SYNTHESES OF 5,10b-ETHANOPHENANTHRIDINE AND RELATED ALKALOIDS OCCURRING IN AMARYLLIDACEAE

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Synthetic works on the titled compounds including the following articles are reviewed.

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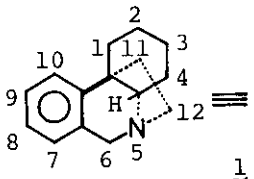
1. Introduction

The Amaryllidaceae alkaloids which go up to over 100 at present are regarded as a single biosynthetic family containing the main skeletal variants from oxidative coupling of the norbelladine precursors (1). They are classified into several skeletally homogeneous subgroups. One of these includes those alkaloids which incorporate the 5,10b-ethanophenanthridine nucleus 1 and is usually referred to as the crinine group after the parent natural alkaloid 2. Recent review (1) of these alkaloids lists about 40 closely related members of this family which includes the alkaloids elaborated from both enantiomorphs of this basic nucleus, e.g. (-)-crinine 2a vs. its (+)-enantiomer, vittatine 2b. Further variations are produced by differences in aromatic substitution and the functional groups attached to rings C and D. Some examples are shown in Chart 1.

Of these, the alkaloids carrying oxygenated function in ring D (5, 6, 10, and 11 in Chart 2) are particularly important in the both biosynthetic and chemical sense since they are possible biosynthetic precursors of other several subgroups such as methanomorphanthridines (cf. 16) and [2]benzopyrano[3,4c]indoles (7, 8, 9, 12, 13, and 14 in Chart 2)(1). These transformations have also been realized chemically (Chart 3). For example, haemanthamine mesylate 15 rearranges under solvolytic conditions such as NaOMe in MeOH to give the alkaloid, manthine 16 (2), and haemanthidine 6 isomerizes on methylation to pretazettine 7 which by base treatment further undergoes internal Cannizzaro reaction giving rise to tazettine 8 (3). 3-Epimacronine 9 is a stable congener of pretazettine (cf. Chart 2).



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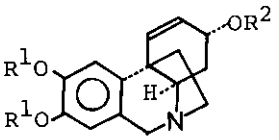
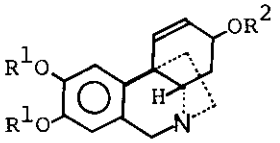
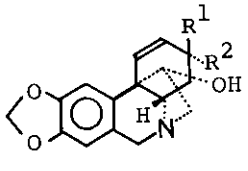
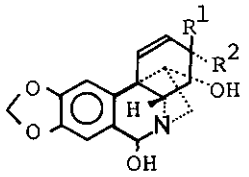


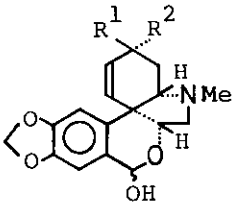


R^1	R^2		
$-CH_2-$	H	2a: crinine	2b: vittatine
$-CH_2-$	CH_3	3a: (-)-buphanisine	3b: (+)-buphanisine
CH_3	H	4a: (-)-maritidine	4b: (+)-maritidine

Chart 1

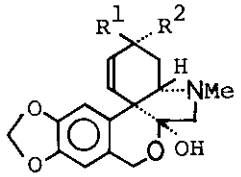


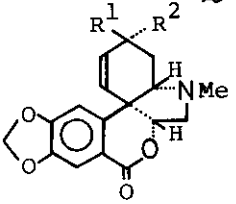




R^1=OMe, R^2=H haemanthamine 5 haemanthidine 6 pretazettine 7

R^1=H, R^2=OMe crinamine 10 6-hydroxycrimamine 11 precriwelline 12





R^1=OMe, R^2=H tazettine 8 3-epimacronine 9

R^1=H, R^2=OMe criwelline 13 macronine 14

Chart 2

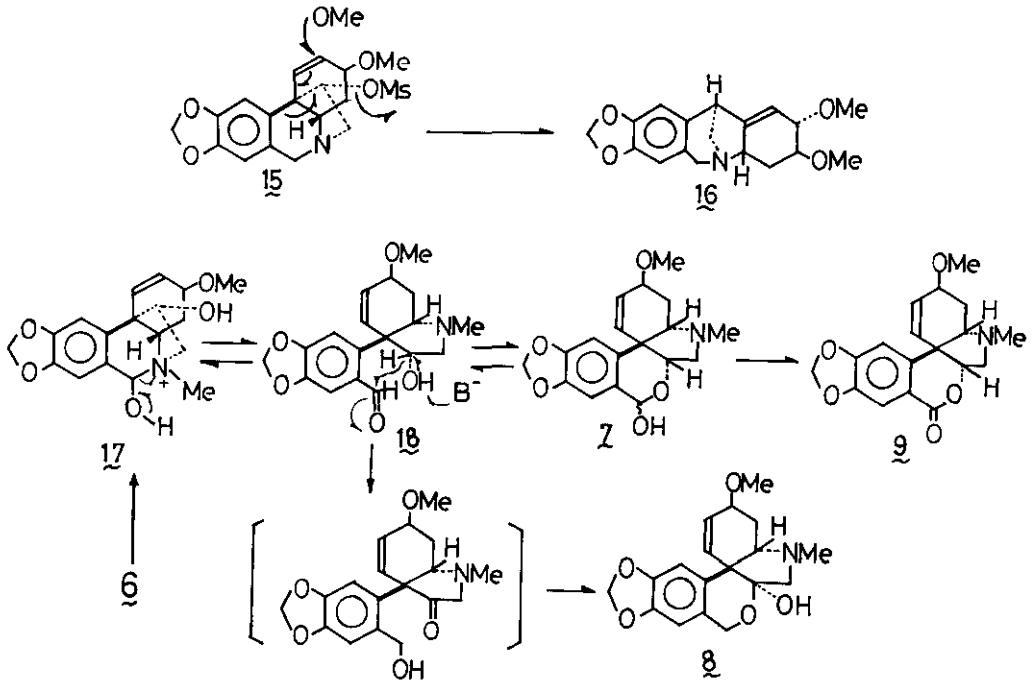


Chart 3

Since the above transformations are usually achieved in excellent yields, synthesis of an appropriately substituted 11-oxygenated crinine alkaloid is promising total synthesis of wide variety of its congeners; the fact which makes synthetic effort of such an 11-oxygenated alkaloid more attractive than that of usual ethanophenanthridine alkaloid.

Synthetic route of the 5,10b-ethanophenanthridine, when regarded to the C-N bond formation as the final step of skeletal make-up, is divided into three main routes shown in Chart 4. The route a realized as Pictet-Spengler (abbreviated as P-S

hereafter) cyclization of a cis-hydroindole a which can be prepared by one of the several routes a_1 to a_3, the latter route a_2 is exemplified by MVK annelation of Δ^2-pyrroline or Diels-Alder cyclization of dioxopyrroline derivative. Therefore these routes a_1-a_3 also provide the general synthetic scheme to the mesembrine alkaloids (such as 19) which occur in Aizoaceae (31). Formation of C-N bond at b is achieved by internal Michael addition (4) of

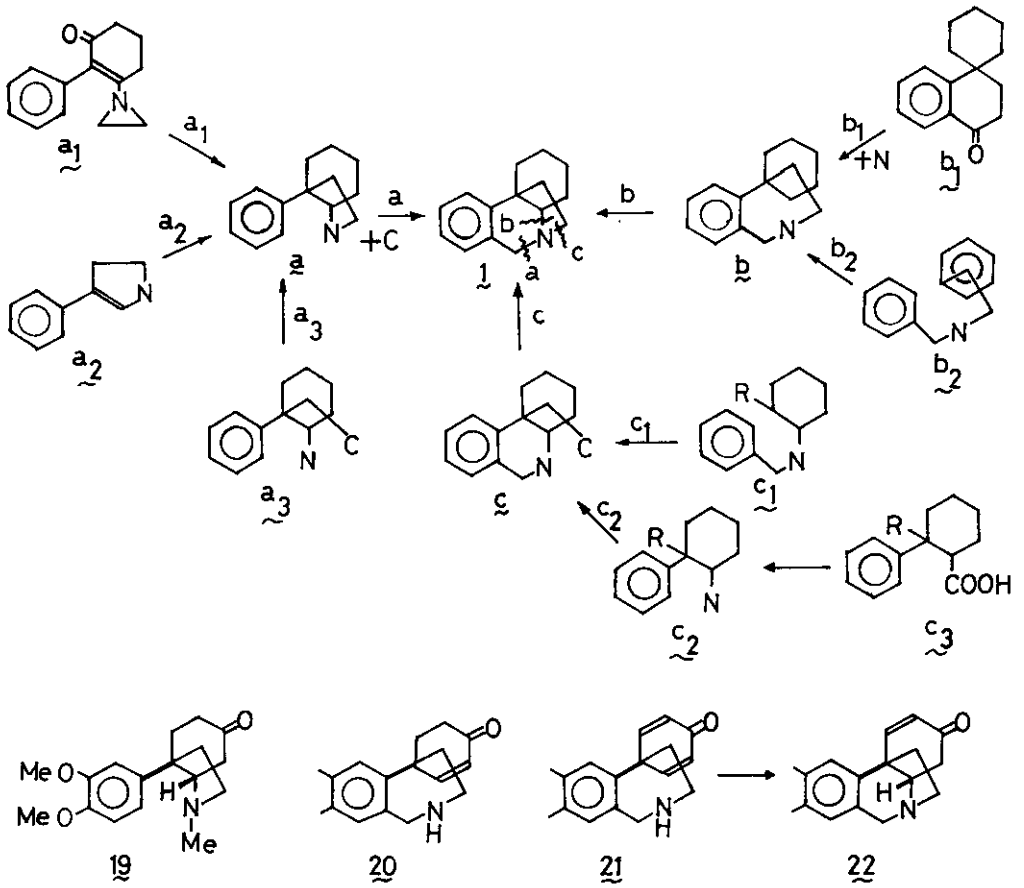


Chart 4

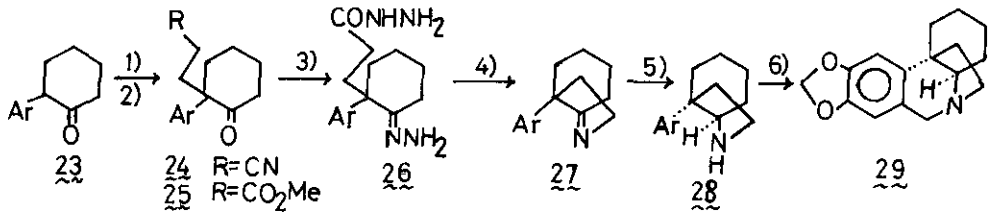
the enone 20 or dienone 21 which can be prepared by the routes b_1 or b_2, the cyclization proceeds in highly stereospecific manner. The latter route b_2 constitutes biogenetic-type synthesis of these alkaloids. Construction of ring D by route c is simple N-alkylation. The intermediate angularly substituted phenanthridine derivative was prepared by the routes c_1 (photo-cyclization) or alternatively c_2, the latter compound c_2 is derivable from a carboxylic acid c_3.

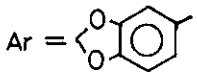
In this text the author will review these synthetic works up to 1978.

2. Syntheses of 5,10b-Ethanophenanthridine Skeleton and Simple Alkaloids

2-1 Crinane

(±)-Crinane 29, the basic skeleton of crinine, was first synthesized by Wildman (4) through P-S cyclization of the cis-octahydroindole 28 which was prepared from 2-(3',4'-methylenedioxyphenyl)-cyclohexanone 23 by several steps (Chart 5). Cyanoethylation of 23 afforded the corresponding cyanoethyl derivative 24 which on methanolysis yielded the methyl ester 25. With hydrazine it gave a hydrazone hydrazide 26 which was decomposed with nitrous acid to a hexahydroindole 27 (43). Catalytic hydrogenation of 27 gave the expected cis-hydroindole 28.

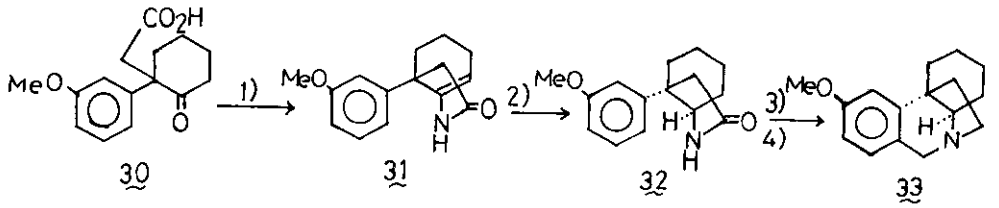




1) CH_2=CHCN, Triton B 2) MeOH-HCl 3) 80%NH_2NH_2 4) HNO_2
5) 10%Pd-C/H_2, $HClO_4$ 6) HCHO-$NaHCO_3$, 20%HCl

Chart 5

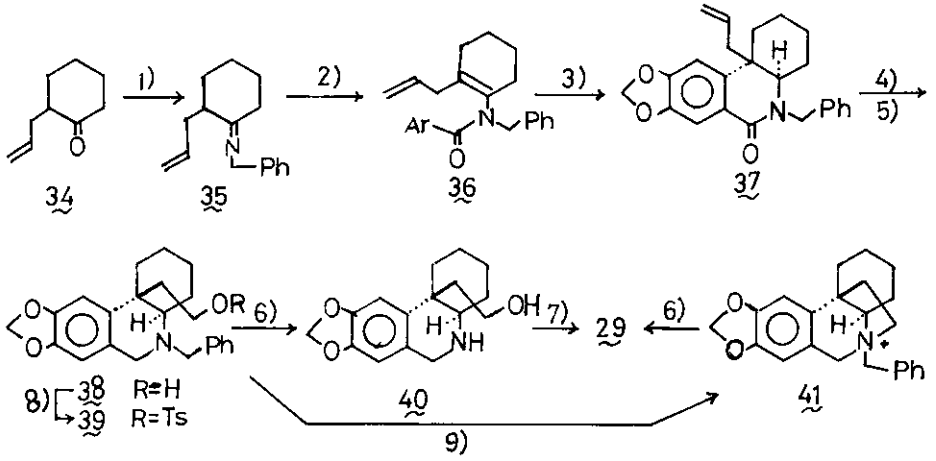
Similar synthesis of crinine-type skeleton by Langlois et al. (5) converts the cyclohexanone derivative 30, with NH_3, to the cyclic enamide 31 which on hydrogenation (Pd/C) gave cis-octahydroindole 32. The conversion of 32 to 33 is followed by the standard method (Chart 6).



1) NH_3 2) Pd-C/H_2 3) LAH 4) P-S

Chart 6

(±)-Crinane synthesis by Ninomiya (6) includes stereoselective photocyclization of the enamide 36 to the trans-hydrophenanthridone 37 as a key step, the former in turn was prepared from 2-allylcyclohexanone 34 in two stages. From 37 the ring D was constructed by ozonolysis, LAH reduction (38), hydrogenolysis (Pd/C) (40), and $SOCl_2$ treatment giving (±)-crinane 29. Alternatively, iodide treatment of tosyl derivative 39 gave a quarternary salt 41 which upon hydrogenolysis yielded 29 (Chart 7).



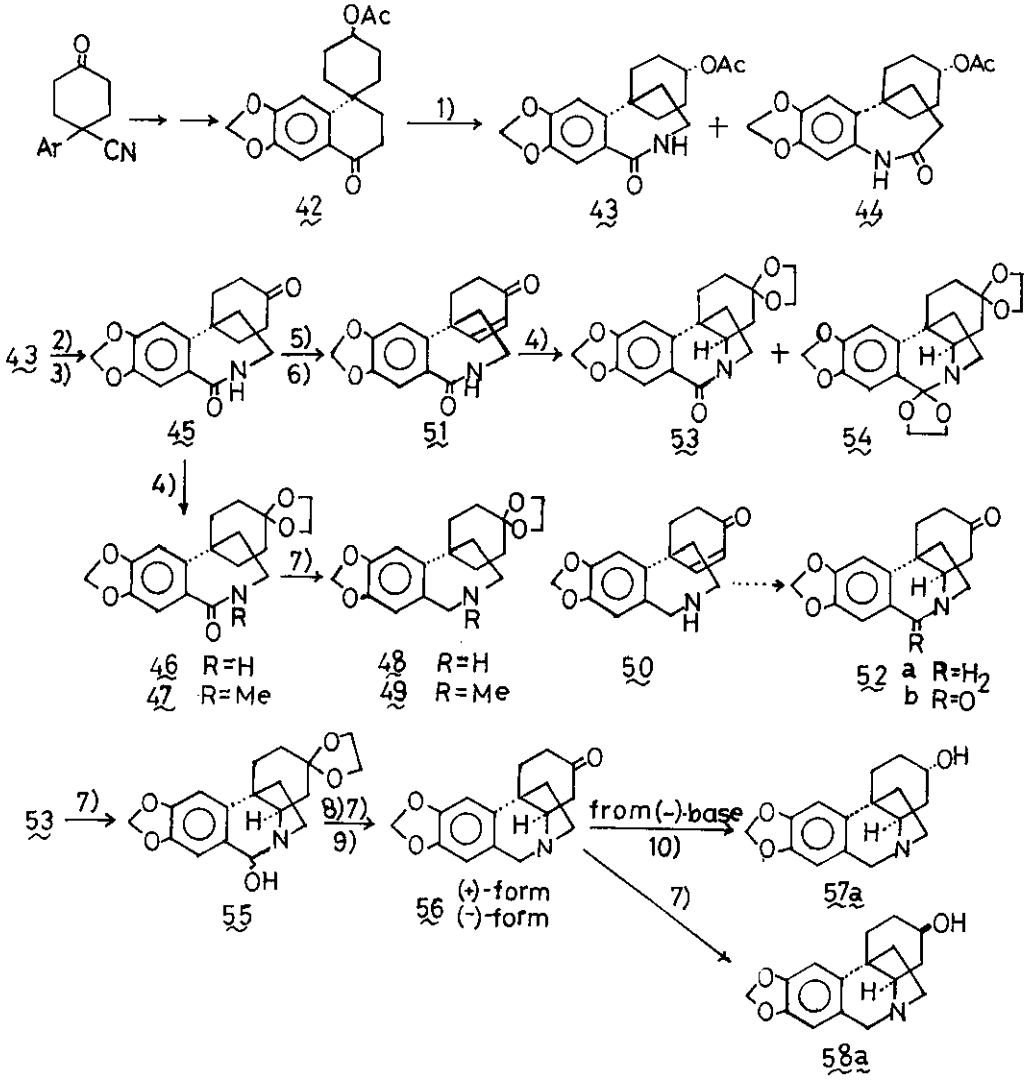
1) $PhCH_2NH_2$ 2) ArCOCl 3) hν 4) O_3 5) LAH 6) Pd-C/H_2
7) $SOCl_2$ 8) TsCl-Py 9) NaI

Chart 7

2-2 Dihydrocrinine

Dihydrocrinine, 3-hydroxycrinane, occurrs as a natural alkaloid, elwesine (1), which was synthesized by several groups.

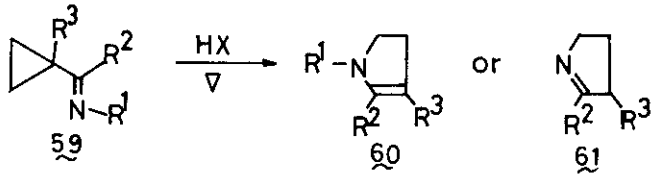
Uyeo and Irie (7,8) found that the tetralone 42 prepared by a series of conventional steps, when submitted to Schmidt reaction, afforded the lactam 43 and the undesired isomer 44 in approximately equal amounts. Their first attempt was transannular Michael addition of 50 to 52a. For this purpose, they attempted to prepare 50. Compound 43 was converted into 46 via 45. LAH reduction of 46 to the desired sec-amine 48 did not give satisfactory results (<5%), although the corresponding tertiary amide 47 was reduced smoothly, and thus the attempts was abandoned.
Their second attempt of direct Michael cyclization of 51 to 52b was again disappointing, the yield of the desired tetracyclic lactam being always less than 5% despite use of various bases. However, ketalization of 51 with ethyleneglycol and p-TsOH afforded a desired cyclized product 53 (major) accompanied with the diacetal 54 (minor). On forming tetracyclic system the carbonyl group near to the bridge-head nitrogen loses amide character (cf. Bredt's rule). Therefore 53 was converted to the tertiary amine by successive treatment with LAH, $SOCl_2$, and LAH (S_N2 replacement of the chloride). Removal of the ketal group afforded (±)-dihydro-oxocrinine 56 which was resolved into (-)- and (+)-base. The (-)-base on Meerwein-Pondorf reduction gave dihydrocrinine (elwesine) 57a, and the (+)-base gave its enantiomer, dihydrovittatine 57b as a sole product respectively. On the contrary, LAH reduction of (-)-dihydro-oxocrinine gave the epimeric alcohol, dihydro-epicrinine 58 exclusively (8)(Chart 8).



1) NaN_3, CCl_3COOH 2) K_2CO_3-EtOH 3) CrO_3-Py 4) $HOCH_2CH_2OH$, TsOH
5) Br_2 6) LiCl-$LiCO_3$, DMF 7) LAH 8) $SOCl_2$ 9) HCl-H_2O 10) $Al(OPr)_3$

Chart 8

Stevens' synthesis (9) of (±)-dihydrocrinine utilizes the acid-catalysed thermally induced rearrangement of cyclopropyl imines 59 to Δ^1- or Δ^2-pyrrolines (60 or 61).



The aldimine 62 prepared from piperonylcyanide in sveral stages was isomerized in 72-80% yield to the pyrroline 63 on heating at 135° with a catalytic amount of NH_4Cl. Annelation was achieved by heating the hydrochloride of 63 with slight excess of MVK in CH_3CN giving rise to cis-octahydroindole 64 (56 — 70%). $NaBH_4$ reduction of 64 afforded a 3:1 mixture of two epimeric alcohols. The major isomer 65 gave, on hydrogenolysis and P-S cyclization, (±)-dihydroepicrinine 58. While, reducing the ketone 64 catalytically (PtO_2 in i-PrOH) provided ratio of 8:1 in favor of the desired alcohol 66, which on debenzylation

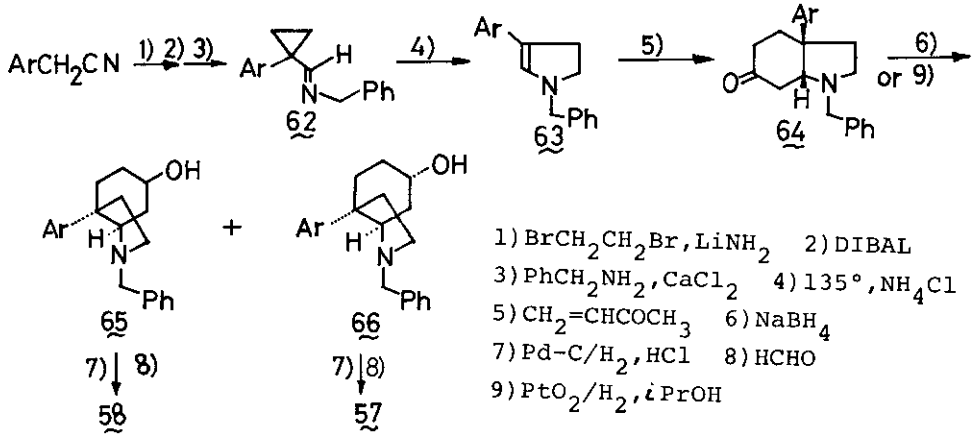


Chart 9

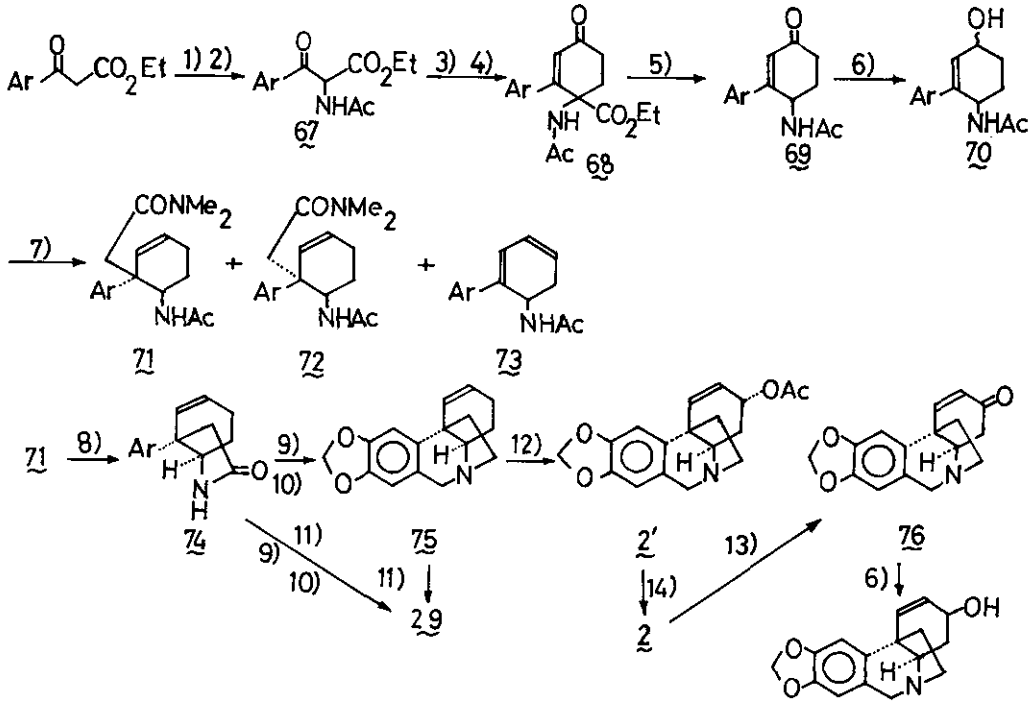
(Pd/C-HCl) and P-S cyclization afforded (±)-dihydrocrinine 57 (Chart 9).

The method presented here has been successfully applied to the total synthesis of mesembrine 19 (10,11).

2-3 Crinine

Crinine includes extra double bond on ring C, its synthesis therefore requires some modifications.

The first synthesis of crinine was achieved by Muxfeldt (12) (Chart 10). Ethyl N-acetyl-piperonylglycinate 67 was condensed with MVK and cyclized to 68.

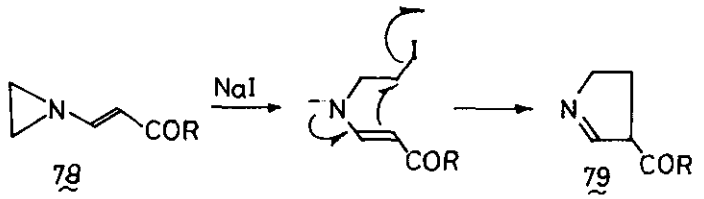


1) $NaNO_2$-AcOH 2) Zn-AcOH, Ac_2O 3) MVK, Triton B 4) ⬡NH, AcOH
5) H_2O 6) $NaBH_4$ 7) $CH_3C(OMe)_2NMe_2$, benzene 8) NaOH-$EtOCH_2CH_2OH$-H_2O
9) LAH 10) HCHO 11) Pd-C/H_2 12) SeO_2, AcOH-Ac_2O 13) CrO_3-Py
14) saponification

Chart 10

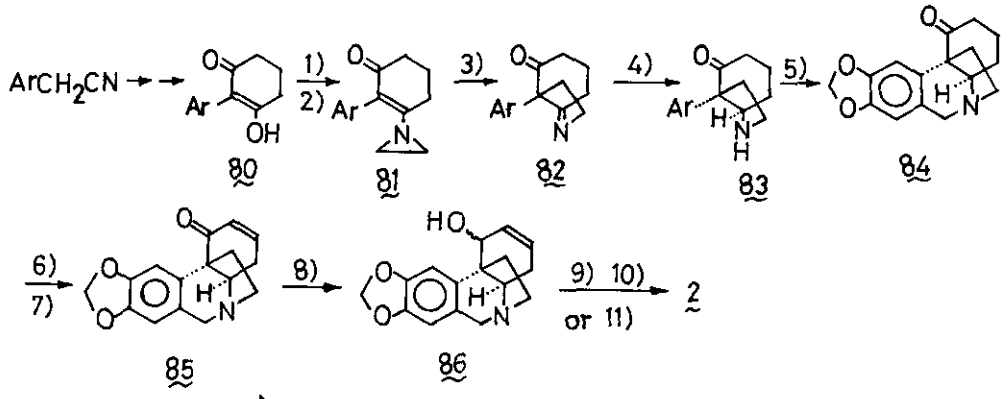
Saponification and decarboxylation of the product gave 69 which was reduced to a mixture of the epimeric alcohols 70. In the crucial step of the synthesis 70 was treated with 1,1-dimethoxy-1-dimethylaminoethane to give a mixture of trans- and cis-diamide (71 and 72) (45%) and the diene 73 (50%). Hydrolysis of the diamide mixture provided the desired cis-hexahydroindole derivative 74, the trans-diamide being remained unchanged under this condition. 74 on catalytic hydrogenation, LAH reduction, and P-S cyclization afforded (±)-crinane 29 thus confirming its stereochemistry. Reduction of 74 with LAH followed by P-S cyclization gave the crinene 75, conversion of which to (±)-crinine 2 was achieved by SeO_2 oxidation ($AcOH-Ac_2O$) and saponification of the resultant acetate. The structure of synthetic crinine was confirmed by oxidation to (±)-oxocrinine 76, which was reduced by $NaBH_4$ to (±)-epicrinine 77.

The second novel route to an oxygenated crinane and hence to crinine presented by Whitlock (13) includes as a crucial step the rearrangement of N-vinylaziridine derivatives 78 to Δ^1-pyrrolines 79 by action of iodide ion.



78 79

The dione 80 was converted successively to the chloride and cyclopropyl-imide 81. The rearrangement was effected by heating 81 with anhydrous NaI in dry diglyme under nitrogen at 145° giving rise to 82 in 55% yield. Catalytic hydrogenation of 82 in ethanol with PtO_2 afforded predominantly the cis-dihydro derivative 83 (75%) accompanied with small amount of the trans-isomer (5.5%). P-S cyclization of the cis-isomer gave (±)-1-oxocrinane 84 (79%). 84 was brominated and dehydrobrominated to 85. The latter was reduced to 86 which, once transformed into O-tosyl ester, gave by solvolysis the expected (±)-crinine 2 in 30% yield together with dehydrated products (Chart 11).



1) PCl_3, $CHCl_3$ 2) NH, Et_3N 3) NaI, 145°, diglyme 4) PtO_2/H_2
5) HCHO-MeOH, 6N-HCl 6) HCl-Et_2O, Br_2-AcOH 7) LiCl-DMF 8) LAH
9) *n*BuLi-THF, TsCl 10) $NaHCO_3$-H_2O 11) 10%HCl

Chart 11

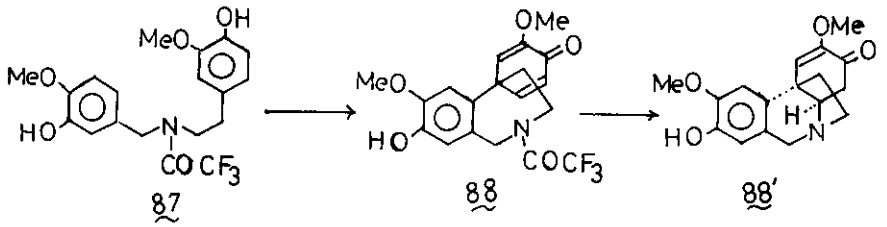
3. Oxidative Coupling of Norbelladine Derivative Leading to Oxocrinine and Its Analog.

Biogenetic-type synthesis of 5,10b-ethanophenantridine alkaloids from an appropriate norbolladine derivative is an attractive problem and several of this attempt have been realized. The reaction employed for this purpose is classified into three categories: a) phenol oxidation with metal salts and complexes, b) anodic oxidation, and c) photolytic cyclization. The results are summarized in Table 1. Pschorr-type cyclization, sometimes useful for other group of alkaloid, is not succeeded synthesizing crinine alkaloids.

3-1 Phenol oxidation

Selection of the oxidizing agent is the crucial point. Early work (14) on the model compound 87 in a two phase oxidation using $FeCl_3$ yielded 12% of the dienone 88. The yield of the coupling product was greatly increased by using $VOCl_3$, thus O-methyl-norbelladine derivative 89 was converted to the dienone 90 in 24% yield (37% based on the recovered starting material) by oxidation in diluted ethereal solution (15). Hydrolysis of 90 gave, with spontaneous transannular cyclization, an enone 91 which on methylation (24%) afforded (±)-oxomaritidine 94. $NaBH_4$ reduction of 94 gave (±)-epimaritidine 95 (64%). Acid treatment of 95 under solvolytic condition caused partial epimerization to the desired product, (±)-maritidine 4 (29%).

The iron complexes, $FeCl_3$-DMF complex and $FeCl_3$-DMSO complex, having the formula $[Fe(DMF)_3Cl_2][FeCl_4]$ and $[Fe(DMSO)_4Cl_2]\cdot[FeCl_4]$ were shown to be more effective when the reactions were



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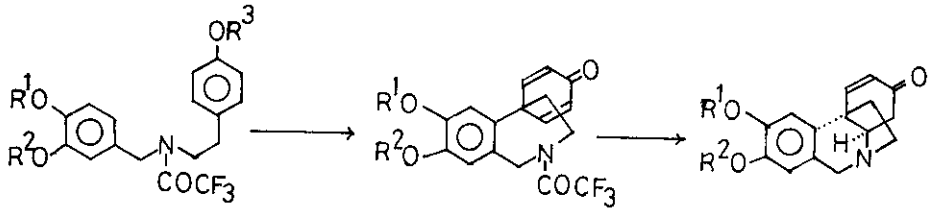


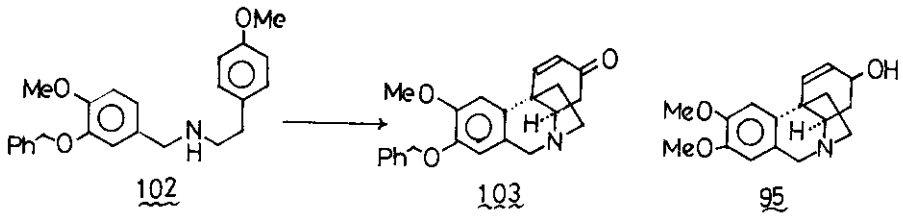
89 R^1=Me, R^2=R^3=H
92 R^1=R^2=R^3=Me
96 R^1,R^2=CH_2, R^3=H
98 R^1,R^2=CH_2, R^3=Me
99 R^1=R^3=Me, R^2=CH_2Ph

90 R^1=Me, R^2=H
93 R^1=R^2=Me
97 R^1,R^2=CH_2

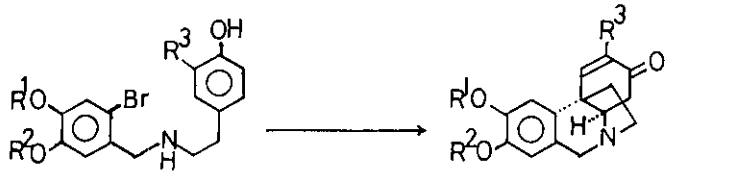
100 R^1=Me, R^2=CH_2Ph

91 R^1=Me, R^2=H
94 R^1=R^2=Me
76 R^1,R^2=CH_2

101 R^1=Me, R^2=CH_2Ph



102 103 95



104 R^1,R^2=CH_2, R^3=OMe
106 R^1=Me, R^2=R^3=H
107 R^1,R^2=CH_2, R^3=H

105 R^1,R^2=CH_2, R^3=OMe
91 R^1=Me, R^2=R^3=H
76 R^1,R^2=CH_2, R^3=H

Chart 12

Starting material	Oxidation method	Product	yield %	lit.
87	$FeCl_3$	88	12	14
89	$VOCl_3$	90	24(37)	15
"	$FeCl_3$-DMF complex	"	35	16,17
"	$FeCl_3$-DMSO complex	"	30	"
96	TTFA	97	19	18
92	Anodic oxidation	93	62	17,19
98	"	97	62	"
99	"	100	60	"
102	"	103	50	"
104	$h\nu$	105	3.3	20,21
106	"	91	3.6	"
107	"	76	5	"

Table 1

carried in a two-phase system of ether and water (16,17). The yields of 89 to 90 were 35% and 30% respectively. The coupling mediated by phenoxonium ion using two electron oxidizing agent was effected conversion of the compound non-phenolic at ring A to the dienone. Thus Schwartz (18) succeeded in synthesis of 97 from 96 in 19% yield using $Tl(OCOCF_3)_3$ (TTFA) as an oxidant in CH_2Cl_2. Hydrolysis of 97 gave (±)-oxocrinine 76.

3-2 Anodic Oxidation

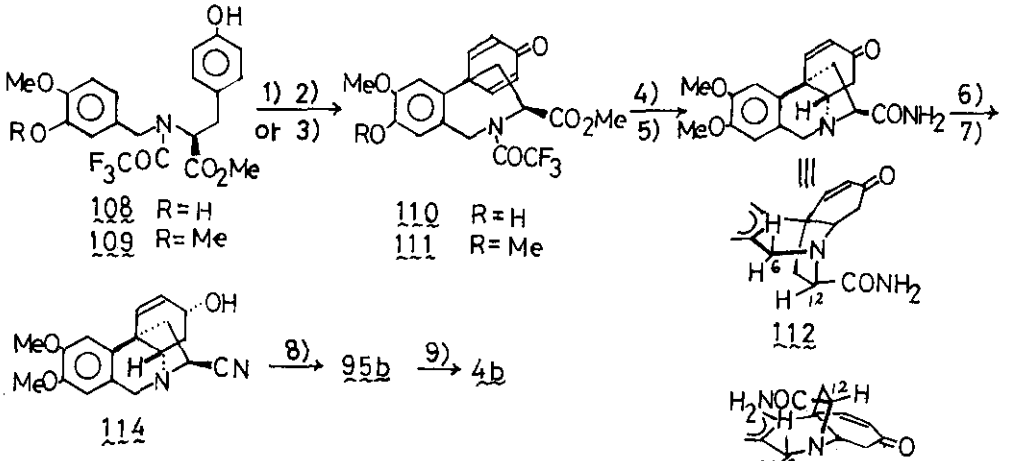
The coupling of non-phenolic norbelladine derivatives 92 and 98 were achieved in high yields by anodic oxidation in CH_3CN with HBF_4 as an electrolyte and Pt as the electrodes giving rise to the dienone 93 and 97 (62% yields), respectively (17,19). It is noteworthy to mention that this method is applicable to the compound 102 which does not carry protecting group on the secondary nitrogen, directly giving the cyclized enone 103 (17).

3-3 Photolytic Cyclization

Photolytic cyclization (20,21) of the phenolic bromo-compound 106 and 107 led to (±)-oxocrinine 76 and (±)-oxomaritidine derivative 91 when irradiated in ethanolic hydroxide solution though the yields were low (5% and 3.6% respectively). The bromo-phenol 104 gave the analogous product 105.

3-4 Asymmetric Synthesis

By application of phenol oxidation asymmetric synthesis of (+)-maritidine was accomplished (22). The TFA derivative 108 prepared from tyrosine and isovaniline by sequence of reactions was oxidized with $FeCl_3$-DMF complex to yield the dienone 110 ($[\alpha]_D$ +146°) (14%). Its O-methyl derivative 111 was also obtained by oxidation of 109 with TTFA in CH_3CN (67%). Amidation



108 R=H
109 R=Me

110 R=H
111 R=Me

112

114

95b

4b

113

1) $FeCl_3$-DMF 2) MeI-*t*-BuOK, DMF 3) TTFA
4) NH_3-MeOH 5) NaOH 6) $POCl_3$-Py 7) $NaBH_4$
8) Na-liq.NH_3 9) 10%HCl

Chart 13

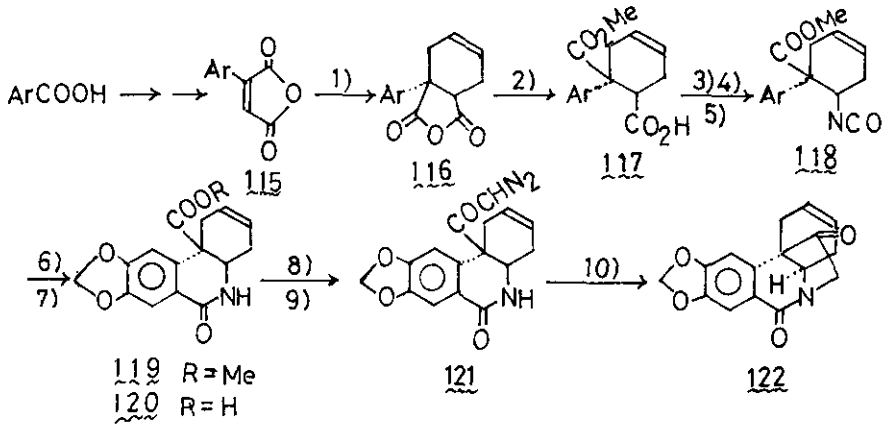
of 111 followed by hydrolysis resulted the enonone 112 ($[\alpha]_D$ +98.6°) as a sole product. This highly specific asymmetric cyclization is ascribed to the difference in steric effects between the methylene group at C_6 and the amide group at C_{12} in 112 and in 113. The isomer 113 would serve severe steric interaction between these groups. 112 was converted to the nitrile and reduced with $NaBH_4$ to 114. The α-cyano group was removed reduction with Na in liq. NH_3 (23) giving in 58% yield (+)-epimaritidine 95b ($[\alpha]_D$ +136°) which was partially epimerized to (+)-maritidine 4b (17%) by refluxing in dilute HCl.

4. Synthesis of 11-Oxygenated 5,10b-Ethanophenanthridines and Functionalization of Ring C

It is obvious that most of the Scheme described above is not directly applicable to the synthesis of 11-oxygenated alkaloids, since they have an extra oxygen on the ethano-bridge, novel scheme should be designed for this purpose. In this Section this problem and, as a rational consequence thereof, the total synthesis of natural alkaloids of this family is discussed.

4-1 Hendrickson's Total Syntheses of Haemanthidine and Tazettine

a) 6,11-Dioxocrinene. 6,11-Dioxocrinene-2 122 was synthesized as follows (24)(Chart 14). 3,4-Methylenedioxyphenylmaleic anhydride 115 provided the Diels-Alder adduct 116 upon condensation with butadiene (63%). The adduct contains the proper cis-orientation of the aryl and hydrogen atom for ring C in the crinine type alkaloids. The anhydride was opened by one eq. mole of NaOMe to form the halfester 117. The formation of more hindered ester is rationalized by assuming the greater steric demands of the solvated carboxylate ion over the methyl ester, thus the kinetic product (isomeric ester) being equilibrated to the more stable salt of 117. Curtius degradation afforded an isocyanate 118 which was cyclized to the lactam 119 with CF_3COOH or with PPA (81.3%). Standard reactions, i.e. hydrolysis, chlorination, and treatment with diazomethane converted 119 to the diazoketone 121 which was cyclized on heating with dry HCl to 6,11-dioxocrinene-2 122.

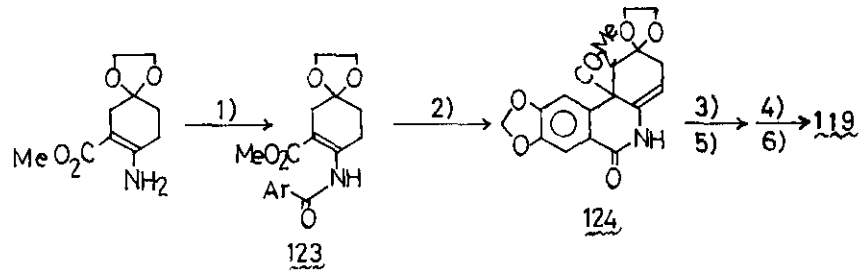


1) $\rightleftharpoons$, Δ 2) NaOMe 3) $(COCl)_2$ 4) NaN_3 5) Δ, toluene
6) CF_3COOH or PPA 7) 40%KOH 8) $SOCl_2$ 9) CH_2N_2 10) HCl

Chart 14

However, stereocontrol for functionalizing ring C of 122 was not successful, reduction of 122 with $NaBH_4$ giving an inseparable mixture of 6,11-diol.

An alternative route to the lactam-acid 120 through photocyclization of the enamide 123 to 124 has been proposed (26), however, it requires multistages for modification of ring C (Chart 15).

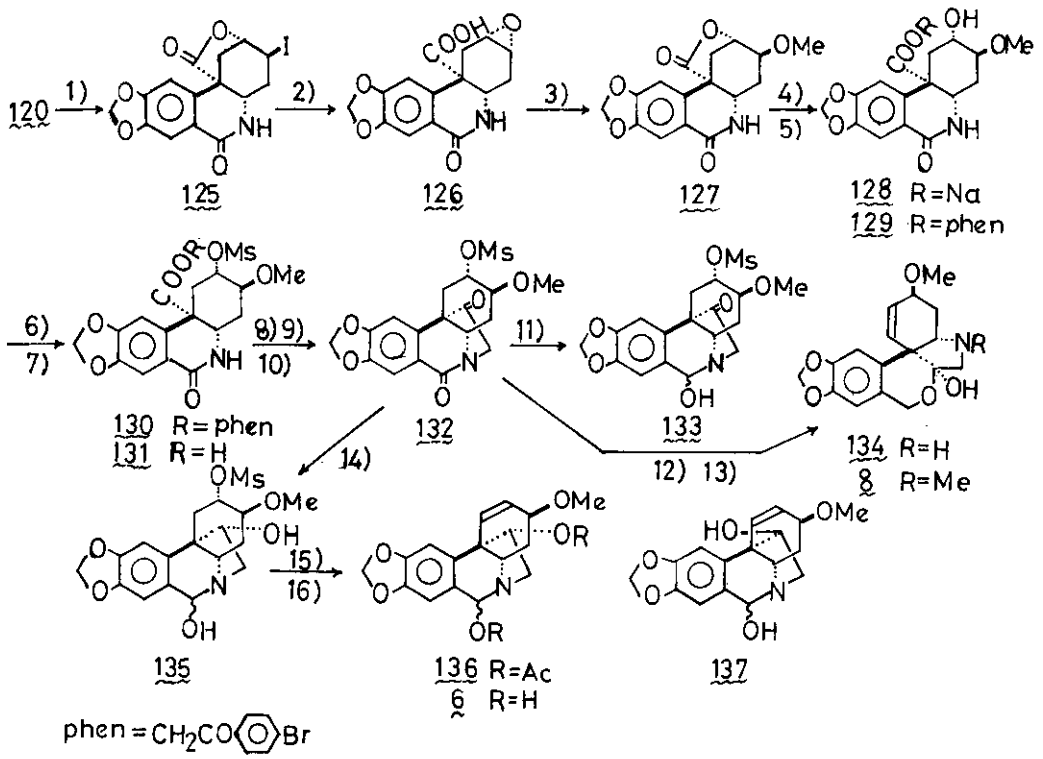


1) ArCOCl 2) $h\nu$ 3) Pd-C/H_2, AcOH 4) Br_2-AcOH
5) $NaBH_4$ 6) Zn-AcOH

Chart 15

b) Haemanthidine and Tazettine. The first total synthesis of haemanthidine 6 and tazettine 8 has been completed (25) starting from the lactam-acid 120 which has the axial carboxyl required to direct the steric course of the functionalization in ring C (Chart 16). The methoxy group cis to aryl was created by converting 120 into the iodo-lactone 125 followed by base treatment to the cis 2,3-epoxy-acid 126, then by its opening with BF_3-MeOH to the methoxy-lactone 127. It was saponified to the acid salt 128 which was directly converted, in order to prevent relactonization on acidification, to the ester 129 by displacement with phenacylbromide in DMF, then mesylated to 130. The homologation of 130 to the crinane derivative 132 was brought about by saponification (powdered KOH in THF) to acid 131, followed by the sequence of reactions described above (120→121→122).

Reduction of 132 with $NaBH_4$ (or $LiBH_4$) in the cold (2 days) gave the carbinolamine 133 in agreement with the expected behaviour of a carbonyl near a bridgehead nitrogen and with the hindered character of C-11 ketone in 132. Since reduction at C-11 in natural 11-oxo derivative yields predominantly wrong 11-epimer (3), the presence of axial mesyl group at C-2 was intended to reverse this trend by steric hindrance. However, when 132 was reduced with $NaBH_4$ in boiling isopropanol followed by basic elimination of the mesylate group, nortazettine 134 was obtained indicating that internal Cannizzaro hydride shift had already occurred in hot borohydride reduction. Methylation of nortazettine 134 is known to give tazettine 8 (3). Therefore 132 was reduced under acidic conditions (refluxing disiamylborane in THF) to give a diol 135 which was



1) I_2-KI, $NaHCO_3$-H_2O 2) NaOH 3) MeOH-BF_3 4) 1.1 eq. 0.1N NaOH
5) *p*-bromophenacyl bromide, DMF 6) MsCl-Py 7) KOH-THF
8) $SOCl_2$ 9) CH_2N_2 10) dry HCl 11) $NaBH_4$ in DME
12) $NaBH_4$ in propanol 13) 40%KOH 14) disiamylborane, THF
15) Ac_2O-BF_3·$2Et_2O$ 16) DBN, 110°

One enantiomeric form (identical with the natural alkaloid) is indicated.

Chart 16

acetylated and subjected to mesylate elimination with hot DBN, then deacetylation with LAH. The sequence gave (±)-haemanthidine 6 (20%) and its 11-epimer 137 (6%).

Overall yield of this 30 sequential reactions with 19 isolations of intermediate products is 0.4%. Stereocontrol at C-11 is the point still to be improved in this synthesis.

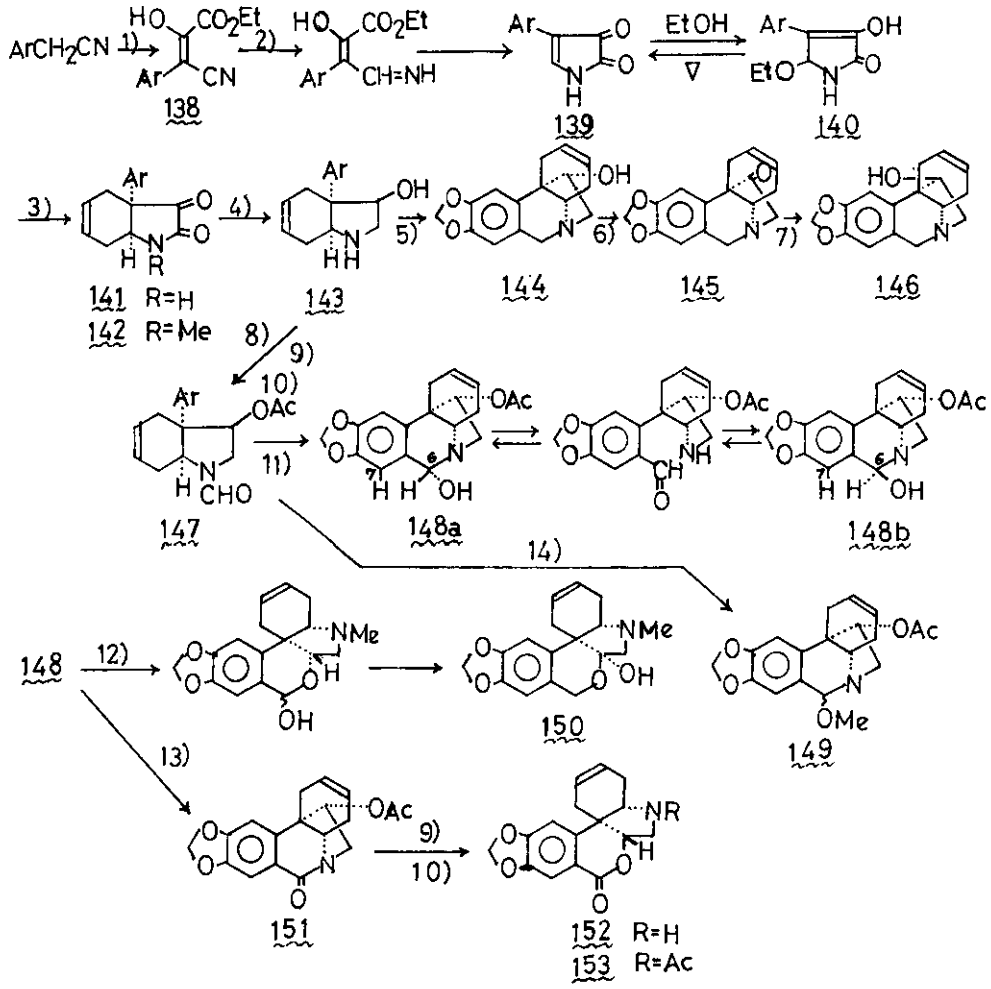
4-2 Tsuda's Synthesis of Haemanthamine, Haemanthidine, and Tazettine

A fully stereocontrolled synthesis of 11-hydroxy-cis-hexahydroindole and hence the synthesis of haemanthamine, haemanthidine, and tazettine, a series of alkaloids were presented (27,28).

a) 11α-Hydroxycrinene-2 (Chart 17). Tsuda's general synthesis of series of alkaloids involves as its key intermediate the tricyclic tetrahydroindole 141, which is susceptible to further functionalization and which has the required cis-fusion. It was prepared by cycloaddition of butadiene in DMSO to the dioxopyrroline derivative 139 (characterized as its ethanol adduct 140) prepared from piperonylcyanide and ethyl oxalate via the pyruvate 138 followed by hydrogenation (ether containing a trace of ethanol). This was easily methylated to 142, a potential intermediate to mesembrine alkaloids (27,29).

LAH reduction of 141 gave the hydroxy-hexahydroindole 143 as a single product (95%) which has the right stereochemistry with that of natural alkaloids as shown below. Apparently hydride attack to the ketone took place from the convex-face.

P-S cyclization of 143 gave in 72% yield (±)-11-hydroxy-crinene-2 144, which corresponds to the natural alkaloid (±)-haemultine (30). The ketone 145 prepared by CrO_3-pyridine oxidation of 144 afforded, on $NaBH_4$ reduction, the isomeric alcohol 146 and the original alcohol 144 in ratio of 2:1. Since haemanthaminone is known to give 11-epihaemanthamine



1) $(CO_2Et)_2$,EtONa 2)Raney Ni/H_2,ether,40 kg/cm^2,70°
3)〜in DMSO,170° 4)LAH 5)HCHO,AcOH 6)CrO_3-Py
7)$NaBH_4$ 8)HCOOAc-Py 9)$NaHCO_3$-MeOH 10)Ac_2O-Py
11)$POCl_3$-xylene,Na_2CO_3-H_2O 12)MeI,2%NaOH
13)MnO_2 in $CHCl_3$ 14)$POCl_3$-xylene,MeOH

Chart 17

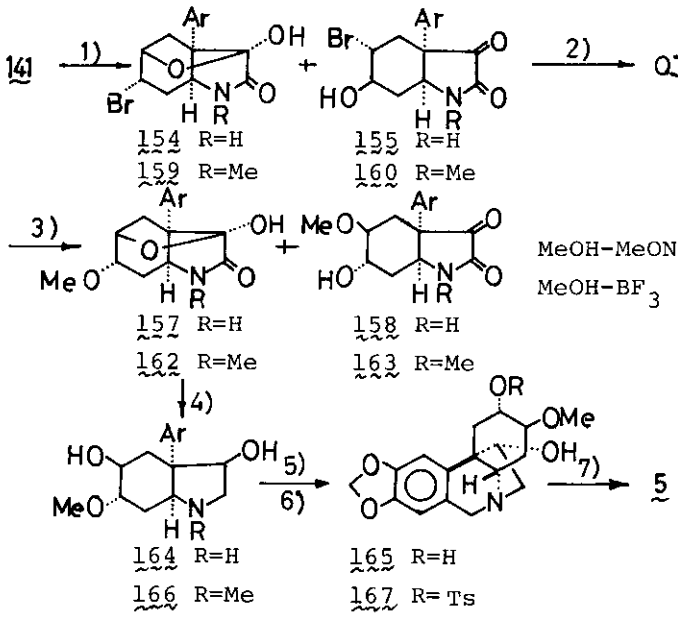
predominantly by hydride reduction (3), the above evidence indicates that 144 (and hence 143) has the stereochemistry of the hydroxyl group identical with that of natural alkaloids.

The skeletal transformations from 143 to various alkaloid types were achieved as follows (32). The alcohol 143 was converted to the N-formyl-O-acetyl derivative 147 by the sequence of reactions shown in Chart 17, and the product was subjected to Bischler-Napieralski (B-N) reaction (heating with $POCl_3$ in xylene). Quenching the reaction mixture with aqueous Na_2CO_3 gave in 80% yield 148 (haemanthidine type) which showed in its n.m.r. spectrum two couples of peaks corresponding to C_7-H and C_6-H (δ6.98, 6.80 and 5.35, 5.11 ppm with ratio of 1:2, respectively), like haemanthidine, indicating that it exist in equilibrated forms 148a and 148b in $CDCl_3$ solution.

Methylation of 148 followed by base treatment (2% NaOH-MeOH) afforded 150 (tazettine type) almost quantitatively. Oxidation of 148 with MnO_2 gave the lactam 151 which on LAH reduction regenerated 148(-OH instead of -OAc), but on hydrolysis with $NaHCO_3$ in MeOH gave 152 (macronine type) with the concomitant skeletal rearrangement, the latter formed the N-acetate 153. On the other hand, quenching the B-N reaction mixture with MeOH afforded O-methyl derivative 149 in 70% yield. This was stable to base treatment but on mild hydrolyis with 50% AcOH furnished 148 in excellent yield proving that -OMe is a good protecting group of C_6-OH.

b) Haemanthamine (Chart 18). Stereospecific introduction of the methoxyl group at C-3 cis to the aryl in the crinane skeleton coupled with the desired functionalization was achieved as follows (27)(Chart 18). On bromohydrination with NBA, 141 was converted into a mixture of the bromoacetal 154 (major) and bromohydrine 155 (minor). The both when kept in MeOH containing 10% NaOMe were transformed into the same epoxy-ketone 156 (70% from 141). The latter upon treatment with BF_3-etherate in MeOH led almost exclusively to the methoxy-ketal 157 (71%) with minor formation of the methoxy-dione 158 (11%)

Model experiment of this epoxy ring opening reaction on the compound 161 revealed interesting results (32) Ring opening

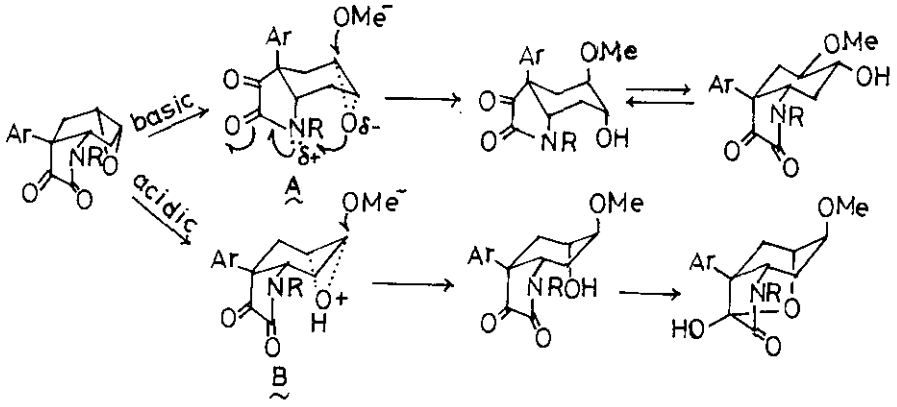


	162(B)	163(A)
MeOH-MeONa	1	: 2
MeOH-BF_3	6	: 1

1) NBA-H_2O-$HClO_4$ 2) MeONa-MeOH 3) MeOH-BF_3;$2Et_2O$ 4) LAH
5) CH_2O-MeOH,AcOH 6) TsCl-Py 7) DBU in DMSO,100°

Chart 18

with hot methanolic NaOMe gave the methoxy-acetal 162 and the methoxy-diketone 163 in 1:2 ratio, while in acidic condition (BF_3-etherate in MeOH) the ratio of 162 of 163 was 6:1. This reversion of stereochemical course of methoxyl introduction can be rationalized by assuming that ring opening in alkaline condition proceeds predominantly through the transition state of the conformation A due to the electrostatic interaction between the positive lactam nitrogen and the negative epoxide oxygen, while in an acidic condition the conformation B becomes dominant due to electrostatic repulsion between the lactam group and the protonated oxygen.



LAH reduction of 157 afforded the diol 164 (90%), again convex-face attack of the hydride took place. However, actual determination of its stereochemistry rests on its conversion into the racemic haemanthamine. Compound 164 under P-S conditions (CH_2O-MeOH followed by AcOH) gave the 5,10b-ethanophenanthridine 165 (50%) and the N-methyl derivative 166 (40%). Tosylation

of 165 at room temperature gave the monotosylate 167 (40%) which upon heating with DBU in DMSO gave (±)-haemanthamine 5 (50%)(27).

Short-cut synthesis of haemanthamine from the 11α-hydroxycrinene 144 was also accomplished (33)(Chart 19). Oxidation of 144 with mCPBA afforded an 1:1 mixture of an α-epoxide 168 and a β-epoxide 169 as their N-oxides, while the same peracid oxidation of the 144-acetate gave the undesired β-epoxide 171 exclusively. Acetylation of the α-epoxide-N-oxide with Ac_2O and pyridine gave, with concomitant reduction of N-oxide group, the acetate 170 which on treatment with BF_3-etherate in MeOH afforded the desired O-methyl derivative 172 as a single product. Sequence of the reactions described above, tosylation, detosylation, and hydrolysis, gave (±)-haemanthamine 5.

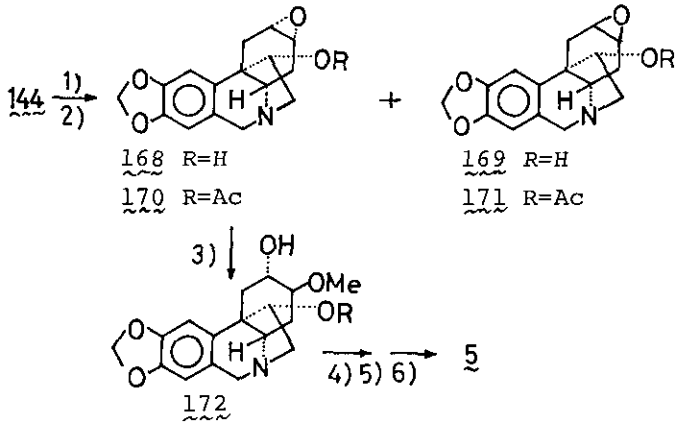
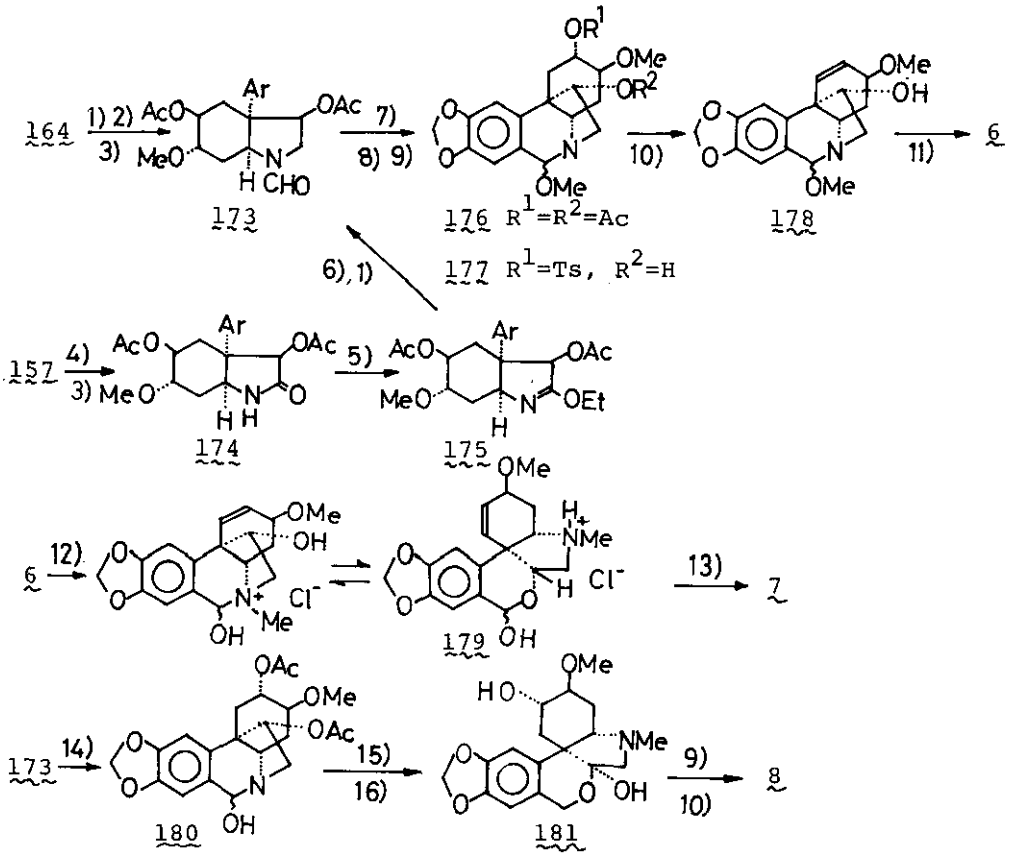


Chart 19

c) Haemanthidine. (±)-Haemanthidine 6 was synthesized as follows. The intermediate diol 164 was converted to the O-acetyl-N-formyl derivative 173 in 78% yield by formylation, hydrolysis, and acetylation. Alternatively it was obtained in better yield (over-all 75%) from the methoxy-acetal 157 by sequence of reactions (34); $NaBH_4$ reduction, acetylation, conversion to imidic ester, $NaBH_4$-$SnCl_4 \cdot 2Et_2O$ reduction (35), and formylation. 173 gives rise, when heated with $POCl_3$ in toluene followed by MeOH treatment, to the methoxy-compound 176 in 70% yield. The latter was hydrolysed, tosylated (64%), and detosylated with DBU in DMSO to yield O-methylhaemanthidine 178, from which (±)-haemanthidine 6 was prepared by hot 50% AcOH treatment (50% from 177).

d) Pretazettine and Tazettine. Methylation of 6 with MeI and conversion of the resulting methiodide to the chloride by ion exchange resin (Amberite IRA-400-Cl^-) gave (±)-prepazettine hydrochloride 179, (=(±)-haemanthidine methochloride) which on basification at pH 8 with ammonia and extraction afforded (±)-pretazettne 7 (34).

Alternative synthesis of (±)-tazettine 8 from the O-acetyl-N-formyl derivative 173 is as follows (28). When the compound 173 was treated with $POCl_3$ in xylene followed by aqueous base the hydroxy derivative 180 was obtained. Rearrangement of its methiodide to 181 required drastic base treatment (hot 20% NaOH). Tosylation of 181 and the subsequent elimination in the above mentioned way gave (±)-tazettine 8.



1) $HCOOAc$-Py 2) $NaHCO_3$-H_2O 3) Ac_2O-Py 4) $NaBH_4$ 5) Et_3OBF_4
6) $NaBH_4$-$SnCl_4$·$2Et_2O$ 7) $POCl_3$ in toluene, MeOH 8) NaOH
9) TsCl-Py 10) DBU 11) 50%AcOH 12) MeI, Amberite IRA-400-Cl^-
13) NH_4OH 14) $POCl_3$ in xylene, Na_2CO_3-H_2O 15) MeI 16) 20%NaOH

Chart 20

4-3 Crinamine, 6-Hydroxycrinamine, Criwelline, and Macronine

These alkaloids have the 3α-methoxy group (trans to aryl group). Stereospecific introduction of this group to the key intermediate 141 and hence total synthesis of the titled alkaloids came from the stereochemical analysis of an ionic addition reaction to a flexible bicyclic system (36).

The author argue that in the halohydrination reaction to 182, the ratio and stereochemistry of the two products (A′ and B′) are depend on the relative ease of the anion introduction to the two convertible transition state conformers (A and B) which are followed from the initial convex-face approach of the cation. The results of bromohydrination to 182 (a and b) given in the previous Section indicate that the conformer A is the preferable transition state, since 183 (a and b) were produced 6 times over 184 (a and b). Similar result was obtained in methoxybromination (NBA-MeOH-H^+) to 182a where 183a was produced over 184a (2:1 ratio).

However, the reaction to the acetoxy-lactam 182c should give the reverse result, since introduction of an anion through the conformer A is hindered by presence of the acetoxyl group (R^2), hence the reaction through the conformer B becoming preferable. Contribution of the boat form C as suggested in many text books

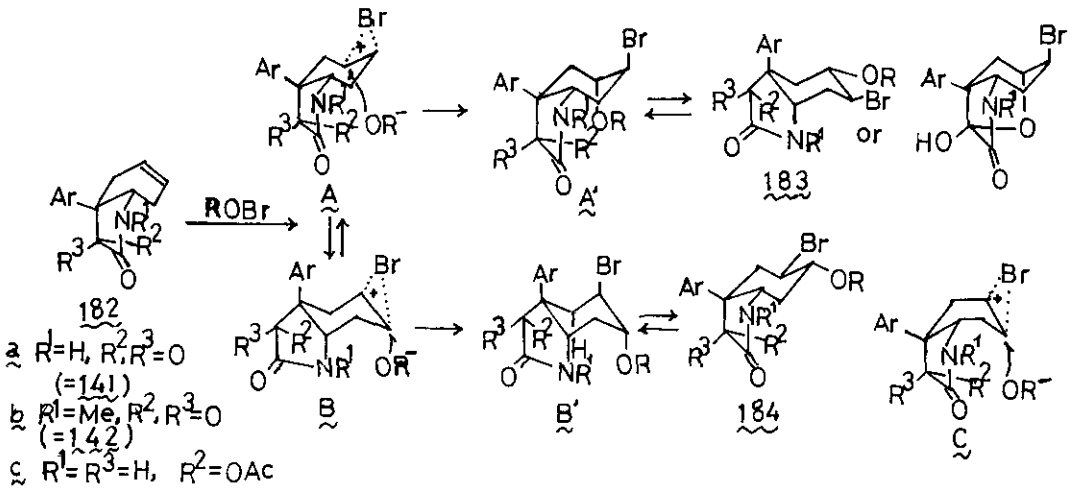
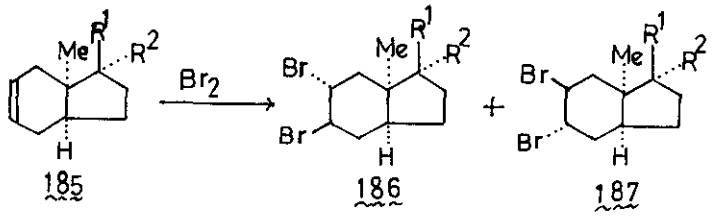


Chart 21

would be negligible since it serves severe steric hindrance for approaching the anion. In fact methoxybromination of 182c gave 183c and 184c in ratio of 1:5.

The validity of the above argument is supported by the result of bromination to the cis-tetrahydroindane derivatives 185a-c (37)(see Table 2).



185 → 186 + 187

	186	187
a R^1,R^2=O	——	98%
b R^1=OAc, R^2=H	48%	46%
c R^1=CH_2OAc, R^2=H	87%	——

Table 2

The methoxy-bromo compound 184c, though it has the correct stereochemistry for the present purpose, could not be dehydrobrominated to the desired 189. This is easily conceivable when considered that the dehydrobromination must occur through the conformation B' where $C_{1\alpha}$-H is seriously hindered from approaching the base. The sequence of reactions, hydrolysis, Jones' oxidation, dehydrobromination with DBU to 188, reduction, and reacetylation converted 184c to 189, but in low yield.

PhSeOMe was expected to react like BrOMe, the PhSe group in the intermediate 190 will be easily removed by cis-elimination (Sharpless method)(38). Thus treatment of 182c with $(PhSe)_2$ and NBA in MeOH followed by 3% H_2O_2 in THF afforded the desired 189 as a sole product (35%).

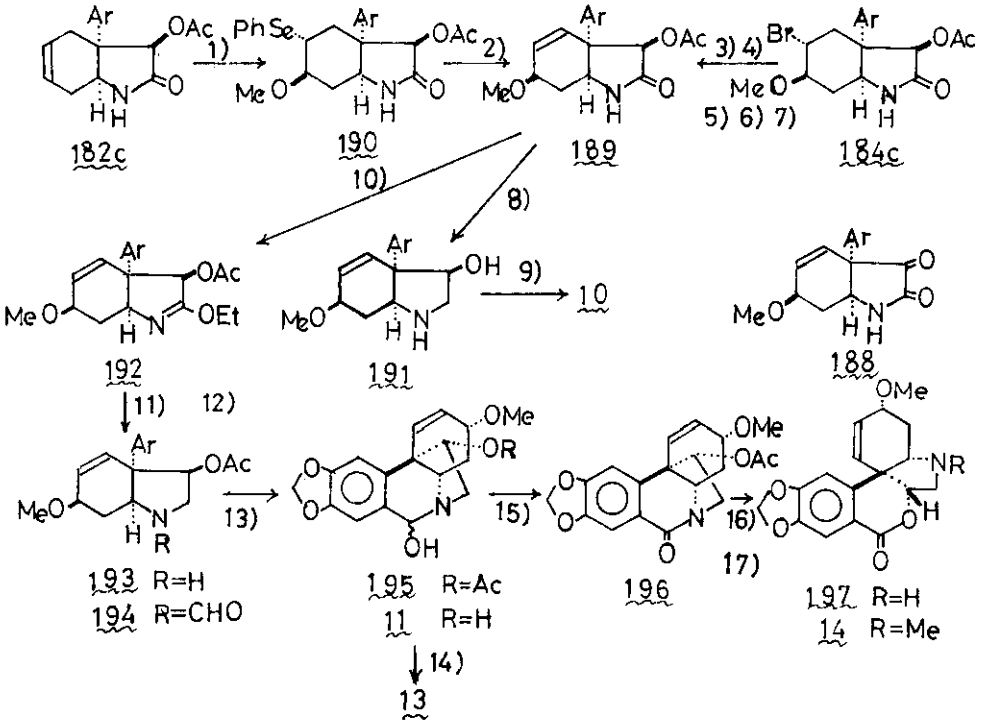
From this properly functionalized intermediate the titled natural alkaloids were synthesised as follows.

Reduction of 189 with LAH gave the amine 191. P-S cyclization of its hydrochloride (heating with 30% HCHO) gave (±)-crinamine 10.

The compound 189 was converted, on treatment with Meerwein reagent, to the imidic ester 192 which on reduction with $NaBH_4$-$SnCl_4 \cdot 2Et_2O$ in glyme (35) gave the amine 193. Heating of its formate 194 with $POCl_3$ in toluene, basification with aqueous NH_4OH gave the acetate 195 which on mild hydrolysis (K_2CO_3-MeOH) furnished (±)-6-hydroxycrinamine 11.

Methylation of 195 and treatment with base in the same manner with transformation of haemanthidine to tazettine afforded (±)-criwelline 13.

Oxidation of 195 with MnO_2 in CH_2Cl_2 gave the lactam 196 (70%), which on short hydrolysis (K_2CO_3-MeOH) and acid treatment of the hydrolysate yielded the lactone 197. Methylation of 197 with HCHO-$NaBH_4$ furnished (±)-macronine 14 (60%).



1) $(PhSe)_2$-NBA-MeOH 2) 3%H_2O_2, THF 3) NaOH 4) Jones' ox.
5) DBU 6) $Zn(BH_4)_2$ 7) Ac_2O-Py 8) LAH 9) HCl, CH_2O 10) Et_3OBF_4
11) $NaBH_4$-$SnCl_4$·$2Et_2O$ 12) HCOOAc-Py 13) $POCl_3$, 14) MeI, NaOH
15) MnO_2 16) K_2CO_3-H_2O 17) CH_2O-$NaBH_4$

Chart 22

5. Narciclasine and Lycoricidine

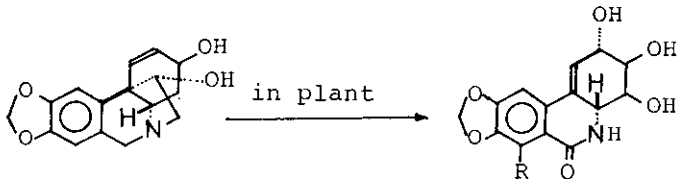
Narciclasine 198 and lycoricidine 199 are antimitotic and growth-inhibiting neutral substances which also occur in Amaryllidaceae and are known to be synthesized in plants from one of an 11-oxygenated 5,10b-ethanophenanthridine alkaloid, 11-hydroxy-vittatine 200, with loss of two-carbons unit (39).

Choice of the key intermediate 141 synthesizing lycoricidine 199 is therefore an interesting subject in somewhat biomimetic sense. Chart 23 illustrates the synthetic scheme of trans- and cis-dihydro-lycoricidine 208(a and b) starting from 141 (40).

This synthesis includes two important synthetic methods: one is B-N type cyclization of the urethan 205 to the lactam 206 by use of $POCl_3$ and $SnCl_4$, and the other is photoremoval of a corboxylate group from the carboxylate ion 207.

Application of the former reaction to 209 gave the lactam-ester 119, Hendrickson's intermediate to haemanthidine in 80% yield (41). The second reaction when applied to the lactam-acid 120 the trans-tetrahydrophenanthridone 210 was obtained exclusively.

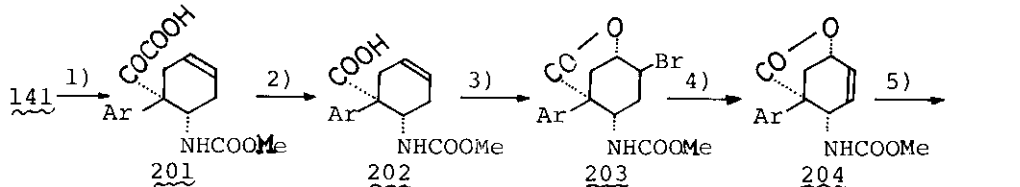
Different and independent synthesis of lycoricidine itself was reported by Ohta et al (42).



200

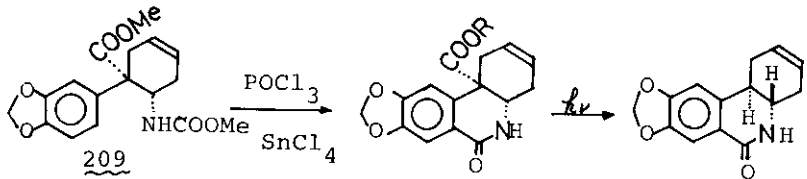
198 R=OH

199 R=H



201 202 203 204

205 206 207 208a,b



209

119 R=Me

120 R=H

210

1)ClCOOMe,KOH in CH_3CN,10%KOH 2)H_2O_2-NaOH 3)NBS in CH_2Cl_2
4)DBU in toluene,100° 5)OsO_4,Ac_2O-Py 6)$POCl_3$,$SnCl_4$
7)NaOH 8) hν

Chart 23

All the method above described for synthesis of 5,10b-ethanophenanthridines and related alkaloids include intriguing synthetic methods and ideas which may be widely applicable to synthesizing not only of this group but also those of other types. Sō far 5,10b-ethanophenanthridine group, synthesis of the ring A substituted alkaloids such as powelline and narciclasine and of the alkaloids with different substitution pattern at ring C such as buphanidrine and bowdensine will be the problems in future.

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