Phytochemistry, 1970, Vol. 9, pp. 157 to 187. Pergamon Press. Printed in England.

REVIEW ARTICLE

ALKALOIDS OF THE MENISPERMACEAE

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(*Received* 30 *June* 1969)

Abstract—The alkaloids of the family Menispermaceae are reviewed. The 198 occurrences of ninety-five alkaloids found in fifty species from twenty-two genera are tabulated and their distribution, structural relations and biosynthesis are discussed.

THE ALKALOIDS of the Menispermaceae were reviewed by Tomita[1] in 1952. Since then the number of alkaloid occurrences reported has doubled and the growth of interest in alkaloid biosynthesis[2-9] and chemical taxonomy[10-12] prompts a new survey of this field. The Menispermaceae are widely distributed[13] in the tropics and have been studied throughout the world, but by far the greatest contribution to our knowledge of their alkaloids has come from the groups of Japanese workers associated with H. Kondo and M. Tomita. The vast majority of alkaloids found in the Menispermaceae and neighbouring families are of the benzylisoquinoline type. Table 1 shows the types of alkaloids found in the major isoquinoline alkaloid-bearing plants. The information shown is drawn largely from the compilation of Boit.[14]

It is seen that although plants of the Menispermaceae are unique in producing the novel hasubanan skeleton, they are otherwise closely related to the Berberidaceae, Papaveraceae, Annonaceae, Rutaceae and Ranunculaceae both in the type and range of alkaloids found. Figures 1–17 illustrate the structures of alkaloids found to date in the Menispermaceae classified under general structural type. A number of reviews have been published discussing

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[3] D. H. R. BARTON and T. COHEN, *Festschr.* Arthur Stoll, 117 (1957).
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TABLE 1. PRINCIPLE ISOQUINOLINE ALKALOID OCCURRENCES

Family	Type										
	1-Benzylisoquinoline	Cularine	Aporphine	Morphine	Hasubanan	Bisbenzylisoquinoline	Protoberberines	Protopine	Phthalideisoquinoline	Benzophenanthridine	Dibenzopyrrocolines
Papaveraceae	√	√	√	√			√		√	√	
Menispermaceae	√		√	√	√	√	√				
Berberidaceae			√			√	√	√	√		
Magnoliaceae	√		√			√					
Ranunculaceae	√		√			√	√		√		
Rutaceae	√		√				√	√		√	
Monimiaceae			√			√					
Annonaceae	√		√			√	√				
Aristolochiaceae			√								
Lauraceae			√								√
Nymphaceae			√								

the chemistry of these groups; 1-benzylisoquinolines,[15] proaporphines,[16] aporphines,[17] protoberberines,[18, 19] morphines,[20] and bisbenzylisoquinolines.[21, 22] The hasubanan alkaloids have not been reviewed, but extensive references to their isolation, structure, and chemistry are given in the list of alkaloid occurrences which follows (Table 2). In addition to these common groups of alkaloids, a few compounds have been isolated which are either uncharacteristic of the Menispermaceae or completely novel (Fig. 17).

It may be noted among the simpler 1-benzylisoquinolines found (Figs. 1–5) that stepharatine (VIIg) is unique in having five aromatic oxygen functions. The pentaoxygenated isoquinoline alkaloids of *Thalictrum* species are well known,[17] but differ from stepharatine in having a trioxygenated isoquinoline ring. As will be discussed later, the hasubanan alkaloids (Fig. 6) and protostephanine (XVII) can be envisaged as arising from a 1-benzylisoquinoline, having one trioxygenated ring, but apart from stepharatine (VIIg) the only

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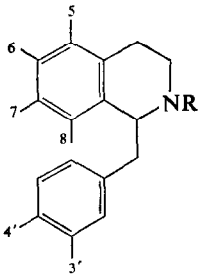
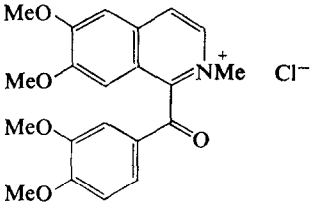


1-Benzyl-tetrahydroisoquinolines (I).

Alkaloid	R	3¹	4¹	6	7
Coclaurine (Ia)	H		OH	OMe	OH
Isococlaurine (Ib)	H		OH	OH	OMe
N-Methylcoclaurine (Ic)	Me		OH	OMe	OH
Laudanine (Id)	Me	OH	OMe	OMe	OMe



1-Benzylisoquinoline
N-Methylpapaveraldinium chloride (II)

FIG. 1. BENZYLISOQUINOLINES.

other compound known in the Menispermaceae with this oxygenation level and pattern is syringaresinol (XXI) isolated from *Sinomenium acutum*.[23] Michelalbine (IVb) and *N*-methylpapaveraldinium (II) cation show oxidation at a benzylic position, as do prometaphanine (VIIIf) and metaphanine (VIIIg). An interesting feature among the aporphine alkaloids (Fig. 3), is that a methylenedioxy bridge in the 1,2-position never co-occurs with 11-substitution although examples have been noted of this type in other plants.[14] The morphine alkaloids of Menispermaceae (Fig. 4) have the opposite absolute configuration to those of the Papaveraceae. The hasubanan alkaloids (Fig. 6), formerly believed to be of the morphine class, have now been shown by X-ray crystallography[24, 25] synthesis of degradation products[26] and transformation of the morphine skeleton into the hasubanan skeleton[27] to have this novel structure.

Among the bisbenzylisoquinolines the unusual structures of insularine (XIIId), insulanoline (XXIIc) and cissampareine (XIIIf) should be noted. The structure of tiliarine (XIIa)

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has been discussed recently,[22] but the position is still not clear as conflicting evidence suggesting a trilobine (XIIc), rather than menisarine (XIIf) dibenzo-*p*-dioxin nucleus, has been put forward.[28] The structure of protostephanine (XVII) has been proved by synthesis.[29, 30] Cocculolidine (XVI) is unusual among lactone *Erythrina* alkaloids[31] in having a γ-lactone moiety, and along with dihydroerysodine (XVIII) is the only example of the *Erythrina* skeleton found outside the genus *Erythrina* (Leguminosae).[14] *Cocculus laurifolius* base *IV* (XVa), cocculine (XVb) and cocculidine (XVc) have a similar skeleton to the lycorine class of Amaryllidaceae alkaloids,[32] but no lycorine alkaloids with a methyl group at the benzylic position are known.

TABLE 2. ALKALOIDS OF THE MENISPERMACEAE

Plant species	Alkaloids present	Formulae	References
Archangelisia flava (L.) Merrill	berberine	(VIa)	33
(= *Menispermum flavum* L.)	palmatine	(VIb)	33
	columbamine	(VIc)	33
	jatrorrhizine	(VId)	33
Archangelisia lemniscata (Miers) Beccari	berberine	(VIa)	1
Burasaia madagascariensis Thou.	palmatine	(VIb)	34
	columbamine	(VIc)	34
	jatrorrhizine	(VId)	34
Chondodendron candicans Sandwith	d-isochondodendrine	(XIIIa)	35
	d-bebeerine	(XIVa)	35
Chondodendron limaciifolium (Diels) Moldenke	d-isochondodendrine	(XIIIa)	36
Chondodendron microphyllum (Eichl.) Moldenke	l-isococlaurine	(Ib)	35
	d-bebeerine	(XIVa)	35
	d-isochondodendrine	(XIIIa)	35
Chondodendron platyphyllum Miers	l-isococlaurine	(Ib)	35
	d-isochondodendrine	(XIIIa)	35
	l-bebeerine	(XIVb)	35
Chondodendron tomentosum Ruiz et Pav	d-isochondodendrine	(XIIIa)	37, 38
	cycleanine	(XIIIb)	37, 38
	norcycleanine	(XIIIc)	38
	d-chondocurine	(XIVg)	37, 38
	d,l-tubocurarine	(XIVi)	37, 38, 39
	d-chondocuranine	(XIVh)	39
	l-curine	(XIVb)	38

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TABLE 2—*continued*

Plant species	Alkaloids present	Formulae	References
Cissampelos insularis Makino	magnoflorine	(IVl)	40
= *Cyclea insularis* (Makino) Diels	cyclanoline	(VIIf)	40
= *Paracyclea insularis* (Makino) Kudo et Yamamoto	cycleanine	(XIIIb)	40, 41
	norcycleanine	(XIIIc)	42
	isochondodendrine	(XIIIa)	40
	insularine	(XIIId)	40, 43
	insulanoline	(XIIIe)	42
Cissampelos pareira L.	cyclanoline	(VIIf)	44
	d-isochondodendrine	(XIIIa)	45, 46
	l-curine	(XIVb)	45, 46, 47
	hayatine (d,l-curine)	(XIVc)	45, 46, 47, 48
	hayatinine = (++), (−−)-4-*O*-methylcurine	(XIVe)	45, 46, 47, 49, 50
	hayatidine = (+−)-4-*O*-methylcurine	(XIVf)	44, 49
	(++)-4-*O*-methylcurine	(XIVd)	51
	cissampareine	(XIIIf)	52
Cissampelos ochiaiana Yamamoto	insularine	(XIIId)	53
(= *Paracyclea ochiaiana* Kudo et Yamamoto)	l-curine	(XIVb)	53
	cycleanine	(XIIIb)	53
	isochondodendrine	(XIIIa)	53
Cissampelos mucronata A. Rich	d-isochondodendrine	(XIIIa)	54
Cocculus hirsutus (L.) Diels	d,l-coclaurine	(Ia)	55
	d-trilobine	(XIIc)	55, 56
Cocculus laurifolius D.C.	d,l-coclaurine	(Ia)	57, 58
	magnoflorine	(IVl)	59

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TABLE 2—*continued*

Plant species	Alkaloids present	Formulae	References
Cocculus laurifolius D.C.	laurifoline	(IVg)	58, 60
	trilobine	(XIIc)	56, 58
	cocculine	(XVb)	61
	cocculidine	(XVc)	61
	dihyroerysodine	(XVIII)	62
	Base *II*	(XIIe)	58
	Base *IV*	(XVa)	58
	coclanoline		63
	subsequently shown to be a mixture of laudanine	(Id)	64
	and d-*N*-methylcoclaurine	(Ic)	64
Cocculus leaeba D.C.	palmatine	(VIb)	65
	oxycanthine	(XIa)	65
Cocculus sarmentosus (Lour.) Diels	cocsarmine	(IVh)	66
	tetrandrine	(Xc)	66
	trilobine	(XIIc)	56, 67
	isotrilobine (homotrilobine)	(XIId)	56, 68
	menisarine	(XIIf)	69
Cocculus trilobus D C.	magnoflorine	(IVl)	70
	trilobine	(XIIc)	56, 71
	isotrilobine	(XIId)	56, 72
	trilobamine (daphnoline)	(XIc)	73
	cocculolidine	(XVI)	74
	normenisarine	(XIIg)	73
Cyclea barbata (Wall.) Miers	isotetrandrine	(Xd)	75
	homoaromoline	(XIc)	75
Cyclea burmanii Hook. et Thoms.	tetrandrine	(Xc)	76
Cyclea peltata Diels	d-tetrandrine	(Xc)	77
	d,l-tetrandrine	(Xc)	77
	fangchinoline	(Xf)	77
	isochondodendrine	(XIIIa)	77

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TABLE 2—*continued*

Plant species	Alkaloids present	Formulae	References
Coscinium blumeanum (Wall.) Miers	palmatine	(VIb)	78
	berberine	(VIa)	78
	jatrorrhizine	(VId)	78
Coscinium fenestratum Colebrooke	berberine	(VIa)	79
Epinetrum cardifolium	isochondodendrine	(XIIIa)	80
	norcycleanine	(XIIIc)	80
	cycleanine	(XIIIb)	80
Epinetrum mangenati	isochondodendrine	(XIIIa)	80
	norcycleanine	(XIIIc)	80
	cycleanine	(XIIIb)	80
Fibraurea chloroleuca Miers	palmatine	(VIb)	78
(= *F. tinctonia* Loureiro)	jatrorrhizine	(VId)	78
Jatrorrhiza palmata Miers	palmatine	(VIb)	81
(= *J. columba* Miers)	columbamine	(VIc)	82
	jatrorrhizine	(VId)	81
Limacia cuspidata Hook.f et Thoms.	limacine	(Xg)	83
	cuspidaline	(IXc)	83
	limacusine	(XIb)	83
Limacia oblongata Miers	limacine	(Xg)	84
	cuspidaline	(IXc)	84
	limacusine	(XIb)	84
Legnephora moorei Miers	menisperine	(IVk)	85
(= *Pericampylus incanus* Miers)	(*N*-methylisocorydinium)		
Menispermum canadense L.	dauricine	(IXa)	86
	tetrandrine	(Xc)	86
Menispermum dauricum D.C.	menisperine	(IVk)	87
	sinomenine	(Va)	88, 89
	acutumine	(VIIIh)	24, 88
	acutumidine	(VIIIi)	24
	tetrandrine	(Xc)	86
	dauricine	(IXa)	87
	daurinoline	(IXb)	90
Parabaena hirsuta (Beccari) Diels	palmatine	(VIb)	91
Pericampylus formosanus Diels	(+)stepharine	(IIIa)	92

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TABLE 2—*continued*

Plant species	Alkaloids present	Formulae	References
Pleogyne australis Benth.	d-isochondodendrine	(XIIIa)	93
(= *P. cunninghamii* Miers)	l-curine	(XIVb)	93
Pycnarrhena manillensis Vidal	pycnamine	(Xb)	94
	isotetrandrine	(Xd)	94
	berbamine	(Xa)	94
	phaeanthine	(Xe)	94
Sinomenium actutum Rehd et Wils	stepharine	(IIIa)	95
(= *S. diversifolium* Diels)	tuduranine	(IVi)	96
	michelalbine	(IVb)	95
	magnoflorine	(IVl)	97
	sinomenine	(Va)	96, 98
	disinomenine	(Vb)	96, 98
	sinoacutine	(Vc)	96, 98, 99
	norsinoacutine	(Vd)	96, 98
	isosinomenine, now shown to be an artefact		100
	acutumine	(VIIIh)	24, 101
	acutumidine	(VIIIi)	24, 102
	sinactine	(VIIg)	101
Stephania capitata Sprengel	stephanine	(IVc)	102
	crebanine	(IVd)	102
	d-dicentrine	(IVe)	102
	cycleanine	(XIIIb)	102
	epistephanine	(XI)f	102
	phanostenine	(IVf)	102
Stephania cepharantha Hayata	cepharamine	(VIIIe)	103
	berbamine	(Xg)	103, 104
	isotetrandrine	(Xd)	103, 105, 106
	homoaromoline	(XIe)	103

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TABLE 2—*continued*

Plant species	Alkaloids present	Formulae	References
Stephania cepharantha Hayata	cycleanine	(XIIIb)	41, 103, 104, 106
	cepharanthine	(XId)	103, 105, 106, 107
Stephania dinklagei Diels	(+)isocorydine	(IVj)	108, 109
	dicentrine	(IVl)	108
	(+)corydine	(IVm)	109
	(−)roemerine	(IVa)	109
Stephania glabra (Roxb.) Miers (= *S. rotunda* Loureiro)	(+)stepharine	(IIIa)	110–113
	(+)pronuciferine	(IIIb)	111, 113
	tuduranine	(IVi)	110
	magnoflorine	(IVl)	114, 115
Stephania glabra (Roxb.) Meirs (= *S. rotunda* Loureiro)	(−)tetrahydropalmatine	(VIIa)	110, 111, 116, 117
	(−)corydalmine	(VIIh)	111
	(−)stepholidine	(VIIc)	111
	stepharatine	(VIIg)	110
	columbamine	(VIc)	115
	palmatine	(VIb)	115, 116
	jatrorrhizine	(VId)	115
	dehydrocorydalmine	(VIe)	115
	stepharanine	(VIf)	115
	cycleanine	(XIIIb)	112, 118
	rotundine, subsequently shown to be tetrahydropalmatine	(VIIa)	119, 120
	gindarine = tetrahydropalmatine	(VIIa)	116, 121
	gindarinine = palmatine	(VIb)	116, 121
Stephania hernandifolia (Willd.) Walp.	isotrilobine	(XIId)	56, 122

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TABLE 2—*continued*

Plant species	Alkaloids present	Formulae	References
Stephania hernandifolia (Willd.) Walp.	fangchinoline	(Xf)	123
	d-tetrandrine	(Xc)	123
	d-l-tetrandrine	(Xc)	123
	d-isochondodendrine	(XIIIa)	123
	4-desmethyl hasubanonine	(VIIIb)	25
	4-desmethylnorhasubanonine	(VIIIc)	25
Stephania japonica (Thunb.) Miers (= *Cocculus japonicus* D.C.)	stepharine	(IIIa)	124
	stephanine	(IVc)	125, 126
	hasubanonine	(VIIId)	27, 127, 128
	homostephanoline	(VIIIa)	27, 125, 128
	metaphanine	(VIIIg)	26, 126, 129
	prometaphanine	(VIIIf)	130, 131
	steponine	(VIIe)	132
	cyclanoline	(VIIIf)	133
	stepholine (= obamegine)	(Xh)	134, 135
	insularine	(XIIId)	136
	epistephanine	(XIf)	125, 135, 137
	hypoepistephanine	(XIg)	135, 137
	stebisimine	(XIh)	138
	protostephanine	(XVII)	126, 127, 139, 140

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TABLE 2—*continued*

Plant species	Alkaloids present	Formulae	References
Stephania sasakii Hayata	*N*-methylpapaveraldinium	(II)	141, 142
	phanostenine	(IVf)	106, 143
	crebanine	(IVd)	106, 143
	steponine	(VIIe)	142
	berbamine	(Xa)	106
	cepharanthine	(XId)	106, 143, 144
Stephania tetrandra S. Moore	cyclanoline	(VIIf)	145
	tetrandrine	(Xc)	145, 146
	fangchinoline	(Xf)	145, 147
Stephania venosa (Blume) Sprengel	d-corydine	(IVm)	148
Tiliacora acuminata Hook. et Thoms.	tiliarine	(XIIa)	28, 149
(= *T. racemosa* Colebr.)	tiliacorine	(XIIb)	150, 151
Tinomiscium petiolare Miers	l-isocorypalmine	(VIIb)	148
Tinospora bakis Miers	palmatine	(VIb)	65
(= *Cocculus bakis* Richard)	bebeerine	(XIVa)	1
Tinospora crispa Miers	berberine	(VIa)	1
(= *Cocculus crispa* D.C.)			
Tinospora rumphii Boerlage	berberine	(VIa)	1

Added in Proof: A new *Erythrina* alkaloid of novel structure has recently been reported in *Cocculus laurifolius* D. C. by Y. INUBUSHI, H. FURUKAWA and M. JU-ICHI, *Tetrahedron Letters* (3) 153 (1969)

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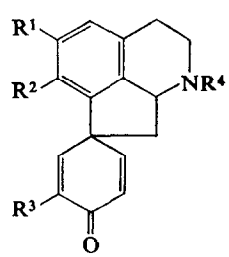
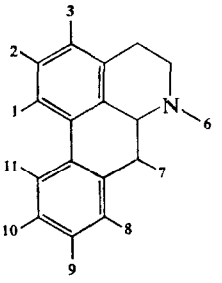


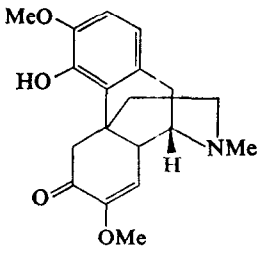
Stepharine (IIIa) $R^1 = R^2 = OMe$, $R^3 = H$, $R^4 = H$
Pronuciferine (IIIb) $R^1 = R^2 = OMe$, $R^3 = Me$, $R^4 = H$

FIG. 2. PROAPORPHINES (III).

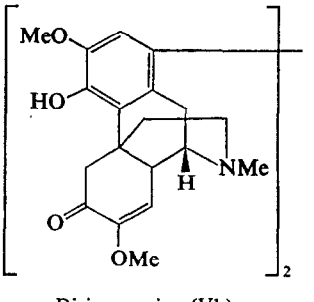


Alkaloid	1	2	6	7	8	9	10	11
Roemerine (IVa)	OCH_2O		Me					
Michelalbine (IVb)	OCH_2O		H	OH				
Stephanine (IVc)	OCH_2O		Me		OMe			
Crebanine (IVd)	OCH_2O		Me		OMe	OMe		
Dicentrine (IVe)	OCH_2O		Me			OMe	OMe	
Phanostenine (IVf)	OCH_2O		Me			OMe	OH	
Laurifoline (IVg)	OH	OMe	$(Me)_2$			OH	OMe	
Cocsarmine (IVh)	OMe	OMe	$(Me)_2$			OMe	OMe	
Tuduranine (IVi)	OMe	OMe	H				OH	
Isocorydine (IVj)	OMe	OMe	Me				OMe	OH
Menisperine (IVk) (= *N*-Methylisocorydinium)	OMe	OMe	$(Me)_2$				OMe	OH
Magnoflorine (IVl)	OH	OMe	$(Me)_2$				OMe	OH
Corydine (IVm)	OMe	OH	Me				OMe	OMe

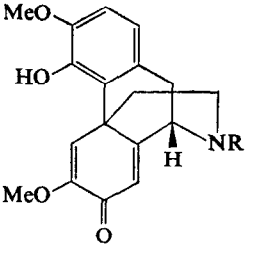
FIG. 3. APORPHINES (IV).



Sinomenine (Va)
(cucoline)



Disinomenine (Vb)
(Dehydrosinomenine)

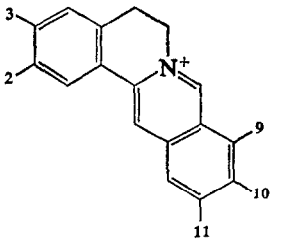


Sinoacutine (Vc) R = Me
Norsinoacutine (Vd) R = H

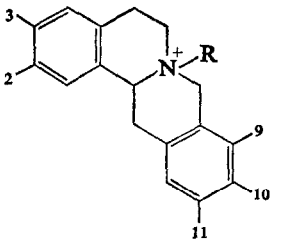
FIG. 4. MORPHINE (V).

The occurrences of the various alkaloids found in the Menispermaceae are shown in Table 2. The information has been drawn initially from the compilations of Tomita[1] and Boit,[14] and from 1960 to the end of 1968 from *Chemical Abstracts*. A few references are included to Japanese papers which have not been abstracted at the time of writing.

The table shows 198 alkaloid occurrences of ninety-five structures in fifty species from twenty-two genera. (Diels[13] describes about 350 species from sixty-three genera.)



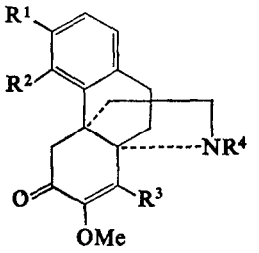
Formula A
Protoberberines (VI)



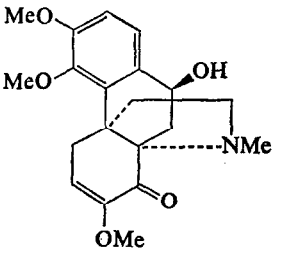
Formula B
Tetrahydroprotoberberines (VII)

Formula A	Formula B	2	3	9	10	11	R
Berberine (VIa)		OCH_2O		OMe	OMe		
Palmatine (VIb)	Tetrahydropalmatine (VIIa)	OMe	OMe	OMe	OMe		—
Columbamine (VIc)	Isocorypalmine (VIIb)	OH	OMe	OMe	OMe		—
Jatrorrhizine (VId)		OMe	OH	OMe	OMe		
Dehydrocorydalmine (VIe)	Corydalmine (VIIh)	OMe	OMe	OMe	OH		
Stepharanine (VIf)	Stepholidine (VIIc)	OH	OMe	OMe	OH		—
	Sinactine (VIId)	OMe	OMe	OCH_2O			—
	Steponine (VIIe)	OMe	OH	OH	OMe		Me
	Cyclanoline (VIIf)	OH	OMe	OH	OMe		Me
	Stepharatine (VIIg)	OMe	OMe	OMe	OMe	OH	

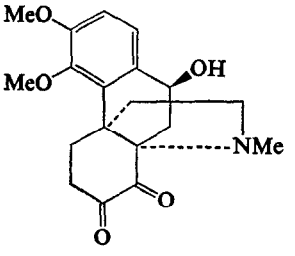
FIG. 5. PROTOBERBERINES.



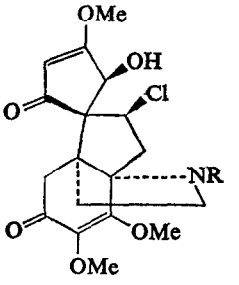
	R^1	R^2	R^3	R^4
Homostephanoline (VIIIa)	OH	OMe	OMe	Me
4-Desmethylhasubanonine (VIIIb)	OMe	OH	OMe	Me
4-Desmethylnorhasubanonine (VIIIc)	OMe	OH	OMe	H
Hasubanonine (VIIId)	OMe	OMe	OMe	Me
Cepharamine (VIIIe)	OMe	OH	H	Me



Prometaphanine
(VIIIf)

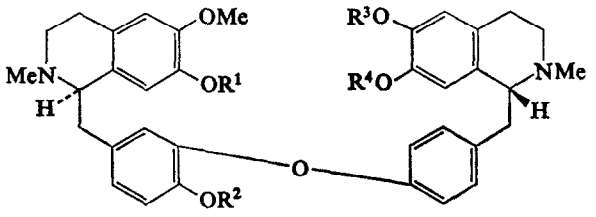


Metaphanine (VIIIg)



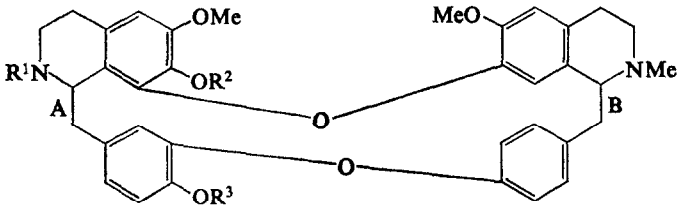
Acutumine (VIIIh) R = Me
Acutumidine (VIIIi) R = H

FIG. 6. HASUBANAN ALKALOIDS (VIII).



Alkaloid	R^1	R^2	R^3	R^4
Dauricine (IXa)	Me	H	Me	Me
Daurinoline (IXb)	Me	H	H	Me
Cuspidaline (IXc)	H	Me	Me	H

FIG. 7. BISCOCLAURINE ALKALOIDS. (i) DAURICINE TYPE ALKALOIDS (IX).



Alkaloid	R^1	R^2	R^3	Configuration	
				A	B
Berbamine (Xa)	Me	Me	H	D	L
Pycnamine (Xb)	Me	Me	H	D	D
Tetrandrine (Xc)	Me	Me	Me	L	L
Isotetrandrine (Xd)	Me	Me	Me	D	L
Phaeanthine (Xe)	Me	Me	Me	D	D
Fangchinoline (Xf)	Me	H	Me	L	L
Limacine (Xg)	Me	H	Me	D	D
Obamegine (Xh)	Me	H	H	D	L

FIG. 8. BISCOCLAURINE ALKALOIDS. (ii) BERBAMINE TYPE (X).

Incompletely Characterized Bases

In addition to the alkaloids shown in Figs. 1–17 the following partially characterized bases have been described.

Anospermum grandifolium[152] Eichl. (*Elissarhena grandifolia*) (Eichl.) Diels. Curare activity in the quaternary fraction.

Archangelisia flava (L.) Merrill (*Menispermum flavum* L.). Schobakunine[33] separated as tetrahydro shobakunine, $C_{20}H_{23}NO_4$, m.p. 140°. (Probably mixture of berberine and palmatine.[19])

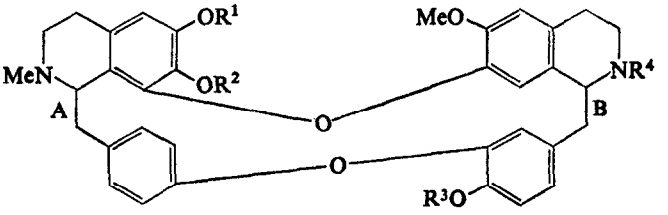
Burasaia madagascariensis Thou. Burasaine,[34] $C_{21}H_{23}O_4N$.

Chondodendron limaciifolium (Diels) Moldenke. Base A,[36] m.p. 270–300°, $C_{34}H_{32}O_4N_2(OMe)_2$. Base B,[36,38] m.p. 230° d., $C_{32}H_{22}O_5N_2(OMe)_3$.

Chondodendron platyphyllum Miers. l-Chondofoline,[35] $C_{35}H_{36}O_6N_2$, α_{5461} −280·6° (0·1 N HCl).

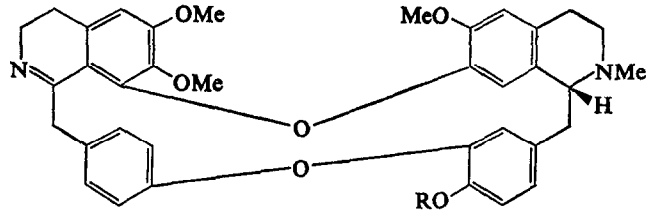
Chondodendron tomentosum Ruiz et Pav. *d*-Tomentocurine,[38,152] m.p. 265°, $C_{36}H_{38}O_6N_2$, $[\alpha]_D$ + 202° (0·1 N HCl).

[152] H. KING, *J. Chem. Soc.* 1945 (1948); 936 (1947).

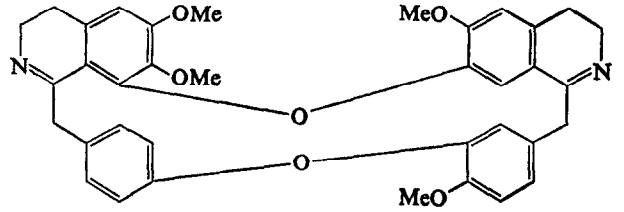


Alkaloid	R^1	R^2	R^3	R^4	Configuration A	Configuration B
Oxycanthine (XIa)	Me	Me	H	Me	L	D
Limacusine (XIb)	Me	H	Me	Me	D	D
Trilobamine (XIc)	Me	H	H	H	L	D
Cepharanthine (XId)	—CH_2—		Me	Me	L	D
Homoaromoline (XIe)	Me	H	Me	Me	L	D

FIG. 9. BISCOCLAURINE ALKALOIDS. (iii) OXYCANTHINE TYPE (XI).



R = Me Epistephanine (XIf)
R = H Hypoepistephanine (XIg)



Stebisimine (XIh)

FIG. 10. BISCOCLAURINE ALKALOIDS. (iii) OXYCANTHINE TYPE (XI).

Cissampelos pareira L. Four uncharacterized bases.[46]

Cocculus laurifolius D.C. Coclamine,[153] m.p. 140–142°, $C_{19}H_{23}O_2N$, $[\alpha]_D^4$ −245°. Contains tertiary nitrogen and $(OMe)_3$. Coclifoline picrate,[153] m.p. 158°, $C_{19}H_{27}O_3N$. $C_6H_3O_7N_3$.

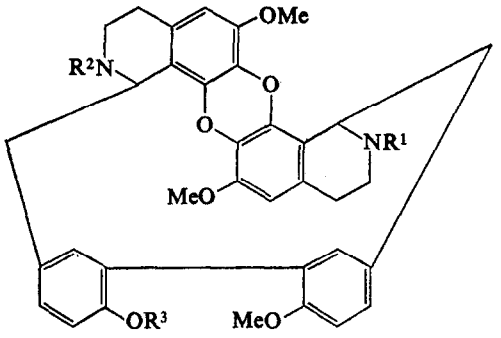
Cyclea burmanii Miers. Burmannine,[154] m.p. 218°, $C_{18}H_{21}O_3N$. Hydrochloride $[\alpha]_D^{28.5}$ + 235·5°. Burmannoline,[154] m.p. 165°, $C_{21}H_{23}O_4N$.

Fibraurea chloroleuca Miers (*F. tinctoria* Loureiro). Fibramine,[155] $C_{25}H_{29}O_7N$, contains $(OMe)_3$, $(OCH_2O)_2$. Hydrochloride, m.p. 196–198°, $[\alpha]_D^{15}$ 273·3°. Fibraminine,[155] m.p. 192–193°, $C_{18}H_{19}O_8N$, $[\alpha]_D^{15}$ 28·3°, contains $(OMe)_4$.

[153] M. TOMITA and H. YAMAGUCHI, *J. Pharm. Soc. Japan* **76**, 1048 (1956); *Chem. Abs.* **51**, 1542 (1957).

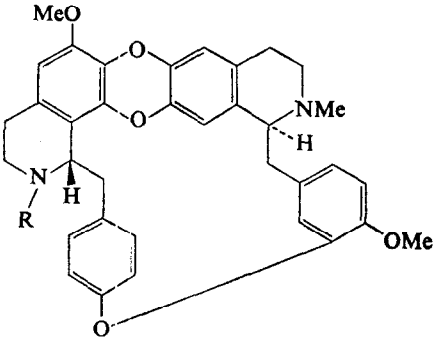
[154] S. P. SARADAMMA, *Bull. Central. Research Inst. Univ. Travancore, Trivandrum* Ser. A, **3**, 55 (1954); *Chem. Abs.* **49**, 11794 (1955).

[155] JEN-HUNG CHU, JUI-CH'UN CH'EN and SHEN-TING SHENG, *Hua Hsuah Hsueh pao.* **28** (2), 89 (1962); *Chem. Abs.* **60**, 6887 (1964).

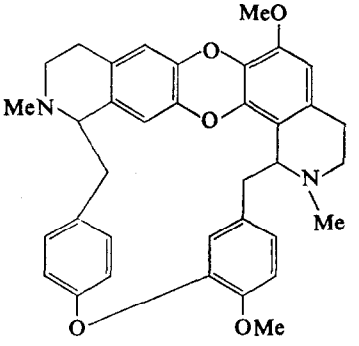


Tiliarine (XIIa) $R^2 = H$ $R^1 = Me$ or vice versa $R^3 = H$
Tiliacorine (XIIb) $R^1 = R^2 = Me$ $R_3 = H$

FIG. 11. BISCOCLAURINE ALKALOIDS. (iv) DIBENZO-*p*-DIOXIN TYPE (XII).



Trilobine (XIIc) R = H
Isotrilobine (XIId) R = Me



Cocculus laurifolius Base *II* (XIIe)

FIG. 12. BISCOCLAURINE ALKALOIDS. (iv) DIBENZO-*p*-DIOXIN TYPE (XII).

Pycnarrhena manillensis Vidal. Ambaline,[156] m.p. 203–204°, $C_{18}H_{21}O_3N$, contains $(OMe)_2$ and NMe. Ambalinine,[156] m.p. 123°, $C_{38}H_{42}N_2O_{10}$, $[\alpha]_D^{26}$ 142–143°, contains a carbonyl function.

Sinomenium acutum Rehd. et Wils. Base *III*,[95] m.p. 194–195°, $C_{23}H_{25}O_6N$, $[\alpha]^{18}$ −74·1° (*c* = 1·0,$CHCl_3$). U.v. 275 nm (log ε 3·55). NMR τ 2·3–3·5 (6H); 6·20 (3H, s); 7·67 (3H, s); 7·73 (3H, s); 7·86 (3H, s). Compound *IV*,[95] m.p. 94–97°, $C_{27}H_{33}O_{11}N$, $[\alpha]_D^{18}$ + 11·3 (*c* = 1, $CHCl_3$). U.v. 278 nm (log ε 3·6), i.r. 1750 cm^{-1}. NMR τ 3·16–3·56 (4H); 4·32 (2H, m); 6·22 (3H, s); 7·5 (3H, s); 7·71 (3H, s); 7·74 (3H, s); 7·94 (3H, s). Diversine,[58] $C_{17}H_{16}O(OH)_2(OMe)_2NMe$, $[\alpha]_D^{17}$ 6·98°. Hydrochloride, m.p. 135–140°.

Stephania abyssinica Dill. et Rich. Neostephanine,[157] m.p. 230–233°, $C_{22}H_{25}NO_6$.

Stephania delavayi Diels. Base,[118] m.p. 150°, $C_{20}H_{24}O_5N$(sic), $[\alpha]_D^{22}$ −240°, has $(OMe)_2$.

Stephania dinklagei Diels. Dinklageine,[158] m.p. 285°, $C_{18}H_{19}O_3N$, $[\alpha]_D$ −24·4°, contains $(OMe)_2$.

Stephania glabra Miers (*S. rotunda* Loureiro). Gindaricine,[116] m.p. 193°, $C_{18}H_{19}O_3N$. Base,[112] m.p. 205, $C_{19}H_{21}O_4N$, $[\alpha]_D^{21}$ −70°, contains (OMe), $_2$OH and carbonyl; gives hexahydro product.

Base A,[117] m.p. 81°, $C_{19}H_{18}O_2N$, $[\alpha]_D$ −88°. Hydrochloride, m.p. 253°, tertiary nitrogen.

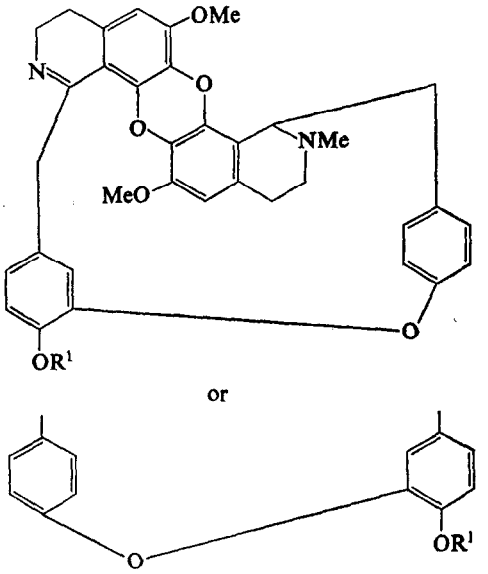
Base B,[117] m.p. 182–183°, $C_{21}H_{25}O_4N$. Hydrochloride, m.p. 232°, contains $(OMe)_3$, OH and NMe.

Base C,[117] m.p. 154° $C_{20}H_{25}O_4N$, $[\alpha]_D$ −72°, contains $(OH)_2(OMe)_2NMe$. I.r., 1697, 1633, 1618 cm^{-1} u.v., 265 nm. Hydrochloride, m.p. 227–228°, gives a tetrahydro-derivative, m.p. 155–156°, i.r., 1732, 1609 cm^{-1}. Base,[118] m.p. 205°, $C_{19}H_{21}O_4N$, $[\alpha]_D^{21}$ −70°, contains $(OMe)_2$ and active H.

[156] A. C. SANTOS and G. Q. QUIBILAN, *Univ. Phillipines Nat. Appl. Sci. Bull.* **3**, 353 (1933); *Chem. Abs.* **28**, 4735 (1934). A. C. SANTOS, *Univ. Phillipines Nat. Appl. Sci. Bull.* **4**, 338 (1935); *Chem. Abs.* **30**, 4171 (1936).

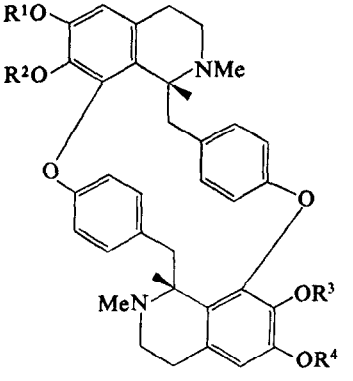
[157] H. L. DE WAAL and E. WEIDEMAN, *Tydskr. Natuurwetenskappe* **2**, 12 (1962); *Chem. Abs.* **59**, 1962 (1961).

[158] P. A. SARTORETTO and F. J. SOWA, *J. Am. Chem. Soc.* **59**, 603 (1937); R. A. PARIS and J. LE MEN, *Ann. Pharm. Fr.* **13**, 200 (1955); *Chem. Abs.* **49**, 11959 (1955).



Menisarine (XIIf) $R^1 = CH_3$
Normenisarine (XIIg) $R^1 = H$

FIG. 13. BISCOCLAURINE ALKALOIDS. (iv) DIBENZO-*p*-DIOXIN TYPE (XII).



Isochondodendrine (XIIIa)	$R^2 = R^3 = H$ $R^1 = R^4 = Me$
Cycleanine (XIIIb)	$R^1 = R^2 = R^3 = R^4 = Me$
Norcycleanine (XIIIc)	$R^3 = H$ $R^1 = R^2 = R^4 = Me$

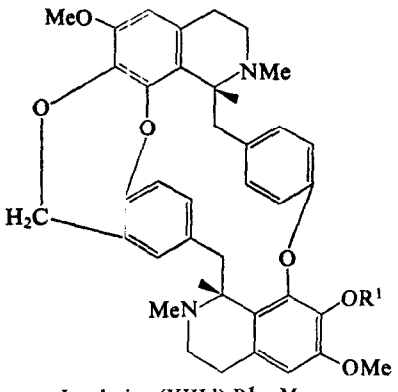
FIG. 14. BISCOCLAURINE ALKALOIDS. (v) ISOCHONDODENDRINE TYPE (XIII).

Stephania hernandifolia (Willd.) Walp. Three bases,[118] one of which $C_{20}H_{25}O_5N$, HI, m.p. 194°; MeI, m.p. 186°; acetate, m.p. 113°. Hernandoline,[159] $C_{20}H_{25}NO_5$.

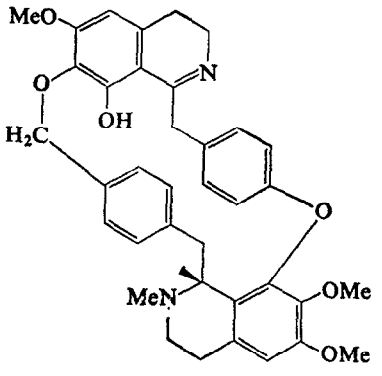
Stephania japonica (Thunb.) Miers (*Cocculus japonicus* D.C.). Base originally called epistephanine[125] which cannot be the same as that now known under this name, $C_{19}H_{21-23}NO_3$, $[\alpha]^{15}$ 19·8° contains $(OMe)_2$, NMe ($C{=}C)_2$ and C=O.

Ψ Epistephanine,[125] m.p. 257°, $C_{16}H_{11}(OMe)_2OH.NMe$. $[\alpha]_D$ 174°. Stephanoline,[125] m.p. 186°, $C_{27}H_{29}N_2O_2(OH)(OMe)_4$ $[\alpha]_D^{17}$ −255°.

[159] I. I. FADELVA, A. D. KUZOVKOV and T. N. IL'INSKAYA, *Khim. Prir. Soedin* **3**, (2), 106 (1967); *Chem. Abs.* **67**, 43966 (1967).

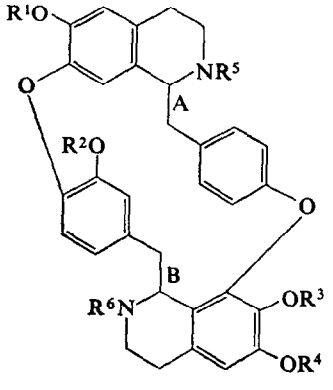


Insularine (XIIId) R^1 = Me
Insulanoline (XIIIe) R^1 = H



Cissampareine (XIIIf)

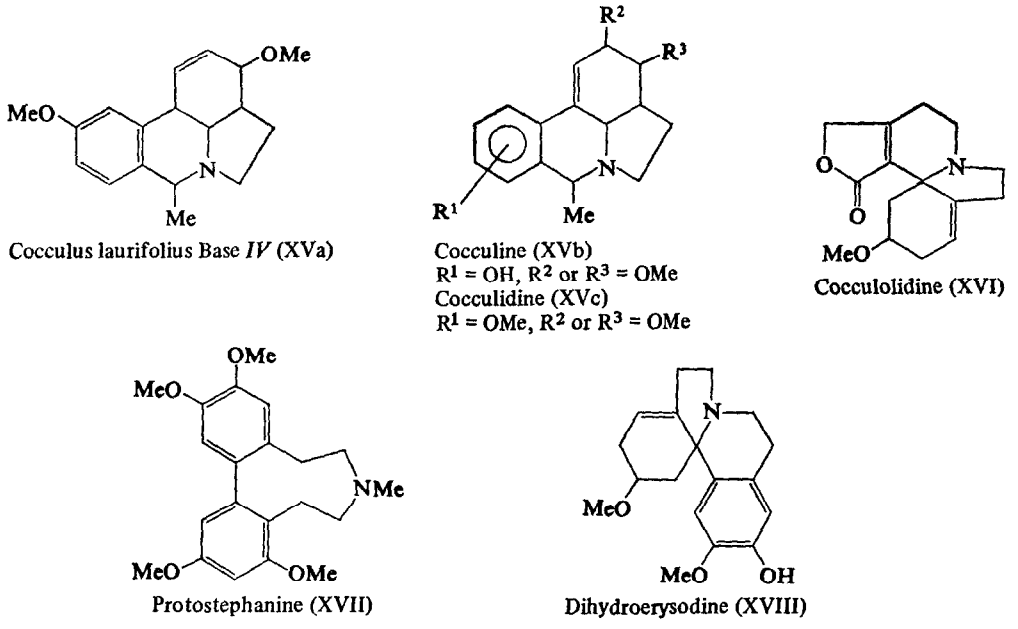
FIG. 15. BISCOCLAURINE ALKALOIDS. (vi) ISOCHONDODENDRINE TYPE (XIII).



Alkaloid	R^1	R^2	R^3	R^4	R^5	R^6	Configuration A	Configuration B
d-Curine (XIVa)	Me	H	H	Me	Me	Me	L	L
l-Curine (XIVb)	Me	H	H	Me	Me	Me	D	D
Hayatine (XIVc) (-d,l-curine)	Me	H	H	Me	Me	Me	D	D
							and	
							L	L
4-*O*-Methylcurine (XIVd)	Me	Me	H	Me	Me	Me	L	L
Hayatinine (XIVe)	Me	Me	H	Me	Me	Me	D	D
							and	
							L	L
Hayatidine (XIVf)	Me	Me	H	Me	Me	Me	D	L
d-Chondocurine (XIVg)	Me	H	Me	H	Me	Me	L	D
d-Chondocurarine (XIVh)	Me	H	Me	H	(Me_2)	$(Me)_2$	D	L
d-Tubocurarine (XIVi)	Me	H	H	Me	$(Me)_2$	$(Me)_2$	L	D

Note: Curine = bebeerine = chondodendrine.

FIG. 16. BISCOCLAURINE ALKALOIDS. (vi) CURINE TYPE (XIV).



Cocculus laurifolius Base *IV* (XVa)

Cocculine (XVb)
R^1 = OH, R^2 or R^3 = OMe
Cocculidine (XVc)
R^1 = OMe, R^2 or R^3 = OMe

Cocculolidine (XVI)

Protostephanine (XVII)

Dihydroerysodine (XVIII)

FIG. 17. MISCELLANEOUS BASES.

Miersine.[124] A new minor alkaloid, m.p. 222°, $C_{20}H_{27}O_6N$ (accurate mass). Mass spectral fragmentation characteristic of hasubanan alkaloids. I.r., 3700 3550, 1725, 1600 cm^{-1}, u.v. 237, 280 nm. Forms internal hemiketal. NMR τ 3·32 (2H, s); 6·09 (3H, s); 6·17 (3H, s); 6·54 (3H, s); 7·40 (3H, s); 4·90 (1H, d, J = 6·5 cps). Base treatment causes loss of water (accurate mass). Tentatively proposed structure on this information and structural analogy (XXXI).

Stephania tetrandra S. Moore. Menisine,[160] m.p. 152°, $C_{19}H_{22}NO_3$, contains $(OMe)_2$. Menisidine,[160] m.p. 176°, $C_{36}H_{41}N_2O_6$, contains $(OMe)_3$. Hangfangchine,[161] m.p. 215–217°, $C_{16}H_{21}NO_6$, $[\alpha]^{18}$ −12·9.

Tiliacora racemosa Colebr. Base A,[162] m.p. 249–250°; MeI, m.p. 255°. Base B,[162] m.p. 275·5° $[\alpha]_D^{30}$ 10·14°. (Found: C, 67·96; H, 5·23; O, 25·56; N, 1·25%.) Also reported a Base A,[163] $C_{17}H_{14}NO_5$, $[\alpha]_D$ = 196°; EtI, m.p. 283°.

Base B,[163] iodide, $C_{19}H_{24}O_3NI$, m.p. 211–214°, $[\alpha]_D$ −18°. Base C, iodide,[173] m.p. 156–159°, $C_{20}H_{26}O_5NI$, $[\alpha]_D$ −10·6. Perchlorate, m.p. 156–159°, $C_{20}H_{26}O_9NCl$, $[\alpha]_D$ −70°. Base D, perchlorate,[163] $C_{20}H_{24}O_8NCl$, m.p. 256°, $[\alpha]_D$ + 122°. Iodide, $C_{20}H_{24}O_4NI$, m.p. 242–244°.

Tiliacora funifera, Oliver. Funiferine,[164] m.p. 232°, $C_{31}H_{24}O_2(OH)(OMe)_3(NMe)_2$, $[\alpha]_D^{22}$ + 184–183°.

Tinospora cardifolia (D.C.) Miers. Two uncharacterized[165] bases.

Triclisia gilleti (De Wild) Staner (*Tiliacora gilleti* De Wild). Triclisine,[166] m.p. 255–256°, $C_{16}H_{31}O_{10}N$, $[\alpha]_D$ + 117°. Tricliseine,[166] m.p. 135°, $C_{33}H_{39-41}O_7N$, $[\alpha]_D$ + 68°. Efirine,[167] m.p. 176°, $C_{38}H_{44}N_2O_7$, and another yellow amorphous base.

[160] T. Q. CHOU, *Chines eJ. Physiol.* **6**, 267 (1935); *Chem. Abs.* **30**, 471 (1936); *Chinese J. Physiol.* **13**, 167 (1938); *Chem. Abst.* **32**, 9092 (1938).

[161] C. F. HSU, *J. Chinese Chem. Soc.* **7**, 123 (1940); *Chem. Abs.* **35**, 5121 (1941); *J. Chinese Chem. Soc.* **17**, 156 (1950); *Chem. Abs.* **46**, 10546 (1952).

[162] N. SARASWATI BAI, *Bull. Central Res. Inst. Univ. Travancore, Trivandrum* Ser. **A3**, 55, 109 (1954); *Chem. Abs.* **49**, 11794 (1955); *Chem. Abs.* **50**, 1056 (1956).

[163] T. K. PALIT, A. C. ROY and M. P. KHARE, *Curr. Sci. (India)* **36** (2), 43–4 (1967); *Chem. Abs.* **66**, 73228 (1967).

[164] A. N. TACKIE and A. THOMAS, *Ghana J. Sci.* **5**, 11 (1965); *Chem. Abs.* **65**, 3922 (1966).

[165] S. N. SEGHAL and D. N. MAJUMDAR, *J. Proc. Inst. Chemists (India)* **31**, 12 (1959); *Chem. Abs.* **54**, 4637 (1960).

[166] E. CASTAGNE, *Congo* 41 (1934); *Chem. Abs.* **29**, 5476 (1935); *Congo* (1) 32, (1935); *Chem. Abs.* **30**, 5359 (1939).

[167] E. DELVAUX, *Bull. agr. Congo. Belg.* **27**, 135 (1936); *Chem. Abs.* **30**, 6129 (1936).

The information tabulated in Table 2 is summarized in Table 3 where the number of occurrences of alkaloids in the principal structural groups is shown for each genus. It will have been noted from Table 2 that different groups of workers have often found a different distribution of alkaloids in the same plant. It is not possible to decide whether the plant material used in such cases was the same, since its source is not always clear. In addition,

TABLE 3. NUMBER OF OCCURRENCES OF EACH ALKALOID GROUP BY GENUS

	Type							
Genus (number of species)	1-Benzylisoquinoline	Proaporphine	Aporphine	Protoberberine	Biscoclaurine	Morphine	Hasubanan	Others
Archangelisia (2)				5				
Burasaia (1)				3				
Chondodendron (5)	2				14			
Cissampelos (4)			1	2	16			
Cocculus (5)	4		4	1	12			5
Coscinium (2)				4				
Cyclea (3)					7			
Epinetrum (2)					6			
Fibraurea (1)				2				
Jatrrorhiza (1)				3				
Limacia (2)					6			
Legnephora (1)			1					
Menispermum (2)			1		5	1	2	
Parabaena (1)				1				
Pericampylus (1)		1						
Pleogyne (1)					2			
Pycnarrhena (1)					4			
Sinomenium (1)		1	3	1		4	2	
Stephania (9)	1	3	12	13	23		7	1
Tiliacora (1)					2			
Tinomiscium (1)				1				
Tinospora (3)				3	1			

even the same plants can give different alkaloids if the growth conditions, season of harvest and isolation technique are varied. These factors also apply to comparison of the genera within the family Menispermaceae. There are also complications caused by the fact that some genera, e.g. *Stephania* and *Chondodendron*, have been investigated more extensively than others, and in some cases the investigations reported were carried out before modern techniques of separation and structural determination were available.

However, despite these reservations concerning the validity of the information for comparison purposes, some interesting observations can be made. Thus, with the exception of the genus *Pericampylus* where the proaporphine, stepharine, is the only recorded alkaloid, every genus has been found to contain a member of at least one of the three main classes—aporphine, protoberberine and biscoclaurine. In some cases representatives of all three classes have been noted. So far, morphine alkaloids have been found only in *Menispermum*

and *Sinomenium* species and hasubanan alkaloids only in *Stephania*, *Sinomenium* and *Menispermum* species. The remainder of the unusual monomeric bases found are in *Cocculus* and *Stephania* species.

The family Menispermaceae has been subdivided in the manner shown in Table 4[168] (only subfamilies containing genera reported in Table 2 are shown). It is interesting to observe the correlations between the alkaloids found and the systematic classification illustrated here. In particular the few hasubanan, morphine, *Erythrina* and novel bases of the Menispermaceae have so far been found only in the subfamily Menispermeae.

TABLE 4. SUB-FAMILIES OF MENISPERMACEAE

Sub-family		Genus
Triclisiae		*Pycnarrhena*, *Tiliacora*, *Triclisia*, *Chondodendron*
Anamirteae		*Coscinium*, *Anamirta*
Fibraureae		*Burasaia*, *Tinomiscium*, *Fibraurea*
Tinosporeae		*Jatrorrhiza*, *Tinospora*
Menispermeae →	Menisperminae →	*Cocculus*, *Sinomenium*, *Menispermum*
	Stephaniinae	*Stephania*
	Cissampelinae →	*Cissampelos*, *Cyclea*

Biosynthesis

Alkaloid biosynthesis has been extensively reviewed[2-9] so that only the broad outlines of skeletal transformations need be mentioned here. All the alkaloids of the family Menispermaceae are either 1-benzylisoquinolines or compounds theoretically derivable from such precursors. The results of incorporation experiments with tyrosine, 3,4-dihydroxyphenylalanine and 3,4-dihydroxyphenethylamine into simple benzylisoquinolines have been discussed recently.[169] The subsequent transformations of the basic skeleton into the various types of monomeric bases considered here, are shown schematically in Chart 1.

A number of aporphine alkaloids, such as dicentrine (IVe) and isocorydine (IVj), can be envisaged as arising by direct oxidative phenolic coupling[3, 5, 8] of reticuline (Ie, R = Me, $3^1 = 7 = OH$, $4^1 = 6 = OMe$) although no such mechanism has been demonstrated so far *in vivo*.* Tuduranine (IVi), stephanine (IVc), roemerine (IVa) and crebanine (IVd) can be

* *Added in Proof*: But see: G. BLASCHKE, *Arch. Pharm* (*Weinheim*) **301**, 432–9 (1968). *Chem. Abst.* **69**, 33548 (1968).

[168] A. ENGLER, *Syllabus der Pflanzen-Familien*, Vol. II, Gebruder Borntraeger, Berlin-Nikolasse (1964).
[169] V. DEULOFEU, J. COMIN and M. J. VERNENGO, in *The Alkaloids* (edited by R. H. F. MANSKE), Vol. X, Academic Press, New York (1968).

envisaged as arising from oxidative phenolic coupling of a benzylisoquinoline to give a proaporphine (III) which might rearrange in a number of ways. Dienone–phenol rearrangement[3] with aryl or alkyl migration, or, after reduction, dienol benzene rearrangement[3] with alkyl or aryl migration, could, in principle, account for the biosynthesis of all the known aporphines after suitable methylations, demethylations and methylenedioxy bridge formations.

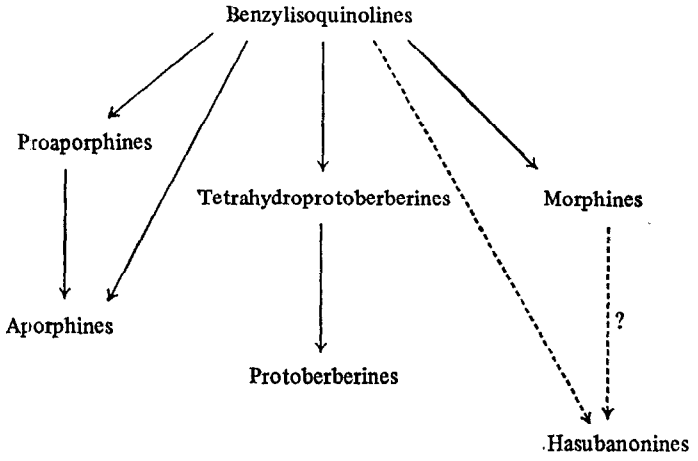


CHART 1.

A number of proaporphine alkaloids have been isolated.[16] Their formation *in vitro* and their rearrangements have been extensively studied.[8, 170–173] Tracer work has been described[174] showing the biosynthesis of the aporphine, isothebaine (IVn, 1 = OH, 2 = 11 = OMe 6 = Me) in *Papaver orientale*, to proceed from the benzylisoquinoline, orientaline (If, $3^1 = 6 = OMe$, $7 = 4^1 = OH$, R = Me), via the proaporphine, orientalinone (IIIc, $R^1 = R^3 = OMe$, $R^2 = OH$). Also the biosynthesis of roemerine (IVa) has been shown to involve coclaurine (Ia) and *N*-methylcoclaurine (Ic) in *P. dubium*.[175] Thus, in the case of the Menispermaceae, one could envisage the transformation of coclaurine (Ia) via isocrotonosine (IIId, $R^1 = OMe$, $R^2 = OH$, $R^3 = H$, $R^4 = H$) to stepharine (IIIa) and pronuciferine (IIIb). By dienone–phenol rearrangement of stepharine (IIIa) tuouranine (IVi) could be produced and this reaction is known *in vitro*.[172] Reduction of isocrotonosine to the corresponding dienol followed by rearrangement of the dienol–benzene type could give rise to roemerine (IVa) and michelalbine (IVb). It is also possible that tuduranine (IVi), along with stephanine (IVc), might arise from orientalinone after reduction and dienol–benzene rearrangement.[4] One expects that further isolation work will reveal new proaporphines in the Menispermaceae.

[170] A. H. JACKSON and J. A. MARTIN, *Chem. Commun.* 142, 420 (1965).
[171] M. SHAMMA and W. A. SLUSARCHYK, *Chem. Commun.* 528 (1965).
[172] M. TOMITA and M. KOZUKA, *J. Pharm. Soc. Japan* **86**, 671 (1966); *Chem. Abs.* **66**, 28947 (1967).
[173] A. R. BATTERSBY and T. H. BROWN, *Proc. Chem. Soc.* 85 (1964). A. R. BATTERSBY, T. H. BROWN and J. H. CLEMENTS, *J. Chem. Soc.* 4550 (1965).
[174] A. R. BATTERSBY, R. T. BROWN, J. H. CLEMENTS and G. G. IVERACH, *Chem. Commun.* 230 (1965). A. R. BATTERSBY and T. H. BROWN, *Chem. Commun.* 170 (1966).
[175] D. H. R. BARTON, D. S. BHAKUNI, G. M. CHAPMAN and G. W. KIRBY, *Chem. Commun.* 259 (1966).

The biosynthesis of morphine alkaloids has been studied extensively[8] and the pathway from norlaudanosoline (Ig, 6 = 7 = 3^1 = 4^1 = OH, R = H) via (–) reticuline (Ie, 3^1 = 7 = OH, 4^1 = 6 = OMe, R = Me) to the morphinandienone, salutaridine [the enantiomer of sinacutine (Vc)] has been well established. In *Sinomenium acutum*, (±) reticuline was shown to be converted by way of sinoacutine (Vc) to sinomenine (Va).[176] Disinomenine (Vb) can be seen to arise by *para-para* coupling of ring A of sinomenine or one of its precursors. The protosinomenine (Ih, 3^1 = 6 = OH, 4^1 = 7 = OMe, R = Me) proposed by Robinson[2] has never yet been found in nature and is not incorporated into sinomenine.[176]

The results of feeding experiments with plants producing protoberberine alkaloids have recently been summarized.[18] Thus it has been shown[177, 178] that the *N*-methyl group of a 1-benzyltetrahydroisoquinoline forms the berberine bridge. The cyclization reaction occurs *ortho* or *para* to a free phenolic group in ring C of the benzylisoquinoline. It has been shown that (+) reticuline is incorporated into berberine (VIa) in *Hydrastis canadensis*,[179] into stylopine in *Chelidonium majus*[180] and that (±) laudanosoline (Ii, 3^1 = 4^1 = 6 = 7 = OH, R = H) is incorporated into berberine in *Berberis japonica*.[181] It was also shown that the two possible monomethylated laudanosolines between laudanosoline and reticuline are incorporated into berberine but protosinomenine is not.[179] On the basis of this work, one might account for the biosynthesis of all the protoberberines in Menispermaceous plants with the exception of stepharatine (VIIg), the novel structure of which was discussed earlier. The pentaoxygenated 1-benzylisoquinoline, which one might propose as a precursor to stepharatine, has an oxygenation pattern hitherto unknown.

The bisbenzyl alkaloids of Menispermaceae are formally derivable by intermolecular oxidative coupling of two coclaurine type units[182] with formation of carbon–oxygen or more rarely carbon–carbon bonds (tiliacorine, XIIb). Thus the oxycanthine, berbamine and isochondodendrine classes and curine can be seen to be derivable directly by coupling and subsequent *O*-methylation. Chondocurine (XIVg) and chondocurarine (XIVh) would require that either norcoclaurine is used for at least one half or that coclaurine is incorporated with a subsequent demethylation step. The same applies to daurinoline (IXb), except that in this case isococlaurine (Ib) could also be considered as a possible precursor for one half.

A few biscoclaurine alkaloids do not fit this simple approach, namely those with a dibenzo-*p*-dioxin nucleus such as trilobine (XIIc) and menisarine (XIIf) and the insularines (XIIId) and (XIIIe) and cissampareine (XIIIf). One approach to the dibenzo-*p*-dioxin system[8] is illustrated with partial structures in Fig. 18. The intermediate (XIXa) is oxidized to the corresponding phenoxonium ion which is then substituted into the ring A to give the ion (XIXb). Reduction then leads to the trilobine type (XIXc). A similar mechanism involving radical substitution could also be considered.[8] Formation of the menisarine type of nucleus can be considered in a similar manner, as shown in Fig. 18 (XIXa) → (XIXd) → (XIXe). The second approach[3] to these two systems is shown in Fig. 19, and involves initial carbon–carbon coupling.

Insularine (XIIId) might be formed from an isochondodendrine type skeleton by involvement of a hydroxymethyl group, as has been suggested in the case of the berberine bridge

[176] D. H. R. Barton, A. J. Kirby and G. W. Kirby, *Chem. Commun.* 52 (1965); *J. Chem. Soc.* (c) 929 (1968).
[177] D. H. R. Barton, R. H. Hesse and G. W. Kirby, *Proc. Chem. Soc.* 223 (1964).
[178] A. R. Battersby, R. J. Francis, M. Hirst and J. Staunton, *Proc. Chem. Soc.* 268 (1963).
[179] D. H. R. Barton, R. H. Hesse and G. W. Kirby, *J. Chem. Soc.* **63**, 79 (1965).
[180] A. R. Battersby, R. J. Francis, E. A. Ruveda and J. Staunton, *Chem. Commun.* 89 (1965).
[181] A. R. Battersby, R. J. Francis, M. Hirst and J. Staunton, *Proc. Chem. Soc.* 268 (1963).
[182] F. Faltis, L. Holzinger, P. Ita and R. Schwarz, *Ber.* **74**, 79 (1941).

cyclization.[183] Cissampareine (XIIIf) could also be derived from an isochondodendrine type as suggested by Kupchan.[52] The skeletal changes involved in these proposed transformations can be illustrated as in Chart 2. Table 5 shows the distribution of the principle types of biscoclaurine alkaloids in genera of the Menispermaceae. It is seen that the isolation work to date in the genus *Cissampelos* shows the co-occurrence of isochondodendrine, insularine

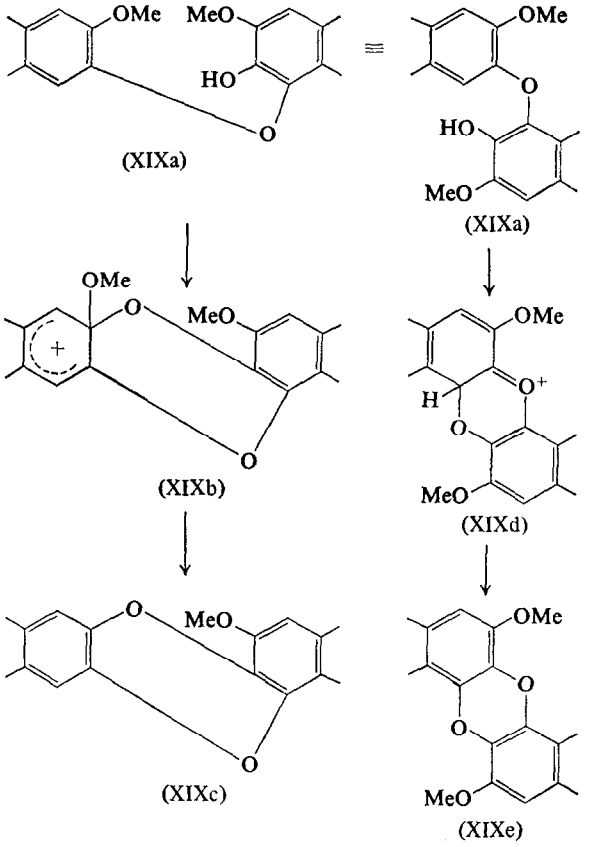


FIG. 18. FORMATION OF THE DIBENZO-*p*-DIOXIN NUCLEUS.

SCHEME I.

and cissampareine, and in the genera *Cocculus* and *Stephania* the co-occurrence of oxycanthines and trilobines, in keeping with the pattern of skeletal changes shown in Chart 2.

It has been shown[184] that (±) coclaurine and (–) *N*-methylcoclaurine are incorporated into epistephanine in *S. japonica*. Successful *in vitro* oxidation of quaternary 1-benzylisoquinolines to bisbenzylisoquinolines has led to the suggestion that these might be the precursors.[185]

Protostephanine (XVII) might arise[14] from phenol coupling of the acyclic precursor (XXII), as shown in Fig. 20. Reduction of the dienone (XXIIIa) to the dienol (XXIIIb)

[183] R. H. F. MANSKE (ed.) and W. R. ASHFORD, in *The Alkaloids* Vol. IV, Academic Press, New York (1954).
[184] D. H. R. BARTON, G. W. KIRBY and A. WIECHERS, *J. Chem. Soc.* (c) (24), 2131 (1966).
[185] B. FRANK and G. BLASCHKE, *Ann.* **668**, 145 (1963).

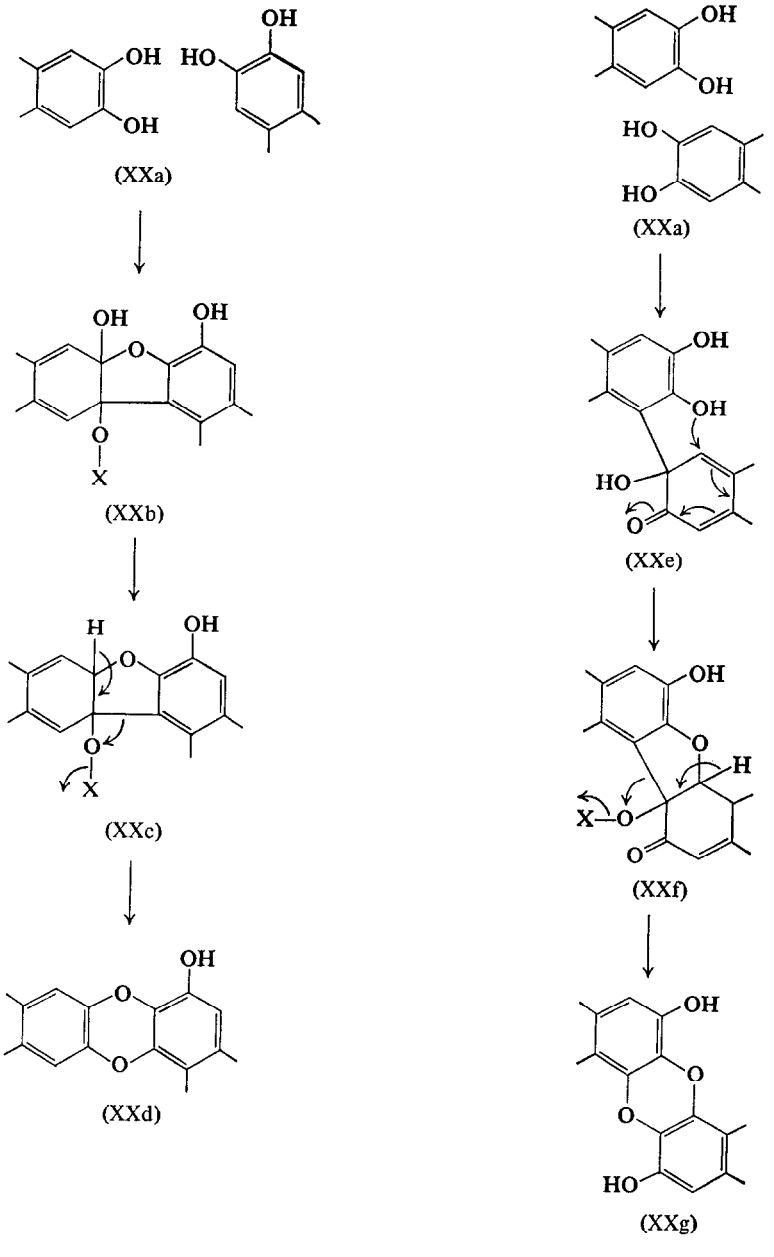


FIG. 19. FORMATION OF THE DIBENZO *p*-DIOXIN NUCLEUS.

SCHEME II.

followed by rearrangement leads to the desired skeleton. An alternative route proposed,[186] illustrated in Fig. 21, starts with the oxidative phenolic coupling of the 1-benzylisoquinoline (XIV) to give the dienone (XVa). Reduction to the dienol (XVb) would allow dienol-benzene

[186] D. H. R. BARTON, *Pure Appl. Chem.* **9**, 35 (1964).

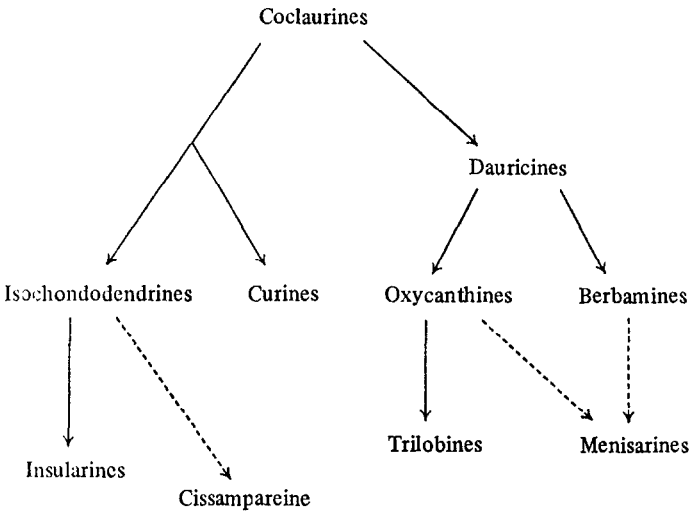


CHART 2.

rearrangement to take place, giving rise, after fragmentation, to the imine (XVII) which is reduced to protostephanine. These transformations have been realized *in vitro*.[29]

Hasubanonine (VIIId) and its relatives might arise[8] by rearrangement of a morphine skeleton, as shown in Fig. 22. Rearrangement of the dienone (XXIX), with assistance from the nitrogen, would give as an intermediate the quaternary compound (XXX), which could be reduced to hasubanonine. The pathway proposed[8] for metaphanine might now be

TABLE 5. DETAILED BREAKDOWN OF BISCOCLAURINE OCCURRENCES

	Type								
	Isochondodendrine	Insularine	Cissampareine	Curine	Dauricine	Oxycanthine	Trilobine	Berbamine	Menisarine
Chondodendron	√			√					
Cissampelos	√	√	√	√					
Cocculus						√	√	√	√
Cyclea	√					√		√	
Epinetrum	√								
Limacia					√	√		√	
Menispermum					√			√	
Pleogyne	√			√					
Pycnarrhena								√	
Stephania	√	√				√	√	√	

slightly modified to include the proposed structure of miersine (XXXI) (see partially charac terized bases *S. japonica*) as in Fig. 23. The compound (XXXI) might be formed by hydroxylation of hasubanonine or one of its precursors.[187] Reduction of the carbonyl group and enol ether hydrolysis leads to (XXXI) which, by elimination of water, could give prometaphanine (VIIIf). Further enol ether hydrolysis would give rise to metaphanine (VIIIg) which readily forms an internal hemi-ketal.

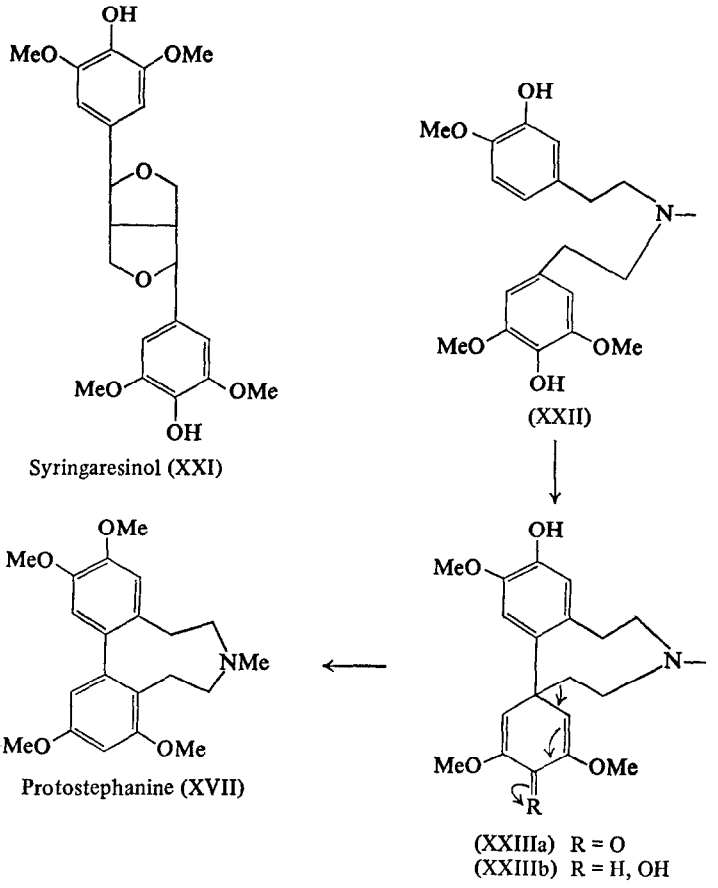


FIG. 20.

It has been suggested[187] that the double dienone (XXXIII) might be formed from the benzylisoquinoline (XXXII) and be a precursor to hasuabanonine, and after extensive rearrangement and degradation to the novel chlorine containing alkaloids acutumidine (VIIIh) and acutumidine (VIIIi). A dienone–phenol rearrangement of the upper ring of dienone (XXXIII), with the alkyl migration indicated "a", could also lead[124] to the intermediate (XXVa) in the proposed scheme for protostephanine, Fig. 21. It might be noted that a similar double dienone (XXXIV) arising from the coupling of a 1-benzylisoquinoline with a trioxygenated benzylbenzene ring (cf. stepharatine, VIIg) could by dienone–phenol

[187] D. H. R. BARTON, A. J. KIRBY and G. W. KIRBY, *J. Chem. Soc.* (c) 929 (1968).

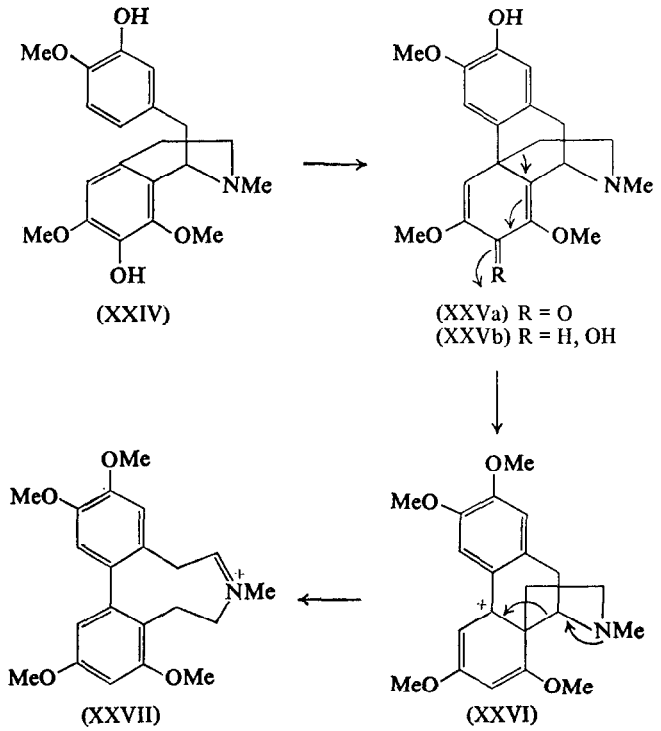

OH
MeO
NMe
MeO
OMe
OH
(XXIV)
OH
MeO
NMe
MeO
OMe
R
(XXVa) R = O
(XXVb) R = H, OH
OMe
MeO
NMe
MeO
OMe
(XXVI)
OMe
MeO
NMe
MeO
OMe
(XXVII)

FIG. 21.

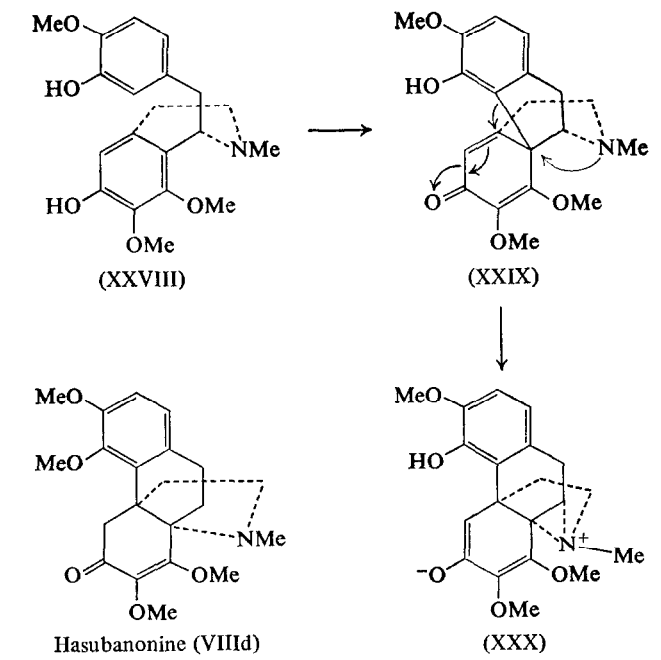
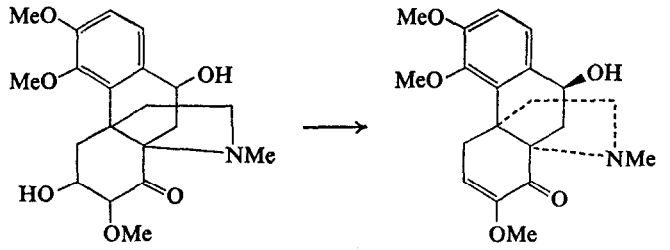
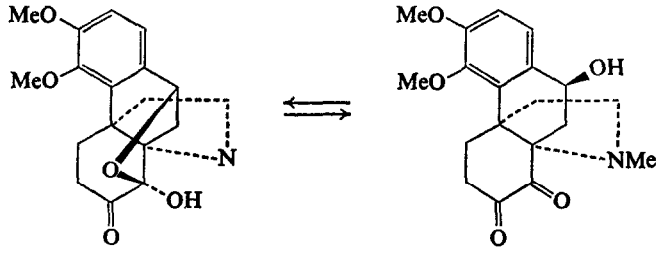

MeO
HO
NMe
HO
OMe
OMe
(XXVIII)
MeO
HO
NMe
O
OMe
OMe
(XXIX)
MeO
MeO
NMe
O
OMe
OMe
Hasubanonine (VIIId)
MeO
HO
N+
Me
-O
OMe
OMe
(XXX)

FIG. 22.

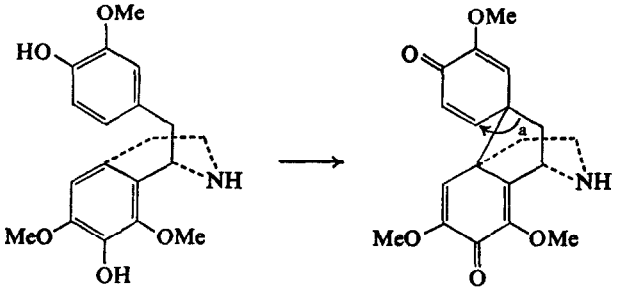


Miersine (XXXI) Prometaphanine (VIIIf)



Metaphanine (VIIIg) Metaphanine (VIIIg)

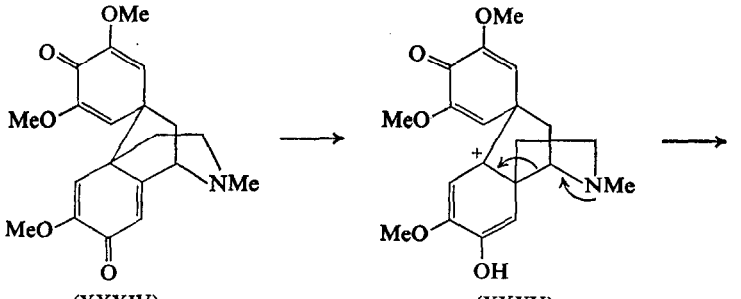
FIG. 23.



(XXXII) (XXXIII)

Acutumine (VIIIh)
Acutumidine (VIIIi)

Hasubanonine (VIIId) (XXVa)



(XXXIV) (XXXV)

FIG. 24.

rearrangement and subsequent fragmentation give rise to intermediate (XXIIIa) proposed in the alternative scheme for protostephanine, Fig. 20.

The biosynthesis of *Erythrina* alkaloids such as dihydroerysodine (XVIII) has been recently discussed[31, 188] and several schemes have been proposed.[2, 3, 189, 190] Experimental

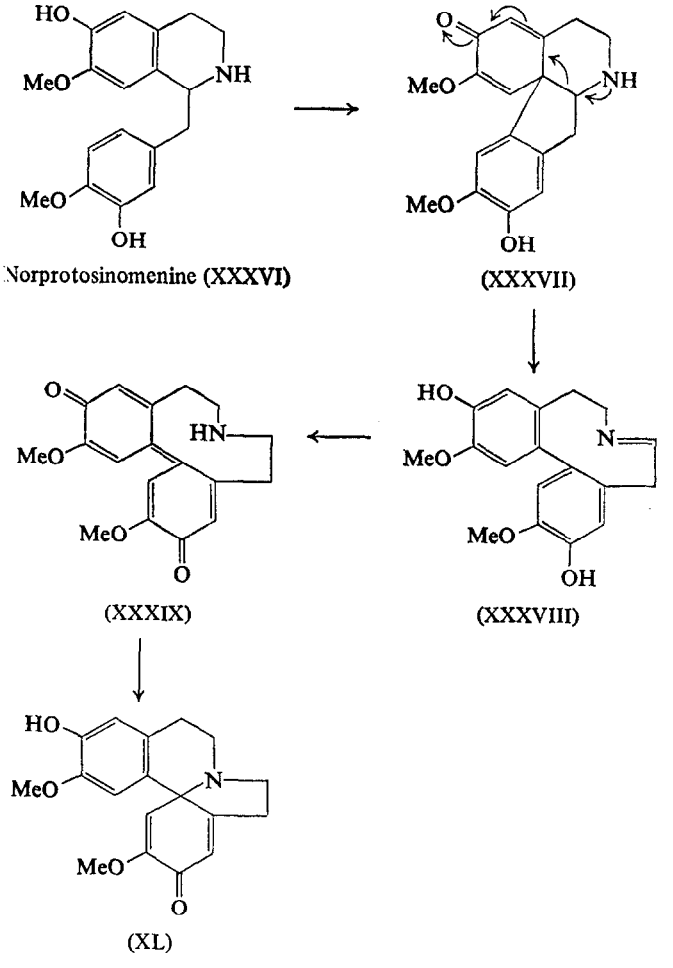


FIG. 25.

evidence has been obtained in support[188] of the scheme shown in Fig. 25. Thus norprotosinomenine (XXXVI) by internal oxidative phenolic coupling gives rise to the dienone (XXXVII) which fragments to the imine (XXXVIII). Michael addition of the nitrogen to the quinone (XXXIX) could then give rise to the erythrinan skeleton. The transformation

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(XXXVII) → (XXXVIII) represents a further way of setting up the protostephanine skeleton (XVII).

It should be noted that in these various biosynthetic proposals the schemes shown are intended to indicate only an overall route whereby the desired molecule could be formed by plausible chemical steps. The intermediates illustrated would not necessarily be involved in the biosynthesis since it is often possible to consider the various transformations in a different sequence. Furthermore, free phenolic positions and secondary amines, which need not be further involved in the reaction scheme, are shown for convenience as being protected by methylation whereas they might be free in the plant or associated with an enzyme surface.

Acknowledgements—The author wishes to thank Professor A. R. Battersby, F.R.S., for his interest and encouragement and Dr. J. S. Staunton and Mr. S. Ruchirawat for helpful and interesting discussions. Grateful acknowledgement is made to the Science Research Council for a maintenance grant.