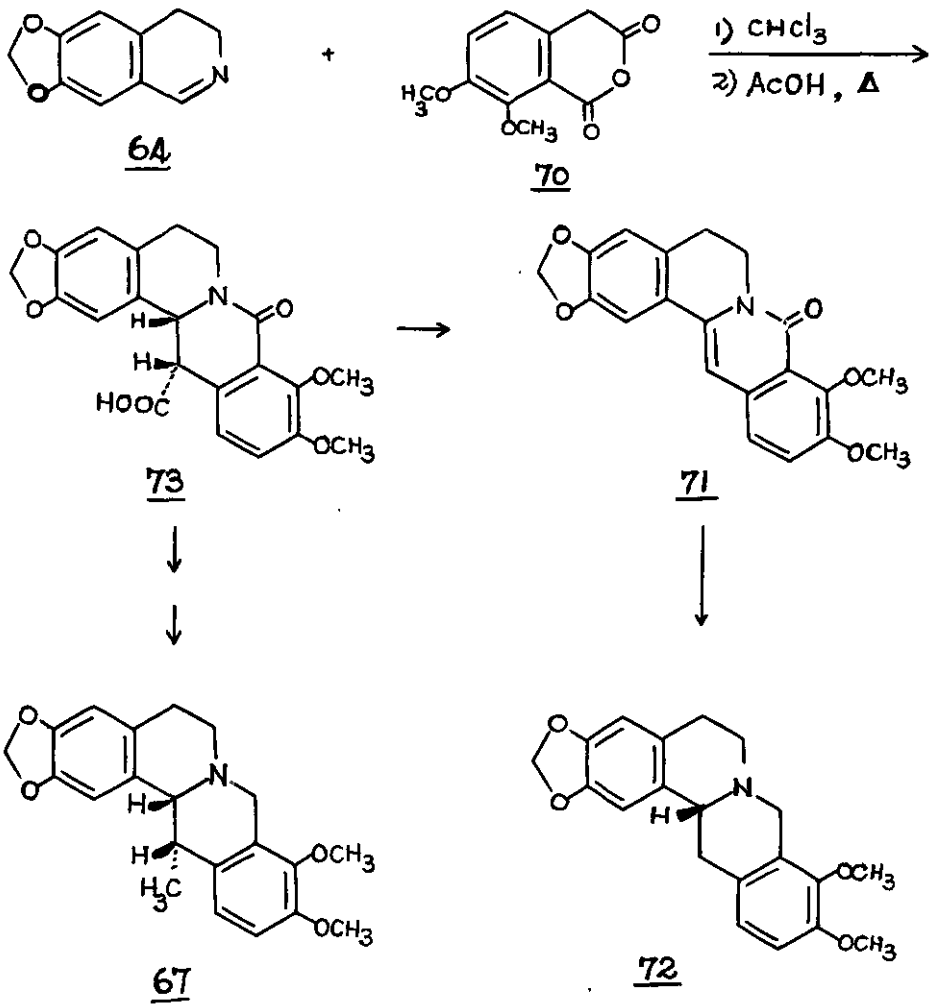
The first successful synthesis utilizing this general method of condensation of dihydroisoquinolines and dioxygenated homophthalic anhydrides is the total synthesis of (±)-corydaline (69)[54], a 9,10-substituted protoberberine, from the



Scheme 10

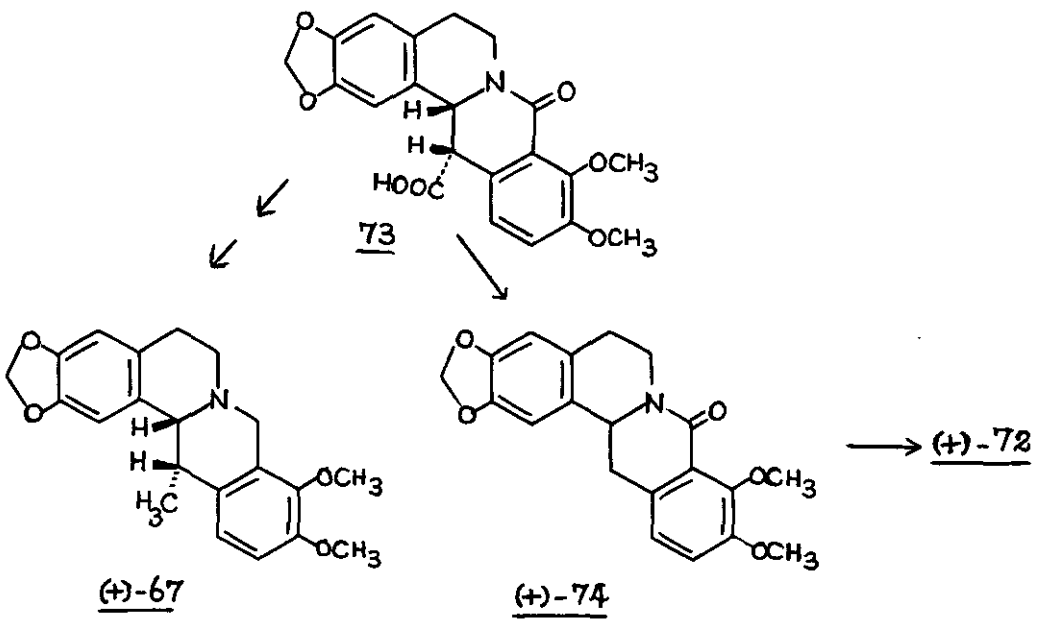
addition product of 6,7-dimethoxy-3,4-dihydroisoquinoline (59) and the homophthalic anhydride 70. The thermodynamically more stable cis isomer was converted into (±)-corydaline as indicated in Scheme 10.

On exactly similar lines Cushman et al.[55] synthesised (±)-thalictricavine (67), berlambine (71) and (±)-canadine (72) from a common intermediate (73). Condensation of norhydrastinine (64) with the homophthalic anhydride (70) proceeded exothermally in chloroform to afford a mixture of cis and trans isomer which was converted to the thermodynamically more stable cis diastereomer 73 on heating in acetic acid. The cis diastereomer 73 was converted into (±)-thalictricavine (67), berlambine (71) and (±)-canadine (72) as shown in Scheme 11.



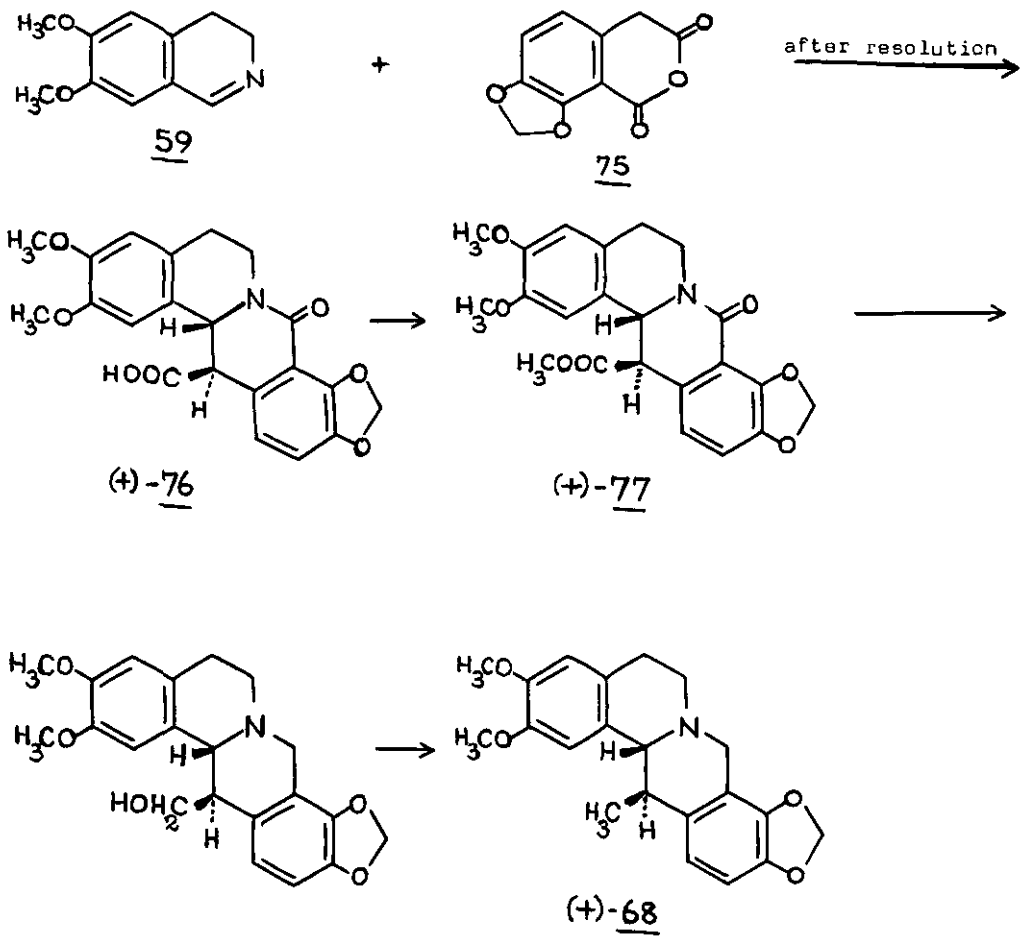
Scheme 11

Further, Cushman et al.[49] converted the (±)-13-carboxy-8-oxotetrahydroprotoberberine (73) into a crystalline salt with (-)-strychnine. Upon recrystallization from acetone pure (+)-isomer could be separated. The free acid (+)-73 yielded an optically impure lactam 74 when heated to 240-244°C for 5 min. Lithium aluminium hydride reduction of 74 gave (±)-canadine (72) as well as impure (+)-canadine whose absolute configuration is known already[56]. This established the absolute configuration of the acid (+)-73. Subsequently, acid 73 was converted into (+)-thalictricavine (67) by established methods (Scheme 10) without affecting any of the asymmetric centres. The absolute configuration of (+)-thalictricavine is therefore 13S, 14R as shown in structure (+)-67.



Imaginatively, Cushman et al. extended this approach to determine the absolute configuration of (+)-thalictrifoline (68)[50]. Condensation of 6,7-dimethoxy-3,4-dihydroisoquinoline 59 with 3,4-methylenedioxyhomophthalic anhydride 75 in chloroform at room temperature proceeded exothermally to yield a diastereomeric mixture of trans and cis 8-oxoberbines from which the major (±)-trans isomer 76 crystallized out in 80% yield. The (±)-trans acid 76 afforded a crystalline salt when treated with (-)-strychnine in ethyl acetate followed by recrystallization from chloroform-ethyl acetate. This salt gave free (-)-trans acid on decomposition.

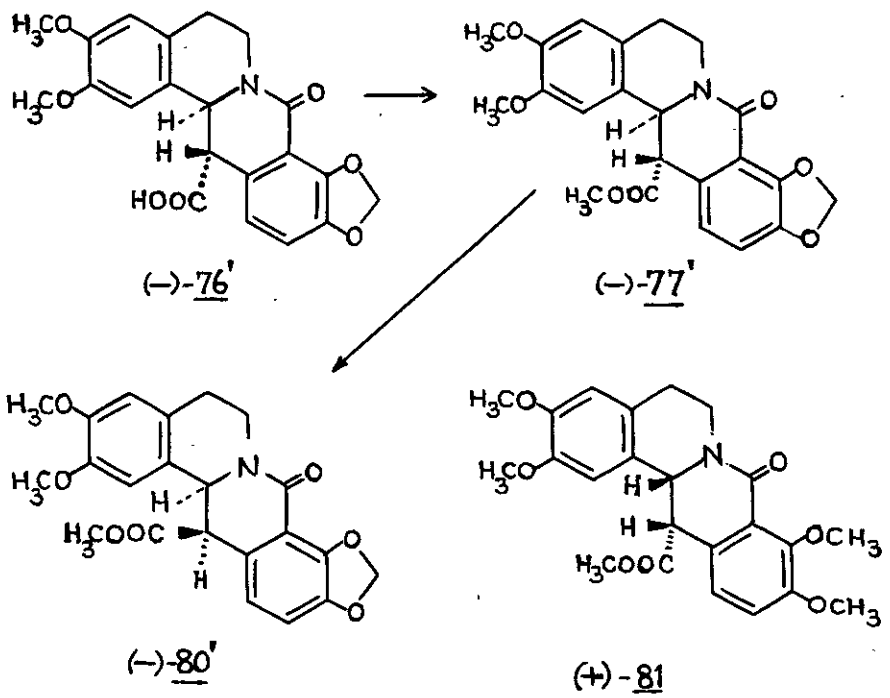
The (+)-trans isomer 76 was obtained by decomposition followed by recrystallization of the mother liquors. The (+)-trans acid 76 was converted into (+)-thalictrifoline (68)(Scheme 12) on lines similar to the synthesis of (+)-thalictricavine(67).



Scheme 12

In order to determine the absolute configurations of the (+)-trans ester 77 and the (-)-trans ester 77', methanolic solution of the (-)-trans ester 77' containing sodium methoxide was stirred at room temperature. This afforded the

(-)-cis ester 80' whose absolute configuration must be opposite to that of (+)-cis ester 81, since the conformations of both of these esters are identical as indicated by their PMR data and the optical rotations are opposite and almost of equal magnitude. The absolute configuration of (+)-cis-81 has already been established (See Scheme 11) as 13S, 14R[50]. Since (+)-thalictrifoline is derived from the (+)-trans ester 77 (Scheme 12), the absolute configuration of thalictrifoline is 13R, 14R as shown in 68.



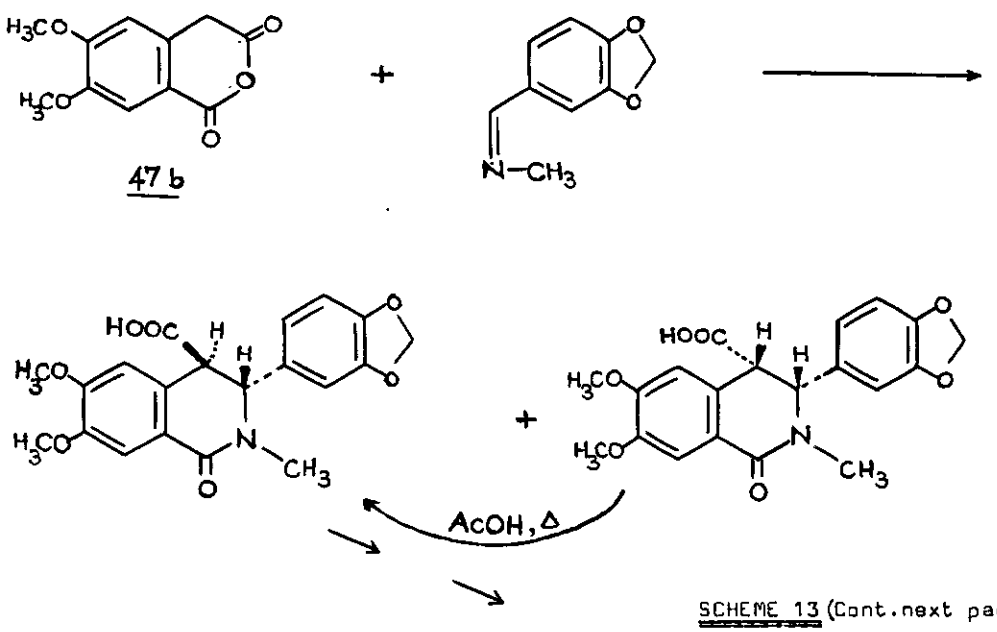
Pai and coworkers, continuing their earlier efforts to synthesize (±)-thalictrifoline (68)[57], now focused their attention on the use of Cushman's elegant method for the synthesis of (±)-thalictrifoline (68). Their efforts were first directed to get the maximum yield of trans-(76) which was utilized in the synthesis of (±)-thalictrifoline (68)[58]. Among the three solvents and different temperatures employed for the condensation of 59 and 75, ethylene chloride at 80°C gave the best result (Table 1). In line with Cushman's observation both the trans and cis isomers were obtained in 4:1 ratio which were separated by fractional crystallization. The major product (trans isomer) was converted into (±)-68 as shown in Scheme 12.

Table 1

No.	Temp. °C	Solvent	Ratio of Trans:Cis By HPLC
1	15	CH_2Cl_2	2:1
2	25	CH_2Cl_2	2:1
3	25	$(CH_2)_2Cl_2$+Et_3N	1.6:1
4	25	$CHCl_3$	2:1
5	25	$(CH_2)_2Cl_2$	2:1
6	35	CH_2Cl_2	2:1
7	35	$(CH_2)_2Cl_2$	2.5:1
8	42	CH_2Cl_2	2.6:1
9	80	$(CH_2)_2Cl_2$	4:1

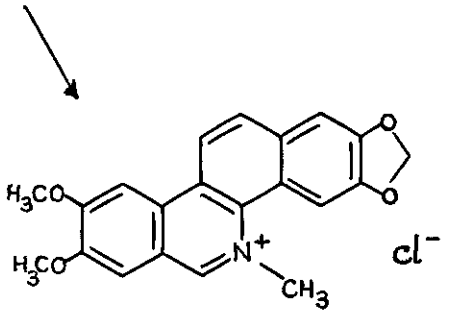
2.6 Synthesis of Benzophenanthridine Alkaloids:

In a new approach to the preparation of benzophenanthridine alkaloids, Cushman and coworkers[59] utilized the condensation of 3,4-methylenedioxybenzylidenemethylamine with the homophthalic anhydride 47b. The product was a mixture of cis and trans isomers in 49% and 39% yield respectively. The kinetic product (cis isomer) was converted into the thermodynamically more stable trans isomer by heating in acetic acid and this trans isomer was further converted into nitidine chloride (82) in several steps (Scheme 13).



SCHEME 13 (Cont.next page)

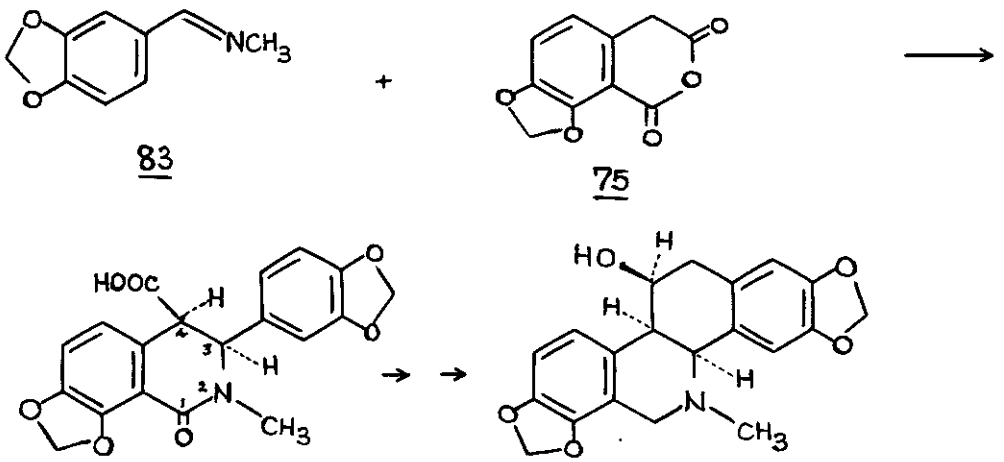
SCHEME 13 (cont)



82

Scheme 13

Similarly, the Schiff base 83 and the homophthalic anhydride 75 afforded a mixture of cis and trans diastereomeric isoquinolinones[60]. When the condensation was performed in refluxing acetonitrile the cis isomer (84) was the major product which was utilized in the total synthesis of (±)-chelidonine (85), also a benzophenanthridine alkaloid.

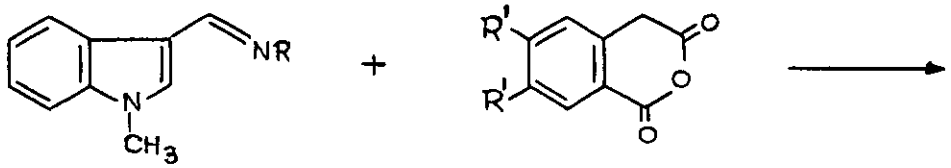


83 + 75 → 84 → 85

2.7 Synthesis of Indole Alkaloids

Haimova et al. extended their studies on the use of Schiff bases to the synthesis of indole alkaloids[61]. Schiff bases of 1-methylindole-3-carboxaldehyde (86 a-d) were prepared and were condensed with homophthalic anhydrides 47a and 47b to give diastereomeric mixtures of 4-carboxy-3-(3'-indolyl)-2-alkyl-3,4-dihydro-1(2H)-isoquinolinones 87 a-d. These acids were readily converted into their methyl esters by reacting with diazomethane. Contrary to their earlier observations[43],

where they observed stereoselective products (trans adduct), in this reaction both cis and trans isomers were obtained. The methyl esters of these diastereomers were separated by silica gel chromatography. The cis and trans configurations were assigned based on PMR spectra. Again, the coupling constant $J_{3,4}$ is larger (~6Hz) for the cis isomer than that for the corresponding trans isomer (~1Hz).



86 a-d

86a R = CH_3

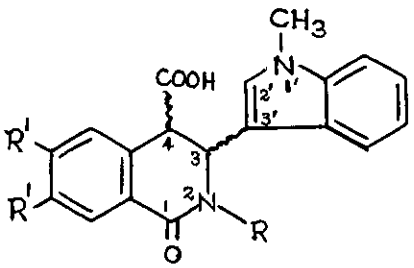
86b R = C_2H_5

86c R = nC_3H_7

86d R = $CH_2C_6H_5$

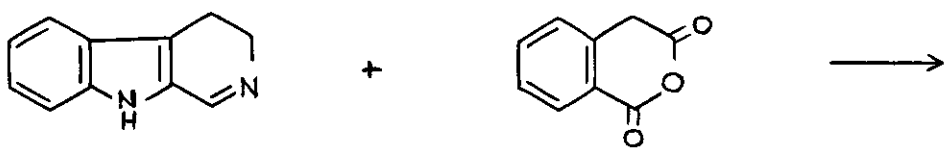
47a R' = H

47b R' = OCH_3

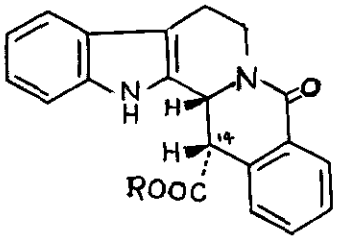


87 a-d

3,4-Dihydro-β-carboline 88 reacted with homophthalic anhydride 47a to give a diastereomeric mixture of cis and trans 14-carboxy-hexadehydroyohimbane 89 and 90 respectively. The relative configurations of 89 and 90 were established on the basis of PMR spectra of their methyl esters. The PMR characteristics of these compounds are similar to those of 13-carboxy-8-oxoberbines (60) discussed earlier[43]. In the cis isomer 89a the methyl protons of the carboxymethyl group resonate at a higher field (δ 3.21) and for the trans isomer 90a the corresponding methyl protons appear at relatively lower field (δ 3.80).



88 47a



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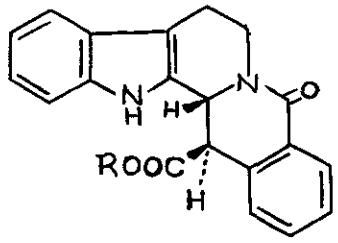


89 R = H

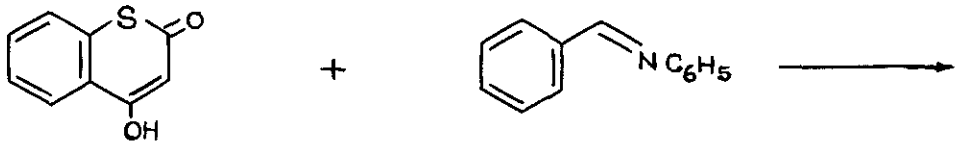
89a R = CH_3

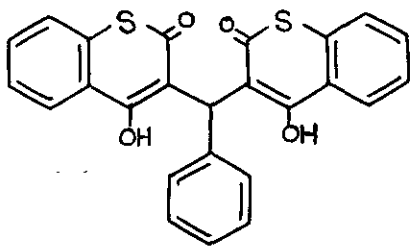
90 R = H

90a R = CH_3

2.8 Addition of Schiff Bases to 4-Hydroxythiocoumarin and 4-Hydroxycoumarin

Merchant et al.[62] reacted 4-hydroxythiocoumarin with benzylideneaniline in glacial acetic acid at 30°C or in methanol at reflux temperature to get 3,3'-benzylidene-bis-4-hydroxythiocoumarin 91 as the product. The same product could be

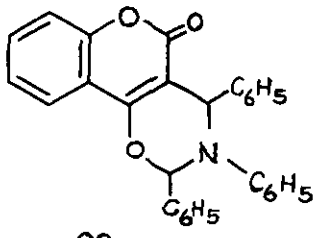




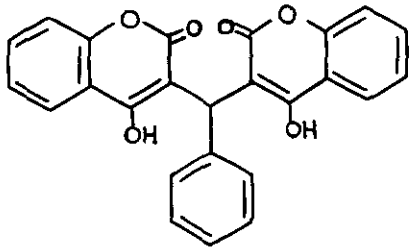
91

obtained when benzaldehyde was used in the place of benzylideneaniline. This observation led the authors to revise the original structure[63] (92) for the

condensation product between 4-hydroxycoumarin and benzylideneaniline, the correct structure being 93.



92

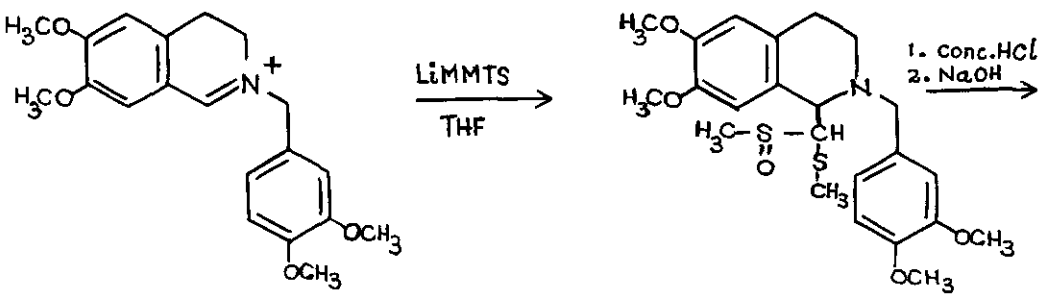


93

3. Reactions of Anions with Iminium Salts for Synthesizing Protoberberines and Phthalide Isoquinolines and Related Alkaloids

3.1 Addition of Lithio Methyl Methylthiomethylsulfoxide (L MMTS)

Anion of methyl methylthiomethylsulfoxide[64] (MMTS) is known to add to iminium salts[65]. MacLean et al.[66] used this reaction for a two step synthesis of dihydroprotoberberines. Appropriately substituted N-benzyl-3,4-dihydroisoquinolinium or N-benzylisoquinolinium salts were used as starting materials in this work.



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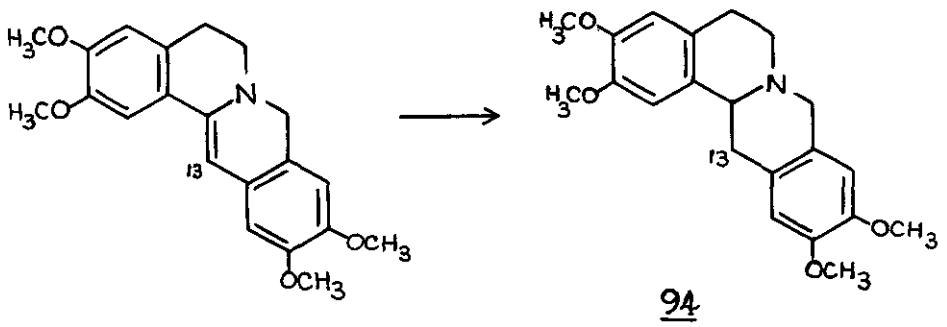
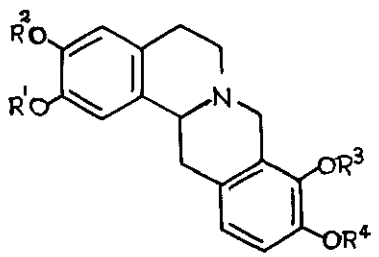
SCHEME 14 (cont.)



94

Scheme 14

A typical synthesis of (±)-xylopinine (94) from N-benzyl-3,4-dihydroisoquinolinium salt is given Scheme 14. It should be noted that the anionic carbon of the nucleophile ends up as C-13 of the protoberberine skeleton. (±)-Tetrahydropalmatine (95), (±)-sinactine (96) and (±)-corydaline (69) were also prepared by using the addition of LiMMTS to N-benzyl-3,4-dihydroisoquinolinium salts.

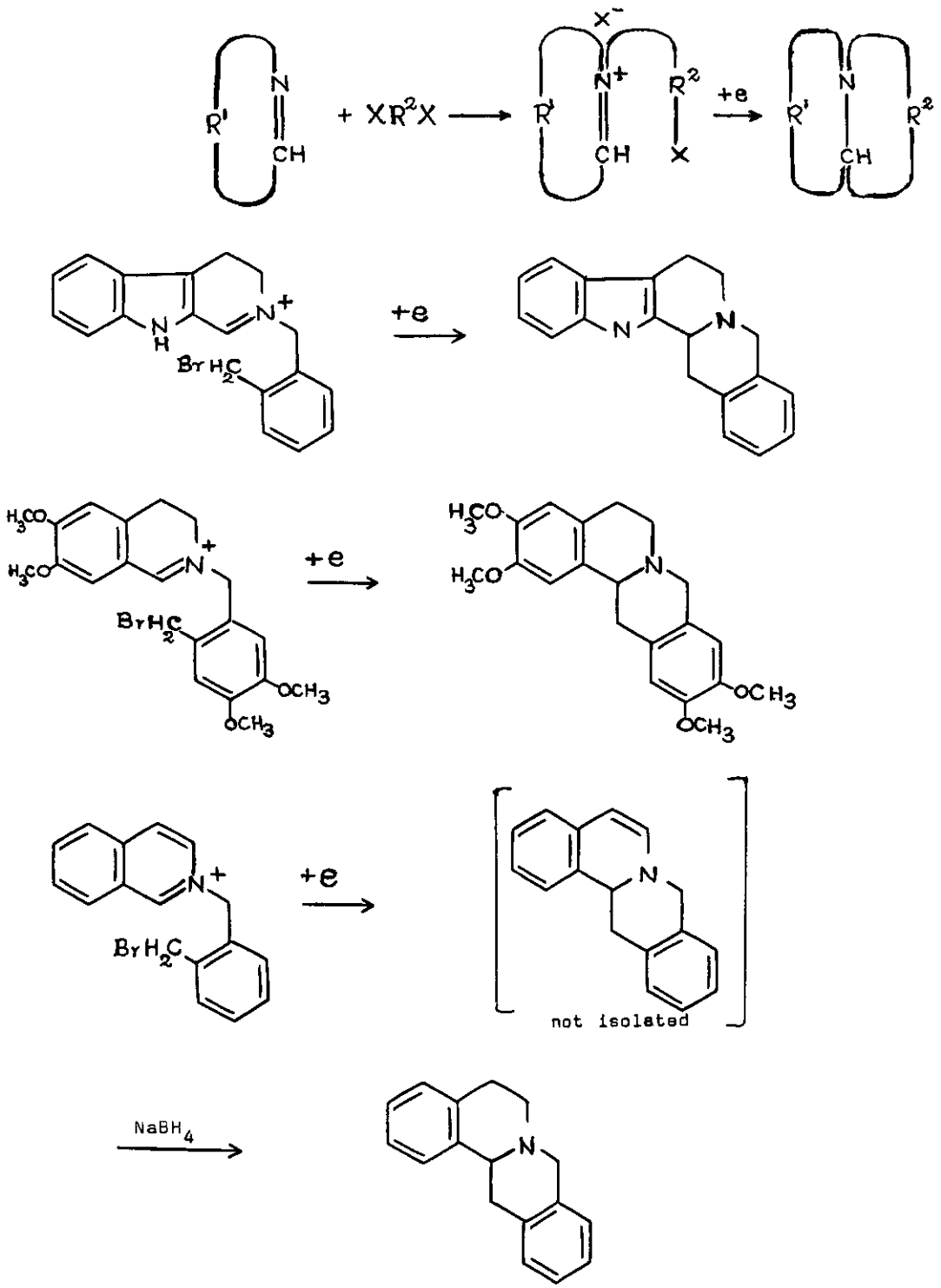


95 $R^1 = R^2 = R^3 = R^4 = CH_3$

96 $R^1 = R^2 = CH_3$ and $R^3R^4 = CH_2$

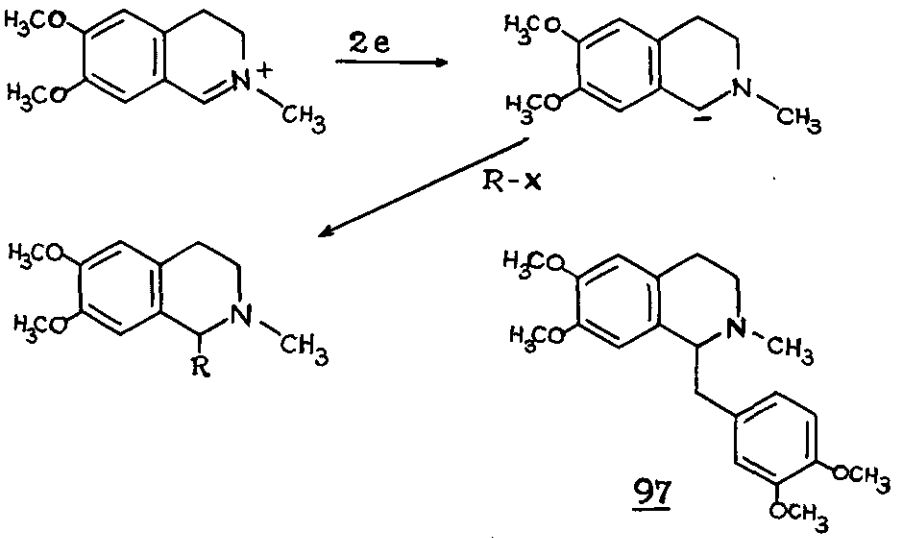
3.2 Electroreductive Addition of Alkyl Halides to Iminium Salts

In 1978, Shono and coworkers reported a novel annelation forming a hetero ring by electroreductive addition of alkyl halides to iminium salts[67]. They used this simple and elegant method for the synthesis of several indole and isoquinoline alkaloids (Scheme 15).



Scheme 15

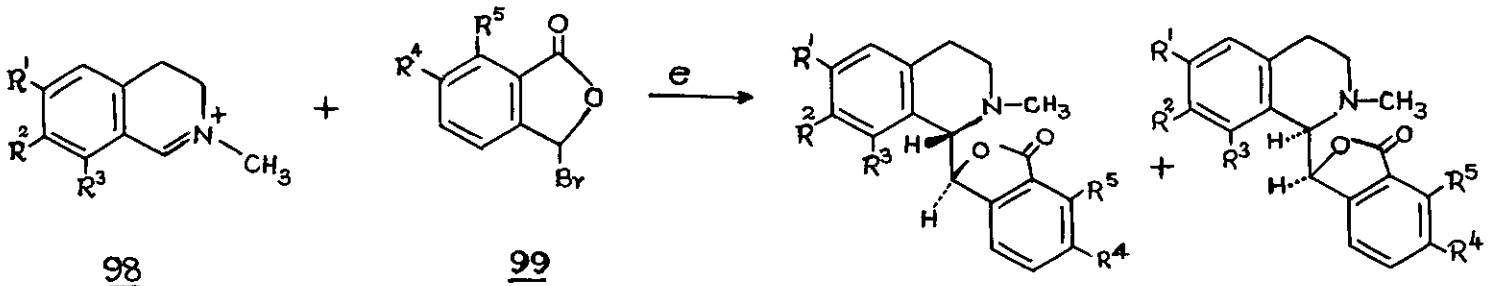
Intermolecular reductive addition of alkyl halides to iminium salts is also possible and alkaloids such as (±)-laudanosine (97) have been synthesised by this method. Incidentally, these authors established the relationship between isolated yields and cathodic potentials and also the reaction mechanism (Scheme 16).



RX = $C_6H_5CH_2Br$	65%
RX = 4-CH_3O-$C_6H_4CH_2Br$	73%
RX = 3,4-diCH_3O-$C_6H_3CH_2Br$	85%
RX = CH_3 I	35%

Scheme 16

Shono and coworkers extended the electroreductive method to practical synthesis of phthalide isoquinolines[68]. In this process the easily accessible components 98 and 99 are coupled to provide 100 in reasonably good yield. In all the cases studied both the diastereomers were obtained in almost equal amounts. It is indeed an ingenious and versatile method to the credit of Shono and coworkers. On these lines, Mooney et al.[69] have shown that phthalide anions add to isoquinolinium salts to yield phthalide isoquinolines, providing an interesting and significant variation to the theme.

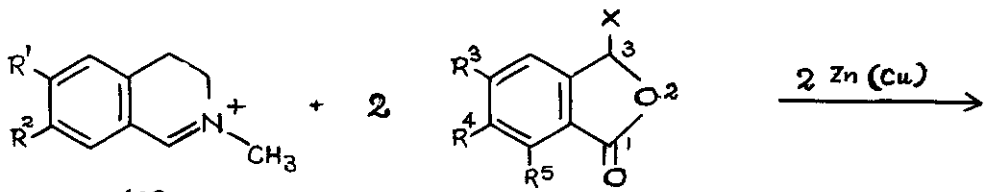


98 + 99 → 100

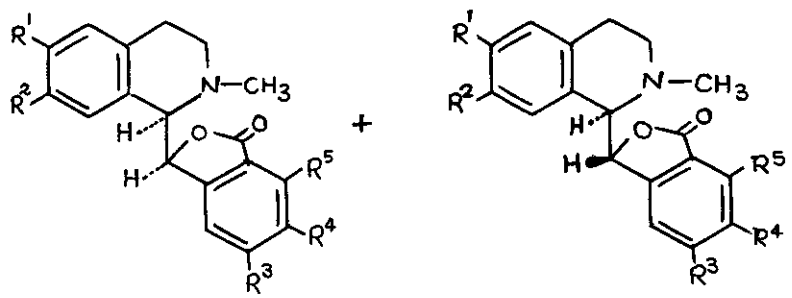
$R^1 = R^2 = OCH_3$, $R^3 = H$	$R^4 = R^5 = H$	40%	28%
$R^1 = R^2 = OCH_3$, $R^3 = H$	$R^4 = R^5 = OCH_3$	42%	35%
$R^1R^2 = OCH_2O$, $R^3 = H$	$R^4 = R^5 = OCH_3$	35%	30%
$R^1 = R^2 = R^3 = OCH_3$	$R^4 = R^5 = OCH_3$	57% (mixture)	
$R^1R^2 = OCH_2O$, $R^3 = OCH_3$	$R^4 = R^5 = OCH_3$	57% (mixture) (dl-Noscapine)	

3.3 Synthesis of Phthalide Isoquinolines and Protoberberines - MacLean's Work

As a follow up work of Shono and Mooney, MacLean[70] reported the coupling of 3-halophthalides 101 with N-methyl-3,4-dihydroisoquinolinium salts 102 in the presence of Zn(Cu) couple or metallic Zn to give a mixture of erythro and threo-N-methylphthalidetetrahydroisoquinolines 103 and 104 respectively. The diastereomers are formed almost in equal amounts as in earlier cases. When the 3-halophthalide was treated with Zn under Reformatsky conditions, followed by introduction of the isoquinolinium salt, no coupling occurred. This observation led the authors to conclude that the reaction proceeded on the metal surface through the formation of a phthalide anion which reacts directly with the iminium salt at the surface. However, a radical mechanism for the reaction has not been ruled out.



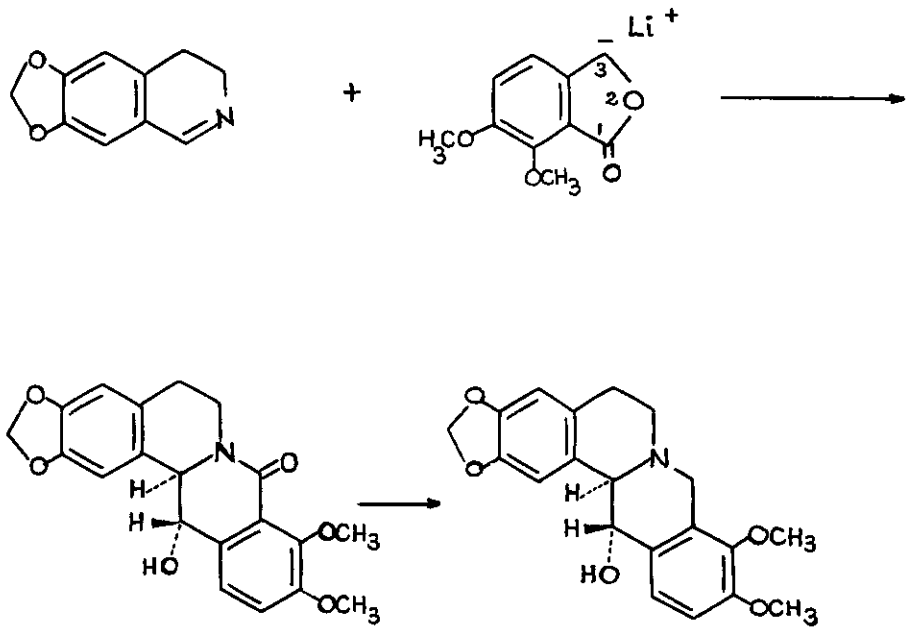
102 101



103 104

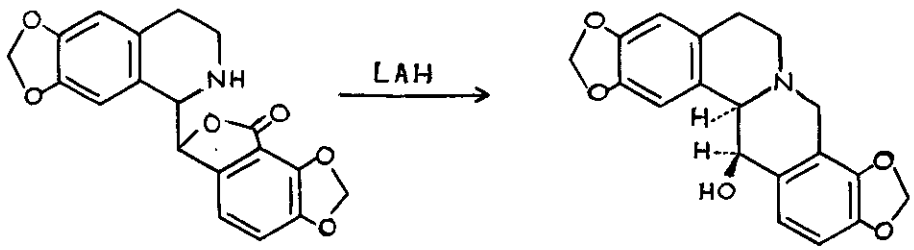
As an interesting variation of this method MacLean et al.[71] found that imines (3,4-dihydroisoquinolines) react with phthalide anions yielding 13-hydroxy-8-

oxotetrahydroprotoberberines in good yield as shown in Scheme 17. The trans relationship of the hydrogen atoms at C-13 and C-14 in the product is apparent from the coupling constants of these hydrogens ($J_{13,14}$=8.4Hz). The high degree of stereoselectivity in this reaction implies that the two components must interact in an "endo" relationship with respect to each other in the formation of

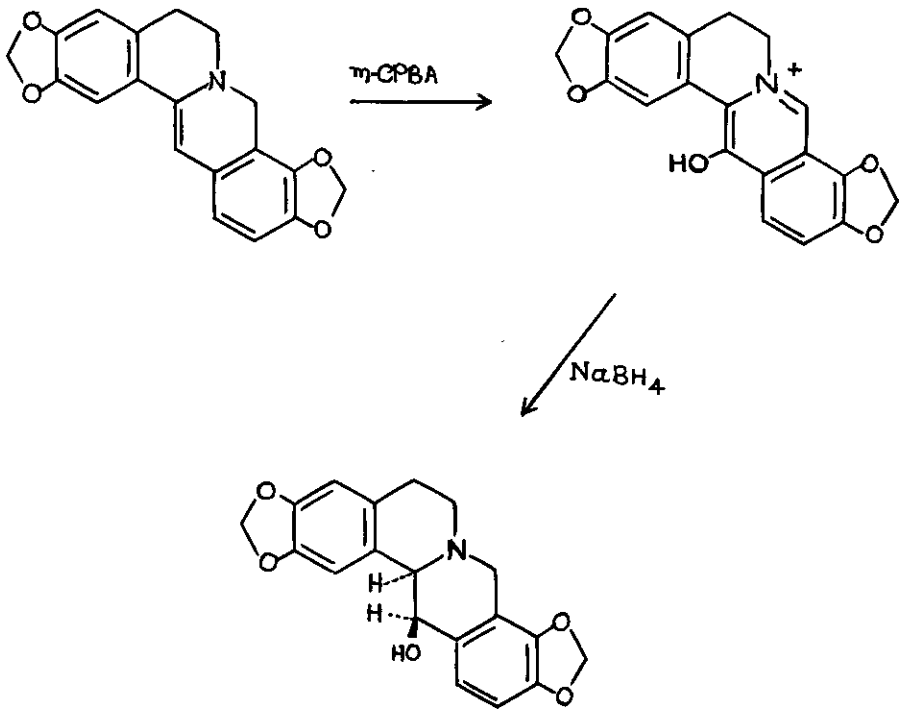


Scheme 17

bonds between C-13 and C-14 and between N and C-8. However, the authors do not rule out the possibility of the other diastereomer being formed or its presence in infinitesimally small amounts. This synthesis of (±)-ophiocarpine bears some similarities to the earliest synthesis of (±)-ophiocarpine from phthalide isoquinoline reported by Govindachari et al[72]. The method of Jeffs[73] involves the reduction of 13-hydroxyberberinium salts which could be obtained by oxidation



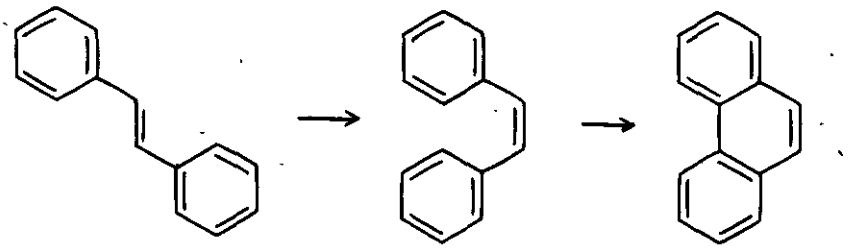
of dihydroberberines (Scheme 18).



Scheme 18

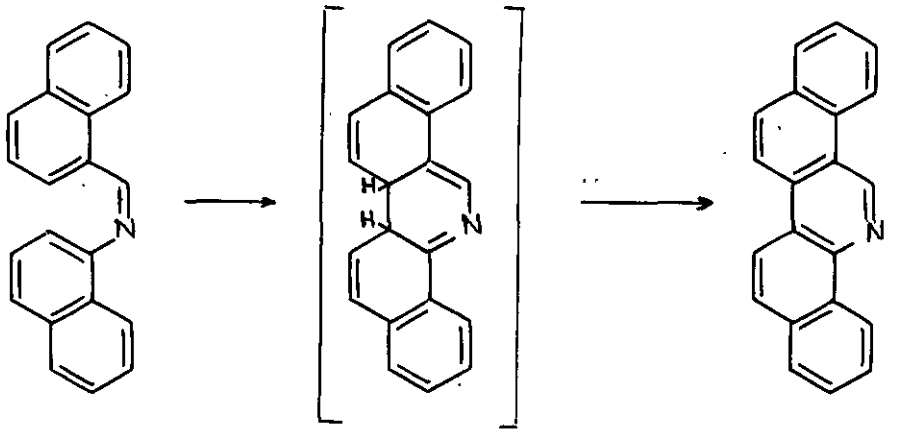
4. Photochemical Reactions of Schiff Bases

The conversion of stilbenes into phenanthrines by oxidative photochemical process has been the object of considerable study (Scheme 19)[74].



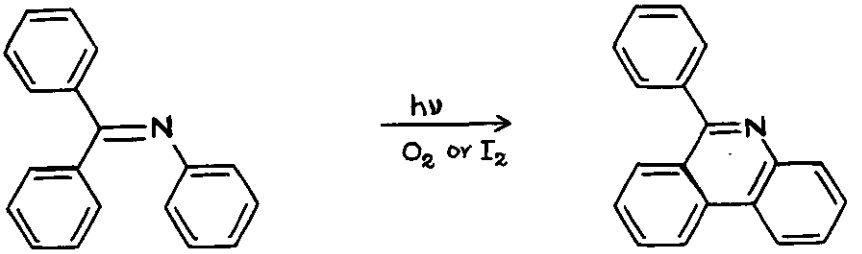
Scheme 19

In recent years there have appeared three reviews entitled the photochemistry of imines[75], photochemistry of the carbon-nitrogen double bond[76], and photochemistry and photocyclization of aryl halides[77]. Photocyclizations and Pschorr-type reactions do not proceed as well with anils or their derivatives as with stilbenes[78]. Several groups have recorded the failure of the photochemical cyclization of benzalaniline itself[79]. However, Cava and Schlessinger[80] reported



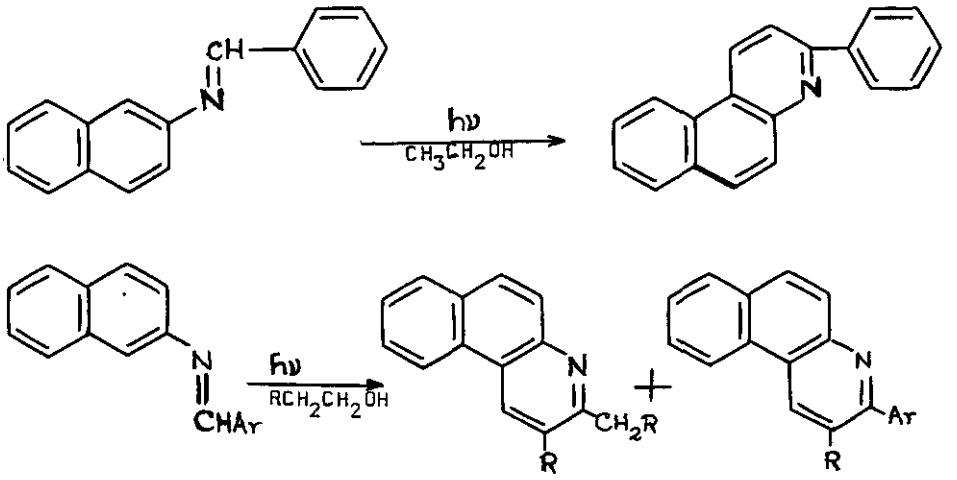
105 106

the photooxidative ring closure of the Schiff base 105 to 106 in the presence of air. This observation prompted Mallory and Wood[81] to reinvestigate the photochemistry of benzalaniline. For the benzalaniline to give phenanthridine, it is necessary to have a considerable photostationary concentration of the cis isomer. This condition was realized by carrying out the reaction at 10°C when the yield was 2%. Alternatively, the Schiff base 107 (from benzophenone and aniline) cyclized upon irradiation in the presence of air or iodine to phenylphenanthridine 108



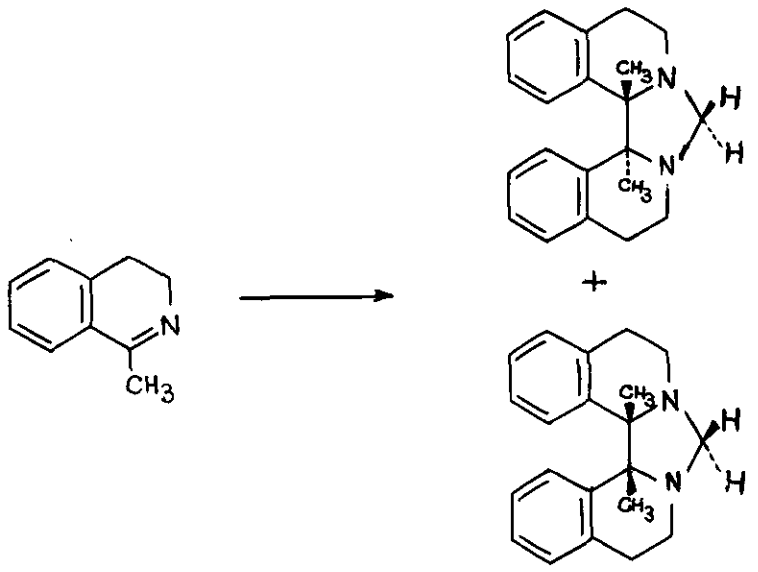
107 108

in good yield. Interestingly, Sternhell et al.[82] observed the incorporation of solvent molecules in the photochemical process. Examples are given in Scheme 20.

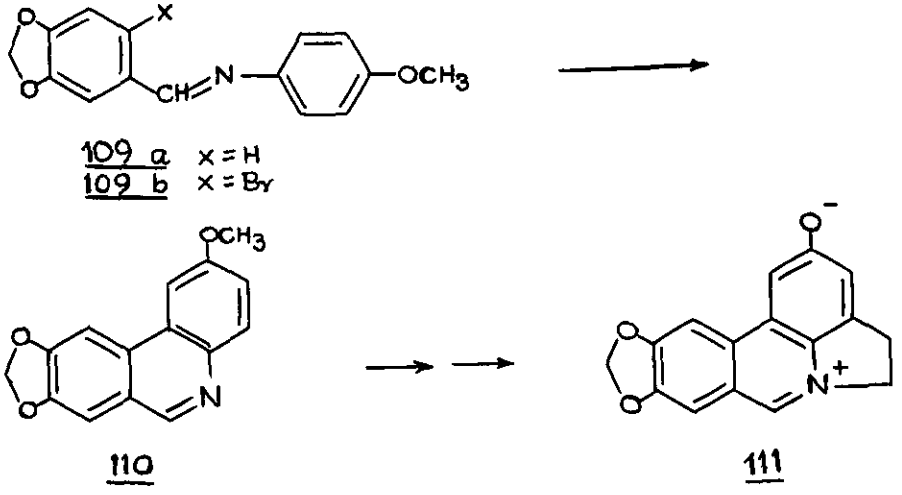


Scheme 20

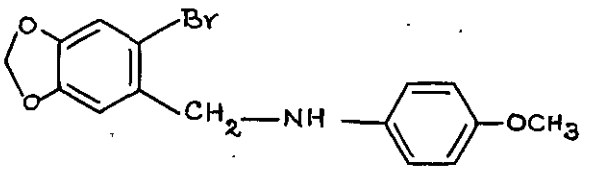
Another example of the incorporation of solvent in the photochemical reactions of Schiff bases is provided by Schmid and Cerutti[82a]. When 1-methyl-3,4-dihydroisoquinoline in dry methanol was irradiated under nitrogen atmosphere two products were formed as shown in next page.



It is interesting to note that in the second example (in Scheme 20) one of the products is from the Schiff base formed by β-naphthylamine and the aldehyde derived from the solvent molecule RCH_2CH_2OH. Irradiation of benzalaniline in conc.H_2SO_4 yielded a mixture of phenanthridine and benzylaniline[83]. Another successful attempt on the photocyclization of Schiff bases was by Natsume and coworkers[84] during their synthesis of the antileukemic activity bearing alkaloid ungeramine 111.

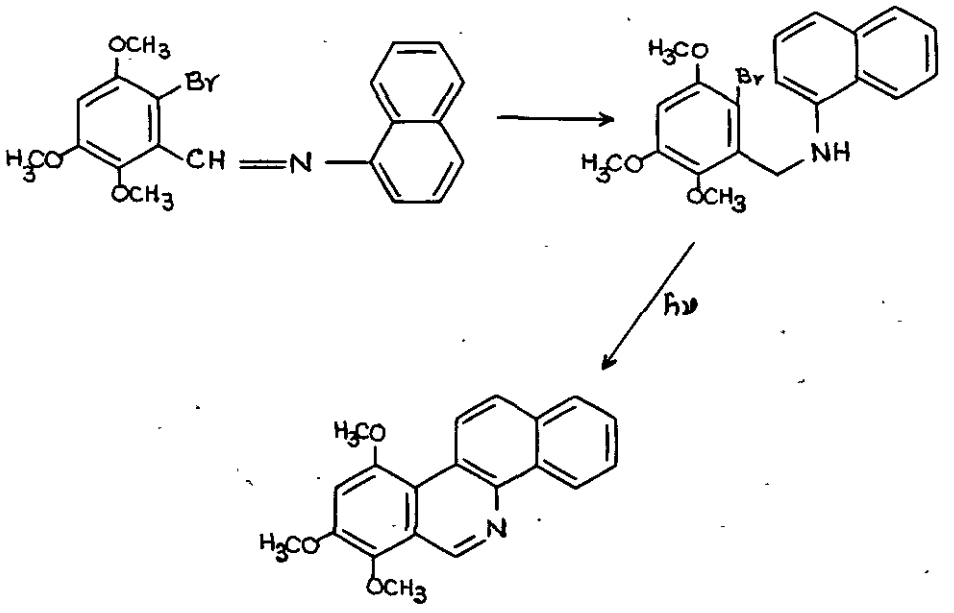


However, Gupta et al.[85] reported the failure of this reaction and hence resorted to an alternative method wherein the Schiff base 109b was reduced with sodium borohydride to give 112 which upon irradiation yielded 110, cyclization and oxidation taking place concomitantly.



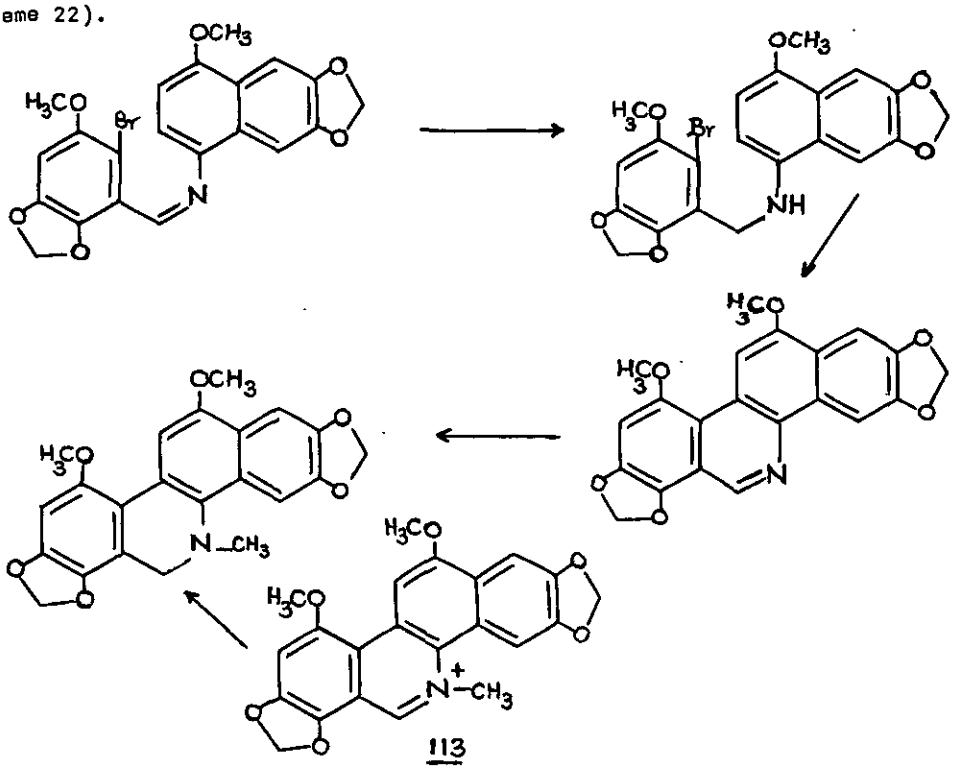
112

Kessar[86] had earlier carried out this type of reaction in an overall yield of 50% in the following sequence (Scheme 21).



Scheme 21

Recently, Takao et al.[87] have accomplished a total synthesis of the alkaloid macarpine 113, utilizing the photocyclization of the reduced Schiff base (Scheme 22).

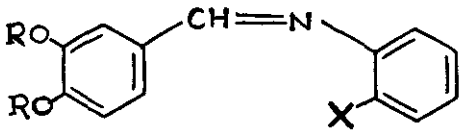


Scheme 22

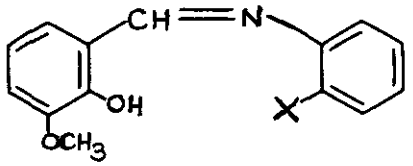
Since there does not seem to be any report on the successful photocyclization of benzylideneanilines in moderate yield for the method to be of any preparative value, we planned the synthesis of a series of Schiff bases with a halogen at the ortho position of the aniline or aldehyde ring. The following anils 114-122 were prepared+ by simple condensation of the aromatic aldehyde and the aniline at around 140°C . Compounds 114 to 122 gave satisfactory analytical and spectral data. Compounds 114, 117 and 121 were subjected to photolysis using a low pressure lamp (254nm) fitted with a quartz filter. When methanol or benzene was used as solvent only the corresponding aldehydes could be obtained as products in all the cases and this type of hydrolysis is already known[98]. Additionally, Schiff bases 117 and 119 were subjected to photochemical reaction using sunlight as the radiation source the reactions being carried out in Pyrex as also in quartz

+ This work forms parts of the theses submitted by B.Sunita, T.Sivakamasundari and B.Premila to the University of Madras (Pachaiyappa's College, Madras) in May, 1981 in partial fulfilment of the M.Sc. degree in Chemistry.

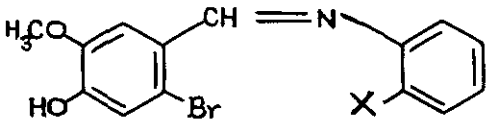
vessels[89]. Using methanol, hexane, acetone and acetone containing benzophenone as solvents only traces of aldehydes could be isolated as products along with the starting materials even after two days. To our disappointment no phenanthridines were found to be formed in any of the above experiments.



114 R = CH_3, X = Cl
115 R = CH_3, X = Br
116 RR = $-CH_2-$, X = Cl

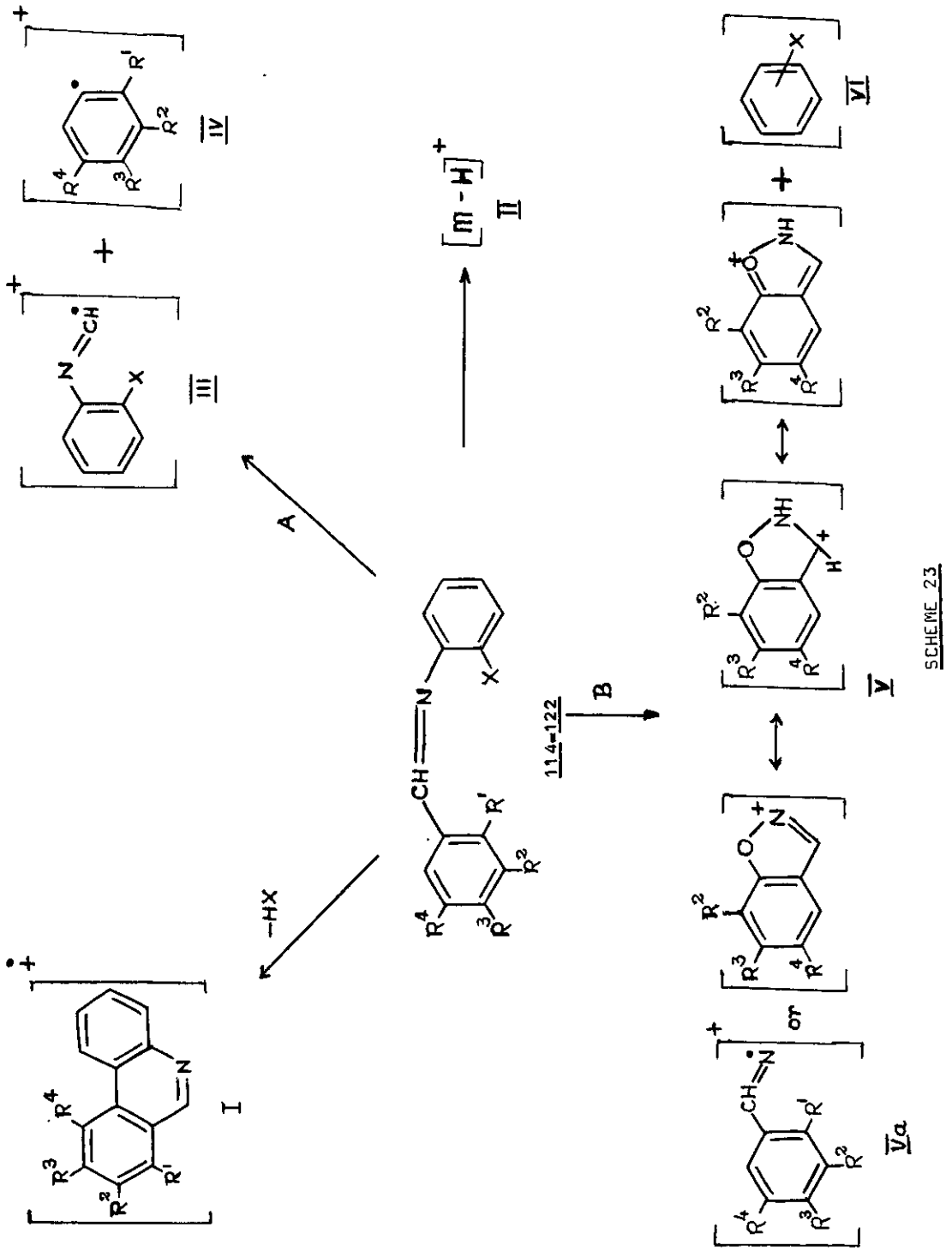


117 X = Cl
118 X = Br
119 X = I
120 X = OCH_3



121 X = H
122 X = Cl

In the meantime, we had occasion to study the mass spectra of these Schiff bases. Studies on the mass spectra of Schiff bases were first reported in 1966[90] where simple mode of fissions and rearrangements of substituted Schiff bases were the object of study. Skeletal rearrangements of the type $(ABC)^+ \longrightarrow (AC)^+ + B$ which are common features of the spectra of compounds having the general structure Ar-X-Y-Ar have also been reported in the case of anils derived from aromatic aldehydes[91]. When an alkyl group is present in the ortho position of the aldehyde part of the Schiff base, C=N bond cleavage accompanied by a transfer of one and/or two hydrogens to the nitrogen containing fragment is a common feature[92]. When the Schiff bases derived from 2-hydroxy-5-methylbenzaldehyde were subjected to mass spectral studies a six-centre H-transfer-McLafferty rearrangement, HCN elimination from M^+ as well as from other fragments and formation of a benzisoxazole cation were observed[93].



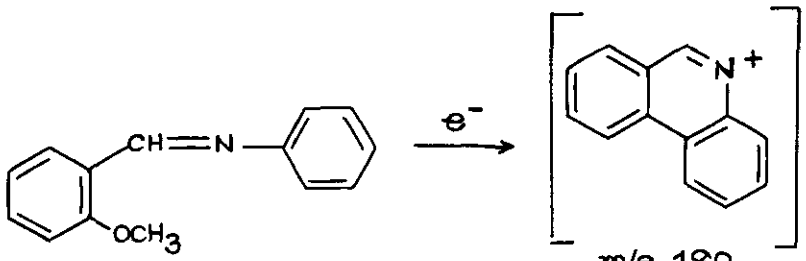
SCHEME 23

Table 2

Compound	Fragments m/e (intensity %)						
	M^+(m/e)(%)	I	II	III	IV	V	VI
117	263(11) 261(19)	226(25)	262(27) 260(96)	138(15) 136(2)	123(2)	150(46)	113(15) 111(42)
118	307(100) 305(85)	226(59)	306(40) 304(26)	184(23) 182(42)	-	150(78)	157(39) 155(85)
119	353(100)	226(22)	-	-	-	150(42)	203(10)
120	257(100)	226(15)	256(22)	134(9)	123(56)	150(33) ($R=OCH_3$)	108(39)
122	343(33) 341(100) 339(86)	226(17)	342(41) 340(76) 338(55)	140(15) 138(36)	203(12) 201(14)	231(10)* 221(11)	113(75) 111(36)
121	307(24) 305(81)	226(32)	306(95) 304(93)	104(30)	203(8) 201(8)	231(100)* 229(98)	77(43)
116	261(34) 259(100)	224(25)	260(41) 258(79)	140(16) 138(26)	121(26)	147(7)*	113(26) 111(26)
114	277(7) 275(20)	239(6)	276(10) 274(19)	140(1) 138(2)	137(5)	165(100)*	113(4) 111(13)
115	321(79) 319(84)	240(32)	320(58) 318(47)	184(26) 182(37)	137(32)	164(27)*	157(32) 155(37)

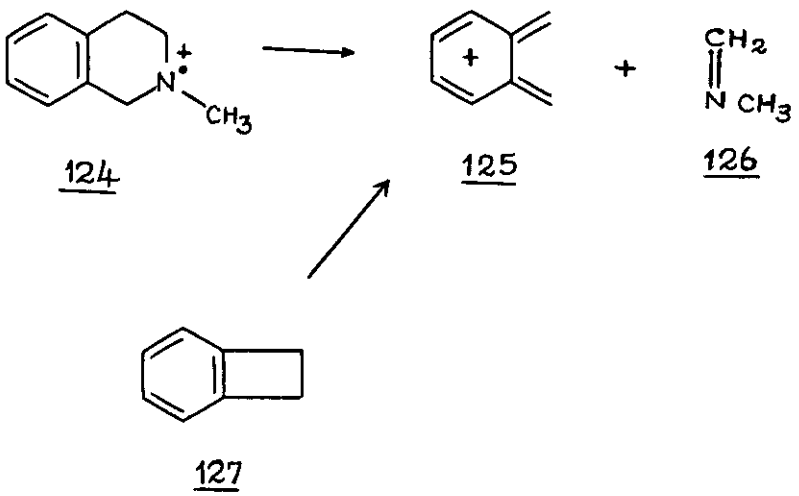
*Va

In the mass spectrum of Schiff base 123, the ion at m/e 180 (relative intensity 5%) could result from the formation of protonated phenanthridine. However, Elias and Gillis[90] make no special mention of this fragment.



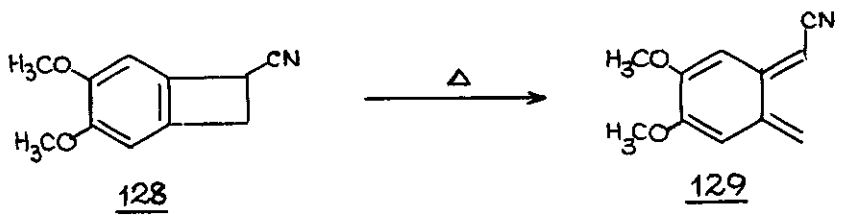
123

To our delight and surprise we found that each one of the Schiff bases 114-122 exhibited a phenanthridine ion fragment of considerable intensity (Scheme 23, Table 2). This naturally turned our attention to the epoch making review article by Professor Kametani[94]. In 1976, Professor Kametani proposed a new and effective synthetic design which he called "Retro Mass Spectral Synthesis". This analysis is based on fragmentation processes in mass spectrometry and he has synthesized several kinds of natural products along the routes determined by this method. He discovered this analysis for the design of a synthetic route from the following assumption: Since fragmentation in the mass spectrometer is a chemical process that results in bond breaking, fragmentation of a compound is sometimes very similar to chemical degradation reactions. These facts indicate that some mass spectral fragmentations parallel chemical degradations and therefore also parallel retro processes of synthetic reactions of organic compounds. It is significant to point out in this review that one of the very first examples that Professor Kametani chose to establish his thesis was the synthesis of 1,2,3,4-tetrahydroisoquinolines from compounds which correspond to ion 125 and fragment 126 formed by retro-Diels-Alder reaction of the molecular ion 124. He considered the benzocyclobutene 127 as the chemical equivalent of

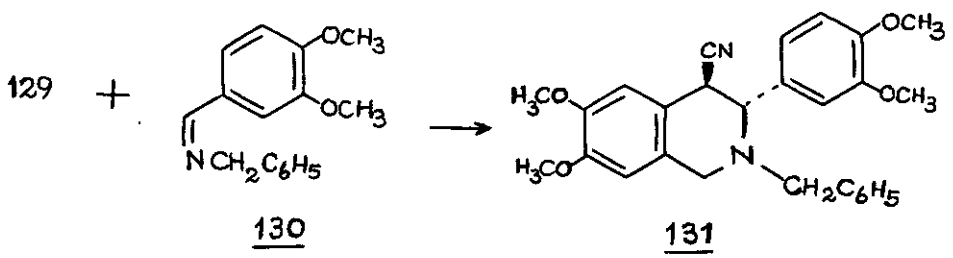


124 125 126 127

ion 125, because benzocyclobutene 127 readily produces o-quinodimethane 125 on heating. Reaction of 128 with the Schiff base 130, the synthon corresponding to fragment 126, at 150-160°C afforded the 1,2,3,4-tetrahydroisoquinoline 131 in both regio and stereselective manner by cycloaddition of the o-quinodimethane 129 to the Schiff base.



128 129



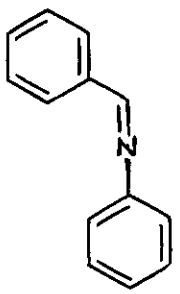
130 131

This has inspired in us the hope, yet unrealized, that under suitable thermal or photolytic conditions, it should be possible to prepare phenanthridines from all the Schiff bases we have prepared.

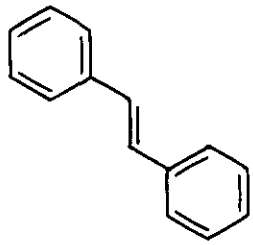
This brings us to the geometrical requirements at the excited state of the anils for the photocyclization to occur.

The ultraviolet spectral behaviour of a molecule is a rather sensitive function of the molecular conformation which to a very good approximation can be described by a single molecular parameter, the rotation of the plane of the phenyl ring about the N-C bond in the case of Schiff bases.

Spectral investigations into the cause of the marked dissimilarity between the UV spectra of benzylideneaniline 132 and the isoelectronic analogues trans



132



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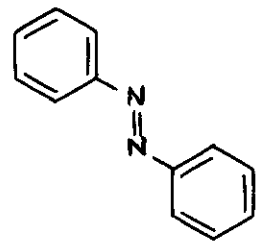


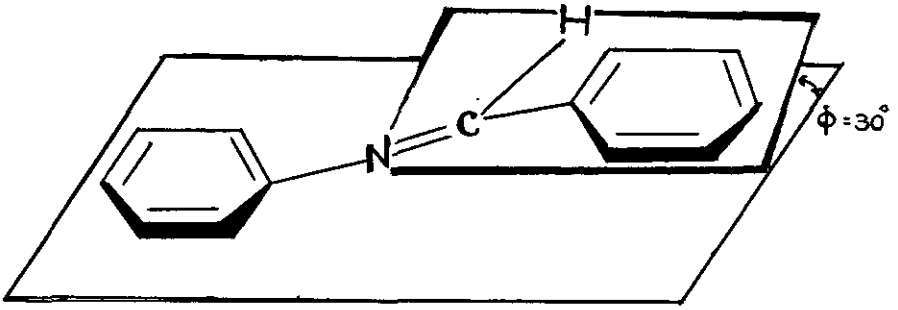
134

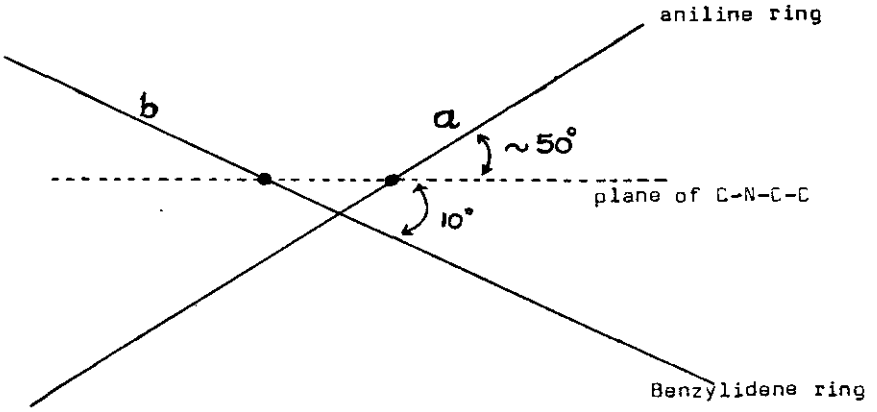
stilbene 133 and trans azobenzene 134[95-100] led to the conclusion that the difference was due to the non-planarity of 132; 133 and 134 being earlier established as nearly planar molecules[101,102].

Indeed, crystal and molecular structure determinations of benzylideneaniline and substituted benzylideneanilines by Bürgi and Dunitz[103,104] on the one hand and Bernstein[105] on the other verified that these molecules exhibited a twist of the aniline ring out of the C-N = C-C plane by 41-55° with a smaller and opposite twist of the benzylidene ring by 10°. This is represented in the following diagram. Since the crystal reflectance UV spectra are similar to the solution spectra it seems likely that the stable conformations of the free molecule are not too different from those occurring in the crystalline state[103].

Hence an investigation of the ultraviolet spectra of the Schiff bases 114-122 was undertaken and compared with the spectra of benzylideneaniline in order to gain an insight into the molecular conformation of these Schiff bases.

The results are given in Table 3.





An inspection of the table indicates that in almost all cases there is a hypsochromic shift (of the band near 310nm) in hexane when compared to the spectra in ethanol. This shows that the excited state of these Schiff bases is more polar than the ground state. In the case of phenolic Schiff bases addition of dilute acid causes a bathochromic shift of the band near 310nm while the band near 285nm undergoes a hypsochromic shift. However, the extent of bathochromic shift

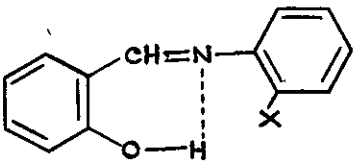


Figure 1

Table 3.

UV Spectral Data of Schiff bases 55-64 in various solvents

λ Values in nm and Extinction coefficients ε are given in parenthesis

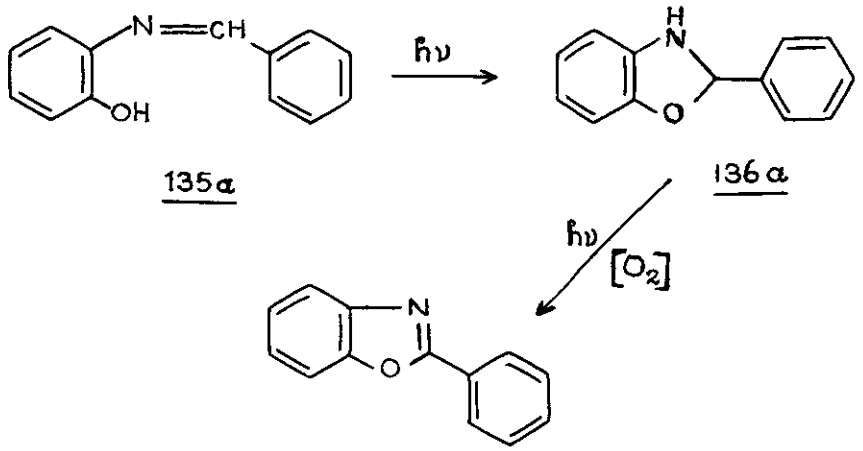
Compound	Ethanol	Ethanol-H_3O^+	Hexane	Con.H_2SO_4
132	310,262 (14770,26064)	282,248 (1592,17740)	308 (3330)	335,275 (18969,3620)
114	320,280,235 (14867,12520,16237)	308,275,230 (8216,9781,15356)	320,280 (13224,13224)	380,245 (11842,5000)
115	320,282,232 (18268,15658,20318)	310,275,230 (10439,12303,20878)	318,280 (18892,18724)	383,243 (21811,7987)
116	325,280,235 (6723,4718,8139)	315,275,232 (3779,3067,7313)	320,276 (18118,15476)	395,245 (17897,5369)
117	315,285,228 (14038,14176,24223)	345,265,218 (3028,11010,23948)	355,310,282 (4082,8164,10295)	352,230 (21471,10460)
118	315,285,228 (12871,14007,22903)	343,265,220 (3218,10789,24228)	360(sh),315,282 (3060,6226,8721)	352,228 (21420,11580)
119	320(sh),288,255,225 (13700,18610,10667,34290)	345,265,220 (3850,13980,32950)	315,285 (17650,29520)	340(sh),233 (14810,15740)
120	340,275,225(sh) (10499,9515,20177)	345,268,220 (3281,13123,26739)	360,335,280 (11282,14417,16568)	365,340(sh),233 (28421,24188,31445)
121	358,290,240 (4840,2504,3388)	325,285,242 (2337,3004,5341)	328,292 (11127,12055)	308,348,248 (15450,11657,8160)
122	335,290,240 (12075,12667,17970)	325,285,242 (6901,10215,18926)	325,285 (15436,19749)	405,350,250 (49030,38842,31220)

(of the band near 310nm) is more when the phenol is ortho to the -CH=N position than when the phenol is in the para position. This is probably due to intramolecular hydrogen bonding between the phenolic hydrogen and nitrogen as shown in figure 1. The PMR spectra of compounds 117-120 support the intramolecular hydrogen bonding where the phenolic hydrogen appears around δ13.00. When concentrated sulfuric acid was used as solvent the band around 310nm shifted very much to longer wavelengths and the band near 285nm disappeared completely.

Dunitz and Bürgi attempted to correlate the structures of benzylideneanilines with their UV spectra[103] but they did not get very far in their attempts[106]. They also dealt with the competing roles of π electron energy and non-bonded interactions influencing the molecular conformation[104]. In view of Dunitz's experience, perhaps the correlation of UV and structure (conformation) could be possible only if the X-ray crystallographic structure of the concerned Schiff base is established. Among the Schiff bases that we have studied, at least the X-ray structures of 115, 120, 121 and 122 would not only be helpful in correlating their UV spectra and structure but also would explain why irradiation of these Schiff bases failed to produce the respective phenanthridines.

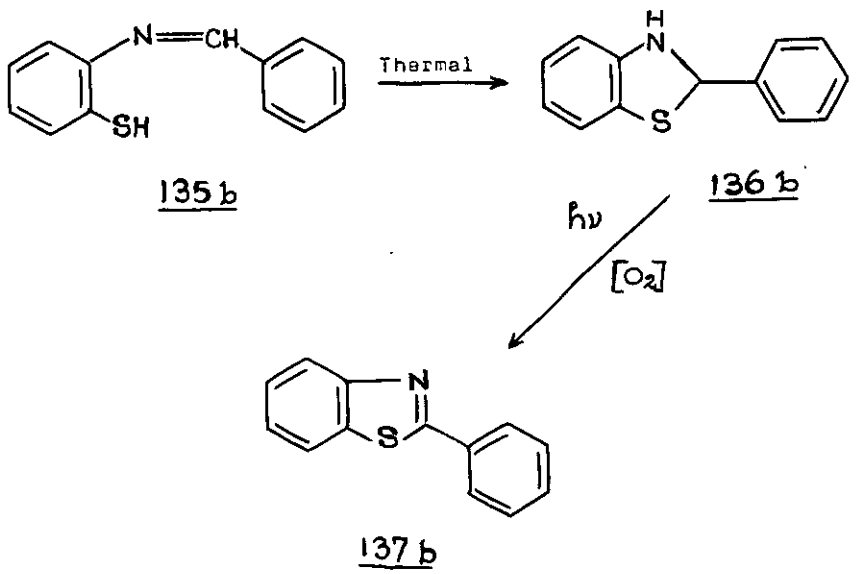
In a different kind of photochemical reaction where stringent conformational requirements are not needed, Grellmann and Tauer[107,108] studied the photochemical cyclizations of benzylideneanilines substituted in the ortho position of the aniline ring. Benzylidene-o-hydroxyaniline (135a), benzylidene-o-mercaptoaniline (135b) and benzylidene-o-aminoaniline (135c) were photocyclized to the respective 2-phenylbenzoxazole (137a), 2-phenylbenzothiazole (137b) and 2-phenylbenzimidazole (137c). The reaction depended on the nature of the solvent used. The mercapto (135b) and amino (135c) derivatives yielded in hexane and in ethanol solutions the corresponding azoles whereas the hydroxy derivative (135a) photohydrolyzed in ethanol into o-hydroxyaniline and benzaldehyde, but in aprotic solvents gave the cyclized reaction products.

In spite of the similarity of the final products the reaction pathways of the three compounds differ substantially. Benzylidene-o-hydroxyaniline (135a) absorbs two photon of energy for the cyclization and oxidation to 137a via 136a (Scheme 24).



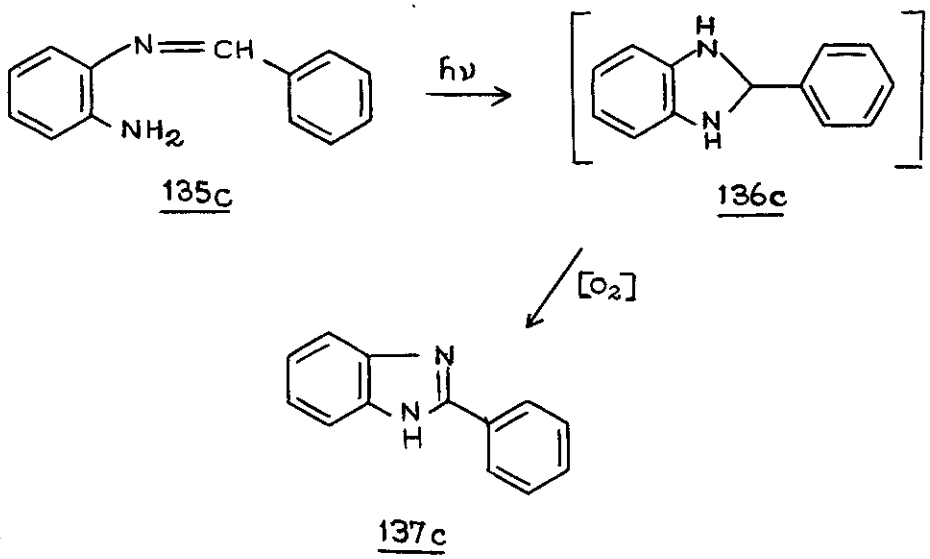
Scheme 24

However, benzylidene-o-mercaptoaniline (135b) exists only in the thiazoline form (136b) which upon irradiation in the presence of oxygen yielded the thiazole (137b) (Scheme 25).



Scheme 25

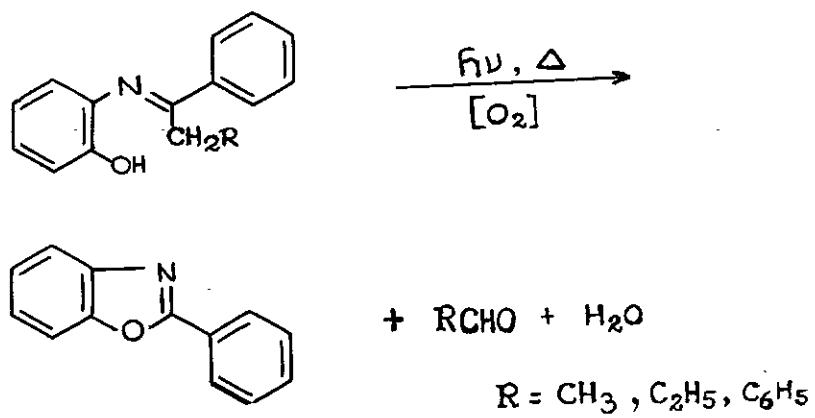
Interestingly, in the case of benzylidene-o-aminoaniline (135c) only one photon of energy is required for the conversion to 2-phenylimidazole (137c). Here 2-phenylimidazoline (136c) is proposed only as a possible intermediate (Scheme 26).



135c 136c 137c

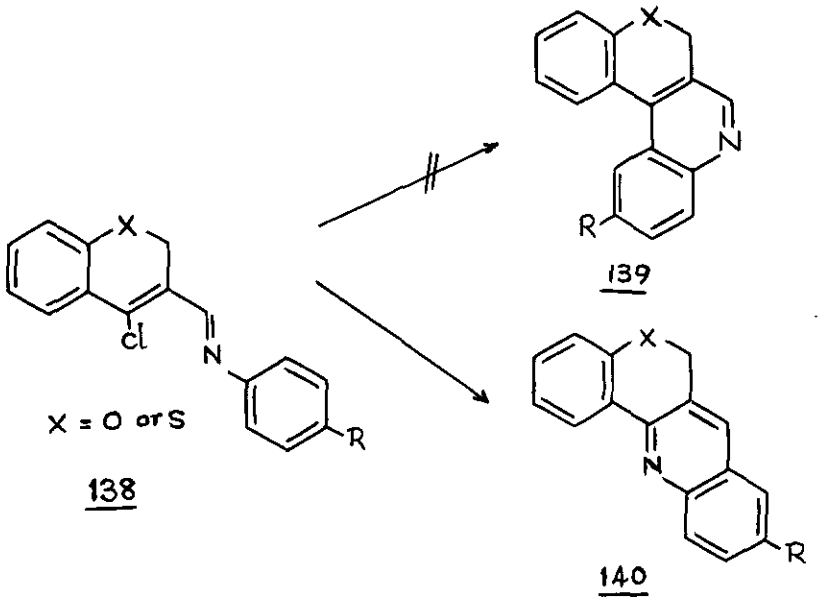
Scheme 26

Schiff bases derived from ketones and ortho hydroxyanilines are converted into benzoxazoles by the absorption of just one photon, but only in the presence of oxygen and only if the aliphatic residue R^1 of the $N=C(R^1R^2)$ bridge contains at least two carbon atoms (Scheme 27)[108].



Scheme 27

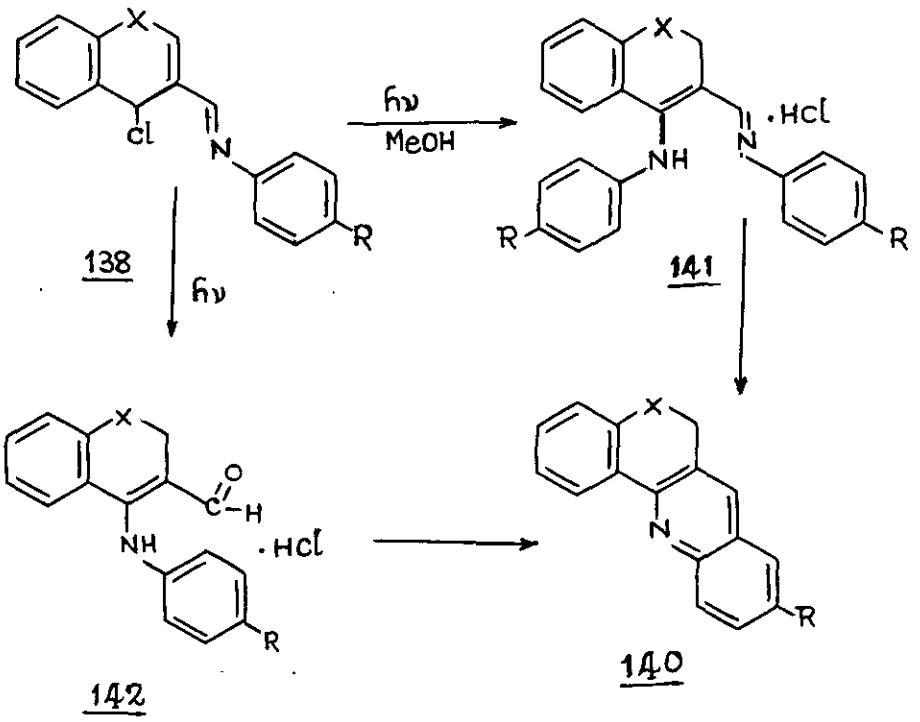
Balasubramanian [109] attempted photocyclization of N-arylimines 138 derived from 4-chloro-3-formyl-(2H)-benzopyrans and benzothiopyrans with the hope of synthesizing 139 but surprisingly ended up with the isolation of 140.



The photochemical transformation of 138 to 140 clearly involves a number of steps and may proceed either through the intermediacy of the enamino-imine 141 arising by a disproportionation of 138 or through the 4-anilino-3-formyl derivative 142 as shown in Scheme 28.

Recently, Mariano[110] has studied the features of excited-state reactions proceeding by single electron transfer pathways using examples taken from recent studies with iminium and related N-heteroaromatic salts. He has observed that in the case of iminium salts, electron-transfer-induced photochemical processes appear to represent reasonably versatile C-C bond-forming methods that can be applied to the synthesis of heterocyclic ring systems.

This brings us to the observation of Professor Padwa[76] in 1977 regarding the photochemical behaviour of Schiff bases: "It is obvious that a great deal more *quantitative work will be necessary* before the nature of these reactions can be fully understood and generalized. The identification of the excited states involved, substituent effects and quantum yields must be determined before a full understanding of this area can be accomplished. It is also apparent that the



Scheme 28

reactions in this field are so rich in variation that the photochemistry of this chromophore will remain intriguing and provide further challenge to the experimentalists as well as the theoretical chemists for a long time to come".

Professor P.S.Mariano echoes the same theme, in 1983, in his Account[110] on *electron-transfer mechanisms in* photochemical transformations of iminium salts. Thus the Schiff base chemistry provides a challenging field of investigation to Theoretical Organic Chemists, X-ray Crystallographers and Synthetic Organic Chemists.

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