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RECENT ADVANCES IN THE CHEMISTRY OF BERBINE ALKALOIDS[‡]

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Abstract - Some aspects of the recent chemical progress in the field of berbine alkaloids have been reviewed.

CONTENTS

I. INTRODUCTION

Berbines[2] comprise a large group of alkaloids both of natural and synthetic origin[3]. A good number of investigations have been carried out owing to their great biological activity[4]. We have been interested in the field of berbine alkaloids for the last few years and wish to give an account of the current chemical progress made in this field. The authors would like to be pardoned for limiting the review to only some aspects of the berbine chemistry.

II. SOLIDALINE - A MODIFIED BERBINE ALKALOID

Solidaline (1) has been isolated from Corydalis solida by Manske et al[5] and

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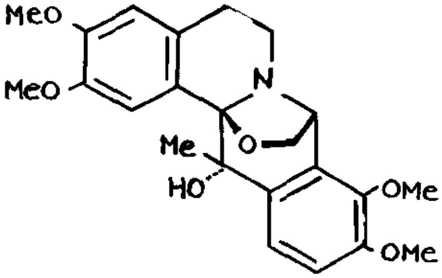
[‡] Dedicated to the memory of late Prof. R.H.F.Manske who expired in Sept.,1977.

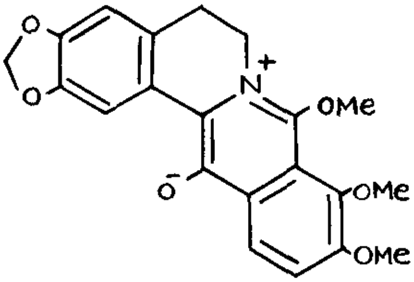
the structure assigned as (1).



(1)

III. THE 8,13-DIOXOBERBINES[6]

Methanolic hydrogen chloride cleaves oxybisberberine, the ferricyanide oxidation dimer of berberine, to afford 8-methoxyberberinephenolbetaine(2)[7,8]. Cleavage of oxybisberberine with pyridine hydrochloride in pyridine gives a 1:1 molar ratio of (6) and (7). Some other reactions are shown in Scheme 1.



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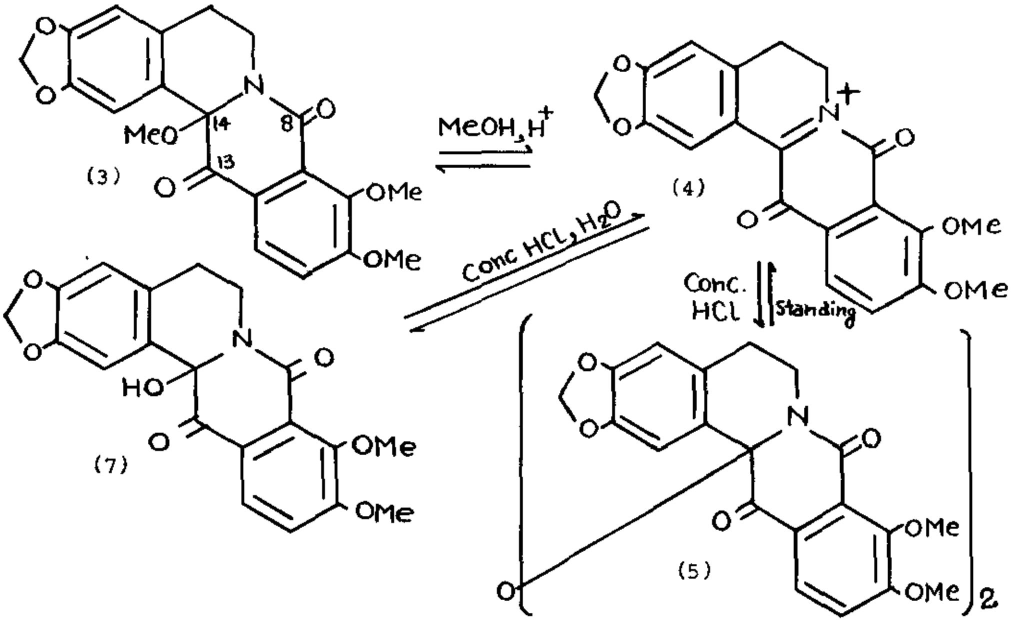
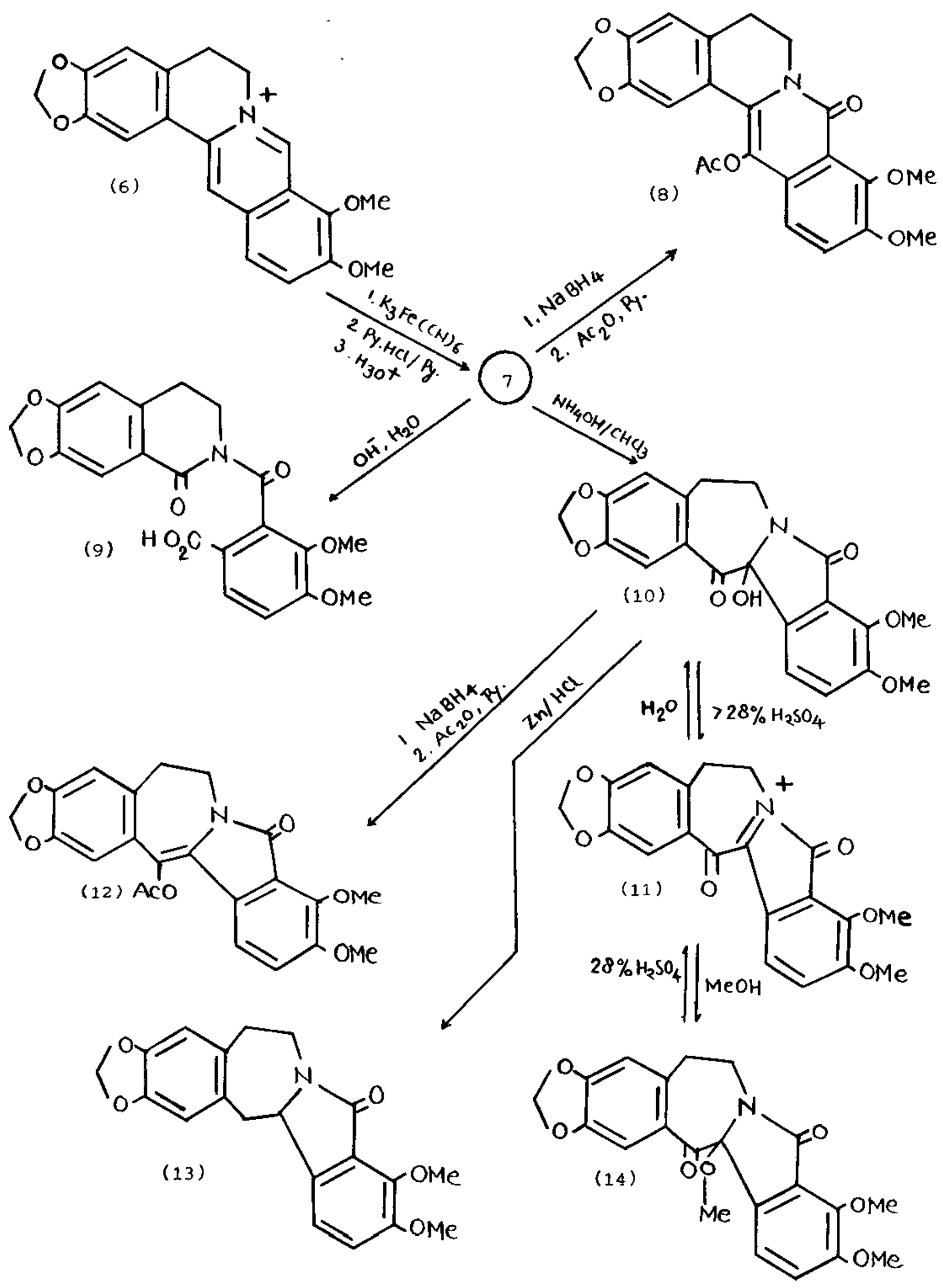



(6)
OMe
OMe
1. $K_3Fe(CN)_6$
2. Py.HCl/Py.
3. H_3O^+
7
1. $NaBH_4$
2. Ac_2O, Py.
(8)
AcO
OMe
OMe
OH^-, H_2O
(9)
HO_2C
OMe
OMe
$NH_4OH/CHCl_3$
(10)
O OH
OMe
OMe
1. $NaBH_4$
2. Ac_2O, Py.
Zn/HCl
H_2O
> 28% H_2SO_4
(11)
OMe
OMe
(12) AcO
OMe
OMe
28% H_2SO_4
MeOH
(13)
OMe
OMe
(14)
Me
OMe
OMe

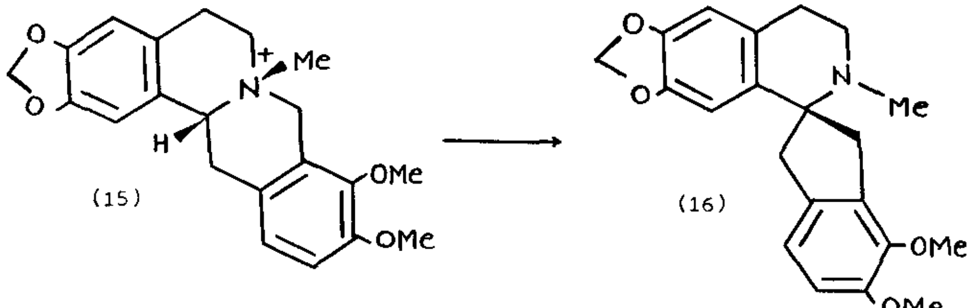
Scheme 1

The present oxidation of berberine at C-8, C-13 and C-14, and the formation of rearranged products such as the aporhoeadane (10), have some analogy in nature. Tetrahydroberbines are known to be converted in plants into benzazepine containing alkaloids such as the rhoeadines[9]. The conversion of (7) to (10) is also reminiscent of the ring expansion which must be involved in the biogenesis of the dimeric benzylisoquinoline alkaloid stepinonine[10].

IV. REACTIONS OF BERBINE ALKALOIDS

The Hofmann degradation has been widely used for the structure elucidation of the berbine alkaloids. In some cases this reaction has been shown to lead to conversion of berbines into protopine[10], benzophenanthridine[11,12] and pavine[13] type alkaloids.

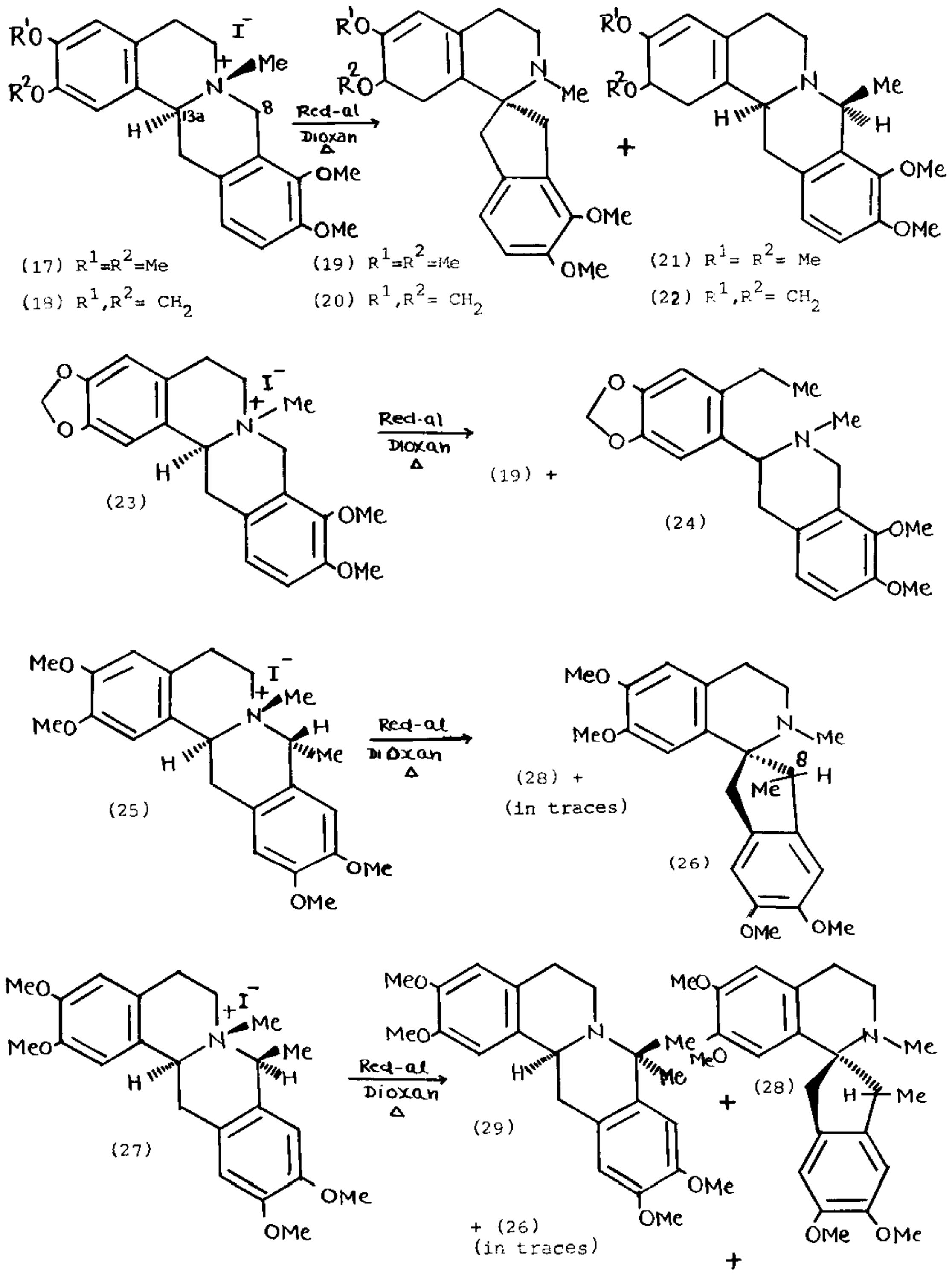
Reactions of the non-phenolic quaternary salts such as (15) with stronger bases as butyl lithium, phenyl lithium, sodium methylsulphinylmethylide, sodium amalgam and lithium aluminium hydride in tetrahydrofuran causes the Stevens type rearrangement to yield the spirobenzylisoquinoline (16) in a good yield, the chirality at C-14 being maintained[14,15] (Scheme 2). A radical anion intermediate has been held responsible for retention of stereochemistry[16,17].



Scheme 2

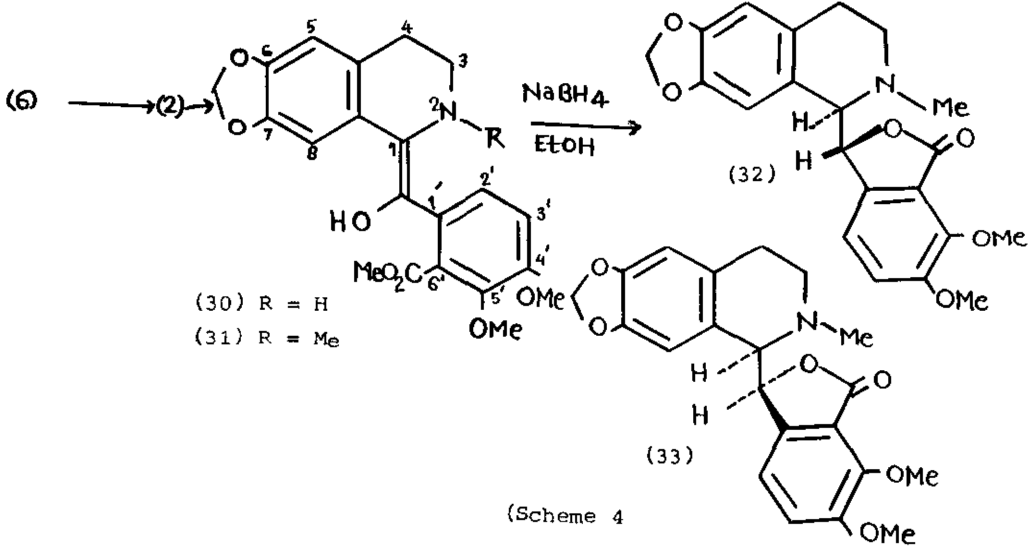
The Stevens rearrangement of berbine methiodides with sodium bis (2-methoxyethoxy)aluminium hydride (Red-al) leads to the formation of spirobenzylisoquinolines and 8-methylberbines. Thus treatment of several berbine methiodides(17, 23, 18, 25, 27) leads to formation of (19, 20, 26, 28) and the 8-methylberbines (21, 22, and 29) (Scheme 3).

Quasi-axially oriented hydrogens at the C-8 and C-14,positions of the berbine methiodide were predominantly abstracted by the complex hydride in hot dioxane. In the case of the trans-quinolizidinium salts the stereochemistry at the C-8


R¹O
R²O
I⁻
Me
N
H
13a
8
OMe
OMe
Red-al
Dioxan
Δ
(17) R¹=R²=Me
(18) R¹,R²= CH₂
(19) R¹=R²=Me
(20) R¹,R²= CH₂
(21) R¹= R²= Me
(22) R¹,R²= CH₂
+
(23)
(19) +
(24)
(25)
(28) +
(in traces)
(26)
(27)
(29)
+ (26)
(in traces)
(28)
MeO
H
Me

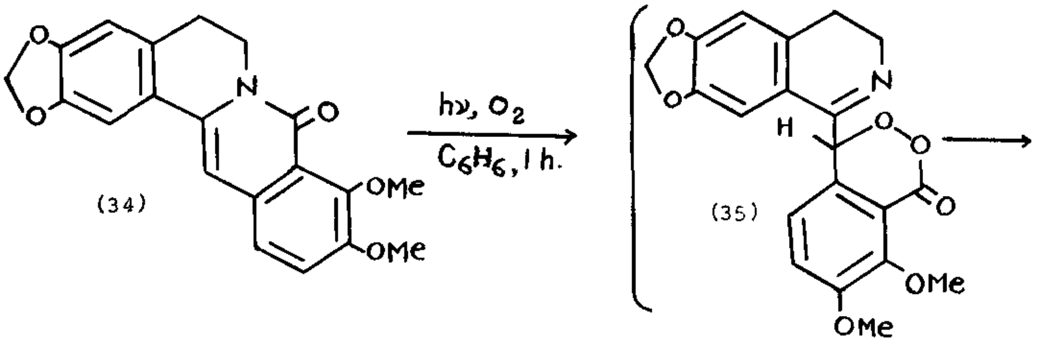
Scheme 3

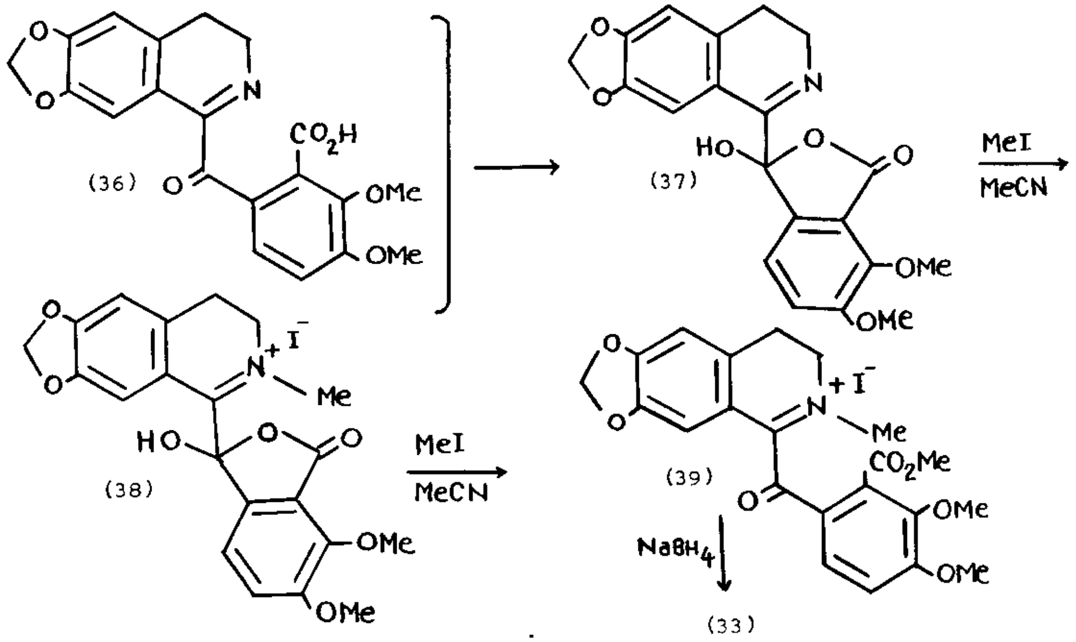
and C-14 positions was retained during the conversion into the spirobenzylisoquinolines, and the 8-methylberbines with inversion of the configuration at the C-8 position. On the other hand, the <u>cis</u>-quinolizidinium salts gave the spirobenzylisoquinolines with retention at the C-8 and inversion at the C-14 position, and the 8-methylberbines with retention at the C-8 position[18].
Berberine (6) has been converted into a 1:2 mixture of (±)-α-hydrastine(32) and (±)-β-hydrastine (33) through the intermediate use of 8-methoxyberberine-phenolbetaine (2)[7](Scheme 4).



(Scheme 4

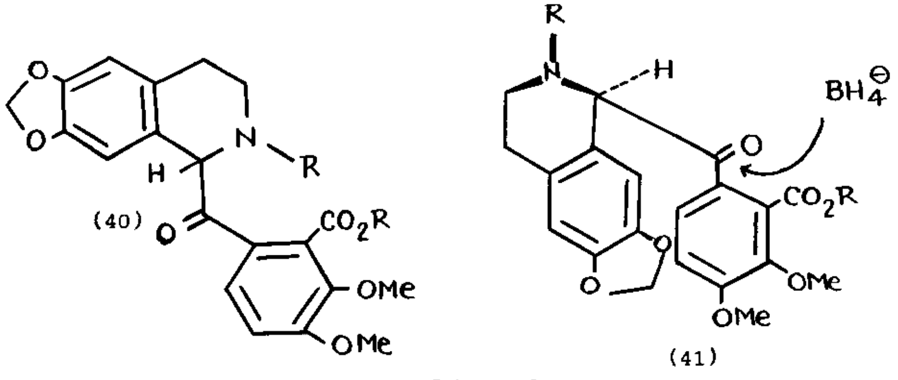
A stereospecific conversion of berberine (6) into (±)-β-hydrastine (33) has been achieved by Shamma <u>et al</u>[19] starting from short photo-oxidation of oxyberberine (34)[20] (Scheme 5).





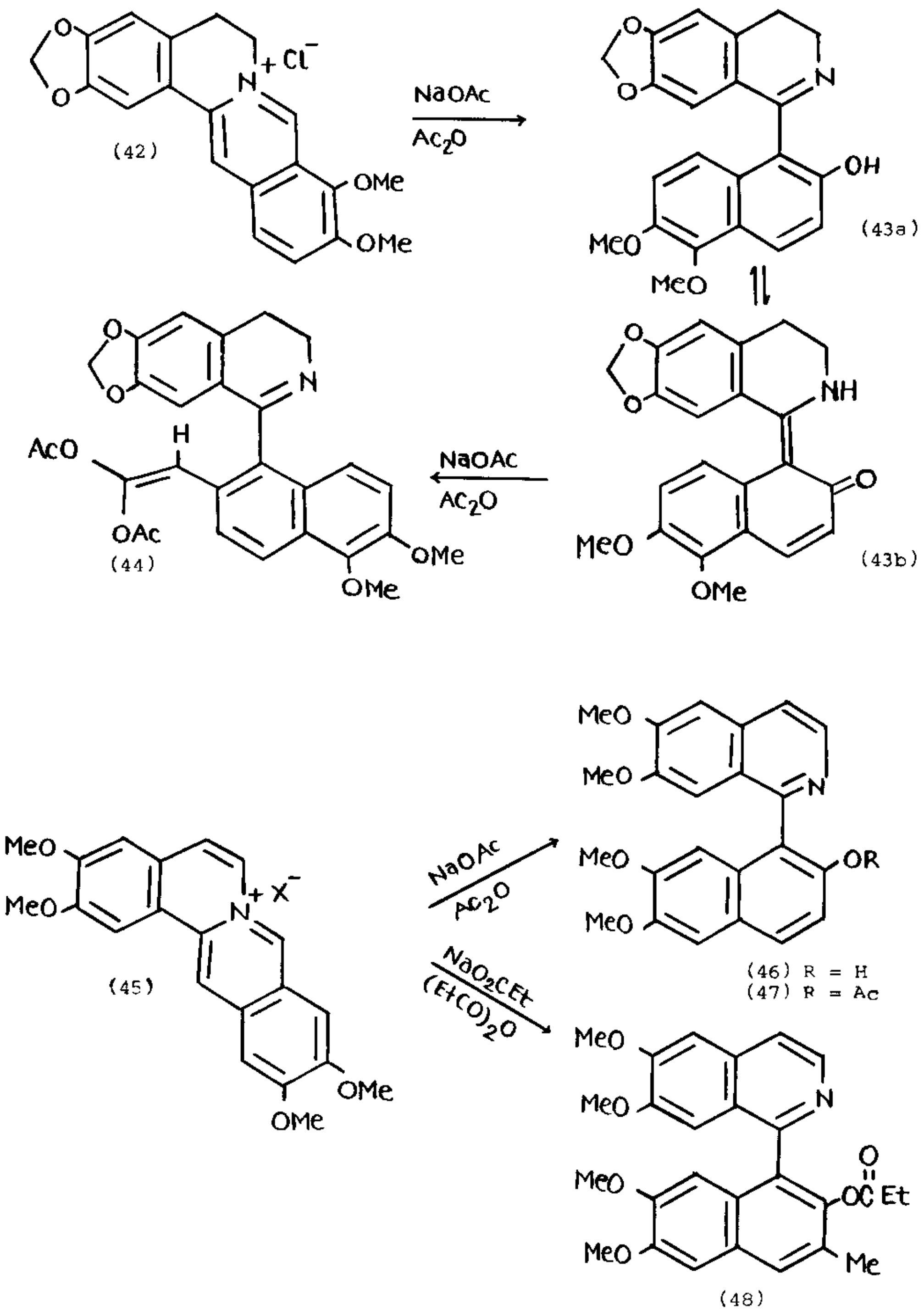
Scheme 5

The high degree of stereospecificity observed in the reduction of (39) is rationalized on the premise that reduction of the iminium double bond proceeds first to furnish the species (40) which exists in preferred conformation (41). Application of Cram's rule[21] with approach of borohydride from less hindered side leads to the product (33) obtained (Scheme 6).



Scheme 6

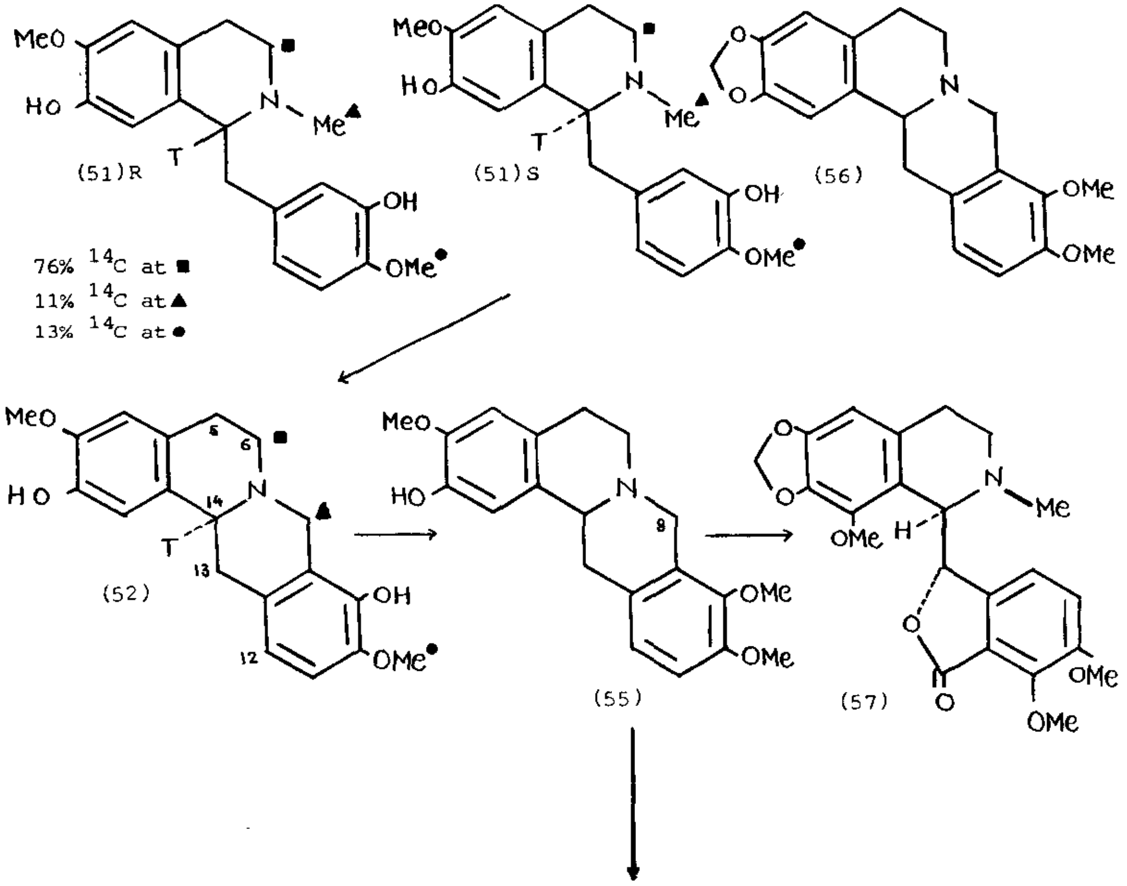
A one step conversion of berbine salts into the naphthalene derivatives has been worked out[22,23]. Thus, berberine chloride (42) upon treatment with sodium acetate-acetic anhydride mixture yields the naphthalene derivatives (43) and(44). In like fashion (45) gives the naphthalenes (46), (47) and (48) (Scheme 7).All these transformations proceed by initial nucleophilic attack of the acetic anhydride anion on the iminium carbon atom.

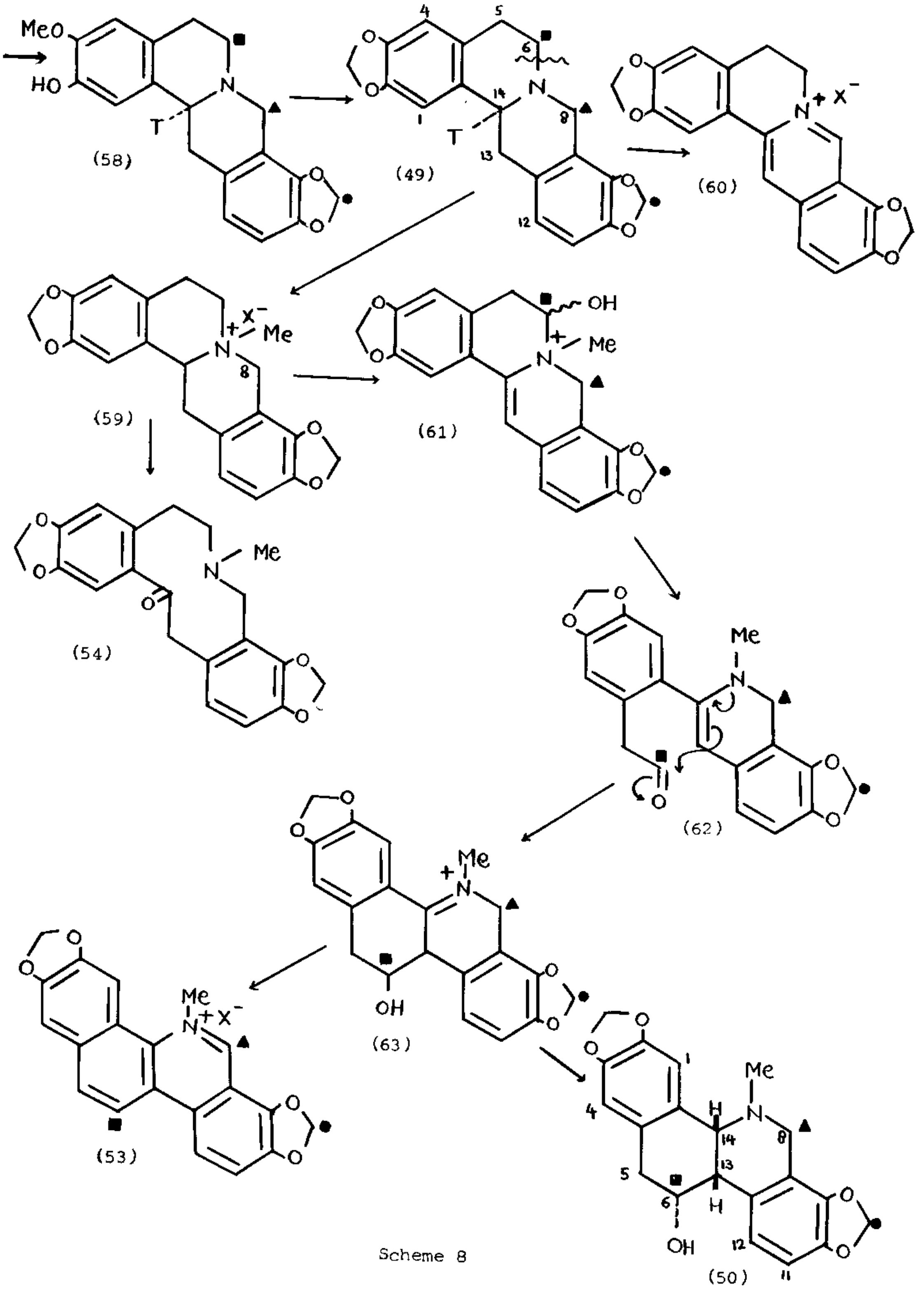


Scheme 7

V. BIOSYNTHESIS OF BERBINES

Various aspects of berbine biosynthesis including berbine bioformation in mammalian tissues have been reviewed by Kametani et al[25]. Several important classes of alkaloids are believed to be derived from berbines in nature[26]. Investigations on the biosynthesis of stylopine (49) in Chelidonium majus using multiply labelled reticuline (51) have further strengthened this belief[27,28]. The major benzophenanthridine alkaloid, chelidonine (50) has been shown to be biosynthesized in C. majus plants from (S)-reticuline (51) via (S)-scoulerine(52) and (S)-stylopine (49) and evidence consistent with a dihydroisoquinoline intermediate like (61) has been presented (Scheme 8). Similar but concise evidence is provided for the same pathway to the aromatic systems like sanguinarine (53). Protopine (54) is shown to be formed in vivo from (S)-scoulerine (52) and (S)-stylopine (49). Role of isocorypalmine (55) and canadine (56) in the biosynthesis of narcotine (57) and berberine (6) in Papaver somniferum plants has been investigated[29].



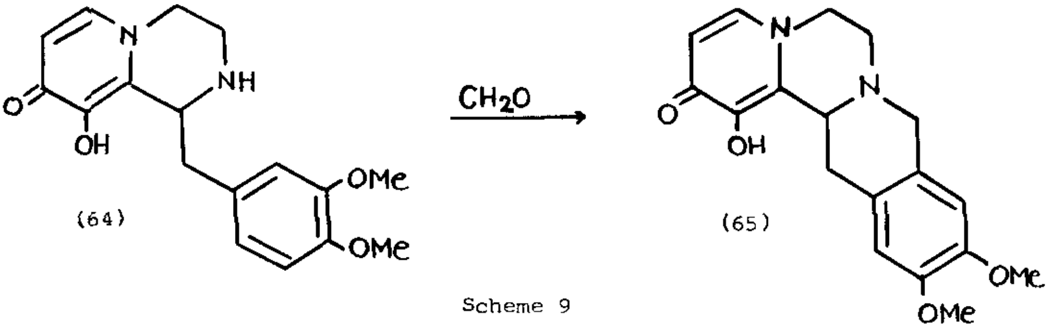

MeO
HO
T
(58)
4
5
6
1
14
8
13
12
T
(49)
X⁻
(60)
X⁻
Me
8
(59)
OH
Me
(61)
Me
(54)
Me
(62)
Me
OH
(63)
Me
X⁻
(53)
1
Me
4
H
14
8
5
13
6
H
OH
12
11
(50)

Scheme 8

VI. SYNTHESES OF BERBINE ALKALOIDS

1. INTRAMOLECULAR MANNICH REACTION

This reaction has been a method of choice for the synthesis of 10,11-disubstituted berbines[25,30]. A pyridine analogue of berbine (65) has been synthesised from the pyrazine (64) by the Mannich type reaction[31] (Scheme 9).



Scheme 9

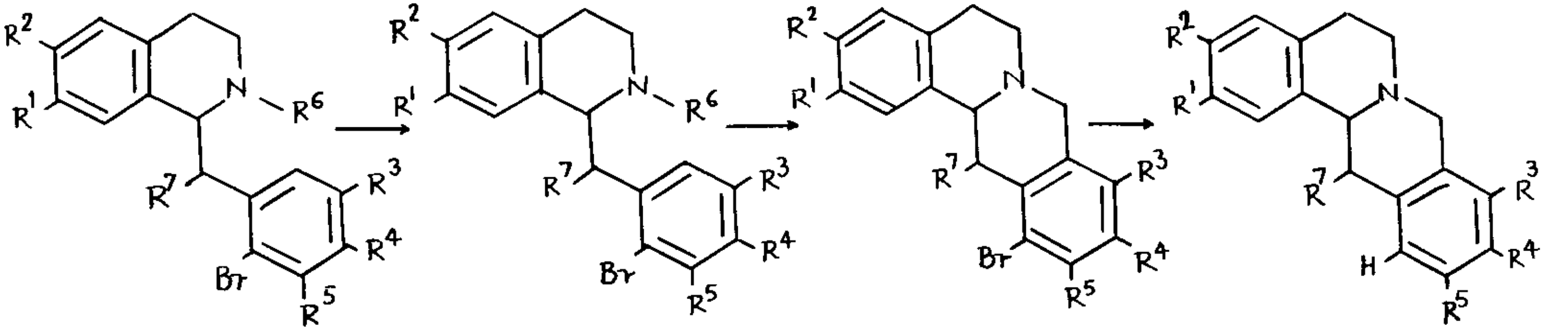
2. MODIFIED BISCHLER-NAPIERALSKI CYCLIZATION-USE OF BROMINE AS A BLOCKING AGENT

The Mannich reaction of the 1-benzyl-tetrahydroisoquinoline sometimes fails to give expected berbine. Thus, the N-formyl derivatives of the type (73-79)from the amines (66-72) were prepared and subjected to phosphoryl chloride cyclization followed by sodium borohydride reduction to give the 12-bromoberbines (80-86) which were converted to the berbines (49, 56, 87, 88, 89, 90, 91). Use of a mixture of phosphorus pentoxide and phosphorus pentabromide gives good yields in the cyclization of the N-formyl compounds[32]. A mixture of phosphorus pentoxide and phosphorus tribromide has also been used[33].

Thus dl-stepholidine (87), dl-13-methyltetrahydropseudocoptisine (88), dl-canadine (56), dl-sinactine (89), dl-stylopine (40) and dl-tetrahydrogroenlandicine (90) were synthesized by Pai et al[32]. Likewise Brochmann-Hanssen et al synthesized dl-discretamine (91)[34] (Scheme 10).

3. SYNTHESIS INVOLVING LACTONES AS INTERMEDIATES

The berbine skeleton has been synthesized using lactones[35,36]. The method though works equally well for the synthesis of both 9,10-[38-39] and 10,11- [37,41] disubstituted berbines yet suffered from the disadvantage of non-feasibility of 7,8-disubstituted 3-isochromanones. In an earlier method of Battersby[43] for the synthesis of 7,8-disubstituted 3-isochromanones, yields were poor. This was due to necessasity of introducing a hydroxymethyl function in a position ortho to a phenolic function[43]. This difficulty in introducing a hydroxymethyl



(66) $R^1 = R^4 = OH$; $R^3 = R^2 = OMe$; $R^5 = R^6 = H$ → (73) $R^6 = CHO$; $R^7 = H$ → (80) $R^6 = R^7 = H$ → (87)

(67) R^1, $R^2 = OCH_2O$; $R^3 = R^6 = H$; $R^7 = Me$; R^4,$R^5 = OCH_2O$ → (74) $R^6 = CHO$ → (81) $R^7 = Me$ → (88)

(68) R^1, $R^2 = OCH_2O$; $R^3 = R^4 = OMe$; $R^5 = R^6 = R^7 = H$ → (75) $R^6 = CHO$ → (82) $R^7 = H$ → (56)

(69) $R^1 = R^2 = OMe$; R^3, $R^4 = OCH_2O$; $R^5 = R^6 = R^7 = H$ → (76) $R^6 = CHO$ → (83) $R^7 = H$ → (89)

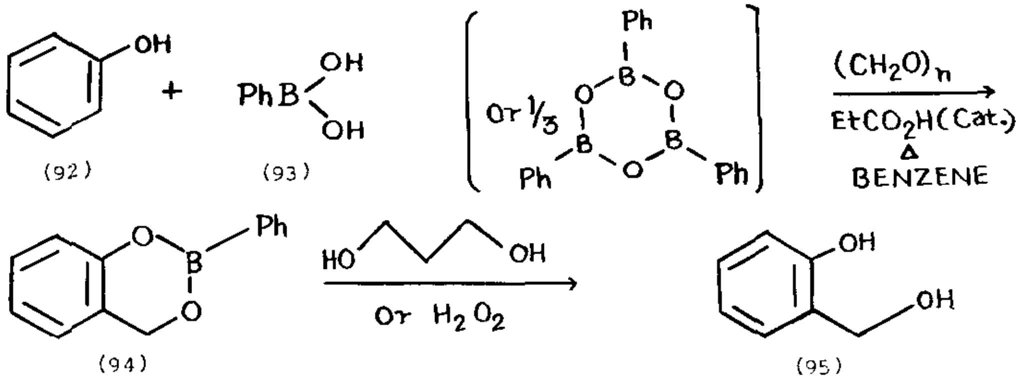
(70) R^1, $R^2 = OCH_2O$; R^3, $R^4 = OCH_2O$; $R^5 = R^6 = R^7 = H$ → (77) $R^6 = CHO$ → (84) $R^7 = H$ → (49)

(71) $R^1 = OMe$; $R^2 = OH$; R^3, $R^4 = OCH_2O$; $R^5 = R^6 = R^7 = H$ → (78) $R^6 = CHO$ → (85) $R^7 = H$ → (90)

(72) $R^1 = R^3 = OMe$; $R^2 = R^4 = OH$; $R^5 = R^6 = R^7 = H$ → (79) $R^6 = CHO$ → (86) $R^7 = H$ → (91)

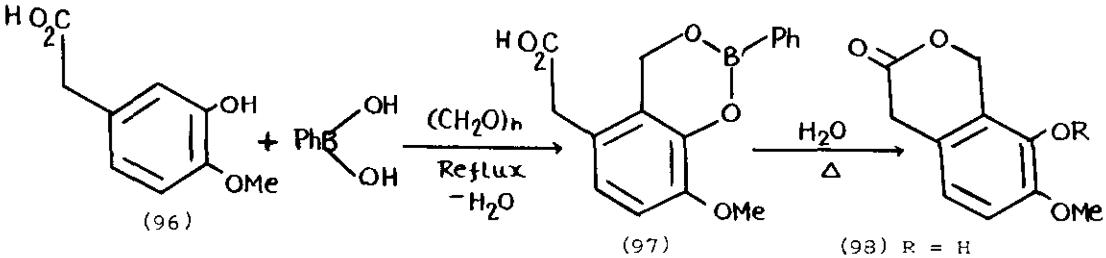
Scheme 10

function required for the synthesis of the desired 7,8-disubstituted lactones (3-isochromanones) has been nicely overcome by an ingenious method of Nagata et al employing benzeneboronic acid and paraformaldehyde[38,44] (Scheme 11).



Scheme 11

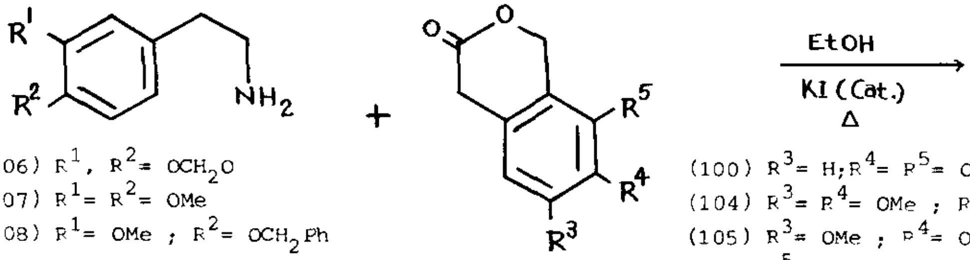
Using this method for example the 3-isochromanones (98), (99) and (100) were prepared, starting from homoisovanillic acid (96) (Scheme 12).



(98) R = H
(99) R = CH_2Ph
(100) R = Me

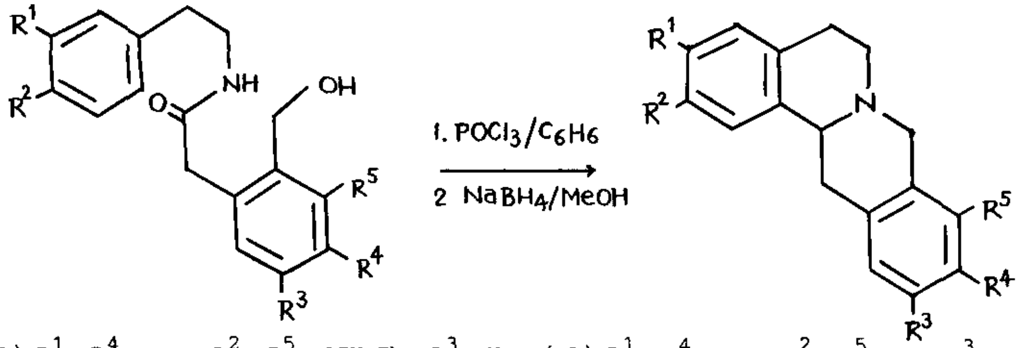
Scheme 12

The alkaloids dl-stepholidine (87)[39], dl-xylopinine (101)[37], dl-tetrahydropalmatine (102)[40], dl-scoulerine (52)[42], dl-canadine (56)[44] and dl-govanine (103)[41] were synthesized likewise (Scheme 13).



(106) $R^1, R^2 = OCH_2O$
(107) $R^1 = R^2 = OMe$
(108) $R^1 = OMe$; $R^2 = OCH_2Ph$

(100) $R^3 = H; R^4 = R^5 = OMe$
(104) $R^3 = R^4 = OMe$; $R^5 = H$
(105) $R^3 = OMe$; $R^4 = OH$; $R^5 = H$



(109) $R^1 = R^4 =$ OMe; $R^2 = R^5 =$ OCH$_2$Ph; $R^3 =$ H	(52) $R^1 = R^4 =$ OMe; $R^2 = R^5 =$ OH; $P^3 =$ H
(110) R^1, $R^2 =$ OCH$_2$O ; $R^4 = R^5 =$ OMe; $R^3 =$ H	(56) $R^1 = R^2 =$ OCH$_2$O; $R^4 = R^5 =$ OMe; $R^3 =$H
(111) $R^1 = R^5 =$ OMe ; $R^2 = R^4 =$ OCH$_2$Ph;$R^3 =$ H	(87) $R^1 = R^5 =$ OMe; $R^2 = R^4 =$ OH;$R^3 =$ H
(112) $R^1 = R^2 = R^3 = R^4 =$ OMe ; $R^5 =$ H	(101) $R^1 = R^2 = R^3 = R^4 =$ OMe ; $R^5 =$ H
(113) $R^1 = R^2 = R^4 = R^5 =$ OMe ; $R^3 =$ H	(102) $R^1 = R^2 = R^4 = R^5 =$ OMe ; $R^3 =$ H
(114) $R^1 = R^3 = R^4 =$ OMe ; $R^2 =$ OCH$_2$Ph; $R^5 =$H	(103) $R^1 = P^3 = R^4 =$ OMe; $R^2 =$ OH ; $R^5 =$ H

Scheme 13

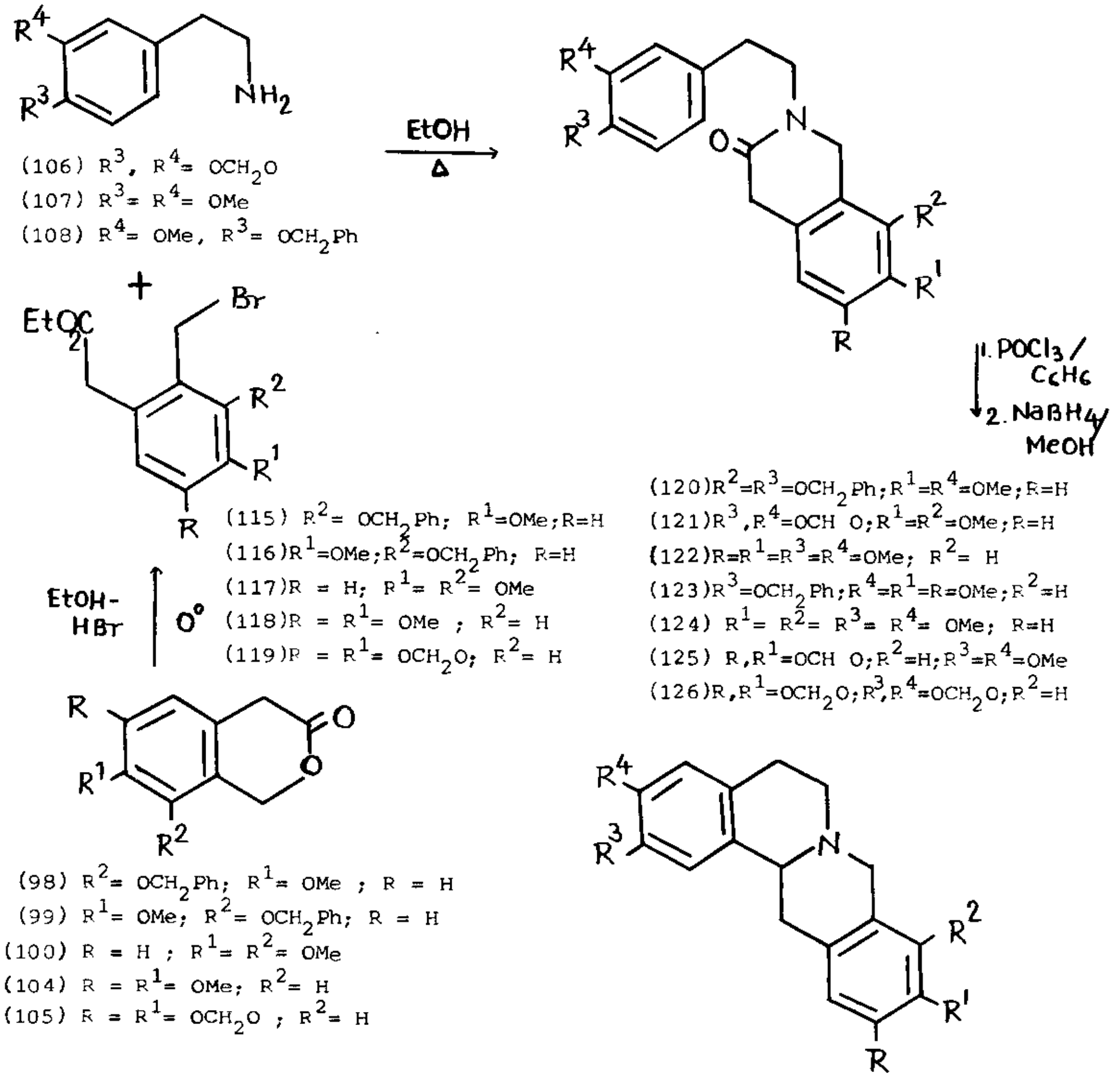
4. THE BROMOESTER SYNTHESIS

The 3-isochromanones (98, 99, 100, 104, 105)[44, 45] on dissolution in ethanolic hydrobromic acid at 0-5° afford the bromoesters (115-119). Condensation of the bromoesters (115-119) with β-phenethylamines (106-108) yields the tricyclic lactams (120-126) which could be converted to the desired berbines(52, 56, 101, 102, 103, 127, 128) by phosphoryl chloride cyclization followed by sodium borohydride reduction in fairly good yields[46-48]. The method works equally well for both 9,10- and 10,11- disubstituted berbines, the substitution pattern of the ring D of berbine being dictated by the substitution on the bromoesters (115-119). This method has been used to synthesize 13-methylberbines[49]. Thus, dl-tetrahydropalmatine (102), dl-xylopinine (101), dl-scoulerine (52), dl-pseudoepitetrahydroberberine (127), dl-isocoptisine(128), dl-canadine (56) and dl-govanine (103) were accordingly synthesized by us (Scheme 14).

5. THE PALLADIUM CATALYZED CARBON MONOXIDE INSERTION METHOD[50]

The idea of this novel synthesis came in our minds from the synthesis of the benzolactams by palladium catalyzed amidation[51] (Scheme 15).

The required key precursor, the 1-(1'-bromobenzyl)tetrahydroisoquinoline(134) was prepared from the known reaction sequence involving the Schotten-Baumann



(106) R^3, R^4= OCH_2O

(107) R^3= R^4= OMe

(108) R^4= OMe, R^3= OCH_2Ph

(115) R^2= OCH_2Ph; R^1=OMe;R=H

(116)R^1=OMe;R^2=OCH_2Ph; R=H

(117)R = H; R^1= R^2= OMe

(118)R = R^1= OMe ; R^2= H

(119)R = R^1= OCH_2O; R^2= H

(120)R^2=R^3=OCH_2Ph;R^1=R^4=OMe;R=H

(121)R^3,R^4=OCH_2O;R^1=R^2=OMe;R=H

(122)R=R^1=R^3=R^4=OMe; R^2= H

(123)R^3=OCH_2Ph;R^4=R^1=R=OMe;R^2=H

(124) R^1= R^2= R^3= R^4= OMe; R=H

(125) R,R^1=OCH_2O;R^2=H;R^3=R^4=OMe

(126)R,R^1=OCH_2O;R^3,R^4=OCH_2O;R^2=H

(98) R^2= OCH_2Ph; R^1= OMe ; R = H

(99) R^1= OMe; R^2= OCH_2Ph; R = H

(100) R = H ; R^1= R^2= OMe

(104) R = R^1= OMe; R^2= H

(105) R = R^1= OCH_2O ; R^2= H

(52) R^2= R^3= OH; R^1= R^4= OMe ; R = H

(56) R^3,R^4= OCH_2O ; R^1= R^2= OMe; R = H

(101)R = R^1= R^3= R^4= OMe; R^2= H

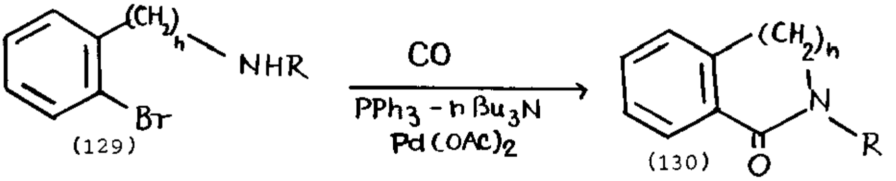
(103)R^3=OH ; R^4= R^1= R = OMe; R^2= H

(102) R^1= R^2= R^3= R^4= OMe ; R = H

(127) R, R^1= OCH_2O ; R^2= H; R^3= R^4 = OMe

(128) R,R^1= OCH_2O , R^3,R^4 = OCH_2O; R^2= H

Scheme 14

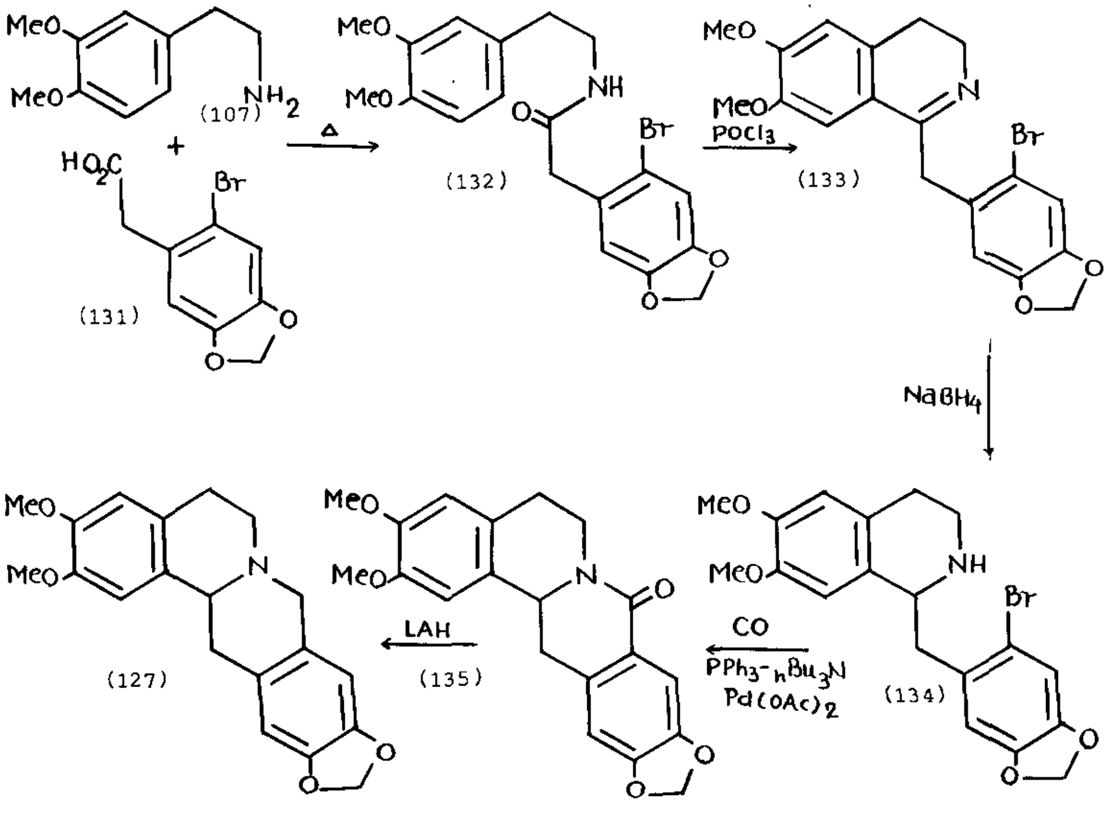


(129)

(130)

Scheme 15

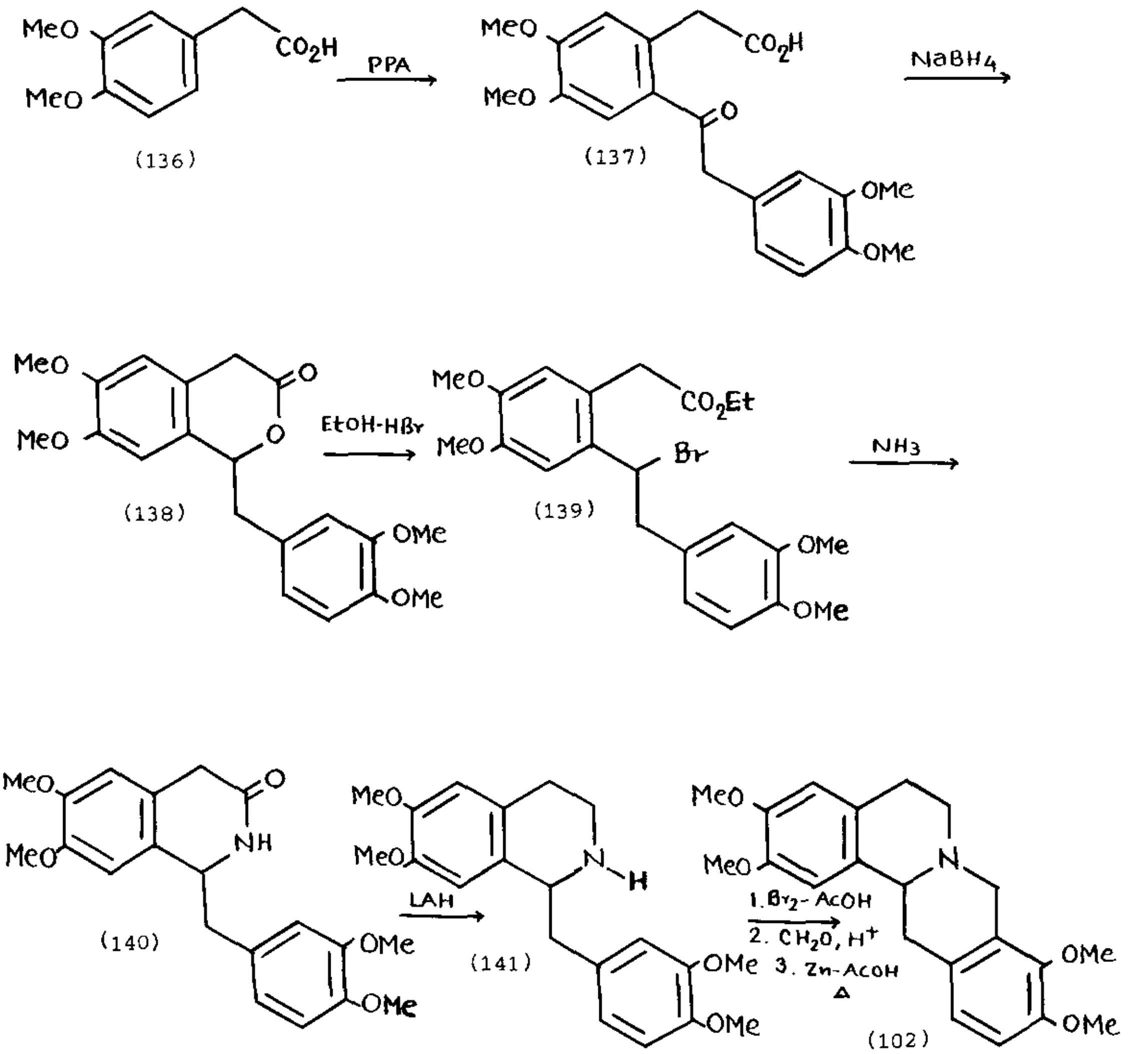
condensation and the Bischler-Napieralski reaction followed by sodium borohydride reduction[52]. Carbon monoxide was mildly inserted in the key precursor (134) at 95° in the presence of catalytic amounts of palladium diacetate and triphenylphosphine assisted by a tertiary amine. The resultant 8-oxoberbine (135) was cleanly reduced to the desired berbine (127) with lithium aluminium hydride (Scheme 16). This method has been extended for the synthesis of various 9,10- disubstituted and 13-substituted berbines[53].



Scheme 16

6. SELF CONDENSATION OF HOMOVERATRIC ACID METHOD[57]

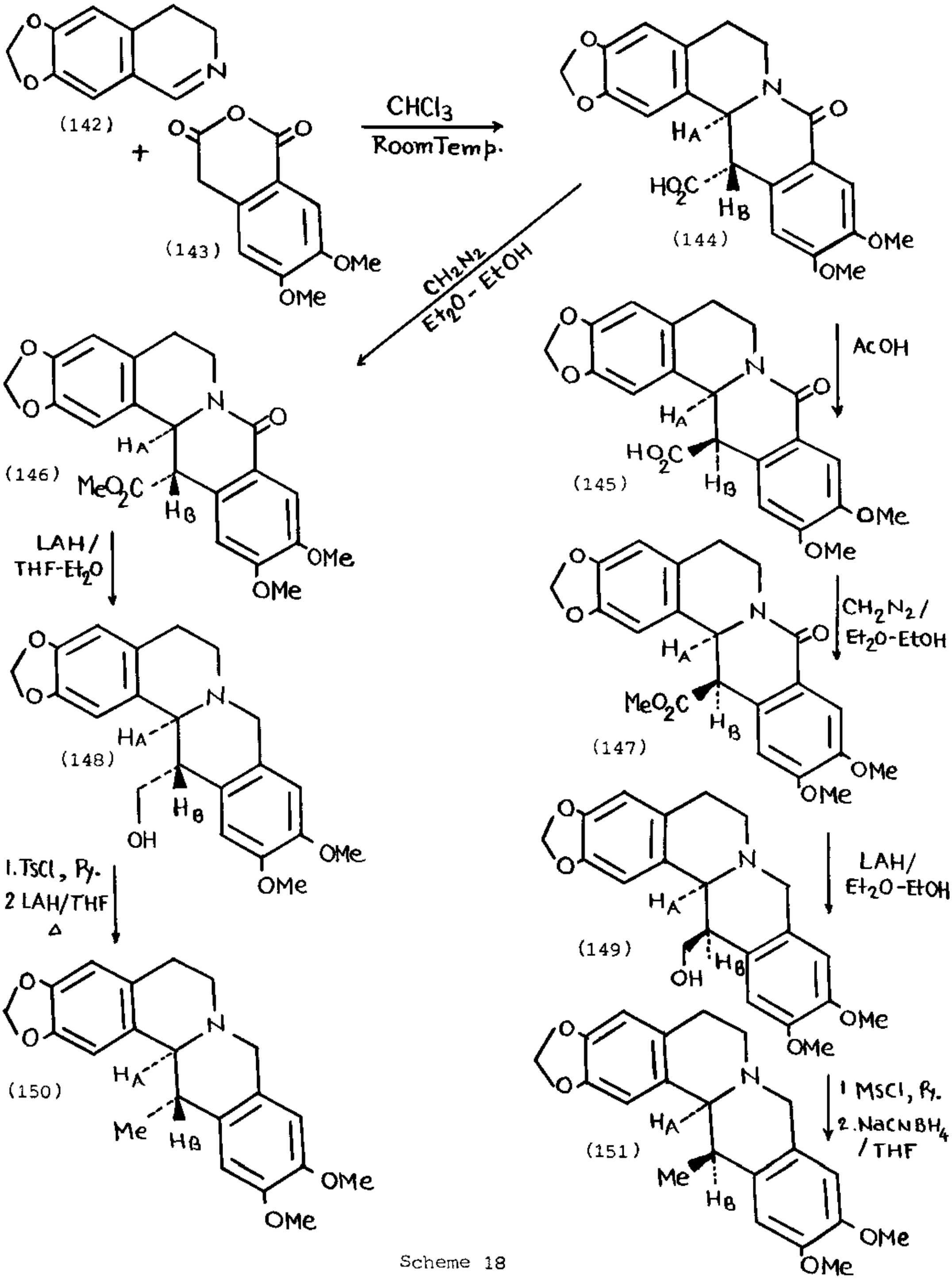
This method of berbine synthesis had its origin in the assumption that berbines can be derived from benzylisoquinolines by the addition of one carbon atom.The isoquinoline alkaloids have been synthesized by self condensation of homoveratric acid (136)[54,55]. The keto acid (137) was reduced with sodium borohydride to afford the 1-benzylisochromanone (138)[56] which was dissolved in ethanolic hydrobromic acid to give the bromoester (139). Treatment of (139) with ammonia followed by lithium aluminium hydride reduction of the resulting isoquinolone (140) gave the isoquinoline (141) which afforded dl-tetrahydropalmatine (102)[57] following procedure of Kametani <u>et al</u>[58] (Scheme 17).



Scheme 17

7. CONDENSATION OF IMINES WITH HOMOPHTHALIC ANHYDRIDES

A convergent synthesis of 13-methylberbines (Scheme 18) involves condensation

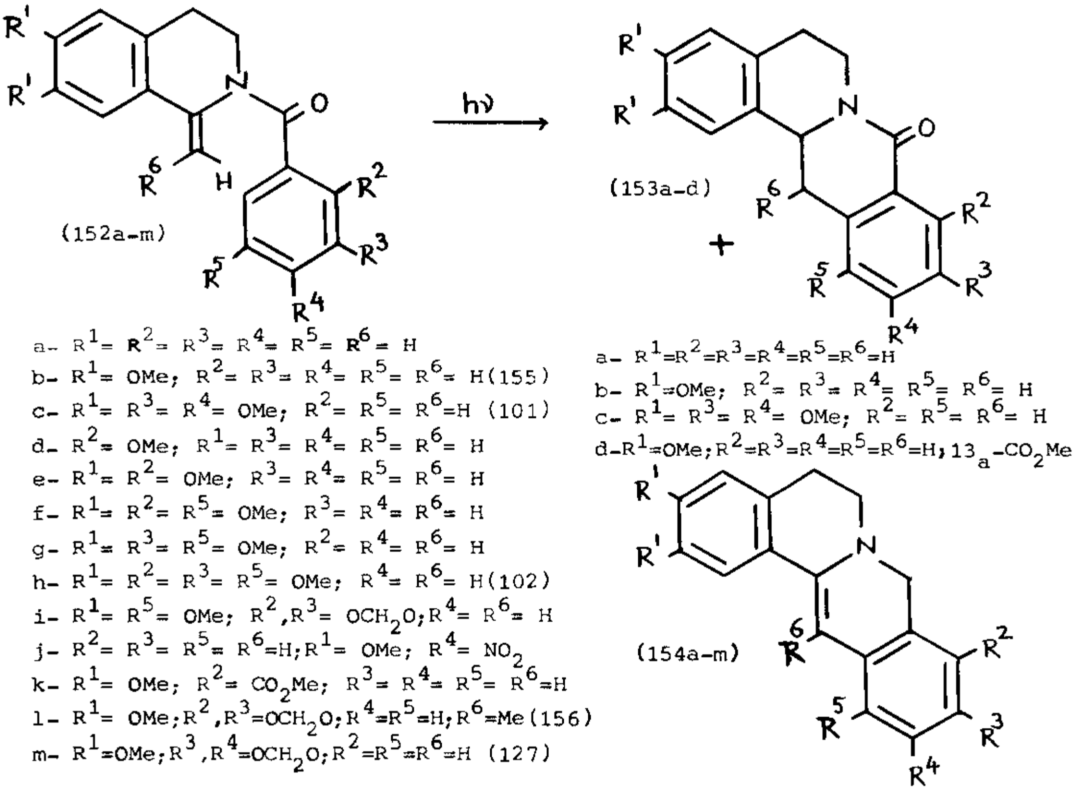


Scheme 18

of the imine (142) and the homophthalic anhydride (143)[59,60], the substitution pattern of the ring D of berbine is dictated by that of the anhydride[61] and stereochemistry at C-13 is controlled by epimerization of the kinetically produced trans(13H,14H)-8-oxoberbine intermediate (144) to the thermodynamically more stable cis(13H, 14H)-isomer (145)[59].

8. PHOTOCYCLIZATION OF ENAMIDES

Two independent groups of workers led by Ninomiya and Lenz have successfully exploited the enamide photocyclization[62,63] for the berbine synthesis[64]. The 2-aroyl-1-methylene-1,2,3,4-tetrahydroisoquinolines (152 a-m) readily photocyclize to the berbin-8-ones (153a-d)[65-67] and the dehydroberbin-8-ones(154a-m). The potential of this route has been established by the synthesis of dl-xylopinine (101)[67-70], dl-tetrahydropalmatine (102)[69], dl-sinactine (89)[69], pseudoepitetrahydroberbine (127)[67], 2,3-dimethoxyberbine (155)[69], dl-cavidine (156)[68] and various halogenated berbines[67] (Scheme 19).



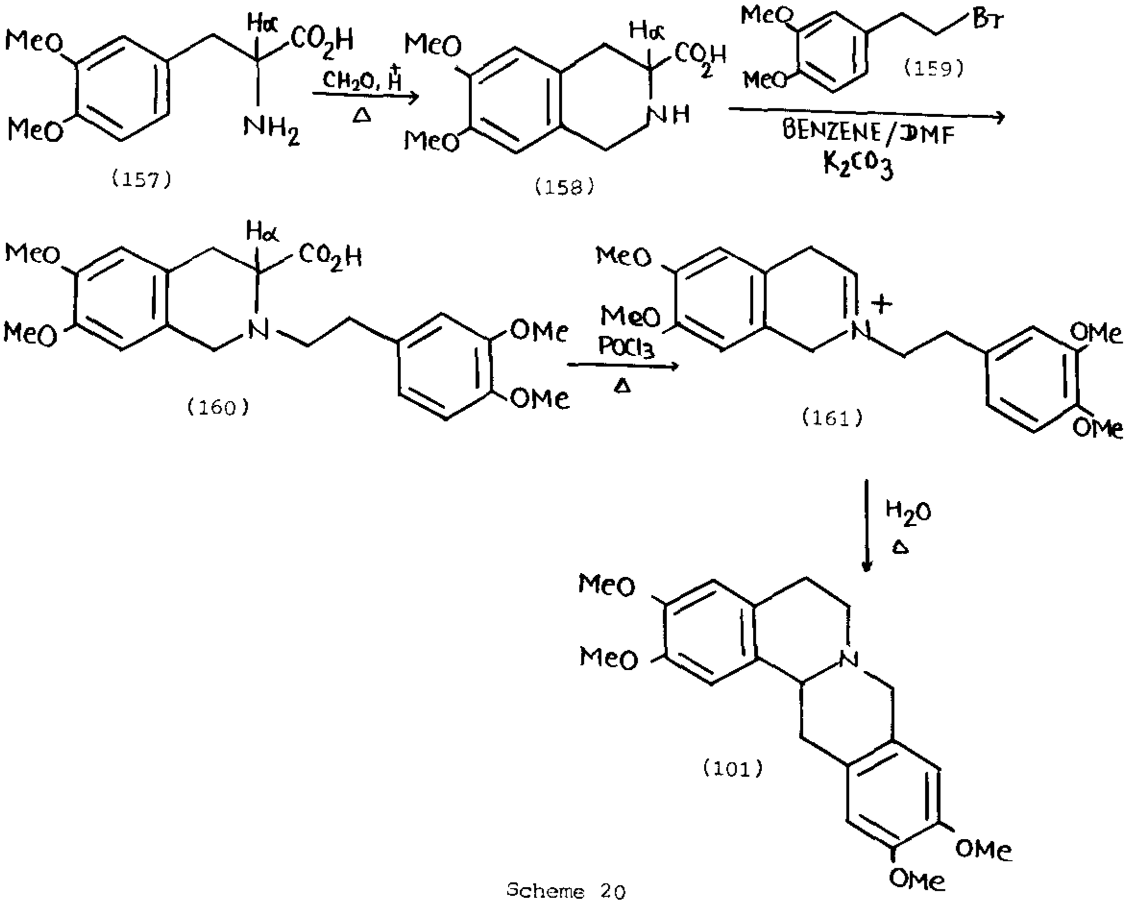
a- $R^1= R^2= R^3= R^4= R^5= R^6= H$
b- $R^1= OMe; R^2= R^3= R^4= R^5= R^6= H$ (155)
c- $R^1= R^3= R^4= OMe; R^2= R^5= R^6=H$ (101)
d- $R^2= OMe; R^1= R^3= R^4= R^5= R^6= H$
e- $R^1= R^2= OMe; R^3= R^4= R^5= R^6= H$
f- $R^1= R^2= R^5= OMe; R^3= R^4= R^6= H$
g- $R^1= R^3= R^5= OMe; R^2= R^4= R^6= H$
h- $R^1= R^2= R^3= R^5= OMe; R^4= R^6= H$ (102)
i- $R^1= R^5= OMe; R^2,R^3= OCH_2O; R^4= R^6= H$
j- $R^2= R^3= R^5= R^6=H; R^1= OMe; R^4= NO_2$
k- $R^1= OMe; R^2= CO_2Me; R^3= R^4= R^5= R^6=H$
l- $R^1= OMe; R^2,R^3=OCH_2O; R^4=R^5=H; R^6=Me$ (156)
m- $R^1=OMe; R^3,R^4=OCH_2O; R^2=R^5=R^6=H$ (127)

a- $R^1=R^2=R^3=R^4=R^5=R^6=H$
b- $R^1=OMe; R^2= R^3= R^4= R^5= R^6= H$
c- $R^1= R^3= R^4= OMe; R^2= R^5= R^6= H$
d- $R^1=OMe; R^2=R^3=R^4=R^5=R^6=H; 13_a-CO_2Me$

Scheme 19

9. IMINIUM SALT[71] CYCLIZATION METHOD

The decarbonylation of α-tertiary amino acids regiospecifically generates iminium salts[72]. These salts cyclize by acid to berbines[73]. The iminium salts are synthesized from various phenylalanines which involve as the key step alkylation of a 1,2,3,4-tetrahydro-6,7-dimethoxy-3-isoquinoline carboxylate. Various C-8 and C-13 methyl berbines have also been synthesized using this method[74] (Scheme 20).



Scheme 20

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