β-Phenylethylamines and the isoquinoline alkaloids

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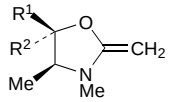
Previous review: 1997, 14, 387

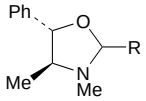
1 β-Phenylethylamines

trans-*N*-Feruloyltyramine has been isolated from *Stephania cepharantha*.[1] The yields of ephedrine and dihydropseudoephedrine from plants derived from axillary buds of *Ephedra gerardiana* and from the parent plants have been compared.[2]

Ephedrine and pseudoephedrine have been condensed with paraformaldehyde to give the oxazolines **1a** and **1b**, respectively,[3] and the oxazolines **2a**, **2b** and **2c** have been prepared



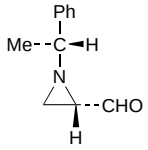
1a R^1 = Ph; R^2 = H
1b R^1 = H; R^2 = Ph



2a R = $CHMe_2$
2b R = Ph
2c R = *p*-Anisyl

from pseudoephedrine.[4] *N*-Cyanomethylephedrine and *N*-cyanomethylpseudoephedrine have been prepared.[5] Complexes of ephedrine and of norephedrine with copper, nickel and cobalt salts have been prepared, the copper derivatives being much the most stable.[6]

Highly diastereoselective additions of lithium alkyls to the (2*S*)-aziridine aldehyde **3** have been achieved, as a result of chelation-controlled carbon–carbon bond formation, to give the alcohols **4**, which have been catalytically reduced selectively to **5**, relatives of ephedrine and pseudoephedrine. Similar reactions have been accomplished with the *R* isomer of **3**.[7]



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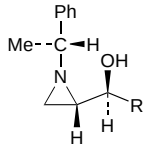

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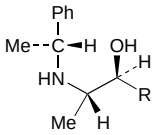

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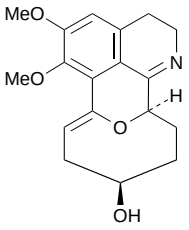
The pharmacological and physiological effects of ephedrine,[8,9,10] of methylephedrine[10] and of pseudoephedrine[11] have been studied.

2 Isoquinolines

The new alkaloids stephaoxocanine **6** and stephaoxocanidine **7** have been isolated from *Stephania cepharantha*.[1,12] These are analogues of excentricine, reported in the previous review, and



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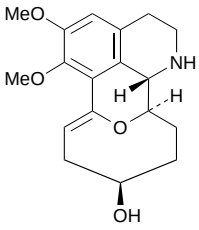

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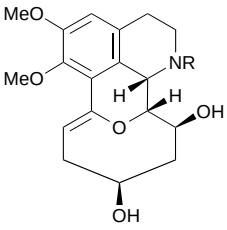
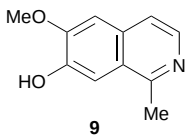


8a R = H
8b R = Me



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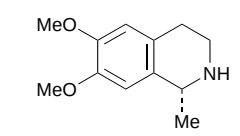
a comparison of the spectra of these three alkaloids has suggested[12] a reversal of the absolute stereochemistry of excentricine from that given in the previous review to **8a**. Methylexcentricine, **8b** on this basis, has been isolated as a new alkaloid from *Stephania excentrica*.[13] 7-*O*-Demethylisosalsolidine **9** has been isolated as a new alkaloid from *Hernandia nymphaeifolia*.[14] *N*-Cyanomethylsalsoline has been prepared.[5]

A convenient process for the synthesis of (±)-carnegine from *N*-methylhomoveratrylamine and acetic acid, by Bischler–Napieralsky cyclisation with polyphosphoric acid and subsequent reduction with sodium borohydride, has been described.[15] A stereospecific synthesis of (*R*)-salsolidine **10** has



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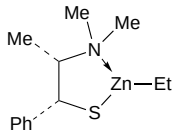

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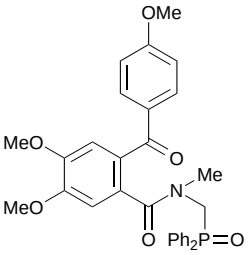

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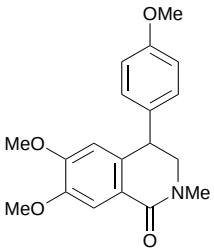


13

been achieved by the catalytic reduction of 1-methyl-6,7-dimethoxy-3,4-dihydroisoquinoline using the chiral zinc complex **11** as catalyst.[16] The benzophenone amide **12** has been cyclised to the 4-aryltetrahydroisoquinolone **13** by potassium hexamethyldisilazide, and the product has been reduced with lithium aluminium hydride to (±)-*O*-methylcherylline.[17]

3 Naphthylisoquinolines

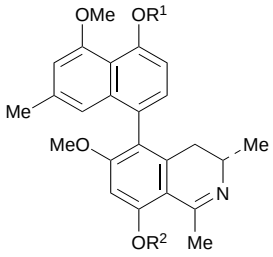
Five new naphthylisoquinoline alkaloids have been isolated from the following plant species:

Ancistrocladus tectorius[18]

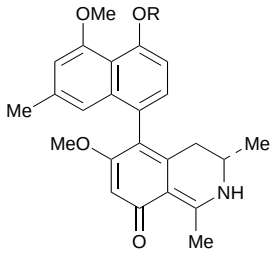
6-*O*-methyl-8-*O*-demethylancistrocladinine **14a**, 6-*O*-methyl-4′-*O*-demethylancistrocladinine **14b** and 6-*O*-methyl-8,4′-*O*-demethylancistrocladinine **14c**

Ancistrocladus korupensis[19]

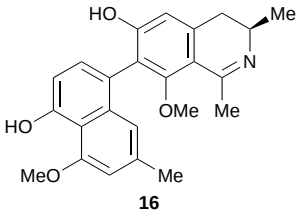
yaoudamine A **16** and its 6-rhamnoside (yaoudamine B).



14a R^1 = Me; R^2 = H
14b R^1 = H; R^2 = Me
14c R^1 = R^2 = H



15a R = Me
15b R = H



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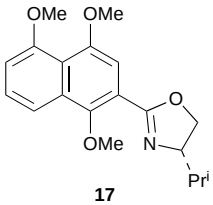
Spectroscopic studies suggest that the free bases **14a** and **14c** exist in the tautomeric keto forms **15a** and **15b**. The absolute stereochemistry of these alkaloids at C-3 has been deduced from their CD spectra and confirmed by the oxidation of **14c** to (3*S*)-aminobutyric acid.[18]

The Grignard reagent **18** has been condensed with the dihydrooxazole **17** and the product has been hydrolysed to the amide **19a**, which was separated into its atropomers in the ratio 6:1, the major component of which was converted into



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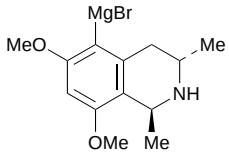

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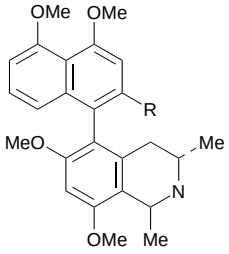
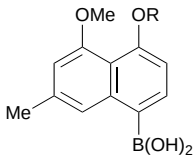
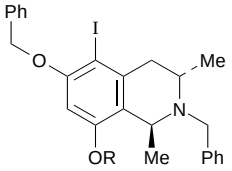


19a R = $CONH_2$
19b R = Me

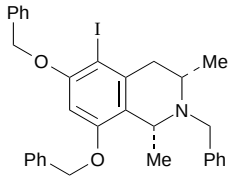
O-methylancistocladine **19b**.[20] The boronic acid derivative **20a** has been condensed with the iodides **21a** and **21b** to give, after reduction and removal of the benzyl groups from oxygen and nitrogen, ancistrobrevine B and korupensamine C.[21] In a similar manner korupensamine D has been prepared from **20b** and **22**.[22] The bromo compound **23** has been coupled with the



20a R = Me
20b R = H



21a R = Me
21b R = CH_2Ph



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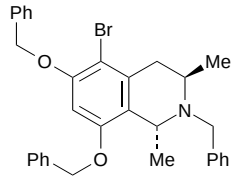

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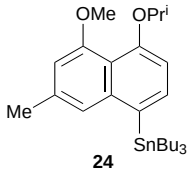

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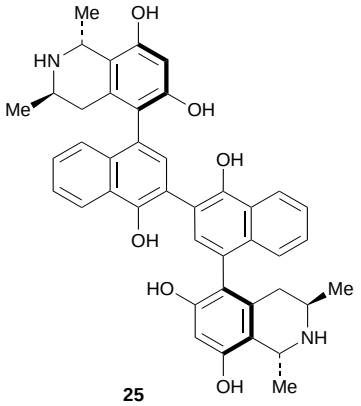
organotin derivative **24** to give *O*-benzylkorupensamines A and B, which have been oxidised by silver oxide and debenzylated to give a mixture of michellamines A, B and C.[23] Palladium-catalysed cross coupling of tetrabenzylkorupensamine A 6′-boronic acid with 6′-bromotetrabenzylkorupensamine B, followed by removal of the benzyl groups, has afforded michellamine B only.[24] A patent has been published covering previously described syntheses of the michellamines, directly and from the korupensamines.[25]

Interest in the antiviral properties of the michellamines has led to the synthesis of analogues of these alkaloids. 4,4′-Didemethoxy-2,2′-didemethylmichellamine B **25**, synthesised by processes analogous to the previously reported direct synthesis of michellamine, inhibits recombinant HIV reverse transcriptase at 60 μg ml^{-1}.[26] The naphthyltin derivative **24** has been converted into **26a**, and oxidation of the related phenol **26b** gave a dimeric quinone, which was reduced to



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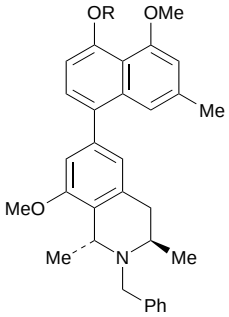
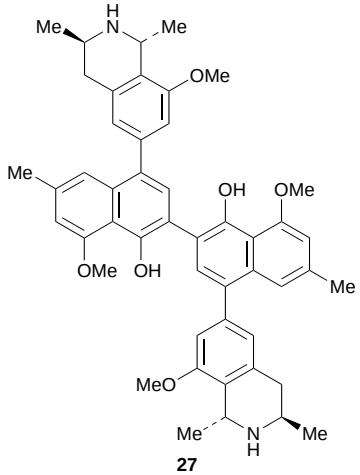
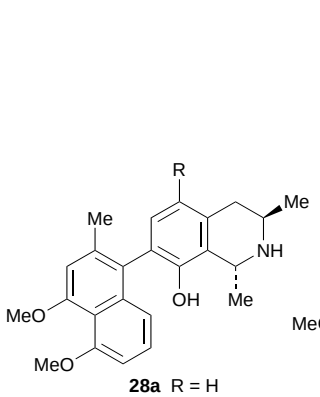


26a R = Pr^{i}
26b R = H

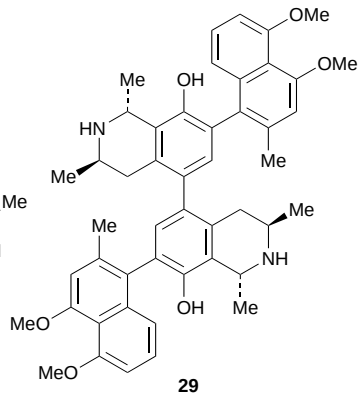


27

pindikamine A **27**, with an unnatural 'skew' structure. This shows no antiviral activity, but is active against *Plasmodium falciparum* at 1.23 μg ml^{-1}, compared with 3.49 μg ml^{-1} for the monomer **26b**.[27] Dioncophylline A **28a** has been brominated to **28b**, the benzyl ether of which was dimerised by *tert*-butyllithium at low temperature to a single rotamer of jozimine A **29**, which equilibrated to a mixture at room temperature. This was found to be active at 0.75 μg ml^{-1} against the asexual erythrocytic stage of *Plasmodium falciparum*; the monomer **28a** is active against the same



28a R = H
28b R = Br



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organism at 1.44 μg ml^{-1}.[28] Antimalarial activity has also been found in 7-epidioncophylline A, 5′-*O*-demethyl-6-*O*-methyl-7-epidioncophylline A, dioncolactone A and dioncophylline C, the last being the most active of the whole group with IC_{50} = 0.014 μg ml^{-1}.[29]

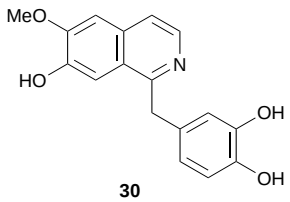
Dioncophylline A and some of its 8-ethers, especially the 8-*O*-benzyl and 8-*O*-(4-bromobenzyl) derivatives, show growth retardant activity against larvae of *Spodoptera littoralis*; studies of other derivatives shows that a free NH group is essential for this activity.[30]

4 Benzylisoquinolines

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

Berber turcomanica[31,32]
papaverine and turcomanine* **30**

Papaver setigerum[33]
laudanosine, papaverine, setigerine* **31a** and setigeridine* **31b**



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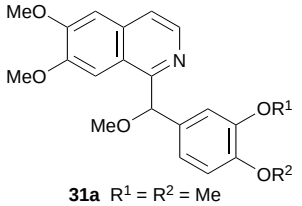
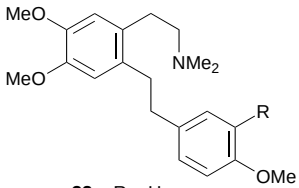
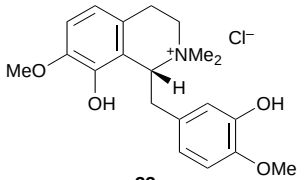


31a $R^1 = R^2 = Me$
31a $R^1R^2 = CH_2$



32a R = H
32b R = OMe



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Polyalthia insignis[34]
polysignine* **32a** and methoxypolysignine* **32b**

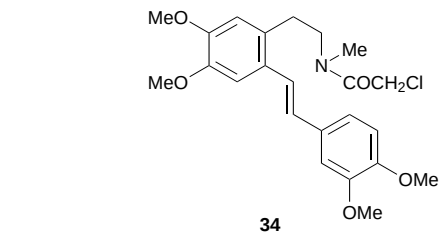
Stephania cepharantha[1,35]
coclaurine, *N*-methylcoclaurine, juziphine, norjuziphine, laudanidine, protosinomenine and reticuline

Stephania excentrica[36]
coclaurine and *N*-methylcoclaurine

Zanthoxylum nitidum[37]
isotembetarine chloride* **33**.

The crystal structure of papaverine[38] and the ^{15}N NMR spectrum of armepavine[39] have been studied. *N*-Chloroacetylnorlaudanosine methine **34**, on photolysis in the presence of oxygen, has given the cyclised lactams **35** and **36**.[40]

The condensation of L-gluconolactone with homoveratrylamine has yielded the amide **37**, which was cyclised, *N*-methylated and reduced to **38a**. Oxidation of this to the aldehyde **38b**, followed by treatment with 3,4-dimethoxyphenyllithium, afforded hydroxy-(*R*)-laudanosine **39a**, which was hydrogenolysed to give (*R*)-(−)-laudanosine **39b**.[41] (*S*)-(−)-Norlaudanosine has been synthesised in good enantiomeric yield by the hydrogenation of 1-(3,4-dimethoxybenzyl)-6,7-dimethoxy-3,4-dihydroisoquinoline in the presence of chiral iridium complexes,[42] and stereoselective reduction of the corresponding 1-(3-hydroxybenzyl) compound has given (*R*)-noranicanine.[43]Bischler–Napieralsky cyclisation of the amide **40**, followed by reduction of the resulting chiral iminium salt and *N*-methylation, has afforded the benzylisoquinoline **41**,[44] which differs from the alkaloid fumarizine, to which this structure has been assigned.[45] The Reissert compound **42** on treatment with 2-benzyloxy-3,4-methylenedioxybenzaldehyde has given **43**, which was



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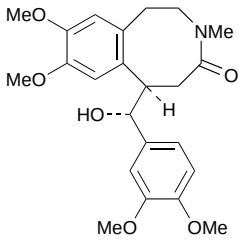

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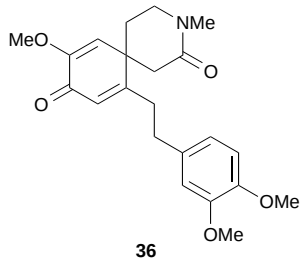

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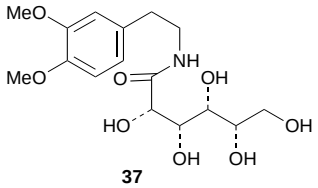

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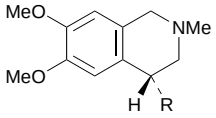
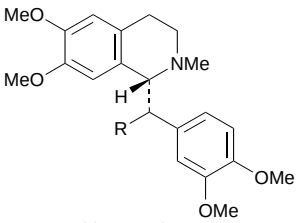
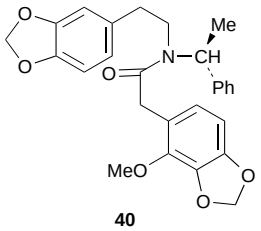


38a R = $[CH(OH)]_4CH_2OH$
38b R = CHO



39a R = OH
39b R = H



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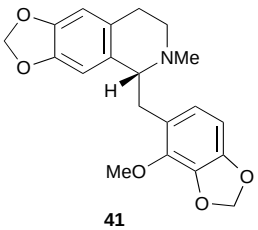

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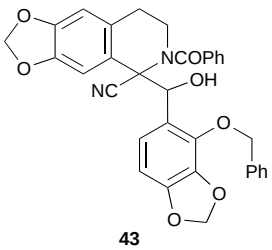

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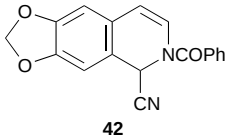

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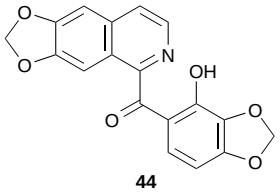


44

converted by conventional methods into **44**, found to be identical with the alkaloid sauvagnine,[46] to which a cularine-like structure has been assigned.

The physiological effects of papaverine[47] and of atracurium[48,49] have been studied.

5 Bisbenzylisoquinolines

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

Berberis crataegina[50]
aromoline, berbamine, isotetrandrine and oxyacanthine

Berberis turcomanica[32]
aromaline and oxyacanthine

Dehaasia triandra[51]
homoaromoline and thalrugosinone

Hernandia nymphaeifolia[14]
vatteamine 2′β-*N*-oxide* **45**

Isopyrum thalictroides[52]
fangchinoline, isopyruthaline* **46** and isopythaline* **47**

Mahonia aquifolium[53]
aquifoline, aromoline, baluchistanamine, berbamine, obamegine and oxyacanthine

Pachygone dasycarpa[54]
angchibangkine* **48**, atherospermoline, cosculine, 2′-norcosculine, daphnoline, fangchinoline, isoboldine, 7-*O*-demethyl-*N*-methylpeinamine, penduline, tetrandrine, tricordatine and 12-*O*-methyltricordatine* **49**

Stephania cepharantha[1]
berbamine, 2-norberbamine, cepharanthine, 2-norcepharanthine, cepharanoline, 2-norcepharanoline, cycleanine, 3,4-dehydrocycleanine* **50**, homoaromoline, isotetrandrine, 2-norisotetrandrine, obaberine, obamegine, secocepharanthine, stephababerine, 3,4-dehydrostephasuberine and thalugosinone.

Angchibangkine **48** represents a new type of bisbenzylisoquinoline alkaloid, having a skeleton isomeric with that of all of the alkaloids of the trilobine group, which have the arrangement of three diphenyl ether linkages shown in **49**. Both angchibangkine and 12-*O*-methylisocordatine show appreciable activity against *Plasmodium falciparum*.

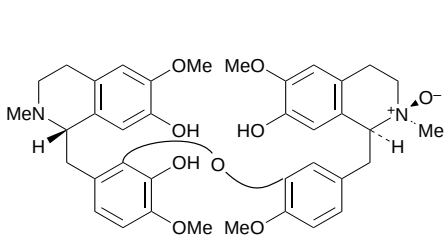
The physiological effects of aquifoline,[53] of aromoline,[53] of baluchistanamine,[53] of berbamine,[53] of fangchinoline,[55] of hernandezine,[56] of obamegine,[53] of oxyacanthine[53] and of tetrandrine[56–75] have been studied.

6 Cularines

Cularine *cis*-*N*-oxide **51a** and sarcocapnine *cis*-*N*-oxide **51b** have been isolated from *Ceratocapnos heterocarpa*, the relative stereochemistry being deduced from studies of the spectra of cularine *cis*- and *trans*-*N*-oxides prepared from the free base.[76]

Clavizepine **5b** has been synthesised from the thioketal **52**, prepared by an internal Ullmann reaction. An elimination reaction converted this into **53a**, which was desulfurised to **53b**, and oxidation of this with osmium tetroxide afforded the diol **54**. Rearrangement of this by sodium hydride gave the aldehyde **55a**, which was converted through the alcohol **55b** and its ester **55c** into the amino acetal **55d**, and this was cyclised and reduced to clavizepine **56**.[77] Following a successful synthesis of dioxoaporphine (Section 18.7), the diphenyl ether **57** was condensed with oxalyl chloride and stannic chloride with simultaneous Bishler–Napieralsky cyclisation of the intermediate **58** to give a mixture of dioxocularine **59**, the ring-contracted **60** (which is an isomer of aristoyagonine) and the dibenzopyran **61**.[78]

Following the identification of sauvagnine as the benzylisoquinoline **44**[46] and of linaresine as rugosinone,[79] the NMR spectra of these alkaloids have been reinterpreted.[46]



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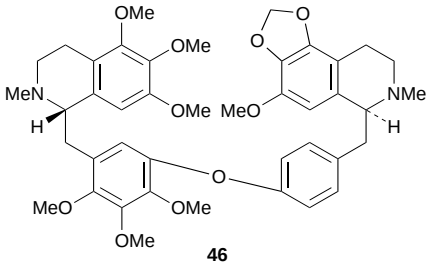

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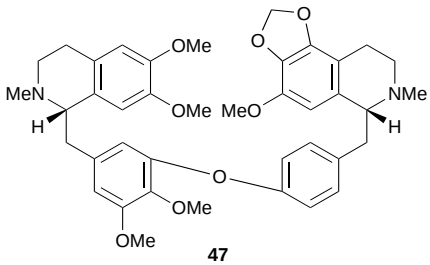

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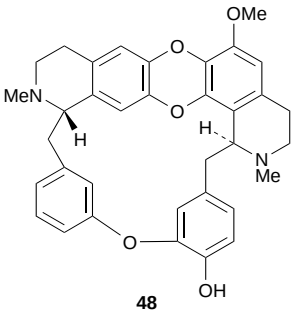

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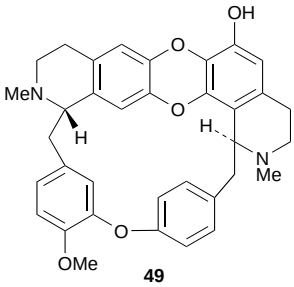

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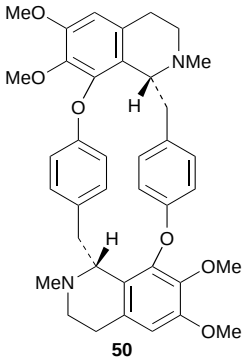

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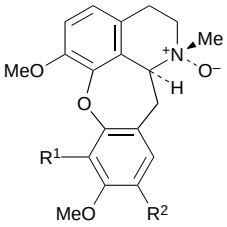
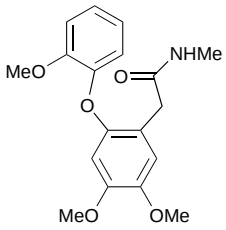


51a R^1 = H; R^2 = OMe
51b R^1 = OMe; R^2 = H



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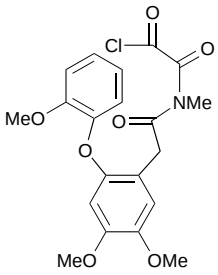

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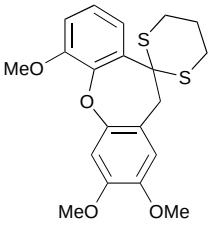
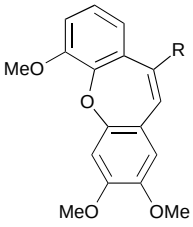
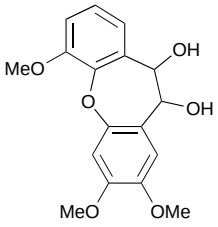


52



53a R = $S(CH_2)_3SH$
53b R = H



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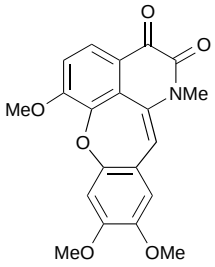

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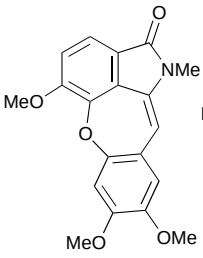

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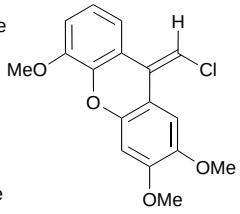
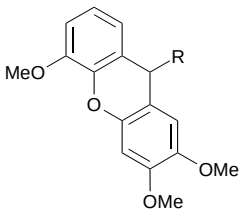
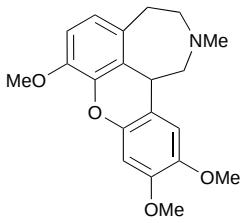


61



55a R = CHO
55b R = CH_2OH
55c R = CH_2OTos
55d R = $NMeCH_2CH(OMe)_2$



56

7 Pavines and isopavines

Amurensinine has been isolated from *Papaver caucasicum* (*P. fugax*)[80] and *N*-methylamurensinine chloride has been isolated as a new alkaloid, together with the free base, from *Meconopsis robusta*.[81]

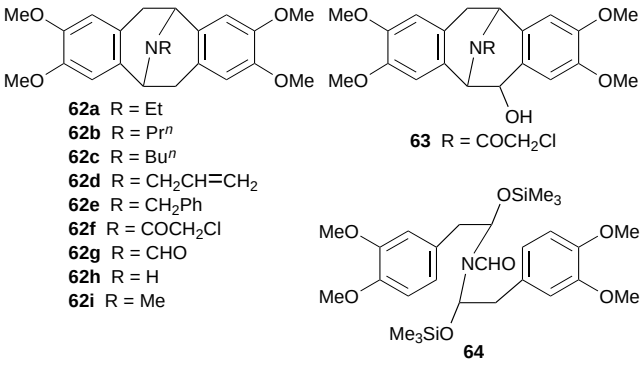
The *N*-alkylpavines **62a–62e** have been prepared by the selective *N*-demethylation of the related *N*-alkyl-*N*-methylpavine quaternary salts by heating in refluxing 2-aminoethanol.[82] Photolysis of *N*-chloroacetylpavine **62f** has afforded **63**.[83]

Homoveratric aldehyde has been condensed with *N*,*N*-bis-di(trimethylsilyl)formamide to give **64**, which has been cyclised to *N*-formylpavine **62g** and this has been hydrolysed to pavine **62h** and reduced to argemonine **62i**.[84] The keto acid **65** has been condensed with (*S*)-phenylglycinol to give the oxazoline **66**, which was reduced by red aluminium at low temperature to the lactam **67a**, which was converted through **67b** into **67c**. Reduction of this gave the hydroxy amide **68**, which was cyclised *via* the iminium ion **69** to pavine **62h**, which was converted through **62g** into (+)-argemonine **62i**.[85]

The antiviral activity of thalimonine has been studied.[86]

8 Berberines and tetrahydroberberines

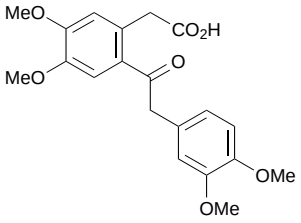
Alkaloids of this group have been isolated from the following plant species, the four marked with asterisks being new alkaloids:



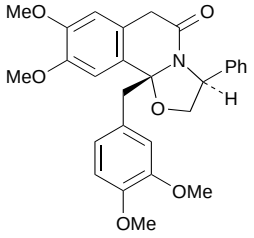
62a R = Et
62b R = Pr^n
62c R = Bu^n
62d R = $CH_2CH{=}CH_2$
62e R = CH_2Ph
62f R = $COCH_2Cl$
62g R = CHO
62h R = H
62i R = Me

63 R = $COCH_2Cl$

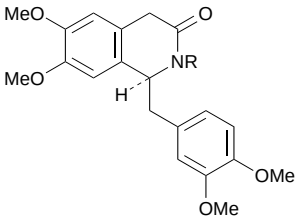
64



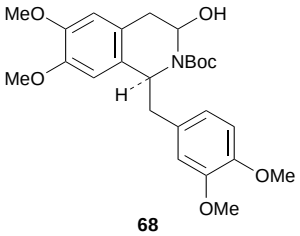
65



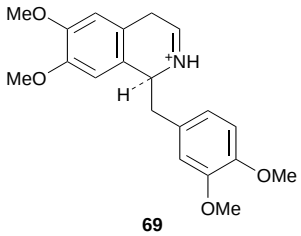
66



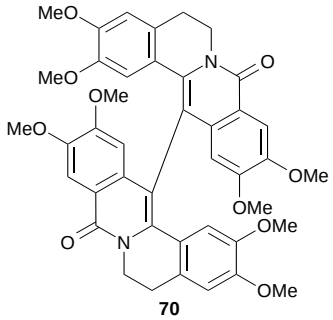
67a R = $CH(Ph)CH_2OH$
67b R = H
67c R = CO_2Bu^t



68



69



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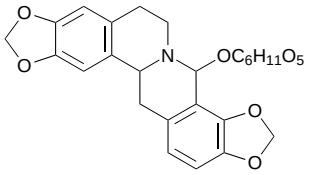

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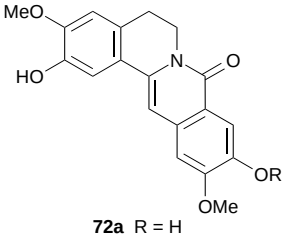
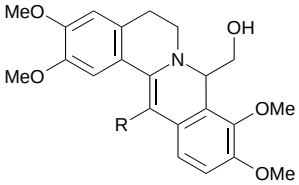
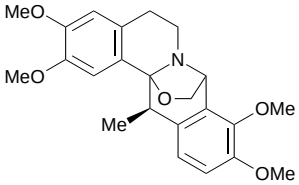


72a R = H
72b R = Me



73a R = H
73b R = Me



74

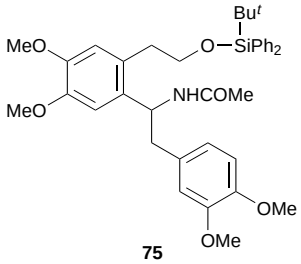
Berberis crataegina[50]
berberine, columbamine, jatrorrhizine and palmatine
Berberis ilicifolia[87]
ilicifoline* **70**
Berberis turcomanica[31,32]
berberine
Corydalis racemosa[88]
tetrahydropalmatine
Eschscholtzia californica[89]
berberine
Fumaria densiflora[90]
coptisine, scoulerine, sinactine, stylopine and *N*-methylstylopine chloride
Fumaria indica[91]
8-hydroxystylopine glucoside* **71**
Hernandia nymphaeifolia[92]
N-methylcoralydine chloride
Meconopsis cambrica[81]
mecambridine and *N*-methylmecambridine chloride
Meconopsis robusta[81]
coptisine and corysamine
Papaver setigerum[33]
coptisine, scoulerine and stylopine
Polyalthia cerasoides[93]
cerasodine* **72a** and cerasonine* **72b**
Stephania cepharantha[1]
scoulerine
Zanthoxylum nitidum[37]
cis-*N*-methylcanadine chloride.

Ilicifoline is the first dimeric berberine of its type to be discovered.

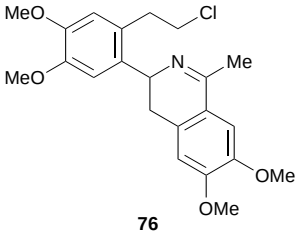
Berberine and its analogues have been shown to react with methanol to give 8-hydroxymethyl compounds such as **73a** and **73b**, and the latter has been further converted in the presence of oxygen into solidaline **74**.[94]

The amide **75** has been cyclised by phosphorus pentachloride *via* **76** to the iminium salt **77**, reduction of which gave coralydine.[95] *N*-Acetyl- and *N*-ethoxy-carbonylhomoveratrylamine and homoveratric acid have been converted, *via* the amides **78a** and **78b**, into **79a** and **79b**, and reduction of these with sodium borohydride, followed by further cyclisation, afforded **77** and **80a**, which were converted into coralydine **80b** and xylopinine **80c**.[15] The chiral benzylic lactam **66** has been reduced to (*S*)-(−)-norlaudanosine, which gave (*S*)-(−)-xylopinine **80c** on condensation with formaldehyde.[85]

The physiological effects of berberine,[96–100] of tetrahydroberberine,[101,102] of *N*-(4-chlorobenzyl)tetrahydroberberine chloride,[103] of coralyne,[104] of govadine,[105] of 12-chloroscoulerine,[106] of stepholidine,[102,107–111] of tetrahydropalmatine[88,102,112,113] and of *N*-benzyltetrahydropalmatine chloride[114] have been studied.



75



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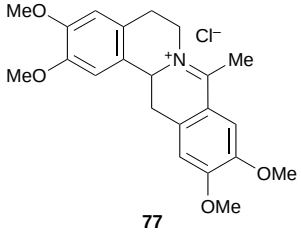

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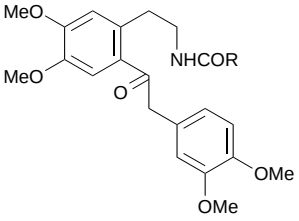
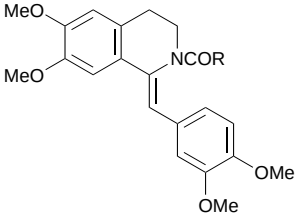
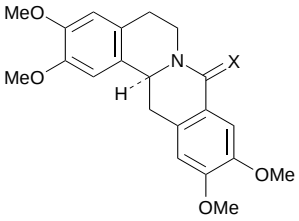


78a R = Me
78b R = OEt



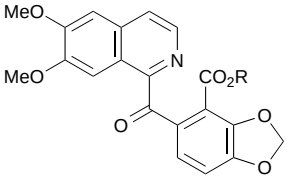
79a R = Me
79b R = OEt



80a X = O
80b X = H,Me
80c X = H,H

9 Secoberberines

Two new secoberberine alkaloids, fumaflorine **81a** and its methyl ester **81b**, have been isolated from *Fumaria densiflora*.[90]



81a R = H
81b R = Me

10 Protopines

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

Eschscholtzia californica[89]
hunnemanine

Fumaria densiflora[90]
cryptopine and protopine

Fumaria indica[91]
pseudoprotopine

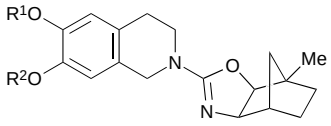
Meconopsis cambrica[81]
allocryptopine and protopine

Meconopsis robusta[81]
allocryptopine, cryptopine and protopine

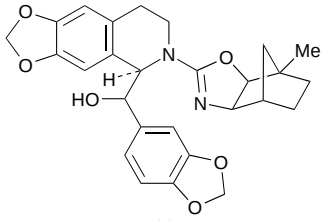
11 Phthalide-isoquinolines

Adlumine and bicuculline have been isolated from *Fumaria densiflora*.[90] The secoberberine fumaflorine **81a**, isolated from the same plant, may also be assigned to this group.

Treatment of the tetrahydroisoquinoline **82a** with methyllithium affords the C-1 anion and this reacts with magnesium bromide to give the C-1 Grignard reagent. This in turn reacts stereoselectively with piperonal to give the *erythro* compound **83** and these processes show more regio- and stereo-selectivity



82a $R^1R^2 = CH_2$
82b $R^1 = R^2 = Me$



83

than similar reactions previously reported with simpler analogues of **82**. The alcohol **83** has been converted as previously reported into the alkaloids egenine and bicuculline, and the dimethoxy compound **82b** has been similarly converted into corlumine.[115]

The physiological effects of adlumine,[116] of bicuculline,[117] of norbicuculline[116] and of hydrastine[118,119] have been studied.

12 Spirobenzylisoquinolines

Fumaricine, fumariline, fumarophycine and parfumine have been isolated from *Fumaria densiflora*.[90]

13 Indanobenzazepines

Fumaritridine, fumaritine and fumarofine have been isolated from *Fumaria densiflora*.[90]

14 Rhoeadines

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

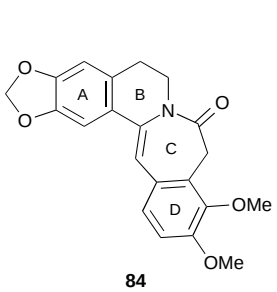
Meconopsis cambrica[81]
papaverrubine C and papaverrubine D

Meconopsis robusta[81]
rhoeadine

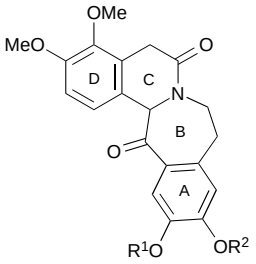
Papaver setigerum[33]
papaverrubines A, B, C, D and E.

15 Other modified berberines

A ring-C homoberberine of a new type, hediamine **84**, has been isolated from *Berberis actinacantha*.[120] Although this has the

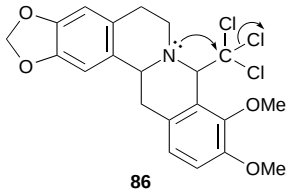


84

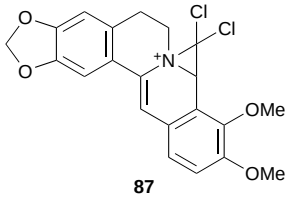


85a $R^1R^2 = CH_2$
85b $R^1 = R^2 = Me$

same carbon–nitrogen skeleton as puntarenine **85a** and saulatine **85b**, the arrangement of substituents show that these two alkaloids are ring-B homoberberines. Puntarenine and saulatine are regarded as artefacts rather than natural alkaloids, puntarenine arising from berberine-chloroform **86** (produced from berberine during extraction of plant material with chloroform and ammonia) *via* the intermediates **87**–**90**,[121]



86



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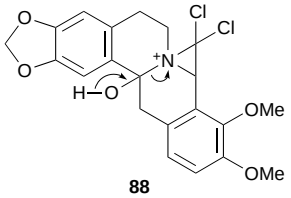

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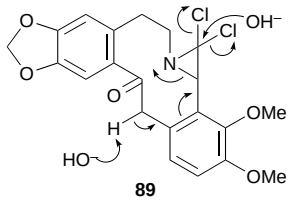
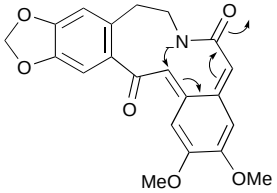


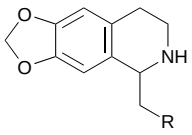
89



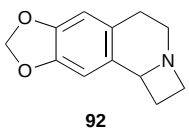
90

and it may be noted that reductive opening of the aziridine ring of **87** and hydrolysis of the *gem*-dichloride would afford hediamine **84**.

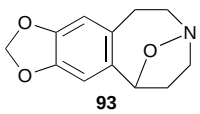
The tetrahydroisoquinoline **91a** has been reduced to **91b**, which was cyclised by phosphorus trichloride to the amine **92**, the *N*-oxide of which suffered Polonovski rearrangement to give the isoxazolidine **93**. Reduction of this gave the alcohol



91a R = CO_2Me
91b R = CH_2OH

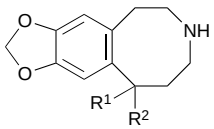


92

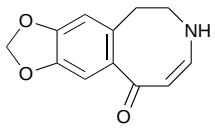


93

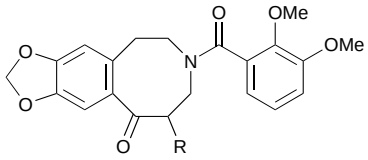
94a, which was converted through the ketone **94b** into the unsaturated ketone **95**. This could not be acylated, but **94a** was *N*-acylated and oxidised to **96a**, which was converted through



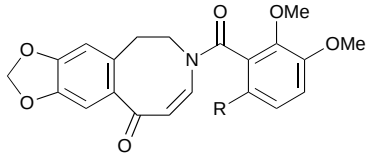
94a $R^1 = H$; $R^2 = OH$
94b $R^1R^2 = O$



95

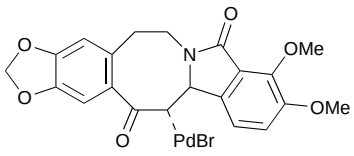


96a R = H
96b R = SPh



97a R = H
97b R = PdBr

96b into **97a**. Conversion of this into the palladium derivative **97b** enabled cyclisation to be effected to give **98**, from which the palladium was eliminated to give magallanesine **99**.[122]



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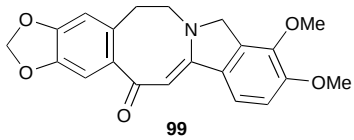


99

16 Emetine and related alkaloids

The likely biological conversion of alangiside into azaberberine alkaloids has been reproduced in the laboratory. Alangiside **100a** has been hydrolysed in a phosphate/citric acid buffer to the aglycone **100b**, which may be assumed to be in equilibrium with **101**, and this, when treated with ammonia and trifluoroacetic acid, was converted into (+)-alagimaridine **102a**. In a similar manner, dihydroalangiside has been converted into (+)-dihydroalangimaridine **102b**.[123]

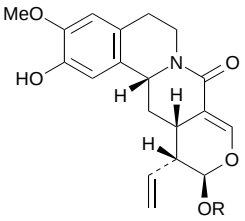
17 Benzophenanthridines

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

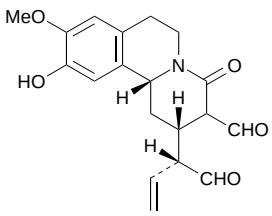
Eschscholtzia californica[89]
sanguinarine

Zanthoxylum nitidum[37]
chelerythrine and nitidine.

The ^{15}N NMR spectra of chelerythrine and sanguilutine have been studied.[124] Fagaridine **103a** has been oxidised to the quinone **104**, reduction of which has afforded 8,10-*O*-demethylsanguilutine **103b**.[125] *O*-Demethylation of oxofagaridine **105a** has given **105b**, partial benzylation of which gave **105c**, and reduction of this with lithium aluminium hydride



100a R = Glucose
100b R = H



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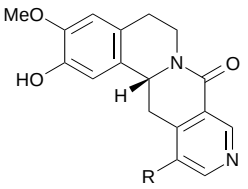
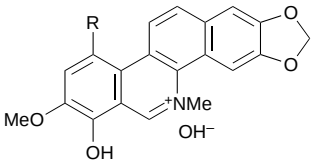
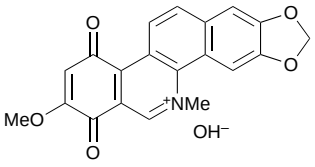


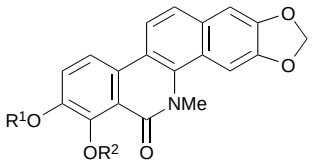
102a R = CH=CH$_2$
102b R = Et



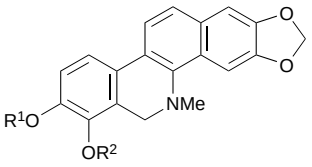
103a R = H
103b R = OH



104

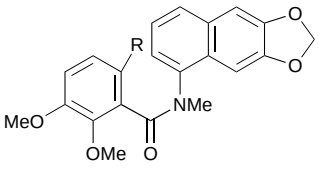


105a R^1 = Me; R^2 = H
105b R^1 = R^2 = H
105c R^1 = CH$_2$Ph; R^2 = H
105d R^1 = R^2 = Me



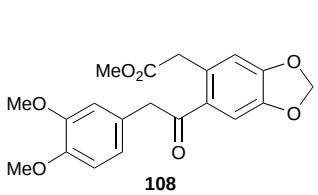
106a R^1 = CH$_2$Ph; R^2 = H
106b R^1 = CH$_2$Ph; R^2 = Me
106c R^1 = H; R^2 = Me

yielded **106a**. *O*-Methylation of this afforded **106b**, which was debenzylated to dihydroisofagaridine **106c**, and this was oxidised to isofagaridine, isomeric with **103a**, confirming the structure of this alkaloid.[126]



107a R = Br
107b R = I

Oxochelerythrine **105d** has been synthesised by the palladium-assisted internal biaryl coupling of the amides **107a** and **107b**.[127] The keto ester **108**, on treatment with benzylamine, acetyl chloride and titanium tetrachloride, gave a mixture of the enamide **109** and the naphthyl amide derivative **110**, and the latter was cyclised by phosphorus oxychloride (but not by phosphorus pentachloride) to 11-acetoxy-*N*-benzylnornitidine **111**.[95] A review of methods of synthesis of benzophenanthridine alkaloids has been published.[128]



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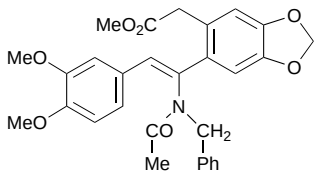

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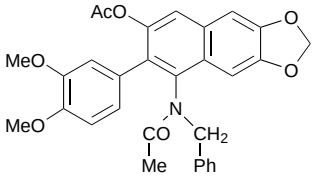

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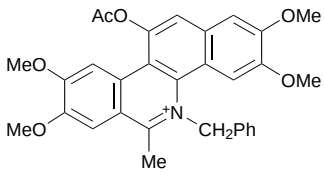

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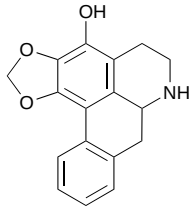

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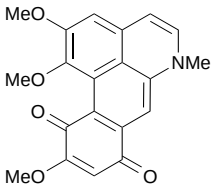

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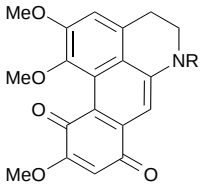
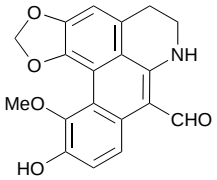


114a R = Me
114b R = H



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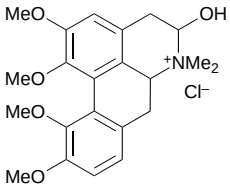

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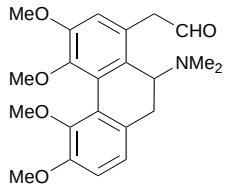

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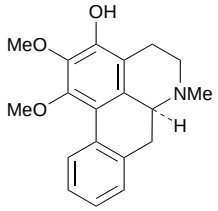

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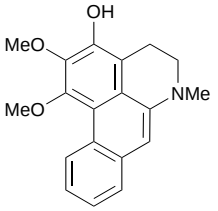


119

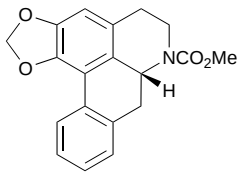
The physiological effects of chelerythrine[129–132] and of sanguinarine[132–135] have been studied.

18 Aporphinoid alkaloids

18.1 Proaporphines

Proaporphine alkaloids have been isolated from the following plant species:

Croton ruizianus[136]
crotsparine and jacularine



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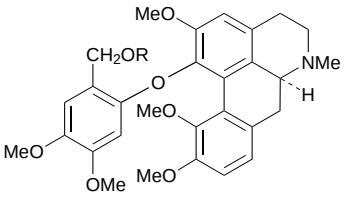
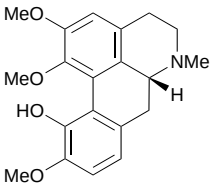


121a R = H
121b R = Me



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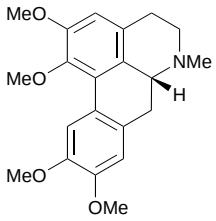

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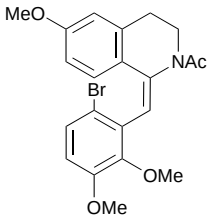

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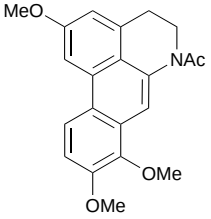

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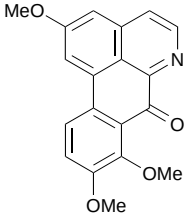
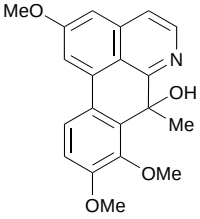
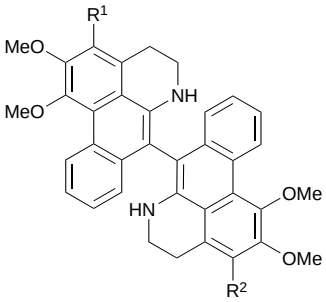


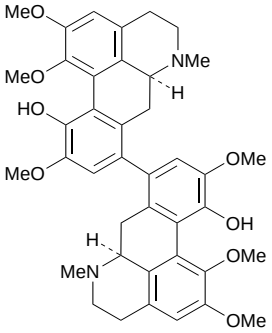
126



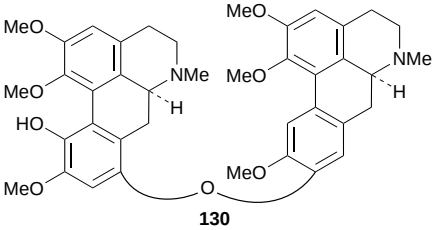
127



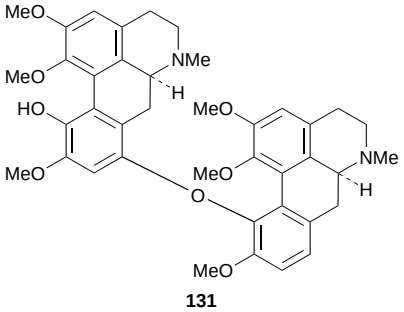
128a $R^1 = R^2 = H$
128b $R^1 = R^2 = OMe$
128c $R^1 = H$; $R^2 = OMe$



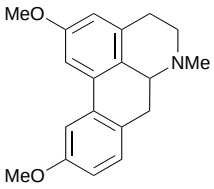
129



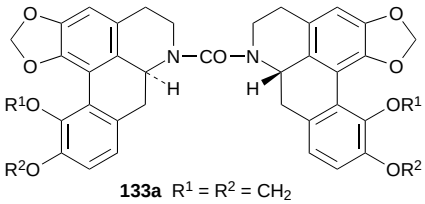
130



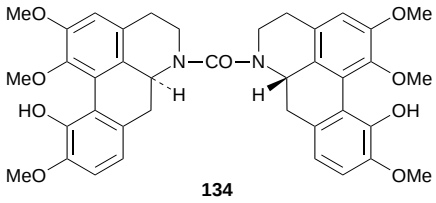
131



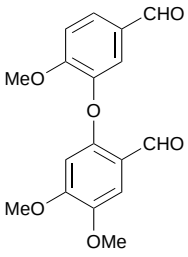
132



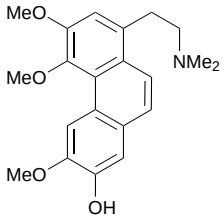
133a $R^1 = R^2 = CH_2$
133b $R^1 = Me$; $R^2 = H$



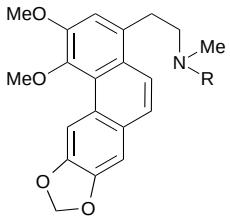
134



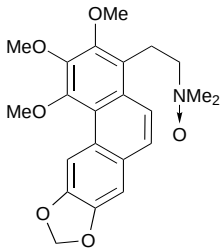
135



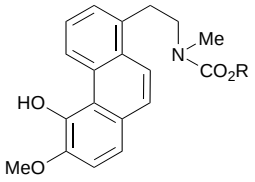
136



137a R = H
137b R = OH



138

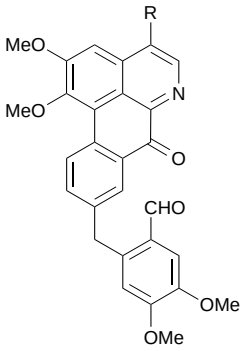


139

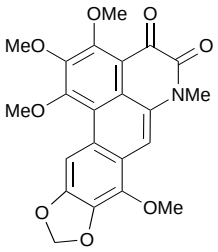
Meconopsis cambrica[81]
mecambrine
Papaver caucasicum[80]
mecambrine
Stephania cepharantha[1,35]
N-methylcrotsparine and stepharine.

18.2 Aporphines

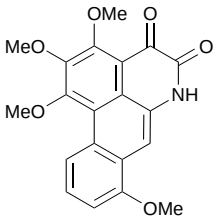
Aporphine alkaloids have been isolated from the following plant species, the eleven marked with asterisks being new alkaloids:
Berberis crataegina[50]
magnoflorine
Berberis turcomanica[32]
glaucine, isocorydine and thalicmidine



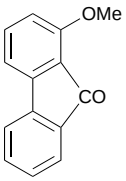
140a R = H
140b R = OMe



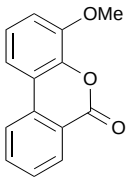
141



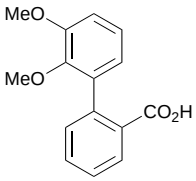
142



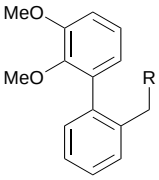
143



144

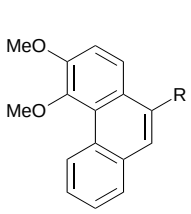


145

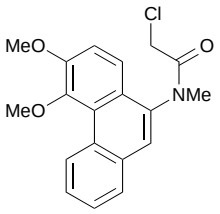


146a R = OH
146b R = Cl
146c R = CN
146d R = CO_2H
146e R = CO–N O

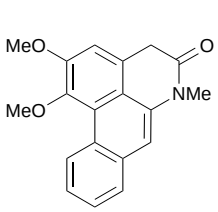
Cissampelos glaberrima[137]
cissaglaberrimine* **112**
Dehaasia triandra[51,138]
dehydroisocorydione* **113**, isocorydione* **114a**, norisocorydione* **114b**, isoboldine, norisocorydine, *N*-methyllaurotetanine, *N*-methyllindcarpine and nantenine
Fumaria densiflora[90]
corytuberine
Hernandia nymphaeifolia[14,92]
hernandaline, 7-formyldehydrohernangine* **115** and *N*-methylovigerine
Magnolia sieboldii[139]
magnoporphine* **116**
Meconopsis cambrica[81]
corytuberine, magnoflorine, mecambroline, roemerine and roemeroline
Meconopsis robusta[81]
corytuberine and magnoflorine



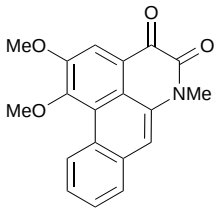
147a R = N O
147b R = OH
147c R = NHMe



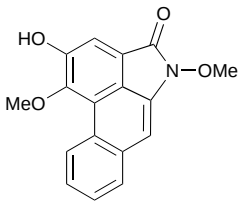
148



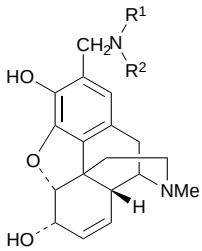
149



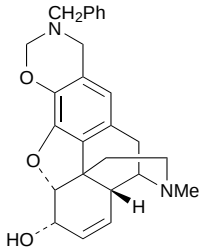
150



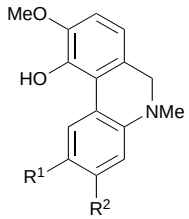
151



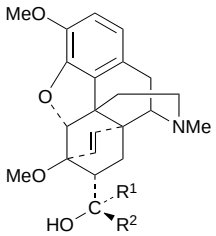
152a $R^1 = R^2$ = Me
152b R^1 = Me; R^2 = Et
152c $R^1 = R^2$ = Et



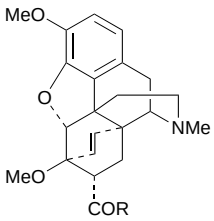
153



154a $R^1 = R^2$ = H
154b R^1 = Cl; R^2 = H
154c R^1 = Br; R^2 = H
154d R^1 = H; R^2 = Cl

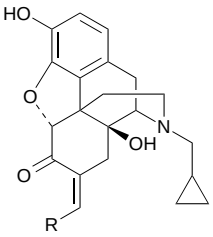


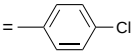
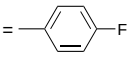
155a R^1 = H; R^2 = Ph
155b R^1 = Ph; R^2 = H
155c R^1 = Me; R^2 = Ph
155d R^1 = Ph; R^2 = Me

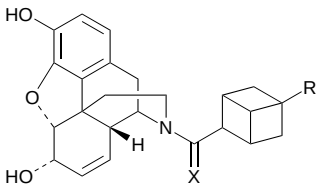


156a R = Ph
156b R = H
156c R = Me

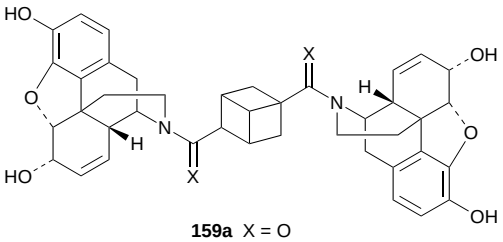
Ocotea benesii[140]
3-hydroxynuciferine* **118**, 3-hydroxydehydronuciferine* **119** and isocorydine
Ocotea holdrigeana[141]
corytuberine, isocorydine and norisocorydine
Papaver caucasicum[80]
nuciferine, nornuciferine and roemerine



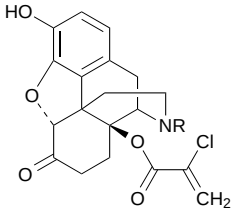
157a R = Ph
157b R = 
157c R = 
157d R = α-Naphthyl
157e R = 9-Anthracenyl
157f R = 3-Pyridyl
157g R = 4-Pyridyl



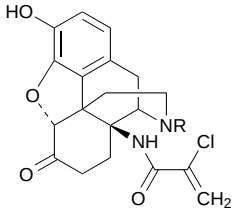
158a X = O; R = CO_2H
158b X = H,H; R = CH_2OH



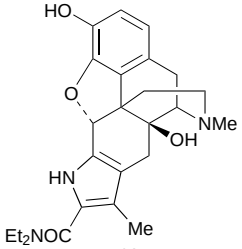
159a X = O
159b X = H,H



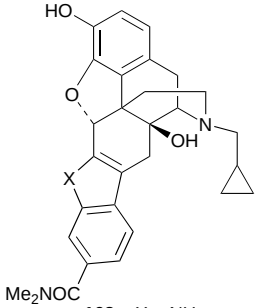
160a R = Me
160b R = CH_2 



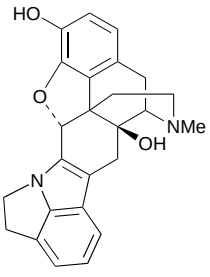
161a R = Me
161b R = CH_2 



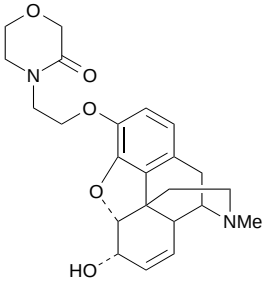
162



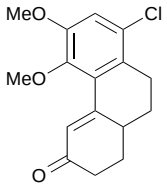
163a X = NH
163b X = O



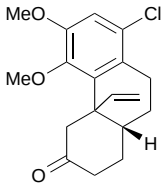
164



165



166



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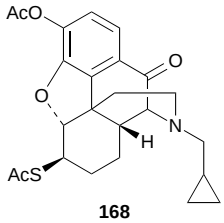
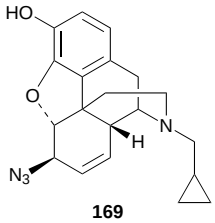
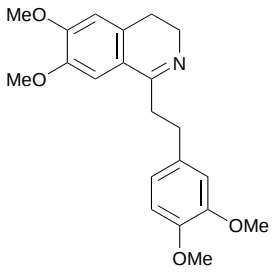


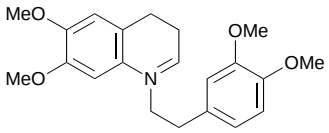
168



169



170



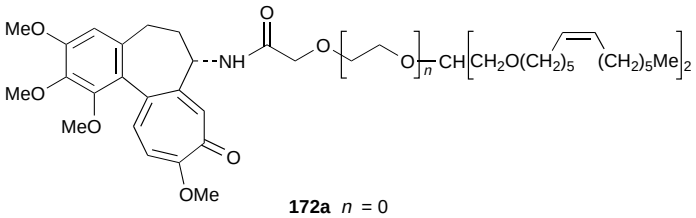
171

Papaver setigerum[33]
corytuberine, isoboldine and magnoflorine

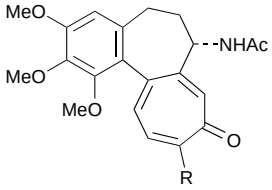
Polyalthia insignis[34]
assimilobine
Rollinia mucosa[142]
anonaine, glaucine, purpureine and romucosine* **120**
Stephania cepharantha[1,35]
anonaine, corydine, isoboldine, isocorydine, isocorytuberine, litsiferine and *N*-methyllaurotetanine
Stephania excentrica[13]
isoboldine and roemerine
Thalictrum fauriei[143]
faurine* **121a** and *O*-methylfaurine* **121b**
Thalictrum simplex[144]
ocoteine, preocoteine, preocoteine *N*-oxide, thalicmidine, thalicmidine *N*-oxide and thalicsimidine
Thalictrum thalictroides[145]
magnoflorine
Xylopia papua[146]
anonaine and xylopine
Zanthoxylum nitidum[37]
magnoflorine and menispermine.

Of the new alkaloids the structure of dehydroisocorydione was confirmed by its preparation from (*S*)-(+)-isocorydine **122** by oxidation with Fremy's salt,[138] and that of romucosine by its preparation from the related secondary base, anonaine, by treatment with methyl chloroformate and trimethylamine.[142] Only an abstract of the paper in which the structure **116** is assigned to magnoporphine is readily available, but the amine salt would be expected to lose a proton to give the aldehydo base **117**; structures analogous to **116** have not previously been assigned to the salts of pseudo bases in the isoquinoline alkaloid series. The alkaloid faurine is probably the product of oxidation of a benzylisoquinoline–aporphine dimer.

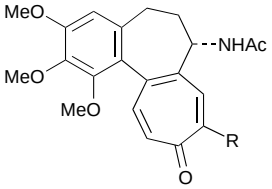
The ^{13}C and ^{15}N NMR spectra of roemeridine have been studied.[124] (*R*)-(−)-Laudanosine, prepared from L-gluconolactone (Section 4) has been oxidised by chromium trioxide to (*R*)-(−)-glaucine **123**.[41] Photocyclisation of the 6′-bromobenzylidenetetrahydroisoquinoline **124** has given the



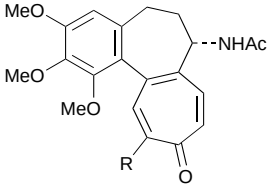
172a n = 0
172b n = 1
172c n = 2
172d n = 3



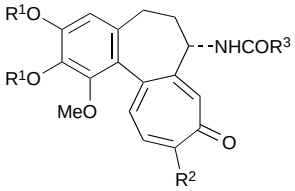
173a R = NH_2
173b R = $NH((CH_2)_2CO_2H$
173c R = $NH(CH_2)_3NH(CH_2)_2CO_2H$



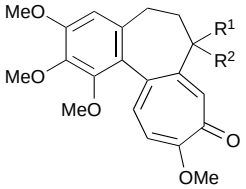
174a R = OMe
174b R = SMe
174c R = SPh



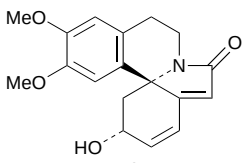
175a R = SMe
175b R = SPh



176 R^1 = H, Glucose, Me; R^2 = OMe, SMe; R^3 = C_1–C_6 Haloalkyl



177a R^1 = H; R^2 = OAc
177b R^1 = H; R^2 = $OCOCF_3$
177c R^1 = H; R^2 = $OCOPr^n$
177d R^1 = H; R^2 = COPh
177e R^1R^2 = O



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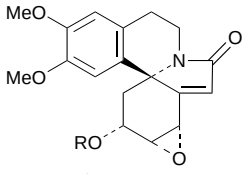
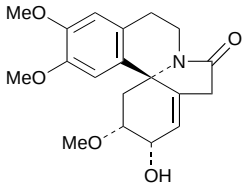


179a R = H
179b R = Me



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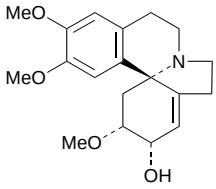

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dehydroaporphine **125** and oxidation of this with Fremy's salt afforded the oxoaporphine **126**, which reacted with methylmagnesium bromide to give (±)-sinomendine **127**.[147]

The physiological effects of boldine[148] and of apomorphine[149–157] and the effects of a series of 11-substituted-(*R*)-aporphines on the dopamine-2A and 5-hydroxytryptamine-1A receptors[158] have been studied. A method for the estimation of apomorphine has been published.[159]

18.3 Dimeric aporphines

Urabaine **128a** and the new 7,7′-dimers 7,7′-bis(dehydro-*O*-methylisopiline) **128b** and 7-dehydronuciferyl-7′-dehydro-*O*-methylisopiline **128c** have been isolated from *Polyalthia bullata*.[160] The first carbon–carbon and carbon–oxygen–carbon coupled aporphines that are direct analogues of the bisbenzylisoquinolines and the benzylisoquinoline–aporphine dimers have been identified in the 8,8′-linked bis-(*S*)-isocorydine **129** and its *R* isomer, the 8,9′-linked dehatriphine **130**[138] and the 8,11′-oxygen-linked *O*-bisisocorydine **131**,[51] all isolated from *Dehaasia triandra*. The structure of 8,8′-bis-(*S*)-isocorydine was confirmed by its preparation from (*S*)-isocorydine by oxidation with manganese trisacetylacetonate.[51] Dehatriphine is formulated as a dimer of isocorydine and *N*-methyllaurotetanine, but an attempt to confirm this by fission of the alkaloid with sodium and liquid ammonia yielded the aporphine **132** as the only identifiable product.[138]

The new carbamides ovigeridimerine **133a**, ovihernangerine **133b** and oviisocorydine **134**, isolated from *Hernandia nymphaeifolia*[14,92] can be formally regarded as aporphine dimers, but are more logically seen as derivatives of simple aporphines.

18.4 Benzylisoquinoline–aporphine dimers

Thalicarpine has been isolated from *Hernandia nymphaeifolia*.[92] Faurine (Section 18.2), oxohernandaline and 4-methoxyoxohernandaline (Section 18.6) are presumably products of oxidation of bases of this group, as may also be the diphenyl ether dialdehyde hernandial **135**, isolated with 4-methoxyoxohernandaline from *Hernandia nymphaeifolia*.[14]

18.5 Phenanthrenes

Secoaporphines, which are derivatives of phenanthrene, have been isolated from the following plant species, the four marked with asterisks being new alkaloids:

Dehaasia triandra[51]
secoxanthoplanine* **136**

Thalictrum simplex[144]
northalicthuberine* **137a**, *N*-hydroxynorthalicthuberine* **137b** thalihazine and thalihazine *N*-oxide* **138**.

The structures of the new alkaloids have been confirmed by the preparation of secoxanthoplanine by the Hofmann degradation of xanthoplanine and by the reduction of thalihazine *N*-oxide to thalihazine. Apocodeine has been converted into a series of alkyloxycarbonylnorapocodeines **139** by treatment with alkyl chloroformates.[161]

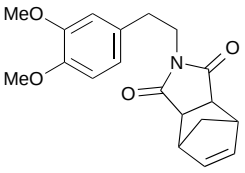
The physiological effects of *N*-allylnorsecoboldine have been studied.[162]

18.6 Oxoaporphines

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

Artabotrys zeylanicus[163]
atherospermidine, lanuginosine, liriodenine, oxobuxifoline and oxocrebanine

Hernandia nymphaeifolia[14,92]
oxohernandaline* **140a** and 4-methoxyoxohernandaline* **140b**



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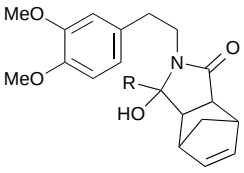

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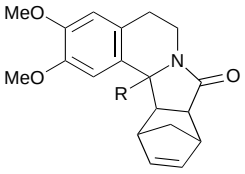

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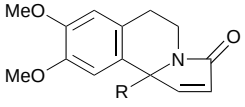

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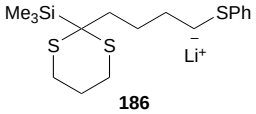

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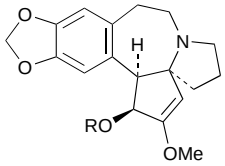
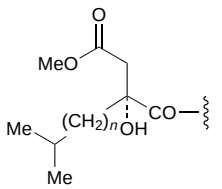
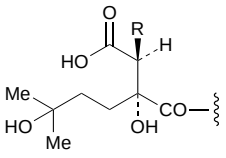


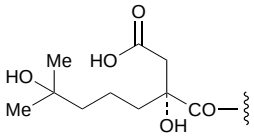
187a R = **188a**
187b R = **188b**
187c R = **188c**
187d R = **189a**
187e R = **189b**
187f R = **190**
187g R = **191**
187h R = **192a**
187i R = **192b**
187j R = **192c**



188a *n* = 1
188b *n* = 3
188c *n* = 4
188d *n* = 2



189a R = H
189b R = OH



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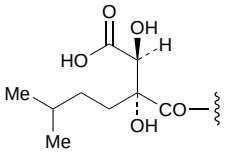

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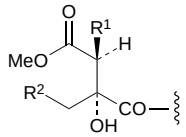


192a R^1 = H; R^2 = Ph
192b R^1 = H; R^2 = CH_2Ph
192c R^1 = OH; R^2 = Ph
192d R^1 = H; R^2 = CH_2CMe_2OH

Papaver caucasicum[80]
liriodenine and lysicamine
Polyalthia insignis[34]
liriodenine, *O*-methylmoschatoline and oxostephanine
Xylopia championi[163]
O-methylmoschatoline.

18.7 Dioxoaporphines

Dioxoaporphine alkaloids have been isolated from the following plant species, the two marked with asterisks being new alkaloids:
Artabotrys zeylanicus[163]
ouregidione and 8-methoxyouregidione* **141**
Xylopia championi[163]
dicentrinone* **142**.

The fluoren-9-one **143** has been oxidised by the Baeyer–Villiger process to the benzocoumarin **144**, which was hydrolysed and methylated to the diphenyl carboxylic acid **145**. Reduction of this with lithium aluminium hydride gave the alcohol **146a**, which was converted through **146b** and **146c** into the acid **146d** and this was further converted through the acid chloride into the amide **146e**. Bischler–Napieralsky cyclisation of this yielded the phenanthrene **147a**, which was converted through **147b** into **147c**. The *N*-chloroacetyl derivative **148** of this was subjected to Friedel–Crafts cyclisation to give deoxycepharadione B **149**, which was oxidised to cepharadione B **150**.[164]

18.8 Aristolochic acids and aristolactams

Aristolochic acids B-II and D-II have been isolated from *Aristolochia manchuriensis*[165] and the new alkaloid piperlactam **151** has been isolated from *Piper puberullum*.[166]

19 Alkaloids of the morphine group

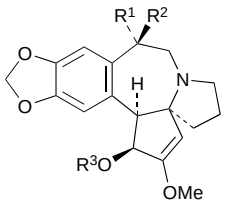
Alkaloids of the morphine–hasubanonine group have been isolated from the following plant species:
Meconopsis cambrica[81]
flavinantine
Papaver caucasicum[80]
salutaridine
Papaver setigerum[33]
codeine, morphine, thebaine and *N*-methylthebaine iodide
Stephania cepharantha[1,35]
aknadicine, aknadinine, aknadilactam, cephakacine, cephamuline, cepharamine, cephasamine, cephatonine, sinoacutine, sinomenine, 14-episinomenine, stephodeline, tannagine and alkaloid FK 3000
Stephania excentrica[13,36]
aknadinine, cephamorphimine and sinococculine.

The ^1H and ^{13}C NMR spectra of codeine[167] and of the *N*-oxides of thebaine[168] and of 14-hydroxycodeinone[168] have been studied, the spectra of the *N*-oxides permitting distinctions to be made between the *cis* and *trans* forms.

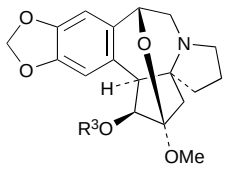
Morphine has been shown to undergo the Mannich reaction with formaldehyde and secondary amines to give the 2-aminomethyl compounds **152a**, **152b** and **152c**; with primary amines the product undergoes further condensation with formaldehyde to give oxazines such as **153**.[169] Codeine and both 6- and 7-halogenated 6-demethoxythebaine have been rearranged to apocodeine **154a** and the halogenated derivatives **154b**, **154c** and **154d**, respectively, in good yield by heating with methanesulfonic acid and methionine.[170]

Calculations of the fully optimised transition states for Diels–Alder additions to thebaine have been made.[171] The 20*S* and 20*R* alcohols **155a** and **155b** have been prepared by the reduction of the ketone **156a** and the reaction of the aldehyde **156b** with phenylmagnesium bromide respectively.[172] Similarly the alcohols **155c** and **155d** have been obtained from the ketones **156c** and **156d** by treatment with phenylmagnesium bromide and with methylmagnesium iodide, respectively.[173]

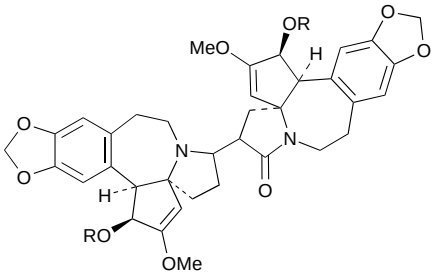
The condensation of naltrexone with the appropriate aldehydes in the presence of piperidine has given the (*E*)-arylidene derivatives **157a**–**157g**, some of which have been converted by ultraviolet light into their *Z* isomers.[174,175] Reaction of normorphine with cubane 1,4-dicarboxylic acid has given the amides **158a** and **159a**, which have been reduced by lithium aluminium hydride to the amines **158b** and **159b**. Of these **159b** does not bind to any of the three opioid receptors and **158b** binds only weakly to the μ and δ receptors, but not to the κ receptor.[176]



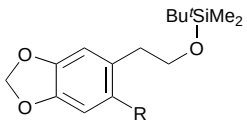
193a R^1 = H; R^2 = OH; R^3 = **188d**
193b R^1 = H; R^2 = OH; R^3 = **188b**
193c R^1 = OH; R^2 = H; R^3 = **188b**



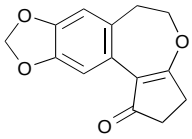
194 R = **187d**



195 R = **191d**



196a R = I
196b R = CHO



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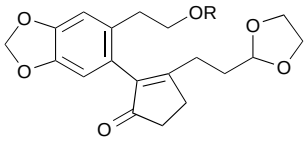
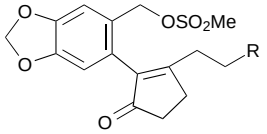
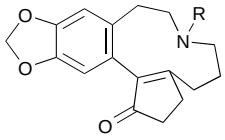


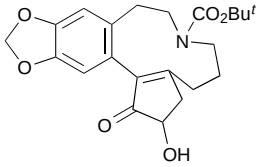
198a R = H
198b R = SO_2Me



199a R = CHO
199b R = CH_2NHCH_2Ph



200a R = CH_2Ph
200b R = CO_2Bu^t
200c R = H



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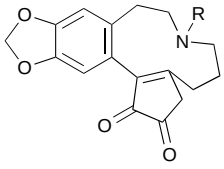
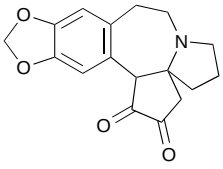


202a R = CO_2CH_2Ph
202b R = H



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Details of the preparation of the following have been published: 3-esters of morphine,[177,178] 14-hydroxydihydrocodeinone and 14-hydroxy-5-methyldihydrocodeinone,[179] 2-chloroacrylyl esters of 14-hydroxydihydromorphinone **160a** and its *N*-cyclopropylmethyl analogue **160b** and the related acylated 14-aminodihydromorphinones **161a** and **161b**,[180] the heterocyclic compounds **162**, **163a**, **163b**, **164** and related compounds,[181–183] and fluorescent derivatives of *N*-benzylnaltrindole,[184] α, β and γ-isomorphine[169] and buprenorphine.[185] The lactam **165** has been isolated as a metabolite of pholcodine in humans.[186]

Methods for the estimation of morphine,[187] morphine 3- and 6-glucuronides,[188] heroin,[187] codeine,[187] naloxone,[189] naltrexone,[190] β-naltrexol,[190] nalbuphine,[191] buprenorphine[192] and dihydroetorphine[193] have been described.

Michael addition of methyl vinyl ketone to 5-chloro-7,8-dimethoxy-1-tetralone, followed by internal aldol condensation and dehydration, has given the unsaturated ketone **166**. Reaction of this with lithium vinylcuprate afforded the B/C *cis*-13-vinylphenanthrene derivative **167**, an intermediate in an earlier synthesis of morphine, thus constituting a formal synthesis of the alkaloid.[194] Methods of synthesis of morphine have been reviewed.[195,196]

The analgesic properties,[197–230] pharmacokinetics[231–234] and metabolism[235–237] of morphine have been studied, as have the effects of the alkaloid on behaviour,[210,238–250] on immune responses,[251–262] on the brain,[263–265] on the brain stem,[266] on the hypothalamus,[267–269] on spinal receptors,[270] on neurones,[271–273] on locomotor activity,[274] on somatosympathetic reflexes,[275] on the heart,[276,277] on coronary bypass grafts,[278] on opioid,[279] monoaminergic[280] and adreno[281] receptors, on respiration,[282] on the gastrointestinal tract,[283,285] on body weight,[286] on tolerance of cold,[287] on the consumption of alcohol,[288] on taste preferences,[215] on the utilisation of glucose,[289] on the inflammatory process,[290,291] on shock,[292] on lymphocytes,[293] on cerebral activity in neonates,[294] on postherpetic neuralgia,[295] and on levels of acetyl choline,[296,297] of cyclic AMP,[298] of adrenocorticotropic hormone,[299] of amylase,[300] of cortisol,[299] of dopamine,[301] of γ-aminobutyric acid,[302,303] of nitric oxide,[304] of proteoglycan[305] and of substance P.[306]

The morphine antagonist properties[307–309] and the paradoxical analgesic effect[310] of *N*-allyl-14-hydroxydihydromorphinone (naloxone) have been studied as have the effects of this compound on behaviour,[311–314] on the brain,[315] on the cardiovascular system,[316–318] on the eye,[319] on the baroreflex,[320] on the intake of sugar,[321] on levels of cortisol,[322] of dopamine,[323–327] of endorphins,[322] of testosterone[328] and of thyrotropin,[329] and on the effects of cocaine,[330] of paracetamol[331] and of non-steroidal anti-inflammatory agents.[332]

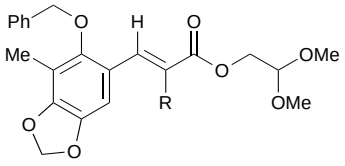
The pharmacological and/or physiological effects of the following have also been studied: morphine 3-glucoside,[333–337] morphine 6-glucoside,[335–339] heroin,[340,341] codeine,[342–346] 3-*O*-ethylmorphine,[347] normorphine,[339] naloxonazine,[348] naltrexone,[349–356] methylnaltrexone,[357,358] nalbuphine,[351,359–365] nalmefene,[366,367] funaltrexamine,[352,368,369] the acetylthio compound **168**,[370] the azide **169**,[371] naltrindole,[369] oripavine,[372] etorphine,[373] dihydroetorphine,[374–376] buprenorphine[377–394] and norbuprenorphine.[394]

20 Phenethylisoquinolines

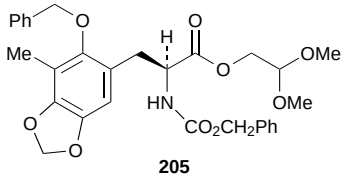
Catalytic reduction of the dihydroisoquinolines **170** and **171** with chiral iridium complexes has afforded (*S*)-norhomolaudanone.[42]

21 Colchicine

N-Deacetylcolchicine has been converted into the lipid derivatives **172a**–**172d**[395] and colchicine has been converted into the amines **173a**–**173c**.[396] Isocolchicine **174a** in methanol or dimethyl sulfoxide undergoes *ipso*-substitution with thiols and their sodium salts to give **174b** and **174c**, which are prone to *tele*-substitution *in situ* to give **175a** and **175b**.[397] Patents for the preparation of compounds of general formulae **176** have been published.[398,399] Derivatives of deacetamidocolchicine of structures **177a**–**177e** have been synthesised and evaluated as antitubulin agents.[400]



204a R = $CO_2CH_2CH{=}CH_2$
204b R = $NHCO_2CH_2Ph$



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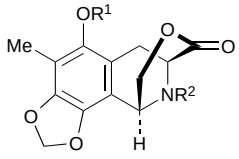
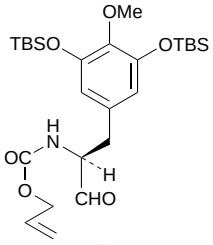
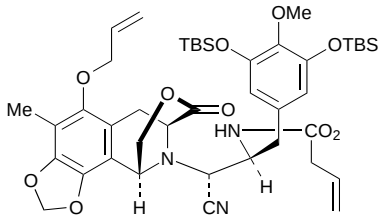




206a $R^1 = CH_2Ph$; $R^2 = CO_2CH_2Ph$
206b $R^1 = R^2 = H$

207



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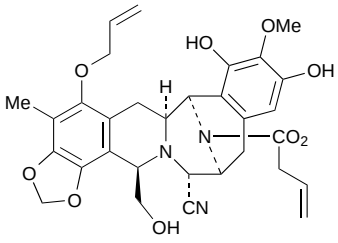

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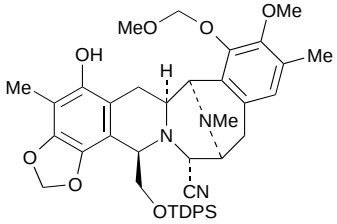

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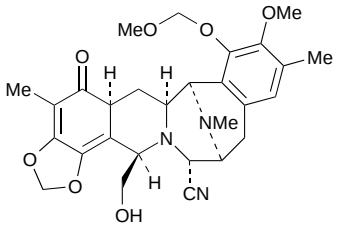

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The physiological effects of colchicine,[401–407] of colchiceine,[408] of β-lumicolchicine[408] and of thiocolchicoside[409] have been studied.

22 *Erythrina* alkaloids

Reviews of the chemistry of the *Erythrina* alkaloids have been published.[410,411]

22.1 Erythrina alkaloids

(±)-Demethylerysotramidine **178**, previously prepared by synthesis, has been epoxidised to **179a**, which was *O*-methylated to **179b**. Reduction of this with stannous iodide has yielded **180**, which on further reduction with lithium aluminium hydride afforded (±)-erythratidine **181**.[412] Treatment of the *N*-substituted maleimide/cyclopentadiene adduct **182** with alkyllithiums affords the hydroxy amides **183**, which can be cyclised to **184**, and retro-Diels–Alder decomposition of these leads to compounds of general structures **185**; the use of the lithium derivative **186** in this process leads to intermediates useful in the synthesis of alkaloids of this group.[413]

22.2 Cephalotaxine and related alkaloids

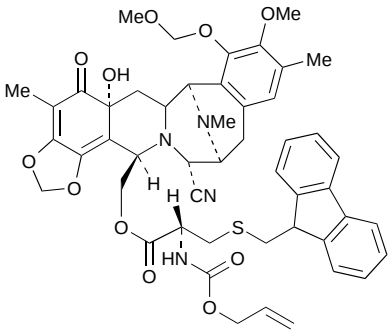
The following new esters of cephalotaxine have been isolated from *Cephalotaxus harringtonia*: nordeoxyharringtonine **187a**,[414] homodeoxyharringtonine **187b**,[414] bishomodeoxyharringtonine **187c**,[414] 5′-*O*-demethylharringtonine **187d**,[415] (3*S*)-hydroxy-5′-*O*-demethylharringtonine **187e**,[415] 5′-*O*-demethylhomoharringtonine **187f**,[415] 5′-*O*-demethylisoharringtonine **187g**,[415] neoharringtonine **187h**,[416] homoneoharringtonine **187i**[416] and (3*S*)-hydroxyneoharringtonine **187j**.[416] In addition the new alkaloids 11-hydroxydeoxyharringtonine **193a**, 11-hydroxyhomodeoxyharringtonine **193b** and 11-hydroxyhomodeoxyharringtonine **193c**,[417] the drupacine ester drupangtonine **194**[418] and the bimolecular alkaloid cephalotaxidine **195**[419] have also been isolated from *Cephalotaxus harringtonia*, together with the known alkaloids cephalotaxine, harringtonine, isoharringtonine, deoxyharringtonine and homoharingtonine.[415]

Drupangtonine is a powerful inhibitor of P388 leukaemic cells,[418] as are 11-hydroxydeoxyharringtonine and 11-hydroxyhomodeoxyharringtonine. All of these alkaloids are less generally cytotoxic than deoxyharringtonine.[417] The anti-tumour effects of harringtonine have also been studied.[420]

A new synthesis of (±)-cephalotaxinone, and therefore of (±)-cephalotaxine, has been reported. Treatment of the aryl iodide **196a** with butyllithium and *N*-formylpiperidine afforded the aldehyde **196b**, which, with 1,2-bis(trimethylsilyloxy)-cyclobutadiene, yielded the enol ether **197**. This, on treatment with the appropriate Grignard reagent, yielded the acetal **198a**, the methylsulfonyl ester of which **198b** was hydrolysed to the aldehyde **199a**, and then reductively aminated to give **199b**. This was hydrolysed and cyclised to **200a**, which was converted by *tert*-butyl carbonate into **200b**. Oxidation of this to **201** followed by further oxidation gave **202a**, and removal of the protecting group from the nitrogen of this resulted in Michael addition of the resulting secondary base to the enone to give (±)-cephalotaxinone **203**.[421] When **200b** was hydrolysed to **200c** it was found that the equilibrium greatly favoured the uncyclised base rather than the tetracyclic base analogous to **203**.

23 Other isoquinolines

A synthesis of optically pure ecteinascidin-743 has been achieved from the unsaturated ester **204a**. This was converted into the unsaturated carbamate **204b**, which was reduced over a chiral rhodium catalyst to the chiral carbamate **205**. This



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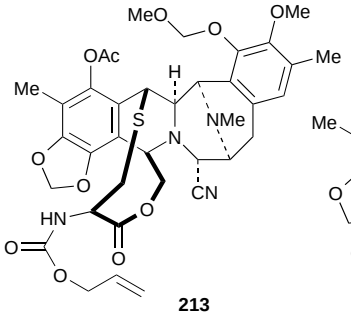

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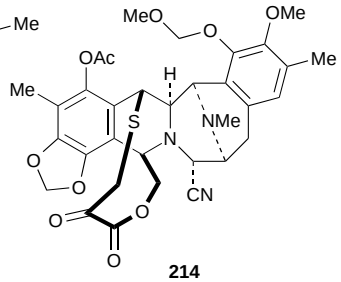

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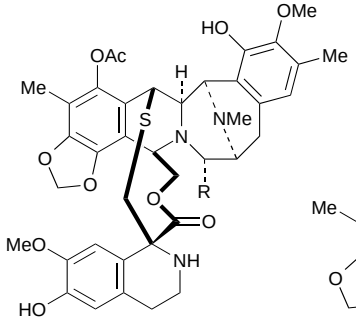
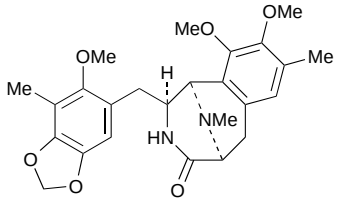


215a R = CN
215b R = OH



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acetal was then cyclised by boron trifluoride to the lactone **206a**, which was converted into **206b**. Reaction of this with the aldehyde **207** in the presence of potassium cyanide, followed by allyl bromide, yielded **208**, which was cyclised by methanesulfonic acid to **209**. This was converted by conventional processes into **210**, which was oxidised to the hydroxy dienone **211**. Conversion of this into the cysteine derivative **212** was followed by cyclisation and further transformation into **213**, which was oxidised to the keto lactone **214**. Pictet–Spengler condensation of this with homovanillylamine yielded ecteinascidin-770 **215a**, which was converted into ecteinascidin-743 **215b** by aqueous silver nitrate.[422] The lactam **216** has been synthesised in an approach to the ecteinascidins.[423]

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