THE INDOLE ALKALOIDS OF JAPANESE PLANTS; STRUCTURES AND REACTIONS

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Indole alkaloids of several Japanese plants have been studied. Some chemical conversion works have also been made utilizing them as the starting materials.

The indole alkaloids which are formed from tryptophan and secologanin via a common intermediate vincoside are mostly produced by the tropical species of Loganiaceae, Apocynaceae and Rubiaceae plants. Some of them, e.g. reserpine, ajmaline and vincristine, are probably among the most important medicinal drugs known in these days.

Before we began our study on the indole alkaloids of Japanese plants, only fragmentary (though of great importance) works had been made in this field. Kondo reported the presence of oxindole alkaloids rhynchophylline (71a) and isorhynchophylline (72a) in Uncaria rhynchophylla Miq.[1] and also characterized formosanine (73) and isoformosanine (74) in U. Kawakamii Hayata which distributes in Formosa.[2] β-Yohimbine (44b) was isolated from an Amsonia species (Apocynaceae) by Kimoto.[3]

In 1965 Haginiwa and Sakai started this series of works from the study of the constituents of Gardneria spp. (Loganiaceae). Four species are known in Japan and one in Formosa.[4]

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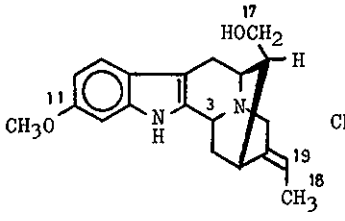
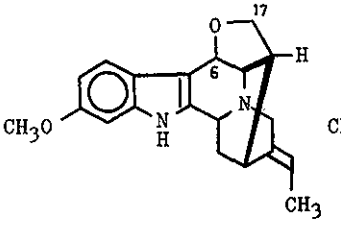
Dedicated to Professor Tsuneo Takemoto on the occasion of his retirement.

Gardneria nutans Sieb. et Zucc.	Group A
Gardneria insularis Nakai	
Gardneria multiflora Makino	Group B
Gardneria Shimadai Hayata	
Gardneria liukiuensis Hatsushima	

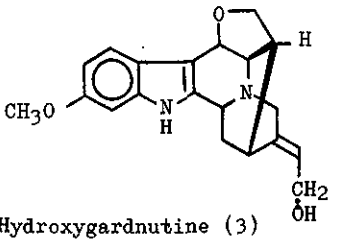
These plants seem to be divided morphologically into two groups (A and B). The plants of the group A bear one to three flowers separatedly on the top of a flower stem, while those of the group B bear the flowers congestedly (three to ten). It is interesting to note that a distinct difference exists in the alkaloidal constituents of the two groups. The constituents of the plants of the group A are shown in Chart 1.



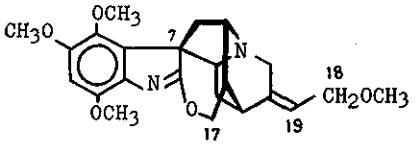
Gardnerine (1)



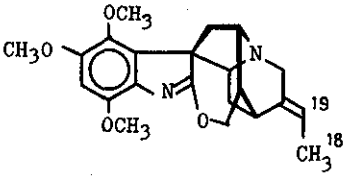
Gardnutine (2)



Hydroxygardnutine (3)



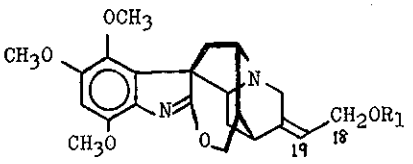
Gardneramine (4)



19-(E)-18-Desmethoxygardneramine (5)

Chart 1. from Gardneria nutans Sieb. et Zucc.

The sarpagine type indoles (1-3) possessing a methoxyl group at $C_{(11)}$ on their aromatic rings are characteristic to this group of plants.[6] Gard-

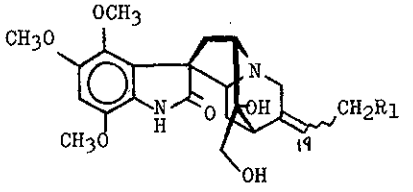


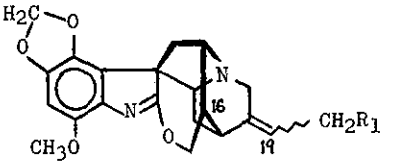
19-(E)-18-desmethoxygardneramine (5)

Gardneramine N-oxide (7)

R_1= CH_3, Gardneramine (4)

R_1= H, 18-Demethylgardneramine (6)

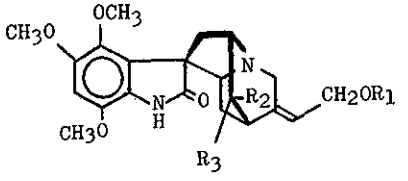




R_1= H, Chitosenine (16(R),19(Z)or(E)) (8)

R_1= OCH_3, Gardfloramine (19(Z)or(E)) (9)

R_1= H, 18-Desmethylgardfloramine (19(Z)or(E)) (10)



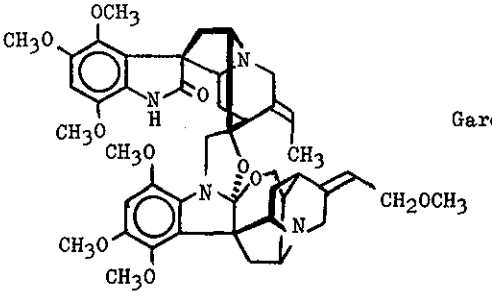
R_1=CH_3, R_2=H, R_3=CH_2OH, Alkaloid I (11)

R_1=CH_3, R_2=CH_2OH, R_3=H, Alkaloid J (12)

R_1=CH_3, R_2=OH, R_3=CH_2OH, Alkaloid N (13)

R_1=H, R_2=H, R_3=CH_2OH, Alkaloid M (14)

R_1=H, R_2=CH_2OH, R_3=H, Alkaloid L (15)



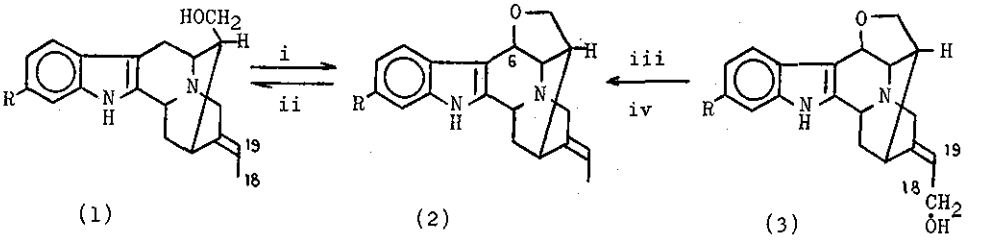
Gardmultine (16)

Chart 2. from Gardneria multiflora Makino. (Loganiaceae) [5,8,10]

nutine (2) and hydroxygardnutine (3) could be regarded as the alkaloids formed by the stepwise oxidation at $C_{(6)}$ and $C_{(18)}$ of 1. This type of alkaloids with the oxygen function at $C_{(6)}$ was found by us for the first time though almost at the same time a similar type alkaloid having $C_{(6)}$-$C_{(17)}$ ether ring was found from a Voacanga species by a research group of Belgium.[7] The structure of gardneramine (4) was elucidated chemically and finally by the X-ray analysis of its cyanobromide.[9] The basic skeleton of 4 is regarded as an oxindole formed by the oxidative rearrangement of a gardnerine type indole.

As shown in Chart 2 quite many alkaloids have been isolated from the plants of the group B. But the only common constituents to the plants of the group A are 4 and 5. All the alkaloids shown in Chart 2 are either oxindoles or the equivalents. No gardnerine type indole alkaloid has been found in this group.[10]

The absolute configuration of 1 was determined by the chemical correlation of the demethoxylated compound with a degradation product of ajmaline.[6] Since 2 and 3 have been connected with 1 as shown in Chart 3, their absolute configuration are also firmly established.[11]



(1) (2) (3)

R= $-OCH_3$

i) CrO_3/ H_2SO_4 or t-BuOCl ii) $LiAlH_4$ iii) HBr-AcOH iv) Zn-AcOH

Chart 3.

In the course of our study on the determination of the geometry of Δ^{19} double bond of 3, an interesting reaction was found to occur at the $C_{(6)}$-$C_{(17)}$ ether ring system under the Huang Minlon reduction conditions. Thus the ether oxygen at $C_{(6)}$ of 2 was lost and the product was proved to be 20.[11] (Chart 4). A possible reaction mechanism is shown in Chart 5. Though we have not succeeded in isolating the intermediate 22, its existence was proved by the fact that a deuterium atom was incorporated to $C_{(17)}$ of 21 when $(CD_2OH)_2$ was used in the place of triethylene glycol in the condition iv. (Chart 4).

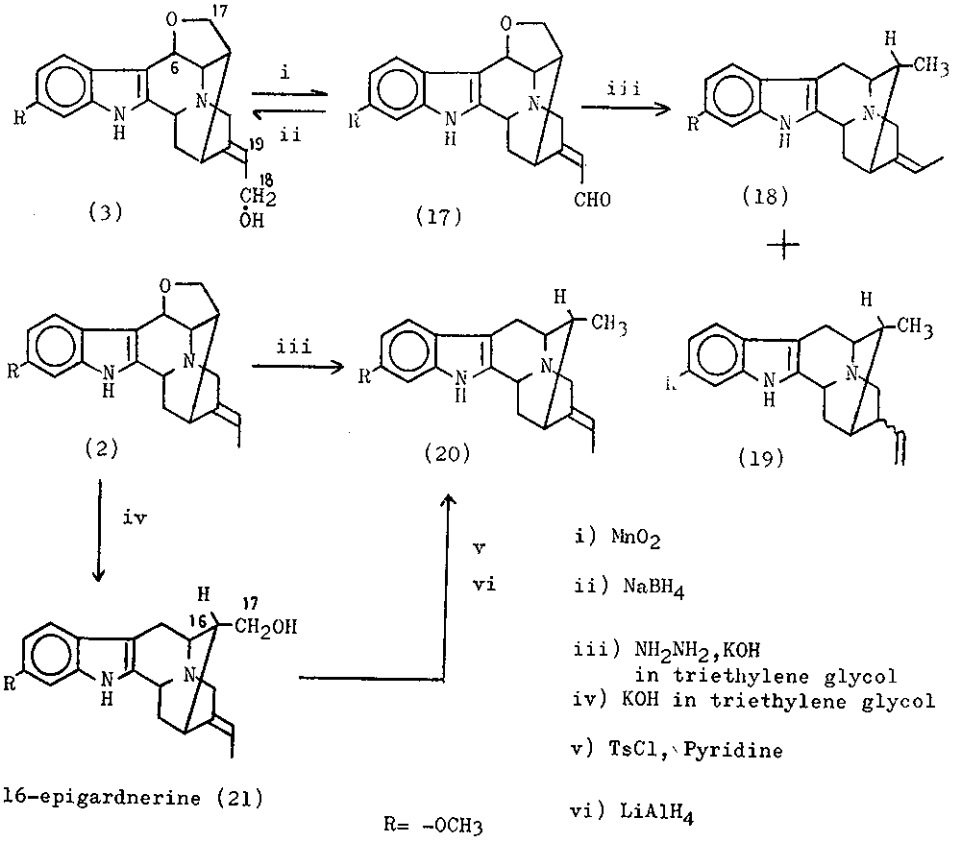
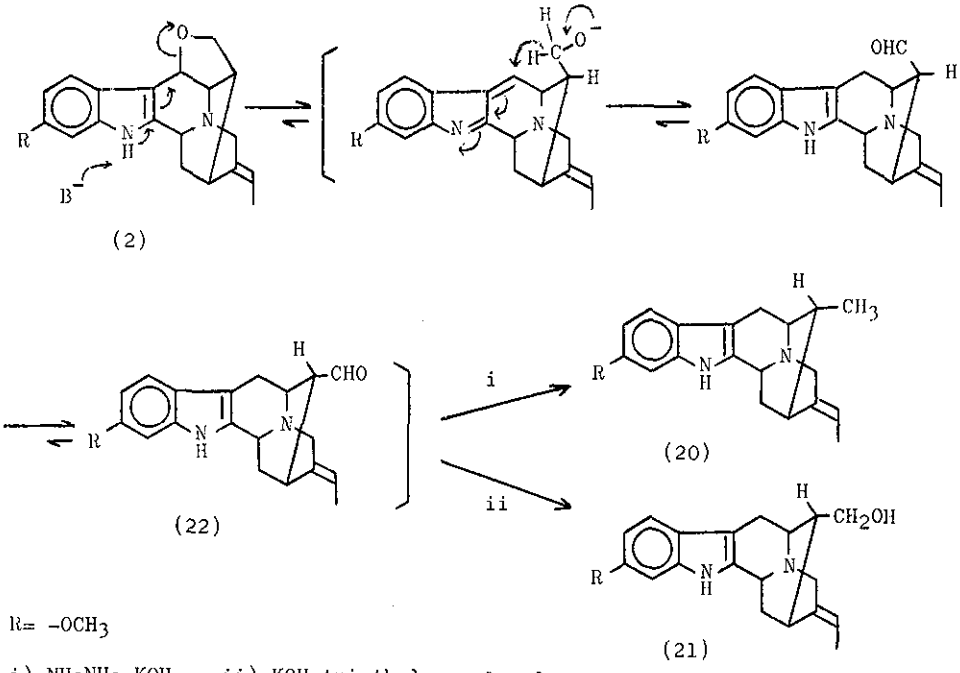


Chart 4.

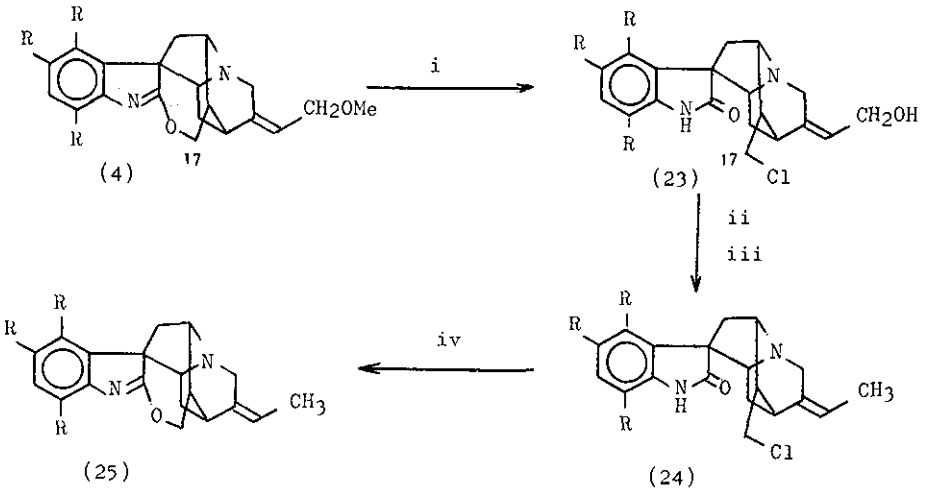


(2) (20) (21) (22)

Chart 5

The configuration of $C_{(19)}=C_{(20)}$ double bond of 5 was determined. Thus Δ^{19}-Z-demethoxygardneramine (25) was prepared from 4 via an allylic alcohol (23), the Δ^{19} configuration of which had been proved to be same as that of the starting material (4). The natural alkaloid 5, however, was not identical with the derived compound 25, and therefore E configuration of 5 was proved. The same conclusion was obtained from NOE experiment.

It is interesting to note that all the Gardneria alkaloids possessing ethylidene side chain (1,2 and 5) have E type geometry at Δ^{19}. On the other hand, in the $C_{(18)}$-oxygenated analogues the geometry was not predictable.



R= $-OCH_3$ i) 2N-HCl , Δ ii) HBr-AcOH iii) Zn-AcOH

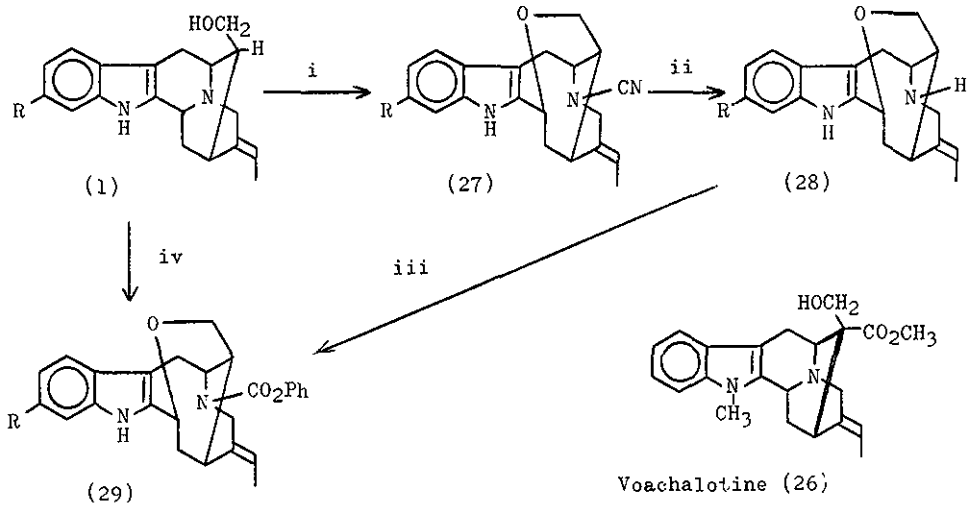
iv) KOH in EtOH

Chart 6.

Thus, while the Δ^{19} geometry of 3 was E that of 4 was Z type.

The above reactions were mostly found in the course of the structure determination and were studied for this aim. We then made some attempts to convert 1 to some other natural alkaloids.

Since the first report by Dolby and Sakai[12] appeared in 1964, several reports concerning the C/D ring cleavage of indole alkaloids have been published. Albright and Goldman[13] used cyanogen bromide in ethanol to cleave the C/D ring of yohimbine derivatives. Pecher et al.[14] used the same reagent to a sarpagine type alkaloid voachalotine (26). Recently we found that chlorocarbonate esters react with various types of alkaloids in a similar manner as cyanogen bromide. (Chart 7).[15]



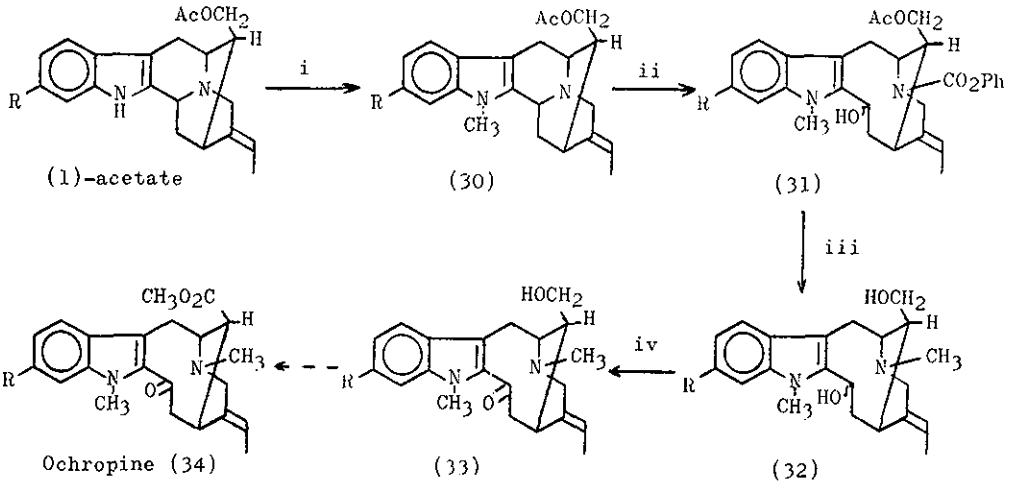
R= $-OCH_3$ i) $BrCN-Na_2CO_3$ in $CHCl_3$ ii) H_2O (NaOH)

iii) $ClCO_2Ph$/ Py. iv) $ClCO_2Ph-Na_2CO_3$ in $CHCl_3$

Chart 7.

One of the advantages of this cleavage reaction using chlorocarbonate esters is that the corresponding $N_{(b)}$-methyl derivatives can be readily obtained by reducing the resulted urethanes with lithium aluminumhydride.

When $N_{(a)}$-methyl-gardnerine acetate (30) was vigorously stirred in the two layers of solvents ($CHCl_3$ (ethanol free) and water) under the presence of phenyl chlorocarbonate an epimeric mixture of alcohol 31 was obtained (70 %). In the route shown in Chart 8, a primary alcohol 33 was prepared. Though conversion of the hydroxymethyl group of 33 to a carbomethoxy group would give a natural compound ochropine (34), we have not succeeded in this final step.

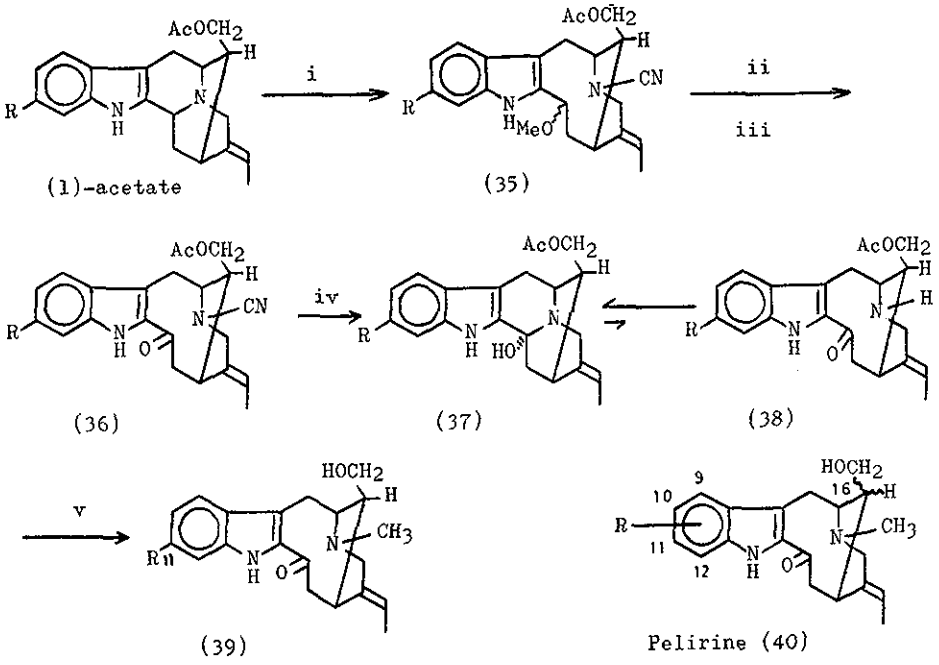


R= -OCH_3 i) CH_3I,$NaNH_2$ in liq.NH_3 ii) $ClCO_2Ph$-Na_2CO_3 in H_2O-$CHCl_3$

iii) $LiAlH_4$ iv) CrO_3-Py

Chart 8.

A natural alkaloid pelirine (40)[16] isolated from the roots of Rauwolfia perakensis has the structure shown in Chart 9, in which the position of the methoxyl group and the configuration of the substituent at $C_{(16)}$ remains undetermined. Conversion of 1 to the compound having one of the possible structures of pelirine was then attempted. (Chart 9). The physical constants and the spectral data of the final compound 39, however, did not agree with the reported values for 40. Nonidentity of their UV spectra strongly suggested that the position of the methoxyl group of 40 was at some place other than $C_{(11)}$. One of the interesting observations in this sequence of reactions was that the N-CN group of 36 was easily removed on mild treatment with aqueous acetic acid containing ammonium acetate to give 38.



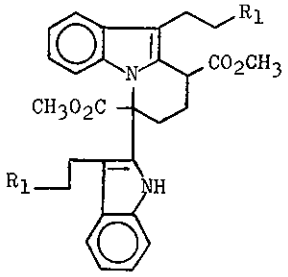
R= $-OCH_3$ i) $BrCN-Na_2CO_3$ in $MeOH-CHCl_3$ ii) t-BuOCl iii) H_2O

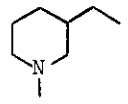
iv) $AcOH-H_2O$/ $AcONH_4$ v) H_2CO, H_2/ Pd-C

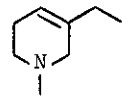
Chart 9.

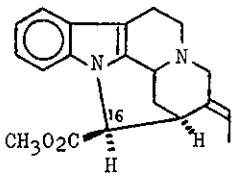
Amsonia elliptica Roem. et Schult (Japanese name; Choji-so) was long known to contain β-yohimbine (44b).[3] A few foreign species have also been reported to contain indole alkaloids : e.g. tabersonine and β-yohimbine in A. angustifolia [17] and eburnamine type alkaloids in A. tabernaemontana[18]. For the purpose of examining the minor constituents we reinvestigated the alkaloidal constituent of A. elliptica. Various types of alkaloids were

newly isolated.[22] (Chart 10). Among them secamine(42) and tetrahydrosecamine (41) were the novel type dimetic alkaloids whose structures were elucidated by Smith et al.[20] in 1968. These alkaloids are known to be formed from the corresponding precursors presecamine(49) and tetrahydropresecamine in an acidic condition. The occurrence of presecamines in the plants has also been proved, though the corresponding monomeric components secodine(48) and dihydrosecodine have not been isolated.[21]

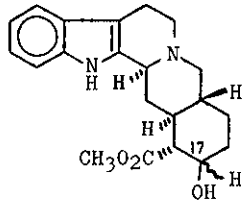


R_1=  Tetrahydrosecamine (41)

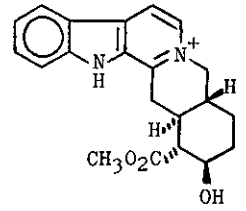
R_1=  Secamine (42)



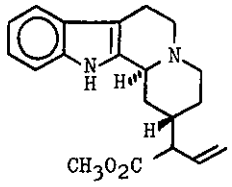
Pleiocarpamine (43)



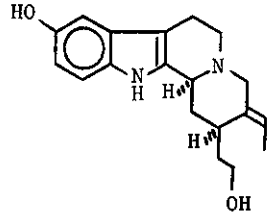
17β-H; Yohimbine (44)a
17α-H; β-Yohimbine (44)b



3,4,5,6-Tetradehydro-β-yohimbine (45)

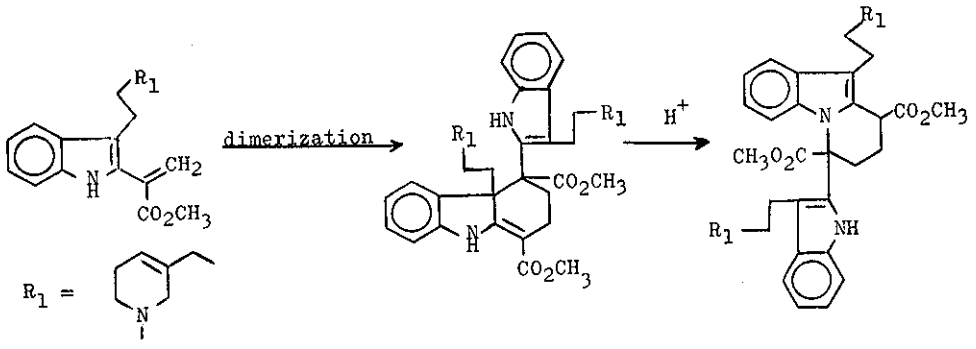


Antirhine (46)a
Antirhine-α-methochloride (46)b



10-Hydroxygeissoschizol (47)

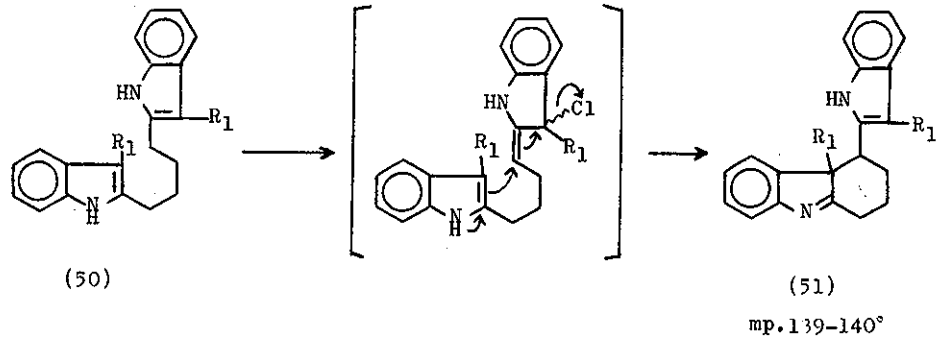
Chart 10 from roots of Amsonia elliptica Roem. et Schult (Apocynaceae)



Secodine (48) Presecamine (49) Secamine (42)

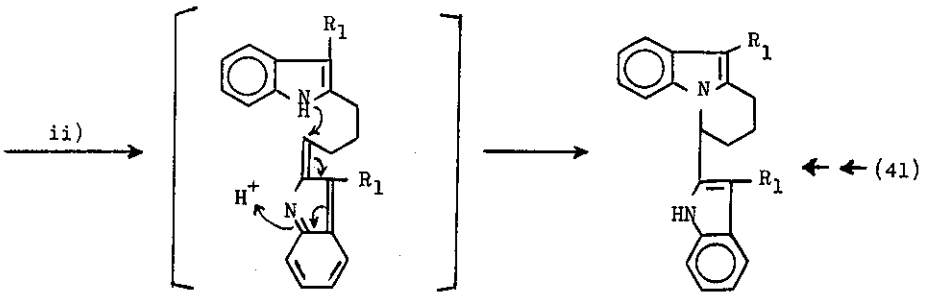
Chart 11

Next our synthetic approach to this group of dimeric alkaloids will be described.[22] (Chart 12).



(50) (51)

mp.139-140°



R_1 = (±) $-CH_2CH_2-N$

(41) : Tetrahydrosecamine

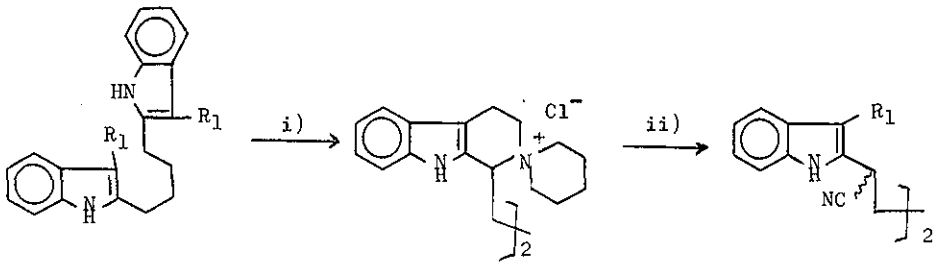
(52) Amorphous

i) 1 mol t-BuOCl, NEt_3 in CH_2Cl_2

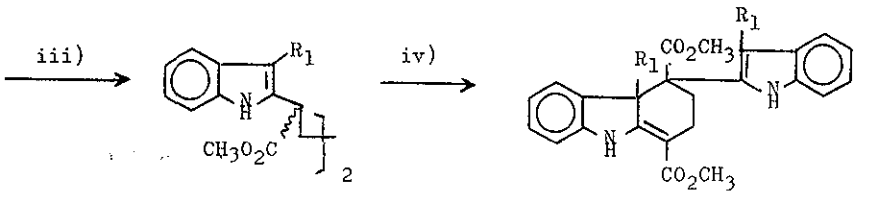
ii) 2N-HCl

Chart 12

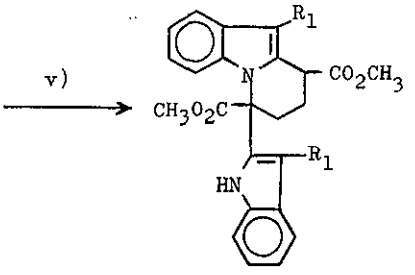
On oxidation of the known bisindole(50) with one molar equivalent of t-butyl hypochlorite at room temperature, a presecamine analogue(51) was obtained. As reported on natural presecamine, 51 rearranged to a compound (52) having the secamine skeleton. The same compound (52) was derived from natural tetrahydrosecamine by the chemical degradation and as the result



(50) (53) (54)



(55) (56)



(57)

R_1 = $-CH_2CH_2-N$⟨ ⟩

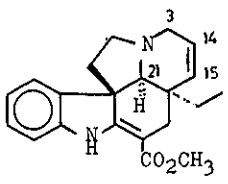
i) more than 2 mols t-BuOCl
ii) NaCN / DMSO
iii) MeOH-HCl-H_2O
iv) 1 mol t-BuOCl
v) H^+

Chart 13

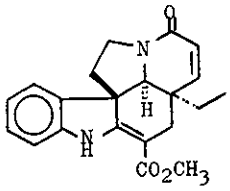
the two specimens were proved to be identical spectrometrically. (Mass, NMR, IR and UV spectra.)

When four molar equivalents of t-butyl hypochlorite was used in the first step of our synthesis, a quarternary salt (53) was obtained in 20 % yield. Making use of 53, we succeeded in synthesizing bisnorethylpresecamine (56) and the corresponding secamine (57). (Chart 13).

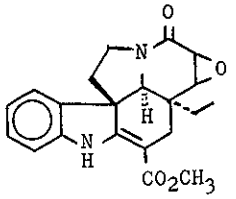
Returning to the subject of the constituents of Amsonia elliptica, the constituents of its seeds were studied. The main base tabersonine (58) and five minor bases were isolated.[23] (Chart 14).



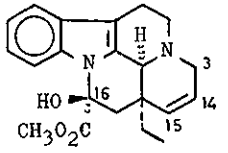
Tabersonine (58)



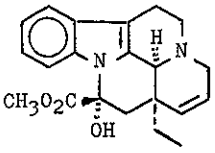
3-Oxotabersonine (59)



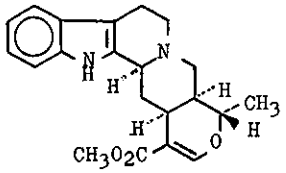
14,15-Epoxy-3-oxo-vincadifformine (60)



Δ^{14}-Vincamine (61)



16-Epi-Δ^{14}-vincamine (62)



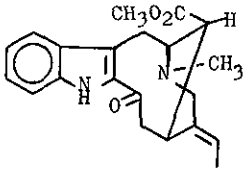
Tetrahydroalstonine (63)

from seed of Amsonia elliptica Chart 14

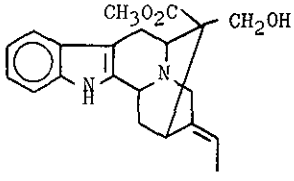
The structure of a new base 3-oxotabersonine (59) was proved by the direct comparison of its dihydroderivative with the synthetic specimen of 3-oxovincadifformine reported by Prof. LeMen.[24] This comparison was made in the labo-

ratory of Prof. LeMen and the two specimens were found to be identical except their optical properties. Furthermore oxidation of 58 with potassium permanganate afforded 3-oxotabersonine which was found to be identical with the above natural base (59). Another new base was elucidated as 14,15-epoxy-3-oxovincadifformine (60) mainly from the NMR evidences.

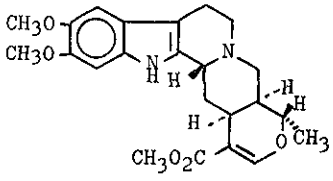
Ochrosia Nakaiana Koidz. is another indole alkaloid containing Apocynaceae plant which grows in Bonin islands locating about 1000Km south of Tokyo. Various types of indole alkaloids were found in this plant as shown in Chart 15. A new base 11-methoxyserpentine (69) was isolated as the anhydronium base



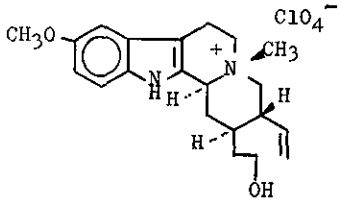
Vobasine (64)



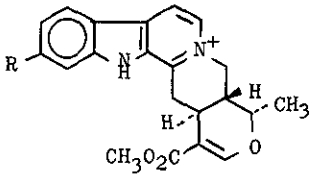
Akuammidine (65)



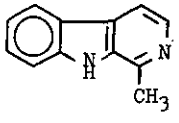
Reserpiline (66)



10-Methoxycorynantheol -β-methoperchlorate(67)



R = H Serpentine(68)
R = OCH_3 11-Methoxyserpentine(69)

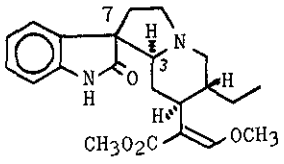


Harman (70)

from bark of Ochrosia Nakaiana Koidz.[25] Chart 15
(Apocynaceae)

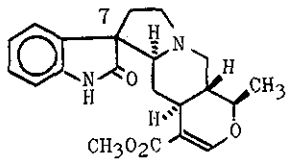
$C_{22}H_{22}N_2O_4$ (M^+, m/e 378) from which the known base tetraphylline was obtained on reduction with sodium borohydride.

The hooks of Uncaria sinensis Oliv. (Rubiaceae) have long been used as an important crude drug in the traditional Chinese medicine. Analysis of the prescriptions suggests that it might have sedative activity. Several plants of this genus can be found in Japan and the surrounding area. Thus U.rhynchophylla Miq. grows in the middle to west part of Japan. In Formosa two species U.Kawakamii Hayata and U.florida Vidal. are found. As described in the beginning of this article Kondo et al. showed the presence of oxindole alkaloids in this genus, i.e. rhynchophylline(71a) and isorhynchophylline(72a)



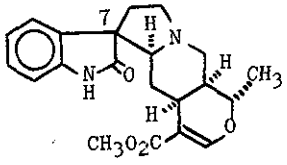
C_7:R Rhynchophylline (71)a

C_7:S Isorhynchophylline (72)a



C_7:R Formosanine (73)

C_7:S Isoformosanine (74)



C_7:R Pteropodine (75)

C_7:S Isopteropodine (76)

Chart 16.

in U.rhynchophylla[1] and formosanine (73) and isoformosanine (74) in U.Kawakamii.[2] We studied the alkaloidal constituents of U.rhynchophylla and U.florida,[26] and some conversion works were made using their constituents. First our works of the constituents of U.florida will be described.

This plant was collected in Formosa and was found to contain pteropodine (75) and isopteropodine (76) in the total yield of about 0.3 %. These two oxindoles are epimeric at $C_{(7)}$. Either 75 or more conveniently a mixture of 75 and 76 was converted into the same epimeric mixture of the iminoethers 77a and 77b on treatment with the Meerwein's reagent ($Et_3O^+BF_4^-$). A 2,3-seco

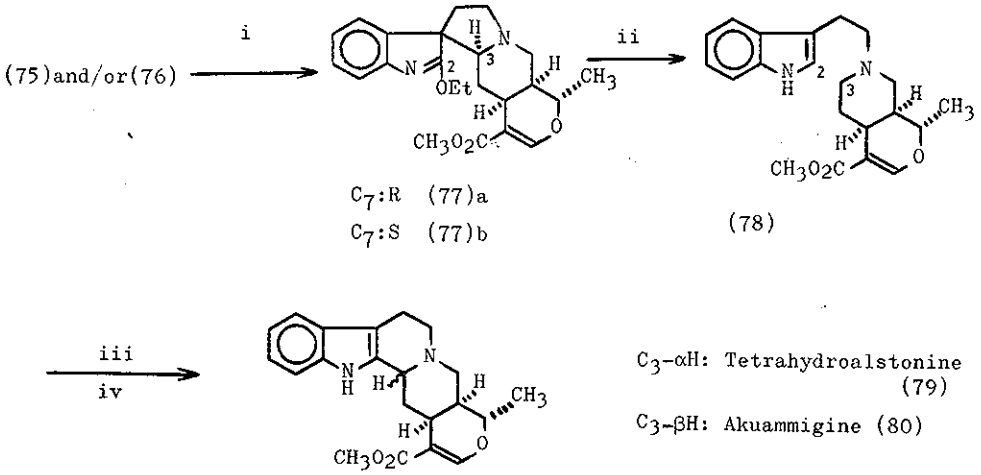
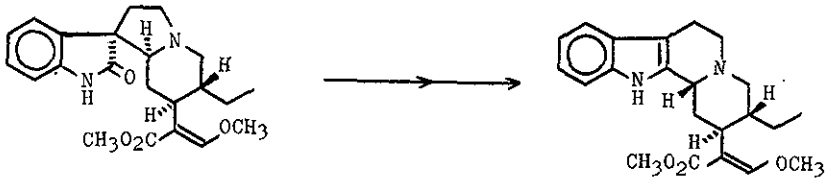


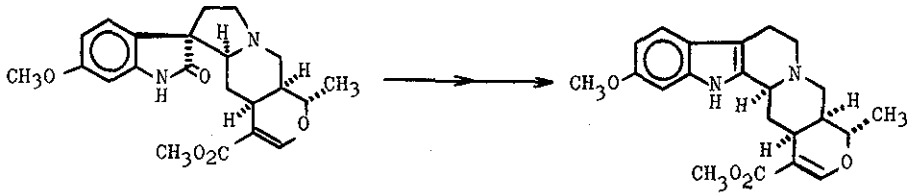
Chart 17.

alkaloid (78) was obtained in one step when the above iminoether mixture was reduced with sodium borohydride in acetic acid at room temperature. The 2,3-seco alkaloid (78) was then submitted to oxidative ring closing reaction using mercuric acetate to form natural tetrahydroalstonine (79) and akuammigine (80). Taylor and Finch[28] succeeded in converting natural indole alka-

loids to the corresponding oxindole alkaloids. Our work was the first example of the inverse change.[27] We further succeeded in converting 72a to hirsutine (93a). Recently this general method was employed by LeMen et al.[29] for converting a new base caboxine A (82) to reserpinine (83) of the known structure.



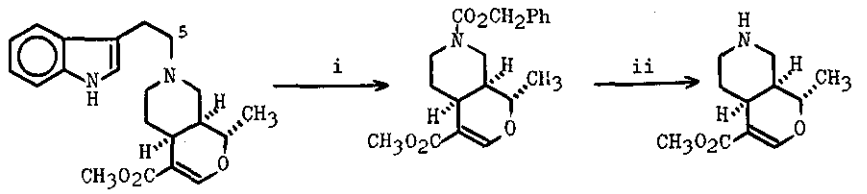
Isorhynchophylline (72)a Hirsutine (93)a



Caboxine A (82) Reserpinine (83)

Chart 18.

A piperidine derivative (85), $[\alpha]_D$ -66°, was obtained in a good yield

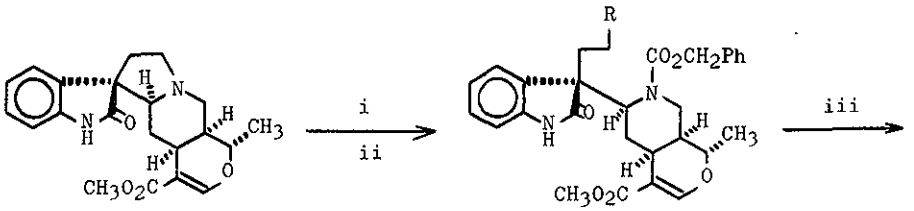


(78) (84) (85)

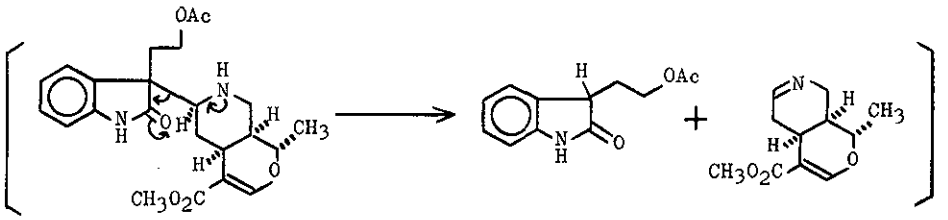
i) $ClCO_2CH_2Ph$ ii) H_2/ Pd-C

Chart 19.

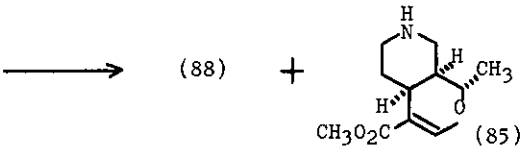
from the 2,3-seco alkaloid (78) by cleaving the $C_{(5)}$-$N_{(b)}$ bond with carbobenzyloxy chloride as shown in Chart 19.[30] When 75 was treated with the same reagent in hot benzene, a chloride (86a) with the cleaved C ring was obtained in 52 % yield. It is interesting to note that 76 did not undergo the same type ring cleavage reaction with carbobenzyloxy chloride. Substitution of the chloride residue of 86a with acetoxyl group followed by catalytic reduction under acidic condition enabled us to obtain the same piperidine derivative (85) as was obtained from 78. The yield of 85 was 60 % from 86a. (Chart 20).



(75) (86) a: R= Cl
b: R= OAc



(87) (88) (89)

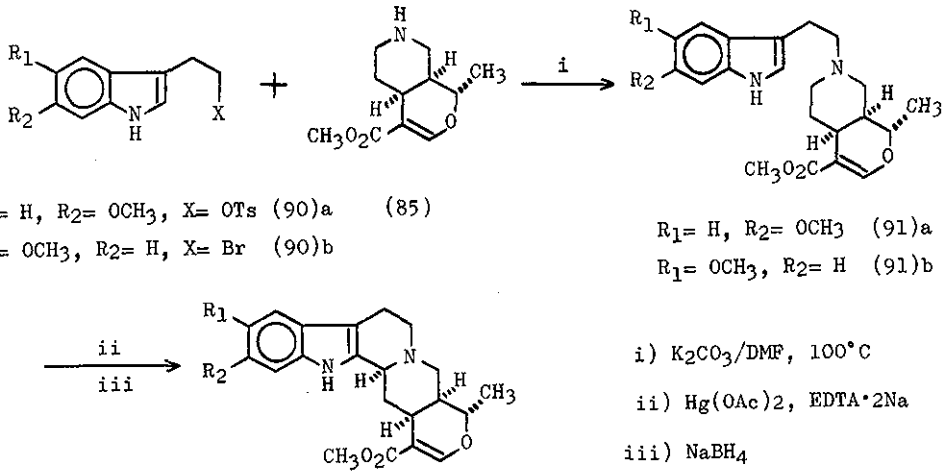


(88) (85)

i) $ClCO_2CH_2Ph$ in benzene
ii) NaOAc in DMSO
iii) H_2/ Pd in aq.AcOH

Chart 20

The partial synthesis of reserpinine (83) [33] and aricine (92) [34] was carried out by using this piperidine (85) as shown in Chart 21.



R_1= H, R_2= OCH_3, X= OTs (90)a (85)
R_1= OCH_3, R_2= H, X= Br (90)b

R_1= H, R_2= OCH_3 (91)a
R_1= OCH_3, R_2= H (91)b

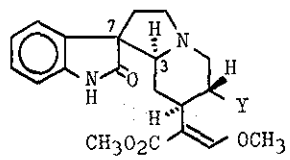
i) K_2CO_3/DMF, 100°C
ii) $Hg(OAc)_2$, EDTA·2Na
iii) $NaBH_4$

R_1= H, R_2= OCH_3 Reserpinine (83)
R_1= OCH_3, R_2= H Aricine (92)

Chart 21.

As stated above U.rhynchophylla has been known to contain rhynchophylline (71a) and isorhynchophylline (72a). But our reinvestigation of the constituents of this plant proved that indoles, hirsutine (93a) and hirsuteine (93b), are contained in almost equal amounts as the above oxindoles.[35] Furthermore two minor bases, akuammigine (80) and geissoschizine methylether (94), were newly isolated from the barks and roots.[36] Geissoschizine methylether (94)was a new base and the structure was proved by catalytic reduction to give a mixture of dihydrocorynantheine (93c) and corynantheidine. The $C_{(3)}$-β H configuration of 93a had been elucidated by Beckett et al. from the various spectral

evidences.[37] We proved this chemically by converting 93a to 93c in hot acetic acid.

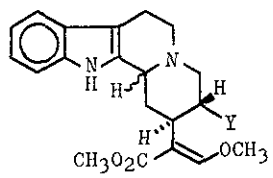


C_7:R, Y= Et Rhynchophylline (71)a

C_7:R, Y=-CH=CH_2 Corynoxeine (71)b

C_7:S, Y= Et Isorhynchophylline (72)a

C_7:R, Y=-CH=CH_2 Isocorynoxeine (72)b

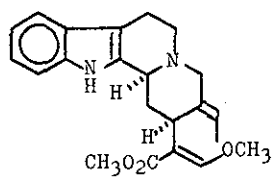


C_3-βH, Y= Et Hirsutine (93)a

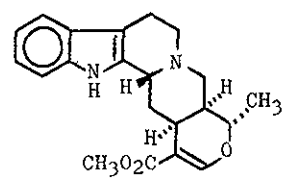
C_3-βH, Y=-CH=CH_2 Hirsuteine (93)b

C_3-αH, Y= Et Dihydrocorynantheine (93)c

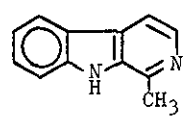
C_3-αH, Y=-CH=CH_2 Corynantheine (93)d



Geissoschizine methyl ether (94)



Akuammigine (80)

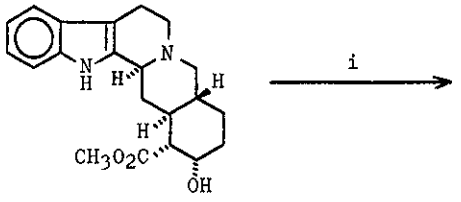


Harman (95) (from hooks)

Chart 22. from roots and bark of Uncaria rhynchophylla Miq.

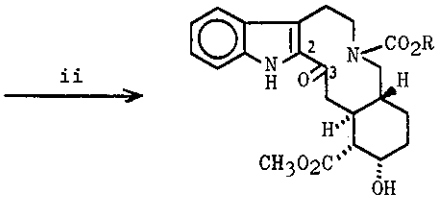
It was described in the earlier part of this article that C/D ring cleavage by chloroformates was successfully made for gardnerine (1) and its derivatives which have sarpagine type skeleton. (Chart 8 and 9). The same type reaction was observed to occur on yohimbinoid alkaloids, e.g. yohimbine

(44a) and reserpine (98), the former has trans- and the latter has cis-fused C/D ring systems. The reaction products were then easily oxidized to 2-acyl indole derivatives (97) and (99) respectively. (Chart 23).



Yohimbine (44)a

(96)
mixture of C_3(R)and(S)



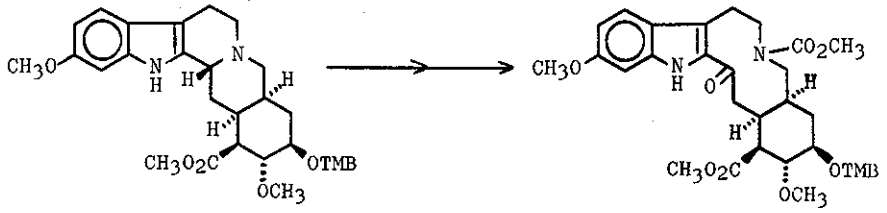
R= Et, mp 178-182° (97)a

R= Ph, mp 190-191° (97)b

R= $PhCH_2$, amorph. (97)c

i) $ClCO_2R/EtOH-CHCl_3-Na_2CO_3$
60-80 % yield

ii) t-BuOCl
30-80 % yield



Reserpine (98)

(99)

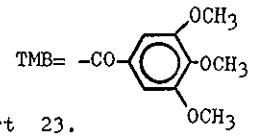
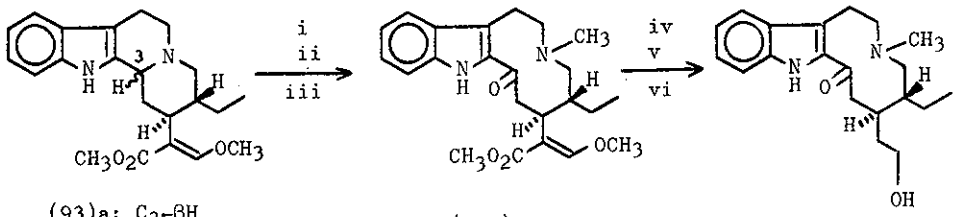


Chart 23.

Sakai[12] already reported the conversion of 93c to dihydroburnamicine (101) via a 2-acyl indole (100) as shown in Chart 24. Basing on the above findings



(93)a: C_3-βH
(93)c: C_3-αH

(100)

Dihydroburnamicine
(101)

i) $Pb(OAc)_4$ ii) CH_3I iii) NaOAc in aq.AcOH iv) $H_2O(OH^-)$
v) $-CO_2$ (H^+) vi) $NaBH_4$

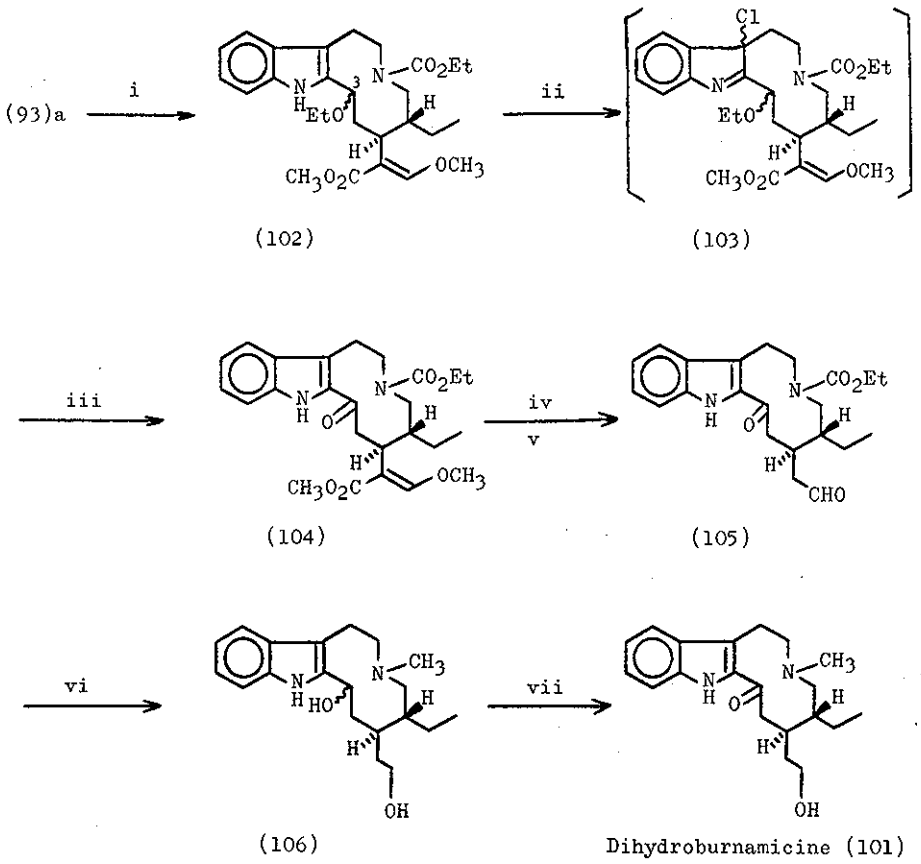
Chart 24.

and making use of hirsutine(93a) as the starting material a new conversion to 101 was attained. (Chart 25).

C/D ring cleavage of 93a was successfully made by use of alkyl chloroformates as on 44a. When the resulting two epimers (102) were treated with t-butyl hypochlorite followed by either filtration of the crude product through alumina column or acid treatment a 2-acyl indole (104) was obtained in a good yield. This compound (104) was then stepwisely treated with alkali and with dilute hydrochloric acid in dioxane to give an aldehyde (105), which was reduced with lithium aluminumhydride to a diol (106). Selective oxidation of the hydroxyl group at $C_{(3)}$ of 106 either with t-butyl hypochlorite or active manganese oxide gave 101.[38] (Chart 25).

As described above geissoschizine methylether (94) was isolated from U.rhynchophylla though the yield was low (0.01 % from dry roots). Using this compound (94) as the starting material the partial synthesis of natural burnamicine (112) was made.

The first attempt along the scheme shown in Chart 24 using lead tetraacetate and methyl iodide was given up owing to the low yields of the each



i) $ClCO_2Et/EtOH-CHCl_3-Na_2CO_3$ ii) t-BuOCl iii) $H_2O(H^+)$ iv) $H_2O(OH^-)$
v) $-CO_2$ (H^+) vi) $LiAlH_4$ vii) t-BuOCl or MnO_2

Chart 25.

reaction step. The route shown in Chart 26 was also ineffective, since the

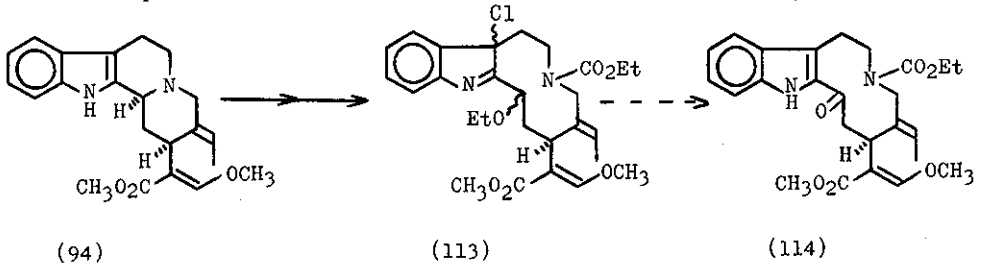
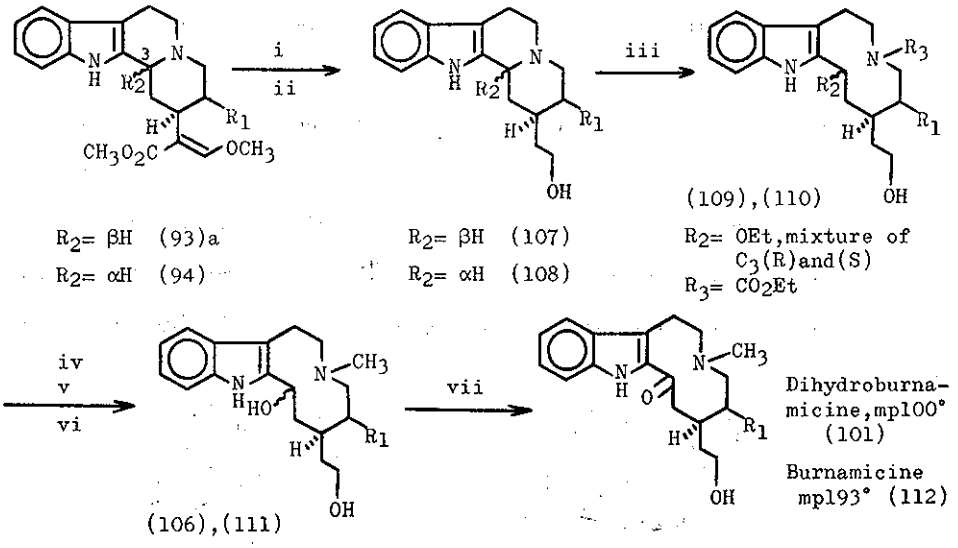


Chart 26.

intermediate (113) was unexpectedly stable and the conversion to 114 under either acidic or basic condition was unsuccessful. (Chart 26).

Ultimately this transformation was accomplished in the route shown in Chart 27. Thus 94 and 93a were converted to geissoschizol (108) and hirsutinol (107) respectively by hydrolysis and decarboxylation of the β-methoxy acrylic ester moiety followed by reduction of the resulting aldehyde to the alcohols. These compounds were then submitted to the ring cleavage reac-



i) $H_2O(H^+)$, ii) $NaBH_4$ iii) $ClCO_2Et/EtOH-CHCl_3-Na_2CO_3$ iv) t-BuOCl
v) $H_2O(H^+)$ vi) $LiAlH_4$ vii) MnO_2

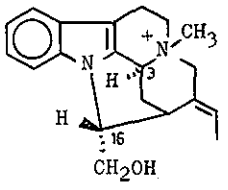
Chart 27.

tion with ethyl chloroformate, and after the subsequent reaction steps 112 and 101 were obtained respectively in good yields.[39]

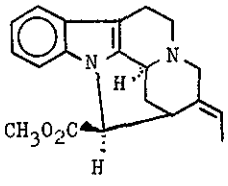
This partial synthesis of 112 from 94 forms the first chemical estab-

lishment of the absolute configuration of natural burnamicine (112). It is interesting to point out here the fact that whereas 101 shows the specific rotation of + 125°, 112 has that of the opposite sign, - 240° (Lit. - 280°). Furthermore the CD spectra of the both compounds show the maxima of the opposite signs. As is evident from the above formation route the absolute configuration of $C_{(15)}$ of the both compounds are same, and therefore the ten membered rings of these compounds are suggested to take up the nearly antipodal conformations in regards to the plane of the 2-acyl indole chromophore.

C-Mavacurine (115), pleiocarpamine (116) and their analogues[40] are members of a group of indole alkaloids of the unique structures in which $N_{(a)}$ and $C_{(16)}$ of corynanthe skeleton are linked. Two different biogenetic pathways have been proposed by Wenkert[41] and Hesse.[42] In regard to the chemical synthesis Boekelheide et al.reported the synthesis of 19,20-dihydronormavacurine.[43]



C-Mavacurine (115)
from Calebassen-Curare,
and Strychnos sp.

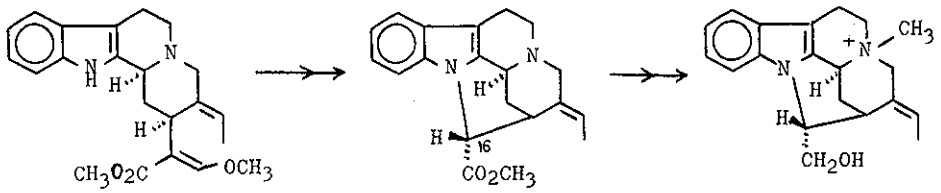


Pleiocarpamine (116)
from Pleiocarpa sp.

Chart 28

Very recently we succeeded in the partial synthesis of 16-epipleiocarpamine (117) from geissoschizine methylether (94), the above stated new alkaloid of U.rhynchophylla.[45] Since in literature 117 has been converted to C-mava-

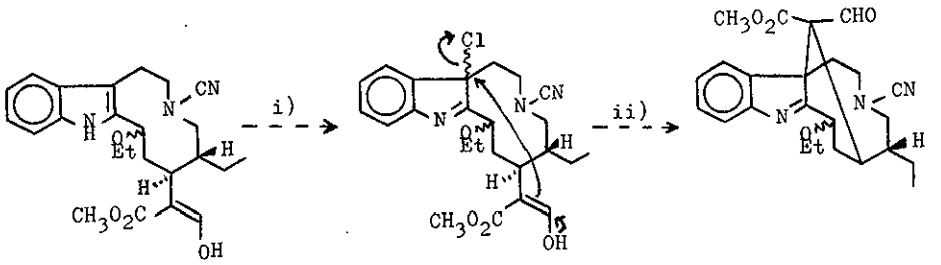
curine (115) our work implies that 115 has been correlated with a corynanthe type alkaloid with the known absolute configuration, and hence the absolute configurations of 117 and 115 have been chemically proved. The outline of this work will be described hereinafter.



Geissoschizine methylether (94) | 16-Epi-pleiocarpamine (117) | C-Mavacurine (115)

Chart 29

Our initial plan was to obtain a picraline type compound by following the reaction pathway shown in Chart 30. For this purpous 93a was demethylated in the usual manner[46] to demethylhirsutine (118) and then its enolic hydroxyl group was protected in the form of ethylcarbonate. Cleavage reaction

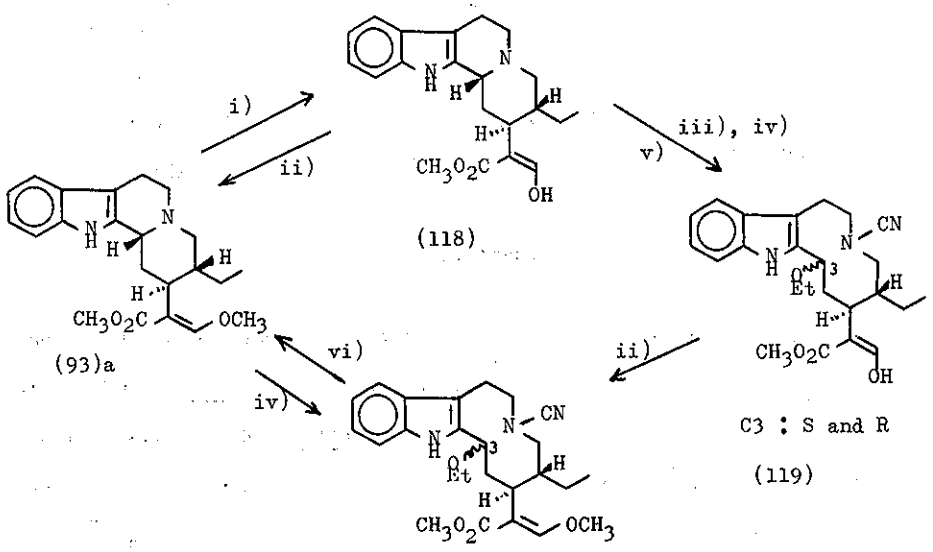


(119) (121) (122)

i) t-BuOCl ii) base

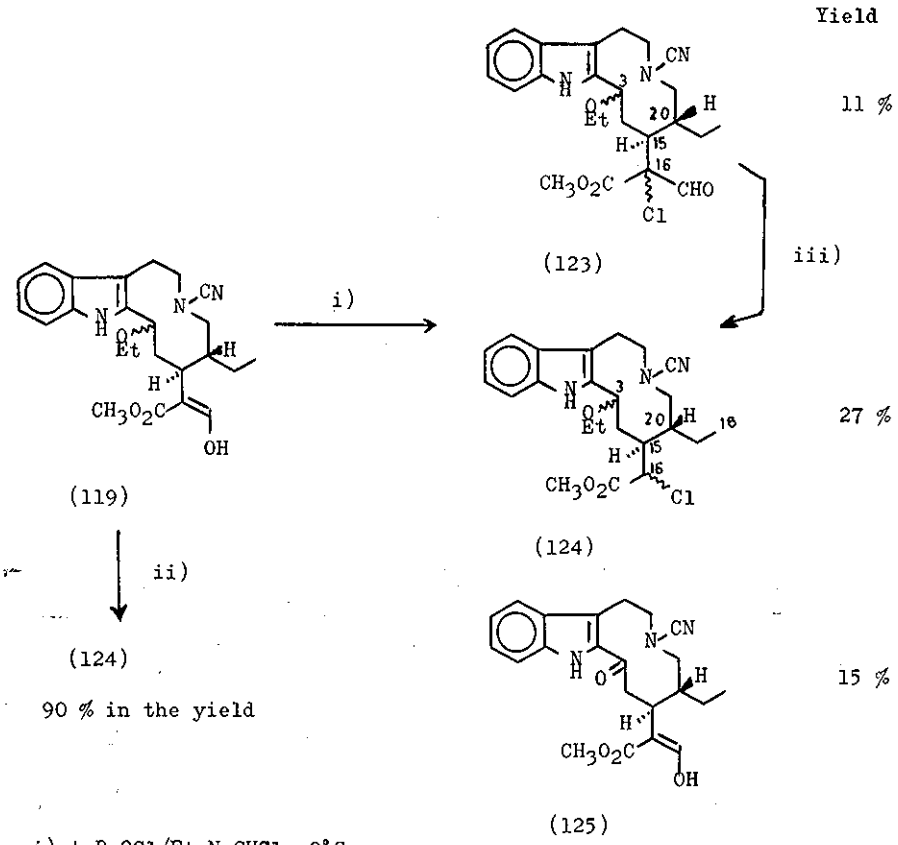
Chart 30

of the resulting compound at C/D ring using cyanogen bromide afforded a 3,4-seco compound (119) in a good yield. In expectation of obtaining a chloroindolenine, 119 was chlorinated with t-butyl hypochlorite. When this reaction was carried out at 0°, however, the desired chloroindolenine was not obtained. Instead of it a 2-acyl indole (125), which was considered to be secondarily formed from 121 in the work-up process, was obtained in 15 % yield. At the



i) HCl-Acetone 0°C ii) CH_2N_2 iii) $ClCO_2Et$ 0°C iv) BrCN/EtOH-$CHCl_3$ /Na_2CO_3 v) aq NaOH/MeOH, r.t. vi) HOAc

Chart 31



i) t-BuOCl/Et_3N-$CHCl_3$ 0°C

ii) t-BuOCl/Et_3N-$CHCl_3$ -78°C

iii) Δ

Chart 32

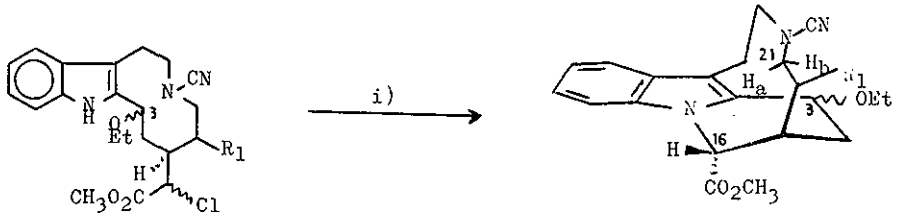
same time $C_{(16)}$-chlorinated compounds 123 and 124 were obtained. Their formation can be explained as the result of the reaction of the hypochlorite with the enol system of 119. Compound 124 was obtained by deformylation of 123 when the latter was heated with finely powdered glass under reduced pressure. Interestingly when the reaction of 119 with t-butyl hypochlorite was carried out using one molar equivalent of the reagent under cooling with dry ice in acetone, 124 was obtained selectively. Though the reaction mechanism is unknown, the same type reaction was found to occur also in the route starting from 94 as described later. Obtaining this compound (124) we began our work to convert it to C-mavacurine type compounds. As 124 is an important intermediate, its NMR data will be shown in Table 1.

	NH	C19 H	C3 H	C16 H	$CO_2\underline{CH_3}$	CH_3(C18)	$-OCH_2\underline{CH_3}$
3-(R) -(124)	8.24 (1H,s)		4.5 (1H,m)	4.24 (1H,d J= 8)	3.80(s) } 3.84(s) } (3H)	0.42(t) } 0.58(t) } (3H)	1.16 (3H,t)
3-(R) -(126)	8.21 (1H,s)	5.48(q) } 5.34(q) } (1H)	4.58 (1H,t)	4.27(d) } 4.24(d) } (1H,J=9)	3.76(s) } 3.68(s) } (3H)	1.62(d) } 1.81(d) } (3H)	1.16 (3H,t)

Table 1 Chemical shift in δ (J in Hz)

Compound 124 derived from 93a was a mixture of four diastereomers arised from the two epimeric centres at $C_{(3)}$ and $C_{(16)}$. On the other hand when 93c was used as the starting material, the reaction with cyanogen bromide gave the product with $C_{(3)}$-R configuration stereoselectively. Therefore compound 124 there obtained was a mixture of two epimers at $C_{(16)}$. The same type of stereoselectivity was observed when 94 having $C_{(3)}$-α H was used as the starting material. The NMR spectra of these products are in reasonable accord

with the above conclusion. In this way $C_{(3)}$-(R,S)-124, $C_{(3)}$-(R)-124 and $C_{(3)}$-(R)-126 were obtained from hirsutine (93a), dihydrocorynantheine (93c) and geissoschizine methylether (94) respectively. All these chlorinated compounds underwent ring formation between $N_{(a)}$ and $C_{(16)}$ on heating at 75° in the presence of sodium hydride in dimethylsulfoxide. In this condition carbomethoxyl group of the products takes up more stable α orientation, which was evidenced by the fact that $C_{(16)}$-epipleiocarpamine (117) was obtained as the final product of the conversion from 94 as described below. Thus $C_{(3)}$-(R,S)-127a, $C_{(3)}$-(R)-127a and $C_{(3)}$-(R)-127b were obtained.

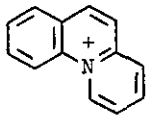


C3 : (S) and (R), R_1 = α-Et (124)

C3 : (R), R_1 = (E) =CH-CH_3 (126)

C3 : (S) and (R), R_1= α-Et(127)a

C3 : (R), R_1= (E) =CH-CH_3 (127)b



(f) m/e 180

i) NaH/DMSO 75°C

Chart 33

The NMR data of $C_{(3)}$-(R)-127a and $C_{(3)}$-(R)-127b are shown in Table 2. Correctness of the assigned structures was supported by the observation that their $C_{(21)}$-H_a are highly shielded by the anisotropic effect of the indole plane.[44] Furthermore, in their mass spectra the characteristic fragment due to benzoquinolizidium ion (f)[44] was observed at m/e 180 besides the expected molecular ion peaks of m/e 395 or 393. The skeletal assignment was also

	C19 H	C3 H	C16 H	CO_2CH_3	$-OCH_2CH_3$	C21 H_a
3-(R) -(127)a		4.86 (1H,t,J=5)	4.67 (1H,d,J=2)	3.84 (3H,s)	3.26 (2H,q,J=7)	-0.96 (1H,m)
3-(R) -(127)b	5.38 (1H,q,J=7)	4.83 (1H,t,J=6)	4.59 ((1H,s)	3.84 (3H,s)	3.26 (2H,q,J=7)	0.10 (1H,d,J=14)

Table 2 Chemical shift in δ (J in Hz)

supported by the UV spectrum (Fig.1), which showed the characteristic absorption curve of C-mavacurine (or pleiocarpamine).

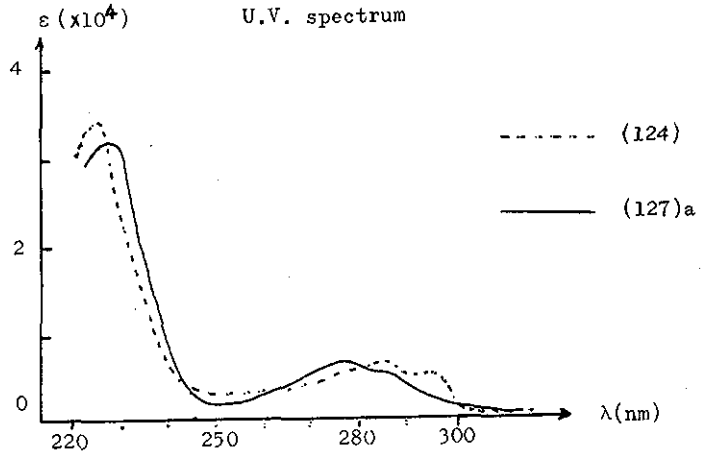
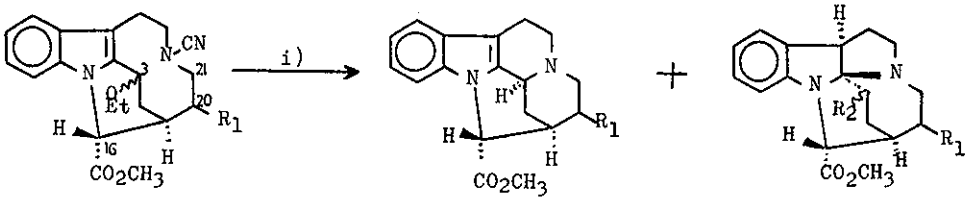


Fig. 1

$^{C}_{(16)}$-Epi-19,20β-dihydropleiocarpamine(128) was obtained when compound (127a) was heated in 95 % aqueous acetic acid in the presence of about 5 molar equivalents of ammonium acetate. In this reaction both $C_{(3)}$-(R)-127a and $C_{(3)}$ (R,S)-127a gave the same mixture of 128 and 129 as the reaction products. Reduction of 128 with lithium aluminumhydride gave a product which should be named as 19,20β-dihydronormavacurine (130a). Comparison of its mass spectral data with those reported for 19,20α-dihydronormavacurine (130b)[44] showed good



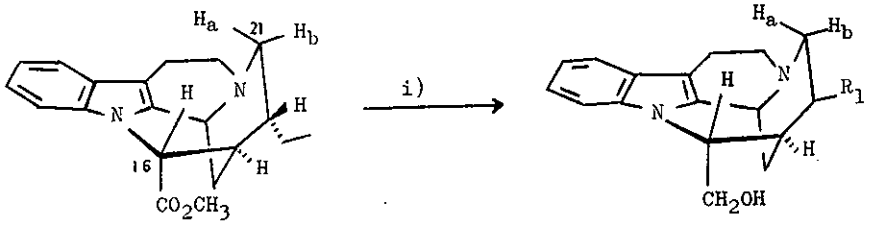
R_1= α-Et (127)a
R_1= (E) =CH-CH_3 (127)b

R_1= α-Et (128)
R_1= (E) =CH-CH_3 (117)

R_1= α-Et, R_2= OAc
(129)

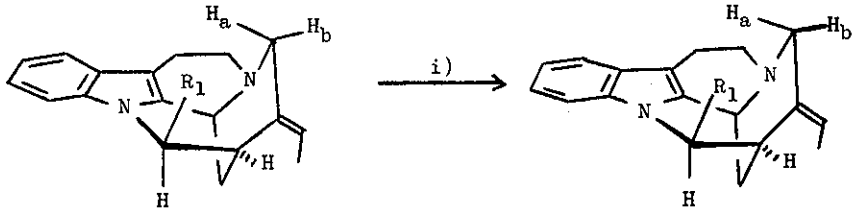
i) 95 % aq-HOAc/NH_4OAc, Δ

Chart 34



(128)

R_1= α-Et (130)a
R_1= β-Et (130)b



R_1= CO_2CH_3
(116)

R_1= CH_2OH
(131)

i) $LiAlH_4$

Chart 35

agreement not only in the ion species but also in their relative intensities. Hesse et al. observed chemical shift difference of 0.63 ppm between $C_{(21)}$-H_a (δ 1.68) of pleiocarpamine (116) and $C_{(21)}$-H_a (δ 1.05) of pleiocarpaminol (131) in their NMR spectra. They ascribed this difference to the anisotropic effect of the carbomethoxyl group of 116. In our compounds, however, the corresponding difference between the chemical shift of $C_{(21)}$-H_a (δ 0.38) of 128 and $C_{(21)}$-H_a (δ 0.41) of 130a was only 0.03 ppm, suggesting the carbomethoxyl group of 128 takes $C_{(16)}$-epi configuration as in $C_{(16)}$-epipleiocarpamine (117). This assumption was finally verified by the fact that the compound (127b), which was derived from 94 in the same way as 127a was derived from 93a, gave 117 on the cyclization as shown in Chart 34. Thus derived 117 showed the following physical properties : $[\alpha]_D$ + 234°; CD λ nm ($\Delta\varepsilon$), 301 (+4.16), 262(+1.96) and 236(-9.47); IR (Fig.2). An authentic specimen of

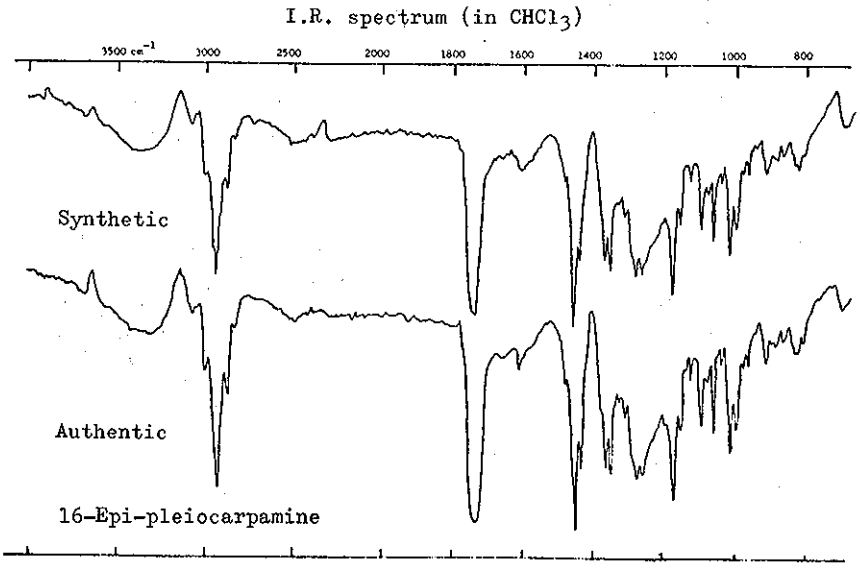


Fig. 2

$C_{(16)}$-epipleiocarpamine (117) was prepared in this laboratory according to the known method reported by Hesse et al. from pleiocarpamine (116) which had been isolated from Amsonia elliptica (Chart 10) and identified with an authentic sample kindly provided by Prof. Schmid. The authentic 117 showed $[\alpha]_D$ + 234° (lit. value) and CD λ nm (Δε); 300(+5.36), 257(+1.91) and 236 (-16.36). These values showed good agreement with those of the partially synthesized material. NMR and IR (Fig.2) spectra of these two specimens were completely superimposable.

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THE INDOLE ALKALOIDS OF JAPANESE PLANTS; STRUCTURES AND REACTIONS

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Indole alkaloids of several Japanese plants have been studied. Some chemical conversion works have also been made utilizing them as the starting materials.

The indole alkaloids which are formed from tryptophan and secologanin via a common intermediate vincoside are mostly produced by the tropical species of Loganiaceae, Apocynaceae and Rubiaceae plants. Some of them, e.g. reserpine, ajmaline and vincristine, are probably among the most important medicinal drugs known in these days.

Before we began our study on the indole alkaloids of Japanese plants, only fragmentary (though of great importance) works had been made in this field. Kondo reported the presence of oxindole alkaloids rhynchophylline (71a) and isorhynchophylline (72a) in Uncaria rhynchophylla Miq.[1] and also characterized formosanine (73) and isoformosanine (74) in U. Kawakamii Hayata which distributes in Formosa.[2] β-Yohimbine (44b) was isolated from an Amsonia species (Apocynaceae) by Kimoto.[3]

In 1965 Haginiwa and Sakai started this series of works from the study of the constituents of Gardneria spp. (Loganiaceae). Four species are known in Japan and one in Formosa.[4]

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Dedicated to Professor Tsunematsu Takemoto on the occasion of his retirement.