β-CARBOLINE ALKALOIDS

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β-Carboline alkaloids are discussed as a unified group.

1. INTRODUCTION

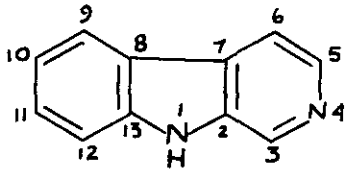
The review by Abramovitch and Spenser[1] in 1964 of the carbolines covered some aspects of this topic, but since that time, several new and exciting developments have occurred especially in the area of naturally produced β-carbolines. In order that a comprehensive picture might be presented, attention will be drawn to some alkaloids which were first isolated more than one hundred years ago and the literature is covered up to September 1974. An overriding consideration which motivated

this review is the fact that the available periodic reviews of alkaloid chemistry, such as the Chemical Society's Specialist Reports, "The Alkaloids", and Manske's volumes, of necessity present a fragmented view of certain areas. An equally important aspect is the fact that several of the currently used classifications of indole alkaloids, for example those used by Boit[2], Hesse[3], and Kompis et al[4], place β-carboline compounds in different sub-groups. Here we have brought together all alkaloids which possess a 8-carbolinium structure and so this review includes cases where the chromophore has been modified by conjugation or by quaternization of N-4, or have more than the basic three aromatic rings. Attention will be drawn to some very recent results of biosynthetic studies which have been carried out on alkaloids in this group, but in view of the very recent comprehensive review of the biosynthesis of indole alkaloids[5], comments will be kept to a minimum.

2. SIMPLE β-CARBOLINES

This group can be further subdivided into type A which have simple substituents, type B containing a vinyl substituent and type C, with a quaternary N-4. As will be noted, the numbering scheme used is that which has been more recently used in view of the more complex alkaloids isolated. Alkaloids in this section are tabulated in TABLE 1 below.

TABLE 1.



Type A.

NAME	SUBSTITUTION					
	C-3	C-5	C-6	C-11	C-12	OTHER
Harman (1)	CH_3	-	-	-	-	-
Harmanine (2)	CH_3	-	-	-	-	N-4→O
Harmol (3)	CH_3	-	-	OH	-	-
10-Methoxyharman (4)	CH_3	-	-	-	-	C-10; CH_3O
Harmine (5)	CH_3	-	-	OCH_3	-	-
Ruine (6)	CH_3	-	-	OCH_3	O-Glu.	-
3-Hydroxymethyl-β-carboline (7)	CH_2OH	-	-	-	-	-
Harman-5-carboxylic acid (8)	CH_3	COOH	-	-	-	-
3-Carbomethoxy-β-carboline (9)	$COOCH_3$	-	-	-	-	-
5-Carbomethoxyharman (10)	CH_3	$COOCH_3$	-	-	-	-
Crenatine (11)	CH_2CH_3	-	OCH_3	-	-	-
Crenatidine (12)	CH_2CH_3	-	OCH_3	-	OCH_3	-
Brevicolline (13)	CH_3	-		-	-	-
Brevicarine (14)	CH_3	-	$(CH_2)_4NHCH_3$	-	-	-
11-carbomethoxy-β-carboline (15)	-	-	-	$COOCH_3$	-	-

TABLE 1 continued ..

Type B.

NAME	SUBSTITUTION					
	C-3	C-5	C-6	C-11	C-12	OTHER
Pavettine (16)	$-CH=CH_2$	-	-	-	-	-
Dehydrocrenatine (17)	$-CH=CH_2$	-	OCH_3	-	-	-
Dehydrocrenatidine (18)	$-CH=CH_2$	-	OCH_3	-	OCH_3	-
6,11-Dimethoxy-3-vinyl-β-carboline (19)	$-CH=CH_2$	-	OCH_3	OCH_3	-	-

Type C.

Melinonine F (20)	CH_3	-	-	-	-	CH_3atN^+-4
10-Methoxy-4-methyl-β-carbolinium chloride (21)	-	-	-	-	-	CH_3atN^+-4, Cl; CH_3O at C-10

Type A

Harman (1)

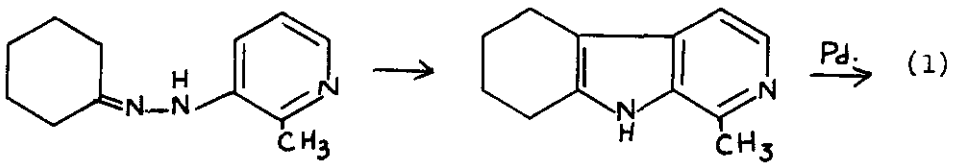
This alkaloid has so far been isolated from 23 plant species belonging to 8 families.

Plant	Family	Reference
Newbouldia sp.	Bignoniaceae	6
Carex sp.	Cyperaceae	7
Elaeagnus sp.	Elaeagnaceae	8
Colligonium minimum	Polygonaceae	9
Passiflora actinea	Passifloraceae	10
P. incarnata	"	10,11,12,33
P. alata	"	10

Harman continued

Plant	Family	Reference
P. alba	Passifloraceae	11
P. bryonioides	"	11
P. capsularis	"	11
P. edulis	"	12
P. eichleriana	"	12
Passiflora quadrangularis	"	12
P. ruberosa	"	11
Ophiorrhiza japonica	Rubiaceae	13
Nauclea diderrichii	"	14
Pauridiantha callicarpoides	"	15
Palicourea alpina	"	16
Sickingia rubra	"	17
Simira klugii	"	18
S. rubra	"	19
Symplocos racemosa	Symplocaceae	20
Zygophyllum fabago	Zygophyllaceae	21

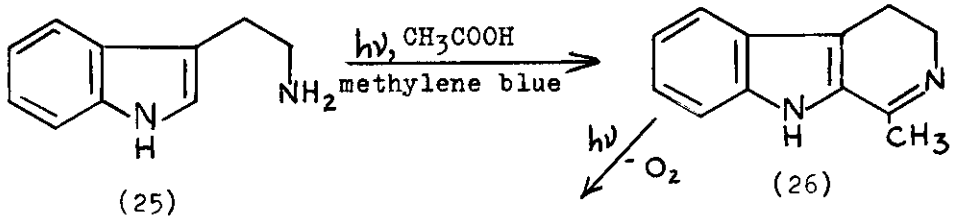
A synthesis by Clemo and Holt[22] illustrates the utility of the Fisher indole synthesis. It consists of the ring closure of the condensation product of 2-methyl-3-hydrazinopyridine (22) and cyclohexanone, namely compound (23), and then conversion of (24) to harman (1).



(1)

(23) (24)

Several other syntheses have been recorded[11,23,24]. Recently, photo-induced dehydrogenation of 5,6-dihydro-β-carboline has been used[25] and a scheme starting from tryptamine (25) has been published by Cauzzo and Jori[26].



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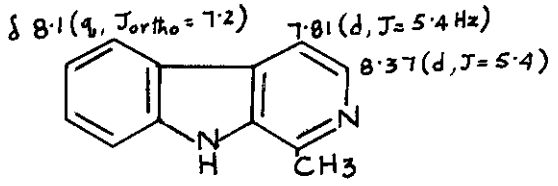
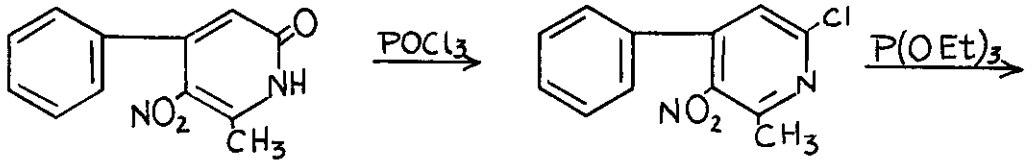


(93% yield)

(1)

A nitrene intermediate has also been utilized by Kametani and his group to synthesise harman[27]. Starting from the nitro derivative (27), harman can be synthesised by a scheme shown below by the application of triethyl phosphite.



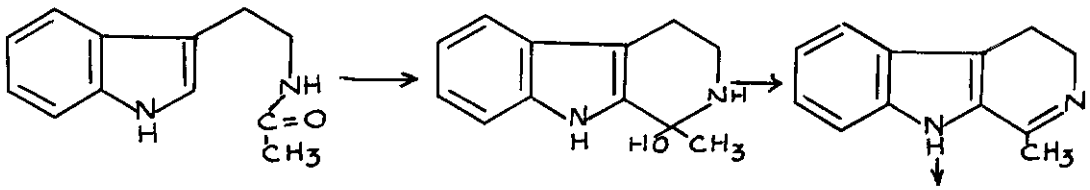
(27)

(1)

In the area of structural elucidation, especially with respect to the determination of the substitution sites in harman and

related systems. the use of nuclear overhauser effect is of interest[28].

Addition of tryptophan to a cell suspension from the roots of Phaseolus vulgaris caused the production of norharman and harman, although this plant does not normally produce these alkaloids[29]. It was theorised that N-acetyl amines played an important role in alkaloid biosynthesis, and N-acetyltyramine (28) was shown to be a precursor for harman[30]. The following scheme was the proposed pathway.



(28) (I)

The general utility of N-acetylamines has however not been demonstrated[31].

Harmanine (2).

This compound has so far been only isolated from Colligonum minimum (Polygonaceae)[32].

Harmol (11-hydroxyharman) (3)

Passiflora incarnata (Passifloraceae)[33], Banisteriopsis inebrians (Malpighiaceae)[34], and Zygophyllum fabago (Zygophyllaceae)[21] have yielded this alkaloid which can be produced from harmine by boiling in HCl[35].

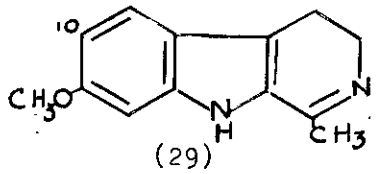
10-Methoxyharman (4)

Virola caspidata (Myristicaceae) is the origin of this alkaloid. The mass spectrum showed m/e 212 (M^+) 198, 197 (base peak), 169, and 168[36].

Harmine (11-Methoxyharman) (5)

Plant	Family	Reference
Peganum harmala	Rutaceae	3
Passiflora incarnata	Passifloraceae	3
Banisteria caapi	Malpighiaceae	3
Banisteriopsis inebrians	"	3
Cabi paraensis	"	3
Banisteriopsis caapii	"	32
B. sp.	"	32
Banisteria lutea	"	37
Calycanthus sp.	Calycanthaceae	38
Tribulus terrestris	Zygophyllaceae	37
Zygophyllum fabago	"	21

Harmine has been produced by oxidising harmaline (29).



(29)

Other syntheses have been recorded[23,39]. It has been shown recently that nitration produced the 10-nitro derivative[40].

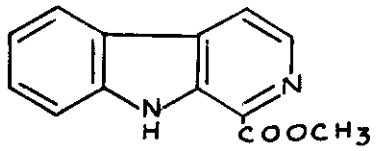
Ruine (6)

MS, NMR, UV were utilized to elucidate the structure of this glycoside. The glycosidic bond was resistant to β-glucosidase at

30°. and had to be cleaved by acid hydrolysis. This alkaloid co-occurs with harmine in both callus tissue and seedlings of Peganum harmala[41]. The NMR spectrum of the tetraacetate ($CDCl_3$) showed that the N-H signal was considerably shielded, and appeared at δ 8.62. Nettleship and Slaytor also demonstrated that ruine was produced from harmine by direct hydroxylation and glycosylation.[41].

3-Hydroxymethyl-β-carboline (7)

This alkaloid from Picrasma ailanthoides (Simaroubaceae)[42] was established on the basis of spectral evidence and its preparation from (30) by reduction with $LiAlH_4$ in tetrahydrofuran.



(30)

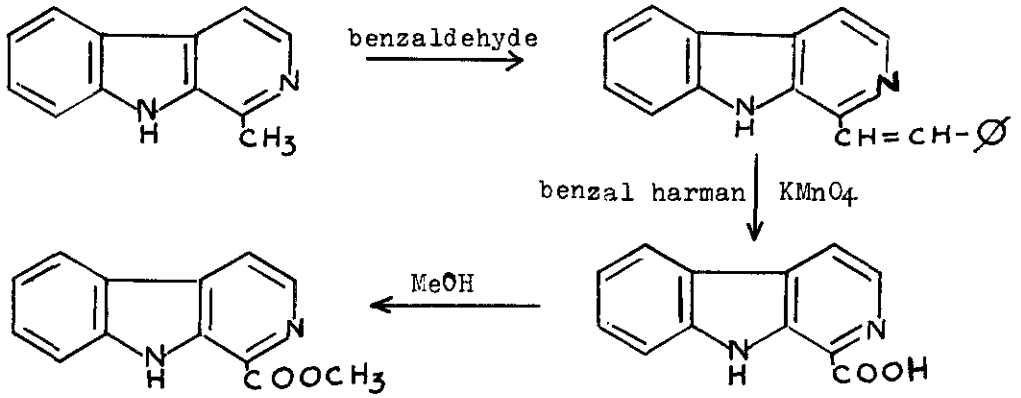
Harman-5-carboxylic acid (8)

In the case of its isolation from Aspidosperma polyneuron (Apocynaceae)[43] this base was obtained by acid hydrolysis of a sugar ester. It has also been isolated from A. exalatum[44]. Spectral data were used in the structure determination, and synthesis has confirmed it[45].

3-Carbomethoxy-β-carboline (9)

Isolation has been from Picrasma crenata[46]; P. ailanthoides[42] (Simaroubaceae), Pleiocarpa mutica[47] (Apocynaceae) and Nauclea diderrichii (Rubiaceae)[14,48] One synthetic route used to confirm

this structure starts with harman (1) and is shown below[49].

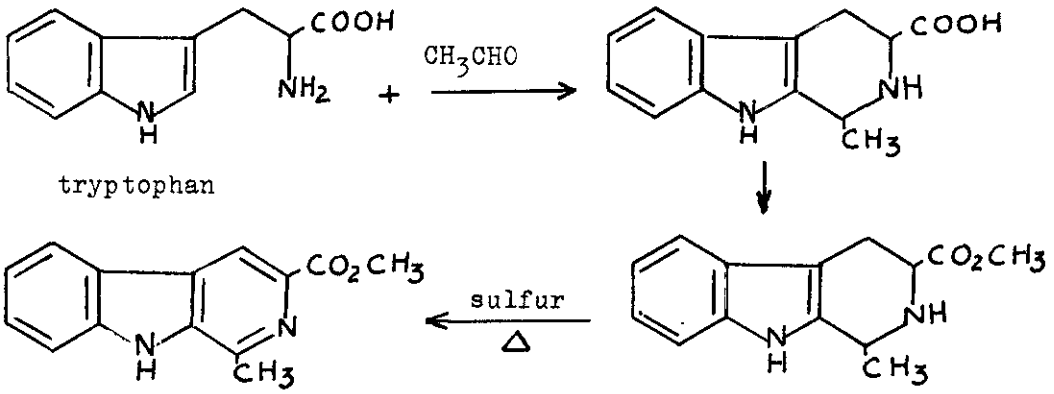


(9)

Another synthesis has been reported, and this utilised established procedures[45].

5-Carbomethoxyharman (10)

Isolation was from Nauclea diderrichii[14] and its synthesis from tryptophan is shown below[45].



(10)

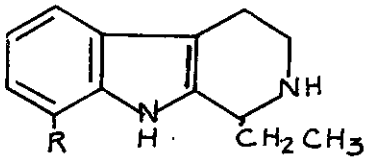
Crenatine (3-Ethyl-6-methoxy-β-carboline)(11)

Plant sources are Picrasma crenata[50,46] and P. javanica (Simaroubaceae)[51]. It was shown that its UV was similar to that of harman and the substitution pattern established by comparison

of its NMR with that of 3-ethyl-β-carboline[51]. The assignment of aromatic signals were assisted by Hückel MO calculations. Protons at C-9 have a net positive charge and so appear at low field while C-12 protons have a net negative charge[46].

Crenatidine (3-Ethyl-6,12-dimethoxy-β-carboline)(12)

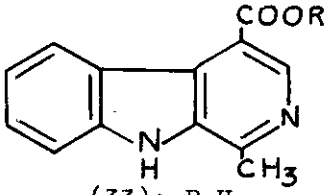
This alkaloid co-occurred with crenatine in Picrasma crenata[46]. The UV resembled that of 3-methyl-12-methoxy-β-carboline, and the N-H in the NMR was shifted upfield ca.1 ppm to δ 8.90. Reduction of both crenatine and crenatidine with Na in absolute EtOH gave compounds (31) and (32) respectively, and MS data were also discussed.



(31); R=H (32); R=OCH_3

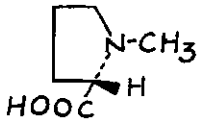
Brevicolline (13)

Carex brevicollis (Cyperaceae) produced this compound, and the stereochemistry indicated in (13A) was based on the following evidence[52].



(33); R=H

(34); R=CH_3



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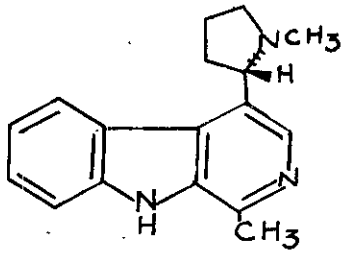


(13A)

When oxidised, brevicolline yielded (33) and its identity was established by synthesis of its methyl ester (34). This synthesis

involved the reaction of methyl indolyl-glycolate with dibenzyl acetamidomalonate in the presence of $NaOCH_3$ to produce firstly dibenzyl carbomethoxyskatylacetamidomalonate. Hydrogenolysis of this latter product was then followed by reaction with polyphosphoric acid and $POCl_3$ to give the desired product.

The configuration shown in structure (13A) was determined by oxidation with potassium ferricyanide and then CrO_3 to yield (-)-hygrinic acid (35). This acid was identical with a specimen obtained on methylation of L-(-)-proline[53].

In the area of biosynthesis, when DL-[2-^{14}C]-tryptophan was administered to Carex brevicollis plants, there was a 0.01% incorporation into brevicolline. 92% of this activity was located in the harman portion of the molecule. Sodium [2-^{14}C] pyruvate showed a 0.017% incorporation (C-3=91%; C-14=0%). With sodium [^{14}C]-formate there was a 0.012% incorporation and the N-methyl having 87% of the activity. [U-^{14}C]-Glutamic acid was very little incorporated.[54]

Brevicarine (14)

Like brevicolline, brevicarine occurs in Carex brevicollis (Cyperaceae)[55]. Brevicarine was prepared from brevicolline by first treating it with PhCOCl, then H_2-Pt, and finally with KOH. Final proof of structure was achieved as follows. The quaternary salt of 3-(1-methylpiperidyl)-2-indole was reacted with the potassium derivative of benzylsulfinylacetone, then the resulting β-ketosulfoxide decomposed to give 8-(methylbenzylamino)-4-(indol-3-yl)-octan-2-one. The oxime of this ketone was cyclised to give 5.6-dihydro-β-carboline, which upon dehydrogenation

afforded a compound identical with the natural brevicarine. The lower homolog was similarly prepared from pyrrolidylindole[56].

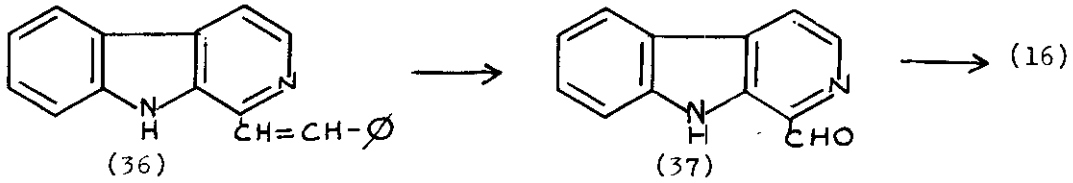
11-Carbomethoxy-β-carboline (15)

This alkaloid was reportedly isolated from Picrasma crenata (Simaroubaceae) and supposedly also present in Pleiocarpa mutica.

Type B.

Pavettine (16)

Pavetta lanceolata (Rubiaceae) was the source of this alkaloid[57]. Hydrogenation yielded 3-ethyl-β-carboline. Synthesis was achieved as follows. The benzal derivative of harman (36) was oxidised with sodium paraperiodate and osmium tetroxide to give 3-formyl-β-carboline (37). Reaction of (37) with methyl-triphenylphosphonium bromide produced pavettine.



(36) (37)

Dehydrocrenatine (6-methoxy-3-vinyl-β-carboline)(17)

It was isolated from Picrasma javanica (Simaroubaceae)[13]. Reduction to the dihydro compound produced a product identical to crenatine (11). 100MHz NMR data were also used to support the proposed structure (17).

Dehydrocrenatidine (18)

This compound occurs in Perriera madagascarienisis (Simaroubaceae)[58] and can be regarded as the C-12 methoxy derivative of dehydrocrenatine.

6,11-Dimethoxy-3-vinyl-β-carboline (19)

This alkaloid co-occurs with dehydrocrenatidine[58].

Type C.

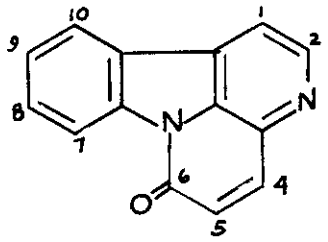
Melinonine F. (20)

This 3,4-dimethyl-β-carboline anhydro base was isolated from Strychnos melinoniana as the chloride[59]. It had a UV with λ_{max}^{EtOH} 253(log ε 4.46), 308(4.27), 377nm(3.67).

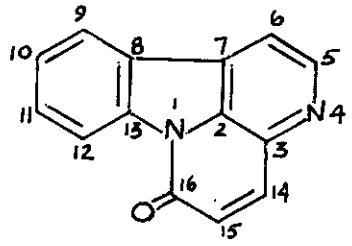
10-Methoxy-4-methyl-β-carbolinium chloride (21)

(21) is the only member of this fairly large group of simple β-carbolines which possess a C-10 substituent. So far isolation has only been from Desmodium gangeticum (Leguminosae)[60].

3. CANTHINE TYPE



[A]

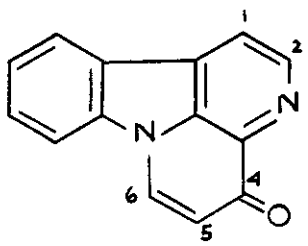


[B]

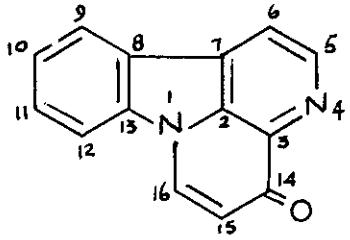
Type A.

Name	Substitution	Structure No.
Canthine-6-one		(38)
5-Methoxycanthin-6-one	C-5, OCH_3	(39)
4-Methylthiocanthin-6-one	C-4, SCH_3	(40)
4,5-Dimethoxycanthin-6-one	C-4,C-5,2xOCH_3	(41)
Nigakinone	C-4,OCH_3,C-5,OH	(42)

Type B.



[C]



[D]

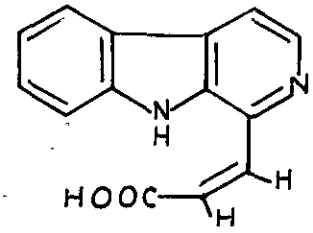
Norisotuboflavine	CH_3,C-6	(43)
Isotuboflavine	CH_3CH_2-,C-6	(44)
Tuboflavine	CH_3CH_2-,C-5	(45)

General structures [A] and [C] represent the Ring Index numbering which has been used for this group. Numbering in structures [B] and [D] conforms to the system used for the simple β-carbolines described earlier in this review. Because half of this group of alkaloids have well established names based on the Ring Index numbering, it has been decided not to alter these names for the purpose of this discussion.

Type A.

Canthin-6-one (38)

Three plants have so far yielded canthin-6-one, namely Pentaceras australis (Rutaceae)[61], Zanthoxylum suberosum (Rubiaceae)[62] and Picrasma crenata (Simaroubaceae)[63]. Early structure proposals were based on the fact that canthin-6-one on oxidation gave 3-carboxy-β-carboline, and the lactam underwent base opening which was reversible to compound (46). The trans-isomer of this acrylic acid derivative obtainable from (46) is however irreversible.

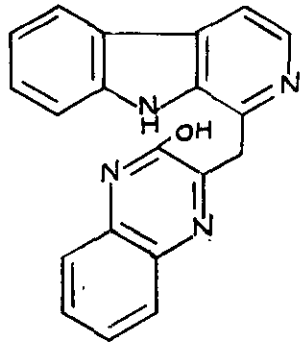


(46)

The UV showed $\lambda_{max}^{dioxane}$ 251 nm (log ε,4.09), 259(4.05), 269(4.03) ~293(3.90), 299(3.91), 347(3.94), 362(4.17) and 3.81(4.14). Hexahydrocanthin-6-one which was previously synthesised[64] has been successfully dehydrogenated to canthin-6-one[65]. A more recent synthesis has been described[66]. Preparation of several canthinone derivatives were reviewed by Abramovitch and Spenser[1].

5-Methoxycanthin-6-one (39)

This alkaloid occurs in Pentaceras australis.[61] Structural assignment was based firstly on the fact that KMnO4 oxidation gave β-carboline-3-carboxylic acid. Also alkali opening of the lactam ring gave β-carbolylmethoxyacrylic acid, a reaction which is reversible. Location of the methoxyl group was established by demethylation followed by condensation of the resulting hydroxy compound with o-phenylenediamine to give the hydroxyquinoxaline (47) and not a phenazine derivative[67].



(47)

This alkaloid has been synthesised by condensing diethyl oxalate with the dilithium derivative of 3-methyl-β-carboline, and the resulting phenol treated with diazomethane[65].

4-Methylthiocanthin-6-one (40)

Pentaceras australis also yields this alkaloid[68]. The presence of sulphur is a rare feature in plant alkaloids. This compound displays low basicity and the UV of the 4-methoxy and 4-methylthiocanthinone are similar, and the only result of the replacement of oxygen by sulphur being that the two longer wavelength bands are displaced ca.10 nm to longer wavelengths with no significant change in intensity.

Treatment of the base with alcoholic alkali gave 2-methylthio-2-(1-β-carboxyl)acrylic acid, followed by the elimination of methyl mercaptan and recyclisation to 4-hydroxycanthin-6-one. Synthesis was as follows: β-carboline-3-carboxylic acid chloride was condensed with magnesium ethoxy derivative of malonic ester, to give, after acid hydrolysis, 4-hydroxycanthin-6-one. Treatment with phosphorus oxychloride followed by heating in a sealed tube with potassium methyl mercaptide gave the natural product[68].

4,5-Dimethoxycanthin-6-one (41)

The structure of this alkaloid from Picrasma ailanthoides (Simaroubaceae) was established by utilizing UV data, functional group analysis and oxidation to β-carboline-3-carboxylic acid[69].

Nigakinone (42)

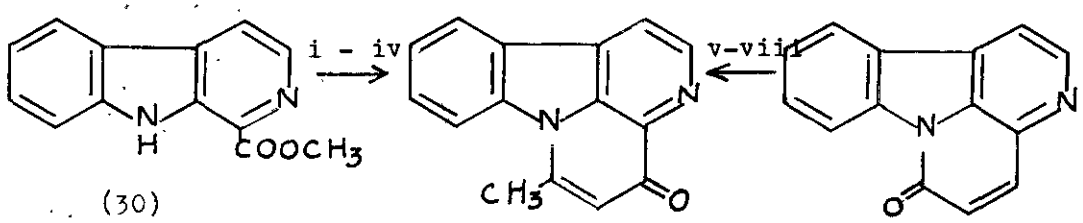
This alkaloid has been found to co-occur with compound (41) in P.ailanthoides[70]. Mainly on the basis of its conversion to methyl-3-

carboline-3-carboxylate, and methylation to 4,5-dimethoxycanthin-6-one (41). structure (42) was assigned.

Type B.

Norisotuboflavine (43)

Plant source was Pleiocarpa mutica (Apocynaceae). Structural assignment was first proposed mainly on the basis of spectral data, especially mass spectrometry, and the detailed spectral discussion involved making a comparison with the co-occurring alkaloid isotuboflavine, which is described below[47]. This alkaloid has now been synthesised from canthin-6-one[71] as well as 3-methoxycarbonyl-β-carboline[72] by schemes summarised below.



(30) (43) (38)

Reagents:

i) $MeCH{=}CHCO_2Me$-NaH;
ii) H^+;
iii) $(CH_3)_3PhN^+Br_3^-$
iv) LiCl
v) H_2-Pd|C
vi) CH_3MgI
vii) CH_3OH-HCl
viii) SeO_2

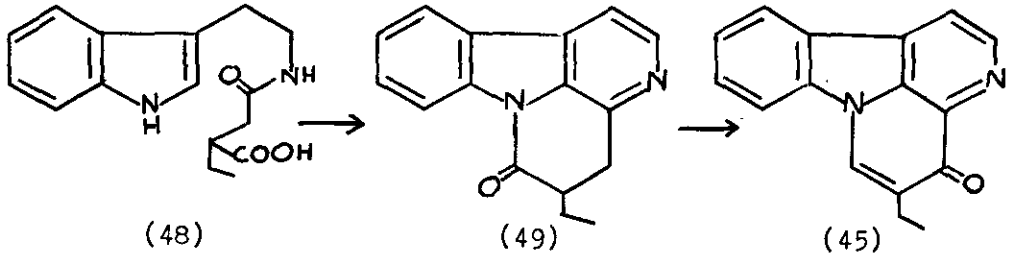
Isotuboflavine (44)

Isotuboflavine co-occurs with norisotuboflavine in Pleiocarpa mutica[47]. Both these alkaloids exhibited identical UV, very similar IR (having a typical pyridone band at 1620 cm^{-1}). Their MS fragmentation was also very similar, and differences observed for this base when compared with that of tuboflavine (45) could

be rationalised by the fact that the ethyl substituent was differently located in ring D.

Tuboflavine (45)

Pleiocarpa tubicina produced this base[47]. This third yellow alkaloid in this series, like the others, exhibits a large bathochromic shift in acid or upon formation of the respective methiodides. Reduction of tuboflavine with $LiAlH_4$ gave a mixture of two compounds, both of which have UV similar to 1-methylharman. Treatment with dilute alkali and then methanolic HCl furnished 3-methoxycarbonyl-β-carboline[73]. Tuboflavine has been synthesised by firstly condensing dl-tryptophan with dl-ethylsuccinic acid to give a mixture of amides. When one of these (48) was cyclised with a mixture of polyphosphoric acid, phosphorus oxychloride and vanadium pentoxide, compound (49) was obtained after palladium charcoal hydrogenation of the crude product along with a larger amount of the 4-ethyl isomer.



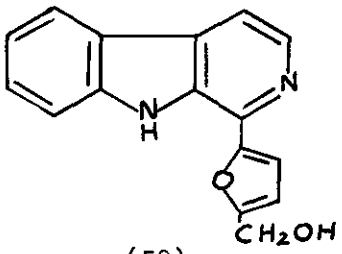
(48) (49) (45)

Compound (49) was reduced with zinc dust in HCl, and then treated with selenium dioxide to yield tuboflavine[66].

4. β-CARBOLINES WITH COMPLEX SUBSTITUENTS AT C-3

Perlolyrine (50)

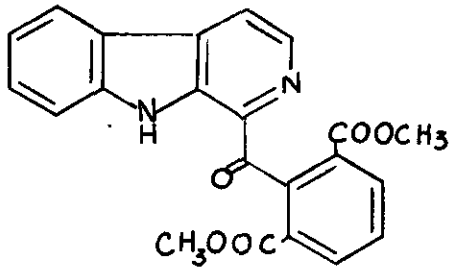
Perlolyrine was isolated from rye-grass, Lolium perenne, (Gramineae)[74,75].



(50)

X-ray analysis of its hydrobromide dihydrate, $C_{16}H_{12}N_2O_2.HBr.2H_2O$ was used to establish its structure. The mass spectrum showed a ready loss of hydroxyl, and ions corresponding to M-CHO, M-CH_3O, and M-C_2H_3O. The loss of -CHO is in keeping with the presence of a furanoid ring. NMR and UV data were analysed by comparison with appropriate models. Synthesis was achieved by reacting 5-acetoxymethyl-2-formylfuran and tryptophan, in a Pictet-Spengler type acid-catalysed ring closure, and perlolyrine was obtained following oxidative dehydrogenation-decarboxylation[75].

Alstonilidine (51)

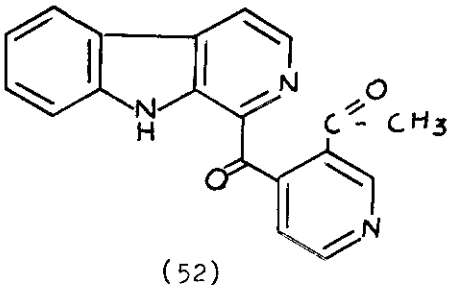


(51)

Alstonia constricta (Apocynaceae) produced this $C_{23}H_{18}N_2O_6$ alkaloid[76]. The UV of this compound showed a λ_{max}^{EtOH} 215, 255, 289, 335 nm, while the IR had an indolic NH at 3520cm^{-1}, methoxycarbonyl (1730cm^{-1}) and an unsaturated carbonyl at 1670 cm^{-1}. MS gave evidence of two methoxycarbonyl residues by showing ions

at m/e 359 (M-59) and m/e 300 (M-118). 100 MHz NMR gave a spectrum in complete agreement with the assigned structure.

Pauridianthine (52)

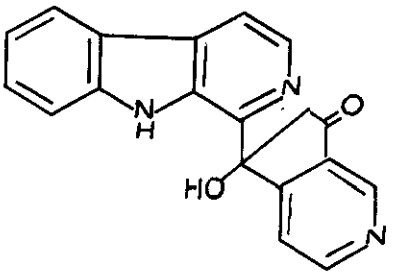


(52)

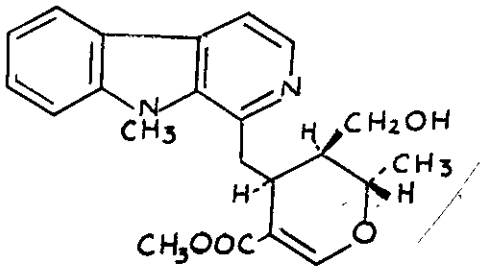
Pauridianthine was isolated from Pauridiantha callicarpoides (Rubiaceae), and on the basis of its UV, 218 nm (log ε 4.66), 285(4.21), 385(3.84), NMR and MS evidence, structure (52) was proposed for this alkaloid.[15]

Pauridianthinine (53)

Two plants, namely Pauridiantha callicarpoides[15] and Stelechantha cauliflora[77] have yielded this alkaloid. The UV is similar to that of harman, 234nm (log ε 4.58), 284(4.16), 347 (3.58) and the IR showed 3300(OH) and 1630cm^{-1}, the latter being assigned to the conjugated carbonyl[15]. Like pauridianthine, the C-9 skeleton of the non-tryptamine portion containing a nitrogen atom makes these compounds interesting from a biosynthetic point of view.



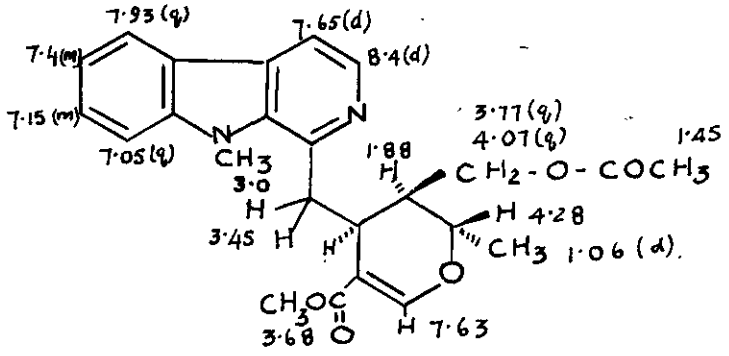
(53)



(54)

Alstonidine (54)

Alstonia constricta (Apocynaceae) produced this alkaloid[78].

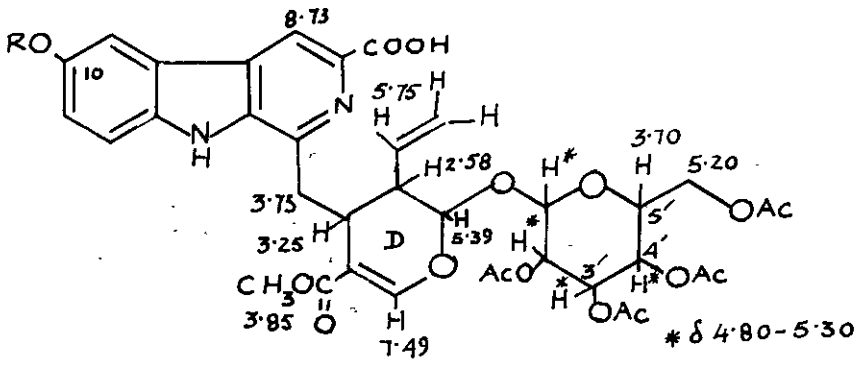


(55)

UV data demonstrated the presence of a methyl substituent on the indole nitrogen, and ruled out any oxygen substitution on the harman portion of the molecule. The conjugated carbomethoxy group could be assigned based on a UV absorption at 235nm and IR bands at 1698 and 1629 cm^{-1}. Boaz et al. suggested structure (54) [*without stereochemical definition*] and biosynthetic considerations were also taken into account. The complete structure has now been proposed based on a detailed NMR study[76], and the spectrum of O-acetylalstonidine (55) in benzene-d6 is summarised in the figure above (δ values).

Cordifoline (56)

Cordifoline is one of many indole alkaloids which have been isolated from Adina sp. and characterised by R. T. Brown and his group. Cordifoline originated from Adina cordifolia (Rubiaceae)[79]. It was obtained pure as its penta-acetate, $C_{38}H_{40}N_2O_{17}$. Structural assignment was based on extensive NMR and MS studies[79]. NMR on the pentaacetate (57) is summarised below:

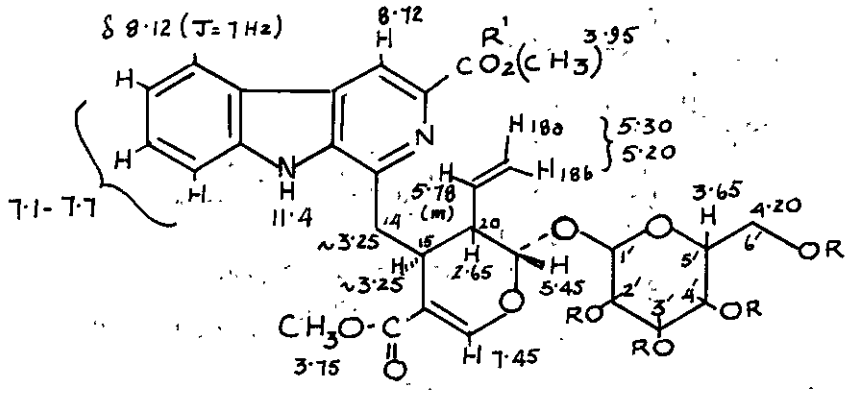


(56) R = H (57) R = Ac

Although there has been no explicit statement, a recent paper by Brown and his group[80] placed the OH group at C-10 and this will be adopted for our considerations. The structural determination of this compound will be discussed in some detail since it laid the ground work for future work on β-carbolinium glycosides of this type. IR bands at 1680 and 1635 cm^{-1} indicated the presence of the CH_3O_2C-CH=CHO chromophore, and this is supported by UV absorption in the 240 nm region, and showing a bathochromic shift in acid solution. Ring D was confirmed in the MS by a pyrylium ion at m/e 165, and the oxonium ion at m/e 331 of the pentaacetate was evidence of the glucose moiety. The NMR data given in summary above was assisted by spin decoupling experiments.

Desoxycordifoline (58)

Adina cordifolia[81] and A. rubescens[80] (Rubiaceae) produced desoxycordifoline. Structural proposal was based on IR, UV and NMR data[81]. Configurational assignments could be made based on 100MHz studies ($CDCl_3$), especially on methyldesoxycordifoline tetraacetate (59)[82] which is shown below.



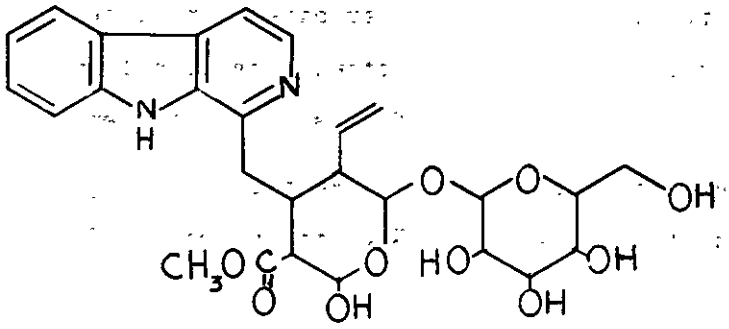
(58) $\overset{1}{R}$=H

(59) R=Ac.[H_1'-H_4', δ4.7→5.20]
[Ac 1.85 → 2.10]

J.	Hz
C-20-21	5
19-20	10
20-15	~3
18a-18b	2
18b-19	17
18b-19	10
17-15	~0.8
6'-6'	12.5
6'-5'	4.5, 2.5

Palinine (60)

This new alkaloid from Palicourea alpina (Rubiaceae) was the first characterised alkaloid from a Palicourea sp.[83]



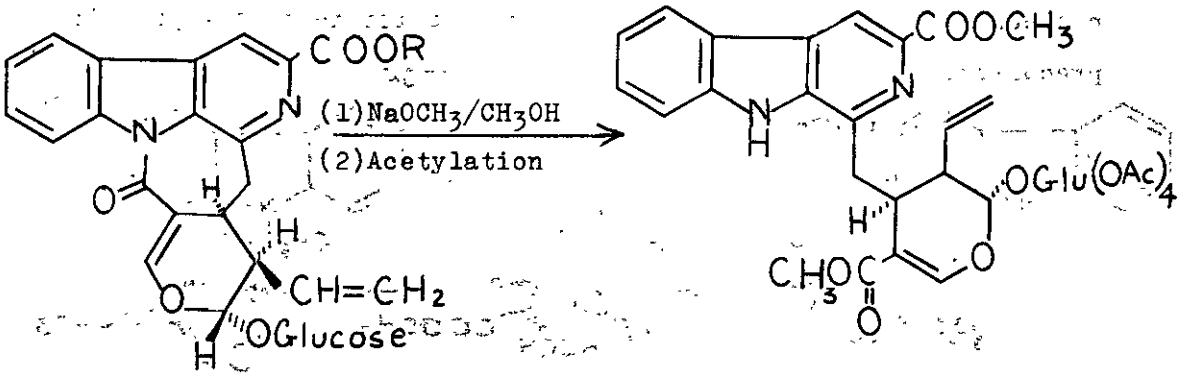
(60)

Palinine, $C_{27}H_{32}N_2O_{10}$, m.p.166.5-168° co-occurs with harman. Hydrolysis with β-glucosidase proved the presence of D-glucose and the proposed structure was based mainly on UV, IR, NMR and MS data of the free alkaloid, its tetra- and penta-acetate derivative.

5. PENTACYCLIC TYPE

Desoxycordifoline lactam (61)

Desoxycordifoline lactam was isolated as its tetraacetate, $C_{37}H_{43}N_2O_{15}$ from Adina rubescens (Rubiaceae)[84] and assigned structure (61).

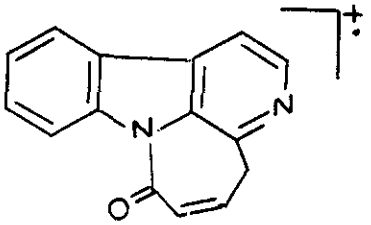


(61) R=H
(62) R=CH_3

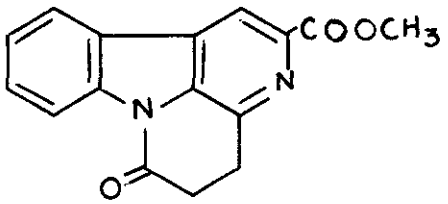
(63)

The UV spectrum with alkali gave a 3-carboxy-β-carboline type chromophore, and was evidence of a lactam. The transformation of (62) to (63) was chemical evidence of this lactam system.

The MS gave the expected glycosidic and β-carboline fragmentation, and a strong peak at m/e 234 ($C_{15}H_{10}N_2O$) was attributable to ion (64).

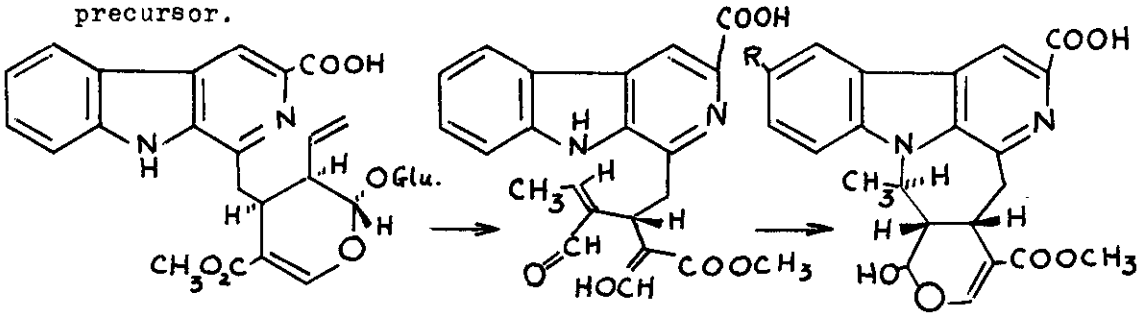


(64)



(65)

Compound (65), namely 2-carbomethoxy-4,5-dihydrocanthin-6-one was synthesised by heating Nb- succinamide of methyl tryptophanate with $POCl_3$ and V_2O_5 in polyphosphoric acid in order to confirm the UV assignment. The authors[84] suggested that desoxycordifoline lactam was biosynthesised from the alkaloid (66) by nucleophilic attack at the C-22 ester function in this glycosidic precursor.

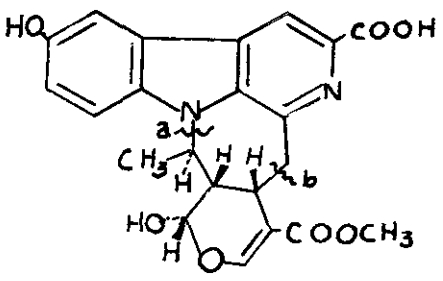


(66) (67) (68) R=OH
(69) R=H

A biogenetic relationship between desoxycordifoline lactam, adifoline (68) and desoxyadifoline (69) was also drawn, in that the aglycone of (66) is in equilibrium with the ring-opened form where a prototropic shift can occur to give an α,β-unsaturated aldehyde (67). An alternative attack by N-1 on C-19 and reclosure of the heterocyclic ring would then generate (69) directly and (68) after further oxidation.

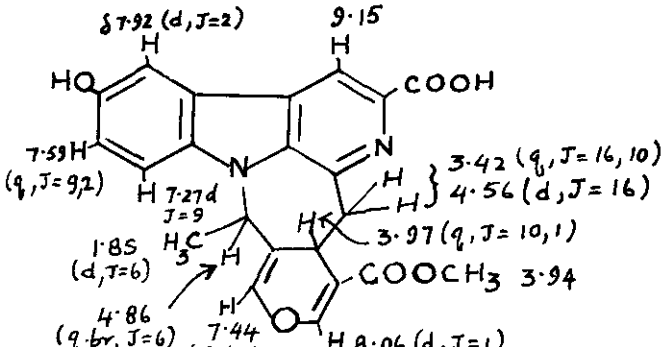
Adifoline (70)

Adifoline co-occurs with desoxycordifoline in Adina cordifolia (Rubiaceae)[85,86]. Earlier workers[85] suggested $C_{22}H_{20}N_2O_8$ as the molecular formula. and showed it was a β-carboline derivative. but more recently $C_{22}H_{20}N_2O_7$ has been shown to be the correct molecular formula. Methylation yielded trimethyladifoline, whereas acetylation gave a diacetate, and so indicated a carboxy group and two phenolic and/or enolic functions.



(70)

[a+b= MS fragmentation]



(71)

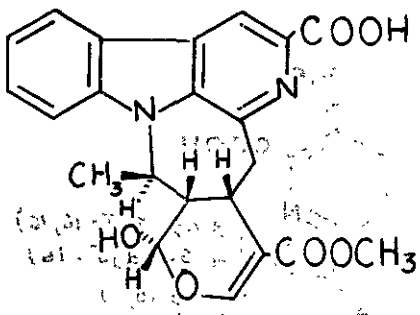
Reduction experiments in conjunction with UV and IR studies indicated a β-alkoxy-α,β-unsaturated ester, and a bathochromic shift in acid suggested a substituted 3-carboxy-β-carboline chromophore. Adifoline was readily dehydrated to anhydroadifoline (71) and NMR and MS studies on this compound as well as adifoline itself fully supported the proposed structure.

10-Desoxyadifoline (72)

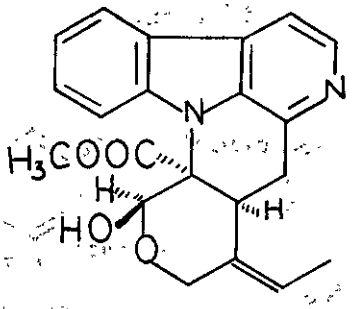
Also in Adina cordifolia (Rubiaceae) is the alkaloid 10-desoxyadifoline[81]. Physical data were utilized for structural elucidation. In the case of the NMR data, these were mainly on the methylated and acetylated derivatives.

3,4,5,6-Tetradehydrotalbotine (73)

Pleiocarpa talbotii (Apocynaceae) has yielded tetradehydrotalbotine (73)[87].



(72)



(73)

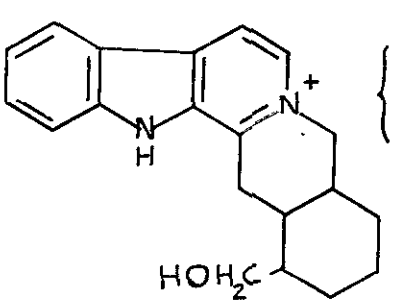
Co-occurring with it were the alkaloids 5,6-dehydrotalbotine and deformyltalbotinic acid methyl ester and all these structures were determined by IR, UV, ORD and MS data.

6. ANHYDRONIUM BASES

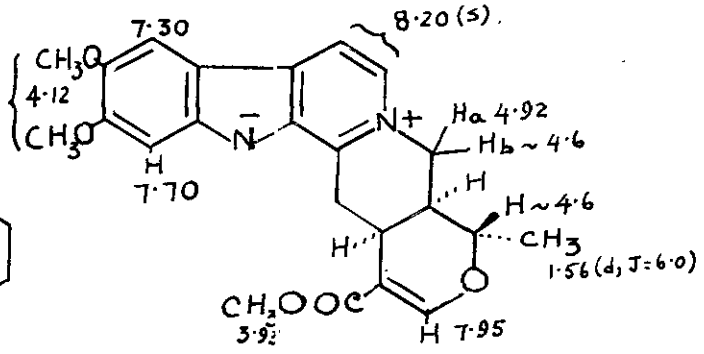
Melinonine E. (74)

This alkaloid was isolated from Strychnos melinoniana (Strychnaceae)[60]. The structure (74) was proposed on extensive

UV studies which utilized appropriate models.



(74)



(75)

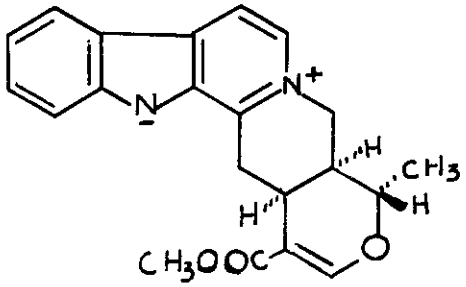
Simple chemical transformations such as acetylation to confirm the primary alcohol were performed[60].

Bleekerine (75)

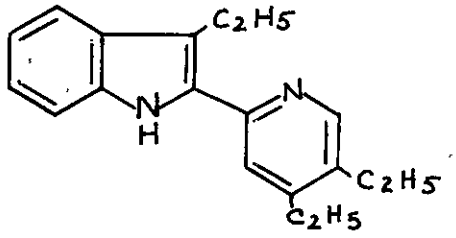
Bleekeria vitiensis (Apocynaceae) produced bleekerine[88]. The mass spectrum (M^+408) showed little fragmentation and confirms the conjugated nature of the molecule. Reduction with $NaBH_4$ in methanol yielded isoreserpiline, and the structure proposed was substantiated by NMR studies (see above,(75)). Lead tetraacetate oxidation produced this alkaloid, albeit, in low yield[88].

Alstonine (76)

This $C_{21}H_{20}N_2O_3$ alkaloid has so far been isolated from several plants, namely Alstonia constricta (Apocynaceae), Rauvolfia hirsuta, R. obscura, R. vomitoria (Apocynaceae) and Vinca rosea (Catharanthaceae)[3]. A gross structure was proposed in 1953[89] and 1951[90], but the stereochemistry shown in structure (76) was based on work by Wenkert and his group[91]. In both this case and that of the following alkaloid serpentine, palladium-maleic acid dehydrogenation experiments which are of general use in determining the stereochemistry of certain indole alkaloids, were used.



(76)

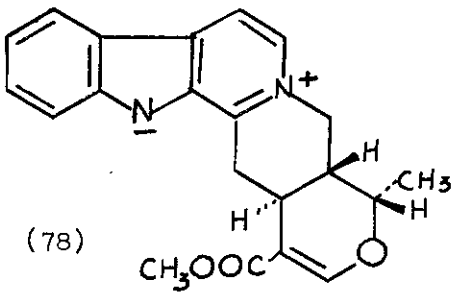


(77)

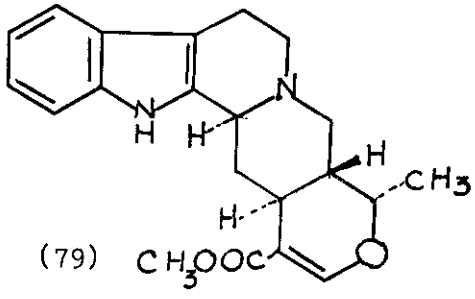
In earlier work leading to a structural proposal, Sharp showed that selenium dehydrogenation yielded alstyrin (77)[92].

Serpentine (78)

Serpentine has been isolated from Rauvolfia hirsuta, R. fruticosa, R. heterophylla, R. ligustrina, R. sellowii, R. serpentina. R. micrantha. R. sumatrana (Apocynaceae). Vinca minor and V. rosea (Catharanthaceae).[3]



(78)

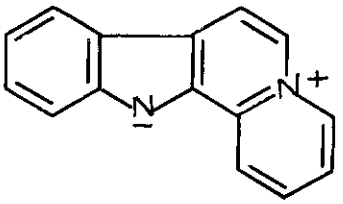


(79)

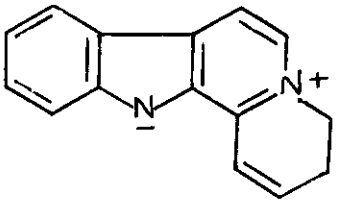
This alkaloid showed a UV, λ_{max} 252 nm (log ε 4.49), 308(4.30), 370(3.61) and many simple chemical transformations such as base hydrolysis and reductions were carried out by Schlittler and co-workers[93]. This alkaloid has been prepared from ajmalicine (79) by oxidation with lead tetraacetate, a process which can be reversed

by catalytic reduction [94]. Serpentine has been the subject of several biosynthetic studies [95-98].

Indolo[2,3-a]pyridocoline (80) and Dihydroindolopyridocoline (81)



(80)

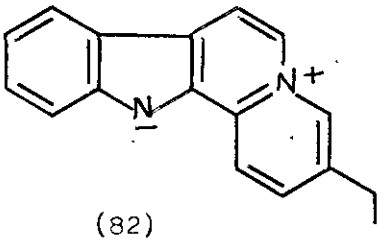


(81)

Isolated from Gonioma kamassi (Apocynaceae) these two anhydronium bases occur in only small amounts [99]. Structural assignment was made with the aid of mass spectrometry. Both bases showed poor fragmentation. Compound (80) showed a molecular ion at m/e 218 (base peak) and the other significant ions appeared at m/e 109 (M^{++}), 190, 191 and 192, the last three being due to the loss of H_2CN, HCN and C_2H_2. (81) showed ions at m/e 220 (M^+), 219 (base peak), 110 (M^{++}), 109.5 (219^{2+}) and small peaks at m/e 191, 192, (219-H_2CN) and 219-HCN respectively. Reduction with zinc powder gave a mixture of products whose MS had 4 or 6 hydrogens more than starting material. and some peaks were characteristic of a tetrahydro-β-carboline moiety.

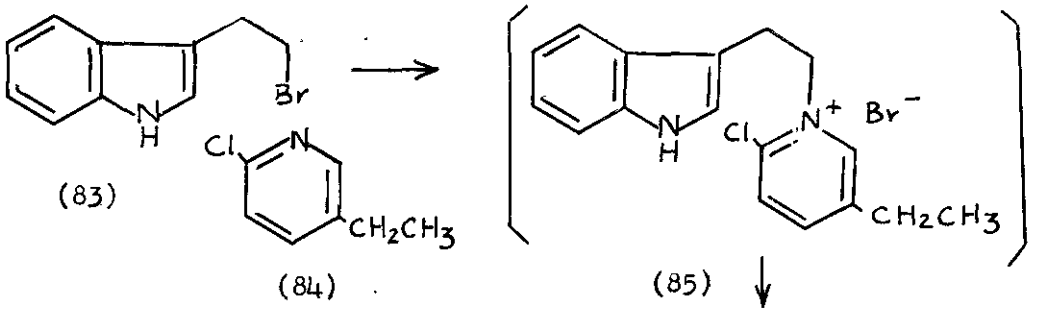
Flavopereirine (Melinonine G) (82)

This $C_{17}H_{14}N_2$ alkaloid was isolated from Geissospermum laeve (Apocynaceae) and Strychnos melinoniana (Strychnaceae) [3].

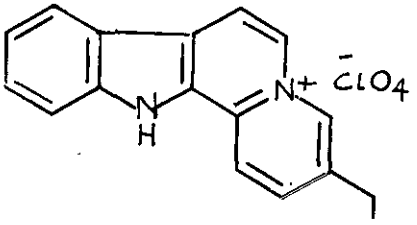


(82)

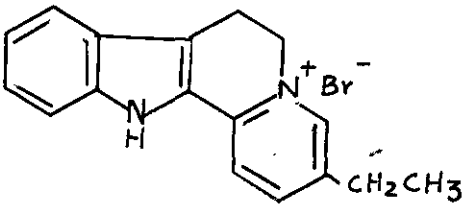
The UV, λ_{max}^{EtOH}, 230 nm (log ε 4.40), 238(4.43), 248(4.39), 294(4.14), 351(4.25), 390(4.14) had its structure elucidated by two research groups[100,101]. Several syntheses have been reported to confirm this structure.[102-109] Two of the most recent of these will be discussed briefly. The method used by Ban and Seo[109] can be summarised as follows: 3-(2-bromoethyl)-indole (83) was condensed with 2-chloro-5-ethylpyridine (84) to give (86) directly, probably via (85). Dehydrogenation afforded flavopereirine perchlorate (82A).



(83) (84) (85)

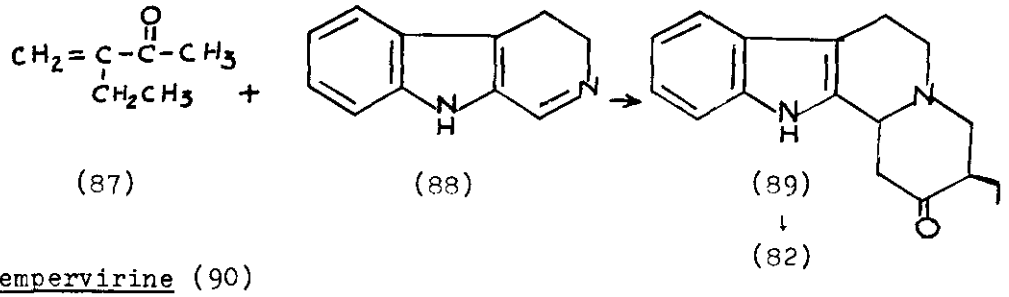


(82A)



(86)

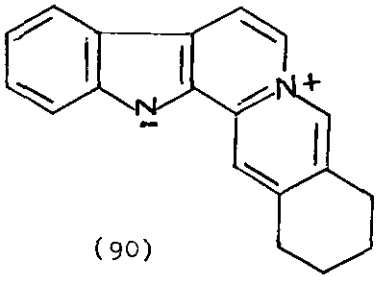
In the second condensation of the α,β-unsaturated ketone (87) with dihydro-β-carboline (88) afforded (89) in good yield. Wolff-Kishner reduction of this product followed by dehydrogenation gave flavopereirine[110].



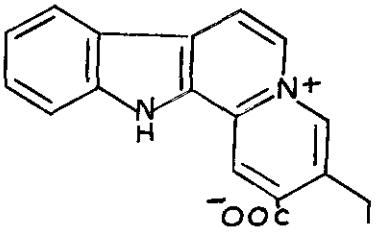
(87) (88) (89) → (82)

Sempervirine (90)

Sempervirine (90) has been isolated from Gelsemium elegans, G. sempervirens (Loganiaceae), Mostuea buchholzii and M.stimulans (Loganiaceae)[3].



(90)



(91)

Structural proposals were based on work from Woodward's laboratory[111], and there are four reports of syntheses[112-115]. The general method used earlier by Ban and Seo[109] was extended to the synthesis of sempervirine[115]. 3-(2-Bromoethyl)indole was condensed with 3-chloro-5,6,7,8-tetrahydroisoquinoline and the product cyclised with $POCl_3$. The final step involved dehydrogenation using tetrachloro-o-benzoquinone.

Flavocarpine (91)

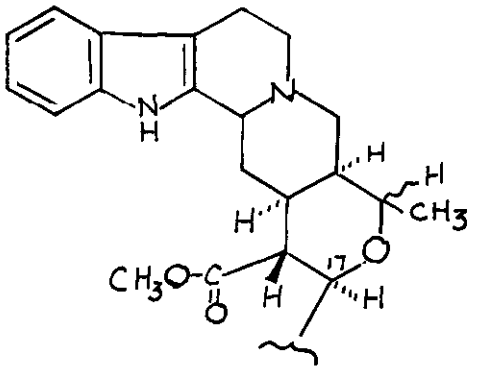
Pleiocarpa mutica (Apocynaceae) is the only plant reported so far which contains flavocarpine[108]. This yellow zwitterionic substance could be decarboxylated to yield flavopereirine. A detailed study of its UV in conjunction with appropriate models established the location of the carboxylic group. The structural proposal was supported by NMR data and MS studies, especially on the reduced compound. Structural confirmation was finally by synthesis. This involved condensation of 3-(2- bromoethyl)indole with 4-carboxamido-2-chloro-5-ethylpyridine and then dehydrogenation, hydrolysis and then passage through ion exchange resin to yield the natural product. This approach is an application of the Ban-Seo method[109].

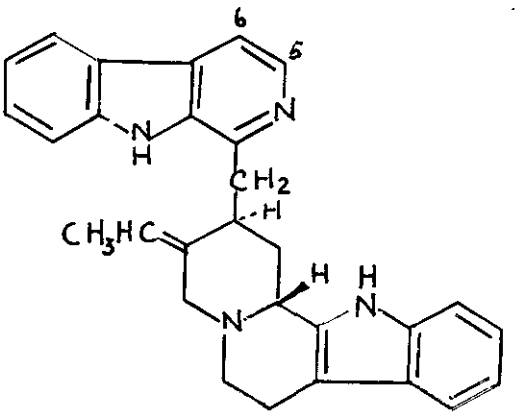
7. DIMERIC ALKALOIDS

Serpentinine (92)

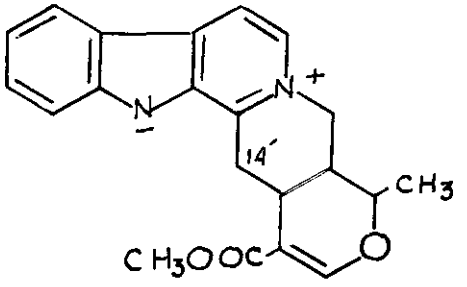
Several Rauvolfia species contain this alkaloid, namely R. degeneri, R. lingustrina, R. mayiensis, R.sandwicensis, R. serpentina, R tetraphylla and R. vomitoria.[3]

Early work on this dimeric alkaloid involved selenium dehydrogenation to yield alstyrine (77) which was obtained also from alstonine (76) under similar conditions. Also KOH fusion gave indole-2-carboxylic acid and 1-oxo-1,2-dihydro-β-carboline.[93]. The UV of this deep yellow base was very instructive in that it suggested an addition spectrum of alstonine and a yohimbine-type compound, and also indicated the presence of only one β-alkoxy-acrylic ester function. This alkaloid and its derivatives have been subject to extensive 220 MHz NMR and MS analysis, and in the case of the latter, some deuteration experiments as well. An early





(93)



(92)

structural proposal involved a link between C-17 and C-14' of the two units, but as pointed out in a comprehensive review of all the available evidence[116], further data are required for structural confirmation, and the partial structure (92) is the current situation.

Usambarensine (93)

A second dimeric structure containing the β-carboline moiety is usambarensine. It co-occurs with 5,6-dihydrousambarensine and their quaternized-N-methylated derivatives in Strychnos usambarensis (Strychnaceae). Structural assignment was based on MS, UV and IR data[117].

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