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PREFACE

This volume of *The Alkaloids: Chemistry and Biology* might be called 'The Brazilian Volume' since each of the three chapters is compiled and written exclusively by Brazilian authors. This is definitely a reflection of the tremendous current Brazilian interest in the investigation and potentiation of their vast array of natural resources, and particularly of alkaloid-bearing plants. In this volume, the recent progress relating to three groups of alkaloids, the protoberberine alkaloids, the *Stemona* alkaloids, and the alkaloids of the plant family Hernandiaceae is reviewed.

The first chapter, by da-Cunha, Fechine, Guedes, Barbosa-Filho, and da Silva is an overview of the protoberberine alkaloids from the aspects of their distribution, very diverse biological activities, and NMR data. This is the first review of this important group of alkaloids in twenty years.

The second chapter is on a group of alkaloids, the *Stemona*, which, considering its overall size, possesses a remarkable number of complex alkaloid skeleta. This area was last reviewed in 1967, and the tremendous changes in this field are presented by Pilli, Rosso, and de Oliveira, from the perspectives of their isolation, structure determination, and biological activity.

Finally, in the third chapter, Conserva, Pereira, and Barbosa-Filho review the numerous alkaloids derived from the plant family Hernandiaceae. Their isolation, structural diversity, and substantial range of biological effects are described and well cataloged.

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—Chapter 1—

PROTOBERBERINE ALKALOIDS

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I. Introduction

The protoberberine alkaloids are comprised of a tetracyclic ring system which is based on the dibenzo[*a,g*]quinolizidine system. These tetracyclic alkaloids are derived from benzylisoquinolines through phenolic oxidation and coupling with the isoquinoline *N*-methyl group, which becomes the ''berberine bridge'' carbon.

Three previous reviews on protoberberine alkaloids were published in this series. The first by R. H. F. Manske and W. R. Ashford in 1954 (*1*), the second in 1967 by P. W. Jeffs (*2*), and the third in 1986 by D. S. Bhakuni and S. Dain (*3*). The progress in the study of protoberberine alkaloids can be observed in Table 1.

This group of alkaloids consists of a series of variations of the main tetracyclic ring system. The most commonly found are: the protoberberines (*sensu strictu*), such as berberine; the tetrahydroprotoberberines, such as tetrahydropalmatine; and 14-oxo derivatives, such as cryptopine. The skeleton types reported in the period covered by this review can be seen in Fig. 1.

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TABLE I.
Progress in the Investigation of Protoberberine Alkaloids.

Data obtained from	Plants studied (families)	Alkaloids described	Number of papers published
Manske's review – 1954	117 (5)	65	254
Jeffs' review – 1967	68 (9)	99	344
Bhakuni's review – 1986	119 (9)	101	378
This work (up to 2001)	310 (13)	138	589

Structure determination in this series, i.e., the correct location of the substituents on the protoberberine ring system, has been a matter of some difficulty. The functional groups (H, OH, OMe, Me, CO, OCH_2O etc.), were located in R_1 to R_{14}.

Plants that contain protoberberine alkaloids are reported to be used as analgesics, antiseptics, sedatives, and stomatics in Chinese folk medicine. In Indian and Islamic folk medicine, such plants are used for bleeding disorders and eye diseases, and as antiseptics, sedatives, stomatics, and uterine muscle depressants. Both quaternary alkaloids and their tetrahydro derivatives possess many substantiated biological and therapeutic effects, e.g., palmatine, jatrorrhizine, and tetrahydropalmatine have been reported to show *in vitro* antimalarial activity. In China, tetrahydropalmatine is used as an analgesic, and has been reported to exhibit bradycardial, hypotensive, and sedative activities (*4*).

II. The Organization of the Data

The data are organized in alphabetical order of alkaloid names, with a list of botanical species and families from which they were isolated. The alkaloids are classified by skeleton type and the substituent groups present. These data are shown in Table II. The biological activities reported for this type of alkaloid are shown in Table III, organized by the alkaloid name, followed by the type of activity reported. The present compilation includes data from most of the papers published between 1986 and 2001. The ^{13}C NMR data are presented in Table IV. Among the 138 alkaloids described in the literature in the period, only 85 have their ^{13}C NMR data reported.

III. Chemotaxonomic Compilation of Protoberberine Alkaloids

Table II shows the distribution of all of the protoberberine alkaloids described in the period. A few interesting observations can be made regarding the analysis of the data presented in Table II.

A. DISTRIBUTION OF PROTOBERBERINE ALKALOIDS AMONG THE FAMILIES AND GENERA WHERE THEY WERE FOUND

It is quite impressive that the vast majority of plant species cited from the family Papaveraceae produce this type of alkaloid. Among the 310 plants studied in the period, 123 belong to this family, from 18 of its genera. In second place appears the

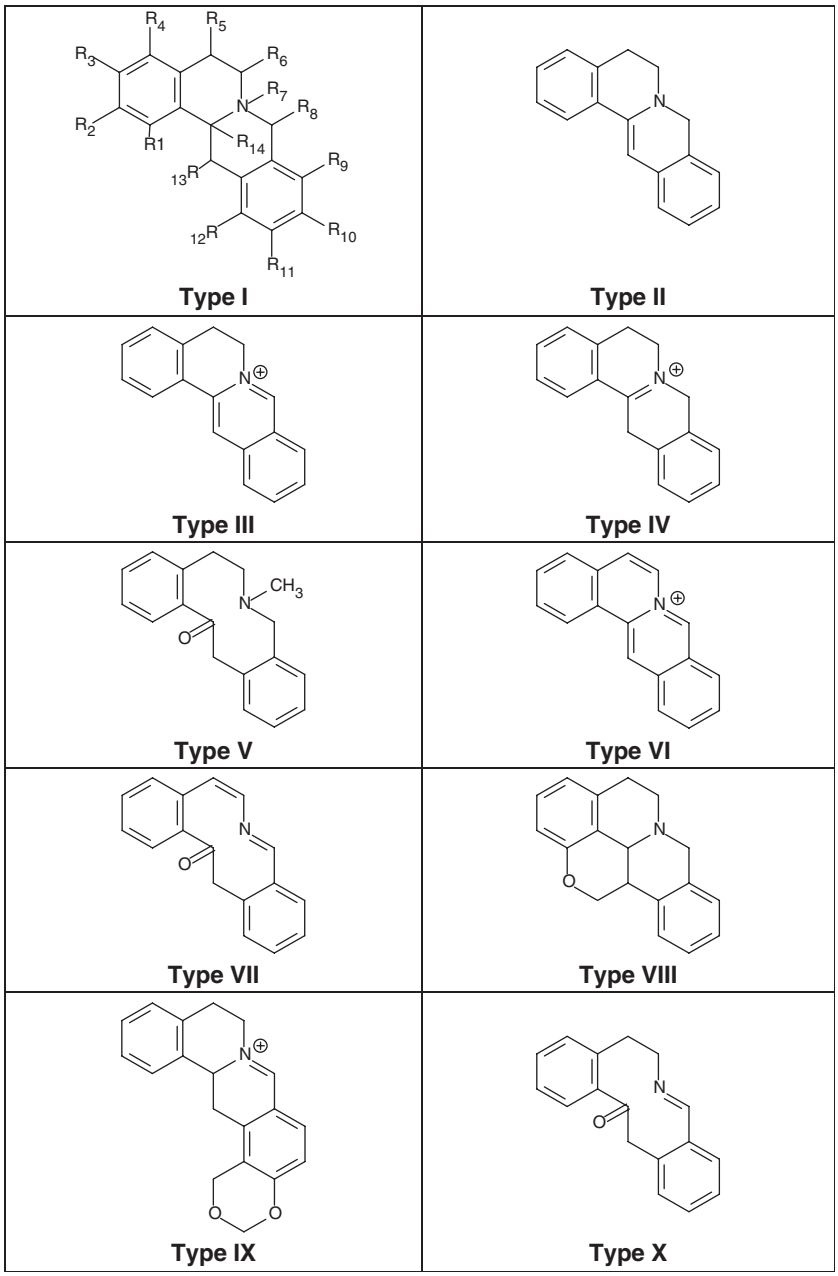


Figure 1. A summary of the skeletons of the protoberberine alkaloids described in this chapter.

TABLE II.

Protoberberine Alkaloids Reported in the Literature between 1986 and 2001.

Alkaloid	Skeleton type	Substance	Substituents	Plant (Family)	References
Alborine	III	1	R_2R_3═OCH_2O, $R_{10}R_{11}$═OMe, $R_{12}CH_2OH$	*Meconopsis punicea* (Papaveraceae)	*4*
Anibacanine	I	2	R_2═OH, R_3═OMe, R_9═OH	*Aniba canelilla* (Lauraceae)	*5*
Anibacanine, α-8-Methyl	I	3	R_2═OH, R_3═OMe, R_8═Me, R_9═OH	*Aniba canelilla* (Lauraceae)	*5*
Anibacanine, pseudo	I	4	R_2═OH, R_3═OMe, R_{11}═OH	*Aniba canelilla* (Lauraceae)	*5*
Anibacanine, pseudo α-8-Methyl	I	5	R_2═OH, R_3═OMe, R_8═Me, R_{11}═OH	*Aniba canelilla* (Lauraceae)	*5*
Anibacanine, pseudo β-8-Methyl	I	6	R_2═OH, R_3═OMe, R_8═Me, R_{11}═OH	*Aniba canelilla* (Lauraceae)	*5*
Anisocycline	III	7	$R_2R_3R_4R_9R_{10}$═OMe	*Anisocycla cymosa* (Menispermaceae)	*6*
Artavenustine	I	8	R_2═OMe, $R_3R_{10}R_{11}$═OH	*Artabotrys venustus* (Annonaceae)	*7*
Berberastine	III	9	R_2R_3═OCH_2O, R_5═OH, R_9R_{10}═OMe	*Coptis chinensis* (Ranunculaceae)	*8*
				Coptis japonica	*9*
				Coptis quinquefolia	*10*
				Coptis sp.	*11*
Berberine	III	10	R_2R_3═OCH_2O, R_9R_{10}═OMe	*Alstonia macrophylla* (Apocynaceae)	*12*
				Andira inermis (Fabaceae)	*13*
				Aquilegia sp. (Ranunculaceae)	*14*
				Aquilegia vulgaris	*15*
				Arcangelisia flava (Menispermaceae)	*16*
				Argemone hybrida (Papaveraceae)	*17*
				Argemone ochroleuca	*18*
				Berberis aemulans (Berberidaceae)	*19*
				Berberis aggregata	*20*
				Berberis arrido-callida	*21*
				Berberis berbeyana	*22*
				Berberis boliviana	*23*

(*continued*)

TABLE II.
Continued.

Alkaloid	Skeleton type	Substance	Substituents	Plant (Family)	References
Berberine *continued*	III	10	R_2R_3═OCH_2O, R_9R_{10}═OMe	*Coptis lutescens*	38
				Coptis omeiensis	37
				Coptis quinquefolia	39
				Coptis ramosa	38
				Coptis sp.	31
				Coptis teetoides	40
				Coptis trifolia	38
				Corydalis caucasica (Papaveraceae)	41
				Corydalis chaerophylla	41
				Corydalis intermedia	42
				Corydalis pallida	43
				Corydalis solida	44
				Corydalis ternata	45
				Corydalis turtschaninovii	46
				Fibraurea chloroleuca (Menispermaceae)	47
				Glaucium arabicum (Papaveraceae)	48
				Mahonia fargesii (Berberidaceae)	49
				Mahonia gracilipes	50
				Meconopsis cambrica (Papaveraceae)	51
				Papaver confine (Papaveraceae)	52
				Papaver dahlianum	53
				Papaver laestadianum	53
				Papaver lapponicum	53
				Papaver pinnatifidum	54
				Papaver radicatum	53
				Papaver rhoeas	52

				Papaver rhopalothece	55
				Papaver stevenianum	56
				Penianthus zenkeri (Menispermaceae)	57
				Phellodendron chinense (Rutaceae)	58
				Phellodendron lavallei	59
				Ranunculus serbicus (Ranunculaceae)	60
				Rollinia mucosa (Annonaceae)	61
				Thalictrum atriplex (Ranunculaceae)	62
				Thalictrum collinum	63
				Thalictrum delavayi	64
				Thalictrum flavum	65
				Thalictrum glandulosissimum	66
				Thalictrum honanense	67
				Thalictrum lankesteri	68
				Thalictrum minus	69
				Thalictrum orientale	70
				Thalictrum petaloideum	71
				Thalictrum przewalskii	72
				Thalictrum rugosum	73
				Thalictrum sessile	74
				Thalictrum smithii	75
				Xanthorhiza simplicissima (Ranunculaceae)	38
				Zanthoxylum monophyllum (Rutaceae)	76
Berberine oxo	II	11	R_2R_3═OCH_2O, R_8═O, R_9R_{10}═OMe	*Arcangelisia gusanlung* (Menispermaceae)	77
				Chelidonium majus (Papaveraceae)	78
				Coptis japonica (Ranunculaceae)	79
Berberine, dihydro *N*-methyl	II	12	R_2R_3═OCH_2O, R_7═CH_3, R_9R_{10}═OMe	*Berberis heteropoda* (Berberidaceae)	80
Berberine, epi	III	13	R_2R_3═OMe, R_9R_{10}═OCH_2O	*Berberis turcomanica* (Berberidaceae)	81
				Coptis chinensis (Ranunculaceae)	82
				Coptis deltoidea	37
				Coptis japonica	37

(*continued*)

TABLE II.
Continued.

Alkaloid	Skeleton type	Substance	Substituents	Plant (Family)	References
Berberine, epi *continued*	III	13	R_2R_3═OMe, R_9R_{10}═OCH_2O	*Coptis omeiensis*	37
				Coptis sp.	11
				Coptis teeta	37
				Coptis trifolia	38
				Nandina domestica (Berberidaceae)	83
				Sinomenium acutum (Menispermaceae)	84
Berberine, proto 1-8-dihydroxy-2-3-9-10-dimethylenedioxy	II	14	R_1R_8═OH, $R_2R_3R_9R_{10}$═OCH_2O	*Thalictrum delavayi* (Ranunculaceae)	64
Berberine, proto-2-3-9-10-imethylenedioxy-8-oxo	II	15	$R_2R_3R_9R_{10}$═OCH_2O, R_8═O	*Thalictrum delavayi* (Ranunculaceae)	64
Berberine, tetrahydro	I	16	R_2R_3═OCH_2O, R_9R_{10}═OMe	*Berberis heteropoda* (Berberidaceae)	85
				Corydalis bulbosa (Papaveraceae)	86
				Rollinia mucosa (Annonaceae)	61
				Sanguinaria canadensis (Papaveraceae)	87
				Zanthoxylum integrifoliolum (Rutaceae)	88
Berberine, tetrahydro *N*-methyl	I	17	R_2R_3═OCH_2O, R_7═Me, R_9R_{10}═OMe	*Sanguinaria canadensis* (Papaveraceae)	87
Berberubine	II	18	R_2R_3═OMe, R_9R_{10}═OCH_2O	*Berberis amurensis* (Berberidaceae)	89
				Berberis cretica	90
				Berberis sibirica	33
				Berberis valdiviana	91
				Fibraurea ochloroleuca (Menispermaceae)	47
				Phellodendron amurense (Rutaceae)	92
				Thalictrum glandulosissimum (Ranunculaceae)	93
Berberubine-8-oxo	II	19	R_2R_3═OCH_2O, R_8═O, R_9═OH, R_{10}═OMe	*Berberis heteropoda* (Berberidaceae)	80

				Berberis sibirica	*33*
				Arcangelisia gusanlung (Menispermaceae)	*94*
Berlambine	II	20	R_2R_3═OCH_2O, R_8═O, R_9R_{10}═OMe	*Berberis empetrifolia* (Berberidaceae)	*29*
				Berberis vulgaris	*95*
				Coscinium fenestratum (Menispermaceae)	*96*
Canadine	I	21	R_2R_3═OCH_2O, R_9R_{10}═OMe	*Berberis cretica* (Berberidaceae)	*90*
				Corydalis ambigua (Papaveraceae)	*97*
				Corydalis intermedia	*42*
				Chelidonium majus (Papaveraceae)	*78*
				Glaucium arabicum (Papaveraceae)	*98*
				Hydrastis canadensis (Ranunculaceae)	*99*
Canadine, oxo	I	22	R_2R_3═OCH_2O, R_8═O, R_9R_{10}═OMe	*Coscinium fenestratum* (Menispermaceae)	*100*
Canadine, *N*-methyl	I	23	R_2R_3═OCH_2O, R_7═Me, R_9R_{10}═OMe	*Glaucium grandiflorum* (Papaveraceae)	*101*
				Hydrastis canadensis (Ranunculaceae)	*102*
Capaurimine	I	24	R_1R_{10}═OH, $R_2R_3R_9$═OMe	*Anomianthus dulcis* (Annonaceae)	*103*
Capaurine	I	25	R_1═OH, $R_2R_3R_9R_{10}$═OMe	*Corydalis incisa* (Papaveraceae)	*97*
				Stephania lincangensis (Menispermaceae)	*104*
Caseadine	I	26	R_1═OH, $R_2R_{10}R_{11}$═OMe	*Ceratocapnos heterocarpa* (Papaveraceae)	*105*
				Dasymaschalon sootepense (Annonaceae)	*106*
Caseadine-*N*-oxide	I	27	R_1═OH, $R_2R_{10}R_{11}$═OMe, R_7═O^-	*Ceratocapnos heterocarpa* (Papaveraceae)	*107*
Caseamine	I	28	R_1R_{11}═OH, R_2R_{10}═OMe	*Anomianthus dulcis* (Annonaceae)	*103*
				Ceratocapnos heterocarpa (Papaveraceae)	*105*
Caseamine-*N*-oxide	I	29	R_1═OH, R_2R_{10}═OMe, R_7═O^-	*Ceratocapnos heterocarpa* (Papaveraceae)	*107*
Cavidine	I	30	R_2R_3═OMe, R_9R_{10}═OCH_2O, R_{13}═Me	*Corydalis ambigua* (Papaveraceae)	*108*
				Corydalis remota	*109*
Cavidine, dehydro	III	31	R_2R_3═OMe, R_9R_{10}═OCH_2O, R_{13}═Me	*Corydalis caucasica* (Papaveraceae)	*41*

(*continued*)

TABLE II.
Continued.

Alkaloid	Skeleton type	Substance	Substituents	Plant (Family)	References
Cavidine, iso apo	I	32	R_2═OMe, R_3═OH, R_9R_{10}═OCH_2O, R_{13}═Me	*Dactylocapnos torulosa* (Papaveraceae)	110
Cerasodine	II	33	R_2R_{10}═OH, R_3R_{11}═OMe, R_8═O	*Polyalthia cerasoides* (Annonaceae)	111
Cerasonine	I	34	R_2═OH, $R_3R_{10}R_{11}$═OMe, R_8═O	*Polialthia cerasoides* (Annonaceae)	111
Cheilanthifoline	I	35	R_2═OH, R_3═OMe, R_9R_{10}═OCH_2O	*Argemone hybrida* (Papaveraceae)	17
				Argemone mexicana	17
				Argemone ochroleuca	112
				Corydalis bungeana (Papaveraceae)	113
				Corydalis caucasica	114
				Corydalis hendersonii	115
				Corydalis hsuchowensis	116
				Corydalis marschalliana	117
				Fumaria densiflora (Papaveraceae)	118
				Papaver fugax (Papaveraceae)	119
Cheilanthifoline, dehydro	III	36	R_2═OH, R_3═OMe, R_9R_{10}═OCH_2O	*Corydalis humosa* (Papaveraceae)	120
Clarkeanidine	I	37	R_1R_9═OH, R_2R_{10}═OMe	*Corydalis clarkei* (Papaveraceae)	121
Columbamine	III	38	R_2═OH, $R_3R_9R_{10}$═OMe	*Berberis aemulans* (Berberidaceae)	19
				Berberis crataegina	26
				Berberis cretica	90
				Berberis dasystachya	19
				Berberis heteropoda	80
				Berberis koreana	122
				Berberis nummularia	123
				Berberis parviflora	124
				Berberis poiretii	19

				Berberis polymorpha	125
				Berberis pruinosa	19
				Berberis sibirica	33
				Berberis turcomanica	126
				Burasaia australis (Menispermaceae)	127
				Burasaia congesta	127
				Coptis quinquefolia (Ranunculaceae)	10
				Coptis sp.	11
				Dioscoreophyllum volkensii (Menispermaceae)	128
				Fissistigma balansae (Annonaceae)	129
				Isopyrum thalictroides (Ranunculaceae)	130
				Mahonia gracilipes (Berberidaceae)	50
				Nandina domestica (Berberidaceae)	83
				Ranunculus serbicus (Ranunculaceae)	131
				Thalictrum glandulosissimum (Ranunculaceae)	66
				Tinospora hainanensis (Menispermaceae)	132
Columbamine, 13-methyl	III	39	R_2═OH, $R_3R_9R_{10}$═OMe, R_{13}═Me	*Corydalis solida* (Papaveraceae)	133
Columbamine, *N*-methyl-tetrahydro	I	40	R_2═OH, $R_3R_9R_{10}$═OMe, R_7═Me	*Tinospora hainanensis* (Menispermaceae)	134
Columbamine, pseudo	III	41	$R_3R_{10}R_{11}$═OMe	*Fibraurea chloroleuca* (Menispermaceae)	101
				Nandina domestica (Berberidaceae)	135
Columbamine, tetrahydro	I	42	R_2═OH, $R_3R_9R_{10}$═OMe	*Corydalis lutea* (Papaveraceae)	136
				Corydalis omeiensis	137
				Liriodendron tulipifera (Magnoliaceae)	138
				Pachypodanthium staudtii (Annonaceae)	139
				Polygala tenuifolia (Polygalaceae)	140
Constrictosine	VII	43	R_3R_{10}═OH, R_{14}═O	*Aristolochia constricta* (Aristolochiaceae)	141
Constrictosine, 3-*O*-methyl	VII	44	R_3═OMe, R_{10}═OH, R_{14}═O	*Aristolochia constricta* (Aristolochiaceae)	141
Constrictosine, 3,5-di-*O*-methyl	VII	45	R_3R_{10}═OMe	*Aristolochia constricta* (Aristolochiaceae)	141
Constrictosine, 5,6-dihydro 3,5-di-*O*-methyl	X	46	R_3R_{10}═OMe, R_{14}═O	*Aristolochia constricta* (Aristolochiaceae)	141

(*continued*)

TABLE II.
Continued.

Alkaloid	Skeleton type	Substance	Substituents	Plant (Family)	References
Constrictosine, 5,6-dihydro	X	47	R_3R_{10}═OH, R_{14}═O	*Aristolochia constricta* (Aristolochiaceae)	*141*
Coptisine	III	48	$R_2R_3R_9R_{10}$═OCH_2O	*Aquilegia* sp. (Ranunculaceae)	*14*
				Berberis amurensis (Berberidaceae)	*142*
				Coptis omeiensis (Ranunculaceae)	*143*
				Coptis ramosa	*38*
				Coptis teeta	*143*
				Coptis trifolia	*38*
				Corydalis ambigua (Papaveraceae)	*144*
				Corydalis caucasica	*41*
				Corydalis dasyptera	*145*
				Corydalis humosa	*144*
				Corydalis intermedia	*42*
				Corydalis nobilis	*42*
				Corydalis omeiensis	*146*
				Corydalis rutifolia	*147*
				Corydalis ternata	*148*
				Corydalis turtschaninovii	*144*
				Corydalis yanhusuo	*144*
				Eschscholzia caespitosa (Papaveraceae)	*42*
				Eschscholzia californica	*42*
				Fumaria muralis (Papaveraceae)	*149*
				Fumaria parviflora	*150*
				Fumaria petteri	*151*
				Fumaria spicata	*149*
				Glaucium arabicum (Papaveraceae)	*48*
				Meconopsis cambrica (Papaveraceae)	*51*

				Papaver albiflorum (Papaveraceae)	*56*
				Papaver argemone	*152*
				Papaver atlanticum	*153*
				Papaver confine	*52*
				Papaver glaucum	*153*
				Papaver nudicaule	*154*
				Papaver orientale	*155*
				Papaver pavonium	*156*
				Papaver pseudo-orientale	*157*
				Papaver rhopalothece	*55*
				Papaver stevenianum	*56*
				Phellodendron amurense (Rutaceae)	*158*
				Phellodendron chinense	*143*
				Thalictrum glandulosissimum (Ranunculaceae)	*66*
				Thalictrum minus	*159*
Coptisine, oxo	II	49	$R_2R_3R_9R_{10}$═OCH_2O, R_8═O	*Chelidonium majus* (Papaveraceae)	*160*
				Coptis japonica (Ranunculaceae)	*161*
				Fumaria vaillantii (Papaveraceae)	*162*
				Thalictrum galndulosissimum (Ranunculaceae)	*93*
Coptisine, dehydro	II	50	$R_2R_3R_9R_{10}$═OCH_2O	*Fumaria indica* (Papaveraceae)	*163*
Coptisine, tetrahydro	I	51	$R_2R_3R_9R_{10}$═OCH_2O	*Chelidonium majus* (Papaveraceae)	*164*
				Corydalis bungeana (Papaveraceae)	*165*
				Corydalis dasyptera	*145*
				Corydalis humosa	*166*
				Corydalis remota	*109*
				Corydalis turtschaninovii	*167*
				Corydalis yanhusuo	*168*
Coreximine	I	52	R_2R_{11}═OH, R_3R_{10}═OMe	*Annona paludosa* (Annonaceae)	*169*
				Cananga odorata (Annonaceae)	*170*
				Corydalis pseudoadunca (Papavearaceae)	*171*
Coreximine, iso	I	53	R_2R_{10}═OMe, R_3R_{11}═OH	*Toddalia asiática* (Rutaceae)	*172*

(*continued*)

TABLE II.
Continued.

Alkaloid	Skeleton type	Substance	Substituents	Plant (Family)	References
Corybulbine	I	54	$R_2R_9R_{10}R_{13}$═OMe, R_3═OH	*Corydalis ambigua* (Papaveraceae)	*108*
				Corydalis remota	*109*
Corycavamine	I	55	R_2R_3═OCH_2O, R_7R_9═Me, R_{14}═O	*Corydalis bulleyana* (Papaveraceae)	*173*
Corycavine	I	56	$R_2R_3R_9R_{10}$═OCH_2O, R_7═Me, R_{13}═Me, R_{14}═OH	*Corydalis bungeana* (Papaveraceae)	*113*
				Corydalis remota	*109*
Corydalidzine	I	57	R_2R_9═OMe, R_3R_{10}═OH, R_{13}═Me	*Corydalis caucasica* (Papaveraceae)	*41*
Corydalmine	I	58	$R_2R_3R_9$═OMe, R_{10}═OH	*Stephania micrantha* (Menispermaceae)	*174*
Corydalmine, dehydro	II	59	$R_2R_3R_9$═OMe, R_{10}═OH	*Annona glabra* (Annonaceae)	*175*
				Stephania succifera (Menispermaceae)	*176*
				Stephania yunnanensis	*177*
Corymotine	I	60	$R_2R_3R_9R_{10}$═OMe, R_{13}═$(Me)_2$	*Corydalis remota* (Papaveraceae)	*109*
Corynoxidine	I	61	$R_2R_3R_9R_{10}$═OMe, R_7═O^-	*Stephania glabra* (Menispermaceae)	*104*
Corypalmine	I	62	$R_2R_9R_{10}$═OMe, R_3═OH	*Corydalis lutea* (Papaveraceae)	*136*
				Glaucium grandiflorum (Papaveraceae)	*178*
Corypalmine, iso	I	63	R_2═OH, $R_3R_9R_{10}$═OMe	*Corydalis marschalliana* (Papaveraceae)	*117*
Corypalmine, iso 8-oxo	I	64	R_2═OH, $R_3R_9R_{10}$═OMe, R_8═O	*Coscinium fenestratum* (Menispermaceae)	*100*
Corypalmine, *trans*-iso *N*-oxide	I	65	R_2═OH, $R_3R_9R_{10}$═OMe, R_7═O^-	*Corydalis tashiroi* (Papaveraceae)	*179*
Corysamine	III	66	$R_2R_3R_9R_{10}$═OCH_2O	*Papaver syriacum* (Papaveraceae)	*180*
Corysamine, tetrahydro	I	67	$R_2R_3R_9R_{10}$═OCH_2O	*Corydalis dasyptera* (Papaveraceae)	*145*
Corytenchine, dehydro	III	68	$R_2R_3R_{10}$═OMe, R_{11}═OH	*Xylopia vieillardii* (Annonaceae)	*181*
Coulteropine	V	69	$R_2R_3R_9R_{10}$═OCH_2O, R_7═Me, R_{14}═O	*Papaver rhoeas* (Papaveraceae)	*182*
Cryptopine	V	70	$R_2R_3R_9R_{10}$═OCH_2O, R_7═Me, R_{14}═O	*Corydalis esquirolii* (Papaveraceae)	*183*
				Corydalis humosa	*120*
				Corydalis nobilis	*42*

				Corydalis omeiensis	*146*
				Corydalis rutifolia	*184*
				Corydalis stewartii	*185*
				Fumaria densiflora (Papaveraceae)	*149*
				Fumaria agraria	*149*
				Fumaria asepala	*186*
				Fumaria muralis	*149*
				Fumaria vaillantii	*162*
				Hypecoum chinense (Papaveraceae)	*187*
				Hypecoum leptocarpum	*188*
				Hypecoum procumbens	*189*
				Papaver argemone (Papaveraceae)	*156*
				Papaver atlanticum	*153*
				Papaver californicum	*152*
				Papaver confine	*52*
				Papaver glaucum	*153*
				Papaver lateritium	*190*
				Papaver nudicaule	*154*
				Papaver rhoeas	*52*
				Papaver rhopalothece	*191*
				Papaver setigerum	*192*
				Thalictrum delavayi (Ranunculaceae)	*193*
				Thalictrum glandulosissima	*93*
Cryptopine, allo	V	71	R_2R_3═OCH_2O, R_7═Me, R_9R_{10}═OMe, R_{14}═O	*Arctomecon californica* (Papaveraceae)	*194*
				Arctomecon humile	*194*
				Arctomecon merriami	*194*
				Caltha palustris (Ranunculaceae)	*14*
				Corydalis bulleyana (Papaveraceae)	*173*
				Corydalis decumbens	*195*
				Corydalis intermedia	*42*
				Corydalis nobilis	*42*

(*continued*)

TABLE II.
Continued.

Alkaloid	Skeleton type	Substance	Substituents	Plant (Family)	References
Cryptopine, allo *continued*	V	71	R_2R_3═OCH_2O, R_7═Me, R_9R_{10}═OMe, R_{14}═O	*Corydalis remota*	196
				Eschscholzia californica (Papaveraceae)	197
				Eschscholzia glauca	198
				Glaucium aleppicum (Papaveraceae)	199
				Glaucium arabicum	48
				Hypecoum leptocarpum (Papaveraceae)	200
				Hypecoum procumbens	188
				Macleaya cordata (Papaveraceae)	201
				Meconopsis robusta (Papaveraceae)	51
				Papaver albiflorum (Papaveraceae)	56
				Papaver argemone	156
				Papaver atlanticum	153
				Papaver confine	52
				Papaver curviscapum	202
				Papaver dahlianum	53
				Papaver glaucum	153
				Papaver laestadianum	53
				Papaver lapponicum	53
				Papaver lecoquii	53
				Papaver nudicaule	154
				Papaver pavonium	203
				Papaver pinnatifidum	54
				Papaver pseudo-orientale	157
				Papaver rhoeas	182
				Papaver stevenianum	56
				Sanguinaria canadensis (Papaveraceae)	201
				Thalictrum minus (Ranunculaceae)	204

Cyclanoline	I	72	R_2R_9═OH, R_3R_{10}═OMe, R_7═Me	*Berberis horrida* (Berberidaceae)	*25*
				Stephania cepharantha (Menispermaceae)	*205*
Dauricoside	I	73	R_2═OMe, R_3R_{10}═OH, R_{11}═OβD-Glu.	*Menispermum dauricum* (Menispermaceae)	*206*
Discretamine	I	74	R_2R_9═OMe, R_2R_{10}═OH	*Anomianthus dulcis* (Annonaceae)	*103*
Discretamine	I	74	R_2R_9═OMe, R_2R_{10}═OH	*Artabotrys maingayi* (Annonaceae)	*207*
				Cyathostemma argentium (Annonaceae)	*208*
				Desmos longiflorus (Annonaceae)	*209*
				Nandina domestica (Berberidaceae)	*83*
				Rollinia leptopetala (Annonaceae)	*210*
Discretamine, dehydro	III	75	R_2R_9═OMe, R_2R_{10}═OH	*Fissistigma balansae* (Annonaceae)	*129*
				Nandina domestica (Berberidaceae)	*83*
				Sinomenium acutum (Menispermaceae)	*84*
				Xylopia vieillardii (Annonaceae)	*181*
Fississaine	III	76	$R_2R_3R_9$═OMe, R_{10}═OH	*Fissistigma balansae* (Annonaceae)	*129*
Govanine	I	77	R_2═OH, $R_3R_{10}R_{11}$═OMe	*Oxymitra velutina* (Annonaceae)	*211*
Groenlandicine	III	78	R_2═OMe, R_3═OH, R_9R_{10}═OCH_2O	*Nandina domestica* (Berberidaceae)	*212*
Gusanlung-A	I	79	R_2R_3═OCH_2O, R_8═O, R_9═OH, R_{11}═OMe	*Arcangelisia gusanlung* (Menispermaceae)	*213*
Gusanlung-B	I	80	R_2R_3═OCH_2O, R_8═O, R_9R_{10}═OMe	*Arcangelisia gusanlung* (Menispermaceae)	*213*
Gusanlung-D	I	81	R_2R_3═OCH_2O, R_8═O	*Arcangelisia gusanlung* (Menispermaceae)	*77*
Hunnemanine	V	82	R_2R_3═OCH_2O, R_7═Me, R_9═OH, R_{10}═OMe, R_{14}═O	*Dactylocapnos torulosa* (Papaveraceae)	*110*
				Eschscholzia californica (Papaveraceae)	*214*
				Hypecoum procumbens (Papaveraceae)	*215*
Jatrorrhizine	III	83	$R_2R_9R_{10}$═OMe, R_3═OH	*Berberis aemulans* (Berberidaceae)	*19*
				Berberis amurensis	*89*
				Berberis angulosa	*21*
				Berberis arrido-callida	*21*
				Berberis candidula	*21*
				Berberis cerasina	*21*
				Berberis dasystachya	*19*
				Berberis dictyophylla	*21*

(*continued*)

TABLE II.
Continued.

Alkaloid	Skeleton type	Substance	Substituents	Plant (Family)	References
Jatrorrhizine *continued*	III	83	$R_2R_9R_{10}$═OMe, R_3═OH	*Berberis francisci-ferdinandii*	*20*
				Berberis gagnepainii	*21*
				Berberis giraldii	*21*
				Berberis ilicifolia	*28*
				Berberis iliensis	*21*
				Berberis koetineana	*21*
				Berberis koreana	*122*
				Berberis laxiflora	*21*
				Berberis mucrifolia	*21*
				Berberis mutabilis	*21*
				Berberis nummularia	*21*
				Berberis oblonga	*216*
				Berberis papillifera	*21*
				Berberis paravirescens	*21*
				Berberis parvifolia	*124*
				Berberis poiretii	*19*
				Berberis polymorpha	*125*
				Berberis pruinosa	*19*
				Berberis pseudothunbergii	*20*
				Berberis serrata	*21*
				Berberis stenophylla	*21*
				Berberis taliensis	*21*
				Berberis turcomanica	*81*
				Berberis valdiviana	*217*
				Berberis vernae	*21*
				Berberis virgetorum	*35*
				Burasaia gracilis (Menispermaceae)	*127*
				Coptis deltoidea (Ranunculaceae)	*143*

				Coptis japonica	*218*
				Coptis lutescens	*38*
				Coptis omeiensis	*37*
				Coptis quinquefolia	*10*
				Coptis ramosa	*38*
				Coptis sp.	*31*
				Coptis teetoides	*40*
				Coptis trifolia	*219*
				Corydalis decumbens (Papaveraceae)	*220*
				Corydalis nobilis	*42*
				Dioscoreophyllum volkensii (Menispermaceae)	*128*
				Fagara chalybea (Rutaceae)	*221*
				Glaucium arabicum (Papaveraceae)	*48*
				Hydrastis canadensis (Ranunculaceae)	*38*
				Mahonia bealei (Berberidaceae)	*222*
				Mahonia gracilipes	*50*
				Penianthus zenkeri (Menispermaceae)	*57*
				Sphenocentrum jollyanum (Menispermaceae)	*223*
				Stephania miyiensis (Menispermaceae)	*224*
				Stephania venosa	*225*
				Thalictrum cultratum (Ranunculaceae)	*226*
				Tinospora cordifolia (Menispermaceae)	*227*
				Zanthoxylum chalybeum (Rutaceae)	*228*
Jatrorrhizine, tetrahydro	I	84	$R_2R_9R_{10}$═OMe, R_3═OH	*Rollinia leptopetala* (Annonaceae)	*210*
Kikemanine	I	85	$R_2R_3R_9$═OMe, R_{10}═OH	*Fissistigma balansae* (Annonaceae)	*129*
				Guatteria schomburgkiana (Annonaceae)	*229*
Lambertine	IV	86	R_2R_3═OCH_2O, R_9R_{10}═OMe	*Berberis vulgaris* Berberidaceae)	*95*
Lienkonine	I	87	$R_2R_3R_{10}$═OMe, R_8═Me, R_9═OH	*Corydalis ochotensis* (Fumariaceae)	*230*
Malacitanine	I	88	R_1═OH, $R_2R_{10}R_{11}$═OMe, R_f═CH_2OH	*Ceratocapnos heterocarpa* (Papaveraceae)	*231*
Manibacanine	I	89	R_2R_3═OMe, R_9═OH	*Aniba canelilla* (Lauraceae)	*5*
Manibacanine, pseudo	I	90	R_2R_3═OMe, R_{11}═OH	*Aniba canelilla* (Lauraceae)	*5*

(*continued*)

TABLE II.
Continued.

Alkaloid	Skeleton type	Substance	Substituents	Plant (Family)	References
Mecambridine	I	91	$R_1R_{10}R_{11}$═OMe, R_2R_3═OCH_2O, R_{12}═CH_2OH	*Meconopsis punicea* (Papaveraceae)	232
				Papaver oreophilum (Papaveraceae)	233
				Papaver pseudo-orientale	157
Muramine	V	92	$R_2R_3R_9R_{10}$═OMe, R_7═Me, R_{14}═O	*Argemone mexicana* (Papaveraceae)	234
				Corydalis decumbens (Papaveraceae)	195
				Corydalis esquirolii	183
				Corydalis omeiensis	137
				Glaucium vitellinium (Papaveraceae)	146
				Papaver californicum (Papaveraceae)	152
				Papaver nudicaule	154
				Papaver radicatum	53
Orientalidine	IX	93	See Fig. 1 Type IX	*Papaver pseudo-orientale* (Papaveraceae)	235
Pallimamine	VIII	94	$R_2R_3R_9R_{10}$═OMe	Corydalis pallida *(Papaveraceae)*	235
Palmatine	III	95	$R_2R_3R_9R_{10}$═OMe	*Anisocycla cymosa* (Menispermaceae)	6
				Asteropyrum cavaleriei (Ranunculaceae)	237
				Berberis aemulans (Berberidaceae)	19
				Berberis brandisiana	24
				Berberis bemeliaefolia	23
				Berberis candidula	19
				Berberis cerasina	21
				Berberis crataegina	26
				Berberis cretica	90
				Berberis dasystachya	19
				Berberis giraldii	21
				Berberis ilicifolia	28
				Berberis koetineana	19
				Berberis laurina	23

(*continued*)

TABLE II.
Continued.

Alkaloid	Skeleton type	Substance	Substituents	Plant (Family)	References
Palmatine *continued*	III	95	$R_2R_3R_9R_{10}$═OMe	*Isopyrum thalictroides* (Ranunculaceae)	130
				Mahonia fargesii (Berberidaceae)	49
				Mahonia gracilipes	50
				Nandina domestica (Berberidaceae)	83
				Papaver atlanticum (Papaveraceae)	153
				Papaver nudicaule	154
				Papaver orientale	155
				Penianthus zenkeri (Menispermaceae)	57
				Phellodendron chinense (Rutaceae)	92
				Phellodendron wilsonii	92
				Ranunculus serbicus (Ranunculaceae)	60
				Sinomenium acutum (Menispermaceae)	84
				Sphenocentrum jollyanum (Menispermaceae)	225
				Stephania cepharantha (Menispermaceae)	248
				Stephania hainanensis	249
				Stephania lincangensis	104
				Stephania micrantha	174
				Stephania miyiensis	224
				Stephania viridiflavens	250
				Thalictrum lankesteri (Ranunculaceae)	68
				Tinospora hainanensis (Menispermaceae)	251
				Tinospora malabarica	252
				Zanthoxylum chalybeum (Rutaceae)	228
Palmatine, dehydro	IV	96	$R_2R_3R_9R_{10}$═OMe	*Annona paludosa* (Annonaceae)	169
				Berberis chitria (Berberidaceae)	253
Palmatine, 7-8-dihydro 8-hydroxy	II	97	$R_2R_3R_9R_{10}$═OMe, R_8═OH	*Enanthia chlorantha* (Annonaceae)	253

Palmatine, pseudo 8-oxo	II	98	$R_2R_3R_{10}R_{11}$=OMe, R_8=O	*Berberis ilicifolia* (Berberidaceae)	*28*
				Stephania suberosa (Menispermaceae)	*254*
Palmatine, oxy	II	99	$R_2R_3R_9R_{10}$=OMe, R_8=O	*Anamirta cocculus* (Menispermaceae)	*255*
				Coscinium fenestratum (Menispermaceae)	*100*
Palmatine, pseudo	I	100	$R_2R_3R_{10}R_{11}$=OMe	*Berberis amurensis* (Berberidaceae)	*89*
				Berberis heterocarpa	*80*
				Penianthus zenkeri (Menispermaceae)	*256*
				Stephania suberosa (Menispermaceae)	*254*
				Xylopia vieillardii (Annonaceae)	*181*
Palmatine, tetrahydro	I	101	$R_2R_3R_9R_{10}$=OMe	*Annona cherimola* (Annonaceae)	*257*
				Annona paludosa	*258*
				Corydalis decumbens (Papaveraceae)	*242*
				Corydalis intermedia	*42*
				Corydalis pallida	*259*
				Corydalis remota	*196*
				Corydalis yanhusuo	*260*
Pessoine	I	102	$R_2R_{10}R_{11}$=OH, R_3=OMe	*Annona spinescens* (Annonaceae)	*264*
Phellodendrine	I	103	R_2R_{11}=OH, R_3R_{10}=OMe, R_7=Me	*Phellodendron chinense* (Rutaceae)	*92*
Polialthiaine, 8-oxo	I	104	$R_2R_9R_{11}$=OH, R_3R_{10}=OMe, R_8=O	*Polyalthia longifolia* (Annonaceae)	*265*
Prechilenine	I	105	R_2R_3=OCH_2O, R_8R_{13}=O, R_9R_{10}=OMe, R_{14}=OH	*Berberis actinacantha* (Berberidaceae)	*266*
Protopine	V	106	$R_2R_3R_9R_{10}$=OCH_2O, R_7=Me, R_{14}=O	*Arctomecon californica* (Papaveraceae)	*194*
				Arctomecon humile	*194*
				Arctomecon merriami	*194*
				Argemone hybrida (Papaveraceae)	*17*
				Argemone mexicana	*267*
				Berberis bumeliaefolia (Berberidaceae)	*23*
				Berberis laurina	*23*
				Berberis valdiviana	*267*
				Ceratocapnos claviculata (Papaveraceae)	*105*
				Ceratocapnos heterocarpa	*105*
				Corydalis amabilis (Papaveraceae)	*268*

(*continued*)

TABLE II.
Continued.

Alkaloid	Skeleton type	Substance	Substituents	Plant (Family)	References
Protopine *continued*	V	106	$R_2R_3R_9R_{10}$═OCH_2O, R_7═Me, R_{14}═O	*Corydalis bulleyana*	173
				Corydalis bungeana	165
				Corydalis hendersonii	115
				Corydalis humosa	120
				Corydalis impatiens	269
				Corydalis integra	270
				Corydalis koidzumiana	243
				Corydalis nobilis	42
				Corydalis omeiensis	146
				Corydalis pallida	259
				Corydalis pseudoadunca	171
				Corydalis ramosa	271
				Corydalis remota	196
				Corydalis rutifolia	147
				Corydalis semenowii	272
				Corydalis stewartii	273
				Corydalis tashiroi	179
				Corydalis ternata	274
				Corydalis thyrsiflora	275
				Corydalis turtschaninovii	167
				Corydalis yanhusuo	276
				Dactylocapnos torulosa (Papaveraceae)	110
				Dicentra peregrina (Papaveraceae)	277
				Dicentra spectabilis	245
				Eomecon chionantha (Papaveraceae)	278
				Fumaria asepala (Papaveraceae)	186
				Fumaria bastardii	279

(*continued*)

TABLE II.
Continued.

Alkaloid	Skeleton type	Substance	Substituents	Plant (Family)	References
Protopine *continued*	V	106	$R_2R_3R_9R_{10}$═OCH_2O, R_7═Me, R_{14}═O	*Papaver rhoeas*	52
				Papaver rhopalothece	55
				Papaver setigerum	192
				Papaver stevenianum	56
				Rupicapnos africana (Papaveraceae)	105
				Sarcocapnos baetica (Papaveraceae)	288
				Sarcocapnos crassifolia	289
				Sarcocapnos enneaphylla	290
				Sarcocapnos saetabensis	291
				Thalictrum delavayi (Ranunculaceae)	64
				Thalictrum foetidum	292
				Thalictrum glandulosissimum	93
				Thalictrum triternatum	293
Protopine, pseudo	V	107	$R_2R_3R_{10}R_{11}$═OCH_2O, R_7═Me, R_{14}═O	*Fumaria indica* (Papaveraceae)	294
				Thalictrum delavayi (Ranunculaceae)	193
				Zanthoxylum integrifoliolum (Rutaceae)	295
Quinolizine-8-one, 5,6,13,13a tetrahydro-9, 10 dimethoxydibenzo (5,6a)	I	108	R_2R_3═OCH_2O, R_8═O, R_9R_{10}═OMe	*Coscinium fenestratum* (Menispermaceae)	296
Quinolizinium, 2,10 dihydroxy-13-oxidodibenzo (a,g)	VI	109	$R_2R_{10}R_{13}$═OH	*Aristolochia arcuata* (Aristolochiaceae)	297
Schefferine	I	110	$R_2R_3R_{10}$═OMe, R_9═OH	*Stephania succifera* (Menispermaceae)	298
Scoulerine	I	111	R_2R_9═OH, R_3R_{10}═OMe	*Annona paludosa* (Annonaceae)	169
				Argemone alba (Papaveraceae)	17
				Argemone albiflora	112

				Argemone hybrida	*17*
				Argemone mexicana	*17*
				Argemone ochroleuca	*112*
				Berberis valdiviana (Berberidaceae)	*217*
				Chelidonium majus (Papaveraceae)	*299*
				Corydalis bungeana (Papaveraceae)	*300*
				Corydalis pseudoadunca	*171*
				Fumaria densiflora (Papaveraceae)	*301*
				Fumaria judaica	*301*
				Nandina domestica (Berberidaceae)	*302*
				Papaver argemone (Papaveraceae)	*156*
				Papaver atlanticum	*153*
				Papaver bracteatum	*303*
				Papaver confine	*52*
				Papaver fugax	*119*
				Papaver orientale	*155*
				Papaver pinnatifidum	*54*
				Papaver rhoeas	*52*
				Papaver setigerum	*192*
				Papaver stevenianu	*56*
Scoulerine, dehydro	III	112	R_2R_9═OH, R_3R_{10}═OMe	*Pseuduvaria indochinensis* (Annonaceae)	*304*
Scoulerine, iso	I	113	R_2R_9═OMe, R_3R_9═OH	*Stephania hainanensis* (Menispermaceae)	*249*
Sinactine	I	114	R_2R_3═OMe, R_9R_{10}═OCH_2O	*Corydalis remota* (Papaveraceae)	*109*
				Dasymaschalon sootepense (Annonaceae)	*106*
				Fumaria densiflora (Papaveraceae)	*301*
				Fumaria muralis	*149*
				Fumaria parviflora	*149*
				Papaver rhoeas (Papaveraceae)	*182*
Spiduxine	I	115	$R_2R_3R_{10}$═OMe, R_{11}═OH , R_{12}═CHO	*Duguetia spixiana* (Annonaceae)	*305*
Spinosine	I	116	R_2R_3═OMe, $R_{10}R_{11}$═OH	*Annona spinescens* (Annonaceae)	*264*
				Desmos yunnanensis (Annonaceae)	*306*

(*continued*)

TABLE II.
Continued.

Alkaloid	Skeleton type	Substance	Substituents	Plant (Family)	References
Stephabinamine	I	117	R_1R_{11}═OH, R_2 R_3R_{10}═OMe	*Stephania suberosa* (Menispermaceae)	254
Stephabine	III	118	R_1═OH, $R_2R_3R_{10}R_{11}$═OMe	*Stephania suberosa* (Menispermaceae)	254
Stephabine, tetrahydro	I	119	R_1═OH, $R_2R_3R_{10}R_{11}$═OMe	*Stephania pierrei* (Menispermaceae)	307
				Stephania suberosa	254
Stepharanine	III	120	R_2R_{10}═OH, R_3R_9═OMe	*Piptostigma fugax* (Annonaceae)	305
				Popowia pisocarpa (Annonaceae)	308
				Sinomenium acutum (Menispermaceae)	309
				Stephania miyiensis (Menispermaceae)	224
				Stephania yunnanensis	177
Stepholidine	I	121	R_2R_{10}═OH, R_3R_9═OMe	*Alphonsea sclerocarpa* (Annonaceae)	310
				Desmos cochinchinensis (Annonaceae)	311
				Liriodendron tulipifera (Magnoliaceae)	138
				Stephania delavayi (Menispermaceae)	312
				Stephania dentifolia	250
				Stephania epigaea	250
				Stephania hainanensis	250
				Stephania intermedia	250
				Stephania kuinanensis	250
				Stephania kwangsiensis	250
				Stephania longa	250
				Stephania longipes	250
				Stephania macrantha	250
				Stephania mashanica	250
				Stephania micrantha	174
				Stephania sp.	313
				Stephania succifera	250
				Stephania viridiflavens	250

				Stephania yunnanensis	250
Stylopine	I	122	$R_2R_3R_9R_{10}$═OCH_2O	*Argemone platyceras* (Papaveraceae)	17
				Chelidonium majus (Papaveraceae)	314
				Corydalis caucasica (Papaveraceae)	114
				Corydalis hendersonii	115
				Corydalis marschalliana	117
				Corydalis pseudoadunca	171
				Fumaria densiflora (Papaveraceae)	306
				Fumaria indica	315
				Fumaria officinalis	149
				Fumaria parviflora	155
				Glaucium oxylobum (Papaveraceae)	316
				Papaver atlanticum (Papaveraceae)	153
				Papaver confine	52
				Papaver dubium	317
				Papaver nudicaule	318
				Papaver setigerum	192
Stylopinium, *N*-methyl	I	123	$R_2R_3R_9R_{10}$═OCH_2O, R_7═Me	Dactylocapnos torulosa (Papaveraceae)	319
Thaicanine	I	124	$R_2R_3R_9R_{10}$═OMe, R_4═OH	*Guatteria schomburgkiana* (Annonaceae)	320
Thaicanine, 8-oxo	I	125	$R_2R_3R_9R_{10}$═OMe, R_8═O	*Conscinum fenestratum* (Menispermaceae)	100
Thaicanine, *N*-methyl	I	126	$R_2R_3R_9R_{10}$═OMe, R_4═OH, R_7═Me	*Anisocycla cymosa* (Menispermaceae)	321
Thaicanine, *N*-*O*-dimethyl	I	127	$R_2R_3R_4R_9R_{10}$═OMe, R_7═$(Me)_2$	*Anisocycla cymosa* (Menispermaceae)	321
Thaicanine, *O*-methyl	I	128	$R_2R_3R_4R_9R_{10}$═OMe	*Parabaena sagittata* (Menispermaceae)	322
Thaipetaline	I	129	$R_2R_3R_9$═OMe, R_{10}═OH	*Fissistigma balansae* (Annonaceae)	129
Thalictricavine	I	130	$R_2R_9R_{10}$═OMe, R_3═OH	*Corydalis ambigua* (Papaveraceae)	97
Thalidastine	III	131	R_2R_3═OCH_2O, R_5R_{10}═OH, R_9═OMe	*Nandina domestica* (Berberidaceae)	83
Thalidastine, deoxy	VI	132	R_2R_3═OCH_2O, R_5R_{10}═OH, R_9═OMe	*Nandina domestica* (Berberidaceae)	83
Thalifendine	III	133	R_2R_3═OCH_2O, R_9═OMe, R_{10}═OH	*Berberis congestiflora* (Berberidaceae)	25
				Berberis polymorpha	125
				Coptis quinquefolia (Ranunculaceae)	10

(*continued*)

TABLE II.
Continued.

Alkaloid	Skeleton type	Substance	Substituents	Plant (Family)	References
Thalifendine *continued*	III	133	R_2R_3═OCH_2O, R_9═OMe, R_{10}═OH	*Fibraurea chloroleuca* (Menispermaceae)	47
				Glaucium arabicum (Papaveraceae)	48
				Papaver dubium (Papaveraceae)	317
				Thalictrum cultratum (Ranunculaceae)	226
				Thalictrum glandulosissimum	66
				Thalictrum honanense	67
				Thalictrum lankesteri	68
Thalifendine, tetrahydro-8-oxo	I	134	R_2R_3═OCH_2O, R_8═O, R_9═OMe, R_{10}═OH	*Hydrastis canadensis* (Ranunculaceae)	323
Thalifendine, tetrahydro-8-oxo acetil	I	135	R_2R_3═OCH_2O, R_8═O, R_9═OMe, R_{10}═$OCOCH_3$	*Hydrastis canadensis* (Ranunculaceae)	323
Thalifendine, chloride	III	136	R_2R_3═OCH_2O, R_9═OMe, R_{10}═OH	*Fibraurea chloroleuca* (Menispermaceae)	324
Xilopinine	I	137	$R_2R_3R_{10}R_{11}$═OMe	*Artabotrys grandifolius* (Annonaceae)	325
				Dasymaschalon sootepense (Annonaceae)	325
Yuanamide	II	138	$R_2R_3R_9R_{10}$═OMe, R_8═O, R_{13}═Me	*Corydalis bulbosa* (Papaveraceae)	326
				Corydalis incisa	97

TABLE III.
Biological Activities Related for Protoberberine Alkaloids in the Literature between 1986 and 2001.

Alkaloid	Biological activity	Active	Inactive	References
Berberine	Acetylcholine receptor binding	X		*327*
	Acetylcholinesterase inhibition	X		*328*
	ACH receptor blocking effect	X		*329*
	Activator protein 1 inhibition	X		*330*
	Adherence inhibition (bacteria to host cells)	X		*331*
	Adrenergic agonist (α)	X		*332*
	Adrenergic agonist (α-2) activity platelets	X		*333*
	Adrenergic receptor blocker (α-1)	X		*328*
	Adrenergic receptor blocker (α-2)	X		*328*
	Adrenergic receptor blocker (α-2) platelets	X		*333*
	Alcohol dehydrogenase inhibition	X		*334*
	Aldehyde reductase I inhibition	X		*334*
	Alkaline phosphatase inhibition	X		*335*
	Amino acid (aromatic) decarboxylase inhibition	X		*336*
	Analgesic activity	X		*337*
	Antiacne activity	X		*338*
	Antimalarial activity *Plasmodium falciparum*	X		*339*
	Antiamnesic activity	X		*340*
	Antiarrhythmic activity	X		*341*
	Anticrustacean activity	X		*342*
	Anticytotoxic activity		X	*343*
	Antidiarrheal activity	X		*344*
	Antieczema effect	X		*345*
	Antifibrillatory activity	X		*346*
	Antigenic activity	X		*347*
	Antihemorrhagic activity	X		*348*
	Antihemostatic activity	X		*349*
	Antihypercholesterolemic activity	X		*350*
	Antihyperglycemic activity	X		*351*
	Antihypoxic effect	X		*352*
	Anti-inflammatory activity	X		*337*
	Anti-ischemic effect	X		*353*
	Antinephritic effect	X		*354*
	Antineurotoxic activity	X		*355*
	Antioxidant activity	X		*356*
	Antiparasitic activity	X		*357*
	Antiproliferation activity	X		*358*
	Antisepticemia activity	X		*347*

(*continued*)

TABLE III.
Continued.

Alkaloid	Biological activity	Active	Inactive	References
Berberine *continued*	Antispermatogenic effect	X		*343*
	Antithrombotic effect	X		*359*
	Antitrypanosomal activity	X		*360*
	Antitumor-promoting activity	X		*361*
	Antiulcer activity	X		*362*
	Apoptosis induction	X		*363*
	Arylamine *N*-acetyltransferase inhibition	X		*364*
	Blood flow increase	X		*365*
	Bone resorption inhibition	X		*366*
	Butyrylcholinesterase inhibition	X		*328*
	Calcium channel agonist	X		*367*
	Calcium ion uptake inhibition	X		*368*
	Calcium level decrease (extracellular)	X		*369*
	Calcium level increase (intracellular)	X		*370*
	Carcinogenesis inhibition	X		*371*
	Cardiac output increased	X		*372*
	Cardiovascular effects (unspecified)	X		*373*
	Cell adhesion inhibition	X		*374*
	Cell attachment enhancement inhibition	X		*375*
	Cell cycle cytotoxicity (G2 phase)	X		*363*
	Cell cycle cytotoxicity (S phase)	X		*376*
	Cell differentiation induction	X		*377*
	Cell invasion inhibition	X		*330*
	Cell morphological alteration	X		*378*
	Cell proliferation inhibition	X		*379*
	Cell transport effects	X		*380*
	Choline acetyltransferase inhibition		X	*328*
	Cholinesterase inhibition	X		*328*
	Chronotropic effect negative	X		*381*
	Complement classical pathway inhibition	X		*382*
	Cytochrome P-450 inhibition	X		*383*
	Delayed type hypersensitivity inhibition		X	*384*
	DNA adduct formation inhibition	X		*385*
	DNA aggregation enhancement	X		*386*
	DNA binding effect	X		*387*
	DNA cleavage inhibition	X		*388*
	DNA intercalating effect	X		*328*
	DNA ligase inhibition		X	*389*
	DNA polymerase I inhibition		X	*390*
	Dopamine metabolism alteration	X		*391*
	Dopamine receptor binding inhibition	X		*392*
	Dopamine synthesis inhibition	X		*336*
	Drug resistance reversal induction	X		*393*

(*continued*)

TABLE III.
Continued.

Alkaloid	Biological activity	Active	Inactive	References
	Electrolyte transport inhibition	X		*395*
	Elastase inhibition	X		*394*
	Electrophysiological effects	X		*396*
	Feeding deterrent (insect)	X		*397*
	GABA receptor blocking effect		X	*398*
	Gene expression induction	X		*380*
	Gene expression inhibition	X		*399*
	Glucocorticoid receptor level increase	X		*400*
	Gluconeogenesis inhibition	X		*401*
	Glutathione-*S*-transferase inhibition	X		*402*
	Hemagglutinin activity inhibition	X		*403*
	Hypoglycemic activity	X		*404*
	Immunologic effects (unspecified)	X		*405*
	Immunosuppressant activity	X		*406*
	Inflammation induction	X		*382*
	Inositol phosphate formation inhibition		X	*407*
	Inotropic effect positive	X		*408*
	Insecticide activity	X		*409*
	Insulin release inhibition	X		*375*
	Intercellular adhesion molecule-1 inhibition	X		*410*
	Interleukin-8 production inhibition	X		*362*
	K^+ outward current inhibition	X		*411*
	Lipase inhibition	X		*412*
	Lipid peroxide formation inhibition	X		*413*
	Lipogenesis inhibition	X		*414*
	Lipoxygenase, 1,2 inhibition		X	*415*
	Lipoxygenase, 5 inhibition		X	*416*
	Lipoxygenase inhibition	X		*417*
	Locomotor activity decrease		X	*340*
	Lymphocyte proliferation inhibition	X		*384*
	RNA-m inhibition	X		*418*
	Membrane binding effect	X		*419*
	Metastasis inhibition	X		*330*
	Microsomal metabolizing system inhibition	X		*401*
	Molluscicidal activity	X		*420*
	Monoamine oxidase inhibition	X		*421*
	Monoamine oxidase inhibition (type A)	X		*422*
	Monooxygenase inhibition		X	*423*
	Monophasic action potential duration increase	X		*411*
	Multidrug resistance enhancement	X		*424*
	Muscarinic agonist activity	X		*332*
	Muscarinic antagonist activity	X		*425*
	Muscarinic receptor binding activity	X		*328*
	Mutagenic activity	X		*426*

(*continued*)

TABLE III.
Continued.

Alkaloid	Biological activity	Active	Inactive	References
Berberine *continued*	Myeloperoxidase inhibition	X		*362*
	Myocardial ischemic	X		*427*
	N-acetyltransferase inhibition	X		*428*
	Neuromuscular blocking activity	X		*429*
	Neuroprotectant effect	X		*430*
	Nicotinic receptor binding activity	X		*328*
	Oncogene expression inhibition	X		*431*
	Osteoclast formation inhibition	X		*366*
	Percutaneous absorption enhancement	X		*432*
	Pharmacokinetic study	X		*433*
	Phosphodiesterase inhibition		X	*434*
	Platelet aggregation inhibition	X		*435*
	Platelet aggregation stimulation	X		*435*
	Potassium channel blocking activity	X		*436*
	Pro-oxidant activity		X	*415*
	Prostaglandin-f-1-α-6-keto synthesis inhibition		X	*437*
	Prostaglandin synthesis inhibition	X		*438*
	Protein kinase activation		X	*439*
	Protein kinase inhibition		X	*439*
	Protein synthesis inhibition	X		*328*
	Radical scavenging effect	X		*440*
	Recombination induction	X		*426*
	Respiration (cellular) stimulant		X	*429*
	Reverse transcriptase inhibition	X		*328*
	RNA binding	X		*441*
	Sclerosing effect	X		*418*
	Serotonin (5-HT) receptor blocking effect	X		*328*
	Serotonin (5-HT) release inhibition	X		*442*
	Sister chromatid exchange stimulation	X		*443*
	Sleep time increased	X		*444*
	Superoxide dismutase stimulation	X		*413*
	Superoxide scavenging activity	X		*388*
	Thiol content decrease	X		*418*
	Thrombocytopoietic activity	X		*445*
	Thromboxane A-2 synthesis inhibition	X		*438*
	Thromboxane B-2 synthesis inhibition	X		*365*
	Topoisomerase I inhibition		X	*446*
	Transpeptidase inhibition	X		*402*
	Tryptophan hydroxylase inhibition	X		*442*
	Tyrosine hydroxylase inhibition	X		*447*
	Ulcerogenic activity	X		*337*
	Vascular cell adhesion molecule-1 inhibition		X	*410*

(*continued*)

TABLE III.
Continued.

Alkaloid	Biological activity	Active	Inactive	References
	Vascular permeability decreased	X		*448*
	Vasorelaxation activity	X		*449*
	Cardiac output decreased	X		*450*
	Adrenergic receptor blocker (α-1)	X		*328*
	Antiallergenic activity	X		*451*
	Antiischemic effect	X		*413*
	Cataleptic effect		X	*452*
	Chloride channel inhibition		X	*453*
	Current inhibition (large cation)		X	*453*
	Dopamine receptor blocking effect	X		*454*
	Elastase inhibition	X		*394*
	Hydroxide radical generation inhibition	X		*455*
	Potassium transport inhibition	X		*456*
	Xanthine oxidase inhibition	X		*457*
Berberine, tetrahydro	Insecticide activity	X		*409*
Berberubine	Topoisomerase II calytic inhibition activity	X		*458*
Canadine	Cytotoxic activity		X	*459*
	Molluscicidal activity		X	*420*
	Reverse transcriptase inhibition		X	*460*
	Smooth muscle relaxant activity		X	*99*
	Smooth muscle stimulant activity	X		*461*
	Antimycobacterial activity		X	*462*
	Antimalarial activity		X	*459*
	Cytotoxic activity	X		*459*
	Insecticide activity	X		*463*
Capaurine	Antigen activation inhibition	X		*464*
	Antimalarial activity	X		*465*
Columbamine	Antiamebic activity	X		*339*
	Antimalarial activity	X		*466*
	Apoptosis inhibition	X		*467*
	Cyclooxygenase inhibition		X	*416*
	Cytotoxic activity	X		*339*
	Dopamine receptor blocking effect	X		*468*
	Lipid peroxide formation inhibition	X		*469*
	Lipoxygenase inhibition	X		*469*
	Lipoxygenase, 5 inhibition		X	*416*
	Reverse transcriptase inhibition	X		*460*
Columbamine, tetrahydro	Adrenergic receptor blocker (α-1)	X		*140*
	GABA receptor blocking effect		X	*468*
	Muscarinic antagonist activity		X	*468*
	Aldose reductase inhibition	X		*470*

(*continued*)

TABLE III.
Continued.

Alkaloid	Biological activity	Active	Inactive	References
Columbamine, tetrahydro *continued*	Platelet aggregation inhibition		X	*471*
Constrictosine	Spasmolytic activity	X		*472*
Constrictosine, 3-O-methyl	Spasmolytic activity	X		*472*
Constrictosine, 3,5-di-*O* methyl	Spasmolytic activity	X		*472*
Constrictosine, 5,6-dihydro-3, 5-di-*O*-methyl	Spasmolytic activity	X		*472*
Constrictosine, 5,6-dihydro	Spasmolytic activity	X		*472*
Coptisine	Antibacterial activity	X	X	*473*
	Antinephritic effect	X		*365*
	Antioxidant activity	X		*356*
	Antispasmodic activity		X	*474*
	Antiulcer activity	X		*475*
	Antiyeast activity	X		*473*
	Blood flow increase		X	*365*
	Butyrylcholinesterase inhibition	X		*365*
	Cytotoxic activity	X		*476*
	DNA ligase inhibition		X	*477*
	DNA polymerase I inhibition		X	*390*
	Elastase inhibition	X		*394*
	GABA receptor blocking effect		X	*398*
	Lipid peroxide formation inhibition	X		*356*
	Lipogenesis inhibition	X		*414*
	Monoamine oxidase inhibition	X		*478*
	Percutaneous absorption enhancement	X		*432*
	Platelet aggregation inhibition	X		*365*
	Reverse transcriptase inhibition		X	*479*
	Serotonin (5-HT) release inhibition		X	*480*
	Thromboxane B-2 synthesis inhibition	X		*365*
	Topoisomerase I inhibition		X	*446*
Coptisine, tetrahydro	Antifungal activity	X		*481*
	Antifungal activity (plant pathogens)		X	*482*
	Binding effect	X		*483*
Coreximine	Antileishmaniasis activity	X		*484*
	Antitrypanosomal activity		X	*484*
	Dopamine receptor blocking effect	X		*484*
	Dopamine uptake inhibition		X	*484*
	Platelet aggregation inhibition		X	*485*
Corybulbine	Antigen activation inhibition	X		*466*

(*continued*)

TABLE III.
Continued.

Alkaloid	Biological activity	Active	Inactive	References
Corybulbine, dehydro	Antimalarial activity	X		*466*
Corydaline	Antifungal activity	X		*486*
	Antigen activation inhibition	X		*464*
	Antiproliferation activity	X		*487*
	Cell migration inhibition	X		*487*
	Elastase inhibition	X		*394*
	Reverse transcriptase inhibition		X	*390*
Corydalidzine	Antigen activation inhibition	X		*464*
Corydalmine	Platelet aggregation inhibition	X		*488*
	Antimalarial activity	X		*307*
	Cytotoxic activity		X	*179*
Corydalmine, *N*-oxide, *cis*	Platelet aggregation inhibition	X		*488*
Corynoxidine	Platelet aggregation inhibition	X		*488*
	Cytotoxic activity		X	*179*
Corypalmine	Antibacterial activity		X	*489*
	Antifungal activity		X	*490*
	Antimycobacterial activity		X	*490*
	Antiyeast activity		X	*490*
	Dopamine receptor blocking effect	X		*491*
	Dopamine uptake inhibition		X	*491*
Corypalmine, iso	Antigen activation inhibition	X		*464*
Corypalmine, *trans*-iso *N*-oxide	Cytotoxic activity		X	*179*
Corypalmine, *N*-oxide, *cis*-iso	Platelet aggregation inhibition	X		*488*
Corysamine	Antimalarial activity	X		*466*
Cryptopine	DNA polymerase I inhibition		X	*390*
	Antiarrhythmic activity		X	*492*
	Antihepatotoxic activity	X		*493*
	Reverse transcriptase inhibition		X	*390*
Cyclanoline	Angiotensin-converting enzyme inhibition	X		*494*
Dauricoside	Platelet aggregation inhibition	X		*495*
Discretamine	Antibacterial activity		X	*489*
	Antiyeast activity		X	*489*
	Adrenergic receptor blocker (α)	X		*496*
	Adrenergic receptor blocker (α-1)	X		*497*
	Spasmolytic activity		X	*496*

(*continued*)

TABLE III.
Continued.

Alkaloid	Biological activity	Active	Inactive	References
Discretine, 10-demethyl	Dopamine receptor blocking effect	X		*491*
Discretine, dehydro	Antiamebic activity	X		*459*
	Cytotoxic activity		X	*459*
Fagarine	Antiproliferation activity	X		*498*
	Cytotoxic activity		X	*499*
	Mutagenic activity	X		*500*
	Phototoxicity	X		*501*
	Platelet aggregation inhibition	X		*502*
	Sister chromatid exchange stimulation	X		*498*
Govadine	Adrenergic receptor blocker (α-1)	X		*503*
	Adrenergic receptor blocker (β)		X	*503*
	Smooth muscle relaxant activity	X		*504*
Groenlandicine	Apoptosis inhibitionin vitro	X		*467*
	Topoisomerase I inhibition	X		*446*
Mecambridine	Analgesic activity	X		*232*
	Anticrustacean activity	X		*342*
	CNS depressant activity	X		*565*
Ophiocarpine	Antibacterial activity		X	*486*
	Antifungal activity		X	*486*
Orientalidine	Antifungal activity	X		*506*
Palmatine	Acetylcholinesterase inhibition	X		*328*
	Adrenergic receptor blocker (α-1)	X		*328*
	Amino acid (aromatic) decarboxylase inhibition		X	*442*
	Analgesic activity	X		*507*
	Antiarrhythmic activity	X		*508*
	Antileishmaniasis activity	X		*509*
	Antimalarial activity	X		*246*
	Antispasmodic activity	X		*510*
	Antispermatogenic effect	X		*511*
	Antitumor-promoting activity	X		*512*
	Antiyeast activity	X		*246*
	Apoptosis induction		X	*376*
	Apoptosis inhibition	X		*467*
	Butyrylcholinesterase inhibition		X	*328*
	Choline acetyltransferase inhibition		X	*328*
	CNS depressant activity	X		*507*
	Cyclo-oxygenase inhibition		X	*416*
	DNA binding effect	X		*376*
	DNA uncoiling stimulation	X		*513*
	Dopamine depletion	X		*514*

(*continued*)

TABLE III.
Continued.

Alkaloid	Biological activity	Active	Inactive	References
	Dopamine metabolism alteration	X		*391*
	Dopamine synthesis inhibition	X		*336*
	Drug resistance reversal induction	X		*393*
	Feeding deterrent (insect)	X		*397*
	Intercalation effect	X		*515*
	Lipase inhibition	X		*412*
	Lipogenesis inhibition		X	*516*
	Lipoxygenase, 5 inhibition		X	*416*
	Locomotor activity decrease	X		*514*
	Monoamine oxidase inhibition	X		*517*
	Monoamine oxidase inhibition (type A)		X	*422*
	Muscarinic receptor binding activity	X		*328*
	Nicotinic receptor binding activity		X	*328*
	Percutaneous absorption enhancement	X		*432*
	Platelet aggregation inhibition	X		*518*
	Protein kinase inhibition		X	*439*
	Serotonin (5-HT) depletion	X		*514*
	Serotonin (5-HT) receptor blocking effect	X		*328*
	Serotonin (5-HT) release inhibition	X		*442*
	Stability study	X		*513*
	Topoisomerase I inhibition	X		*513*
	Topoisomerase II inhibition		X	*515*
	Tryptophan hydroxylase inhibition	X		*442*
	Tyrosine hydroxylase inhibition	X		*519*
Palmatine, 7-8-dihydro 8-hydroxi	Antiulcer activity	X		*520*
Palmatine, dihydro	Antispermatogenic effect	X		*511*
Palmatine, tetrahydro	ATP-ase (Na^+/k^+) inhibition		X	*521*
	Analgesic activity	X		*507*
	Antibacterial activity	X		*486*
	Antigen activation inhibition	X		*464*
	Antiyeast activity		X	*522*
	Cytotoxic activity	X		*179*
	DNA ligase inhibition		X	*477*
	Platelet aggregation inhibition	X		*243*
	Protein expression stimulation	X		*523*
	Toxic effect (general)	X		*524*
	Adrenergic receptor blocker (α-1)	X		*328*
	Antiallergenic activity		X	*451*

(*continued*)

TABLE III.
Continued.

Alkaloid	Biological activity	Active	Inactive	References
Palmatine, tetrahydro *continued*	Antiischemic effect	X		*525*
	Antimalarial activity	X		*246*
	Binding effect	X		*483*
	Calcium channel blocker	X		*526*
	Calcium level increase (intracellular)	X		*527*
	Cardiovascular effects (unspecified)	X		*528*
	Dopamine receptor blocking effect	X		*529*
	Dopamine uptake inhibition	X		*530*
	Drug addiction inhibition	X		*531*
	Drug resistance reversal induction	X		*393*
	Hypotensive activity	X		*532*
	Inotropic effect negative	X		*533*
	Monoamine oxidase inhibition	X		*517*
	Mutagenic activity		X	*534*
	Neuroexcitatory activity	X		*535*
	Norepinephrine levels decreased	X		*536*
	Potassium transport inhibition		X	*537*
	Spasmolytic activity	X		*532*
	Tyrosine hydroxylase stimulation	X		*529*
Palmatine, tetrahydro *N*-methyl	Antimalarial activity		X	*538*
Palmatrubine, tetrahydro	Reverse transcriptase inhibition		X	*460*
Pessoine	Antitrypanosomal activity	X		*539*
Phellodendrine	Antibody formation suppression		X	*540*
	Antihepatotoxic activity	X		*541*
	Antinephritic effect	X		*542*
	Immunomodulator activity	X		*543*
	Delayed type cutaneous hypersensitivity inhibition	X		*543*
Protopine	Alcohol dehydrogenase inhibition		X	*334*
	Aldehyde reductase I inhibition	X		*334*
	Aldose reductase inhibition	X		*470*
	Alpha-amylase inhibition	X		*544*
	Aminopyrine-*N*-demethylase induction	X		*545*
	Antiamebic activity	X		*459*
	Antiamnesic activity	X		*544*
	Antihepatotoxic activity	X		*301*
	Antihistamine activity		X	*546*
	Antimalarial activity	X		*459*

(*continued*)

TABLE III.
Continued.

Alkaloid	Biological activity	Active	Inactive	References
	Antiototoxicity activity	X		*547*
	Antispermatogenic effect	X		*548*
	Antithrombotic effect	X		*549*
	Antitrypanosomal activity		X	*270*
	Arachidonate metabolism inhibition	X		*550*
	ATP levels decreased	X		*551*
	Blood viscosity decreased	X		*552*
	Butyrylcholinesterase inhibition		X	*274*
	Calcium ion release inhibition	X		*553*
	Calcium ion uptake inhibition	X		*553*
	Cerebral blood flow increased	X		*554*
	Choleretic activity	X		*555*
	Chronotropic effect negative	X		*556*
	Chronotropic effect positive		X	*557*
	Cyclic AMP phosphodiesterase inhibition		X	*558*
	Cyclic GMP stimulation	X		*554*
	Cytochrome P-450 induction	X		*545*
	Dopamine receptor binding inhibition	X		*392*
	Enzyme effects	X		*559*
	Fibrinogen conversion inhibition		X	*549*
	GABA receptor modulatory effect	X		*398*
	Hypotensive activity	X		*560*
	Inositol phosphate formation inhibition	X		*551*
	Inotropic effect negative	X		*556*
	Inotropic effect positive		X	*557*
	Intercellular adhesion molecule-1 inhibition		X	*410*
	Lipid peroxide formation inhibition	X		*545*
	Molluscicidal activity	X		*561*
	NADPH cytochrome P-450 reductase stimulation	X		*545*
	Opiate potentiation	X		*562*
	Platelet activating factor inhibition	X		*550*
	Platelet aggregation inhibition	X		*488*
	Prostaglandin inhibition		X	*549*
	Prothrombin time increased		X	*549*
	Receptor binding stimulant	X		*492*
	Serotonin (5-HT) secretion inhibition	X		*554*
	Sleep time increased	X		*545*
	Spasmolytic activity	X		*563*
	Thromboxane A-2 synthesis inhibition		X	*554*

(*continued*)

TABLE III.
Continued.

Alkaloid	Biological activity	Active	Inactive	References
Protopine *continued*	Thromboxane B-2 synthesis induction	X		*564*
	Vascular cell adhesion molecule-1 inhibition		X	*410*
	Vasodilator activity	X		*564*
Protopine, pseudo	Antifungal activity	X		*486*
	Dopamine receptor binding inhibition	X		*64*
Scoulerine	Antifungal activity	X		*486*
Sinactine	Anticrustacean activity		X	*565*
Sinactine, *N*-methyl	Anticrustacean activity	X		*565*
Solidaline	Antigen activation inhibition	X		*464*
Stephabine, tetrahydro	Antimalarial activity	X		*465*
Stepholidine	Antibacterial activity		X	*489*
	Antimycobacterial activity		X	*489*
	Antiyeast activity		X	*489*
	Adrenergic receptor blocker (α-1)	X		*566*
	Antiischemic effect	X		*566*
	Antipyretic activity	X		*567*
	Binding effect	X		*483*
	Calcium channel blocker	X		*568*
	Calcium ion release inhibition	X		*569*
	Calcium level increase (intracellular)	X		*527*
	Cataleptic effect	X		*570*
	CNS effects (general)	X		*571*
	DNA synthesis inhibition	X		*572*
	Dopamine increase	X		*572*
	Dopamine metabolism alteration	X		*572*
	Dopamine receptor blocking effect	X		*574*
	Dopamine receptor upregulation	X		*575*
	Dopamine release inhibition	X		*576*
	Dopamine-releasing activity	X		*577*
	Dopaminergic effect	X		*574*
	Drug addiction		X	*567*
	Drug resistance reversal induction	X		*393*
	Glutamate-oxaloacetate-transaminase inhibition	X		*529*
	Hypotensive activity	X		*578*
	Miscellaneous effects	X		*579*
	Narcotic activity	X		*567*
	Neuroexcitatory activity	X		*580*
	Neuroprotectant effect	X		*581*
	Potassium transport inhibition		X	*582*

(*continued*)

TABLE III.
Continued.

Alkaloid	Biological activity	Active	Inactive	References
	Spasmolytic activity	X		*583*
	Tranquilizing effect	X		*570*
Stylopine	Antigen activation inhibition	X		*464*
	Antitrypanosomal activity		X	*584*
	Antimalarial activity		X	*585*
	Antitrypanosomal activity		X	*584*
	Aldose reductase inhibition	X		*470*
	Antifungalactivity (plant pathogens)		X	*482*
	Antipsychotic activity	X		*482*
	Cytotoxic activity	X		*314*
	GABA receptor modulatory effect	X		*398*
	Histamine release inhibition	X		*586*
	Insecticide activity	X		*587*
	Intercellular adhesion molecule-1 inhibition		X	*410*
	Platelet aggregation inhibition	X		*471*
	Vascular cell adhesion molecule-1 inhibition		X	*410*
Thaicanine	Antimalarial activity	X		*465*
	Cytotoxic activity	X		*588*
Thalifendine	Antiamebic activity	X		*339*
	Anticrustacean activity		X	*516*
	Antimalarial activity	X		*459*
	Cytotoxic activity		X	*589*
Thalifendine, tetrahydro-8-oxo	Antibacterial activity		X	*323*
	Antiyeast activity		X	*323*
Yuanamide	Antigen activation inhibition	X		*464*

Berberidaceae with 61 species from three genera, followed by the Menispermaceae with 42 species from 14 genera, and the Ranunculaceae with 37 species from nine genera. Figure 2 shows the distribution of the protoberberine alkaloids among the families from which they were isolated, showing also the number of genera and the species studied in each family and the number of citations.

1. Annonaceae

The family Annonaceae contains the largest number of genera investigated among the 13 families studied. In the period covered by this review, 20 genera and 30 different species of the Annonaceae were reported as producing protoberberine alkaloids. However, only 47 citations have appeared in the literature regarding protoberberines from this family. The genus *Annona* was the most studied, yielding eight citations from four species, followed by the genus *Fissistigma* with five citations from a single species.

TABLE IV.
Chemical Shift Data of the Protoberberine Alkaloids Shown in Table II.

Carbon	Compound					
	2	**3**	**4**	**5**	**6**	**10**
1	111.5	113.1	111.7	113.2	112.7	105.4
2	144.0	145.1	144.2	145.1	145.0	147.6
3	145.7	146.4	145.4	146.5	146.5	149.7
4	110.8	112.4	110.8	112.4	112.1	108.4
4a	125.1	126.6	125.7	126.8	127.1	130.6
5	28.1	30.0	29.0	30.1	30.3	26.3
6	51.3	47.8	51.6	48.0	48.3	55.1
8	53.3	55.5	58.1	59.4	60.0	145.4
8a	120.9	121.1	125.2	132.5	132.0	121.3
9	152.9	153.8	127.0	128.8	128.5	143.6
10	111.6	112.9	113.7	114.1	114.3	150.3
11	126.6	127.5	155.8	155.7	155.5	126.6
12	119.5	121.1	115.1	115.3	115.1	123.5
12a	135.2	136.3	135.5	136.1	137.1	132.9
13	35.8	36.0	36.8	36.7	37.9	120.1
14	58.7	50.6	59.4	50.7	59.5	137.4
14a	129.4	132.7	130.4	132.5	131.9	120.4
OCH_2O	–	–	–	–	–	102.0
3-OMe	55.5	56.5	55.8	56.2	55.8	–
9-OMe	–	–	–	–	–	61.9
10-OMe	–	–	–	–	–	57.0
8-Me	–	14.9	–	18.1	22.5	–
Solvent	$CDCl_3$	CD_3CN	$CDCl_3$	CD_3CN	CD_3CN	DMSO-d_6
Refer.	*5*	*5*	*5*	*5*	*5*	*76*

Carbon	Compound				
	11	**14**	**16**	**18**	**19**
1	104.6	104.4	105.5	108.6	104.0
2	147.3	145.9	146.4	148.6	141.6
3	148.4	147.1	146.2	148.6	146.4
4	107.8	107.6	108.4	111.1	107.1
4a	129.9	110.0	127.4	130.7	109.6
5	28.6	28.1	29.1	25.9	28.4
6	39.3	39.0	51.5	55.2	39.1
8	160.0	156.4	53.9	144.1	164.0
8a	123.6	131.6	127.4	118.8	129.9
9	151.3	148.6	150.4	151.2	149.0
10	149.5	148.3	144.9	141.0	147.5
11	118.9	113.9	111.3	119.8	114.9
12	122.2	119.1	124.1	123.3	120.0

(*continued*)

TABLE IV.
Continued.

Carbon	Compound				
	11	**14**	**16**	**18**	**19**
12a	132.3	129.5	128.0	132.8	128.9
13	101.2	102.4	35.9	128.3	103.6
14	119.3	135.0	59.7	137.0	133.6
14a	135.5	123.2	130.3	121.9	122.1
OCH_2O	101.3	101.2/102.2	100.9	100.4	100.6
2-OMe	–	–	–	56.0	–
3-OMe	–	–	–	55.7	–
9-OMe	61.5	–	60.2	–	–
10-OMe	56.8	–	55.8	–	56.7
8-Me	–	–	–	–	–
Solvent	DMSO-d_6	$CDCl_3$	$CDCl_3$	$CDCl_3$	$CDCl_3$
Refer.	*324*	*64*	*223*	*223*	*77*

Carbon	Compound				
	21	**22**	**23**	**27**	**28**
1	105.3	106.1	107.7	149.3	143.0
2	145.9	146.5	147.6	148.5	146.0
3	145.7	146.4	148.9	117.3	110.3
4	108.1	108.5	109.8	110.8	118.8
4a	127.5	128.8	122.1	122.9	128.0
5	29.4	29.8	22.6	24.4	29.3
6	51.2	38.2	52.1	55.3	47.9
8	53.7	162.5	59.1	72.2	57.0
8a	128.4	123.4	120.1	122.9	127.2
9	144.9	153.0	145.6	110.2	110.3
10	150.0	150.1	151.6	146.7	145.3
11	110.8	115.2	114.1	144.1	144.8
12	123.6	122.0	123.9	108.9	115.3
12a	127.5	130.8	122.3	121.7	125.8
13	36.2	39.1	33.6	35.7	31.5
14	59.4	55.2	65.0	66.0	55.7
14a	130.6	128.7	125.2	121.2	124.8
OCH_2O	100.5	101.0	102.0	–	–
2-OMe	–	–	–	56.2	56.2
9-OMe	59.9	61.5	61.1	–	–
10-OMe	55.6	56.2	56.7	55.6	55.9
11-OMe	–	–	–	56.0	–
N-Me			50.2	–	–
Solvent	$CDCl_3$	$CDCl_3$	DMSO-d_6	$CDCl_3$	DMSO-d_6
Refer.	*99*	*100*	*102*	*107*	*105*

(*continued*)

TABLE IV.
Continued.

Carbon	Compound			
	29	**33**	**35**	**38**
1	146.7	101.1	106.8	114.9
2	145.1	145.4	145.2	143.7
3	119.8	146.0	145.0	150.4
4	113.5	106.9	110.7	109.4
4a	120.9	129.1	130.4	133.6
5	23.4	27.9	29.2	23.6
6	54.0	39.7	51.5	55.6
8	69.8	161.8	53.0	144.8
8a	120.5	122.2	116.9	117.4
9	110.8	111.6	144.0	148.0
10	145.1	146.7	143.3	149.9
11	141.7	151.6	111.8	126.5
12	108.7	113.7	121.1	123.3
12a	118.8	131.8	128.7	128.2
13	34.1	105.3	36.3	119.8
14	65.2	119.4	59.4	138.3
14a	117.2	135.9	126.0	121.4
OCH_2O	–	–	101.1	101.8
2-OMe	56.1	–	–	–
3-OMe	–	56.0	55.9	56.9
9-OMe	–	–	–	61.8
10-OMe	56.1	–	–	56.3
11-OMe	–	56.2	–	–
13-Me	–	–	–	–
Solvent	$CDCl_3$	$CDCl_3$	CD_3OD	$CDCl_3$
Refer.	*107*	*111*	*110*	*127*

Carbon	Compound					
	40	**43**	**44**	**45**	**46**	**47**
1	111.5	113.4	111.6	111.5	113.8	113.5
2	145.7	113.9	112.2	112.0	111.8	113.5
3	147.4	154.1	159.0	158.7	158.0	154.7
4	111.2	107.8	106.8	106.6	106.1	107.8
4a	121.3	132.3	132.8	132.7	132.7	132.7
5	23.8	118.6	116.9	116.8	21.0	19.9
6	61.7	137.9	137.8	137.8	50.1	50.0
8	61.8	139.4	140.1	140.0	139.1	139.1
8a	120.2	115.7	115.7	126.6	126.5	126.5
9	146.0	106.9	107.0	102.9	102.9	103.7
10	151.5	154.1	154.3	156.1	156.1	152.0

(*continued*)

TABLE IV.
Continued.

Carbon	Compound					
	40	**43**	**44**	**45**	**46**	**47**
11	113.5	113.8	113.9	113.0	113.0	114.0
12	124.3	119.8	120.0	114.5	114.5	116.5
12a	121.4	122.4	122.5	122.7	128.7	128.7
13	28.9	50.0	49.0	50.0	50.0	50.0
14	66.0	189.3	189.3	185.0	185.0	184.4
14a	121.6	129.5	129.7	129.7	128.7	128.7
3-OMe	56.3	–	57.2	57.1	57.1	–
9-OMe	61.8	–	–	–	–	–
10-OMe	56.0	–	–	57.1	57.0	–
N-Me	39.4	–	–	–	–	–
Solvent	$CDCl_3$	CD_3OD	CD_3OD	CD_3OD	CD_3OD	CD_3OD
Refer.	*134*	*141*	*141*	*141*	*141*	*141*

Carbon	Compound					
	58	**59**	**60**	**64**	**65**	**72**
1	108.6	108.6	111.2	111.9	113.9	113.2
2	146.5	148.6	144.4	144.5	151.0	143.8
3	147.5	148.6	146.3	145.4	147.4	147.6
4	114.5	111.1	111.4	110.6	111.4	113.5
4a	126.3	130.7	124.4	128.4	122.6	122.8
5	28.9	25.9	29.9	29.5	24.9	24.5
6	51.5	55.2	49.4	38.3	57.8	54.9
8	53.8	144.1	53.8	162.7	65.3	61.7
8a	127.7	118.8	124.4	123.5	120.1	125.1
9	147.5	151.2	147.7	153.1	145.5	145.7
10	143.4	141.0	149.7	150.1	145.2	150.1
11	111.4	119.8	112.1	115.3	112.5	113.5
12	124.7	123.3	112.1	122.1	123.4	114.5
12a	127.8	132.8	124.4	130.9	123.6	125.1
13	36.1	128.3	40.7	38.9	35.6	34.9
14	59.4	137.0	60.2	55.9	70.4	68.6
14a	129.5	121.9	124.4	126.8	123.4	122.0
2-OMe	58.3	55.7	55.8	–	–	–
3-OMe	57.0	56.0	55.8	55.8	55.9	57.7
9-OMe	63.0	–	56.0	61.5	60.5	–
10-OMe	–	–	56.0	56.5	56.0	57.2
N-Me	–	–	–	–	–	52.0
Solvent	$CDCl_3$	DMSO-d_6	$CDCl_3$	$CDCl_3$	$CDCl_3$	CF_3COOD
Refer.	*176*	*176*	*109*	*100*	*179*	*321*

(*continued*)

TABLE IV.
Continued.

Carbon	Compound					
	73	**74**	**79**	**80**	**81**	**82**
1	110.8	110.0	106.1	106.0	107.3	108.1
2	148.8	147.2	145.9	146.6	135.0	148.0
3	149.2	146.4	147.7	146.7	147.0	149.3
4	117.3	116.2	107.8	108.5	107.5	109.9
4a	126.4	127.7	129.1	128.6	126.5	132.5
5	27.9	29.2	29.0	29.8	29.7	28.0
6	51.9	51.8	37.8	39.1	42.0	55.4
8	57.4	54.5	161.4	162.5	162.0	54.4
8a	124.9	126.8	122.3	123.5	117.3	127.0
9	115.4	144.7	149.7	153.0	128.7	146.2
10	149.0	148.8	145.7	150.1	127.9	147.8
11	147.5	115.8	118.9	115.4	127.1	111.6
12	120.0	124.4	122.1	121.9	126.8	121.3
12a	126.4	129.2	128.2	128.7	124.6	119.0
13	35.4	36.8	37.7	38.2	33.5	35.0
14	61.3	59.9	54.4	55.2	49.4	197.0
14a	126.2	129.2	129.3	130.8	126.5	132.5
OCH_2O	–	–	100.5	101.0	100.9	102.6
2-OMe	57.4	56.1	–	–	–	–
9-OMe	–	59.6	–	61.5	–	–
10-OMe	–	–	60.5	56.2	–	56.5
N-Me	–	–	–	–	–	41.8
Solvent	C_5D_5N	C_5D_5N	$CDCl_3$	$CDCl_3$	$CDCl_3$	$CDCl_3$
Refer.	*206*	*210*	*213*	*213*	77	*110*

Carbon	Compound					
	83	**84**	**86**	**89**	**90**	**95**
1	110.9	108.9	108.3	111.3	111.0	108.8
2	149.3	147.8	143.5	147.5	147.0	149.1
3	149.6	146.7	145.3	147.4	147.0	150.1
4	116.2	114.5	105.3	108.5	108.3	110.9
4a	130.2	126.8	126.6	126.7	126.4	133.5
5	29.0	29.2	36.9	28.9	28.7	26.7
6	57.5	51.7	57.6	51.4	51.1	56.0
8	145.1	54.0	57.0	53.5	57.9	145.1
8a	119.2	127.0	132.8	121.7	124.8	118.9
9	151.5	146.7	149.6	152.0	126.7	151.8
10	145.1	143.7	147.5	112.2	113.5	144.0
11	122.8	111.7	121.2	126.8	155.9	123.6
12	125.6	125.0	120.2	120.9	114.8	126.4

(*continued*)

TABLE IV.
Continued.

Carbon	Compound					
	83	**84**	**86**	**89**	**90**	**95**
12a	128.1	128.0	137.2	136.2	135.1	128.0
13	119.2	36.3	26.3	36.7	36.6	120.5
14	134.9	59.6	150.2	59.0	59.2	137.8
14a	120.9	129.8	123.3	129.0	129.6	121.6
OCH_2O	–	–	101.4	–	–	–
2-OMe	58.3	56.1	–	56.0	55.7	56.5
9-OMe	–	–	–	55.8	55.4	56.9
10-OMe	62.9	60.8	61.9	–	–	62.0
N-Me	57.0	56.3	56.2	–	–	55.7
Solvent	$CDCl_3$	$CDCl_3$	DMSO-d_6	$CDCl_3$	$CDCl_3$	$CDCl_3$
Refer.	*223*	*210*	*95*	*5*	*5*	*127*

Carbon	Compound					
	97	**96**	**98**	**102**	**104**	**106**
1	105.6	108.6	105.6	111.3	113.1	108.1
2	147.9	143.3	149.0	144.0	147.0	146.4
3	149.2	145.2	149.2	145.0	147.7	148.1
4	111.9	111.7	107.9	110.5	112.2	110.5
4a	127.4	126.4	131.1	124.7	128.5	136.2
5	30.0	36.9	28.8	27.7	29.5	31.8
6	51.8	56.9	41.2	51.0	37.1	57.9
8	73.6	56.9	160.7	57.4	169.1	50.9
8a	114.9	132.9	118.8	124.3	124.0	118.1
9	146.5	149.9	109.0	111.7	156.9	146.1
10	149.7	148.4	153.6	143.0	134.9	145.9
11	114.6	121.1	146.3	143.3	156.3	106.7
12	118.6	120.0	111.3	114.9	106.0	125.1
12a	129.5	137.3	122.3	124.6	125.4	129.0
13	97.1	26.0	110.6	34.8	38.6	46.6
14	137.6	151.2	136.8	59.2	55.1	195.0
14a	123.5	123.3	133.4	129.2	134.5	138.2
OCH_2O	–	–	–	–	–	101.2/100.8
2-OMe	56.5	56.4	56.2	55.0	–	–
3-OMe	56.9	56.1	55.8	55.9	55.9	–
9-OMe	62.0	61.1	61.9	–	–	–
10-OMe	55.7	56.1	55.3	56.2	60.2	–
11-OMe	–	–	–	56.1	–	–
N-Me	–	–	–	–	–	41.5
Solvent	$CDCl_3$	$DMSO-d_6$	DMSO-d_6	$CDCl_3$	C_5D_5N	$CDCl_3$
Refer.	*127*	*253*	*95*	*28*	*265*	*271*

(*continued*)

TABLE IV.
Continued.

Carbon	Compound					
	107	**108**	**109**	**116**	**122**	**123**
1	108.3	106.0	107.9	108.8	105.6	109.0
2	146.5	147.0	154.3	147.2	145.1	147.3
3	147.5	147.0	113.4	147.7	146.3	148.6
4	110.0	108.5	113.0	111.1	108.4	107.1
4a	138.3	129.0	136.6	125.7	127.8	121.7
5	32.0	39.1	118.3	27.8	29.6	–
6	58.1	39.1	137.2	50.9	51.3	–
8	52.0	163.0	138.6	57.4	53.0	–
8a	117.9	122.8	122.2	124.1	117.0	–
9	111.9	152.2	106.6	112.2	146.0	144.5
10	146.3	149.5	152.5	142.9	143.3	146.7
11	145.9	115.5	119.4	143.3	106.8	108.9
12	120.5	121.4	114.0	114.6	121.0	121.0
12a	123.5	131.0	131.7	124.6	128.6	121.5
13	48.1	38.0	188.7	34.9	36.5	33.6
14	180.7	61.2	115.5	59.4	59.8	65.3
14a	140.5	129.0	131.4	128.4	130.8	124.8
OCH_2O	100.5/191.0	101.0	–	–	100.8/101.0	102.1/101.7
2-OMe	–	–	–	55.2	–	–
3-OMe	–	–	–	55.7	–	–
9-OMe	–	55.0	–	–	–	–
10-OMe	–	56.1	–	–	–	–
N-Me	42.5	–	–	–	–	50.0
Solvent	DMSO-d_6	$CDCl_3$	Me_2CO-d_6	$CDCl_3$	$CDCl_3$	CD_3OD
Refer.	*294*	*296*	*297*	*264*	*271*	*319*

Carbon	Compound						
	124	**126**	**127**	**128**	**134**	**135**	**136**
1	100.6	108.4	106.0	104.6	106.0	106.0	105.3
2	150.4	148.8	151.5	150.8	146.7	146.7	149.3
3	133.5	153.6	142.0	140.5	146.5	146.6	149.6
4	146.3	146.0	153.6	151.8	108.5	108.6	108.3
4a	114.8	122.0	123.5	121.4	128.7	128.5	130.4
5	23.1	19.3	19.0	23.6	29.8	29.6	27.4
6	50.9	53.3	52.1	51.2	38.2	38.2	55.0
8	54.1	68.1	59.9	54.0	162.4	161.9	144.2
8a	127.7	122.0	113.1	127.7	Not detected	123.7	121.5
9	150.2	152.6	151.3	150.3	149.0	152.6	141.3
10	145.0	145.2	145.7	145.1	147.3	137.2	147.6

(*continued*)

TABLE IV.
Continued.

Carbon	Compound						
	124	**126**	**127**	**128**	**134**	**135**	**136**
11	111.0	115.8	113.6	111.0	118.1	126.0	130.9
12	123.7	126.3	123.5	123.8	122.7	122.2	123.3
12a	128.6	128.5	127.1	128.7	130.5	125.4	132.6
13	36.2	35.0	33.9	36.4	39.0	39.4	120.2
14	59.5	67.9	64.8	59.5	55.3	54.9	136.7
14a	133.7	119.8	119.7	133.6	128.6	128.6	122.0
OCH_2O	–	–	–	–	101.0	101.1	101.9
2-OMe	55.9	56.7	56.1	55.9	–	–	–
3-OMe	61.0	62.1	60.7	60.6	–	–	–
4-OMe	–	–	61.7	60.9	–	–	–
9-OMe	60.2	62.1	60.9	60.2	62.3	62.1	61.2
10-OMe	55.9	56.8	56.6	56.2	–	–	–
N-Me	–	51.6	50.3	–	–	–	–
Acetato	–	–	–	–	–	169.2/20.7	–
Solvent	$CDCl_3$	CF_3COOD	$CDCl_3$	$CDCl_3$	$CDCl_3$	$CDCl_3$	$CDCl_3$
Refer.	*322*	*321*	*321*	*322*	*100*	*100*	*324*

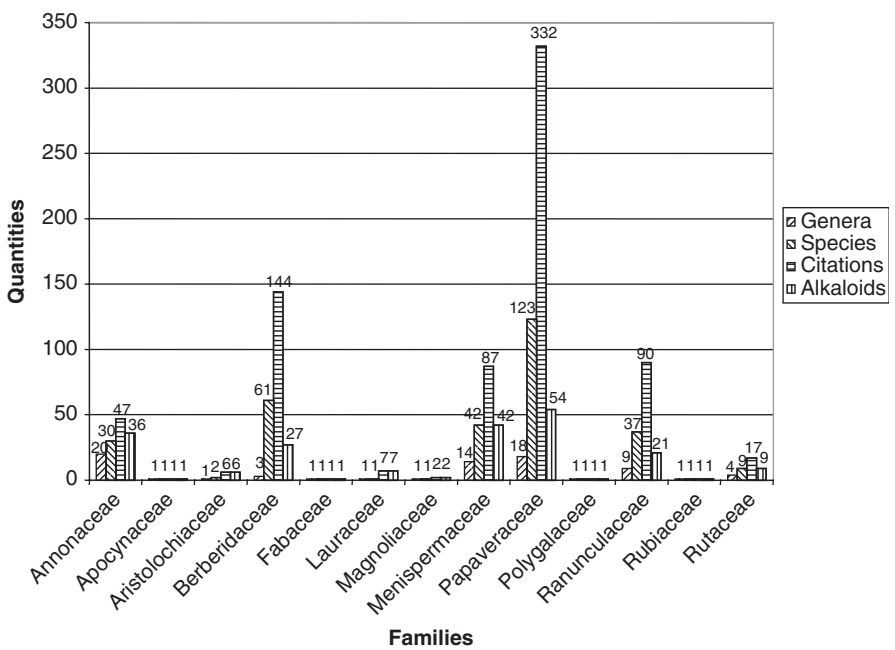


Figure 2. Families reported as producers of protoberberine alkaloids.

2. Apocynaceae

Only one plant in this family was cited as producing protoberberine alkaloids, *Alstonia macrophylla* (*12*), yielding the alkaloid berberine.

3. Aristolochiaceae

Only two species from the same genus were studied and yielded six different alkaloids.

4. Berberidaceae

From three genera of this family, a total of 61 species were studied, generating 144 citations with a total of 27 different alkaloids. The genus *Berberis* has the most significant contribution, with 126 citations from 57 species, followed by *Nandina* with 11 citations from one species, and *Mahonia* with eight citations from three species.

5. Fabaceae

Only one alkaloid from one species was described as being isolated from this family. Berberine has been reported as isolated from *Andira inermis* (*13*).

6. Lauraceae

Surprisingly, from a family known for producing many different kinds of alkaloids, only one species was reported in the literature as producing protoberberine alkaloids. From *Aniba canelilla* seven different protoberberines were isolated (*5*).

7. Magnoliaceae

Only two alkaloids were described as isolated from *Liriodendron tulipifera* (*138*).

8. Menispermaceae

This is one of the most studied families regarding the production of protoberberine alkaloids. From 42 species of 14 different genera, there are 87 citations of 42 different protoberberine alkaloids. The genus *Stephania* is the most studied, with a total of 23 species generating 42 citations, followed by the genera *Arcangelisia* (2 species), *Coscinium* (1 species), and *Fibraurea* (2 species) with 6 citations each.

9. Papaveraceae

This is by far the richest family in terms of protoberberine alkaloids. 123 species from 18 different genera were studied and produced 54 different alkaloids in 332 citations (45% of the total number of citations of this type of alkaloid in the period covered by this review). The genus *Corydalis* has the largest number of citations, with a total of 121 from 38 species, followed by *Papaver* with 95 from 29 species, and *Fumaria* with 35 citations from 17 species. *Corydalis* is the second richest single genus in terms of citations regarding protoberberine alkaloids.

10. Polygalaceae

This is another family with only one citation from a single species. The alkaloid tetrahydrocolumbamine was isolated form *Polygala tenuifolia* (*140*).

11. Ranunculaceae

This family had 37 species from nine genera studied and yielding protoberberine alkaloids. The genus with the largest contribution was *Thalictrum* with 17 species studied and 34 citations, followed by *Coptis* with 12 species and 40 citations.

12. Rubiaceae

Another family with only a single species studied. Protopine was isolated from *Galium aparine* (*283*).

13. Rutaceae

This family, from nine different species in the four genera studied, yielded a total of nine different alkaloids in 17 citations.

B. MOST CITED PROTOBERBERINE ALKALOIDS

Among the 138 protoberberine alkaloids cited in the period covered by this review, a few are more widely distributed than the others. Berberine is the most cited alkaloid with 90 citations from plants of seven families and 20 genera, followed by protopine with 85 citations from plants of four families and 16 genera. The 138 different alkaloids were found in 741 citations. Thus, berberine alone appears in 12.1% of all the publications regarding protoberberine alkaloids. It is interesting to observe that 84 alkaloids (60.4% of the total) appeared only once in the review.

Regarding the distribution between the plant families, berberine is again the most distributed protoberberine alkaloid, appearing in seven (53.8%) of the 13 plant families covered by this review.

Figure 3 shows the ten most cited protoberberine alkaloids and their distribution among the families and genera, which will be discussed below.

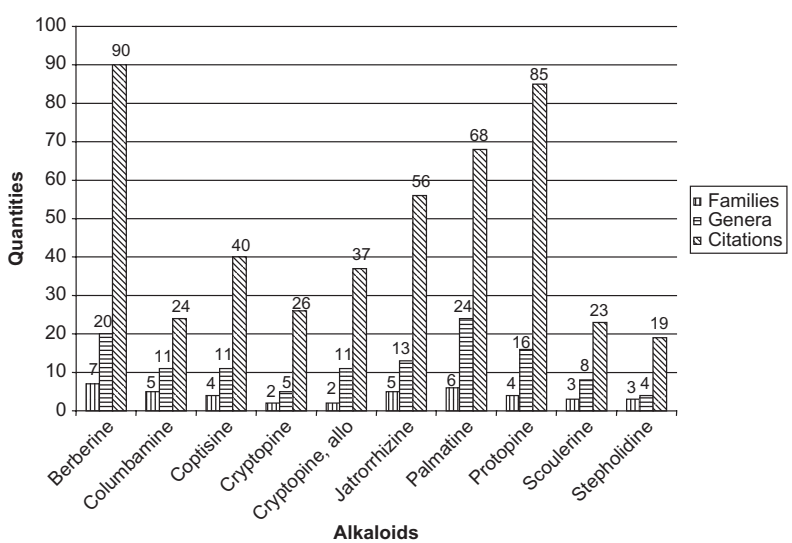
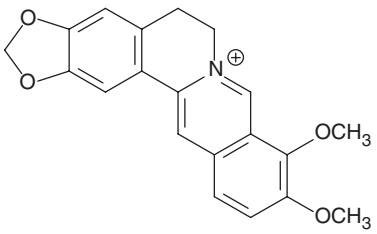


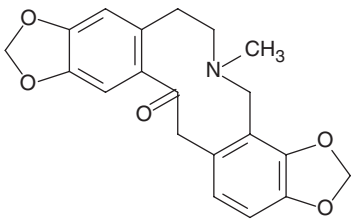
Figure 3. The ten most cited protoberberine alkaloids during the period covered by this review.

1. Berberine



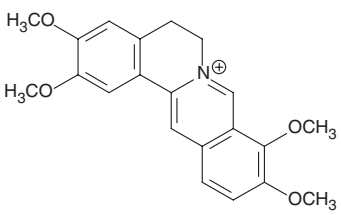
As stated above, berberine is the most cited protoberberine alkaloid in the period covered by this review. From the seven plant families from which it has been isolated, the family Berberidaceae shows the greatest number of citations, with 34 citations. It is important to note that among the 34 citations from the family, 32 were from the genus *Berberis*.

2. Protopine



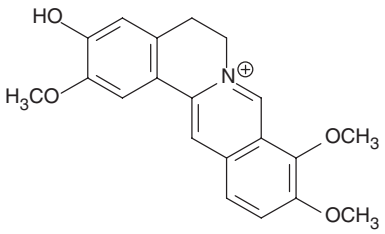
Protopine is the second most cited alkaloid in this review, with 85 citations (11.5%), from plants of four different families and 16 genera. The genus *Corydalis* with 22 citations (25.9%) has the largest contribution, followed by *Papaver* with 19 (22.4%) and *Fumaria* with 11 citations (12.9%).

3. Palmatine



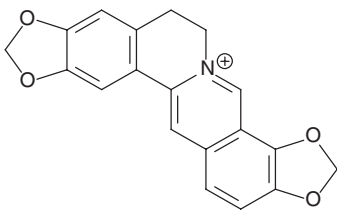
The third most cited alkaloid in this review is palmatine, appearing 68 (9.2%) times from plants in six families and 24 genera. The genus *Berberis* appears as the largest contributor with 22 citations (32.4%), followed by *Corydalis* with 12 (17.6%).

4. Jatrorrhizine



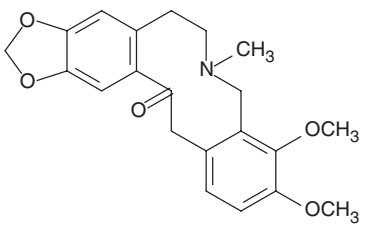
Appearing 56 times (60.7%), jatrorrhizine is the fourth most cited alkaloid in this review, where it is distributed among the plants of five families and 13 genera. The genus *Berberis*, with 34 citations, yielded more citations of this alkaloid than all other genera together. In second place, appears the genus *Coptis* with nine citations (16.1%).

5. Coptisine



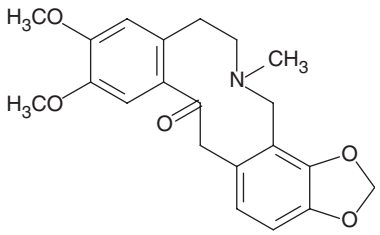
Coptisine is the fifth largest contributor to the protoberberine literature. It appears 40 times (5.4%) being isolated from plants of four different families and 11 different genera. The genera *Corydalis* and *Papaver* each have 11 citations (27.5%), followed by *Coptis* and *Fumaria* with four citations each.

6. Cryptopine, Allo



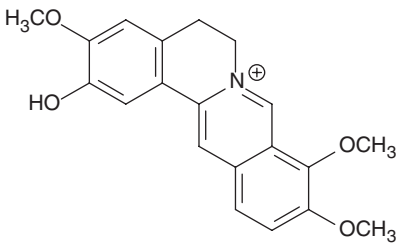
With 37 citations (4.5%) from two families and 11 genera in the period, allocryptopine is the sixth most cited protoberberine alkaloid. The genus *Papaver* with 17 citations (45.9%) is the main contributor, followed by *Corydalis* with five (13.5%), and *Arctomecon* and *Hypecoum* each with three citations (8.2%).

7. Cryptopine



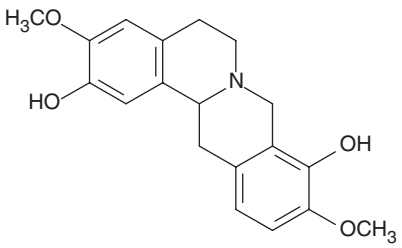
The seventh main contributor in terms of citations is cryptopine, being cited 26 times (3.5%) from plants in two families and from five genera. The main genus is *Papaver* with ten citations (38.5%), followed by *Corydalis* with six (23.1%), and *Fumaria* with five citations (19.2%).

8. Columbamine



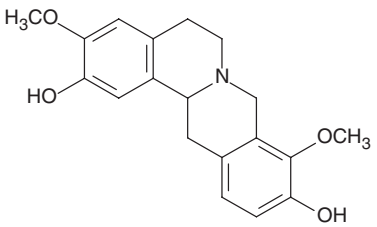
Columbamine is the eighth most cited alkaloid in this review. It appears 24 times (3.2%) from plants of five families and 11 genera. The main genus is *Berberis* with 13 citations (50.0%), followed by *Burasaia* with two (8.3%).

9. Scoulerine



With 23 citations (3.1%) from plants of three families and eight genera, scoulerine comes in ninth place in terms of citations. *Papaver* appears as the main genus with ten citations (43.5%), followed by *Argemone* with five (21.7%).

10. Stepholidine



Stepholidine is the tenth most cited alkaloid in the review, with 19 citations (2.6%) from plants in three families and four genera. The main genus is *Stephania*, responsible for 16 citations (84.2%). It was also cited from the genera *Alphonsea*, *Desmos*, and *Liriodendron*, with one citation each.

IV. Biological Activity of the Protoberberine Alkaloids

The pharmacological investigations being carried out with the protoberberine alkaloids have been showing, as the years advance, a growing and relevant number of very important biological activities.

Based on the data compiled between 1986 and 2001, one can effectively observe that very simple living systems, such as bacteria and fungi, and more complex organic systems, have shown susceptibility to the diverse biological activities exercised by the protoberberine alkaloids. This fact denotes the number of possibilities that can arise in the near future for the utilization of this class of alkaloids as tools to benefit health care, in the area of experimental pharmacology, or even as preventive or curative therapeutic agents.

The uses related so far can be classified into a number of important biological areas, as can be seen below.

A. AGAINST PATHOGENIC AGENTS

A number of different activities against pathogenic agents are already attributed to this class of alkaloids. They are used as antiseptic (*347*), antiparasitic (*357*), antitrypanosomal (*360*), insecticide (*409*), moluscicidal (*420*), antifungal (*509*), and antileishmaniasis agents (*484*), among many other activities.

B. SPECIFIC ORGANIC SYSTEMS

Another important group of activities attributed to the protoberberine alkaloids is those related to specific organic systems.

1. Central Nervous System

In the central nervous system (CNS), analgesic activity (*337*), anticonvulsant (*339*), antiamnesic (*340*), antineurotoxic (*355*), narcotic (*568*), and chemical mediators receptor blocker, such as GABAergic (*398*), have already been described. The inhibition

of various enzymes involved in very important physiological processes, are also part of the substantial series of actions provided by these alkaloids.

2. Autonomous Nervous System

Effects with the autonomous nervous system have also merited attention. Over the cardiovascular system: antiarrhythmic (*341*), antieschemic (*353*), antihemorrhagic (*348*), antifibrillatory (*346*), PAF inhibition (*435*), vasorelaxant (*449*), and hypotensive activities (*532*) are some of the important biological effects reported for the protoberberine alkaloids in the period covered by this review. Also important to mention are the metabolic effects: hypoglycemic (*351,404*), antihypercholesterolemic (*350*), bone resorption inhibition (*366*), osteoclast formation inhibition (*366*), lipase and lipogenesis inhibition (*412,414*), and prostaglandin synthesis inhibition (*438*), are a few of the reported activities related to metabolism.

3. Enzymatic System

Enzymes, such as alcohol dehydrogenase (*334*), aldehyde reductase (*334*), acetyltransferase (*364*), acetyl and butyrylcholinesterase (*328*), cytochrome P-450 (*383*), and the lipoxygenases (*415–417*), were significantly inhibited in the presence of some protoberberine alkaloids. It is also relevant to cite the large number of either blocking or activating activities over ion channels, especially the calcium and potassium channels, located in numerous cells (*367,368,411,436*), besides the actions over diverse pharmacological receptors. Agonist and antagonist activities regulating the adrenergic, cholinergic (muscarinic and nicotinic), dopaminergic, serotoninergic, and other systems have also been reported (*328,332,333,336,392,422,514*).

4. Immunologic System

Actions on the immunologic system are also described for these alkaloids: induction and inhibition of gene expression (*380,399*), antiinflammatory (*337,400*), antigenic (*347*), antioxidant (*356*), antiproliferative (*356*), antitumoral (*361*), antisystem complement (*382*), apoptosis induction (*363*), and many others.

5. Digestive System

At the level of the digestive system, some relevant actions were reported: antidiarrhetic (*344*), antiulcer (*362*), electrolyte transport inhibition (*395*), and smooth muscle relaxant effects (*472*), are some of the activities described.

As the study of the protoberberine alkaloids is continuously expanding, other biological activities will undoubtedly be either reported or evaluated in more detail in the near future, foreseeing an optimization and growth of the knowledge already consolidated. A complete list of all of the biological activities reported for the protoberberine alkaloids is presented in Table III.

V. ^{13}C NMR Data of the Protoberberine Alkaloids

^{13}C NMR spectroscopy is a very important tool for the identification or structure elucidation of organic compounds. However, among the 138 alkaloids described in the literature in the period, only 85 (61.2%) have their ^{13}C NMR data reported. The complete list of all ^{13}C NMR assignments for the alkaloids which have their data reported is presented in Table IV.

VI. Summary

Following the previous reviews published by Manske (1954), Jeffs (1967), and Bhakuni (1986), it is easy to see that the research on these alkaloids has grown substantially. This review covers the period from 1986 to 2001, and it shows that there were 589 citations describing studies on the phytochemistry and/or biological activities of 138 protoberberine alkaloids isolated from 310 plants from 13 families. Among the families cited as producers of protoberberine alkaloids, a simple analysis of Fig. 1, calls attention to the vast majority of citations from plants of the family Papaveraceae with 332 citations (45% of the total), followed by the family Berberidaceae with 144 citations (19%), and the family Ranunculaceae with 90 citations (12%). In terms of the number of different protoberberine alkaloids isolated from the families, again the family Papaveraceae comes in first place with 54 different alkaloids (39%), followed by the family Menispermaceae with 42 (30%), and the family Annonaceae with 36 (26%) different alkaloids. Chart 1 also shows that the families Apocynaceae, Fabaceae, Polygalaceae, and Rubiaceae each had only one alkaloid of this type described in the period.

Regarding the different alkaloids described in the period, analysis of Chart 2, shows that among the 138 alkaloids cited in the period, berberine comes in first place with 90 citations from 7 families and 20 genera, followed by protopine with 85 citations from 4 families and 16 genera, and palmatine from 6 families and 24 genera. A large number of alkaloids were described only once in the period.

The wide range of different biological activities described for the protoberberine alkaloids in the period is striking. Table III shows all the types of activities for which these alkaloids were evaluated. It was observed that some protoberberine alkaloids act against some pathogenic agents, with very important activities such as antiparasitic, antitrypanosomal, and antileishmaniasis. Other very important biological activities are observed on different specific organic systems. Activities such as analgesic, anticonvulsant, antiamnesic, narcotic (central nervous systems), antiarrhythmic, antihemorrhagic, hypotensive (autonomous nervous system), antiinflammatory, antioxidant, antitumoral (immunologic system), antidiarrhetic, antiulcer, smooth muscle relaxant (digestive system), not to mention many other important activities, are found for this class of alkaloids.

VII. Conclusions

The phytochemical and biological activities investigations on protoberberine alkaloids are continuously showing that this type of alkaloid could give rise to important therapeutic agents. Plants containing these alkaloids are used worldwide in traditional medicine for the treatment of numerous diseases. The results of the diverse biological evaluations performed on this class of natural products also point to their importance in terms of templates for new therapeutic agents.

Acknowledgments

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—Chapter 2—

THE *STEMONA* ALKALOIDS

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I. Introduction

The Stemonaceae (order Dioscoreales) is a small, monocotyledonous family with three small genera: *Croomia* (Southeastern North America and Japan), *Stemona* (Southeast Asia through Malaysia to North Australia), and *Stichoneuron* (Southeast Asia, including the Malay Peninsula) (*1*). Herbal extracts from various plants belonging to the Stemonaceae family have been used for the treatment of respiratory diseases and as antihelmintics in China and other East Asian countries for thousands of years. Amongst them, three species of the *Stemona* genus (*S. tuberosa*, *S. japonica*, and *S. sessilifolia*), which comprises about 25 species and represents the largest genus of the Stemonaceae family, have been officially listed in the 2000 Edition of the Chinese Pharmacopoeia as antitussive traditional Chinese medicinal herbs (*2*). Since the roots of several species are widely used as insecticides and for medicinal purposes, they are sold in local markets and herb shops. As an example, the dried roots of *S. japonica, S. sessilifolia*, or *S. tuberosa* (known as "*Bai Bu*" in traditional Chinese medicine, "*Bach Bo*" in Vietnam, or "*Non Tai Yak*" and "*Pong Mot Ngam*" in Thailand) contain several alkaloids, such as tuberostemonine, stenine, isostemonamine, stemonine, and protostemonine, and are used to suppress excitation of the respiratory center and inhibit the coughing reflex (*3–5*). The active principles are claimed to exert antituberculous, antibacterial, antifungal, and antihelminthic effects. "*Bai Bu*" displays a pesticide effect against *Pediculus capitus*, and the alcohol based extract is used as an insecticide and household spraying agent (*6*). However, because of the similarity of the fleshy tuberous roots, the same vernacular names are often used for different species, and even for representatives from other plant families. Caution is therefore recommended in order

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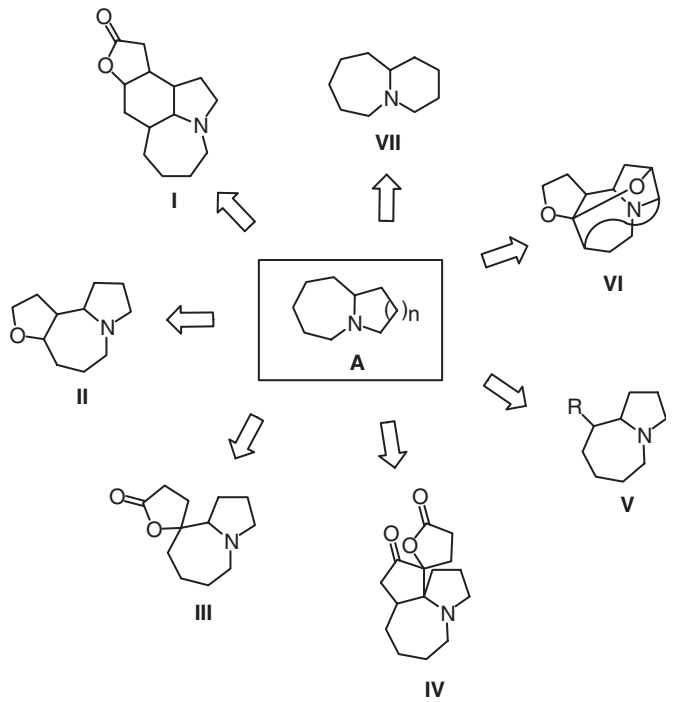


Figure 1. *Stemona* alkaloid groups.

to properly classify plant material for studies or practical applications in agriculture and medicine (*3–5*).

Despite their long history in traditional medicine, phytochemical studies on the Stemonaceae family have been limited to 14 species. Notwithstanding, these studies have provided structurally unique alkaloids which have sparked interest regarding their chemical and biological properties. Most of the *Stemona* alkaloids are structurally characterized by the presence of a pyrrolo[1,2-*a*]azepine (also known as perhydroazaazulene or 4-azaazulene) or, as revealed recently, a pyrido[1,2-*a*]azepine nucleus (Fig. 1). The *Stemona* alkaloids represent a class of polycyclic alkaloids with relatively complex structures which emerged from the structural elucidation of its first representative, tuberostemonine (Fig. 2) in the 1960s (*7*). Götz and Strunz reviewed this class of alkaloids in 1975 covering the structural elucidation of tuberostemonine, stenine, oxotuberostemonine, stemonine, protostemonine, stemofoline, and tuberostemonine A (*7*). Additionally, the physical data of 11 representatives of this family possessing unknown structures were also described. The field was reviewed again in 2000 covering literature data up to 1998 (*8*). The pyrrolo[1,2-*a*]azepine ring system is also present in alkaloid 275A which has been isolated from the skin of a Colombian poison frog, *Dendrobates lehmanni* (*9*). A limited number of *Stemona* alkaloids either lack or have a hidden pyrrolo[1,2-*a*]azepine architecture which can only be revealed on cleavage or formation of C–C bonds. This review focuses on the structural classification, isolation and structural elucidation, biological activity, and total synthesis of the *Stemona* alkaloids

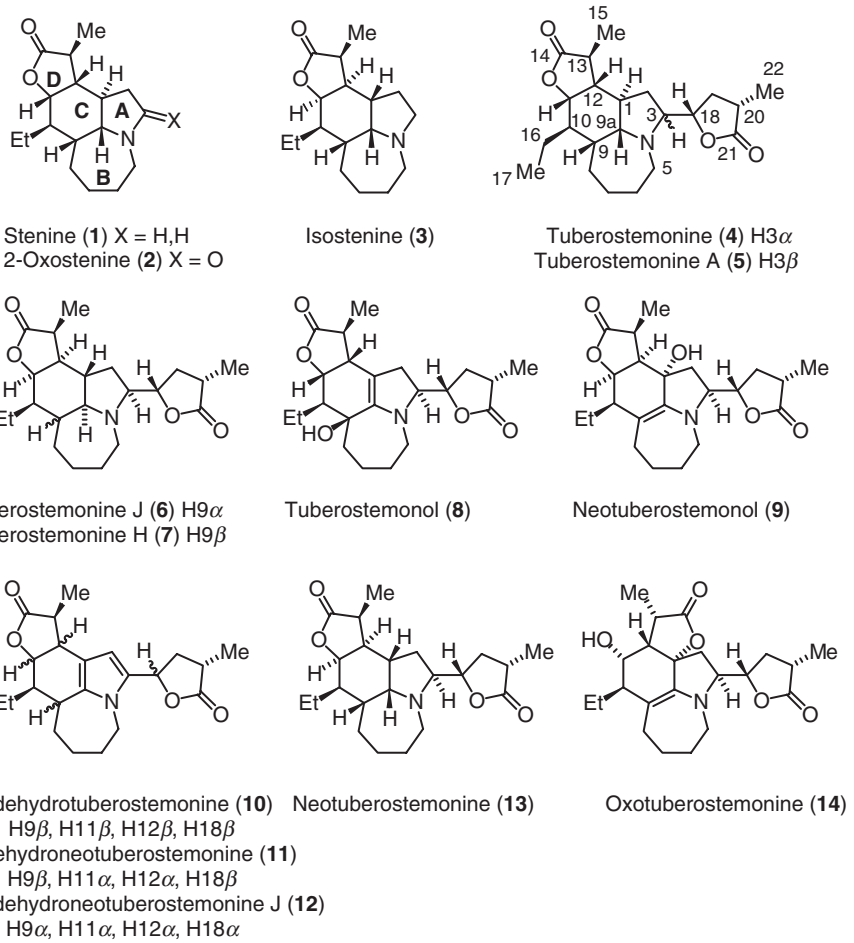


Figure 2. *Stemona* alkaloids of the stenine group (**1**–**14**).

reported so far in the literature. Although dihydrophenanthrenes and stilbenoids, particularly several phenylbenzofurans, have been isolated from *Stemona* species (*S. collinsae* and *Stemona* cf. *pierrei*) and are of interest in their own right, these compounds are not included in the present review (*10,11*).

II. Structural Classification

The *Stemona* alkaloids are structurally characterized by the presence of either an exposed or hidden pyrrolo[1,2-*a*]azepine ($n = 1$) moiety (*8*), also named perhydroazaazulene (*12*) or 4-aza-azulene (*13*), or a pyrido[1,2-*a*]azepine ($n = 2$) nucleus (**A**, Fig. 1) and currently comprises 68 alkaloids.

Xu and coworkers have previously suggested that the *Stemona* alkaloids can be separated into eight structural groups according to the sites of connection between the

basic ring and the side chain (*13*). However, these authors have only specified the maistemonine (*13*), tuberostemonine (*14*), croomine (*14*), and protostemonine (*15*) groups. Until 1998, only 42 *Stemona* alkaloids were reported in the literature, which were classified into six groups according to their structural features (*8*). Since then, 26 new *Stemona* alkaloids were isolated which led us to organize them into eight groups (Fig. 1): stenine (**I**), stemoamide (**II**), tuberostemospironine (**III**), stemonamine (**IV**), parvistemoline (**V**), stemofoline (**VI**), containing the pyrrolo[1,2-*a*]azepine nucleus characteristic of the majority of the *Stemona* alkaloids, stemocurtisine (**VII**) which displays the pyrido[1,2-*a*]azepine nucleus, and a miscellaneous group (**VIII**) either lacking or featuring a hidden pyrrolo[1,2-*a*]azepine moiety.

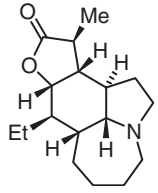
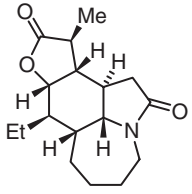
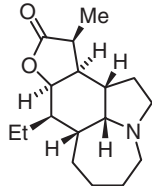
The numbering system of the structures was based on that described in the literature (*12,13,16,17*), although in some cases the numbering of some alkaloids may differ from that originally published in order to provide a consistent numbering system for all representatives in each group.

A. STENINE GROUP

The alkaloids from the stenine group can be structurally represented by the tetracyclic skeleton, furo[2,3-*h*]pyrrolo[3,2,1-*jk*][1]benzazepin-10-(2*H*)-one (**I**, Fig. 1) except for oxotuberostemonine (**14**) which features a rearranged butyrolactone ring (D ring). This group currently comprises 14 *Stemona* alkaloids: stenine (**1**) (*7,19*), 2-oxostenine (**2**) (*19*), isostenine (**3**) (*20*), also named as neostenine (*2*), tuberostemonine (**4**) (*7,12,21,22,29*), tuberostemonine A (**5**) (*7*), tuberostemonine J (**6**) (*2*), tuberostemonine H (**7**) (*2*), tuberostemonol (**8**) (*12*), neotuberostemonol (**9**) (*19,23*), didehydrotuberostemonine (**10**) (*12*), also named as bisdehydrotuberostemonine (*14*), bisdehydroneotuberostemonine (**11**) (*14,20,24*), *epi*-bisdehydroneotuberostemonine J (**12**) also designated as *epi*-bisdehydrotuberostemonine J (*2*), neotuberostemonine (**13**) (*2,14,20,23,24*), also named as tuberostemonine LG (*25*), and oxotuberostemonine (**14**) (*7,26*) (Fig. 2, Table I). Another stenine alkaloid named stemonine LG was reported in the literature (*27*), but with only partial stereochemical assignment. Later, Dao and coworkers (*25*) referring to this alkaloid as tuberostemonine LG, established its structure by X-ray analysis and showed it to be identical to neotuberostemonine (**13**).

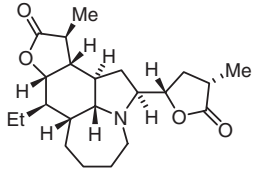
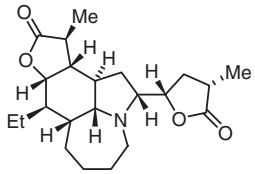
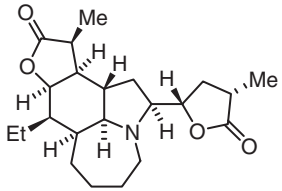
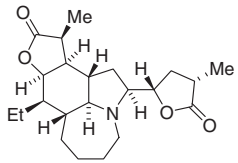
Stenine (**1**) was first isolated from the roots of *S. tuberosa* as a crystalline solid, but only partial NMR data were then reported (*18*). After completion of its total synthesis (Section III), ^{1}H- and ^{13}C-NMR data (Tables II and III) became available for stenine (**1**), although without assignments. The absolute configuration of stenine (**1**) was first established through its chemical conversion to derivatives of tuberostemonine (**4**) (*18*), whose absolute configuration was revealed after X-ray diffraction analysis (heavy-atom method) of its methobromide dihydrate ($C_{23}H_{36}NO_4Br \cdot 2H_2O$) (*7,29*) and later by asymmetric synthesis (*30,31*) (Section III). During the studies toward the elucidation of the structure of tuberostemonine (**4**) by chemical methods, Edwards and coworkers (*26*), and later Götz and coworkers (*21*), carried out its oxidation with potassium permanganate and isolated a lactam with the molecular formula $C_{17}H_{25}NO_3$, which was later also isolated from *S. sessilifolia* and assigned the structure of 2-oxostenine (**2**) (*19*). The same lactam was isolated from the oxidative cleavage of the C3–C18 bond in tuberostemonine A (**5**), thus revealing the absolute configuration depicted for tuberostemonine A (**5**) in Fig. 2 (*7*). Unfortunately, a complete set of NMR data is lacking for 2-oxostenine (**2**), as well as for tuberostemonine A (**5**).

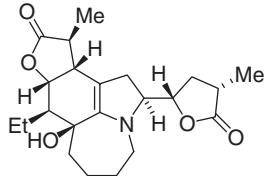
TABLE I.
Stenine Type *Stemona* Alkaloids: Occurrence and Properties.

Structure	Alkaloid/Source	Physical data
	**Stenine (1)** Source: *S. tuberosa* Lour. (roots) (*18*); *S. sessilifolia* Franch. & Sav. (roots) (*19*)	mp: 65–67°C (*18*) $[\alpha]_D = -30.2°$ (MeOH) (*18*) IR, MS, Elemental analysis (*18*) ^{1}H-NMR (partial data) (*18*)
	**2–Oxostenine (2)** Source: *S. sessilifolia* Franch. & Sav. (roots) (*19*)	not reported
	**Isostenine (3)** also named **Neostenine** Source: *S. collinsae* Craib. (roots) (*20*); *S. tuberosa* Lour. (roots) (*2*)	mp: 213–215°C (*20*) mp: 90–92°C (*2*) $[\alpha]_D = +92°$ ($CHCl_3$, $c = 0.6$) (*20*) $[\alpha]_D = +73.6°$ (20°C, MeOH, $c = 0.1$) (*2*) IR, EIMS (*2,20*) HRMS (*2,20*) ^{1}H-NMR (*2,20*) ^{13}C-NMR (*2,20*) nOe data (*20*)

(*continued*)

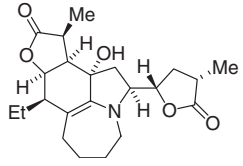
TABLE I.
Continued.

Structure	Alkaloid/Source	Physical data
	**Tuberostemonine (4)** Source: *S. tuberosa* Lour. (tissue not reported) (*7,21*); (roots) (*12*); (roots and rhizomes) (*22*); *S. sessilifolia* Franch. & Sav. (tissue not reported) (*7*)	mp: 86–88°C (*12,21*) mp: 66–68°C (for **4**.MeOH) (*21*) $[\alpha]_D = -25.4°$ (21°C, Me_2CO, $c = 0.059$) (*12*) IR, Elemental analysis (*21*) EIMS (*12*) X-ray crystallographic analysis of methobromide dihydrate (*29*)
	**Tuberostemonine A (5)** Source: *S. sessilifolia* Franch. & Sav. (rhizomes) (*7*)	not reported
	**Tuberostemonine J (6)** Source: *S. tuberosa* Lour. (roots) (*2*)	mp: 180–182°C (*2*) $[\alpha]_D = +36.4°$ (20°C, MeOH, $c = 0.1$) (*2*) HRMS, EIMS (*2*) ^{1}H-NMR (*2*) ^{13}C-NMR (*2*)
	**Tuberostemonine H (7)** Source: *S. tuberosa* Lour. (roots) (*2*)	mp: 183–185°C (*2*) $[\alpha]_D = +77.6°$ (20°C, MeOH, $c = 0.1$) (*2*) IR, HRMS, EIMS (*2*) ^{1}H-NMR (*2*) ^{13}C-NMR (*2*)



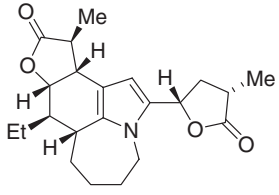
Tuberostemonol (8)
Source: *S. tuberosa* Lour. (roots) (*12*)

Amorphous (*12*) $[\alpha]_D = +33.54°$ (20°C, MeOH, $c = 0.3$) (*12*)
IR, EIMS, Elemental analysis (*12*)
^{1}H-NMR (*12*)
^{13}C-NMR (*12*)
nOe data (*12*)



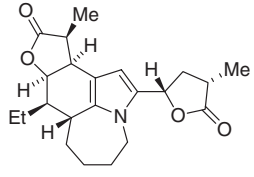
Neotuberostemonol (9)
Source: *S. tuberosa* Lour. (herbal sample) (*23*);
S. sessilifolia Franch. & Sav. (roots) (*19*)

mp: 195–197°C (*23*)
HRMS, EIMS, IR (*23*)
X-ray crystallographic analysis (*23*)
^{1}H-NMR (*23*)
^{13}C-NMR (*23*)



Didehydrotuberostemonine (10)
also named **bisdehydrotuberostemonine** (*14*)
Source: *S. tuberosa* Lour. (roots) (*12*)

mp: 176–178°C (*12*)
$[\alpha]_D = +105.96°$ (8°C, C_6H_6, $c = 0.1$) (*12*)
IR, EIMS (*12*)



Bisdehydroneotuberostemonine (11)
Source: *S. tuberosa* Lour. (roots) (*14*);
S. collinsae Craib. (roots) (*20*)

mp: 172–174°C (*14,20*)
$[\alpha]_D = -32°$ (18.5°C, EtOH, $c = 1.0$) (*14*)
$[\alpha]_D = -32°$ (25°C, EtOH, $c = 0.6$) (*20*)
IR, EIMS (*14,20*)
HRMS (*14*)
^{1}H-NMR (*14,20*)
^{13}C-NMR (*14*)
nOe data (*14*)

(*continued*)

TABLE I.
Continued.

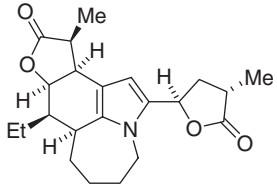
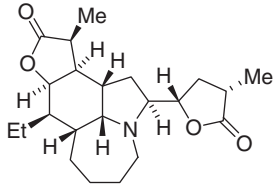
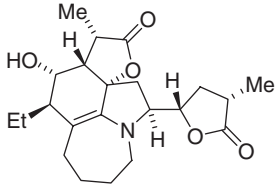
Structure	Alkaloid/Source	Physical data
	***epi*-Bisdehydroneotuberostemonine J (12)** Source: *S. tuberosa* Lour. (roots) (*2*)	mp: 186–188°C (*2*) $[\alpha]_D = -16.1°$ (20°C, MeOH, $c = 0.1$) (*2*) IR, HRMS, EIMS (*2*) ^{1}H-NMR (*2*) ^{13}C-NMR (*2*)
	**Neotuberostemonine (13)** also named **Tuberostemonine LG** (*25*) Source: *S. tuberosa* Lour. (roots) (*2,14*); (herbal sample) (*23*); *S. collinsae* Craib. (roots) (*20*)	mp: 160.5–162°C (*14,20*) mp: 160–161°C (*25*) $[\alpha]_D = +66°$ (18.5°C, EtOH, $c = 1.4$) (*14*) $[\alpha]_D = +66°$ (25°C, EtOH, $c = 0.6$) (*20*) $[\alpha]_D = +83°$ (20°C, MeOH, $c = 0.1$) (*2*) X-ray crystallographic analysis (*25*) IR, EIMS (*14,20,23*) Elemental analysis (*14*) ^{1}H-NMR (*14,20*) ^{13}C-NMR (*2,14*) nOe data (*14*)
	**Oxotuberostemonine (14)** Source: *S. sessilifolia* Franch. & Sav. (roots) (*26*); *S. tuberosa* Lour. (tissue not reported) (*7*)	mp: 217°C (*26*) IR, UV (*26*) X-ray crystallographic analysis (*32*)

TABLE II.

^{1}H-NMR Chemical Shifts (δ in ppm and multiplicity) and Coupling Constants (J, Hz) for the Stenine Alkaloid Group.

Hydrogen	**3**[i] (*20*)		**3**[i] (*2*)		**6**[i] (*2*)		**7**[i] (*2*)		**8**[i] (*12*)	
	δ	J	δ	J	δ	J	δ	J	δ	J
H1	2.65 ddd	4.0, 6.0, 10.5	1.30–2.00 m	–	1.40–2.10 m	–	1.30–2.00 m	–	–	–
H2	2.32 m	–	1.30–2.00 m	–	1.40–2.10 m	–	1.30–2.00 m	–	1.99 dd	5.5, 13.0
	1.82 m	–	–	–	–	–	–	–	1.39 dd	10.7, 13.0
H3	4.20 dt	10.0, 20.2	2.45 m	–	3.02 m	–	3.20 m	–	3.49 ddd	5.5, 7.8, 10.7
	3.03 m	–	–	–	–	–	–	–	–	–
H5	3.60 dt	5.3, 12.4	2.89 m	–	2.98 m	–	2.84 m	–	2.58 ddd	5.5, 5.5, 12.0
	2.95 m	–	2.81 m	–	2.74 m	–	2.78 m	–	2.48 ddd	2.0, 12.0, 12.0
H6	2.32 m	–	1.30–2.00 m	–	1.40–2.10 m	–	1.30–2.00 m	–	1.82 m	–
	1.95 m	–	–	–	–	–	–	–	1.56 m	–
H7	1.91 m	–	1.30–2.00 m	–	1.40–2.10 m	–	1.30–2.00 m	–	2.10 m	–
	1.62 m	–	–	–	–	–	–	–	2.00 m	–
H8	2.06 m	–	1.30–2.00 m	–	1.40–2.10 m	–	1.30–2.00 m	–	1.82 m	–
	1.70 m	–	–	–	–	–	–	–	1.56 m	–
H9	2.06 m	–	1.30–2.00 m	–	1.40–2.10 m	–	1.30–2.00 m	–	–	–
H9a	3.36 br s	–	3.22 m	–	3.02 m	–	3.01 m	–	–	–
H10	2.53 m	–	1.30–2.00 m	–	1.40–2.10 m	–	1.30–2.00 m	–	2.09 m	–
H11	4.59 t	3.1	4.50 m	–	4.46 m	–	4.57 m	–	4.67 dd	8.0, 11.2
H12	2.18 m	–	1.30–2.00 m	–	1.40–2.10 m	–	1.30–2.00 m	–	2.67 dd	8.0, 11.6
H13	2.95 m	–	2.27 m		2.74 m	–	2.61 m	–	2.26 dq	7.0, 11.6
H15	1.22 d	7.2	1.20 d	7.2	1.18 d	7.5	1.18 d	7.2	1.30 d	7.0
H16	1.70 m	–	1.30–2.00 m	–	1.40–2.10 m	–	1.30–2.00 m	–	1.72 m	–
	1.39 m	–	–	–	–	–	–	–	1.36 m	–
H17	1.02 t	7.4	0.97 t	7.5	1.01 t	7.5	1.00 t	7.2	0.99 t	7.6
H18	–	–	–	–	4.39 m	–	4.37 ddd	4.6, 5.9, 10.5	4.43 ddd	7.3, 7.5, 7.8
H19	–	–	–	–	2.25 m	–	2.35 m	–	2.15 ddd	7.5, 9.0, 13.2
	–	–	–	–	1.40–2.10 m	–	1.30–2.00 m	–	1.93 ddd	5.5, 7.3, 13.2
H20	–	–	–	–	2.50 m	–	2.45 m	–	2.67 ddq	5.5, 7.5, 9.0
H22	–	–	–	–	1.22 d	7.5	1.22 d	7.2	1.29 d	7.5

(*continued*)

TABLE II.
Continued.

Hydrogen	**9**[ii] (*23*)		**11**[i] (*14*)		**12**[i] (*2*)		**13**[i] (*14*)	
	δ	J	δ	J	δ	J	δ	J
H1	–	–	–	–	–	–	1.75 m	–
H2	2.33 m	–	5.95 s	–	5.97 s	–	1.65 m	–
	1.72 m	–	–	–	–	–	–	–
H3	3.69 dt	6.8, 10.7	–	–	–	–	3.30 dd	7.7, 14.0
H5	3.60 ddd	2.8, 4.8, 12.2	4.20 br ddd	1.0, 5.0, 15.0	4.24 m	–	3.05 dd	nr
	2.90 dd	7.6, 12.2	3.73 br dd	11.4, 15.0	3.79 m	–	2.92 dd	nr
H6	1.96 m	–	1.93 m	–	3.06 m	–	1.67 m	–
	1.54 m	–	1.30 m	–	1.16 m	–	–	–
H7	1.84 m	–	2.03 m	–	2.08 m	–	1.64 m	–
	1.36 m	–	1.45 m	–	1.47 m	–	1.48 m	–
H8	1.77 m	–	1.30 m	–	1.95 m	–	1.91 m	–
	1.51 m	–	1.10 ddd	3.2, 8.2, 11.7	–	–	1.65 m	–
H9	–	–	2.73 m	–	3.01 m	–	1.85 m	–
H9a	–	–	–	–	–	–	3.17 dd	3.8, 3.9
H10	3.22 dt	4.0, 11.4	1.90 m	–	1.47 m	–	1.72 m	–
H11	5.09 dd	4.0, 8.6	4.62 br d	5.0	4.67 m	–	4.51 dd	3.0, 3.3
H12	2.99 t	8.6	3.51 dd	5.0, 7.1	3.56 dd	5.0, 5.8	2.07 ddd	3.3, 6.7, 15.0
H13	2.40 br q	7.6	2.95 dq	7.1, 7.3	2.70–2.90 m	–	2.88 dq	6.7, 7.1
H15	1.41 d	7.6	1.30 d	7.3	1.37 d	7.0	1.23 d	7.1
H16	1.69 m	–	1.75–1.85 m	–	1.80 m	–	1.65 m	–
	–	–	–	–	–	–	1.35 m	–
H17	0.98 t	7.2	1.03 t	7.5	1.06 t	7.0	0.99 t	7.3
H18	4.25 ddd	5.6, 7.4, 10.7	5.33 dd	5.2, 11.2	5.36 dd	5.0, 11.0	4.38 ddd	5.5, 7.7, 11.2
H19	2.25 m	–	2.77 ddd	5.2, 5.4, 11.7	2.80 m	–	2.36 ddd	5.5, 13.3, 15.2
	1.47 m	–	2.15 ddd	11.2, 11.7, 11.9	2.07 m	–	1.45 dd	11.2, 15.2
H20	2.68 dq	7.0, 14.4	2.80 ddq	5.4, 6.9, 11.9	2.70–2.90 m	–	2.59 ddq	5.3, 7.0, 12.1
H22	1.19 d	7.0	1.35 d	6.9	1.35 d	7.0	1.26 d	7.0

[i] $CDCl_3$.
[ii] C_5D_5N.

TABLE III.

^{13}C-NMR Chemical Shifts (δ, ppm) for the Stenine Alkaloid Group.

Carbon	δ								
	3[i] (*20*)	**3**[i] (*2*)	**6**[i] (*2*)	**7**[i] (*2*)	**8**[i] (*12*)	**9**[ii] (*23*)	**11**[i] (*14*)	**12**[i] (*2*)	**13**[i] (*14*)
C1	36.70	39.79	38.38[iii]	41.90[vi]	114.0	77.05	107.1	108.59	37.4
C2	28.71	30.65	32.40	31.15	37.8	38.63	108.7	107.13	32.8
C3	56.04	56.44	64.59	77.97	65.4	66.73	137.7	137.58	66.6
C5	57.91	56.28	50.09	54.70	54.6	52.40	44.8	44.85	50.0
C6	25.79	28.86	33.27[iv]	27.34[vii]	30.8	26.98	28.6	35.04[ix]	29.8
C7	20.68	21.70	29.45	24.10	28.0	26.59	29.2	28.58	23.2
C8	28.58	28.67	30.62[iv]	27.10[vii]	32.1	30.09	35.1	28.88[ix]	28.9
C9	32.63	37.81	34.77	41.10	130.0	106.52	36.1	36.10[x]	36.3
C9a	72.17	71.52	66.28	67.46	121.1	151.00	127.8	126.60	66.2
C10	37.09	34.79	34.52	35.31	48.8	41.26	34.9	34.87	34.8
C11	78.28	79.87	80.28	80.67	82.7	80.37	80.8	80.89	80.4
C12	40.27	43.04	41.11	44.14	51.9	51.51	39.6	39.57	41.8
C13	42.50	43.38	45.80	47.22	36.6	38.59	41.9	41.90	42.5
C14	178.45	180.24	179.26	179.45	179.2	179.13	178.7	178.87	179.3
C15	10.16	10.67	11.60[v]	11.61[viii]	16.8	18.52	15.0	11.39[xi]	10.2
C16	21.47	21.63	25.45	21.17	26.4	21.99	23.2	23.25	21.1
C17	10.78	11.84	12.90[v]	11.88[viii]	11.5	13.11	11.4	11.88[xi]	11.2
C18	–	–	81.18	79.24	79.5	83.37	71.7	71.70	78.9
C19	–	–	34.30	33.42	32.7	34.45	30.8	30.97	34.5
C20	–	–	45.05[iii]	44.84[vi]	34.1	35.18	44.8	41.80[x]	34.9
C21	–	–	179.18	179.10	179.3	179.24	178.7	178.87	179.1
C22	–	–	14.80	15.05	16.2	15.15	11.8	14.97	14.8

[i]$CDCl_3$.
[ii]C_5D_5N.
[iii–xi]Assigned signals may be interchangeable within each pair.

Isostenine (**3**) has been isolated from *S. collinsae*, an indigenous *Stemona* species from Vietnam, the structure of which was established mainly by NMR spectroscopy (*20*). An alkaloid later isolated from *S. tuberosa* in a bioactivity-directed phytochemical analysis was named neostenine and the same structure as isostenine (**3**) was proposed (*2*). Although the same structure has been assigned to these two alkaloids, inspection of their physical [isostenine: mp 213–215°C (ref. *20*, experimental section), $[\alpha]_D = +92°$ ($CHCl_3$, $c = 0.6$); neostenine: mp 90–92°C, $[\alpha]_D = +73.6°$ (MeOH, $c = 0.1$)] and spectroscopic data (^{1}H- and ^{13}C-NMR) does not support their identity and a structural reinvestigation seems to be in order.

The structures of tuberostemonine J (**6**) and tuberostemonine H (**7**) which differ only by the stereochemistry at C-9 were assigned by spectroscopic studies, and confirmed by X-ray crystallographic analyses (*2*). While these two alkaloids display similar ^{1}H-NMR data, their ^{13}C-NMR spectra differ significantly as revealed by, among others, the deshielding of C1 (3.5 ppm), C3 (13.4 ppm), C5 (4.6 ppm), and C9 (6.3 ppm), and the shielding of C6 (5.9 ppm), C7 (5.3 ppm), and C8 (3.5 ppm) of tuberostemonine H (**7**) in comparison with the corresponding carbons in tuberostemonine J (**6**). The impressive deshielding at C3 in the ^{13}C-NMR spectrum of tuberostemonine H (**7**) is not present in its ^{1}H-NMR data which reveal a moderate deshielding effect (0.18 ppm) for H3 when compared with tuberostemonine J (**6**), and is not easily accounted for based only on structural or conformational changes.

The relative configurations of tuberostemonol (**8**) and neotuberostemonine (**13**) were established by 2D-NMR studies (*12,14*). Neotuberostemonol (**9**) was isolated from *S. tuberosa* and from *S. sessilifolia*. Its relative configuration was established by X-ray crystallographic analysis, while its absolute configuration was inferred from the known configuration of tuberostemonine (**4**) through biogenetic considerations (*23*). Inspection of the NMR data of tuberostemonol (**8**) and neotuberostemonol (**9**) reveals both H5 and one of the hydrogens at C2 deshielded in neotuberostemonol (**9**) as a result of the isomeric nature of the double bond in these two alkaloids. Additionally, significant deshielding of H10, H11, H12, and H13 in neotuberostemonol (**9**) is also observed due to the difference in the ring junction at C11–C12 and the position of the double bond. The ^{13}C-NMR data for tuberostemonol (**8**) and neotuberostemonol (**9**) display the expected differences at C1 and C9a, but the chemical shift for C9 in tuberostemonol (**8**) (130.0 ppm) is rather surprising, particularly when compared to the corresponding carbon (C1) in neotuberostemonol (**9**) (77.05 ppm). Also noteworthy are the shielding at C10 and C16 (7.5 and 4.4 ppm, respectively) and the deshielding at C18 (3.9 ppm) in neotuberostemonol (**9**) when compared to tuberostemonol (**8**).

The structure of didehydrotuberostemonine (**10**) was identified by direct comparison of its physical and chemical data with those obtained from the oxidation products of tuberostemonine (**4**), but NMR data for didehydrotuberostemonine (**10**) are not available (*12*). Comparison of the ^{1}H-NMR chemical shifts of bisdehydroneotuberostemonine (**11**), isolated from *S. tuberosa* (*14*) and from *S. collinsae* (*20*), and *epi*-bisdehydroneotuberostemonine J (**12**), isolated from bioactivity-directed fractionation of the crude extract of *S. tuberosa* and whose structure was claimed to be established by X-ray crystallographic analysis (*2*), reveals a significant deshielding effect at H5 in both alkaloids when compared to the other members of this group as a result of the ring current of the pyrrole moiety. Rather unusual is the deshielding of one of the H6 (3.06 ppm) in *epi*-bisdehydroneotuberostemonine J (**12**) which also displays H8 and

H9 as being less shielded than the corresponding hydrogens in bisdehydroneotuberostemonine (**11**). It should be noted that in another reference (*20*), H2 in bisdehydroneotuberostemonine (**11**) is wrongly reported (δ 9.96). Inspection of the ^{13}C-NMR data indicates that the largest differences in chemical shifts are for C6 [more shielded in bisdehydroneotuberostemonine (**11**)] and C8 [more shielded in *epi*-bisdehydroneotuberostemonine J (**12**)], incidentally or not, by roughly the same amount (~6 ppm). Bisdehydroneotuberostemonine (**11**) has been also isolated from *S. collinsae,* a *Stemona* species indigenous to Vietnam (*20*), and characterized by comparison of its melting point, specific optical rotation, infrared and mass spectra, and partial ^{1}H-NMR data with those reported previously, although with significant differences in the chemical shift of H2 and H12 (*14*). The stereochemistry at C10 of bisdehydroneotuberostemonine (**11**) was not depicted in the report on its original isolation (*14*), but a β-configuration of the ethyl group was indicated in subsequent reports (*20,24*).

The structure of neotuberostemonine (**13**) was solved by X-ray diffraction analysis by Dao and coworkers, who referred to this alkaloid as tuberostemonine LG (*25*). Neotuberostemonine (**13**) differs from tuberostemonine H (**7**) only by its configuration at C9a, and the most apparent differences in their ^{1}H-NMR data are for H5α and 9a, which are more deshielded in neotuberostemonine (**13**) when compared with the corresponding signals in tuberostemonine H (**7**). The differences observed in their ^{13}C-NMR data are considerably more prominent: significant shielding effects are observed for C1, C3, C5, C9, C12, C13, and C20 in neotuberostemonine (**13**), which are rather unexpected as these two alkaloids differ only by the stereochemistry at C9a.

Except for stenine (**1**), 2-oxostenine (**2**), and isostenine (**3**) also named neostenine, all the other members have an α-methyl-γ-butyrolactone ring attached to C3 in the pyrrolidine ring A. Interestingly, the configurations at C10 (ethyl group), C13 (methyl group), C18, and C20 are conserved in the whole group, except in *epi*-bisdehydroneotuberostemonine (**12**), where inversion of the C18 configuration is observed. Stenine (**1**), 2-oxostenine (**2**), tuberostemonine (**4**), tuberostemonine A (**5**), tuberostemonol (**8**), and didehydrotuberostemonine (**10**), show a *cis* relationship between H11, H12, and the methyl group at C13 in the lactone ring D, while the remaining alkaloids in this group display *cis* hydrogens at H11 and H12 disposed *trans* to the methyl group at C13. Additionally, tuberostemonine A (**5**) is the only *Stemona* alkaloid to display an inverted configuration at C3 to which the α-methyl-γ-butyrolactone ring is attached. The *cis*-B/C and *cis*-C/D ring junctions are dominant in the stenine group, except for tuberostemonine H (**7**) where rings B and C are *trans*-fused. Oxotuberostemonine (*7*) (**14**, Fig. 2) has been isolated from *S. tuberosa* and from *S. sessilifolia*, and its structure was established by X-ray diffraction analysis (*32*). NMR data for oxotuberostemonine (**14**) are still lacking in the literature. Oxotuberostemonine (**14**) possesses a structure closely related to the stenine group, but with the oxygen atom of the lactone ring D relocated from C11 to C1. Additionally, oxotuberostemonine (**14**) displays a hydroxyl group at C11 and a double bond at C9–C9a as neotuberostemonol (**9**). Except for the opposite configuration at C11, both structures can be correlated via the relocation of the γ-butyrolactone ring involving the hydroxyl groups at C1 and C11. Götz (*7*) pointed out the possibility that oxotuberostemonine (**14**) is an artifact formed by the air oxidation of tuberostemonine (**4**), since it has also been obtained from the mild oxidation of tuberostemonine (**4**) with mercuric acetate, or by air oxidation of tuberostemonine (**4**) on standing for several months, and may be isolated from the mother liquors of the crude alkaloid (*21*).

B. STEMOAMIDE GROUP

This group of *Stemona* alkaloids displays the basic tricyclic skeleton of 2*H*-furo[3,2-*c*]pyrrolo[1,2-*a*]azepine (**II**, Fig. 1), and is currently represented by 13 alkaloids (Fig. 3, Table IV): stemoamide (**15**) (*12*), stemonine (**16**) (*7,11,15,28,34*), neostemonine (**17**) (*15,24*), bisdehydroneostemonine (**18**) (*15,24,34*), protostemonine (**19**) (*7,15,36,43*), dehydroprotostemonine (**20**) (*36*), oxyprotostemonine (**21**) (*36*), didehydroprotostemonine (**22**) (*15,24,34*), isoprotostemonine (**23**) (*15,24,35*), stemocochinin (**24**) (*37*), tuberostemoamide (**25**) (*19,37,38*), sessilifoliamide A (**26**) (*19*), and stemoninine (*39–41*) (**27**) (Fig. 3). Some members of this group (**16–19**, **22**, and **23**) have been reported as protostemonine-type alkaloids (*15*). Before the isolation of neostemonine (**17**), the name neostemonine was applied to **18** (*34*), but after that the latter was changed to its

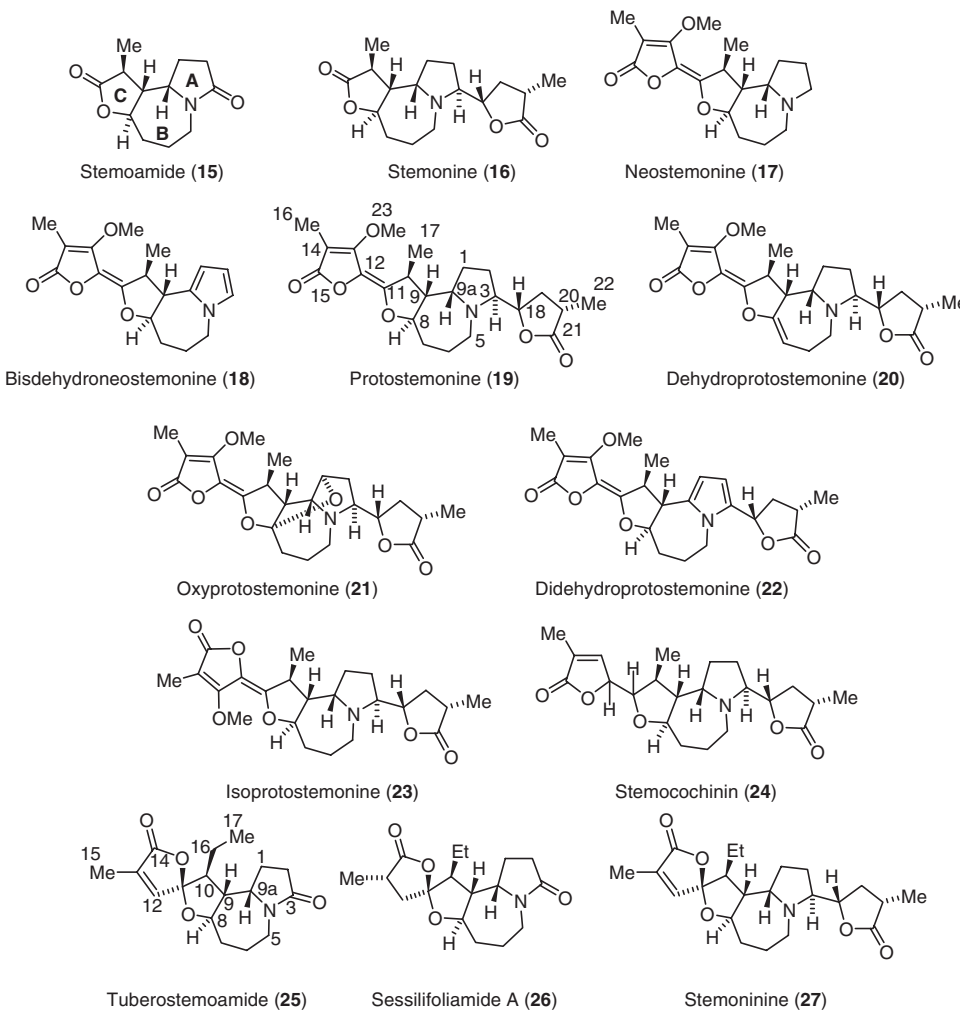
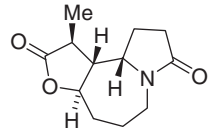
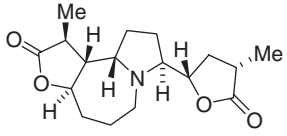
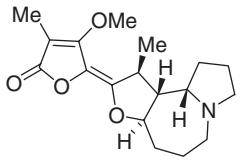
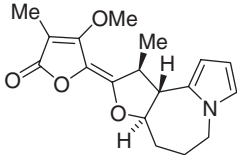


Figure 3. *Stemona* alkaloids of the stemoamide group (**15**–**27**).

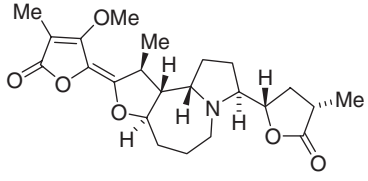
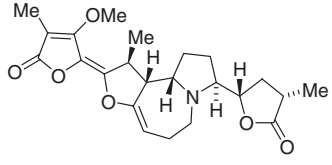
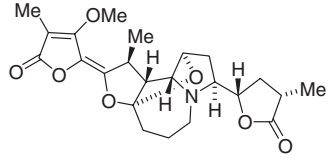
TABLE IV.

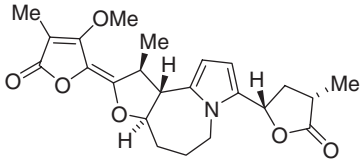
Stemoamide type *Stemona* alkaloids: Occurrence and Properties.

Structure	Alkaloid/Source	Physical data
	**Stemoamide (15)** Source: *S. tuberosa* Lour. (roots) (*12*)	Amorphous (*12*) $[\alpha]_D = -28.1°$ (21.6°C, MeOH, $c = 0.125$) (*12*) IR, HRMS, EIMS (*12*) ^{1}H-NMR (*12*) ^{13}C-NMR (*12*)
	**Stemonine (16)** Source: *S. japonica* Miq. (roots) (*7,15*); *S.* cf. *pierrei* Gagnep. (roots and rhizomes) (*11*)	mp: 148–150°C (*15*) mp: 275°C (for **16**.HBr.½H_2O (*28*) X-ray crystallographic analysis (*28*) UV (*43*) IR (*15,43*) EIMS (*15*) ^{1}H-NMR (*15*) ^{13}C-NMR (*33*)
	**Neostemonine (17)** Source: *S. japonica* Miq. (roots) (*15*)	mp: 198–200°C (for **17**.HCl) (*15*) $[\alpha]_D = +245°$ (EtOH, $c = 1.3$) (*15*) EIMS, FABMS, IR (*15*) ^{1}H-NMR (*15*) ^{13}C-NMR (*15*) Elemental analysis (*15*)
	**Bisdehydroneostemonine (18)** previously named **Neostemonine** Source: *S. japonica* Miq. (roots) (*15,34*)	mp: 218–221°C (*15,34*) $[\alpha]_D = +187°$ (EtOH, $c = 0.033$) (*15,34*) IR (*15,34*) EIMS (*15*) HRMS (*34*) ^{1}H-NMR partial data (*34*) ^{1}H-NMR (*15*) ^{13}C-NMR (*15,34*)

(*continued*)

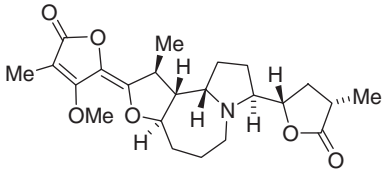
TABLE IV.
Continued.

Structure	Alkaloid/Source	Physical data
	**Protostemonine (19)** Source: *S. japonica* Miq. (roots) (*7,15,34*); *S. kerrii* Craib. (roots) (*36*); *S. cochinchinensis* Gagnep. (roots) (*36*); *S. mairei* (tissue not reported) (*35*); *S.* cf. *pierrei* (roots and rhizomes) (*11*)	mp: 170–172°C (*15*) X-ray crystallographic analysis (*36,44*) UV (*36,43*) IR (*15,36,43*) EIMS (*15*) ^{1}H-NMR (*15,36*) ^{13}C-NMR (*15,36*)
	**Dehydroprotostemonine (20)** Source: *S. kerrii* Craib. (roots) (*36*); *S. curtisii* Hook.f. (roots) (*36*)	Amorphous (*36*) $[\alpha]_D = +72°$ (20°C, MeOH, $c = 0.3$) (*36*) IR, EIMS, HRMS, UV (*36*) ^{1}H-NMR (*36*) ^{13}C-NMR (*36*)
	**Oxyprotostemonine (21)** Source: *S. kerrii* Craib. (roots) (*36*); *S. curtisii* Hook.f. (roots) (*36*)	Amorphous (*36*) $[\alpha]_D = +142°$ (20°C, MeOH, $c = 0.2$) (*36*) IR, EIMS, HREIMS, UV (*36*) ^{1}H-NMR (*36*) ^{13}C-NMR (*36*)



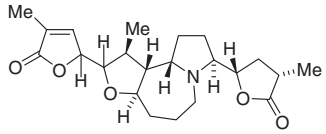
Didehydroprotostemonine (22) (*34*)
also named **Bisdehydroprotostemonine** (*15*)
Source: *S. japonica* Miq. (roots) (*15,34*)

mp: 192–194°C (*15,34*)
$[\alpha]_D = +169°$ (EtOH, $c = 0.81$) (*15*)
$[\alpha]_D = +169.5°$ (EtOH, $c = 0.81$) (*34*)
IR, EIMS (*15,34*)
^{1}H-NMR (*15*)
^{13}C-NMR (*15,34*)
nOe data (*15,34*)



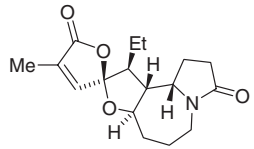
Isoprotostemonine (23)
Source: *S. japonica* Miq. (roots) (*15,34*)

mp: 165–167°C (*15,34*)
$[\alpha]_D = -23.6°$ (EtOH, $c = 0.47$) (*15,34*)
IR, EIMS (*15*)
HRMS (*15,34*)
^{1}H-NMR partial data (*34*)
^{1}H-NMR (*15*)
^{13}C-NMR (*15,34*)
nOe data (*15*)



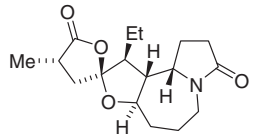
Stemocochinin (24)
Source: *S. kerrii* Craib. (roots) (*36*);
S. cochinchinensis Gagnep. (roots) (*36*);
S. curtisii Hook.f. (roots) (*36*)

Amorphous (*36*)
$[\alpha]_D = -52°$ (20°C, MeOH, $c = 0.2$) (*36*)
IR, EIMS (*36*)
^{1}H-NMR (*36*)
^{13}C-NMR (*36*)



Tuberostemoamide (25) (*37*)
also named **Stemoninoamide** (*19,38*)
Source: *S. tuberosa* Lour. (roots) (*37,38*);
S. sessilifolia Franch. & Sav. (roots) (*19*)

mp: 155–157°C (*37,38*)
$[\alpha]_D = +94°$ (MeOH, $c = 0.06$) (*37*)
$[\alpha]_D = -94°$ (MeOH, $c = 0.06$) (*38*)
EIMS (*38*)
HRMS (*37*)
IR (*37,38*)
^{1}H-NMR (*37,38*)
^{13}C-NMR (*37,38*)



Sessilifoliamide A (26)
Source: *S. sessilifolia*
Franch. & Sav. (roots) (*19*)

mp: 166–168°C (*19*)
$[\alpha]_D = -128°$ (27°C, $CHCl_3$, $c = 0.35$) (*19*)
IR, HRMS, EIMS,
X-ray crystallographic analysis (*19*)
^{1}H-NMR (*19*)
^{13}C-NMR (*19*)

current name, bisdehydroneostemonine (**18**) (*15*). Additionally, bisdehydroneostemonine (**18**) has been depicted in the literature with *cis*-fused B and C rings (*24*). Alkaloid **15** has been wrongly reported as stemonamide (*42*), while structures **22** and **25** have also been named as bisdehydroprotostemonine (*15*) and stemoninoamide (*19,38*), respectively, and on two occasions the stereochemistry at C11 was not depicted (*37,38*). Lin and coworkers have reported opposite optical rotation values ($[\alpha]_D$ $+94^\circ$ $c = 0.06$, MeOH (*37*), and $[\alpha]_D$ -94° c=0.06, MeOH (*38*)) for tuberostemoamide (**25**). The alkaloid stemoninine (**27**) was referred to as stemoninoine (*37,38*) and stemoninone (*37*).

The alkaloids **16**, **19–24**, and **27** display an α-methyl-γ-butyrolactone ring attached to C3 in the pyrrolidine ring A. Moreover, the *trans* ring fusion of the B/C rings, the *cis* relationship between the hydrogens at C9 and C9a, and the *S* absolute configuration at C10 are noteworthy stereochemical features of this group of alkaloids. The *Stemona* alkaloids **17–23** have a disubstituted lactone ring attached to ring C at C11 by a double bond. Dehydroprotostemonine (**20**) and protostemonine (**19**) differ structurally by the presence of a double bond at C7–C8 in the former. Stemocochinin (**24**) lacks the methoxy substituent at the C13 and the double bond between C11 and C12 (stereochemistry at C11 and C12 not known) in comparison with protostemonine (**19**) (*36*). Alkaloids **25–27** display a spirolactone ring fused at C11. Interestingly, these three alkaloids have an ethyl substituent at C10 instead of the methyl substituent found in the other members of this group. Surprisingly, isoprotostemonine (**23**) has the disubstituted lactone ring disposed with the opposite geometry around the exocyclic double bond when compared to the other members of the group. In fact, this is the only structural difference between protostemonine (**19**) and isoprotostemonine (**23**). Protostemonine (**19**) has been previously converted to its hydrate hydrochloride, which afforded stemoninine (**27**) on K_2CO_3 treatment or vacuum pyrolysis (*7*), and oxidation of **19** with Ag_2O afforded bisdehydroprotostemonine (**22**) (*15*). The only structural difference between tuberostemoamide (**25**) and sessilifoliamide A (**26**) resides in the absence of the double bond between C12–C13 with an α-oriented methyl group at C13 in the latter.

The relative configuration of stemoamide (**15**) was originally proposed based on comparison of its NMR data with those available for stemoninine (**27**) (*12,39*). Eventually, the structure of stemoamide (**15**) was confirmed by total synthesis (Section III), which also contributed to validate the stereochemical assignment for stemoninine (**27**).

The absolute stereochemistry of stemonine (**16**) was revealed by X-ray analysis of its hydrobromide hemihydrate by considering anomalous dispersion effects (*28*). The ^{13}C-NMR data for stemonine (**16**) has been reported without assignments (*33*).

Neostemonine (**17**) and bisdehydroneostemonine (**18**) are represented by their relative configuration obtained from NMR studies and comparison of their ^{1}H-NMR data with those of protostemonine (**19**) and didehydroprotostemonine (**22**), respectively (*15*). The structures of dehydroprotostemonine (**20**) and stemocochinin (**24**) were also established by comparison of their NMR data with those of protostemonine (**19**), while the analytical data of oxyprotostemonine (**21**) was compared with those of dehydroprotostemonine (**20**) (*36*). X-Ray crystallographic analysis unambiguously established the relative configuration of sessilifoliamide A (**26**) (*19*). The absolute configuration of sessilifoliamide A (**26**) was determined through a modified Mosher's method (*19*). Protostemonine (**19**) was described by Xu and coworkers (*15*) and its absolute

configuration was established by X-ray crystallography of its chloroform solvate (*36*), while the relative stereochemistry of stemoninine (**27**) was revealed from NMR studies (*39*). The relative configuration of didehydroprotostemonine (**22**) was obtained from the comparison of its NMR data with those of protostemonine (**19**) and isolation from the Ag_2O oxidation of protostemonine (**19**) (*15*). Comparison of the NMR data (Tables V and VI) of isoprotostemonine (**23**) and protostemonine (**19**) revealed the former alkaloid to have the relative configuration represented in Fig. 3 (*15,34*).

Tables V and VI show the ^{1}H and ^{13}C-NMR data, respectively, of the stemoamide-type *Stemona* alkaloids. Examination of the ^{1}H-NMR data for neostemonine (**17**) reveals H8 and H9a surprisingly shielded (2.57 and 2.22 ppm, respectively) (*15*) as compared to the other members of this group bearing the same structural features. Also, H9 and H10 are reported to be at 4.18 and 4.27 ppm, respectively, in neostemonine (**17**), and at 2.29 and 2.48 ppm, respectively, in stemoamide (**15**). It seems that the reassignment of the H8, H9, H9a, and H10 signals in the ^{1}H-NMR spectrum of neostemonine (**17**) is in order. Additionally, the chemical shifts and multiplicities of the signals assigned to the methyl groups (C16 and C17), and the methoxyl group in neostemonine (**17**) reported by Xu and coworkers (*15*) should be revised. Most probably, the singlet reported at 2.05 ppm is due to the methyl group at C14, while the doublet at 1.40 ppm should be assigned to the methyl group at C10.

The assignments in the ^{1}H-NMR spectrum of bisdehydroneostemonine (**18**) were not correct due to a misnumbering of the structure in the original report of its isolation (*15*), as revealed by the H10 signal which is missing, and other assignments which are clearly erroneous in the original publication.

Protostemonine (**19**) and isoprotostemonine (**23**) differ structurally by the arrangement around the double bond at C11–C12 (*Z*- and *E*-isomers, respectively), but the changes in the ^{1}H-NMR data are subtle (*15*). In the ^{13}C-NMR spectra of these two alkaloids, the chemical shifts of C10, C11, C12, and of the methyl group attached at C14 and the methoxyl group are particularly diagnostic of the two geometric isomers: C10 and C11 are about 2 ppm shielded, while the methyl group attached to C14 is 2.5 ppm deshielded in protostemonine (**19**) as compared to isoprotostemonine (**23**) (*15,34*).

The presence of a double bond at C7–C8 in dehydroprotostemonine (**20**) significantly shields C5, C9, C10, and C11 in the ^{13}C-NMR spectrum when compared to protostemonine (**19**). It is also apparent that the chemical shifts of the methyl groups at C10 and C14 have been reversed in the original assignment of the ^{13}C-NMR spectrum of dehydroprotostemonine (**20**) when compared to the corresponding signals in protostemonine (**19**) and other alkaloids bearing similar structural features, as pointed out by Greger and coworkers (*36*). The presence of an unsaturation at C7–C8 in dehydroprotostemonine (**20**) does not bring any remarkable change in its ^{1}H-NMR spectrum when compared to the parent protostemonine (**19**), except for the expected changes at H7 and its proximity (H6 and H9) (*36*).

The presence of an oxygen bridge between C1 and C8 in oxyprotostemonine (**21**) impacts more heavily on the chemical shifts of H1, H2, and H9, and one of the H5 and H19 signals in the ^{1}H-NMR spectrum when compared with the corresponding signals of protostemonine (**19**), but the differences are much clearer when one compares their ^{13}C-NMR spectra. Besides the expected deshielding at C1 and C8 for oxyprotostemonine

TABLE V.

^{1}H-NMR Chemical Shifts (δ, ppm) and Coupling Constants (J, Hz) for the Stemoamide Alkaloid Group.

Hydrogen	**15**[i] (*12*)		**16**[i] (*15*)		**17**[i,ii] (*15*)		**18**[i,ii] (*15*)		**19**[i] (*15*)	
	δ	J	δ	J	δ	J	δ	J	δ	J
H1	1.93 m	–	nr	nr	2.24 m	–	5.98 d	2.1	1.92 m	–
	1.61 m	–	nr	nr	1.85 m	–	–	–	1.55 m	–
H2	2.32 m	–	nr	nr	2.25 m	–	6.03 dd	2.1, 3.1	1.89 m	–
	–	–	nr	nr	2.05 m	–	–	–	1.48 m	–
H3	–	–	3.28 br dd	nr	3.67 ddd	nr	6.60 dd	3.1	3.27 ddd	nr
H5	4.01 ddd	2.1, 4.7, 14.2	3.51 dd	nr	3.35 m	–	4.07 dd	5.2, 10.4	3.48 dd	4.0, 15.5
	2.55 ddd	1.5, 12.5, 14.2	2.88 dd	nr	3.10 ddd	3.0, 6.4, 15.8	–	–	2.92 dd	7.1, 15.2
H6	1.75 m	–	nr	nr	3.35 m	–	3.85 dd	11.6, 14.4	1.65 m	–
	1.41 m	–	nr	nr	2.14 m	–	1.76 m	–	1.50 m	–
H7	1.62 m	–	nr	nr	1.85 m	–	2.57 m	–	2.32 m	–
	–	–	nr	nr	1.62 m	–	1.80 ddd	nr	1.50 m	–
H8	4.09 ddd	2.9, 10.2, 11.1	4.12 ddd	nr	2.57 m	–	2.07 m	–	4.08 ddd	3.4, 10.4, 14.3
H9	2.29 ddd	6.4, 11.1, 12.4	nr	nr	4.18 ddd	3.7, 10.7, 10.8	3.77 ddd	3.7, 10.3, 14.3	2.19 ddd	4.1, 9.5, 10.4
H9a	3.88 ddd	6.3, 6.4, 11.1	3.65 ddd	nr	2.22 ddd	nr	–	–	3.73 m	–
H10	2.48 dq	6.7, 12.4	nr	nr	4.27 m	–	2.91 dd	10.2, 10.3	2.89 m	–
H12	–	–	1.20 d[iii]	7.0	–	–	–	–	–	–
H13	–	–	4.17 ddd	nr	–	–	–	–	–	–
H14	–	–	2.60 m[iii]	–	–	–	–	–	–	–
H15	–	–	nr	nr	–	–	–	–	–	–
H16	–	–	nr	nr	2.91 dq	6.8, 10.1	3.49 dq	6.5, 10.2	2.04 s	–
H17	1.18 d	6.7	1.25 d[iii]	7.0	2.05 s	–	2.07 s	–	1.41 d	6.6
H18	–	–	–	–	1.40 d	6.8	1.51 d	6.5	4.15 ddd	5.4, 5.5, 11.1

H19	–	–	–	–	4.10 s	–	4.16 s	–	2.35 m	–
	–	–	–	–	–	–	–	–	1.52 m	–
H20	–	–	–	–	–	–	–	–	2.60 ddq	7.0, 8.5, 12.0
H22	–	–	–	–	–	–	–	–	1.23 d	7.0
H23	–	–	–	–	–	–	–	–	4.10 s	–

Hydrogen	**20**[i] (*36*)		**21**[i] (*36*)		**22**[i] (*15*)		**23**[i] (*15*)	
	δ	*J*	*δ*	*J*	*δ*	*J*	*δ*	*J*
H1	1.78 m	–	4.76 ddd	2.3, 2.3, 2.3	5.95 d	3.8	1.89 ddd	nr
	1.42 m	–	–	–	–	–	1.55 m	–
H2	1.88 m	–	2.25 m	–	6.13 d	3.8	1.87 m	–
	1.38 m	–	1.74 m	–	–	–	1.48 m	–
H3	3.23 ddd	6.0, 8.0, 9.0	3.31 ddd	4.0, 5.5, 9.3	–	–	3.24 ddd	7.3, 7.5, 11.5
H5	3.37 m	–	3.08 m	–	4.37 dd	5.6, 14.7	3.50 dd	4.8, 14.8
	3.34 m	–	2.97 m	–	3.82 dd	11.3, 14.7	2.89 dd	11.2, 14.8
H6	2.56 m	–	1.70 m	–	1.85 m	–	1.65 m	–
	2.10 m	–	1.44 m	–	1.55 m	–	1.50 m	–
H7	5.24 m	–	2.25 m	–	2.47 m	–	2.32 m	–
	–	–	1.74 m	–	2.10 m	–	1.50 m	–
H8	–	–	–	–	3.70 ddd	3.7, 10.2, 10.9	4.18 ddd	nr
H9	3.43 m	–	2.55 d	5.3	3.10 t	10.2	2.12 ddd	5.3, 10.3, 10.4
H9a	3.74 ddd	4.9, 4.9, 10.1	3.60 d	2.0	–	–	3.69 ddd	5.6, 10.6, 10.7
H10	2.99 dq	3.5, 7.1	3.08 m	–	3.53 dq	6.5, 10.2	3.01 dq	6.7, 10.5
H12	–	–	–	–	–	–	–	–
H13	–	–	–	–	–	–	–	–
H14	–	–	–	–	–	–	–	–
H15	–	–	–	–	–	–	–	–

(*continued*)

TABLE V.
Continued.

Hydrogen	**20**[i] (*36*)		**21**[i] (*36*)		**22**[i] (*15*)		**23**[i] (*15*)	
	δ	*J*	*δ*	*J*	*δ*	*J*	*δ*	*J*
H16	2.07 s	–	2.08 s	–	2.05 s	–	2.01 s	–
H17	1.31 d	7.1	1.37 d	7.0	1.51 d	6.5	1.32 d	6.7
H18	4.10 ddd	5.3, 8.0, 11.2	4.23 ddd	4.1, 5.6, 9.7	5.50 dd	5.2, 11.0	4.14 ddd	nr
H19	2.35 ddd	5.3, 8.6, 12.6	2.30 ddd	5.8, 9.1, 12.4	2.70 ddd	nr	2.36 ddd	nr
	1.54 ddd	11.2, 11.4, 12.6	1.80 m	–	2.15 m	–	1.52 m	–
H20	2.60 m	–	2.68 m	–	2.85 m	–	2.58 ddq	nr
H22	1.26 d	7.1	1.30 d	7.1	1.25 d	7.1	1.24 d	6.9
H23	4.14 s	–	4.15 s	–	4.25 s	–	4.10 s	–

Hydrogen	**24**[i] (*36*)		**25**[i] (*37*)		**26**[i] (*19*)		**27**[i] (*39*)	
	δ	*J*	*δ*	*J*	*δ*	*J*	*δ*	*J*
H1	1.81 m	–	1.68 m	–	1.98 m	–	1.75 m	–
	1.55 m	–	1.61 m	–	1.67 m	–	1.50 m	–
H2	1.91 m	–	2.12 m	–	2.37 m	–	1.80 m	–
	1.37 m	–	–	–	–	–	1.35 m	–
H3	3.21 ddd	6.4, 7.7, 10.1	–	–	–	–	3.25 ddd	5.5, 7.0, 10.0
H5	3.44 ddd	~1.0, 5.3, 15.6	4.05 ddd	2.9, 2.9, 14.2	3.61 brd	14.0	3.41 dd	9.0, 15.5
	2.88 ddd	~1.0, 11.1, 15.6	2.65 ddd	1.0, 12.5, 14.2	2.64 brt	12.4	2.86 dd	11.5, 15.5
H6	1.54 m	–	1.70 m	–	1.69 m	–	1.57 m	–
	1.37 m	–	1.42 m	–	1.44 m	–	1.33 m	–
H7	2.06 m	–	1.97 m	–	2.09 m	–	2.03 m	–
	1.27 m	–	1.71 m	–	1.53 m	–	1.43 m	–
H8	3.80 m	–	4.00 ddd	nr	3.90 ddd	2.6, 9.9, 10.6	3.93 ddd	3.5, 9.5, 11.0

H9	2.00 m	–	2.59 ddd	5.7, 9.6, 11.83	2.52 m	–	2.43 ddd	5.5, 9.5, 11.0
H9a	3.64 ddd	4.9, 4.9, 9.8	3.97 m	–	4.00 m	–	3.68 dt	6.0, 6.0, 9.5
H10	2.20 m	–	2.37 m	–	1.93 m	–	1.93 ddd	5.5, 7.0, 12.0
H11	3.77 m	–	–	–	–	–	–	–
H12	4.90 ddq	2.7, 2.7	6.62 d	1.5	2.36 m	–	6.59 d	2.0
	–	–	–	–	1.97 m	–	–	–
H13	7.00 dq	2.7, 2.7	–	–	2.93 m	–	–	–
H15	–	–	1.91 s	–	1.25 d	7.2	1.85 d	2.0
H16	1.95 dd	2.7, 2.7	1.42 m	–	1.56 m	–	1.60 m	–
	–	–	–	–	–	–	1.28 m	–
H17	1.08 d	6.6	0.86 t	7.6	1.01 t	7.7	0.77 t	7.5
H18	4.14 ddd	5.3, 7.9, 11.2	–	–	–	–	4.14 ddd	5.5, 7.0, 10.0
H19	2.36 ddd	5.3, 8.4, 12.6	–	–	–	–	2.31 ddd	5.5, 9.0, 12.0
	1.52 ddd	11.2, 11.5, 12.6	–	–	–	–	1.43 m	–
H20	2.60 m	–	–	–	–	–	2.54 ddq	7.0, 9.0, 12.0
H22	1.26 d	7.1	–	–	–	–	1.17 d	7.0

[i] $CDCl_3$ (nr = not reported).

[ii] The authors suggest the partial reassignment of the ^{1}H-NMR data for the alkaloid neostemonine (**17**): H8 4.18 ddd (3.7, 10.7, 10.8), H9 2.22 ddd, H9a 4.27 m, H10 2.91 dq (6.8, 10.1), H16 2.05 s, H17 1.40 d (6.8), H18 and H19 not present, and H23 4.10 s, and for the alkaloid bisdehydroneostemonine (**18**): H10 3.49 dq (6.5, 10.2), H16 2.07 s, H17 1.51 d (6.5), H18, and H19 not present, and H23 4.16 s.

[iii] Signals not assigned in Ref. *15*.

TABLE VI.
^{13}C-NMR Chemical Shifts (δ, ppm) for the Stemoamide Alkaloid Group.

Carbon	δ											
	15[i] (*12*)	**17**[i] (*15*)	**18**[i] (*15*)	**19**[i] (*34*)	**20**[i] (*36*)	**21**[i] (*36*)	**22**[i] (*15*)	**23**[i] (*15*)	**24**[i] (*36*)	**25**[i] (*37*)	**26**[i] (*19*)	**27**[i] (*39*)
C1	30.43	23.4	104.8	26.46	27.0	87.9	103.4	26.5	26.9	34.62	22.10	26.3
C2	34.84	26.8	106.6	27.23	26.7	33.0	106.9	27.2	27.0	35.71	30.80	26.5
C3	173.83	52.4	122.6	64.33	63.6	66.3	132.1	64.4	64.3	173.75	174.00	63.4
C5	40.00	49.8	49.3	46.53	43.8	50.8	45.3	46.6	47.4	40.20	40.30	45.6
C6	22.31	17.5	26.3	20.59	22.6	20.8	25.6	20.2	20.2	21.95	25.60	20.2
C7	25.45	32.6	34.1	33.65	99.7	32.4	34.1	34.3	35.4	25.49	36.10	35.3
C8	77.45	81.6	86.1	82.45	154.1	120.7	85.5	82.5	80.7	80.59	79.70	81.1
C9	52.50	52.1	52.2	55.53	47.8	57.0	51.9	54.2	55.2	49.60	52.00	52.4
C9a	55.85	60.5	128.7	58.76	65.1	69.8	129.8	58.4	59.0	56.05	56.40	58.3
C10	37.12	40.1	39.8	39.42	37.7	39.6	39.4	41.7	39.6	51.71	49.40	51.2
C11	177.21	146.9	148.7	148.90	145.8	146.7	148.4	150.8	83.4	113.53	114.60	113.5
C12	–	125.1	122.6	124.40	123.5	125.7	125.4	125.7	80.5	143.90	38.90	144.4
C13	–	163.0	165.4	163.13	163.1	162.9	163.1	163.8	146.2	134.02	34.50	133.5
C14	–	97.4	98.0	96.86	97.1	97.6	97.6	98.3	131.0	171.12	178.80	171.3
C15	–	170.0	167.9	169.92	169.9	169.8	169.9	168.5	174.4	10.40	15.20	10.3
C16	–	19.8	19.3	20.59	9.1	9.1	19.2	18.1	10.9	20.16	21.20	20.0
C17	13.87	9.1	9.2	8.97	22.4	22.0	9.1	8.5	15.9	12.74	12.90	12.7
C18	–	–	–	83.94	84.3	82.3	71.4	83.3	84.0	–	–	82.4
C19	–	–	–	34.19	34.5	34.1	34.8	34.3	34.4	–	–	34.1
C20	–	–	–	34.73	35.0	35.9	35.9	34.8	35.0	–	–	34.7
C21	–	–	–	179.14	179.5	179.3	178.7	179.2	179.6	–	–	179.1
C22	–	–	–	14.74	14.9	15.0	14.9	14.9	14.9	–	–	14.8
C23	–	60.5	58.9	58.76	59.0	58.9	58.8	59.5	–	–	–	–

[i]$CDCl_3$.

(**21**) and some other noticeable shifts in C2 to C5, the most striking change is at C9a which is remarkably deshielded (11 ppm) in oxyprotostemonine (**21**) when compared with the corresponding carbon in protostemonine (**19**).

In addition to the expected H11 (3.77 ppm) and H12 (4.90 ppm) signals in stemocochinin (**24**) which are not present in protostemonine (**19**), comparison of the ^{13}C-NMR spectra of protostemonine (**19**), and stemocochinin (**24**) reveals C7 shielded and C8 deshielded in protostemonine (**19**) while the methyl group at C10 is significantly deshielded and the one at C14 is considerably shielded in stemocochinin (**24**) when compared with the corresponding carbons in protostemonine (**19**).

Tuberostemoamide (**25**), featuring a spirobutyrolactone ring replacing the carbonyl group at C11 and an ethyl substituent at C10, displays ^{1}H-NMR data very close to the corresponding data for stemoamide (**15**), except for the signals corresponding to the ethyl substituent at C10, the olefinic hydrogen at C12, and the methyl group at C13 present in tuberostemoamide (**25**). More diagnostic signals can be found in the ^{13}C-NMR spectra of these compounds: the most striking difference is the chemical shift of C10 which is deshielded ~14 ppm (C1 and C8 are also deshielded by 3–4 ppm), while C9 is shielded by ~3 ppm in tuberostemoamide (**25**).

Comparison of the ^{1}H-NMR spectra of tuberostemoamide (**25**) and sessilifoliamide A (**26**) reveals the expected changes due to the hydrogenation of the double bond present at C12–C13 in tuberostemoamide (**25**). Differences are also observed for one of the H1 and H5 signals and at H10, H15, and H17. Besides the expected differences in the ^{13}C-NMR spectra of tuberostemoamide (**25**) in comparision with sessilifoliamide A (**26**) due to the presence of two saturated carbons at C12 and C13 in sessilifoliamide A (**26**), remarkable shielding effects at C1 (~ 12 ppm) and C2 (5 ppm) and deshielding at C7 (~ 10 ppm) in sessilifoliamide A (**26**) are observed.

Comparison of the ^{1}H-NMR spectra of tuberostemoamide (**25**) and stemoninine (**27**) reveals that in the latter, one of the H5 signals is shielded (stemoamide numbering). Significant differences are observed between their ^{13}C-NMR spectra, with the most striking one being the deshielding effect at C5 and C7, and some shielding at C1, C2, and C6 of stemoninine (**27**).

C. TUBEROSTEMOSPIRONINE GROUP

The tuberostemospironine group of *Stemona* alkaloids is characterized by a spiro[furan-2-(5*H*),9′[9*H*]pyrrolo[1,2-*a*]azepin]-5-one nucleus which displays a spiro γ-lactone at C9 of the basic ring system (**III**, Fig. 1) and is comprised of seven members: tuberostemospironine (**28**) (*12*), croomine (**29**) (*45–47*), stemospironine (**30**) (*33*), stemotinine (**31**) (*47*), isostemotinine (**32**) (*47*), stemonidine (**33**) (*7,47*), and didehydrocroomine (**34**) (*46*) (Fig. 4, Table VII). The *Stemona* alkaloids **29**, **31–33** have been reported as croomine-type alkaloids (*14*). The absolute configurations of croomine (**29**) (*45*) and stemospironine (**30**) (*33*) were established by X-ray analyses (heavy-atom method). The only structural difference between croomine (**29**) and stemospironine (**30**) is the presence of a methoxyl substituent at C8 in the latter, revealed by the extra oxygenated carbon (85.2 ppm) and the methoxyl group (58.0 ppm) in the ^{13}C-NMR spectrum of the latter. Although only partial ^{1}H-NMR data (Table VIII) are reported for stemospironine (**30**)

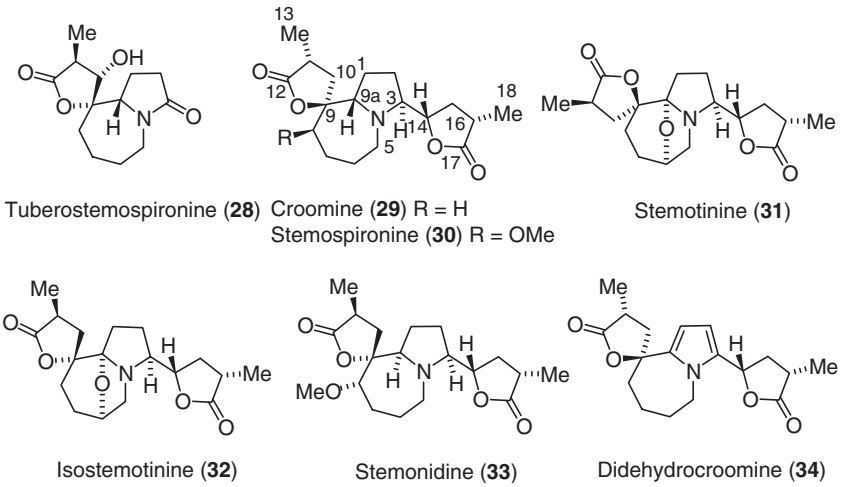


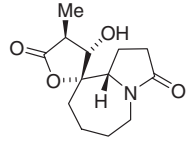
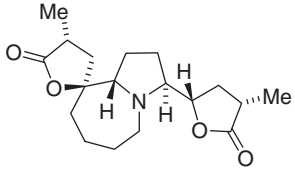
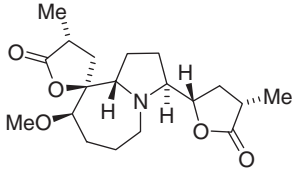
Figure 4. *Stemona* alkaloids of the tuberostemospironine group (**28**–**34**).

(*33*), comparison of its ^{13}C-NMR data (Table IX) with those described for stemonidine (**33**) (*47*) reveals remarkable coincidences to the extent that allows one to consider them identical. The possible identity of these alkaloids is reinforced by the similarities of their melting points: 283–284°C for stemospironine hydrobromide (recrystallized from methanol-ethyl acetate) (*33*) and 278°C for stemonidine hydrobromide (*47*).

The relative configurations of the alkaloids tuberostemospironine (**28**), stemotinine (**31**), and isostemotinine (**32**) were established by 2D-NMR studies. Tuberostemospironine (**28**) is the only representative of this group that bears a carbonyl group at C3, with the corresponding deshielding effects at H2 and H5 in its ^{1}H-NMR spectrum when compared with the other members. The hydroxyl group at C10 is evident from the inspection of its ^{1}H-NMR (doublet at 3.77 ppm) and ^{13}C-NMR (78.29 ppm) spectra. The presence of the spirooxygenated carbon at C9, characteristic of this group of alkaloids, is revealed by the signal at 87.52 ppm. In the ^{1}H-NMR spectrum of croomine (**29**), the presence of the α-methyl-γ-butyrolactone ring attached at C3 is apparent from the signal at 4.32 ppm, an extra methyl group (1.27 ppm) and the hydrogen at C16 (2.61 ppm). The structure of didehydrocroomine (**34**), for which only partial ^{1}H-NMR data are available (*46*), was proposed based on its formation from croomine (**29**) after Ag_2O oxidation (*46*). The structural difference between stemotinine (**31**) and isostemotinine (**32**) is the opposite configuration of the oxygenated spirocyclic carbon (C9) which imparts moderate shielding (0.51 ppm) in one of the H10 signals of isostemotinine (**32**). The presence in the ^{13}C-NMR spectra of stemotinine (**31**) and isostemotinine (**32**) of a quaternary carbon (106.9 and 106.6 ppm, respectively) attached to two heteroatoms (C9a) is a unique feature of these two alkaloids.

In this group, tuberostemospironine (**28**) is the only alkaloid which lacks the α-methyl-γ-butyrolactone ring appended to C3 of the pyrrolidine ring A. Croomine (**29**), stemospironine (**30**), stemotinine (**31**), and didehydrocroomine (**34**) display an opposite stereochemistry at C9 to that found in tuberostemospironine (**28**), isostemotinine (**32**), and stemonidine (**33**). Curiously, stemotinine (**31**) and isostemotinine (**32**) have an oxygen bridge between C9a and C6.

TABLE VII.
Tuberostemospironine type of *Stemona* alkaloids: Occurrence and Properties

Structure	Alkaloid/Source	Physical data
	**Tuberostemospironine (28)** Source: *S. tuberosa* Lour. (roots) (*12*)	mp: 245–246°C (*12*) $[\alpha]_D = -30°$ (16°C, MeOH, $c = 0.02$) (*12*) IR, EIMS, Elemental analysis (*12*) ^{1}H-NMR (*12*) ^{13}C-NMR (*12*)
	**Croomine (29)** Source: *C. heterosepala* Okuyama (roots and rhizomes) (*45*); *C. japonica* Miq. (roots) (*46*)	bp: 210–215°C (2×10^{-3} mmHg) (*45*) $[\alpha]_D = +9.8°$ (18°C, $CHCl_3$, $c = 0.11$) (*45*) $[\alpha]_D = +9.6°$ (20°C, $CHCl_3$, $c = 0.1$) (*46*) EIMS, IR (*45,46*) HRMS, UV, Elemental analysis, X-ray crystallographic analysis (*45*) ^{1}H-NMR (*45–47*) ^{13}C-NMR (*45*) Data for croomine picrate: mp: 125°C (*45*) IR, MS (*45*) Data for croomine methiodide: mp: 188°C (*45*) IR, MS (*45*)
	**Stemospironine (30)** Source: *S. japonica* Miq. (leaves and stems) (*33*)	mp: (dec) 283–284°C (for **30**.HBr) (*33*) $[\alpha]_D = -8.2°$ (27°C, $CHCl_3$, $c = 0.92$) (*33*) IR, MS, CIMS, X-ray crystallographic analysis (*33*) Elemental analysis (**30**.HBr) (*33*) ^{1}H-NMR partial data (*33*) ^{13}C-NMR (*33*)

(*continued*)

TABLE VII.
Continued.

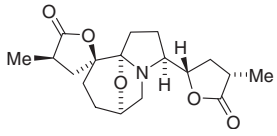
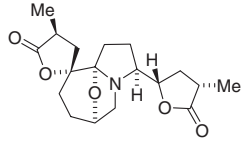
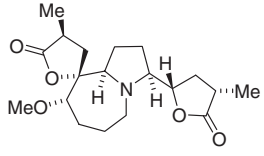
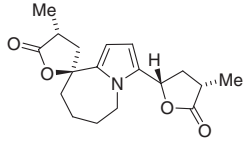
Structure	Alkaloid/Source	Physical data
	**Stemotinine (31)** Source: *S. tuberosa* Lour. (roots) (*47*)	mp: 207–208°C (*47*) $[\alpha]_D = +91.7°$ (22°C, MeOH, $c = 1.1$) (*47*) IR, CD, MS, Elemental analysis (*47*) ^{1}H-NMR (*47*) ^{13}C-NMR (*47*) nOe data (*47*)
	**Isostemotinine (32)** Source: *S. tuberosa* Lour. (roots) (*47*)	mp 245–246°C (*47*) $[\alpha]_D = +47.5°$ (22°C, MeOH, $c = 0.6$) (*47*) IR, CD (*47*) ^{1}H-NMR (*47*) ^{13}C-NMR (*47*) nOe data (*47*)
	**Stemonidine (33)** Source: *S. tuberosa* Lour. (roots) (*47*); *S. ovata* (syn. *S. japonica*) (tissue not reported) (*7*)	mp 116°C (*7*) mp 119°C (free base) (*47*) mp 278°C (for **33**.HBr) (*47*) $[\alpha]_D = -8°$ (conditions not reported) (*7*) $[\alpha]_D = -5.4°$ (24°C, acetone, $c = 0.9$) (*47*) IR, CD, HRMS (*47*) ^{1}H-NMR (*47*) ^{13}C-NMR (*47*) nOe data (*47*)
	**Didehydrocroomine (34)** Source: *C. japonica* Miq. (roots) (*46*)	mp: 172–174°C (*46*) $[\alpha]_D = +66.23°$ (31°C, MeOH, $c = 0.06$) (*46*) IR, EIMS (*46*) ^{1}H-NMR partial data (*46*)

TABLE VIII.

^{1}H-NMR Chemical Shifts (δ, ppm) and Coupling Constants (J, Hz) for the Tuberostemospironine Alkaloid Group.

Hydrogen	**28**[i] (*12*)		**31**[i] (*47*)		**32**[i] (*47*)		**33**[i] (*47*)	
	δ	J	δ	J	δ	J	δ	J
H1	1.90 m	–	1.86 m	–	1.88 m	–	nr	nr
	2.01 m	–	1.91 m	–	1.92 m	–	nr	nr
H2	2.24 m	–	1.72 m	–	1.60 m	–	nr	nr
	2.25 m	–	1.98 m	–	2.15 m	–	nr	nr
H3	–	–	2.86 ddd	5.8, 8.8, 10.8	2.93 ddd	6.1, 7.8, 10.8	3.30 ddd	6.8, 6.8, 7.4
H5	2.80 ddd	1.0, 12.7, 13.2	3.00 ddd	1.4, 6.3, 10.7	3.04 dd	6.3, 10.4	3.10 m	–
	3.83 ddd	2.9, 3.6, 13.2	3.22 d	10.7	3.20 d	10.4	–	–
H6	1.65 m	–	4.59 m	1.4, 2.0, 2.0, 6.3	4.68 ddd	2.0, 2.0, 6.3	nr	nr
	1.29 m	–	–	–	–	–	–	–
H7	1.51 m	–	1.81 m	5.9, 12.6, 13.5	nr	nr	nr	nr
	1.90 m	–	1.62 bdd	1.8, 5.4, 12.6	nr	nr	nr	nr
H8	1.57 m	–	1.55 ddt	1.8, 1.8, 5.9, 13.5	nr	nr	3.22 dd	2.4, 6.8
	–	–	2.34 dt	5.4, 13.5, 13.5	nr	nr	nr	nr
H9a	3.70 dd	6.4, 9.8	–	–	–	–	3.77 dd	6.6, 8.0
H10	3.77 d	10.2	2.61 dd	11.6, 14.6	2.10 dd	10.0, 13.1	2.47 dd	11.0, 14.0
	–	–	1.70 dd	6.3, 14.6	1.71 dd	12.6, 13.1	1.63 dd	8.0, 14.0
H11	2.49 dq	7.0, 10.2	2.81 ddq	6.3, 7.7, 11.6	2.80 ddq	7.7, 10.0, 12.6	2.71 ddq	7.8, 8.0, 11.0
H13	1.15 d	7.0	1.34 d	7.7	1.28 d	7.7	1.31 d	7.8
H14	–	–	4.26 ddd	5.4, 8.8, 11.3	4.14 ddd	5.4, 7.8, 11.3	4.38 ddd	5.4, 6.8, 11.3
H15	–	–	1.48 ddd	11.3, 12.6, 12.6	1.58 ddd	11.3, 12.6, 12.6	1.50 ddd	11.3, 12.6, 12.6
	–	–	2.36 ddd	5.4, 9.0, 12.6	2.36 ddd	5.4, 9.0, 12.6	2.38 ddd	5.4, 9.0, 12.6
H16	–	–	2.67 ddq	7.5, 9.0, 12.6	2.66 ddq	7.5, 9.0, 12.6	2.62 ddq	7.5, 9.0, 12.6
H18	–	–	1.26 d	7.5	1.28 d	7.5	1.27 d	7.5
H19	–	–	–	–	–	–	3.40 s	–

(*continued*)

TABLE VIII.
Continued.

29[i,ii] (*47*)		**30**[i,ii] (*33*)		**34**[i,ii] (*46*)	
δ	*J*	*δ*	*J*	*δ*	*J*
4.32 ddd	5.4, 6.8, 11.3	4.2–4.6 m	–	6.03 d	3.9
3.50 dd	7.8, 8.2	3.5–3.9 m	–	6.01 d	3.9
3.36 ddd	6.8, 6.8, 7.4	3.4 s	–	5.52 dd	4.0, 7.9
3.12 m	–	1.29 d	7.0	2.74 dd	4.3, 12.3
2.72 ddq	7.8, 7.9, 10.9	1.25 d	6.5	1.90 dd	12.1, 12.3
2.61 ddq	7.5, 9.0, 12.6	–	–	1.33 d	7.1
2.45 dd	10.9, 13.5	–	–	1.27 d	7.0
2.37 ddd	5.4, 9.0, 12.6	–	–	–	–
1.65 dd	7.9, 13.5	–	–	–	–
1.51 ddd	11.3, 12.6, 12.6	–	–	–	–
1.32 d	7.8	–	–	–	–
1.27 d	7.5	–	–	–	–

[i] $CDCl_3$ (nr = not reported).
[ii] The assignment of the ^{1}H-NMR data for compounds **30** and **34** not available.

TABLE IX.
^{13}C-NMR Chemical Shifts (δ, ppm) for the Tuberostemospironine Alkaloid Group.

δ					
28[i] (*12*)	**29**[i,ii] (*45*)	**30**[i,ii] (*33*)	**31**[i,ii] (*47*)	**32**[i,ii] (*47*)	**33**[i,ii] (*47*)
175.40	179.28	179.5	179.7	179.0	179.4
175.08	179.28	179.5	179.2	178.6	179.3
87.52	89.27	90.5	106.9	106.6	90.5
78.29	80.43	85.2	85.3	83.3	85.2
67.59	68.82	80.0	83.1	82.9	80.1
41.17	66.87	67.7	77.9	77.3	67.6
40.41	48.61	63.1	71.4	71.7	63.2
29.95	40.82	58.0	58.0	58.0	57.9
28.66	37.41	48.9	36.4	38.2	48.8
25.85	35.87	35.7	35.3	35.2	35.6
21.49	34.81	35.0	35.1	34.2	35.0
20.64	34.81	35.0	33.7	33.9	34.9
11.86	27.67	34.6	31.6	29.9	34.6
–	26.86	27.0	29.8	29.7	27.1
–	26.29	26.5	28.5	29.4	26.5
–	22.07	25.7	28.0	26.6	25.7
–	17.85	22.4	18.5	15.5	22.4
–	14.85	17.5	14.8	14.9	17.5
–	–	14.8	–	–	14.8

[i] $CDCl_3$.
[ii] The assignment of the ^{1}C-NMR data for compounds **29–33** not available.

D. STEMONAMINE GROUP

Previously reported as the maistemonine group (*13*), this group is characterized by the tetracyclic spiro[1*H*-cyclopenta[*b*]pyrrolo[1,2-*a*]azepine-11(10*H*),2′(5′*H*)-furan]-5′,10-dione skeleton with a spirolactone ring at C12 (**IV**, Fig. 1), and may be found in both absolute configurations. The stemonamine group includes the following *Stemona* alkaloids: stemonamine (**35**) (*13*), isostemonamine (**36**) (*13*), stemonamide (**37**) (*13,24*), isostemonamide (**38**) (*13,24*), maistemonine (**39**) (*13,35,48*), and oxymaistemonine (**40**) (*13,35,48*) (Fig. 5, Table X). The literature (*49*) also reports the name protostemotinine when referring to structure **39**, despite the difference in the melting points reported for maistemonine (**39**) (*13*) (mp 205–207°C) and protostemotinine (*49*) (mp 214–246°C). The relative configuration of protostemotinine was established by X-ray analysis (*49*). The alkaloids maistemonine (**39**) and oxymaistemonine (**40**) were first reported to display the *R* absolute configuration at C9a (*48*). Later on, their correct structures were revealed by conversion of maistemonine (**39**) to stemonamide (**37**) (*13*). Curiously, stemonamine (**35**) and isostemonamine (**36**) were identified as optically inactive alkaloids and stemonamine (**35**) displayed racemic pairs of molecules X-ray analysis (*50*).

Inspection of the ^{1}H-NMR data for stemonamine (**35**) reveals one of its H1, H3, and H6 hydrogens deshielded, and one of its H2 and H5 hydrogens shielded, compared to

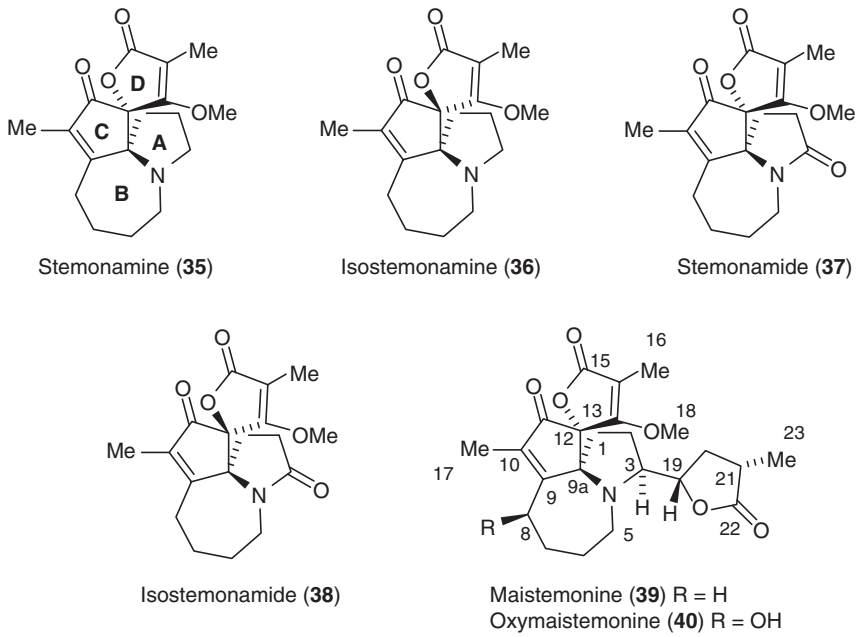


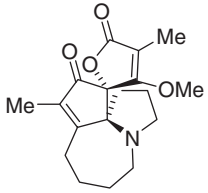
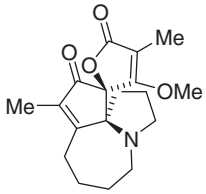
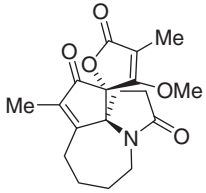
Figure 5. *Stemona* alkaloids of the stemonamine group (**35**–**40**).

the corresponding signals in isostemonamine (**36**). In the ^{13}C-NMR spectra of these two alkaloids, the most diagnostic signals are C1, C8, and C12 which are shielded (3.4, 2.3 and 3.1 ppm, respectively), and C13 and C14 which are deshielded (1.6 and 4.9 ppm, respectively) in isostemonamine (**36**). In both alkaloids, C9 displays a rather unusual chemical shift (174.7 and 176.0 ppm), and for isostemonamine (**36**) the signal corresponding to C11 is missing in its ^{13}C-NMR spectra (Tables XI and XII).

The relative configurations of stemonamide (**37**) and isostemonamide (**38**) were established by NMR studies. The ^{1}H-NMR data for stemonamide (**37**) and isostemonamide (**38**) are very similar (chemical shifts and multiplicities) and the striking difference in the chemical shifts of the two H5 signals in both of them, when compared to the other members of this group, may be attributed to the presence of the carbonyl group at C3 in these two alkaloids. The ^{13}C-NMR data shows C2, C8, and C12 deshielded and C14 shielded in stemonamide (**37**) in comparison to isostemonamide (**38**). When one compares the ^{1}H-NMR data available for stemonamine (**35**) and stemonamide (**37**), one finds in the ^{1}H-NMR spectrum of stemonamide (**37**) the expected deshielding effects at H1, H2, H5, and H7 due to the introduction of the carbonyl group at C3. In the ^{13}C-NMR spectrum, C1 and C5 are deshielded in stemonamine (**35**) when compared to the corresponding carbons in stemonamide (**37**) while a shielding effect is observed for C2, C6, C7, and C8 of stemonamine (**35**). The relative configuration of oxymaistemonine (**40**) was obtained by comparison of its NMR data with those for maistemonine (**39**), with the former displaying an extra hydroxyl group attached to C8. Their ^{13}C-NMR data are very similar, except for

TABLE X.

Stemonamine Type *Stemona* Alkaloids: Occurrence and Properties.

Structure	Alkaloid/Source	Physical data
	**Stemonamine (35)** Source: *S. japonica* Miq. (roots) (*13*,*50*)	mp: 172–174°C (*50*) mp: 148–150°C (for **35**.HCl.2H_2O) (*50*) mp: 184–190°C (for **35**.HBr.2H_2O) (*50*) mp: 169–171°C (*13*) IR, UV, X-ray crystallographic analysis (*50*) ^{1}H-NMR (*13*) ^{13}C-NMR (*13*)
	**Isostemonamine (36)** Source: *S. japonica* Miq. (roots) (*13*,*50*)	mp: 165–169°C (*50*) mp: 155–157°C (*13*) ^{1}H-NMR (*13*) ^{13}C-NMR (*13*)
	**Stemonamide (37)** Source: *S. japonica* Miq. (roots) (*13*)	mp: 182.5–184°C (*13*) $[\alpha]_D = -120°$ (EtOH, $c = 0.79$) (*13*) IR, EIMS, HRMS (*13*) ^{1}H-NMR (*13*) ^{13}C-NMR (*13*)

(*continued*)

TABLE X.
Continued.

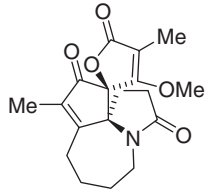
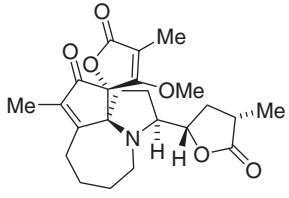
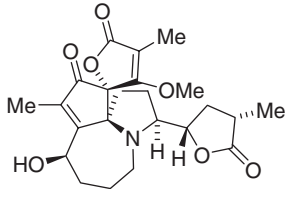
Structure	Alkaloid/Source	Physical data
	**Isostemonamide (38)** Source: *S. japonica* Miq. (roots) (*13*)	mp: 234–236°C (*13*) $[\alpha]_D = -177°$ (EtOH, $c = 0.37$) (*13*) IR, EIMS, HRMS (*13*) ^{1}H-NMR (*13*) ^{13}C-NMR (*13*) nOe data (*13*)
	**Maistemonine (39)** also named **Protostemotinine** Source: *S. mairei* K. Krause (roots) (*48*); *S. japonica* Miq. (roots) (*13*); *S. sessilifolia* Miq. (Franch. & Sav.) (roots and rhizomes) (*49*)	mp: 205–207°C (*13,48*) mp: 214–246°C (*49*) $[\alpha]_D = -28.77°$ (16°C, MeOH, $c = 0.75$) (*48*) IR, HRMS (*48,49*) X-ray crystallographic analysis (*49*) ^{1}H-NMR (*49*) ^{13}C-NMR (*48,49*)
	**Oxymaistemonine (40)** Source: *S. mairei* K. Krause (roots) (*48*)	mp: 217–219°C (*48*) $[\alpha]_D = +44.6°$ (16°C, MeOH, $c = 0.46$) (*48*) HRMS (*48*) ^{13}C-NMR (*48*)

TABLE XI.

^{1}H-NMR Chemical Shifts (δ, ppm) and Coupling Constants (J, Hz) for the Stemonamine Alkaloid Group.

Hydrogen	**35**[i] (*13*)		**36**[i] (*13*)		**37**[i] (*13*)		**38**[i] (*13*)		**39**[i] (*49*)	
	δ	J	δ	J	δ	J	δ	J	δ	J
H1	1.85 m	–	1.73 m	–	2.59 ddd	nr	2.59 dd	7.2, 13.2	2.00 dd	6.7, 11.7
	1.75 m	–	1.52 ddd	nr	1.95 ddd	nr	1.90 ddd	9.2, 12.8, 13.2	1.82 m	–
H2	1.85 m	–	2.34 dd	5.7, 12.7	2.37 dd	8.8, 14.6	2.32 ddd	9.2, 12.8, 16.4	1.82 m	–
	–	–	1.73 m	–	2.28 dd	7.9, 14.6	2.26 ddd	nr	1.41 m	–
H3	3.10 m	–	3.17 m	–	–	–	–	–	3.30 ddd	5.5, 7.6, 10.6
	3.05 ddd	nr	2.82 dd	6.3, 13.5	–	–	–	–	–	–
H5	3.10 m	–	3.17 m	–	4.18 br d	14.6	4.14 br d	10.8	3.48 br d	16.3
	2.75 m	–	3.08 dd	2.7, 15.6	2.83 br t	12.9	2.95 m	–	2.80 m	–
H6	2.10 m	–	1.75 m	–	1.82 br d	10.5	1.77 br d	10.5	1.75 m	–
	1.39 m	–	1.36 bdd	3.2, 14.3	1.40 m	–	1.36 m	–	1.42 m	–
H7	1.85 m	–	1.98 m	–	2.13 m	–	2.10 m	–	1.93 m	–
	1.20 ddd	nr	1.13 m	–	1.32 m	–	1.26 m	–	1.30 m	–
H8	2.87 ddd	nr	2.81 m	–	2.98 dd	5.7, 13.0	2.93 dd	5.6, 12.2	2.80 m	–
	2.10 m	–	1.98 m	–	2.14 m	–	2.10 m	–	2.20 m	–
H16	2.00 s	–	2.06 s	–	2.00 s	–	2.06 s	–	1.92 s	–
H17	1.76 s	–	1.73 s	–	1.85 s	–	1.74 s	–	1.69 s	–
H18	3.96 s	–	4.11 s	–	3.97 s	–	4.13 s	–	3.91 s	–
H19	–	–	–	–	–	–	–	–	3.78 ddd	5.1, 7.7, 10.8
H20	–	–	–	–	–	–	–	–	2.28 m	–
	–	–	–	–	–	–	–	–	1.43 m	–
H21	–	–	–	–	–	–	–	–	2.49 m	–
H23	–	–	–	–	–	–	–	–	1.16 d	7.0

[i] $CDCl_3$.

nr = not reported.

TABLE XII.
^{13}C-NMR Chemical Shifts (δ, ppm) for the Stemonamine Alkaloid Group.

Carbon	δ					
	35[i] (*13*)	**36**[i] (*13*)	**37**[i] (*13*)	**38**[i] (*13*)	**39**[i] (*48*)	**40**[i] (*48*)
C1	38.8	35.4	29.8	29.4	35.26	35.34
C2	26.8	27.7	31.9	29.7	25.82	25.22
C3	51.5	51.0	168.6	168.7	62.98	61.76
C5	49.0	49.2	41.3	42.4	46.72	45.15
C6	24.6	24.2	27.5	27.7	25.11	32.67
C7	24.4	24.2	27.4	26.8	24.55	32.44
C8	29.6	27.3	30.2	27.9	27.88	66.56
C9	174.7	176.0	170.8	171.7	172.15	171.80
C9a	77.4	75.4	74.6	73.5	78.89	78.05
C10	135.2	134.6	137.0	136.6	135.71	135.53
C11	198.4	–[ii]	196.5	196.9	197.29	197.20
C12	91.6	88.5	90.0	86.4	91.17	92.00
C13	171.6	173.2	170.8	172.6	172.86	173.00
C14	97.6	102.5	99.8	102.8	96.63	96.28
C15	174.7	176.0	175.7	174.6	174.09	174.10
C16	9.0	9.2	9.1	9.2	8.42	8.06
C17	8.2	8.0	8.4	8.3	7.69	8.05
C18	58.7	59.3	59.2	59.8	58.45	58.90
C19	–	–	–	–	83.54	82.52
C20	–	–	–	–	33.46	33.75
C21	–	–	–	–	34.26	35.35
C22	–	–	–	–	178.70	178.91
C23	–	–	–	–	14.48	14.43

[i]$CDCl_3$.
[ii]This signal did not appear in the ^{13}C-NMR spectrum.

C6, C7, and C8 which are deshielded in oxymaistemonine (**40**) when compared to maistemonine (**39**) (*48*). Stemonamine (**35**) and stemonamide (**37**) differ from isostemonamine (**36**) and isostemonamide (**38**), respectively, only by the absolute configuration at C12. All the members of this group show the *S* absolute configuration at C9a and the α-methyl-γ-butyrolactone ring attached to C3 is found only in the alkaloids maistemonine (**39**) and oxymaistemonine (**40**).

E. PARVISTEMOLINE GROUP

The parvistemoline alkaloids are characterized by the lack of B/C ring fusion and by the presence of a substituent attached to C9 of the [1,2-*a*]azepine nucleus. This group comprises the alkaloids parvistemoline (**41**) (*16*), parvistemonine (**42**) (*51,52*), didehydroparvistemonine (**43**) (*16*), sessilifoliamide B (**44**) (*19*), sessilifoliamide C (**45**) (*19*), sessilifoliamide D (**46**) (*19*), and neostemodiol (**47**) (*34*) (Fig. 6, Table XIII). The substituent at C9 may be either a hexahydro-2,6-dimethyl-5-oxofuro[3,2-*b*]furan-3-yl moiety

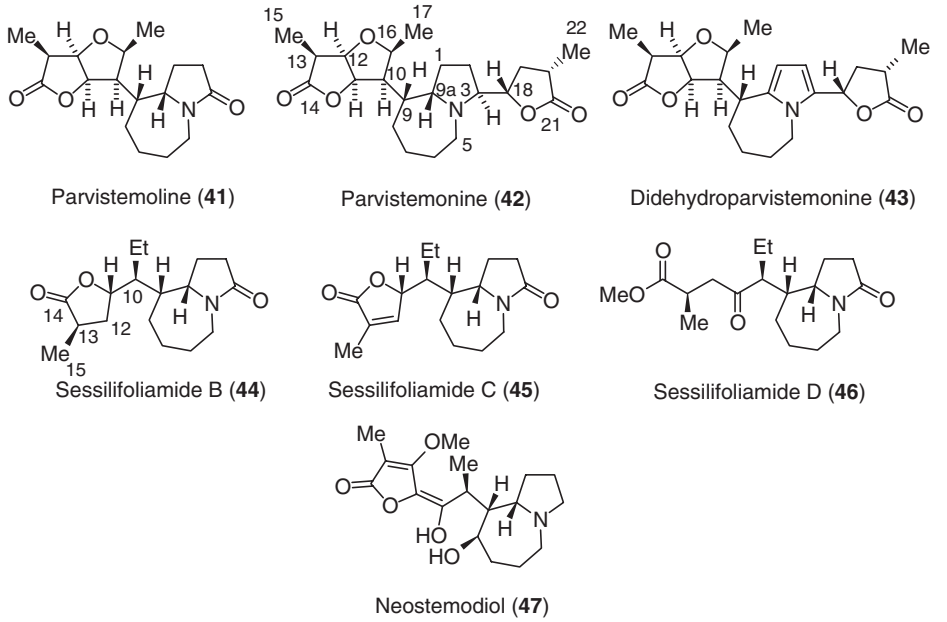


Figure 6. *Stemona* alkaloids of the parvistemoline group (**41**–**47**).

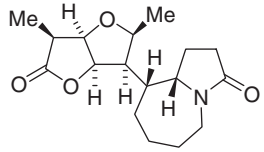
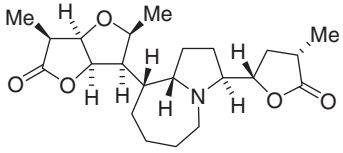
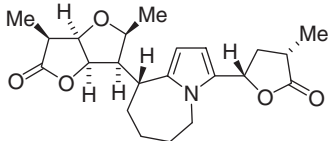
[parvistemoline (**41**), parvistemonine (**42**), and didehydroparvistemonine (**43**)], an α-methyl-γ-propyl-butyrolactone moiety with different levels of unsaturation attached directly to C9 [sessilifoliamide B (**44**), sessilifoliamide C (**45**), and neostemodiol (**47**)], or an acyclic substituent containing a γ-oxocarboxylic acid-derived motif [sessilifoliamide D (**46**)] (**V**, Fig. 1).

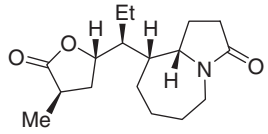
Parvistemonine (**42**) and didehydroparvistemonine (**43**) have an α-methyl-γ-lactone ring positioned at C3. The structures of these alkaloids were established by a combination of spectroscopic methods (*16*,*36*,*51*), and by oxidation of parvistemonine (**42**) to didehydroparvistemonine (**43**) with Ag_2O (*16*). The striking differences in almost all of the signals in the ^{13}C-NMR data (Table XV) of parvistemoline (**41**) and parvistemonine (**42**) ranging from less than 1 ppm (C11, C15, and C16) to 11.1 ppm (C10), compared to the chemical shift differences observed previously for alkaloids which differ only in the replacement of the carbonyl at C3 by the α-methyl-γ-butyrolactone ring, makes the current structural assignment for these alkaloids doubtful.

The aromatic nature of ring A in didehydroparvistemonine (**43**) imposes severe deshielding at C1, C2, C3, and C9a, moderate deshielding at C6, C8, C13, and C20, and significant shielding at C5, C10, and C16 when the ^{13}C-NMR spectra of didehydroparvistemonine (**43**) and parvistemonine (**42**) are compared.

The ^{1}H-NMR data (Table XIV) of sessilifoliamide B (**44**) and sessilifoliamide D (**46**) are similar, although some expected differences at H10, H12, H13, and H16, which appear more deshielded in sessilifoliamide D (**46**) as the result of the presence of the ketone functionality at C11 in sessilifoliamide D (**46**), are observed. The same trend is seen

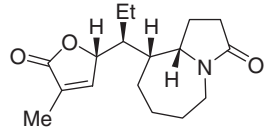
TABLE XIII.
Parvistemoline Type *Stemona* Alkaloids: Occurrence and Properties.

Structure	Alkaloid/Source	Physical data
	**Parvistemoline (41)** Source: *S. parviflora* Wright C. H. (roots) (*16*)	mp: 241–243°C (*16*) $[\alpha]_D = -24.72°$ (20°C, MeOH, $c = 0.042$) (*16*) IR, MS (*16*) ^{1}H-NMR (*16*) ^{13}C-NMR (*16*) nOe data (*16*)
	**Parvistemonine (42)** Source: *S. parviflora* Wright C. H. (roots) (*51*); *Stemona* sp. (roots) (*36*)	mp: 295–296°C (*51*) $[\alpha]_D = +26.6°$ (21.5°C, MeOH, $c = 0.456$) (*51*) CD (*51*) IR (*36,51*) HRMS (*51*) ^{1}H-NMR (*36,51*) ^{13}C-NMR (*36,51*) nOe data (*51*)
	**Didehydroparvistemonine (43)** Source: *S. parviflora* Wright C. H. (roots) (*16*)	mp: 220–222°C (*16*) $[\alpha]_D = -280°$ (20°C, MeOH, $c = 0.1$) (*16*) IR, MS (*16*) ^{1}H-NMR (*16*) ^{13}C-NMR (*16*)



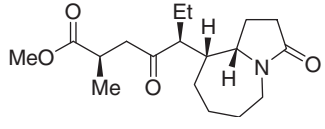
Sessilifoliamide B (44)
Source: *S. sessilifolia* Franch. & Sav. (roots) (*19*)

Colorless oil (*19*)
$[\alpha]_D = -43°$ (24°C, $CHCl_3$, $c = 0.10$) (*19*)
IR, HRMS (*19*)
^{1}H-NMR (*19*)
^{13}C-NMR (*19*)



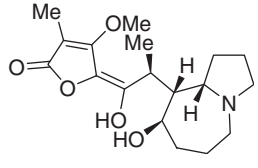
Sessilifoliamide C (45)
Source: *S. sessilifolia* Franch. & Sav. (roots) (*19*)

Colorless oil (*19*)
$[\alpha]_D = -140°$ (26°C, $CHCl_3$, $c = 0.17$) (*19*)
IR, HRMS, EIMS (*19*)
^{1}H-NMR (*19*)
^{13}C-NMR (*19*)



Sessilifoliamide D (46)
Source: *S. sessilifolia* Franch. & Sav. (roots) (*19*)

Colorless oil (*19*)
$[\alpha]_D = -94°$ (26°C, $CHCl_3$, $c = 0.16$) (*19*)
IR, HRMS, EIMS (*19*)
^{1}H-NMR (*19*)
^{13}C-NMR (*19*)



Neostemodiol (47) also named **Stemodiol**
Source: *S. japonica* Miq. (roots) (*34*)

mp: 198–200°C (*34*)
$[\alpha]_D = +245°$ (EtOH, $c = 0.13$) (*34*)
IR, EIMS (*34*)
^{13}C-NMR (*34*)

TABLE XIV.

^{1}H-NMR Chemical Shifts (δ, ppm) and Coupling Constants (J, Hz) for the Parvistemoline Alkaloid Group.

Hydrogen	**41**[i] (*16*)		**42**[i] (*36*)		**42.HBr**[ii] (*51*)		**43**[i] (*16*)	
	δ	J	δ	J	δ	J	δ	J
H1	2.23 m	–	1.74 m	–	2.04 m	–	6.07 d	3.7
	1.89 m	–	1.60 m	–	–	–	–	–
H2	2.45 m	–	1.91 m	–	2.13 m	–	5.81 d	3.7
	2.23 m	–	1.49 m	–	1.68 m	–	–	–
H3	–	–	3.49 m	–	3.79 ddd	6.5, 9.7, 11.0	–	–
H5	4.03 ddd	3.0, 3.0, 14.0	3.41 m	–	3.52 ddd	2.0, 4.0, 12.7	4.19 ddd	2.2, 2.3, 12.8
	2.63 ddd	2.3, 12.7, 14.0	2.90 ddd	<1, 11.8, 15.4	3.30 m	–	3.84 ddd	2.0, 12.0, 12.8
H6	1.45 m	–	1.71 m	–	1.80 m	–	1.98 m	–
	–	–	1.51 m	–	–	–	–	–
H7	1.45 m	–	1.76 m	–	1.80 m	–	1.24 m	–
	–	–	1.45 m	–	1.43 m	–	0.88 m	–
H8	1.72 m	–	1.78 m	–	1.94 m	–	1.57 m	–
	–	–	1.43 m	–	1.68 m	–	–	–
H9	1.73 m	–	2.19 m	–	2.25 m	–	3.10 ddd	2.5, 7.9, 10.4
H9a	3.75 ddd	5.2, 5.5, 10.7	3.44 m	–	3.72 ddd	4.3, 8.1, 12.4	–	–
H10	2.42 m	–	2.07 ddd	4.5, 7.3, 12.0	2.27 ddd	3.8, 6.8, 7.4	2.87 ddd	4.1, 7.4, 7.9
H11	4.98 dd	4.3, 4.5	5.04 dd	4.5, 4.6	4.91 dd	3.8, 3.9	5.02 dd	4.1, 4.1
H12	4.64 dd	4.5, 5.5	4.33 d	4.6	4.49 dd	3.8, 3.9	4.68 dd	4.1, 5.2
H13	2.73 dq	5.5, 6.8	2.74 q	8.1	2.72 dq	5.8, 7.2	2.74 dq	5.2, 7.4
H15	1.20 d	6.8	1.29 d	8.1	1.05 d	7.2	1.30 d	7.4
H16	4.31 dq	6.9, 7.5	4.27 dq	6.6, 7.3	4.30 dq	6.7, 6.8	4.60 dq	6.5, 7.4
H17	1.23 d	7.5	1.21 d	6.6	1.05 d	6.7	0.95 d	6.5
H18	–	–	4.21 ddd	5.5, 6.5, 11.5	4.55 ddd	5.5, 9.7, 11	5.37 dd	5.2, 11.0
H19	–	–	2.35 ddd	5.5, 8.5, 12.6	2.45 ddd	5.5, 8.4, 12.5	2.66 ddd	5.2, 8.3, 12.5
	–	–	1.56 ddd	11.5, 11.5, 12.6	1.56 ddd	11.0, 12.2, 12.5	2.19 ddd	11.0, 11.5, 12.5
H20	–	–	2.60 m	–	2.66 ddq	7.7, 8.4, 12.2	2.74 ddq	7.0, 8.3, 11.5
H22	–	–	1.26 d	7.1	1.09 d	7.7	1.33 d	7.0

Hydrogen	**44**[i] (*19*)		**45**[i] (*19*)		**46**[i] (*19*)	
	δ	*J*	*δ*	*J*	*δ*	*J*
H1	1.93 m	–	1.95 m	–	1.91 m	–
	1.68 m	–	1.67 m	–	1.63 m	–
H2	2.36 m	–	2.38 m	–	2.35 m	–
	–	–				
H5	4.05 br d	14.0	4.04 br d	13.9	4.00 br d	14.0
	2.64 br t	12.4	2.66 br t	12.3	2.65 dt	1.5, 13.5
H6	1.75 m	–	1.72 m	–	1.69 m	–
	1.46 m	–	1.45 m	–	1.40 m	–
H7	1.91 m	–	1.88 m	–	1.78 m	–
	1.25 m	–	1.34 m	–	1.25 m	–
H8	1.64 m	–	1.68 m	–	1.28 m	–
	1.38 m	–	1.35 m	–	1.13 m	–
H9	2.12 m	–	2.20 m	–	2.28 m	–
H9a	3.82 m	–	3.93 m	–	3.85 m	–
H10	1.51 m	–	1.67 m	–	2.48 m	–
H11	4.69 dt	3.6, 7.6	5.16 br d	1.9	–	–
H12	2.27 m	–	7.02 d	1.4	2.89 dd	7.9, 18.0
	1.96 m	–	–	–	2.53 dd	5.3, 18.0
H13	2.70 m	–	–	–	2.96 m	–
H15	1.30 d	7.5	1.94 d	1.5	1.18 d	7.1
H16	1.50 m	–	1.36 m	–	1.62 m	–
	–	–	1.20 m	–	–	–
H17	1.00 t	7.3	0.85 t	7.4	0.83 t	7.5
H18	–	–	–	–	3.67 s	–

[i] $CDCl_3$.
[ii] CD_3OD.

TABLE XV.
^{13}C-NMR Chemical Shifts (δ, ppm) for the Parvistemoline Alkaloid Group.

Carbon	δ							
	41[i] (*16*)	**42**[i] (*36*)	**42.HBr**[ii] (*51*)	**43**[i] (*16*)	**44**[i] (*19*)	**45**[i] (*19*)	**46**[i] (*19*)	**47**[i] (*34*)
C1	29.03	26.7	25.83	106.75	22.7	22.0	21.1	23.37
C2	30.61	26.8	26.38	106.03	30.9	30.8	30.7	26.82
C3	174.09	63.6	69.44	127.60	174.4	174.4	174.3	52.41
C5	40.73	46.3	52.75	45.06	40.6	40.6	40.7	49.79
C6	25.75	24.6	22.74	28.23	29.2	28.8	29.0	17.52
C7	22.07	27.0	27.76	28.27	29.7	29.4	29.5	32.58
C8	28.78	28.6	27.76	32.82	24.5	24.5	26.1	81.62
C9	41.21	39.4	36.34	34.54	42.9	43.3	42.4	52.10
C9a	59.56	62.8	70.25	139.43	61.2	60.8	59.4	60.54
C10	38.80	49.9	50.46	36.08	46.1	44.2	55.0	40.14
C11	83.71	84.3	84.31	83.72	79.6	82.1	211.1	146.88
C12	79.89	84.0	77.47	78.12	34.5	148.3	47.2	125.07
C13	48.30	44.8	41.88	48.78	34.5	130.4	34.2	162.97
C14	178.22	179.6	179.25	178.93	180.0	174.3	176.1	97.36
C15	19.54	19.3	19.42	18.30	16.6	10.7	17.1	170.00
C16	76.90	77.3	77.24	71.89	20.4	19.1	22.8	19.80
C17	9.90	14.9	9.17	8.94	13.6	13.3	11.0	9.11
C18	–	83.1	80.79	79.90	–	–	51.9	60.54
C19	–	34.1	35.36	34.69	–	–	–	–
C20	–	34.9	35.37	41.57	–	–	–	–
C21	–	179.5	179.35	178.32	–	–	–	–
C22	–	14.9	14.74	14.93	–	–	–	–

[i] $CDCl_3$.
[ii] CD_3OD.

in the ^{13}C-NMR spectra for C8, C10, C11, C12, and C16 which appear less shielded in sessilifoliamide D (**46**), while its C9a, C14, and C17 signals are shielded when compared to sessilifoliamide B (**44**). The differences in the ^{1}H-NMR spectra of sessilifoliamide B (**44**) and sessilifoliamide C (**45**) are mainly due to the incorporation of the unsaturation in the γ-butyrolactone ring of sessilifoliamide C (**45**): H10, H11, H12, and H15 are deshielded in sessilifoliamide C (**45**), while shielding is observed at its H17 signal (methyl group). In the ^{13}C-NMR spectra, the main diagnostic signals to distinguish between sessilifoliamide B (**44**) and sessilifoliamide C (**45**) are C11, C12, and C13, which are deshielded in sessilifoliamide C (**45**), while significant shielding (5.9 ppm) is observed at C15 (methyl group) as compared to the corresponding signal in sessilifoliamide B (**44**). The relative configurations of sessilifoliamide B (**44**), sessilifoliamide C (**45**), and sessilifoliamide D (**46**) have been firmly established by chemical correlation with derivatives of sessilifoliamide A (**26**, stemoamide group), the structures of which were determined by X-ray crystallographic analysis. The absolute configurations of the sessilifoliamides were established by the modified Mosher method (*19*).

Neostemodiol (**47**) and neostemonine (**17**) (Fig. 3), both isolated from *S. japonica*, may be biogenetically related, as neostemodiol (**47**) can be formally derived from neostemonine (**17**) by cleavage of the tetrahydrofuran ring present in the latter through the addition of the elements of water.

F. STEMOFOLINE GROUP

The stemofoline group comprises some of the structurally more complex representatives of the *Stemona* alkaloids, and currently ten alkaloids have been described: stemofoline (**48**) (*17,22,53,54*), oxystemofoline (**49**) (*17*), methoxystemofline (**50**) (*17*), 2′-hydroxystemofoline (**51**) (*22,36*), 16,17-didehydro-16(*E*)-stemofoline (**52**)[a] (*22,54*), also named as didehydrostemofoline, 1′,2′-didehydrostemofoline or asparagamine A (*5,55*), 16,17-didehydro-4(*E*),16(*E*)-stemofoline (**53**) (*54*), parvistemoninine (**54**) (*52*), parvistemoninol (**55**) (*52*), (11*S*,12*R*)-dihydrostemofoline (**56**)[a] (*56*), and stemoburkilline (**57**) (*56*) (Fig. 7, Table XVI). They feature a pentacyclic skeleton with an oxygen bridge between C2 and C8 and a carbon–carbon bond between C3 and C7 of the parent pyrrolo[1,2-*a*]azepine ring system, with a β-methoxy-α-methyl-α,β-unsaturated γ-butyrolactone appended at C11, except for stemoburkilline (**57**) which displays a tetracyclic core resulting from the formal cleavage of the C11-oxygen bond. In fact, the removal of the oxygen atom bridging C2 and C8, the bond between C3 and C7, and the side chain at C3 of alkaloids **48–50** formally leads to the stemoamide alkaloid neostemonine (**17**) (Fig. 3).

The absolute configuration of stemofoline (**48**) was established by X-ray analysis of its hydrobromide monohydrate (heavy-atom method) (*53*), while the alkaloids oxystemofoline (**49**) and methoxystemofoline (**50**) had their relative configurations assigned after 2D-NMR studies (*17*).

^{1}H- and ^{13}C-NMR data (Table XVII and Table XVIII, respectively) have been reported for stemofoline (**48**), oxystemofoline (**49**), 2′-hydroxystemofoline (**51**), and 16,17-didehydro-16(*E*)-stemofoline (**52**), while for methoxystemofoline (**50**) only complete

[a]The numbering used by the authors in the isolation report (*54,56*) differs from the one adopted by us. In order to avoid any ambiguity, the original nomenclature in Refs *54* and *56* are used.

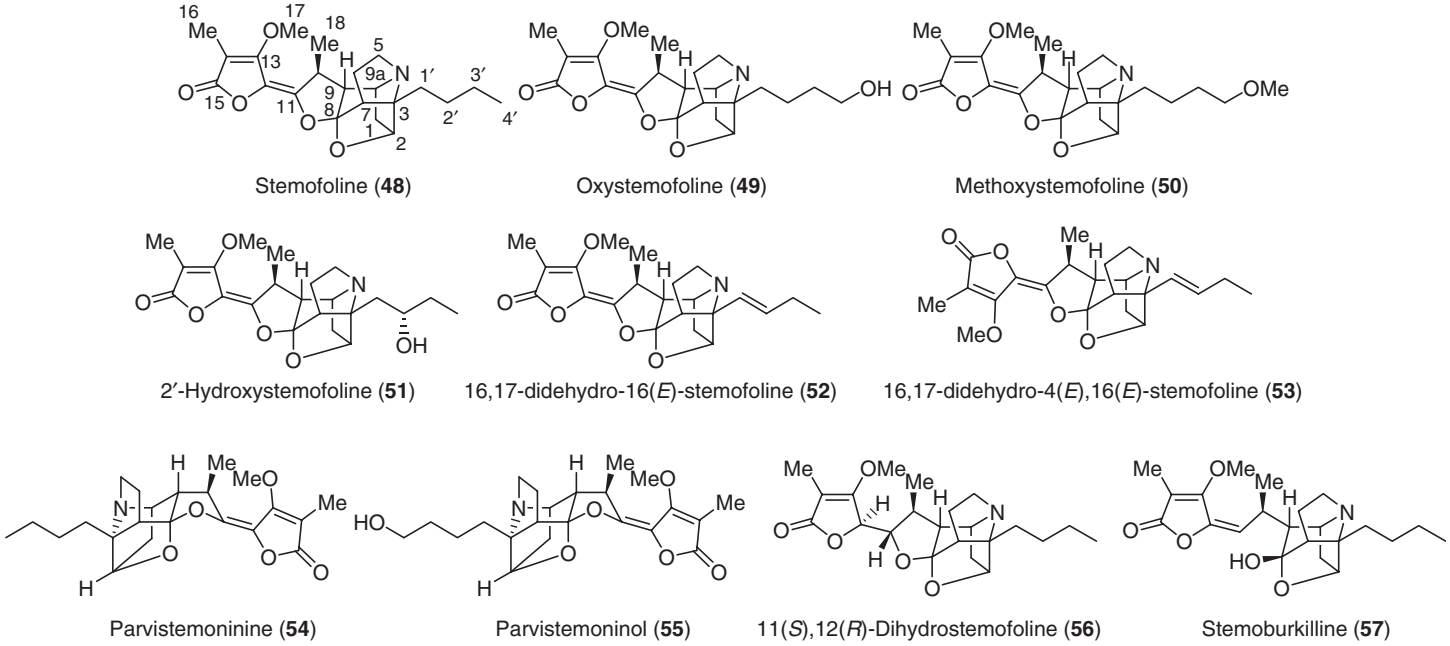
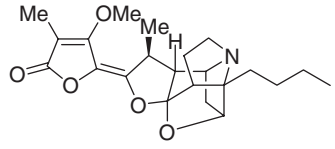
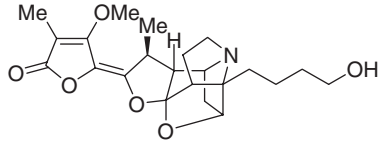
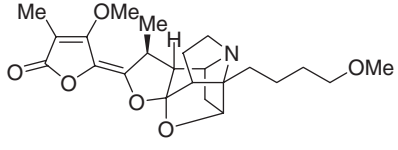


Figure 7. *Stemona* alkaloids of the stemofoline group (**48**–**57**).

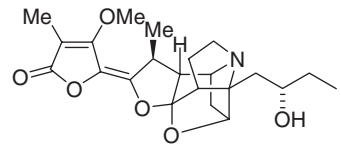
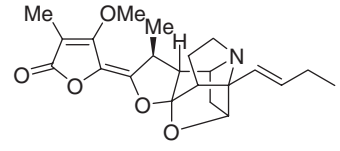
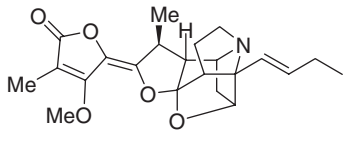
TABLE XVI.

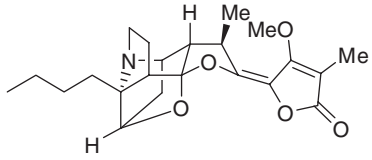
Stemofoline type *Stemona* alkaloids: Occurrence and Properties.

Structure	Alkaloid/Source	Physical data
	**Stemofoline (48)** Source: *S. japonica* Miq. (stems and leaves) (*53*); *S. parviflora* Wright C. H. (roots) (*17*); *S. collinsae* Craib (roots and/or rhizomes) (*22,54,55*); *S. curtisii* Hook.f. (roots and leaves) (*36*); *S. cochinchinensis* Gagnep. (roots and leaves) (*36*); *S. burkillii* Prain (roots) (*56*)	mp: 87–89°C (*53*) mp: (dec) 224°C (for **48**.HBr) (*53*) $[\alpha]_D = +273°$ (MeOH) (*53*) $[\alpha]_D = +270°$ (20°C, MeOH, $c = 0.8$) (*55*) UV (*53,55*) X-ray crystallographic analysis For **48**.HBr.H_2O (*53*) IR (*17,53,55*) MS, HRMS (*55*) CD (*17*) ^{1}H-NMR (*17,54,55*) ^{13}C-NMR (*17,55*)
	**Oxystemofoline (49)** Source: *S. parviflora* Wright C. H. (roots) (*17*)	mp: 224–226°C (*17*) $[\alpha]_D = +106°$ (20°C, MeOH, $c = 0.1$) (*17*) IR, EIMS, CD (*17*) ^{1}H-NMR (*17*) ^{13}C-NMR (*17*)
	**Methoxystemofoline (50)** Source: *S. parviflora* Wright C. H. (roots) (*17*)	mp: 180–182°C (*17*) $[\alpha]_D = +75.6°$ (21.6°C, MeOH, $c = 0.037$) (*17*) IR, EIMS, CD (*17*) ^{1}H-NMR partial data (*17*) ^{13}C-NMR (*17*)

(*continued*)

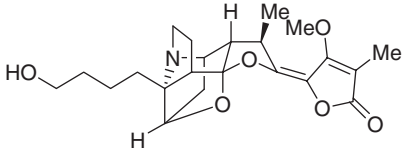
TABLE XVI.
Continued.

Structure	Alkaloid/Source	Physical data
	**2′-Hydroxystemofoline (51)** Source: *S. collinsae* Craib. (roots and rhizomes) (*22*); *S. curtisii* Hook.f. (roots) (*36*); *S. cochinchinensis* Gagnep. (roots) (*36*); *S. burkillii* Prain (roots) (*56*)	$[\alpha]_D = +197°$ (20°C, MeOH, $c = 0.5$) (*22*) $[\alpha]_D = +195°$ (20°C, MeOH, $c = 0.3$) (*55*) IR, UV, EIMS, HRMS (*55*) FDMS (*22*) X-ray crystallographic analysis (for **51**.H_2O) (*55*); (for **51**.CH_2Cl_2) (*55*) ^{1}H-NMR (*22,55*) ^{13}C-NMR (*22,55*)
	**16,17-didehydro-16(*E*)-stemofoline (52)** also named **didehydrostemofoline** and **1′,2′-didehydrostemofoline (asparagamine A)** Source: *S. collinsae* Craib. (roots) (*54*); (roots and rhizomes) (*22*)	Colorless crystals (*54*) mp: 172–174°C (*54*) $[\alpha]_D = +230°$ (18°C, MeOH, $c = 0.74$) (*54*) $[\alpha]_D = +210°$ (20°C, MeOH, $c = 0.5$) (*55*) X-ray crystallographic analysis (for **52**.MeOH) (*55*) IR, HRMS, EIMS, UV (*54,55*) ^{1}H-NMR (*54,55*) ^{13}C-NMR (*22,55*)
	**16,17-didehydro-4(*E*),16(*E*)-stemofoline (53)** Source: *S. collinsae* Craib. (roots) (*54*)	Colorless glassy resin (*54*) $[\alpha]_D = +130°$ (18°C, MeOH, $c = 0.01$) (*54*) IR, UV, EIMS (*54*) ^{1}H-NMR (*54*)



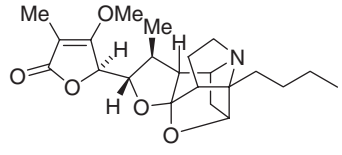
Parvistemoninine (54)
Source: *S. parviflora* Wright C. H. (roots) (*52*)

mp: 76–78°C (*52*)
$[\alpha]_D = -256.6°$ (MeOH) (*52*)



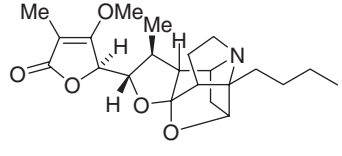
Parvistemoninol (55)
Source: *S. parviflora* Wright C. H. (roots) (*52*)

mp: 224–226°C (*52*)
$[\alpha]_D = +106°$ (MeOH) (*52*)



(11*S*,12*R*)-Dihydrostemofoline (56)
Source: *S. burkillii* Prain (roots) (*56*)

Yellow–brown gum (*56*)
$[\alpha]_D = +38.9°$ (26°C, $CHCl_3$, $c = 0.35$) (*56*)
IR, HRMS (*56*)
^{1}H-NMR (*56*)
^{13}C-NMR (*56*)



Stemoburkilline (57)
Source: *S. burkillii* Prain (roots) (*56*)

Yellow–brown gum (*56*)
$[\alpha]_D = +37.5°$ (26°C, $CHCl_3$, $c = 0.28$) (*56*)
IR, HRMS (*56*)
^{1}H-NMR (*56*)
^{13}C-NMR (*56*)

TABLE XVII.

^{1}H-NMR Chemical Shifts (δ, ppm) and Coupling Constants (J, Hz) for the Stemofoline Alkaloid Group.

Hydrogen	**48**[i] (*54*)		**49**[ii] (*17*)		**51**[i] (*22*)		**52**[i] (*54*)	
	δ	J	δ	J	δ	J	δ	J
H1	1.7–2.0 m	–	1.98 m	–	2.05 d	15.0	1.7–2.0 m	–
	–	–	1.73 m	–	1.85 m	–	–	–
H2	4.25 br s	–	4.23 m	–	4.36 br s	–	4.20 br s	–
H5	~3.0–3.1 m	–	3.14 m	–	3.25 ddd	5.3, 10.6, 13.7	~2.95–3.1 m	–
	–	–	3.01 m	–	3.02 ddd	4.8, 8.8, 13.7	–	–
H6	1.7–2.0 m	–	1.96 m	–	1.97 m	–	1.7–2.0 m	–
	–	–	1.85 ddd	2.5, 7.4, 11.9	1.89 m	–	–	–
H7	2.7 d	6.4	2.68 dd	2.5, 6.1	2.65 s	–	2.84 d	5.8
H9	1.7–2.0 m	–	1.81 m	–	1.82 dd	3.6, 9.8	1.7–2.0 m	–
H9a	3.49 br s	–	3.47 m	–	3.34 br s	–	3.50 br s	–
H10	~3.1 m	–	3.10 dq	6.5, 7.5	3.11 dq	6.5, 9.8	~3.1 m	–
H16	2.07 s	–	2.06 s	–	2.08 s	–	2.07 s	–
H17	4.13 s	–	4.13 s	–	4.14 s	–	4.14 s	–
H18	1.37 d	6.4	1.36 d	6.5	1.38 d	6.5	1.38 d	6.4
H1′	1.5–1.6 m	–	1.52–1.72 m	–	1.74 dd	2.0, 14.2	5.50 d	15.6
	–	–	–	–	1.64 dd	10.6, 14.2	–	–
H2′	1.5–1.6 m	–	1.57 m	–	3.63 m	–	5.78 dt	6.4, 15.6
H3′	1.5–1.6 m	–	1.61 m	–	1.52 m	–	~2.05 m	–
	–	–	–	–	1.43 m	–	–	–
H4′	0.91 t	7.0	3.56 t	6.2	0.95 t	7.3	0.99 t	7.3
OH	–	–	–	–	6.60 br s	–	–	–

Hydrogen	**53**[i] (*54*)		**56**[i] (*56*)		**57**[i] (*56*)	
	δ	*J*	*δ*	*J*	*δ*	*J*
H1	1.7–2.0 m	–	1.99 m	–	1.99 m	–
	–	–	1.63 dd	3.0, 7.5	1.80 m	–
H2	4.22 br s	–	4.22 br s	–	4.38 br s	–
H5	~3.0–3.2 m	–	3.14 m	–	3.27 m	–
	–	–	3.01 m	–	3.09 m	–
H6	1.7–2.0 m	–	1.82 m	–	1.93 m	–
	–	–	1.72 m	–	–	–
H7	2.86 d	6.1	2.45 d	6.0	2.34 d	5.9
H9	1.7–2.0 m	–	1.64 dd	3.0, 12.0	1.85 m	–
H9a	3.52 br s	–	3.44 br s	–	3.60 br s	–
H10	~3.1 m	–	2.61 m	–	3.18 m	–
H11	–	–	3.79 dd	3.0, 9.0	5.50 d	10.0
H12	–	–	4.60 br s	–	–	–
H16	2.07 s	–	2.01 br s	–	2.07 s	–
H17	4.13 s	–	4.11 s	–	4.13 s	–
H18	1.46 d	6.7	1.08 d	6.5	1.08 d	6.8
H1′	5.50 d	15.6	1.56 t	8.0	1.67 m	–
	–	–	–	–	1.60 m	–
H2′	5.78 dt	6.4, 15.6	1.40 m	–	1.39 m	–
	–	–	1.23 m	–	1.29 m	–
H3′	~2.05 m	–	1.33 m	–	1.36 m	–
H4′	0.99 t	7.9	0.87 t	7.0	0.92 t	6.8

[i] $CDCl_3$.
[ii] $(CD_3)_2CO$.

TABLE XVIII.
^{13}C-NMR Chemical Shifts (δ, ppm) for the Stemofoline Alkaloid Group.

Carbon	δ							
	48[i] (*22*)	**48**[ii] (*17*)	**49**[iii] (*17*)	**50**[i] (*17*)	**51**[i] (*22*)	**52**[i] (*22*)	**56**[i] (*56*)	**57**[i] (*56*)
C1	33.3	30.78	33.66	33.01	33.7	32.9	33.4	32.9
C2	78.6	77.70	79.14	78.61	78.7	79.7	78.2	79.8
C3	82.8	82.07	82.87	83.04	82.7	83.1	82.2	82.9
C5	47.6	46.83	47.97	46.06	47.1	48.0	47.4	46.5
C6	27.3	32.57	33.90	31.51	26.6	26.9	26.5	25.3
C7	49.9	49.70	51.03	50.11	52.7	51.2	50.5	55.4
C8	112.7	112.28	112.66	113.52	112.0	112.8	111.8	105.7
C9	47.6	46.50	48.08	47.44	47.6	47.6	47.3	44.2
C9a	60.9	59.97	61.52	61.02	60.8	60.9	61.0	63.4
C10	34.6	34.07	35.42	36.25	34.4	34.6	33.1	28.4
C11	148.4	148.71	148.45	149.82	147.8	148.4	86.3	114.7
C12	127.9	126.46	127.97	128.29	128.0	128.0	76.5	141.9
C13	162.8	162.73	163.10	163.50	162.7	162.8	170.3	161.8
C14	98.6	97.27	99.04	98.80	98.8	98.6	98.5	99.1
C15	169.7	168.70	169.53	170.48	169.6	169.7	174.5	170.5
C16	9.2	8.44	9.00	8.68	9.2	9.2	8.7	8.7
C17	58.8	59.01	59.57	59.42	58.8	58.8	58.8	59.3
C18	18.3	17.43	18.31	16.19	18.3	18.3	14.8	18.7
C19	–	–	–	58.55	–	–	–	–
C1′	26.7	25.96	27.06	26.50	36.1	126.5	31.5	30.2
C2′	31.6	22.36	22.08	21.92	71.2	133.4	27.2	27.5
C3′	23.1	26.64	32.21	29.97	30.6	25.3	23.2	23.7
C4′	14.0	13.69	62.03	72.45	9.7	13.5	13.9	14.1

[i]$CDCl_3$.
[ii]C_5D_5N.
[iii]$(CD_3)_2CO$.

^{13}C-NMR data (*17*) and for 16,17-didehydro-4(*E*),16(*E*)-stemofoline (**53**) only ^{1}H-NMR data (*54*), are available.

Comparison of the ^{1}H-NMR data of stemofoline (**48**), oxystemofoline (**49**), and 2′-hydroxystemofoline (**51**) reveals only small differences in the chemical shifts, except for the hydrogens of the side chain attached to C3. The same observations hold for the ^{13}C-NMR data of these alkaloids. The ^{1}H-NMR spectra of 16,17-didehydro-16(*E*)-stemofoline (**52**) and 16,17-didehydro-4(*E*),16(*E*)-stemofoline (**53**) basically differ only by the chemical shift of the methyl at C10 which appears slightly shielded (1.38 ppm) in 16,17-didehydro-16(*E*)-stemofoline (**52**) as compared to the corresponding signal (1.46 ppm) in 16,17-didehydro-4(*E*),16(*E*)-stemofoline (**53**). As photoisomerization of 16,17-didehydro-4(*E*),16(*E*)-stemofoline (**53**) to 16,17-didehydro-16(*E*)-stemofoline (**52**) was achieved under fluorescent light, the possibility that 16,17-didehydro-16(*E*)-stemofoline (**52**) is an artifact derived from 16,17-didehydro-4(*E*),16(*E*)-stemofoline (**53**) cannot be ruled out at this point. Comparison of the ^{1}H-NMR data of 16,17-didehydro-16(*E*)-stemofoline (**52**) with those of stemofoline (**48**) reveals, besides the expected differences for the signals

corresponding to the side chain, the H7 doublet less shielded (2.84 ppm) in 16,17-didehydro-16(*E*)-stemofoline (**52**) as compared to stemofoline (**48**) (2.7 ppm). As to their ^{13}C-NMR data, the more significant differences appear at C7, which appears more deshielded in 16,17-didehydro-16(*E*)-stemofoline (**52**), and in the side chain attached to C3. Only melting point and specific optical rotation data are available for parvistemoninol (**55**) (*52*) and they are identical to those reported for oxystemofoline (**49**) (*17*). Inspection of the two structures proposed for these two alkaloids reveals their enantiomeric relationship. As the absolute configuration has not been firmly established it seems that oxystemofoline (**49**) and parvistemoninol (**55**), both isolated from the roots of *S. parviflora* Wright C. H., might be regarded as identical alkaloids.

The structure of (11*S*,12*R*)-dihydrostemofoline (**56**) was established by high resolution mass spectrometry (which indicated it to be a stemofoline derivative) and by NMR spectroscopy, where two additional signals at δ 3.79 and 4.60 ppm were observed in comparison to stemofoline (**48**). The *cis* configuration of H11 and the methyl group at C10 followed from NOESY experiments, and the 11*S*,12*R* configuration was assigned by comparison with the spectroscopic data available for the *syn* hydrogenation derivative of stemofoline (**48**) (*56*).

High resolution mass spectrometric analysis of stemoburkilline (**57**) showed the same molecular formula as (11*S*,12*R*)-dihydrostemofoline (**56**), but its ^{1}H-NMR data indicated the presence of an olefinic proton (δ 5.5 ppm) coupled to an adjacent methine hydrogen (H10). Extensive 2D-NMR analyses showed that stemoburkilline (**57**) was the C-ring opened product of stemofoline (**48**). Its *E*-configuration was assigned on the basis of the assumption that **57** arises from **56** via an *anti*-elimination process (*56*).

G. STEMOCURTISINE GROUP

While all of the previous alkaloids display the pyrrolo[1,2-*a*]azepine moiety as their hallmark, the stemocurtisine group is characterized by the presence of the pyrido[1,2-*a*]azepine nucleus. This group comprises six alkaloids: stemocurtisine (**58**) (*57*), also named as pyridostemin (*36*), stemokerrin (**59**) (*36*), methoxystemokerrin-*N*-oxide (**60**) (*36*), oxystemokerrin (**61**) (*36*), oxystemokerrin-*N*-oxide (**62**) (*36*), and stemocurtisinol (**63**) (*58*) (Fig. 8, Table XIX).

The first alkaloid to be reported was stemocurtisine (**58**), isolated from the roots of *S. curtisii,* the structure of which was established by X-ray crystallography. The piperidine ring adopts a chair-like conformation, and it displays an ether bridge involving C1 and C9. The acetal-like nature of C9 is confirmed by the presence of a signal at 120.5 ppm in its ^{13}C-NMR spectrum. The absolute configuration is not known, but it is assumed to be the same as the one in those alkaloids with the same C/D ring substructure [stemofoline (**48**)] (*57*). The same alkaloid was also isolated from the roots of *Stemona* sp. (*36*).

Stemokerrin (**59**) was isolated from the roots of *S. kerri* (HG 889) and its relative configuration was firmly established by X-ray crystallography, which revealed the pyrido[1,2-*a*]azepine substructure and the *Z* configuration of the double bond at C12–C13, which is also present in other *Stemona* alkaloids, such as protostemonine (**19**) and stemofoline (**48**) (*36*). The presence of a 1′-hydroxypropyl substituent (or its *O*-methyl derivative) attached to C4 is another distinct feature of this group of *Stemona* alkaloids [except for stemocurtisine (**58**)]. Comparison of the ^{13}C-NMR data of stemocurtisine (**58**)

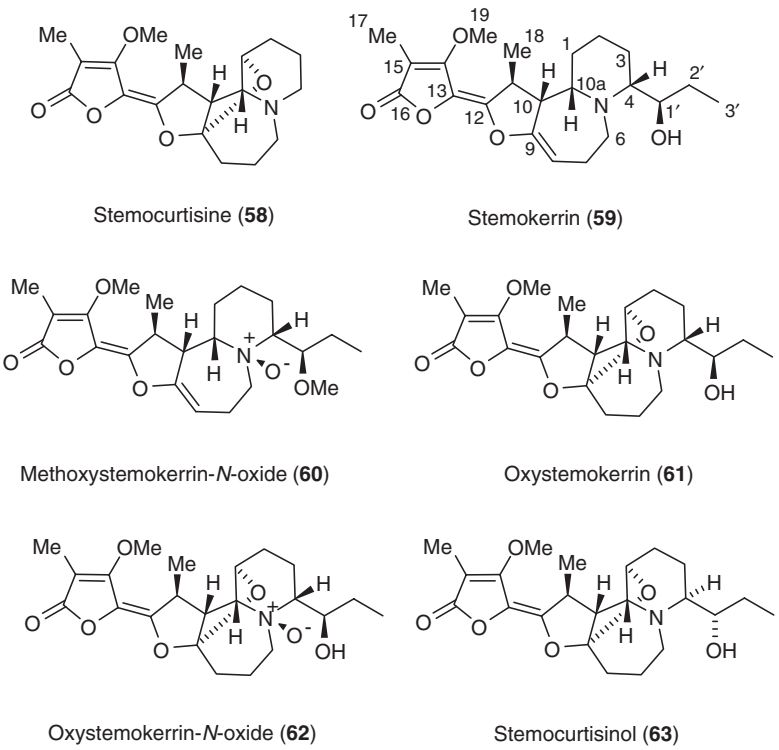


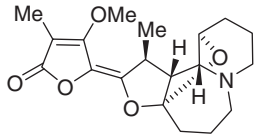
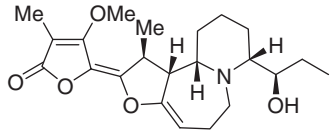
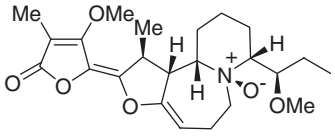
Figure 8. *Stemona* alkaloids of the stemocurtisine group (**58**–**63**).

and stemokerrin (**59**) reveals major differences in the chemical shifts of the carbon atoms forming the A/B ring (C1 to C10), and small changes for the carbons of the remaining rings which are conserved in both alkaloids. Particularly noteworthy is C6 in stemocurtisine (**58**) which is significantly deshielded as compared to the correspondending signal in stemokerrin (**59**), probably due to the deshielding effect of the lone electron pair of its bridging oxygen atom. The same trend is also observed for H6 in the ^{1}H-NMR spectrum of stemocurtisine (**58**) which appears deshielded in comparison to the corresponding signal in stemokerrin (**59**). Methoxystemokerrin-*N*-oxide (**60**) was also isolated from the roots of *S. kerrii* (HG 892) and displayed 2D-NMR connectivities identical to those observed for stemokerrin (**59**), except for a methoxy group replacing the hydroxyl group at C1′ of stemokerrin (**59**). However, most of the chemical shifts in the ^{1}H-NMR spectrum of methoxystemokerrin-*N*-oxide (**60**) appeared downfield as compared to the corresponding signals in stemokerrin (**59**), particularly those assigned to the A and B rings. The chemical shifts of C4, C6, and C10a are particularly deshielded (up to 16.5 ppm) in the ^{13}C-NMR spectrum of methoxystemokerrin-*N*-oxide (**60**). The NMR data combined with the FAB-HRMS (molecular ion compatible with the molecular formula $C_{23}H_{33}O_6N$) and EIMS (loss of the C4 side chain and an additional loss of an oxygen atom) led to the assignment of the structure of methoxystemokerrin-*N*-oxide (**60**) (Tables XX and XXI).

Oxystemokerrin (**61**) was also isolated from the roots of *S. kerrii* (HG 889) and it displayed ^{1}H-NMR data similar to those reported for stemocurtisine (**58**), except for

TABLE XIX.

Stemocurtisine Type *Stemona* Alkaloids: Occurrence and Properties.

Structure	Alkaloid/Source	Physical data
	**Stemocurtisine (58)** also named **Pyridostemin** Source: *S. curtisii* Hook.f. (roots) (*57,58*); *Stemona* sp. (roots and leaves) (*36*)	Amorphous (*36*) mp: 149–151°C (*57*) $[\alpha]_D = +473°$ (20°C, MeOH, $c = 0.4$) (*36*) $[\alpha]_D = +334°$ (25°C, $CHCl_3$, $c = 0.66$) (*57*) IR, HRMS (*36,57*) UV, EIMS (*36*) X-ray crystallographic analysis (*57*) EIMS (*36*) ^{1}H-NMR (*36,57*) ^{13}C-NMR (*36,57*)
	**Stemokerrin (59)** Source: *S. kerrii* Craib. (roots) (*36*)	mp: 138–141°C (*36*) $[\alpha]_D = +136°$ (20°C, MeOH, $c = 0.3$) (*36*) IR, UV, EIMS, HRMS, X-ray crystallographic analysis (*36*) ^{1}H-NMR (*36*) ^{13}C-NMR (*36*)
	**Methoxystemokerrin-*N*-oxide (60)** Source: *S. kerrii* Craib. (roots) (*36*)	Amorphous (*36*) $[\alpha]_D = +255°$ (20°C, MeOH, $c = 0.2$) (*36*) IR, UV, EIMS, HRFABMS (*36*) ^{1}H-NMR (*36*) ^{13}C-NMR (*36*)

(*continued*)

TABLE XIX.
Continued.

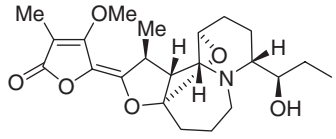
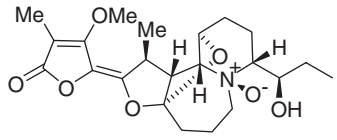
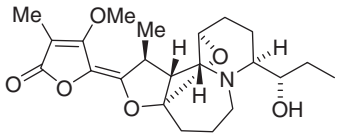
Structure	Alkaloid/Source	Physical data
	**Oxystemokerrin (61)** Source: *S. kerrii* Craib. (roots) (*36*); *Stemona* sp. (roots and leaves) (*36*); *S. curtisii* Hook.f. (roots and leaves) (*36*)	Amorphous (*36*) $[\alpha]_D = +289°$ (20°C, MeOH, $c = 0.4$) (*36*) IR, EIMS, FDMS, UV (*36*) ^{1}H-NMR (*36*) ^{13}C-NMR (*36*)
	**Oxystemokerrin-*N*-oxide (62)** Source: *S. kerrii* Craib. (roots) (*36*); *S. curtisii* Hook.f. (leaves) (*36*); *Stemona* sp. (leaves) (*36*)	Amorphous (*36*) $[\alpha]_D = +247°$ (20°C, MeOH, $c = 0.3$) (*36*) IR, EIMS, FDMS, UV (*36*) ^{1}H-NMR (*36*) ^{13}C-NMR (*36*)
	**Stemocurtisinol (63)** Source: *S. curtisii* Hook.f. (roots) (*58*)	Mp: 209–211°C (*58*) $[\alpha]_D = +233°$ (25°C, $CHCl_3$, $c = 0.334$) (*58*) IR, X-ray crystallographic analysis, HREIMS (*58*) ^{1}H-NMR (*58*) ^{13}C-NMR (*58*)

TABLE XX.

^{1}H-NMR Chemical Shifts (δ, ppm) and Coupling Constants (J, Hz) for the Stemocurtisine Alkaloid Group.

Hydrogen	**58**[i] (*36*)		**59**[i] (*36*)		**60**[i] (*36*)		**61**[ii] (*36*)	
	δ	J	δ	J	δ	J	δ	J
H1	4.00 ddd	2.0, 2.0, 3.5	1.73 dddd	4.4, 13.2, 13.2, 13.2	1.93 m	–	4.03 ddd	1.0, 1.0, 2.0
	–	–	1.04 dm	13.2	1.72 m	–	–	–
H2	2.20 ddm	2.0, 14.9	1.91 dm	13.2	1.65 m	–	2.19 m	–
	1.62 dddd	3.5, 5.5, 13.1, 14.9	1.49 m	–	1.57 m	–	1.81 m	–
H3	1.82 ddddd	4.5, 4.5, 13.3, 13.3, 13.3	1.40 dddd	4.2, 13.2, 13.2, 13.2	1.92 m	–	1.64 m	–
	1.20 ddddd	<1, 2.1, 4.7, 7.5, 13.3	1.25 m	–	1.72 m	–	1.34 m	–
H4	2.98 m	–	2.60 m	–	3.26 m	–	2.59 ddd	1.9, 9.0, 11.8
	2.92 m	–	–	–	–	–	–	–
H6	3.38 ddd	<1, 12.6, 15.8	2.70 ddd	1.5, 10.5, 12.5	3.36 ddd	<1.0, 11.5, 11.5	3.36 m	–
	2.97 m	–	2.56 m	–	2.63 ddd	<1.0, 5.1, 11.5	3.06 ddd	≤1.0, 11.5, 15.5
H7	2.01 m	–	2.22 m	–	3.31 m	–	1.95 m	–
	1.65 m	–	2.17 m	–	1.95 m	–	1.74 m	–
H8	2.37 ddd	1.6, 5.3, 13.3	5.48 ddd	2.0, 5.0, 9.0	5.39 ddd	1.8, 4.7, 8.7	2.22 m	–
	1.74 ddd	5.6, 12.0, 13.3	–	–	–	–	1.87 m	–
H10	2.66 d	5.0	3.15 br s	≤2.0	4.53 br s	–	2.88 d	4.8
H10a	3.42 d	2.0	2.83 dm	12.5	3.21 m	–	3.50 br s	–
H11	3.06 dq	5.0, 6.9	2.92 dq	2.0, 7.1	2.88 dq	1.6, 7.1	3.20 dq	4.8, 6.9
H17	2.07 s	–	2.08 s	–	2.09 s	–	2.10 s	–
H18	1.37 d	6.9	1.32 d	7.1	1.39 d	7.1	1.45 d	6.9
H19	4.14 s	–	4.17 s	–	4.18 s	–	4.25 s	–
H1′	–	–	3.40 ddd	2.7, 8.3, 9.8	4.13 m	–	3.59 ddd	3.1, 7.7, 9.0
H2′	–	–	1.59 ddq	2.7, 7.5, 13.7	1.69 m	–	1.72 ddq	3.1, 7.4, 14.1
	–	–	1.26 m	7.5, 9.8, 13.7	1.37 m	–	1.43 ddq	7.4, 7.7, 14.1
H3′	–	–	1.01 t	7.5	1.03 t	7.3	1.03 t	7.4
H4′	–	–	–	–	3.50 s	–	–	–

(*continued*)

TABLE XX.
Continued.

Hydrogen	**62**[ii] (*36*)		**63**[i] (*58*)	
	δ	J	δ	J
H1	4.38 br s	–	4.05 s	–
	–	–	–	–
H2	2.11 m	–	1.95 m	–
	2.02 m	–	1.73 dd	5.8, 12.3
H3	1.98 m	–	1.96 m	–
	1.94 m	–	1.36 m	–
H4	3.31 ddd	2.5, 9.0, 11.5	2.53 m	–
H6	4.04 m	–	3.48 m	–
	3.55 ddd	<1.0, 6.5, 12.6	2.92 dd	4.5, 15.5
H7	2.62 m	–	1.99 m	–
	1.96 m	–	1.65 m	–
H8	2.20 m	–	2.36 dd	4.1, 13.0
	2.10 m	–	1.76 dd	5.8, 13.0
H10	3.38 d	3.7	2.70 d	4.7
H10a	3.93 br s	–	3.40 s	–
H11	3.18 dq	4.8, 6.8	3.07 qui	6.1
H17	2.10 s	–	2.07 s	–
H18	1.48 d	6.8	1.38 d	7.0
H19	4.26 s	–	4.15 s	–
H1′	4.08 m	–	3.50 m	–
H2′	1.69 m	–	1.60 m	–
	1.47 m	–	1.25 m	–
H3′	1.04 t	7.4	1.02 t	7.3

[i]$CDCl_3$.
[ii]CD_3OD.

TABLE XXI.
^{13}C-NMR Chemical Shifts (δ, ppm) for the Stemocurtisine Alkaloid Group.

Carbon	δ					
	58[i] (*36*)	**59**[i] (*36*)	**60**[i] (*36*)	**61**[ii] (*36*)	**62**[ii] (*36*)	**63**[i] (*58*)
C1	75.5	16.9	23.8	76.8	77.0	75.4
C2	26.9	24.8	23.3	28.1	22.5	22.4
C3	18.8	19.2	23.2	30.8	23.0	18.4
C4	53.6	69.9	84.3	65.8	79.4	65.5
C6	53.0	39.7	56.2	44.2	61.9	54.8
C7	27.0	25.8	18.7	27.4	19.7	25.8
C8	33.9	100.2	98.2	34.8	32.6	33.5
C9	120.5	157.4	157.9	121.8	154.1	120.1
C10	57.1	52.8	44.2	57.4	52.3	56.9
C10a	62.0	62.4	78.5	66.4	85.4	57.5
C11	39.3	38.9	38.5	41.0	40.2	39.3
C12	147.3	146.8	146.1	150.2	148.2	146.8
C13	125.0	123.2	123.6	126.2	120.7	125.0
C14	162.9	163.1	162.9	165.4	165.2	162.7
C15	97.5	97.2	97.6	97.9	98.3	97.5
C16	169.9	169.8	169.7	172.8	172.6	169.7
C17	9.1	9.2	9.2	8.9	8.9	9.2
C18	22.5	22.1	21.7	22.6	22.8	22.6
C19	–	59.0	59.2	60.0	60.0	58.9
C1′	–	70.1	78.7	73.1	73.7	67.9
C2′	–	26.9	26.0	28.2	28.5	26.4
C3′	–	9.8	11.1	10.1	8.8	10.3
C4′	–	–	57.9	–	–	–

[i] $CDCl_3$.
[ii] CD_3OD.

extra signals due to the 1′-hydroxypropyl side chain attached at C4. The presence of this carbon chain is evident from a comparison of its ^{13}C-NMR data with those of stemokerrin (**59**), with a moderate deshielding observed for C1′, C2′, and C3′ in oxystemokerrin (**61**) probably due to the oxygen bridge involving C1 and C9. Oxystemokerrin-*N*-oxide (**62**) was also isolated from the roots of *S. kerrii* (HG 889) and displayed the same connectivities in the 2D-NMR analyses, as shown by oxystemokerrin (**61**). The chemical shifts in the ^{1}H- and ^{13}C-NMR spectra of oxystemokerrin-*N*-oxide (**62**) appeared downfield in comparison with the corresponding signals in oxystemokerrin (**61**), particularly for C4, C6, and C10a (differences up to 19 ppm were observed in the ^{13}C-NMR spectra), and points toward a similar relationship as observed for stemokerrin (**59**) and methoxystemokerrin-*N*-oxide (**60**). The spectroscopic evidence, combined with the mass spectrometry data, led to the assignment of the structure of oxystemokerrin-*N*-oxide (**62**).

Stemocurtisinol (**63**) was isolated from the roots of *S. curtisii*, and its relative configuration was established by X-ray structural analysis (*58*). Stemocurtisinol (**63**)

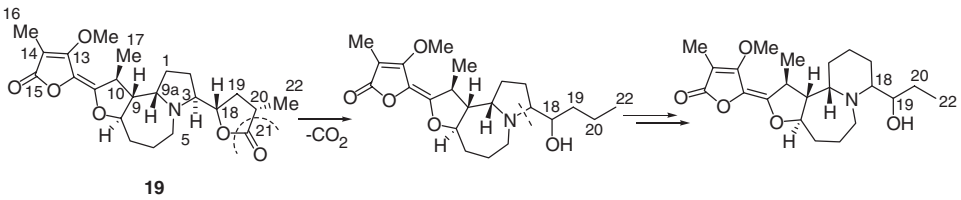


Figure 9. Biogenetic connections between the pyrrolo- and pyridoazepine nuclei (*36*).

differs from oxystemokerrin (**61**) only by the configurations at C4 and C1′ of the side chain attached at C4. Comparison of their ^{13}C-NMR spectra reveals significant shielding at C2 (5.7 ppm), C3 (12.4 ppm), C10a (8.9 ppm), and C1′ (5.2 ppm), and deshielding at C6 (10.2 ppm) in stemocurtisinol (**63**).

The co-occurrence of pyrrolo- and pyridoazepines in the *Stemona* species studied by Hofer and Greger, together with the presence of the more widespread protostemonine (**19**), led these authors to put forth a biogenetic hypothesis connecting these two families of *Stemona* alkaloids (*36*) (Fig. 9). Starting from protostemonine (**19**), hydrolysis of the lactone ring, followed by decarboxylation may lead to a 1′-hydroxybutyl side chain appended at C3 of the pyrroloazepine ring. The construction of the pyridoazepine moiety would then arise from the cleavage of the C3-*N* bond and the formation of a C1′-*N* bond, leaving a propyl residue which is present in stemokerrin (**59**), methoxystemokerrin-*N*-oxide (**60**), oxystemokerrin (**61**), oxystemokerrin-*N*-oxide (**62**), and stemocurtisinol (**63**), but absent in stemocurtisine (**58**).

H. MISCELLANEOUS GROUP

The miscellaneous group includes five Stemona alkaloids: parvistemoamide (**64**) (*16,52*), tuberostemoninol (**65**) (*37,38*), neotuberostemoninol (**66**) (*23*), tuberostemonone (**67**) (*12,19,59*), and parvineostemonine (**68**) (*60*). (Fig. 10, Table XXII)

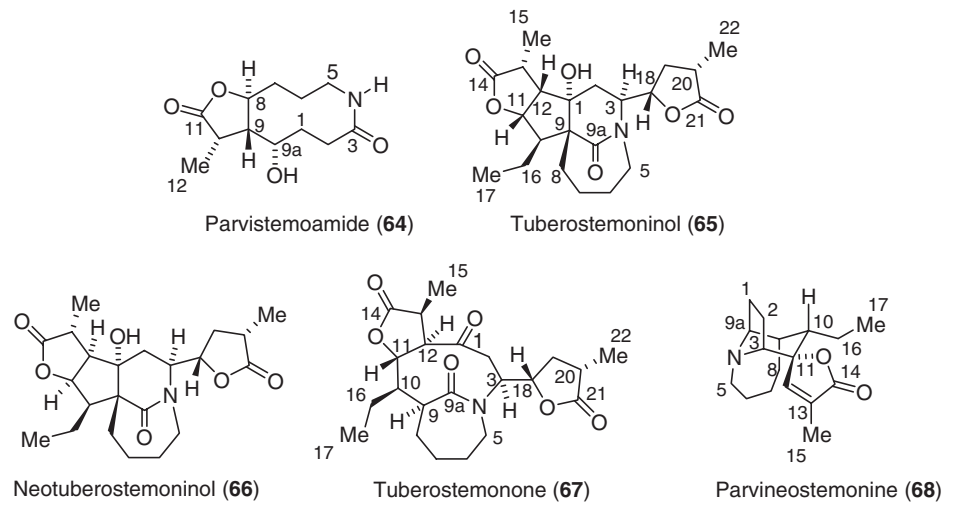
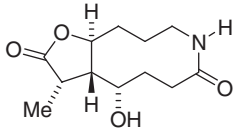
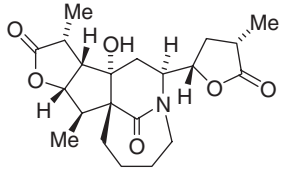
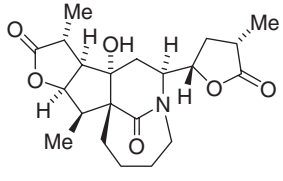


Figure 10. *Stemona* alkaloids of the miscellaneous group (**64**–**68**).

TABLE XXII.
Miscellaneous Type *Stemona* Alkaloids: Occurrence and Properties.

Structure	Alkaloid/Source	Physical data
	**Parvistemoamide (64)** Source: *S. parviflora* Wright C. H. (roots) (*16*)	mp: 197–198°C (*16,52*) $[\alpha]_D = -211.2°$ (20°C, MeOH, $c = 0.25$) (*16*) IR, MS, Elemental analysis (*16*) ^{1}H-NMR (*16*) ^{13}C-NMR (*16*) nOe data (*16*)
	**Tuberostemoninol (65)** Source: *S. tuberosa* Lour. (roots) (*37,38*)	mp: 217–219°C (*37,38*) $[\alpha]_D = +124°$ (MeOH, $c = 0.83$) (*37,38*) MS, HRMS, X-ray crystallographic analysis (*37*) EIMS (*38*) IR (*37,38*) ^{1}H-NMR (*37,38*) ^{13}C-NMR (*37,38*) nOe data (*37,38*)
	**Neotuberostemoninol (66)** Source: *S. tuberosa* Lour. (herbal sample) (*23*)	mp: 190–192°C (*23*) IR, HRMS, EIMS, X-ray crystallographic analysis (*23*) ^{1}H-NMR (*23*) ^{13}C-NMR (*23*)

(*continued*)

TABLE XXII.
Continued.

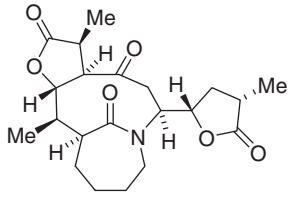
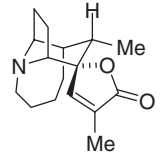
Structure	Alkaloid/Source	Physical data
	**Tuberostemonone (67)** Source: *S. tuberosa* Lour. (roots) (*12,59*); *S. sessilifolia* Franch. & Sav. (roots) (*19*)	mp: 208–209°C (*12,59*) $[\alpha]_D = +134.8°$ (8°C, $CHCl_3$, $c = 0.1$) (*12,59*) X-ray crystallographic analysis (*59*) IR, HRMS (*12,59*) EIMS (*12*) ^{1}H-NMR (*12,59*) ^{13}C-NMR (*12,59*) nOe data (*12*)
	**Parvineostemonine (68)** Source: *S. parviflora* Wright (stems and leaves) (*60*)	Amorphous (*60*) IR, HRMS, UV, EIMS (*60*) ^{1}H-NMR (*60*) ^{13}C-NMR (*60*)

TABLE XXIII.

^{1}H-NMR Chemical Shifts (δ, ppm) and Coupling Constants (J, Hz) for the Miscellaneous Group.

Hydrogen	**64**[i] (*16*)		**65**[iii] (*37,38*)		**66**[ii] (*23*)	
	δ	J	δ	J	δ	J
H1	1.62 dddd	1.0, 10.8, 10.8, 11.4	–	–	–	–
	2.10 dddd	5.8, 5.8, 6.4, 11.4	–	–	–	–
H2	2.40 m	–	2.18 dd	12.9, 13.02	2.17 m	–
	–	–	2.00 dd	3.9, 13.02	2.49 m	–
H3	–	–	4.24 ddd	3.90, 9.0, 12.90	4.37 dt	4.0, 10.0
H5	4.13 ddd	2.1, 2.3, 14.1	3.94 ddd	3.72, 12.06, 15.0	3.31 dd	7.6, 11.9
	2.56 ddd	2.2, 12.4, 14.1	3.57 ddd	5.40, 5.40, 15.0	3.91 dt	6.8, 11.9
H6	1.83 m	–	1.61 m	–	1.46 m	–
	1.48 m	–	1.41 m	–	1.61 m	–
H7	2.39 m	–	1.82 m	–	1.52 m	–
	1.50 m	–	1.41 m	–	1.71 m	–
H8	4.19 ddd	2.8, 10.1, 10.7	1.68 ddd	5.58, 8.62, 12.30	1.20 m	–
	–	–	1.26 dddd	2.3, 3.0, 12.3, 12.30	2.13 m	–
H9	2.41 ddd	6.4, 6.7, 10.7	–	–	–	–
H9a	3.98 ddd	6.4, 6.4, 10.8	–	–	–	–
H10	2.58 dq	6.7, 7.1	3.18 m	–	3.60 br d	3.6
H11	–	–	4.64 dd	5.1, 7.86	5.15 dd	5.6, 6.0
H12	1.28 d	7.1	2.54 d	7.86	3.56 dd	6.8, 11.8
H13	–	–	3.15 q	7.68	3.22 dq	4.0, 7.6
H15	–	–	1.50 d	7.68	1.57 d	7.6
H16	–	–	2.51 m	–	1.85 dq	7.6, 14.8
	–	–	1.30 m	–	2.36 dq	7.6, 14.8
H17	–	–	1.15 t	7.32, 7.56	1.11 t	7.6
H18	–	–	4.72 dd	5.1, 9.0, 10.14	4.72 ddd	4.8, 10.0, 10.4
H19	–	–	2.51 ddd	5.1, 8.36, 12.0	1.34 m	–
	–	–	1.30 ddd	10.14, 12.0, 12.0	2.45 m	–
H20	–	–	2.81 ddq	7.02, 8.36, 12.09	2.82 dq	7.0, 14.4
H22	–	–	1.14 d	7.02	1.13 d	7.0

[i] $CDCl_3$.
[ii] C_5D_5N.
[iii] DMSO-d_6.

(*continued*)

TABLE XXIII.
Continued.

Hydrogen	**67**[i] (*59*)		**68**[i] (*60*)	
	δ	J	δ	J
H1	–	–	1.55 m	–
	–	–	2.06 m	–
H2	2.38 dd	3.7, 12.2	1.67 m	–
	3.19 dd	12.2, 12.2	1.94 m	–
H3	5.40 ddd	3.7, 5.7, 12.2	2.97 bd	6.9
H5	3.81 ddd	2.9, 9.2, 12.1	3.12 m	–
	3.51 ddd	2.6, 4.6, 12.1	3.61 m	–
H6	1.91 m	–	1.75 m	–
	1.77 m	–	1.89 m	–
H7	1.51 m	–	1.71 m	–
	1.75 m	–	2.02 m	–
H8	1.70 m	–	1.34 m	–
	1.52 m	–	1.87 m	–
H9	3.04 ddd	[ii]	1.81 m	–
H9a	–	–	3.72 bd	6.9
H10	2.32 m	–	1.98 m	–
H11	5.10 dd	7.1, 9.9	–	–
H12	3.56 dd	7.7, 9.9	6.88 d	1.4
H13	2.91 dq	7.0, 7.7	–	–
H15	1.30 d	7.0	1.92 d	1.4
H16	1.80 m	–	1.01 m	–
	1.27 m	–	1.26 m	–
H17	0.92 dd	7.2, 7.4	0.80 t	7.4
H18	4.45 ddd	5.7, 5.7, 10.9	–	–
H19	1.78 m	–	–	–
	2.50 ddd	nr	–	–
H20	2.71 m	–	–	–
H22	1.23 d	7.1	–	–

[i] $CDCl_3$.
[ii] In reference (*12*), H9 appears at 3.08 ppm (ddd, $J = 1.8$, 9.2 and 11.0 Hz).

The relative configuration for parvistemoamide (**64**) was obtained by 2D-NMR studies, but it has been depicted differently in the literature (*16,52*). In addition to structure **64**, Xu and coworkers have also represented parvistemoamide (**64**) with a different configuration between the substituents in the lactone ring (C9 and C10) and for the stereocenter at C9a (*16,52*). The structure of tuberostemoninol (**65**), isolated from the roots of *S. tuberosa*, features a rearranged skeleton formed by the formal cleavage of the C1–C9a bond in tuberostemonine (**4**), formation of a C1–C9 bond, and oxidation of the C1 and C9a atoms. Its structure was proposed based mainly on NMR techniques (*38*) and confirmation by X-ray diffraction analysis is claimed (*37*). Neotuberostemoninol (**66**) was also isolated from the same *Stemona* species, and its relative configuration was established by comparison with the spectroscopic data available for tuberostemoninol (**65**) and X-ray crystallographic analysis. Comparison of their ^{1}H-NMR data (Table XXIII) reveals major differences in the chemical shifts of one of the H2, H8, and H16, as well as for H10, H11, and H12 signals. In the ^{13}C-NMR spectra, the most striking difference is in the chemical shift of C6 which appears extremely shielded (18.85 ppm) in neotuberostemoninol (**66**), while moderate chemical shift differences are observed for C10, C11, C12, and C13 (Table XXIV). Besides the unusual *trans* ring fusion involving the

TABLE XXIV.
^{13}C-NMR Chemical Shifts (δ, ppm) for the Miscellaneous Group.

Carbon	**64**[i] (*16*)	**65**[ii] (*37,38*)	**66**[iii] (*23*)	**67**[i] (*12*)	**68**[i] (*60*)
	δ	δ	δ	δ	δ
C1	22.56	81.7	83.17	205.00	28.2
C2	34.77	32.7	33.74	44.56	27.1
C3	176.30	58.7	59.79	56.25	66.2
C5	40.22	47.6	48.57	39.67	46.6
C6	25.58	26.2	18.85	23.71	28.3
C7	30.58	30.4	27.92	21.09	24.2
C8	77.60	28.4	27.52	26.06	27.3
C9	37.29	61.4	61.52	51.47	38.4
C9a	55.78	185.0	184.66	176.57	57.0
C10	52.64	50.0	48.29	44.56	38.1
C11	179.70	87.1	84.72	79.41	89.6
C12	17.20	52.2	54.79	59.78	153.0
C13	–	34.4	37.89	39.67	130.6
C14	–	180.6	179.04	178.18	174.2
C15	–	17.1	15.06	15.15	10.7
C16	–	35.0	33.77	18.87	17.2
C17	–	13.4	13.01	12.16	11.9
C18	–	76.8	77.51	77.01	–
C19	–	35.0	36.14	34.10	–
C20	–	34.5	35.52	35.50	–
C21	–	179.1	178.63	178.80	–
C22	–	14.7	13.15	14.79	–

[i]$CDCl_3$.
[ii]C_5D_5N.
[iii]DMSO-d_6.

nine-membered ring and the α-methyl-γ-butyrolactone ring, tuberostemonone (**67**), whose structure was firmly established by X-ray crystallography, it features a nine-membered ring which can be derived by the oxidative cleavage of the C1–C9a bond in tuberostemonine (*59*).

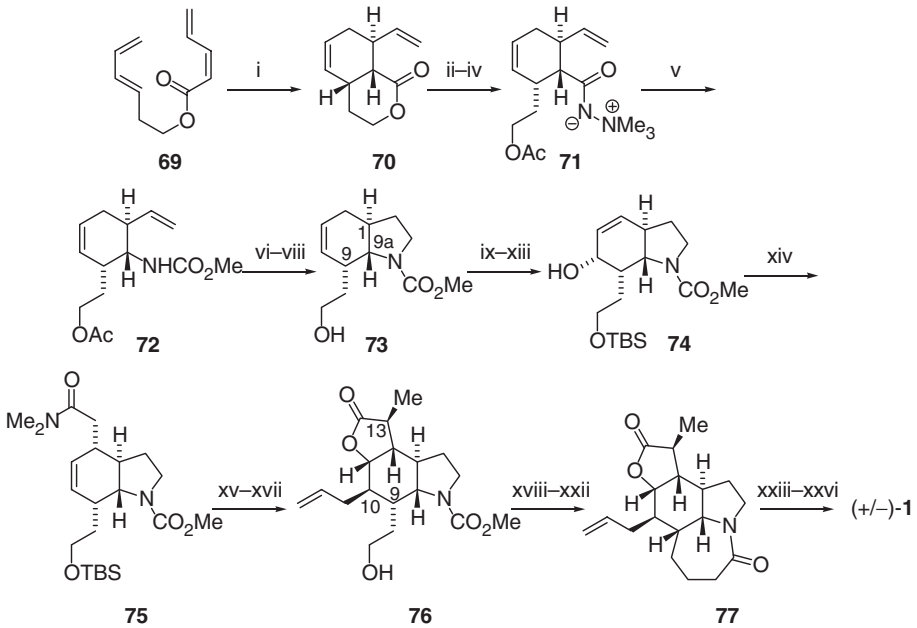
The structure of parvineostemonine (**68**) was established by spectroscopic methods, which features a spirotetracyclic structure with a two-carbon bridge involving C3 and C9 of the pyrroloazepine moiety. One of these carbons (C11) is part of a spirobutenolide ring (ring D), while the other (C10) bears an ethyl substituent.

III. Synthesis

A. STENINE GROUP

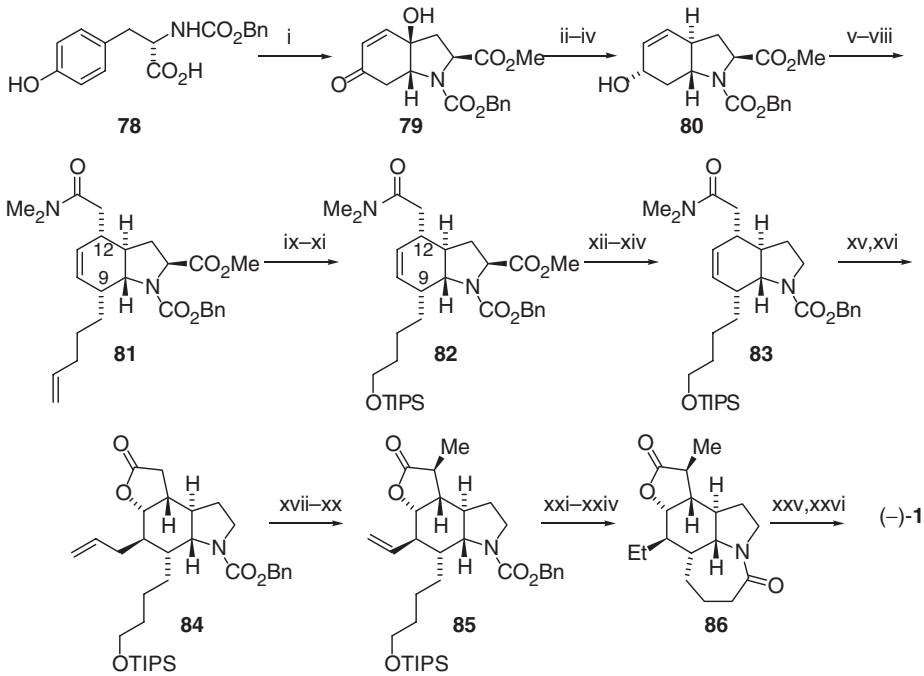
Stenine (**1**) was the first representative of this group of *Stemona* alkaloids to yield to total synthesis. Hart and Chen have described the first total synthesis of racemic stenine (**1**) (*61,62*). The construction of the advanced intermediate **76** containing the ACD substructure was initiated with an intramolecular Diels–Alder reaction (**69**→**70**, Scheme 1). The yield of bicyclic lactone **70** was 67% when the reaction was conducted in chloroform on a 2.0 mmol scale using 4.0 mmol of Et_2AlCl in a sealed tube at 80°C for 20 h, but dropped to 49% when carried out on a larger scale (110 mmol tetraene **69** and 170 mmol of Et_2AlCl) in refluxing toluene. Hofmann rearrangement (**71**→**72**, Scheme 1) set the stage for ring A formation and a 83% yield was obtained for hexahydroindole **73**, accompanied by a 13% yield for the corresponding acetate which was hydrolyzed to **73** with a 85% yield (94% overall yield) (Scheme 1). Claisen-Eschenmoser rearrangement (**74**→**75**, Scheme 1) and iodolactonization completed the assembly of tricyclic intermediate **76**. Ring B was finally put in place after homologation of the side chain at C9 and intramolecular lactam formation (**76**→**77**, Scheme 1). The first total synthesis of racemic stenine (**1**) was completed in 26 steps from **69** with ~8% overall yield after conversion of the allylic residue at C10 to the requisite ethyl substituent and the adjustment of the oxidation level at ring B (Scheme 1).

Wipf and coworkers (*30*) have reported the first asymmetric synthesis of (−)-stenine (**1**) based on an efficient preparation of a hydroindolenone intermediate through the oxidation of *N*-carbobenzyloxy tyrosine with hypervalent iodine which was followed by the reduction of the corresponding π-allyl palladium intermediate (**78**→**80**, Scheme 2). The last step required extensive experimentation and the use of catalytic tris(dibenzylideneacetone)dipalladium(0) chloroform complex, tributylphosphine and triethyl ammonium formate at 60°C under strictly anaerobic conditions, gave a 68% yield of *trans*-hexahydroindole **80**. The stereogenic center at C9 was established through enolate alkylation, and the acetamido side chain at C12 by a Claisen-Eschenmoser rearrangement (**80**→**81**, Scheme 2). Selective cleavage of the terminal olefin was accomplished with Sharpless asymmetric dihydroxylation followed by sodium periodate cleavage of the corresponding diol. Reductive decarboxylation (**82**→**83**, Scheme 2) set the stage for the iodolactonization reaction, followed by a stereoselective radical allylation (**83**→**84**, Scheme 2) and enolate alkylation, a sequence of events which resembles the approach by Hart and Chen (*61,62*). The azepine ring was formed through intramolecular nitrogen acylation, and the total synthesis was completed by the reduction of lactam **86** to afford (−)-**1** in 26 steps from Cbz-tyrosine (**78**) and ~1.0% overall yield.



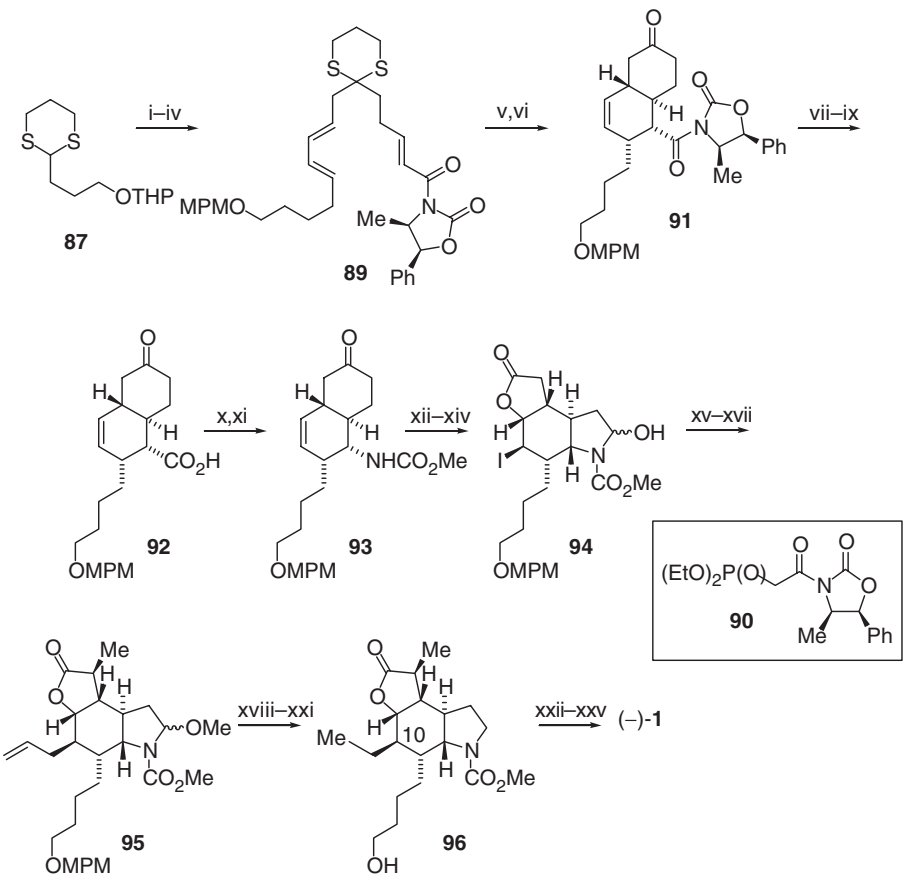
Scheme 1. *Reagents and Conditions:* (i) Et_2AlCl, $CHCl_3$, 80°C (67%); (ii) N_2H_4, H_2O, MeOH, reflux (87%); (iii) MeI, K_2CO_3, MeOH, reflux (100%); (iv) AcCl, 0°C to rt (100%); (v) mesitylene, reflux; then, MeOH, reflux (94%); vi) 9-BBN, THF, 0°C to rt; then $NaBO_3.4H_2O$ (95%); (vii) MsCl, Et_3N, CH_2Cl_2, 0°C to rt (100%); (viii) MeLi, THF, −78°C to rt (94%); (ix) Jones' reagent, acetone, 0°C (83%); (x) I_2, THF-H_2O, aq. $NaHCO_3$, 0°C to rt (95%); (xi) DBU, toluene, reflux (98%); (xii) *t*-BuOH, MeOH, $NaBH_4$, 50°C (100%); (xiii) TBSCl, Et_3N, CH_2Cl_2, DMAP, rt (97%); (xiv) $MeC(OMe)_2NMe_2$, xylenes, reflux (93%); (xv) I_2, THF, H_2O, rt (75%); (xvi) $CH_2{=}CHCH_2SnBu_3$, AIBN, C_6H_6, reflux (83%); (xvii) LDA, MeI, THF, HMPA, −78°C (87%); (xviii) DMSO, $(COCl)_2$, CH_2Cl_2, −78°C then Et_3N (99%); (xix) $Ph_3P{=}CHCO_2Et$, $CHCl_3$, reflux (91%); (xx) Red-Al, CuBr, THF, butan-2-ol, −78 to −20°C (85%); (xxi) Me_3SiI, $CHCl_3$, rt (94%); (xxii) mesitylene, reflux (91%); (xxiii) OsO_4 (cat.), $NaIO_4$, THF, H_2O, rt (84%); (xxiv) $HSCH_2CH_2SH$, SiO_2-$SOCl_2$, CH_2Cl_2, rt (100%); (xxv) (p-$MeOC_6H_4PS_2)_2$, CH_2Cl_2, rt (100%); (xxvi) W-2 Raney-Ni, EtOH, reflux (80%).

The stereocontrolled total synthesis of (−)-stenine (**1**) developed by Morimoto and coworkers (*31,63*) (Scheme 3) relies on the asymmetric, intramolecular Diels-Alder cycloaddition of the (*E,E,E)*-triene **89** prepared by alkylation of the lithium anion of dithiane **87** with (*E,E*)-dienylchloride **88** (the corresponding alcohol was prepared in four steps and 44% overall yield from 1,5-pentanediol). Complete *endo* and good facial selectivity was observed in the dimethylaluminum chloride promoted diastereoselective [4 + 2] cycloaddition which provided the key intermediate **91** in 68% yield from **89**, after exposure of the carbonyl group. While the *endo* transition state is considered to be more favored than the *exo* one due to a repulsive 1,3-diaxial-like interaction involving the diene and the 1,3-dithianyl protecting group, the facial selectivity resulted from the *s-cis* conformation of the dienophile displaying the 1,3-oxazolidinyl coordinated to the Lewis acid. A Curtius rearrangement (**92**→**93**) installed the necessary carbamate function which,



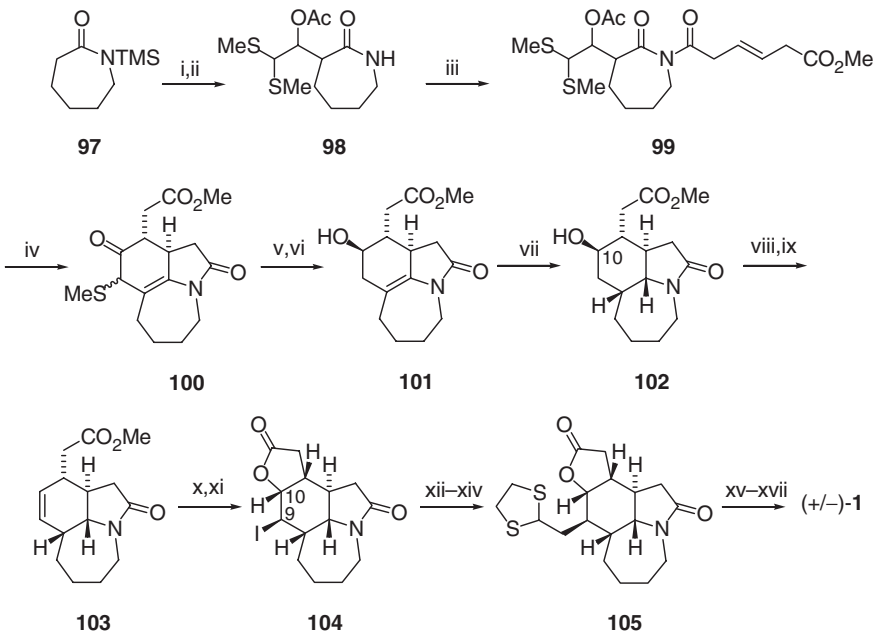
Scheme 2. *Reagents and Conditions:* (i) $PhI(OAc)_2$, MeOH, $NaHCO_3$, 23°C (54%); (ii) Bz_2O, CH_2Cl_2, pyridine, DMAP, reflux (90%); (iii) $NaBH_4$, $CeCl_3.7H_2O$, MeOH, THF, rt (99%); (iv) $Pd_2(dba)_3.CHCl_3$, THF, *n*-Bu_3P, HCO_2H, Et_3N, 60°C (68%); (v) TPAP (cat.), NMO, CH_2Cl_2, MS 4 Å, −20°C to rt (90%); (vi) KHMDS, toluene, −80°C; then, $CH_2{=}CH(CH_2)_3$ OTf, THF, −60°C (34% yield, 51% based on recovered starting material); (vii) $NaBH_4$, $CeCl_3.7H_2O$, THF, MeOH, 40°C (91%); (viii) $MeC(OMe)_2NMe_2$, xylenes, reflux (85%); (ix) AD-mix-*β*, *t*-BuOH, H_2O; then, $NaIO_4$, *t*-BuOH, H_2O, rt (82%); (x) $NaBH_4$, THF, MeOH (93%); (xi) TIPSCl, imidazole, DMAP (cat.), CH_2Cl_2, rt (100%); (xii) LiOH, THF, MeOH, H_2O, 40°C (90%); (xiii) $PhOP(O)Cl_2$, C_6H_5SeH, Et_3N, THF, 0 to 22°C; (xiv) *n*-Bu_3SnH, AIBN (cat.), xylenes, 130°C (79%, 2 steps); (xv) I_2, H_2O, THF, pH 5.5, 21°C (85%); (xvi) $CH_2{=}CHCH_2SnBu_3$, AIBN (cat.), 80°C (90%); (xvii) LDA, THF, HMPA, MeI, −78°C (87%); (xviii) OsO_4 (cat.), $NaIO_4$, THF, H_2O, *t*-BuOH, 0 to 21°C; (xix) $NaBH_4$, THF, MeOH, −40°C (63%, 2 steps); (xx) *o*-$(NO_2)PhSeCN$, *n*-Bu_3P, THF, 0°C; then, H_2O_2, THF, 21°C (87%); (xxi) HF, CH_3CN, 0°C; (xxii) Dess-Martin periodinane, CH_2Cl_2, 21°C; then, THF, 2-methylbut-2-ene, $NaClO_2$, aq. Na_2HPO_4, 0°C; (xxiii) H_2, $Pd(OH)_2/C$, MeOH, 21°C; (xxiv) $C_6F_5P(O)Ph_2$, CH_2Cl_2, 21°C (71%, 4 steps); (xxv) $(p\text{-}MeOC_6H_4PS_2)_2$, CH_2Cl_2, 21°C (93%); (xxvi) Raney-Ni, EtOH, 21°C (78%).

after construction of ring D via an iodolactonization reaction, was used to implement ring A of (−)-stenine (**93**→**94**). The final stages of the synthesis featured the installation of the ethyl substituent at C10 and the construction of ring B through intramolecular *N*-alkylation. Overall, the total synthesis of (−)-stenine (**1**) proceeded in 30 steps with ~1% overall yield from 1,5-pentanediol (longest route) or in 25 steps with ~2% overall yield from dithiane **87** (shortest route) (Scheme 3).



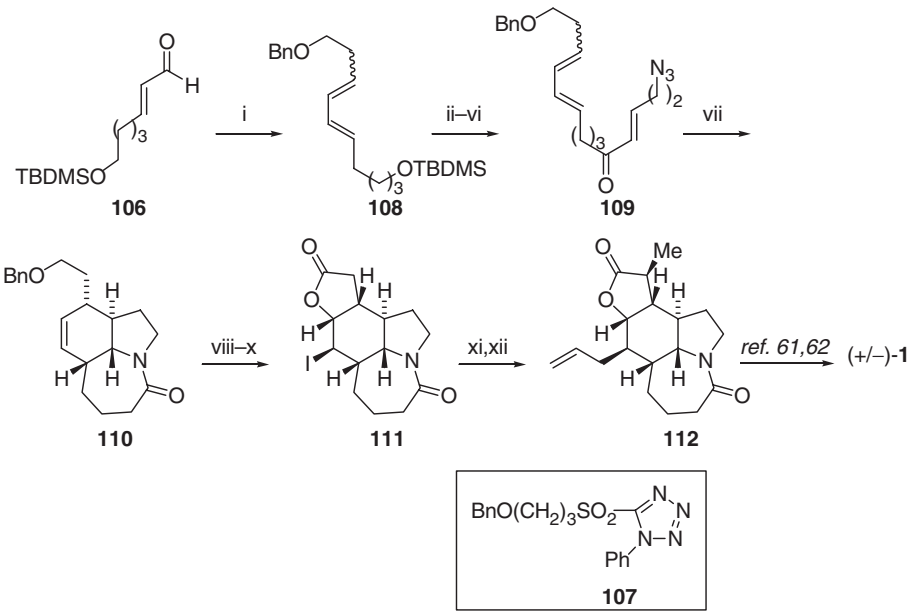
Scheme 3. *Reagents and Conditions:* (i) *n*-BuLi, THF, −25°C; then, (*E,E*)-MPMO$(CH_2)_4$CH═CHCH═$CHCH_2Cl$ (**88**), HMPA, −78°C to rt; (ii) *p*-TsOH (cat.), MeOH, THF, rt (68%, 2 steps); (iii) SO_3.pyr, DMSO, Et_3N, THF, 0°C to rt (85%); (iv) **90**, Et_3N, LiCl, THF, 0°C to rt (90%); (v) Me_2AlCl, CH_2Cl_2, −20°C to rt (85%); (vi) $AgNO_3$, *N*-chlorosuccinimide, CH_3CN, H_2O, 0°C (80%); (vii) LiSEt, THF , 0°C (91%); (viii) Et_3SiH, 10% Pd-C, 0°C to rt (100%); (ix) $NaClO_2$, NaH_2PO_4, 2-methylbut-2-ene, *t*-BuOH, H_2O, 0°C to rt (100%); (x) $(PhO)_2P(O)N_3$, DMF, Et_3N, 60°C; (xi) MeOH, CuCl (cat.), rt (82%, 2 steps); (xii) TMSCl, NaI, CH_3CN, Et_3N, 50°C; (xiii) MCPBA, hexanes, CH_2Cl_2, −15°C to rt; (xiv) H_5IO_6, THF, H_2O, rt; then, I_2, $NaHCO_3$, rt (50%, 3 steps); (xv) CSA (cat.), $CH(OMe)_3$, MeOH, CH_2Cl_2, rt (90%); (xvi) CH_2═$CHCH_2SnBu_3$, AIBN (cat.), toluene, 80°C (80%); (xvii) LDA, THF, HMPA, −78°C; then, MeI, −78°C (73%); (xviii) Et_3SiH, $BF_3.OEt_2$, CH_3CN, 0°C (82%); xix) OsO_4 (cat.), $NaIO_4$, THF, H_2O, rt (75%); (xx) $HSCH_2CH_2SH$, $BF_3.OEt_2$, CH_2Cl_2, −15°C (81%); (xxi) W2 Raney-Ni, EtOH, reflux (85%); (xxii) MsCl, Et_3N, CH_2Cl_2, 0°C (88%); (xxiii) NaI, acetone, reflux (98%); (xxiv) TMSI, CH_2Cl_2, rt; (xxv) CH_3CN, reflux (70%, 2 steps).

Padwa and Ginn (*64*) devised an approach to (+/−)-stenine (**1**) where the azepine ring would be installed at an early point of the synthetic scheme, a distinct feature from previous syntheses which relied on the initial construction of the hydroindole portion with the closure of the seven-membered azepine ring postponed until the end of the synthesis



Scheme 4. *Reagents and Conditions:* (i) LDA, THF, 0°C; then $(MeS)_2CHCHO$, −78°C; (ii) Ac_2O, −78°C to rt (80%, 2 steps); (iii) (*E*)-$MeO_2CCH_2CH{=}CHCH_2COCl$, CH_2Cl_2, MS, 25°C (85%); (iv) DMTSF, CH_3CN, −40°C (80%); (v) Ni-Ra, EtOH (95%); (vi) $NaBH_4$, $CeCl_3$, MeOH (77%); (vii) $[Ir(cod)pyr(Pcy_3)]PF_6$, H_2, CH_2Cl_2 (80%); (viii) MsCl, CH_2Cl_2, Et_3N, 0°C; (ix) DBU, toluene, reflux (64%, 2 steps); (x) LiOH, THF, H_2O, 0°C; (xi) I_2, CH_3CN (59%, 2 steps); (xii) $CH_2{=}CHCH_2SnBu_3$, AIBN, benzene, reflux (59%); (xiii) OsO_4 (cat.), $NaIO_4$, THF, H_2O, rt; (xiv) $HSCH_2CH_2SH$, $BF_3.OEt_2$, −15°C (50%, 2 steps); (xv) Lawesson′s reagent, CH_2Cl_2, 25°C (77%); (xvi) W2 Ni–Ra, EtOH, reflux (93%); (xvii) i. LDA, THF, HMPA, −78°C; ii. MeI (65%).

(Scheme 4). This strategy secured a rapid and efficient access to the tricyclic intermediate **100** displaying rings A, B, and C of (+/−)-stenine (**1**). The synthesis started with the aldol reaction of the lithium enolate of 1-trimethylsilyl-azepan-2-one (**97**) with 2,2-bis(methanesulfanyl)acetaldehyde, followed by acetylation, which afforded **98** as a 4:1 mixture of diastereoisomers. Methylsulfenylation of one of the methylthio groups of *N*-acyl lactam **99** with DMTSF led to a thionium-promoted cyclization, followed by acetic acid loss from the dihydrofuran intermediate to afford an amidofuran. This compound could not be isolated under the conditions of its formation, as it rapidly rearranged to afford azepinoindole **100** in 80% yield as a 1:1 mixture of diastereoisomers at the stereogenic center bearing the methylthio substituent. The mixture of unsaturated lactams **100** underwent desulfurization with Ni–Ra, followed by stereoselective carbonyl reduction and hydrogenation with Crabtree′s catalyst to provide the saturated hydroxy lactam **102** which displayed the desired *trans* and *cis* relationships between rings A/C and B/C, respectively. The stereochemistry of lactam **102** was established by X-ray diffraction analysis and the stereochemical outcome was rationalized by the directing effect of the hydroxyl group at C10 in **101** thus securing rapid access to the correct stereochemistry of

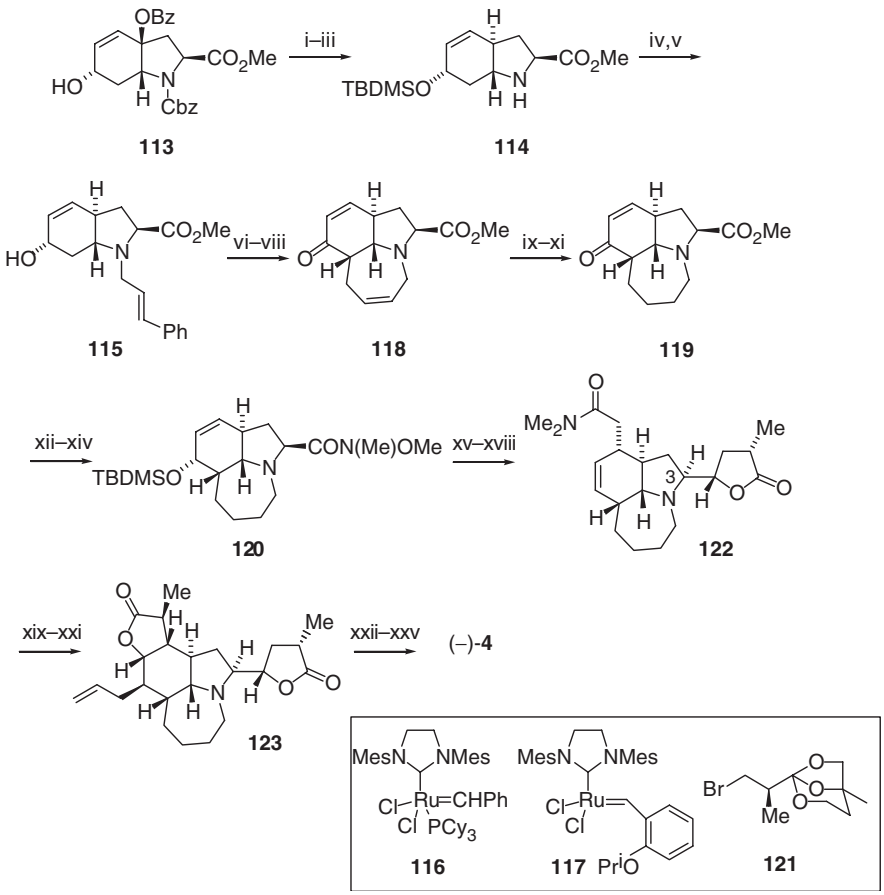


Scheme 5. *Reagents and Conditions:* (i) **107**, LiHMDS, THF, −78°C (90%); (ii) PPTS, EtOH; (iii) $(COCl)_2$, DMSO, Et_3N; (iv) $(MeO)_2P(O)CH_2Li$, −78°C; (v) TPAP, NMO, MS; (vi) $Ba(OH)_2 \cdot 8H_2O$, $N_3CH_2CH_2CHO$ (55%, 5 steps); (vii) $MeAlCl_2$, CH_2Cl_2, reflux (79% overall, 43% for **110**); (viii) Na, NH_3(l); (ix) CrO_3, H_2SO_4; (x) I_2, $NaHCO_3$ (80%, 3 steps); (xi) $CH_2{=}CHCH_2SnBu_3$, AIBN, benzene; (xii) LiHMDS, MeI (72%, 2 steps).

the azepino indole moiety of stenine (**1**). The previous functional group manipulation set the stage for the iodolactonization reaction devised to install ring D. The final operation required installation of the ethyl substituent at C9 which was carried out as previously described by Hart and coworkers (*61,62*). Overall, (+/−)-stenine (**1**) was prepared in 17 steps and ~2% overall yield from 1-trimethylsilyl-azepan-2-one (**97**).

Aubé and Golden (*65*) have demonstrated the utility of a combined intramolecular Diels-Alder/intramolecular Schmidt reaction to construct the azepinoindole intermediate **110** (Scheme 5). The Lewis acid-catalyzed tandem intramolecular Diels-Alder/Schmidt reaction required azidodiene **109**, which was prepared after five steps as a 85:15 mixture of diastereoisomers from diene **108** via a modified Julia olefination between aldehyde **106** (prepared in 5 steps and 94% overall yield from 1,5-pentanediol) and sulfone **107** (prepared in four steps and 84% overall yield from 1,3-propanediol). The key synthetic transformation afforded azepinoindole **110** in 43% yield, whose structure was confirmed by X-ray crystallographic analysis, along with two isomeric lactams (24% and 12% yield). After exposure of the primary hydroxyl group and its oxidation to the corresponding carboxylic acid, iodolactonization provided the installation of ring D (**111**). Following allylation at C10 and methylation of the butyrolactone **112**, the formal synthesis of (+/−)-stenine (**1**) was achieved in 17 steps with an overall yield of 11.6% from 1,5-pentanediol or in 12 steps with an overall yield of 12.3% from aldehyde **106**.

The first total synthesis of (−)-tuberostemonine (**4**) was described by Wipf and coworkers (*66*). The oxidation of *N*-carbobenzyloxy tyrosine with hypervalent iodine afforded, after benzoylation of the tertiary hydroxyl group, bicyclic **113** which was employed by Wipf and coworkers in their synthesis of (−)-stenine (Scheme 2) and served here as the scaffold for the installation of the stereogenic centers of (−)-tuberostemonine (**4**) (Scheme 6). Substitution of PBn_3 for the previously used PBu_3 allowed them to



Scheme 6. *Reagents and Conditions:* (i) $Pd_2(dba)_3$, $CHCl_3$, Et_3N, HCO_2H, PBn_3, THF, 65°C (93%); (ii) TBDMSCl, imidazole, DMAP, CH_2Cl_2 (97%); (iii) Et_3SiH, $Pd(OAc)_2$, Et_3N, CH_2Cl_2 (90%); (iv) (*E*)-PhCH═CHCH$_2$Br, K_2CO_3, toluene, 60°C (96%); (v) TBAF, THF, rt (96%); (vi) TPAP, NMO, CH_2Cl_2 (88%); (vii) KHMDSA, CH_2═CHCH$_2$I, −90°C (66%); (viii) **116** (cat.), CH_2Cl_2, reflux (92%); (ix) PhSH, Et_3N, CH_2Cl_2 (91%); (x) $(PPh_3)_3RhCl$, H_2, EtOH, CH_2Cl_2, rt; (xi) DBU, CH_2Cl_2, rt (89%); (xii) $CeCl_3.7H_2O$, $NaBH_4$, THF, MeOH, 0°C (71%); (xiii) TBDMSCl, imidazole, DMAP, CH_2Cl_2, rt (79%); (xiv) (MeO)NHMe.HCl, Me_2AlCl, CH_2Cl_2, rt (94%); (xv) **121**, LIDBB (95%); (xvi) L-Selectride, THF, −78°C (80%); (xvii) TsOH, MeOH (70%); (xviii) $Me_2NC(OMe)_2Me$, xylenes, 135°C (78%); (xix) PhSeCl, CH_3CN (67%); (xx) CH_2═CHCH$_2SnPh_3$, AIBN, 95°C (70%); (xxi) LDA, THF, HMPA, MeI, −78°C (76%); (xxii) **116** (cat.), allyltritylamine, DIEA, toluene, 110°C (85%); (xxiv) **117** (cat.), TsOH, CH_2Cl_2, CH_2═CH_2, reflux (81%); (xxv) Pd/C, H_2, MeOH (97%).

carry out the Pd(0)-mediated reduction of hydroindolenone **113** on a gram scale without compromising the yield. After protection of the allylic alcohol and deprotection of the nitrogen, *N*-alkylation of hydroindole **114**, and deprotection of the secondary hydroxyl group afforded **115** in five steps and 75% overall yield from **113**. Oxidation of **115** to the corresponding ketone allowed the diastereoselective allylation of the corresponding potassium enolate. Once the two olefin appendages were installed, intramolecular olefin ring-closing metathesis was efficiently carried out with Grubb's catalyst **116**. The tricyclic intermediate **118** had its double bond in the azepino ring removed after a three-step sequence (81% yield), which included a transient protection of the enone double bond by the conjugate addition of thiophenol. Enone **119** was stereoselectively reduced under Luche–Gemal conditions, and the secondary hydroxyl group was protected as the corresponding *tert*-butyldimethylsilyl ether before the conversion of the methyl ester residue to the corresponding Weinreb′s amide **120**.

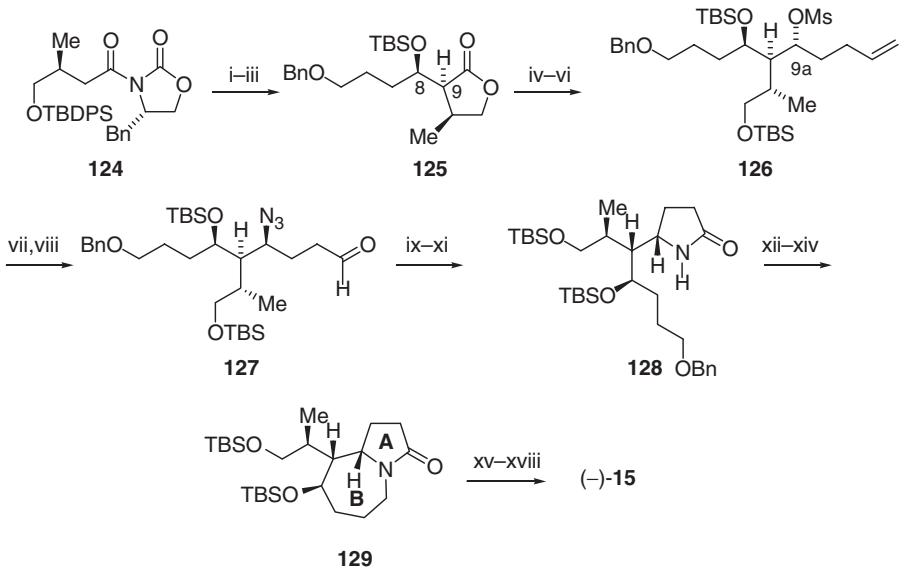
The installation of the butyrolactone substituent at C3 started with the addition of the lithiated form of the ortho ester **121** to **120**. The γ-butyrolactone core was installed after stereoselective reduction of the ketone moiety and exposure to TsOH in methanol. Claisen rearrangement afforded **122** which resisted attempts to undergo iodocyclization, but afforded tetracylic **123** after selenolactonization followed by Keck allylation and α-methylation. The total synthesis of (−)-tuberostemonine (**4**) was concluded after 25 steps and in 1.7% overall yield from **113** after isomerization of the allyl group and cross-metathesis with ethylene promoted by ruthenium catalyst **117** to provide the terminal vinyl group which was stereoselectively hydrogenated.

B. STEMOAMIDE GROUP

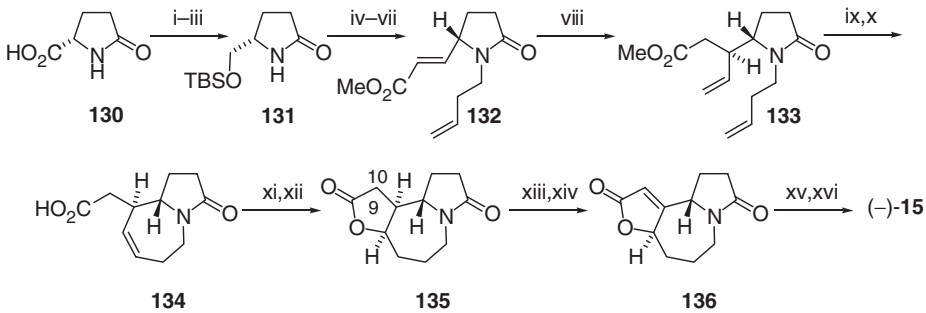
The tricyclic alkaloid stemoamide (**15**) is a typical representative of this group of *Stemona* alkaloids and it has been synthesized several times over the last few years, including some very efficient approaches.

Williams and coworkers (*67*) succeeded in preparing (−)-stemoamide (**15**) starting from commercially available methyl (*R*)-3-hydroxy-2-methylpropionate, which was homologated and coupled with (*S*)-4-benzyloxazolidin-2-one to afford the chiral imide **124** (seven steps, 85% overall yield). Asymmetric boron aldol reaction with 4-benzyloxybutyraldehyde installed the stereogenic centers at C8 and C9 (**125**, Scheme 7). The correct stereochemistry at C9a was established after chain elongation, reduction with lithium triethylborohydride (exclusively from the carbonyl *si* face), mesylation (**125**→**126**, Scheme 7), and methanesulfonate displacement with sodium azide, which proceeded with inversion of configuration (**126**→**127**, Scheme 7). At this point, all the carbons and the stereogenic centers of (−)-stemoamide (**15**) were in place, and the remaining steps were dedicated to the formation of rings A, B, and C, and the functional group interconversions (Scheme 7). The first total synthesis of (−)-stemoamide (**15**) was then completed in 18 steps and 6.6% overall yield from **124**, and in 25 steps from methyl-(*R*)-3-hydroxy-2-methylpropionate with an overall yield of 5.6%.

Pyroglutamic acid (**130**) was employed in the total synthesis of (−)-stemoamide (**15**) by Sibi and Subramanian (Scheme 8) (*68*). After its conversion to the *tert*-butyldimethylsilyl ether **131**, *N*-alkylation with 4-bromo-1-butene and chain extension via a Wittig reaction set the stage for the key stereoselective addition of vinyl copper



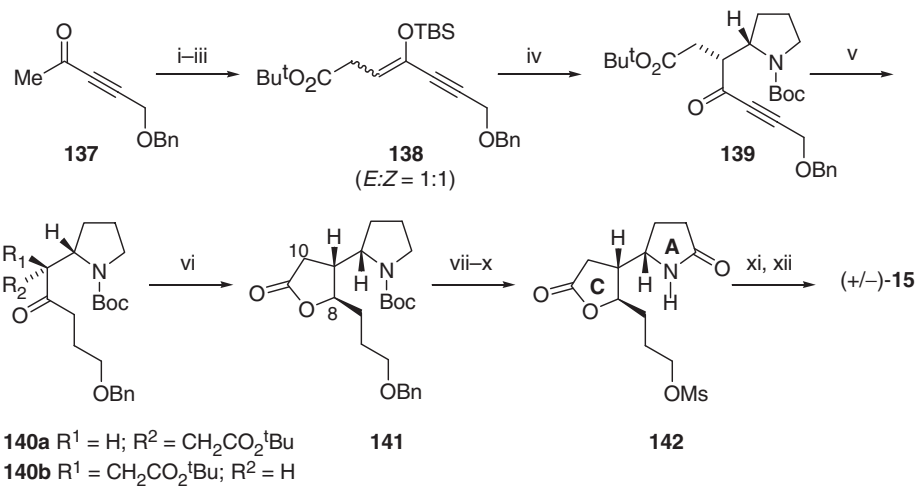
Scheme 7. *Reagents and Conditions:* (i) *n*-Bu_2BOTf, CH_2Cl_2, Et_3N, −78 to 0°C; then, 4-benzyloxybutyraldehyde, −78 to 0°C (88%); (ii) aq. HF, CH_3CN, rt; sat. aq. $NaHCO_3$, K_2CO_3 (82%); (iii) TBDMSOTf, collidine, CH_2Cl_2, −78°C to rt (97%); (iv) 4-iodobut-1-ene, *t*-BuLi, Et_2O, −100 to −78°C; then, TBDMSOTf, collidine, −78 °C to rt (78%); (v) $LiEt_3BH$, THF, −78°C to rt (91%); (vi) MsCl, pyridine, rt (96%); (vii) NaN_3, HMPA, rt; (viii) O_3, CH_2Cl_2, MeOH, −78°C; then, Me_2S, −78°C to rt (49%, 2 steps); (ix) $NaClO_2$, $NaH_2PO_4.H_2O$, CH_3CN, *t*-BuOH, H_2O, 2-methylbut-2-ene, 0°C; (x) CH_2N_2, Et_2O, 0°C (96%, 2 steps); (xi) PPh_3, THF, H_2O, reflux (87%); (xii) H_2, 10% Pd/C, EtOH; (xiii) MsCl, pyridine, rt; (xiv) NaH, THF, rt (71%, 3 steps); (xv) $HF.Et_3N$, CH_3CN, rt (63%); (xvi) Dess-Martin periodinane, pyridine, CH_2Cl_2, rt; (xvii) TBAF, THF, rt (94%, 2 steps); (xviii) PDC, CH_2Cl_2, reflux (80%).



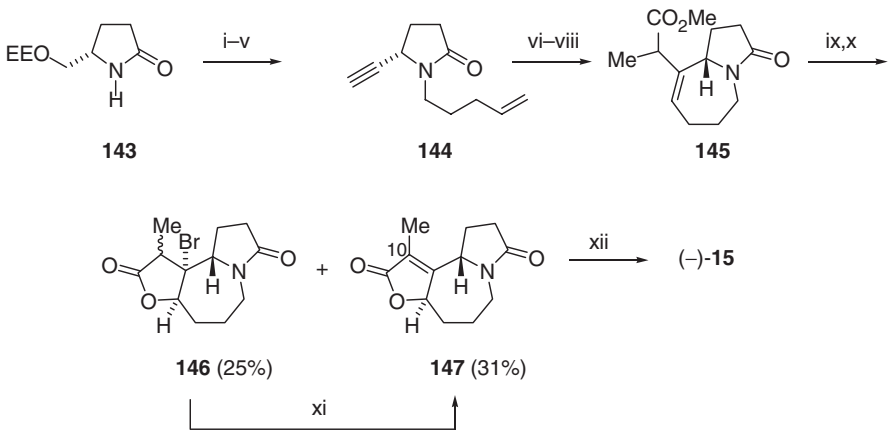
Scheme 8. *Reagents and Conditions:* (i) $SOCl_2$, MeOH; (ii) $NaBH_4$; (iii) TBSCl (92%); (iv) NaH, 4-bromo-1-butene (80%); (v) TBAF (95%); (vi) Swern oxidation; (vii) $Ph_3P{=}CHCO_2Me$ (73%, two steps); (viii) $CH_2{=}CHMgBr$, CuBr.DMS, LiBr, −78°C (81%); (ix) Grubbs type II catalyst (6 mol%), CH_2Cl_2, reflux (95%); (x) 1N NaOH, MeOH (83%); (xi) 5% $NaHCO_3$, I_2 (91%); (xii) *n*-Bu_3SnH, AIBN, toluene (70%); (xiii) LiHMDS, PhSeBr (81%); (xiv) H_2O_2 (76%); (xv) $NaBH_4$, $NiCl_2$ (78%); (xvi) LiHMDS, MeI, THF (70%).

reagent which stereoselectively afforded **133** with the opposite configuration at C9 required for (−)-stemoamide (**15**). Ring-closing metathesis reaction with Grubbs-type catalyst proceeded with an excellent yield to provide the bicyclic intermediate **134** after basic hydrolysis. After iodocyclization, dehalogenation under radical conditions provided the key tricyclic lactam **135** in good yield. The final steps involved epimerization at C9 (via selenoxide elimination and stereoselective reduction of the double bond), and methylation at C10 via a modification of the Narasaka procedure. (−)-Stemoamide (**15**) was obtained after 16 steps from (*S*)-pyroglutamic acid (**130**) and in *ca*. 7% overall yield (Scheme 8).

Kohno and Narasaka (*42*) devised a short synthesis of (+/−)-stemoamide (**15**), mistakenly designated as (+/−)-stemonamide by these authors, by applying the oxidative coupling reaction of 2-tributylstannyl *N*-Boc pyrrolidine with silyl enol ethers (Scheme 9). A 65% yield of the key intermediate **139** was produced as a mixture of stereoisomers which led to a separable mixture of diastereoisomers (**140a**:**140b** = 4:1) on hydrogenation of the acetylenic bond (Scheme 9). The formation of **139** is rationalized through the addition of silyl enol ether **138** (*E*:*Z*=1:1) to an intermediate *N*-acyliminium ion derived from *N*-Boc-2-tributylstannylpyrrolidine (Scheme 9). The stereogenic center at C8 was established after $NaBH_4$ reduction of **140a** which afforded a 59% yield of γ-lactone **141**. A 25% yield of the alcohol with the wrong stereochemistry at C8 was also obtained which was converted to **141** through a 3-step sequence. In the final steps of the synthesis, ring B was formed by intramolecular nitrogen alkylation, and the correct stereochemistry at C10 was established by stereoselective methylation of the lithium enolate of the γ-lactone. This concise approach required 12 steps from 5-benzyloxy-3-pentyn-2-one (**137**) and provided (+/−)-stemoamide (**15**) with an ~2% overall yield.



Scheme 9. *Reagents and Conditions:* (i) TBSCl, Et_3N, NaI, CH_3CN, 50°C (92%); (ii) *t*-Butyl-2-(tributilstannyl)acetate, TBACN, EtCN, K_2CO_3, MS 4 Å, 0°C (85%); (iii) TBSCl, Et_3N, NaI, CH_3CN, 50°C (60%); (iv) 1-(*t*-butoxycarbonyl)-2-(tributylstannyl)pyrrolidine, CAN, MS 4 Å, EtCN, −45°C (65%); (v) H_2, 10% Pd/C, MeOH, rt (90%, **140a**:**140b** = 4:1); (vi) **140a**, $NaBH_4$, THF, MeOH, rt (59%); (vii) 10% Pd/C, MeOH, HCO_2H, rt (89%); (viii) MsCl, Et_3N, CH_2Cl_2, rt (96%); (ix) RuO_2 (cat.), $NaIO_4$, AcOEt, H_2O, rt (60%); (x) 1 M HCl-AcOEt, rt (89%); (xi) NaH, THF, rt (62%); (xii) LDA, THF, −78°C; then, MeI, −78°C to rt (59%).

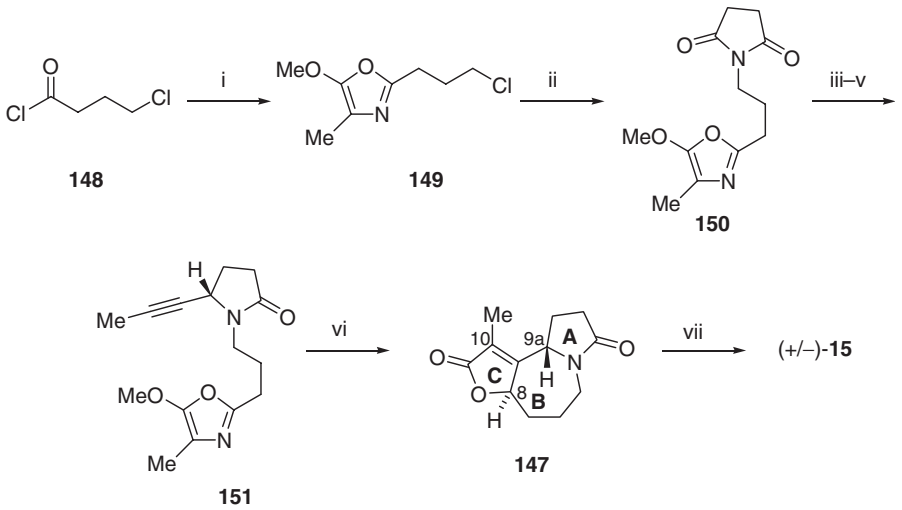


Scheme 10. *Reagents and Conditions:* (i) NaH, DMF, 5-bromopent-1-ene (89%); (ii) TsOH, MeOH (91%); (iii) $(COCl)_2$, DMSO, Et_3N; (iv) CBr_4, Ph_3P; (v) *n*-BuLi, THF, −98°C (72%, 3 steps); (vi) LDA, HMPA, THF, $ClCO_2Me$, −98°C (59%); (vii) $Cl_2Ru[P(C_6H_{11})_3]_2CHPh$, CH_2Cl_2, rt (87%); (viii) $NaBH_4$, MeOH (85%); (ix) NaOH, MeOH, H_2O; (x) $CuBr_2$ on Al_2O_3 (**146**, 25% and **147**, 31%); (xi) Et_3N, rt, **147** (50% from **145**); (xii) $NaBH_4$, $NiCl_2.6H_2O$, MeOH (76%).

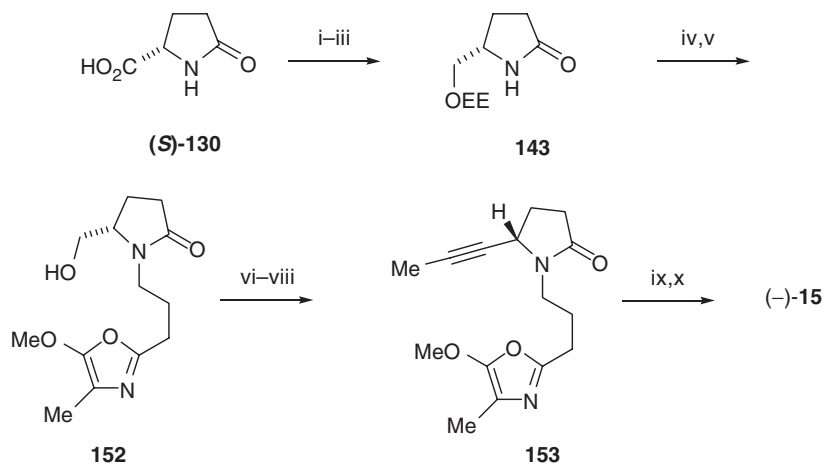
A concise and efficient approach to (−)-stemoamide (**15**) based on an intramolecular enyne metathesis was developed by Kinoshita and Mori (*69,70*). Starting from lactam **143**, prepared in two steps from (−)-pyroglutamic acid, the acetylene **144** was obtained in five steps and 58% overall yield (Scheme 10). The construction of ring B was efficiently accomplished by enyne metathesis (87% yield) using a catalytic amount of Grubb's catalyst (**144**→**145**, Scheme 10). Reduction to the saturated ester, followed by bromolactonization of the mixture of epimeric carboxylic acids, afforded the unsaturated lactone **147** (31% yield) and the corresponding bromolactone **146** (25% yield) which could be converted to **147** (50% overall yield from **145**) by treatment with Et_3N. The correct stereochemistry at C10 was established by reduction of **147** with $NaBH_4$ in the presence of $NiCl_2.6H_2O$ in methanol to give (−)-stemoamide (**15**) in 12 steps as 9.7% overall yield from **143**, and in 14 steps and 9% overall yield from (−)-pyroglutamic acid.

By far the most concise and efficient approach to (+/−)-stemoamide (**15**) was developed by Jacobi and Lee (*71,72*) and featured an intramolecular Diels-Alder/retro Diels–Alder cycloaddition between the 2-methoxyoxazole and acetylenic moieties in **151** followed by equilibration to set the correct relative configuration at C8 and C9a (**151**→**147**, Scheme 11). The stereochemistry at C9 and C10 was established after nickel boride reduction of the unsaturated butyrolactone ring and epimerization at C10 to afford a 73% yield of (+/−)-stemoamide (**15**), together with its epimer at C9 and C10. Overall, the total synthesis of (+/−)-stemoamide (**15**) was achieved in seven steps from 4-chlorobutyryl chloride (**148**) and in ∼20% overall yield.

The approach was extended to the synthesis of (−)-stemoamide (**15**) from enantiomerically pure alkyne oxazole **153**, prepared from (*S*)-pyroglutamic acid



Scheme 11. *Reagents and Conditions:* (i) $CH_3CH(NH_2)CO_2Me$, C_5H_5N; then, P_2O_5 (80%); (ii) succinimide, NaH (97%); (iii) $NaBH_4$; (iv) MeOH, H^+ (72%, 2 steps); (v) $CH_3C{\equiv}CSnBu_3$, $BF_3.OEt_2$ (92%); (vi) diethylbenzene, reflux (53%); (vii) $NaBH_4$, $NiCl_2$, MeOH, −30°C (73%).

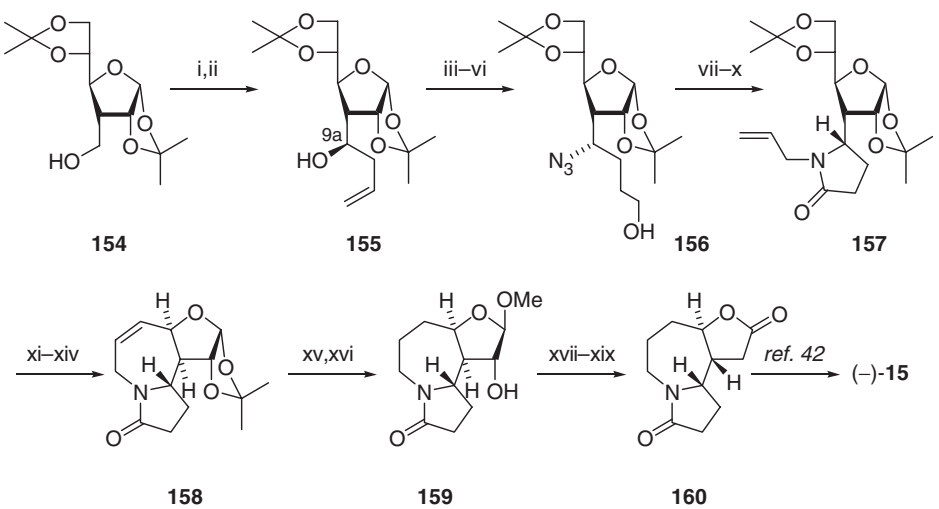


Scheme 12. *Reagents and Conditions:* (i) $SOCl_2$, MeOH; (ii) $NaBH_4$ (83%, 2 steps); (iii) $CH_2{=}$ CHOEt, $CHCl_3$, Cl_3CCO_2H (cat.), rt (93%); (iv) NaH, DMF, 0°C; then, 2-(3-chloroperoyl)oxazole (**149**), 70°C (67%); (v) TsOH (cat.), MeOH (83%); (vi) $(COCl)_2$, DMSO, CH_2Cl_2, −78°C; then, Et_3N, −78°C to rt; (vii) $(MeO)_2P(O)CHN_2$, THF, *t*-BuOK, −78°C (65%); (viii) MeI, LDA, THF, HMPA, −78°C (32%); (ix) diethylbenzene, 182°C (52%); (x) $NaBH_4$, $CeCl_3$ (73%).

(Scheme 12) (*72*). The preparation of **153** from oxazole was initially investigated via the Corey–Fuchs protocol. Low yields were observed, in part due to difficulties associated with the removal of triphenylphosphine oxide produced during the coupling process. Eventually, this problem was solved by employing hexamethylphosphorous

triamide (HMPT), a modification of the Corey–Fuchs procedure, which produced water soluble hexamethylphosphoramide (HMPA). Low yields were also observed in the conversion of the geminal dibromide formed in the previous step to the corresponding alkyne oxazole which was converted to **153** after alkylation. For preparative purposes, **153** was obtained via the Gilbert procedure (coupling with the potassium anion of dimethyl(diazomethyl)phosphonate) which afforded better yields and is less prone to cause epimerization at labile stereocenters. Thermolysis of **153** in diethylbenzene and reduction provided (−)-**15** in 10 steps and ~3% overall yield from (*S*)-pyroglutamic acid (**130**).

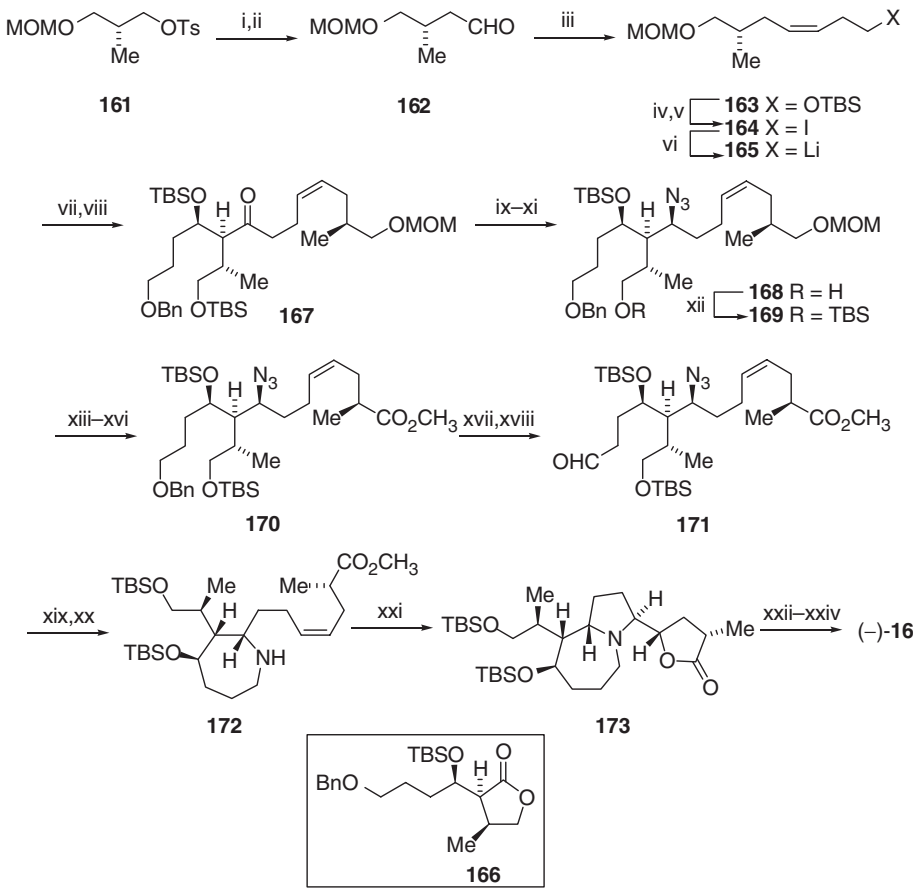
A formal synthesis of (−)-stemoamide (**15**) from allofuranose **154**, prepared from D-glucose diacetonide in three steps, was described by Gurjar and Reddy (*73*) and features the creation of the stereogenic center at C9a via a stereoselective zinc-mediated allylation (Scheme 13). The pyrrolidinone ring was then constructed after introduction of the azido functionality and proper adjustment of the oxidation state of the unsaturated side chain in **156**. A ring-closing metathesis reaction installed the seven-membered azepino ring and the hydroxyl group present in **159** was removed under the Barton–McCombie conditions. γ-Lactone **160**, the precursor of (+/−)-stemoamide (**9**) in the Kohno and Narasaka synthesis (*42*), was then prepared by oxidation with MCPBA and $BF_3.OEt_2$. The synthesis



Scheme 13. *Reagents and Conditions:* (i) $(COCl)_2$, DMSO, Et_3N, −78°C (80%); (ii) allyl bromide, Zn, satd. NH_4Cl, THF or $(CH_2{=}CHCH_2)_2Zn$, THF-Et_2O, −78°C (81%); (iii) $BH_3.(CH_3)_2S$, THF, 0°C to rt, then NaOAc, H_2O_2 (65%); (iv) TBSCl, imidazole, CH_2Cl_2, rt (90%); (v) MsCl, Et_3N, CH_2Cl_2, 0°C to rt (85%); (vi) NaN_3, DMF, 75–85°C (77%); (vii) $NaClO_2$, DMSO, NaH_2PO_4, H_2O, 0°C to rt (95%); (viii) CH_2N_2, 50% KOH soln., Et_2O, −20°C (94%); (ix) 10% Pd/C, H_2, MeOH, rt (87%); (x) allyl bromide, 50% KOH soln., C_6H_6, TBAI, rt (74%); (xi) 0.8% H_2SO_4, MeOH, rt (84%); (xii) MsCl, Et_3N, CH_2Cl_2, 0°C (70%); (xiii) NaI, ethyl methyl ketone, reflux (66%); (xiv) Grubb′s catalyst, CH_2Cl_2, reflux (83%); (xv) 10% Pd/C, H_2, MeOH, rt (85%); (xvi) Amberlyst-15, MeOH, reflux (70%); (xvii) Im_2CS, toluene, reflux; xviii) *n*-Bu_3SnH, AIBN, toluene, reflux (45%, two steps); (xix) MCPBA, $BF_3.OEt_2$, CH_2Cl_2, 0°C to rt (30%).

of tricyclic intermediate **160** was accomplished in 19 steps from **154** with ~0.4% overall yield.

The first total synthesis of (−)-stemonine (**16**) was reported by Williams and coworkers (Scheme 14) (*74*) through the construction of a fully functionalized acyclic



Scheme 14. *Reagents and Conditions:* (i) NaCN, DMSO, 70°C; (ii) DIBAL, Et_2O, −78°C to rt, then H_3O^+ (86%); (iii) $TBSO(CH_2)_3PPh_3Br$, KHMDS, Et_2O, −78°C; then, **162**; (iv) TBAF, THF, 0°C to rt; (v) PPh_3, I_2, imidazole, CH_2Cl_2 (80%); (vi) *t*-BuLi, -78 °C; (vii) **166**, Et_2O, −78°C; (viii) TBSOTf, collidine, −78°C to rt (86%); (ix) $LiEt_3BH$, THF, −78°C to rt (94% yield, *anti:syn* = 17:1); (x) MsCl, pyridine, rt (95%); (xi) NaN_3 (3 equiv.), 15-crown-3 (3 equiv.), HMPA, rt (65%); (xii) TBSOTf, collidine, −78°C (97%); (xiii) Me_2BBr, CH_2Cl_2, Et_3N, −78°C (76%); (xiv) Dess-Martin periodinane, $NaHCO_3$, CH_2Cl_2, rt; (xv) $NaClO_2$, NaH_2PO_4, *t*-BuOH, CH_3CN, 2-methyl-2-butene, 0°C; (xvi) CH_2N_2, Et_2O (83%, 3 steps); (xvii) DDQ, CH_2Cl_2, *t*-BuOH, H_2O, rt (56%); (xviii) Dess-Martin periodinane, $NaHCO_3$, CH_2Cl_2, rt (86%); (xix) $EtPPh_2$, benzene, rt; (xx) $NaBH_4$, THF, MeOH (70%); (xxi) I_2, CH_2Cl_2, Et_2O, rt (42%); (xxii) TBAF, THF, rt (77%); (xxiii) Dess-Martin periodinane, $NaHCO_3$, CH_2Cl_2, rt (69%); (xxiv) aq. CrO_3, H_2SO_4, acetone, THF, rt (68%).

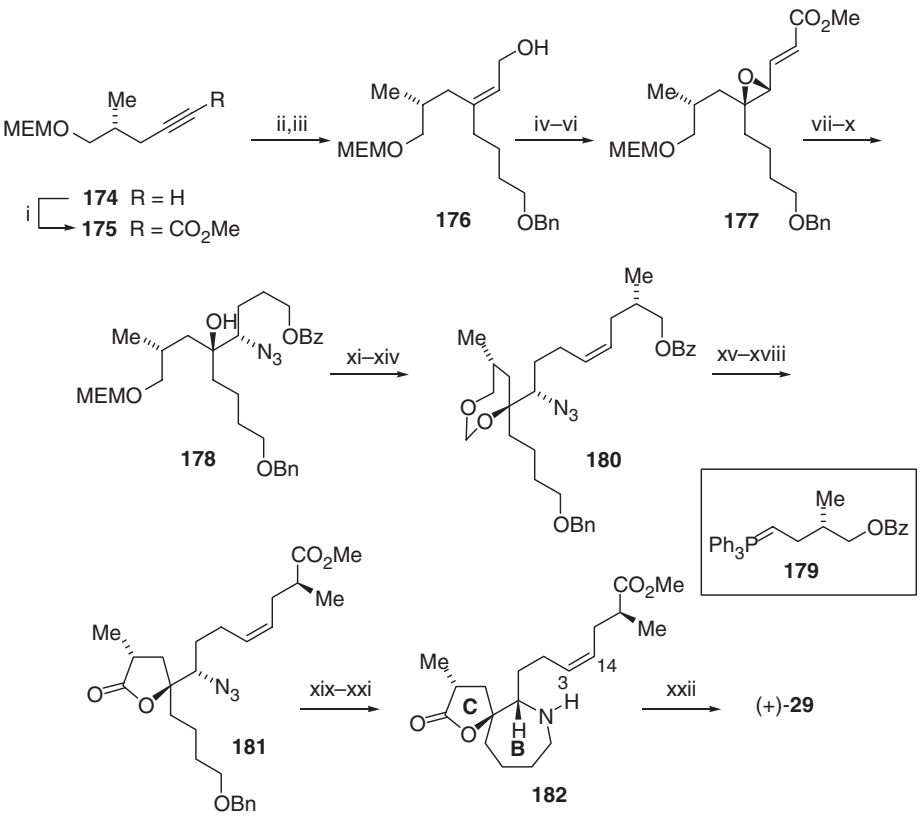
carbon chain before carrying out sequential ring closure reactions via intramolecular aza-Wittig and iodocyclization reactions. The synthesis of (−)-stemonine (**16**) was carried out in 24 steps (longest linear sequence) from **161** with an overall yield of 1%, and this features a very efficient construction of the perhydroazepine and γ-butyrolactone rings via iodine-induced cyclization with the formation of an aziridinium intermediate which is opened by the carboxymethyl group.

C. TUBEROSTEMOSPIRONINE GROUP

(+)-Croomine (**29**), a prototypical example of the tuberostemospironine group, was the first S*temona* alkaloid to yield to total synthesis. In 1989, Williams and coworkers (*75*) disclosed its total synthesis featuring an intermolecular Staudinger reaction followed by an iodoamination step to construct the pyrrolo[1,2-*a*]azepine nucleus and the γ-butyrolactone ring attached at C3 (Scheme 15). As in the total synthesis of (−)-stemoamide by the same group (*67*), Williams and coworkers started with methyl (*S*)-2-methyl-3-hydroxy propionate which was converted to acetylene **174** after four steps with a 72% overall yield. Sharpless asymmetric epoxidation of (*E*)-trisubstituted allylic alcohol **176** and a two-carbon homologation of the corresponding aldehyde provided epoxide **177** which set the stage for the regioselective epoxide opening with lithium azide (**177**→**178**, Scheme 15). Chain homologation (**178**→**180**, Scheme 15) and γ-lactone formation (**180**→**181**, Scheme 15) was followed by ring B formation through an intramolecular Staudinger reaction (**181**→**182**, Scheme 15). Rings A and D were formed in a single step by iodoamination of bicyclic intermediate **182**, an impressive transformation which also set the correct stereochemistry at C3 and C14, and yielded (+)-croomine (**29**) in 25% yield from **182** which was recovered at 50–60% yield. The first total synthesis of (+)-croomine (**29**) was carried out in 22 steps and ~1% overall yield from alkyne **174**, and 26 steps and about 0.6% overall yield from methyl (*S*)-2-methyl-3-hydroxy propionate (**174**).

A shorter and more efficient route to (+)-croomine (**29**) was devised by Martin and Barr (*76*) who employed the vinylogous Mannich addition of 2-silyloxyfuran **184** to a chiral *N*-acyliminium ion derived from (*S*)-pyroglutamic acid to connect rings A and C and to set the correct stereochemistries at C9 and C9a (**184**→**186**, Scheme 16). The stereochemistry at C11 was set after hydrogenation of the double bond in ring C (**186**→**187**, Scheme 16), probably directed by the basic nitrogen of the pyrrolidine ring. Ring B was constructed through an intramolecular nitrogen alkylation (**187**→**188**, Scheme 16). The thermally unstable acid chloride from intermediate **188** gave rise to the corresponding iminium ion which was trapped with 2-triisopropylsilyloxy-3-methylfuran. This second vinylogous Mannich transformation (**188**→**189**, Scheme 16) afforded a 47% combined yield of the desired isomer **189** and its C14 epimer (2:1 ratio) which were readily separated. The desired adduct **189** was submitted to stereoselective hydrogenation to afford (+)-croomine (**29**) in 8 steps and approximately 5% overall yield from the silyloxyfuran **183**.

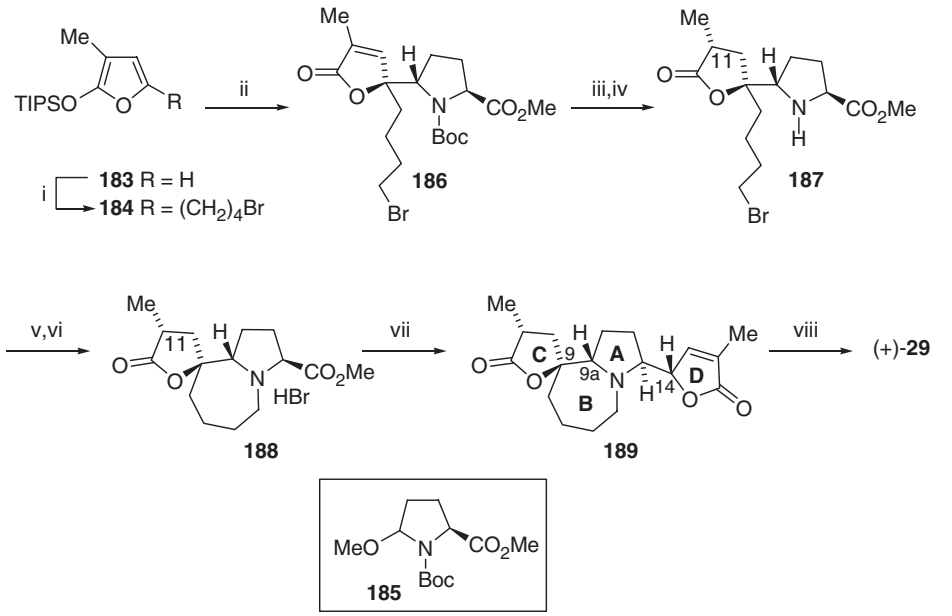
Despite the remarkable brevity of the asymmetric synthesis of (+)-croomine (**29**) (*76,77*), an even shorter route was devised by Martin and coworkers by postponing the hydrogenation of the C10–C11 double bond (Scheme 17). In fact, cyclization of **190** in *N*-methylmorfoline (NMM) afforded tricyclic pyrroloazepine **191**, which after acid hydrolysis and decarboxylation provided the corresponding minimum intermediate which was treated with 2-triisopropylsilyloxy-3-methylfuran to give the tetracyclic



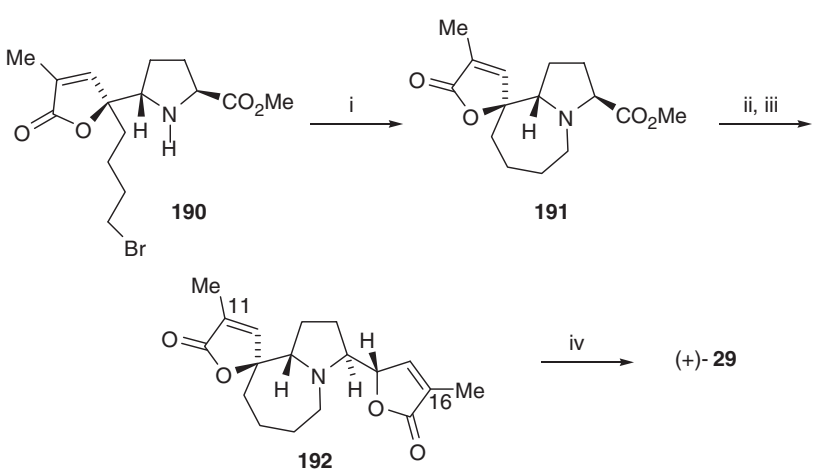
Scheme 15. *Reagents and Conditions:* (i) *n*-BuLi, THF, −78 to 0°C; then, $ClCO_2Me$, −78°C, (63%); (ii) $BnO(CH_2)_3MgBr$, DMS.CuBr, TMEDA, Et_2O, −78°C (95%); (iii) DIBAL-H, CH_2Cl_2, −78°C (98%); (iv) $Ti(OiPr)_4$ (cat.), D-DIPT (cat.), *t*-BuOOH, MS 4 Å, CH_2Cl_2, −50°C (83%); (v) $(COCl)_2$, DMSO, CH_2Cl_2, Et_3N, −78 to 0°C; (vi) $Ph_3P{=}CHCO_2Me$, 0°C to rt (89%, 2 steps); (vii) $LiBH_4$, Et_2O, MeOH, 0°C (81%); (viii) 5% Rh/Al_2O_3, H_2, THF (62%); (ix) BzCl, Et_3N, CH_2Cl_2, 0°C to rt (97%); (x) LiN_3, DMPU, 110°C (94%); (xi) $BF_3.OEt_2$, CH_2Cl_2, 0°C (81%); (xii) LiOH, THF, aq. MeOH (97%); (xiii) $(COCl)_2$, DMSO, CH_2Cl_2, Et_3N, −78 to 0°C (91%); (xiv) **179**, KO*t*-Bu, THF, −10°C (70-81%); (xv) aq. HBF_4, MeOH (72%); (xvi) LiOH, THF, MeOH, H_2O, 22°C (86%); (xvii) Jones' reagent, THF, 0°C; (xviii) CH_2N_2, Et_2O (78%, 2 steps); (xix) BCl_3, CH_2Cl_2, −78 to 0°C; then, MeOH, −78°C (77%); (xx) $(COCl)_2$, DMSO, CH_2Cl_2, Et_3N, −78 to 0°C (92%); (xxi) Ph_3P, THF, 22 °C; then, $NaBH_4$, MeOH (90%); (xxii) I_2, CH_2Cl_2, Et_2O, 22°C (25%).

pyrroloazepine **192** and its C14 epimer as a 2:1 mixture of diastereoisomers. Catalytic hydrogenation under acid conditions provided (+)-croomine (**29**) as the only isolable product in 81% yield.

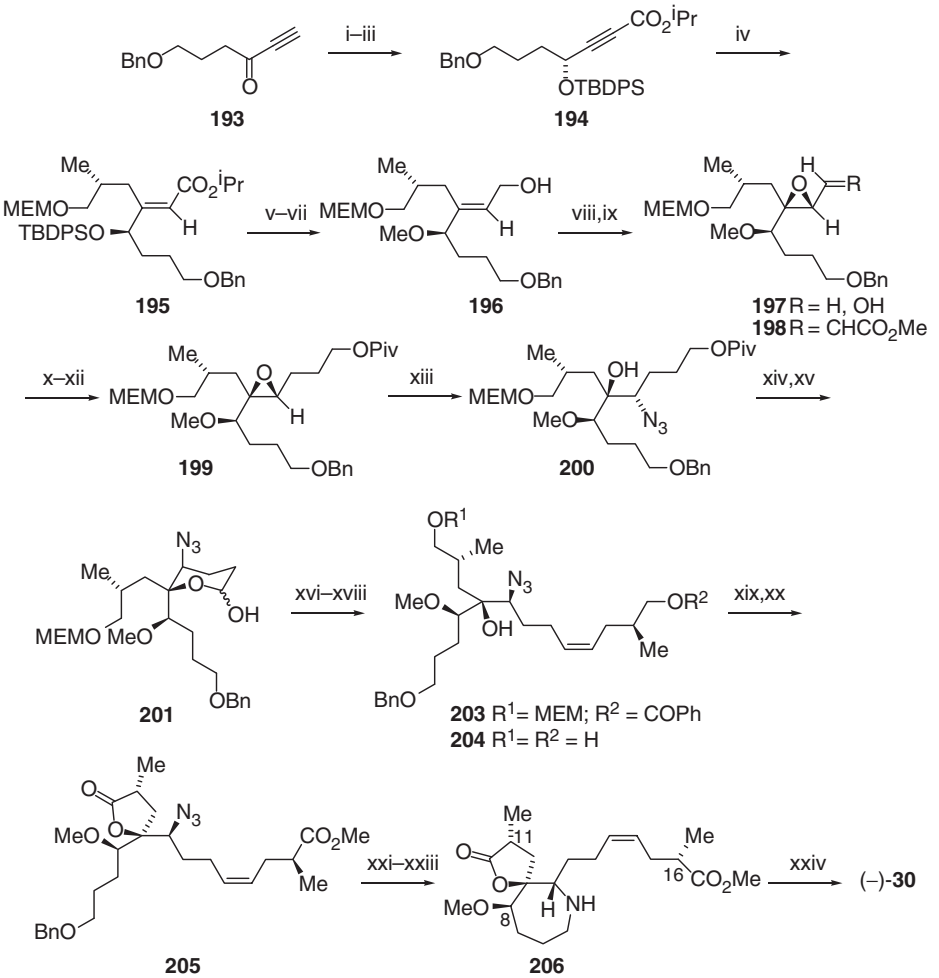
The first total synthesis of stemospironine (**30**), a structurally complex *Stemona* alkaloid, was accomplished by Williams and coworkers (*78*) (Scheme 18), using the same strategy successfully applied by the same group for the total synthesis of croomine and



Scheme 16. *Reagents and Conditions:* (i) *s*-BuLi, TMEDA, THF, 0°C; then, $BrCH_2(CH_2)_2CH_2Br$ (83%); (ii) **185**, 5% TIPSOTf, CH_2Cl_2, 0°C (32%); (iii) CF_3CO_2H, CH_2Cl_2, rt; (iv) 3% Rh/C, H_2, EtOAc, EtOH (> 96%, 2 steps); (v) *N*-methylmorpholine, DMF, reflux; (vi) 3 M aq. HBr, 60°C (74%, 2 steps); (vii) $POCl_3$, DMF, rt; then, **183** (~32%); (viii) 10% Pd-C, H_2, 10% HCl/EtOAc (85%).



Scheme 17. *Reagents and Conditions:* (i) *N*-methylmorfoline, DMF, 160°C (51%); (ii) 3N HBr, 60°C; (iii) $POCl_3$, DMF, rt; then, 2-triisopropylsilyloxy-3-methylfuran (26%); (iv) H_2, 10% Pd-C, EtOH, HCl (81%).



Scheme 18. *Reagents and Conditions:* (i) (*R*)-Alpine Borane, THF, −10°C to rt (95%, 88% ee); (ii) TBDPSCl, imidazole, CH_2Cl_2, rt (80%); (iii) *n*-BuLi, $ClCO_2iPr$, THF, −78°C (90%); (iv) (*S*)-$MEMOCH_2CH(CH_3)CH_2MgBr$, CuBr.DMS, THF, −78°C to rt (70%); (v) TBAF, THF, rt (90%); (vi) NaH, MeI, DMF (85%); (vii) DIBAL-H, CH_2Cl_2, −78°C (92%); (viii) $Ti(OiPr)_4$, CaH_2, SiO_2, (−)-DIPT, *t*-BuOOH, CH_2Cl_2, −20°C, 72 h (85–90%, 4:1 mixture of isomers); (ix) Dess-Martin periodinane, pyridine, CH_2Cl_2; then, $Ph_3P{=}CHCO_2CH_3$ (60%, 2 steps); (x) 5% Rh-Al_2O_3, H_2, THF (85%); (xi) $LiBH_4$, CH_3OH, Et_2O (90%); (xii) PivCl, pyridine, DMAP (91%); (xiii) LiN_3, NH_4Cl, DMPU, 130°C (83%); (xiv) LiOH, THF, MeOH, H_2O (94%); (xv) Swern oxidation (97%); (xvi) KO*t*-Bu, (*S*)-$Ph_3P^+(CH_2)_2CH(CH_3)CH_2OBzI^-$ (**202**), THF, −10°C (77%); (xvii) HCl, THF, rt (85%); (xviii) LiOH, THF, H_2O, MeOH (88%); (xix) Jones′ reagent, THF, −10°C; (xx) CH_2N_2, Et_2O, 0°C (80%, 2 steps); (xxi) BCl_3, CH_2Cl_2, −78°C to rt (60%); (xxii) Dess-Martin periodinane, CH_2Cl_2 (80%); (xxiii) PPh_3, THF; then, $NaBH_4$, MeOH, rt (60%); (xxiv) I_2, CH_2Cl_2, Et_2O, rt (30%).

stemoamide (*78*). This approach features the construction of a fully functionalized acyclic carbon chain, followed by sequential ring closures. For this particular target, the stereochemistry at C11 and C16 was designed to come from (*S*)- and (*R*)-methyl 3-hydroxy-2-methylpropionate, respectively.

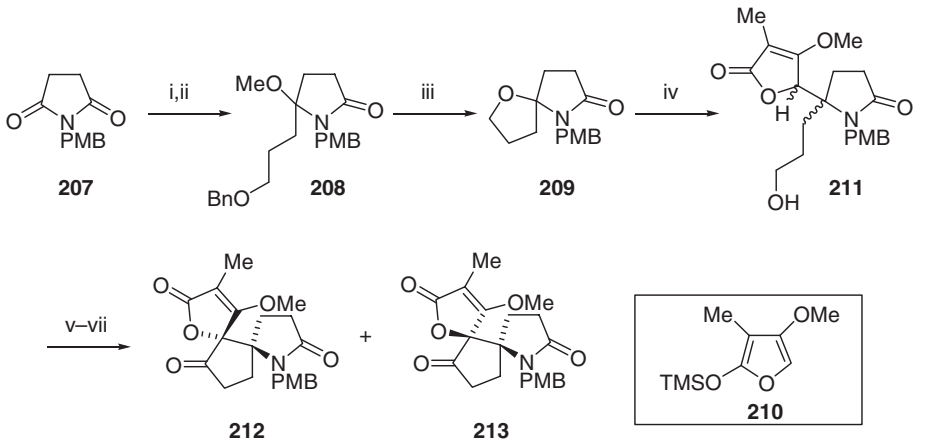
(*R*)-Alpine borane reduction of the propargylic ketone **193** resulted in the corresponding alcohol (88% ee) displaying the stereogenic center at C8 (stemospironine numbering). After hydroxyl group protection and acylation of the terminal acetylene, propargylic ester **194** underwent stereoselective Cu(I)-catalyzed conjugate addition of a Grignard reagent (prepared from (*S*)-methyl 3-hydroxy-2-methylpropionate) to afford the (*E*)-α,β-unsaturated ester **195**. After functional group manipulations, allylic alcohol **196** underwent Sharpless asymmetric epoxidation with (−)-DIPT to provide a 4:1 mixture of stereoisomers. The major isomer was isolated by flash silica gel chromatography and was converted to the (*E*)-α,β -unsaturated ester **198**. Reduction to the corresponding primary alcohol and protection as the pivalic ester provided epoxide **199** which underwent epoxide opening with lithium azide in DMPU with solid ammonium chloride at 130°C to provide azido alcohol **200** in 83% yield. Exposure of the primary alcohol and Swern oxidation led to a 3:1 ratio of lactols **201** and the corresponding hydroxyaldehyde. Treatment of this equilibrating mixture with triphenylphosphorane derived from **202** provided exclusively the *Z*-alkene **203**. Acid removal of the MEM protecting group and basic hydrolysis of the benzoate ester provided triol **204**. Jones' oxidation, followed by esterification with diazomethane, provided lactone **205** in 80% yield (two steps). Cleavage of the benzyl ether at low temperature with BCl_3, followed by Dess–Martin oxidation, gave the key azido aldehyde intermediate for the aza-Wittig step. Upon exposure to triphenylphosphine, the corresponding aza-ylide underwent the aza-Wittig reaction to provide a seven-membered imine for the *in situ* reduction with sodium borohydride. Iodine-promoted, stereoselective double cyclization of azepine **206** provided (−)-stemospironine (**30**) in reproducible 30% yield via the anchimeric assistance of the tertiary nitrogen of the pyrrolo azepine intermediate and iodide-promoted cleavage of the methyl ester.

Comparisons of the spectral data of synthetic and natural (−)-stemospironine (**30**) showed these two substances to be identical. Williams and coworkers also compared the NMR data for natural stemonidine (**33**), isolated by Xu and coworkers (*47*) in 1982 from the roots of *S. tuberosa*, with those of natural and synthetic stemospironine (**30**). This revealed striking similarities between these two samples casting doubt on the structure assigned for the alkaloid stemonidine (**33**).

The first total synthesis of (−)-stemospironine (**30**) was carried out in 24 steps and less than 1% overall yield from propargylic ketone **193**, prepared in two steps from 4-benzyloxybutenal (*78*).

D. STEMONAMINE GROUP

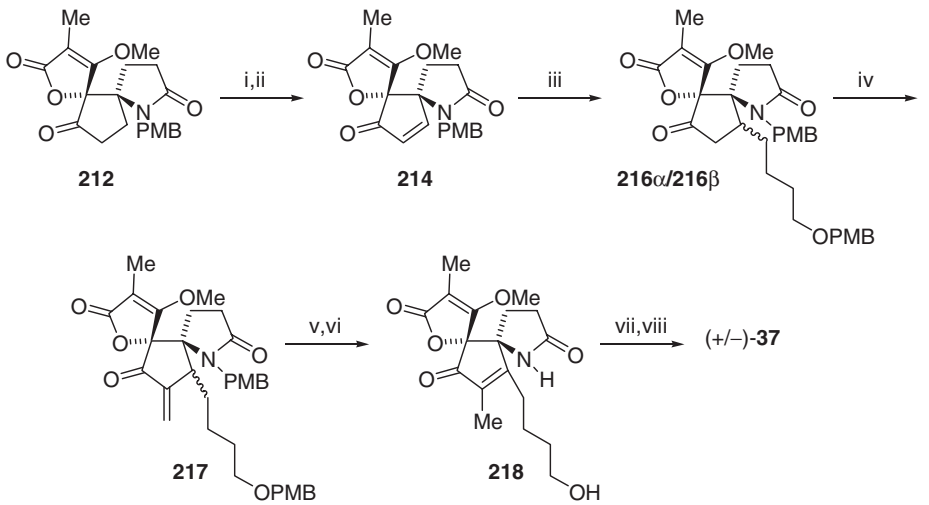
The first total syntheses of (+/−)-stemonamide (**37**) and (+/−)-isostemonamide (**38**) were carried out by Kende and coworkers (*79,80*) based on *N*-acyliminium chemistry (Scheme 19). The key tricyclic intermediates **212** (for stemonamide) and **213** (for isostemonamide) were rapidly constructed via the addition of silyloxyfuran **210** to the *N*-acyliminium ion precursor **209**, prepared in three steps and 81% overall yield from *N*-4-methoxybenzylsuccinimide (**207**). The resulting mixture of diastereoisomeric alcohols **211** (1:2 mixture) underwent oxidation to the corresponding aldehydes under Swern



Scheme 19. *Reagents and Conditions:* (i) $BnO(CH_2)_3MgBr$, Et_2O, reflux; (ii) PPTS, MeOH, rt (90%, 2 steps); (iii) H_2, Pd/C, MeOH, rt (90%); (iv) **210**, $BF_3.Et_2O$, CH_2Cl_2, rt (82%); (v) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2; (vi) DBU, CH_2Cl_2, rt; (vii) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2 (70%, 3 steps).

conditions. DBU-mediated aldol spirocyclization afforded tricyclic ketones **212** and **213** as a 1:1 mixture which were readily separated by column chromatography.

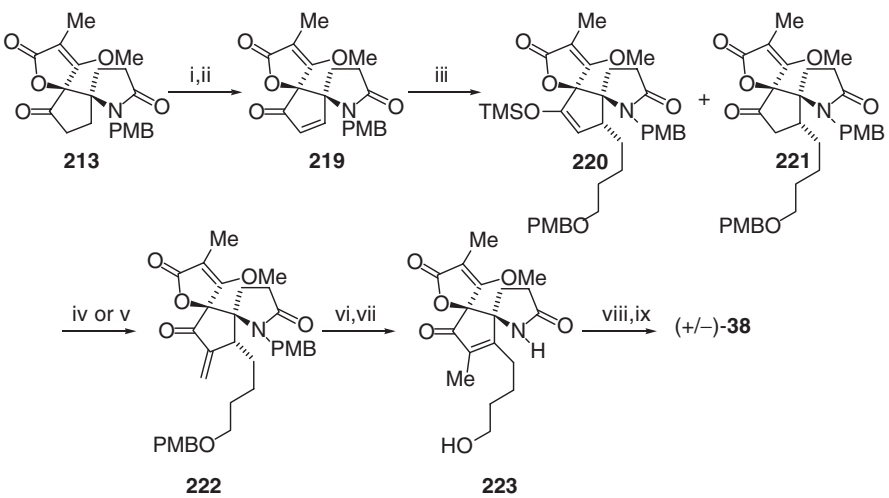
The total synthesis of (+/−)-stemonamide (**37**) (Scheme 20) proceeded from **212** via the Saegusa oxidation of the corresponding silyl enol ether to provide the



Scheme 20. *Reagents and Conditions:* (i) TBDMSOTf, collidine, toluene, 0°C to rt (80%); (ii) $Pd(OAc)_2$, O_2, DMSO, 80°C (93%); (iii) $PMBO(CH_2)_4MgBr$ (**215**), 5% CuBr.Me_2S, TMSCl, HMPA, THF, −78°C (74%, 6.4:1 mixture of **216***α*/**216***β*); (iv) KH, $Me_2N^+{=}CH_2CF_3CO_2^-$, THF, 0°C to rt (67%); (v) CAN, CH_3CN–H_2O (80%); (vi) $RhCl_3.xH_2O$, EtOH-H_2O, reflux (66%); (vii) MsCl, DMAP, pyridine, CH_2Cl_2, 0°C (71%); (viii) NaH, THF, rt (46%).

α,β-unsaturated ketone **214** in 93% yield. With the requisite unsaturated double bond installed, the stage was set for the Cu(I)-catalyzed conjugate addition of Grignard reagent **215** carrying the four-carbon segment necessary for the construction of the azepine ring. The best experimental conditions involved the use of HMPA and TMSCl as additives and afforded ketones **216**α and **216**β in 74% yield and 6.4:1 molar ratio. Tricyclic ketone **216**α underwent a Mannich reaction to introduce the exocyclic double bond in **217** (67% yield). The initial unsuccessful attempts to isomerize the double bond to the endocyclic position with rhodium trichloride hydrate were assigned to steric factors. After removal of both PMB groups with cerium(IV) ammonium nitrate, the isomerization was achieved in 66% yield. Alcohol **218** was uneventfully transformed to (+/−)-stemonamide (**37**) after mesylation and intramolecular displacement (33% yield, two steps). In summary, the first total synthesis of (+/−)-stemonamide was carried out in 15 steps with 1.3% overall yield from *N*-4-methoxybenzylsuccinimide (**207**) (*80*).

The total synthesis of (+/−)-isostemonamide (**38**) (Scheme 21) proceeded from **213** according to the sequence described for (+/−)-stemonamide (**37**) (Scheme 20) in 16 steps and in ~3.5% overall yield from **207**. In the Cu(I)-mediated addition of Grignard reagent **215** to the α,β-unsaturated ketone **219** only α-attack was observed, and ketone **221** and the corresponding silyl enol ether **220** were formed in 32% and 57% yield, respectively. Both compounds were converted to the α-methylene lactone **222** under treatment with the Mannich reagent *N*,*N*-dimethylformaldimmonium trifluoroacetate, albeit under different experimental conditions (*80*).



Scheme 21. *Reagents and Conditions:* (i) TBDMSOTf, collidine, toluene, 0°C to rt (68%); (ii) $Pd(OAc)_2$, O_2, DMSO, 80°C (89%); (iii) $PMBO(CH_2)_4MgBr$ (**215**), 5% $CuBr.Me_2S$, TMSCl, HMPA, THF, −78°C (**220**, 57%, **221**, 32%); (iv) from **220**: $Me_2N^+{=}CH_2CF_3CO_2^-$, CH_2Cl_2, rt (96%); (v) from **221**: $Me_2N^+{=}CH_2CF_3CO_2^-$, KH, THF (85%); (vi) CAN, CH_3CN-H_2O (75%); (vii) $RhCl_3.xH_2O$, EtOH-H_2O, reflux (69%); (viii) MsCl, DMAP, pyridine, CH_2Cl_2; 0°C (83%); (ix) NaH, THF, rt (70%).

E. STEMOFOLINE GROUP

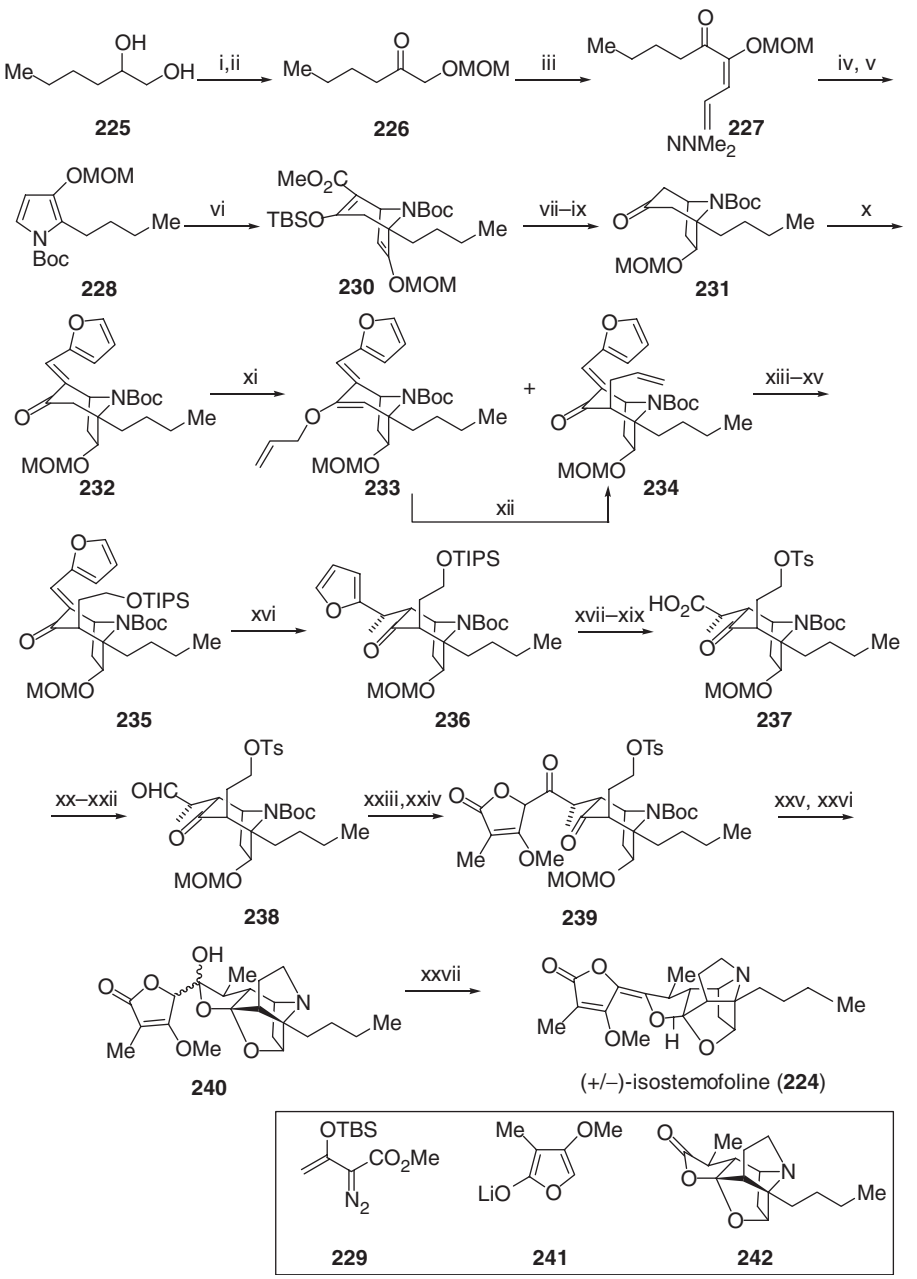
The first total synthesis of the intricate *Stemona* alkaloid (+/−)-isostemofoline (**224**)[b] was reported by Kende and coworkers (*81*) starting from 1,2-hexanediol (**225**) which was straightforwardly converted to **227** (Scheme 22) (*82*). Reductive cyclization with sodium hydrosulfite in refluxing aqueous ethanol, and protection of the unstable pyrrole as *tert*-butyl carbamate, afforded **228** in five steps with 12% overall yield. The key bicyclic ketone **231** was assembled by [4 + 3] cycloaddition of pyrrole **228** and diazoester **229** promoted by rhodium octanoate dimer, followed by enol silane deprotection, *exo*-specific hydrogenation, and nucleophilic decarboxylation (47% overall yield). Sodium methoxide-catalyzed aldol condensation of ketone **231** and furfural provided the α,β-unsaturated ketone **232** whose olefin configuration was established by nOe studies. Allylation of **232** provided a 2.4:1 mixture of ketone **234** and the corresponding allylic enol ether **233**, which could be converted to the former via a stereoselective Claisen rearrangement.

Protected keto alcohol **235** was prepared via oxidative cleavage, and $Zn(BH_4)_2$ reduction of the aldehyde provided the primary alcohol which spontaneously cyclized to the corresponding hemiketal. Treatment with TIPSCl and imidazole afforded the TIPS-protected keto alcohol **235** (three steps, 48% overall yield). Conjugate addition was successfully carried out with MeLi and DMPU in ether to provide **236** as a single diastereoisomer. *O*-Desilylation and tosylation of the primary alcohol was followed by ozonolysis of the furyl substituent to provide carboxylic acid **237** in 53% overall yield. The conversion of carboxylic acid **237** to the corresponding aldehyde **238** required formation of the mixed anhydride, $NaBH_4$ reduction to the primary alcohol, and Dess–Martin periodinane oxidation (30% overall yield).

Installation of the butenolide appendage was carried out by addition of the lithium anion of 4-methoxy-3-methyl-2(5*H*)furanone (**241**) to aldehyde **238** to provide a 2:1 mixture of diastereoisomeric alcohols **239**, which was converted to a 2:1 mixture of diastereoisomeric ketones after Dess–Martin oxidation. Treatment of the respective ketones with trifluoroacetic acid, followed by adjustment of the pH to 10, triggered a tandem triple cyclization to give stemofoline hydrate **240** in 67% yield. Dehydration of **240** proved surprisingly difficult due to the propensity for **240** to undergo retro-aldolization to provide pentacyclic lactone **242**. Treatment of **240** with triflic anhydride provided a 12% yield of a single dehydration product (along with 24% of pentacyclic ketone **242**) which proved to be identical by TLC and ^{1}H-NMR spectroscopy with an authentic sample of natural isostemofoline. The synthetic sample was compared and shown to be identical to isostemofoline (**224**).

The first total synthesis of (+/−)-isostemofoline (**224**) (Scheme 22) was accomplished in 27 steps and in less than 0.1% overall yield from 1,2-hexanediol featuring a [4 + 3] cycloaddition of a substituted *N*-Boc pyrrole and a vinyl diazoester, the use of a furyl substituent as a surrogate of a carboxylic acid residue, and the formation of an (*E*)-conjugate butenolide via dehydration of the corresponding alcohol (*81*).

[b]The isolation of isostemofoline (**224**) by Professor Yang Ye has been informed (*81*), *but literature data on its isolation and structural elucidation were not available.*



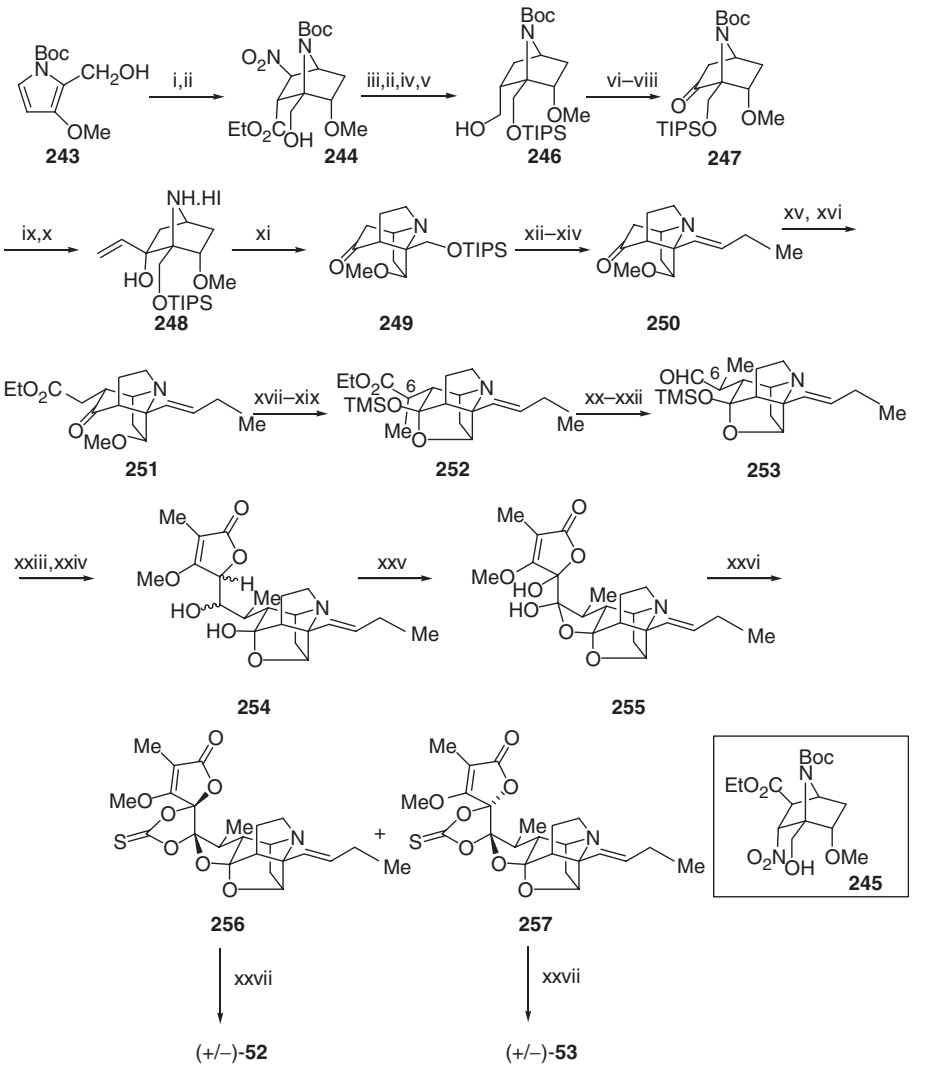
Scheme 22. *Reagents and Conditions:* (i) aq. NaOCl, HOAc (65%); (ii) MOMCl, *i*-Pr_2NEt, CH_2Cl_2, 0°C to rt (93%); (iii) $Me_2NN{=}CHCHO$, KOEt (80%); (iv) $Na_2S_2O_4$, EtOH, H_2O, 90°C (35%); (v) $(Boc)_2O$, DMAP, CH_3CN (72%); (vi) **229**, rhodium octanoate dimer, pentane, reflux (90%); (vii) Bu_4NF, THF (65%); (viii) H_2, 5% Pd/C, MeOH (90%); (ix) H_2O, DMSO, 150°C (90%); (x) furfuraldehyde, NaOH, MeOH, H_2O, reflux (90%); (xi) LiHMDS, DMPU

(*contd*)

The synthesis of (+/−)-didehydrostemofoline (**52**) and (+/−)-isodidehydrostemofoline (**53**), displaying the unique 1-azatricyclo[5.3.0.0^{4,10}]decane and 4-methoxy-3-methyl-5-tetrahydrofuran-2-ylidene-2(5*H*)furanone moieties, by Overman and coworkers (*82*) centered on the construction of the key intermediate **247** by an aza-Cope-Mannich rearrangement (Scheme 23). The synthesis started with a Diels-Alder reaction of the readily available pyrrole **243** (prepared in two steps and >95% yield from 3-methoxypyrrole carboxaldehyde) and ethyl (*E*)-3-nitroacrylate which afforded a mixture of two stereoisomers which underwent hydrogenation to give the bicyclic nitroester **244** in 73% yield, together with the corresponding regioisomer **245** (13%). The azabicycloheptane **244** structure was confirmed by X-ray crystallographic analysis of its methyl ester. After serving to activate the dienophile, the nitro group was removed by treatment with DBU, followed by hydrogenation. The primary alcohol was protected as the TIPS ether, and the ester residue was reduced to the primary alcohol **246** in order to carry out the requisite one-carbon removal via oxidation to the corresponding aldehyde with Dess–Martin periodinane, formation of the corresponding silyl enol ether and ozonolysis (37% overall yield from **244**). After vinyl addition to ketone **247** and *N*-Boc deprotection, the stage was now set for the key tandem iminium ion formation, [3,3]-sigmatropic rearrangement, and Mannich cylization which provided azatricyclo[5.3.0.0^{4,10}]decanone **249** in nearly quantitative yield. Once an efficient route to **249** was secured, the (*E*)-butenyl side chain present in **250** was introduced uneventfully via Julia–Kocienski olefination, while a two-carbon homologation was carried out via the alkylation of the kinetic lithium enolate of ketone **250** with ethyl iodoacetate, followed by DBU-catalyzed epimerization. Cleavage of the methyl ether in **251** with BBr_3 allowed lactol formation which, after silylation, underwent alkylation via the lithium enolate of the ethyl ester side chain affording a 54% overall yield of **252**. X-Ray diffraction analysis of the corresponding primary alcohol revealed the incorrect configuration at C6 (didehydrostemofoline numbering) which could be fixed via oxidation of the aforementioned alcohol to the corresponding aldehyde and equilibration in the presence of silica (or DBU) to provide aldehyde **253** as a 94:6 mixture of separable epimers from which the major epimer **253**, with the correct configuration at C6, could be isolated as a 68% yield.

The introduction of the tetrahydrofuranylidene butenolide unit was achieved starting with the addition of the lithium anion of 4-methoxy-3-methyl-2(5*H*)furanone (**241**) (Scheme 22), followed by acid cleavage to provide lactol **254** which was oxidized with an excess of *o*-iodoxybenzoic acid (IBX) in DMSO to yield **255**. Condensation with thiophosgene at −50°C provided a 3.5:1 mixture of cyclic thiocarbonates **256** and **257** as a 68% yield, the ratio depending on the reaction temperature. Finally, thiocarbonate **256** was converted to (+/−)-didehydrostemofoline (**52**) in 66% yield after treatment with trimethyl phosphate at 120°C, while (+/−)-isodidehydrostemofoline was isolated in 64% yield from thiocarbonate **257**.

(1.1 equiv.), THF, 0°C; then allyl iodide, rt (91%); (xii) toluene, reflux (86%); (xiii) K_2OsO_4, $NaIO_4$, Et_2O, H_2O, rt; (xiv) $Zn(BH_4)_2$, THF, −10°C (52%, 2 steps); (xv) TIPSCl, imidazole, DMF (93%); (xvi) MeLi (2.2 equiv.), DMPU (1.1 equiv.), Et_2O, −40°C (85%); (xvii) Bu_4NF, THF (90%); (xviii) TsCl, pyridine, $CHCl_3$ (90%); (xix) O_3, CH_2Cl_2, Me_2S (65%); (xx) *i*-BuOCOCl, *N*-methylmorpholine, THF, 0°C; (xxi) $NaBH_4$, MeOH; (xxii) Dess–Martin periodinane, CH_2Cl_2 (30%, 3 steps); (xxiii) **241**, THF, −78°C (56%); (xxiv) Dess-Martin periodinane, CH_2Cl_2 (61%); (xxv) TFA; (xxvi) satd. aq. $NaHCO_3$ (67%); (xxvii) Tf_2O, CH_2Cl_2 (12%).



Scheme 23. *Reagents and Conditions:* (i) (*E*)-$NO_2CH{=}CHCO_2Et$, rt; (ii) H_2, Pd/C, EtOAc, rt (**244**: 73%; **245**: 13%); (iii) DBU, CH_2Cl_2, rt; (iv) TIPSOTf, 2,6-lutidine, CH_2Cl_2; (v) DIBAL-H, toluene, −78°C (51% overall); (vi) Dess–Martin periodinane, CH_2Cl_2, rt; (vii) TIPSOTf, Et_3N, CH_2Cl_2, −78°C; (viii) O_3, MeOH–CH_2Cl_2 (72% overall); (ix) $CH_2{=}CHMgBr$, $CeCl_3$, THF, −78°C; (x) TMSI, 2,6-lutidine, 0°C to rt, MeOH (85%); (xi) $(CH_2O)_n$, toluene-CH_3CN, 80°C (94%); (xii) TBAF, THF, rt; (xiii) SO_3.py, Et_3N, DMSO, rt; (xiv) $C_7H_5N_4SO_2nPr$, KHMDS, DME, −55°C (70% overall); (xv) LDA, THF; ICH_2CO_2Et, −10 °C; (xvi) DBU, toluene, 130°C (67% overall); (xvii) BBr_3, CH_2Cl_2, −78°C to −10°C; aq. NaOH; (xviii) TMS-imidazole, 130°C; (xix) LDA, MeI, THF-DMPU, −45°C (54% overall); (xx) DIBAL-H, CH_2Cl_2, −78°C (98%); (xxi) Dess-Martin periodinane, rt; (xxii) SiO_2, $CHCl_3$, rt (54% overall); (xxiii) **241**, THF, −78°C; (xiv) aq. HCl, $CHCl_3$–MeOH, rt (93%); (xxv) IBX, DMSO, 55°C (55%); (xxvi) $CSCl_2$, DMAP, CH_2Cl_2, −50°C (68%, **254:255**=3.5:1); (xxvii) $P(OMe)_3$, 120°C (66% for **256**, and 64% for **257**).

Overall, the first total synthesis of (+/−)-didehydrostemofoline (**52**) was carried out in 27 steps from *N-terc*-butoxycarbonyl-1-hydroxymethyl-3-methoxy pyrrrole with less than 1% yield featuring a Diels–Alder and an aza-Cope-Mannich reaction as the key transformations in the first preparation of a member of the stemofoline family of *Stemona* alkaloids possessing the *Z* configuration of the tetrahydrofuranylidene butenolide substituent.

IV. Biological Activity

The remarkable insecticide, vermifuge, and anticough activities reported for the *Stemona* extracts in the traditional medicine system of China and Japan (*6,7,24,33,83* have motivated the study of the biological activity of the crude extracts of some *Stemona* species, as well as of the isolated alkaloids.

The basic methanolic extract from the fresh leaves of *S. japonica* showed strong insecticidal activity against *Bombix mori* L. (silk worm larvae) (*33*). The insecticidal activity of the methanolic extracts from the leaves and roots of *S. tuberosa* and *S. collinsae* were investigated against the larvae of *Spodoptera littoralis* Boisduval (*22*). Bioassays were carried out using different methodologies (chronic feeding, leaf disk choice, and contact toxicity) in order to compare the different bioactive properties. Both extracts from *S. collinsae* were shown to be more active, but more toxic, than those from *S. tuberosa* on the basis of chronic feeding bioassays. The leaf disk choice test revealed strong antifeedant activity for *S. collinsae* and remarkable repellence for *S. tuberosa* (*22*). The lipophilic crude extracts from the leaves and roots of *S. curtisii, S. cochinchinensis, S. kerrii*, and the unidentified species HG 915 (*Stemona* sp.) were also bioassayed against *Spodoptera littoralis* (polyphagous pest insect) on the basis of the chronic feeding test. *S. curtisii* and *S. cochinchinensis* extracts were the most active followed by moderate insecticidal activity for *S. kerrii*, and only a weak effect for the *Stemona* sp. (*36*). A moderate larvicidal activity was found when the crude extract from the roots of *S. curtisii* was evaluated against the mosquito larvae *Anopheles minimus* Ho (*58*).

The biological activities of some *Stemona* alkaloids were also evaluated in order to find the active principles of *Stemona* species. Tuberostemonine (**4**) was the first *Stemona* alkaloid to have its biological activity tested. The anthelminthic activity of this alkaloid was detected against *Angiostrongylus cantonensis, Dipylidium caninun*, and *Fasciola hepatica* with an effect on the motility of these helminthic worms (*83*). Tuberostemonine (**4**) was pointed out as the bioactive principle responsible for the insecticidal activity of *S. tuberosa*, with activity levels comparable to those of azadirachtin, after being tested against the larvae of *Spodoptera littoralis* (*22*). The action of tuberostemonine (**4**) on the neuromuscular transmission in crayfish (a model for studying the mechanism of drug action in the mammalian central nervous system) was also investigated, revealing that this alkaloid depressed glutamate-induced responses at similar concentrations of those of established glutamate inhibitors (*83*). The alkaloids stemonine (**16**), stemospironine (**30**) and stemofoline (**48**) had their insecticidal activity tested against the fourth instar silk worm larvae (*Bombix mori* L). Stemofoline (**48**) was 10^4 times more potent than the alkaloids stemonine (**16**) and stemospironine (**30**) (*33*). On the other hand, these three alkaloids showed no activity against the fifth instar larvae of *Mamestra brassicae* (cabbage army worm) (*33*). The antifeeding activity of neostemonine (**17**) and isoprotostemonine (**23**) was tested against the last-instar larvae of *Spodoptera litura* showing little activity. Additionally, no antimicrobial and antiviral activities were

detected for these two alkaloids (*15*). The *Stemona* alkaloids didehydrostemofoline (**52**) (also named 16,17-didehydro-16(*E*)-stemofoline), identified as the major alkaloid of *S. collinsae*, exhibited higher toxicity than the co-occurring alkaloids stemofoline (**48**) and 2′-hydroxystemofoline (**51**) when these three alkaloids were tested against *Spodoptera littoralis* on the basis of the diet feeding test (*22*). Stemofoline (**48**) and didehydrostemofoline (**52**) showed higher activities than those of Pyrethrum extract when the contact toxicity tests were carried out (*22*). The stemocurtisine-type alkaloids stemocurtisine (**58**), also named as pyridostemin, stemokerrin (**59**), methoxystemokerrin-*N*-oxide (**60**), oxystemokerrin (**61**), and oxystemokerrin-*N*-oxide (**62**), the stemoamide-type alkaloids protostemonine (**19**), oxyprotostemonine (**21**), dehydroprotostemonine (**20**) and stemocochinin (**24**), and parvistemonine (**42**), a parvistemoline-type alkaloid, were also tested against *Spodoptera littoralis* on the basis of the chronic feeding test (*36*). Oxystemokerrin (**61**) and dehydroprotostemonine (**20**) displayed the strongest insecticidal activity amongst the *Stemona* alkaloids tested. The presence of the unsaturated 4-methoxy-3-methyl-2-furanone moiety seemed to be very important for the observed biological activity since a strong decrease of the insecticidal activity was observed for both stemocochinin (**24**) and parvistemonine (**42**) (*36*). The insecticidal and anti-feedant activities of the alkaloids stemofoline (**48**) and 16,17-didehydro-16(*E*)-stemofoline (**52**) (also named didehydrostemofoline) were tested against the third instar larvae of *Plutella xylostella*, showing higher activity for **52** (*54*). The alkaloids oxyprotostemonine (**21**), stemocurtisine (**58**), and stemocurtisinol (**63**), isolated from the roots of *S. curtisii*, had their larvicidal activities evaluated against *Anopheles minimus* Ho. In this case, oxyprotostemonine (**21**) was identified as the most active alkaloid (*58*).

The antitussive activity of the aqueous and alkaloid extracts from the roots of *S. tuberosa*, and five isolated stenine-type alkaloids: neostenine, also named isostenine (**3**), tuberostemonine J (**6**), tuberostemonine H (**7**), *epi*-bisdehydroneotuberostemonine J (**12**) and neotuberostemonine (**13**), were evaluated in a guinea pig cough model. The alkaloid extract showed much more potent activity than the aqueous extract, indicating that the *Stemona* alkaloids are responsible for the antitussive activity of *S. tuberosa*. Neotuberostemonine (**13**) was the most active alkaloid, followed by neostenine, also named isostenine (**3**), tuberostemonine H (**7**), and tuberostemonine J (**6**) (*2*).

The antitumoral activity of the crude extracts from *S. tuberosa* and *S. collinsae* was evaluated against eight cell lines of the medullary thyroid carcinoma (MTC). *S. tuberosa* induced an enhancement of apoptosis while *S. collinsae* showed only an antiproliferative effect (*84*).

V. Natural Sources

The Stemonaceae is so far the only source of the *Stemona* alkaloids. A typical *Stemona* alkaloid, named asparagamine A (**52**), was isolated from the roots of *Asparagus racemosus* Willd (Asparagaceae). Later on, a comparative study with 44 *Stemona* and nine *Asparagus* species strongly suggested that *Asparagus* has no *Stemona* alkaloids and had been confused with the *Stemona* genus (*22*).

The phytochemical investigation of the Stemonaceae is restricted to the genera *Stemona* and *Croomia* (Table XXV), and no chemical studies are reported for the genus *Stichoneuron*. Although this small family comprises more than 30 species, the literature reports the phytochemical study of only 14 species (12 species of *Stemona* and 2 species of

TABLE XXV.
Stemona Alkaloids from Stemonaceae Species.

Stemonaceae species	*Stemona* alkaloids (tissue) (reference)	Group
S. tuberosa Lour.	Stenine (**1**) (roots) (*18*)	Stenine (**I**)
	Isostenine/Neostenine (**3**) (roots) (*2*)	
	Tuberostemonine (**4**) (tissue not reported) (*7,21*); (roots and rhizomes) (*22*)	
	Tuberostemonine J (**6**) (roots) (*2*)	
	Tuberostemonine H (**7**) (roots) (*2*)	
	Tuberostemonol (**8**) (roots) (*12*)	
	Neotuberostemonol (**9**) (herbal sample) (*23*)	
	Didehydrotuberostemonine (**10**) (roots) (*12*)	
	Bisdehydroneotuberostemonine (**11**) (roots) (*14*)	
	epi-Bisdehydroneotuberostemonine J (**12**) (roots) (*2*)	
	Neotuberostemonine/Tuberostemonine LG (**13**) (roots) (*2,14*); (herbal sample) (*23*)	
	Stemoamide (**15**) (roots) (*12*)	Stemoamide (**II**)
	Tuberostemoamide/Stemoninoamide (**25**) (roots) (*37,38*)	
	Tuberostemospironine (**28**) (roots) (*12*)	Tuberostemospironine (**III**)
	Stemotinine (**31**) (roots) (*47*)	
	Isostemotinine (**32**) (roots) (*47*)	
	Stemonidine (**33**) (roots) (*47*)	
	Tuberostemoninol (**65**) (roots) (*37,38*)	Miscellaneous (**VIII**)
	Neotuberostemoninol (**66**) (herbal sample) (*23*)	
	Tuberostemonone (**67**) (roots) (*12,59*)	
	Oxotuberostemonine (**14**) (tissue not reported) (*7*)	
S. sessilifolia Franch. & Sav.	Stenine (**1**) (roots) (*19*)	Stenine (**I**)
	2-Oxostenine (**2**) (roots) (*19*)	
	Tuberostemonine (**4**) (tissue not reported) (*7*)	
	Tuberostemonine A (**5**) (rhizomes) (*7*)	
	Neotuberostemonol (**9**) (roots) (*19*)	

(*continued*)

TABLE XXV.
Continued.

Stemonaceae species	*Stemona* alkaloids (tissue) (reference)	Group
	Tuberostemoamide/Stemoninoamide (**25**) (roots) (*19*)	Stemoamide (**II**)
	Sessilifoliamide A (**26**) (roots) (*19*)	
	Stemoninine (**27**) (roots) (*39*)	
	Maistemonine/Protostemotinine (**39**) (roots and rhizomes) (*49*)	Stemonamine (**IV**)
	Sessilifoliamide B (**44**) (roots) (*19*)	Parvistemoline (**V**)
	Sessilifoliamide C (**45**) (roots) (*19*)	
	Sessilifoliamide D (**46**) (roots) (*19*)	
	Tuberostemonone (**67**) (roots) (*19*)	Miscellaneous (**VIII**)
	Oxotuberostemonine (**14**) (roots) (*26*)	
S. collinsae Craib.	Isostenine/Neostenine (**3**) (roots) (*20*)	Stenine (**I**)
	Bisdehydroneotuberostemonine (**11**) (roots) (*20*)	
	Neotuberostemonine/Tuberostemonine LG (**13**) (roots) (*20*)	
	Stemofoline (**48**) (roots and rhizomes) (*22*); (roots) (*54*)	Stemofoline (**VI**)
	2′-Hydroxystemofoline (**51**) (roots and rhizomes) (*22*)	
	16,17-didehydro-16(*E*)-stemofoline/Didehydrostemofoline (**52**) (roots and rhizomes) (*22*); (roots) (*54*)	
	16,17-didehydro-4(*E*),16(*E*)-stemofoline (**53**) (roots) (*54*)	
S. japonica Miq.	Stemonine (**16**) (roots) (*7,15*)	Stemoamide (**II**)
	Neostemonine (**17**) (roots) (*15*)	
	Bisdehydroneostemonine (**18**) (roots) (*15,34*)	
	Protostemonine (**19**) (roots) (*7,15,34*)	
	Didehydroprotostemonine/Bisdehydroprotostemonine (**22**) (roots) (*15,34*)	
	Isoprotostemonine (**23**) (roots) (*15,34*)	
	Stemospironine (**30**) (leaves and stems) (*33*)	Tuberostemospironine (**III**)
	Stemonidine (**33**) (tissue not reported) (*7*)	

	Stemonamine (**35**) (roots) (*13,50*)	Stemonamine (**IV**)
	Isostemonamine (**36**) (roots) (*13,50*)	
	Stemonamide (**37**) (roots) (*13*)	
	Isostemonamide (**38**) (roots) (*13*)	
	Maistemonine/Protostemotinine (**39**) (roots) (*13*)	
	Neostemodiol/Stemodiol (**47**) (roots) (*34*)	Parvistemoline (**V**)
	Stemofoline (**48**) (stems and leaves) (*53*)	Stemofoline (**VI**)
S. cf. pierrei Gagnep.	Stemonine (**16**) (roots and rhizomes) (*11*)	Stemoamide (**II**)
	Protostemonine (**19**) (roots and rhizomes) (*11*)	
S. cochinchinensis Gagnep.	Protostemonine (**19**) (roots) (*36*)	Stemoamide (**II**)
	Stemocochinin (**24**) (roots) (*36*)	
	Stemofoline (**48**) (roots) (*36*)	Stemofoline (**VI**)
	2′-Hydroxystemofoline (**51**) (roots) (*36*)	
S. mairei K. Krause	Protostemonine (**19**) (tissue not reported) (*35*)	Stemoamide (**II**)
	Maistemonine/Protostemotinine (**39**) (roots) (*48*)	Stemonamine (**IV**)
	Oxymaistemonine (**40**) (roots) (*48*)	
S. kerrii Craib.	Protostemonine (**19**) (roots) (*36*)	Stemoamide (**II**)
	Dehydroprotostemonine (**20**) (roots) (*36*)	
	Oxyprotostemonine (**21**) (roots) (*36*)	
	Stemocochinin (**24**) (roots) (*36*)	
	Stemokerrin (**59**) (roots) (*36*)	Stemocurtisine (**VII**)
	Methoxystemokerrin-*N*-oxide (**60**) (roots) (*36*)	
	Oxystemokerrin (**61**) (roots) (*36*)	
	Oxystemokerrin-*N*-oxide (**62**) (roots) (*57*)	
S. curtisii Hook.f.	Dehydroprotostemonine (**20**) (roots) (*36*)	Stemoamide (**II**)
	Oxyprotostemonine (**21**) (roots) (*36*)	
	Stemocochinin (**24**) (roots) (*36*)	
	Stemofoline (**48**) (roots) (*36*)	Stemofoline (**VI**)
	2′-Hydroxystemofoline (**51**) (roots) (*36*)	
	Stemocurtisine/Pyridostemin (**58**) (roots) (*57*)	Stemocurtisine (**VII**)
	Oxystemokerrin (**61**) (roots) (*36*)	
	Stemocurtisinol (**63**) (roots) (*58*)	

(*continued*)

TABLE XXV.
Continued.

Stemonaceae species	*Stemona* alkaloids (tissue) (reference)	Group
S. parviflora Wright C. H.	Parvistemoline (**41**) (roots) (*16*)	Parvistemoline (**V**)
	Parvistemonine (**42**) (roots) (*51*)	
	Didehydroparvistemonine (**43**) (roots) (*16*)	
	Stemofoline (**48**) (roots) (*17*)	Stemofoline (**VI**)
	Oxystemofoline (**49**) (roots) (*17*)	
	Methoxystemofoline (**50**) (roots) (*17*)	
	Parvistemoninine (**54**) (roots) (*52*)	
	Parvistemoninol (**55**) (roots) (*52*)	
	Parvistemoamide (**64**) (roots) (*16*)	Miscellaneous (**VIII**)
	Parvineostemonine (**68**) (stems and leaves) (*60*)	
Stemona sp.	Stemoninine (**27**) (tissue not reported) (*40,41*)	Stemoamide (**II**)
	Parvistemonine (**42**) (roots) (*36*)	Parvistemoline (**V**)
	Stemocurtisine/Pyridostemin (**58**) (roots) (*36*)	Stemocurtisine (**VII**)
	Oxystemokerrin (**61**) (roots) (*36*)	
Stemona burkillii Pain	2′-Hydroxystemofoline (**51**) (roots) (*36*)	Stemocurtisine (**VII**)
	Stemofoline (**48**) (roots) (*17*)	
	11(*S*),12(*R*)-Dihydrostemofoline (**58**) (roots) (*56*)	
	Stemoburkilline (**59**) (roots) (*56*)	
C. heterosepala Okuyama	Croomine (**29**) (roots and rhizomes) (*45*)	Tuberostemospironine (**III**)
C. japonica Miq.	Croomine (**29**) (roots) (*46*)	Tuberostemospironine (**III**)
	Didehydrocroomine (**34**) (roots) (*46*)	

Croomia). Most *Stemona* alkaloids were isolated from the roots, but chemical investigations have also involved rhizomes, leaves and stems, as well as herbal samples (Table XXV).

S. tuberosa provided most of the isolated *Stemona* alkaloids, followed by *S. japonica*, and *S. sessilifolia*. The phytochemical study of *Croomia* is restricted to *C. heterosepala* and *C. japonica*, from which only two *Stemona* alkaloids were isolated [croomine (**29**) and didehydrocroomine (**34**)], both from the tuberostemospironine group (**III**). Alkaloids from the stemoamide group (**II**) were found in eight of the twelve investigated *Stemona* species, while the alkaloids from the other groups were isolated from only two to four *Stemona* species (Table XXV).

The elucidation of the complex structures of the *Stemona* alkaloids involved mainly ^{1}H and ^{13}C-NMR, and X-ray analysis (Section II).

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—Chapter 3—

ALKALOIDS OF THE HERNANDIACEAE: OCCURRENCE AND A COMPILATION OF THEIR BIOLOGICAL ACTIVITIES

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I. Introduction

According to Dahlgren's classification, the position of the Hernandiaceae family is: Plantae (Kingdom), Magnoliophyta (Division), Magnoliopsidae (Class), Magnoliidae (Subclass), Magnoliiflorae (Superorder), Laurales (Order) (*1*). Plants of this family are trees, shrubs, or scandent lianas. The leaves are alternate, simple, or compound, peltate (often, in *Hernandia*), or not peltate; if compound, palmate. The flowers are aggregated in ''inflorescences'' (*2*).

The family Hernandiaceae comprises about 4–5 genera distributed in the tribes Gyrocarpoidea (*Gyrocarpus* Jacq. and *Sparattanthelium* Mart.) and Hernandoidea [*Halomazonia* Capuron (syn. *Hernandia* L.), *Hernandia* L., *Illigera* Blume, and *Valvanthera* CT. White (syn. *Hernandia* L.)] (*3*). The species are geographically distributed in subtropical to tropical areas, occurring in Southeast Asia, Northeast Australia, Central and South America, and West Africa (*2*). Among them, only *Gyrocarpus*, *Hernandia*, and *Sparattanthelium* are found in Brazil (*4*). Species of these genera are used medicinally in various ways. In particular, plants belonging to the genus *Gyrocarpus* are used in Tonga and Venda for induration of the entire breast not associated with pain or redness, to treat

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watery vaginal discharge (*5*), and a decoction of the dried roots is used to wash wounds, for diarrhea, and to cover wounds (*6*).

The genus *Hernandia* is represented by more than seventy species mainly growing in tropical areas (*7*) and they are renowned for their medicinal properties. The stem bark of *H. voyronii* Jum. is widely used in Madagascar as an adjuvant to chloroquine in treating malaria (*8,9*), the leaves of *H. nymphaeifolia* (Presl.) Kubitzki are used in Tonga to treat postpartum hemorrhage, retained placenta, and also to expel retained blood clots from the uterus (*5*), and the leaves of *H. sonora* L. are used in Guadalupe to purify the blood when spots appear on the skin (*10*).

The genus *Sparattanthelium* has been little investigated chemically. Only two species have been studied so far (Table I). From the stem bark of *S. uncigerum* (Meissn.) Kubitzki (*11*) and *S. amazonum* Martius (*12*), species that occur in South America, six aporphine (**I**) and two benzylisoquinoline [(+)-coclaurine (**II.2**) and (+)-reticuline (**II.8**)] alkaloids were isolated (Table I). Among them, (−)-roemrefidine (**I.47**) showed *in vitro* activity against both resistant and sensitive strains of *Plasmodium falciparum*, and *in vivo* against *P. berghei*, and exhibited weak cytotoxicity against CA-KB, Hep-2, and HeLa human cell lines (*12*). Actinodaphnine (**I.1**), launobine (**I.23**), and laurotetanine (**I.26**), at 100 μg/mL, showed significant inhibition of platelet aggregation induced by arachidonic acid, collagen, PAF (*13*), and ADP (*14*). Actinodaphnine (**I.1**) also exhibited marked vasorelaxant activity in rat thoracic aorta induced by high K^+ and norepinephrine (*14*).

About thirty *Illigera* species are known from tropical Africa to Madagascar and East Asia (*15*). Studies have revealed that extracts of *I. luzonensis* (Presl.) Merr. exhibit significant biological activity, e.g., antispasmodic, analgesic, antifebrile, and local anesthetic effects (*14*). So far, only five species of this genus have been investigated (Table I) and some of the alkaloids isolated showed significant biological activities.

Sixty-eight alkaloids found in the Hernandiaceae showed weak, moderate, or strong activities for the treatment of numerous diseases. Table II shows a compilation of these biological activities.

II. Classification of the Alkaloids of the Hernandiaceae

The plants of the Hernandiaceae are recognized as sources of lignans (*7,13,16–18*), terpenoids (*13,19,20*), flavonoids (*19,21*), and alkaloids (Table I). This latter group constitutes the largest class of chemical constituents in this family. Phytochemical investigation of this family has revealed the occurrence of about 128 alkaloids (Table I) belonging to seventeen different structural types, which are classified as indicated in Chart I.

These structural types were isolated in the species that occur in Africa (types **I**, **Ib**, **II**, **IIId**, **VIII**, and **X**), Asia (all types, except **VIII**, **X**, and **XVI**), Europe, South America (types **I** and **II**), and Central America (types **I**, **Ib**, and **II**). In this family, the bisbenzylisoquinolines have the second most numerous (17 alkaloids), the subtypes **IIIa**, **IIIc**, and **IIId** are restricted to the genus *Gyrocarpus*, while **III** and **IIIb** occur in *Hernandia*. In the genus *Sparattanthelium* only aporphines (**I**) and benzylisoquinolines (**II**) are present, while in the genus *Illigera* four types were found (**I**, **Ib**, **II** and **XVI**) (Table I).

TABLE I.
Alkaloids Isolated from Hernandiaceae Species.

Substance name	Skeleton type	Subst. number	Species name	Part of plant	Geographical distribution	Refs.
Actinodaphnine	**I**	**I.1**	*H. guianensis* Aubl.	Leaf	Guyana	*18*
			H. ovigera L. var. m*ascarenensis* Meissn.	Leaf	New Hebrides	*51*
			I. khasiana C. B. Clarke	Stem	China	*53*
			I. luzonensis (Presl.) Merr.	Stem	Taiwan	*14*
			S. uncigerum (Meissn.) Kubitzki	Stem bark	Guyana	*11*
(+)-Actinodaphnine	**I**	**I.1**	*H. cordigera* Vieill.	Leaf	France	*54*
			I. pentaphylla Welw.	Entire plant	Nigeria	*15*
(−)-Actinodaphnine	**I**	**I.1**	*I. parviflora* Dunn	Entire plant	China	*55*
Ambrimine	**IIIb**	**IIIb.1**	*H. peltata* Meissn.	Not specified	New Hebrides	*56*
				Trunk bark	New Hebrides	*51*
(+)-Ambrimine	**IIIb**	**IIIb.1**	*H. peltata* Meissn.	Trunk bark	Not stated	*47*
Atheroline	**Ib**	**Ib.1**	*H. nymphaeifolia* (Presl.) Kubitzki	Trunk bark	Taiwan	*13*,*22*
			H. sonora L.	Root bark	Taiwan	*57*
			I. pentaphylla Welw.	Entire plant	Nigeria	*15*
(+)-Auroramine	**IV**	**IV.1**	*G. americanus* Jacq.	Leaf	Not stated	*33*
Backebergine	**II**	**II.1**	*H. sonora* L.	Root bark	Taiwan	*57*
(−)-Bebeerine	**XV**	**XV.1**	*H. ovigera* L.	Not specified	New Hebrides	*51*
(+)-Boldine	**I**	**I.2**	*I. pentaphylla* Welw.	Entire plant	Nigeria	*16*
Bulbocapnine	**I**	**I.3**	*H. ovigera* L.	Stem bark	Not stated	*27*
			I. luzonensis (Presl.) Merr.	Stem	Taiwan	*14*
Catalpifoline	**I**	**I.4**	*H. catalpifolia* Britt. & Harris	Bark	Antilles	*27*,*58*
			H. jamaicensis Britt. & Harris	Bark	Jamaica	*59*
(+)-Coclaurine	**II**	**II.2**	*S. uncigerum* (Meissn.) Kubitzki	Stem bark	Guyana	*11*
(+)-Corytuberine	**I**	**I.5**	*H. sonora* L.	Root bark	Taiwan	*57*

(*continued*)

TABLE I.
Continued.

Substance name	Skeleton type	Subst. number	Species name	Part of plant	Geographical distribution	Refs.
3-Cyano-4-methoxy-pyridine	**XIII**	**XIII.1**	*H. nymphaeifolia* (Presl.) Kubitzki	Leaf	Iriomote Island (Japan)	*60*
Dehydrohernandaline	**Ia**	**Ia.1**	*H. nymphaeifolia* (Presl.) Kubitzki	Trunk bark	Taiwan	*13*
			H. sonora L.	Root bark	Taiwan	*57*
Dehydrothalicarpine	**VIb**	**VIb.1**	*H. ovigera* L.	Root bark	Taiwan	*35,36,61*
6a,7-Dehydrothalmelatine	**VIb**	**VIb.2**	*H. peltata* Meissn.	Trunk bark	Not stated	*47*
Demethylsonodione	**IX**	**IX.1**	*H. sonora* L.	Stem bark	Taiwan	*32*
Dicentrine	**I**	**I.6**	*I. luzonensis* (Presl.) Merr.	Stem	Taiwan	*14*
Dicentrinone	**Ib**	**Ib.2**	*I. luzonensis* (Presl.) Merr.	Stem	Taiwan	*14*
			I. pentaphylla Welw.	Entire plant	Nigeria	*15*
			H. sonora L.	Root bark	Taiwan	*57*
(+)-*O*,*O*-Dimethylcorytuberine [= *O*-dimethylcorytuberine]	**I**	**I.7**	*H. catalpifolia* Britt. & Harris	Bark	Antilles	*27*
			H. jamaicensis Britt. & Harris	Bark	Jamaica	*59*
Domesticine	**I**	**I.8**	*G. americanus* Jacq.	Stem bark	Samoa	*3*
Efatine	**IIIb**	**IIIb.2**	*H. peltata* Meissn.	Not specified	New Hebrides	*56*
(+)-Efatine	**IIIb**	**IIIb.2**	*H. peltata* Meissn.	Trunk bark	Not stated	*47*
7-Formyldehydrohernangerine	**Ia**	**Ia.2**	*H. nymphaeifolia* (Presl.) Kubitzki	Trunk bark	Taiwan	*34*
7-Formyldehydronornantenine	**Ia**	**Ia.3**	*H. nymphaeifolia* (Presl.) Kubitzki	Stem bark	Taiwan	*62*
			H. sonora L.	Root bark	Taiwan	*57*
7-Formyldehydroovigerine	**Ia**	**Ia.4**	*H. sonora* L.	Root bark	Taiwan	*57*
N-Formyldehydroovigerine	**Ia**	**Ia.5**	*H. nymphaeifolia* (Presl.) Kubitzki	Trunk bark	Taiwan	*26*

(+)-*N*-Formylhernangerine	**I**	**I.9**	*H. nymphaeifolia* (Presl.) Kubitzki	Trunk bark	Taiwan	*63*
(+)-*N*-Formylnornantenine	**I**	**I.10**	*H. nymphaeifolia* (Presl.) Kubitzki	Trunk bark	Taiwan	*63*
(+)-*N*-Formylovigerine	**I**	**I.11**	*H. nymphaeifolia* (Presl.) Kubitzki	Trunk bark	Taiwan	*63*
(−)-Grisabine	**IIIa**	**IIIa.1**	*G. americanus* Jacq.	Stem bark	Samoa	*3*
(+)-Gyroamericine	**IIId**	**IIId.1**	*G. americanus* Jacq.	Stem bark	Samoa	*3*
Gyrocarpine	**IIIc**	**IIIc.1**	*G. americanus* Jacq.	Stem bark	Samoa	*3*
(−)-Gyrocarpine	**IIIc**	**IIIc.1**	*G. americanus* Jacq.	Leaf	Not stated	*33*
(+)-Gyrocarpusine	**IIIc**	**IIIc.2**	*G. americanus* Jacq.	Stem bark	Samoa	*3*
(−)-Gyrolidine	**IIIc**	**IIIc.3**	*G. americanus* Jacq.	Stem bark	Samoa	*3*
(+)-Hebridamine	**VII**	**VII.1**	*H. peltata* Meissn.	Bark	Not stated	*46*
			H. peltata Meissn.	Trunk bark	Not stated	*47*
Hernagine	**I**	**I.12**	*H. nymphaeifolia* (Presl.) Kubitzki	Leaf	Iriomote Island (Japan)	*60*
			H. ovigera L. var. *mascarenensis* Meissn.	Stem bark	Reunion Island	*64*
(+)-Hernagine	**I**	**I.12**	*H. cordigera* Vieill.	Stem bark	New Caledonia	*65*
			H. cordigera Vieill.	Stem bark	New Caledonia	*66*
			H. nymphaeifolia (Presl.) Kubitzki	Leaf	Taiwan	*27*,*51*
			H. ovigera L. var. *mascarenensis* Meissn.	Twig	New Hebrides	*51*
			H. peltata Meissn.	Leaf, Stem bark	New Hebrides	*67*
Hernandaline	**I**	**I.13**	*H. nymphaeifolia* (Presl.) Kubitzki	Trunk bark	Taiwan	*13*, *22*
(+)-Hernandaline	**I**	**I.13**	*H. nymphaeifolia* (Presl.) Kubitzki	Trunk bark	Green Island (Taiwan)	*25*
			H. ovigera L.	Stem bark	New Hebrides	*27*,*51*,*58*
			H. sonora L.	Seeds	Not stated	*7*
Hernandine	**I**	**I.14**	*H. bivalvis* Benth.	Not specified	Malaysia	*68*,*69*
			H. catalpifolia Britt. & Harris	Stem bark	Antilles	*27*
			H. ovigera L.	Bark	New Hebrides	*70*

(*continued*)

TABLE I.
Continued.

Substance name	Skeleton type	Subst. number	Species name	Part of plant	Geographical distribution	Refs.
Hernandonine	**Ib**	**Ib.3**	*H. jamaicensis* Britt. & Harris	Stem bark	Jamaica	*59*
			H. nymphaeifolia (Presl.) Kubitzki	Trunk bark	Taiwan	*13*,*22*,*63*
				Trunk bark	Green Island (Taiwan)	*25*
				Stem bark	Taiwan	*62*
			H. papuana C.T. White	Stem bark	Not stated	*71*
			H. ovigera L.	Root bark	Taiwan	*35*,*36*,*61*
				Trunk bark	China	*72*
			H. ovigera L. var. *mascarenensis* Meissn.	Leaf	Reunion Island	*64*
			H. sonora L.	Root bark	Taiwan	*57*
Hernangerine [=Nandigerine]	**I**	**I.15**	*H. nymphaeifolia* (Presl.) Kubitzki	Trunk bark	Taiwan	*22*
			H. ovigera L.	Root bark	Taiwan	*36*
				Trunk bark	China	*72*
			H. papuana C.T. White	Bark	Not stated	*71*
(+)-Hernangerine [=(+)-Nandigerine]	**I**	**I.15**	*H. sonora* L.	Root bark	Taiwan	*57*
Hernanymphine	**Ib**	**Ib.4**	*H. nymphaeifolia* (Presl.) Kubitzki	Stem bark	Taiwan	*62*
Hernovine	**I**	**I.16**	*H. catalpifolia* Britt. & Harris	Bark	Antilles	*27*
			H. guianensis Aubl.	Stem bark	Guyana	*18*
			H. jamaicensis Britt. & Harris	Stem bark	Jamaica	*59*
			H. nymphaeifolia (Presl.) Kubitzki	Trunk bark	Taiwan	*22*
			H. ovigera L.	Stem bark	New Hebrides	*51*
				Trunk bark	China	*70*,*72*

			H. ovigera L. var. *mascarenensis* Meissn.	Stem bark	Reunion Island	*64*
			H. peltata Meissn.	Leaf, Stem bark	New Hebrides	*67*
			I. luzonensis (Presl.) Merr.	Stem	Taiwan	*14*
			I. luzonensis (Presl.) Merr.	Root + Stem	Taiwan	*36*
(+)-Hernovine	**I**	**I.16**	*H. nymphaeifolia* (Presl.) Kubitzki	Trunk bark	Taiwan	*26*
			I. parviflora Dunn	Entire plant	China	*55*
Herveline A	**VIII**	**VIII.1**	*H. voyronii* Jum. (syn. *Hazomalania* voyronii R. Capuron)	Entire plant	Madagascar	*48*
				Stem bark	Madagascar	*8,9*
Herveline B	**VIII**	**VIII.2**	*H. voyronii* Jum.	Stem bark	Madagascar	*8,9*
Herveline C	**VIII**	**VIII.3**	*H. voyronii* Jum. (syn. *Hazomalania voyronii* R. Capuron)	Entire plant	Madagascar	*48*
			H. voyronii Jum.	Stem bark	Madagascar	*8,9*
Herveline D	**VIII**	**VIII.4**	*H. voyronii* Jum.	Stem bark	Madagascar	*9*
Herveline HB	**VIII**	**VIII.5**	*H. voyronii* Jum.	Entire plant	Madagascar	*48*
7-Hydroxy-6-methoxy-1-methylisoquinoline	**XII**	**XII.1**	*H. nymphaeifolia* (Presl.) Kubitzki	Trunk bark	Taiwan	*34*
(+)-*N*-Hydroxyhernangerine	**I**	**I.17**	*H. nymphaeifolia* (Presl.) Kubitzki	Trunk bark	Taiwan	*26*
(+)-*N*-Hydroxyovigerine	**I**	**I.18**	*H. nymphaeifolia* (Presl.) Kubitzki	Trunk bark	Taiwan	*63*
(+)-Isoboldine	**I**	**I.19**	*H. cordigera* Vieill.	Leaf	France	*54*
(+)-Isocorydine [= Artabotrine, Luteanine]	**I**	**I.20**	*H. catalpifolia* Britt. & Harris	Stem bark	Antilles	*27*
			H. cordigera Vieill.	Stem bark	New Caledonia	*65,66*
				Leaf	France	*54*
			H. jamaicensis Britt. & Harris	Bark	Jamaica	*59*
			H. nymphaeifolia (Presl.) Kubitzki	Leaf	Iriomote Island (Japan)	*60*
			H. ovigera L.	Stem bark	New Hebrides	*27,58,70*

(*continued*)

TABLE I.
Continued.

Substance name	Skeleton type	Subst. number	Species name	Part of plant	Geographical distribution	Refs.
			H. peltata Meissn.	Leaf, Bark	New Hebrides	*67*
(−)-Isotetrandrine	**IIId**	**IIId.2**	*G. americanus* Jacq.	Stem bark	Samoa	*3*
Laetanine	**I**	**I.21**	*H. voyronii* Jum.	Stem bark	Madagascar	*9*
Laetine	**I**	**I.22**	*H. peltata* Meissn.	Trunk bark	Not stated	*47*
(+)-Laetine	**I**	**I.22**	*H. nymphaeifolia* (Presl.) Kubitzki	Trunk bark	Taiwan	*22*
Lanuginosine	**Ib**	**Ib.5**	*I. pentaphylla* Welw.	Entire plant	Nigeria	*15*
Laudanosine	**II**	**II.3**	*H. voyronii* Jum.	Stem bark	Madagascar	*9*
(+)-Laudanidine	**II**	**II.4**	*H. papuana* C.T. White	Bark	Not stated	*71*
Launobine	**I**	**I.23**	*I. khasiana* C.B. Clarke	Stem	China	*53*
			I. luzonensis (Presl.) Merr.	Stem	China	*53*
				Not specified	Taiwan	*73*
			S. uncigerum (Meissn.) Kubitzki	Stem bark	Guyana	*11*
(+)-Laurelliptine	**I**	**I.24**	*I. pentaphylla* Welw.	Entire plant	Nigeria	*15*
Laurolitsine	**I**	**I.25**	*H. catalpifolia* Britt. & Harris	Bark	Antilles	*27*,*58*
Laurotetanine	**I**	**I.26**	*H. guianensis* Aubl.	Stem bark	Guyana	*18*
			H. jamaicensis Britt. & Harris	Bark	Jamaica	*59*
			H. nymphaeifolia (Presl.) Kubitzki	Trunk bark	Taiwan	*13*
			H. nymphaeifolia (Presl.) Kubitzki	Leaf	Iriomote Island (Japan)	*60*
			H. ovigera L.	Stem bark	New Hebrides	*27*,*58*
			I. pulchra Blume	Entire plant	Not stated	*74*
			S. uncigerum (Meissn.) Kubitzki	Stem bark	Guyana	*11*
(+)-Laurotetanine	**I**	**I.26**	*H. cordigera* Vieill.	Leaf	France	*54*
			H. cordigera Vieill.	Stem bark	New Caledonia	*65*, *66*
			H. nymphaeifolia (Presl.) Kubitzki	Trunk bark	Taiwan	*26*

			H. peltata Meissn.	Leaf, bark	New Hebrides	*67*
			I. pentaphylla Welw.	Entire plant	Nigeria	*15*
Limacine	**IIId**	**IIId.3**	*G. americanus* Jacq.	Stem bark	Samoa	*3*
(−)-Limacine	**IIId**	**IIId.3**	*G. americanus* Jacq.	Leaf	Not stated	*33*
(+)-Limacusine	**IIIc**	**IIIc.4**	*G. americanus* Jacq.	Stem bark	Samoa	*3*
Lindcarpine	**I**	**I.27**	*H. voyronii* Jum.	Stem bark	Madagascar	*9*
(+)-Lindcarpine	**I**	**I.27**	*I. pentaphylla* Welw.	Entire plant	Nigeria	*15*
Liriodenine	**Ib**	**Ib.6**	*I. luzonensis* (Presl.) Merr.	Stem	Taiwan	*14*
(+)-Litseferine	**I**	**I.28**	*I. parviflora* Dunn	Entire plant	China	*55*
Lysicamine	**Ib**	**Ib.7**	*I. pentapylla* Welw.	Entire plant	Nigeria	*15*
Magnocurarine	**II**	**II.5**	*G. americanus* Jacq.	Stem bark	Not stated	*27,3*
(+)-Magnoflorine	**I**	**I.29**	*H. nymphaeifolia* (Presl.) Kubitzki	Trunk bark	Taiwan	*26*
(+)-Malekulatine	**IIIb**	**IIIb.3**	*H. nymphaeifolia* (Presl.) Kubitzki	Trunk bark	Taiwan	*22*
			H. peltata Meissn.	Stem bark	New Hebrides	*31*
			H. sonora L.	Root bark	Taiwan	*57*
(+)-Maroumine	**IV**	**IV.2**	*G. americanus* Jacq.	Leaf	Not stated	*33*
N-Methylactinodaphnine	**I**	**I.30**	*I. luzonensis* (Presl.) Merr.	Stem	Taiwan	*14*
(+)-*N*-Methylactinodaphnine	**I**	**I.30**	*H. cordigera* Vieill.	Leaf	France	*54*
N-(*N*-Methyl-carbamoyl)-*O*-methylbulbocapnine	**I**	**I.31**	*H. nymphaeifolia* (Presl.) Kubitzki	Trunk bark	Taiwan	*13*
N-Methylcoclaurine	**II**	**II.6**	*G. americanus* Jacq.	Stem bark	Samoa	*3*
N-Methylcorydaldine	**XI**	**XI.1**	*H. nymphaeifolia* (Presl.) Kubitzki	Trunk bark	Green Island (Taiwan)	*25*
			H. ovigera L.	Twig	Indonesia	*16*
				Not specified	Not stated	*75*
N-Methyl-6,7-dimethoxy-isoquinoline	**XI**	**XI.2**	*H. ovigera* L.	Not specified	Not stated	*75*
				Stem bark	New Hebrides	*58*
N-Methyl-5,6-dimethoxy-phthalimide	**XVII**	**XVII.1**	*H. nymphaeifolia* (Presl.) Kubitzki	Trunk bark	Taiwan	*34*
(+)-*N*-Methylhernangerine [=*N*-Methylnandigerine]	**I**	**I.32**	*H. nymphaeifolia* (Presl.) Kubitzki	Stem bark	Taiwan	*62*
			H. ovigera L.	Trunk bark	China	*72*
			H. sonora L.	Root bark	Taiwan	*57*

(*continued*)

TABLE I.
Continued.

Substance name	Skeleton type	Subst. number	Species name	Part of plant	Geographical distribution	Refs.
N-Methylhernovine	**I**	**I.33**	*H. guianensis* Aubl.	Stem bark	Guyana	*18*
				Leaf	Guyana	*18*
				Root bark	Guyana	*18*
			H. ovigera L.	Trunk bark	China	*72*
(+)-*N*-Methylhernovine	**I**	**I.33**	*H. nymphaeifolia* (Presl.) Kubitzki	Trunk bark	Taiwan	*26*
			H. ovigera L.	Stem bark	New Hebrides	*27*
				Fruit	New Hebrides	*51*
			H. peltata Meissn.	Leaf, Stem bark	New Hebrides	*67*
N-Methyllaurotetanine	**I**	**I.34**	*H. catalpifolia* Britt. & Harris	Stem bark	Antilles	*27*
			H. nymphaeifolia (Presl.) Kubitzki	Leaf	Iriomote Island (Japan)	*60*
				Trunk bark	Taiwan	*22*
			H. voyronii Jum.	Stem bark	Madagascar	*9*
			H. peltata Meissn.	Leaf, Bark	New Hebrides	*67*
(+)-*N*-Methyllaurotetanine	**I**	**I.34**	*H. cordigera* Vieill.	Leaf	France	*54*
(+)-*N*-Methyllindcarpine	**I**	**I.35**	*I. pentaphylla* Welw.	Entire plant	Nigeria	*15*
N-Methylnandigerine [=*N*-Methylhernangerine]	**I**	**I.32**	*H. guianensis* Aubl.	Stem bark	Guyana	*18*
				Root bark	Guyana	*18*
				Leaf	Guyana	*18*
			H. jamaicensis Britt. & Harris	Stem bark	Jamaica	*59*
			H. nymphaeifolia (Presl.) Kubitzki	Bark	Taiwan	*62*
			H. ovigera L.	Trunk bark	New Hebrides	*27*,*70*,*72*
			H. ovigera L. var. *mascarenensis* Meissn.	Stem bark	Reunion Island	*64*
			H. peltata Meissn.	Leaf, Stem bark	New Hebrides	*67*
(+)-*N*-Methylovigerine	**I**	**I.36**	*H. catalpifolia* Britt. & Harris	Stem bark	Antilles	*27*
			H. jamaicensis Britt. & Harris	Bark	Jamaica	*59*

			H. nymphaeifolia (Presl.) Kubitzki	Trunk bark	Green Island (Taiwan)	*25*
			H. ovigera L.	Trunk bark	China	*70*,*72*
O-Methylbulbocapnine	**I**	**I.37**	*I. luzonensis* (Presl.) Merr.	Stem	Taiwan	*14*
O-Methyllimacusine	**IIIc**	**IIIc.5**	*G. americanus* Jacq.	Stem bark	Samoa	*3*
O-Methyloxobulbocapnine	**Ib**	**Ib.8**	*H. nymphaeifolia* (Presl.) Kubitzki	Trunk bark	Taiwan	*22*
N,*O*-Dimethylnandigerine	**I**	**I.38**	*H. catalpifolia* Britt. & Harris	Bark	Antilles	*27*
4-Methoxyoxohernandaline	**Ib**	**Ib.9**	*H. nymphaeifolia* (Presl.) Kubitzki	Trunk bark	Taiwan	*34*
Nandigerine [=Hernangerine]	**I**	**I.15**	*H. catalpifolia* Britt. & Harris	Stem bark	Antilles	*27*
			H. cordigera Vieill.	Stem bark	New Caledonia	*65*
			H. guianensis Aubl.	Stem bark	Guyana	*18*
			H. jamaicensis Britt. & Harris	Stem bark	Jamaica	*59*
			H. nymphaeifolia (Presl.) Kubitzki	Leaf	Iriomote Island (Japan)	*60*
			H. ovigera L.	Root bark	Taiwan	*35*,*61*
				Stem bark	China	*27*,*70*,*72*
			H. ovigera L. var. *mascarenensis* Meissn.	Leaf	Reunion Island	*64*
				Stem bark	Reunion Island	*64*
			H. papuana C.T. White	Stem bark	Not stated	*71*
			H. peltata Meissn.	Leaf, Stem bark	New Hebrides	*67*
(+)-Nandigerine [=(+)-Hernangerine]	**I**	**I.15**	*H. cordigera* Vieill.	Stem bark	New Caledonia	*66*
(+)-Neolitsine	**I**	**I.39**	*H. cordigera* Vieill.	Leaf	France	*54*
(+)-Norboldine	**I**	**I.40**	*I. pentaphylla* Welw.	Entire plant	Nigeria	*15*
(+)-Nordicentrine	**I**	**I.41**	*I. pentaphylla* Welw.	Entire plant	Nigeria	*15*
Nordomesticine	**I**	**I.42**	*S. uncigerum* (Meissn.) Kubitzki	Stem bark	Guyana	*11*

(*continued*)

TABLE I.
Continued.

Substance name	Skeleton type	Subst. number	Species name	Part of plant	Geographical distribution	Refs.
Norisocorydine	**I**	**I.43**	*H. catalpifolia* Britt. & Harris	Stem bark	Antilles	*27*,*58*
			H. voyronii Jum.	Stem bark	Madagascar	*9*
			S. uncigerum (Meissn.) Kubitzki	Stem bark	Guyana	*11*
			H. peltata Meissn.	Leaf, Stem bark	New Hebrides	*67*
(+)-Norisocorydine	**I**	**I.43**	*H. cordigera* Vieill.	Stem bark	New Caledonia	*65*
(+)-Nornantenine	**I**	**I.44**	*H. cordigera* Vieill.	Leaf	France	*54*
				Stem bark	New Caledonia	*65*,*66*
			H. nymphaeifolia (Presl.) Kubitzki	Leaf	Iriomote Island (Japan)	*60*
			H. peltata Meissn.	Leaf, Stem bark	New Hebrides	*67*
			H. ovigera L.	Trunk bark	New Hebrides	*70*
Norpredicentrine	**I**	**I.45**	*H. voyronii* Jum.	Stem bark	Madagascar	*9*
Norsonodione	**IX**	**IX.2**	*H. sonora* L.	Stem bark	Taiwan	*32*
Northalicarpine	**VI**	**VI.1**	*H. peltata* Meissn.	Trunk bark	Not stated	*47*
(+)-2′-Northalicarpine	**VI**	**VI.2**	*H. peltata* Meissn.	Stem bark	Not stated	*47*
(+)-6-Northalicarpine	**VI**	**VI.3**	*H. peltata* Meissn.	Bark	Not stated	*46*
				Trunk bark	Not stated	*47*
Northalifoline	**XI**	**XI.3**	*H. nymphaeifolia* (Presl.) Kubitzki	Trunk bark	Taiwan	*26*
(+)-Nymphaedaline	**II**	**II.7**	*H. nymphaeifolia* (Presl.) Kubitzki	Trunk bark	Taiwan	*22*
Ocobotrine	**X**	**X.1**	*H. voyronii* Jum.	Stem bark	Madagascar	*8*,*9*
(+)-Ovigeridimerine	**V**	**V.1**	*H. nymphaeifolia* (Presl.) Kubitzki	Trunk bark	Taiwan	*34*
			H. ovigera L.	Root bark	Taiwan	*35*,*36*
Ovigerine	**I**	**I.46**	*H. guianensis* Aubl.	Stem bark, Leaf	Guyana	*18*
			H. nymphaeifolia (Presl.) Kubitzki	Leaf	Iriomote Island (Japan)	*60*

			H. nymphaeifolia (Presl.) Kubitzki	Trunk bark	Taiwan	*22*
			H. ovigera L. var. *mascarenensis* Meissn.	Leaf	New Hebrides	*51*
(+)-Ovigerine	**I**	**I.46**	*H. catalpifolia* Britt. & Harris	Stem Bark	Antilles	*27*
			H. cordigera Vieill.	Stem bark	New Caledonia	*65*,*66*
			H. jamaicensis Britt. & Harris	Stem bark	Jamaica	*59*
			H. ovigera L.	Root bark	Taiwan	*61*
				Stem bark	New Hebrides	*27*,*51*
			H. peltata Meissn.	Leaf, Stem bark	New Hebrides	*51*,*67*
			H. sonora L.	Root bark	Taiwan	*57*
Ovihernangerine	**V**	**V.2**	*H. nymphaeifolia* (Presl.) Kubitzki	Trunk bark	Green Island (Taiwan)	*25*
Oviisocorydine	**V**	**V.3**	*H. nymphaeifolia* (Presl.) Kubitzki	Trunk bark	Green Island (Taiwan)	*25*
(+)-2′-*N*-Oxidethalicarpine	**VI**	**VI.4**	*H. peltata* Meissn.	Bark	Not stated	*46*
				Trunk bark	Not stated	*47*
(+)-2′β-*N*-Oxidevateamine	**III**	**III.1**	*H. nymphaeifolia* (Presl.) Kubitzki	Trunk bark	Taiwan	*13*,*34*
Oxocrebanine [=1,2-Methylene-dioxy-8,9-dimethoxyquino-lin-7-one]	**Ib**	**Ib.10**	*H. ovigera* L.	Stem	New Hebrides	*51*
			I. pentaphylla Welw.	Entire plant	Nigeria	*15*
Oxohernandaline	**Ib**	**Ib.11**	*H. nymphaeifolia* (Presl.) Kubitzki	Trunk bark	Green Island (Taiwan)	*25*
7-Oxohernangerine	**Ib**	**Ib.12**	*H. nymphaeifolia* (Presl.) Kubitzki	Trunk bark	Taiwan	*13*,*22*
				Stem bark	Taiwan	*62*
7-Oxohernangine	**Ib**	**Ib.13**	*H. nymphaeifolia* (Presl.) Kubitzki	Trunk bark	Taiwan	*13*,*22*
				Stem bark	Taiwan	*62*
Oxonantenine	**Ib**	**Ib.14**	*H. nymphaeifolia* (Presl.) Kubitzki	Leaf	Iriomote Island (Japan)	*60*
				Stem bark	Not stated	*51*

(*continued*)

TABLE I.
Continued.

Substance name	Skeleton type	Subst. number	Species name	Part of plant	Geographical distribution	Refs.
			I. pentaphylla Welw.	Entire plant	Nigeria	*15*
Oxothalicarpine	**VIa**	**VIa.1**	*H. ovigera* L.	Root bark	Taiwan	*35*,*36*
(−)-Pallidine	**X**	**X.2**	*H. voyronii* Jum.	Stem bark	Madagascar	*9*
(−)-Phaeanthine	**IIId**	**IIId.4**	*G. americanus* Jacq.	Leaf	Not stated	*33*
				Stem bark	Samoa	*3*
(+)-Pronuciferine	**XIV**	**XIV.1**	*G. americanus* Jacq.	Leaf	Not stated	*33*
Pycnamine	**IIId**	**IIId.5**	*G. americanus* Jacq.	Leaf, Bark	Madagascar	*27*
Reticuline	**II**	**II.8**	*G. americanus* Jacq.	Stem bark	Samoa	*3*
			H. guianensis Aubl.	Stem bark	Guyana	*18*
(+)-Reticuline	**II**	**II.8**	*H. cordigera* Vieill.	Stem bark	New Caledonia	*65*,*66*,*78*
				Leaf	France	*54*
			H. guianensis Aubl.	Root bark	Guyana	*18*
			H. jamaicensis Britt. & Harris	Bark	Jamaica	*59*
			H. nymphaeifolia (Presl.) Kubitzki	Trunk bark	Taiwan	*13*,*26*
			H. ovigera L.	Stem bark	New Hebrides	*27*
				Fruit	New Hebrides	*51*
			H. ovigera L. var. *mascarenensis* Meissn.	Twig	New Hebrides	*51*
			H. peltata Meissn.	Bark	New Hebrides	*31*
				Leaf	New Hebrides	*51*,*67*
			H. sonora L.	Stem bark	New Hebrides	*51*
			H. voyronii Jum.	Stem bark	New Hebrides	*51*
			I. parviflora Dunn	Entire plant	China	*55*
			S. uncigerum (Meissn.) Kubitzki	Stem bark	Guyana	*11*

(−)-Roemrefidine	**I**	**I.47**	*S. amazonum* Martius	Stem bark	Bolivia	*12*
			S. uncigerum (Meissn.) Kubitzki	Stem bark	Guyana	*11*
Sonodione	**IX**	**IX.3**	*H. sonora* L.	Stem bark	Taiwan	*32*
Thalicarpine	**VI**	**VI.5**	*H. ovigera* L.	Root bark	Taiwan	*35*,*36*,*61*
(+)-Thalicarpine	**VI**	**VI.5**	*H. nymphaeifolia* (Presl.) Kubitzki	Trunk bark	Taiwan	*13*
				Trunk bark	Green Island (Taiwan)	*25*
			H. peltata Meissn.	Trunk bark	Not stated	*47*
Thalifoline	**XI**	**XI.4**	*H. nymphaeifolia* (Presl.) Kubitzki	Trunk bark	Taiwan	*22*,*26*
			H. peltata Meissn.	Trunk bark	Not stated	*47*
(+)-Thalmelatine	**VI**	**VI.6**	*H. peltata* Meissn.	Trunk bark	Not stated	*47*
Thaliporphinemethine	**XVI**	**XVI.1**	*I. pentaphylla* Welw.	Entire plant	Nigeria	*15*
(+)-Vanuatine	**III**	**III.2**	*H. peltata* Meissn.	Trunk bark	New Hebrides	*31*
				Trunk bark	Not stated	*47*
(+)-Vateamine	**III**	**III.3**	*H. peltata* Meissn.	Trunk bark	New Hebrides	*31*
(+)-Vilaportine	**VIa**	**VIa.2**	*H. peltata* Meissn.	Trunk bark	Not stated	*46*,*47*
Xanthoplanine	**I**	**I.48**	*H. ovigera* L.	Stem bark	New Hebrides	*27*,*51*
			H. peltata Meissn.	Stem bark	New Hebrides	*51*
			H. sonora L.	Stem bark	New Hebrides	*51*

TABLE II.
Biological Activity of the Alkaloids found in the Hernandiaceae Species.

Alkaloid number	Biological activity/method/route/concentration or dose used	Refs.
I.1	**Analgesic** – (mouse) vs. acetic acid-induced writhing (IP, ED_{50} 42.17 mg/kg) and (SC, ED_{50} 40.12 mg/kg); (IP, mouse, hot plate) at 40.0 mg/kg and at 1.0 mg/kg.	*76*
	Antiplatelet – *in vitro* at 100.0 μg/mL, induced by ADP, arachidonic acid, collagen, and PAF.	*14*
	Antipyretic – (IP, rabbit) vs. *Colibacillus* (at 50.0 mg/kg) and peptone-induced fever (at 30.0 mg/kg).	*76*
	Antiviral – *in vitro* (Cell culture, virus-herpes simplex), ED_{50} 7.5 μM.	*77*
	Cytotoxic – *in vitro* (Cell culture) vs. cells-Vero (IC_{50} 47.5 and 107.0 μM), CA-HeLa (IC_{50} 30.9 μM), non-cancer 3T3 cells (IC_{50} 66.4 μM), melanoma-SK-Mel-5 (IC_{50} 25.7 μM), Leuk-HL60 (IC_{50} 15.4 μM).	*77–79*
	Hypothermic – *in vivo* (IP) at 20.0 mg/kg (mouse), 30.0 mg/kg (rat), and 50.0 mg/kg (rabbit).	*76*
	Platelet aggregation inhibition – *in vitro* at 100.0 μg/mL, induced by ADP, arachidonic acid, collagen, and PAF; (rabbit) at 50.0 μg/mL, induced by arachidonic acid.	*80,81*
	Smooth muscle relaxant – *in vitro* (rabbit, aorta), conc. used not stated.	*81*
	Vasodilator – (rat, aorta) at 100.0 μg/mL, induced contractions by potassium and norepinephrine.	*14*
I.1 (+)-Form	**Platelet aggregation inhibition** – *in vitro* (rabbit) at 100.0 μg/mL, induced by ADP, arachidonic acid, collagen, and PAF.	*82*
	Smooth muscle relaxant – *in vitro* (rat, aorta) at 100.0 μg/mL, induced contractions by potassium and norepinephrine.	*82*
Ib.1	**Platelet aggregation inhibition** – *in vitro* at 100.0 μM, induced by PAF.	*13*
	Vasorelaxant – *in vitro* (rat, aorta) at 100.0 μM, induced contractions by potassium and norepinephrine.	*22*
XV.1	**Antitrypanosomal** – *in vitro* (*Trypanosoma cruzi*) at 50.0 μg/mL.	*52*
	Protein kinase inhibition – *in vitro*, conc. used not stated, vs. avian MLCK.	*83*
I.2	**Antimalarial** – *in vitro* against *Plasmodium falciparum* D-6 (IC_{50} 2130 ng/mL) and W-2 (IC_{50} 1470 ng/mL).	*85*
	Platelet aggregation inhibition – *in vitro* (rabbit) at 100.0 μg/mL, induced by ADP, arachidonic acid, collagen, and PAF.	*82*
	Protein kinase inhibition – *in vitro* vs. rat liver CAK (IC_{50} 82.0 μM), avian MLCK (IC_{50} 12.0 μM), and rat brain PKC (conc. used not stated).	*83*

	Smooth muscle relaxant – *in vitro* (rat, aorta) at 100.0 μg/mL, induced contractions by K^+ and norepinephrine.	*82*
I.3	**Antibacterial** – *in vitro* (Agar plate, conc. used not stated) against *Bacillus anthracis* and *Corynebacterium diphtheriae*.	*86*
	Anticonvulsant – *in vivo* (SC, mouse) induced convulsion by harman (ED_{50} 7.3 mg/kg) and picrotoxin (ED_{50} 22.0 mg/kg).	*87*
	Antimycobacterial – *in vitro* (Agar plate) against *Mycobacterium smegmatis*, MIC 1.0 mg/mL.	*88*
	Antiplatelet – *in vitro* at 100.0 μg/mL, induced by ADP, arachidonic acid, collagen, and PAF.	*14*
	Antiyeast – *in vitro* against *Candida albicans*, MIC 1.0 mg/animal.	*88*
	Barbiturate potentiation – *in vivo* (SC, mouse), ED_{50} 7.8 mg/kg.	*87*
	Chromosome aberrations induced – *in vitro* (Cell culture, cells-hamster-lung) at 100.0 μg/mL.	*89*
	Hypothermic – *in vivo* (SC, mouse), ED_{50} 5.6 mg/kg.	*87*
	Intraocular pressure increased – *in vivo* (IV, rabbit), 20.0 mg/animal.	*90*
	Lipid peroxidase inhibition – *in vitro*, conc. used not stated, vs. Fe(II)/Ascorbate, CCl_4/NADPH or Fe(III)ADP/NADPH.	*91*
	Lipid peroxidase formation inhibition – *in vitro* at 100.0 μM.	*92*
	Lipid peroxidase formation – *in vitro* (microsomes – rat-liverR), IC_{50} 12.5 μM, induced lipid peroxidation by Fe^{2+}/Cysteine.	*93*
	Nociceptive response reduction – *in vivo* (SC, mouse), hot plate test (ED_{50} 26.0 mg/kg) and phenylquinone induced writhing (ED_{50} 27.0 mg/kg).	*87*
	Protein kinase inhibition – *in vitro*, conc. used not stated, vs. wheat germ CDPK and rat liver CAK, and rat brain PKC, and avian MLCK, IC_{50} 30.0 μM.	*83*
	Radical formation effect – *in vitro* at 100.0 μM. Degradation of deoxyribose in Fe^{3+}-EDTA-H_2O system assayed. Effect inhibited by superoxide dismutase, catalase and mannitol but enhanced by ascorbate.	*92*
	Spontaneous activity reduction – *in vivo* (SC, mouse), ED_{50} 4.6 mg/kg.	*87*
	Toxicity assessment (Quantitative) – *in vivo* (SC, mouse), LD_{50} 195.0 mg/kg.	*94*
	Tyrosine hydroxylase inhibition – *in vitro* using bovine adrenal tyrosine kinase at 200.0 μM.	*95*
I.4	**Antiamebic** – *in vitro* (Agar plate) against *Entamoeba histolytica*, IC_{50} 147.0 μM.	*96*
	Antimalarial – *in vitro* (Agar plate) against *Plasmodium falciparum*, IC_{50} 24.1 μM.	*96*

(*continued*)

TABLE II.
Continued.

Alkaloid number	Biological activity/method/route/concentration or dose used	Refs.
II.2	**Antipsychotic** – *in vivo* (IV, rat), dose not stated. Studies involved conflict and learning behavior.	*97*
	Cataleptic effect – in humans (intraventricular, mouse) at 25.0 μg/animal. Prostate posture and ptosis observed.	*98*
	Dopamine uptake inhibition – *in vivo* (mouse, neuron), route and dose not stated. Effect seen in sympathetic nerve cells.	*99*
	Neuromuscular blocking – *in vitro* (frog, sciatic nerve-sartorius muscle), ED_{50} 467.0 μg/mL, induced contractions by Ach.	*100*
	Tranquilizing effect – *in vivo* (intraventricular, mouse) at 25.0 μg/animal vs. apomorphine or meta-amphetamine-induced increase in locomotor activity.	*98*
Ia.1	**Platelet aggregation inhibition** – *in vitro* at 100.0 μM, induced by arachidonic acid and PAF.	*13*
I.6	**Adrenergic receptor blocker (Alpha)** – *in vitro* (rat, aorta), conc. used not stated; (Alpha-1) - *in vitro* (rat, aorta) at 10.0 nM/L, induced contraction by phenylephrine.	*101*
	Antiarrythmic – *in vitro* (rat, cells cardiac myocyte) at 3.0 μM. Compound prolongs action potential duration-50, decreases max. rate of polarization and inhibits late outward current.	*102*
	Antiatherosclerotic, antiarrythmic, and antihypertensive – (oral, human adult), dose not stated.	*103*
	Antifungal – *in vitro* (Agar plate) at 15.0 μg/mL against *Cladosporium herbarum*.	*104*
	Antiplatelet – *in vitro* at 100.0 μg/mL, induced by ADP, arachidonic acid, collagen, and PAF.	*14*
	Antispasmodic – *in vitro*, IC_{50} 45.8 μM, human prostatic tissue was used, induced contractions by norepinephrine; and (unspecified type) at 100.0 nM vs. transmural field stimulated contraction.	*105*
	Cell proliferation inhibition – *in vitro* (Cell culture, splenocytes mouse) vs. cells – CTLL-2 (IC_{50} 0.5 μg/mL), Con-A (IC_{50} 2.2 and 9.2 μg/mL) and interleukin-2 (IC_{50} 9.2 μg/mL) stimulations.	*106*
	Chromosome aberrations induced – *in vitro* (Cell culture, cells hamster-Lung) at 15.0 μg/mL. Metabolic activation has no effect on the results.	*89*

	Cytotoxic – *in vitro* (Cell culture) vs. CA-HeLa (IC_{50} 33.3 μM), non-cancer 3T3 (IC_{50} 35.1 μM), melanoma-SK-MEL-5 (IC_{50} 36.3 μM), and Leuk-HL-60 (IC_{50} 28.3 μM); vs. Leuk-P388 and melanoma-B16 (IC_{50} 2.7 μg/mL), Leuk-L1210 (IC_{50} 1.2 μg/mL), and CA-adenocarcinoma-colon-C26 (IC_{50} 1.3 μg/mL), and vs. Leuk-L1210 (IC_{50} 13.8 μg/mL), melanoma-B16 (IC_{50} 14.3 μg/mL), CA-Bladder-MBC2 (IC_{50} 18.0 μg/mL), and CA-adenocarcinoma-colon-C26 (IC_{50} 14.0 μg/mL).	*79*,*106*
	Hypercholesterolemic, hypotriglyceridemia and **hypotensive** – *in vivo* (intragastric, rat) at 5.0 mg/kg. Wistar-Kyoto and spontaneously hypertensive animals were dosed 2× daily for 4 weeks. Total cholesterol and LDL reduced while HDL increased.	*107*
	Molluscicidal - *in vitro* (*Biomphalaria glabrata*), LC_{100} 2.5 ppm.	*108*
	Mutagenic – *in vitro* (Agar plate) against *Salmonella typhimurium* TA-98 and TA-100, conc. used not stated.	*109*
	Plant restitution inhibitor – *in vitro* (rat, spleen) at 10.0 nM/L, induced by phenylephrine.	*101*
	Platelet aggregation inhibition – *in vitro* (rabbit) at 300.0 μM, induced by arachidonic acid and collagen.	*110*
	Sodium channel blocking effect – *in vitro* (rat, cells-cardiac myocyte), IC_{50} 3.0 μM. Compound reduced transient outward Na current.	*111*
	Spasmolytic – *in vivo* (intragastric, rat, aorta) at 5.0 mg/kg, induced contractions by phenylephrine. No effect seen on Ach or nitroprusside-induced contraction.	*107*
	Spasmolytic – *in vitro* (guinea pig, ileum) at 10.0 μM, induced contractions by Ach and KCl, (rat, aorta) at 10.0 μM, induced contractions by KCl and phenylephrine, and (rat, aorta) at 9.0 μM, induced contractions by norepinephrine.	*110*,*111*
Ib.2	**Antileishmaniasis** – *in vitro* against *Leishmania donovani* (IC_{50} 55.5 μM, amastigotes; and IC_{50} 30.0 μM, promastigotes).	*112*
	Antimalarial – *in vitro* (*Plasmodium falciparum*), IC_{50} 189.2 μM.	*112*
	Cytotoxic – *in vitro* (Agar plate) at 49.0 μg/mL vs. RS-322 yeast strain.	*114*
	Cytotoxic – *in vitro* (Cell culture), CA-P-388 at 100.0 μM vs. wild type and camptothecin-resistant mouse leukemia cells; also CA-9KB), IC_{50} 10.4 μM.	*107*,*114*, *109–112*
	Topoisomerase I inhibition – *in vitro* at 100.0 μM.	*114*
	Vasodilatador – *in vitro* (rat, aorta) at 100.0 μg/mL, induced contractions by norepinephrine.	*14*

(*continued*)

TABLE II.
Continued.

Alkaloid number	Biological activity/method/route/concentration or dose used	Refs.
I.8	**Aldol reductase inhibition** – *in vitro* (lens), IC_{50} 0.76 mM.	*115*
	Chromosome aberrations induced – *in vitro* (Cell culture, cells-hamster-lung) at 40.0 μg/mL. Metabolic activation has no effect on the results.	*89*
Ia.5	**Bacterial stimulant** – *in vitro* (Cell culture, Leuk-P388), IC_{50} 0.3 μg/mL.	*26*
	Cytotoxic – *in vitro* (Cell culture) vs. CA-KB-16 (IC_{50} 0.072 μg/mL), CA-A549 (IC_{50} 0.4 μg/mL), and human colon cancer cell line HT-29 (IC_{50} 0.5 μg/mL).	*26*
IIIc.1	**Antibacterial** – *in vitro* (*Gardnerella vaginalis*) at 10.0 μg/mL.	*116*
	Antiprotozoan – *in vitro* (*Leishmania braziliensis* and *L. donovani*) at 10.0 μg/mL).	*116*
	Antitrypanosomal – *in vitro* (*Trypanosoma cruzi*) at 50.0 and 25.0 μg/mL and *Oscillatoria tenuis* at 250.0 μg/mL.	*52*,*117*, *118*
I.13	**Hypotensive**	*27*
	Platelet aggregation inhibition – *in vitro* at 50.0 μM, induced by thrombin, arachidonic acid, collagen, and PAF.	*13*
	Vasorelaxant – *in vitro* (rat, aorta) at 100.0 μM, induced contractions by potassium and norepinephrine.	*22*
I.13 (+)-Form	**Cytotoxic** – *in vitro* (Cell culture) vs. Leuk-P-388 (IC_{50} 3.060 μg/mL), CA-KB-16 (IC_{50} 2.818 μg/mL), CA-A549 (IC_{50} 2.929 μg/mL), and human colon cancer cell line HT-29 (IC_{50} 1.761 μg/mL); (Cell culture, CA-9KB), conc. used not given.	*25*,*119*
Ib.3	**Antiviral** – (Cell culture, virus HIV-1), IC_{50} 16.3 μM.	*30*
	Cytotoxic – *in vitro* (Cell culture) vs. Leuk-P-388 (IC_{50} <1.0 ng/mL), CA-KB-16 (IC_{50} 0.634 μg/mL), CA-A549 (IC_{50} 0.092 μg/mL), and human colon cancer cell line HT-29 (IC_{50} 0.348 μg/mL); vs. GLC-82 cells (IC_{50} 7.6 μM), cells-HCT (IC_{50} 8.2 μM).	*25*,*120*
I.15 and	**Antioxidant** – ($IC_{0.200}$ 12.29 μM) in scavenging stable free radical, DPPH.	*22*
I.15 (+)-Form	**Platelet aggregation inhibition** – *in vitro* at 300.0 μM, induced by thrombin, and collagen, and arachidonic acid.	*32*,*121*
	Vasorelaxation – *in vitro* (rat, aorta) at 100.0 μM, induced contractions by potassium and norepinephrine.	*22*

I.16	**Antiplatelet** – *in vitro* at 100.0 μg/mL, induced by ADP, arachidonic acid, collagen, and PAF.	*14*
	Vasorelaxation – *in vitro* (rat, aorta) at 300.0 μM, induced contractions by Potassium and norepinephrine.	*22*
I.16	**Antioxidant** – ($IC_{0.200}$ 12.4 μM) in scavenging stable free radical, DPPH.	*22*
(+)-Form	**Cytotoxic** – *in vitro* (Cell culture) vs. Leuk-P388 (IC_{50} 0.2 μg/mL); CA-KB-16 (IC_{50} 12.9 μg/mL), CA-A549 (IC_{50} 14.3 μg/mL), and human colon cancer cell line HT-29 (IC_{50} 6.0 μg/mL).	*26*
	Platelet aggregation inhibition – *in vitro* at 100.0 μM, induced by ADP, arachidonic acid (IC_{50} 167.7 μM), collagen, and PAF.	*121*
VIII.1	**Antimalarial** – *in vitro* (*Plasmodium falciparum*), conc. used not stated. Reverses chloroquine resistance.	*8*
	Antimalarial – *in vitro* (*Plasmodium falciparum*), IC_{50} 3.28 μM) vs. chloroquine-resistant strain FCM-29/Cameroon; *in vivo* (route not given, mouse, *Plasmodium yoelii*) at 10.0 mg/kg, vs. chloroquine-resistant strain N-67.	*9*
	Antimalarial – *in vitro* (cell culture, *Plasmodium falciparum*), IC_{50} 3.282 μM.	*48*
	Drug resistance reversal induction – *in vivo* (*Plasmodium yoelii*) at 10.0 mg/kg. Compound increased effectiveness of drug chloroquine vs. drug-resistant parasite strain.	*9*
VIII.2	**Antimalarial** – *in vitro* (*Plasmodium falciparum*), conc. used not stated. Reverses chloroquine resistance (*P. falciparum*), IC_{50} 1.68 μM vs. chloroqine-resistant strain FCM-29/Cameroon.	*8*,*9*
	Antimalarial – *in vivo* (route not given, mouse, *Plasmodium yoelii*) at 10.0 mg/kg vs. chloroquine-resistant strain N–67.	*9*
	Drug resistance reversal induction – *in vivo* (*Plasmodium yoelii*) at 10.0 mg/kg. Compound increased effectiveness of drug chloroquine vs. drug-resistant parasite strain.	*9*
VIII.3	**Antimalarial** – *in vitro* (*Plasmodium falciparum*), conc. used not stated. Reverses chloroquine resistance; (*P. falciparum*, IC_{50} 2.81 μM) vs. chloroquine-resistant strain FCM-29/Cameroon, and at 1.50 μM. Compound decreased IC_{50} value of Herveline D. A mixture of pure compounds was used to obtain the reported effect.	*8*,*9*
	Antimalarial – *in vitro* (Cell culture, *Plasmodium falciparum*, IC_{50} 3.168 μM). Also potentiated effect of chloroquine.	*48*
VIII.4	**Antimalarial** – *in vitro* (*Plasmodium falciparum*, IC_{50} 2.22 μM) vs. chloroquine-resistant strain FCM-29/Cameroon; *in vivo* (*P. falciparum*, IC_{50} 0.53 μM) in mixture with harveline C vs. chloroquine resistant strain FCM-29/Cameroon.	*9*
	Drug resistance reversal induction – *in vitro* (*Plasmodium falciparum*) at 12.54 μM. Compound reduced IC_{50} value of chloroquine when tested against drug-resistant parasite strain.	*9*

(*continued*)

TABLE II.
Continued.

Alkaloid number	Biological activity/method/route/concentration or dose used	Refs.
VIII.5	**Antimalarial** – *in vitro* (Cell culture, *Plasmodium falciparum*), IC_{50} 1.687 μM. Also potentiated effect of chloroquine.	*48*
	Cytotoxic – *in vitro* (Cell culture, HeLa cells), IC_{50} 14.2 μM.	*48*
I.17	**Cytotoxic** – *in vitro* (Cell culture) vs. Leuk-P388 (IC_{50} 2.0 μg/mL), CA-KB-16 (IC_{50} 0.6 μg/mL), and human colon cancer ell line HT-29 (IC_{50} 1.6 μg/mL), and CA-A549), (IC_{50} 6.3 μg/mL).	*26*
I.19	**Antibacterial** – *in vitro* (Agar plate) at 5.0 μg/disc against *Escherichia coli*, *Pseudomonas aeruginosa*, and *Staphylococcus aureus*.	*122*
	Antifungal – *in vitro* (Agar plate, *Phytophthora infestans*) at 5.0 μg/disc.	*122*
	Antimalarial – *in vitro* against *Plasmodium falciparum* D-6 (IC_{50} 668.0 ng/mL) and W-2 (IC_{50} 904.0 ng/mL).	*85*
I.20	**Antiarrhythmic** – *in vivo* (IV, rat) at 5.0 mg/kg induced by Barium, Calcium or aconitine (IV, rabbit) at 10.0 mg/kg, by $CHCl_3$-adrenaline (IV, guinea pig), dose not stated, and by ouabain.	*123*
	Antiarrhythmic – *in vivo* (IV, guinea pig) at 10.0 mg/kg, induced by ouabain (IV, rat), at 5-20 mg/kg by Barium and aconitine (IV, rabbit), and at 10.0 mg/kg by $CHCl_3$ and epinephrine.	*123*
	Antispasmodic – *in vitro* (guinea pig, bile duct), conc. not stated, induced contractions by Ach, histamine, angiotensin, and K^+.	*124*
	Butyrocholinesterase inhibition – *in vitro* (species not stated) at 0.1 mM/L.	*125*
	Cholinesterase inhibition – *in vitro* (species not stated) at 10.0 mM/L. Butyrylcholinesterase measured.	*125*
	Chronotropic effect negative – *in vivo* (IV, rat) at 10.0 mg/kg.	*123*
	Cytotoxic – *in vitro* (Cell culture) vs. CA-RS 322 YK-Rad-52 (at 2.16 μg/mL), CA-RS 321-Rad-321 (1.20 μg/mL), and Leuk-P388 (IC_{50} 1.59 μM).	*126*
	Hypotensive – *in vivo* (IV, dog) at 3.0 mg/kg. Effect of short duration.	*127*
	Inotropic effect negative – *in vitro* (guinea pig, muscle papillary) at 1.83 μM. Antagonized calcium response.	*123*
	Platelet aggregation inhibition – *in vitro* (rabbit) at 100.0 μg/mL, induced by ADP, PAF, arachidonic acid, and collagen.	*82*
	Respiratory stimulant effect – *in vivo* (IV, dog) at 3.0 mg/kg.	*127*

	Smooth muscle relaxant – *in vitro* (rat, aorta) at 20.0 μg/mL; (mouse) vs. vas deferens (at 424.0 μM) inhibited twitch response to field stimulation and at 212.0 μM, enhanced the twitch response to field stimulation.	*82*,*128*
	Spasmolytic – *in vitro* (mouse, conc. used not stated, vas deferens) induced contractions by KCl and norepinephrine.	*128*
	Toxicity assessment (Quantitative) – *in vivo* (IV, mouse), LD_{50} 49.5 mg/kg.	*129*
	Uterine stimulant effect – *in vitro* (rabbit and guinea pig, uterus), conc. used not stated, unspecified conditions.	*129*
IIId.2	**Analgesic** – *in vivo* (IP, mouse), dose not stated.	*130*
	Antiamebic – *in vitro* (Agar plate, *Entamoeba histolytica*), IC_{50} 22.2 μM.	*131*
	Anticytotoxic – *in vitro* (Cell culture, CA-mammary-MM2) ID_{50} 38.0 μg/mL, vs. TAK (an antitumor immunomodulator)-induced polymorphonuclear leukocyte tumoricidal activity against the MM2 ascites tumor.	*132*
	Antihemolytic – *in vitro* (human adult, membrane-erythrocyte) at 10.0 μM, vs. hypotonic hemolysis.	*133*
	Antiinflammatory – *in vivo* (IP, rat) dose not stated, (IP, mouse), route and dose not given, and (External, mouse) at 1.0 mg/ear, induced inflammation by arachidonic acid and tetradecanoyl-phorbol-13-acetate.	*130*,*134*,*135*
	Antiinflammatory – *in vitro* at 10.0 μg/mL, monocyte 90% cytokine production inhibition.	*136*
	Antileishmaniasis – *in vivo* against *Leishmania amazonensis* (SC and intrapaw, mouse) at 100.0 and 200.0 mg/kg; *Leishmania venezuelensis* (intrapaw, mouse) at 100.0 mg/kg.	*137*
	Antileishmaniasis – *in vitro* against *Leishmania donovani*, IC_{50} 2.22 μM.	*138*
	Antimalarial – *in vitro* against *Plasmodium falciparum* (IC_{50} 0.07 μg/mL), K-1 (IC_{50} 0.16 μM), and W-2 (ED_{50} 88.0 nM)	*131*,*139*,*140*
	Antimycobacterial – *in vitro* (Broth culture) against *Mycobacterium tuberculosis*, MIC 0.15 mg/mL and at 0.15 mg/mL; (Agar plate) against *Mycobacterium smegmatis*, MIC 100.0 μg/mL.	*141*,*142*
	Antiproliferation – *in vitro* (Cell culture, cells-colon 26), IC_{50} 19.1 μg/mL.	*143*
	Antitrypanosomal – *in vivo* (IG, mouse) *Trypanosoma cruzi* at 100.0 mg/kg; *in vitro* against *T. brucei brucei*, IC_{50} 1.45 μM.	*138*,*144*
	Antitumor – *in vivo* (IP, mouse) vs. CA-Ehrlich-Ascites (at 100.0 mg/kg) and sarcoma 180 (solid) at 125.0 mg/kg.	*42*
	Antitumor-promoting – *in vivo* (External, mouse) at 2.0 μM/ear, induced carcinogenesis by 12-O-tetradecanoylphorbol-13-acetate (TPA) and DMBA.	*135*

(*continued*)

TABLE II.
Continued.

Alkaloid number	Biological activity/method/route/concentration or dose used	Refs.
	Calcium channel blocker – *in vitro* (pig, sarcolemma cardiac), IC_{50} 1.2 μM. Compound inhibits binding of diltiazem, D-600, fluspirilene and nitrendipine. Inhibition of diltiazem binding correlates with Ca^{2+} uptake inhibition.	*145*
	Calcium ion uptake inhibition – *in vitro* (rat, cells-anterior pituitary). IC_{50} 15.0 μM. Effect assayed in GH3 cells whose calcium uptake is stimulated by KCl.	*145*
	Cell migration inhibition – *in vitro* (Cell culture, cells-colon 26), IC_{50} 19.0 μg/mL.	*143*
	Cell proliferation stimulation – *in vitro* (Cell culture) at 0.01 μg/mL vs. murine hair apparatus.	*146*
	Cytotoxic – *in vitro* (Cell culture) vs. HeLa cells (ED_{50} 5.8 μg/mL), CA-colon-human (ED_{50} 10.5 μg/mL), CA-human-breast BC-1 (ED_{50} 5.4 μg/mL), fibrosarcoma HT-1080 (ED_{50} 11.0 μg/mL), CA-lung-1 (ED_{50} 10.0 μg/mL), melanoma-SK-MEL-2 (ED_{50} 19.5 μg/mL), CA-9KB (ED_{50} 6.6 μg/mL and 10.6 μM), Leuk-P388 (ED_{50} 5.6 μg/mL), CA-A-431 (ED_{50} 8.4 μg/mL), CA-prostate-LNCA-P (ED_{50} 9.4 μg/mL), CA-human-mammary ZR-75-1 (ED_{50} 5.0 μg/mL), CA-9KB-V-1 (ED_{50} 1.5 μg/mL).	*42*,*140*,*147*
	Dopamine uptake inhibition – *in vitro* (synaptosomes-rat-brain), IC_{50} 4.2 μM.	*148*
	Histamine release inhibition – *in vitro* (rat, sarcolema-black) at 0.1 mM. Assay done on given cells after passive sensitization with mouse monoclonal anti-dinitrophenyl IGE antibody, and exposure to DNP-bovine gammaglobulin.	*149*
	Histidine decarboxylase induction – *in vivo* (IP, mouse) at 3.2 mg/kg vs. LPS-induced HDC activities.	*150*
	Interleukin-1 formation inhibition – *in vitro*, IC_{50} 3.4 μM/L.	*151*
	Interleukin-1 formation inhibition – *in vitro*, monocyte, at 1.0 μg/mL.	*136*
	Miscellaneous effects – *in vitro*, displaced 3H-SCH 23390 (IC_{50} 33.3 μM and displaced 3H-Raclopride (IC_{50} 0.67 μM) from their specific dopaminergic binding sites to rat striatal membranes.	*152*
	Muscle effects (unspecified) – *in vitro* (rat, aorta) vs. KCl (ID_{50} (24 h) 23.3 μM and histamine (ID_{50} (24 h) 22.3 μM).	*153*
	Nitric oxide release inhibition – *in vitro* at 5.0 μg/mL vs. thioglycollate and BCG induced macrophages.	*154*

	Pharmacokinetic study – *in vivo* (intragastric, rat), dose variable at 12.5 to 50.0 mg/kg and 100.0 to 250.0 mg/kg. Parameters such as AUC, clearance and volume of distribution were determined for doses.	*155*
	Phospholipase A2 antagonist – *in vitro* (rat, mast cell) at 20.0 μM. Compound inhibits the A2 activation induced by 2,4-dinitrophenyl group conjugated bovine serum albumin (DNP-BSA) in cells sensitized with anti-DNP IGE and by compound 48/80.	*156*
	Plaque-forming cell suppression – *in vivo* (IP, mouse) at 50.0 mg/kg. The response to sheep red blood cell immunization was assayed.	*157*
	Receptor regulating effect (unspecified) – *in vitro* (rat, cortex cerebral) at 1.0 μM vs. prazocin binding inhibition.	*153*
	Smooth muscle relaxant – *in vitro*, IC_{50} 10.0 mM, induced contraction by noradrenaline.	*158*
	Spasmolytic – *in vitro* (rat, aorta), IC_{50} 3.0 μM, induced contractions by K^+.	*159*
	Superoxide inhibition – *in vitro* (neutrophils) at 20.0 μM, induced superoxide generation by formylmethionyl-leucyl-phenylalanine, opsonized zymsan, arachidonic acid, and phorbol myristate acetate.	*160*
	Toxicity assessment (Quantitative) – *in vivo* (IP, mouse), LD_{50} 160.0 mg/kg.	*42*
	Tumor necrosing factor inhibition – *in vitro* IC_{50} 4.3 μM/L; (monocyte) at 3.3 μg/mL.	*136*,*151*
	Uterine relaxation effect – *in vitro* (rat, uterus), induced contractions by K^+ (IC_{50} 27.0 μM), Ach (IC_{50} 39.0 μM), and oxytocin (IC_{50} 49.0 μM).	*161*
Ib.5	**Antibacterial** – *in vitro* (Agar plate) at 200.0 μg/disc against *Bacillus cereus, B. subtilis, Staphylococcus aureus, Salmonella paratyphia, Vibrio cholera, Shigella boydii, S. flexneri, S. dysenteriae*.	*162*
	Antibacterial – *in vitro* (Agar plate) at 10.0 μg/disc against *Bacillus cereus*, *B. coagulans*, *B. megaterium*, *B. subtilis*, *Xanthomonas campestris*, *Micrococcus luteus*, *M. roseus*, *Staphylococcus albus*, *S. aureus*, *S. epidermides*, *S. epidermidis* ATCC-12228 (MIC 50.0 μg/mL), *Streptococcus faecalis*, *S. pneumoniae*, *S. mutans*, *Agrobacterium tumefaciens*, *Citrobacter freundii*, *Enterobacter aerogenes*, *Escherichia coli*, *Klebsiella pneumoniae*, *Neisseria gonorrhea*, *Proteus mirabilis*, *P. vulgaris*, *Pseudomonas aeruginosa*, *Salmonella typhi*, *S. typhimurium*, *and Serratia marcescens*.	*163*,*164*
	Antifungal – *in vitro* (Agar plate) against *Rhizopus oryzae*, *R. oligosporus*, *Trichoderma* species at 200.0 μg/disc.	*162*
	Antitrichomonal – *in vitro* (Agar plate, *Trichomonas vaginalis*) at 10.0 μg/disc.	*163*
	Antiyeast – *in vitro* (Agar plate, *Candida albicans*), IC_{50} 45.0 μg/mL.	*165*

(*continued*)

TABLE II.
Continued.

Alkaloid number	Biological activity/method/route/concentration or dose used	Refs.
II.3	**Adrenergic receptor blocker** (Alpha-1) – *in vitro* (rat, membrane-cerebral cortex) at 5.92 μM.	*166*
	Alcohol dehydrogenase and aldehyde reductase I inhibition – (20%, *in vitro* at 0.15 mM).	*167*
	Antihypertensive – *in vivo* (IV, rat) at 3.0 mg/kg vs. methoxamine-induced in blood.	*166*
	Antimalarial – *in vitro* (*Plasmodium falciparum*), IC_{50} 26.72 μM, vs. chloroquine-resistant strain FCM-29/Cameroon.	*9*
	Convulsivant – *in vivo* (IV, dog), dose not stated.	*168*
	Cyclic AMP stimulation – *in vitro* (guinea pig, striatum) at 100.0 μM vs. forskolin-stimulated camp level.	*169*
	Diltiazem binding inhibition – *in vitro* (rat, membrane-cerebral cortex) at 26.3 μM.	*166*
	Drug resistance reversal induction – *in vitro* (*Plasmodium falciparum*) at 21.01 μM. Compound reduced IC_{50} of drug chloroquine when tested against drug-resistant parasite strain and *in vivo* (mouse, route not given, *Plasmodium yoelii*) at 10.0 mg/kg. Compound increased effectiveness of drug chloroquine against drug-resistant parasite strain.	*9*
	Intraocular pressure reduction – *in vivo* (IV, rabbit) at 10.0 mg/animal.	*90*
II.4	**Spasmolytic** – *in vitro* (rat, aorta) at 50.0 μg/mL, induced contractions by norepinephrine.	*170*
I.23	**Antiplatelet** – *in vitro* at 100.0 μg/mL, induced by ADP, arachidonic acid, collagen, and PAF.	*14*
I.25	**Antihuman immunodeficiency virus** (HIV-1) integrase – (IC_{50} 7.7 μM).	*30*
	Antimalarial – *in vitro* against *Plasmodium falciparum* D-6 (IC_{50} 1240 ng/mL) and W-2 (IC_{50} 1680 ng/mL).	*85*
	Platelet aggregation inhibition – *in vitro* at 100.0 μg/mL, induced by PAF, and arachidonic acid (IC_{50} 149.2 μg/mL).	*121*
I.26	**Antiarrythmic** – *in vivo* (IV, dog) at 5.0 mg/kg, induced arrythmia by adrenalin.	*171*
	Antioxidant – *in vitro* at 10.4 μM.	*22*
	Antiviral – *in vitro* (Cell culture, virus-Poliovirus II), ED_{50} 31.0 μM vs. vaccinal strain Sabin II.	*78*
	Curarizant	*27*

	Platelet aggregation inhibition – *in vitro* induced by arachidonic acid (at 20.0 μM), PAF and collagen (at 100.0 μM).	*13*
	Vasorelaxation – *in vitro* (rat, aorta) at 100.0 μM, induced contractions by Potassium.	*22*
I.26	**Antioxidant** – (IC_{0200} 10.4 μM) in scavenging stable free radical, DPPH.	*22*
(+)-Form	**Antimalarial** – *in vitro* against *Plasmodium falciparum* DD2 (IC_{50} 3900 ng/mL) and *P. falciparum* W-2 (IC_{50} 2530 ng/mL).	*85*
	Cytotoxic – *in vitro* (Cell culture) vs. Leuk-P388 (IC_{50} 0.2 μg/mL), CA-KB-16 (IC_{50} 6.2 μg/mL), CA-A549 (IC_{50} 3.3 μg/mL), and human colon cancer cell line HT-29 (IC_{50} 1.8 μg/mL).	*26*
	Platelet aggregation inhibition – *in vitro* (rabbit) at 100.0 μg/mL, induced by ADP, arachidonic acid, collagen, and PAF.	*82*
	Smooth muscle relaxant – *in vitro* (rat, aorta) at 100.0 μg/mL, induced contractions by Potassium and norepinephrine.	*22*,*82*
	Spasmolitic – *in vitro* (rat, aorta), induced contractions by Potassium (IC_{50} 19.8 μM) and phenylephrine (IC_{50} 36.8 μM). Effect not antagonized by indometacin or nifedipine.	*172*
IIId.3	**Antibacterial** – *in vitro* (Agar plate, conc. not stated) against several Gram-positive and Gram-negative bacteria, and *Gardnerella vaginalis* at 10.0 μg/mL.	*116*,*173*
	Antimalarial – *in vitro* against *Plasmodium falciparum* chloroquine resistant (IC_{50} 789.0 nM), FCB-1 (IC_{50} 1.27 μM), K-1 (IC_{50} 1.35 μg/mL), vs. lymphoblasts-CCRF-CEM (IC_{50} 3.5 μM), and T9-96 (IC_{50} 0.24 μg/mL).	*174*,*175*
	Antiprotozoan – *in vitro* against *Leishmania braziliensis* and *L. donovani* at 10.0 μg/mL.	*116*
	Antitrypanosomal – *in vitro* against *Trypanosoma cruzi*, trypomastigote forms of the Y strain (LC_{50} < 0.1 mM); *T. cruzi* at 50.0 and 250.0 μg/mL, and *in vivo* (intragastric, mouse) at 100.0 mg/kg.	*117*,*118*, *144*,*176*
	Sister chromatid exchange stimulation – *in vitro* (human adult, lymphocytes) at 5.0 μg/mL.	*118*
IIId.3 (−)-Form	**Antimalarial** – *in vitro* (Agar plate) against *Plasmodium falciparum* D-6 (IC_{50} 52.7 μg/mL and 86.0 nM) and W-2 (IC_{50} 164.0 μg/mL and 263.0 nM).	*140*,*177*
	Cytotoxic – *in vitro* (Cell culture) vs. human CA-9KB (ED_{50} 161.0 μM and 9.8 μg/mL), Leuk-P388 (ED_{50} 0.25 μg/mL), CA-9KB-V-1 (ED_{50} 11.0 μg/mL).	*140*,*177*
IIIc.4	**Antimalarial** – *in vitro* against *Plasmodium falciparum* D-6 (IC_{50} 64.0 nM) and W-2 (IC_{50} 192.0 nM).	*140*
	Cytotoxic – *in vitro* (human CA-9KB cells), ED_{50} 4.11 μM.	*140*

(*continued*)

TABLE II.
Continued.

Alkaloid number	Biological activity/method/route/concentration or dose used	Refs.
Ib.6	**Amino acid (aromatic) decarboxylase inhibition** – *in vivo* (Cell culture, cells-PC-12) at 10.0 μM.	*178*
	Antiarrhythmic – *in vitro* (rat, heart) at 0.3 μM, induced arrhytimia by ischemia.	*179*
	Antibacterial – *in vitro* (Agar plate) against *Staphylococcus aureus* (MIC 100.0 μg/mL or 1.0 mg/mL), *S. aureus* methicillin resistant strain 19 (IC_{50} 2.0 μg/mL), and *Bacillus subtilis* (at 1.0 mg/mL).	*165*,*180*,*181*
	Antibacterial – *in vitro* (Agar plate) at 10.0 μg/disc against *Agrobacterium tumefaciens*, *Bacillus cereus*, *B. coagulans*, *B. subtilis*, *B. megaterium*, *Citrobacter freundii*, *Enterobacter aerogenes*, *Escherichia coli*, *Klebsiella pneumoniae*, *Micrococcus luteus*, *M. roseus*, *Neisseria gonorrhea*, *Proteus mirabilis*, *P. vulgaris*, *Pseudomonas aeruginosa*, *Salmonella typhimurium*, *S. typhi*, *Serratia marcescens*, *Staphylococcus albus*, *S. aureus*, *S. epidermidis*, *Streptococcus faecalis*, *S. pneumoniae*, *S. mutans*, and *Xanthomonas campestris*.	*163*
	Antibacterial – *in vitro* (Agar plate) against *Bacillus subtilis* (MIC 6.0 and 1.0 μg/mL) and *Staphylococcus aureus,* (MIC 2.0 and 25.0 μg/mL).	*182*,*183*
	Antibacterial – *in vitro* (Broth culture) against *Staphylococcus aureus*, *S. epidermidis*, *Streptococcus faecalis*, *S. pyogenes* (MIC 25.0 mg/L), and *Bacillus subtilis* (MIC 6.0 mg/L).	*184*
	Anticrustacean – *in vitro* (*Artemia salina*, larvae) LD_{50} 1.1 μg/mL. Assay system is intended to predict for antitumor activity.	*185*
	Antifungal – *in vitro* (Agar plate) against *Cladosporium cladosporioides* (at 1.33 mg/SQ CM), *C. gloeosporioides* (IC_{90} 200.0 μg/mL), and *Aspergillus niger* at 1.0 mg/mL.	*180*,*181*
	Antifungal – *in vitro* (Agar plate) at 5.0 μg/mL, fungal species not given.	*186*
	Antifungal – *in vitro* (Broth culture) against *Microsporum gypseum* (MIC 3.12 μg/mL) and *Trichophyton mentagrophytes* (MIC 3.12 and 0.78 μg/mL).	*187*
	Antifungal – *in vitro* (Agar plate) against *Trichophyton mentagrophytes* (MIC 2.0 μg/mL), *T. rubrum* (MIC 1.0 μg/mL), *Trichophyton* species and *Aspergillus fumigatus* (MIC 25.0 μg/mL), *Syncephalestrum racemosum* (MIC 3.1μg/mL).	*183*
	Antifungal – (plant pathogens) *in vitro* (Agar plate, conc. used not stated) against *Plasmopora viticola*, and *Botrytis fabae*.	*183*

Antileishmaniasis – *in vitro* against *Leishmania braziliensis, L. donovani*, and *L. amazonensis*, IC_{100} 100.0 μg/mL.	*188*
Antileishmaniasis – *in vitro* (Agar plate) against *Leishmania major* (IC_{100} 3.12 μg/mL), *L. donovani* (IC_{100} 3.12 and 5.0 μg/mL), *L. braziliensis*, and *L. amazonensis* (IC_{100} 5.0 μg/mL).	*189*,*190*
Antileishmaniasis – *in vitro* against *Leishmania donovani*, IC_{50} 15.0 μM (promastigotes) and IC_{50} 72.4 μM (amastigotes).	*112*
Antimalarial – *in vitro* (*Plasmodium falciparum*), IC_{50} 25.1 to 54.5 μM.	*112*,*191*
Antimycobacterial – *in vitro* (Agar plate, *Mycobacterium smegmatis*) at 1.0 mg/mL.	*181*
Antimycobacterial – *in vitro* against *Mycobacterium phlei* (MIC 12.0 μg/mL).	*182*
Antimycobacterial – *in vitro* (Agar plate or Broth culture) against *Mycobacterium phlei* (MIC 12.0 mg/L).	*184*
Antiplatelet – *in vitro* at 100.0 μg/mL induced by ADP, arachidonic acid, collagen, and PAF.	*14*
Antitrichomonal – *in vitro* (Agar plate, *Trichomonas vaginalis*) at 10.0 μg/disc.	*163*
Antitrypanosomal – *in vitro* at 250.0 μg/mL against *Trypanosoma cruzi* and *Trypanosoma brucei* (IC_{100} 50.0 μg/mL).	*188*,*189*
Antiviral – *in vitro* (Cell culture, virus-herpes simplex) ED_{50} 7.0 μM.	*77*
Antiyeast – *in vitro* (Agar plate) against *Candida albicans* (IC_{50} 3.5 μg/mL), *Cryptococcus neoformans* (IC_{50} 2.0 μg/mL), *Saccharomyces cerevisiae* (at 1.0 mg/mL), and *Saccharomyces cerevisiae* Rad 52 (IC_{50} 16.7 μg/mL).	*165*,*181*,*192*
Antiyeast – *in vitro* against *Candida albicans* (Agar plate, MIC 50.0 μg/mL) and (Broth culture, MIC 3.1μg/mL).	*182*,*193*
Antiyeast – *in vitro* (Agar plate) against *Candida albicans* (MIC 8.0 μg/mL) and *Pyricularia oryzae* (conc. used not stated).	*183*
Antiyeast – (intraportal) against *Candida albicans* (MIC 3.12 μg/mL); (IP, mouse) at 0.5 mg/kg, and oral at 12.5 mg/kg.	*194*
Antiyeast – *in vitro* (Broth culture) against *Candida albicans* (MIC 500 mg/L) and conc. used not stated.	*184*
Calcium channel blocker – *in vitro* (Cell culture, cells-cardiac myocyte), IC_{50} 2.5 μM.	*179*
Chronotropic effect negative – *in vitro* (rat, atrium) at 3.8 μM.	*179*
Cytotoxic – *in vitro* (Cell culture) vs. CA-9KB (ED_{50} 1.6 and <4.0 μg/mL).	*195*,*196*
Cytotoxic – *in vitro* (Cell culture) vs. CA-9KB (ED_{50} 1.0 μg/mL), CA-A549 (ED_{50} 0.72 μg/mL), CA-HCT-8 (ED_{50} 0.7 μg/mL), Leuk-P388 (ED_{50} 0.57 μg/mL), and Leuk-L1210 (ED_{50} 2.33 μg/mL).	*197*

(*continued*)

TABLE II.
Continued.

Alkaloid number	Biological activity/method/route/concentration or dose used	Refs.
	Cytotoxic – *in vitro* (Cell culture) vs. CA-9KB (ED_{50} 1.0 μg/mL), CA-A549 (ED_{50} 0.72 μg/mL), CA-HCT-8 (ED_{50} 0.70 μg/mL), Leuk-P388 (ED_{50} 70.57 and 0.70 μg/mL), and Leuk-L1210 (ED_{50} 2.33 and 0.57 μg/mL).	*198*,*199*
	Cytotoxic – *in vitro* (Cell culture, cells-Vero), IC_{50} 48.0 μM.	*77*,*78*
	Cytotoxic – *in vitro* (Cell culture) vs. CA-A549 (ED_{50} 1.2 μg/mL), CA-SK-OV-3 (ED_{50} 2.0 μg/mL), human melanoma cell line SK-MEL-2 (ED_{50} 1.5 μg/mL), Cells-XF-498 (ED_{50} 1.8 μg/mL), CA-HCT-15 (ED_{50} 2.2 μg/mL), and cells-Vero (IC_{50} 1.0 μg/mL).	*189*,*200*
	Cytotoxic – *in vitro* (Cell culture) vs. CA-9KB (ED_{50} 1.0 μg/mL), CA-A549 (ED_{50} 0.72 μg/mL), CA-HCT-8 (ED_{50} 0.70 μg/mL), Leuk-P388 (ED_{50} 0.57 μg/mL), Leuk-L1210 (ED_{50} 2.33 μg/mL).	*201*
	Cytotoxic – *in vitro* (Cell culture) vs. Leuk-P388 (ED_{50} 0.8 and <2.5 μg/mL), and CA-9KB (ED_{50} 1.7 and <2.5 μg/mL).	*202*,*203*
	Cytotoxic – *in vitro* (Cell culture) vs. CA-A549 (ED_{50} 0.72 μg/mL), CA-HCT-8 (ED_{50} 0.7 μg/mL), CA-9KB (ED_{50} 1.0 μg/mL), Leuk-P388 ED_{50} 0.57 μg/mL), and Leuk-L1210 (ED_{50} 2.33 μg/mL).	*204*
	Cytotoxic – *in vitro* (Cell culture) vs. CA-9KB (IC_{50} 26.9 μM, ED_{50} 3.8, 3.1, and 3.5 μg/mL).	*112*,*205–207*
	Dopamine release inhibition – *in vivo* (Cell culture, cell-PC12), IC_{50} 8.4 μM.	*178*
	Dopamine uptake inhibition – *in vitro* (rat, synaptosomes-rat-brain), IC_{50} 31.2 μM).	*148*
	Hypotensive – *in vivo* (IV, dog) at 3.0 mg/kg.	*127*
	Inositol phosphate formation inhibition – *in vitro* (Cell culture, muscle-trachealis) at 10.0 mg vs. carbachol-induced inositol phosphate accumulation.	*208*
	Inotropic effect positive – *in vitro* (rat, atrium) at 3.8 μM, 4-aminopyridine but not prazosin, propanolol, verapamil or carbachol inhibited effect.	*179*
	Muscarinic antagonist – *in vitro* (guinea pig, trachea) at 30.0 μM vs. carbachol.	*209*
	Muscarinic antagonist – *in vitro* (Cell culture, muscle-trachealis) at 2.2 μM. Displaces labeled N-methylscopolamine. Data best fit by 2-site binding model.	*208*
	Muscarinic antagonist – *in vivo* (rat), conc. used not stated.	*210*
	Mutagenic – *in vitro* (Agar plate, conc. used not stated) against *Salmonella typhimurium* TA100 and TA98.	*109*

	Mutagenic – *in vitro* against *Salmonella typhimurium* TA98 and TA100 at 4.0 μg/plate. Metabolic activation was required.	*211*
	Platelet activating factor receptor-binding inhibition – *in vitro* at 9.1 μg/mL.	*212*
	Platelet aggregation inhibition – *in vitro* (rabbit) at 25.0 μg/mL, induced by ADP, arachidonic acid, collagen, and PAF.	*82*
	Platelet aggregation inhibition – *in vitro*, induced by epinephrine (IC_{50} 67.0 μM), and arachidonic acid (IC_{50} 44.0 μM).	*212*
	Potassium (IC_{50} 2.8 μM) and **Sodium** (IC_{50} 0.7 μM) **channel blocking** – *in vitro* (Cell culture, cells-cardiac myocyte). Transient outward K^+ channel affected.	*179*
	Respiratory stimulant effect – *in vivo* (IV, dog) at 3.0 mg/kg.	*127*
	Spasmolytic – *in vitro* (Cell culture, muscle-tracheal) at 10.0 μM. Response curve shifted to right.	*208*
	Spasmolytic – *in vitro* (Cell culture, aorta), induced contractions by norepinephrine (IC_{50} 23.0 μM) and K^+ (IC_{50} 32.0 μM).	*213*
	Topoisomerase II inhibition – *in vitro* (Cell culture) vs. SV40-infected CV-1 cells at 5.0 μM and IC_{50} 0.11 μM.	*214*,*215*
	Toxicity assessment (Quantitative) – *in vivo* (IV, mouse), LD_{50} 120 mg/kg.	*194*
	Tyrosine hydroxylase inhibition – *in vivo* (Cell culture, cells-PC12) at 10.0 μM.	*178*
	Vasodilator – *in vivo* (IV, rat), dose not stated.	*216*
Ib.7	**Antibacterial** – *in vitro* (Agar plate) against *Bacillus subtilis*, conc. used not stated.	*217*
	Antibacterial – *in vitro* (Agar plate) against *Bacillus subtilis* (MIC 3.0 μg/mL) and *Staphylococcus aureus* (MIC 25.0 μg/mL).	*182*,*183*
	Antibacterial – *in vitro* (Broth culture) against *Staphylococcus aureus* (MIC 25.0 μg/mL), *S. epidermidis* (MIC 12. mg/L), *Bacillus subtilis* (MIC 3.0 mg/L), *Streptococcus pneumoniae* (IC_{90} 25.0 mg/L).	*184*
	Antibacterial – *in vitro* (Broth culture) against *Streptococcus faecalis* (MIC 50.0 mg/L and IC_{90} 50.0 mg/L), *S. pyogenes* (MIC 50.0 mg/L), *Staphylococcus aureus*, *S. epidermides*, *S. pyogenes*, and *Listeria monocytogenes* (IC_{90} 50.0 mg/L).	*184*
	Antifungal – (Agar plate, conc. used not stated) against *Botrytis cinerea, Saprolegnia asterophora*, and *Staphylococcus aureus*.	*184*,*217*
	Antifungal – *in vitro* (Agar plate) against *Trichophyton mentagrophytes* (MIC 12.5 μg/mL).	*183*
	Antileishmaniasis – *in vitro* against *Leishmania major* and *L. donovani* (IC_{100} 25.0 μg/mL).	*189*

(*continued*)

TABLE II.
Continued.

Alkaloid number	Biological activity/method/route/concentration or dose used	Refs.
	Antimycobacterial – *in vitro* (Agar plate) against *Mycobacterium phlei* (MIC 12.0 μg/mL) and *M. smegmatis* (MIC 12.5 μg/mL).	*182–184*
	Antitrypanosomal – *in vitro* against *Trypanosoma brucei* (IC_{100} 25.0 μg/mL).	*189*
	Antiyeast – *in vitro* (Agar plate) against *Saccharomyces cerevisiae* (MIC 12.5 μg/mL) and *Candida albicans* (MIC 100.0 mg/L and conc. used not stated).	*183*,*184*,*192*
	Barbiturate potentiation – *in vivo* (mouse), route not given, at 1.0 mg/kg.	*218*
	CNS depressant – *in vivo* (IP, mouse), dose used not stated.	*218*
	Cytotoxic – *in vitro* (Cell culture) vs. hepatoma-HEP-G-2 (IC_{50} 8.4 μg/mL), CA-HEP-2 (IC_{50} 3.4 μg/mL), and cells-Vero (IC_{50} 8.0 μg/mL).	*189*,*219*
	Mutagenic – *in vitro* (Agar plate, conc. used not stated) against *Salmonella typhimurium* TA100.	*109*
	Tranquilizing effect – *in vivo* (IP, mouse) at 3.0 mg/kg.	*220*
II.5	**Anticytotoxic** – *in vitro* (Cell culture, CA-mammary-MM2), ID_{50} 8.7 μg/mL, TAK (an antitumor immunomodulator)-induced polymorphonuclear leukocyte tumoricidal.	*132*
	Curarizant	*27*
	Hypotensive – *in vivo* (IV, rat, dog, cat and rabbit), dose not stated.	*221*,*222*
	Cytotoxic – *in vitro* (Cell culture) vs. Leuk-P388 (IC_{50} 0.2 μg/mL, CA-A549 and human colon cancer cell line HT-29 (IC_{50} 13.0 and 13.5 μg/mL).	*26*
	Vasorelaxant – *in vitro* (rat, aorta) at 300.0 μM, induced contractions by norepinephrine.	*22*
IIIb.3	**Antimalarial** – *in vitro* against *Plasmodium falciparum* D-6 (IC_{50} 61.0 nM) and W-2 (IC_{50} 164.0 nM).	*140*
	Antioxidant – ($IC_{0.200}$ 3 μM) in scavenging stable free radical, DPPH.	*22*
	Cytotoxic – *in vitro* (Cell culture, CA-9KB), ED_{50} 29.9 μM.	*140*
	Platelet aggregation inhibition – *in vitro* at 100.0 μM, induced by thrombin, arachidonic acid, collagen, and PAF.	*32*
	Vasorelaxant – *in vitro* (rat, aorta) at 30.0 μM, induced contractions by potassium and norepinephrine.	*22*
I.30	**Adrenergic receptor blocker** (Alpha-1) – *in vitro* (Cell culture, cell-A10-Murine) at –log (conc.) 7.55 M.	*223*
	Antiplatelet – *in vitro* at 100.0 μg/mL, induced by ADP, arachidonic acid, collagen, and PAF.	*14*
	Inositol phosphate formation inhibition – *in vitro* (rat, aorta) at 1.0 μM, induced by norepinephrine.	*223*

	Platelet aggregation inhibition – *in vitro* induced by ADP, collagen (100.0 μg/mL), and arachidonic acid (100.0 and 50.0 μg/mL).	*80*,*81*
	Serotonin receptor blocking effect – *in vitro* (rat, aorta) at 30.0 μM.	*223*
	Smooth muscle relaxant – *in vitro* (rabbit, aorta), conc. used not stated.	*81*
	Spasmolytic – *in vitro* (rat, aorta), induced by indomethacin (at 7.11 M), and vas deferens (at 5.01 M), induced by clonidine.	*223*
I.30 (+)-Form	**Platelet aggregation inhibition** – *in vitro* (rabbit) at 20.0 and 100.0 μg/mL, induced by ADP, arachidonic acid, collagen, and PAF.	*14*,*82*
	Selective α1–adrenoceptor antagonist	*223*
	Smooth muscle relaxant – *in vitro* (rat, aorta) at 100.0 μg/mL, induced contractions by K^+ and norepinephrine.	*82*
II.6	**Antimalarial** – *in vitro* against *Plasmodium falciparum* D-6 (IC_{50} 2730 ng/mL) and W-2 (IC_{50} 3810 ng/mL).	*85*
	Histamine release inhibition – *in vitro* (rat, Leuk-RBL 2H3) at 0.2 mM.	*149*
	Interleukin-1 formation inhibition – *in vitro*, IC_{50} 11.6 μM/L.	*151*
	Spasmolitic activity – *in vitro* (rat, aorta), IC_{50} 32.0 μM.	*159*
	Tumor necrosing factor inhibition – *in vitro* IC_{50} 16.4 μM/L.	*151*
XI.1	**Cytotoxic** – *in vitro* (Cell culture) vs. Leuk-P388 (IC_{50} 0.218 μg/mL), CA-KB-16 (IC_{50} 0.989 μg/mL), CA-A549 (IC_{50} 2.137 μg/mL), and human colon cancer cell line HT-29 (IC_{50} 0.928 μg/mL).	*25*
I.32	**Antioxidant** – ($IC_{0.200}$ 24.9 μM) in scavenging stable free radical, DPPH.	*22*
	Platelet aggregation inhibition – *in vitro* at 300.0 μM, induced by PAF, thrombin, arachidonic acid, and collagen.	*32*
	Vasorelaxant – *in vitro* (rat, aorta) at 100 μM, induced contractions by high K^+ and norepinephrine.	*22*
I.33	**Platelet aggregation inhibition** – *in vitro* at 100.0 μg/mL, induced by collagen, arachidonic acid, and PAF.	*121*
I.34	**Antifungal** – *in vitro* (Agar plate) against *Polyporus* species, *Pleurotus ostreatus, Phialophora malinii, Ceratocystis* sp., and *Fusarium oxysporum* at 0.06%.	*224*
	Antiviral – *in vitro* (Cell culture, virus-Poliovirus II) vs. vaccinal strain Sabin II, ED_{50} 15.0 μM.	*78*,*225*
	Cytotoxic – *in vitro* (Cell culture, virus-poliovirus-Sabin), LC_{50} 250.0 μM.	*225*
	Vasorelaxant – *in vitro* (rat, aorta), induced contractions by potassium (at 30.0 μM) and norepinephrine (at 10.0 μM).	*22*

(*continued*)

TABLE II.
Continued.

Alkaloid number	Biological activity/method/route/concentration or dose used	Refs.
I.34	**Antimalarial** – *in vitro* against *Plasmodium falciparum* D-6 (IC_{50} 7150 ng/mL) and W-2 (IC_{50} 2700 ng/mL).	*85*
(+)-Form	**Platelet aggregation inhibition** – *in vitro* (rabbit) at 100.0 μg/mL, induced by ADP, collagen, arachidonic acid, and PAF.	*82*
	Smooth muscle relaxant – *in vitro* (rat, aorta) at 100.0 μg/mL, induced contractions by K^+ and norepinephrine.	*82*
I.32	**Platelet aggregation inhibition** – *in vitro* (rabbit) induced by ADP, collagen, PAF, and arachidonic acid (at 300.0 mM and 100.0 μg/mL).	*82*,*226*
	Smooth muscle relaxant – *in vitro* (rat, aorta) at 100.0 μg/mL, induced contractions by K^+ and norepinephrine.	*82*
I.36 (+)-Form	**Cytotoxic** – *in vitro* (Cell culture) vs. Leuk-P388 (IC_{50} 0.191 μg/mL), CA-KB-16 (IC_{50} 0.332 μg/mL), CA-A549 (IC_{50} 0.469 μg/mL), and human colon cancer cell line HT-29 (IC_{50} 0.90 μg/mL).	*25*
	Platelet aggregation inhibition – *in vitro* at 100.0 μg/mL, induced by collagen (IC_{50} 193.5 μM).	*121*
	Vasorelaxation – *in vitro* (rat, aorta), induced contractions by potassium (at 30.0 μM) and norepinephrine (at 10.0 μM).	*22*
I.37	**Antiplatelet aggregation inhibition** – *in vitro* at 100.0 μg/mL, induced by ADP, collagen, arachidonic acid, and PAF.	*14*
	Platelet aggregation inhibition – *in vitro* (rabbit) at 100.0 and 300.0 μM, induced by ADP, arachidonic acid, collagen, and PAF.	*82*,*110*
	Spasmolitic – *in vitro* (rat, aorta) at 120.0 μM, induced contractions by K^+ and norepinephrine.	*110*
Ib.8	**Antiplatelet** – *in vitro* at 100.0 μg/mL, induced by ADP, arachidonic acid, collagen, and PAF.	*14*
	Platelet aggregation inhibition – *in vitro* (rabbit, aorta) at 300.0 μM, induced by arachidonic acid and collagen.	*110*
	Platelet aggregation inhibition – *in vitro* (rabbit, aorta) induced by ADP, arachidonic acid, collagen, and PAF (at 100.0 μM).	*82*
	Spasmolytic – *in vitro* (rat, aorta) at 120.0 μM, induced contractions by K^+ and norepinephrine.	*110*
I.42	**Antileishmaniasis** – *in vitro* against *Leishmania braziliensis* (ID_{50} (24 h) 50.0 μg/mL), *L. amazonensis*, and *L. donovani* (IC_{100} 25.0 μg/mL).	*188*
	Antitrypanosomal – *in vitro* at 250.0 μg/mL against *Trypanosoma cruzi*.	*188*

I.43	**Antimalarial** –*in vitro* against *Plasmodium falciparum* D-6 and W-2 (IC_{50} 1990 ng/mL).	*85*
I.44	**Antibacterial** – *in vitro* (Agar plate, conc. used not stated) against *Staphylococcus aureus*.	*184*
	Antibacterial – *in vitro* (Broth culture) against *Streptococcus pyogenes* and *Bacillus subtilis* (MIC 50.0 mg/L).	*184*
	Antileishmaniasis – *in vitro* against *Leishmania mexicana* (IC_{50} 24.0 μM) and *L. panamensis* (IC_{50} 15.0 μM).	*227*
	Antimycobacterial – *in vitro* (Agar plate and Broth culture, conc. not stated) against *Mycobacterium phlei* (MIC 12.0 mg/L).	*184*
	Antiyeast – *in vitro* (Agar plate and Broth culture, conc. used not stated) against *Candida albicans* (MIC 3.0 mg/L).	*184*
	Serotonin (5-HT) antagonist – *in vitro*, conc. used not stated.	*228*
XI.3	**Cytotoxic** – *in vitro* (Cell culture, CA-A549), IC_{50} 30.5 μg/mL.	*26*
I.46	**Platelet aggregation inhibition** – *in vitro* induced by PAF, thrombin, and collagen (at 300.0 μM), and arachidonic acid (at 150 μM).	*32*
	Vasorelaxation – *in vitro* (rat, aorta) induced contractions by K^+ (at 10.0 μM) and norepinephrine (at 30.0 μM).	*22*
V.2	**Cytotoxic** – *in vitro* (Cell culture) vs. human colon cancer cell line HT-29 (IC_{50} 10.2 μg/mL), Leuk-P388 (IC_{50} 1.0 μg/mL), CA-KB-16 (IC_{50} 0.239 μg/mL), and CA-A549 (IC_{50} 1.57 μg/mL).	*25*
V.3	**Cytotoxic** – *in vitro* (Cell culture) vs. Leuk-P388 (IC_{50} 1.489 μg/mL), CA-A549 (IC_{50} 2.146 μg/mL), and human colon cancer cell line HT-29 (IC_{50} 4.152 μg/mL).	*25*
III.1	**Antioxidant** – ($IC_{0.200}$ 3 μM) in scavenging stable free radical, DPPH.	*22*
	Platelet aggregation inhibition – *in vitro* induced by arachidonic acid and collagen (at 20.0 μM), and PAF (at 50.0 μM).	*13*
	Vasorelaxation – *in vitro* (rat, aorta) at 150.0 μM induced contractions by potassium and norepinephrine.	*22*
Ib.10	**Platelet aggregation inhibition** – *in vitro* (rabbit) at 25.0 μg/mL, induced by ADP, arachidonic acid, collagen, and PAF.	*82*
Ib.11	**Cytotoxic** – *in vitro* (Cell culture) vs. Leuk-P388 (IC_{50} 12.56 μg/mL), CA-KB-16 (IC_{50} 5.3 μg/mL), CA-A549 (IC_{50} 27.13 μg/mL).	*25*
Ib.12	**Antiviral** – *in vitro* (Cell culture, virus-HIV-1), IC_{50} 18.2 μM.	*30*
	Platelet aggregation inhibition – *in vitro* at 100.0 μM, induced by arachidonic acid and collagen.	*13*
	Vasorelaxation – *in vitro* (rat, aorta) at 100.0 μM, induced contractions by potassium and norepinephrine.	*22*

(*continued*)

TABLE II.
Continued.

Alkaloid number	Biological activity/method/route/concentration or dose used	Refs.
Ib.13	**Antioxidant** – ($IC_{0.200}$ 8.6 μM) in scavenging stable free radical, DPPH.	*22*
	Platelet aggregation inhibition – *in vitro* at 20.0 μM induced by arachidonic acid and PAF.	*13*
	Vasorelaxation – *in vitro* (rat, aorta) at 30.0 μM, induced contractions by Potassium and norepinephrine.	*22*
Ib.14	**Antibacterial** – *in vitro* (Agar plate) against *Staphylococcus aureus* (MIC 12.5 μg/mL).	*182*
	Antifungal – *in vitro* (Agar plate) against *Trichophyton mentagrophytes* (MIC 12.5 μg/mL).	*182*
	Antimycobacterial – *in vitro* (Agar plate) against *Mycobacterium smegatis* (MIC 6.3 μg/mL).	*182*
	Antiyeast – *in vitro* (Agar plate) against *Saccharomyces cerevisae* (MIC 12.5 μg/mL).	*182*
IIId.4	**Antiamebic** – *in vitro* (Agar plate) against *Entamoeba histolytica* (IC_{50} 17.4 μM).	*131*
	Antibacterial – *in vitro* (Agar plate, conc. used not stated) against several Gram-positive and Gram-negative organisms.	*173*
	Antibacterial – *in vitro* (Agar plate) against *Gardnerella vaginalis* at 50.0 μg/mL.	*116*
	Antileishmaniasis – *in vitro* against *Leishmania donovani* (IC_{50} 1.57 μM and at 50.0 μg/mL) and *L. braziliensis* at 10.0 μg/mL.	*116*,*138*
	Antimalarial – *in vitro* against *Plasmodium falciparum* K-1 (IC_{50} 1.46 μM).	*131*
	Antimalarial – *in vitro* against *Plasmodium falciparum* at 1.43 μg/mL and IC_{50} 1.41 μg/mL.	*139*,*229*
	Antiparasitic – *in vitro* against *Plasmodium falciparum* K-1 (IC_{50} 365.8 nM) and T9-96 (IC_{50} 704.9 nM).	*230*
	Antitrypanosomal – *in vitro* against *Trypanosoma brucei brucei* (IC_{50} 1.73 μM) and *T. cruzi* at 50.0 μg/mL.	*117*,*138*
	Calcium channel blocker – *in vitro* (pig, sarcolemma cardiac), IC_{50} 1.6 μM. Compound inhibits binding of diltiazem, D-600, fluspirilene and nitrendipine. Inhibition of diltiazem binding correlates with Ca^{2+} uptake inhibition.	*145*
	Calcium ion uptake inhibition – *in vitro* (rat, cells-anterior pituitary), IC_{50} 17.0 μM. Effect assayed in GH3 cells whose calcium uptake is stimulated by KCl.	*145*
	Cytotoxic – *in vitro* (Cell culture) vs. CA-9KB (IC_{50} 43.6 μM and IC_{50} 72.8 μg/mL).	*131*,*230*
IIId.5	**Antimalarial** – *in vitro* against *Plasmodium falciparum* K-1 (IC_{50} 0.83 μM).	*131*
	Antimalarial – *in vitro* against *Plasmodium falciparum* at 0.15 μg/mL.	*229*
	Cytotoxic – *in vitro* (Cell culture, CA-9KB), IC_{50} 31.9 μM.	*131*
II.8	**Analgesic** – *in vivo* (IP, mouse) at 10–20 mg/kg. Increase in latent period of tail-flick response.	*231*

	Antifungal – *in vitro* (Agar plate) at 500.0 μg/mL against *Trichophyton rubrum* and *Microsporum gypseum*.	*232*
	Antimalarial – *in vitro* against *Plasmodium falciparum* D-6 (IC_{50} 5800 ng/mL) and W-2 (IC_{50} 3650 ng/mL).	*85*
	CNS depressor – *in vivo* (IP, mouse and rat) at 100.0 mg/kg vs. rotarod, open-field active-avoidance assays.	*233*
	CNS stimulant – *in vivo* (IP, mouse) at 10.0–20.0 mg/kg. Enhancement of locomotor activity, piloerection, irritability, alertness, compulsive biting of cage wires and tremors.	*231*
	Convulsvant – *in vivo* (IP, mouse) at 30-40 mg/kg. Tetanic convulsions characterized by hind limb extension. Pre-treatment with mephenesin totally prevented the convulsions; and (ventral lymph sac, frog) at 40.0 mg/kg. Tetanic convulsions in decorticated frogs.	*231*
	Dopamine receptor blocking effect – *in vitro* (rat male, Corpora striata) at 0.01 mM.	*234*
	Drug resistance reversal induction – *in vitro* (*Plasmodium falciparum*) at 11.39 μM. Compound reduced IC_{50} value of chloroquine when tested against drug-resistant parasite strain.	*22*
	Hair stimulant effect – *in vitro* (mouse) at 0.01 μg/mL. Stimulated proliferation of cultured cells from murine hair apparatus.	*235*
	Pyretic – *in vivo* (IP, rat) at 5–20 mg/kg.	*231*
	Sleep (spontaneous) potentiation – *in vivo* (IP, mouse male) at 100.0 mg/kg, induced narcosis by barbiturate.	*233*
	Spasmolytic – *in vitro* (rat, uterus) induced contractions by Ach (at 2.4 μM) and Calcium (at 5.9 μM); and (rat, vas deferens), IC_{50} 474.0 μM, induced contractions by K^+.	*236*
	Toxicity assessment (Quantitative) – *in vivo* (IP, mouse male, LD_{50} 56.0 and 251.0 mg/kg) and (IP, rat male) at 216.0 mg/kg.	*231*,*233*
	Uterine relaxation effect – *in vitro* (rat, uterus) induced contractions by K^+ (at 61.0 nM) and Calcium (ED_{50} 0.825 mM).	*237*
II.8	**Antimalarial** – *in vitro* against *Plasmodium falciparum* D-6 (ED_{50} 4.05 μg/mL) and W-2 (ED_{50} 4.47 μg/mL).	*238*
(+)-Form	**Antioxidant** – *in vitro* ($IC_{0.200}$ 2.1 μM) in scavenging stable free radical, DPPH.	*22*
	Antipsychotic – *in vivo* (IV, rat), dose not stated. Studies involved conflict and learning behavior.	*97*
	Antisickling – *in vitro* at 50.0 μM induced aggregation by collagen.	*13*
	AbTP-ase – (Mg^{++}, ID_{50} 7.08 mM) and ATP-ase (NA^+/K^+, ID_{50} 6.03 mM) inhibition *in vitro* (rat, brain).	*239*
	Cataleptic effect – *in vivo* (intraventricular, mouse) at 100.0 μg/animal.	*98*
	Dopamine receptor blocking effect – *in vitro* (rat, striatum), IC_{50} 0.47 μM.	*240*
	Dopamine uptake inhibition – *in vitro* (rat, striatum), IC_{50} 39.4 μM.	*240*
	Inotropic effect negative – *in vitro* (guinea pig, heart) at 0.25 mM.	*241*

(*continued*)

TABLE II.
Continued.

Alkaloid number	Biological activity/method/route/concentration or dose used	Refs.
	Neuromuscular blocking – *in vitro* (frog, sciatic nerve-sartorius muscle), ED_{50} 93.2 μg/mL vs. Ach-induced contractions.	*100*
	Platelet aggregation inhibition – *in vitro* induced by ADP, PAF (at 100.0 μM) and arachidonic acid (at 50.0 and 100.0 μM).	*13*,*170*
	Smooth muscle stimulant – *in vitro* (guinea pig), conc. used not stated. Contraction not inhibited by mepryramine or atropine.	*242*
	Tranquilizing effect – *in vivo* (intraventricular, mouse) at 100.0 μg/mL, induced increase in locomotor activity by apomorphine but not metamphetamine.	*98*
	Vasoralaxation – *in vitro* (rat, aorta) at 300.0 μM induced contractions by potassium and norepinephrine.	*22*
I.47	**Antimalarial** – *in vitro* against resistant (IC_{50} 0.58 μM) and sensitive (IC_{50} 0.71 μM) strains of *Plasmodium falciparum*, and *in vivo* against strain NK65 *P. berghei* (IC_{50} 5.98 mg/kg) in mice.	*12*
VI.5	**Analgesic** – *in vivo* (intragastric, rat) at 50.0 mg/kg.	*45*
	Antibacterial – *in vitro* (Agar plate) against *Staphylococcus aureus* (MIC 1.0 mg/mL).	*243*
	Antidiuretic – *in vivo* (intragastric, rat) at 50.0 mg/kg.	*45*
	Antimycobacterial – *in vitro* (Agar plate, *Mycobacterium smegmatis*), MIC 100.0 μg/mL.	*243*,*244*
	Antispasmodic – (Unspecified type) *in vitro* (rat, uterus nonpregnant) at 40.0 μg/mL, induced spasms by vasopressin.	*37*
	Antitumor – *in vivo* (mouse, Leuk-L1210), route and dose not given. A thalicarpine resistant strain was used and the activity was restored when cyclophosphamide was given after thalicarpine. A combination therapy with BCNU, CCNU, 5-fluorouracil, or methotrexate was ineffective; (IP and SC, rat, lymphoma-NK/LY) at 50.0 mg/kg.	*38*,*39*
	Antitumor – *in vivo* (IP and SC, rat, lymphoblasts-NC-37-C6, sarcoma-Yoshida ASC, sarcoma-WM256-IM) at 50.0 mg/kg.	*39*
	Antitumor – *in vivo* (IP, dose not stated) rat (sarcoma WM-256) and mouse (CA-Ehrlich-Ascites, sarcoma-37, sarcoma-180, CA-Lewis Lung).	*245*
	Antitumor – *in vivo* (IP, mouse) CA-Ehrlich-Ascites and Lymphoma-NK/LY (at 250.0 mg/kg), Leuk-L1210 and CA-Lewis Lung (dose not stated).	*40*,*41*

Antitumor – *in vivo* (IP, mouse), dose variable, tumor system not stated. *246*,*247*
Antitumor – *in vivo* (IP, rat) vs. sarcoma-WM-256 (dose not stated) and Leuk-L1210 (at 200.0 mg/kg). *228*,*249*
Antitussive – *in vivo* (IV, dog) at 1.0 mg/kg, cough induced by nerve stimulation. *250*
Antiyeast – *in vitro* (Agar plate, *Candida albicans*), MIC 1.0 mg/mL. *243*
Barbiturate potentiation – *in vivo* (IP, mouse), dose not stated. *251*
Cell cycle cytotoxity – *in vitro* (G1 and G2 + M Phases, cell culture) at 100.0 μg/mL, CA-Ovarian-O-342 and CA-Ovarian-O-342/Cisplatin resistant; (G2 Phase, cell culture) *in vitro* at 2.0 μM, Leuk-P388 and Leuk-P388 (ADR-resistant). Compound enhanced effect of adriamycin or effect seen only when compound and adriamycin exposure were concurrent. *252*,*253*
Cytotoxic – *in vitro* (Cell culture, Leuk-L1210), conc. used not stated; sarcoma-9 and cells-monkey-kidney-CV-1 (at 50.0 μg/mL). *254*,*255*
Cytotoxic – *in vitro* (Cell culture) vs. CA-Ovarian-O-342 (IC_{50} 24.0 μg/mL), CA-Ovarian-O-342/Cisplatin resistant (IC_{50} 12.0 μg/mL). In both case effects seen enhanced by hyperthermia. *256*
Cytotoxic – *in vitro* (Cell culture) vs. HeLa cells (ED_{50} 2.5 μg/mL) and CA-9KB (ED_{50} 2.1 μg/mL). *42*,*43*
Cytotoxic – *in vitro* (Cell culture) vs. cells-Glioma-T406 (ID_{50} 5.1 μg/mL) and cells-Glioma-GW-27 (ID_{50} 8.2 μg/mL). *44*
Cytotoxic – *in vitro* (Cell culture) at 40.0 μg/mL vs. CA-Ovarian-O-342 and CA-Ovarian-O-342/Cisplatin resistant. Additive or synergistic effect with cisplatin. *256*
Cytotoxic – *in vitro* (Cell culture) vs. CA-ovarian-O-342 (ID_{50} 39.3 μg/mL) and CA-Ovarian-O-342/Cisplatin resistant (ID_{50} 27.3 μg/mL). *257*
Cytotoxic – *in vivo* (IP, mouse), dose not stated. Toxin for lymphocytes at 1/22 of the LD_{50}. *258*
Cytotoxic – *in vitro* (Cell culture, Sarcoma-WM-256), conc. used not stated. Drug administrated while entrapped in liposomes, which intensified its cytotoxic activity. *259*
Cytotoxic – *in vitro* (Cell culture) vs. lymphoma TLX5 (ED_{50} 0.8 and 0.3 μg/mL), sarcoma-WM-256 (ED_{50} 5.0 and 1.5 μg/mL). The title compound was incorporated with liposomes. *260*
Cytotoxicity enhancement – *in vitro* (Cell culture) at 8.0 μM vs. CA-mammary-MCF-7. *261*
Cytotoxicity inhibition – *in vitro* (Cell culture) at 8.0 μM vs. CA-mammary-MCF-7. Taxol cytotoxicity inhibition. *261*
DNA scission effect – *in vitro* (Cell culture) at 40.0 μg/mL vs. CA-Ovarian-O-342/Cisplatin resistant. *262*
DNA synthesis inhibition – *in vitro* (Cell culture, microsomes) at 1.0, 5.0, 10.0 and 15.0 mg/mL. *263*

(*continued*)

TABLE II.
Continued.

Alkaloid number	Biological activity/method/route/concentration or dose used	Refs.
	Drug resistance reversal induction – *in vitro* (Cell culture, Leuk-P388 (ADR-resistant) at 2.0 μM. At 1 h exposure to compound reduced ID_{50} of adriamycin from 10.8 to 1.4 μM and at 24 hours exposure reduced ID_{50} from 3.5 to 0.07 μM.	*253*
	Emetic – *in vivo* (IP, cat) at 25.0 mg/kg.	*45*
	Hematopoietic – *in vivo* (IP, rat and mouse), dose variable, caused a transient decrease in the number of leukocytes and lymphocytes but did not affect hemoglobin or erythrocytes given at the LD_{50} and the maximal threshold limit dose.	*264*
	Hemotoxic – *in vivo* (IP, mouse), dose not stated.	*258*
	Hypertensive – *in vivo* (IV, dog both sexes) at 2.0 mg/kg.	*37*
	Hypotensive – *in vivo* (IV, cat) at 0.5 mg/kg.	*45*
	Interaction with DNA – *in vitro* (ant leafcutter), dose not stated.	*265*
	Intestinal motility inhibition – *in vivo* (IP, rat) at 200.0 mg/kg. The delay in passage of intestinal contents was measured.	*266*
	Metastasis inhibition – *in vivo* (IP, mouse - lung metastasis), dose not stated.	*267*
	Multidrug resistance inhibition – *in vitro* (Cell culture) vs. CA-mammary-MCF-7/ADR (LD 84.0 μM). Interactions with adriamycin, etoposide, taxol and CI941 were studied.	*261*
	Multidrug resistance inhibition – *in vitro* (Cell culture, CA-mammary-MCF-7/ADR) at 2.0 μM. Compound acts via glycoprotein inhibition.	*268*
	Mutagenic – *in vitro* (cell culture, microsomes), dose variable. Frequent breaks at chromosome and chromatid levels. Metaphase block, tetraploid metaphase seen.	*263*
	Pharmacokinetic study – human's adult (IV, infusion) at 300.0 mg/SQ M body surface. Plasma decay and urinary excretion studied in 19 patients at doses of 300 to 1900 mg/SQ M body surface. Plasma decay triexponential with terminal phase half-life of 198–1386 hours; urinary excretion is low and erratic.	*127*
	Protein synthesis inhibition – *in vitro* (Cell culture, sarcoma 180), conc. used not stated.	*269*
	Smooth muscle relaxant – *in vitro* (rabbit, ileum) at 10.0 μg/mL.	*37*
	Thymidine uptake inhibition – *in vitro* (Cell culture, HeLa cells), ID_{50} 5.0 μM.	*270*

	Toxic effect (general) – *in vivo* (IP, mouse), dose variable. Toxic symptoms were reported.	*271*
	Toxicity assessment (Quantitative) – *in vivo* (IV, cat), MLD 10.0 mg/kg, and LD_{90} 82.5 mg/kg. Ataxia, muscular weakness, convulsions, mydriasis, salivation, lacrimation, respiratory disturbances were observed.	*45*,*255*
	Toxicity assessment (Quantitative) – *in vivo*, rat male (IV: LD_{50} 78.0 and LD_{10} 58.3 mg/kg; Oral: LD_{50} 1.5 mg/kg), mouse male (IV: LD_{90} 103.6 mg/kg; LD_{50} 58.6 mg/kg and LD_{10} 19.2 mg/kg).	*255*,*272*
	Toxicity assessment (Quantitative) – *in vivo* (IP) rat male (LD_{90} 270.0 mg/kg, LD_{10} 175.0 mg/kg), sarcoma-WM-256 (LD_{50} 215.0 and LD_{10} 168.0 mg/kg). Ataxia, muscular weakness, convulsions, mydriasis, salivation, lacrimation, respiratory disturbances were observed.	*255*
	Toxicity assessment (Quantitative) – *in vivo* (IP), rat (LD_{50} 0.310 mg/kg), mouse (LD_{50} 0.325 mg/kg).	*273*,*274*
	Toxicity assessment (Quantitative) – *in vivo* (IV, dog), minimum toxic dose 319.0 mg/SQ M Body surface.	*272*
	Toxicity assessment (Quantitative) – in humans (IV, human adult), maximum tolerated dose 1.10 GM/SQ M Body surface.	*272*
	Uridine uptake inhibition – *in vitro* (Cell culture, HeLa cells) at 5.0 μM.	*270*
	Uterine relaxation effect – *in vivo* (rat, uterus non-pregnancy) at 40.0 μg/mL.	*37*
	Weight loss – *in vivo* (IP, rat) at 170.0 mg/kg. Control group weight increased 261%. Drug-treatment group increased 66.7%.	*275*
VI.5 (+)-Form	**Cytotoxic** – *in vitro* (Cell culture) vs. Leuk-P388 (IC_{50} 3.769 μg/mL), CA-A549 (IC_{50} 3.917 μg/mL), and human colon cancer cell line HT-29 (IC_{50} 1.897 μg/mL), and CA-KB-16 (IC_{50} 3.365 μg/mL).	*25*
	Platelet aggregation inhibition – induced by thrombin, arachidonic acid (at 50.0 μM), and collagen and PAF at 20.0 μg/mL.	*13*
	Vasorelaxant – *in vitro* (rat, aorta) at 50.0 μM, induced contractions by Potassium and norepinephrine.	*22*
XI.4	**Cytotoxic** – (Cell culture) vs. CA-KB-16 (IC_{50} 0.9 μg/mL), CA-A549 IC_{50} 1.5 μg/mL), and human colon cancer cell line HT-29 (IC_{50} 1.7 μg/mL).	*26*
	Vasorelaxant – *in vitro* (rat, aorta) at 50.0 μM, induced contractions by Potassium and norepinephrine.	*22*
VI.6	**Antimycobacterial** – *in vitro* (Agar plate, *Mycobacterium smegmatis*), MIC 100.0 μg/mL.	*243*

Hernandiaceae

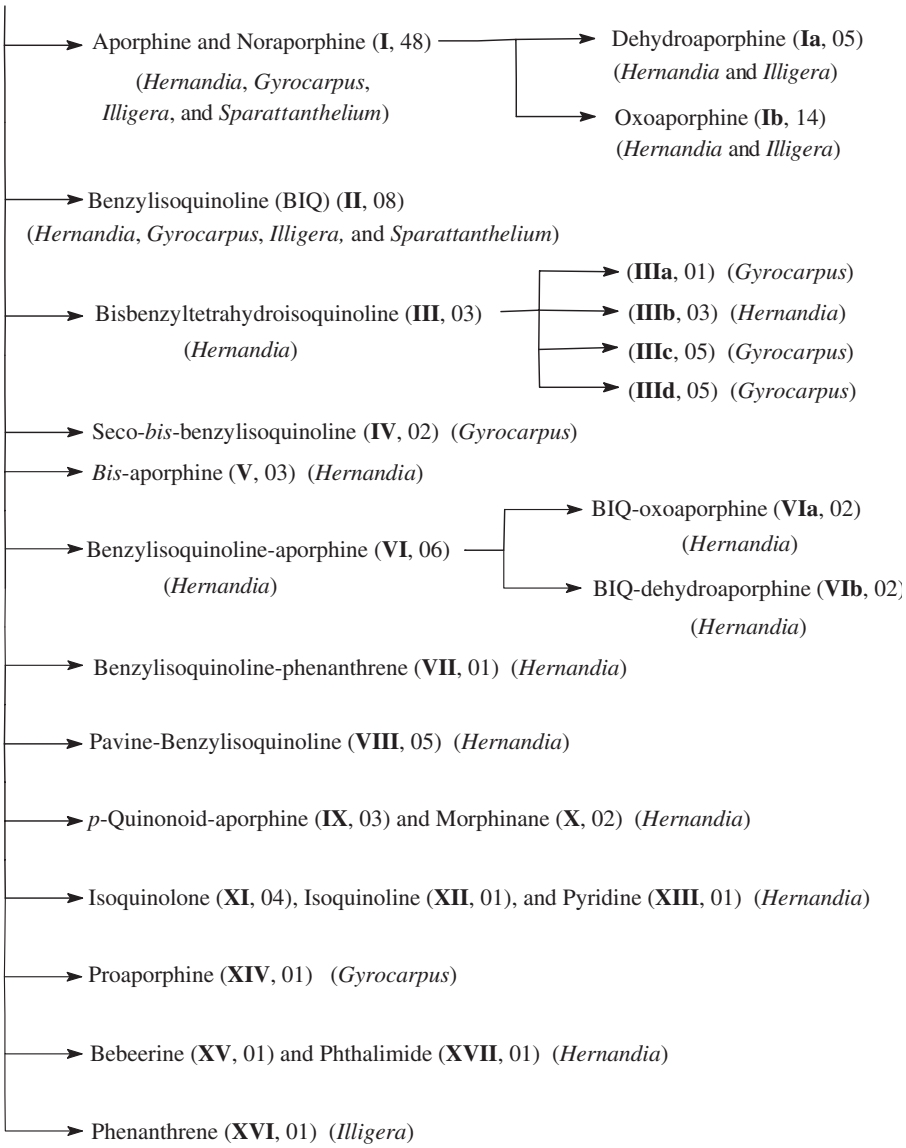
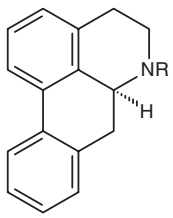
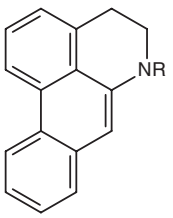


Chart I. Basic skeleta of the alkaloids isolated from the Hernandiaceae, locator code, total number by skeleton type, and distribution in the genus.

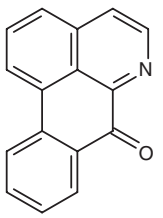
A. TYPE I – APORPHINE, NORAPORPHINE, DEHYDROAPORPHINE, AND OXOAPORPHINE ALKALOIDS



I



Ia

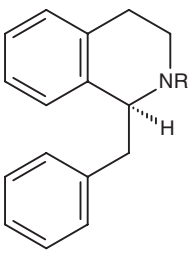


Ib

The aporphine and noraporphine (type **I**) alkaloids are the most numerous (48 alkaloids) and occur in all of the genera studied (*Gyrocarpus, Hernandia, Illigera*, and *Sparattanthelium*), while the dehydroaporphine (subtype **Ia**, with 14 alkaloids) and oxoaporphine (subtype **Ib**, with 5 alkaloids) alkaloids were found in only two of them (*Hernandia* and *Illigera*) (Table I; see also Appendix).

Several of these alkaloids have biological activity (Table II). Among them, inhibition of the contractions induced by norepinephrine and high K^+ [laurotetanine (**I.26**), *N*-methyllaurotetanine (**I.43**), hernandaline (**I.13**), 7-oxohernangine (**Ib.13**) (*22*), and *N*-methylactinodaphnine (**I.30**) (*23*)]; antioxidant in scavenging stable free radicals (DPPH) [hernangerine (**I.15**), (+)-hernovine (**I.16**), *N*-methylhernangerine (**I.32**), laurotetanine (**I.26**), and 7-oxohernangine (**Ib.13**) (*22*)], antiplatelet aggregation induced by PAF, arachidonic acid, and collagen [hernangerine (**I.15**), ovigerine (**I.46**), *N*-methylhernangerine (**I.32**) (*24*), laurotetanine (**I.26**), 7-oxohernangine (**Ib.13**) (*22*), and hernandaline (**I.13**) (*13*), hernovine (**I.16**), actinodaphnine (**I.1**), *N*-methylactinodaphnine (**I.30**), launobine (**I.23**), dicentrine (**I.6**), *O*-methylbulbocapnine (**I.37**), and liriodenine (**Ib.6**) (*25*)], cytotoxity *in vitro* against carcinogenic cell lines [hernandonine (**Ib.3**), ovigerine (**I.46**), (+)-*N*-methylovigerine (**I.36**), *N*-formyldehydroovigerine (**Ia.5**) (*25,26*)], antimalarial *in vitro* activity against resistant and sensitive strains of *Plasmodium falciparum* and *in vivo* against *Plasmodium berghei* [(−)-roemrefidine (**I.47**) (*12*)], vasorelaxant [actinodaphnine (**I.1**) and dicentrinone (**Ib.2**) (*14*)], curarizant [laurotetanine (**I.26**) (*27*)], narcotic, adrenolitic, convulsant, and in the treatment of Parkinson's disease [bulbocapnine (**I.3**) (*27*)].

B. TYPE II – TETRAHYDROBENZYLISOQUINOLINE ALKALOIDS

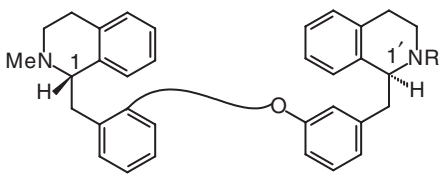


II

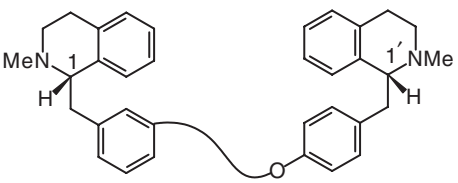
More than 100 alkaloids of this type are distributed throughout the families Lauraceae, Magnoliaceae, Menispermaceae, Papaveraceae, Ranunculaceae, Berberidaceae, and Annonaceae (*28*). In the Hernandiaceae, this type (**II.1-II.8**) occurs in all genera so far investigated. The genera in which they were most commonly found were *Hernandia* (21 citations) followed by *Gyrocarpus* (4 citations), *Sparattanthelium* (2 citations), and *Illigera* (1 citation) (Table I and Chart I).

Biological activity is attributed to some of these alkaloids. Among them, magnocurarine (**II.5**) i.e., curarizant (*27*), laudanosine (**II.3**), and (+)-reticuline (**II.8**) exhibited *in vitro* weak antimalarial activity against a resistant strain of *P. falciparum*, and displayed *in vivo* (*P. yoellii* N67) chloroquine-potentiating action against a chloroquine-resistant strain of *P. falciparum* in a dose dependent manner (*9*). (+)-Reticuline (**II.8**) also showed complete inhibition of platelet aggregation induced by arachidonic acid and collagen, and was an effective antioxidant in scavenging stable free radicals, DPPH (*13,22*). It did not show, at 300 μM, any inhibitory effect on aortic contractions caused by norepinephrine and by high K^+ (*22*) (Table II).

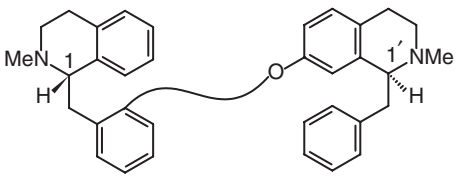
C. TYPE III – BISBENZYLTETRAHYDROISOQUINOLINE ALKALOIDS



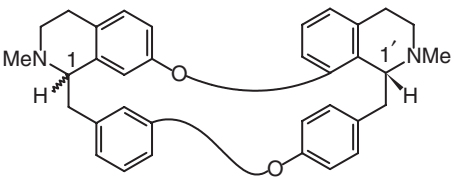
III



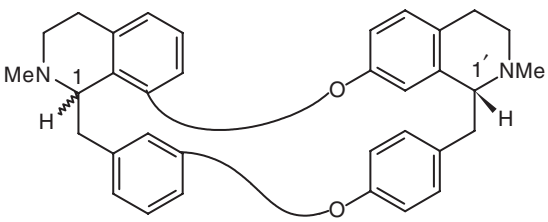
IIIa



IIIb



IIIc



IIId

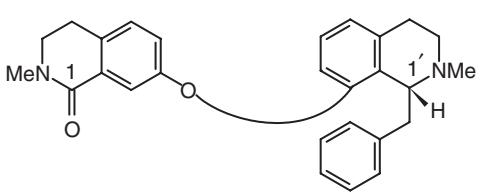
Bisbenzyltetrahydroisoquinolines are a large and diverse group of natural alkaloids that occur in many plant species, particularly in members of the Menispermaceae (*28*), Monimiaceae (*29*), Annonaceae, Berberidaceae, and Ranunculaceae (*30*). Many of these alkaloids may be divided into two broad categories, depending on whether they are derived biogenetically from coclaurine (**II.2**) or reticuline (**II.8**) by different modes of phenolic oxidative coupling (*31*) tail-to-tail linkage biphenyl-ether, head-to-head or both. Seventeen bisbenzylisoquinoline alkaloids (Table I) were found in the Hernandiaceae, and in this work, they were divided into five subtypes (**III** and **IIIa–IIId**) according to the mode of coupling, and the number and position of the bonds between the two units:

(a) One bond [Biphenyl ether bridge tail-to-tail [10–11′ (**III**) or 11–12′ (**IIIa**)] or biphenyl ether bridge head-to-tail [10–7′ (**IIIb**)];
(b) Two bonds [Biphenyl ether head-to-head (**IIIc**: 7–8′; **IIId**: 8–7′) and diphenyl tail-to-tail (11–12′ for both)].

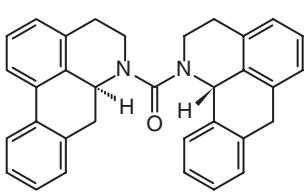
In the Hernandiaceae, these alkaloids are particularly found in the *Hernandia* (6 alkaloids) and *Gyrocarpus* (11 alkaloids) (Table I and Chart I). In each genus these alkaloid types differ by substitution pattern, nature of oxygenated substituents, and mainly by the number of biphenyl-ether linkages, and the configuration of the chiral centers (C-1 and C-1′). With the exception of (−)-grisabine (**IIIa.1**), which was isolated from stem bark of *G. americanus* Jacq., all the other alkaloids containing a bond of the biphenyl ether tail-to-tail (**III**) or biphenyl ether head-to-tail (**IIIb**)] type were isolated from *Hernandia* species. Those that occur in *Gyrocarpus* species possess two bonds involving linkages of the biphenyl ether head-to-head and biphenyl ether tail-to-tail (**IIIc** and **IIId**) type.

Bisbenzyltetrahydroisoquinoline alkaloids have been shown to possess a variety of interesting biological activities (Table II), including complete or partial inhibition of platelet aggregation induced by arachidonic acid, collagen, and PAF (*13,32*), antioxidant activity in scavenging stable free radicals, DPPH (*22*), complete or partial inhibition of rat thoracic aortic contractions caused by norepinephrine and by high K^+ (*22,32*), potent antiplasmodial activities *in vitro* against chloroquine sensitive and resistant strains of *Plasmodium falciparum* (*30*), and cytotoxic activity against cultured mammalian cells (*25,30*).

D. TYPES IV AND V – SECO-*BIS*-BENZYLISOQUINOLINE AND *BIS*-APORPHINE ALKALOIDS



IV

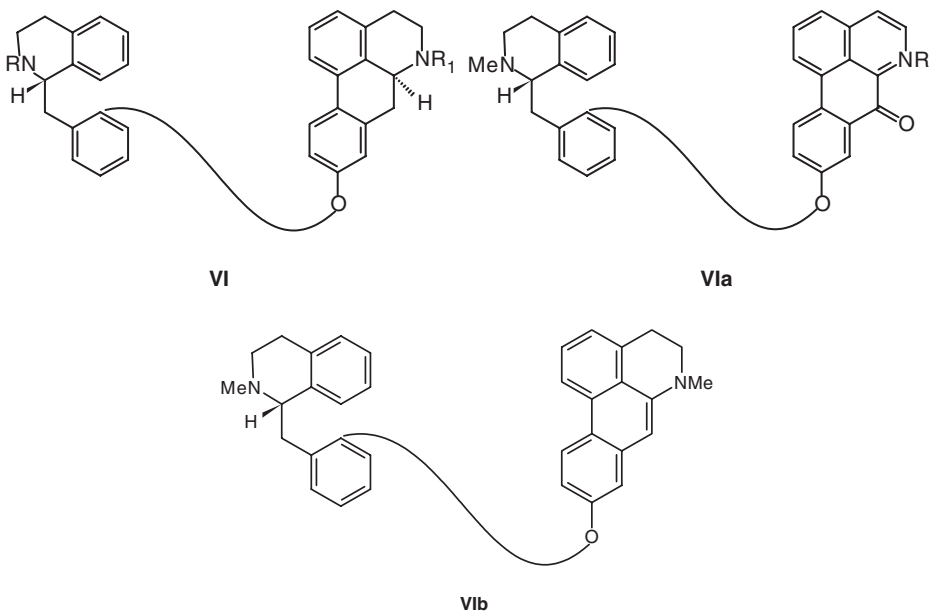


V

Seco-*bis*-benzylisoquinoline alkaloids (**IV.1–IV.2**), isolated only from the stem bark and leaves of *G. americanus* (*3,33*) (Table I), are considered an odd case. According to Duté *et al.* (*33*), these substances are most probably catabolic products formed by oxidative cleavage of the less hindered benzylic bond of the (+)-*O*-methyllimacusine (**IIIc.5**) or (−)-gyrolidine (**IIIc.3**) yielding (+)-auroramine (**IV.1**) and (−)-gyrocarpine (**IIIc.1**) or (+)-gyrocarpusine (**IIIc.2**) to afford (+)-maroumine (**IV.2**). In fact, under laboratory conditions, the acetyl derivative of (−)-gyrocarpine (**IIIc.1**) in the presence of $KMnO_4$ and acetone afforded the acetyl derivative of (+)-maroumine (**IV.2**) (*33*).

Only three *bis*-aporphine alkaloids (**V.1–V.3**) were isolated from the two *Hernandia* species found in Taiwan, the trunk bark of *H. nymphaeifolia* (Presl.) Kubitzki (*25,34*) and the root bark of *H. ovigera* L. (*35,36*). Two of them [ovihernangerine (**V.2**) and oviisocorydine (**V.3**)], possess cytotoxic activity *in vitro* against human colon cancer cell lines (*25*) (Table II). (+)-Ovigeridimerine (**V.1**), at 50.0 μM, does not inhibit *in vitro* the platelet aggregation induced by arachidonic acid, collagen, and PAF (*13*) and the vasorelaxing effect caused by K^+ and norepinephrine (*22*).

E. TYPE VI – BENZYLISOQUINOLINE-APORPHINE, BENZYLISOQUINOLINE-OXOAPORPHINE, AND BENZYLISOQUINOLINE-DEHYDROAPORPHINE ALKALOIDS



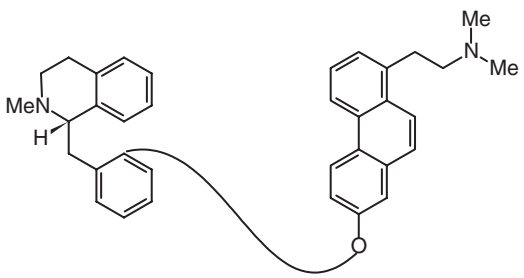
VI **VIa**

VIb

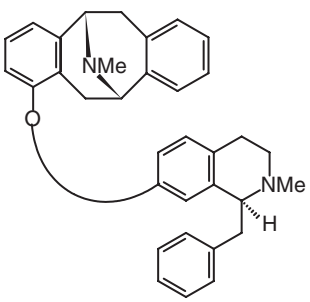
Alkaloid dimers of the benzylisoquinoline-aporphine (**VI.1**–**VI.6**), benzylisoquinoline-oxoaporphine (**VIa.1**–**VIa.2**), and benzylisoquinoline-dehydroaporphine (**VIb.1**–**VIb.2**) type seem to originate biogenetically from the oxidative coupling of two units of reticuline (**II.8**), followed by a second oxidative coupling to afford to the final product (*28*). In the Hernandiaceae, these structural types are restricted to the genus *Hernandia* (Table I and Chart I). Among them, thalicarpine (**VI.5**) possesses a variety of biological

activities (Table II), such as antispasmodic (*37*), antitumoral (*27,38–41*), cytotoxic (*42–44*), hypotensor non-cholinergic (*27,45*), and exhibited complete inhibition of the platelet aggregation induced by PAF and collagen (*13*).

F. TYPES VII AND VIII – BENZYLISOQUINOLINE-PHENANTHRENE AND PAVINE-BENZYLISOQUINOLINE ALKALOIDS



VII

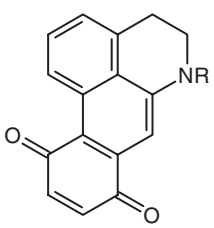


VIII

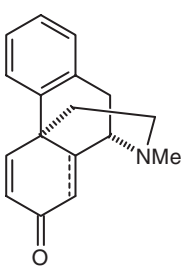
In the Hernandiaceae, only one benzylisoquinoline-phenanthrene alkaloid [(+)-hebridamine (**VII.1**)] was isolated from *H. peltata* Meissn. (*46,47*). This structural type is probably derived biogenetically from the oxidative coupling of two units of reticuline (**II.8**).

Five isoquinoline alkaloid dimers with pavine and tetrahydrobenzylisoquinoline moieties, known as hervelines A–D (**VIII.1–VIII.4**) and HB (**VIII.5**), have been isolated from the stem bark of *Hernandia voyronii* Jum. (*8,9,48*), used as an adjuvant to chloroquine in Malagasy herbal practice and against chronic malaria (*8,9*). Two of them, harvelines B (**VIII.2**) and C (**VIII.3**) reversed *in vitro* chloroquine resistance to the resistant strain of *P. falciparum* (*9*) and exhibited moderate antimalarial activity (*8,9,48*). Harveline HB (**VIII.5**), an alkaloid whose structure has not been determined, also potentiated the effect of chloroquine and showed weak *in vitro* cytotoxicity against HeLa cells (*48*).

G. TYPES IX AND X – *p*-QUINONOID-APORPHINE AND MORPHINANE ALKALOIDS



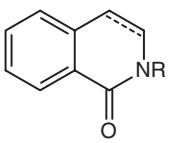
IX



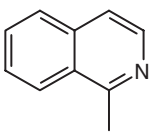
X

Alkaloids of the *p*-quinonoid-aporphine (**IX.1–IX.3**) type are present in *H. sonora* L. (*32*), while the morphinane (**X.1–X.2**) type, also known as promorphine alkaloids, occurs only in *H. voyronii* Jum. (*8,9*). These alkaloids did not inhibit platelet aggregation *in vitro* induced by thrombin, arachidonic acid, collagen, and PAF (*32*) (Table II).

H. TYPES XI AND XII – ISOQUINOLONE AND ISOQUINOLINE ALKALOIDS



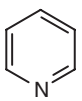
XI



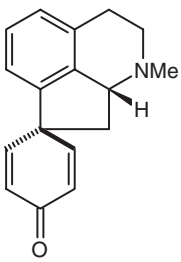
XII

Isoquinoline alkaloids are formed by the reaction of phenylethylamine and formaldehyde, followed by cyclization (*28*). Menachery has reviewed the occurrence and properties of this structural type of alkaloids (*49*). In the Hernandiaceae, only five such alkaloids (**XI.1–XI.4** and **XII.1**) have so far shown restricted occurrence in a few species of *Hernandia* (Table I). Among them, *N*-methylcorydaldine (**XI.1**) showed cytotoxic activity *in vitro* against P-388, CA-KB-16, CA-A549 cells, and the human colon cancer cell line HT-29 (*25*) and northalifoline (**XI.3**) exhibited weak *in vitro* cytotoxity against CA-A549 cells (*26*) (Table II).

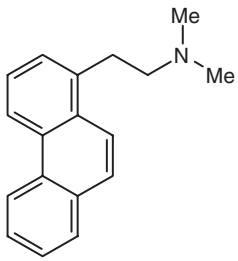
I. TYPES XIII, XIV AND XVI – PYRIDINE, PROAPORPHINE, AND PHENANTHRENE ALKALOIDS



XIII



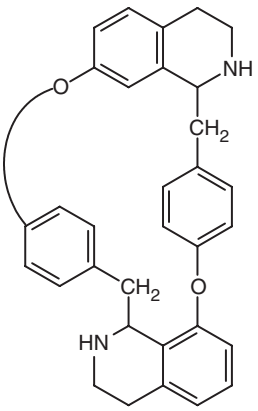
XIV



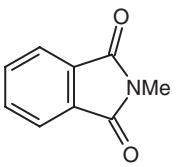
XVI

A few alkaloids with pyridine (**XIII**), proaporphine (**XIV**), and phenanthrene (**XVI**) nuclei were also found in the *Hernandia*, *Gyrocarpus*, and *Illigera* species, respectively (Table I). Phenanthrene alkaloids, also known as "seco-aporphines," are a very rare type, probably formed biogenetically from an aporphine precursor through the opening of ring B (*28*). Castedo and Tojo have reviewed their chemistry (*50*). From the family Hernandiaceae only thaliporphinemethine (**XVI.1**) was isolated from *I. pentaphylla* Welw. (*51*).

J. TYPES XV AND XVII – BEBEERINE AND PHTHALIMIDE ALKALOIDS



XV



XVII

In Hernandiaceae, only one example of each structural type (**XV.1** and **XVII.1**) was found in *H. ovigera* L. (*52*) and *H. nymphaeifolia* (Presl.) Kubitzki (*34*). (−)-Bebeerine, at 50.0 μg/mL, was active *in vitro* against *Trypanosoma cruzi* (*53*).

III. Summary

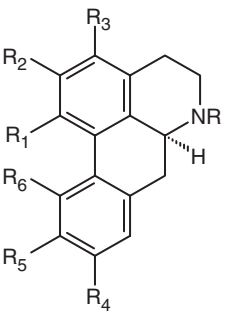
The present work is a review of articles published in the literature (275 references) regarding alkaloids isolated from plants of the family Hernandiaceae and their biological activity. The chemistry of this family has been reviewed previously, but since the last review (published in 1971) (*27*), new species have been chemically investigated and several different structural types of alkaloids have been isolated.

IV. Conclusions

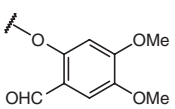
About 20 species distributed in four genera (*Gyrocarpus*, *Hernandia*, *Illigera*, and *Sparattanthelium*) have been investigated for their alkaloid content. The genus *Hernandia* was the most studied (12 species) followed by *Illigera* (5 species), *Sparattanthelium* (2 species), and *Gyrocarpus* (1 species). A total of 128 alkaloids with seventeen different chemical types have been isolated so far. The predominance of aporphines is striking (62 alkaloids) followed by bisbenzylisoquinolines (17 alkaloids), benzylisoquinoline-aporphine, benzylisoquinoline-oxoaporphine, benzylisoquinoline-dehydroaporphine (10 alkaloids together), and benzylisoquinoline (8 alkaloids). Only one structural type of alkaloid, pavine-benzyltetrahydroisoquinoline (**VIII**), is restricted to the family and was found only in *Hernandia voyronii* Jum. Isolated alkaloids from the Hernandiaceae are potentially useful worldwide for the treatment of numerous diseases.

Appendix

TYPE I – APORPHINE AND NORAPORPHINE ALKALOIDS



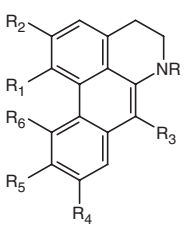
I.1 R═R$_3$═R$_6$═H, R$_1$R$_2$═OCH$_2$O, R$_4$═OH, R$_5$═OMe
I.2 R═Me, R$_1$═R$_5$═OMe, R$_2$═R$_4$═OH, R$_3$═R$_6$═H
I.3 R═Me, R$_1$R$_2$═OCH$_2$O, R$_3$═R$_4$═H, R$_5$═OMe, R$_6$═OH
I.4 R═R$_3$═R$_4$═H, R$_1$═R$_2$═R$_5$═R$_6$═OMe
I.5 R═Me, R$_2$═R$_5$═OMe, R$_1$═R$_6$═OH, R$_3$═R$_4$═H
I.6 R═Me, R$_1$R$_2$═OCH$_2$O, R$_3$═R$_6$═H, R$_4$═R$_5$═OMe
I.7 R═Me, R$_1$═R$_2$═R$_5$═R$_6$═OMe, R$_3$═R$_4$═H
I.8 R═Me, R$_1$═OH, R$_2$═OMe, R$_3$═R$_6$═H, R$_4$R$_5$═OCH$_2$O
I.9 R═CHO, R$_1$R$_2$═OCH$_2$O, R$_3$═R$_4$═H, R$_5$═OH, R$_6$═OMe
I.10 R═CHO, R$_1$═R$_2$═OMe, R$_3$═R$_6$═H, R$_4$R$_5$═OCH$_2$O
I.11 R═CHO, R$_1$R$_2$═R$_5$R$_6$═OCH$_2$O, R$_3$═R$_4$═H
I.12 R═R$_3$═R$_4$═H, R$_1$═R$_2$═R$_6$═OMe, R$_5$═OH

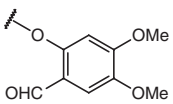
I.13 R═Me, R$_1$═R$_2$═R$_5$═OMe, R$_3$═R$_6$═H, R$_4$═ 

I.14 R═R$_4$═H, R$_1$R$_2$═OCH$_2$O, R$_3$═R$_6$═OMe, R$_5$═OH
I.15 R═R$_3$═R$_4$═H, R$_1$R$_2$═OCH$_2$O, R$_5$═OH, R$_6$═OMe
I.16 R═H, R$_1$═R$_6$═OMe, R$_2$═R$_5$═OH, R$_3$═R$_4$═H
I.17 R═R$_5$═OH, R$_1$R$_2$═OCH$_2$O, R$_3$═R$_4$═H, R$_6$═OMe
I.18 R═OH, R$_1$R$_2$═R$_5$R$_6$═OCH$_2$O, R$_3$═R$_4$═H
I.19 R═Me, R$_1$═R$_4$═OH, R$_2$═R$_5$═OMe, R$_3$═R$_6$═H
I.20 R═Me, R$_1$═R$_2$═R$_5$═OMe, R$_3$═R$_4$═H, R$_6$═OH
I.21 R═R$_3$═R$_6$═H, R$_1$═R$_4$═OMe, R$_2$═R$_5$═OH
I.22 R═R$_3$═R$_4$═H, R$_1$═OMe, R$_2$═OH, R$_5$R$_6$═OCH$_2$O
I.23 R═R$_3$═R$_4$═H, R$_1$R$_2$═OCH$_2$O, R$_5$═OMe, R$_6$═OH
I.24 R═R$_3$═R$_6$═H, R$_1$═R$_4$═OH, R$_2$═R$_5$═OMe
I.25 R═R$_3$═R$_6$═H, R$_1$═R$_5$═OMe, R$_2$═R$_4$═OH
I.26 R═R$_3$═R$_6$═H, R$_1$═R$_2$═R$_5$═OMe, R$_4$═OH
I.27 R═R$_3$═R$_4$═H, R$_1$═R$_5$═OMe, R$_2$═R$_6$═OH
I.28 R═R$_3$═R$_6$═H, R$_1$R$_2$═OCH$_2$O, R$_4$═OMe, R$_5$═OH
I.29 R═(Me)$_2$, R$_1$═R$_6$═OH, R$_2$═R$_5$═OMe, R$_3$═H

I.30 R═Me, R_1R_2═OCH_2O, R_3═R_6═H, R_4═OH, R_5═OMe
I.31 R═$CONHCH_3$, R_1R_2═OCH_2O, R_3═R_4═H, R_5═R_6═OMe
I.32 R═Me, R_1R_2═OCH_2O, R_3═R_4═H, R_5═OH, R_6═OMe
I.33 R═Me, R_1═R_6═OMe, R_2═R_5═OH, R_3═R_4═H
I.34 R═Me, R_1═R_2═R_5═OMe, R_3═R_6═H, R_4═OH
I.35 R═Me, R_1═R_5═OMe, R_2═R_6═OH, R_3═R_4═H
I.36 R═Me, R_1R_2═R_5R_6═OCH_2O, R_3═R_4═H
I.37 R═Me, R_1R_2═OCH_2O, R_3═R_4═H, R_5═R_6═OMe
I.38 R═$(Me)_2$, R_1R_2═OCH_2O, R_3═R_4═H, R_5═R_6═OMe
I.39 R═Me, R_1R_2═R_4R_5═OCH_2O, R_3═R_6═H
I.40 R═R_3═R_6═H, R_1═R_5═OMe, R_2═R_4═OH
I.41 R═R_3═R_6═H, R_1R_2═OCH_2O, R_4═R_5═OMe
I.42 R═R_3═R_6═H, R_1═OH, R_2═OMe, R_4R_5═OCH_2O
I.43 R═R_3═R_4═H, R_1═R_2═R_5═OMe, R_6═OH
I.44 R═R_3═R_6═H, R_1═R_2═OMe, R_4R_5═OCH_2O
I.45 R═R_3═R_6═H, R_1═R_4═R_5═OMe, R_2═OH
I.46 R═R_3═R_4═H, R_1R_2═R_5R_6═OCH_2O
I.47 R═$(Me)_2$, R_1R_2═OCH_2O, R_3═R_4═R_5═R_6═H
I.48 R═$(Me)_2$, R_1═R_4═OH, R_2═R_5═OMe, R_3═R_6═H

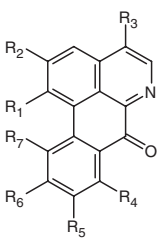
Subtype **Ia** – *Dehydroaporphine Alkaloids*



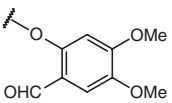
Ia.1 R═Me, R_1═R_2═R_5═OMe, R_3═R_6═H, R_4═ 

Ia.2 R═R_4═H, R_1R_2═OCH_2O, R_3═CHO, R_5═OH, R_6═OMe
Ia.3 R═R_6═H, R_1═R_2═OMe, R_3═CHO, R_4R_5═OCH_2O
Ia.4 R═R_4═H, R_1R_2═R_5R_6═OCH_2O, R_3═CHO
Ia.5 R═CHO, R_1R_2═R_5R_6═OCH_2O, R_3═R_4═H

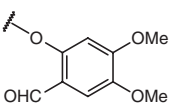
Subtype **Ib** – *Oxoaporphine Alkaloids*



Ib.1 $R_1{=}R_2{=}R_6{=}OMe$, $R_3{=}R_4{=}R_7{=}H$, $R_5{=}OH$
Ib.2 $R_1R_2{=}OCH_2O$, $R_3{=}R_4{=}R_7{=}H$, $R_5{=}R_6{=}OMe$
Ib.3 $R_1R_2{=}R_6R_7{=}OCH_2O$, $R_3{=}R_4{=}R_5{=}H$
Ib.4 $R_1{=}R_3{=}R_4{=}R_7{=}H$, $R_2{=}OMe$, $R_5R_6{=}OCH_2O$
Ib.5 $R_1R_2{=}OCH_2O$, $R_3{=}R_4{=}R_6{=}R_7{=}H$, $R_5{=}OMe$
Ib.6 $R_1R_2{=}OCH_2O$, $R_3{=}R_4{=}R_5{=}R_6{=}R_7{=}H$
Ib.7 $R_1{=}R_2{=}OMe$, $R_3{=}R_4{=}R_5{=}R_6{=}R_7{=}H$
Ib.8 $R_1R_2{=}OCH_2O$, $R_3{=}R_4{=}R_5{=}H$, $R_6{=}R_7{=}OMe$

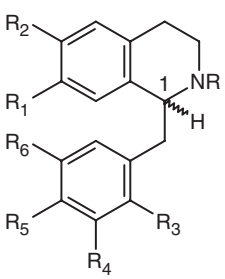
Ib.9 $R_1{=}R_2{=}R_3{=}R_6{=}OMe$, $R_4{=}R_7{=}H$, $R_5{=}$ 

Ib.10 $R_1R_2{=}OCH_2O$, $R_3{=}R_6{=}R_7{=}H$, $R_4{=}R_5{=}OMe$

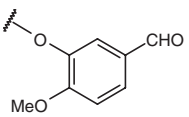
Ib.11 $R_1{=}R_2{=}R_6{=}OMe$, $R_3{=}R_4{=}R_7{=}H$, $R_5{=}$ 

Ib.12 $R_1R_2{=}OCH_2O$, $R_3{=}R_4{=}R_5{=}H$, $R_6{=}OH$, $R_7{=}OMe$
Ib.13 $R_1{=}R_2{=}R_7{=}OMe$, $R_3{=}R_4{=}R_5{=}H$, $R_6{=}OH$
Ib.14 $R_1{=}R_2{=}OMe$, $R_3{=}R_4{=}R_7{=}H$, $R_5R_6{=}OCH_2O$

TYPE II – BENZYLISOQUINOLINE ALKALOIDS



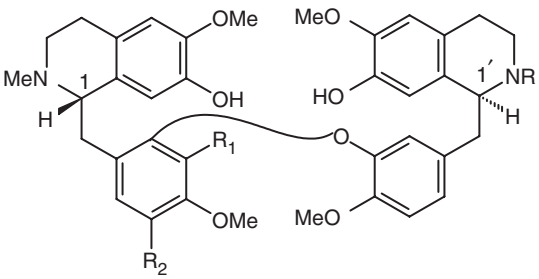
II.1 $R{=}R_3{=}R_4{=}R_5{=}R_6{=}H$, $R_1{=}R_2{=}OMe$
II.2 $R{=}R_3{=}R_4{=}R_6{=}H$, $R_1{=}R_5{=}OH$, $R_2{=}OMe$, (1β)
II.3 $R{=}Me$, $R_1{=}R_2{=}R_4{=}R_5{=}OMe$, $R_3{=}R_6{=}H$
II.4 $R{=}Me$, $R_1{=}R_2{=}R_5{=}OMe$, $R_3{=}R_4{=}H$, $R_6{=}OH$
II.5 $R{=}(Me)_2$, $R_1{=}R_5{=}OH$, $R_2{=}OMe$, $R_3{=}R_4{=}R_6{=}H$, (−OH)
II.6 $R{=}Me$, $R_1{=}R_5{=}OH$, $R_2{=}OMe$, $R_3{=}R_4{=}R_6{=}H$, (1β)

II.7 $R{=}Me$, $R_1{=}R_4{=}OH$, $R_2{=}R_5{=}OMe$, $R_6{=}H$, $R_3{=}$ 

II.8 $R{=}Me$, $R_1{=}R_4{=}OH$, $R_2{=}R_5{=}OMe$, $R_3{=}R_6{=}H$, (1α)

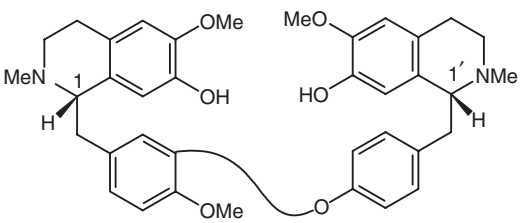
TYPE III – BISBENZYLISOQUINOLINE ALKALOIDS

Subtype **III** *(biphenyl ether bridge 10 → 11′)*



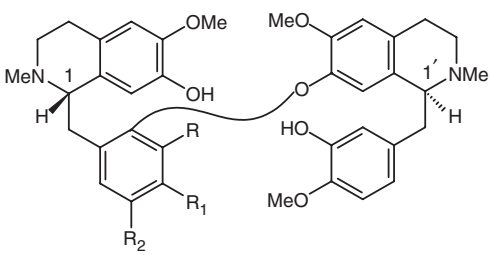
III.1 R═(Me,O⁻), R_1═OH, R_2═H
III.2 R═Me, R_1═H, R_2═OMe
III.3 R═Me, R_1═OH, R_2═H

Subtype **IIIa** *(biphenyl ether bridge 11 → 12′)*



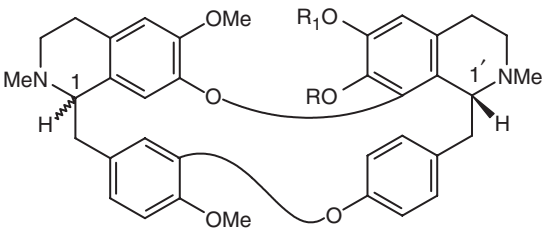
IIIa.1 (1S,1′R)

Subtype **IIIb** *(biphenyl ether bridge 10 → 7′)*



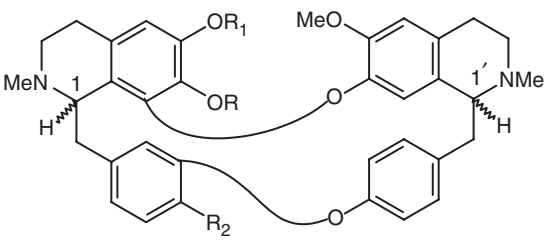
IIIb.1 R═OH, R_1═OMe, R_2═H
IIIb.2 R═OMe, R_1═OH, R_2═H
IIIb.3 R═H, R_1═R_2═OMe

Subtype **IIIc** *(biphenyl ether bridge 7 → 8′ and 11 → 12′)*



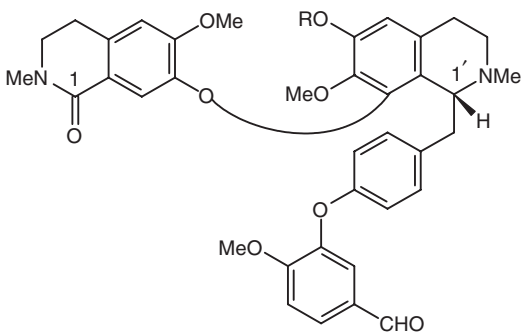
IIIc.1 R═Me, R_1═H, (1β)
IIIc.2 R═Me, R_1═H, (1α)
IIIc.3 R═R_1═Me, (1β)
IIIc.4 R═H, R_1═Me, (1α)
IIIc.5 R═R_1═Me, (1α)

Subtype **IIId** *(biphenyl ether bridge 8 → 7′ and 11 → 12′)*



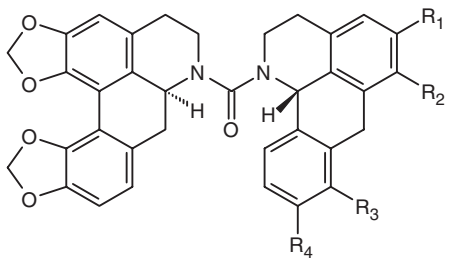
IIId.1 R═Me, R_1═H, R_2═OMe, (1α,1′β)
IIId.2 R═R_1═Me, R_2═OMe (1α,1′α)
IIId.3 R═H, R_1═Me, R_2═OMe, (1α,1′β)
IIId.4 R═R_1═Me, R_2═OMe, (1α,1′β)
IIId.5 R═R_1═Me, R_2═OH, (1α,1′β)

TYPE IV – SECO-*BIS*-BENZYLISOQUINOLINE ALKALOIDS



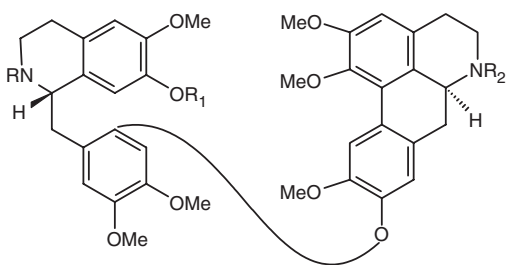
IV.1 R═Me
IV.2 R═H

TYPE V – BIS-APORPHINE ALKALOIDS



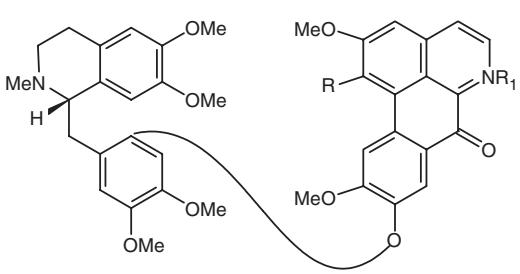
V.1 R_1R_2═R_3, R_4═OCH_2O
V.2 R_1R_2═OCH_2O, R_3═OMe, R_4═OH
V.3 R_1═R_2═R_4═OMe, R_3═OH

TYPE VI – BENZYLISOQUINOLINE-APORPHINE ALKALOIDS



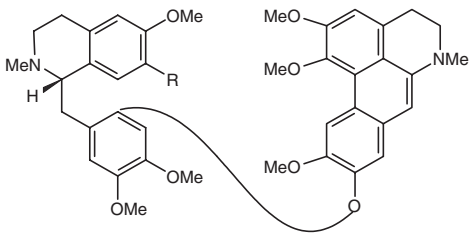
VI.1 R═H, R_1═R_2═Me
VI.2 R═R_2═Me, R_1═H
VI.3 R═R_1═Me, R_2═H
VI.4 R═(Me, O^-), R_1═R_2═Me
VI.5 R═R_1═R_2═Me
VI.6 R═R_2═Me, R_1═H

Subtype **VIa** – *Benzylisoquinoline-oxoaporphine Alkaloids*



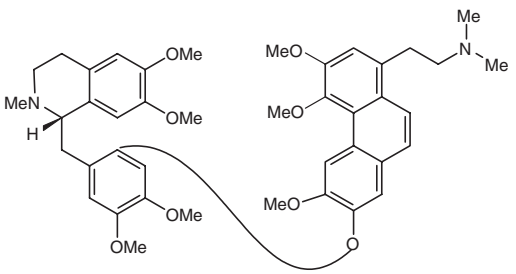
VIa.1 R═OMe, R_1═No group
VIa.2 R═O^-, R_1═Me

Subtype **VIb** – *Benzylisoquinoline-oxoaporphine Alkaloids*



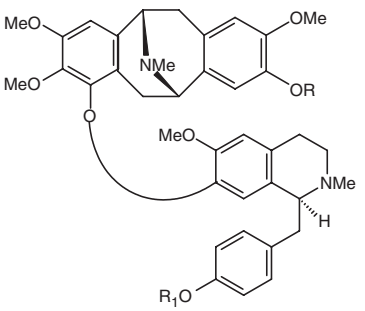
VIb.1 R═OMe
VIb.2 R═OH

TYPE VII – BENZYLISOQUINOLINE-PHENANTHRENE ALKALOID



VII.1

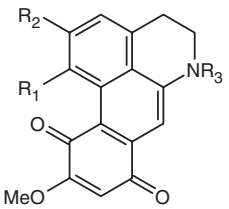
TYPE VIII – PAVINE-BENZYLISOQUINOLINE ALKALOIDS



VIII.1 R═Me, R_1═H
VIII.2 R═H, R_1═Me
VIII.3 R═R_1═Me

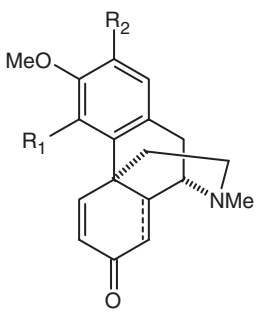
VIII.4 R═R_1═H
VIII.5 Structure not found

TYPE IX – *p*-QUINONOID-APORPHINE ALKALOIDS



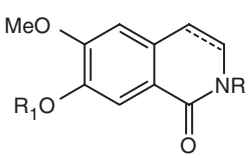
IX.1 R_1═OH, R_2═OMe, R_3═Me
IX.2 R_1═R_2═OMe, R_3═H
IX.3 R_1═R_2═OMe, R_3═Me

TYPE X – MORPHINANE ALKALOIDS



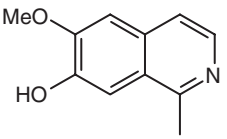
X.1 R_1═OH, R_2═H, $\Delta^{8,14\text{-dihydro}}$
X.2 R_1═H, R_2═OH, $\Delta^{8,14}$

TYPE XI – ISOQUINOLONE ALKALOIDS



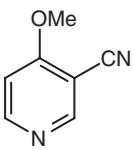
XI.1 R═R_1═Me, $\Delta^{3,4\text{-dihydro}}$
XI.2 R═R_1═Me, $\Delta^{3,4}$
XI.3 R═R_1═H, $\Delta^{3,4\text{-dihydro}}$
XI.4 R═H, R_1═Me, $\Delta^{3,4\text{-dihydro}}$

TYPE XII – ISOQUINOLINE ALKALOID

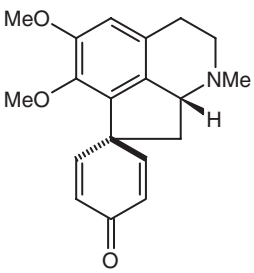


XII.1

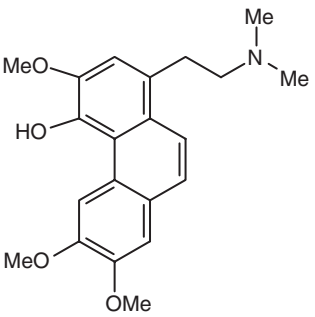
TYPES XIII (PYRIDINE), XIV (PROAPORPHINE), AND XVI (PHENANTHRENE) ALKALOIDS



XIII.1

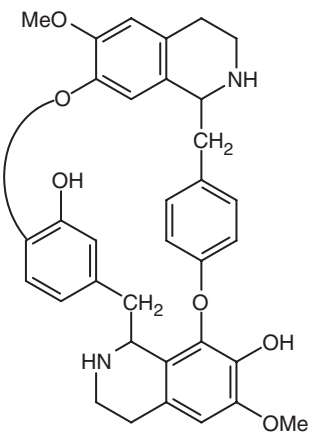


XIV.1

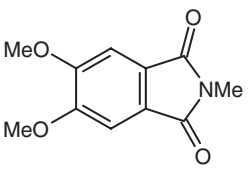


XVI.1

TYPES XV (BEBEERINE) AND XVII (PHTHALIMIDE) ALKALOIDS



XVI.1



XVII.1

List of the Alkaloids Isolated from Hernandiaceae Species

I.1 Actinodaphnine, or (+)-Actinodaphnine, or (−)-Actinodaphnine
I.2 (+)-Boldine
I.3 Bulbocapnine
I.4 Catalpifoline
I.5 (+)-Corytuberine
I.6 Dicentrine
I.7 (+)-*O*,*O*-Dimethylcorytuberine [= *O*-dimethylcorytuberine]
I.8 Domesticine
I.9 (+)-*N*-Formylhernangerine
I.10 (+)-*N*-Formylnornantenine
I.11 (+)-*N*-Formylovigerine
I.12 Hernagine or (+)-Hernagine
I.13 Hernandaline or (+)-Hernandaline
I.14 Hernandine
I.15 Hernangerine [= Nandigerine]; (+)-Hernangerine [= (+)-Nandigerine]
Nandigerine [= Hernangerine]; (+)-Nandigerine [= (+)-Hernangerine]
I.16 Hernovine or (+)-Hernovine
I.17 (+)-*N*-Hydroxyhernangerine
I.18 (+)-*N*-Hydroxyovigerine
I.19 (+)-Isoboldine
I.20 (+)-Isocorydine [= Artabotrine, Luteanine]
I.21 Laetanine
I.22 Laetine or (+)-Laetine
I.23 Launobine
I.24 (+)-Laurelliptine
I.25 Laurolitsine
I.26 Laurotetanine or (+)-Laurotetanine
I.27 Lindcarpine or (+)-Lindcarpine
I.28 (+)-Litseferine
I.29 (+)-Magnoflorine
I.30 *N*-Methylactinodaphnine or (+)-*N*-Methylactinodaphnine
I.31 *N*-(*N*-Methyl-carbamoyl)-*O*-methylbulbocapnine
I.32 (+)-*N*-Methylhernangerine [= *N*-Methylnandigerine] or
N-Methylnandigerine [= *N*-Methylhernangerine]
I.33 *N*-Methylhernovine or (+)-*N*-Methylhernovine
I.34 *N*-Methyllaurotetanine or (+)-*N*-Methyllaurotetanine
I.35 (+)-*N*-Methyllindcarpine
I.36 (+)-*N*-Methylovigerine
I.37 *O*-Methylbulbocapnine
I.38 *N*,*O*-Dimethylnandigerine
I.39 (+)-Neolitsine
I.40 (+)-Norboldine
I.41 (+)-Nordicentrine
I.42 Nordomesticine
I.43 Norisocorydine or (+)-Norisocorydine
I.44 (+)-Nornantenine
I.45 Norpredicentrine

I.46 Ovigerine or (+)-Ovigerine
I.47 (−)-Roemrefidine
I.48 Xanthoplanine
Ia.1 Dehydrohernandaline
Ia.2 7-Formyldehydrohernangerine
Ia.3 7-Formyldehydronornantenine
Ia.4 7-Formyldehydroovigerine
Ia.5 *N*-Formyldehydroovigerine
Ib.1 Atheroline
Ib.2 Dicentrinone
Ib.3 Hernandonine
Ib.4 Hernanymphine
Ib.5 Lanuginosine
Ib.6 Liriodenine
Ib.7 Lysicamine
Ib.8 *O*-Methyloxobulbocapnine
Ib.9 4-Methoxyoxohernandaline
Ib.10 Oxocrebanine [= 1,2-Methylenedioxy-8,9-dimethoxy-quinolin-7-one]
Ib.11 Oxohernandaline
Ib.12 7-Oxohernangerine
Ib.13 7-Oxohernangine
Ib.14 Oxonantenine
II.1 Backebergine
II.2 (+)-Coclaurine
II.3 Laudanosine
II.4 (+)-Laudanidine
II.5 Magnocurarine
II.6 *N*-Methylcoclaurine
II.7 (+)-Nymphaedaline
II.8 Reticuline or (+)-Reticuline
III.1 (+)-2′β-*N*-Oxidevateamine
III.2 (+)-Vanuatine
III.3 (+)-Vateamine
IIIa.1 (−)-Grisabine
IIIb.1 Ambrimine or (+)-Ambrimine
IIIb.2 Efatine or (+)-Efatine
IIIb.3 (+)-Malekulatine
IIIc.1 Gyrocarpine or (−)-Gyrocarpine
IIIc.2 (+)-Gyrocarpusine
IIIc.3 (−)-Gyrolidine
IIIc.4 (+)-Limacusine
IIIc.5 *O*-Methyllimacusine
IIId.1 Gyroamericine
IIId.2 (−)-Isotetrandrine
IIId.3 Limacine or (−)-Limacine
IIId.4 (−)-Phaeanthine
IIId.5 Pycnamine
IV.1 (+)-Auroramine
IV.2 (+)-Maroumine

V.1 (+)-Ovigeridimerine
V.2 Ovihernangerine
V.3 Oviisocorydine
VI.1 Northalicarpine
VI.2 (+)-2′-Northalicarpine
VI.3 (+)-6-Northalicarpine
VI.4 (+)-2′-*N*-Oxidethalicarpine
VI.5 Thalicarpine or (+)-Thalicarpine
VI.6 (+)-Thalmelatine
VIa.1 Oxothalicarpine
VIa.2 (+)-Vilaportine
VIb.1 Dehydrothalicarpine
VIb.2 6a,7-Dehydrothalmelatine
VII.1 (+)-Hebridamine
VIII.1 Herveline A
VIII.2 Herveline B
VIII.3 Herveline C
VIII.4 Herveline D
VIII.5 Herveline HB
IX.1 Demethylsonodione
IX.2 Norsonodione
IX.3 Sonodione
X.1 Ocobotrine
X.2 (−)-Pallidine
XI.1 *N*-Methylcorydaldine
XI.2 *N*-Methyl-6,7-dimethoxy-isoquinoline
XI.3 Northalifoline
XI.4 Thalifoline
XII.1 7-Hydroxy-6-methoxy-1-methylisoquinoline
XIII.1 3-Cyano-4-methoxy-pyridine
XIV.1 (+)-Pronuciferine
XV.1 (−)-Bebeerine
XVI.1 Thaliporphinemethine
XVII.1 *N*-Methyl-5,6-dimethoxy-phthalimide

Acknowledgments

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