β-Phenylethylamines and the isoquinoline alkaloids

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This review covers β-phenylethylamines and isoquinoline alkaloids that are derived from them, including further products of oxidation, condensation with formaldehyde and rearrangement, some of which do not contain an isoquinoline system, together with naphthylisoquinoline alkaloids, which have a different biogenetic origin. The occurrence of the alkaloids, with the structures of new bases, together with their reactions, syntheses and biological activities are reported. The literature from July 2000 to June 2001 is reviewed, with 495 references cited.

1 β-Phenylethylamines

β-Phenylethylamines and amides have been isolated from the following plant species, the eleven marked with asterisks being new alkaloids:

Allium tuberosum[1]
N-cis-feruloyldopamine (tuberosine A)* **1**, *N-trans*-feruloyldopamine (tuberosine B)* **2** and *N-trans*-coumaroyltyramine* **3**
Annona glabra[2]
N-trans-coumaroyltyramine and *N-trans*-feruloyltyramine
Aristolochia mollissima[3]
N-cis-coumaroyltyramine* **4** and *N-trans*-coumaroyltyramine
Balanites aegyptica[4]
N-cis-feruloyltyramine and *N-trans*-feruloyltyramine
Mollinedia marliae[5]
N-trans-feruloyltyramine
Paliurus ramossisimus[6]
paliurine A* **5a**, paliurine B* **5b**, paliurine C* **6**, paliurine D* **7a**, paliurine E* **7b** and paliurine F* **8**
Turbinicarpus alonsoi[7]
hordenine, *N*,*O*,*O*-trimethyldopamine and *N*-methyltyramine
Zanthoxylum integrifolium[8]
alfileramine and integramine* **10**

Of the new alkaloids integramine **10** can be regarded as the product of Hofmann degradation of alfileramine and the paliurines (above) have obvious structural similarities to integerrimine **9** and waltherines A, B and C, reported in the previous review though, unlike these four compounds, they are not derived from tyrosine.

The chromium tricarbonyl complex of 1,2,3-trimethoxybenzene reacts with the anion of acetonitrile to give, after removal of the chromium tricarbonyl, the nitrile **11a**, which can be reduced to mescaline **11b**.[9]

The tartrate esters of ephedrine and pseudoephedrine have been found to be useful derivatives for the resolution of synthetic racemic mixtures of these alkaloids.[10] Ephedrine has been acylated at the amino group rather than at the hydroxy group by *N*-acetylaminobenzenesulfonyl chloride[11] and by 4-nitrobenzoyl chloride.[12] Reduction of the dibenzylaminopropiophenone **12** with borane has afforded 80% excess of the *erythro* alcohol, hydrogenolytic cleavage of which yielded[18] fluoronorephedrine **13**.[13] Methods of estimating ephedrine and of norephedrine in plasma have been reported.[14]

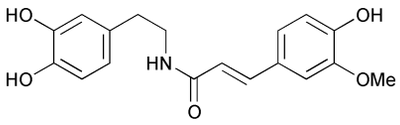
The pharmacological properties and physiological effects of ephedrine[15–18] and of pseudoephedrine[19–21] have been studied.

2 Isoquinolines

Simple isoquinoline alkaloids have been isolated from the following plant species:

Alangium lamarckii[22]
salsoline
Annona purpurea[23]
thalifoline
Iseia luxurians[24]
iseluxine **14**
Turbinicarpus alonsoi[7]
pellotine

 DOI: 10.1039/b009713f



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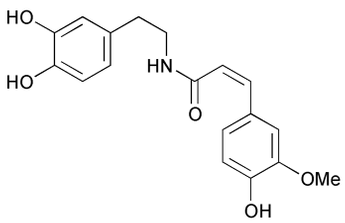

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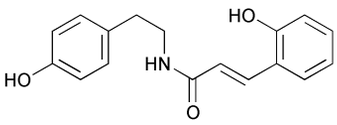

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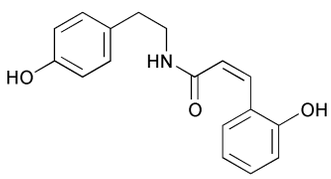

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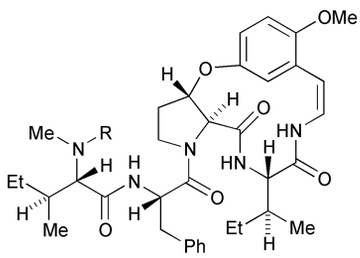
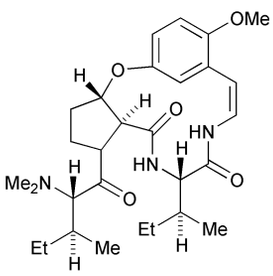
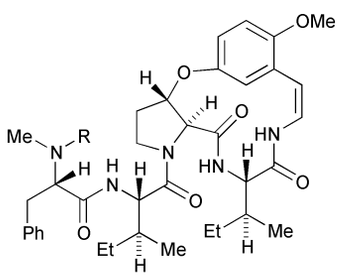
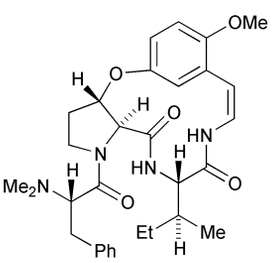




5a R = Me
5b R = H

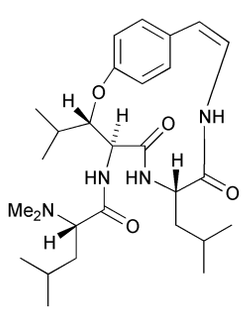
6





7a R = Me
7b R = H

8



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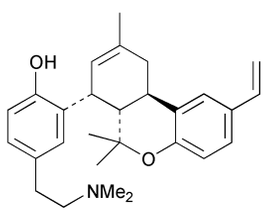

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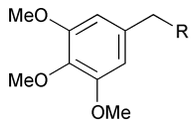
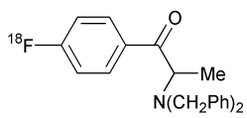


11a R = CN
11b R = CH_2NH_2



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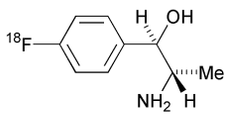

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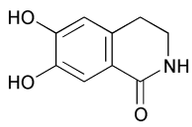
Iseluxine, which is a new alkaloid, is the first of this group to be found with unsubstituted hydroxy groups at positions 6 and 7 and is a simple product of cyclisation of dopamine.



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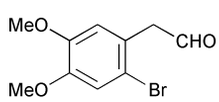
2-Bromohomoveratric aldehyde **15** has been condensed with the amino-alcohol **16** to give the cyclic carbinolamine ether **17**, reduction of which afforded the amino alcohol **18**. This has been further condensed with a variety of aldehydes to give the cyclic carbinolamine ethers **19a**–**19e**, which have been cyclised by butyllithium, followed by a Lewis acid, to give the (1*R*)-tetrahydroquinolines **20** in three-fold excess over their (1*S*) isomers. The (1*R*) compounds derived from **19b**–**19e** have been further converted into (*R*)-carnegine **21b**, (*R*)-*O*-methylarmepavine **21c**, (*R*)-laudanosine **21d** and (*R*)-homolaudanosine **21e** and the non-chiral *O*-methylcorpalline **21a** has been prepared in the same way.[25]



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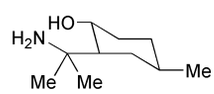

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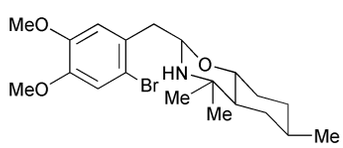

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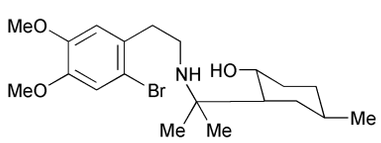
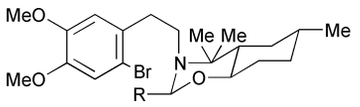
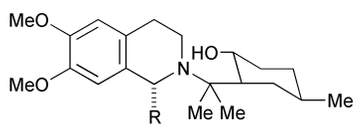


18

The imine **22**, prepared from 2-allylveratraldehyde and 4-methoxy-1-naphthyltyramine, on treatment with methyllithium in the presence of the chiral ligand **23** forms, through a three-component complex, the (*R*) chiral amine **24**. Hydroboration of this affords the alcohol **25**, which can be cyclised to the tetrahydroisoquinoline **26a**. This can be cleaved by ammonium cerium^{III} nitrate and acetic anhydride to **26b**, hydrolysis of which yields (*R*)-salsolidine **26c**.[26] A synthesis of (*S*)-salsolidine **27** in 86% enantiomeric excess has been achieved by an enantioselective protonation of the related lithium salt in the presence of the chiral amine **28**.[27] A simple tetrahydrooxazaphenalene lactone containing the ABC ring system of the alkaloid stephaoxocanine **29** and the related excentricine has been synthesised.[28]



19a R = H
19b R = Me
19c R = CH_2–(3,4-dimethoxyphenyl)
19d R = CH_2–(3,4,5-trimethoxyphenyl)
19e R = CH_2CH_2–(3,4,5-trimethoxyphenyl)



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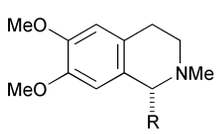
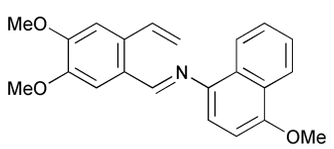


21a R = H
21b R = Me
21c R = CH_2–(3,4-dimethoxyphenyl)
21d R = CH_2–(3,4,5-trimethoxyphenyl)
21e R = CH_2CH_2–(3,4,5-trimethoxyphenyl)



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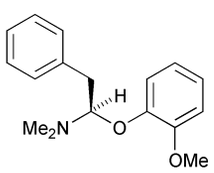

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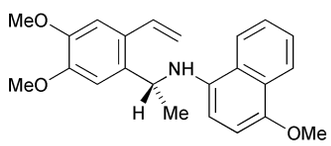

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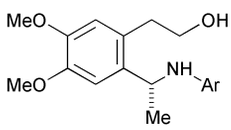

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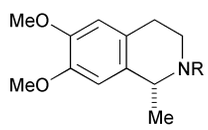


26a R = 4-methoxy-1-naphthyl
26b R = Ac
26c R = H

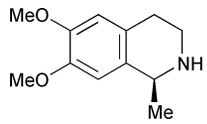
Syntheses of the isomeric 4-aryltetrahydroisoquinoline alkaloids cherylline **30a** and latifine **30b** have been achieved by closure of the isoquinoline ring between an aryl halide and an amide enolate.[29]

3 Naphthylisoquinolines

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

Ancistrocladus ealaensis[30]
ancistroealaine A* **31** and ancistroealaine B* **32**

Ancistrocladus likoko[31]
ancistrolikokine A* **33**, ancistrolikokine B* **34**, ancistrolikokine C* **34** and korupensamine A



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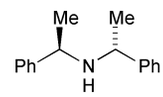

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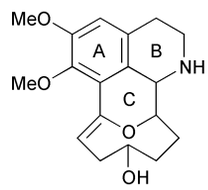

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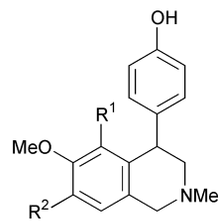
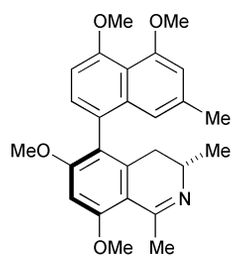


30a R^1 = H, R^2 = OH
30b R^1 = OH, R^2 = H

Ancistrocladus tectorius[32]
ancistrotectoriline A* **36**, ancistrotectoriline B* **37**, 6-*O*-methyl-4′-*O*-demethylancistrocladine* **38** and 6-*O*-methyl-4′-*O*demethylhamatine* **39**

Triphyophyllum peltatum[33]
dioncophylline D, 8-*O*-methyldioncophylline D, dioncophyllinol D and 8-*O*-methyldioncophyllinol D* **40a**



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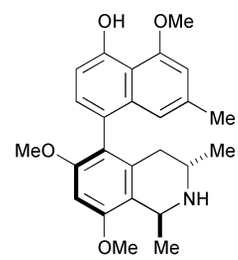

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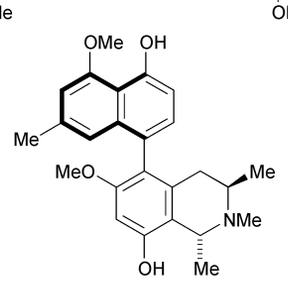

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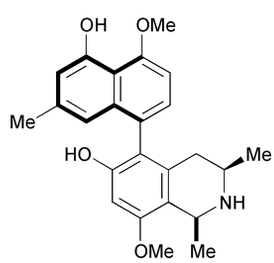

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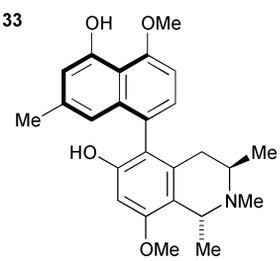
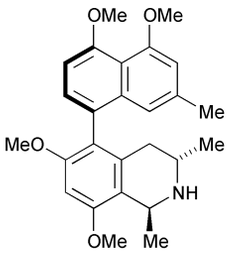


35

Following the assignment of the structure **40a** to 8-*O*-methyldioncophyllinol D, it was shown that dioncophylline D and 8-*O*-methyldioncophylline D have similar 7,6′-coupled structures **41a** and **41b** respectively rather than the 7,8′-coupled structures previously assigned to these alkaloids. Similarly dioncophyllinol D has been reformulated as **40b**.[33]

Jozipeltine A **44**, a dimer of dioncopeltine A **42a** not so far encountered in plants, has been prepared. Oxidation of *N*,*O*-dibenzyldioncopeltine A **42b** with silver oxide gave the quinone **43**, which was reduced to the diphenol and debenzylated to



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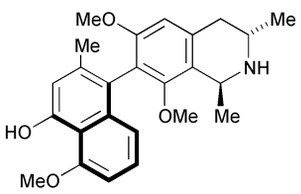

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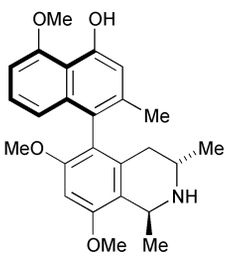

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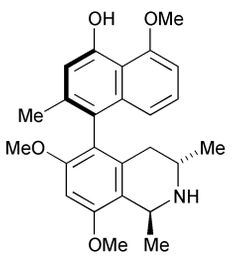

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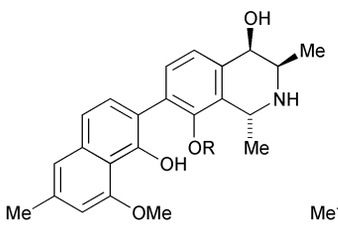
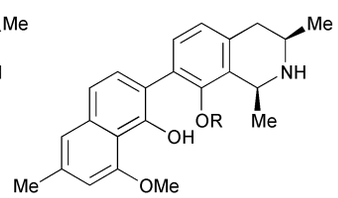


40a R = Me
40b R = H



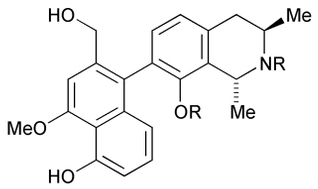
41a R = H
41b R = Me

jozipeltine A **44**. This compound shows greatly enhanced antimalarial activity compared with dioncopeltine A, its IC_{50} against *Plasmodium falciparum* being 42 ng ml^{-1}.[34] A new, nonsymmetric 6′,8-dimer, jozimine B **46** has been prepared in good yield by the nonphenolic oxidative dimerisation of ancistrocladine **45** by lead tetraacetate and boron trifluoride; the imine **47** is also produced as a minor product in this reaction. This dimer also has greatly enhanced antimalarial activity compared with its parent monomer.[35] Lead tetraacetate and phenyliodine^{III} bis(trifluoroacetate) have been used to achieve a convenient one-step dimerisation of dioncophylline B **48** to the unnatural dimer jozimine D **49**, of korupensamine A to michellamine A and of korupensamine B to michellamine C.[36]

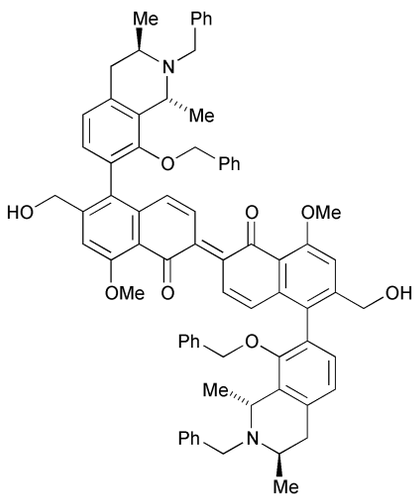
The chromium carbonyl complex **50a** has been combined with the naphthylboronic acid **51** to give, after removal of the chromium carbonyl, the phenylnaphthalene **52**, the cyclic ketal of which was opened to give **53a**, which was converted through **53b** into **54a**, **54b** and **54c**. Bischler–Napieralsky cyclisation of **54c** afforded the dihydroisoquinoline **55**, which was reduced to *O*,*O*-dimethylkorupensamine A, **56a** and its C-1 epimer.[37] A similar sequence of reactions starting from **50b** gave, after removal of the isopropyl groups, korupensamine A **56b** and its C-1 epimer.[38] The amine **57** has been converted into a mixture of the tetrahydroisoquinolines **58** and **59** and **58** has been further converted through **60a**, **60b** and **60c** into the 7-bromo compound **61**. Coupling of this with the tributylstannylnaphthalene **62** by the Stille process afforded *N*-benzyl-*O*,*O*-bis(methoxymethyl)dioncophylline B **63**, which was hydrolysed and debenzylated to dioncophylline B **48**.[39]

4 Benzylisoquinolines

1-Benzylisoquinoline alkaloids have been isolated from the following plant species, that marked with an asterisk being a new alkaloid:



42a R = H
42b R = CH_2Ph



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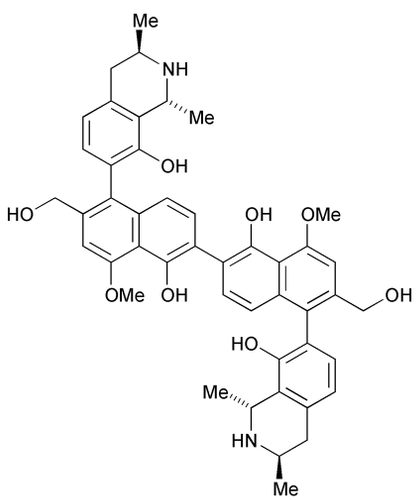

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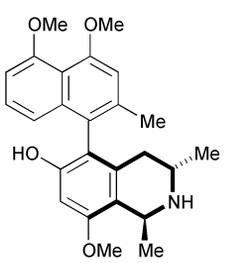
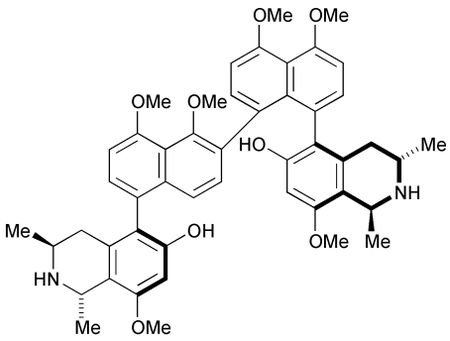


45

Annona purpurea[23]
reticuline
Hernandia nymphaefolia[40]
reticuline
Isopyrum thalictroides[41]
reticuline
Miliusa velutina[42]
reticuline



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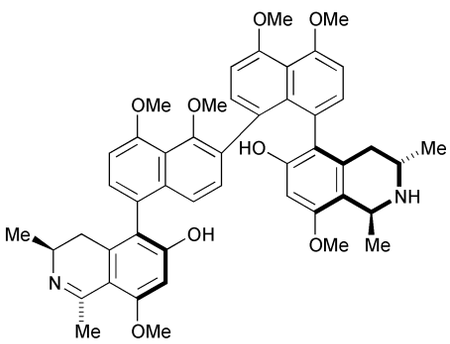

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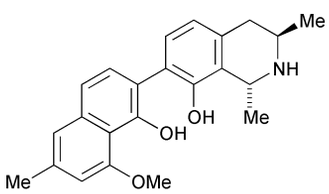

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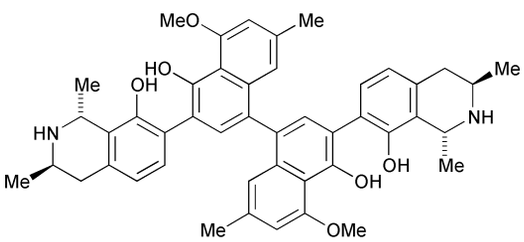
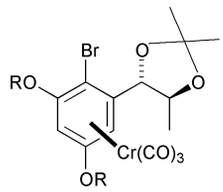


49

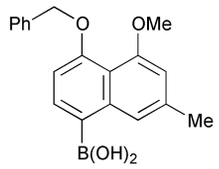
Monodora junodii[43]
norgorchacoine* **64**
Papaver triniifolium[44]
crykonisine

The structures of polysignine **67a** and methoxypolysignine **67b** have been confirmed by their preparations from *O*-methylarmepavine **65a** and laudanosine **65b** by the treatment of these alkaloids with methyl chloroformate, followed by reduction of the resulting carbamates **66a** and **66b** catalytically and with lithium aluminium hydride.[45]

Nitration of *N*-formylnorlaudanosine **68** with nitric and acetic acids has afforded the dinitro compound **69**, together with the simpler compounds **74** and **75**. Direct nitration at C-5 and C-2′ with hydrolysis of the C-6 methoxy group to give **69** is unexceptional, but compounds **74** and **75** must be formed by scission of the isoquinoline system, presumably through the intermediate **70**, which could then suffer ring opening to the iminium salt **72**, hydrolysis of which would give **74** and **75**. The possibility that the dinitro compound could be **71**, formed by recyclisation of the iminium salt **72** *ortho* rather than *para* to the methoxy group, was eliminated by studies of NMR spectra.[46]



50a R = Me
50b R = iPr



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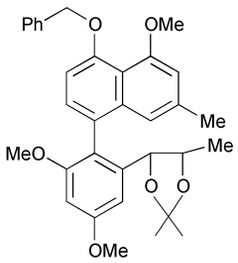

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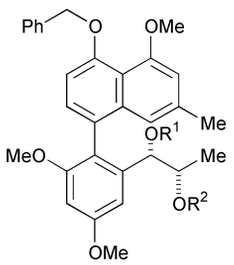
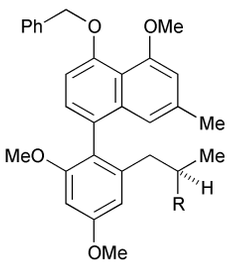
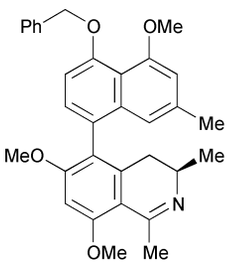


53a R^1 = iPr R^2 = H
53b R^1 = H R^2 = Bu^tSiMe_3



54a R = N_3
54b R = NH_2
54b R = NHAc



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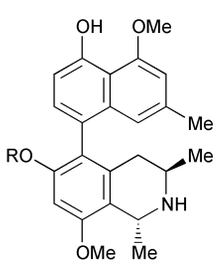
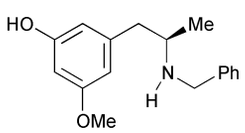


56a R = Me
56b R = H



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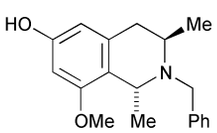

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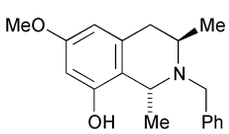

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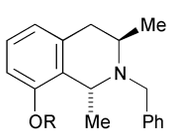
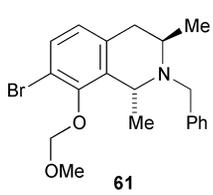
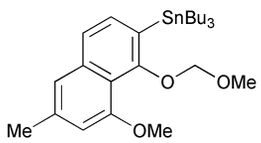


60a R = Me
60b R = H
60c R = CH_2OMe



61

Reaction of the lithium salt of 3,4-dimethoxybenzyl 1-methoxy-2-naphthyl sulfoxide with 6,7-dimethoxy-3,4-dihydroquinoline *N*-oxide has given the hydroxamine **76**, from which (±)-laudanosine **65b** was prepared by reduction.[47] (*R*)-(+)-Laudanosine **21d** has been synthesised from **19d** (see section 2).[25] 1,2-Dehydrolaudanosine hydrochloride reacts with the bromoketone **78** to give the pyrroloisoquinoline **79a**, which may be converted into the aldehyde **79b**, by the Vilsmeier reaction. Hydrolyis of the methanesulfonyl ester **79b** yields the hemiacetal **80**, mild oxidation of which affords *O*,*O*,*O*-trimethyllamellarin G **81**. Oxidation of **80** with manganese dioxide gives only a poor yield of **81**, the main product being the quinone **82**.[48]



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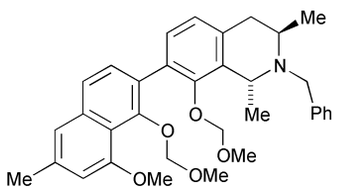

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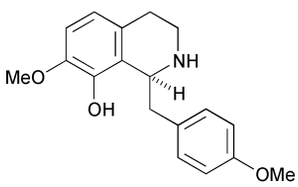

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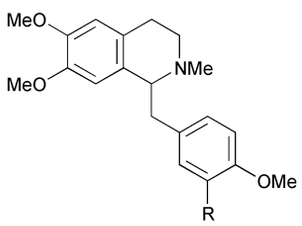
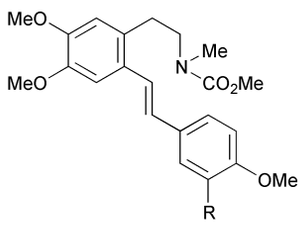
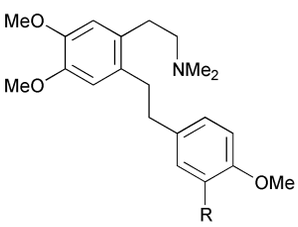


65a R = H
65b R = OMe



66a R = H
66b R = OMe



67a R = H
67b R = OMe

The pharmacological properties and physiological effects of papaverine[49–54] and of atracurium[55–57] have been studied.

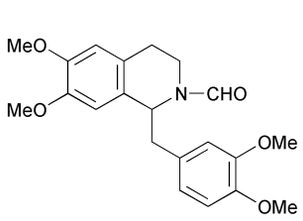
5 Bisbenzylisoquinolines

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

Guatteria boliviana[58]
(−)-antioquine* **83**, guatteboline***84**, pangkorimine, philogaline***85**, puertogaline A* **86a**, puertogaline B* **86b** and sepeerine

Hernandia nymphaefolia[40]
thalicarpine and vateamine 2′β-*N*-oxide

Isolona ghesquireina[59]
chondrofoline, (−)-curine and isochondodendrine



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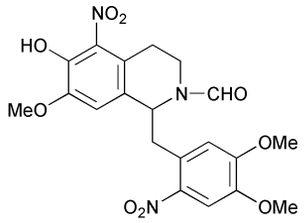

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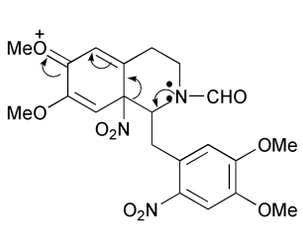

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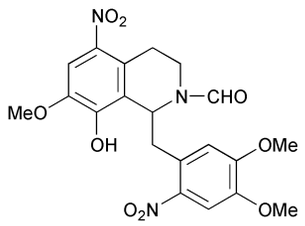

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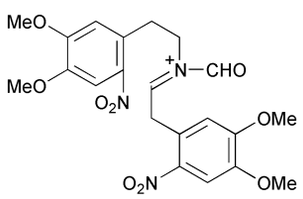

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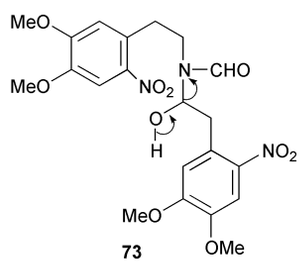

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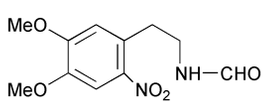

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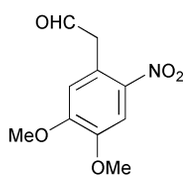

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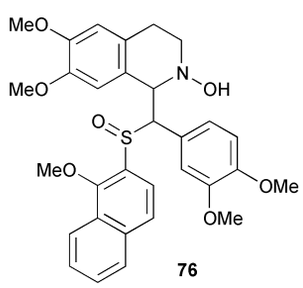

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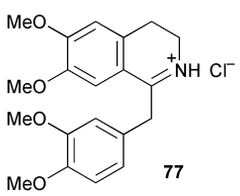

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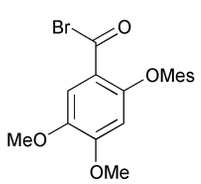

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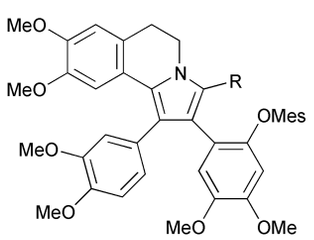


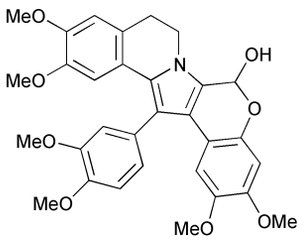
79a R = H
79b R = CHO

Isopyrum thalictroides[41]
isopyruthaldine* **87**, isopythaldine***88** and isothalmidine* **89**

Sciadotenia toxifera[60]
cavanine* **90**

Thalictrum orientale[61]
fangchinoline

(−)-Antioquine is a new alkaloid, although the (+)-isomer has been encountered previously. The structures of the new



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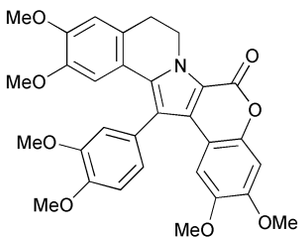

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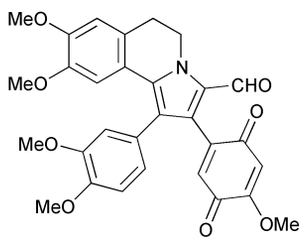

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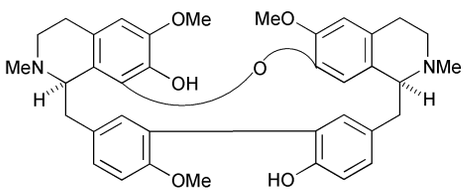

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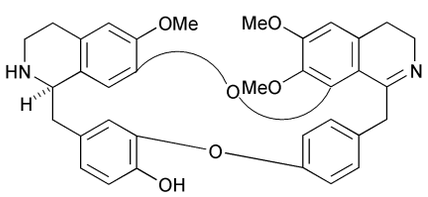


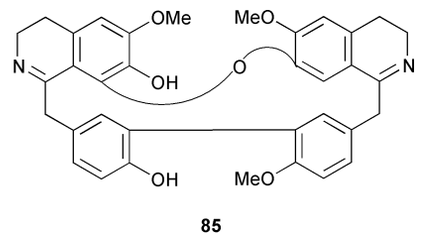
84

alkaloids of the group have been determined on the basis of their NMR spectra and optical properties alone. The structures assigned to the alkaloids of *Isopyrum thalictroides* bear no obvious relationship to those of other alkaloids recently isolated from the same species. Isothalmidine **89** is the first bisbenzylisoquinoline to be reported with a head-to-tail biphenyl linkage. Isopyruthaldine **87** and isopythaldine **88** are likewise unusual in that they purportedly are tail-to-tail diners linked through a methylene group rather than directly or through oxygen as in all other cases. Presumably their biogenesis must involve condensation of two different benzylisoquinolines with formaldehyde or equivalent. Their nearest structural analogues are the head-to-tail dimers cycloatjehine and cycloatjehenine, in which the units are linked through -O-CH_2-. Further study of the of the structures of these alkaloids would be welcome.

A review of the bisbenzylisoquinoline alkaloids has been published.[62] The pharmacological properties and physiological effects of (−)-antioquine,[58] of cepharanthine,[64,65] of chondrofoline,[59] of curine,[59] of isochondodendrine,[59] of guatteboline,[58] of *N*-methylberbamine,[63] of philogaline,[58] of puertogalines A and B,[58] of tetrandrine,[66–80] of tiliacorine,[81] and of tubocurarine[82–85] have been studied.

6 Benzopyrrocolines

The 2′-bromobenzyl-3,4-dihydroisoquinolines **91a** and **91b** have been cyclised, by heating with potassium carbonate, to the



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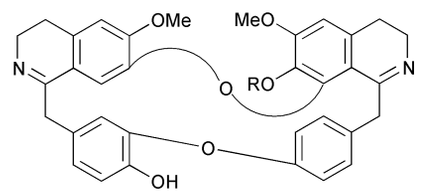
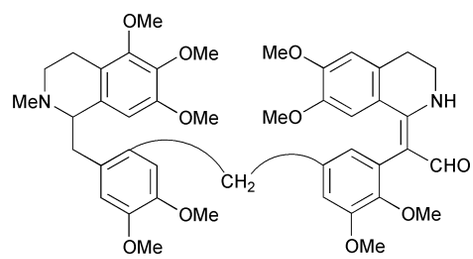


86a R = H
86b R = Me



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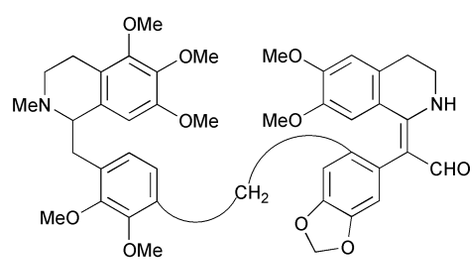

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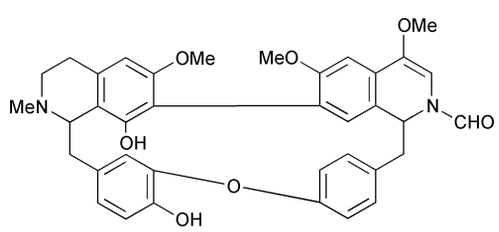

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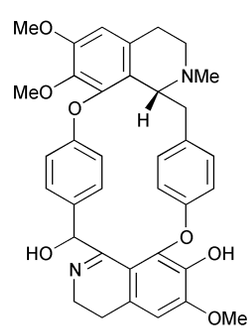
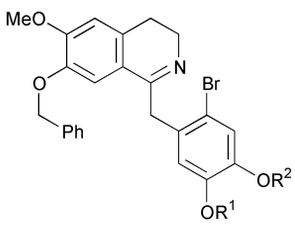
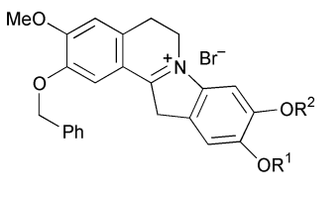


90

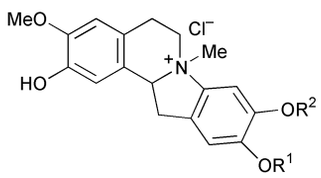
indolo[2,1-*a*]dihydroisoquinolinium salts **92a** and **92b**, which have been reduced catalytically and *N*-methylated to the benzopyrrocoline alkaloids (±)-cryptaustoline **93a** and (±)-cryptowoline **93b**.[86]



91a $R^1 = R^2 = Me$
91b $R^1 R^2 = CH_2$



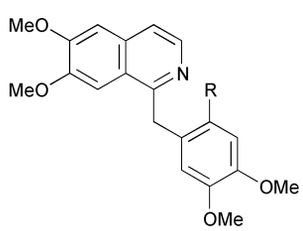
92a $R^1 = R^2 = Me$
92b $R^1 R^2 = CH_2$



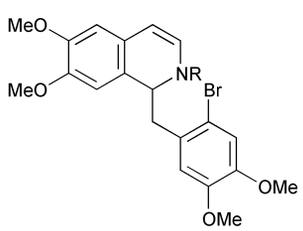
93a $R^1 = R^2 = Me$
93b $R^1 R^2 = CH_2$

7 Pavines and isopavines

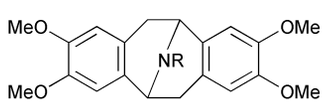
Bromination of papaverine **94a** to 2′-bromopapaverine **94b**, followed by reduction with tributyltin hydride, gave 2′-bromo-1,2-dihydropapaverine **95a**, which with ethyl chloroformate gave the carbamate **95b**. This was cyclised by tetraphenylpalladium in the presence of sodium formate to *N*-ethoxycarbonylpavine **96a**, which was reduced by lithium aluminium hydride to (±)-argemonine **96b**.[87] In a related process the same alkaloid was synthesised from the methiodide of **94b** by a radical cyclisation, followed by reduction and *N*-methylation.[88]



94a R = H
94b R = Br



95a R = H
95b $R = CO_2Et$

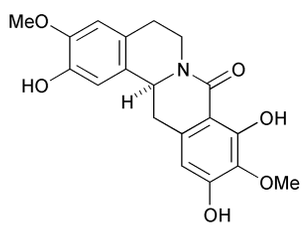


96a $R = CO_2Et$
96b R = Me

8 Berberines and tetrahydroberberines

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

Annona glabra[2]
dehydrocorydalmine and kikemanine
Asteropyrum cavaleriei[89]
berberine, berberubine and palmatine
Isopyrum thalictroides[41]
columbamine and palmatine
Lindera glauca[90]
canadine (tetrahydroberberine)
Papaver triniifolium[44]
cheilanthifoline, isocorypalmine, sinactine and *N*-methylsinactine
Polyalthia longifolia[91]
8-oxopolyalthiaine* **97**
Rollinia leptopetala[92,93]
discretamine and tetrahydrojatrorrhizine
Thalictrum acutifolium[94]
acutiaporberine* **98**
Thalictrum orientale[61]
berberine
Zanthoxylum taediosum[95]
isocorypalmine, kikemanine, scoulerine, tetrahydropalmatine and *cis*-*N*-methyltetrahydropalmatine



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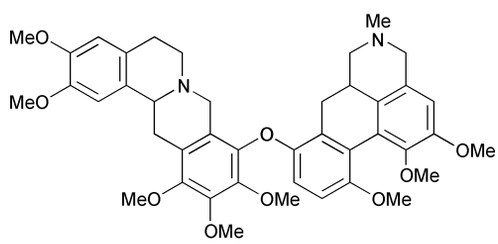


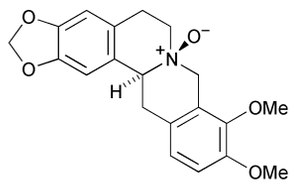
98

Acutiaporberine **98** is the first reported example of a dimer of an aporphine alkaloid and a tetrahydroberberine alkaloid similar to the bisbenylisoquinolines, aporphine–benzylisoquinoline dimers and aporphine dimers.

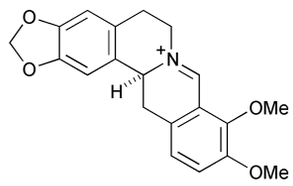
The influence of various media on the fluorescence of berberine chloride and implications for assays of the alkaloid[96] and the absorption and reduction of berberine at the mercury electrode[97] have been studied.

trans-Canadine *N*-oxide **99**, when subjected to the Polonovski–Potier reaction has been shown to give a mixture of 7,8-dehydrocanadine **100** and the isomeric 13,14-dehydro compound **101**, but in the presence of potassium cyanide 8β-cyano-canadine **102a** is formed. Both 8β-cyanocanadine and 7,8-dehydrocanadine on treatment with methyl iodide yield 8β-methylcanadine **102b** Under similar conditions, in the absence or presence of potassium cyanide, *cis*-canadine *N*-oxide **103** gives only 7,8-dehydrocanadine **100**, though on neutralisation of the reaction product small amounts of 5α-hydroxycanadine **104a** and 5β-hydroxycanadine **104b** are also formed. Similar results have been obtained with the *N*-oxides of thalictricavine and xylopinine.[98]

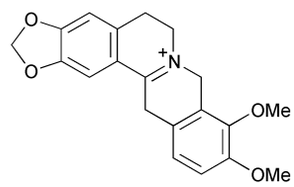
The treatment of the 2′-bromobenzyltetrahydroisoquinoline **105a** with *n*-butyllithium affords the tetrahydroberberine **107a**. 8-Oxotetrahydropalmatine **106**, though not isolated from the reaction products, is assumed to be an intermediate in this reaction since it independently reacts very rapidly with *n*-butyllithium to give **107a** in high yield. Under similar conditions **105a** reacts with *tert*-butyllithium to give only **108** and with *sec*-butyllithium to give the analogue of **108**, together with



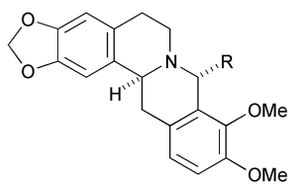
99



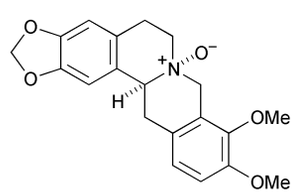
100



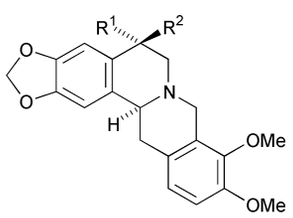
101



102a R = CN
102b R = Me

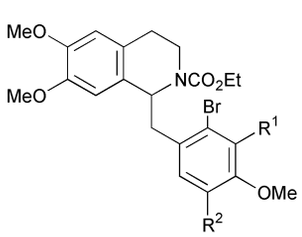


103

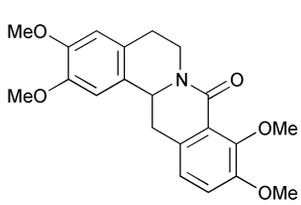


104a R^1 = OH, R^2 = H
104b R^1 = H, R^2 = OH

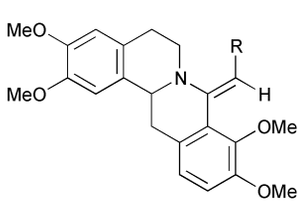
109. With methyllithium **105a** yields **107b**, which is reduced by sodium borohydride to **110a**. In a similar manner (±)-coralydine **110b** has been prepared from **105b**.[99]



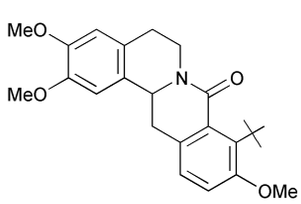
105a R^1 = OMe, R^2 = H
105b R^1 = H, R^2 = OMe



106



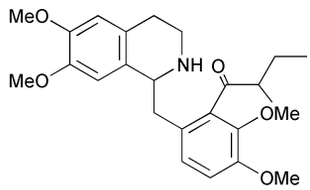
107a R = nPr
107b R = H



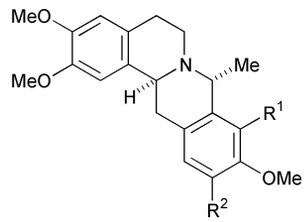
108

The 3-methoxytetrahydroisoquinoline **111** reacts with *O*-methyleugenol **112** and boron trifluoride to give **113**, which may be oxidised by osmium tetroxide to the diol **114** and then further by periodic acid to the aldehyde **115a**. Reduction of this to the alcohol **115b**, followed by hydrolysis and debenzylation affords the amino-alcohol **116**, which is cyclised to (±)-schefferine **117** by the Mitsunobu reaction.[100] 2-(2′-Bromophenylethyl)isocarbostyrils **118** have been cyclised to 8-oxoberberines **119** in good yield by tributyltin hydride.[88]

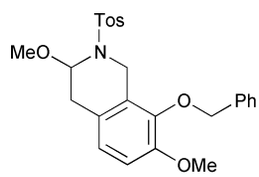
The pharmacological properties and physiological effects of berberine,[101–109] of canadine,[110,111] of stepholidine,[110,112] of



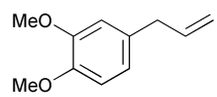
109



110a R^1 = OMe, R^2 = H
110b R^1 = H, R^2 = OMe



111



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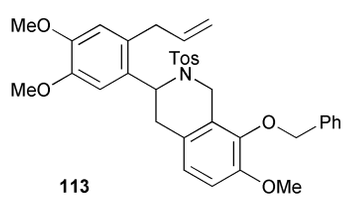
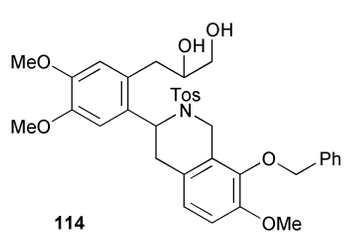


113



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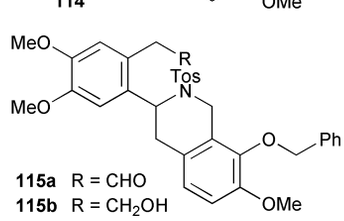


115a R = CHO
115b R = CH_2OH

tetrahydropalmatine[113–115] and of benzyltetrahydropalmatine[116] have been studied.

9 Protopines

Alkaloids of the protopine group have been isolated from the following plant species:

Glaucium corniculatum[117]
allocryptopine and protopine
Glaucium flavum[117]
allocryptopine and protopine
Zanthoxylum integrifolium[8]
allocryptopine and pseudoprotopine

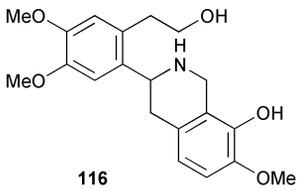
10 Phthalide–isoquinolines

α-Narcotine has been isolated from *Papaver triniifolium*.[44] *N*-Substituted derivatives of nornarcotine, such as **120**, have been prepared as potential adjuvants for vaccines[118] and simpler analogues, such as **121**, have been shown to act as modulators of the $GABA_A$ receptor.[119]

The physiological effects of bicuculline have been studied.[120–126]

11 Spirobenzylisoquinolines

The new alkaloid 8-*O*-acetylcorysolidine **122** has been isolated, together with corysolidine and isoochotensine, from *Corydalis ochotensis*.[127]



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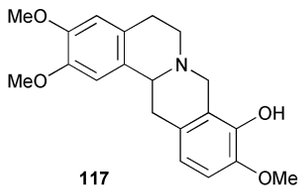

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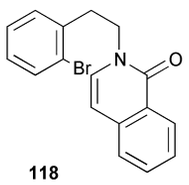
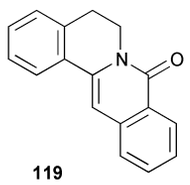


118



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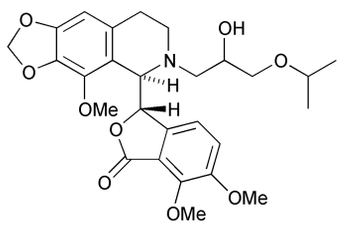

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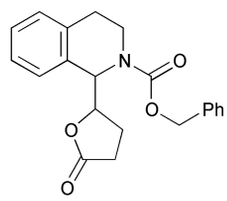

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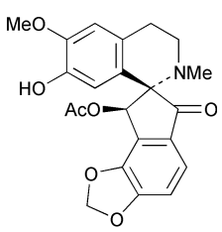
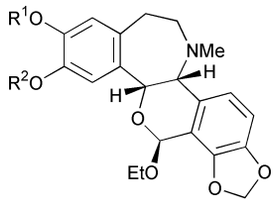


122

12 Rhoeadines

Rhoeadine, rhoeagenine, oreodine and oreogenine have been isolated from *Papaver triniifolium*, together with the new alkaloids *O*-ethylrhoeagenine **123a** and *O*-ethyloreogenine **123b**, which may be artefacts.[44]



123a $R^1 R^2 = CH_2$
123b $R^1 = R^2 = Me$

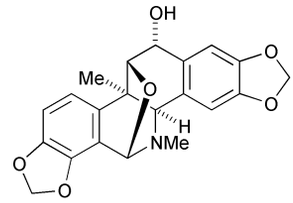
13 Benzophenanthridines

Benzophenanthridine alkaloids have been isolated from the following plants species, that marked with an asterisk being a new alkaloid:

Corydalis incisa[128]
corynoline, acetylcorynoline, 6-oxocorynoline, corynoloxine, 12-hydroxycorynoloxine* **124** and luguine
Glaucium flavum[117]
chlerythrine and sanguinarine

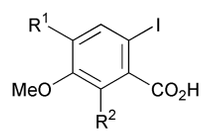
The conformation of chelidonine in deuteriochloroform has been studied by NMR spectroscopy.[129] *O*-(4-[^{18}F]-Fluorobenzoyl)chelidonine has been prepared for possible use as an antitumour agent.[130]

Reaction of the iododimethoxybenzoic acid **125a** with the naphthylamine **126** gives the amide **127a**, the methoxymethyl derivative of which **127b** is cyclised in good yield by palladium^{II}

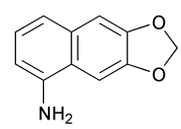


124

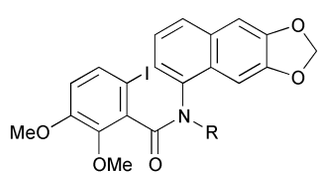
acetate and triphenylphosphine to the benzophenanthridine **128a**, together with a small amount of the alternative benzazepine **129**.[131,132] The lactam **128a** may be hydrolysed to **128b**, which is convertible through **131** into norchelerythrine **130a** by previously described methods. The trifluoromethylsulfonyloxy group has been shown to be as good a leaving group as iodine in this process.[131] Nornitidine **131b** may be prepared in a similar manner from **125b**.[131,132] A similar cyclisation of **127c** yields **128c**, which has been converted into chelerythrine **132**.[133] In approaches to alternative syntheses of benzophenanthridine alkaloids the isoquinolone **133** has been cyclised by acids to the simple unsubstitued analogue of **128c**.[134]



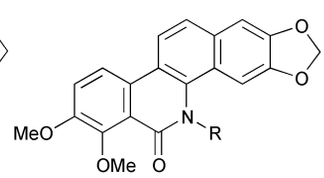
125a $R^1 = H$, $R^2 = OMe$
125b $R^1 = OMe$, $R^2 = H$



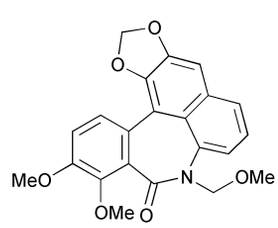
126



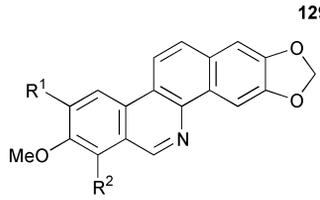
127a R = H
127b R = CH_2OMe
127c R = Me



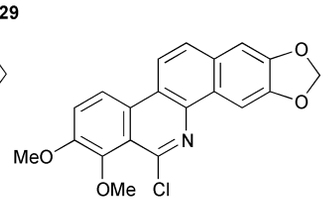
128a R = CH_2OMe
128b R = H
128c R = Me



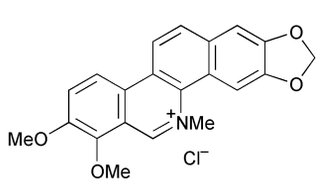
129



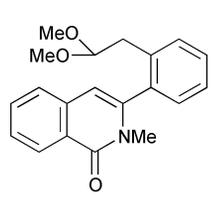
130a $R^1 = H$, $R^2 = OMe$
130b $R^1 = OMe$, $R^2 = H$



131



132

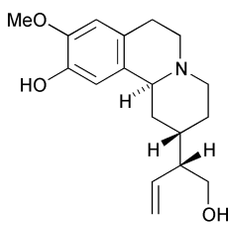


133

The physiological effects of chelerythrine[135] and of sanguinarine[136,137] have been studied.

14 Emetine and related alkaloids

Alangiside, alangine **134**, cephaeline, 2′-*N*-(1-deoxy-D-fructopyranosyl)-cephaeline, 10-*O*-demethylcephaeline, isocephaeline, neocephaeline, protoemetine, protoemetinol, psychotrine, tubulosine, 1′,2′-dehydrotubulosine, deoxytubulosine and isotubulosine have been isolated from *Alangium lamarckii*.[22] Alangine is reported as an alkaloid for the first time. In the last review the structure **134** was incorrectly assigned to neocephaeline.

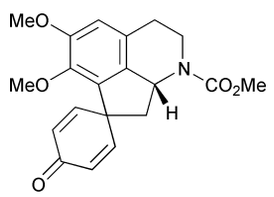


134

15 Aporphinoid alkaloids

15.1 Proaporphines

The proaporphine alkaloid stepharine has been isolated from *Annona glabra*[2] and from *Annona purpurea*[23] and the new alkaloid promucosine **135** has been isolated from *Annona purpurea*.[23]



135

15.2 Aporphines

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

Annona glabra[2]
anonaine, *N*-formylanonaine, annobraine*__136a__, nordomesticine and nornuciferine

Annona purpurea[233]
apoglaziovine, isocorydine, lirindine, norglaucine, norpurpureine, northalbaicaline, romucosine F* **137**, romucosine G* **138** and thalicsimidine

Asteropyrum cavaleriei[89]
magnoflorine

Fissistigma glaucescens[138]
xylopine and *N*-acetylxylopine

Glaucium corniculatum[117]
corydine, isocorydine, glaucine and thalicmidine

Glaucium flavum[117]
corydine, isoboldine, isocorydine and glaucine

Hernandia nymphaefolia[40]
N-(*N*-methylcarbamoyl)-*O*-methylbulbocapnine* **139**, hernandaline and laurotetanine

Isopyrum thalictroides[41]
isocorydine

Lettowianthus stellatus[139]
lettowianthine* **136a** and 11-methoxylettowianthine* **136b**

Lindera glauca[90]
boldine, norboldine, nantenine and 3-chloro-*N*-formylnornantenine* **140**

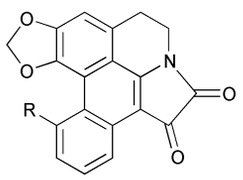
Miliusa velutine[42,140]
isocorydine, isocorydine-*N*-oxide* **141** and norcorydine

Rollinia leptopetala[92]
anonaine and roemerine

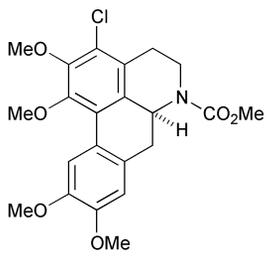
Stephania dinklagei[141]
corydine

Thalictrum acutifolium[94]
acutiaporberine* **98**

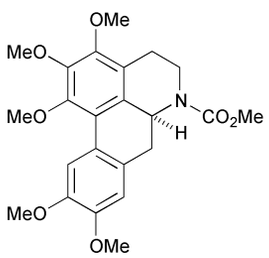
Thalictrum orientale[61]
fuzitine



136a R = H
136b R = OMe



137



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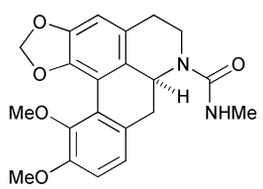

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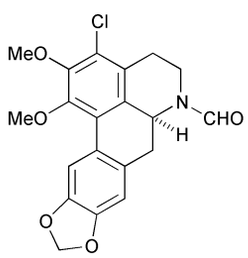

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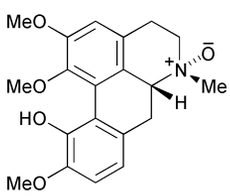
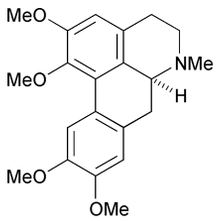


141

Annobraine and lettowianthine, isolated from different species, have been assigned the same structure **136a**. The separation and identification of the components of a mixture of nine aporphine alkaloids by a coupled system of high pressure liquid chromatography and NMR spectroscopy has been demonstrated.[142]

Glaucine **142** has been demethylated by hydrobromic acid at room temperature to a mixture of lirioferine **143a**, thaliporphine **144a**, *N*-methyllaurotetanine **144b** and bracteoline **143b**, though better yields were obtained at elevated temperatures.[143] Bischler–Napieralsky ring closure of the amide **145** has given the dihydroisoquinolinium salt **146**, which was reduced to **147a**, and on treatment with methyl chloroformate this yielded **147b**, which was cyclised by tributyltin hydride to give (±)-cathaformine **148**.[144] The efficacy of various oxidising agents in the dimerisation of dehydrowilsonirine **149** to bipowine **150** and the further oxidation of this to the extended quinone bipowinone **151** have been studied.[145]

The pharmacological properties and physiological effects of boldine,[146–149] of dicentrine,[150] of nantenine and of apomorphine[151–169] have been studied. Two glucuronides of apomorphine have been prepared[170] and several (*R*)-aporphines related to apomorphine have been prepared by ring expansion



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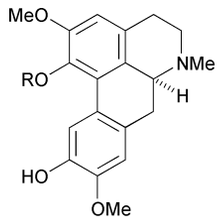
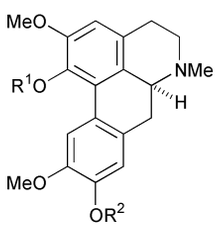
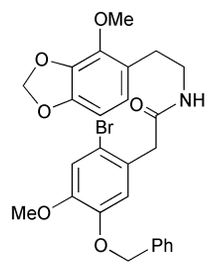


143a R = H
143b R = Me



144a R^1 = H, R^2 = Me
144b R^1 = Me, R^2 = H



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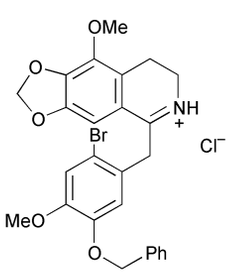

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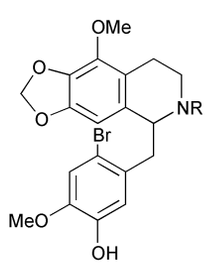
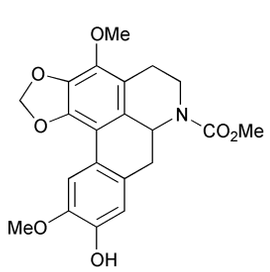


147a R = H
147b R = CO_2Me



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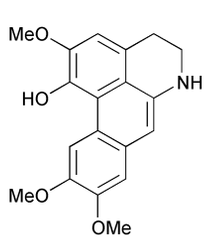

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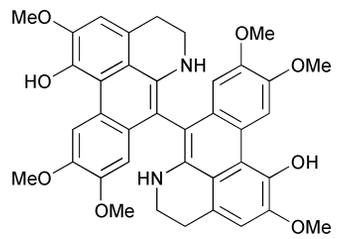

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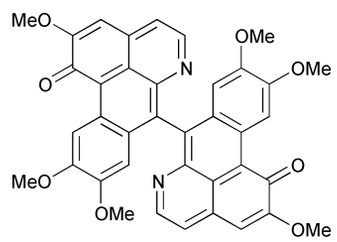

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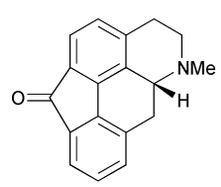
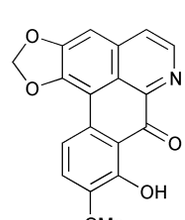


152

Hernandia nymphaefolia[40]
oxohernangine
Lindera glauca[90]
lysicamine
Miliusa velutina[42]
liriodenine
Stephania dinklagei[141]
dicentrinone, liriodenine, *N*-methyliriodendronine **154a** and *N*,2-*O*-dimethylliriodendronine **154b**



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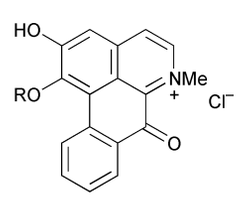


154a R = H
154b R = Me

of the ketone **152** in the quest for activity at serotonin 5-HT_{1A} and 5-HT_7 and dopamine D_{2A} receptors.[171]

15.3 Oxoaporphines

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

Annona glabra[2]
liriodenine and lysicamine
Annona purpurea[23]
liriodenine, lysicamine, oxoglaucine and oxopurpureine
Fissistigma glaucescens[138]
atherospermidine, fissiceine* **153**, liriodenine, kuafumine, oxocrebanine and oxoglaucine
Glaucium flavum[117]
corunnine
Guatteria boliviana[58]
lanuginosine

15.4 Dioxoaporphines

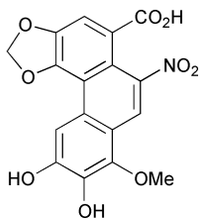
Dioxoaporphine alkaloids have been isolated from the following plant species:

Aristolochia mollissima[3]
cepharadione A and 4,5-dioxodehydroasimilobine
Fissistigma balansae[172]
noraristolodine and norcepharadione B
Fissistigma glaucescens[18]
noraristolodione and norcepharadione B
Fissistigma oldhamii[171]
noraristolodione and norcepharadione B

15.5 Aristolochic acids

Aristolochic acids and their esters have been isolated from the following plant species, that marked with an asterisk being a new acid:

Aristolochia curcurbitifolia[173]
7-hydroxyaristolochic acid* **155** and aristolochic acid III methyl ester
Aristolochia kaempferi[174]
aristolochic acid Ia methyl ester
Aristolochia mollissima[3]
aristolochic acids I, II and IVa, aristoloterpenates I and III and aristophyllide A

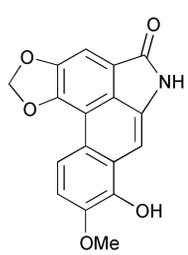


155

15.6 Aristolactams

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

Aristolochia curcurbitifolia[173]
cepharanone C* **156**
Aristolochiia kaempferi[174]
aristoliukine C
Aristolochia mollissima[3]
aristolactam *N*-β-D-glucoside, aristolactams AII and AIIIa, aristolactam C *N*-β-D-glucoside* **157** and aristoliukines A and B
Fissistigma balansae[172]
aristolactams AII, AIIIa, BII, BIII, and FII, enterocarpam I, goniothalactam, piperolactams A and C and stigmalactam* **158**
Fissistigma glaucescens[138]
aristolactams AII, BII and BIII, goniothalactam and piperolactam A
Fissistigma oldhamii[171]
aristolactams AII, AIIIa, BII, BIII and FII, enterocarpam I, goniothalactam, piperolactams A and C and stigmalactam **158**



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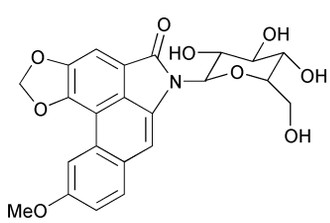
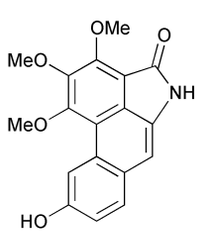


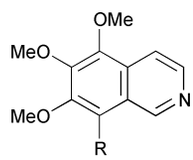
157



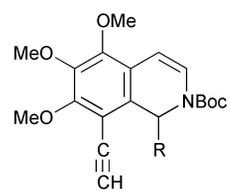
158

15.7 Azafluoranthenes and related tropolones

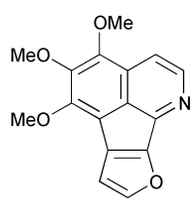
Syntheses of the tropolone alkaloids imerubrine, isoimerubrine and grandirubrine have been achieved starting from 5,6,7-trimethoxyisoquinoline, following a successful synthesis of colchicine by similar methods (section 18). The isoquinoline **159a** was converted through **159b**, into the Reissert compound **160a**, which was reduced and hydrolysed to **160b** and this was converted by stages into the furan **161**. A [4+3]cycloaddition of 3,3-dimethoxy-2-trimethylsilyloxypropene to **161** yielded a mixture of the adducts **162a** and **163** and of these **162a** suffered a ready elimination to the tropolone ether imerubrine **164**, though a similar reaction could not be achieved with **163**. Reaction of the furan **161** with 1,1,3-trichloropropanone, followed by reduction, gave the bridged cycloheptenone **165**, from which the oxygen was eliminated to give the cycloheptatrienone **166**. Oxidation of **165** with phenyliodine^{III} diacetate in methanolic potassium hydroxide afforded the dimethyl ketal of **162b**, which was hydrolysed to **162b** and elimination of the oxygen bridge from this yielded grandirubrine **167a**. Methylation of grandirubrine afforded a mixture of imerubrine **164** and isoimerubrine **167b**. *O*-Methylation of the dimethyl ketal of **162b**, followed by hydrolysis, afforded a route to **162a** without the formation of **163**.[175]



159a R = I
159b R = C≡CH



160a R = CN
160b R = CHO



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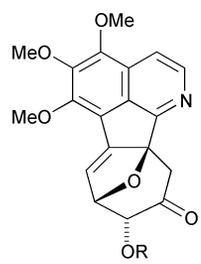
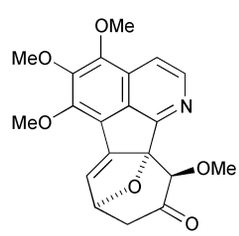


162a R = Me
162b R = H



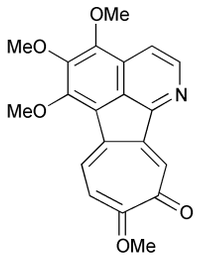
163

16 Alkaloids of the morphine group

Pallidine, norpallidine and *O*-methylflavinantine have been isolated from *Annona purpurea*[23] and *O*-methylflavinantine has also been isolated from *Croton menthodorus*.[176] Hyserpine, a new alkaloid that may be regarded as a degradation product of hasubanonine, isolated from *Hyserpa neocaledonica*, is described in section 20.

Methods of estimating morphine,[177–179] esters of morphine,[180] buprenorphine,[181,182] norbuprenorphine,[182] naltrexone[183] and naltrexol[183] have been described.

Photochemical *N*-demethylation of 14-acetoxycodeinone **168a** in the presence of oxygen and tetraphenylporphin has been achieved with *O*,*N*-acyl migration to give *N*-acetyl-14-hydroxycodeinone **168b**.[184] 1-Fluorocodeine **169a** and 1-fluorodihydrocodeine have been prepared by the thermolysis of the diazonium fluoroborates derived from 1-aminocodeine **169b** and 1-aminodihydrocodeine.[185] The 3-hydroxy group in morphine has been replaced by a series of amino groups. Morphine **170a** was converted into the 3,6-*tert*-butyldiphenylsilyl



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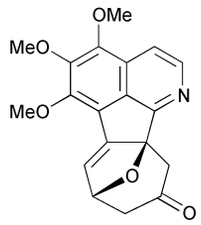

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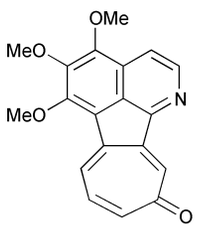

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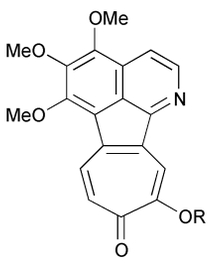
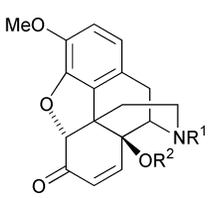
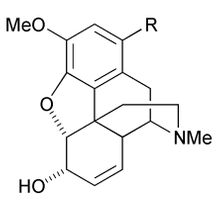


167a R = H
167b R = Me

ether **170b**, which was hydrolysed to the 6-ether **170cc**. The trifluoromethanesulfonyl ester of this **171**, on heating with amines and sodium *tert*-butoxide suffered replacement of the ester group and desilylation of the products yielded the 3-amino-3-deoxymorphines **172a**–**172e**.[186] Oxidation of 3-*O*-methylnaloxone with ammonium cerium^{III} nitrate has given 10α-hydroxy-3-*O*-methylnaloxone **173** which on further oxidation yielded 10-oxo-3-*O*-methylnaloxone **174a**, which was demethylated to 10-oxonaloxone **174b**.[187] The preparation and use of these compounds and their 14-deoxy analogues has been covered by a patent.[188] The 14-aminodihydrocodeinone derivative **175a** has been converted through **175b** into **175c**, the phenyltetrazolyl ether of which was cleaved to give **176**. This was hydrolysed and converted into the amide **177**.[189]

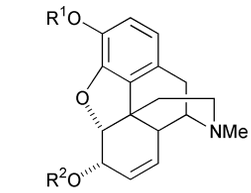


168a R^1 = Me, R^2 = Ac
168b R^1 = Ac, R^2 = H

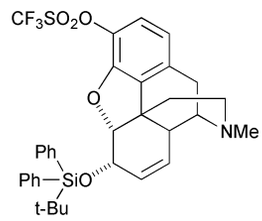


169a R = F
169b R = NH_2

Photochemical oxidation of thebaine affords the enedione-aldehyde **180** together with a smaller amount of the benzofuran **181**. These compounds are believed to arise by the addition of singlet oxygen to the diene system of the alkaloid to give **178**, which collapses through the related iminium salt to the enamine **179**, followed by hydrolysis to **180**. This enedione is stable to heat and is converted into the benzofuran **181** by a non-oxidative photochemical cleavage rather than by a retro Diels–Alder reaction. The enedione **180** is reduced by sodium borohydride in methanol to both diastereoisomers of the triol **182**, catalytically to the alcohol **183** and finally to the isomers of the triol **184a**, and by sodium borohydride and boron trifluoride to the alcohols **184b** and **184c**. The acetal **185** has been isomerised to the ketal **186**, also available directly from **180**, which is reduced by sodium borohydride to the disatereoisomeric alcohols **187**. Sodium borohydride and boron trifluoride reduce the *cis*-diol **182** to a mixture of the *cis*-diol **184c** and the alcohol **188**. Although the 6,14-peroxide **178** has not been isolated from the oxidation of thebaine its quaternary *N*-methyl trifluoromethanesulfonate, which is stable at room temperature over an extended period, has been obtained by the photo-



170a $R^1 = R^2 = H$
170b $R^1 = R^2 = tBuPh_2Si$
170c R^1 = H, $R^2 = tBuPh_2Si$



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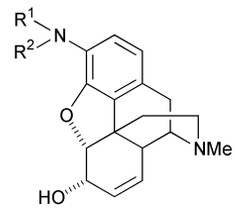
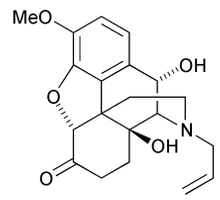


172a $R^1 = R^2 = H$
172b R^1 = H, R^2 = Me
172c $R^1 = R^2$ = Me
172d R^1 = H, R^2 = Ph
172e R^1 = H, $R^2 = CH_2Ph$



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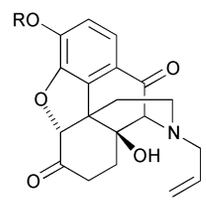
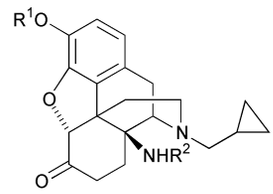
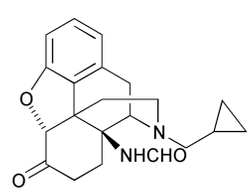


174a R = Me
174b R = H



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



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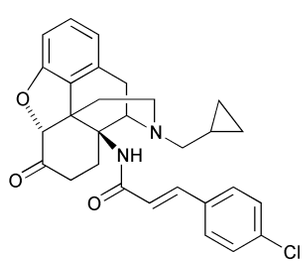
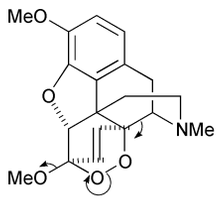


177

oxidation of *N*-methylthebaine trifluoromethanesulfonate. This peroxide is converted by warm trifluoroacetic acid into the quaternary salt **189b** of 14-hydroxycodeinone and the hydroperoxide **189a** has been spectroscopically identified as an intermediate in this hydrolysis.[190]

The 7α-ketone **190** and its 7β-epimer have been equilibrated to a 2 : 1 mixture of the two by perchloric acid. The related *tert*-butyl ketones are similarly equilibrated to an equimolecular mixture. This equilibration occurs during the Schmidt reaction of the ketone **190** with perchloric acid and sodium azide, which gives a 2 : 1 mixture of the amide **191** and its 7β-isomer.[191]

Details of the preparation of the following have been published: morphine 6-glucuronide,[192] dihydromorphinone,[193] dihydrocodeinone,[193] 14-hydroxycodeinone,[190] 14-hydroxydihydrocodeinone,[194] hydrazones of general structure **192**, derived from *N*-aminonorcodeine,[195] naltrexone *O*,*O*-distearate[196] the amide **193**, derived from β-naltrexamine,[197] pyrroles of general structures **194a** and **194b**,[198] the indoles **195**[199]



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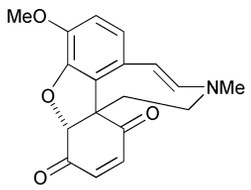

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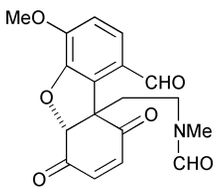

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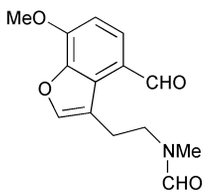

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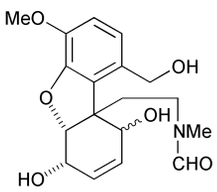

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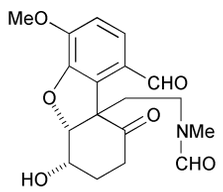

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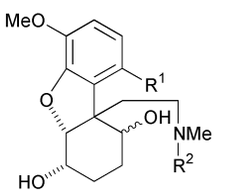
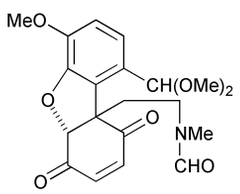


184a $R^1 = CH_2OH$, $R^2 = CHO$
184b $R^1 = CH_2OH$, $R^2 = Me$
184c $R^1 = R^2 = Me$



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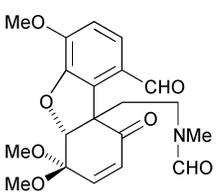

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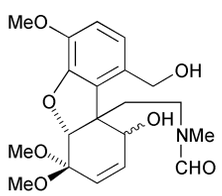

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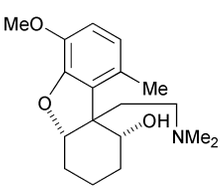

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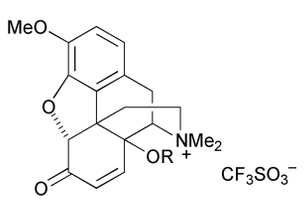
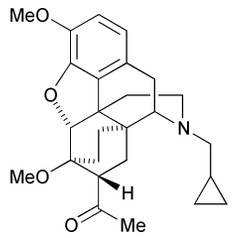


189a R = OH
189b R = H



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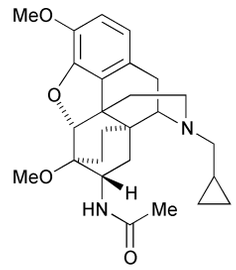

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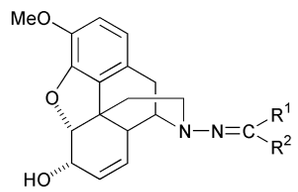

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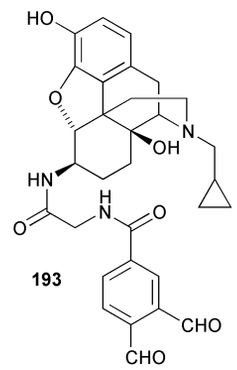

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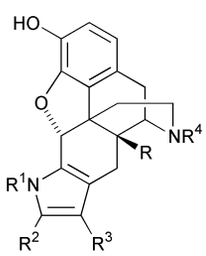
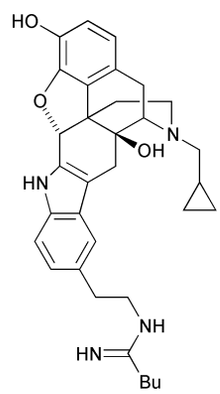


194a R = H
194b R = OH



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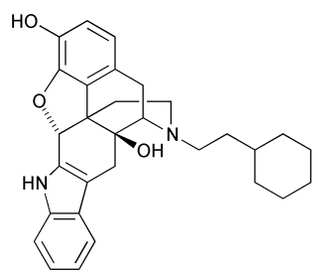

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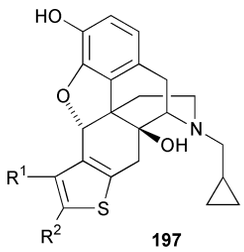
and **196**,[200] thiophenes, pyridines and quinolines of general structures **197**,[201] **198**, **199**,[202] and **200**,[203] the normorphine derivative **201**,[204] dehydrobuprenorphine **202**,[205] alkyl ethers of alcohols of general structure **203**,[206] the phenols **204**[207] and **205**,[208] the amides **206**, **207**,[209] and **208**[210] and the quaternary indolinodeoxycodeine salt **209**.[211]

Alternative approaches to intermediates in previously reported syntheses of morphine and its derivatives have been discussed,[212–214] and syntheses of the alkaloid have been reviewed.[215,216]

The analgesic properties,[217–277] the pharmacokinetics and the metabolism[278–281] of morphine have been studied, as have the effects of the alkaloid on behaviour,[234,282–295] on immune responses,[296–301] on the brain,[302] on the cardiovascular system,[303,304] on the gastrointestinal tract,[305–309] on neurones,[310–316] on blood cells,[317–320] on the regulation of temperature,[321,322] on respiration,[323] on locomotor activity,[324,325] on the intake of food,[326] on the thalamus,[327] on the pituitary gland,[301] on the spinal cord,[328] and spinal injuries,[329] on lung receptors,[330] on the foetus,[331] on the newborn,[332] on the utilisation of glucose,[333] on the intake of saccharin,[334] on pruritus,[335,336] on peritonitis,[337] on feline immunodeficiency virus,[338] on intracellular pH,[339] on macrophage apoptosis,[340] on calcium channels,[341] on adrenoreceptors,[342] on nicotinic receptors,[343] on messenger RNA,[344–346] on nitrite production,[347–349] on gene expression,[350,351] on susceptibility to *Salmonella typhimurum*,[352] on levels of dopamine,[353]



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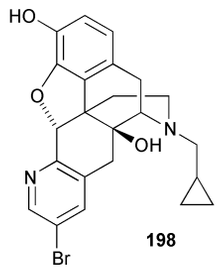

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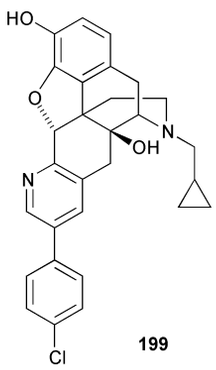

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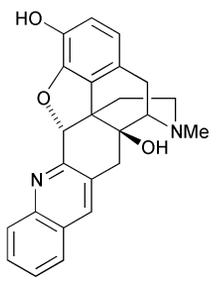

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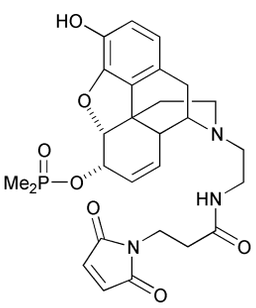

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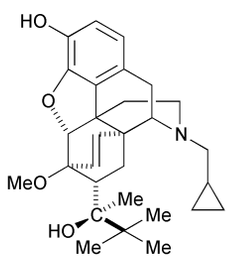

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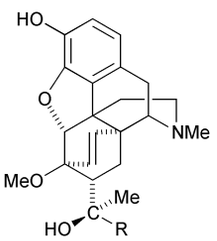

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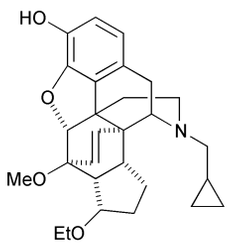

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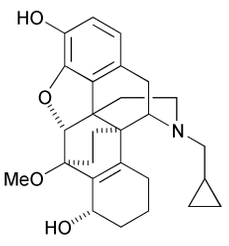
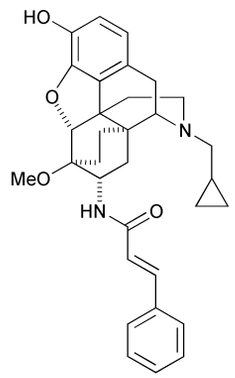


205

of opioid peptides,[354] of calcitonin,[355] of corticosterone,[356] of interleukins,[356,357] of oxytocin[358,359] and of substance P[355] and on the effects of apomorphine,[360] of amikacin,[361] of caffeine,[362] of cocaine,[363] of *N*-methyl-3,4-methylenedioxyamphetamine,[363] and of naloxone.[364]

The morphine-antagonist actions of naloxone have been studied,[365–369] as have the effects of this compound on behaviour,[366] on the development of tolerance to morphine,[370] on neurones,[371–375] on brain injuries,[376] on cerebral blood flow,[377]



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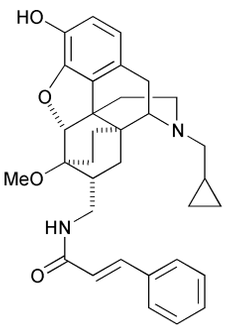

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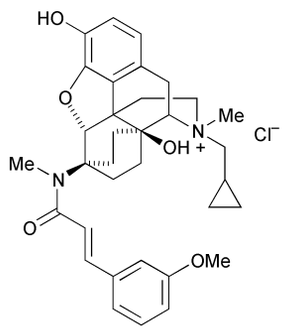

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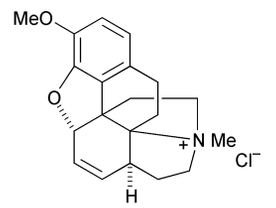


209

on reflexes,[378,379] on the spinal cord,[380] on the cardiovascular system,[381] on lactate and pyruvate metabolism,[382] on antioxidant enzyme activity,[382] on levels of adrenocorticotropin,[383] and of dopamine,[384] and on the effects of amikacin,[361] of buprenorphine,[385] of diazepam,[386] of methotrexate[386] and of pentobarbital.[386]

The pharmacological properties and physiological effects of the following have also been studied: *O*,*O*-diacetylmorphine (heroin),[387–404] morphine 3-glucuronide,[278,405] morphine 6-glucuronide,[278,326,406,407] dihydromorphinone,[408,409] 14-hydroxydihydromorphinone,[410] codeine,[411–418] dihydrocodeinone,[417] naltrexone,[410,419–431] methylnaltrexone,[432] naloxone benzylhydrazone,[433] nalbuphine,[434–436] nalmefene,[437–441] naltrindole,[442] 5′-guanidinonaltrindole,[443] 7′-(2,3-diformylphenylcarboxamido)-naltrindole [7′-(phthalaldehydecarboxamido)naltrindole],[444] β-funaltrexamine,[445] norbinaltorphimine,[446] etorphine,[447,448] dihydroetorphine,[449,450] buprenorphine,[434,451–459] *O*-methylflavinantine,[176] and (+)-morphine.[460]

A review of the use of opiates in medicine has also been published.[461]

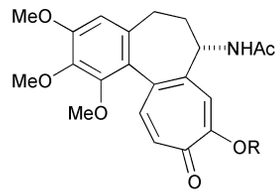
17 Phenethylisoquinolines

(*R*)-Homolaudanosine **21e** has been synthesised from **19e** as described in section 2.[25]

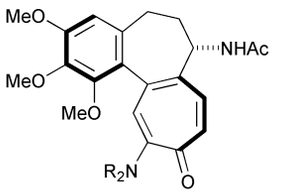
18 Colchicine and related alkaloids

Atropisomeric colchicinoids have been prepared for the first time. Isocolchicine **210a** and its relatives **210b** and **210c**, on treatment with ammonia and with amines, gives the atropisomeric amines **211** and **212**, which in some cases are stable and in others are rapidly equilibrated. The isomers have been distinguished by their dichroic properties. Colchicine **213a**, under similar conditions, affords the regioisomeric amines **214** and **215**.[462]

9-Tolylsulfonyloxycolchicoside **210c** reacts rapidly with the anion of dimethyl malonate in dimethyl sulfoxide to give the lactone **216**, whereas the isomeric 10-tolylsulfonyloxy compound **213b** reacts very slowly under identical conditions to give the isomeric lactone **217**. Neither of these reactions occurs in hydroxylic solvents.[463]



210a R = Me
210b R = Et
210c R = SO_2–Me



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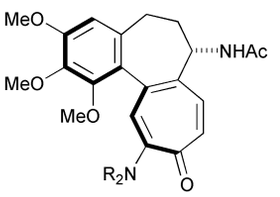

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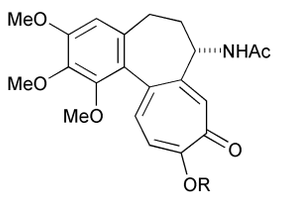
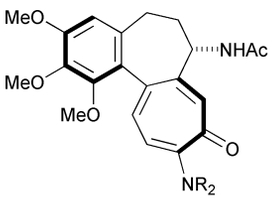


213a R = Me
213b R = SO_2–Me



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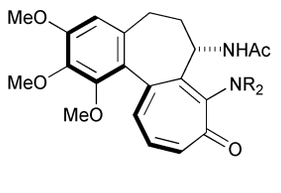

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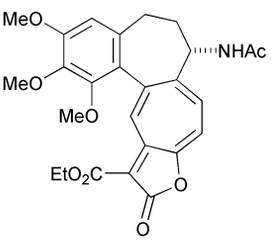

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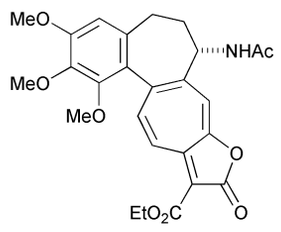

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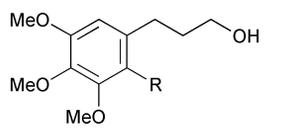
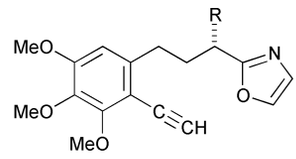
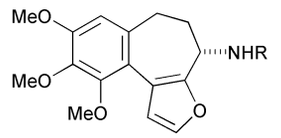


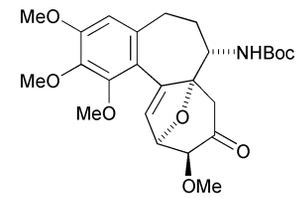
218a R = I
218b R = C≡H



219a R = OH
219b R = N_3
219c R = NHAc



220a R = Ac
220b R = Boc



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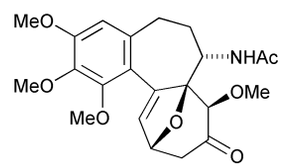

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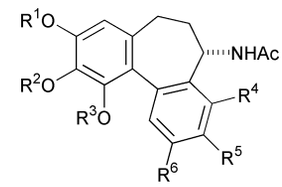


223a $R^1 = R^6 = H$
$R^2 = R^3 = Me$
$R^4 = OH$, $R^5 = OMe$

223b $R^1 = R^2 = R^3 = Me$
$R^4 = R^6 = H$
$R^5 = CO_2Me$

A synthesis of colchicine **213a** has been achieved from the alcohol **218a**. This was converted into the acetylene **218b** which was converted into the oxazole **219a** and this was further converted through **219b** and **219c** into the furan **220a**, also available by an alternative, though similar, route. The furan **220a** was converted into the related **220b**, which underwent a [4+3]cycloaddition reaction with the α-methoxytrimethylsilyloxyallyl cation (generated *in situ* from the trimethylsilyl enol ether of pyruvic aldehyde) to give **221**. This was smoothly cleaved to *N*-benzyloxycarbonyl-*N*-deacetylcolchicine, which was hydrolysed and acetylated to give colchicine **213a**. The furan **220a** also underwent [4+3]addition of 3,3-dimethoxy-2-trimethylsilyloxypropene, but the undesired regioisomer **222** was the sole product of the reaction.[464]

A patent for the preparation of ring-contracted colchinoids similar to colchibiphenyline **223a** and salimine **223b** of general structure **223** has been published.[465]

The physiological effects and other properties of colchicine have been studied.[466–477]

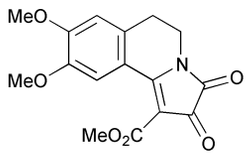
19 *Erythrina* alkaloids

19.1 Erythrinanes

The isomeric 15 and 16 β-D-glucosides of erysopine have been isolated for the first time, together with erysodine β-D-glucoside, erysotramidine, erysotrine, erysovine, erythraline and 8-oxoerythraline, from *Erythrina latissima*.[478]

A modified synthesis of (±)-erysotrine **228**, with a three-fold increase in overall yield, has been reported. Diels–Alder addition of the dioxopyrroline **224** to 1-methoxy-3-trimethylsilyloxybutadiene, followed by reduction of the adduct with lithium borohydride and hydrolysis, afforded the erythrinane **225**, which was converted into **226**. Reduction of this with sodium borohydride gave the 3α-alcohol **227a** and its 3β-isomer in a 9 : 1 ratio. *O*-Methylation of **227a** gave (±)-erysotramidine **227b**, which was reduced by lithium aluminium hydride to (±)-erysotrine **228**. Peracid oxidation of **227a** yielded the 4,5 α-epoxide **229a**, the methyl ether of which **229b** was converted by samarium^{II} iodide into the allylic alcohol **230**, which was reduced by lithium aluminium hydride and aluminium chloride to (±)-erythatidine **231** (80%) and (±)-erysotrine **228** (16%). The epoxide **229b** could not be prepared from erysotramidine **227b** The dienone **226** was oxidised by alkaline hydrogen peroxide to the 4,5α and 4,5β epoxides, which were reduced to **229a** and its 3β-epimer and to the 4,5β-epoxide isomers of these alcohols.[479]

In a new approach to the erythrinane ring system the methylthioacetamide **232** has been oxidised by manganese dioxide in



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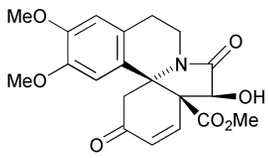

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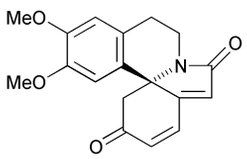

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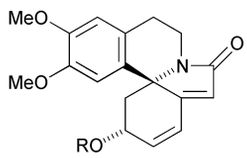
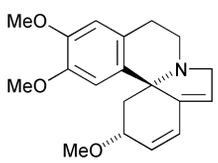


227a R = H
228b R = Me



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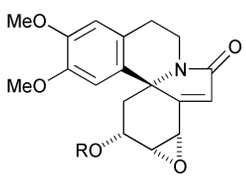
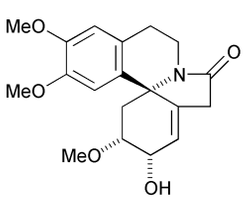


229a R = H
229b R = Me



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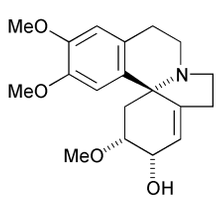

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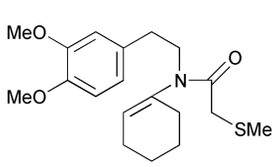
the presence of copper^{II} acetate to give a mixture of **233** and **234**, whereas in the presence of copper^{II} trifluoromethanesulfonate the product was the saturated erythrinane **235**.[480]



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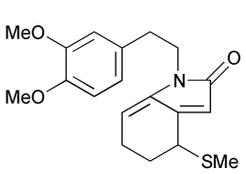

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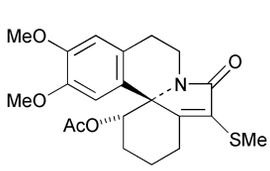

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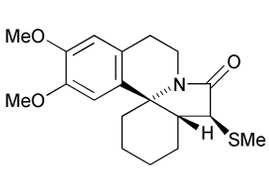


235

The effects of β-erythroidine and of dihydro-β-erythroidine on behaviour have been studied.[481]

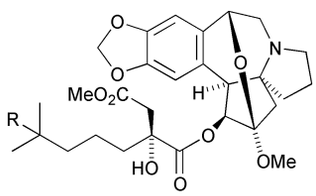
19.2 Homoerythrinanes

3-Epischellhammericine and 3-epitaxodine have been isolated from *Cephalotaxus harringtonia*.[482]

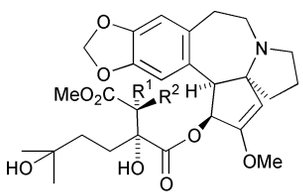
19.3 Cephalotaxine and related alkaloids

Cephalotaxine, 11-hydroxycephalotaxine, demethylcephalotaxinone, drupacine, harringtonine, deoxyharringtonine, homodeoxyharringtonine, isoharringtonine and the new alkaloids cephalezomine A **236a**, cephalezomine B **236b**, cephalezomine C **237a**, cephalezomine D **237b**, cephalezomine E **238a** and cephalezomine F **238b** have been isolated from *Cephalotaxus harringtonia*. The structures of the new alkaloids were deduced from their spectra.[482] The mono- and di-acetyl esters of 11-hydroxycephalotaxine have been prepared.[483] An improved preparation of the α-keto-acid **239**, an intermediate in the synthesis of homoharringtonine, has been reported.[484]

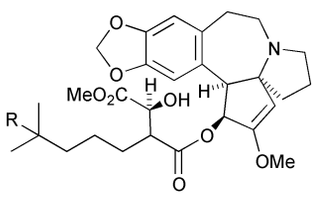
The physiological and antitumour effects of homoharringtonine have been studied.[485,486]



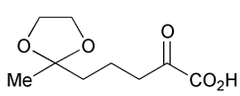
236a R = OH
236b R = H



237a R^1 = H, R^2 = OH
237b R^1 = OH, R^2 = H



238a R = OH
238b R = H

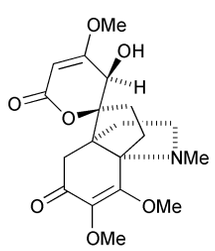


239

20 Other isoquinolines

Hyserpine **240**, which is not an isoquinoline but which can be regarded as a degraded hasubanonine, has been isolated from *Hyserpa neocaledonica*.[487]

Buzonamine, a defensive secretion of the millipede *Buzonium crassipes*, has been assigned the octahydroisoquinoline structure **241**.[488]



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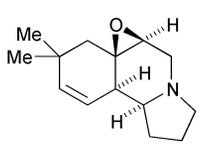

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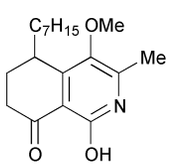
Antidesmone, from *Antidesmona membranaceum* and *A. venosum*, originally assigned the tetrahydroisoquinoline structure **242**, has been shown to be the pyridone **243**.[489]



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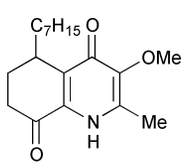
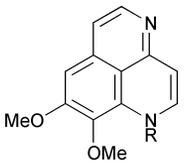


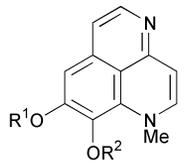
243

Syntheses of aaptamine **244a**, *N*-methylaaptamine **244b**, isoaaptamine **245a** and its regioisomer **245b** have been reported.[490]

Jorumycin **246**, which is a relative of the saframycins, has been isolated from the marine organism *Jorunna funebris*.[491] It is

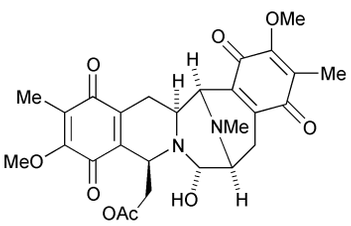


244a R = H
244b R = Me

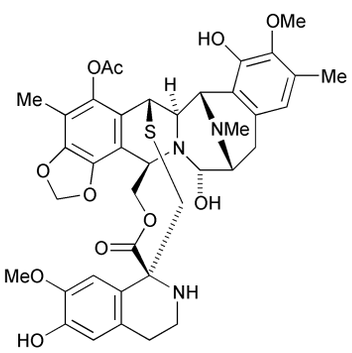


245a R^1 = Me, R^2 = H
245b R^1 = H, R^2 = Me

a cytotoxic agent slightly less potent than the related ecteinascidin E743 **247**. Syntheses of analogues of the saframycins[492,493] and ecteinascidins[494] and a synthesis of ecteinascidin E743 **247** from cyanosafracin B[495] have been reported.



246



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