β-Phenylethylamines and the isoquinoline alkaloids

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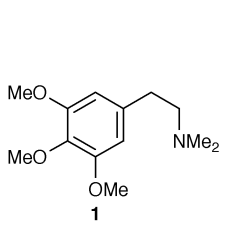

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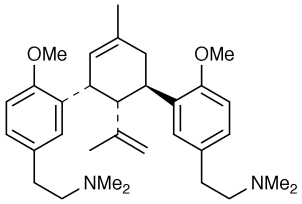

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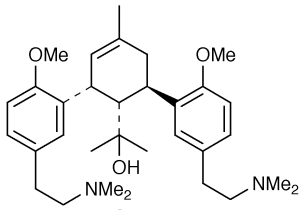

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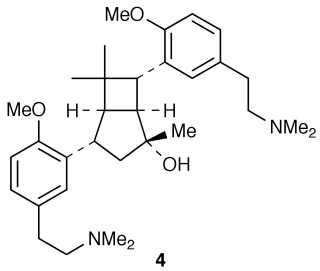

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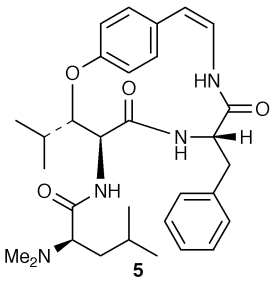

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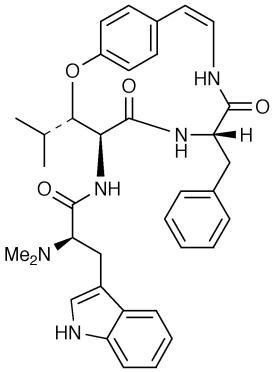

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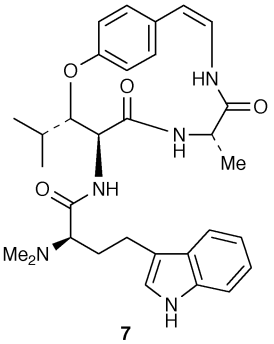

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1 Introduction

Reviews of the occurrence of isoquinoline alkaloids in some plant species[1,2] and of recent developments in the chemistry and synthesis of alkaloids of these groups[3–6] have been published.

2 β-Phenylethylamines

β-Phenylethylamine, tyramine, *N*-methyltyramine, hordenine, mescaline, *N*-methylmescaline and *N*,*N*-dimethylmescaline **1**, which is reported as an alkaloid for the first time, have been isolated from an unspecified species of *Turbinocarpus*[7] and *N-trans*-feruloyltyramine has been isolated from *Cananga odorata*.[8] The *N*-oxides of the known alkaloid culantraramine **2** and the unknown culantraraminol **3**, together with the related avicennamine **4** have been isolated as new alkaloids from *Zanthoxylum avicennae*.[9] Three novel amides of dehydrotyramine have been isolated from *Aaltheria douradinha*[10,11] as waltherine A **5**, waltherine B **6** and waltherine C **7**, and the related alkaloids integerrimine **8** and anorldiamine 27-*N*-oxide **9** have been obtained from *Heisteria nitida*.[12] Of these waltherines A and B are also phenylethylamines by their derivation from phenylalanine; in waltherine C **7**, integerrimine **8** and anorldiamine **9** phenylalanine has been replaced by alanine, leucine and proline respectively. The oxoisoaporphine alkaloid tyraminoporphine (see section 14.8) is also a derivative of tyramine. *N*-Benzoyl-β-phenylethylamine **10** has been isolated as muricatisine from *Oxytropis muratica* and *Oxytropis puberula*, its structure being confirmed by its synthesis from aminoacetophenone.[13]

Physico-chemical studies have shown that *N*-methylephedrine **11** reacts with sulfinyl chlorides, alone and in the

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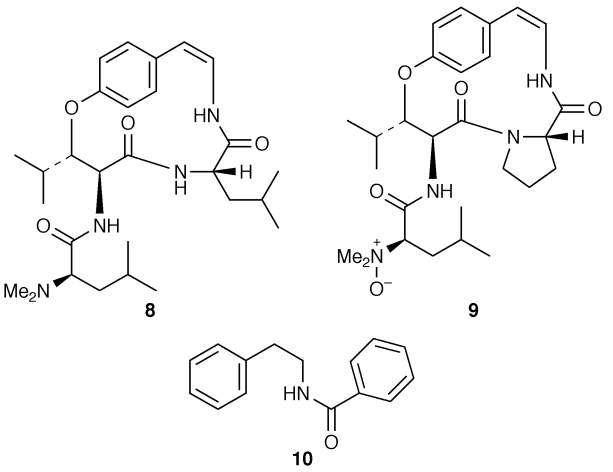
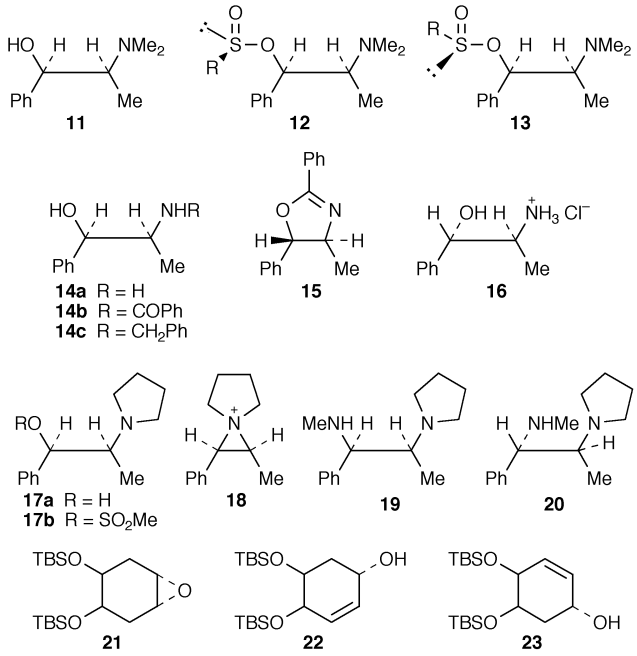
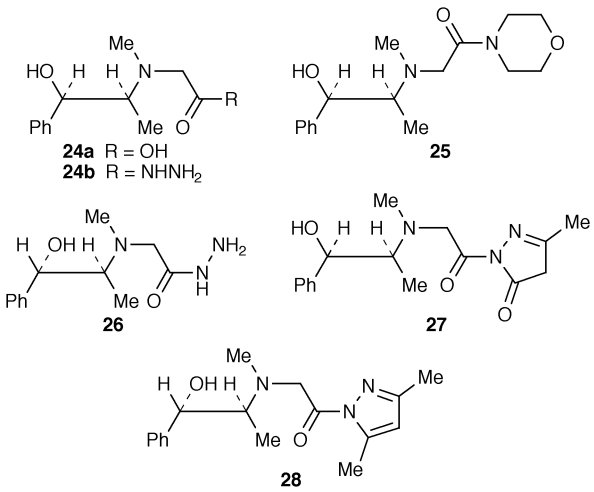


presence of tertiary bases, to give mixtures of the diastereoisomeric sulfinate esters **12** and **13**, the ratio (up to 9 : 1) depending on the acid chloride.[14] *N*-Benzoylnorephedrine **14b** has been cyclised to the oxazole **15**, acid hydrolysis of which affords norpseudoephedrine **16** in excellent yield. Norephedrine **14a** with 1,4-dibromobutane gives the pyrrolidine **17a**, the methanesulfonyl ester of which, **17b**, is easily converted into the spiroaziridinium salt **18**, which reacts with methylamine to give **19**. In the same way norpseudoephedrine **16** gives the diastereoisomeric diamine **20**. The bases **19** and **20** control the opening of the epoxide **21** by butyllithium to give the enols **22** and **23** respectively.[15]



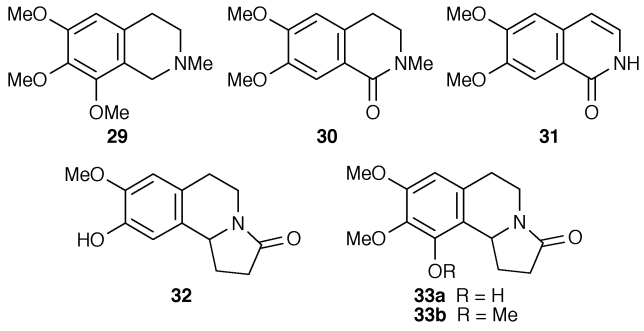
N-Ephedrinylacetic acid **24a** and the related hydrazine **24b** have been prepared from ephedrine *via* the amide **25**.[16] Pseudoephedrinylacethydrazide **26** has been prepared in the same way from pseudoephedrine.[17] The hydrazides **24b** and **26** have been condensed with ethyl acetoacetate and with acetylacetone to give the pyrazolone **27** and the pyrazole **28**, respectively, and their diastereoisomers.[17] *N*-Benzylnorephedrine **14c** has been found to be an efficient ligand for ruthenium catalysed asymmetric transfer hydrogenations of functionalised ketones[18] and poly-[*N*-(4-ethynylbenzyl)ephedrine] to be an effective catalyst for the enantioselective addition of the dialkylzincs to aromatic aldehydes.[19] *N*-Methylenedioxyphenylacetyl-(+)-pseudoephedrine has been used as the starting material for a chiral synthesis of hexahydrobenzophenanthidines (section 13). A patent for the preparation of pseudoephedrine salicylate has been published.[20]



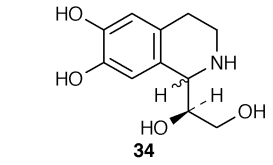
The pharmacological properties and physiological effects of ephedrine,[21–30] of norephedrine,[31] of pseudoephedrine[27,32] and of *N*-methyltyramine[33] have been studied.

3 Isoquinolines

Anhalinine, anhalonidine, pellotine and the new alkaloid *O*-methylanhalidine **29** have been isolated from an unspecified species of *Turbinocarpus*.[7] The new alkaloids *N*-methylcorydaldine **30** and dehydrocorydaldine **31** have been isolated, together with corydaldine, thalifoline and northalifoline, from *Aristolochia elegans*.[34] The novel lactam erythrinarbine **32**, which is an analogue of the known cactus alkaloids peyoglutam **33a** and mescalolactam **33b**, has been isolated from *Erythrina arborescens*.[35]



The aerial oxidation of dopamine in the presence of ferric ions has been shown to involve oxidative fission of the side chain, with the production of formaldehyde and 3,4-dihydroxybenzaldehyde, which undergoes Pictet–Spengler condensation with unchanged amine to give the 6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline.[36] Dopamine has been condensed with D-glyceraldehyde to give the diastereoisomers of **34**.[37] Condensation of (2*R*)-*N*-glyoxyloxybornane 10,2-sultam with dopamine, followed by reduction and *O*,*N*-methylation of the product has afforded (*S*)-(+)-*N*-methylcalycotomine **35a**.[38] Cyclisation of the diamide formed from homoveratrylamine and L-(+)-tartaric acid yields the dihydroisoquinoline **36**, which can be reduced with sodium borohydride, further cyclised, reduced and acetylated to the bis-tetrahydroisoquinoline **37**. Hydrolysis of the *O*-acetyl groups of this, followed by periodate oxidation, then affords an aldehyde, reducible to (*S*)-*N*-acetylcalycotomine **35b**.[39] (*S*)-Calycotomine **35c** has also been obtained by a two-step reduction of the chiral amide **38**.[40] (*R*)-Salsolidine **39** has been prepared by the reduction of 6,7-dimethoxy-3,4-dihydroisoquinoline with the complex formed from sodium borohydride and the chiral phthalimide **40**.[41] (*R*)-Salsolidine has also been synthesised by the asymmetric addition of methyllithium to 6,7-dimethoxy-3,4-dihydroiso-



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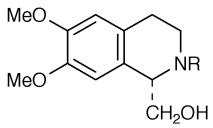
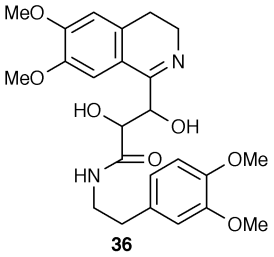


35a R = Me
35b R = Ac
35c R = H



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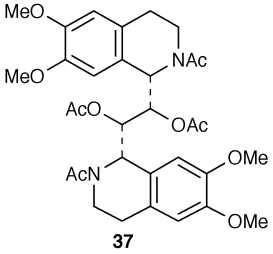

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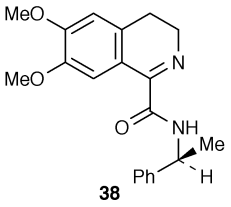

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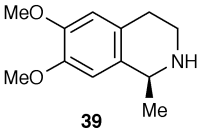

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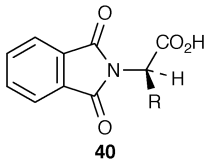

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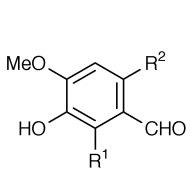
quinoline.[42] *N*-Sulfonylhomoveratrylamines have been cyclised with esters of α-chloro-α-phenylselenoacetic and propionic acids in the presence of Lewis acids, with varying degrees of stereoselectivity using chiral sulfonamides or esters, and this has led to a synthesis of (±)-calycotomine **35c**.[43]

The 4-phenylisoquinoline alkaloids cherylline **46a** and latifine **46b** have been synthesised from isovanillin by bromination to **41a** and **41b**; reduction of these to the alcohols, Fries rearrangement of the esters **42a** and **42b**, and debromination gives the ketones **43a** and **43b**. Oxidation of these to the carboxylic acids was then followed by conversion into the amides **44a** and **44b**, which were cyclised to the isoquinolones **45a** and **45b** and these were reduced to the alkaloids **46a** and **46b**.[44]

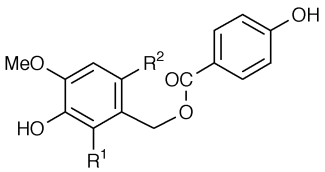
4 Naphthylisoquinolines

The new alkaloids ancistrorobertsonine B **47**, ancistrorobertsonine C **48**, ancistrorobertsonine D **49** and 1,2-dehydroancistrorobertsonine D **50** have been isolated from *Ancistrocladus robertsoniorum*.[45]

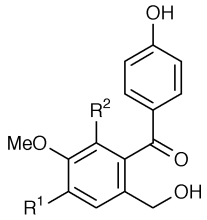
Korupensamine A **56a** has been synthesised from the ester **51** by cyclisation to the lactone **52**, which was reduced with lithium aluminium hydride to the alcohol **53a**, the isopropyl ether of which was oxidised to the aldehyde **53b**. Stobbe condensation of this with diethyl succinate afforded the diester **54**, which was cyclised by acetic anhydride to the naphthalene **55a**. This was converted through **55b** and **55c** into **55d**, removal of the protecting isopropyl and benzyl groups from which afforded korupensamine A **56a**. Its rotamer, korupensamine B, was prepared in the same way from the rotational isomer of **53a**.[46] Korupensamine A, korupensamine B, korupensamine C **56b**, korupensamine D **57** and ancistrobrevine B **58** have been synthesised by coupling of the tetrahydroisoquinolines **59a**, **59b** and **59c** with the naphthylboronic acids **60a** and **60b** and removal of the *O* and *N* protecting groups.[47] A similar biaryl coupling synthesis of korupensamine A has also been reported.[48]



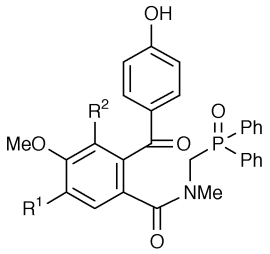
41a R^1 = Br, R^2 = H
41b R^1 = H, R^2 = Br



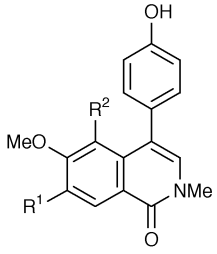
42a R^1 = Br, R^2 = H
42b R^1 = H, R^2 = Br



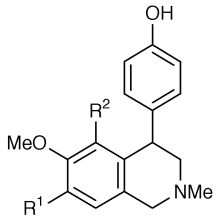
43a R^1 = OH, R^2 = H
43b R^1 = H, R^2 = OH



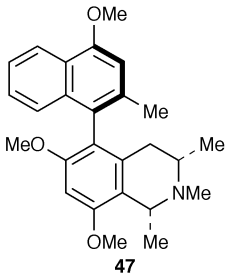
44a R^1 = OH, R^2 = H
44b R^1 = H, R^2 = OH



45a R^1 = OH, R^2 = H
45b R^1 = H, R^2 = OH



46a R^1 = OH, R^2 = H
46b R^1 = H, R^2 = OH



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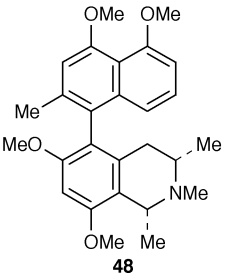

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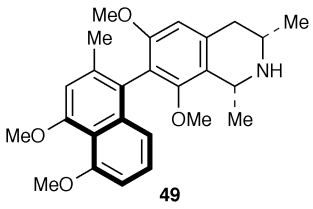

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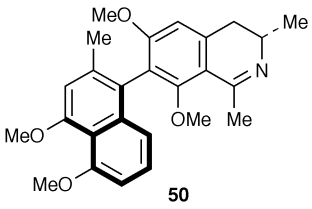

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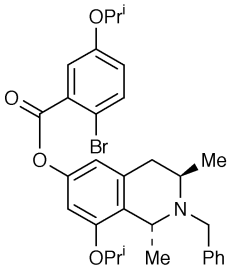
Oxidation of *N*,*O*,*O*-tribenzylkorupensamine A with silver oxide and catalytic reduction of the resulting dimeric quinone, which also removed the benzyl groups, gave michellamine A **61a**. *O*,*O*-Dibenzylkorupensamine D has been similarly converted into **61b**, an analogue of michellamine A which has not so far been encountered as a natural product.[47] The oxygen analogue **62** of michellamine has been prepared in the same way from a synthetic oxygen analogue of korupensamine A.[49]

A synthesis of the acetogenic isoquinoline alkaloid gentrymine B **63a**, related to this group, from 3,4-dimethoxyphenylacetone has been reported. The formation of this alkaloid by the inversion of gentrymine A **63b** in acid has been formulated as involving a retro-Michael reaction as in **63**.[50]

5 Benzylisoquinolines

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



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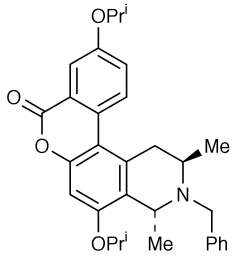

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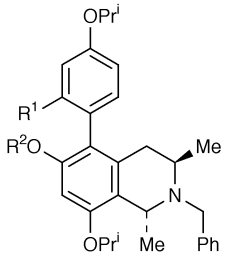
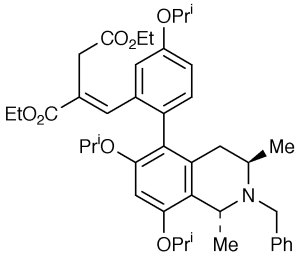


53a $R^1 = CH_2OH$, $R^2 = H$
53b $R^1 = CHO$, $R^2 = Pr^i$



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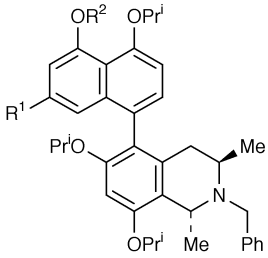
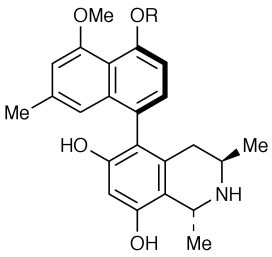
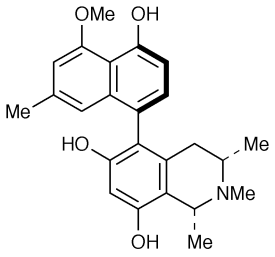


55a $R^1 = CO_2Et$, $R^2 = Ac$
55b $R^1 = CH_2OH$, $R^2 = H$
55c $R^1 = CH_2OH$, $R^2 = Me$
55d $R^1 = R^2 = Me$



56a R = H
56b R = Me



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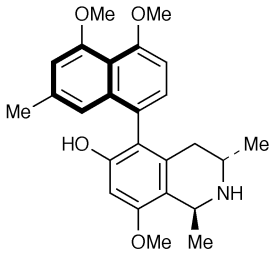

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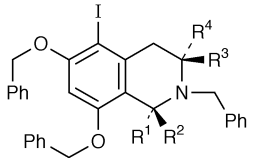
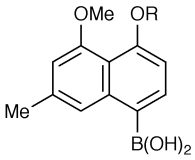


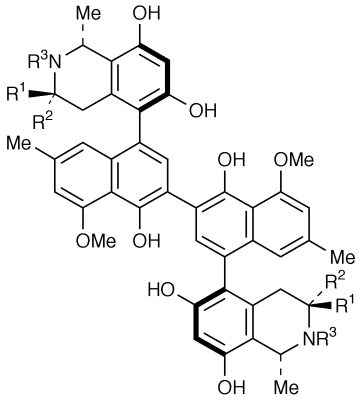
59a $R^1 = R^3 = Me$, $R^2 = R^4 = H$
59b $R^1 = R^3 = H$, $R^2 = R^4 = Me$
59c $R^1 = R^4 = H$, $R^2 = R^3 = Me$



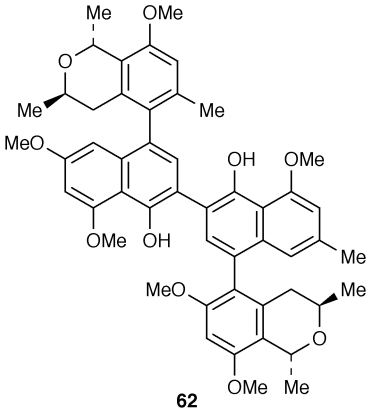
60a R = Me
60b R = CH_2OMe

Cananga odorata[8]
reticuline
Glaucium leiocarpum[51]
N-methylcoclaurine
Gnetum parviflorum[52]
higenamine, *N*-methylhigenamine* **64** and *N*-methylhigenamine *N*-oxide*
Romneya coulteri[53]
escholinine
Stephania cepharantha[54]
dehydroreticuline* **65** and oblongine

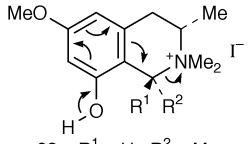
The ^{15}N NMR spectra of alkaloids of the group have been studied.[55] Papaverine methiodide has been found to react with hydroxylamine to give papaverine *N*-oxide in moderate yield,



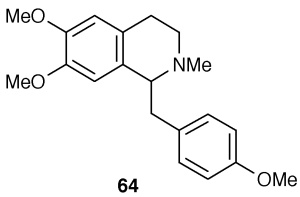
61a $R^1 = Me$, $R^2 = R^3 = H$
61b $R^1 = H$, $R^2 = R^3 = Me$



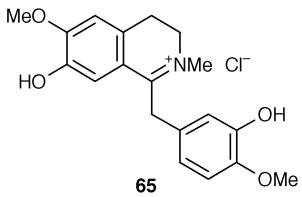
62



63a $R^1 = H$, $R^2 = Me$
63b $R^1 = Me$, $R^2 = H$



64

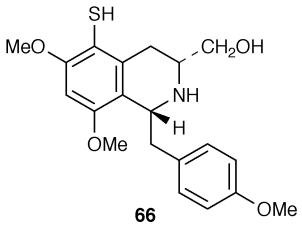


65

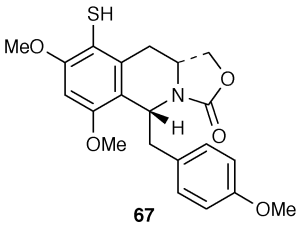
without the production of any detectable intermediate.[56] The photolysis of papaverine *N*-oxide in polar solvents has been studied.[57] An X-ray crystallographic study of the solvation of *O*-tetraethyl-1,2-dehydronorlaudanosoline in ethanol, benzene and hydrochloric acid has been reported.[58]

The trimethyl ether of imbricatine, derived from the star fish *Dermasteria imbricata*,[59] has been synthesised. *N*-Acylation of 2-(4-methoxybenzyl)thio-3,4-dimethoxyphenylalanine methyl ester with 4-methoxyphenylacetyl chloride, followed by Bischler–Napieralsky cyclisation and reduction, afforded the tetrahydroisoquinoline **66**, which was condensed with diethyl carbonate to give **67** and this reacted with 4-bromo-1-methylimidazole-5-carbaldehyde to give **68a**. Reduction of this to the alcohol **68b**, followed by reaction with the lithium salt of 2-isopropyl-2,5-dihydropyridazine afforded **69**, which was hydrolysed and oxidised to **70a** and this was converted through **70b** into *O*,*O*,*O*-trimethylimbricatine **70c**.[60] The biological conversion of 6′-bromo-1,2-dehydroreticuline into 12-bromotetrahydropalmatine in *Cocculus laurifolius* has been observed[61] (see section 8).

The pharmacological properties and physiological effects of papaverine,[62,63] of higenamine,[64] of laudanosine,[65] of atra-



66



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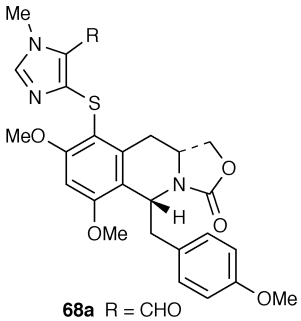
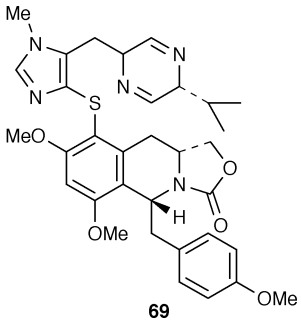
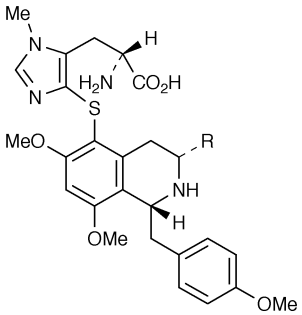


68a R = CHO
68b R = CH_2OH



69



70a R = CH_2OH
70b R = CHO
70c R = CO_2H

curium,[65–68] of mivacurium[67–69] and of a series of acylaminobenzyltetrahydroisoquinolines[70,71] have been studied.

6 Bisbenzylisoquinolines

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

Cyclea peltata[72]
berbamine, curine, cycleanine, cycleanoline, isochondodendrine and tetrandrine

Isopyrum thalictroides[73]
fangchinoline, isopyruthaline, isopythaline, (±)-isothalictrine* **71**, (+)-isothalicrine* **72** and (±)-isothalirine* **73**

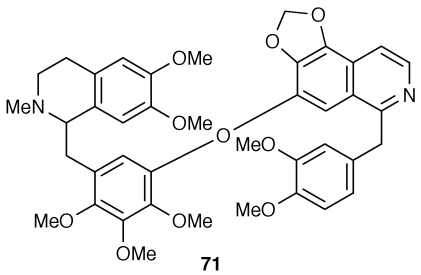
Menispermum dauricum[74]
dauricine, dauricoline and dauricicoline*

Stephania cepharantha[54,75]
berbamine, cepharanthine, cepharanoline, isotetrandrine and 2′-*N*-methylisotetrandine

Stephania rotunda[76]
cycleanine

Benzylisoquinoline-tetrahydroberberine and benzylisoquinoline–aporphine dimers have been isolated from *Thalictrum longistylum* and from *Thalictrum faurei* respectively (see sections 8 and 14.3).

Of the new alkaloids isothalirine, with a 7′,10 head-to-tail diphenyl linkage is of the same type as malekulatine, but isothalictrine and isothalicrine, which have a 7′,11 head-to-tail linkage, represent a structural variant not previously found in this series. 2-Methoxy-5,4′-bis(methoxycarbonyl)diphenyl ether, which is probably a metabolite of a bisbenzylisoquinoline alkaloid, has been isolated from *Aristolochia elegans*.[34] The recent chemistry of alkaloids of this group has been reviewed.[5]



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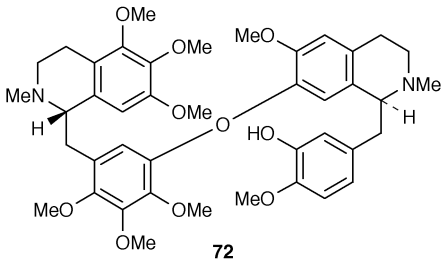
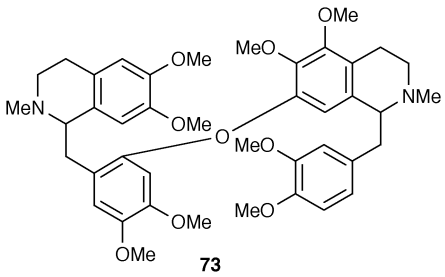


72



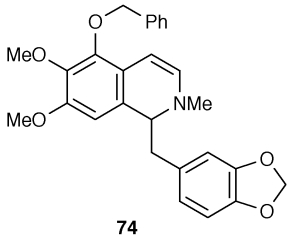
73

The pharmacological properties and physiological effects of berbamine,[62,77–80] of cepharanthine,[81,82] of daphnoline,[81] of dauricine,[83,84] of fangchinoline[85,86] of tetrandrine,[85–101] of tiliacorine[102] and of tubocurarine[103] have been studied, and an *ab initio* quantum chemistry analysis of the stereo-electronic properties of daphnoline, gyrocarpine, malekulatine, obaberine and phaeanthine has been used to explain the antileishmanial activity of these alkaloids.[104]

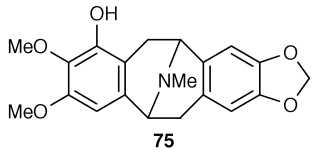
7 Pavines and isopavines

An aporphine–pavine dimer, fauripavine, has been isolated from *Thalictrum faurei*[105] (see section 14.3). Recent chemistry of the alkaloids of this group has been reviewed.[5]

The ^{15}N NMR spectra of some pavine alkaloids have been analysed.[55] (±)-4-Hydroxyeschscholtzidine **75** has been prepared by the cyclisation and debenzylation of the 1,2-dihydroisoquinoline **74**.[106]



74



75

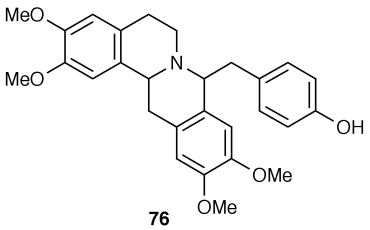
8 Berberines and tetrahydroberberines

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

Argemone mexicana[107]
cheilanthifoline

Glaucium grandiflorum[108]
N-methylcanadine chloride

Gnetum parviflorum[52]
8-(4-hydroxybenzyl)xylopinine* **76**
Romneya coulteri[53]
coulteroberbinone* **77**
Stephania cepharantha[54]
cis-*N*-methylcapaurine chloride* **78a**, cyclanoline (cissamine), stephacarine chloride* **78b** and steponine
Stephania miyiensis[109]
corydalmine, jatrorrhizine, 4-*O*-demethyljatrorrhizine* **79**, stepharanine, stepharine and tetrahydropalmatine
Thalictrum longistylium[110]
longiberine* **80a** and *O*-methyllongiberine* **80b**
Tinospora hainanensis[111]
columbamine, *trans*-*N*-methyltetrahydrocolumbamine and cyclanoline



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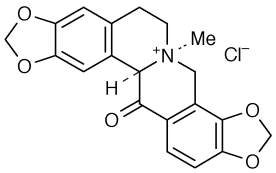
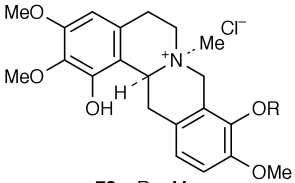
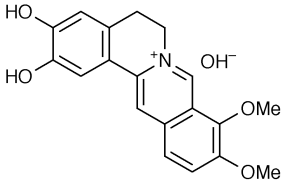


77



78a R = Me
78b R = H



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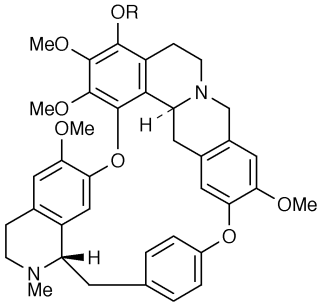
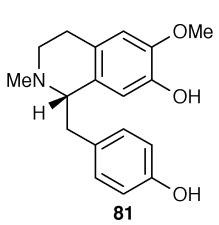


80a R = H
80b R = Me
80c R = Et

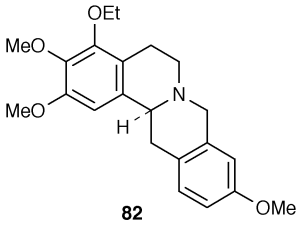
The two new alkaloids longiberine and *O*-methyllongiberine are the first reported dimeric alkaloids of the benzylisoquinoline–tetrahydroberberine group. Their structures were determined by the fission of *O*-ethyllongiberine **80c** with sodium and liquid ammonia to give (*S*)-(+)-*N*-methylcoclaurine **81** and a (*S*)-tetrahydroberberine identified as **82** from its spectra. The structures were confirmed by the synthesis of longiberine **80a** from the bisbenzylisoquinoline alkaloid thalidazine **83a**, *via* **83b**, **83c** and **83d**, the last of which can undergo closure of the tetrahydroberberine system by a Mannich reaction with only one of the benzylisoquinoline units, giving norlongiberine, which is easily methylated to longiberine.[110]

A patent for the extraction of berberine from plants has been published.[112] The ^{15}N NMR spectra of several tetrahydroberberines,[55] and the influence of surface oxygen on the adsorption of alkaloids of this group on charcoal[113] have been studied and an X-ray crystallographic study has confirmed the absolute and relative stereochemistry of cyclanoline bromide **84**.[114]

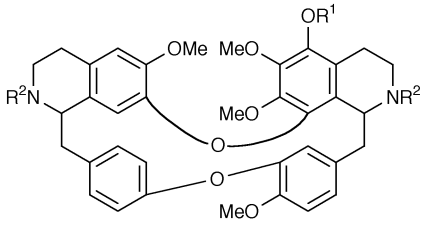
Berberine has been shown to react with sodium hydroxide to give 8-oxoberberine **86** and dihydroberberine **87** as a result of Cannizzaro reaction of the initially formed aldehyde **85**; a small



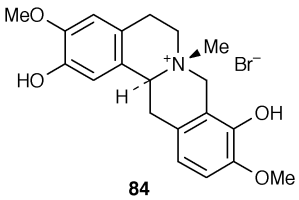
81



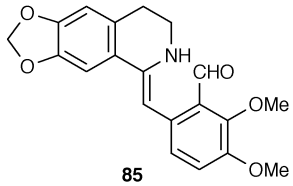
82



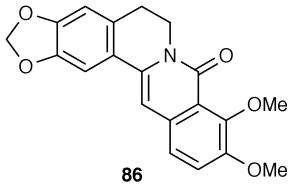
83a R^1 = H, R^2 = Me
83b R^1 = Ac, R^2 = Me
83c R^1 = Ac, R^2 = $CO_2CH_2CCl_3$
83d R^1 = Ac, R^2 = H



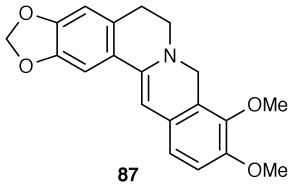
84



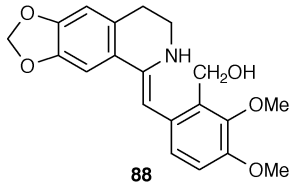
85



86

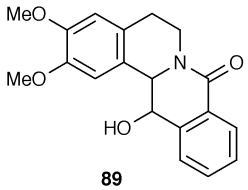


87

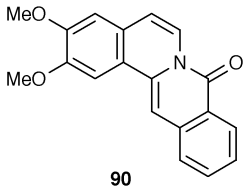


88

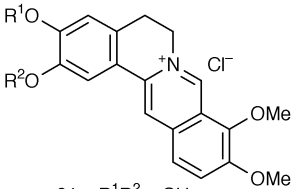
amount of the alcohol **88** was also detected.[115] 13-Hydroxy-*O*-methyl-8-oxobharatamine **89** has been dehydrated and dehydrogenated to the lactam **90**.[116] Prolonged irradiation of berberine **91a** and palmatine **91b** in methanolic hydrogen chloride in the absence of oxygen has given the 8-hydroxymethyldihydro compounds **92a** and **92b** which, on reduction gave 8-hydroxymethylcanadine **93a** and 13-hydroxymethyltetrahydropalmatine **93b**. The same reactions with 13-methyl-



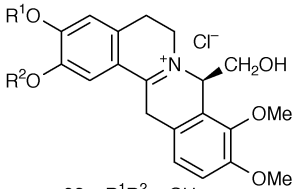
89



90

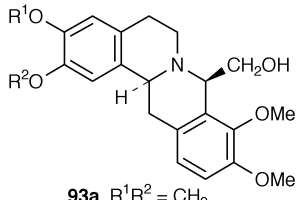


91a R^1R^2 = CH_2
91b R^1 = R^2 = Me

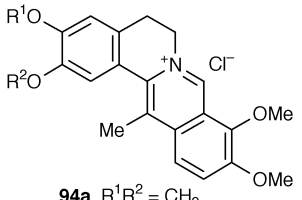


92a R^1R^2 = CH_2
92b R^1 = R^2 = Me

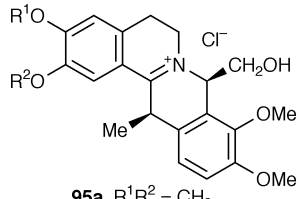
berberine **94a** and dehydrocorydaldine **94b** gave, *via* **95a** and **95b**, 13-hydroxymethylthalictricavine **96a** and **96b** in high yield, with no trace of any other isomer. The high stereoselectivity lies in the radical coupling process, not in the reduction, the 13-methyl group adopting a pseudoequatorial position with the 9-methoxy group then favouring *syn* addition at position 8. The initial product **95b** of irradiation of dehydrocorydaldine, when stirred under oxygen at pH 6, was converted into a mixture of (±)-solidaline **97** and its epimer **98**. These reactions and the spectra of **97** and **98** effectively eliminate **99** previously regarded as a possible structure for solidaline. Attempts to convert dihydroberberinium chloride **100** into 13-hydroxymethylcanadine **101a**, an analogue of the alkaloid zijinlongine **101b**, failed.[117]



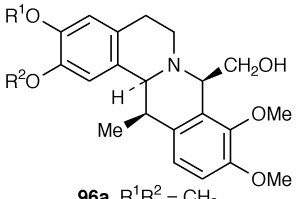
93a $R^1R^2 = CH_2$
93b $R^1 = R^2 = Me$



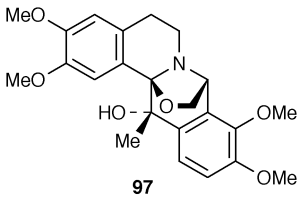
94a $R^1R^2 = CH_2$
94b $R^1 = R^2 = Me$



95a $R^1R^2 = CH_2$
95b $R^1 = R^2 = Me$



96a $R^1R^2 = CH_2$
96b $R^1 = R^2 = Me$



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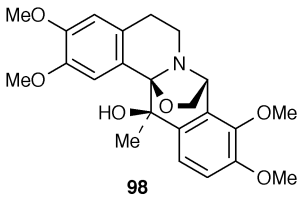

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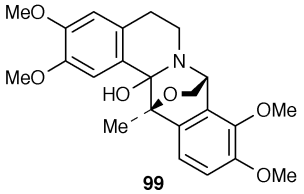
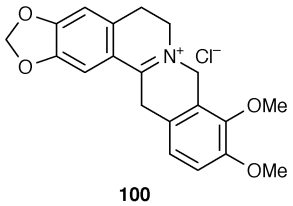
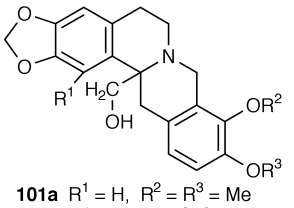


99

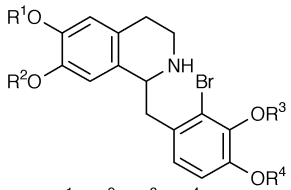


100

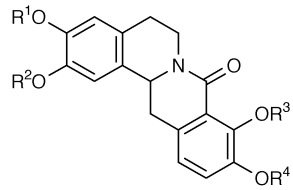


101a $R^1 = H$, $R^2 = R^3 = Me$
101b $R^1 = OMe$, $R^2R^3 = CH_2$

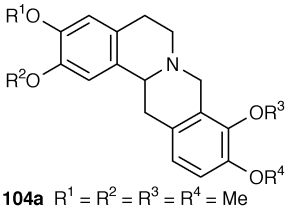
Palladium-catalysed carbonylation of the 1-(2′-bromobenzyl)tetrahydroisoquinolines **102a–d** has afforded the 8-oxotetrahydroberberines **103a–d**, which were reduced by lithium aluminium hydride to tetrahydropalmatine **104a**, sinactine **104b**, canadine **104c** and stylopine **104d**; xylopinine, the 2,3,10,11-tetramethoxy isomer of **104a**, has been synthesised in a similar way.[118] Bischler–Napieralsky ring closure of the amide **105** in the presence of oxalyl chloride and Lewis acids is accompanied by Friedel–Crafts reaction with formation of the α-ketolactam **106**, which can be oxidised to 8-oxopseudopalmatine **107**.[119] The secondary amine **108**, when subjected to Friedel–Crafts acylation with chloro(methylthio)acetyl chloride, affords the lactam **109a**, reduction of which yields



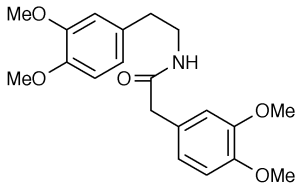
102a $R^1 = R^2 = R^3 = R^4 = Me$
102b $R^1 = R^2 = Me$, $R^3R^4 = CH_2$
102c $R^1R^2 = CH_2$, $R^3 = R^4 = Me$
102d $R^1R^2 = R^3R^4 = CH_2$



103a $R^1 = R^2 = R^3 = R^4 = Me$
103b $R^1 = R^2 = Me$, $R^3R^4 = CH_2$
103c $R^1R^2 = CH_2$, $R^3 = R^4 = Me$
103d $R^1R^2 = R^3R^4 = CH_2$



104a $R^1 = R^2 = R^3 = R^4 = Me$
104b $R^1 = R^2 = Me$, $R^3R^4 = CH_2$
104c $R^1R^2 = CH_2$, $R^3 = R^4 = Me$
104d $R^1R^2 = R^3R^4 = CH_2$



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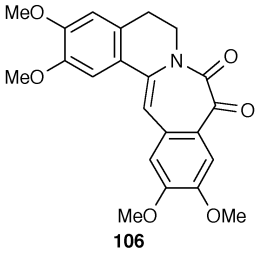

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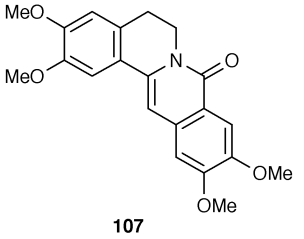
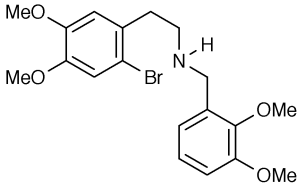


107

109b, and Bischler–Napieralsky cyclisation of this, followed by reduction, gives tetrahydropalmatine **104a**. A similar sequence of reactions using α-chloro-α-(methylthio)propionyl chloride leads to 13-methyltetrahydropalmatine (corydalmine).[120] Reduction of the enamide **110**, followed by hydrolysis, affords *O*-methyl-8-oxobharatamine 13a-carboxylic acid **111**.[121] Photocyclisation of the 1-benzylidenetetrahydroisoquinolines **112a** and **112b** has given the pseudoberberines **113a** and **113b**.[122] 6′-Bromo-1,2-dehydroreticuline chloride **114** has been converted into the 12-bromo derivative of tetrahydropalmatine **104a** in *Cocculus laurifolius*.[61] A patent for the production of 8,13-substituted berberines such as **115** has been published.[123]



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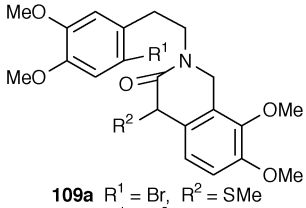
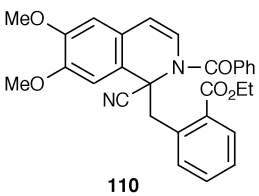


109a R^1 = Br, R^2 = SMe
109b $R^1 = R^2 = H$



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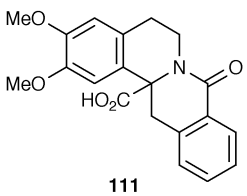
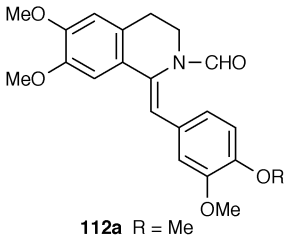
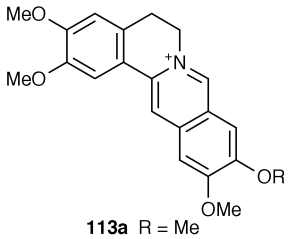


111

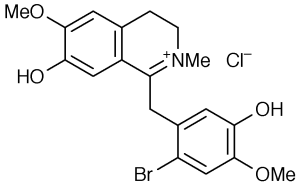
The pharmacological properties and physiological effects of berberine,[124–132] of 8-(4-chlorobenzyl)tetrahydroberberine,[133,134] of coralyne,[135] of palmatine,[130] of tetrahydropalmatine,[136–138] of 8-(4-chlorobenzyl)tetrahydropalmatine,[139] of phellodendrine,[140] of 12-chloroscoulerine,[141] and of stepholidine,[142,143] and the antimalarial activities of seventeen quaternary alkaloids of the group[144] have been studied.



112a R = Me
112b R = H



113a R = Me
113b R = H



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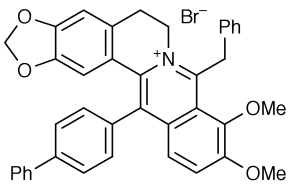


115

9 Protopines

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

Argemone mexicana[107]
protopine

Eomecon chinantha[145]
allocryptopine and protopine

Glaucium grandiflorum[108]
allocryptopine and protopine

Glaucium leiocarpum[51]
allocryptopine and protopine

Glaucium oxylobum[146]
allocryptopine and protopine

The pharmacological properties and physiological effects of protopine have been studied.[147–149]

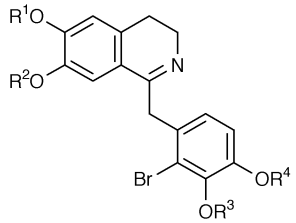
10 Phthalide–isoquinolines

Oxidation of the 1-benzyl-3,4-dihydroisoquinolines **116a–d** with singlet oxygen affords the corresponding ketones **117** in good yield. The methiodides of these, when reduced with excess of sodium borohydride, gave 32:1 mixtures of the *erythro* and *threo* alcohols **119** and **120**. Catalytic reduction of the methiodides gave the ketones **118**, which were reduced by sodium borohydride to the same mixtures of **119** and **120**, and carbonyl insertion into these afforded the racemic phthalide alkaloids cordrastine-II **121a**, corlumine **121b**, β-hydrastine **121c**, bicuculline **121d**, cordrastine-I **122a**, adlumine **122b**, α-hydrastine **122c** and adlumidine **122d**. Under the same conditions, but in the absence of carbon monoxide, the *erythro* alcohols **119** suffered dehydration and loss of the *N*-methyl group to give the dibenzopyrrocolines **123a–d**, but the *threo* isomers were recovered unchanged, as were the 2′- and 6′-bromolaudanosines **124a** and **124b**. The ketones **118** were found to be sensitive to air, and the tetramethoxy compound was rapidly converted into *N*-methylcorydaldine **30** and 2-bromoveratric acid by oxygen in methanol. Similarly **119a** was converted into the dihydroisoquinolinium salt **125** and 2-bromoveratric acid by the mild oxidant copper(II) chloride.[118]

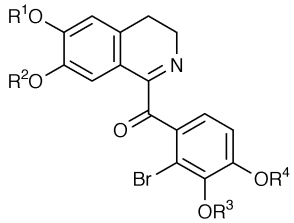
The pharmacological properties and physiological effects of bicuculline have been studied.[150–153]

11 Other modified berberines

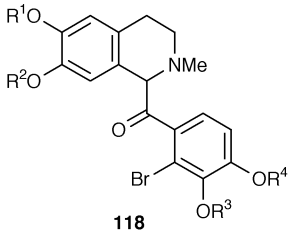
A new synthesis of lennoxamine **130** has been reported. The amide **126** was cyclised to the lactam **127**, which, on condensation with piperonal, gave **128**. Catalytic reduction of this, followed by acid-catalysed cyclisation, gave dehydrolennoxamine **129**, which afforded lennoxamine **130** on catalytic reduction.[154] In a model experiment **131** has been cyclised by tributyltin hydride to an analogue of lennoxamine.[155]



116a $R^1 = R^2 = R^3 = R^4 = Me$
116b $R^1 = R^2 = Me$, $R^3R^4 = CH_2$
116c $R^1R^2 = CH_2$, $R^3 = R^4 = Me$
116d $R^1R^2 = R^3R^4 = CH_2$



117



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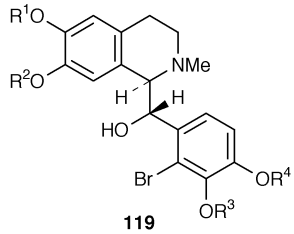

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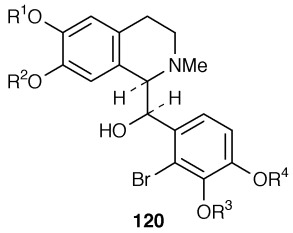

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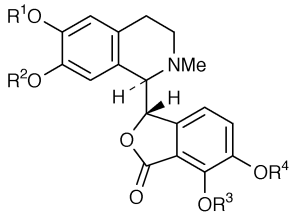
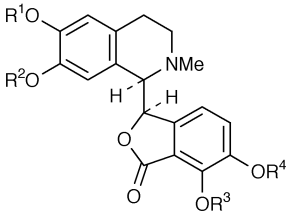
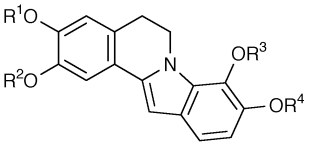


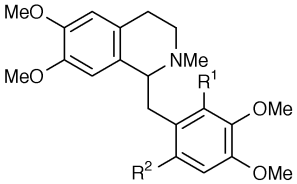
121a $R^1 = R^2 = R^3 = R^4 = Me$
121b $R^1 = R^2 = Me$, $R^3R^4 = CH_2$
121c $R^1R^2 = CH_2$, $R^3 = R^4 = Me$
121d $R^1R^2 = R^3R^4 = CH_2$



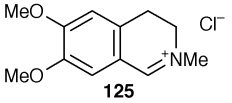
122a $R^1 = R^2 = R^3 = R^4 = Me$
122b $R^1 = R^2 = Me$, $R^3R^4 = CH_2$
122c $R^1R^2 = CH_2$, $R^3 = R^4 = Me$
122d $R^1R^2 = R^3R^4 = CH_2$



123a $R^1 = R^2 = R^3 = R^4 = Me$
123b $R^1 = R^2 = Me$, $R^3R^4 = CH_2$
123c $R^1R^2 = CH_2$, $R^3 = R^4 = Me$
123d $R^1R^2 = R^3R^4 = CH_2$

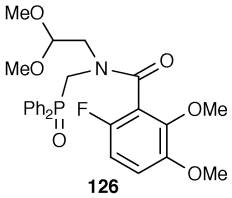


124a $R^1 = Br$, $R^2 = H$
124b $R^1 = H$, $R^2 = Br$



125

A synthesis of (+)-ribasine **139b** has been accomplished starting from the chiral aminolactone **132**. Alkylation of this with homopiperonyl bromide gave the lactone **133** in greater than 99% diastereoisomeric purity, since the phenyl group of **132** is forced to adopt the axial configuration, hindering attack on the same face of the molecule. Hydrolysis of **133** afforded **134a**, which was brominated to **134b** and the *N*-phenylfluorenyl derivative of this was condensed with formaldehyde to give the oxazolidinone **135**. This was cyclised by butyllithium to the aminoindanone **136** with complete enantiomeric purity.



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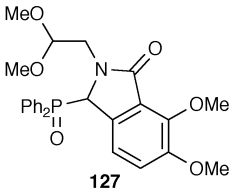

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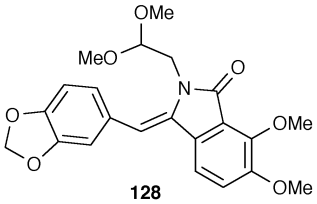

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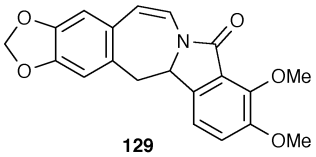

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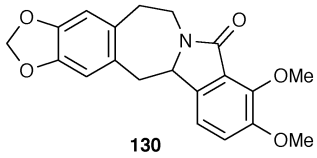

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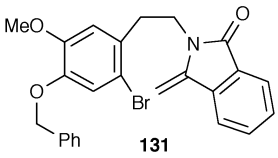

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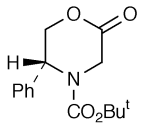

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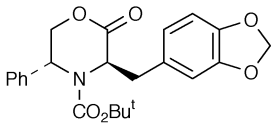

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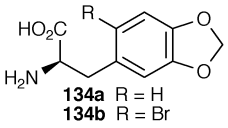
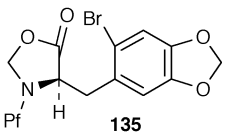
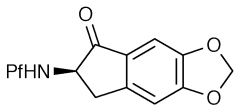


134a R = H
134b R = Br



135

Treatment of this with the lithium salt of ethyl dimethoxy-*o*-toluate afforded the lactone **137**, the *cis* isomer of which (90%) was reduced to the hemiacetal **138**, which gave norribasine **139a** on treatment with trifluoroacetic acid. *N*-Methylation of **139a** gave (+)-ribasine **139b**.[156] In a model approach to ribasine **140** has been converted into **141** by treatment with *N*-methylbenzaldimine.[157]



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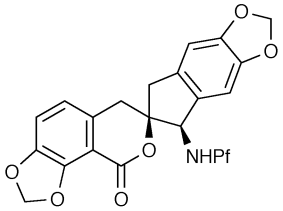

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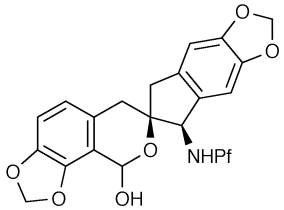

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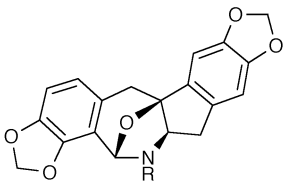
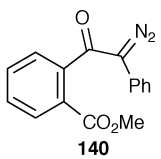


139a R = H
139b R = Me



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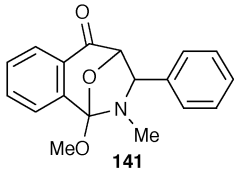
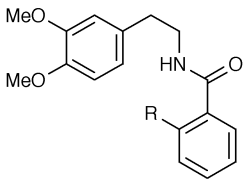
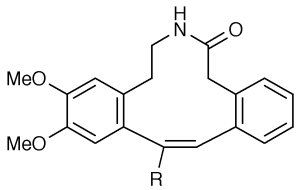


141

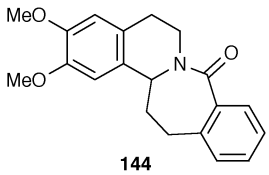
Isomeric homoprotoberberine systems have been synthesised from the amide **142a** *via* **142b**, which was cyclised by tributyltin hydride to the *E* and *Z* isomers of the olefin **143a**, which were reduced to **143b**. Of these the *E*-isomer of **143b** was cyclised to **144** and the *Z*-isomer to **145**.[158]



142a R = I
142b R = C≡C–SiMe$_3$



143a R = SiMe$_3$
143b R = H



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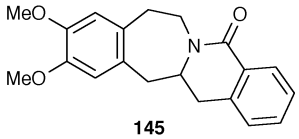


145

12 Emetine and related alkaloids

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

Alangium kurzii[159]

alangiside and *N*-deacetyl-6-*O*-methylipecosidic acid* **146**

Alangium lamarckii[160]

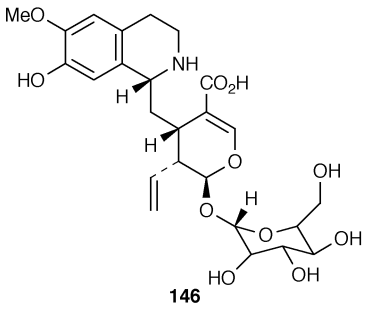
1′,2′-dehydrotubulosine* **147**

Cephaelis acuminata[160,161]

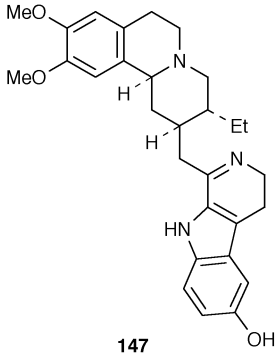
2′-*N*-(1-deoxy-β-D-fructopyranosyl)cephaeline* **149**, 10-*O*-demethylcephaeline, 7′-*O*-demethylcephaeline* **150a**, emetine, isocephaeline, neocephaeline* **150b**, protoemetine, 9-*O*-demethylprotoemetinol and psychotrine

Pogonopsis speciosus[162]

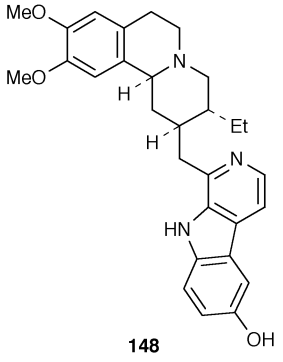
psychotrine, tubulosine and 1′,2′,3′,4′-dehydrotubulosine* **148**



146



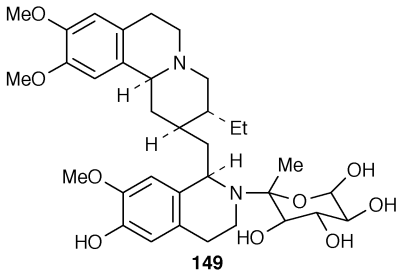
147



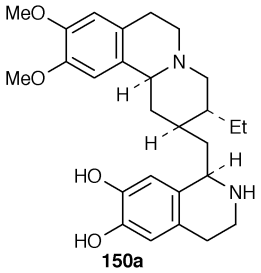
148

13 Benzophenanthridines

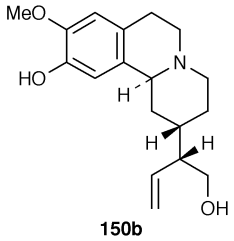
Benzophenanthridine alkaloids have been isolated from the following plant species, the two marked with asterisks being new alkaloids:



149

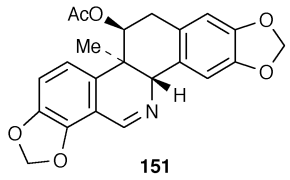


150a



150b

Argemone mexicana[107]
norsanguinarine
Chelidonum majus[163]
chelidonine
Corydalis ambigua[164]
corynicine* **151**, corynoline and acetylcorynoline
Corydalis incisa[164]
corynicine, corynoline and acetylcorynoline
Eomecon chinantha[145]
chelerythrine and sanguinarine
Fagara xanthoxylides[165]
fagaridine
Glaucium oxylobum[146]
8-acetonyldihydrosanguinarine
Macleaya cordata[166]
isofagaridine (decarine)
Zanthoxylum myriacanthum[167]
nornitidine and 8-demethoxy-7-methoxynornitidine* **152**
Zanthoxylum rugosum[168]
chelerythrine



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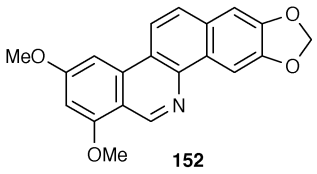
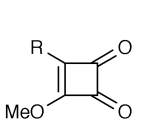


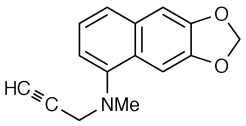
152

Recent chemistry of the alkaloids of the group has been reviewed[5,169] and the ^{15}N NMR spectra of eight of the alkaloids have been analysed.[55,170] Chelerythrine bisulfate on heating has been shown to undergo competing *O* and *N* demethylation.[171] Sanguinarine in aqueous alkali undergoes disproportionation of the initially formed pseudobase to give dihydrosanguinarine and 6-oxodihydrosanguinarine,[172] of which a further synthesis by a previously reported method has been recorded.[173]

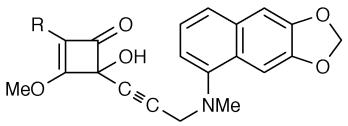
The acetylenic amine **154** reacts with the diketones **153a** and **153b** to give the alcohols **155a** and **155b**, which can be cyclised to the phenolic benzophenanthridines **156a** and **156b** and of these **156b** has been converted into the alkaloid chelilutine **157**.[174] A stereocontrolled synthesis of 12α-methyl-*trans*-hexahydrobenzophenanthridines has been accomplished starting from the *N*-acyl-(+)-pseudoephedrine **158a**. Allylation of this gave the ester **158b** in high diastereoisomeric excess, and this was hydrolysed to the (*S*)-amino acid **159**, the acid chloride of which with methylenedioxybenzene yielded the ketone **160**. This was subjected to reductive ammination with benzylamine to give the (*S*,*S*)-amine **161** almost exclusively. Pictet–Spengler condensation of this with formaldehyde



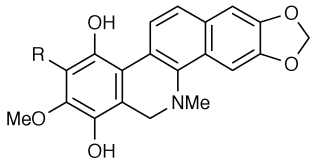
153a R = OMe
153b R = H



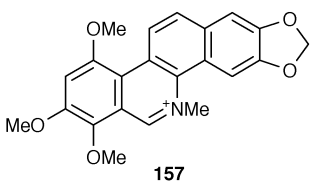
154



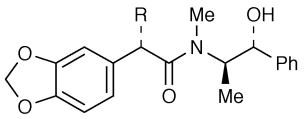
155a R = OMe
155b R = H



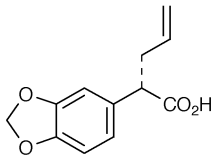
156a R = OMe
156b R = H



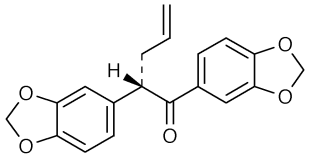
157



158a R = H
158b R = $CH_2CH{=}CH_2$



159



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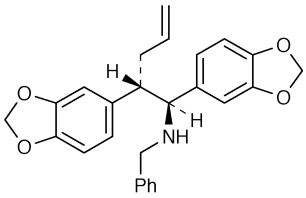
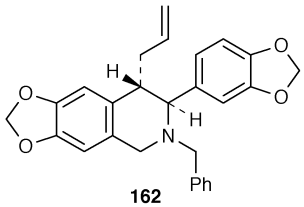
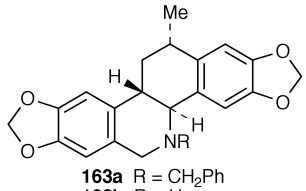


161

afforded the tetrahydroisoquinoline **162**, which was cyclised by phosphoric acid to the hexahydrobenzophenanthridine **163a**, further converted into **163b** and **163c**.[175]



162



163a R = CH_2Ph
163b R = H
163c R = Me

The pharmacological properties and physiological effects of chelerythrine[176] and of sanguinarine[62] have been studied.

14 Aporphinoid alkaloids

14.1 Proaporphines

The proaporphine alkaloids stepharine and pronuciferine have been isolated from *Artabotrys uncinatus*[177] and *Stephania cepharantha*[75] respectively.

14.2 Aporphines

Aporphine alkaloids have been isolated from the following plant species, the ten marked with asterisks being new alkaloids:
Artabotrys uncinatus[177]
anonaine, artabonatine A* **164**, artabonatine B* **165**, asimilobine and norunshinsunine

Cananga odorata[8]
anaxagorine, anonaine, asimilobine, nornuciferine, *N*-acetylnornuciferine* **166**, ushinsunine and ushinsunine *N*-oxide* **167**

Cissampelos glaberrima[178]
cissaglaberrimine

Cyclea peltata[72]
magnoflorine

Enantia chlorantha[179]
dehydronuciferidine* **168a** and dehydronornuciferidine* **168b**

Glaucium grandiflorum[108]
corydine, isocorydine and isocorytuberine

Glaucium leiocarpum[51]
dehydronorglaucine, glaucine, *N*-methylglaucine, lastourvilline and predicentrine

Magnolia denudata[180]
anonaine and glaucine

Magnolia grandiflora[180]
anonaine, glaucine and roemerine

Magnolia kobus[180]
glaucine

Magnolia obovata[180]
anonaine and roemerine

Magnolia soulangeana[180]
anonaine, glaucine and roemerine

Magnolia stellata[180]
glaucine and roemerine

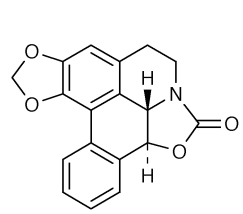
Magnolia tripetala[180]
anonaine, glaucine, isolaureline *N*-oxide and roemerine

Sciadotenia toxifera[181]
N-formylnoranolobine* **169**

Stephania cepharantha[54,75]
asimilobine, *N*-methylasimilobine-2-*O*-β-D-glucoside* **170**, cassythicine, crebanine, dehydrocrebanine, dehydrostephanine, dicentrine, isolaureline, magnoflorine, menispermine, nuciferine, roemerine, stephanine, stesakine, stesakine-9-*O*-β-D-glucoside* **171** and *N*-methylstesakine chloride* **172**

Stephania venosa[182]
dehydrocrebanine and dehydrostephanine

(*S*)-(+)-Boldine **173a** has been halogenated to give **173b**–**173f**; with iodine **173g** was not obtained. The halides **173b**–



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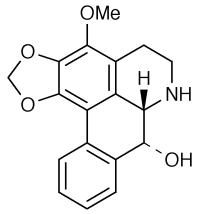

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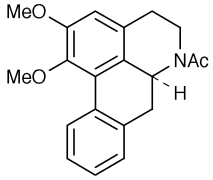

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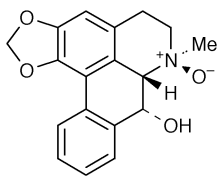

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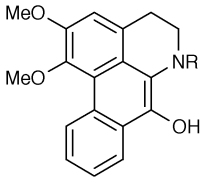
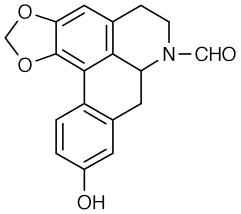


168a R = Me
168b R = H



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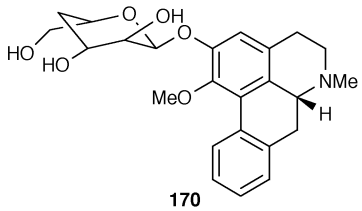

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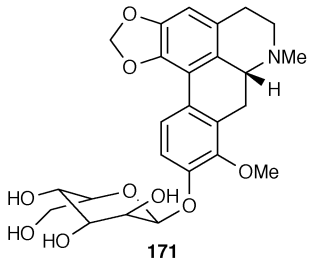

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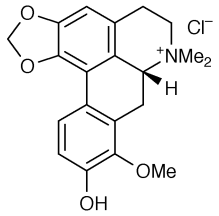
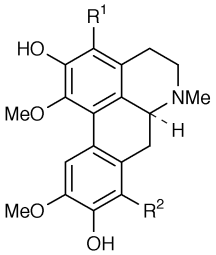
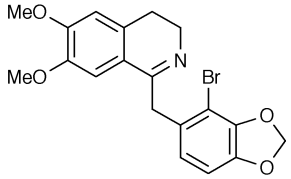


172

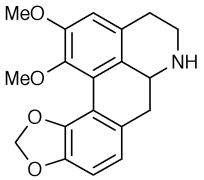
173d have greater affinity for the D_1 than for the D_2 dopaminergic receptor.[183] Radical cyclisation of the 2′-bromobenzyl-3,4-dihydroisoquinoline **174** affords the aporphrine **175**, together with a smaller amount of the dibenzopyrrocoline **123b**.[184]



173a $R^1 = R^2 = H$
173b $R^1 = Cl$, $R^2 = H$
173c $R^1 = Br$, $R^2 = H$
173d $R^1 = I$, $R^2 = H$
173e $R^1 = R^2 = Cl$
173f $R^1 = R^2 = Br$
173g $R^1 = R^2 = I$



174



175

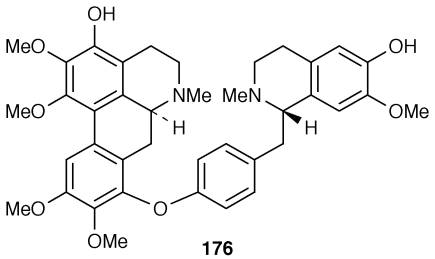
The pharmacological properties and physiological effects of apomorphine,[185–202] of glaucine,[203] of hernovine,[204] of magnoflorine[140] and of 7-hydroxydehydrothalicsimidine[204] have been studied.

14.3 Aporphine–benzylisoquinoline dimers

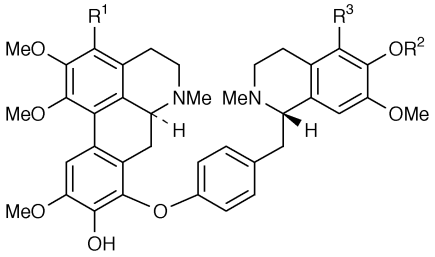
Five new aporphine–benzylisoquinoline dimers, namely 3-hydroxy-6′-*O*-demethyl-9-*O*-methylthalifaboramine (3-*O*-demethylthalifarazine) **176**, 3-hydroxythalifaboramine **177a**, 6′-*O*-demethylthalifaboramine **177b**, 3,5′-dihydroxythalifaboramine **177c**, 5′-hydroxythalifaboramine **177d** and 3-hydroxy-6′-*O*-demethylthalifaboramine **177e** have been isolated from *Thalictrum faberi*.[205] A further four new alkaloids, faurithaline **178a**, 3-methoxyfaurithaline **178b**, fauridine **179** and the pavine fauripavidine **180** have been isolated from *Thalictrum faurei*.[105] Faurithaline and fauripavine represent novel linkages of the two units in this series. The alkaloids **177c** and **177d** have a novel substitution pattern, being the first of the group derived from 5,6,7-oxygenated benzylisoquinolines, but **176**, **177a** and **177e** are analogues of several alkaloids previously isolated from *Thalictrum cultratum* and, like these, show potent cytotoxic and antimalarial activity.[205]

14.4 Phenanthrenes

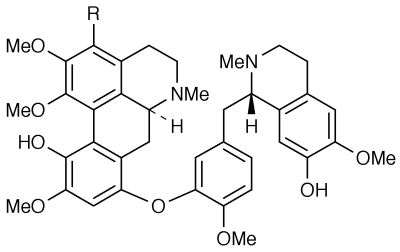
Secoglaucine has been isolated from *Glaucium leiocarpum*.[51] The electronic spectra of taspine have been studied.[206]



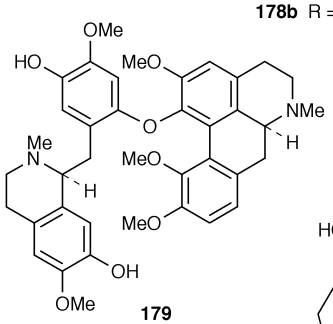
176



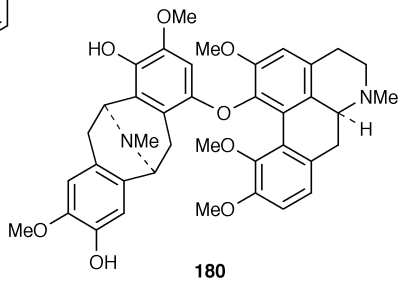
177a R^1 = OH, R^2 = Me, R^3 = H
177b R^1 = R^2 = R^3 = H
177c R^1 = R^3 = OH, R^2 = Me
177d R^1 = H, R^2 = Me, R^3 = OH
177e R^1 = OH, R^2 = R^3 = H



178a R = H
178b R = OMe



179



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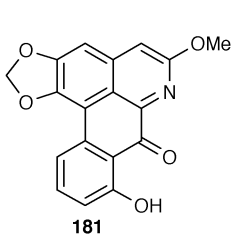
14.5 Oxoaporphines

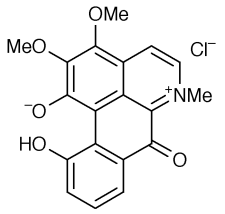
Oxoaporphine alkaloids have been isolated from the following plant species, the two marked with asterisks being new alkaloids:

Alphonsea mollis[207]
8-hydroxy-5-methoxyliriodenine* **181**
Alphonsea monogyma[208]
liriodenine
Artabotrys uncinatus[177]
liriodenine
Cananga odorata[8]
liriodenine and lysicamine
Glaucium leiocarpum[51]
oxoglaucine
Glaucium oxylobum[146]
dicentrinone
Magnolia denudata[180]
liriodenine
Magnolia grandiflora[180]
liriodenine
Magnolia obovata[180]
liriodenine
Magnolia soulangeana[180]
liriodenine
Magnolia stellata[180]
liriodenine
Magnolia tripetala[180]
liriodenine
Sciadotenia toxifera[181]
sciaferine* **182**

and 4-deoxydihydronorouregidione **183a** and its 3-*O*-demethyl analogue **183b**, two oxoaporphines of a novel type, have been isolated from *Mitrephora maingayi*.[209]

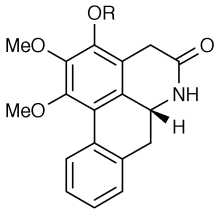


181

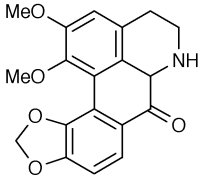


182

2′-Bromobenzoyl-3,4-dihydroisoquinolines of general type **117** have been cyclised by tributyltin hydride to 8-oxoporphines such as **184**, reducible to 8-hydroxyaporphines **185**.[184]



183a R = Me
183b R = H



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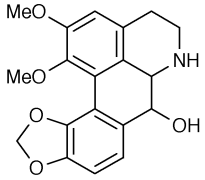
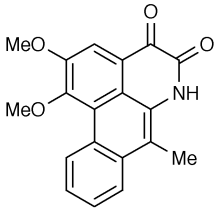


185

14.6 Dioxoaporphines

Dioxoaporphine alkaloids have been isolated from the following plant species, that marked by an asterisk being a new alkaloid:

Glaucium leiocarpum[51]
dihydropontevedrine
Goniothalamus griffithii[210,211]
griffithidione* **186**
Mitrephora maingayii[209]
uregidione



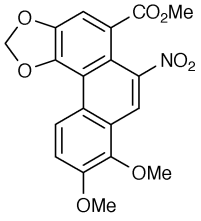
186

14.7 Aristolochic acids and aristolactams

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

Aristolochia bracteata[212]
aristolochic acid A
Aristolochia contorta[212]
aristolochic acid A
Aristolochia curcurbitifolia[213]
7-methoxyaristolochic acid A methyl ester* **187**
Aristolochia debilis[212]
aristolochic acid A
Aristolochia heterophylla[212,214]
aristolochic acid A and aristolactam C-IV* **188**
Aristolochia mollissima[212]
aristolochic acid A

In addition the lactone aristolide C **189**, which is presumably a metabolite of 7-methoxyaristolochic acid A, has been isolated from *Aristolochia curcubitifolia*.[213]



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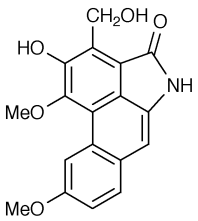

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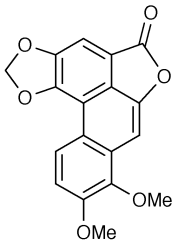
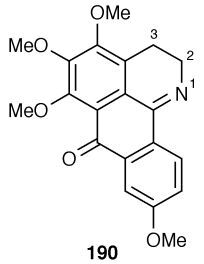


189

A synthesis of aristolactam A-IIIa (goniothalactam) has been reported.[215]

14.8 Oxoisoaporphines

Dauriporphine and the new alkaloids 2,3-dihydrodauriporphine **190** and tyraminoporphine **191** have been isolated from *Menispermum dauricum* grown in a medium containing ketoconazole, an inhibitor of cytochrome P-450. These alkaloids were not produced in the absence of ketoconazole, except in the presence of the bisbenzylisoquinoline alkaloid aromoline, when dauriporphine and dihydrodauriporphine were formed. The structure of tyraminoporphine was proved by an X-ray crystallographic study.[216]



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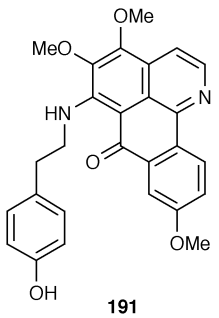
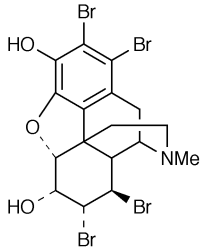


191

15 Alkaloids of the morphine group

Methods of estimating morphine,[217–223] morphine 3 and 6-glucuronides,[219,221,223] 6-*O*-acetylmorphine,[217] 3,6-*O*-diacetylmorphine,[220,223,224] codeine[216] and naltrexone[225] have been described. Bromination of morphine gives, in acetic acid, 1,2-dibromo-6-*O*-acetylmorphine, but a mixture of 1,2,7α,8β- and 1,2,7β,8α-tetrabromodihydromorphine **192** and **193** in hydrobromic acid.[226] Under similar conditions in acetic acid codeine gives 1-bromocodeine, but a mixture of 1,7α,8β-tribromo-, 1,7β,8α-tribromo- and 1,2,7α,8β-tetrabromocodeine under ultraviolet light.[227]



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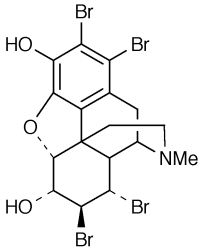
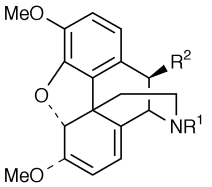
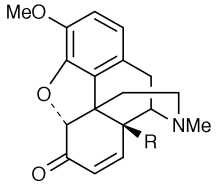


193

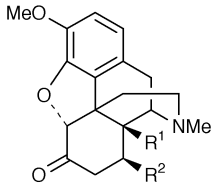
N-Phenylnormorphine, *N*-phenylnorcodeine and *N*-phenylnorthebaine **194a** have been prepared from the corresponding secondary bases and triphenylbismuth in the presence of copper(II) acetate.[228] Codeinone **195a** has been oxidised to 14-hydroxycodeinone **195b** by dimethylperacetic acid and by cobalt(III) acetate in greater than 50% yield.[229] In the preparation of **195b** from thebaine **194b** and hydrogen peroxide 10-hydroxythebaine and 8β,14β-dihydroxydihydrocodeinone **196a** have been identified as by-products.[230] 14-(3-Methylbut-2-enyl)dihydrocodeinone **196b**, on ozonolysis, afforded the keto-aldehyde **196c**, which undergoes internal aldol condensation in alkali to give the ketone **197**.[231] The photo-oxidation of thebaine to the keto-aldehyde **198** has been covered by a patent.[232]



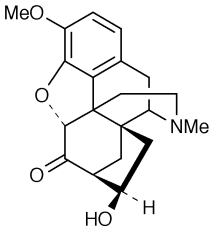
194a R^1 = Ph, R^2 = H
194b R^1 = Me, R^2 = H
194c R^1 = Me, R^2 = OH



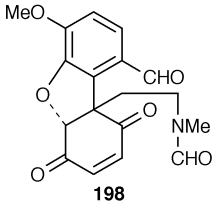
195a R = H
195b R = OH



196a R^1 = R^2 = OH
196b R^1 = $CH_2CH{=}CMe_2$, R^2 = H
196c R^1 = CH_2CHO, R^2 = H
196d R^1 = OH, R^2 = H, MeO = HO
NMe = $NCH_2C_3H_5$

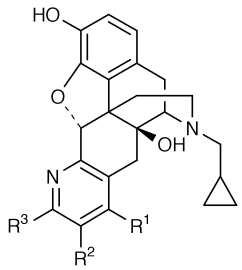


197

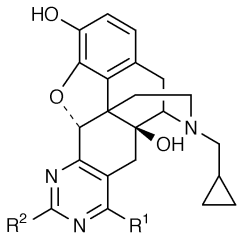


198

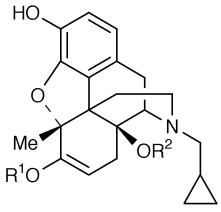
Naltrexone **196d** has been condensed with 3-dimethylaminoacrolein, with 3-dimethylamino-2-phenylacrolein and with β-dimethylaminopropiophenone to give the pyridinomorphinans **199a**, **199b** and **199c** and with cinnamaldoxime to give **199d**. 7-Benzylidenenaltrexone reacts with 1-acetonylpyridinium chloride to give **199e** and with formamidoxime to give the pyrimidinomorphinan **200a**. 7-(Dimethylaminomethylene)-naltrexone reacts with amidines to give the pyrimidinomorphinans **200b**, **200c** and **200d**.[233] Other analogues of **199** and **200** have also been prepared.[233,234] The enol methyl and ethyl ethers of naltrexone have been alkylated to give the 5β-methyl compounds **201a**–**201d**.[235]



199a $R^1 = R^2 = R^3 = H$
199b $R^1 = R^3 = H$, $R^2 = Ph$
199c $R^1 = R^2 = H$, $R^3 = Ph$
199d $R^1 = Ph$, $R^2 = R^3 = H$
199e $R^1 = Ph$, $R^2 = H$, $R^3 = Me$

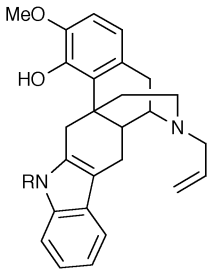


200a $R^1 = Ph$, $R^2 = H$
200b $R^1 = H$, $R^2 = Ph$
200c $R^1 = H$, $R^2 = Me$
200d $R^1 = R^2 = H$

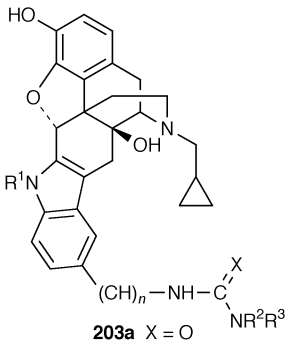


201a $R^1 = Me$, $R^2 = H$
201b $R^1 = Et$, $R^2 = H$
201c $R^1 = R^2 = Me$
201d $R^1 = R^2 = Et$

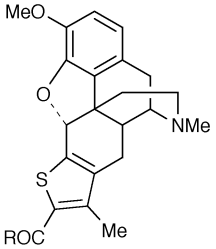
Details of the preparation of the following, by previously described routes, have been published: ethers of *N*-alkylnormorphines,[236] 6-*O*-methyl-6,14-peroxycodeine,[237] 14-hydroxydihydrocodeinone,[238] its hydrazone, and semicarbazone and their 14-*O*-alkyl ethers,[239] esters of naloxone and of naltrexone,[240] ketals of naltrexone,[241] the indoles **202a**, **202b**, **203a** and **203b**[242,243] and other related compounds,[244] the thiophenes **204a**, **204b** and **204c**,[245] the 6,14-*endo*-ethenotetrahydrothebaines **205a**, **205b** and **205c**,[246,247] esters of **205c** and its homologues,[248] the phenol **206**[249] and the isomeric olefines **207a** and **207b**.[250]



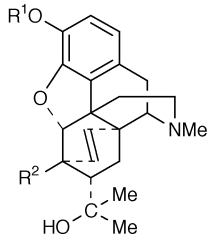
202a R = H
202b R = Me



203a X = O
203b X = NH

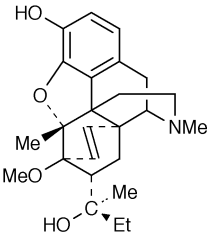


204a R = OH
204b R = OMe
204c R = NPr^i_2

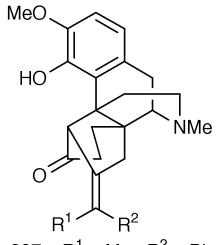


205a $R^1 = Me$, $R^2 = OH$
205b $R^1 = Me$, $R^2 = NH_2$
205c $R^1 = H$, $R^2 = OMe$

Stereo-controlled asymmetric syntheses of natural (−)-codeine and of (+)-codeine have been reported. The hydroxymethylenetetralone **208** undergoes Michael addition to buten-3-one to give the racemic α,β-unsaturated ketone **209**

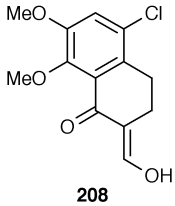


206



207a $R^1 = Me$, $R^2 = Ph$
207b $R^1 = Ph$, $R^2 = Me$

together with its β,γ-unsaturated isomer, which is easily equilibrated with **209**. Racemic **209** was resolved to give pure **209** on cellulose acetate, the unwanted enantiomer being easily racemised for further resolution. (−)-**209** reacted with vinylmagnesium cuprate to furnish **210a** in high yield, the 7-bromo derivative of which, **210b**, was cyclised to **211**. Hydroboration of the cyclic ketal of **211**, followed by oxidation, afforded **212a**, reducible to **212b**, which reacted directly with *N*-methylbenzenesulfonamide to give **213a**. Bromination of this with *N*-bromosuccinimide gave **213b**, which was dehydrobrominated to **214** and this was cyclised to the ketal, hydrolysis of which afforded (−)-dihydrocodeinone **215**, previously converted into (−)-codeine.[251]



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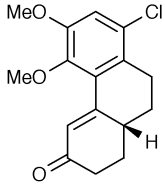

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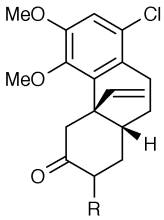
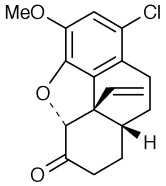


210a R = H
210b R = Br



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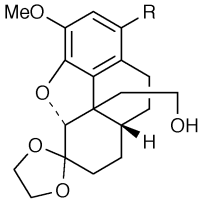
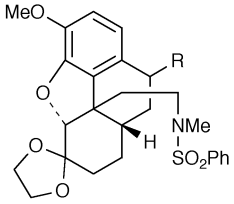
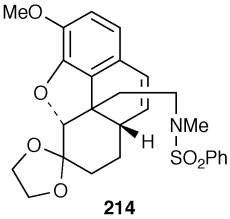


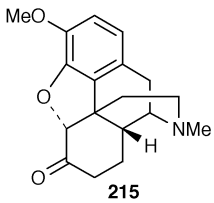
212a R = Cl
212b R = H



213a R = H
213b R = Br



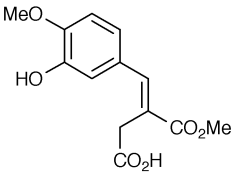
214



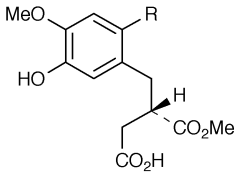
215

Stobbe condensation of isovanillin with dimethyl succinate yielded **216**, which was reduced over a chiral rhodium catalyst to give **217a** in 94% enantiomeric excess. Bromination of this to **217b**, followed by cyclisation led to the tetralone **218a**, which was converted into **218b** and this on Michael addition to buten-3-one yielded **218c**, which was cyclised to the lactol **219**.

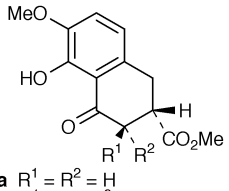
Internal aldol condensation of this in alkali was accompanied by dehydration and hydrolysis, to give only one isomer of an acid that was esterified to **220a**. Bromination of this to **220b**, followed by cyclisation (presumably *via* the isomeric β,γ-unsaturated ketone) afforded **221**. Catalytic reduction of this involved loss of the carbonyl group, but prior reduction with sodium borohydride afforded the alcohol **222a** in 22-fold excess over a diastereoisomer. The related diazoketone **222b** was then cyclised by dirhodium(II) tetrakis(acetamide) to the ketone **223**, the oxime of which on Beckmann rearrangement furnished a 10:1 mixture of **224** and the product of the alternative rearrangement. Hydrolysis and oxidation of **224** yielded **225a**, which was converted through **225b** into the unsaturated ketone **226**, which gave (+)-codeine **227** on reduction with lithium aluminium hydride.[252]



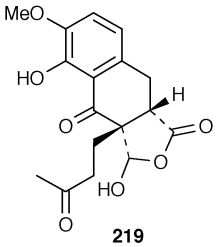
216



217a R = H
217b R = Br



218a $R^1 = R^2 = H$
218b $R^1 = H$, $R^2 = CHO$
218c $R^1 = CH_2CH_2COCH_3$, $R^2 = CHO$



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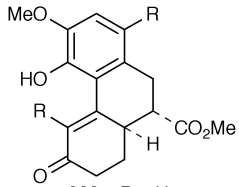
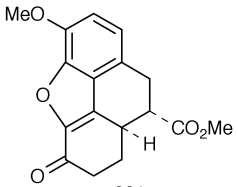


220a R = H
220b R = Br



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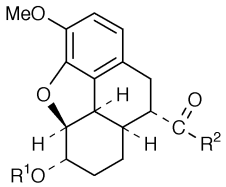
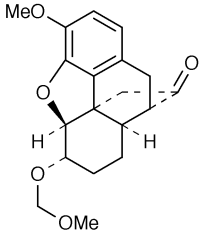


222a $R^1 = H$, $R^2 = OMe$
222b $R^1 = CH_2OMe$, $R^2 = CHN_2$



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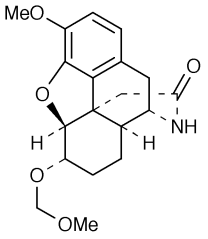
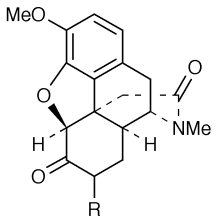
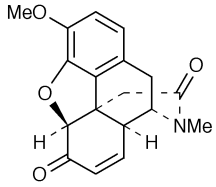


224



225a R = H
225b R = SePh



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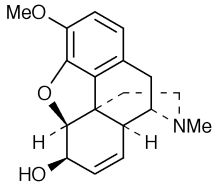

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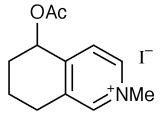

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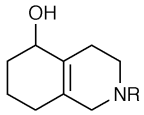
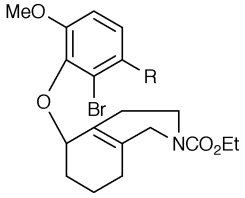
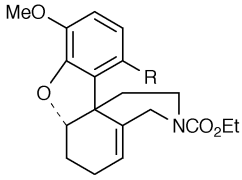


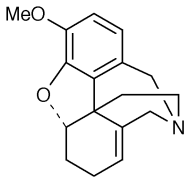
229a R = Me
229b R = CO_2Et



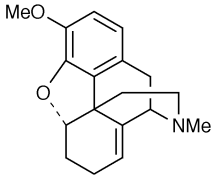
230a R = CHO
230b R = CH_2OH
230c R = $CH_2OSiMe_2Bu^t$



231a R = $CH_2OSiMe_2Bu^t$
231b R = CH_2OH
231c R = CH_2Cl



232



233

The 5,6,7,8-tetrahydroisoquinolinium salt **228** has been reduced to **229a** and the related **229b** reacted with bromoisovanillin to give **230a**, reduced to **230b**. Cyclisation of the protected **230c** afforded **231a**, which was converted through **231b** and **231c** into the tertiary base **232**. The methiodide of this, on treatment with phenyllithium, suffered Stevens rearrangement to give (±)-deoxycodeine D **233**.[253]

The analgesic properties,[254–304] pharmacokinetics[305–307] and metabolism[307–310] of morphine have been studied, as have the effects of the alkaloid on behaviour,[311–323] on the brain,[324,325] on the cardiovascular system,[326,327] on neurones,[261,328–333] on locomotor activity,[334,335] on immune responses,[336–341] on respiration,[342–344] on the gastrointestinal tract,[345,346] on the newborn,[347,348] on life expectancy,[349] on body weight,[350] on sexual organs,[350,351] on appetite,[352] on pulmonary[353] and peritoneal[354] inflammation, on spinal reflexes,[355] on synaptic transmission,[356,357] on sciatic nerve injury,[358] on the intake of alcohol[359] and of sugar,[360] on apoptosis,[361] on responses to HIV,[362] on neuroblastoma cells,[363] on the formation of RNA,[364] on the activity of heme oxygenase,[365] on levels of acetylcholine,[366–368] of dynorphin,[364] of dopamine,[369] of cyclic-AMP,[370] of cortisol,[371] of corticosterone,[372] of follicle stimulating hormone,[349] of luteinising hormone,[349] of interleukin-6,[372] of melatonin,[373] of nitric oxide,[374,375] of orphanin,[325] of prolactin,[371] of phospholipase-C,[376] of substance P,[377] of serotonin,[369] of testosterone,[349] and of thyroid hormones,[371] and on responses to cocaine[378] and to oxytocin.[379]

The morphine antagonist actions of naloxone have been studied,[380–386] as have the effects of this compound on behaviour,[321,387,388] on the cardiovascular system,[389,390] on the gastrointestinal tract,[391] on locomotor activity,[392] on appetite[388] and food intake,[393] on the eye,[394] on learning and memory,[389] on the metabolism of glucose,[395] on the transfer of morphine across the placenta,[396] on recovery from stroke,[397] on the self-administration of heroin,[398] on the activity of the neurofilament gene,[399] on levels of corticosteroids,[392,400] of

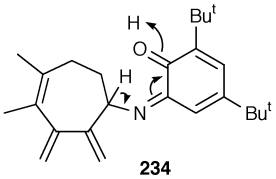
parathyroid hormones[401] and of reactive oxygen species,[402] and on the effects of alcohol,[403,404] of ketamine[405] and of stress.[406]

The pharmacological properties and physiological effects of the following have also been studied: 3,6-*O*-diacetylmorphine,[320,407–409] morphine 3-glucuronide,[307,410,411] morphine 6-glucuronide,[307,411,412] morphinone,[308] dihydromorphinone,[413,414] codeine,[415,416] dihydrocodeinone,[279,417] naloxonazine,[385] naltrexone,[359,384,387,418–436] *N*-methylnaltrexone,[437,438] 7-benzylidenenaltrexone,[439] nalbuphine,[413,440,441] β-funaltrexamine,[422] naltrindole[438,442–445] *O*-methylnaltrindole,[446] binaltorphimine,[424,447] norbinaltorphimine,[418,448–450] etorphine,[451–453] dihydroetorphine,[453] buprenorphine,[413,430,453–465] and the Diels–Alder adduct of thebaine and *N*-phenylmaleimide.[466]

16 Colchicine and related alkaloids

Colchicine, 2-*O*-demethylcolchicine, demecolcine, 2-*O*-demethyldemecolcine, β-lumicolchicine, 2-*O*-demethyl-β-lumicolchicine and 2-*O*-demethylcolchifoline have been isolated from *Colchicum autumnale*.[467,468]

The use of 3,5-di(*tert*-butyl)-1,2-benzoquinone in the oxidative deammination of *N*-deactylcolchicine and *N*-deacetylthiocolchicine has given the compounds **237a**–**237d**, presumably *via* intermediates with the part-structures **234** and **235**, oxidised to **236**, with final oxidation of **237a** to **237b** and **237c** to **237d**.[469] Colchicine reacts with chloroethylamine to give the aziridine **238a** and the tertiary base **238b**,[470] and *N*-deacetylthiocolchicine has been converted into **239**.[471] Irradiation of colchicone has given β-lumicolchicone **240**, but thiocolchicone is not similarly affected.[472] The allocolchinoid ketones **241a** and **241b** have been prepared from the corresponding amines; the former has been demethylated to all four *O*-demethyl compounds[473] and the oxime of the latter, on Beckmann rearrangement afforded the isomeric lactams **242** and **243**.[474] ESR studies have detected a radical anion intermediate in the cathodic reduction of colchicine[475] and a correction has been made to the stereochemistry of the laevorotatory colchinoids and allocolchinoids.[476]



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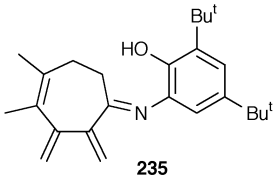

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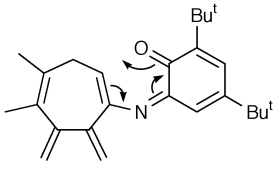
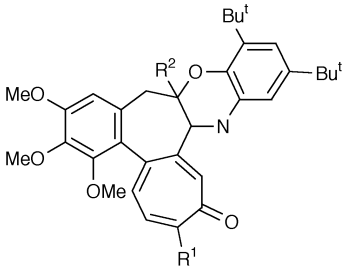


236



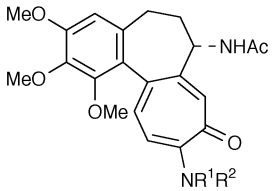
237a R^1 = OMe, R^2 = H
237b R^1 = OMe, R^2 = OH
237c R^1 = SMe, R^2 = H
237d R^1 = SMe, R^2 = OH

The physiological effects of colchicine[477–485] and of thiocolchiside[486] have been studied.

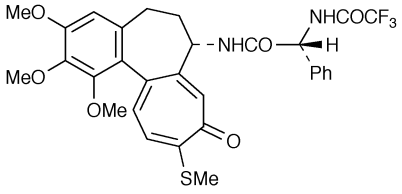
17 *Erythrina* alkaloids

17.1 Erythrinanes

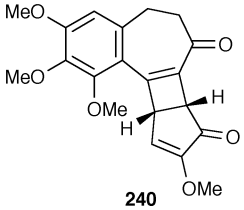
Alkaloids of the erythrinane group have been isolated from the following plant species, the four marked with asterisks being new alkaloids:



238a R^1R^2 = CH_2CH_2
238b R^1 = R^2 = CH_2CH_2Cl



239



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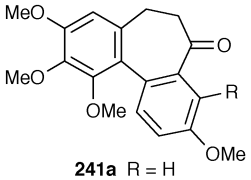
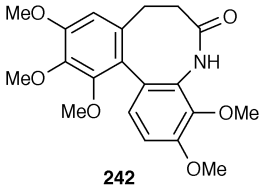
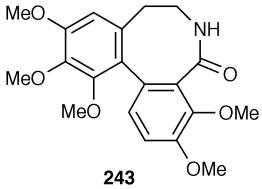


241a R = H
241b R = OMe



242

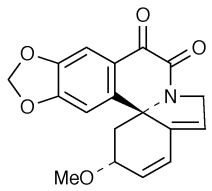


243

Erythrina bidwillii[487]
10,11-dioxoerythraline* **244** and 8-oxoerythraline epoxide* **245**

Erythrina crista-galli[488]
crystamidine, erysotramidine, 11-hydroxyerysotrine, erythrabine and erythrinine

Erythrina variegata[488,489]
crystamidine, erysotramidine, 11-hydroxyerysotrine, erythrinine, erythrosotidienone* **246a** and erythromotidienone* **246b** or **246c**



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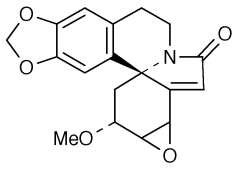
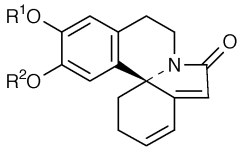


245

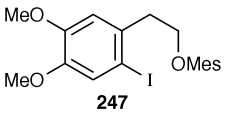
Reaction of the ester **247** with the tetrahydroindole **248** has given **249**, cyclisation of which afforded **250**, which was converted by simple steps into 2-epierythrinitol **251**.[490]

17.2 Cephalotaxine and related alkaloids

Cephalotaxine and drupacine have been isolated from *Cephalotaxus harringtonia*.[491] Treatment of cephalotaxine with the racemic mixed anhydride **252** gave a 3:2 mixture of the (2′*R*)-anhydrohomoharringtonine **253** and its (2′*S*) epimer, which were easily separated. Opening of the tetrahydropyran ring of **253** with hydrogen bromide gave (2′*R*)-(−)-6′-bromo-6′-deoxyhomoharringtonine **254a**, which was hydrolysed to homoharringtonine **254b**.[492] A patent for the preparation of esters of cephalotaxine has been published.[493]



246a $R^1R^2 = CH_2$
246b $R^1 = Me$, $R^2 = H$
246c $R^1 = H$, $R^2 = Me$



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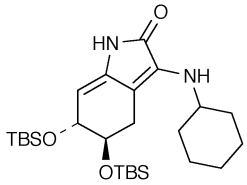

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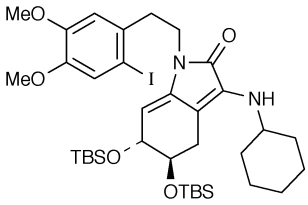

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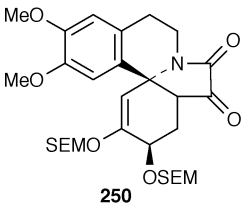

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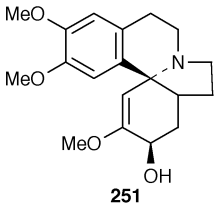

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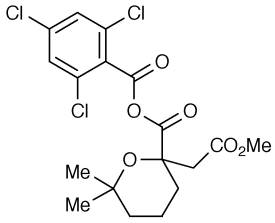

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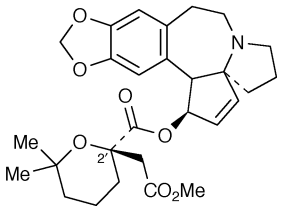
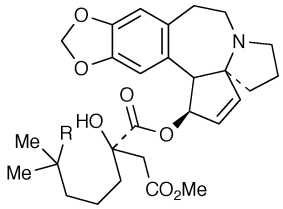
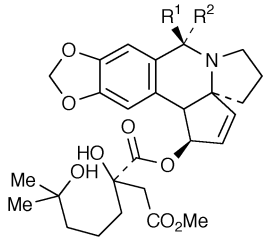


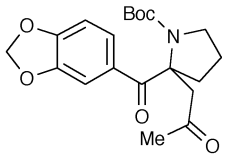
253



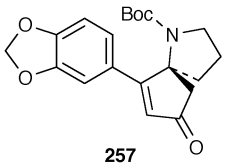
254a R = Br
254b R = OH



255a $R^1 = Me$, $R^2 = H$
255b $R^1 = H$, $R^2 = Me$



256



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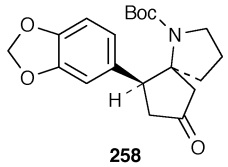

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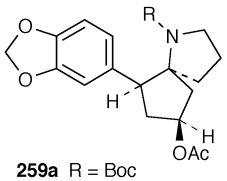
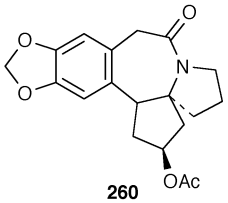


259a R = Boc
259b R = H
259c $R = COCH_2SMe$



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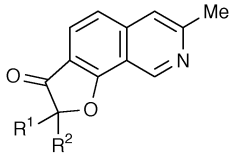

261a $R^1 = CHMe_2$, $R^2 = H$
261b $R^1R^2 = CMe_2$
261c $R^1 = CHMe_2$, $R^2 = OH$

Homoharringtonine *N*-oxide has been rearranged by heat to the bases **255a** and **255b**.[491] Internal aldol condensation of the diketone **256** gave **257**, which was reduced catalytically to **258** and then with sodium borohydride to the alcohol, which was acetylated to **259a**. This was converted into **259b** and then into **259c**, and cyclisation of this gave **260**, which can be converted into cephalotaxine, constituting a formal synthesis of the alkaloid.[494]

The physiological effects of homoharringtonine have been studied.[495–498]

18 Other isoquinolines

Three unusual isoquinolines **261a**, **261b** and **261c**, referred to as TMC 120A, 120B and 120C respectively, with no obvious relationship to alkaloids of any other group, have been isolated from *Aspergillus ustus TC 1118*.[499]

A review of isoquinolinequinone compounds such as saframycin and naphthyridomycin has been published.[500] The physiological effects of ecteinascidin 743 have been studied[501,502] and a patent covering the preparation of this substance and its analogues has been published.[503]

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