ON THE USE OF LACTONES AS BUILDING BLOCKS IN THE ALKALOID SYNTHESIS - A REVIEW[‡]

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Abstract - Recent alkaloid syntheses involving the lactones have been reviewed with particular reference to isoquinoline and indole alkaloids.

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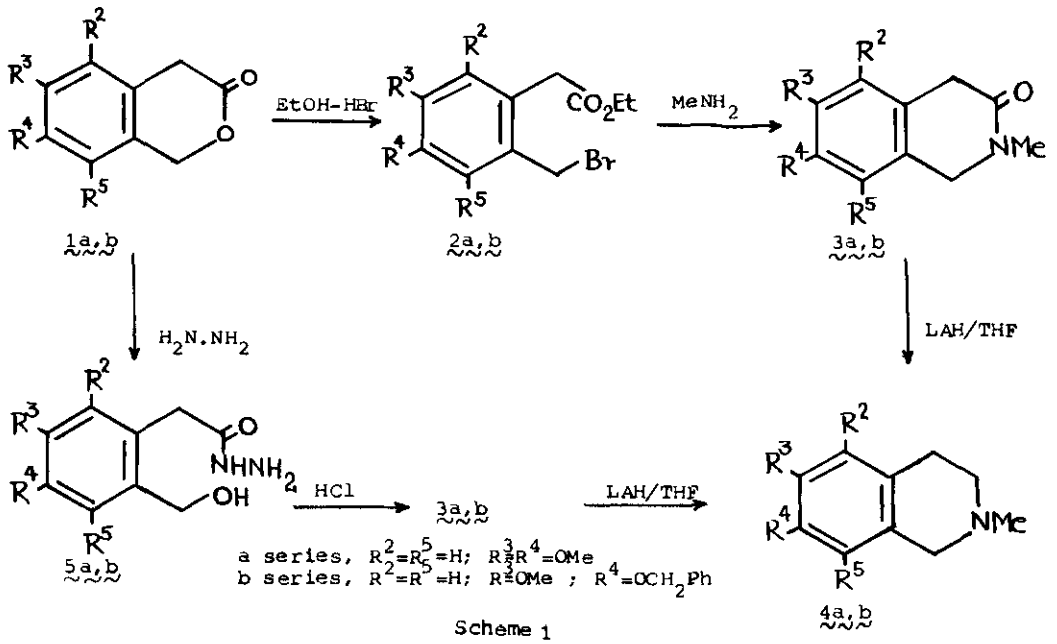
‡ Dedicated to the memory of late Professor Robert B. Woodward (1917-1979).

I. INTRODUCTION

The lactones, a fascinating group of oxygen heterocycles have variously been used in the syntheses of alkaloids of a number of groups such as the isoquinolines, yohimbanes, deserpidines, spirooxindoles, steroidal alkaloids and cinchona alkaloids. In the recent past we have been active in the field of alkaloid synthesis and here wish to present a critical account of the work done on the alkaloid syntheses involving the lactones. The review though may fail to incorporate many more results, will be of interest to a worker in searching newer lactone based syntheses of the alkaloids.

II. 1,2,3,4-TETRAHYDROISOQUINOLINE GROUP

The simple tetrahydroisoquinoline alkaloids have been synthesized using the 3-isochromanones. The lactone (1a) on treatment with ethanolic hydrogen bromide afforded the bromoester (2a). Condensation of the ester (2a) with methylamine gave the 3-oxoisoquinoline (3a) which on lithium aluminium hydride reduction gave the alkaloid O-methylcorypalline[1] (4a). Likewise, corypalline (4b) was synthesized using the lactone[2] (1b) (Scheme 1).



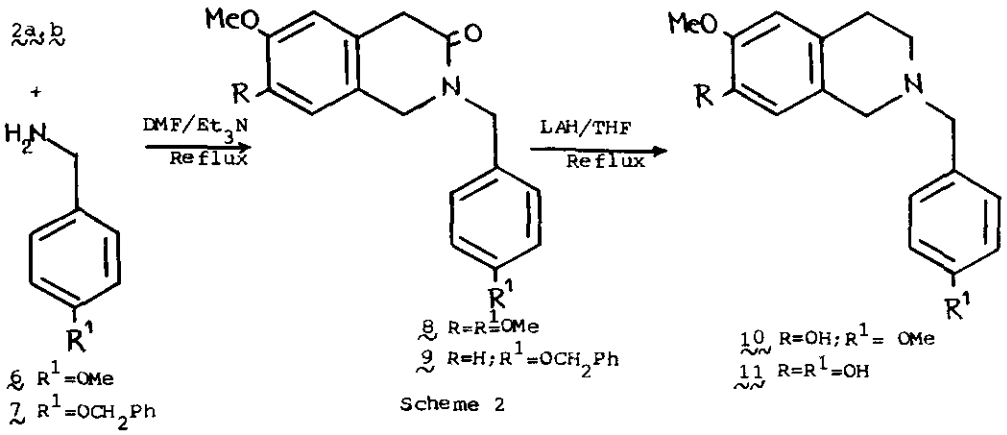
Scheme 1

Treatment of the lactones (1a,b) with hydrazine afforded the hydrazides (5a,b) which upon treatment with hydrochloric acid give the lactams (3a,b) which could

be converted to the isoquinolines (4a,b) by lithium aluminium hydride reduction[3] (Scheme 1).

III. N-BENZYL-1,2,3,4-TETRAHYDROISOQUINOLINE GROUP

Two alkaloids *sendaverine* (10) and *corgoine* (11) have been isolated from plants of the family Fumariaceae[4-6]. Condensation of the bromoester (2a) with the benzylamine (6) gave the tricyclic lactam (8) which on reduction with lithium aluminium hydride gave sendaverine[7] (10). Likewise *corgoine* (11) was synthesized by condensation of the bromoester (2b) with the benzylamine (7) followed by reduction and debenzylation of the resulting 3-oxo derivative[8] (9) (Scheme 2).



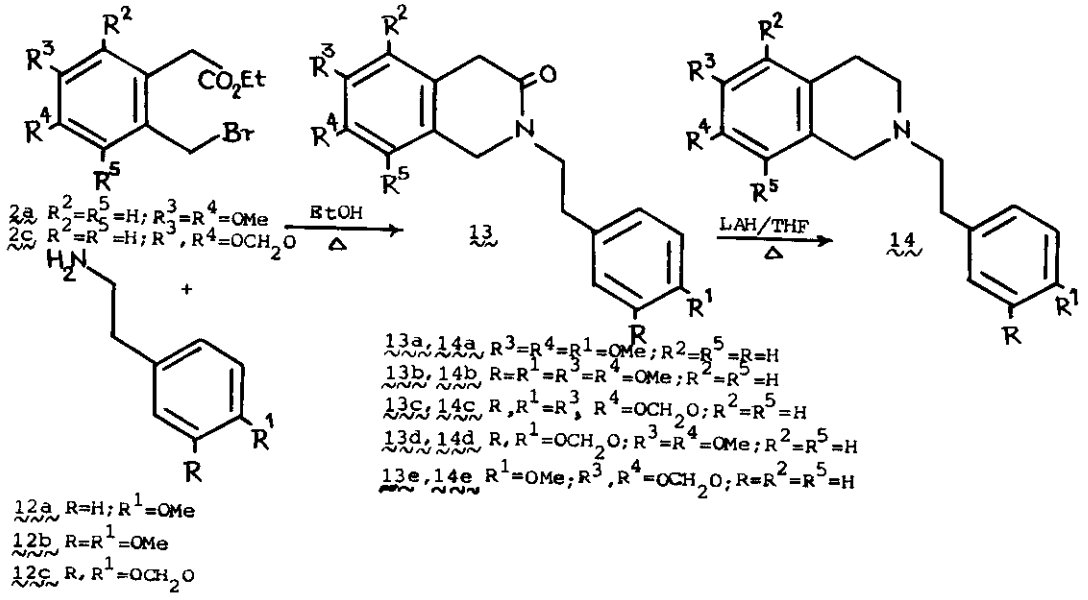
Scheme 2

IV. *N-PHENETHYL-1,2,3,4-TETRAHYDROISOQUINOLINE GROUP*

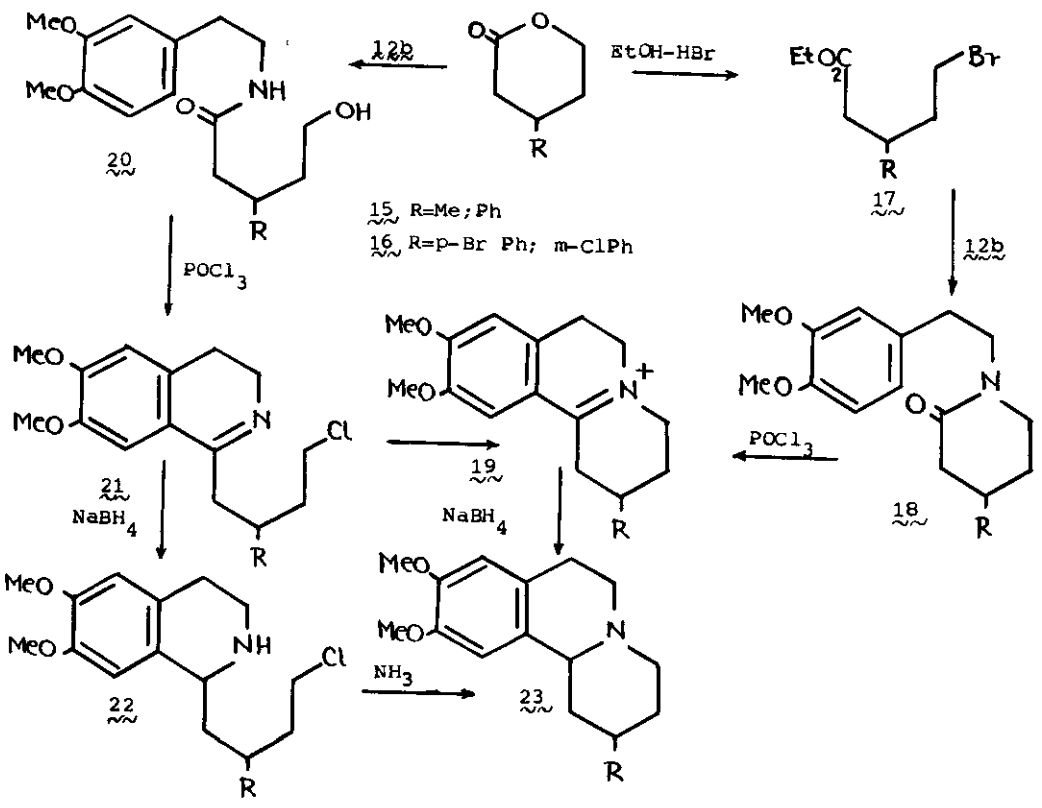
A group of alkaloids of purely synthetic origin has been reported to possess important hypotensive activity[9]. The bromoesters (2a, 2c) prepared from the corresponding 3-isochromanones by dissolution in ethanolic hydrogen bromide on condensation with the phenethylamines (12a-c) gave the lactams (13a-e) which on lithium aluminium hydride reduction gave the corresponding N-phenethylisoquinolines[10] (14a-e) (Scheme 3).

V. BENZO-, INDOLOQUINOLIZINE AND BENZOINDOLIZINE GROUP

A number of 2-substituted-1,3,4,6,7,11b-hexahydro-9,10-dimethoxy-2H-benzo[a]quinolizines and 1,2,3,4,6,7,12,12b-octahydroindolo[2,3,-a]quinolizines have been prepared starting from 3-substituted valerolactones, the preparation requiring five stages[11] (Scheme 4). The 3-substituted δ-valerolactones[12] were



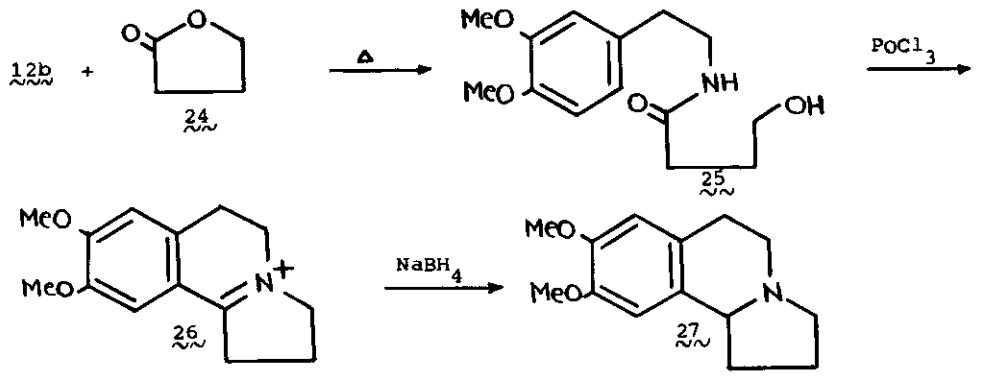
Scheme 3



Scheme 4

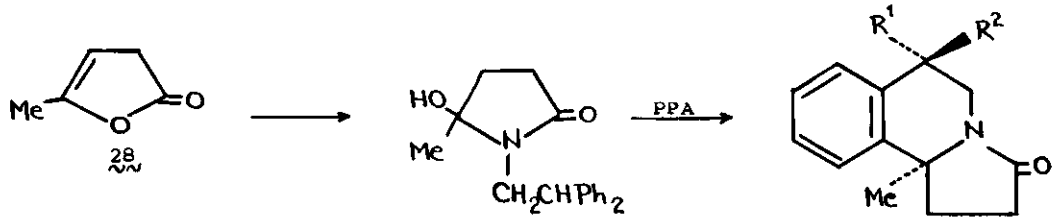
prepared from corresponding glutaric acids by reduction of the carboxylic acid groups[13,14]. The conversion of the lactones (15, 16) to the substituted pyridones (18) required too high a temperature[15], if carried out directly and therefore was performed via bromovalerates[16] (17).

Benz(g)indolizines have been prepared using the γ-butyrolactone (24). The butyramide (25) on phosphoryl chloride cyclization followed by sodium borohydride reduction afforded the benz(g)indolizine[17] (27) (Scheme 5).



Scheme 5

A recent highly stereoselective synthesis of benzindolizines[18] consisting in iminium ion cyclization begins with condensing δ-angelicalactone[19] (28) with 2,2-diphenylethylamine to get an acyl iminium ion precursor (29) which on polyphosphoric acid cyclization gave chiefly one diastereoisomer[18] (30) (Scheme 6).

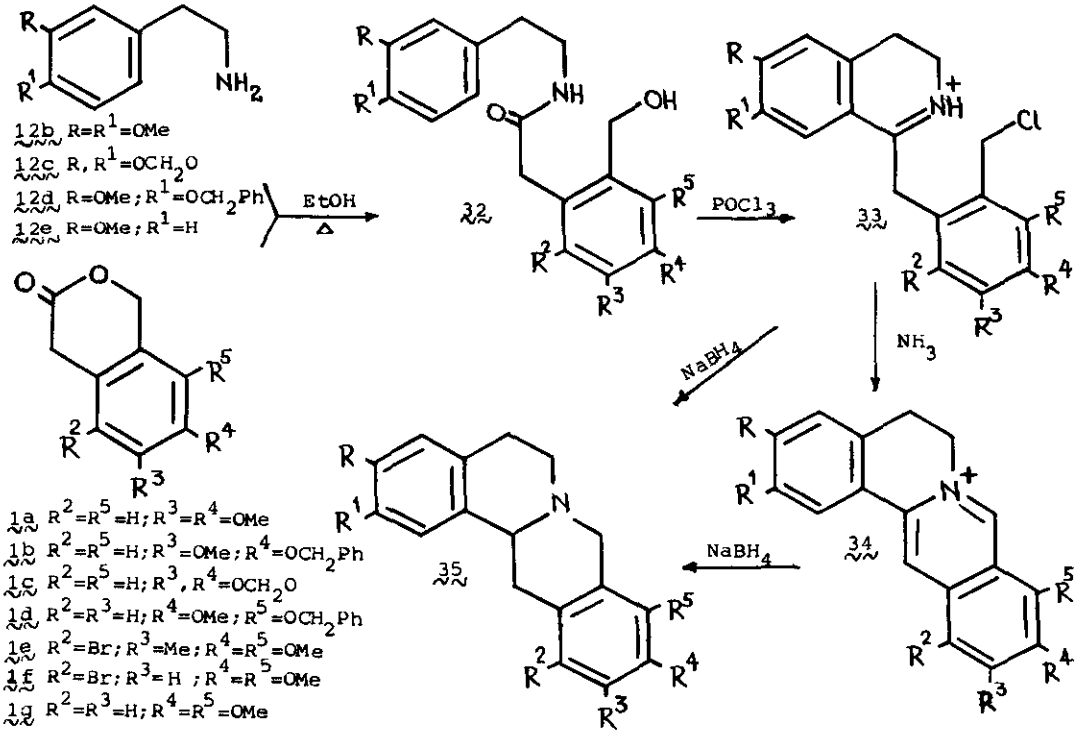


Scheme 6

VI. BERBINE GROUP

The berbine[20] alkaloids have been synthesized using the lactones. Condensation

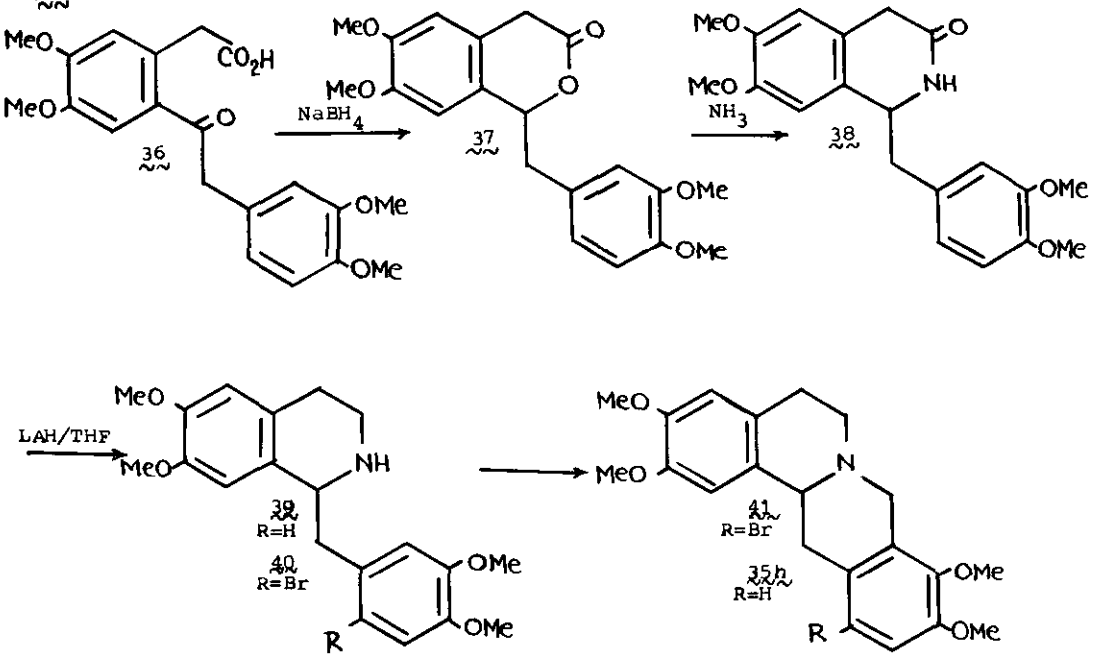
of the 3-isochromanones (1a-f) with the phenethylamines (12b-d) afforded the hydroxymethylphenyl acetamides (32a-f). Phosphoryl chloride cyclization of the amides (32a-f) followed by sodium borohydride reduction afforded the berbines[21-27] (35a-f). Alternatively, treatment of the dihydroisoquinoline salts (33a-f) with ammonia afforded the berberinium salts (34a-f) which on sodium borohydride reduction afforded the berbines (35a-f). This method has also been used to prepare the bromoberbines[28] (35e-f) which on reductive debromination afforded the berbines (35g-h) (Scheme 7).



32, 33, 34, 35	R	R^1	R^2	R^3	R^4	R^5
a	OMe	OMe	H	H	H	H
b	OMe	OMe	H	OMe	OMe	H
c	OMe	OH	H	OMe	OMe	H
d	OMe	OH	H	H	OMe	OH
e	OMe	OMe	Br	Me	OMe	OMe
f	OMe	OMe	Br	H	OMe	OMe
g	OMe	OMe	H	Me	OMe	OMe
h	OMe	OMe	H	H	OMe	OMe
i	OMe	H	H	H	OMe	OMe

Scheme 7

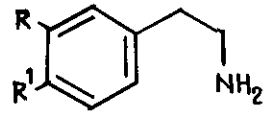
The 1-(3,4-dimethoxybenzyl)-6,7-dimethoxy-3-isochromanone[29] (37) prepared from the keto acid[30-32] (36) has been utilized to prepare the berbine (35h). The lactone (37) on treatment with ammonia afforded (38) which could be converted to dl-tetrahydropalmatine[33] (35h) through the 12-bromotetrahydroisoquinoline[33] (40) (Scheme 8).



Scheme 8

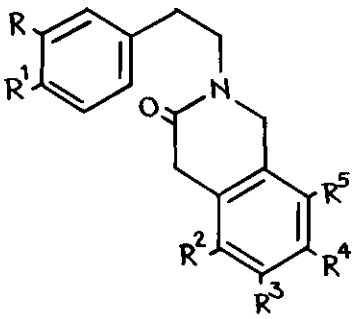
The bromoesters (2a-h) have been employed in berbine synthesis. Condensation of the bromoesters (2a-h) with β-phenethylamines (12b-f) afforded the tricyclic lactams (13b-k) which on phosphoryl chloride cyclization followed by sodium borohydride reduction afforded the berbines (35b-k) in fairly good yields. The method worked equally well for both 9,10- and 10,11-disubstituted berbines, the substitution pattern of the ring D of the berbine being dictated by the substitution on the bromoesters (2a-h). Thus, dl-xylopinine (35b), dl-govanine (35c), dl-scoulerine (35d), dl-pseudoepitetrahydroberberine (35e), dl-isocoptisine (35f), dl-canadine (35g), dl-3-hydroxy-9,10-dimethoxyberbine (35i), dl-2,3,10-trimethoxyberbine (35j) and dl-2,3,11-trimethoxyberbine (35k) were accordingly prepared by us[34-39] (Scheme 9).

The 3-isochromanone (37) on treatment with ethanolic hydrogen bromide gave the corresponding bromoester (42) which could be converted to the berbine[40] (40h)

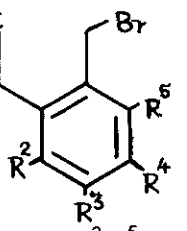


12b R=R^1=OMe
12c R, R^1=OCH$_2$O
12d R=OMe; R^1=OCH$_2$Ph
12e R=OMe; R^1=H
12f R=OCH$_2$Ph; R^1=H

EtOH
Δ



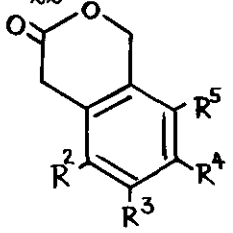
13b R=R^1=R^3=R^4=OMe; R^2=R^5=H
13c R=R^3=R^4=OMe; R^1=OCH$_2$Ph; R^2=R^5=H
13d R=R^4=OMe; R^1=R^5=OCH$_2$Ph; R^2=R^3=H
13e R=R^1=OMe; R^3, R^4=OCH$_2$O; R^2=R^5=H
13f R, R^1=R^3, R^4=OCH$_2$O; R^2=R^5=H
13g R, R^1=OCH$_2$O; R^4, R^5=OMe; R^2=R^3=H
13h R=R^1=R^4=R^5=OMe; R^2=R^3=H
13i R=OCH$_2$Ph; R^4=R^5=OMe; R^1=R^2=R^3=H
13j R^1=R= R^4=OMe; R^3=R^5=H; R^2=H
13k R=R^1=R^3=OMe; R^2=R^4= R^5=H

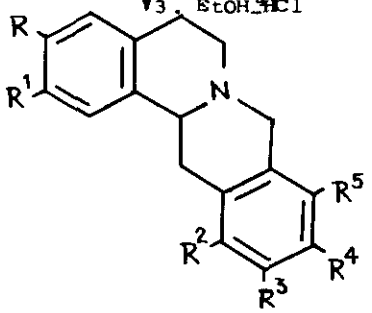


EtOH-HBr

2a R^2=R^5=H; R^3=R^4=OMe
2b R^2=R^5=H; R^3=OMe; R^4=OCH$_2$Ph
2c R^2=R^5=H; R^3, R^4=OCH$_2$O
2d R^2=R^3=H; R^4=OMe; R^5=OCH$_2$Ph
2g R^2=R^3=H; R^4=R^5= OMe
2h R^2=R^4=R^5=H; R^3=OMe

1. POCl$_3$/C$_6$H$_6$
2. NaBH$_4$/MeOH
3. EtOH-HCl



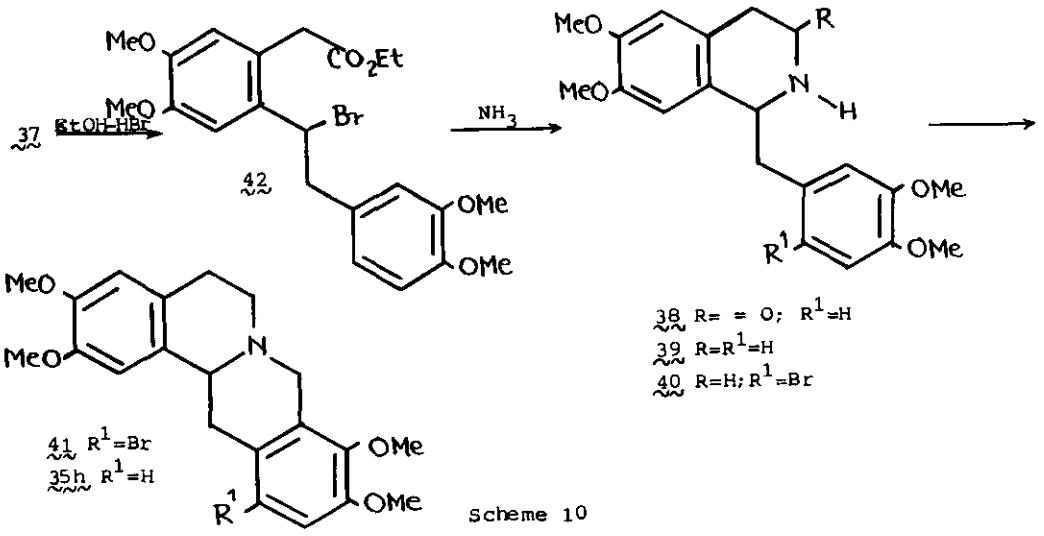


1a R^2= R^5= H ; R^3= R^4= OMe
1b R^2= R^5= H ; R^3= OMe ; R^4=OCH$_2$Ph
1c R^2= R^5= H; R^3, R^4=OCH$_2$O
1d R^2= R^3= H; R^4= OMe; R^5=OCH$_2$Ph
1g R^2= R^3= H; R^4= R^5= OMe
1h R^2= R^4= R^5= H; R^3= OMe

35b R=R^1=R^3=R^4=OMe; R^2=R^5=H
35c R=R^3=R^4=OMe; R^1=OH; R^2=R^5=H
35d R=R^4=OMe; R^1=R^5=OH; R^2=R^3=H
35e R=R^1=OMe; R^3, R^4=OCH$_2$O; R^2=R^5=H
35f R, R^1=R^3, R^4=OCH$_2$O; R^2=R^5=H
35g R, R^1=OCH$_2$O; R^4=R^5=OMe; R^2=R^3=H
35h R=R^1=R^4=R^5=OMe; R^2=R^3=H
35i R=OH; R^4=R^5=OMe; R^1=R^2=R^3=H
35j R^1=R=R^4=OMe; R^2=R^3=R^5=H
35k R=R^1=R^3=OMe; R^2=R^4=R^5=H

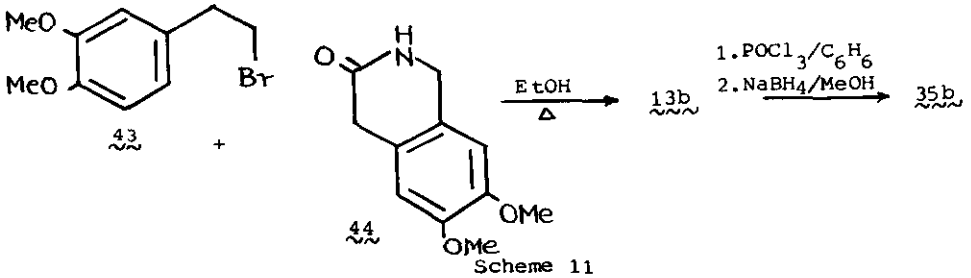
Scheme 9

(Scheme 10).



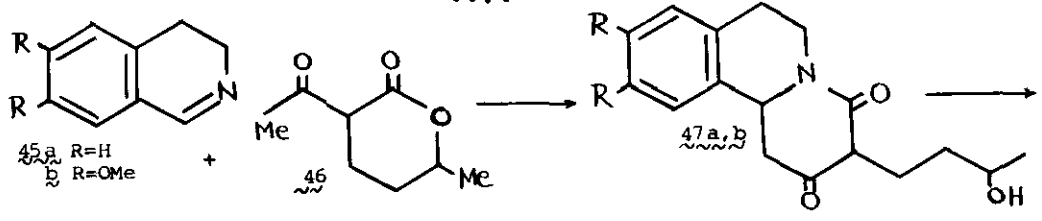
Scheme 10

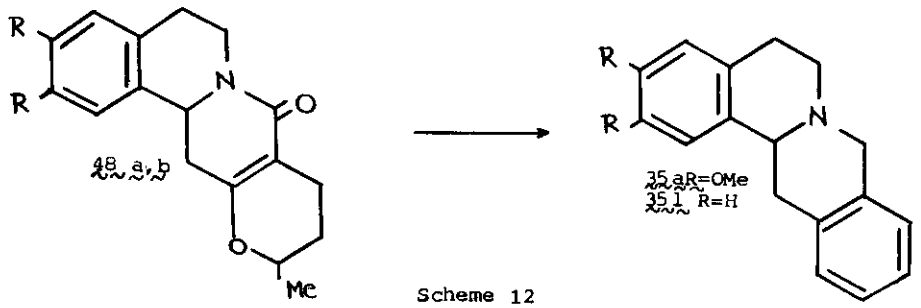
The 3(2H)-isoquinolone (44) prepared from the corresponding 3-isochromanone (1a) has been effectively used to get the berbine (35b). Condensation of the phenethyl bromide (43) with the 3(2H)-isoquinolone (44) gave the lactam (13b) which on phosphoryl chloride cyclization followed by sodium borohydride reduction gave dl-xylopinine[41] (35b) (Scheme 11).



Scheme 11

An alternative synthesis of the berbines involved the condensation of the azomethines (45a,b) with acetyl-δ-lactone (46) to get the lactams (47) which could be converted to the berbine (35a,l) in four operations[42] (Scheme 12).

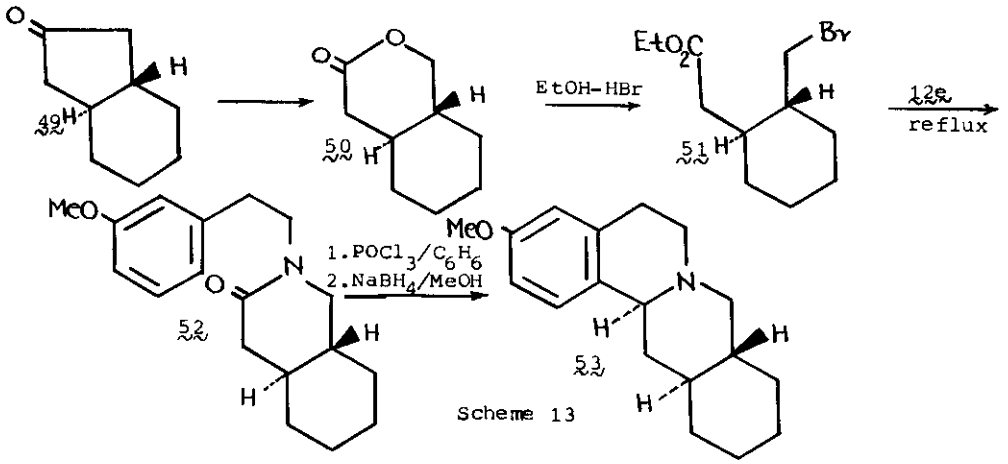




Scheme 12

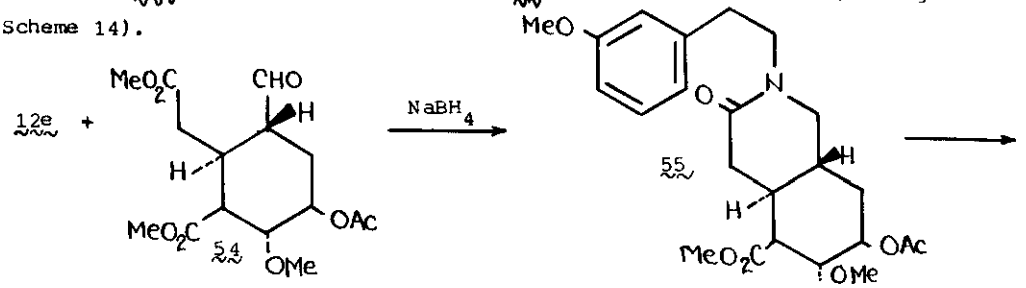
VII. BERBANE, ALLOBERBANE AND EPIALLOBERBANE GROUP

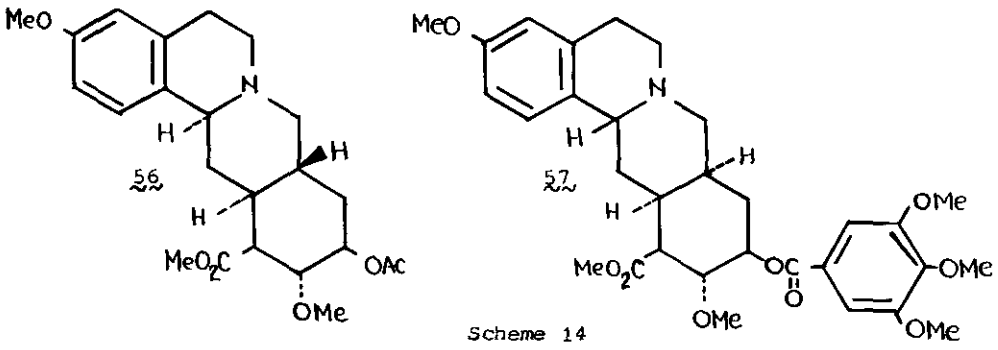
The lactone of dl-trans-2-hydroxymethylhexahydrophenylacetic acid[43] (50) prepared by perbenzoic acid oxidation of dl-trans-2-hydrindone[44] (49) on treatment with ethanolic hydrobromic acid gave ethyl dl-trans-2-bromomethylhexahydrophenyl acetate (51). Condensation of the ester (51) with phenethyl amine (12e) afforded the lactam (52) which on phosphoryl chloride cyclization followed by sodium borohydride reduction produced the berbane[9] (53) (Scheme 13).



Scheme 13

Likewise the alloberbane (56) and epialloberbane (57) were prepared condensing the amine (12e) with the aldehydoester (54) prepared from corresponding lactone[9] (Scheme 14).

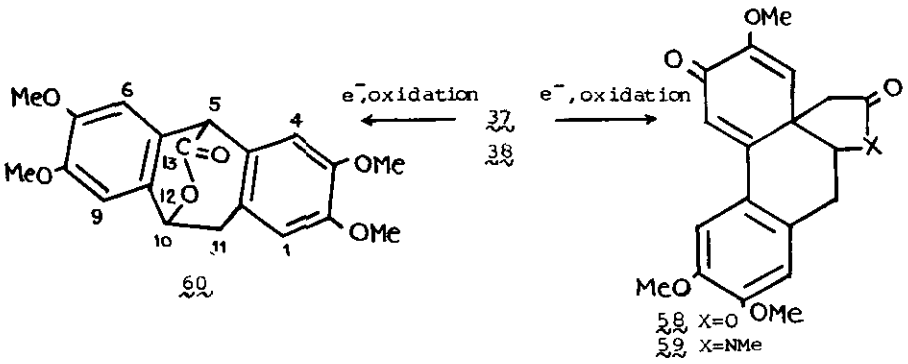




Scheme 14

VIII. PHENANTHRENE AND ISOPAVINE GROUP

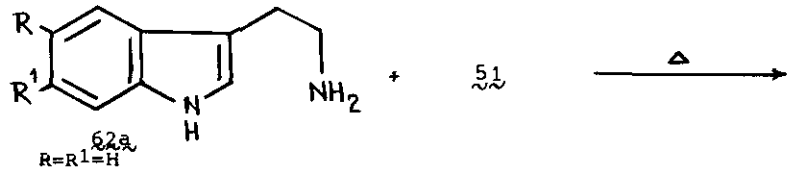
The lactone (37) on anodic oxidation in dichloromethane-trifluoroacetic acid with tetrabutylammonium tetrafluoborate as a supporting electrolyte gave epoxyethanophenanthrene[29] (58). The same spirodienone (58) was isolated when (37) was oxidized with vanadium oxyfluoride using same solvents. An analogues dienone (59) was prepared from lactam (38) using same oxidants. Electrode oxidation of (37) in acetonitrile with quarternary ammonium salts gave an lactonic analogue of the alkaloid isopavine[29] (60) (Scheme 15).

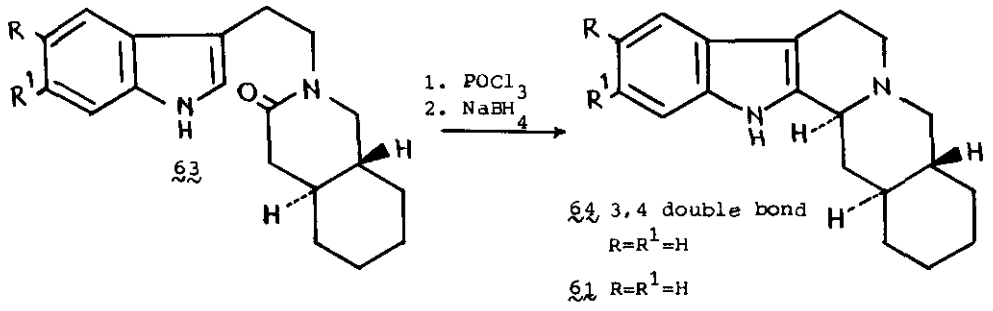


Scheme 15

IX. YOHIMBANE AND HEXADEHYDROYOHIMBANE GROUP

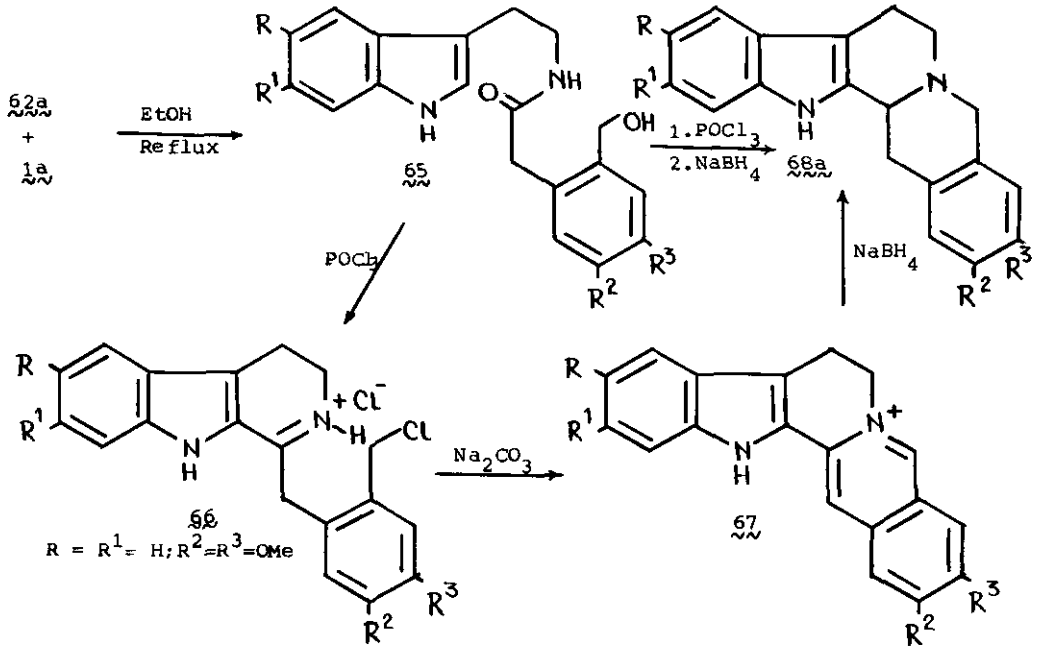
A stereospecific synthesis of dl-yohimbane (61) begins with the condensation of the bromoester (51) with tryptamine[43,45] (62a) (Scheme 16).





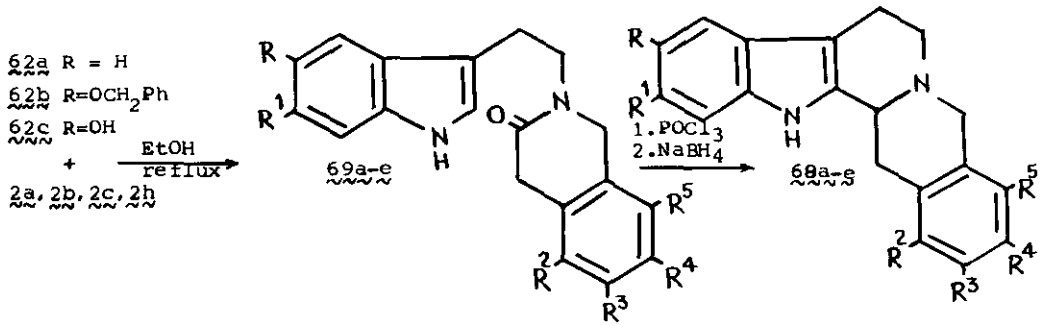
Scheme 16

The yohimbane synthesis has also been accomplished using 3-isochromanones and their derivatives[46-48]. Condensation of tryptamine (62a) with 3-isochromanone (1a) afforded the phenylacetamide (65) which on phosphoryl chloride cyclization followed by sodium borohydride reduction gave the hexadehydroyohimbane (68a). Alternatively the β-carbolinium chloride (66) may be cyclized with sodium carbonate to give (67) which could be reduced to the yohimbane (68a) (Scheme 17). The sulphur[49] and oxygen[50] containing anologues of yohimbane (68a) have also been prepared.



Scheme 17

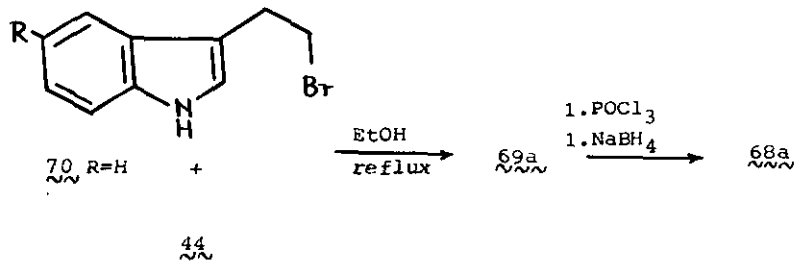
A recent synthesis of the hexadehydroyohimbane alkaloids involves the condensation of the bromoesters (2b-c, 2h) with substituted tryptamines (62a-c)to give the tetracyclic lactams (69a-e) which could be converted to the yohimbanes (68a-e)[51-53] (Scheme 18).



a R=R1=R2=R5=H; R3=R4=OMe
b R=R1=R2=R4=R5=H; R3=OMe
c R=R1=R2=R5=H; R3, R4=OCH2O
d R=R1=R2=R5=H; R3=OMe; R4=OCH2Ph
e R=OCH2Ph; R2=R5=H; R3=R4=OMe; R1=H

Scheme 18

Another approach to the yohimbane skeleton involved the condensation of the indolylethyl bromide (70) with 3(2H)-isoquinolone (44) prepared from corresponding 3-isochromanone (1a). The resulting tetracyclic lactam (69a) could be converted to the hexadehydroyohimbane[54] (68a) (Scheme 19).

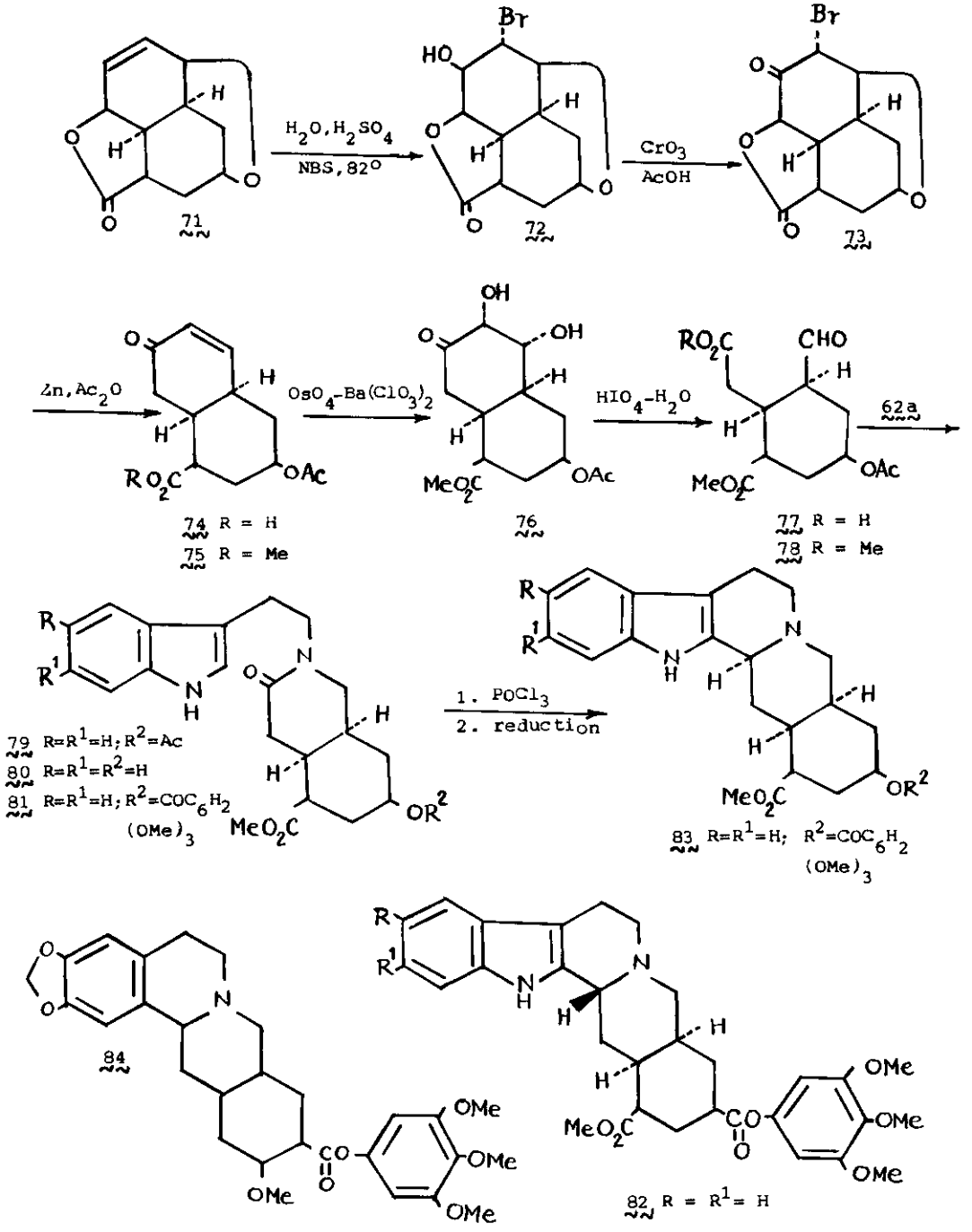


Scheme 19

X. DESERPIDINE, ISODESERPIDINE AND DEPYRROLODESERPIDINE GROUP

3β, 5β-epoxy-8β-hydroxy-1,2,3,4,5,8,9α,10α-octahydro-1β-naphthoic acid lactone (71) has been employed to get 17-demethoxydeserpidine (82) and 17-demethoxy-3-

Isodeserpidine[55] (83) (Scheme 20).

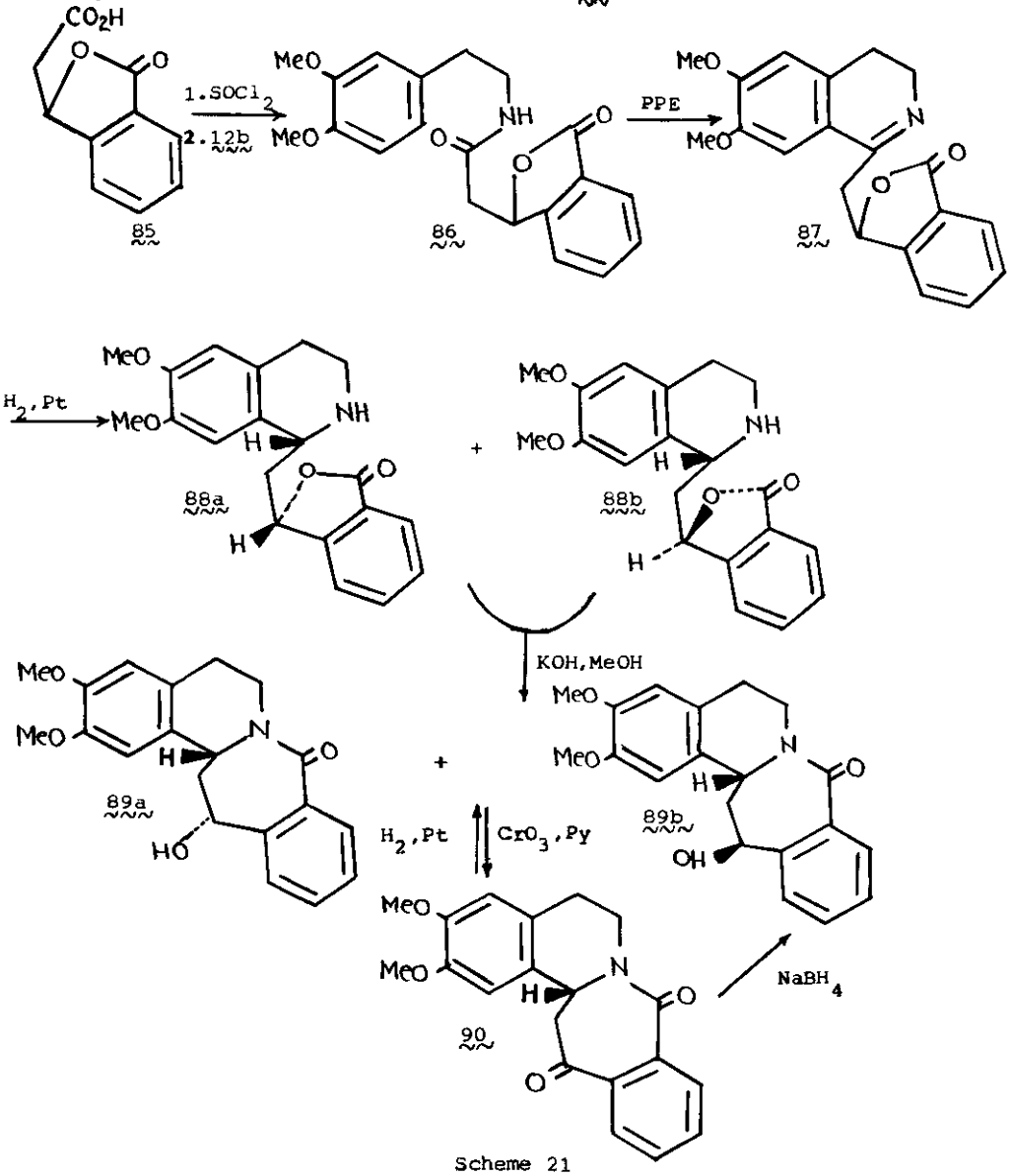


Scheme 20

dl-10,11-Methylenedioxydepyrrolodeserpidine[56] (84) has been prepared from the Woodward's methyl-2-β-carbomethoxy-3α-methoxy-4 -acetoxy-6β-formylcyclohexyl-1β-acetate and phenethylamine[56] (12c).

XI. HOMOPROTOBERBERINE GROUP

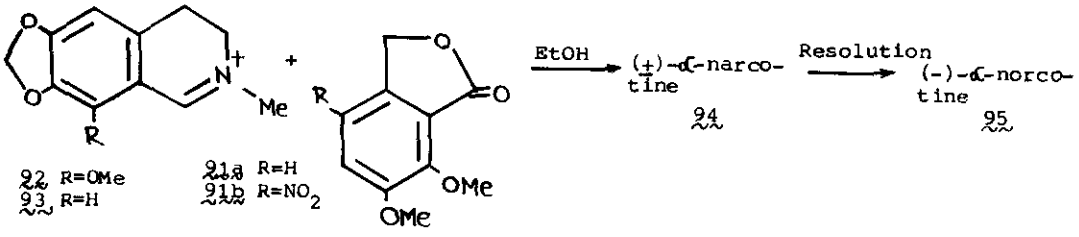
The homoprotoberberines[57] are yet to be discovered in plants. A scheme for their synthesis involves a lactonic acid[58] (85) (Scheme 21).



Scheme 21

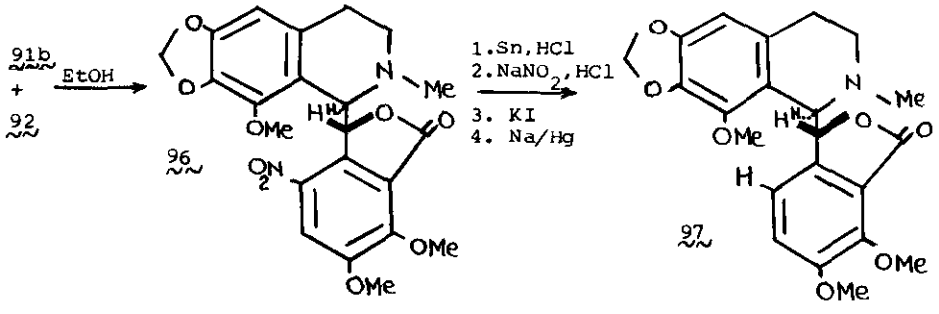
XII. PHTHALIDE ISOQUINOLINE[59] GROUP

(-)-α-Narcotine (95) has been synthesized using meconine[60] (91a) (Scheme 22).



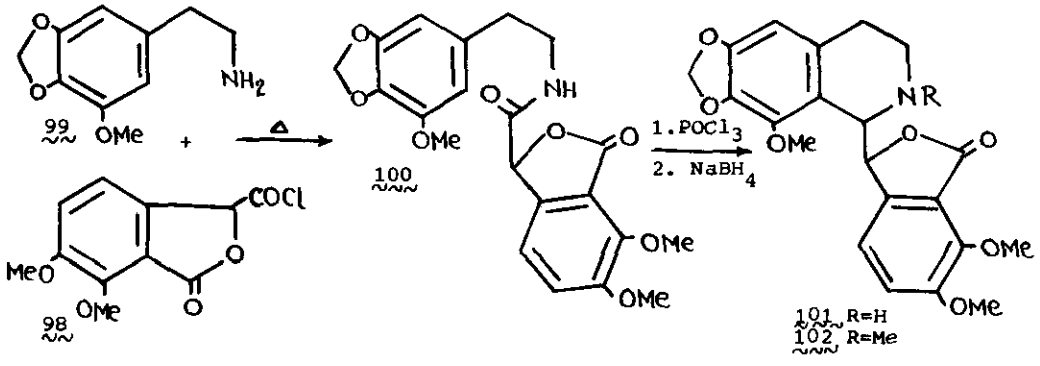
Scheme 22

Hope and Robinson synthesized (±)-β-narcotine (97) starting from condensation of cotarnine (92) with nitromeconine[61] (91b, R = NO_2) (Scheme 23).



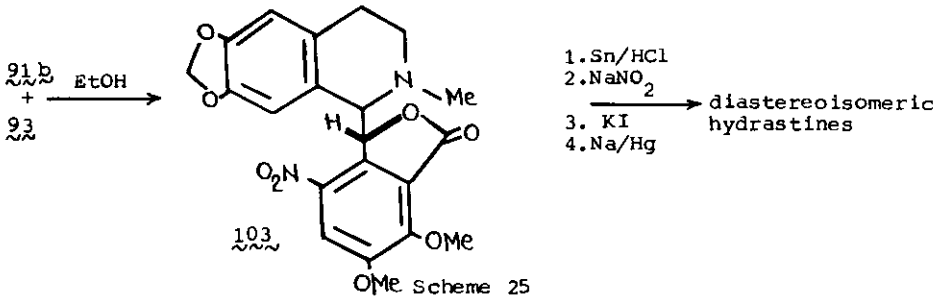
Scheme 23

dl-Narcotine (102) has been synthesized by condensation of meconine chloride (98) with the phenethylamine (99). The resulting amide (100) on phosphoryl chloride cyclization followed by sodium borohydride reduction gave α- and β-nornarcotines (101) which on methylation gave α- and β-narcotines[62,63] (102) (Scheme 24).



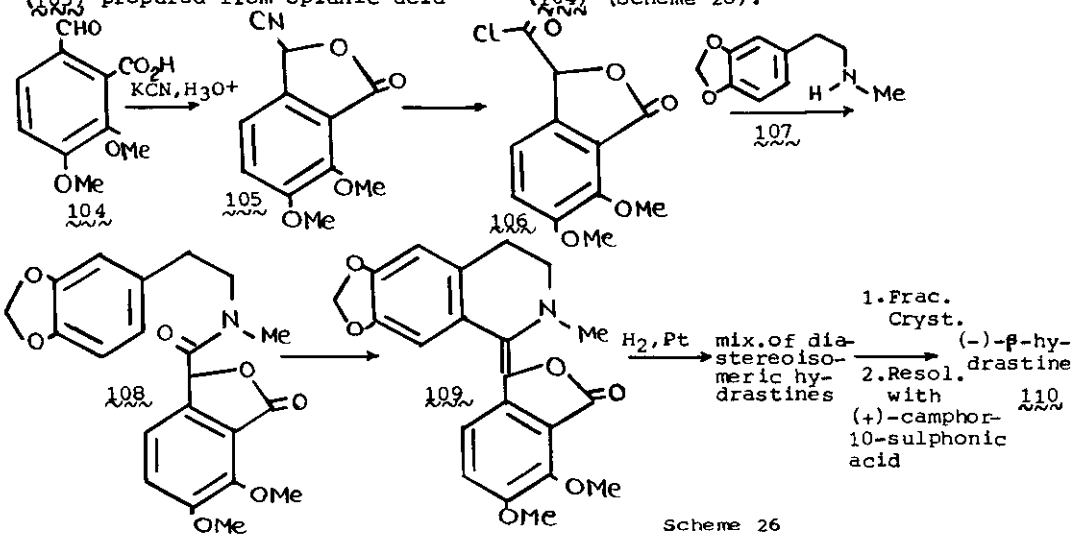
Scheme 24

A parallel synthesis of hydrastines has also been achieved[64,65] (Scheme 25).



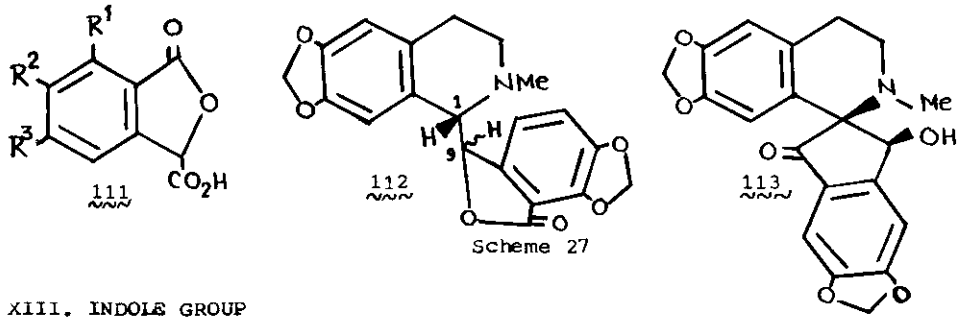
Scheme 25

An improved synthesis of (-)-β-hydrastine (110) involved the use of the lactone (105) prepared from opianic acid[66,67] (104) (Scheme 26).



Scheme 26

Phthalide-3-carboxylic acid (111) has also found application in the synthesis of the alkaloids adlumidine (112) and corydaine[68] (113) (Scheme 27).

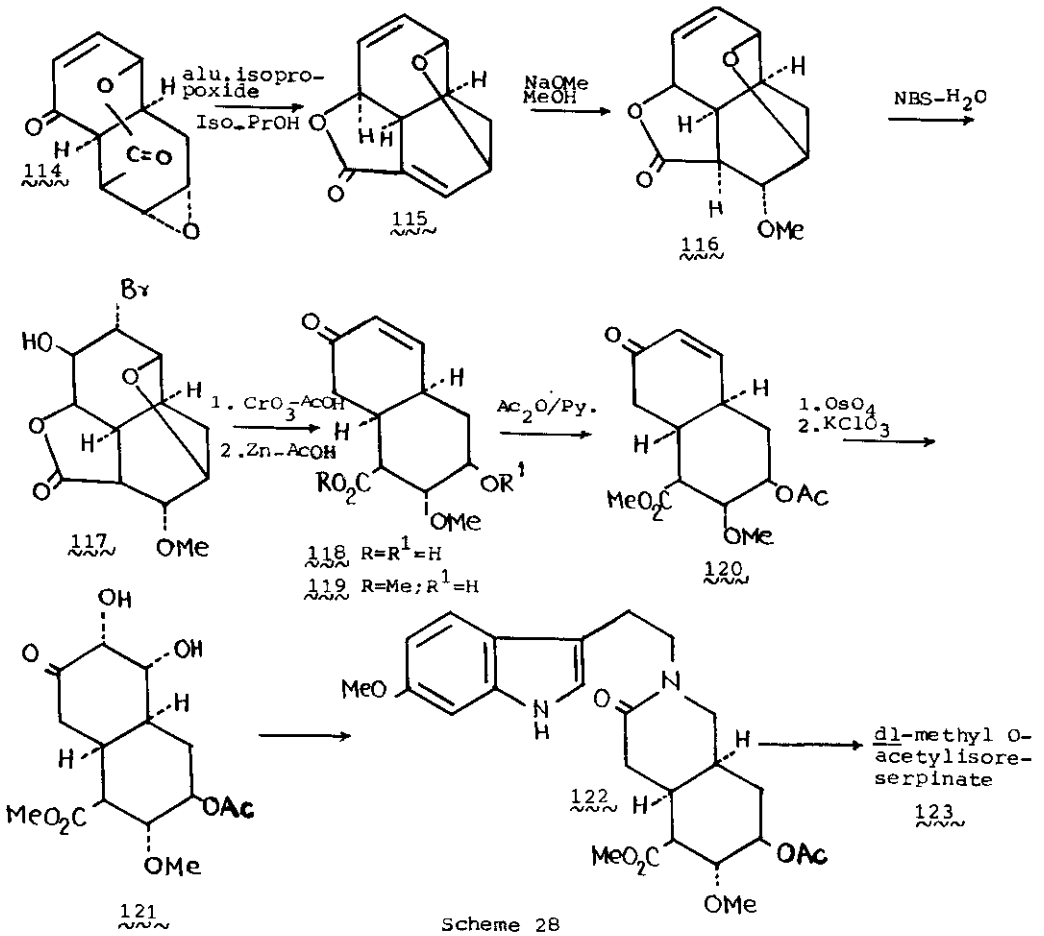


Scheme 27

XIII. INDOLE GROUP

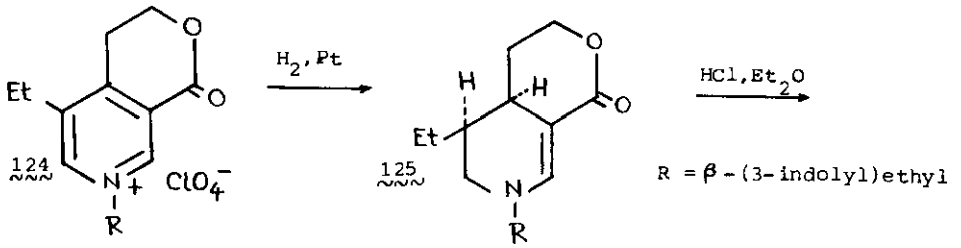
Woodward et al synthesized reserpine (124) employing the lactone (114). The lactone (114) on successive treatment with aluminium isopropoxide and sodium

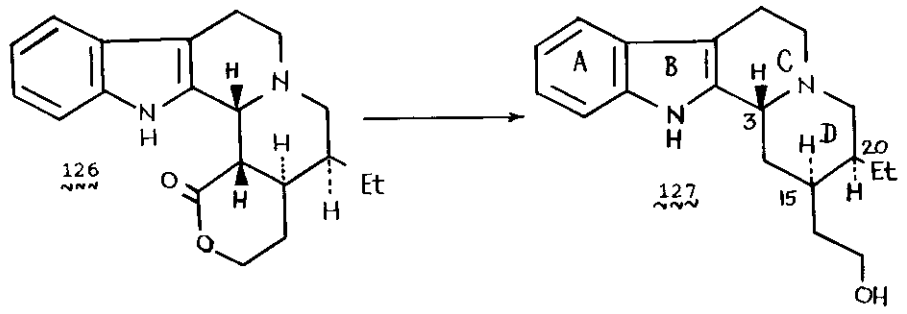
methoxide gave the lactone[69] (116), the key intermediate which contained all five asymmetric carbon atoms of ring E of reserpine (124) properly oriented. Successive treatments of lactone (116) gave dl-methyl-o-acetylisoreserpinate[70] (123) (Scheme 28).



Scheme 28

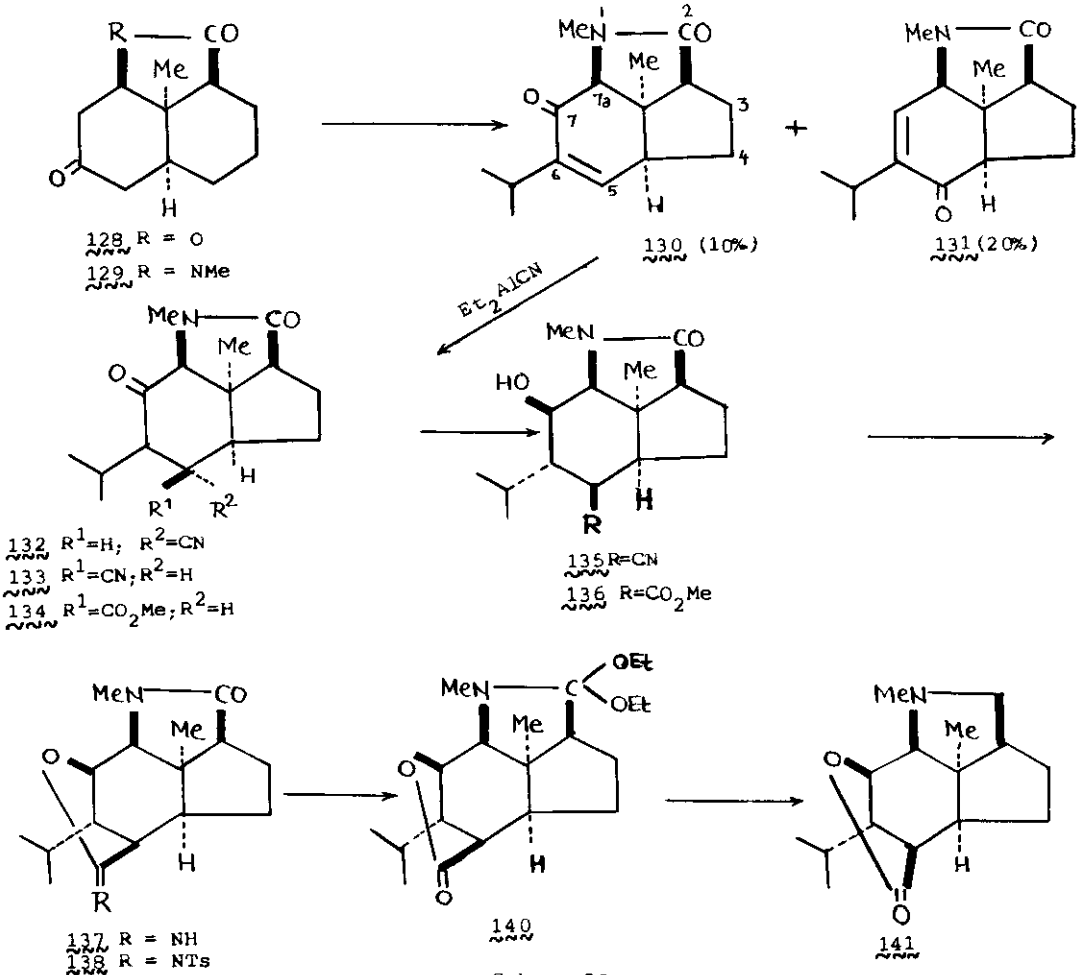
A synthesis of alkaloid dl-corynantheidol[71,72] (127) utilizes the pyridine lactone[71,72] (124) (Scheme 29).





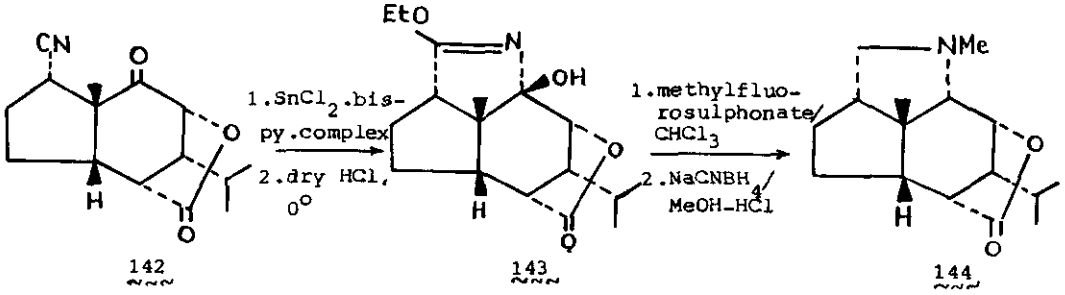
Scheme 29

Dendrobine[73] (141), a sesquiterpene alkaloid from Dendrobium nobile L. having a picrotoxane skeleton has been synthesized from the lactone[74,75] (128) (Scheme 30).



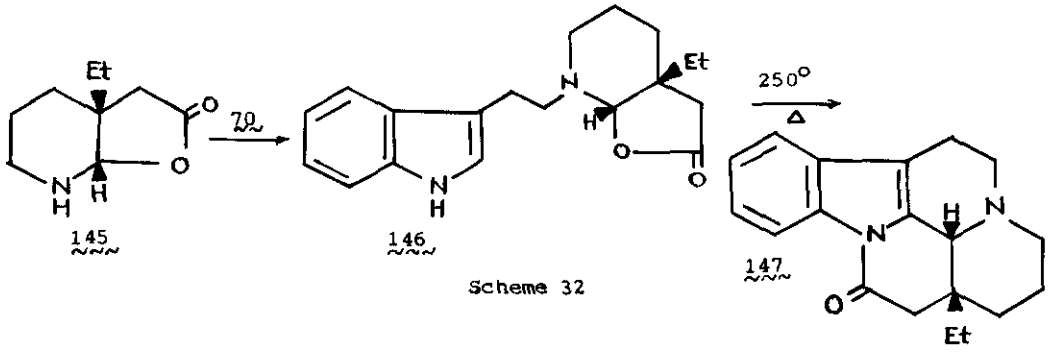
Scheme 30

Borch et al successfully converted the lactone (142) to 8-epidendrobine[76] (144) (Scheme 31).



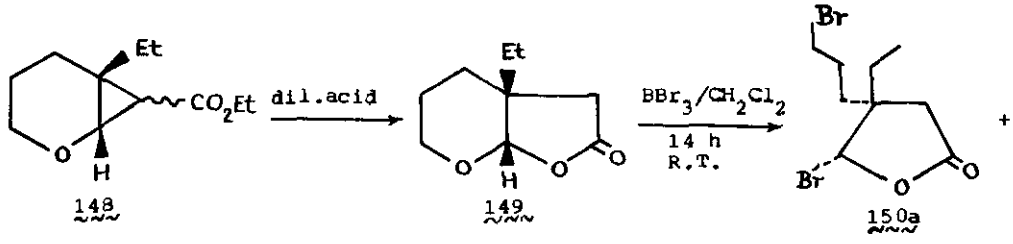
Scheme 31

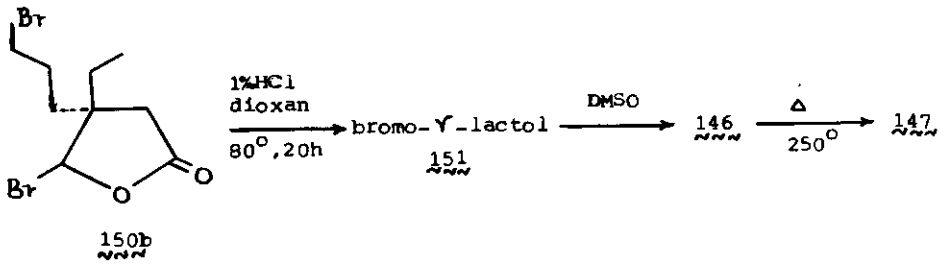
A short synthesis of eburnamonine[77] (147) has been achieved from the carbinolamine-γ-lactone (145). N-alkylation of the lactone (145) with tryptophyl bromide (70) gave the lactone (146). Thermolysis of (146) yielded dl-eburnamonine[78] (147) (Scheme 32).



Scheme 32

Alternatively, the ester (148) on acid hydrolysis gave the lactone (149) which on bromination with borontribromide in methylenedichloride gave a mixture of two dibromides (150a,b). The dibromides on treatment with dilute hydrochloric acid in dioxan gave a bromo-γ-lactol (151) which reacted with tryptamine to give the lactone (146) which was pyrolysed to eburnamonine[78] (147) (Scheme 33).

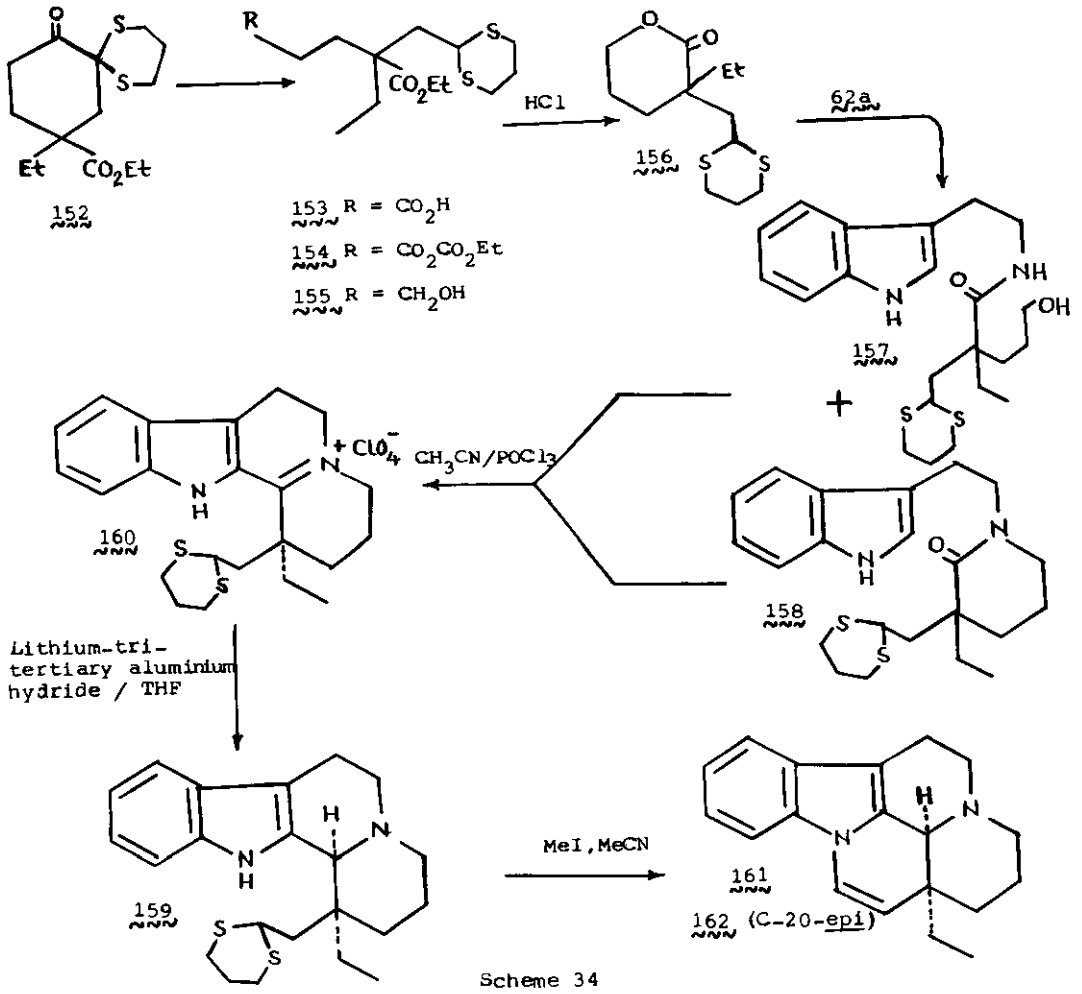




150b 151 146 147

Scheme 33

The C-9 lactone (156) prepared from the cyclic dithioacetal[79] (152) in five steps consisting of ring cleavage, ethoxycarbonylation, reduction and cyclization has been used to synthesize dl-eburunamenine (161) and epieburunamenine[80] (162) (Scheme 34).



152

153 R = CO_2H

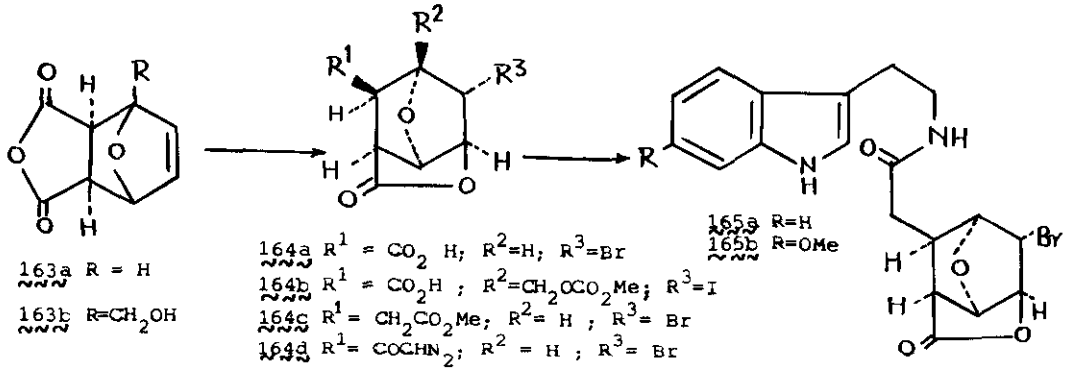
154 R = CO_2CO_2Et

155 R = CH_2OH

156 157 158 160 159 161 162 (C-20-epi)

Scheme 34

an approach to skeleton of Rauwolfia alkaloids[81] involves lactonic intermediates. The hydrolysis of the adducts (163a,b) followed by halolactonization[81a,b] gave (164a-d). The Arndt-Eistert reaction of (164a) (R^1 = CO_2H, R^2=H, R^3=Br) gave (164c). The diazoketone (164d) was condensed with tryptamine (62a) and 6-methoxytryptamine (62b) to give (165)[81] (Scheme 35).



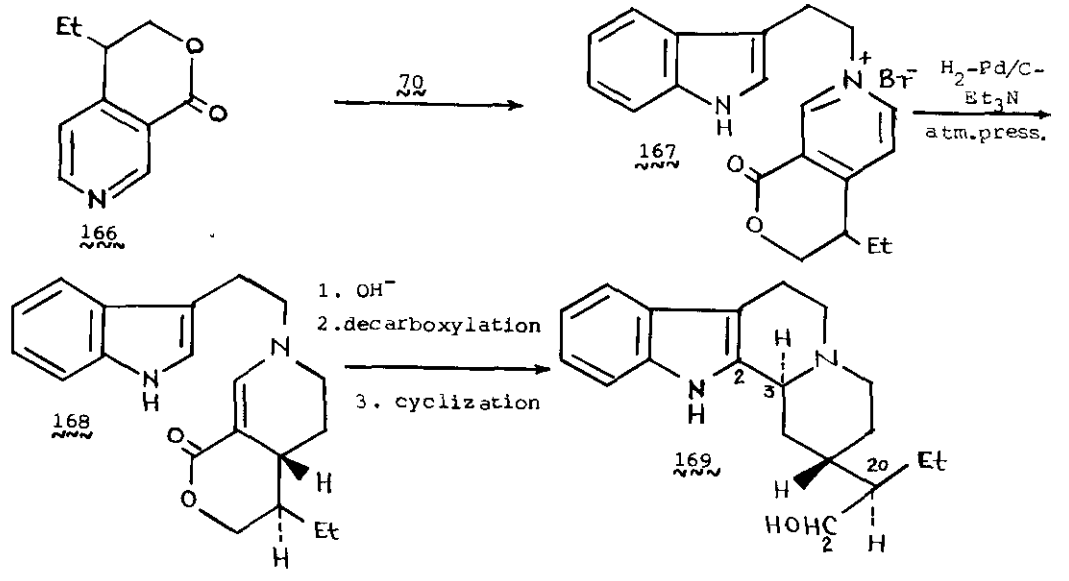
163a R = H
163b R=CH_2OH

164a R^1 = CO_2H; R^2=H; R^3=Br
164b R^1 = CO_2H ; R^2=CH_2OCO_2Me; R^3=I
164c R^1= CH_2CO_2Me; R^2= H ; R^3= Br
164d R^1= $COCHN_2$; R^2 = H ; R^3= Br

165a R=H
165b R=OMe

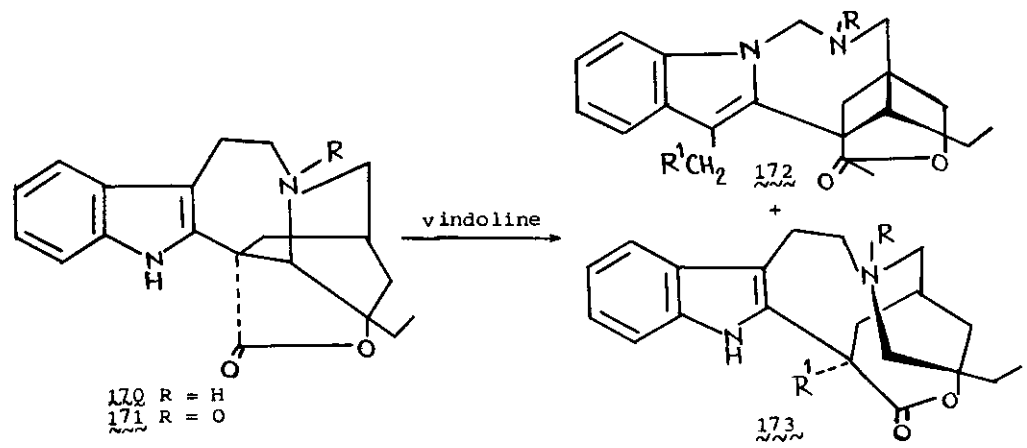
Scheme 35

A general method of synthesis of the indole alkaloids uses the lactone (166) which could be converted in three steps to an antirhine derivative[82] (169) (Scheme 36).



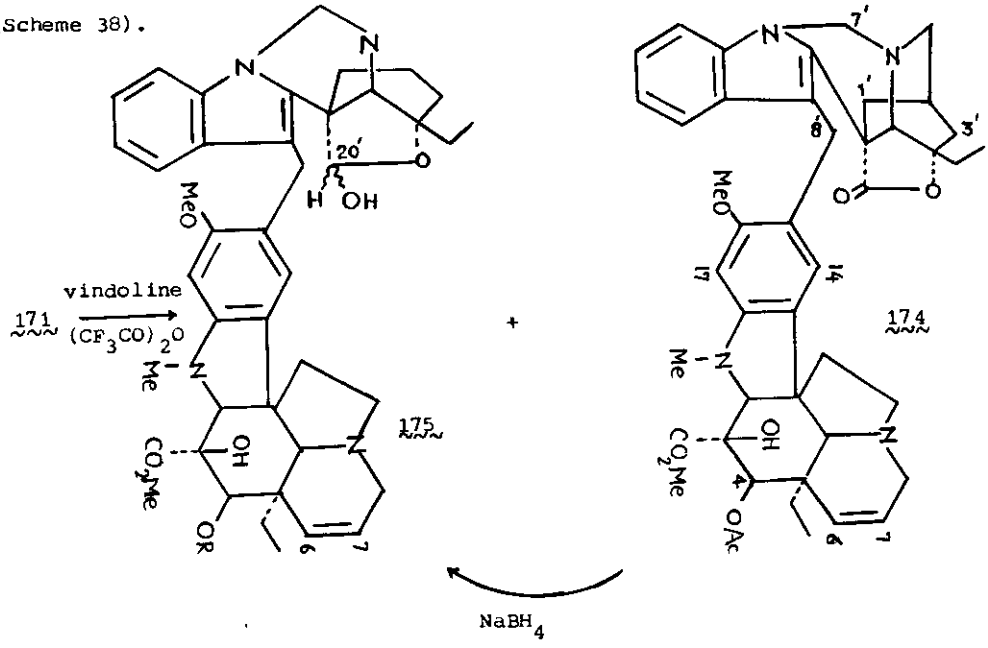
Scheme 36

Catharanthine lactone[83] (170) has been coupled with vindoline to get derivatives of the type (172) and (173)[83] (Scheme 37).



Scheme 37

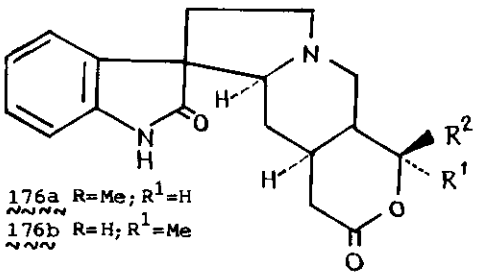
N-oxide derivative of catharanthine lactone (171; R=O) has been coupled with vindoline to provide the rearranged dimeric products (174) and (175)[84-86] (Scheme 38).



Scheme 38

XIV. SPIROOXINDOLE GROUP

The spirooxindole alkaloids dl-formosanine, dl-isoformosanine have been prepared from lactonic intermediates (176a) and dl-mitraphylline and dl-isomitraphylline from the lactone[87] (176b) (Scheme 39).

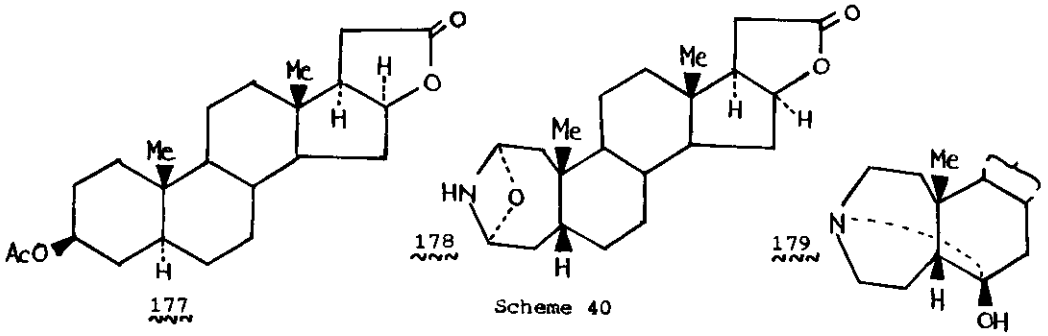


176a R=Me; R^1=H
176b R=H; R^1=Me

Scheme 39

XV. STEROIDAL ALKALOID GROUP

The pregnanoic acid lactone (177) has been used in the synthesis of salamander alkaloids samandaridine (178) and cycloneosamandaridine (179) which has the revised 3,6-cyclic carbinolamine structure (179). Reformatski reaction of 3β, 16β-diacetoxyandrost-5-en-17-one with bromomethylacetate and subsequent dehydration and hydrogenation gave methyl 3β, 16β-diacetoxy-5α-pregnan-21-oate which was cyclized in methanol containing aqueous alkali to give lactone[88] (177) (Scheme 40).

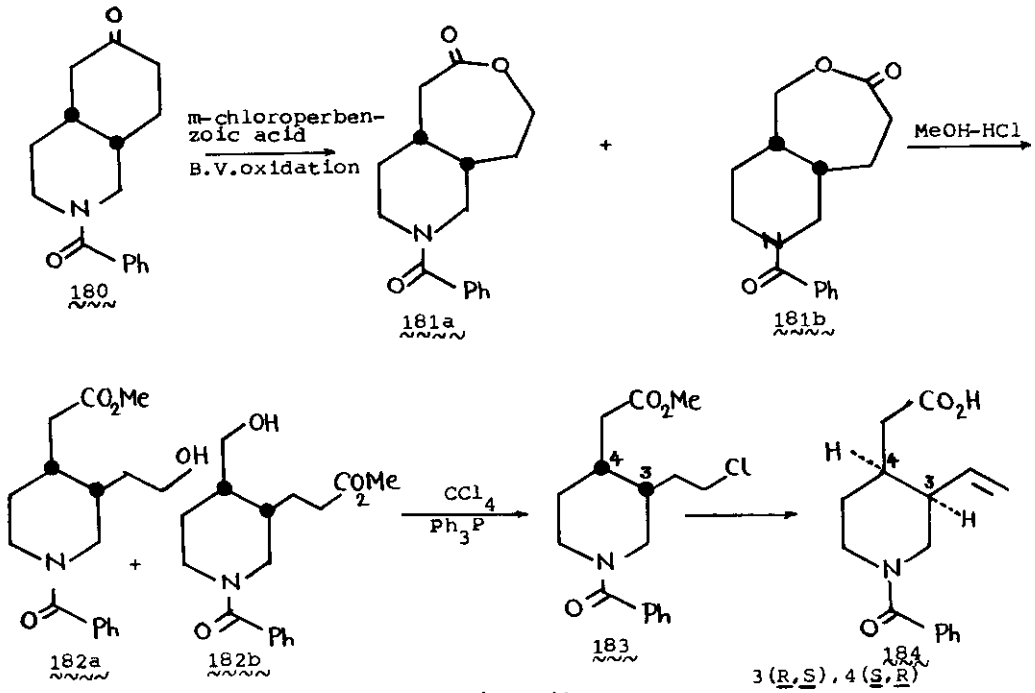


Scheme 40

XVI. QUINUCLIDINE GROUP

The quinuclidine ring with three chiral centres is the characteristic feature of the cinchona alkaloids and elaboration of this ring system is the key for successful total synthesis[89,90]. All recent synthesis of cinchona alkaloids[91-94] utilize the noranalogue of homomeroquinene[95,96]; the 3(R)-vinyl-4(S)-piperidineacetic acid(meroquinene)which is also a degradation product of cinchonine[97]. Racemic cis-N-benzoyl-meroquinene (184) has been synthesized from the lactone (181). The acetic acid

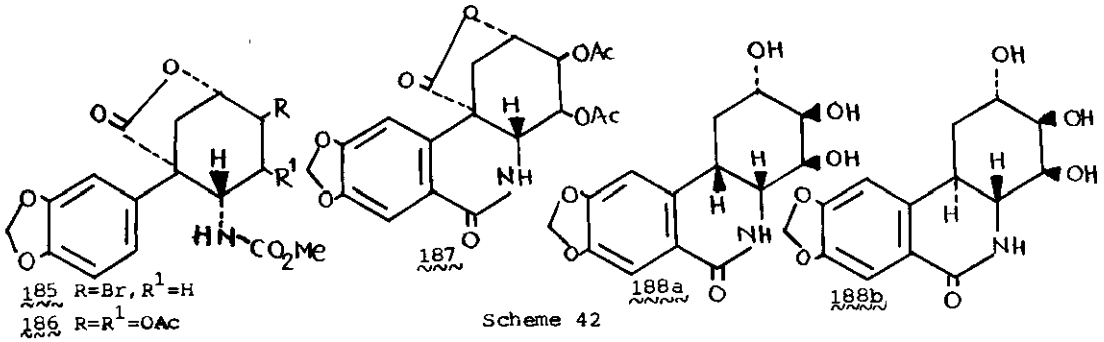
and vinyl side chains of (184) were formed by a Baeyer-Villiger oxidation of (180), opening of the lactone (181a,b) to the hydroxyester (182a,b) and elimination[98] (Scheme 41).



Scheme 41

XVII. ETHANOPHENANTHRIDINE ALKALOID GROUP

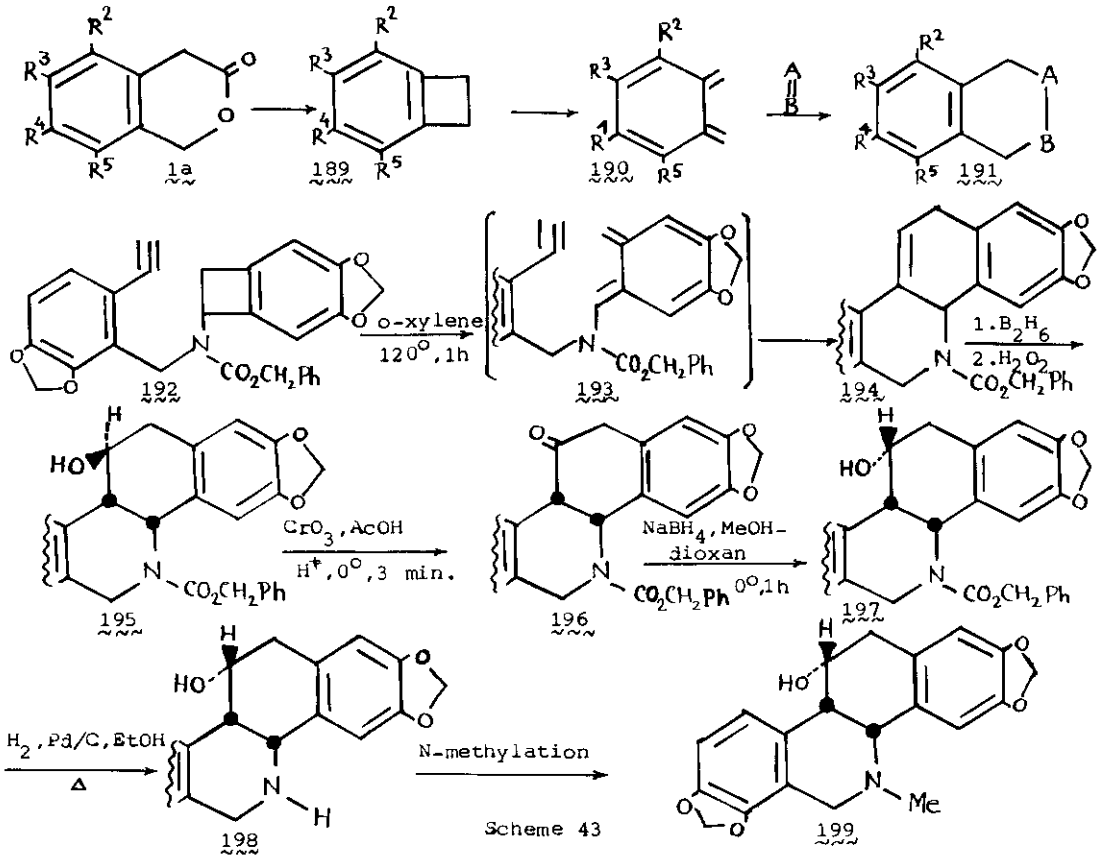
The bromolactone (185) on dehydrobromination, oxidation with osmium tetraoxide and acetylation afforded diacetyl lactone (186). A modified Bischler-Napieralski cyclization of (186) gave the lactam (187). Successive hydrolysis and irradiation of (187) followed by acetylation and hydrolysis gave cis- and trans-dihydrolycorricidine[99] (188a,b) (Scheme 42).



Scheme 42

XVIII. BENZOPHENANTHRIDINE ALKALOID GROUP

A recent synthesis of chelidonine[100] (199) involves the benzoxyclobutene[101] (189), a novel method for their preparation based on thermolysis of 3-isochromanones[102] has recently been described (Scheme 43).



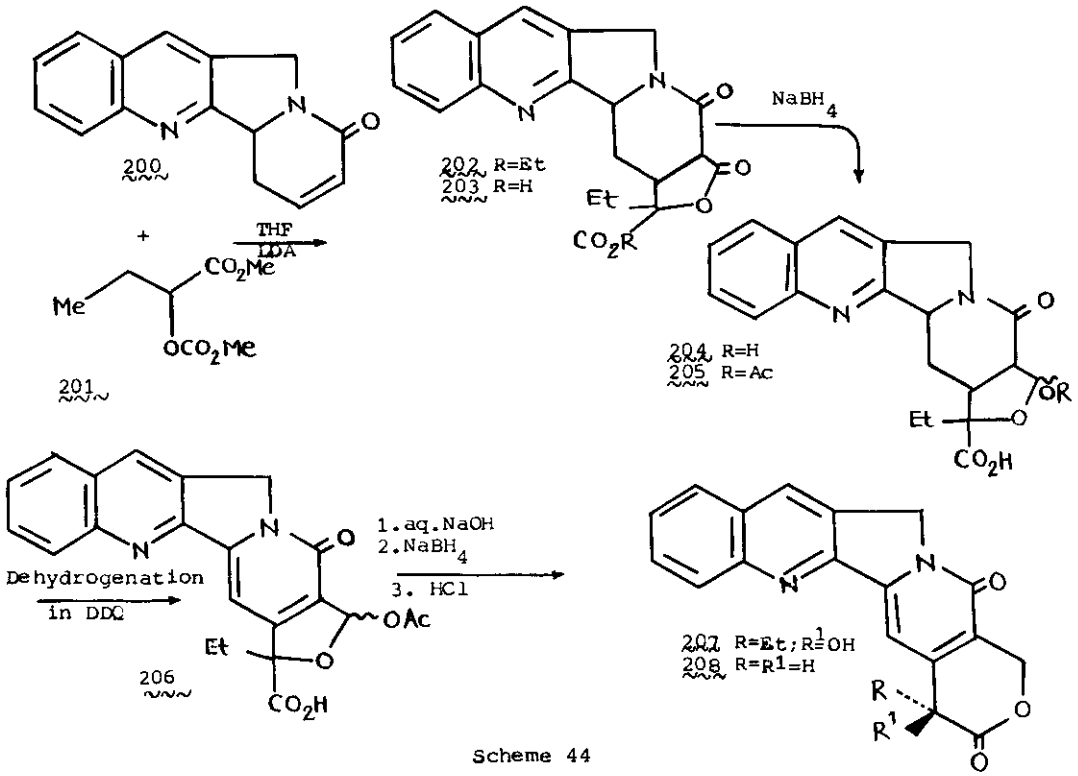
Scheme 43

XIX. UNCLASSIFIED ALKALOID GROUP[103]

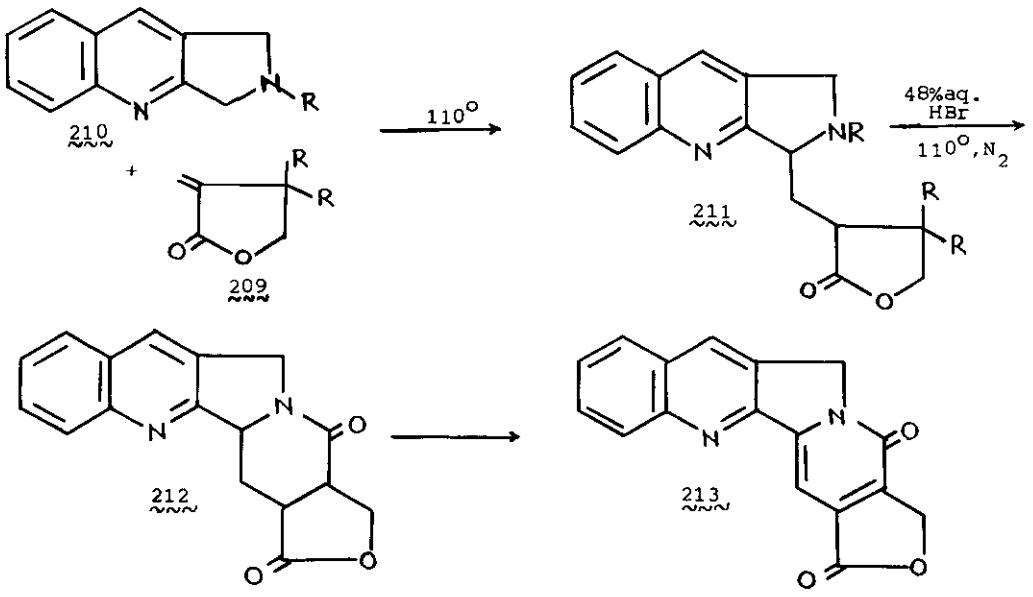
Camptothecin[104], (207) an antitumour alkaloid has been synthesized from lactone (202). The synthesis featured a novel method for the fusion of a γ-lactone ring to a pre-existing conjugated carbonyl system[105]. The lactone (202) on hydrolysis, reduction with sodium borohydride, acetylation and dehydrogenation in dicyanodichloroquinone gave (206) which afforded camptothecin(207) by hydrolysis, reduction with sodium borohydride and acidification (Scheme 44).

α-Methylene-$\beta\beta$-diethoxycarbonyl-γ-butyrolactone[106] (209) has been employed to get an important precursor (213) to camptothecin[107] (207) (Scheme 45).

Several DE and CDE ring analogues of camptothecin(207) have been synthesized from lactones. The lactone (214) was converted to camptothecin analogue(215)

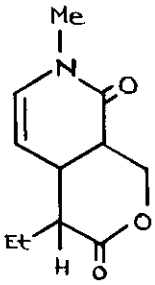


Scheme 44

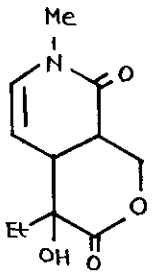


Scheme 45

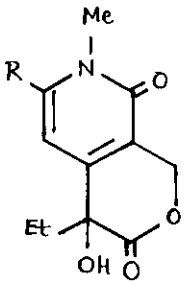
by oxidation with oxygen and alkali in the presence of triethylphosphite[108] (Scheme 46). Four DE (216 a-c) and CDE (217) ring analogues were prepared.



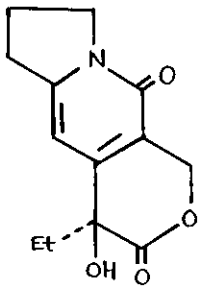
214



215



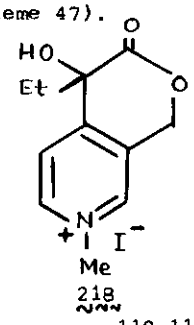
216a R=H
216b R=CO_2Me
216c R=Ph



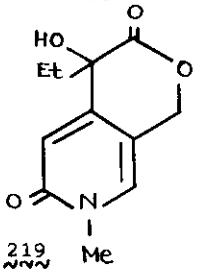
217

Scheme 46

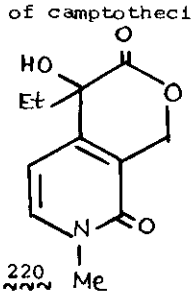
Pyranopyridinone[109] (218) methiodide on oxidation gave pyranopyridinedione (219) rather than the isomeric pyranopyridinedione (220) of camptothecin[109] (207) (Scheme 47).



218



219

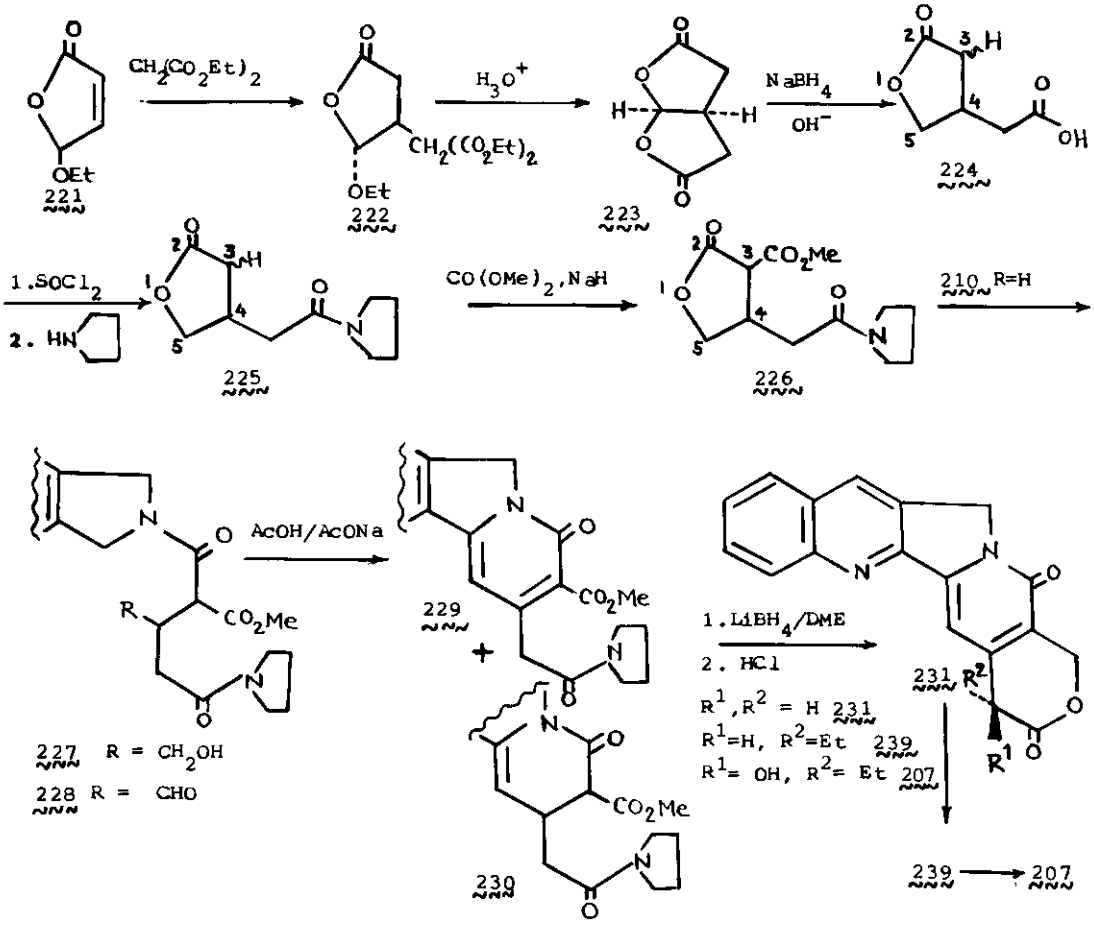


220

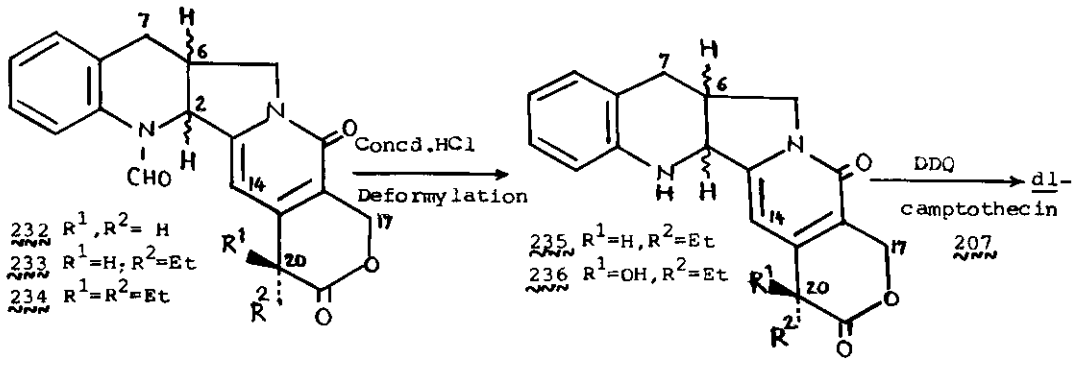
Scheme 47

Ethoxylactone[110-114] (221) was smoothly converted to the trans-adduct (222) by a Michael addition of diethylmalonate. Acid hydrolysis of (222) gave the bis-lactone (223). Reduction of (223) using sodiumborohydride under alkaline conditions gave acid (224) which was converted via its acid chloride to the corresponding pyrrolidinyl amide (225). The amide (225) was methoxycarbonylated to the required butenolide (226) by treatment with sodium hydride and dimethyl-carbonate. Condensation of the butenolide (226) with the pyrroloquinoline[115] (210) gave the corresponding hydroxyamide (227) which could be converted to deethyldeoxycamptothecin[110] (231). Transformation of (231) to deoxycamptothe-cin[116,119] (239) and to camptothecin (207) have been reported by several groups of workers[117] (Scheme 48).

Another synthesis of dl-camptothecin (207) devised by Sugasawa et al involved the lactone[118] (232). This method as outlined in scheme 49 consisted in deformy-lating the crude epimeric mixture of the lactone (233) by treatment with



Scheme 48

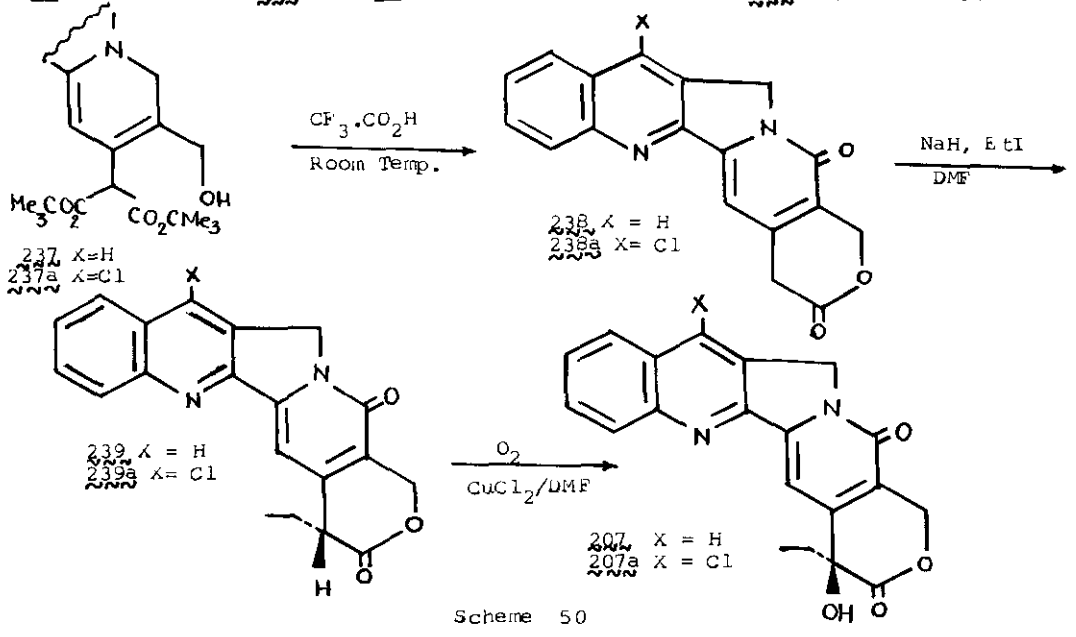


Scheme 49

concentrated hydrochloric acid to give (235) followed by direct oxygenation of (235) with oxygen to afford an epimeric mixture of (236) and dehydrogenation of (236) with dichlorodicyanoquinone to give dl-camptothecin[118] (207). This method, however, suffered from the disadvantage of the unavoidable coformation of the diethyllactone (234) in the ethylation of the lactone (232) to (233) with sodium hydride and ethyl iodide in dimethylformamide (Scheme 49).

Recently, employing an one-step ethylation-oxygenation method[119] Sugasawa et al have improved the yield of monoethyllactone (233) by approximately 1.6 times over the previous method[119].

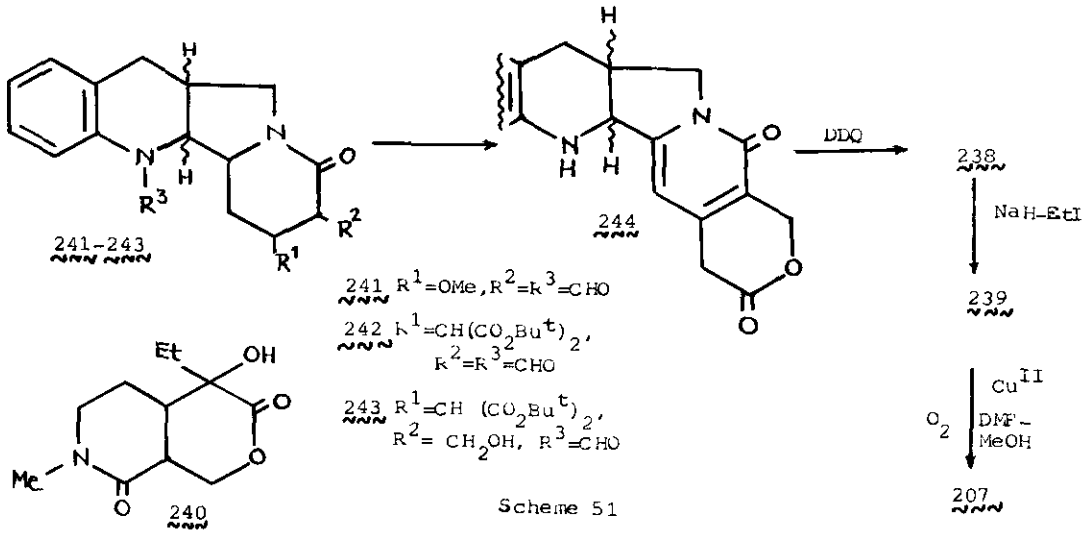
A biogenetically patterned conversion[120] of the lactones (238, 238a) has been exploited for the synthesis of dl-camptothecin (207) and its 7-chloroanalogue (207a). The carbinols (237, 237a) on treatment with trifluoroacetic acid at room temperature afforded the lactones (238, 238a) which on ethylation with sodium hydride-ethyl iodide followed by oxygenation of the resulting deoxy-camptothecins (239, 239a) with oxygen in presence of cupric chloride afforded dl-camptothecin (207) and dl-7-chlorocamptothecin[120] (207a) (Scheme 50).



Scheme 50

In another synthesis of dl-camptothecin (207) a D-E ring analogue, the 4-hydroxypyridine lactone (240) was synthesized[121,122]. The tetracyclic biformyl intermediate[116,122] (241) gave the pyridonemalonate (242) on treatment with di-tert-butylmalonate and sodium hydride in dioxan which on sodium borohydride

reduction gave (243). Treatment of (243) with concentrated hydrochloric acid led to lactone (244) by simultaneous lactone formation and deformylation. Dehydrogenation of (244) with dichlorodicyanoquinone in dioxan gave the lactone (238) which upon ethylation with sodium hydride and ethyl iodide gave dl-deoxy-camptothecin (239). (239) was converted to dl-camptothecin (207) by passing oxygen in presence of triethylamine and copper acetate in dimethylformamide-methanol (Scheme 51).



241-243

241 R^1=OMe, R^2=R^3=CHO

242 R^1=CH$(CO_2Bu^t)_2$, R^2=R^3=CHO

243 R^1=CH $(CO_2Bu^t)_2$, R^2= CH_2OH, R^3=CHO

244

238

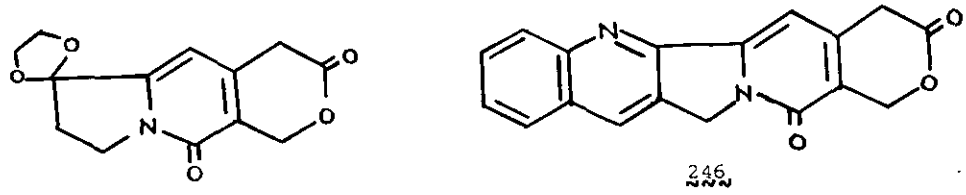
239

207

240

Scheme 51

Yet another synthesis of dl-camptothecin[123] (207) uses the tricyclic lactone (245) prepared by a series of reactions in which most of the steps gave satisfactory yields. Hydrolysis with aqueous oxalic acid and condensation with anthranilaldehyde gave (246) which could be transformed to dl-camptothecin[123] (207) (Scheme 52).



245

246

Scheme 52

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