

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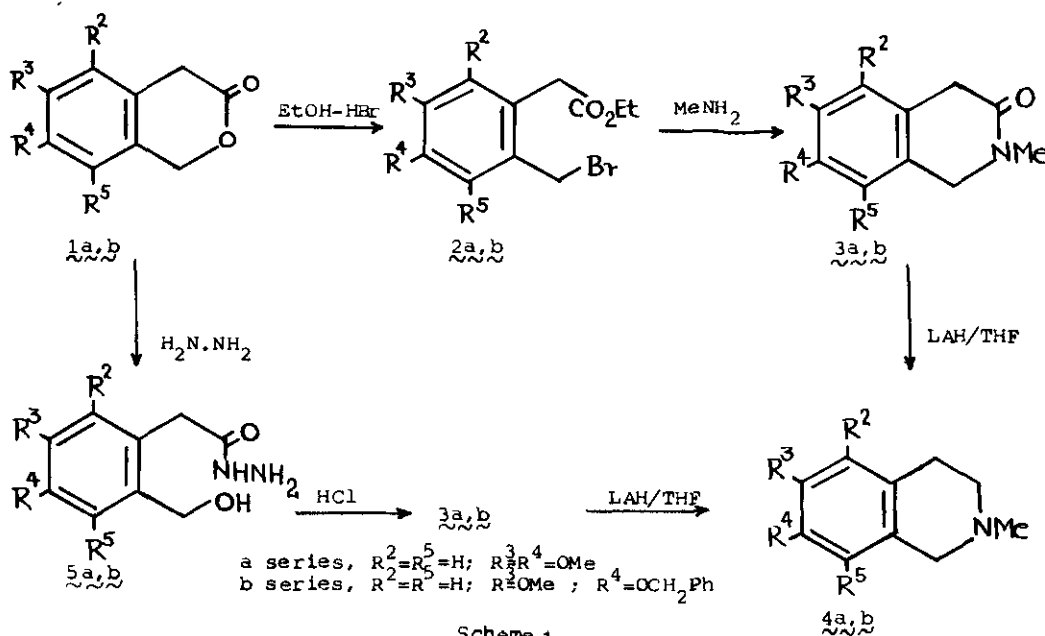
[†] Dedicated to the memory of late Professor Robert B. Woodward
(1917-1979).

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-oxoisquinoline (3a) which on lithium aluminium hydride reduction gave the alkaloid O-methylcorypalline¹ (4a). Likewise, corypalline (4b) was synthesized using the lactone² (1b) (Scheme 1).

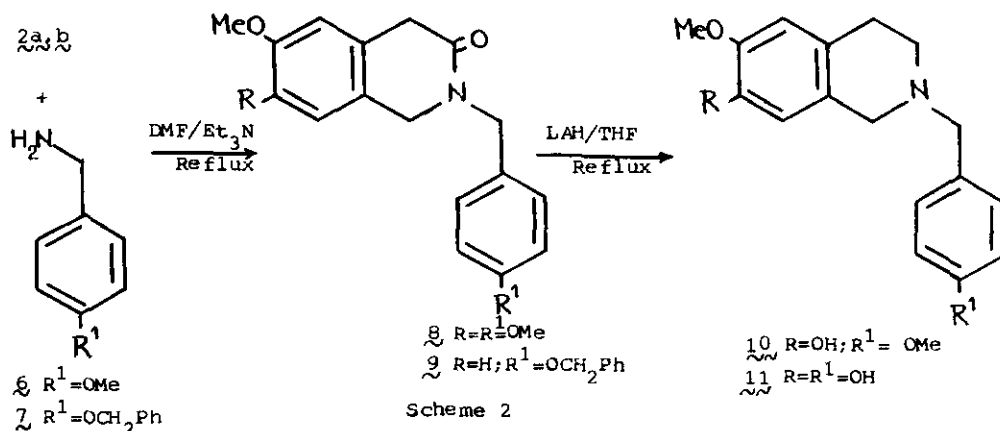


Treatment of the lactones (1a,b) with hydrazine afforded the hydrazides (5a,b) which upon treatment with hydrochloric acid give the lactams (3a,b) which could

be converted to the isoquinolines (4a,b) by lithium aluminium hydride reduction³ (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 Pumariaceae⁴⁻⁶. Condensation of the bromoester (2a) with the benzylamine (6) gave the tricyclic lactam (8) which on reduction with lithium aluminium hydride gave sendaverine⁷ (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 derivative⁸ (9) (Scheme 2).

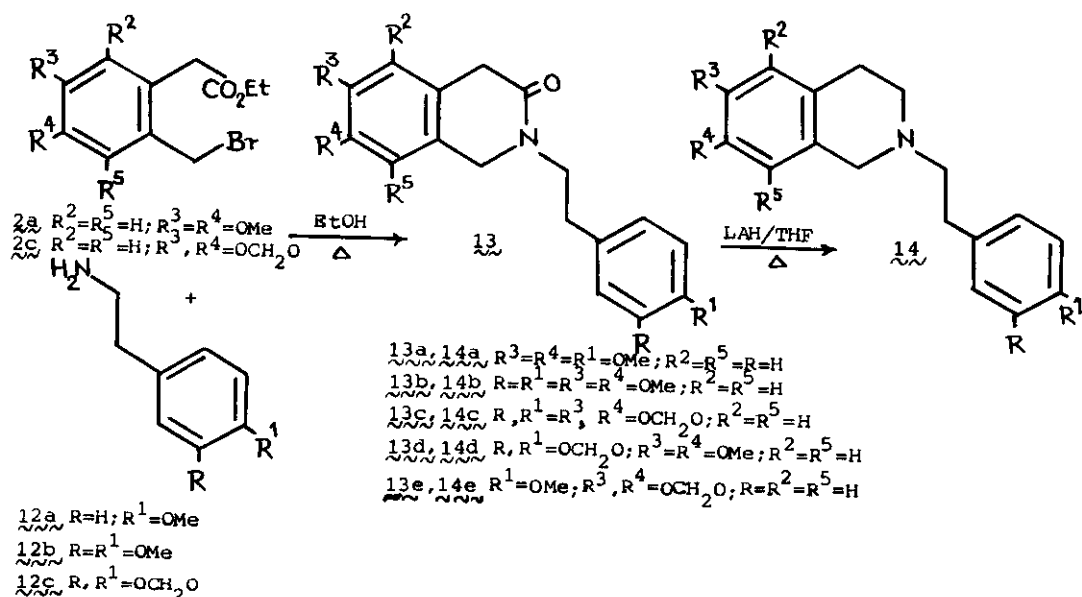


IV. N-PHENETHYL-1,2,3,4-TETRAHYDROISOQUINOLINE GROUP

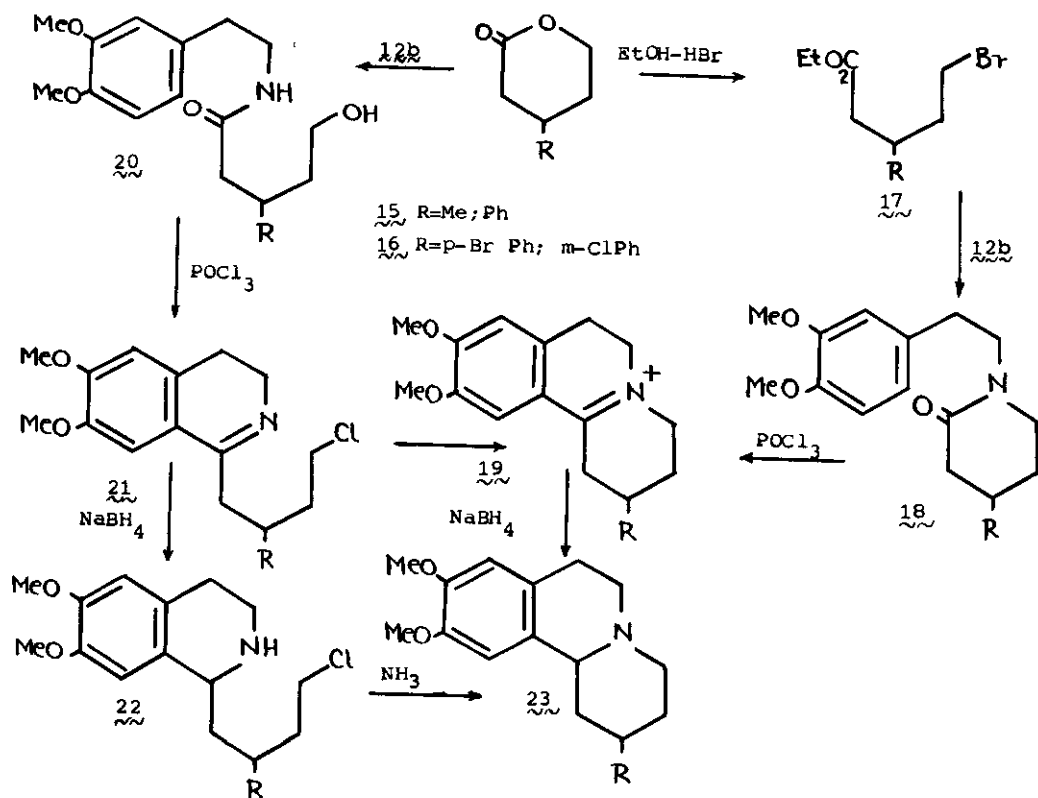
A group of alkaloids of purely synthetic origin has been reported to possess important hypotensive activity⁹. The bromoesters (2a, 2c) prepared from the corresponding 3-isochromanones by dissolution in ethanolic hydrogen bromide on condensation with the phenethylamines (12a-c) gave the lactams (13a-e) which on lithium aluminium hydride reduction gave the corresponding N-phenethylisoquinolines¹⁰ (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 stages¹¹ (Scheme 4). The 3-substituted δ -valerolactones¹² were



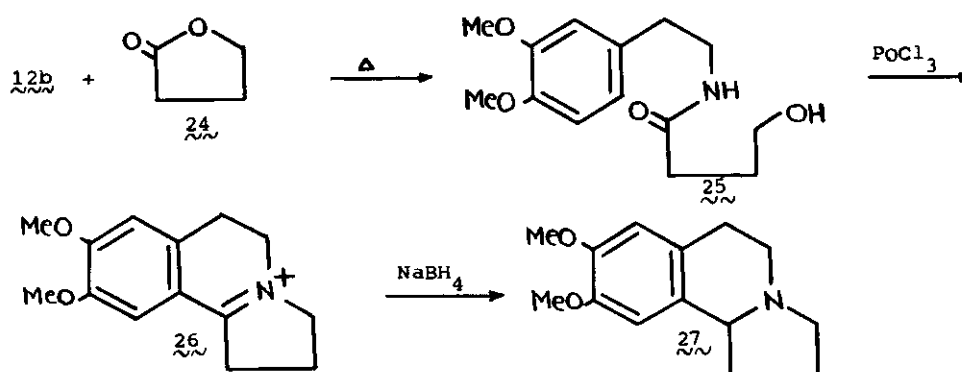
Scheme 3



Scheme 4

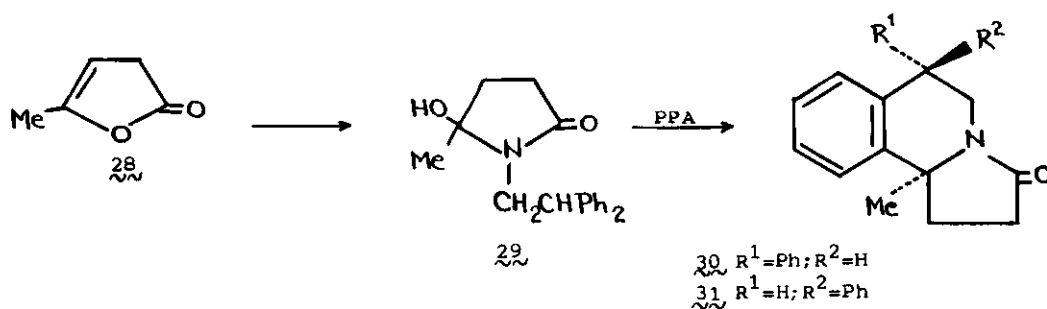
prepared from corresponding glutaric acids by reduction of the carboxylic acid groups^{13,14}. The conversion of the lactones (15,16) to the substituted pyridones (18) required too high a temperature¹⁵, if carried out directly and therefore was performed via bromovalerates¹⁶ (17).

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)indolizine¹⁷ (27) (Scheme 5).



Scheme 5

A recent highly stereoselective synthesis of benzindolizines¹⁸ consisting in iminium ion cyclization begins with condensing δ -angelicalactone¹⁹ (28) with 2,2-diphenylethylamine to get an acyl iminium ion precursor (29) which on polyphosphoric acid cyclization gave chiefly one diastereoisomer¹⁸ (30) (Scheme 6).

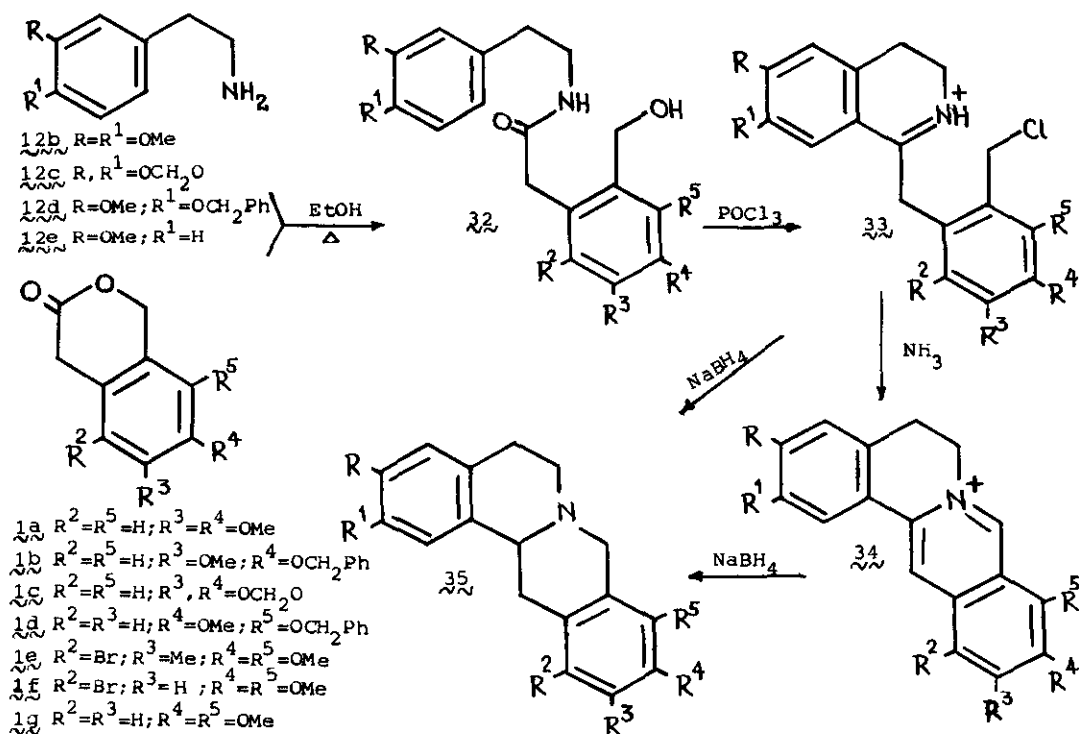


Scheme 6

VI. BERBINE GROUP

The berbine²⁰ alkaloids have been synthesized using the lactones. Condensation

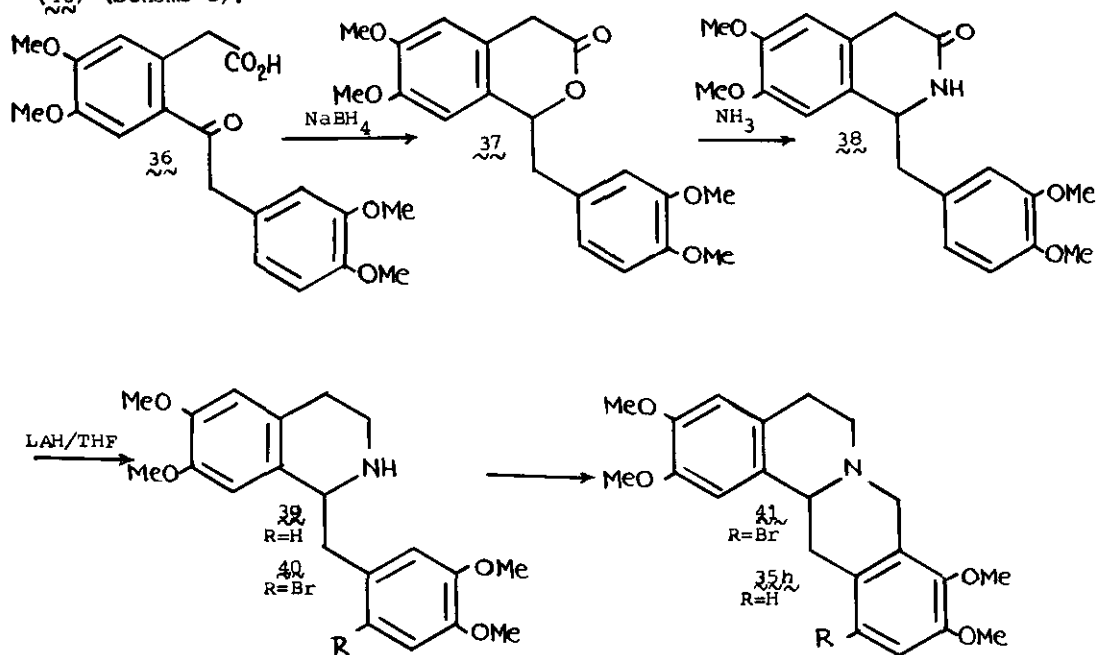
of the 3-isochromanones (1a-f) with the phenethylamines (12b-d) afforded the hydroxymethylphenyl acetamides (32a-f). Phosphoryl chloride cyclization of the amides (32a-f) followed by sodium borohydride reduction afforded the berberines²¹⁻²⁷ (35a-f). Alternatively, treatment of the dihydroisoquinoline salts (33a-f) with ammonia afforded the berberinium salts (34a-f) which on sodium borohydride reduction afforded the berberines (35a-f). This method has also been used to prepare the bromoberberines²⁸ (35e-f) which on reductive debromination afforded the berberines (35g-h) (Scheme 7).



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

Scheme 7

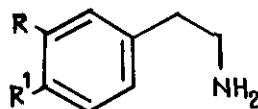
The 1-(3,4-dimethoxybenzyl)-6,7-dimethoxy-3-isochromanone²⁹ (37) prepared from the keto acid³⁰⁻³² (36) has been utilized to prepare the berbine (35h). The lactone (37) on treatment with ammonia afforded (38) which could be converted to dl-tetrahydropalmatine³³ (35h) through the 12-bromotetrahydroisoquinoline³³ (40) (Scheme 8).



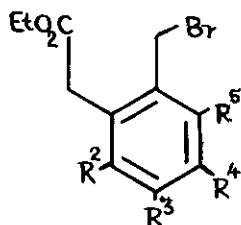
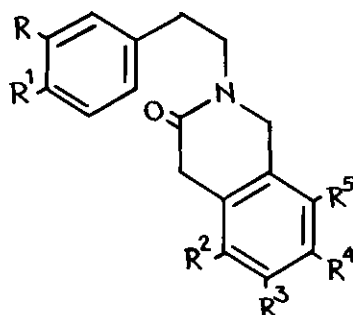
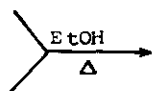
Scheme 8

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 us³⁴⁻³⁹ (Scheme 9).

The 3-isochromanone (37) on treatment with ethanolic hydrogen bromide gave the corresponding bromoester (42) which could be converted to the berbine⁴⁰ (40h)

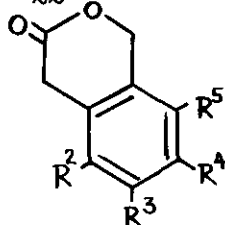


- $\sim\sim\sim$ 12b, R=R¹=OMe
 $\sim\sim\sim$ 12c, R, R¹=OCH₂O
 $\sim\sim\sim$ 12d, R=OMe; R¹=OCH₂Ph
 $\sim\sim\sim$ 12e, R=OMe; R¹=H
 $\sim\sim\sim$ 12f, R=OCH₂Ph; R¹=H



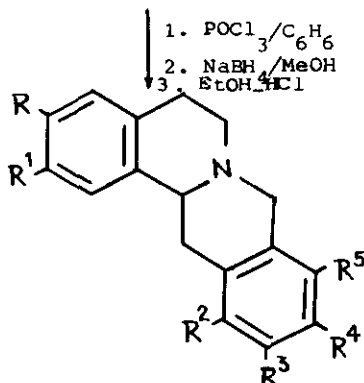
EtOH-HBr

- $\sim\sim\sim$ 2a, R²=R⁵=H; R³=R⁴=OMe
 $\sim\sim\sim$ 2b, R²=R⁵=H; R³=OMe; R⁴=OCH₂Ph
 $\sim\sim\sim$ 2c, R²=R⁵=H; R³, R⁴=OCH₂O
 $\sim\sim\sim$ 2d, R²=R³=H; R⁴=OMe; R⁵=OCH₂Ph
 $\sim\sim\sim$ 2g, R²=R³=H; R⁴=R⁵=OMe
 $\sim\sim\sim$ 2h, R²=R⁴=R⁵=H; R³=OMe



- $\sim\sim$ 1a, R²=R⁵=H; R³=R⁴=OMe
 $\sim\sim$ 1b, R²=R⁵=H; R³=OMe; R⁴=OCH₂Ph
 $\sim\sim$ 1c, R²=R⁵=H; R³, R⁴=OCH₂O
 $\sim\sim$ 1d, R²=R³=H; R⁴=OMe; R⁵=OCH₂Ph
 $\sim\sim$ 1g, R²=R³=H; R⁴=R⁵=OMe
 $\sim\sim$ 1h, R²=R⁴=R⁵=H; R³=OMe

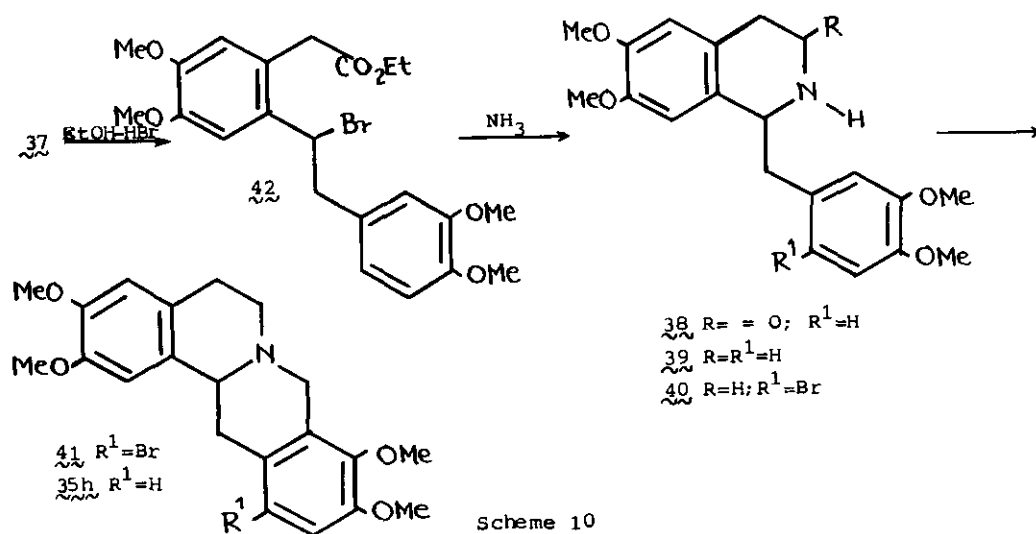
- $\sim\sim\sim$ 13b, R=R¹=R³=R⁴=OMe; R²=R⁵=H
 $\sim\sim\sim$ 13c, R=R³=R⁴=OMe; R¹=OCH₂Ph; R²=R⁵=H
 $\sim\sim\sim$ 13d, R=R⁴=OMe; R¹=R⁵=OCH₂Ph; R²=R³=H
 $\sim\sim\sim$ 13e, R=R¹=OMe; R³, R⁴=OCH₂O; R²=R⁵=H
 $\sim\sim\sim$ 13f, R, R¹=R³, R⁴=OCH₂O; R²=R⁵=H
 $\sim\sim\sim$ 13g, R, R¹=OCH₂O; R⁴, R⁵=OMe; R²=R³=H
 $\sim\sim\sim$ 13h, R=R¹=R⁴=R⁵=OMe; R²=R³=H
 $\sim\sim\sim$ 13i, R=OCH₂Ph; R⁴=R⁵=OMe; R¹=R²=R³=H
 $\sim\sim\sim$ 13j, R¹=R= R⁴=OMe; R³=R⁵=H; R²=H
 $\sim\sim\sim$ 13k, R=R¹=R³=OMe; R²=R⁴=R⁵=H



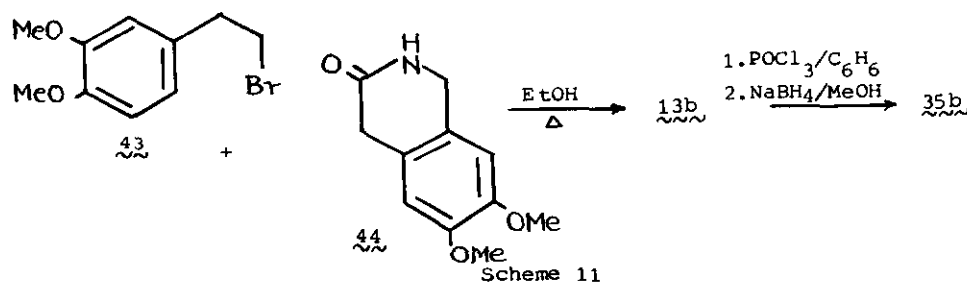
- $\sim\sim\sim$ 35b, R=R¹=R³=R⁴=OMe; R²=R⁵=H
 $\sim\sim\sim$ 35c, R=R³=R⁴=OMe; R¹=OH; R²=R⁵=H
 $\sim\sim\sim$ 35d, R=R⁴=OMe; R¹=R⁵=OH; R²=R³=H
 $\sim\sim\sim$ 35e, R=R¹=OMe; R³, R⁴=OCH₂O; R²=R⁵=H
 $\sim\sim\sim$ 35f, R, R¹=R³, R⁴=OCH₂O; R²=R⁵=H
 $\sim\sim\sim$ 35g, R, R¹=OCH₂O; R⁴=R⁵=OMe; R²=R³=H
 $\sim\sim\sim$ 35h, R=R¹=R⁴=R⁵=OMe; R²=R³=H
 $\sim\sim\sim$ 35i, R=OH; R⁴=R⁵=OMe; R¹=R²=R³=H
 $\sim\sim\sim$ 35j, R¹=R=R⁴=OMe; R²=R³=R⁵=H
 $\sim\sim\sim$ 35k, R=R¹=R³=OMe; R²=R⁴=R⁵=H

Scheme 9

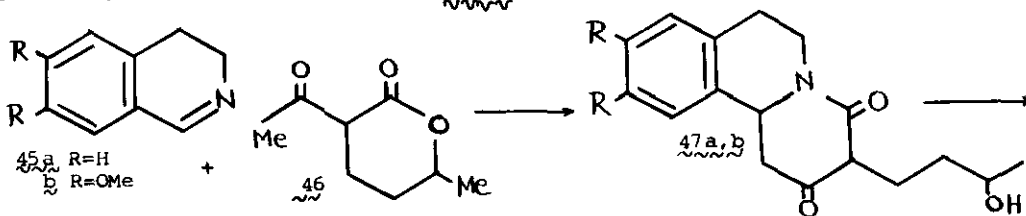
(Scheme 10).

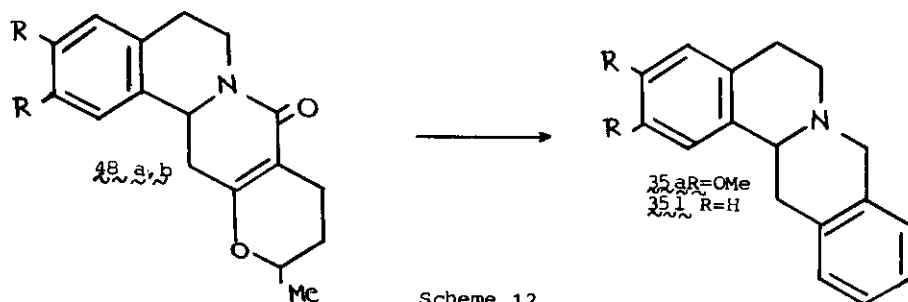


The 3(2H)-isoquinolone (44) prepared from the corresponding 3-isochromanone (1a) has been effectively used to get the berbine (35b). Condensation of the phenethyl bromide (43) with the 3(2H)-isoquinolone (44) gave the lactam (13b) which on phosphoryl chloride cyclization followed by sodium borohydride reduction gave dl-xylopinine⁴¹ (35b) (Scheme 11).



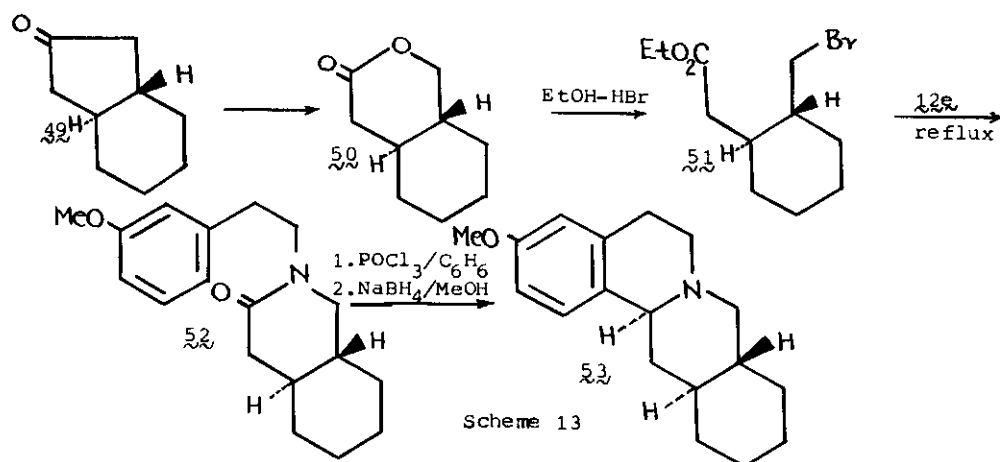
An alternative synthesis of the berbines involved the condensation of the azomethines (45a,b) with acetyl- δ -lactone (46) to get the lactams (47) which could be converted to the berbine (35a,1) in four operations⁴² (Scheme 12).



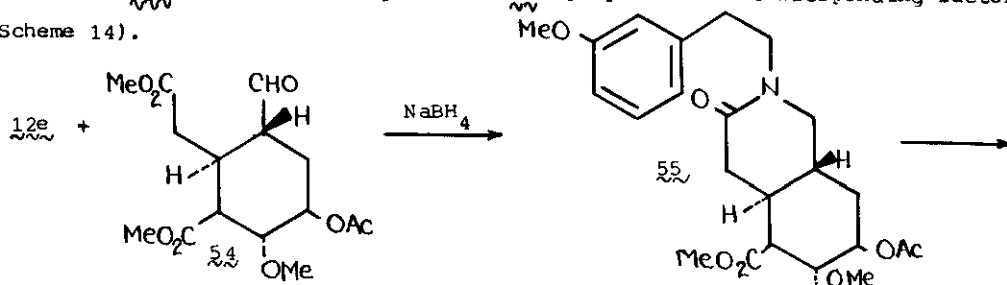


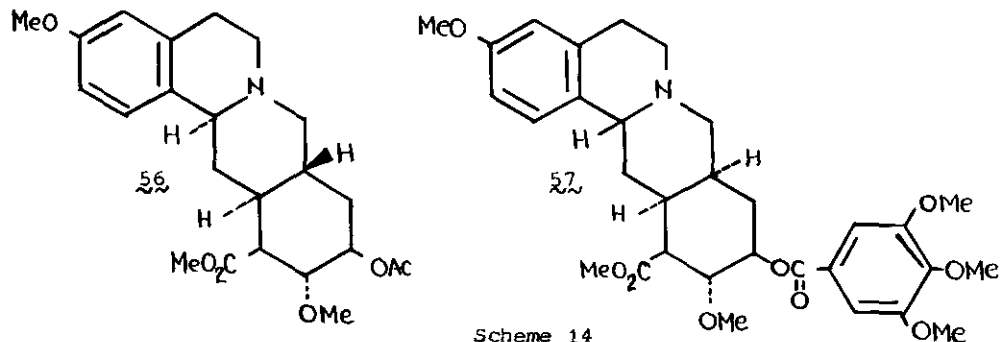
VII. BERBANE, ALLOBERBANE AND EPIALLOBERBANE GROUP

The lactone of dl-trans-2-hydroxymethylhexahydrophenylacetic acid⁴³ (50) prepared by perbenzoic acid oxidation of dl-trans-2-hydrindone⁴⁴ (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 berbane⁹ (53) (Scheme 13).



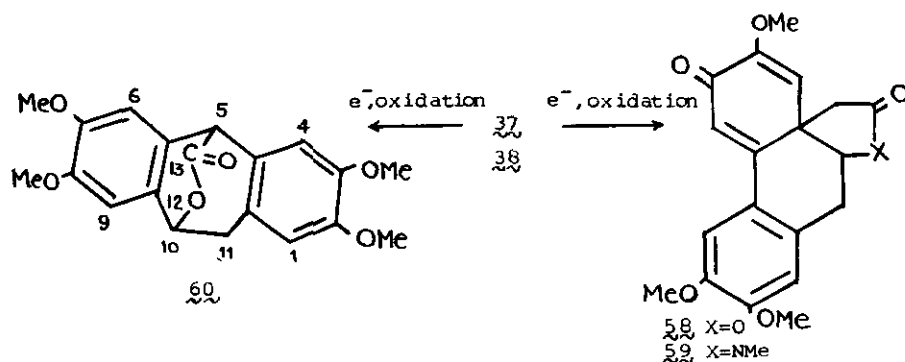
Likewise the alloberbane (56) and epialloberbane (57) were prepared condensing the amine (12e) with the aldehydoester (54) prepared from corresponding lactone⁹ (Scheme 14).





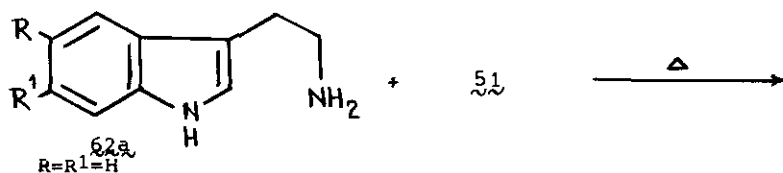
VIII. PHENANTHRENE AND ISOPAVINE GROUP

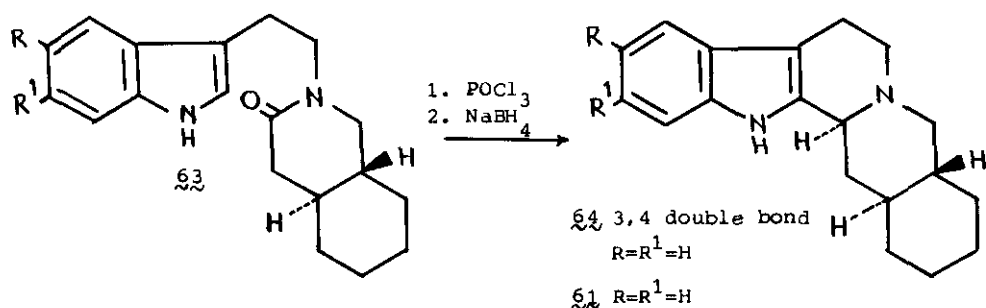
The lactone (37) on anodic oxidation in dichloromethane-trifluoroacetic acid with tetrabutylammonium tetrafluoroborate as a supporting electrolyte gave epoxyethanophenanthrene²⁹ (58). The same spirodienone (58) was isolated when (37) was oxidized with vanadium oxyfluoride using same solvents. An analogues dienone (59) was prepared from lactam (38) using same oxidants. Electrode oxidation of (37) in acetonitrile with quaternary ammonium salts gave a lactonic analogue of the alkaloid isopavine²⁹ (60) (Scheme 15).



IX. YOHIMBANE AND HEXADEHYDROYOHIMBANE GROUP

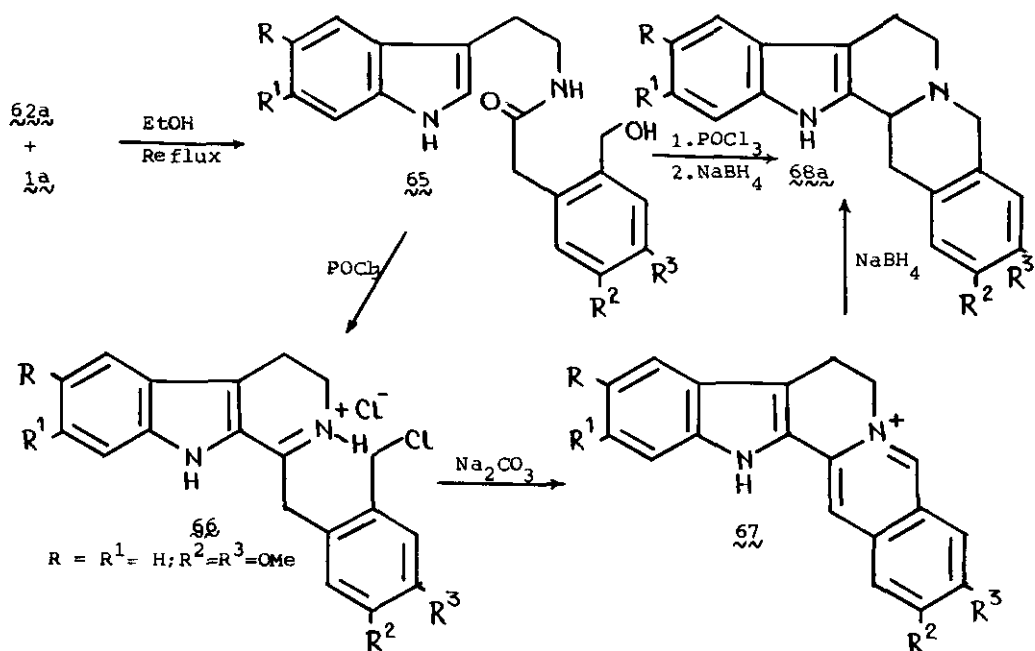
A stereospecific synthesis of *dl*-yohimbane (61) begins with the condensation of the bromoester (51) with tryptamine^{43, 45} (62a) (Scheme 16).





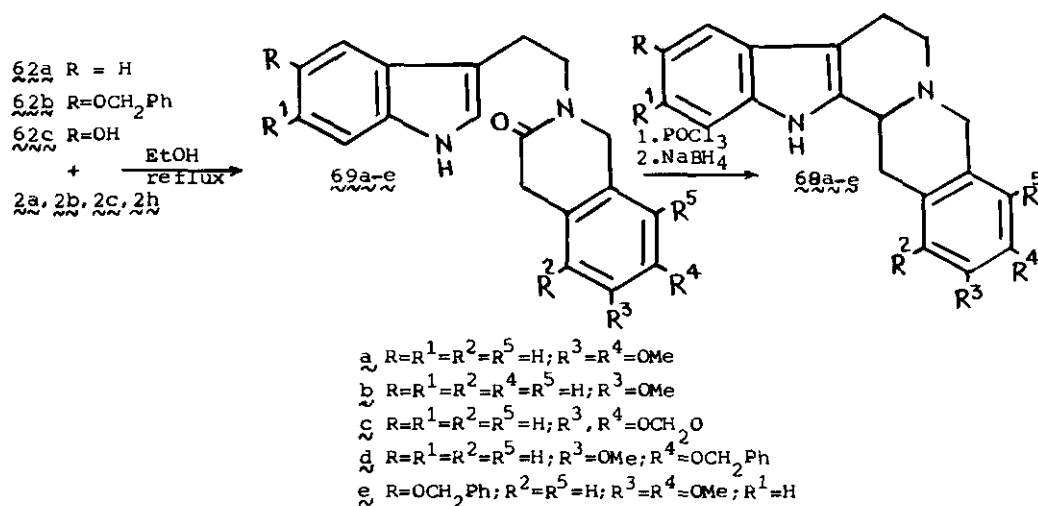
Scheme 16

The yohimbane synthesis has also been accomplished using 3-isochromanones and their derivatives⁴⁶⁻⁴⁸. Condensation of tryptamine (62a) with 3-isochromanone (1a) afforded the phenylacetamide (65) which on phosphoryl chloride cyclization followed by sodium borohydride reduction gave the hexadehydro-yohimbane (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 sulphur⁴⁹ and oxygen⁵⁰ containing analogues of yohimbane (68a) have also been prepared.



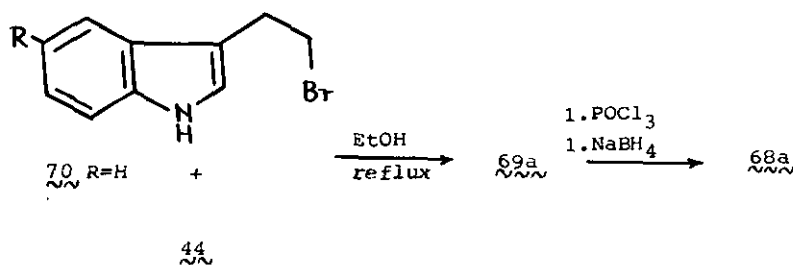
Scheme 17

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).



Scheme 18

Another approach to the yohimbane skeleton involved the condensation of the indolyethyl bromide (70) with 3(2H)-isoquinolone (44) prepared from corresponding 3-isochromanone (1a). The resulting tetracyclic lactam (69a) could be converted to the hexadehydroyohimbane⁵⁴ (68a) (Scheme 19).

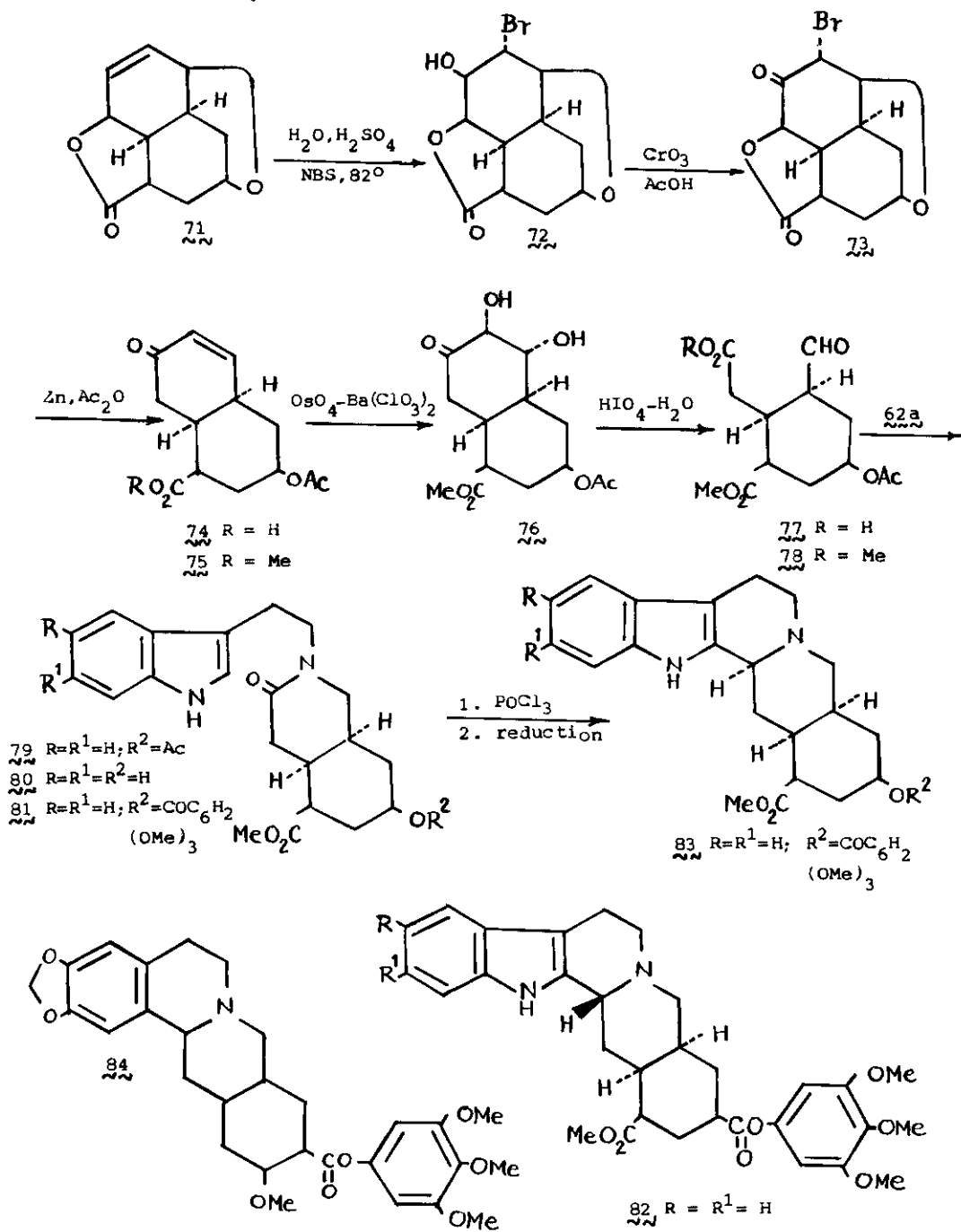


Scheme 19

X. DESERPIDINE, ISODESERPIDINE AND DESPYRROLODESERPIDINE GROUP

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

Isodeserpidine⁵⁵ (83) (Scheme 20).

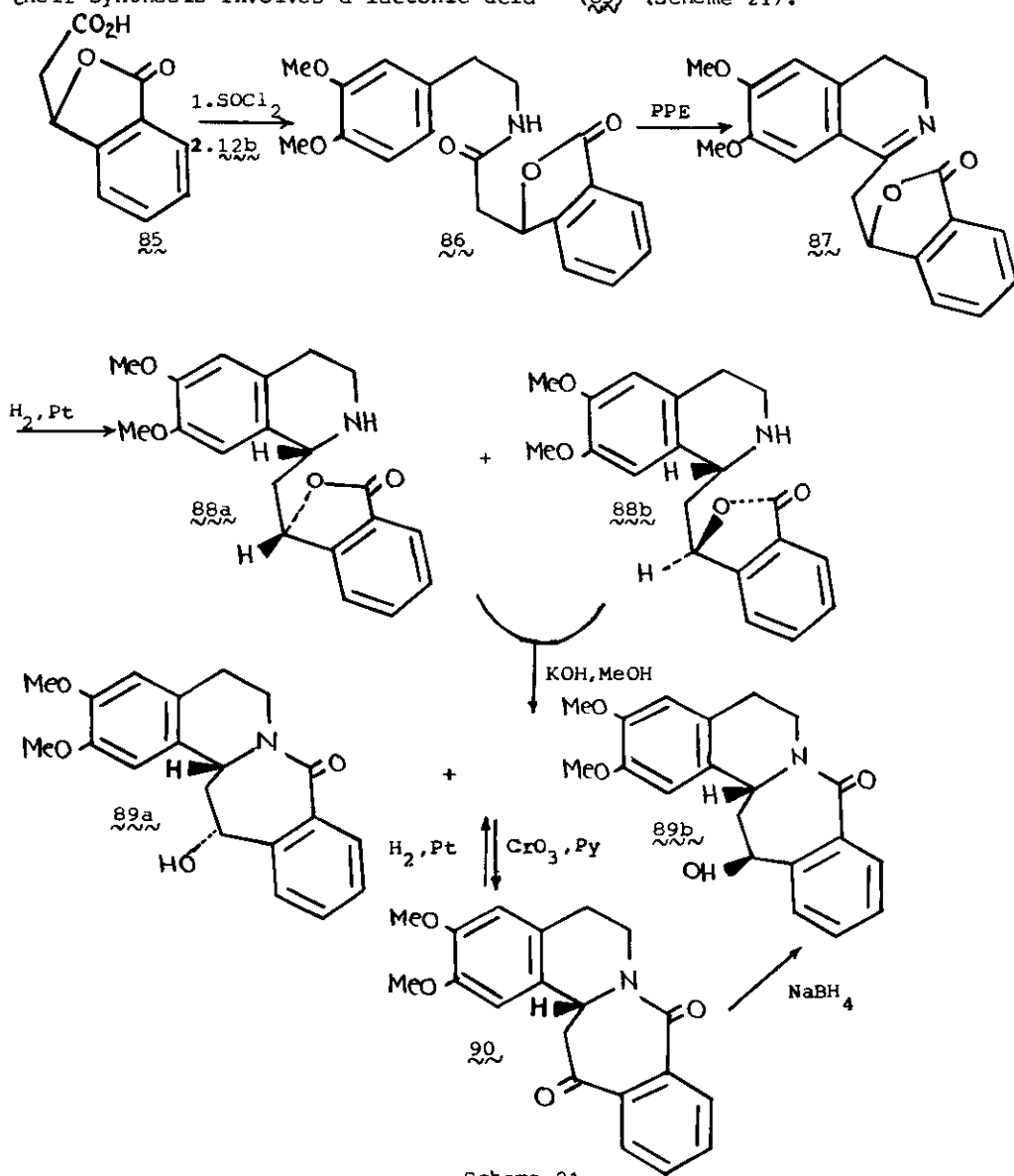


Scheme 20

dl-10,11-Methylenedioxydepyrrolodeserpidine⁵⁶ (84) has been prepared from the woodward's methyl-2- β -carbomethoxy-3 α -methoxy-4-acetoxy-6 β -formylcyclohexyl-1 β -acetate and phenethylamine⁵⁶ (12c).

XI. HOMOPROTOBERBERINE GROUP

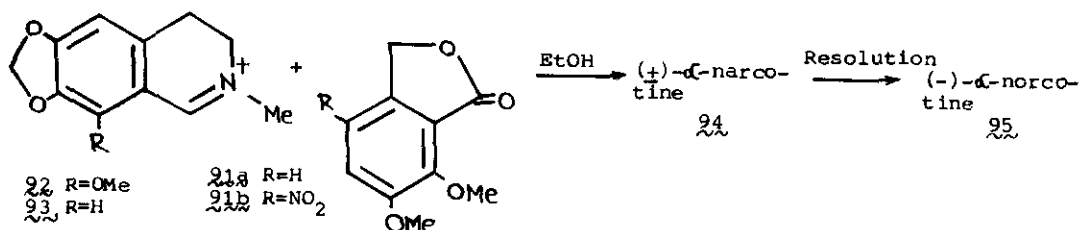
The homoprotoberberines⁵⁷ are yet to be discovered in plants. A scheme for their synthesis involves a lactonic acid⁵⁸ (85) (Scheme 21).



Scheme 21

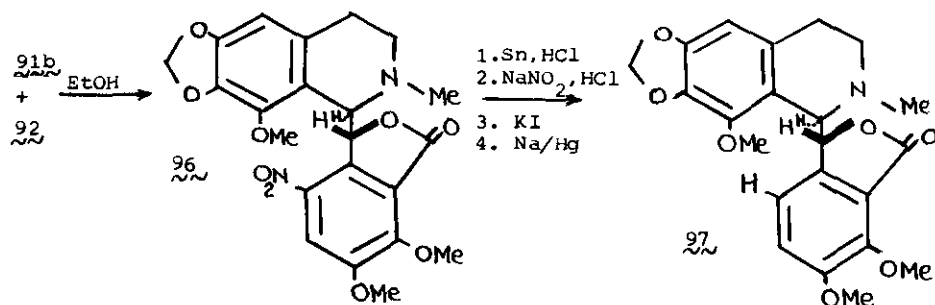
XII. PHTHALIDE ISOQUINOLINE⁵⁹ GROUP

(-)- α -Narcotine (95) has been synthesized using meconine⁶⁰ (91a) (Scheme 22).



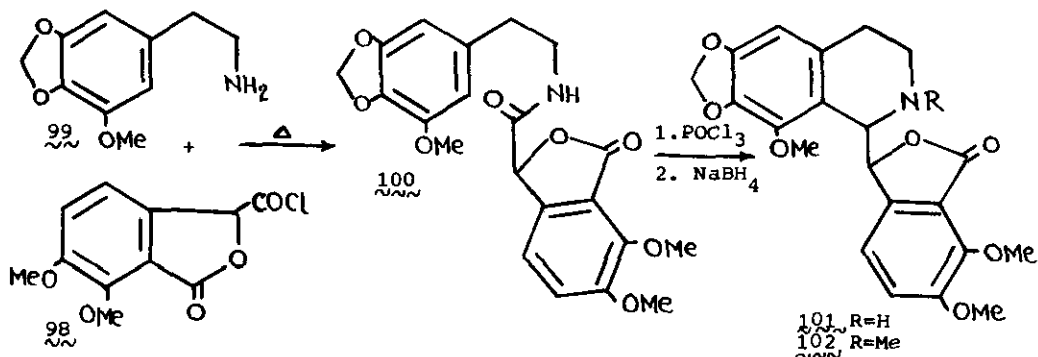
Scheme 22

Hope and Robinson synthesized $(\pm)$ - β -narcotine (97) starting from condensation of cotarnine (92) with nitromeconine⁶¹ (91b, R = NO₂) (Scheme 23).



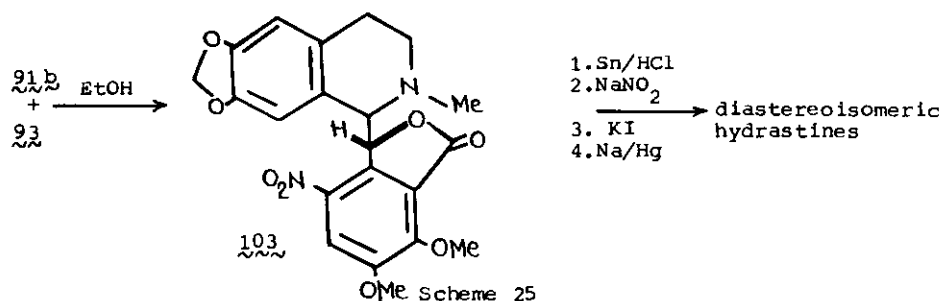
Scheme 23

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).

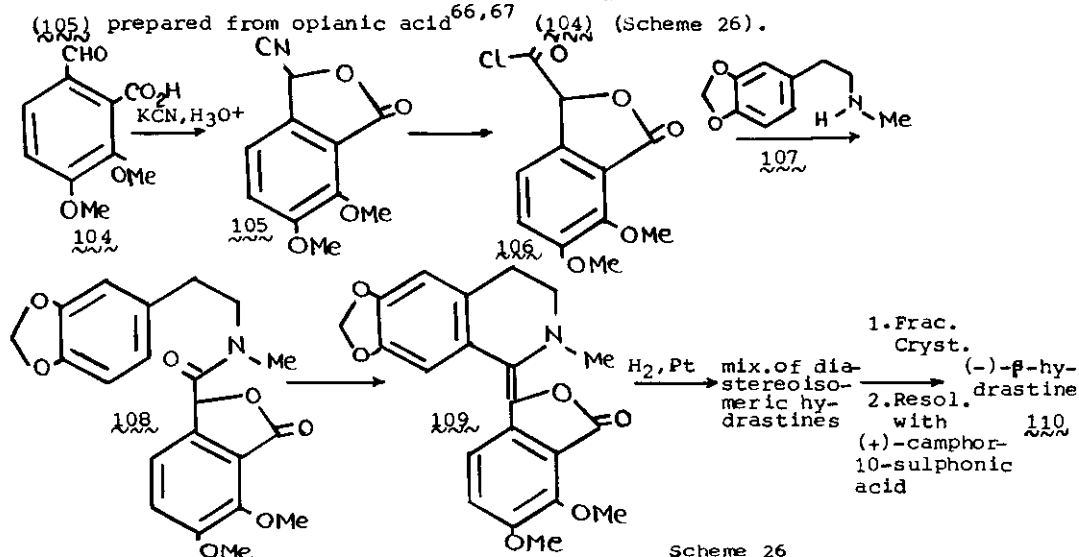


Scheme 24

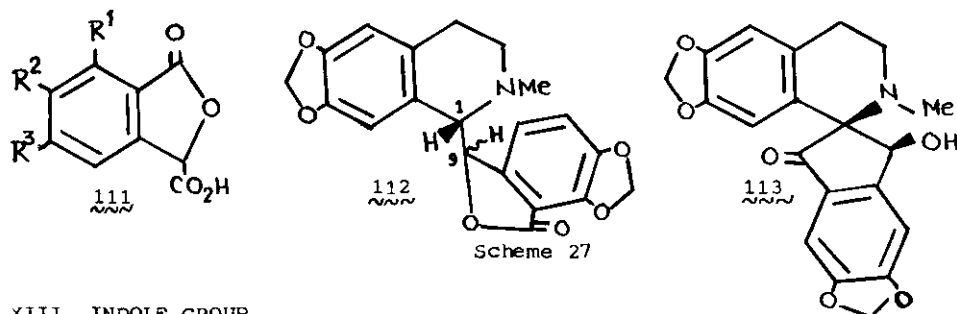
A parallel synthesis of hydrastines has also been achieved^{64,65} (Scheme 25).



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



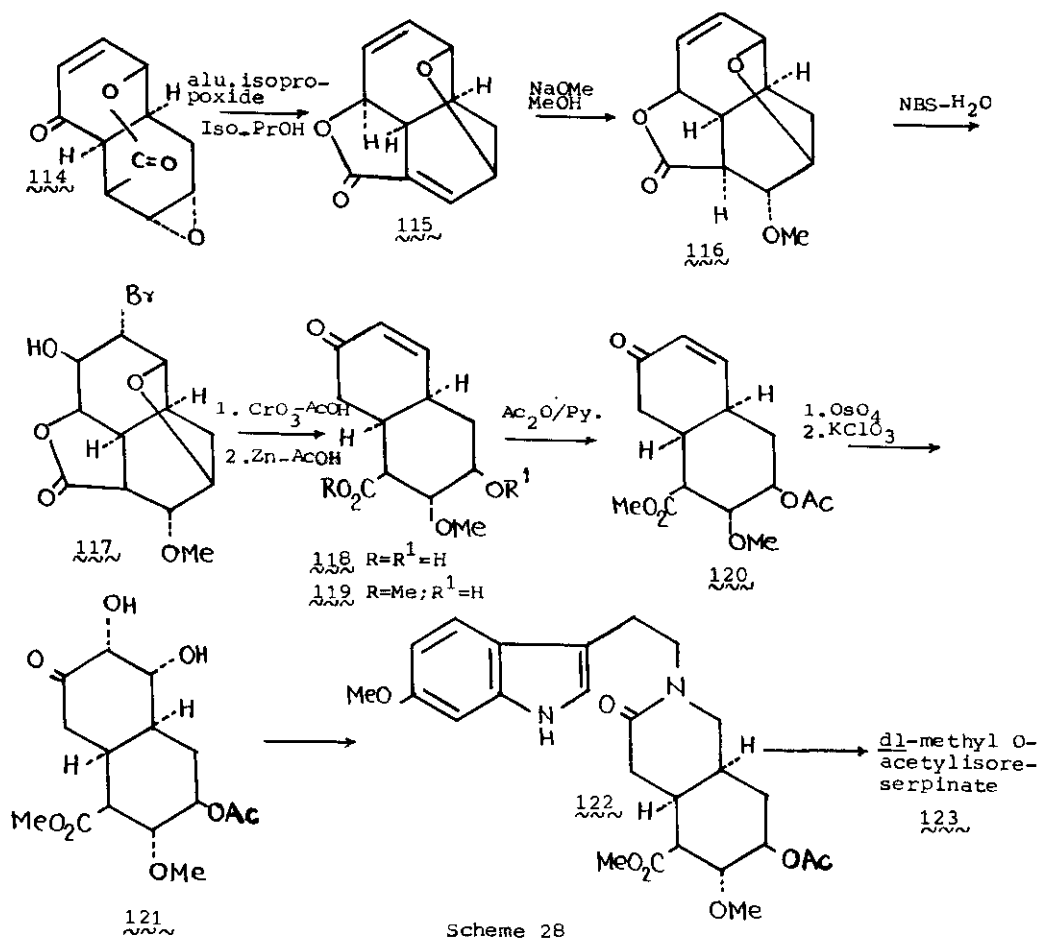
Phthalide- α -carboxylic acid (111) has also found application in the synthesis of the alkaloids adlumidine (112) and corydaine⁶⁸ (113) (Scheme 27).



XIII. INDOLE GROUP

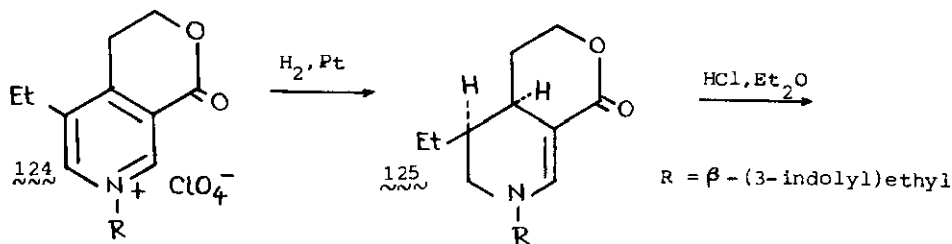
Woodward *et al* synthesized reserpine (124) employing the lactone (114). The lactone (114) on successive treatment with aluminium isopropoxide and sodium

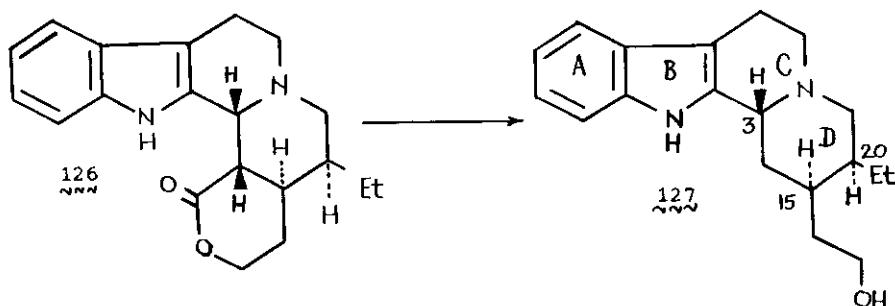
methoxide gave the lactone⁶⁹ (116), the key intermediate which contained all five asymmetric carbon atoms of ring E of reserpine (124) properly oriented. Successive treatments of lactone (116) gave dl-methyl-o-acetylserpinate⁷⁰ (123) (Scheme 28).



Scheme 28

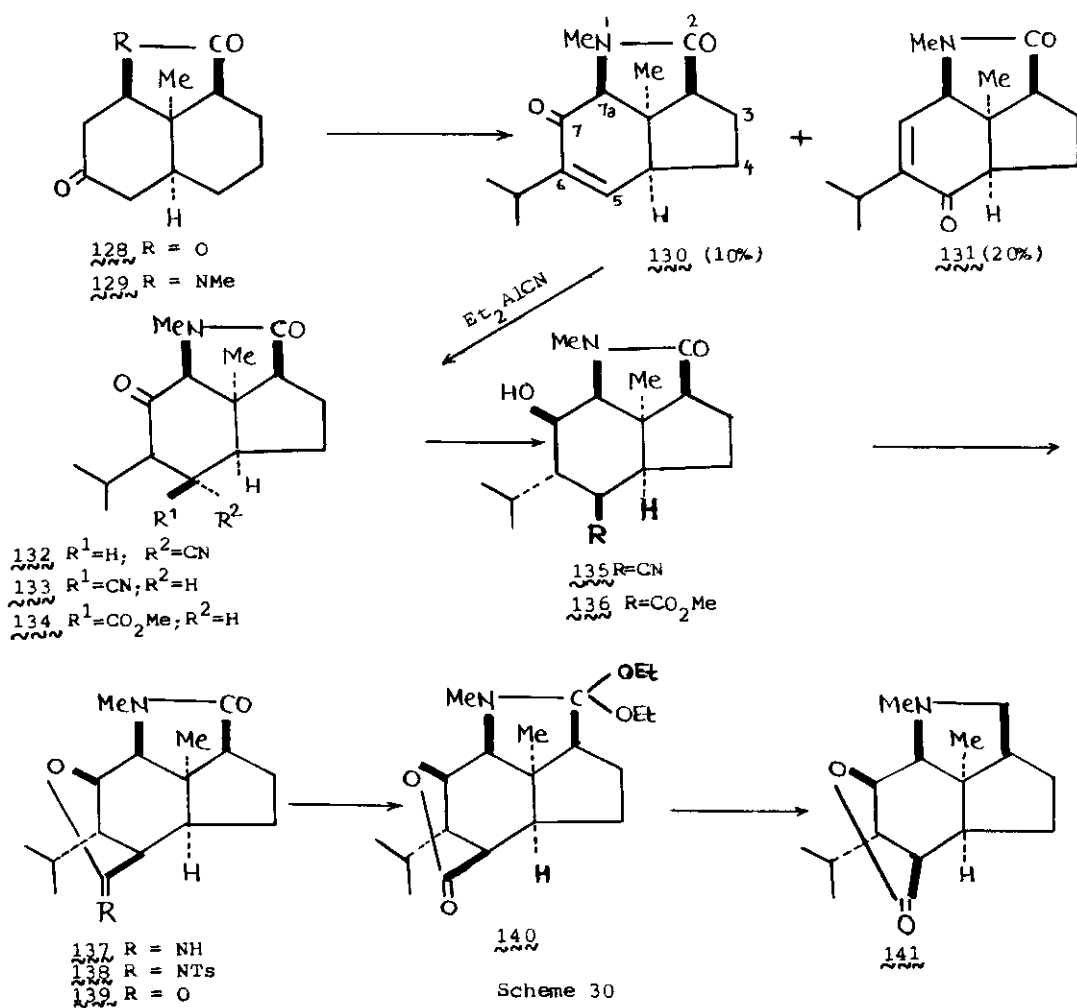
A synthesis of alkaloid dl-corynantheidol^{71,72} (127) utilizes the pyridine lactone^{71,72} (124) (Scheme 29).





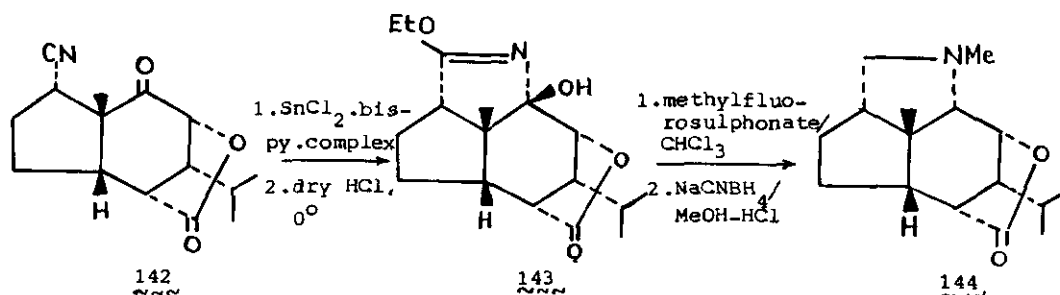
Scheme 29

Dendrobine⁷³ (141), a sesquiterpene alkaloid from *Dendrobium nobile* L. having a picrotoxane skeleton has been synthesized from the lactone^{74,75} (128) (Scheme 30).



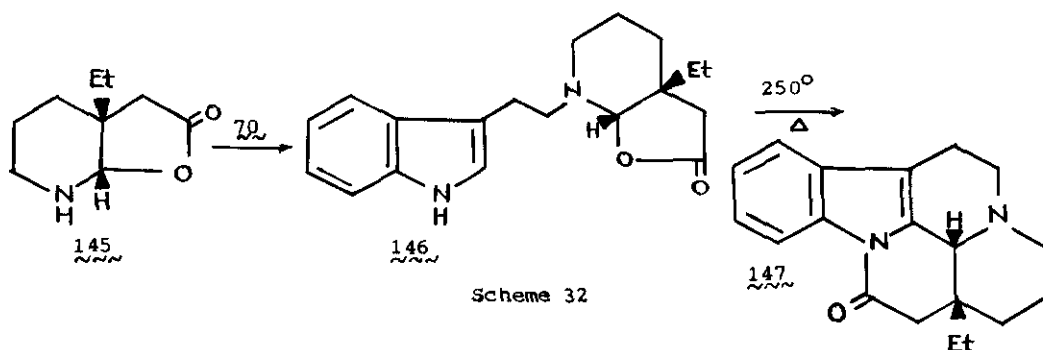
Scheme 30

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



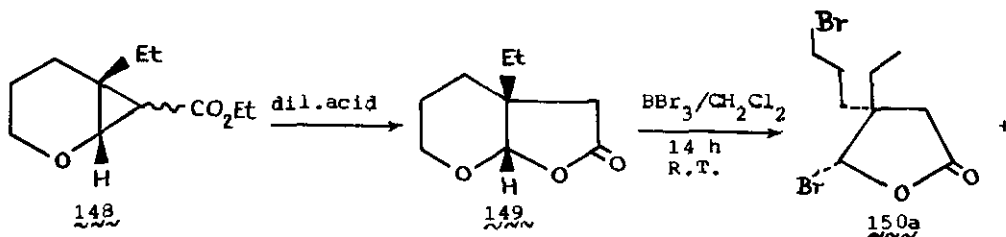
Scheme 31

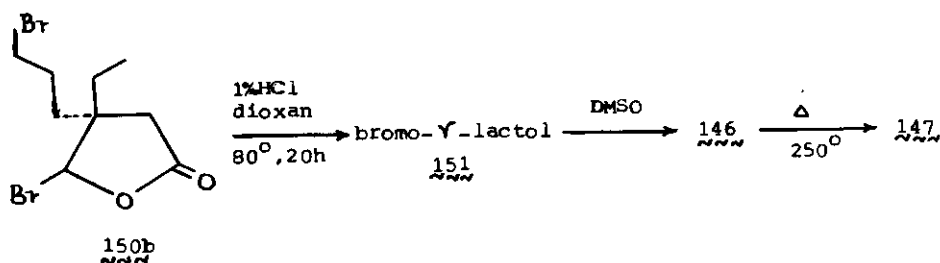
A short synthesis of eburnamonine⁷⁷ (147) has been achieved from the carbinolamine- γ -lactone (145). N-alkylation of the lactone (145) with tryptophyl bromide (70) gave the lactone (146). Thermolysis of (146) yielded *dl*-eburnamonine⁷⁸ (147) (Scheme 32).



Scheme 32

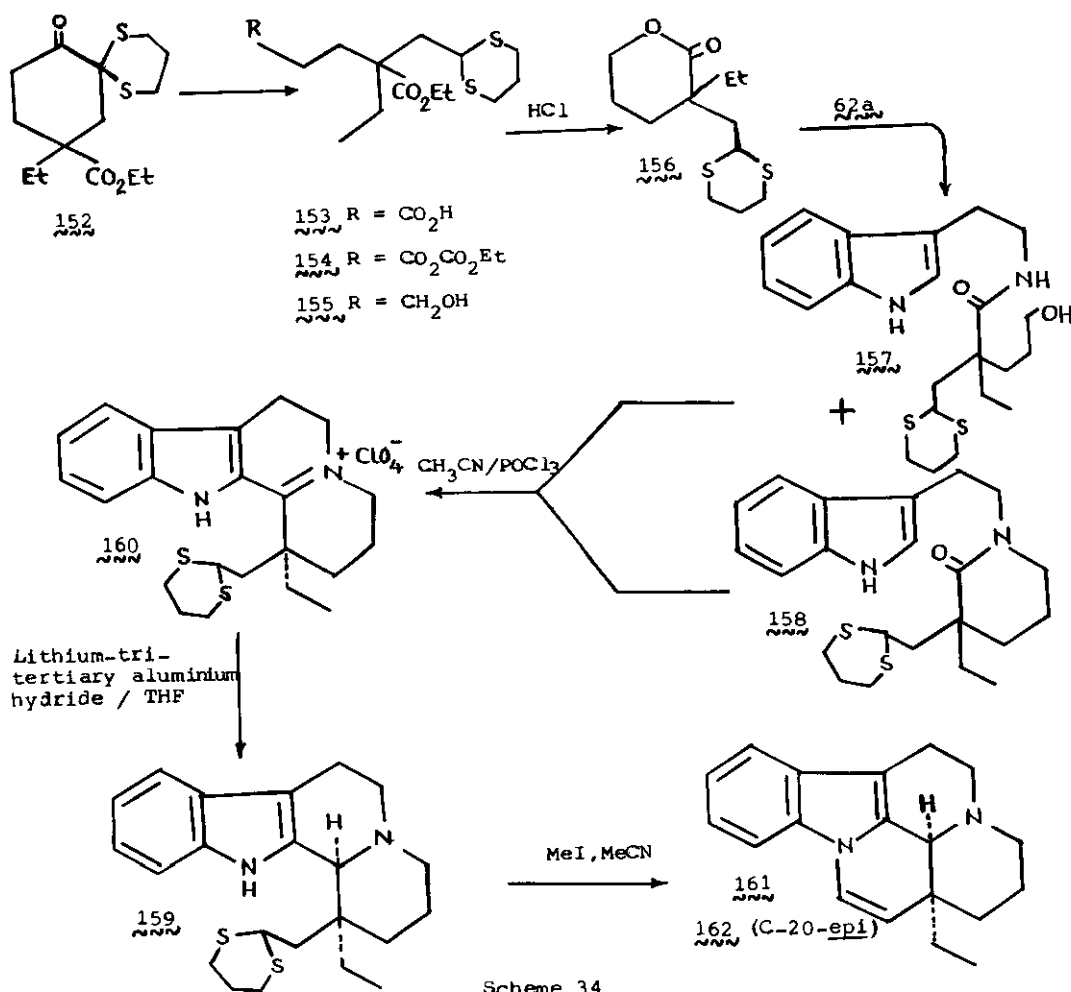
Alternatively, the ester (148) on acid hydrolysis gave the lactone (149) which on bromination with borontribromide in methylenedichloride gave a mixture of two dibromides (150a,b). The dibromides on treatment with dilute hydrochloric acid in dioxan gave a bromo- γ -lactol (151) which reacted with tryptamine to give the lactone (146) which was pyrolysed to eburnamonine⁷⁸ (147) (Scheme 33).





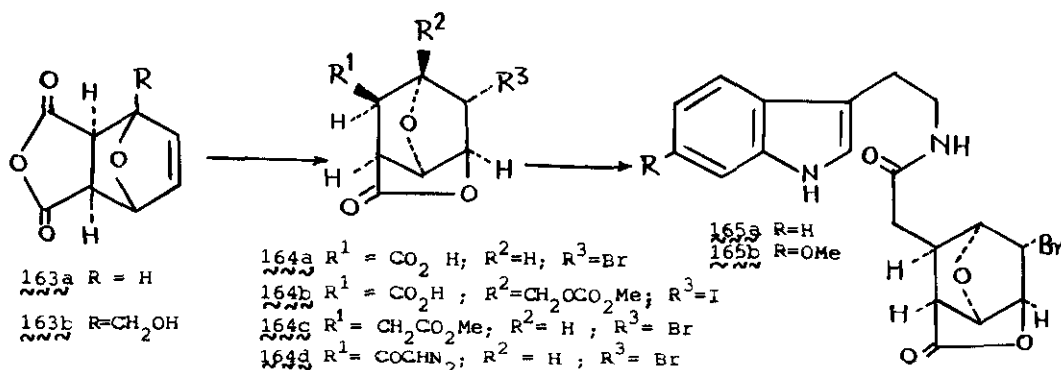
Scheme 33

The C-9 lactone (156) prepared from the cyclic dithioacetal⁷⁹ (152) in five steps consisting of ring cleavage, ethoxycarbonylation, reduction and cyclization has been used to synthesize *dl*-eburunamenine (161) and *epi*eburunamenine⁸⁰ (162) (Scheme 34).



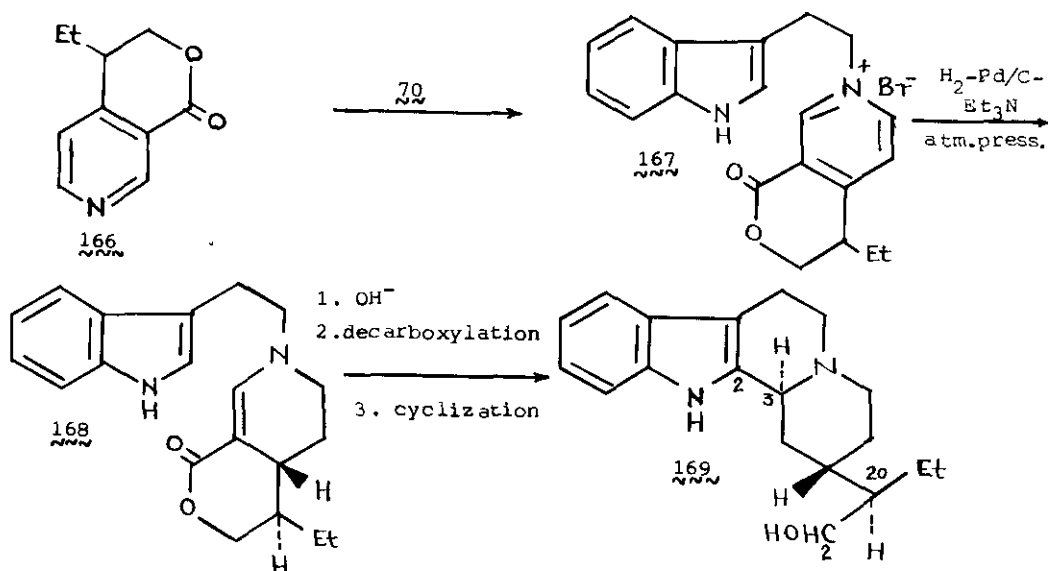
Scheme 34

an approach to skeleton of Rauwolfia alkaloids⁸¹ involves lactonic intermediates. The hydrolysis of the adducts (163a,b) followed by halolactonization^{81a,b} gave (164a-d). The Arndt-Eistert reaction of (164a) ($R^1 = \text{CO}_2\text{H}$, $R^2 = \text{H}$, $R^3 = \text{Br}$) gave (164c). The diazoketone (164d) was condensed with tryptamine (62a) and 6-methoxytryptamine (62b) to give (165)⁸¹ (Scheme 35).



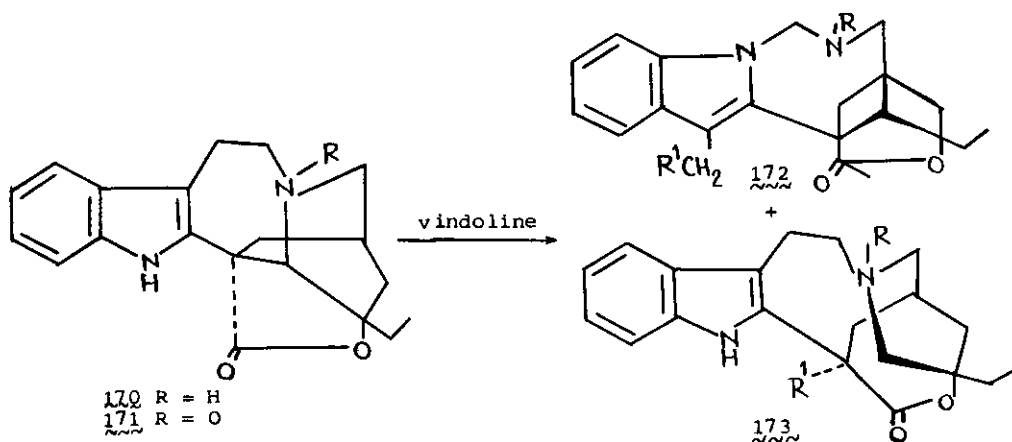
Scheme 35

A general method of synthesis of the indole alkaloids uses the lactone (166) which could be converted in three steps to an antirrhine derivative⁸² (169) (Scheme 36).



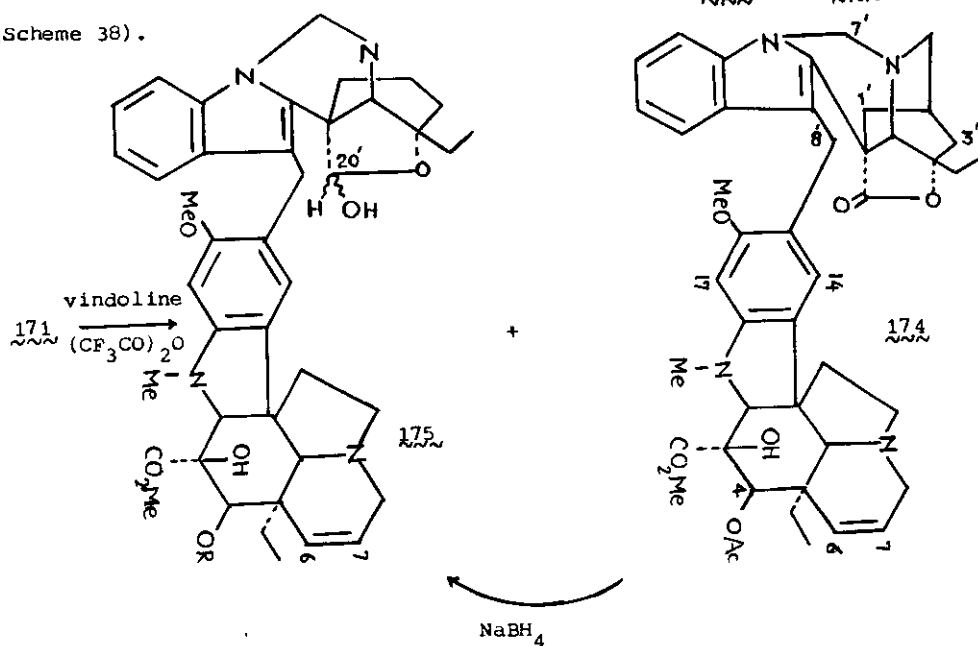
Scheme 36

Catharanthine lactone⁸³ (170) has been coupled with vindoline to get derivatives of the type (172) and (173)⁸³ (Scheme 37).



Scheme 37

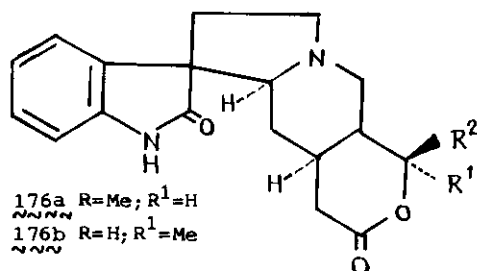
N-oxide derivative of catharanthine lactone (171; R=O) has been coupled with vindoline to provide the rearranged dimeric products (174) and (175)⁸⁴⁻⁸⁶ (Scheme 38).



Scheme 38

XIV. SPIROOXINDOLE GROUP

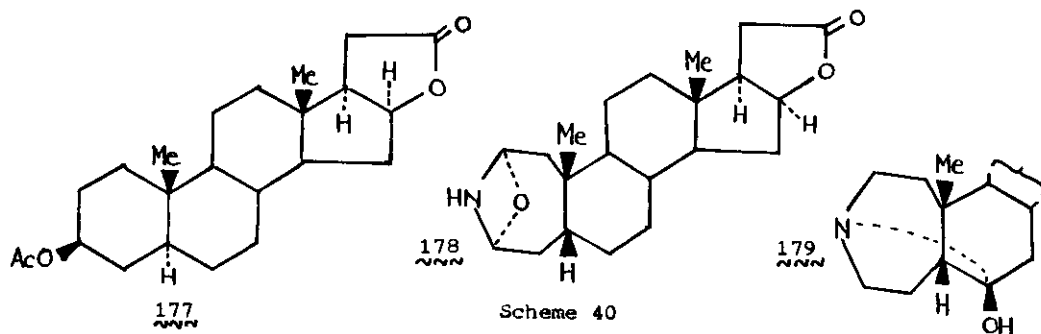
The spirooxindole alkaloids dl-formosanine, dl-isoformosanine have been prepared from lactonic intermediates (176a) and dl-mitraphylline and dl-iso-mitraphylline from the lactone⁸⁷ (176b) (Scheme 39).



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 3 β , 16 β -diacetoxyandrost-5-en-17-one with bromomethylacetate and subsequent dehydration and hydrogenation gave methyl 3 β , 16 β -diacetoxy-5 α -pregnan-21-oate which was cyclized in methanol containing aqueous alkali to give lactone⁸⁸ (177) (Scheme 40).

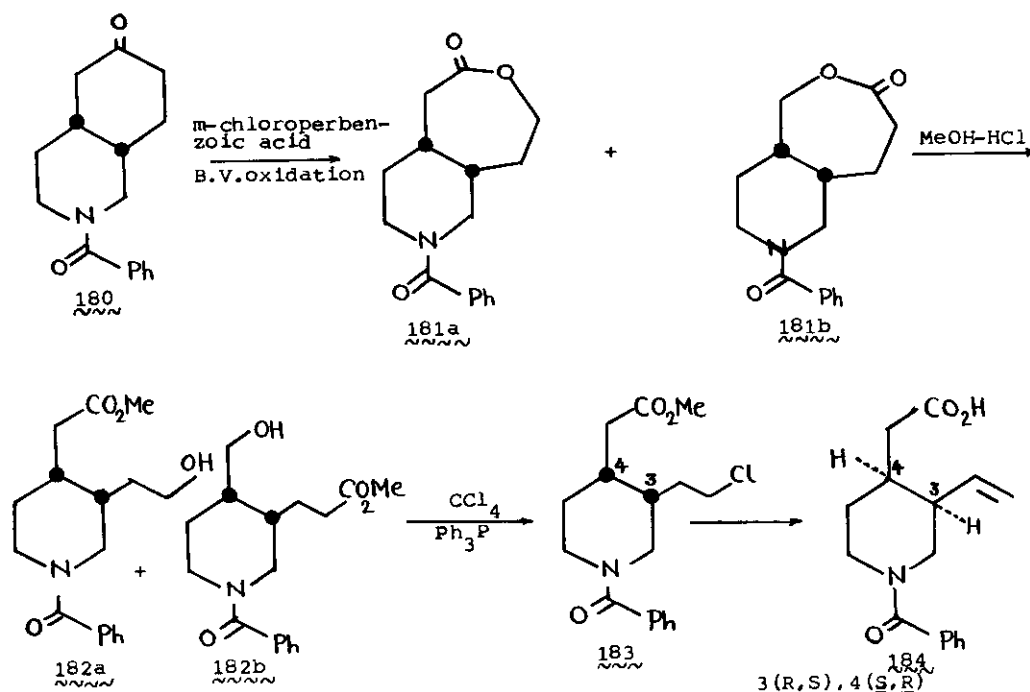


Scheme 40

XVI. QUINUCLIDINE GROUP

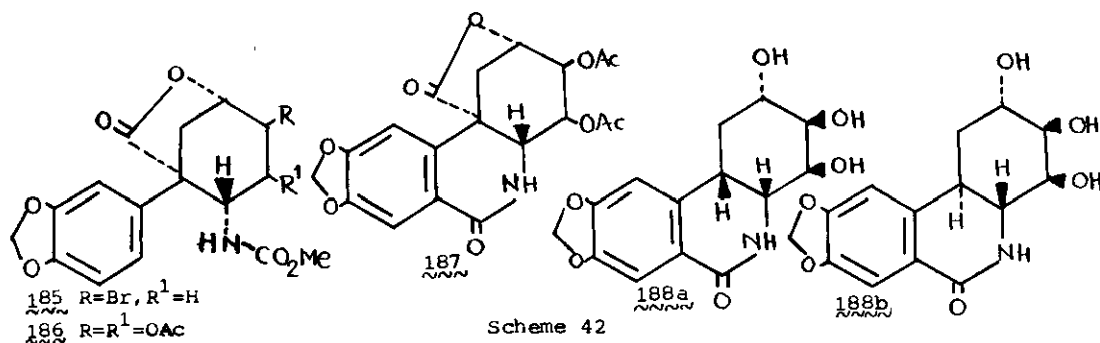
The quinuclidine ring with three chiral centres is the characteristic feature of the cinchona alkaloids and elaboration of this ring system is the key for successful total synthesis^{89,90}. All recent synthesis of cinchona alkaloids utilize the noranalogue of homomeroquinene⁹¹⁻⁹⁴; the 3(R)-vinyl-4(S)-piperidineacetic acid(meroquinene)^{95,96} which is also a degradation product of cinchonine⁹⁷. 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 elimination⁹⁸ (Scheme 41).



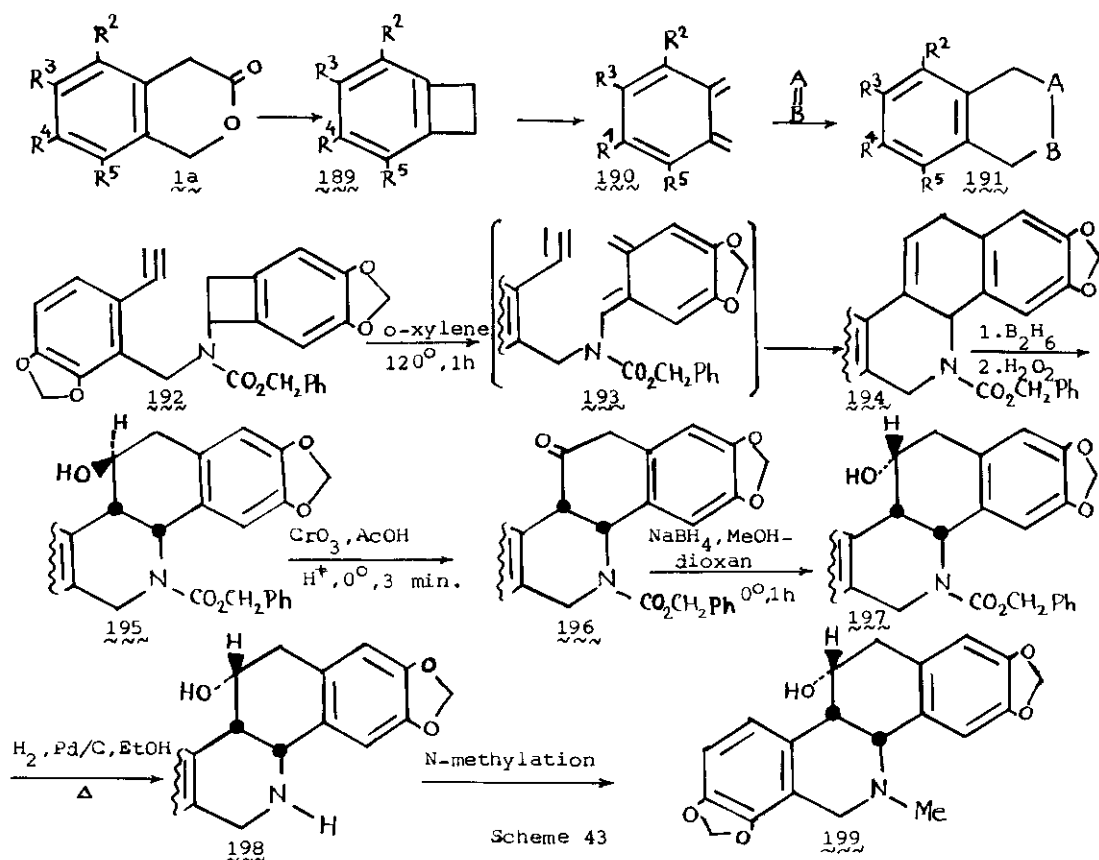
XVII. ETHANOPHENANTHRIDINE ALKALOID GROUP

The bromolactone (185) on dehydrobromination, oxidation with osmium tetroxide 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*-dihydrolycorricidine⁹⁹ (188a,b) (Scheme 42).



XVIII. BENZOPHENANTHRIDINE ALKALOID GROUP

A recent synthesis of chelidonine¹⁰⁰ (199) involves the benzoxyclobutene¹⁰¹ (189), a novel method for their preparation based on thermolysis of 3-isochromanones¹⁰² has recently been described (Scheme 43).

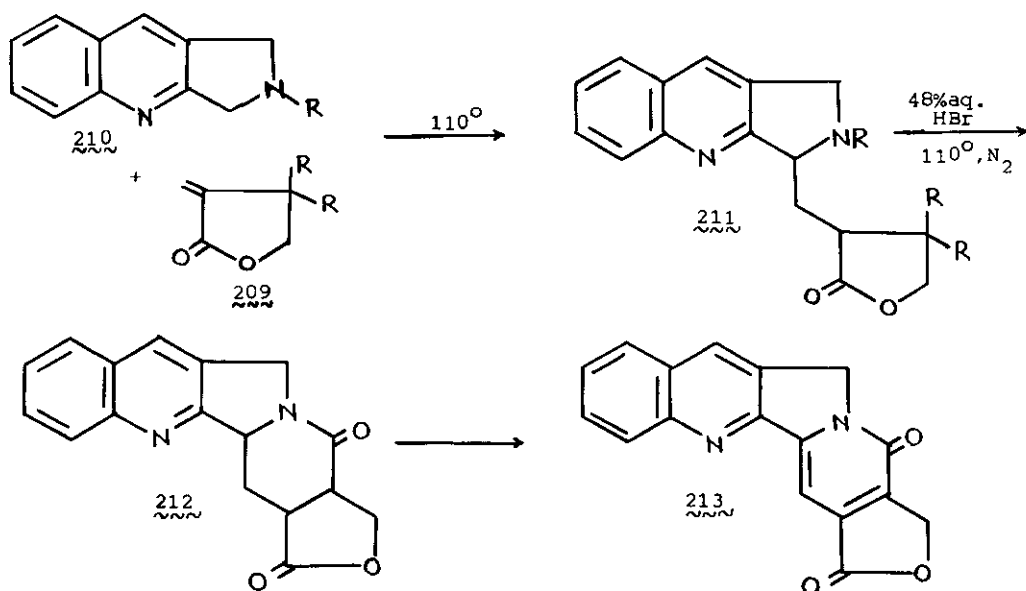
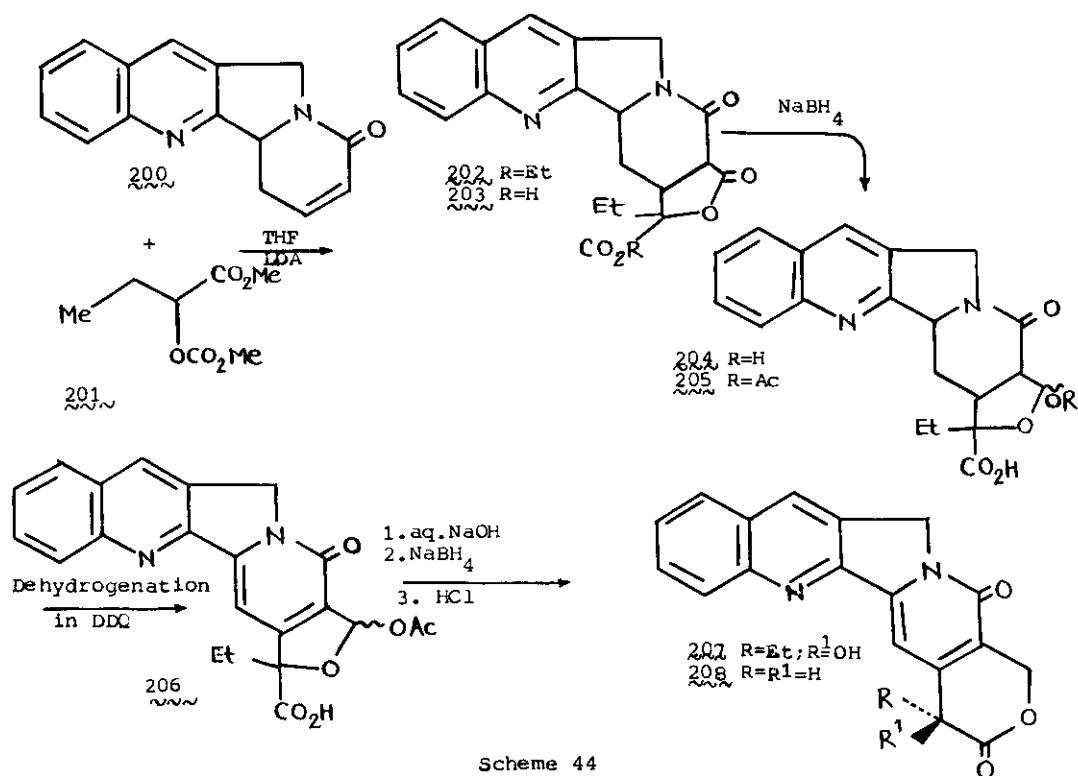


XIX. UNCLASSIFIED ALKALOID GROUP¹⁰³

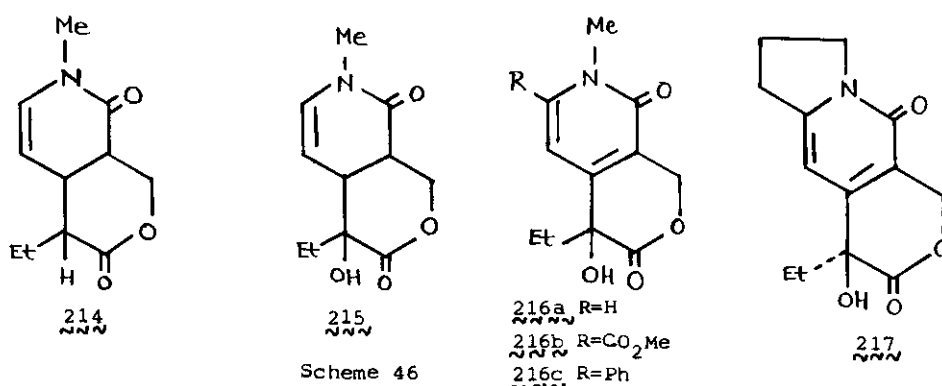
Camptothecin¹⁰⁴, (207) an antitumour alkaloid has been synthesized from lactone (202). The synthesis featured a novel method for the fusion of a γ -lactone ring to a pre-existing conjugated carbonyl system¹⁰⁵. The lactone (202) on hydrolysis, reduction with sodium borohydride, acetylation and dehydrogenation in dicyanodichloroquinone gave (206) which afforded camptothecin(207) by hydrolysis, reduction with sodium borohydride and acidification (Scheme 44).

δ -Methylene- $\beta\beta$ -diethoxycarbonyl- γ -butyrolactone¹⁰⁶ (209) has been employed to get an important precursor (213) to camptothecin¹⁰⁷ (207) (Scheme 45).

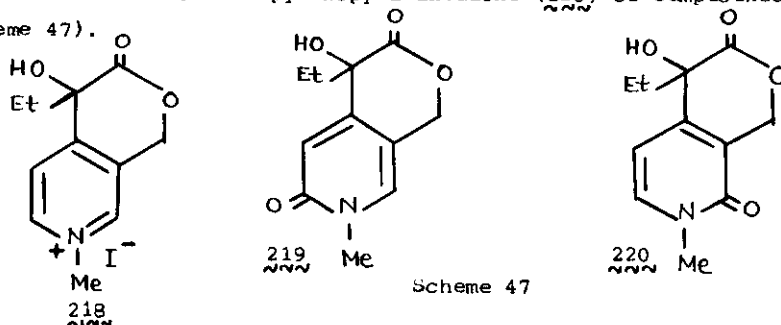
Several DE and CDE ring analogues of camptothecin(207) have been synthesized from lactones. The lactone (214) was converted to camptothecin analogue(215)



by oxidation with oxygen and alkali in the presence of triethylphosphite¹⁰⁸ (Scheme 46). Four DE (216a-c) and CDE (217) ring analogues were prepared.

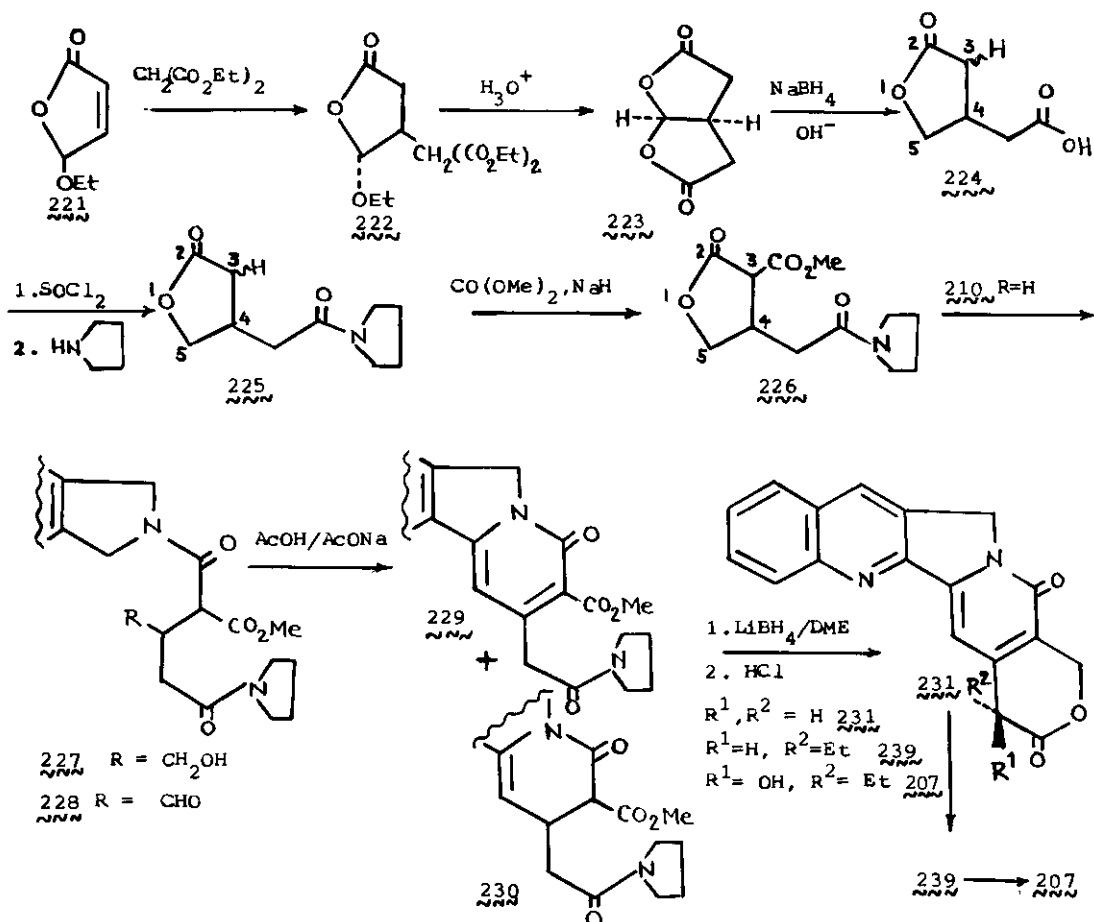


Pyranopyridinone¹⁰⁹ (218) methiodide on oxidation gave pyranopyridinedione (219) rather than the isomeric pyranopyridinedione (220) of camptothecin¹⁰⁹ (207) (Scheme 47).

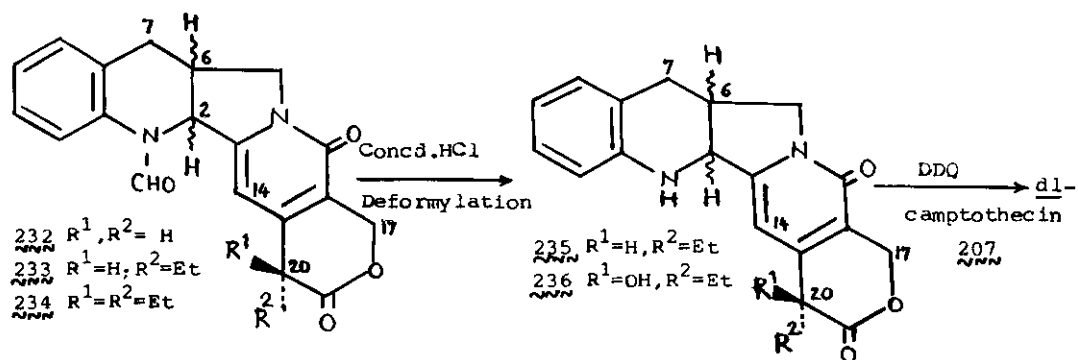


Ethoxylactone¹¹⁰⁻¹¹⁴ (221) was smoothly converted to the trans-adduct (222) by a Michael addition of diethylmalonate. Acid hydrolysis of (222) gave the bis-lactone (223). Reduction of (223) using sodiumborohydride under alkaline conditions gave acid (224) which was converted via its acid chloride to the corresponding pyrrolidinyl amide (225). The amide (225) was methoxycarbonylated to the required butenolide (226) by treatment with sodium hydride and dimethylcarbonate. Condensation of the butenolide (226) with the pyrroloquinoline¹¹⁵ (210) gave the corresponding hydroxyamide (227) which could be converted to deethyldeoxycamptothecin¹¹⁰ (231). Transformation of (231) to deoxycamptothecin^{116,119} (232) and to camptothecin (207) have been reported by several groups of workers¹¹⁷ (Scheme 48).

Another synthesis of dl-camptothecin (207) devised by Sugawara *et al* involved the lactone¹¹⁸ (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

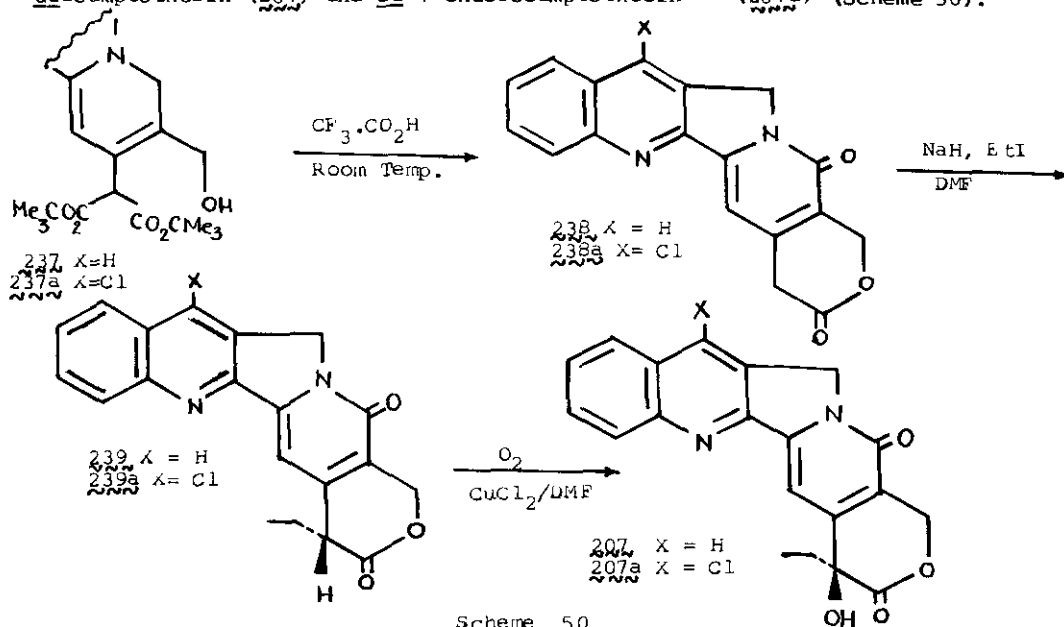


Scheme 49

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-camptothecin¹¹⁸ (207). This method, however, suffered from the disadvantage of the unavoidable coformation of the diethyl lactone (234) in the ethylation of the lactone (232) to (233) with sodium hydride and ethyl iodide in dimethylformamide (Scheme 49).

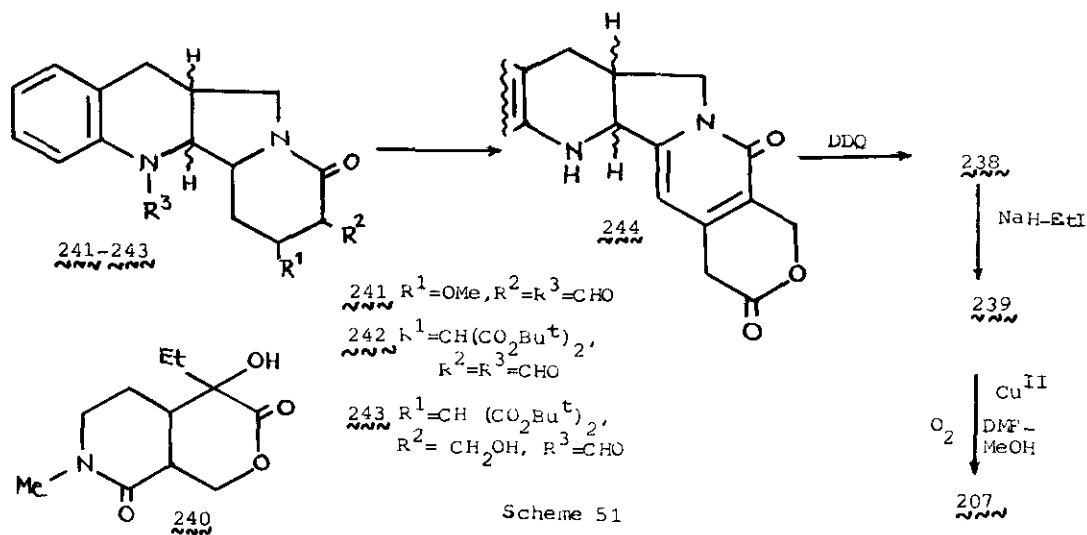
Recently, employing an one-step ethylation-oxygenation method¹¹⁹ Sugasawa *et al* have improved the yield of monoethyl lactone (233) by approximately 1.6 times over the previous method¹¹⁹.

A biogenetically patterned conversion¹²⁰ 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 deoxycamptothecins (239, 239a) with oxygen in presence of cupric chloride afforded dl-camptothecin (207) and dl-7-chlorocamptothecin¹²⁰ (207a) (Scheme 50).

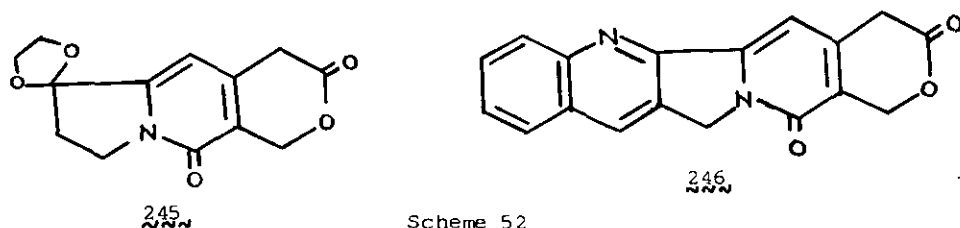


In another synthesis of dl-camptothecin (207) a D-E ring analogue, the 4-hydroxypyridine lactone (240) was synthesized^{121,122}. The tetracyclic biformal intermediate^{116,122} (241) gave the pyridonemalonate (242) on treatment with di-*tert*-butylmalonate and sodium hydride in dioxan which on sodium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



Yet another synthesis of dl-camptothecin¹²³ (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-camptothecin¹²³ (207) (Scheme 52).



ACKNOWLEDGEMENT

We thank Dr. K.C.Srivastava, Hygiejnisk Institut, Odense University, Denmark and Dr. H.Gutmann and Dr. U.Solms of F.Hoffmann La Roche and Co., Basel

for their valuable help in literature collection and gift of chemicals respectively. Thanks are also due to Professors S.P.Tandon and R.D.Tiwari, both Ex-Head of our department for their constant encouragement. We also express our gratitude to Drs. J.S.Chauhan, Ashok Pandey, and R.N.Choudhary of our Department and Mr. T.K.Rai and Mr. R.K.Jaiswal for their valuable help in preparation of the manuscript. The award of a Senior Research Fellowship from CSIR, New Delhi to G.D.P. is gratefully acknowledged.

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Received, 22nd August, 1980