β-Phenylethylamines and the isoquinoline alkaloids

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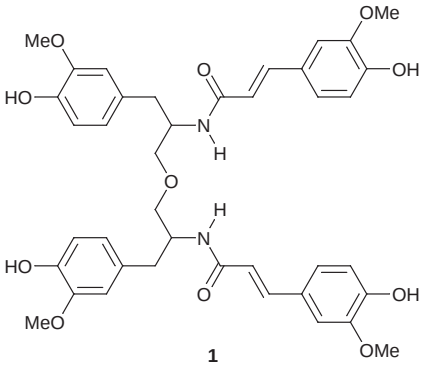
A comprehensive review of the chemistry of the alkaloids within the scope of this review, other than those of the morphine group, has been pubished.[1]

1 β-Phenylethylamines

N-trans-Feruloyltyramine has been isolated from *Tinospora cordifolia*.[2] The novel bimolecular alkaloid cherinonaine, isolated from *Annona cherimola*, has been assigned the structure **1** on the basis of its NMR spectra and of its fission to *trans*-ferulic acid and 4-hydroxy-3-methoxyamphetamine.[3] The new alkaloid densine **2**, isolated from *Berberis densiflora*,[4] is structurally a β-phenylethylamine, but, since it is doubtless derived from dehydrosalsolidine **3**, it is more properly classified with the isoquinoline alkaloids.

The treatment of pseudoephedrine with (*R*)-α-fluoropropionamide has afforded the amide **4**, α-*C*-alkylation of which proceeds with a high degree of stereoselectivity and hydrolysis of the products gives the corresponding chiral acids.[5] The physico-chemical properties of soap solutions generated by ephedrine and pseudoephedrine myristates, which form bimolecular fibres in water,[6] and the crystal structure of *N*-cyanomethylpseudoephedrine[7] have been studied.

The pharmacological properties and physiological effects of ephedrine,[8–11] of (+)- and (±)-norephedrine[12] and of pseudoephedrine[13] have been studied.



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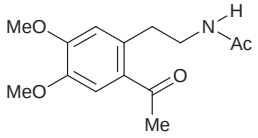

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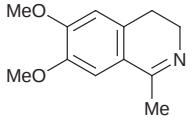

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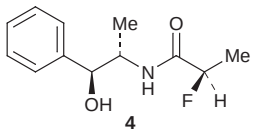

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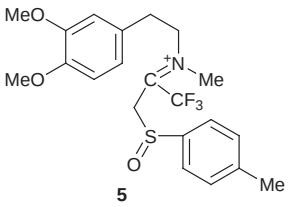
2 Isoquinolines

O-Methylcorypalline has been isolated from *Berberis densiflora*[4] and from *Phoebe minutiflora*[14] and stephaoxocanidine has been isolated from *Stephania cepharantha*.[15] A review of the alkaloids of cacti of *Gymnocalycium* species has been published.[16] An X-ray crystallographic study of corydaldine has been reported.[17] The iminium salt **5** has been cyclised to the (1*R*)-tetrahydroisoquinoline **6**.[18]



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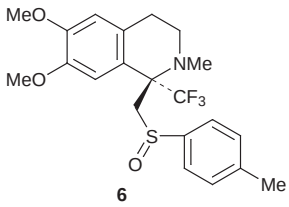

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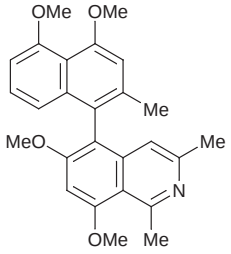
3 Naphthylisoquinolines

Naphthylisoquinoline alkaloids have been isolated from the following plant species, the thirteen marked with asterisks being new alkaloids:

Ancistrocladus cochinchinensis[19]
ancistrocladinine, 6-*O*-methylhamateine* **7**, 6-*O*-methylhamatinine* **8b**, hamatinine **8a**, 7-*epi*-ancistrobrevine D* **9a**, 6-*O*-demethyl-7-*epi*-ancistrobrevine D* **9b** and 6-*O*-demethyl-8-*O*-methyl-7-*epi*-ancistrobrevine D* **9c**

Ancistrocladus guineaensis[20]
ancistrotectorine, ancistroguineine A* **10** and ancistroguineine B* **11**

Ancistrocladus korupensis[21,22]



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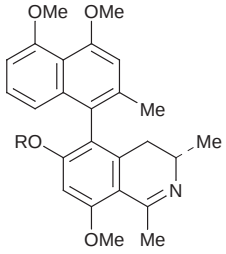
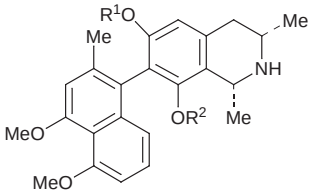
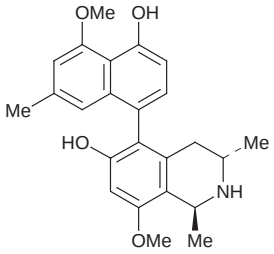


8a R = H
8b R = Me



9a R^1 = Me, R^2 = H
9b R^1 = R^2 = H
9c R^1 = H, R^2 = Me



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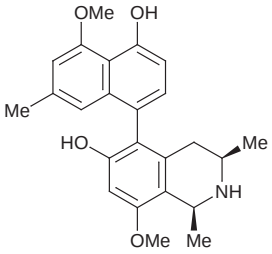

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korupensamine E* **12**, michellamine D* **13**, michellamine E* **14**, michellamine F* **15**, yaoudamine A* **16** and yaoudamine B* **17**

Ancistrocladus robertsoniorum[23]

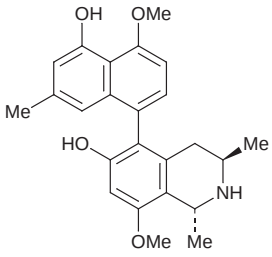
ancistrobrevine B, ancistrocladine, ancistrorobertsonine* **18** and hamatine.

The structures of the new alkaloids have been determined by spectroscopic studies, by the correlation of **9a**, **9b** and **9c** with 7-*epi*-ancistrobrevine D and by the degradation of ancistroguineine A to the amino acids **19** and **20**.[20]

The absolute configuration of dioncophylline A **21** has been confirmed by an anomalous X-ray dispersion crystal analysis of the 5-bromo-*N*,*O*-dibenzyl derivative[24] and the configurations of several of the alkaloids at the biaryl axis has been determined by studies of long range nuclear Overhauser effects.[25] The Fourier transform Raman spectra of the alkaloids from *Ancistrocladus heyneanus* have been examined.[26]

The enzyme involved in the bimolecular coupling of korupensamines A and B to give michellamines A and C has been identified and partially purified. It has been shown to be a single polypeptide and it effects the first dimerisation of the korupensamines to be achieved without protection of the hydroxy and secondary amino groups.[27] Following previous practice, with protection of the hydroxy and amino groups, dioncophylline C **22** has been oxidised to the bimolecular josimine C **23**, which is an analogue of the michellamines but has not been encountered as a natural product.[28]

Dioncophylline C **22** has been found to effect a complete cure of *Plasmodium berghei* malaria, even of strains resistant to conventional antimalarials, at a dosage of 50 mg kg^{-1} over four days, without toxic effects. Dioncopeltine A is also effective against the same organism.[29] *N*,*N*-Dimethyldioncophylline A iodide has been found to have enhanced antiplasmodial activity over the free secondary base.[30] A review of the biological



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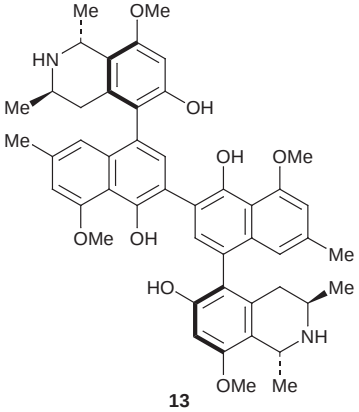

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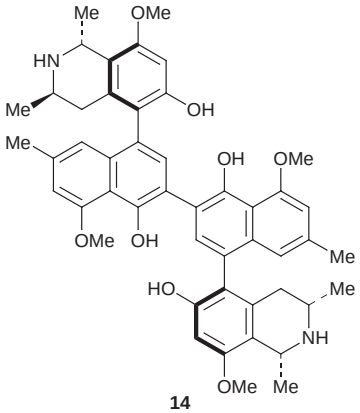

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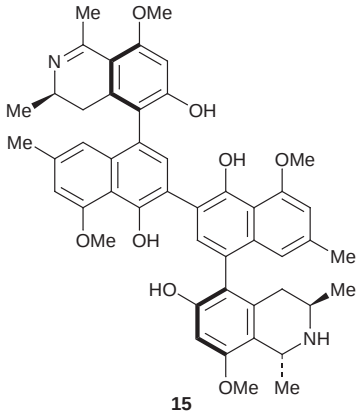

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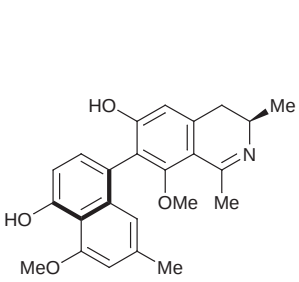

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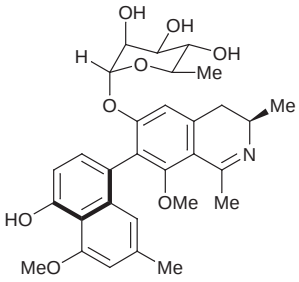

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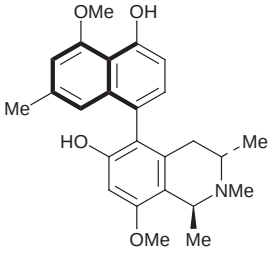

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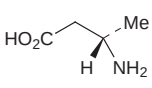

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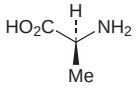

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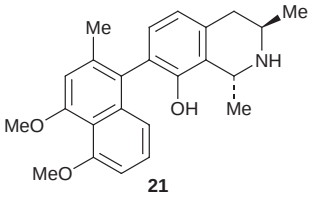

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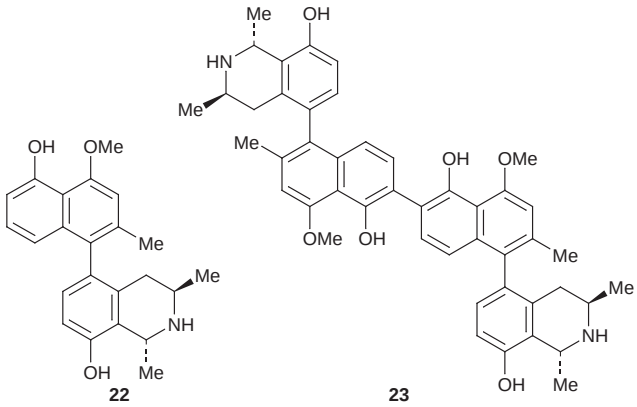


22 **23**

activities of the naphthylisoquinoline alkaloids has been published.[31] A series of analogues of the michellamines, in which the tetrahydroisoquinoline system has been replaced by a variety of simple aromatic systems, have been found to exhibit no activity against human immunodeficiency virus.[32]

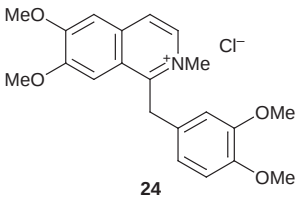
4 Benzylisoquinolines

1-Benzylisoquinoline alkaloids have been isolated from the following plant species, the two marked with asterisks being new alkaloids:

Annona cherimola[33]
orientaline

Aristolochia triangularis[34]
oblongine

Berberis densiflora[4]
densiberine* **24**



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Cocculus laurifolius[35]
coclaurine

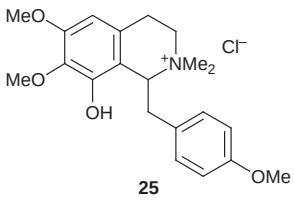
Croton celtidifolius[36]
laudanidine and reticuline

Phoebe minutiflora[14]
armepavine, *N*-methylarmepavine, coclaurine, *N*-methylisococlaurine, juziphine, norjuziphine, laudanidine and reticuline

Papaver triniifolium[37]
militanthaline* **25** and papavarine

The novel 2-benzylisoquinoline alkaloid numularine **26** has been isolated from *Berberis numularia*.[38]

The ^{1}H, ^{13}C and ^{15}N NMR spectra of (−)-armepavine have been studied[39] and an X-ray crystallographic study of the same alkaloid has been reported.[39] The anion of papaverinol has been methylated to give the alkaloid setigerine **27**.[40] Laudanosoline hydrobromide has been oxidised by ferric chloride in aqueous



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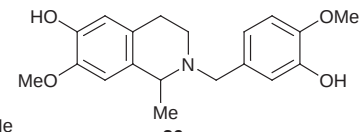

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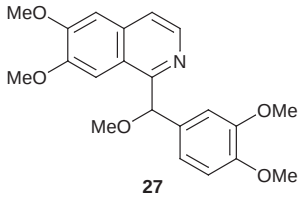

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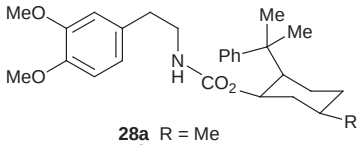
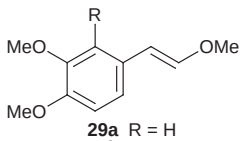
ethanol buffered with sodium acetate to give an 80% yield of an aporphine that gave glaucine on *O*-methylation (see section 16.2).[41]

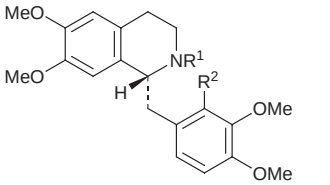
Pictet–Spengler cyclisation of the enol methyl ether of 3,4-dimethoxyphenylacetaldehyde **29a** with the (−)-8-phenylmenthyl carbamate **28a** affords a marked enantiomeric excess of the (1*R*)-tetrahydroisoquinoline **30a**, reduction of which with lithium aluminium hydride affords (*R*)-(+)-laudanosine **30b**, which is the enantiomer of the natural alkaloid. Improved stereoselectivity was achieved using **29b** in place of **29a**. Since the (+)-8-phenylmenthol is not readily available, the corresponding carbamates of (−)-*trans*-2-(α-cumenyl)cyclohexanol **28b** and its (+)-enantiomer have been converted into 2′-bromo-(1*R*)-laudanosine **30c** and its (1*S*)-isomer.[42]



28a R = Me
28b R = H



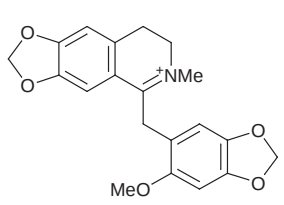
29a R = H
29b R = Br



30a R^1 = O_2C-(–)-8-Phenylmenthyl, R^2 = H
30b R^1 = Me, R^2 = H
30c R^1 = Me, R^2 = Br

In the previous review it was reported that the benzylisoquinoline **32a** is not identical with the alkaloid fumarizine, to which this structure had previously been assigned. This alkaloid is also not identical with the isomeric base **32b**, obtained by the asymmetric reduction of the iminium salt **31**.[43] In a similar manner the alkaloid dehassiline, to which the structure **33** has been assigned,[44] has been shown to be different from the product of reduction of the iminium salt **34**.[45] (*R*)-(+)-Norroefractine **35** has been synthesised and shown to be a selective ligand at the dopamine D_2 receptor, where it displaces raclopride.[46]

The 3,4-dihydroisoquinoline **36**, prepared by Bischler–Napieralsky ring closure, on treatment with base and methyl 2-methoxymethoxy-5-methoxybenzoate affords the ketone **37**, which reacts with ethyl bromoacetate to give the ester **38a**, easily converted into **38b**. Treatment of this with triethylamine effects cyclisation to lamellarin D **39a**, which can be demethylated to lamellarin H **39b**.[47] In an alternative approach to this



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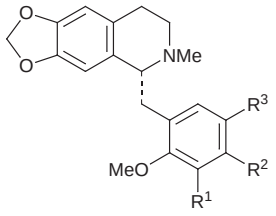
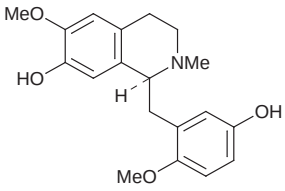


32a $R^1R^2 = OCH_2O$, $R^3 = H$
32b $R^1 = H$, $R^2R^3 = OCH_2O$



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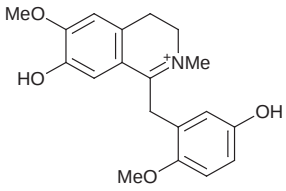

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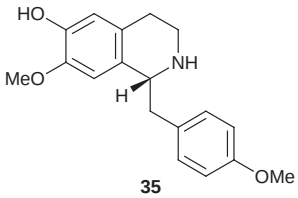

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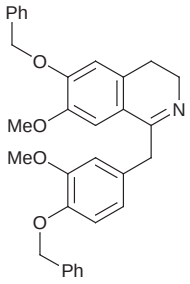
system the dihydroisoquinolinium salt **40** has been cyclised by base to **41a**, which was selectively cleaved by aluminium chloride to lamellarin K **41b**.[48]



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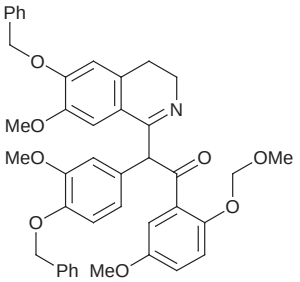

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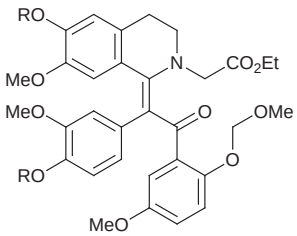
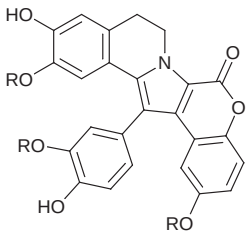
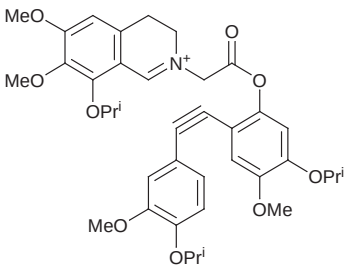


38a R = CH_2Ph
38b R = H



39a R = Me
39b R = H



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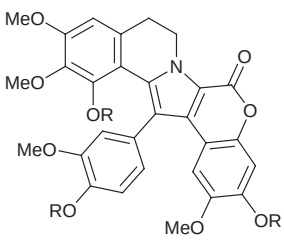


41a R = Pr^i
41b R = H

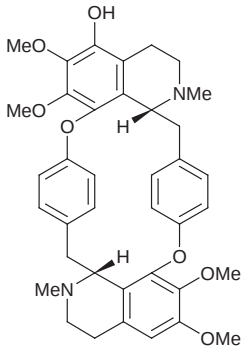
The pharmacological properties and physiological effects of atracurium,[49–52] of higenamine[53] and of papaverine[54,55] and the effects of *O*-methylarmepavine and of reticuline on the replication of poliomyelitis virus[56] have been studied, and a method of estimation of atracurium has been described.[57]

5 Bis-benzylisoquinolines

Bis-benzylisoquinoline alkaloids have been isolated from the following plant species, the four marked with asterisks being new alkaloids:

Anisocyla jollyana[58]

cycleanine, cycleanine-2-*N*-oxide, dehydroapateline, fastrine* **42**, homoaromoline, isochondodendrine, jollyanine* **43**, limacusine, limacusine-2′-*N*-oxide and *O*-methylcosculine



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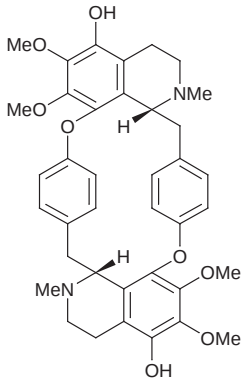


43

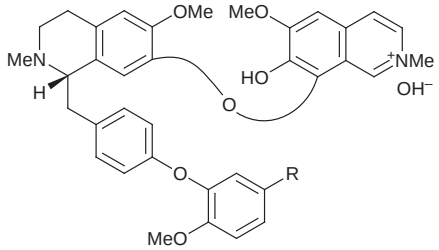
Berberis densiflora[4]

oxyacanthine

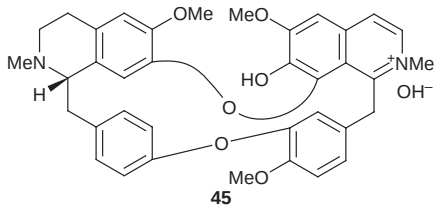
Stephania tetrandra[59]

fenfangjine H* **44a** and fenfangjine I* **44b**.

Fastrine and jollyanine are the first head-to-tail linked bis-benzylisoquinoline alkaloids bearing an oxygen substituent at position 5 to be discovered. The structures of the new alkaloids were determined by spectroscopic methods. Fenfangjines H and I are secobis-benzylisoquinoline alkaloids clearly formed by oxidative cleavage of fenfangjine D **45**, previously isolated



44a R = CH_2OH
44b R = CHO

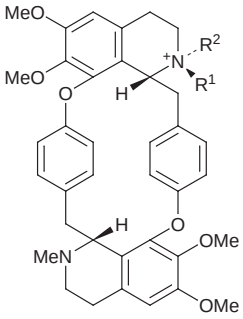


45

from the same plant.[60] These two alkaloids were shown to be inhibitors of the angiotensin-I converting enzyme.[59]

Cycleanine has been oxidised by *m*-chloroperbenzoic acid to a mixture of the 2α and 2β *N*-oxides **46a** and **46b**.[61]

The pharmacological properties and physiological effects of bebeerine,[62] of berbamine,[63,64] of *O*-benzoyl, *O*-ethyl, *O*-butyl and *O*-4-ethoxybutyl-berbamines[65] of tetrandrine[66–72] and of tubocurarine[73] and the antitrypanosmal activities of curine, of

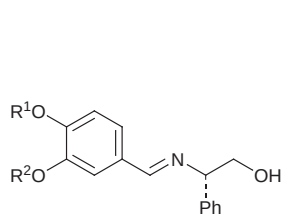


46a R^1 = Me, R^2 = O^-
46b R^1 = O^-, R^2 = Me

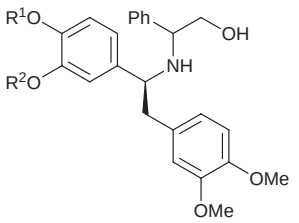
cycleanine, of isotetrandrine, of limacine and of phaeanthine[74] have been studied.

6 Pavines and isopavines

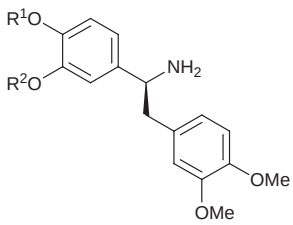
Condensation of phenylglycinol with veratric aldehyde and with piperonal affords the imines **47a** and **47b**, and these have been found to react with 3,4-dimethoxybenzylmagnesium



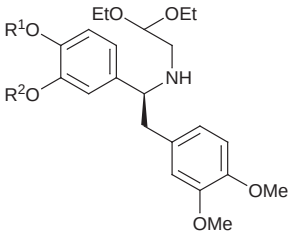
47a R^1 = R^2 = Me
47b R^1R^2 = CH_2



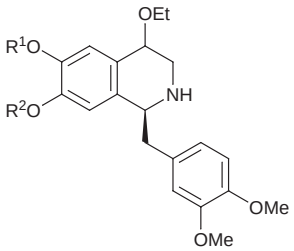
48a R^1 = R^2 = Me
48b R^1R^2 = Me



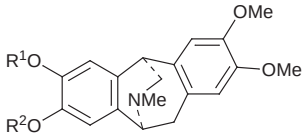
49a R^1 = R^2 = Me
49b R^1R^2 = CH_2



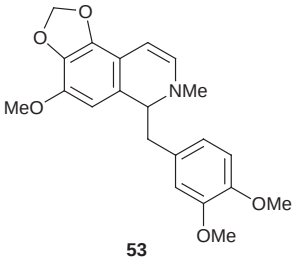
50a R^1 = R^2 = Me
50b R^1R^2 = CH_2



51a R^1 = R^2 = Me
51b R^1R^2 = CH_2



52a R^1 = R^2 = Me
52b R^1R^2 = Me



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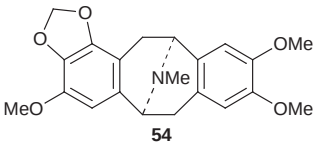

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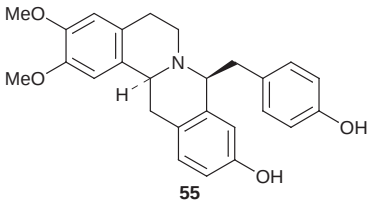
chloride with a high degree of steroespecificity to give the 1,2-diarylethylamines **48a** and **48b** with the (*S*,*S*) forms in 95% excess, and these were cleaved by hydrogenolysis to **49a** and **49b**. Alkylation of these with bromoacetaldehyde diethyl acetal afforded **50a** and **50b**, which were cyclised by acid through the intermediate 4-ethoxytetrahydroisoquinolines **51a** and **51b** to the isopavine secondary bases, which were *N*-methylated to (−)-*O*-methylthalisopavine **52a** and (−)-amurensinine **52b**.[75] Acid-catalysed cyslisation of the dihydroisoquinoline **53** has afforded the racemic isopavine, which was resolved to give (−)-thalimonine **54**, confirming the assignments of the positions of the substituents in this alkaloid.[76]

7 Berberines and tetrahydroberberines

Alkaloids of the berberine group have been isolated from the following plant species, the three marked with asterisks being new alkaloids:

Annona cherimola[33]
kikenamine

Aristolochia constricta[77]
the unnamed base **55***



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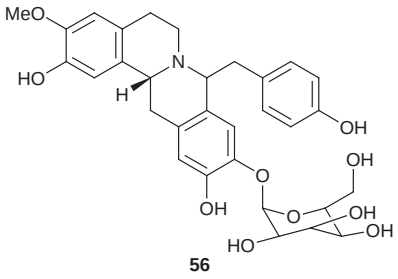
Aristolochia gigantea[78]
the unnamed glucoside **56*** and the *cis*-*N*-oxide **57***



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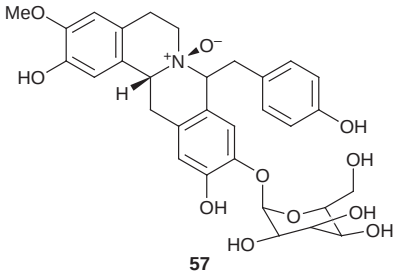

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Berberis densiflora[4]
berberine

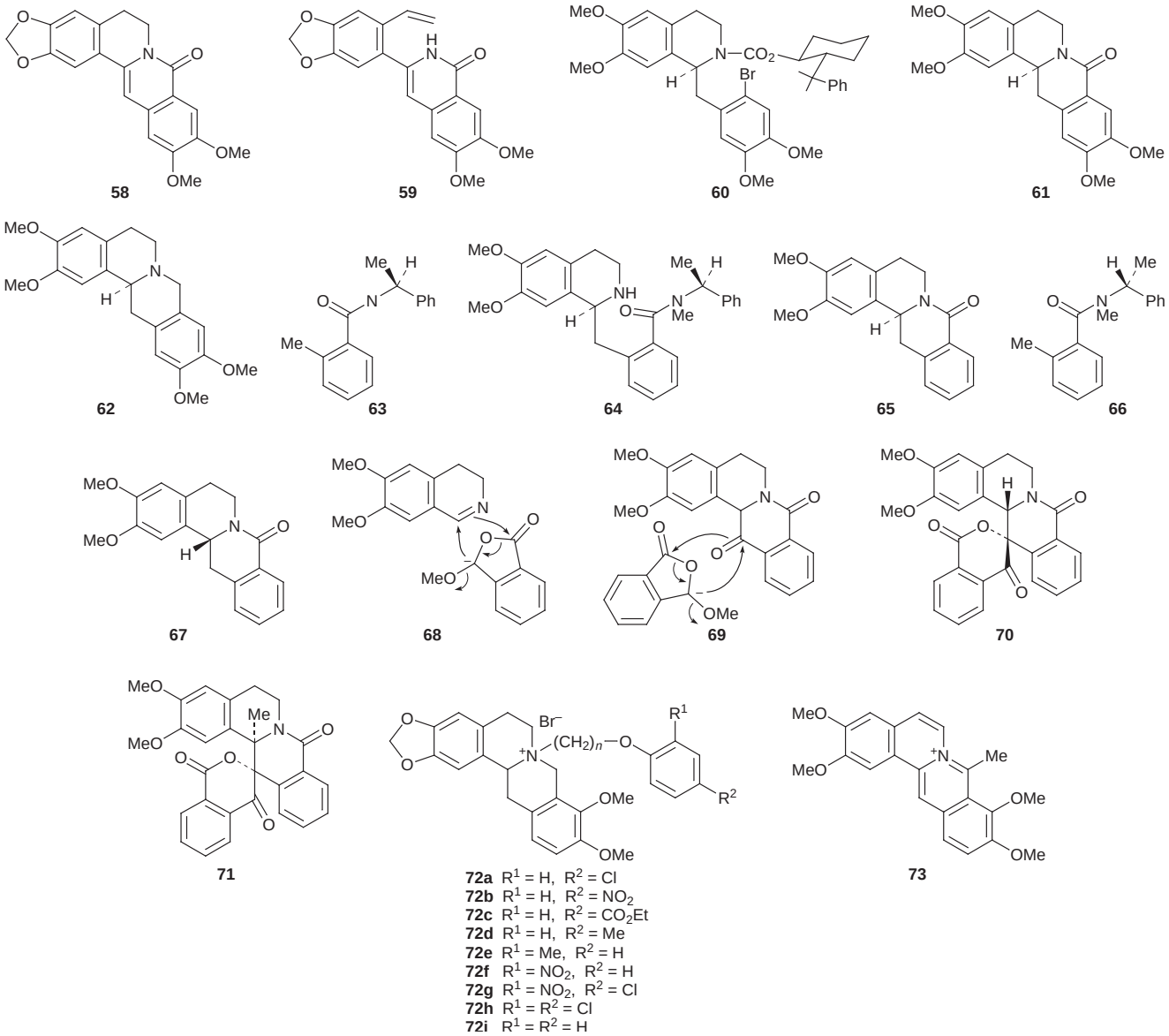
Berberis stenophylla[79]
berberine

Corydalis dasypterma[80]
coptisine, tetrahydrocoptisine, corysamine and tetrahydrocorysamine

Papaver pseudo-orientale[81]
mecambridine and orientalidine.

A method for the estimation of berberine in body fluids has been described.[82]

The 8-oxopseudoberberine **58** has been cleaved by sodium hydride to the olefin **59**, which has been converted into the

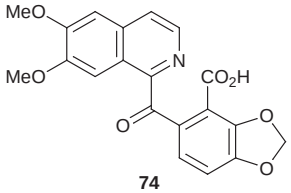


benzophenanthridine alkaloid oxonitidine[83] (see section 15). The chiral carbamate **60**, prepared from (1*S*)-norlaudanosine, has been cyclised by *tert*-butyllithium to 8-oxoxylopinine **61**, which, on reduction with Redal, afforded (*S*)-(−)-xylopinine **62**.[42] In a model approach to the chiral synthesis of tetrahydroberberines the anion of the chiral *o*-toluamide **63** has been condensed with 3,4-dimethoxy-3,4-dihydroisoquinoline (dehydroheliamine) to give a mixture of the amide **64** and the (*S*)-lactam **65**, the latter being the sole product under certain conditions. In a similar way the enantiomeric toluamide **66** yielded the (*R*)-lactam **67**.[84] Dehydroheliamine also reacts with the anion of 3-methoxyphthalide **68** giving, *via* **69**, the 13-spiro-8-oxoberberine **70**. The similar reaction with dehydrosalsolidine **3** affords **71**, with the opposite configuration at position 13a.[85] Quaternary tetrahydroberberinium salts of structures **72a**–**i**, in which $n = 2$ and 3, have been prepared and examined as cardiac antiarrhythmic agents.[86] A patent claiming the use of coralyne **73** and its analogues as topoisomerase inhibitors has been published.[87]

The pharmacological properties and physiological effects of berberine,[88–95] of 8-oxoberberine,[96] of tetrahydroberberine,[97] of berberrubine,[92] of palmatine,[92] of 7-chlorobenzyltetrahydropalmatinium salts,[98] of 13-hydroxytetrahydropalmatine,[92] of 13-alkyltetrahydropalmatines up to the hexyl compound[92] and of stepholidine[99,100] have been studied.

8 Secoberberines

The new secoberberine alkaloid fumaflorine **74** has been isolated from *Fumaria densiflora*.[101]



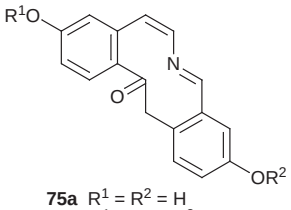
74

9 Protopines

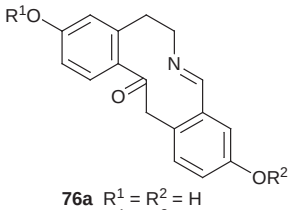
Alkaloids related to protopine have been isolated from the following plant species, the four marked with asterisks being new alkaloids:

Aristolochia constricta[77]
constrictosine* **75a**, *O*-methylconstrictosine* **75b**, *O*,*O*-dimethylconstrictosine* **75c**, 5,6-dihydroconstrictosine* **76a** and *O*,*O*-dimethyl-5,6-dihydroconstrictosine* **76b**

Berberis densiflora[4]
allocryptopine



75a $R^1 = R^2 = H$
75b $R^1 = Me$, $R^2 = H$
75c $R^1 = R^2 = Me$



76a $R^1 = R^2 = H$
76b $R^1 = R^2 = Me$

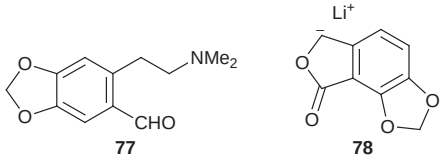
Glaucium fimbrilligerum[102]
protopine
Papaver fugax[103]
protopine.

The substitution pattern of the new alkaloids from *Aristolochia constricta* is unprecedented in this group and their origin from tyrosine is possibly in doubt since the original tyrosine hydroxy group is missing from the left hand half of the system. These alkaloids all cause a significant dose-dependent reduction in contractions of isolated guinea pig ileum induced by electricity, acetylcholine and histamine.[77] The physiological effects of allocrypropine have been studied.[104]

10 Phthalide-isoquinolines

α-Narcotine and narceine have been isolated from *Papaver triniifolium*.[37] The alkaloid fumaflorine **74**, isolated from *Fumaria densiflora*, could also be regarded as a member of this group.

An X-ray crystallographic study of racemic narlumicine hydrobromide has confirmed the relative stereochemistry as that shown in **79**[105] and a synthesis of the alkaloid has been effected by the reaction of the aldehyde **77** with the lithium salt of the appropriate phthalide **78**.[106]



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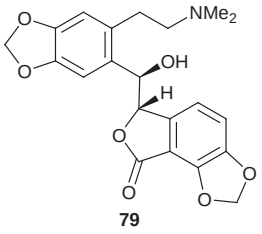

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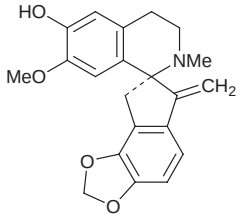
A method for the estimation of narcotine in body fluids has been described.[107] The pharmacological properties and physiological effects of narcotine[108,109] and of bicuculline[110] have been studied.

11 Spirobenzylisoquinolines

The chemistry of the alkaloids of this group isolated from *Fumaria* species has been reviewed.[111] In an attempt to repeat a previously reported synthesis[112] of ochotensine **80**, cyclodehydration of the acids **81a** and **81b** with polyphosphoric acid has been found to give only the acid anhydrides **82a** and **82b**, rather than the ketones **83a** and **83b**.[113]

12 Indanobenzazepines

The first synthesis of the 6,7-indano-3,4-benzazepine system encountered in the alkaloids ribasine **93a**, himalayine **93b** and ribasidine **93c** has been reported.[114] 2-Cyanobenzyl bromide



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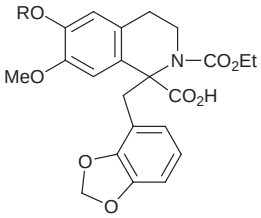
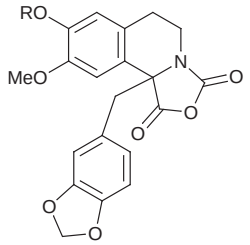
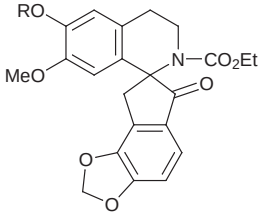


81a R = CO_2Et
81b R = Me



82a R = CO_2Et
82b R = Me



83a R = CO_2Et
83b R = Me

84a was converted through **84b** into the lithium derivative **84c**, which was condensed with the aminoindanone **85** to give the amino alcohol **87** in 91% yield, together with the related diastereoisomer (7%). Acid hydrolysis of this afforded only the elimination product **88a** and its geometrical isomer, but basic hydrolysis afforded mainly the indanobenzazepine **89**, together with 25% of the olefin **88b**. Reduction of the lactam **89** with bis(methylthio)boron hydride yielded the alcohol **90a**, which was converted only with difficulty into **90b**. The alcohol **90a** was oxidised by Fremy's salt to **91a**, which was cleaved by trifluoroacetic acid to the norribasine analogue **91b**, isolated as an equilibrium mixture with the imine **92**. Natural norribasine **93d** does not equilibrate with the corresponding imine.

13 Rhoeadines

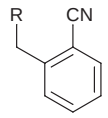
Two new alkaloids of the rhoeadine group, triniifoline **94a** and *O*-ethyltriniifoline **94b** have been isolated from *Papaver triniifolium*.[37]

14 Emetine and related alkaloids

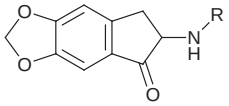
The following new alkaloids have been isolated from *Alangium lamarckii*:[115,116] 6′-*O*-β-D-glucopyranosylalangiside **95**, 3′-*O*-β-D-glucopyranosylalangiside **96**, 6′-α-D-glucopyranosylalangiside **97a**, 6′-*O*-α-D-glucopyranosyl-3-*O*-demethyl-2-*O*-methylalangiside **97b**, 6′-*O*-α-D-xylopyranosylalangiside **98** and the diastereoisomeric methoxy compounds **99a** and **99b**. The structures of these alkaloids were determined on the basis of their NMR spectra. The methoxy compounds **99a** and **99b**, which have been found to be produced from alangiside on long storage of the alkaloid in methanol, are clearly products of oxidation of the alkaloid, being simple derivatives of the dialdehyde **100**, which has been reasonably postulated as an intermediate in the biotransformation of alangiside into the azaberberine alkaloid alangimaridine **101**. Both **99a** and **99b** are converted into alangimaridine under conditions identical with those normally used in the extraction of alkaloids from plant material.[116]

15 Benzophenanthridines

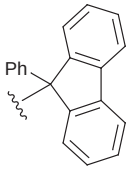
Benzophenanthridine alkaloids have been isolated from the following plant species:
Papaver nudicaule[117]
chelidonine
Zanthoxylum roifolium[118]



84a R = Br
84b R = TeBu^n
84c R = Li



85 R = **86**



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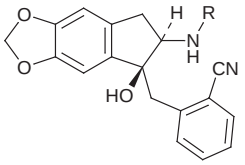
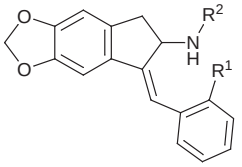
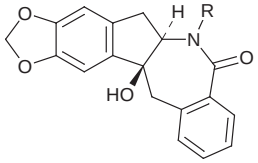


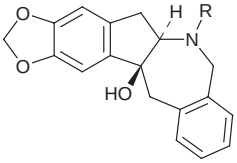
87 R = **86**



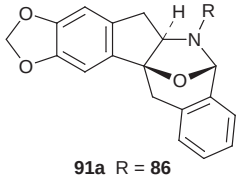
88a R^1 = $CONH_2$, R^2 = **86**
88b R^1 = CN, R^2 = **86**



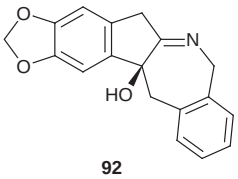
89 R = **86**



90a R = **86**
90b R = H



91a R = **86**
91b R = H



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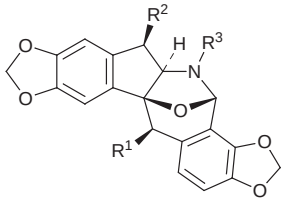
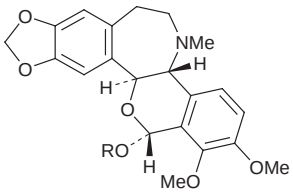


93a R^1 = R^2 = H, R^3 = Me
93b R^1 = H, R^2 = OH, R^3 = Me
93c R^1 = OH, R^2 = H, R^3 = Me
93d R^1 = R^2 = R^3 = H

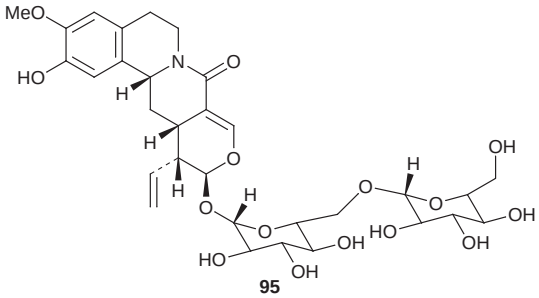


94a R = H
94b R = Et

dihydronitidine, 6-oxonitidine and zanthoxyline **102**.

Zanthoxyline, which is a new alkaloid, has an unusual substitution pattern, being the first alkaloid of the group not to bear an oxygen substituent at position 8. The conformation of methyl (+)-corydalate **103** has been studied by NMR spectroscopy and the *trans*-stereochemistry has been confirmed.[119] Photo-oxidation of sanguinarine has been shown to give 6-oxosanguinarine **104**.[120]

Sanguilutine, on treatment with potassium cyanide, gives 6-cyanodihydrosanguilutine **105a** and treatment with sodium carbonate yields 6-hydroxydihydrosanguilutine **105b**, which in non-polar solvents spontaneously loses water to give the bimolecular amine ether **106**, the structure of which has been confirmed by X-ray crystallography. The related dimeric amine **107** is formed directly from sanguilutine and ammonia.[121]



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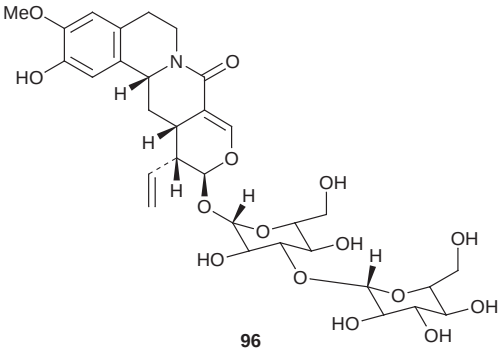

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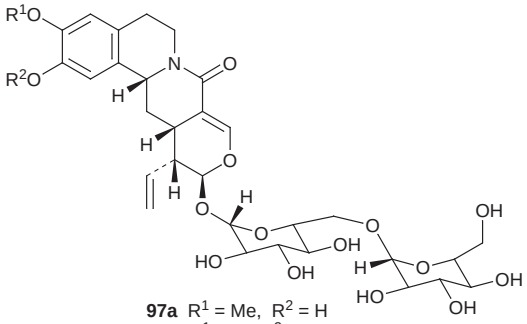
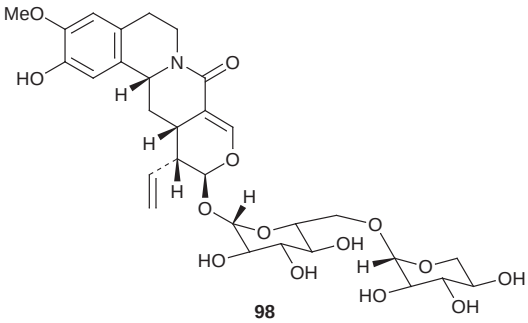


97a R^1 = Me, R^2 = H
97b R^1 = H, R^2 = Me



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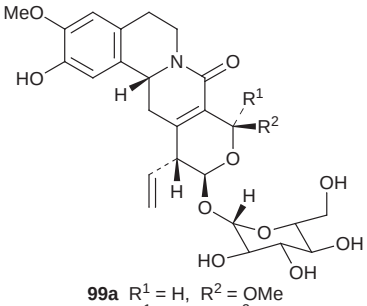
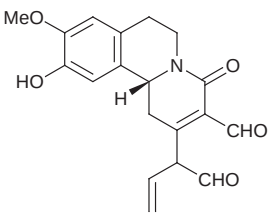


99a R^1 = H, R^2 = OMe
99b R^1 = OMe, R^2 = H



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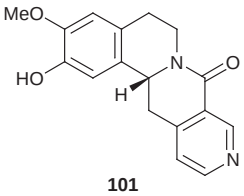

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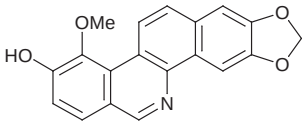

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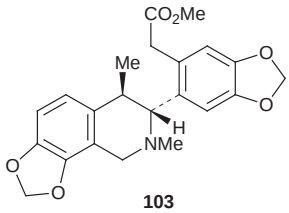

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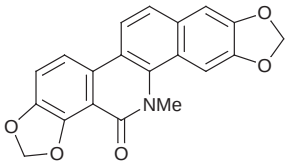

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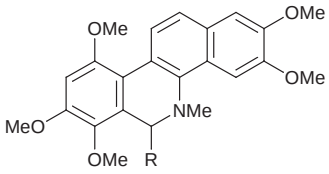
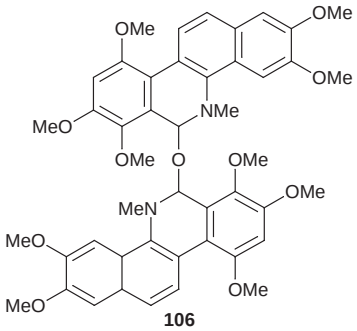


105a R = CN
105b R = OH



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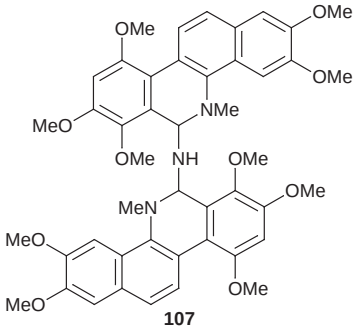
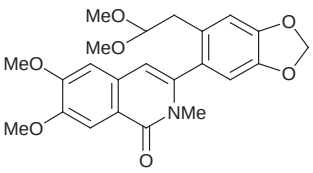
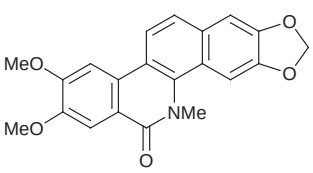


107

A synthesis of 6-oxonitidine **109** has been achieved from the 8-oxopseudoberberine **58** by cleavage with sodium hydride to the olefin **59**, followed by *N*-methylation and oxidation with thallium(III) nitrate in methanol to the acetal **108**, which was cyclised by acid to **109**.[83]



108



109

The pharmacological properties and physiological effects of chelerythrine have been studied.[122]

16 Aporphinoid alkaloids

16.1 Proaporphines

Proaporphine alkaloids have been isolated from the following plant species:

Annona cherimola[33]
stepharine

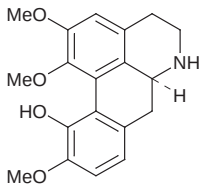
Papaver fugax[103]
pronuciferine

Papaver triniifolium[37]
mecambrine and *N*-methylcrotonosine.

16.2 Aporphines

Aporphine alkaloids have been isolated from the following plant species, the five marked with asterisks being new alkaloids:

Annona cherimola[33]
anolobine, anonaine, *N*-formylanonaine, asimilobine, *N*-methylasimilobine, isocorydine, laurotetanine, *N*-methyllaurotetanine, norisocorydine* **110**, norushinsunine, ushinsunine and xylopine

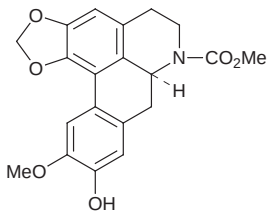


110

Aristolochia triangularis[34]
magnoflorine and *N*,*N*-dimethyllindecarpine

Berberis densiflora[4]
glaucine, isocorydine and thalicmidine

Cassytha filiformis[123]
actinodaphnine, cassamedine, cassameridine, cassythicine, cathafiline* **111**, cathaformine* **112** and isoboldine



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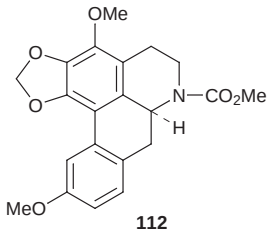


112

Cocculus laurifolius[35]
isoboldine and norisoboldine

Corydalis dasyptera[80]
corytuberine

Croton celtidifolius[36]
isoboldine

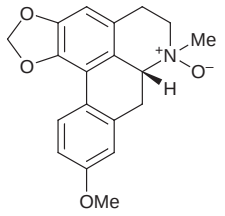
Glaucium fimbrilligerum[102]
bulbocapnine, isocorydine, lindecarpine and thaliporphine

Illigera luzonensis[124]
actinodaphine, *N*-methylactinodaphnine, bulbocapnine, *O*-methylbulbocapnine, dicentrine, hernovine and launobine

Magnolia obovata[125]
anonaine, isolaureline *N*-oxide* **113** and roemerine

Papaver fugax[103]
roemerine

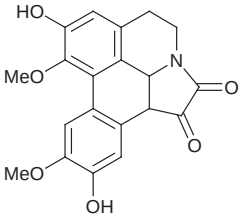
Papaver pseudo-orientale[81]
bracteoline and isothebaine



113

Phoebe formosana[126]

N-formylanonaine, *N*-formyldehydroanonaine and laurodionine* **114**



114

Phoebe minutiflora[14]

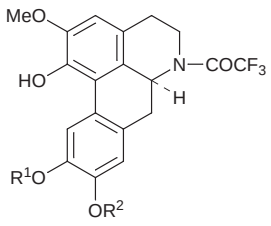
corytuberine, isoboldine, laurolitsine and norisocorydine **110**

Telitoxicum glaziovii[127]

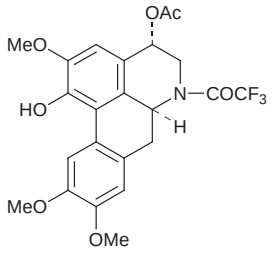
imenine.

A review of alkaloids isolated from *Thalictrum* species has been published.[128]

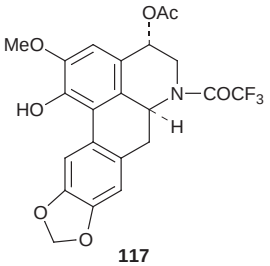
Oxidation of *N*-trifluoroacetylwilsonine **115a** and of *N*-trifluoroacetylnordomesticine **115b** with lead tetraacetate has afforded the 4 α-acetoxy compounds **116** and **117**, respectively,



115a $R^1 = R^2 = Me$
115b $R^1,R^2 = CH_2$



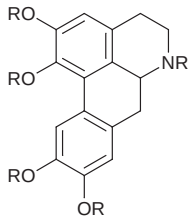
116



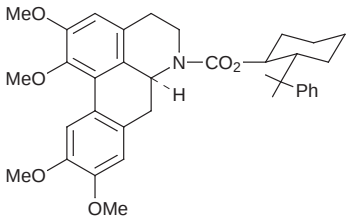
117

with no trace of the 4 β-isomers.[129] A kinetic study of the oxidation of boldine by singlet oxygen has been published.[130] Methods for the estimation of apomorphine, apocodeine and their glucuronides,[131,132] and of boldine[133] have been described. The acid-catalysed rearrangement of thebaine in mercaptans has yielded sulfur-containing derivatives of apomorphine and apocodeine (see section 17).

In syntheses of alkaloids of the group, racemic laudanosoline has been oxidised with alcoholic ferric chloride buffered with sodium acetate to *O*,*O*-didemethyllaurolitsine **118a**, which has been methylated to (±)-glaucine **118b**.[41] The (*S*)-2′-bromolaudanosine derivative **60** has been cyclised by tributyltin hydride



118a R = H
118b R = Me



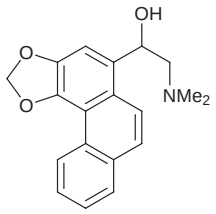
119

to (*S*)-*N*-2-*trans*-(α-cumenyl)cyclohexyloxycarbonylnorglaucine **119**, which on reduction with lithium aluminium hydride afforded (*S*)-glaucine **118b**.[42]

The pharmacological properties and physiological effects of actinodaphnine,[124] of *N*-methylactinodaphnine,[124] of apomorphine,[134–147] of boldine,[56] of isoboldine,[56] of bulbocapnine,[124] of *O*-methylbulbocapnine,[124] of cassythicine,[56] of dicentrine,[124] of guatterine,[56] of glaucine,[148] of hernovine,[124] of launobine,[124] of laurolitsine,[148] of *N*-methyllaurotetanine[56] and of pachystaudine[56] have been studied.

16.3 Phenanthrenes

N-Methylsecoglaucine (glaucine methine) has been isolated from *Phoebe minutiflora*[14] and the new alkaloid fenfangjine F **120** has been isolated from *Stephania tetrandra*.[59] Fenfangjine



120

F is the first phenanthrene alkaloid of the aporphinoid group to be discovered bearing a hydroxy group in the side-chain. The stereochemistry of the alcoholic group has not been determined.

Laurolitsine **121a** has been *N*-alkylated to the tertiary bases **121b**, **121c** and **121d** and solvolysis of these with aqueous ammonium acetate has given the phenanthrenes **122a**, **122b** and **122c**. Mannich condensation of these amino phenols with formaldehyde yielded the homologues **123b**, **123c** and **123d** of the alkaloid litebamine **123a**.[149]

16.4 Oxoaporphines

Oxoaporphine alkaloids have been isolated from the following plant species:

Annona cherimola[33]

liriodenine, lysicamine, oxoanolobine, oxoglaucine and oxoxylopine

Cassytha filiformis[123]

lysicamine

Guatteria lehmanii[150]

lysicamine

Illigera luzonensis[124]

dicentrinone and liriodenine

Magnolia obovata[125]

lanuginosine and liriodenine

Telitoxicum glaziovii[127]

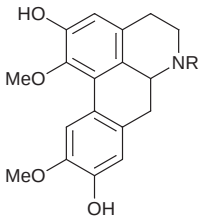
O-methylmoschatoline, splendidine and teliglazine **124**

Zizyphus jujuba[151]

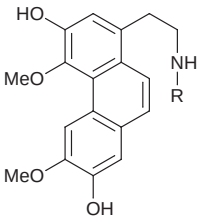
lysicamine.

The quaternary betaine teliglazine is a new alkaloid.

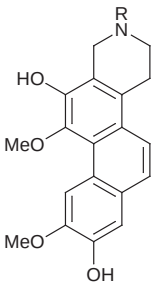
Dicentrinone and liriodenine have been found to inhibit significantly platelet aggregation.[124]



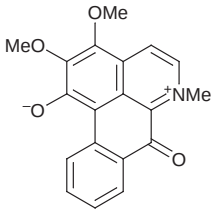
121a R = H
121b R = Pr^n
121c R = Pr^i
121d R = Bu^i



122a R = Pr^n
122b R = Pr^i
122c R = Bu^i



123a R = Me
123b R = Pr^n
123c R = Pr^i
123d R = Bu^i



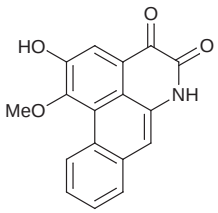
124

16.5 Dioxoaporphines

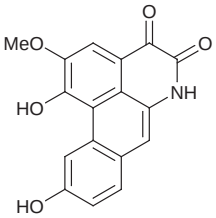
Dioxoaporphine alkaloids have been isolated from the following plant species, the two marked with asterisks being new alkaloids:

Aristolochia triangularis[34]

cepharadione A, 4,5-dioxodehydroasimilobine* **125** and triangularine I* **126**



125



126

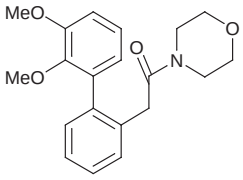
Telitoxicum glaxiovii[127]

dioxodehydroasimilobine **125** and ouregidione.

In an approach to the synthesis of alkaloids of this group the amide **127** was cyclised to **128a**, which was converted through **128b** into **128c**, but this was found to be unsuitable for further elaboration. However the benzocoumarin **129** was methylated to the ester **130a**, which was converted successively through the alcohol **130b**, the halide **130c**, the nitrile **130d**, the acid **130e** and the chloride **130f**, into the amide **131**, which when subjected to Friedel–Crafts cyclisation with oxalyl chloride gave dioxodehydrocorydine **133**, *via* the intermediate **132**.[152]

16.6 Aristolochic acids and aristolactams

Aristolochic acid D, aristolactams Ia, IIa, AIa, AII, AIIIa, BII and CII and the new 9-methoxyaristolactam Ia 6-(β-D-glucosylpyranosyl)-β-D-glucoside **134** have been isolated from *Aristolochia triangularis*.[34]



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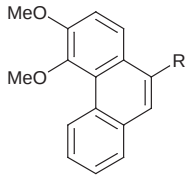
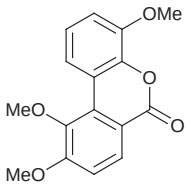


128a R = N O

128b R = OH
128c R = NH_2



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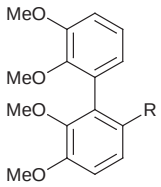
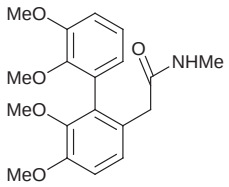


130a R = CO_2Me
130b R = CH_2OH
130c R = CH_2Cl
130d R = CH_2CN
130e R = CH_2CO_2H
130f R = CH_2COCl



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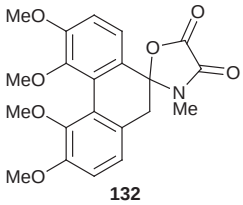

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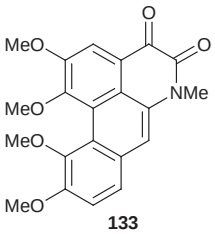
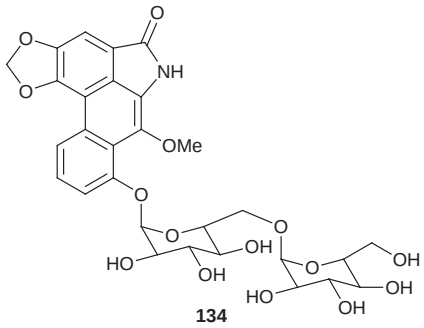


133

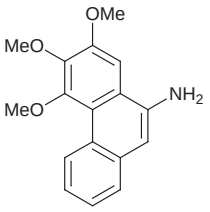


134

Although 9-aminophenanthrenes were found to be unsuitable materials for the synthesis of dioxoaporphines, they are easily converted into aristolactams. The amine **135** was converted into piperolactam C **136** by butyllithium and carbon monoxide in 43% yield.[153] In a new approach to the synthesis of aristolactams, suitably substituted 2-bromobenzoic acids **137** have been converted into *N*-[(diphenylphosphinoyl)methyl]benzamides **138**, which, when subjected to aryne-mediated cyclisation gave anions of 1*H*-isoindolinones **139** and these, in the presence of 2-bromoaryl aldehydes **140** afforded the arylidene derivatives **141**, which could be further cyclised by tributyltin hydride to *N*-benzylaristolactams **142a**, readily cleaved to aristolactams. In this way **137a** and **140a** were converted into cepharanone B **142b**; **137a** and **140b** were converted into taliscanine **142c**; **137a** and **140c** were converted into enterocarpam II **142d** and **137b** and **140b** afforded velutinam **142e**.[154–156]

16.6 Azafluoranthenes

Telitoxine has been isolated from *Telitoxicum glaziovii*.[127]



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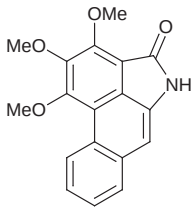

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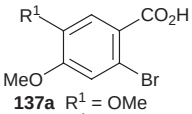
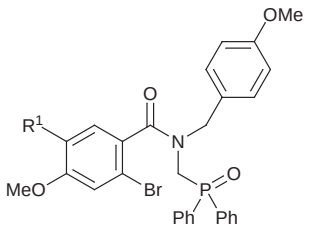


137a R^1 = OMe
137b R^1 = OCH_2Ph



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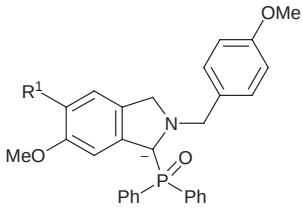

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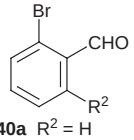
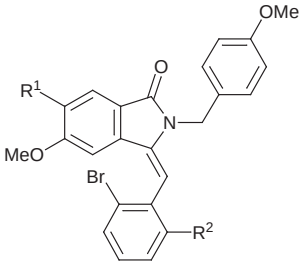
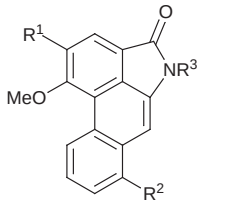
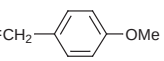


140a R^2 = H
140b R^2 = OMe
140c R^2 = OCH_2Ph



141



142a R^3 = CH_2  OMe

142b R^1 = OMe, R^2 = R^3 = H
142c R^1 = R^2 = OMe, R^3 = H
142d R^1 = OMe, R^2 = OH, R^3 = H
142e R^1 = OH, R^2 = OMe, R^3 = H

17 Alkaloids of the morphine group

Alkaloids of the morphine group have been isolated from the following plant species, the two marked with asterisks being new alkaloids:

Croton chilensis[157]

flavinantine, *O*-methylflavinantine and isosalutaridine

Glaucium fimbrilligerum[102]

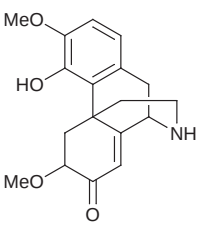
salutaridine

Papaver fugax[103]

salutaridine and thebaine

Papaver pseudo-orientale[81]

5,6-dihydronorsalutaridine* **143**



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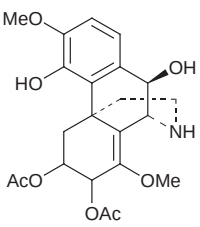


144

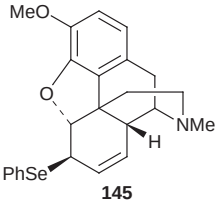
Stephania tetrandra[59]

fenfangjine G* **144**.

Fenfangjine G, which is a hydroxylated form of alkaloid FK 3000, is the first of 48 morphinan alkaloids to be found to bear an oxygen substituent at C-10), although such substitution is common in the rearranged hasubanonine sub-group.

Methods of detection and estimation of morphine,[159–161] of 6-*O*-acetylmorphine,[159] of dihydromorphine,[161] of codeine,[159] of dihydrocodeine,[161] of dihydronorcodeine,[161] of naloxone,[162] of naltrexone[163] and of nalmefene[164] have been reported.

A process for the solid state methylation of morphine to codeine using phenyltrimethylammonium salts has been described.[165] The preparation of pseudocodeine by the solvolysis of α-chlorocodide involves tedious and difficult separation from other isomers of codeine and gives poor overall yields. In an improved preparation of this compound codeine has been converted into the 6 β-selenide **145**, which on treatment with hydrogen peroxide is oxidised to the selenoxide **146**, which suffers a spontaneous [2,3]-sigmatropic rearrangement to give the 8β-selenooxy ether **147a**, which can be hydrolysed by potassium hydroxide to pseudocodeine **147b** with an overall yield of 38% from codeine.[166] Morphine hydrochloride has been shown to react with paraformaldehyde to give the 2-hydroxymethyl compound **148** in alkaline solution and to give the cyclic acetal **149**, together with 2,2′-methylenebismorphine, in neutral solution.[167]



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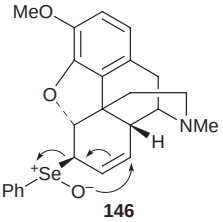

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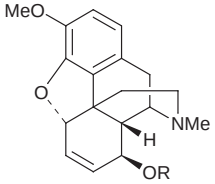
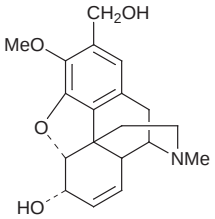


147a R = SePh
147b R = H



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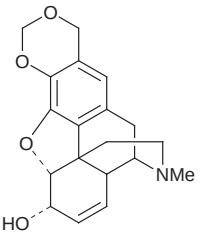
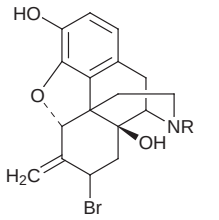


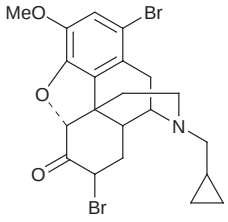
149

Naloxone and naltrexone, under the conditions of the Wittig reaction with (triphenylphosphonium)methylide have afforded products with physical properties corresponding to those previously reported, but shown to be their 3-*O*-methyl ethers rather than the 6-methylene compounds **150a** and **150b** previously claimed.[168] *O*-Methylnaltrexone reacts with bromine to give the 1,7-dibromide **151**, which with thiourea affords the aminothiazole **152a**, from which the bromine can be removed to give **152b**.[169] Naltrexone and naloxone have also been converted into their enol ethers **153a**–**d**, which are derivatives of dihydrothebaine.[170] Ketones such as **154a** have been prepared and these on treatment with hydrazine yield an inseparable mixture of the pyrazoles **154b** and **155a** and with phenylhydrazine to give a separable mixture of **154c** and **155b**.[171]

The preparation of northebaine from nordihydrocodeinone *via* nordihydrothebaine has been improved.[172] Thebaine **156a** is reduced to dihydrothebaine **157a** by diimide. However, 6-demethoxythebaine **156b** is not converted into deoxycodeine C **157b**, but into a mixture of deoxycodine D **158** and dihydrodeoxycodeine D **159** with this reagent.[173] Thebaine has been found to react as a dieneophile with the diene **160**, generated *in situ* by the thermal cleavage of the benzocyclobutene **161**. Of the two trisubstituted double bonds in **156a** that at the 8,14 position is less under the influence of the electron-donating methoxy group and the Diels–Alder reaction affords the adduct **162**; in the absence of the 8,14 double bond dihydrothebaine



150a R = CH_2—CH=CH_2
150b R = CH_2— 



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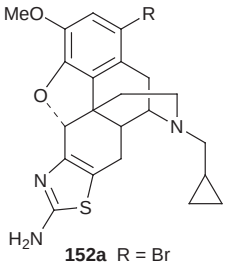
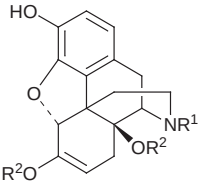
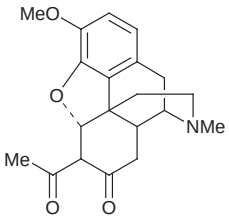


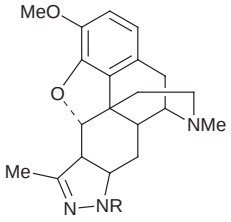
152a R = Br
152b R = H



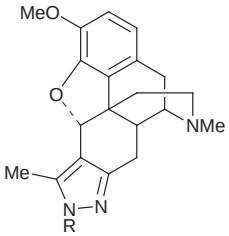
153a R^1 = CH_2—  , R^2 = Me
153b R^1 = CH_2—  , R^2 = Et
153c R^1 = $CH_2CH{=}CH_2$, R^2 = Me
153d R^1 = $CH_2CH{=}CH_2$, R^2 = Et



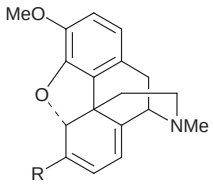
154a



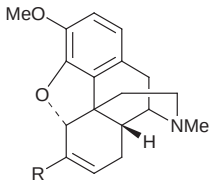
154b R = H
154c R = Ph



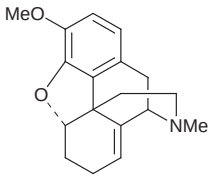
155a R = H
155b R = Ph



156a R = OMe
156b R = H
156c R = SCN



157a R = OMe
157b R = H



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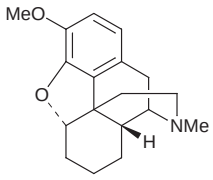

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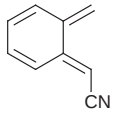

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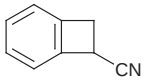

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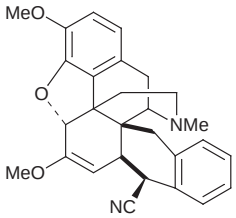

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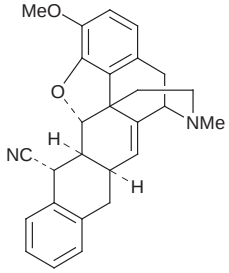

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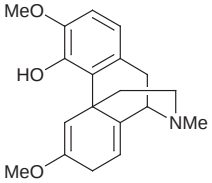

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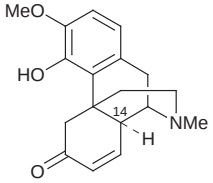

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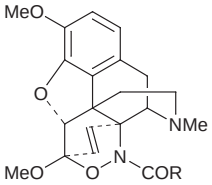

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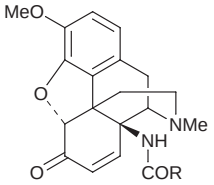

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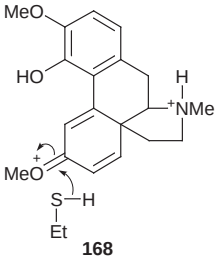

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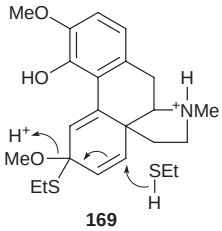

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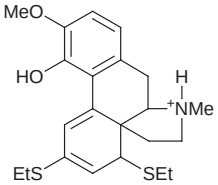

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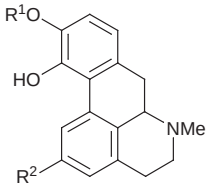


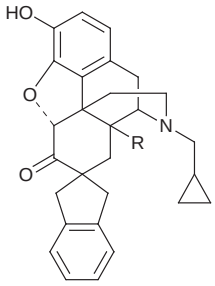
171a R^1 = Me, R^2 = SEt
171b R^1 = H, R^2 = SEt
171c R^1 = Me, R^2 = SCN

157a does not react. Similar addition of the diene to 6-demethoxythebaine **156b** occurs at the less hindered 6,7 double bond to give **163**. The reaction of deoxycodeine C **157b** with the diene has not been reported.[173] Acid-catalysed hydrolysis of dihydrothebaine-ϕ **164** under most conditions affords the kinetically controlled product, which is the ketone β-thebainone **165**, but conditions have been described that afford the thermodynamically more stable C-14 epimer of **165**.[174] Thebaine undergoes normal Diels–Alder reaction as a diene with acylnitroso compounds to give adducts **166**, hydrolysable by acids to the 14-substituted codeinones **167**.[175]

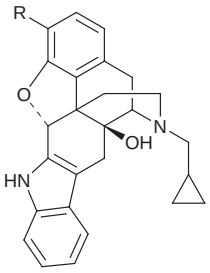
Thebaine is rearranged to morphothebaine by concentrated aqueous acids, but with methanesulfonic acid in ethanethiol the initial rearranged ion **168**, in the absence of water, reacts with the thiol to give **169** and then **170**, which is the product at 20 °C and is further rearranged at 90 °C to the apocodeine derivative **171a** after 30 minutes and to the apomorphine **171b** after two hours.[176] Similar reactions have been observed with *N*-propylnorthebaine.[177] Rearrangement of 6-isothiocyanato-6-demethoxythebaine **156c** in acids affords the derivative **171c**.[178]

Details of the preparation of the following have been given: morphine 3,6-diglucuronide,[179,180] the spiro compounds **172a** and **172b** and their naphthalene and perylene analogues,[181] *N*-

phenyl-14-hydroxydihydronorcodeinone dimethylene ketal,[182] and the 3-deoxynaltrindole analogues **173a**–**g**.[183] In addition a



172a R = H
172b R = OH

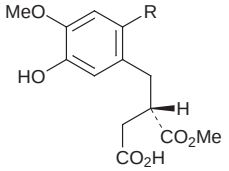


173a R = H
173b R = Me
173c R = CH=CH$_2$
173d R = Ph
173e R = *p*-hydroxyphenyl
173f R = *p*-anisyl
173g R = 2-furyl

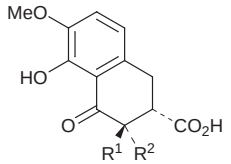
variety of patents have been published covering derivatives of morphine and codeine and of their 14-hydroxy derivatives[184–196] and of Diels–Alder adducts of thebaine.[197,198] The validity of some of these must be questionable as they cover compounds and processes well described many years ago.

A chiral synthesis of (+)-morphine, the mirror image of the natural alkaloid, has been reported. Stobbe condensation of isovanillin with dimethyl succinate, followed by catalytic reduction of the resulting unsaturated ester over a chiral rhodium catalyst afforded the diacid monoester **174a** in 94% enantiomeric excess. This, on bromination, gave **174b**, which was cyclised to the tetralone **175a**. Condensation of this with methyl formate yielded **175b**, which underwent Michael addition to methyl vinyl ketone to give **175c**, which cyclised to the lactol **176**. Internal aldol condensation of this was accompanied by hydrolysis to give **177**, the stereochemistry of which was determined by X-ray crystallography, and this was brominated to **178** and cyclised to **179**. Hydrogenation of this removed the ketonic carbonyl group, but reduction with sodium borohydride, followed by hydrogenation, yielded the ester **180a**, which was converted into the diazoketone **180b**, and this was cyclised by rhodium acetate to the pentacyclic ketone **181**. The oxime of this ketone, on Beckmann transformation, yielded the lactam **182**, which was *N*-methylated, hydrolysed and oxidised to **183a**. This was converted through **183b** into the α,β-unsaturated ketone **184**, which was reduced by lithium aluminium hydride to (+)-codeine **185a**, which gave (+)-morphine **185b** on demethylation.[199]

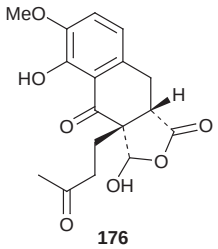
The analgesic properties,[200–239] antispastic effects[229] and pharmaco-dynamics[240–244] of morphine have been studied, as have the effects of the alkaloid on behaviour,[245–258] on immune responses,[259–264] on respiration,[265–267] on the cardiovascular system,[268–270] on the gastro-intestinal tract,[271,272] on locomotor activity,[273–275] on exercise endurance,[276] on learning,[277] on memory,[278] on cognitive performance,[279] on neurones,[280] on blood monocytes,[281] on platelets,[282] on recovery from coronary surgery,[283] on motion sickness,[284] on the expression of messenger RNA in the spinal cord,[285] on the production of proteins,[286] on the binding of DNA to proteins,[387] on apoptosis of splenocytes,[288] on the consumption of alcohol,[289] on the growth hormone receptor,[290] on opiate receptors,[291] on invertase activity,[90] on levels of oxytocin,[292] of interleukin-1β converting enzyme,[293] of nitric oxide,[294] of nitric oxide synthetase,[295] of firefly luciferase[296] and on the effects of amphetamine,[297] of apomorphine,[298] of bicuculline,[110] of cocaine,[297,299–301] of chlordiazepoxide,[302] of chlorpromazine,[302] of grisopam,[302] of nerisopam,[302] and of haloperidol.[252] The effects of L-type calcium channel blockers on the physiological effects of morphine have also been studied.[303] A



174a R = H
174b R = Br



175a $R^1 = R^2 = H$
175b $R^1 = H$, $R^2 = CHO$
175c $R^1 = CH_2CH_2COCH_3$, $R^2 = CHO$



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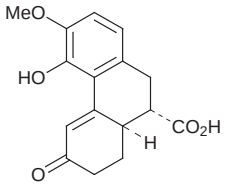

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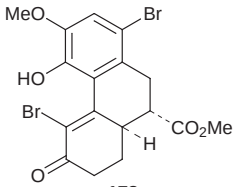

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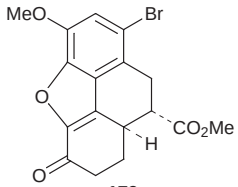

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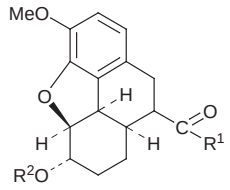
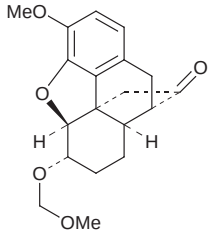


180a R^1 = OMe, R^2 = H
180b $R^1 = CHN_2$, $R^2 = CH_2OMe$



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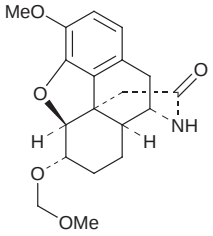

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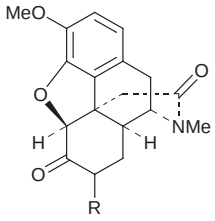
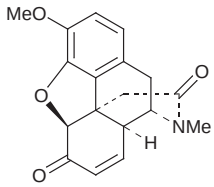


183a R = H
183b R = SePh



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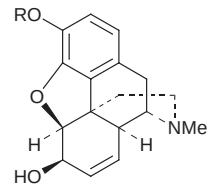


185a R = Me
185b R = H

patent has been claimed covering the use of the diclofenac salt of morphine for the relief of pain.[304]

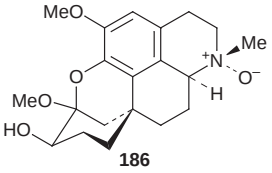
The morphine antagonist actions of naloxone have been studied,[306,306] as have the effects of this compound on behaviour,[256,300,308,309] on responses to stress,[310] on immune responses,[311] on neurones,[312] on opiate receptors,[313,314] on appetite,[315] on acute alcohol intoxication,[316] on cerebral blood flow,[270] on the release of histamine[317] and on the effects of benzodiazepines[318] and of methadone.[319]

The pharmacological and physiological effects of the following have also been studied: morphine 3-*O*-glucuronide,[320–323] morphine 6-*O*-glucuronide,[321–328] 6-*O*-acetylmorphine,[296] 3,6-*O*,*O*-diacetylmorphine,[296,328] codeine,[330–334] codeine glu-

curonide,[334] dihydrocodeine,[335] dihydromorphinone,[336] dihydrocodeinone,[337] 14-hydroxydihydromorphinone,[338] 14-hydroxydihydrocodeinone,[339,340] naltrexone,[270,305,309,341–356] *O*-methylnaltrexone,[357] nalbuphine,[358] nalmefene,[351,359] naltrindole,[348,351,360] binaltorphimine,[361] β-funaltrexamine,[362,363] *N*-chloracetyl-6 β-naltrexamine,[364] etorphine,[365,366] dihydroetorphine,[367] buprenorphine[319,368–385] and the morphinan alkaloid stephodeline.[386]

18 Phenethylisoquinolines

Merenderine and the new alkaloid robustamine *cis*-*N*-oxide **186** have been isolated from *Merendera robusta*.[387]



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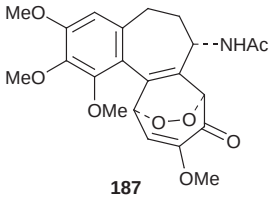
19 Colchicine and related alkaloids

Colchicine has been shown to undergo Diels–Alder addition of singlet oxygen to give the 8,12-*endo*-peroxide **187**, and a similar adduct has been formed with *N*-phenyl-1,2,4-triazoline



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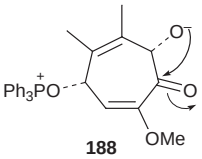

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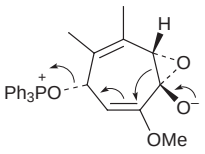

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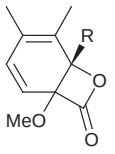
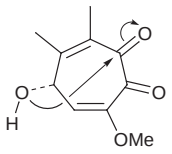


190a R = H
190b R = OH



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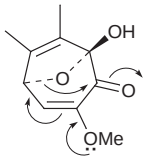

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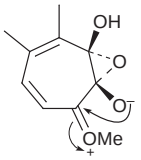

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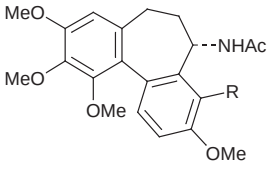
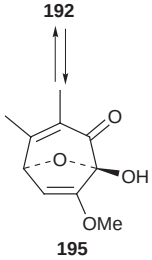


194a R = H
194b R = OH



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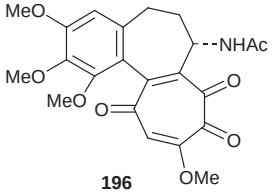
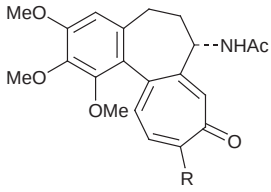


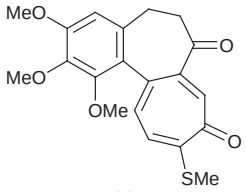
196

dione.[388] The peroxide **187** reacts with triphenylphosphine at 20 °C to give *O*-methyl-*N*-acetylcolchinol **194a**, probably *via* the intermediates represented by the part-structures **188**, **189** and **190a**, and on silica gel in methanol and dichloromethane it is transformed into the alkaloid androbiphenylline **194b**, presumably *via* **191**, **192**, **193** and **190b**. The intermediate of part-structure **192**, interconvertible with **195**, has been obtained, together with colchicine-8,12-dione **196**, on rearrangement of **187** with triethylamine. The dione **196** must arise by an oxidation, which probably involves the abstraction of hydride ion from **191**.[389]

10-*O*-*p*-Tolylsulfonylcolchiceine **197a** is converted into the halides **197b**, **197c** and **197d** on heating with lithium halides in methanol in the presence of boron trifluoride. 9-*O*-*p*-Tolylsulfonylisocolchiceine behaves similarly.[390] A patent has been published covering the preparation of heterocyclic compounds **199** from oxodeacetamidothiocolchicine **198**.[391] The unsaturated lactone **200** has been shown to undergo a novel addition reaction with 1,3-dienes, giving the ester **201** with 2,3-dimethylbuta-1,3-diene.[392] Beckmann transformation of the oxime of the ketone **198** involves ring expansion and contraction to give the isoxazole **202**.[393]



197a R = –OSO$_2$–Me
197b R = Cl
197c R = Br
197d R = I



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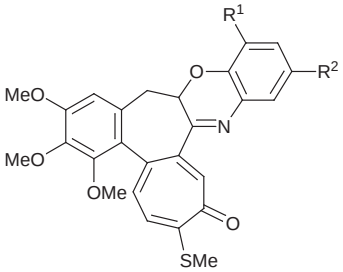
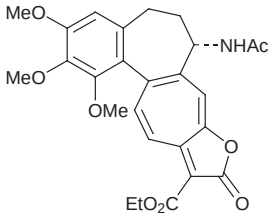


199a R^1 = Bu^t, R^2 = H
199b R^1 = F, R^2 = Bu^t



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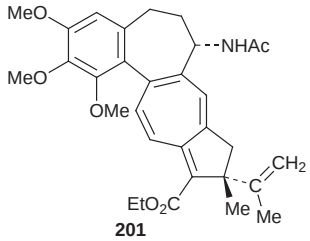

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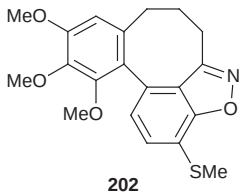


202

An X-ray crystallographic study of speciosine has confirmed the previously accepted structure of this alkaloid.[394]

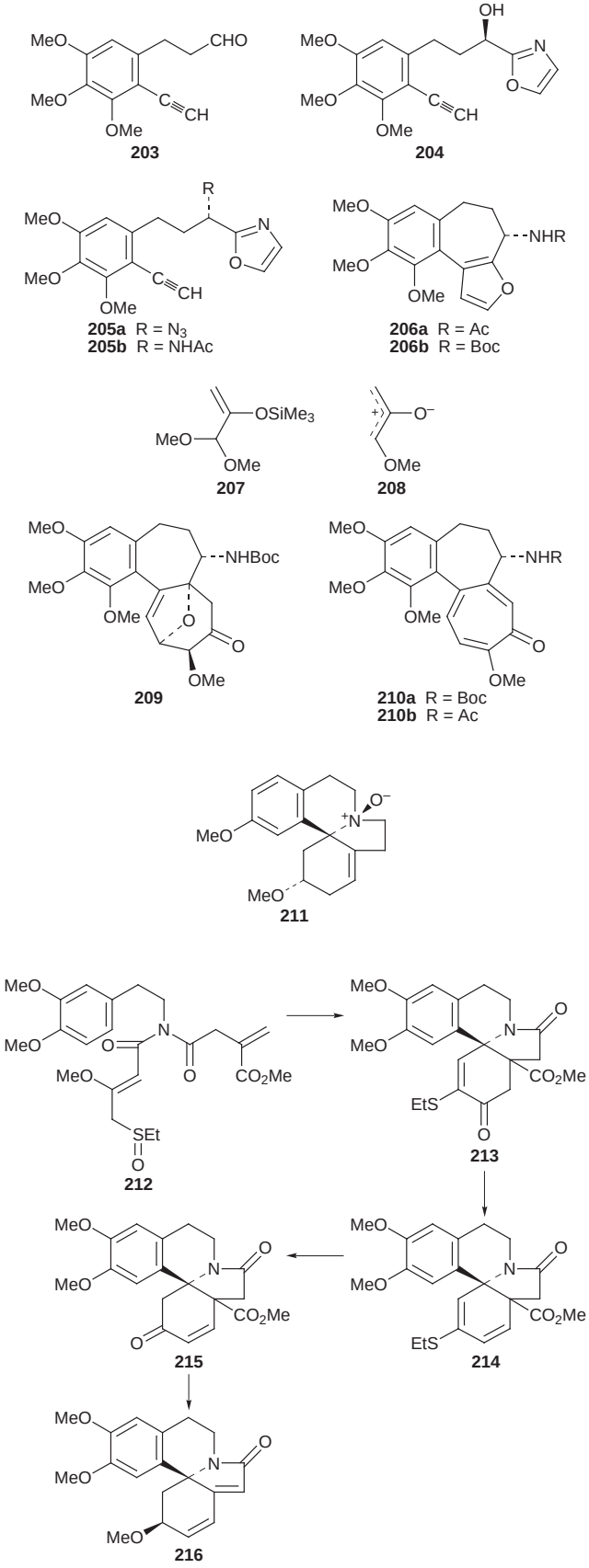
A new synthesis of colchicine started from the aldehyde **203**, which, with the anion of the borane complex of oxazole, afforded the racemic alcohol **204**. This was oxidised and chirally reduced to the (*R*)-form in 90% enantiomeric excess. This was converted through the azide **205a** into the acetylamino compound **205b**, which was thermally cyclised to **206a**. The related **206b** was then treated with the mesomeric zwitterion **208** (prepared from **207**), when [4 + 3]-cycloaddition afforded **209**. (The wrong regioisomer was formed from **206a** and **208**). Elimination of the oxide bridge from **209** yielded **210a**, which was hydrolysed and acetylated to colchicine **210b**.[395]

The pharmacological properties and physiological effects of colchicine,[396–404] of 2-*O*-demethylcolchicine,[401] of 3-*O*-demethylcolchicine,[401] of isocolchicine,[398] of colchiceine[398] and of colchamine[405] have been studied.

20 *Erythrinan* alkaloids

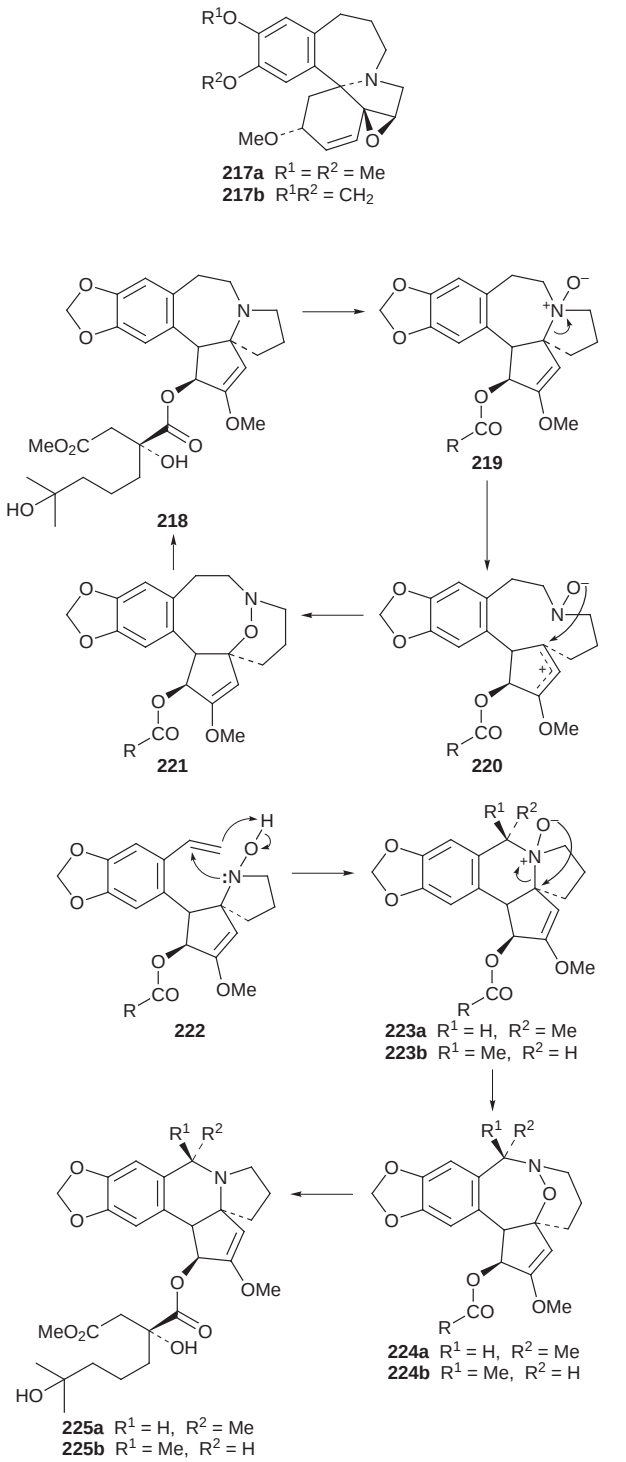
20.1 Erythrinan alkaloids

Cocculine and the new alkaloid cocculine *N*-oxide **211** have been isolated from *Cocculus laurifolius*.[35]



Scheme 1

In a new synthesis of the erythrinane system the imide **212** has been cyclised in one process, by trifluoroacetic anhydride and triethylamine, followed by boron trifluoride, to **213** as a single isomer in 83% yield. This was converted into the diene **214**, which was hydrolysed to the unsaturated ketone **215**, previously converted into (±)-erysotramidine **216** (Scheme 1).[406]



Scheme 2

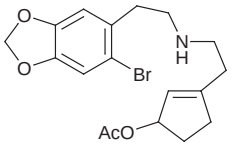
20.2 Homoerythrinan alkaloids

Wilsonirine **217a** and the new alkaloid fortunine **217b** have been isolated from *Cephalotaxus fortunei*.[407]

20.3 Cephalotaxine alkaloids

11-Hydroxycephalotaxine has been isolated from *Cephalotaxus fortunei*.[407] A review of the alkaloids of this group has been published.[408]

Homoharringtonine **218** has been oxidised to a mixture of the diastereoisomeric *N*-oxides **219**. Both of these on heating at 105 °C afforded the same products, namely **221** (formed *via* **220**) and **224a** and **224b**, presumably formed from the product of Cope degradation of **222** (not isolated) *via* **223a** and **223b**. These cyclic '*N*-oxide ethers', when reduced with zinc and



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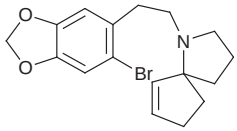

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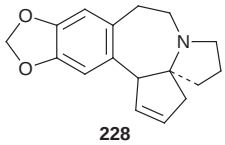

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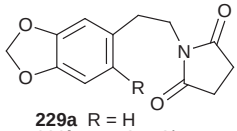
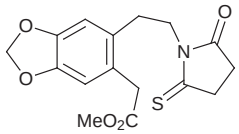
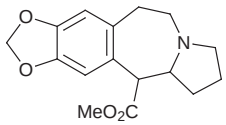


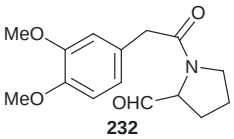
229a R = H
229b R = CH_2Cl
229c R = CH_2CN
229d R = CH_2CO_2Me



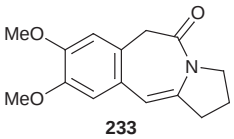
230



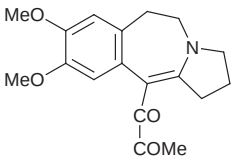
231



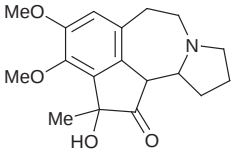
232



233



234



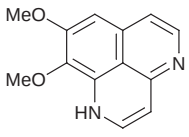
235

acetic acid, afforded homoharringtonine **218** and its isomers **225a** and **225b** (Scheme 2). All of these compounds showed much weaker activity than homoharringtonine against P-388 leukaemia cells.[409]

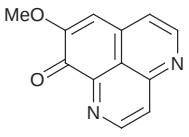
In approaches to the synthesis of cephalotaxine the amine **226** has been cyclised to **227** and further to **228** over palladium,[410] and **229a** has been converted through **229b**–**d** into **230**, the carbanion of which was cyclised to **231**.[411] Homoveratrylamine and (±)-prolinol have afforded the amide **232**, which was cyclised to **233**, and reduction of this lactam and condensation of the product with pyruvic acid yielded the diketone **234**, which was cyclised to the ring system **235**, isomeric with that found in cephalotaxine.[412]

21 Other isoquinolines

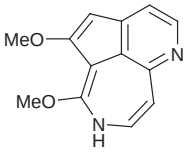
Aaptamine **236**, demethoxyoxyaaptamine **237** and the clearly related new base aaptosine **238**, have been isolated from the



236



237



238

Okinawan sponge *Aaptos aaptos*. Aaptosine does not show the potent toxicity against P-388 and A-549 tumour cells exhibited by aaptamine and demethyloxyaaptamine.[413]

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