β-Phenylethylamines and the isoquinoline alkaloids

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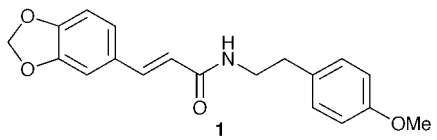
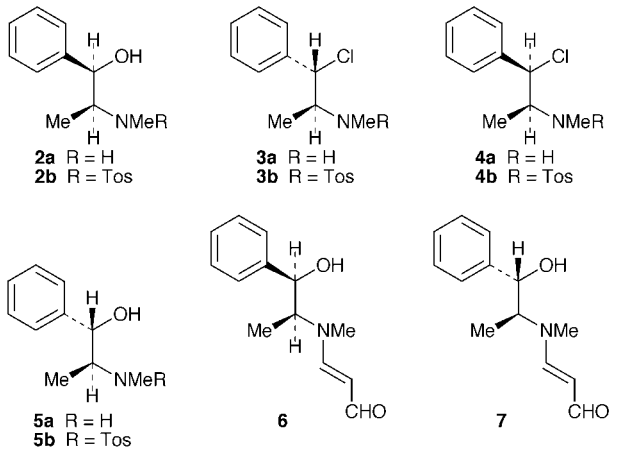
1 β-Phenylethylamines

Hordenine has been isolated from *Anomianthus dulcis*[1] and the new alkaloid armatamide **1**, which has been hydrolysed to β-(4-methoxyphenyl)ethylamine and 3,4-methylenedioxycinnamic acid, has been isolated from *Zanthoxylum armatum*.[2]



1

The conformational analysis of ephedrine and of pseudoephedrine[3] and the crystal structure of ephedrine (*S*)-*tert*-butylsulfinylacetate[4] have been studied. The reaction of ephedrine **2a** with thionyl chloride in the absence of a solvent has been shown to proceed by the S_N2 mechanism with 100% inversion, to give **3a**, whereas the corresponding *N*-toluenesulfonyl compound **2b** reacts by the S_Ni mechanism, with 100% retention of configuration, to give **4b**. Pseudoephedrine **5a**, under the same conditions, gives a mixture of the *erythro* and *threo* compounds **4a** and **3b** by S_N1 substitution and the *N*-toluenesulfonyl compound **5b** gives a mixture of **4b** and **5a**.[5] Ephedrine and pseudoephedrine have been found to add to propargyl (prop-2-ynyl) alcohol, with oxidation, in the presence of manganese dioxide, to give the isomeric aldehydes **6** and **7**.[6] A method for the estimation of *N*-methylephedrine has been published.[7]



2a R = H
2b R = Tos

3a R = H
3b R = Tos

4a R = H
4b R = Tos

5a R = H
5b R = Tos

6

7

The pharmacological and physiological effects of ephedrine[8–15] and of *N*,*N*-dimethyltryptamine[16] have been studied.

2 Isoquinolines

Simple isoquinolines have been isolated from the following plant species:

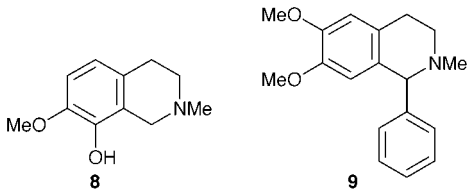
Annona cherimola[17]
doryphornine and thalifoline
Berberis turcomanica[18]
turcomanine **8**
Berberis vulgaris[19]
thalifoline
Fumaria bastardii[20]
corydaldine and oxohydrastinine
Hypecoum leptocarpum[21]
oxohydrastinine
Thalictrum przewalskii[22]
N-methylcorydaldine.

Of these turcomanine is a new alkaloid derived from 7,8-dihydroxyisoquinoline, the only other alkaloids of that type being lemaireocerine, dehydrolemaireocerine, bisdehydrolemaireocerine (isobackebergine) and tepenine. In addition the new 1-phenyltetrahydroisoquinoline alkaloid **9** (unnamed) has been isolated from *Adhatoda vasica*[23] and the novel 5,6,7,8-tetrahydroisoquinolines hyeronine A **10a** and hyeronine B **10b**, in which the stereochemistry at C-6 has not been determined, have been isolated from *Hyeronima oblonga*.[24]

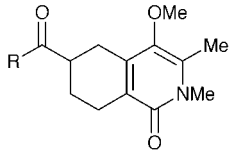
Racemic coreximine **13** has been synthesised by the reaction of hydrastinine **11** with the lithium salt **12**, followed by hydrolysis of the product; a 6% excess of the (+)-isomer was obtained using the menthyl ester analogue of **12**.[25]

3 Naphthylisoquinolines

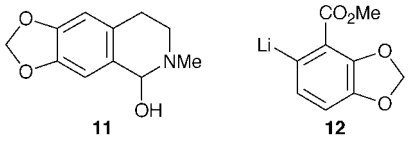
Naphthylisoquinoline alkaloids have been isolated from the following plant species, the six marked with asterisks being new alkaloids:



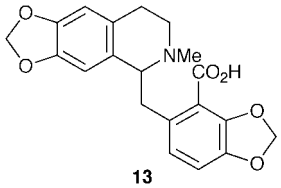
8 **9**



10a R = C_7H_{15}
10b R = C_5H_{11}

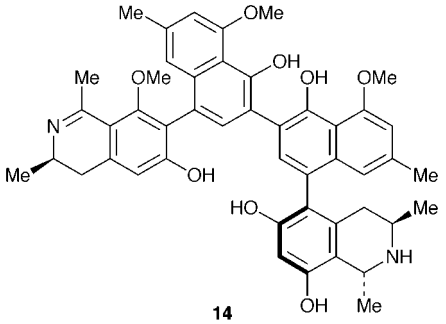


11 **12**



13

Ancistrocladus korupensis[26]
korundamine A* **14**
Ancistrocladus robertsonorium[27]
ancistrobrevine B, ancistrocladine, ancistrorobertsonine A* **15** and hamatine
Triphyophyllum peltatum[28–30]
dioncophylline D* **16a**, 8-*O*-methyldioncophylline D* **16b**, 5′-*O*-demethyldioncophylline A* **17a** and dioncophyllinol* **18**.



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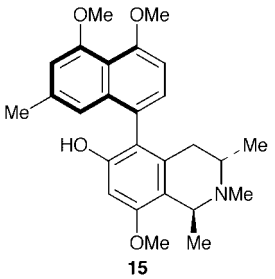
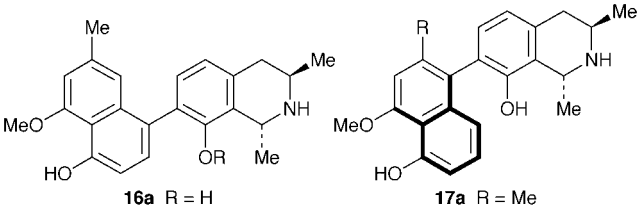


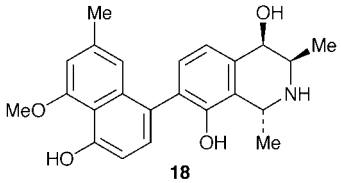
15

Of the new alkaloids the absolute stereochemistry of dionocophylline D was determined by oxidation to D-alanine and (*R*)-3-aminobutyric acid[28] and of 5′-*O*-methyldioncophylline A by an X-ray crystallographic study of its 5-bromo-*N*,*O*,*O*-tribenzyl derivative and by partial synthesis from dioncopeltine A.[29] The absolute configurations of the known isoancistrocladine **19** and its rotamer, isohamatine, have been



16a R = H
16b R = Me

17a R = Me
17b R = CH_2OH



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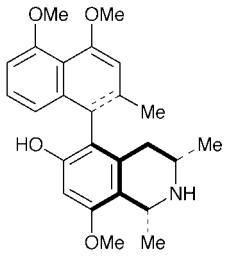
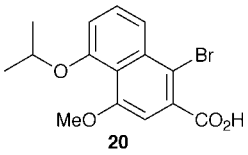


19

determined from their CD spectra.[31] Dionocophyllinol is the first 4-hydroxytetrahydroisoquinoline reported in this series, and korundamine A is the first unsymmetrical dimer of a 5-naphthyl and a 7-naphthylisoquinoline. The latter alkaloid shows antiviral activity against HIV-1 and antimalarial activity against *Plasmodium falciparum*.[26] Michellamines A, B and C and korupensamines A and B have been separated by HPLC, and the enzymatic oxidation of korupensamine B to michellamine C has been confirmed.[32]

The bromo-acid **20** and the phenol **21** have been coupled through the ester **22** to give the lactone **23a**, which was converted through **23b** into dioncolactone A **23c**. Reduction of **23b** with the complex of borane and the (*S*)-oxazaborolidine **24**



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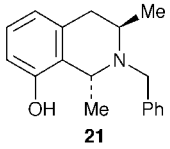

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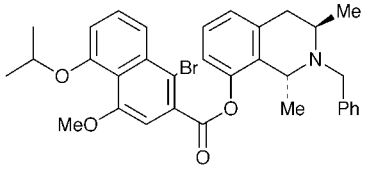

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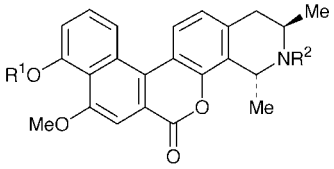
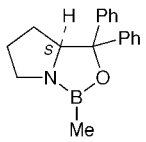


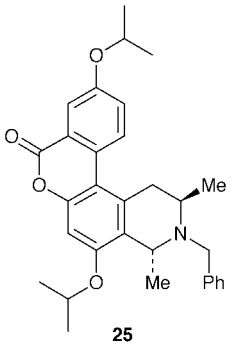
23a R^1 = Pr^i, R^2 = CH_2Ph
23b R^1 = H, R^2 = CH_2Ph
23c R^1 = R^2 = H



24

afforded over 95% enantiomeric excess of *N*-benzyldioncopeltine A, easily converted into dioncopeltine A **17b** and into 5′-*O*-dimethyldioncophylline A **17a**. The unwanted atropomer produced in the reduction of **23b** was easily converted back into **23b** for further use.[33] Using a similar approach the lactone **25** was reduced to the alcohol **26**, from which the naphthalene system was constructed to afford a synthesis of korupensamines A and B **27**,[34] which have also been synthesised by the palladium-mediated coupling of the bromo-compound **28** with the boronic acid **29**, followed by removal of the protecting benzyl group.[35]

Octadehydromichellamine **32**, which contains no asymmetric carbon atom, is not preparable by the dehydrogenation of



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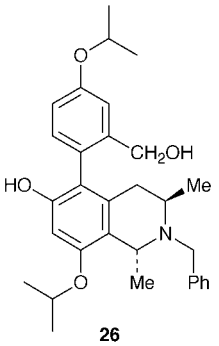

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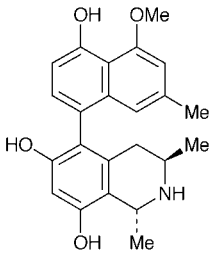

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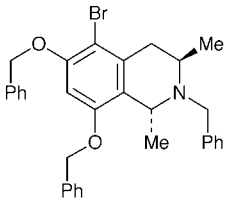

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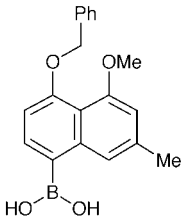
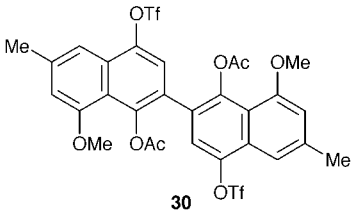


29

michellamines A, B or C, but has been synthesised by the coupling of **30**, available from previous syntheses of michella-



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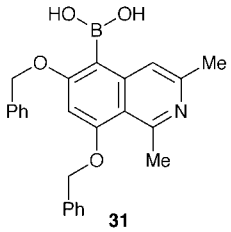

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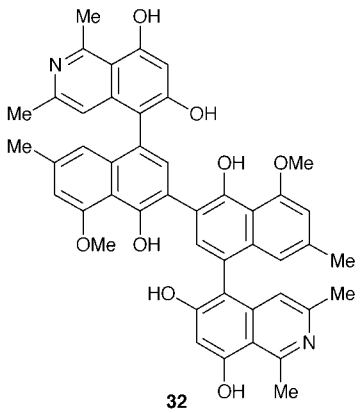


32

mines, with the boronic acid **31**. It shows antiviral and cytotoxic activity against HIV-1 of the same order as that of michellamine B, but its activities against both chloroquine-resistant and chloroquine-sensitive strains of *Plasmodium falciparum* are significantly greater than those of the alkaloid.[36] Other syntheses of alkaloids of this group have been reviewed.[37]

4 Benzylisoquinolines

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

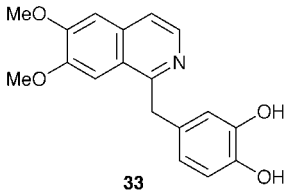
Anonianthus dulcis[1]
reticuline

Berberis turcomanica[38]
turcomanidine* **33**

Fumaria bastardii[20]
juziphine

Orophea hexandra[39]
reticuline

Thalictrum przewalskii[22]
thalprzewalskiinone* **34**



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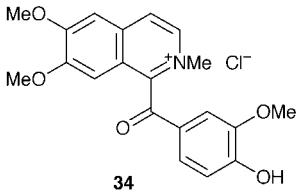
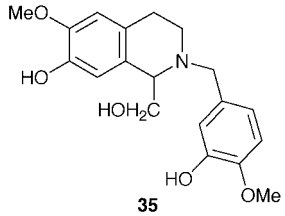
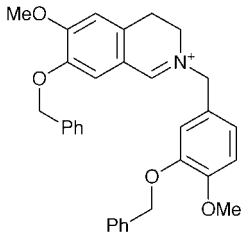


34

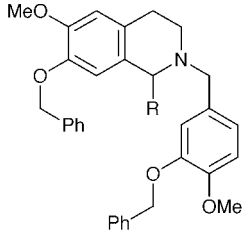
The new 2-benzylisoquinoline alkaloid heterocarpine **35** has been isolated from *Ceratocapnos heterocarpa* and its structure has been confirmed by its synthesis from the iminium salt **36**, through the tetrahydroisoquinolines **37a**, **37b** and **37c**.[40]



35

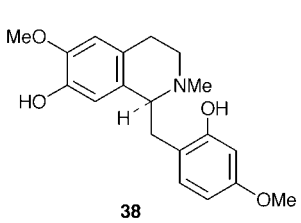


36



37a R = CN
37b R = $CONH_2$
37c R = CO_2Me

It was reported in the previous review that dehassiline, assigned the structure **39**, is not identical with the base of this



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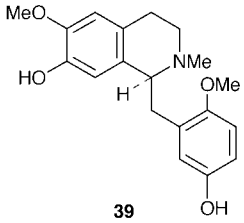


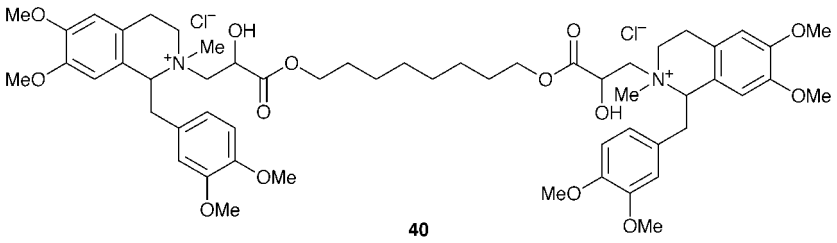
39

structure prepared by synthesis; a further study has shown that it is not identical with the isomeric base **38**, prepared by the stereoselective reduction of the related 3,4-dihydroisoquinolinium salt.[41] The bis-quaternary salt **40**, which is an analogue of atracurium has been prepared from tetrahydropapaverine.[42] Electrolytic cyclisations of the halides **41a**, **41b** and **41c** have afforded the aporphine alkaloid dehydroroemerine **42**.[43]

A review of the isolation, determination of structure and syntheses of alkaloids of *Papaver* species has been published.[44] The pharmacological and physiological effects of papaverine[45] and of atracurium[46–51] have been studied.

5 Bisbenzylisoquinolines

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



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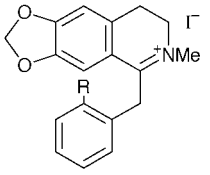
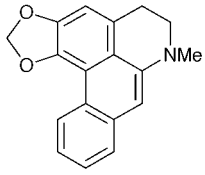


41a R = Cl
41b R^1 = Br
41c R = I



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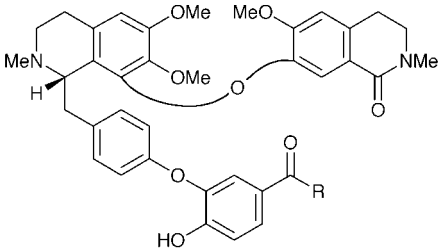
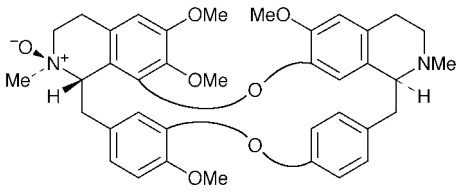


43a R = H
43b R = OMe

Berberis vulgaris[19]
aromoline, baluchistanamine **43a**, berbamine, isotetrandrine, obaberine, obamegine, oxyacanthine and tejedine* **43b**.
Stephania tetrandra[52]
fenfangjine A* **44**, fenfangjine B* **45a** and fenfangjine C* **45b**.



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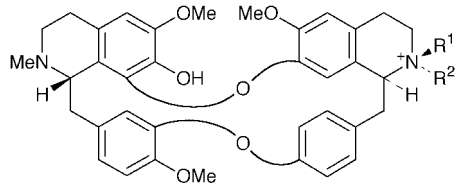
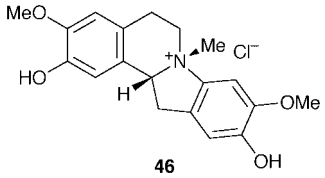


45a R^1 = Me, R^2 = O^-
45b R^1 = O^-, R^2 = Me

The pharmacological and physiological effects of berbamine,[53–57] of *O*-(4-ethoxybutyl)berbamine,[58] of cepharanthine,[59,60] of dauricine,[61,62] of daurisoline,[63–65] of fangchinoline,[66–68] of tetrandrine[66,68–81] and of tubocurarine[82,83] and the esterolytic activity of tubocurarine[84] have been studied.

6 Dibenzopyrrocolines

A new alkaloid of the dibenzopyrrocoline group, mangochinine, which is 10-*O*-demethylcryptaustoline **46**, has been isolated from *Magnolia chingii*. Its structure was deduced from the spectra of its *O*,*O*-diacetyl ester and its absolute configuration from ORD studies.[85]



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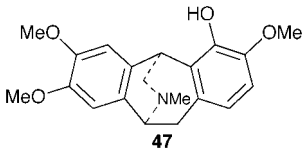
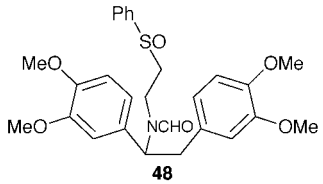
7 Pavines and isopavines

The new alkaloid isothalisopavine **47**, which has been isolated from *Thalictrum minus*,[86] is the first unsymmetrically substituted isopavine alkaloid to be reported, though a similar orientation of substituents has been observed in the pavine alkaloids munitagine, neocaryachine, platycerine and *O*-methylplatycerine. *N*-Methylcaryachine and *N*-methylneocaryachine salts have been isolated from cultures of callus cells of *Cryptocarya chinensis*.[87]

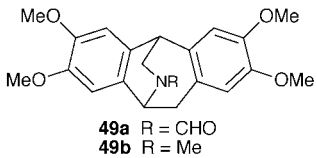


47

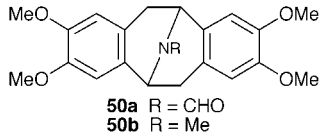
The substituted formamide **48** has been cyclised by tetrafluoroacetic anhydride and boron trifluoride to give *N*-formylisopavine **49a**, which was reduced to (±)-thalisopavine **49b**, and *N*-formylpavine **50a** and hence (±)-argemonine **50b** has been prepared by the similar cyclisation of the 1,2-dihydroisoquinoline **51**.[88]



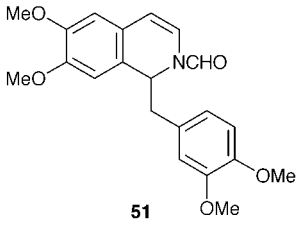
48



49a R = CHO
49b R = Me



50a R = CHO
50b R = Me

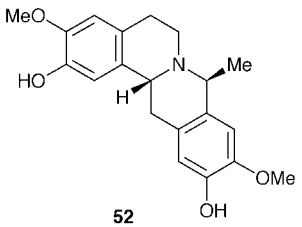


51

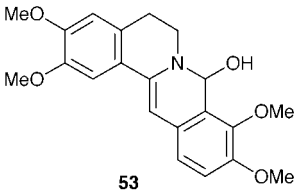
8 Berberines and tetrahydroberberines

Alkaloids of the berberine group have been isolated from the following plant species, the four marked with asterisks being new alkaloids:
Anomianthus dulcis[1]
capaurine, caseamine and discretamine
Berberis turcomanica[38]
N-methylcorydaline chloride

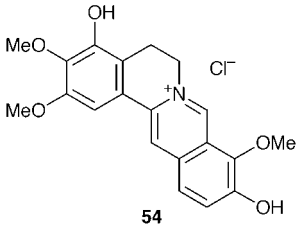
Berberis vulgaris[19]
berberine, 8-oxyberberine, jatrorrhizine and palmatine
Croton hemiargyreus[89]
hemiargyrine* **52**



52



53

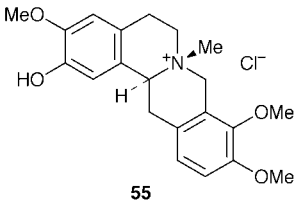


54

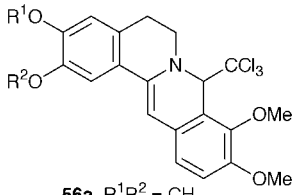
Enantia chlorantha[90]
hydroxydihydropalmatine* **53**
Fissistigma balansae[91]
columbamine, dehydrodiscretamine, fissiaine* **54**, kikemanine and thaipetaline
Fumaria agraria[92]
coptisine, palmatine, sinactine, stylopine and *N*-methylstylopine chloride
Fumaria bastardii[20]
stylopine and tetrahydropalmatine
Fumaria capreolata[92]
coptisine, sinactine and stylopine
Fumaria densiflora[92]
coptisine, palmatine, sinactine, stylopine and *N*-methylstylopine chloride
Fumaria muralis[92]
coptisine, palmatine, sinactine and stylopine
Fumaria officinalis[92]
coptisine, palmatine, sinactine, stylopine and *N*-methylstylopine chloride
Fumaria parviflora[92]
coptisine, sinactine, stylopine and *N*-methylstylopine chloride
Fumaria vaillantii[92]
coptisine, palmatine, sinactine and stylopine
Phellodendron amurense[93]
berberine
Stephania rotunda[94]
tetrahydropalmatine
Thalictrum przewalskii[22]
berberine and pseudocoptisine
Tinospora hainanensis[95]
N-methyltetrahydrocolumbamine chloride* **55**

In addition 8-trichloromethyldihydroberberine **56a** and 8-trichloromethyldihydropalmatine **56b**, which are presumed to be artifacts of the solvent extraction process, have been isolated from *Berberis oblonga* and *Berberis integerrima*.[96] The structures of these[96] and of tetrahydropalmatine hydrate[94] were confirmed by X-ray crystallographic studies.

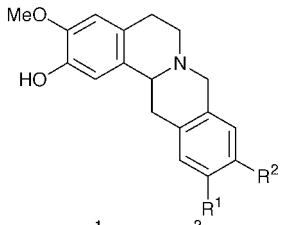
Govadine **57a** has been synthesised by the photo-catalysed cyclisation of **58**,[97] and bharatamine **57b** has been synthesised in the same way from the simpler **59**.[98] Cyclisation of the acetylenes **60a** and **60b** has afforded the macrocyclic lactams **61** and **62** respectively, both of which were stereospecifically cyclised by hydriodic acid to the oxyberberine analogue **63** in very good yield. In marked contrast with this the cyclisation of **60b** with tetrabutylammonium fluoride gave a quantitative yield



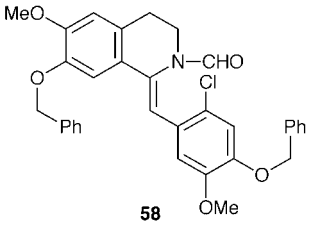
55



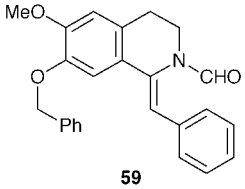
56a $R^1R^2 = CH_2$
56b $R^1 = R^2 = Me$



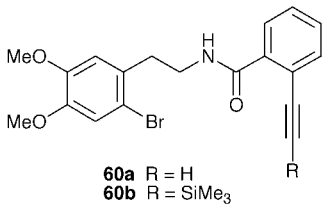
57a R^1 = OMe, R^2 = OH
57b $R^1 = R^2$ = H



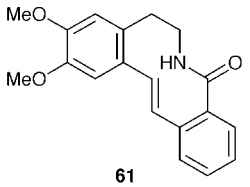
58



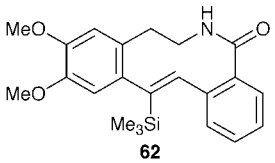
59



60a R = H
60b R = $SiMe_3$



61



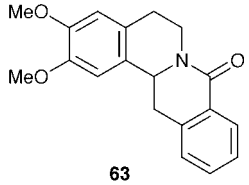
62

of the isoindolobenzazepine **64**, which is an analogue of the alkaloid lennoxamine (section 13).[99] The silylated lactam **62** has been oxidised by the dimethyldioxirane **65a** to the epoxide **66**, which was cyclised by hydrochloric acid to the unsaturated lactam **67**. The same sequence of reactions with the unsilylated lactam **61** afforded the hydroxylated lactam **68**. The (*Z*)-isomer of the (*E*)-lactam **61** reacted more sluggishly with an excess of the oxidising agent **65a**, eventually giving a mixture of the tetrahydroberberine **69** and the isoindolobenzazepine **70**, which are analogues of the alkaloids prechilenine and chilenine respectively. Oxidation of **62** with **65a** involved some fission of the veratrole ring to give **71** in addition to **66**, but the bulkier dioxirane **65b** was unable to attack the styrenoid double bond and only the diester **72** was obtained.[100]

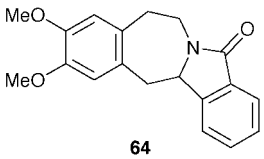
The pharmacological properties and physiological effects of berberine,[101–103] of palmatine,[104,105] of tetrahydropalmatine,[106] and of stepholidine[106–108] have been studied, and the synthetic berberine **73** and its close analogues have been tested as potential antimicrobial agents.[109]

9 Secoberberines

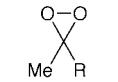
Four new secoberberine alkaloids, leptopine **74a**, leptopidine **74b**, leptopinine **75** and leptopidinine **76**, have been isolated from *Hypecoum leptocarpum*.[21] Their structures were deduced from their spectra. Leptopine **74a** and leptopidinine **76** would be



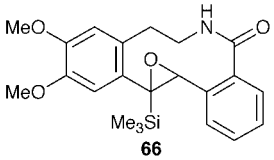
63



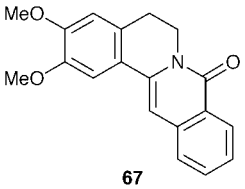
64



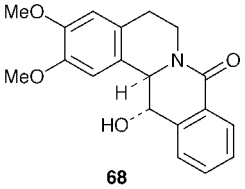
65a R = Me
65b R = CF_3



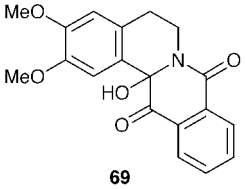
66



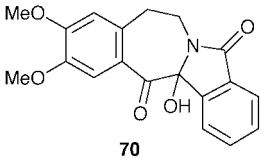
67



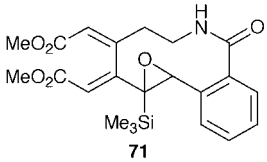
68



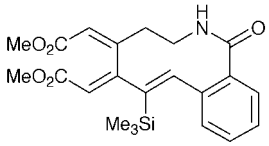
69



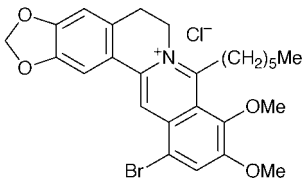
70



71

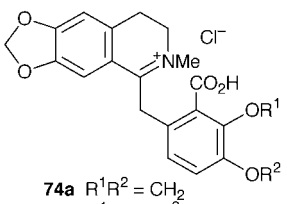


72

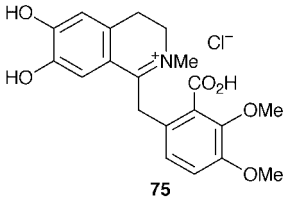


73

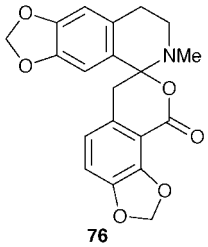
expected to be readily interconverted, but their ultraviolet spectra, and their behaviour on thin layer chromatography, in both aqueous and methanolic sodium hydroxide and hydrochloric acid were not identical.[21]



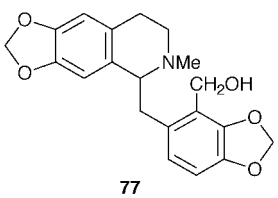
74a $R^1R^2 = CH_2$
74b R^1 = H, R^2 = Me



75



76



77

(±)-Coreximine **13** has been synthesised from hydrastinine **11** as described in section 2, and a similar synthesis of (±)-corydalisol **77** has also been achieved.[110]

10 Protopines

Alkaloids of the protopine group have been isolated from the following plant species:
Fumaria agraria[92]
cryptopine and protopine
Fumaria bastardii[20]
protopine
Fumaria capreolate[92]
cryptopine and protopine
Fumaria densiflora[92]
cryptopine
Fumaria muralis[92]
protopine
Fumaria officinalis[92]
protopine
Fumaria parviflora[92]
cryptopine and protopine
Fumaria vaillantii[92]
cryptopine and protopine
Hypercoum leptocarpum[21]
protopine
Thalictrum triternatum[111]
allocryptopine and protopine.

X-Ray crystallographic studies of α and β-allocryptopine confirm that these are polymorphic forms of the same substance.[112]

11 Phthalide-isoquinolines

Phthalide-isoquinoline alkaloids have been isolated from the following plant species:
Fumaria agraria[92]
adlumiceine and adlumidiceine
Fumaria bastardii[20]
bucuculline, corlumine and β-hydrastine
Fumaria capreolata[92]
adlumiceine and adlumidiceine
Fumaria densiflora[92]
adlumiceine and adlumidiceine
Fumaria muralis[92]
adlumiceine and adlumidiceine
Fumaria officinalis[92]
adlumiceine and adlumidiceine
Fumaria parviflora[92,113]
adlumiceine, adlumidiceine, corledine, corlumidine and α-hydrastine
Fumaria vaillantii[92]
adlumiceine and adlumidiceine

The pharmacological properties and physiological effects of bicuculline[114–116] and of narcotine[117] have been studied.

12 Spirobenzylisoquinolines

Spirobenzylisoquinolines alkaloids have been isolated from the following plant species:
Fumaria agraria[92]
fumaricine, fumariline, fumaritine, fumarophycine, *O*-methylfumarophycine and parfumine
Fumaria bastardii[20]
fumariline, fumaritine and *O*-methylfumarophycine
Fumaria capreolate[92]
fumaricine, fumariline, fumaritine, fumarophycine, *O*-methylfumarophycine and parfumine
Fumaria densiflora[92]
fumaricine, fumariline, fumarophycine, *O*-methylfumarophycine and parfumine
Fumaria muralis[92]
fumaricine, fumaritine, fumariline and parfumine
Fumaria officinalis[92]

fumaricine, fumariline, fumaritine, fumarophycine, *O*-methylfumarophycine and parfumine

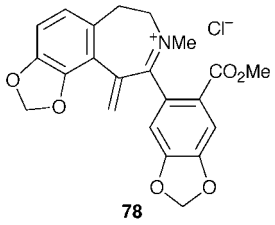
Fumaria parviflora[92]
fumariline, fumaritine, *O*-methylfumarophycine and parfumine

Fumaria vaillantii[92]
fumaricine, fumarophycine, *O*-methylfumarophycine and parfumine

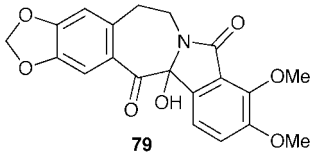
Hypecoum leptocarpum[21]
isohyperectine.

13 Other modified berberines

Chilenine has been isolated from *Berberis vulgaris*[19] and a new alkaloid, leptocarpinine, which has been assigned the arylbenzazepine structure **78** on the basis of its spectra, has been

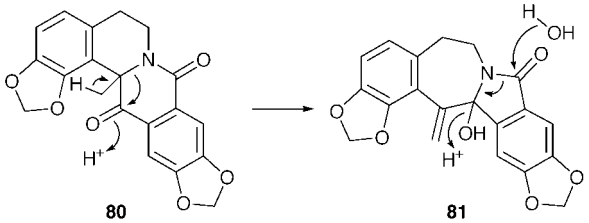


78

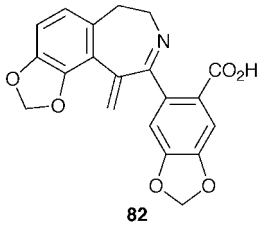


79

isolated from *Hypercoum leptocarpum*.[21] Apart from the additional methylene group, **78** has the skeleton of a hydrolysed chilenine **79** and might be expected to be derived from a secoberberine alkaloid in a manner similar to the derivation of chilenine from berberine. However the orientation of substituents in **78** and **79** is different and the substitution pattern of any putative precursor of **78**, such as **80**, which could be



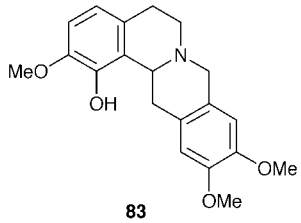
80 **81**



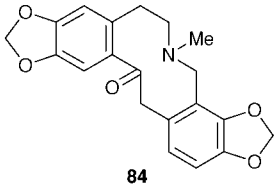
82

converted into **78** through **81** and **82**, is observed only in the alkaloid caseadine **83**. The very much more common 2,3,9,10-substitution pattern is observed in all of the alkaloids (protopine **84**, isohyperectine **85**, leptopine **74a**, leptopinine **74b**, leptopidine **75** and leptopidinine **76**) isolated together with leptocarpinine, from *Hypecoum leptocarpum* suggesting that this alkaloid more probably has the structure **86**. Structures deduced entirely from spectra have occasionally had to be revised, most recently those of fumarizine and dehassiline. Though 13a *C*-methylated tetrahydroberberines have not so far been reported, alkaloids with *C*-methyl groups in the other benzylic positions 8 and 13 are known and the introduction of such a group into **80** or an isomer presents no biogenetic problem.

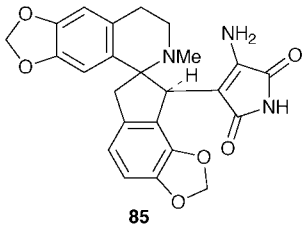
The acetylenic amide **87** has been cyclised to the isoindole **88**, oxidation of which gave the vicinal diol **89a**, the



83



84



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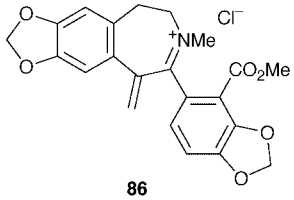
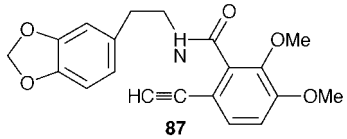
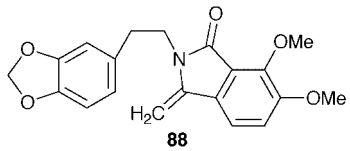


86

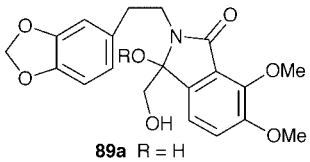
monomethyl ether of which **89b** was cyclised to the isoindoloquinoline **90**. Rearrangement of this afforded dehydrolennoxamine **91**, which was hydrogenated to lennoxamine **92**.[118] The synthesis of analogues of chilenine and lennoxamine from macrocyclic acetylenes is reported in section 8.



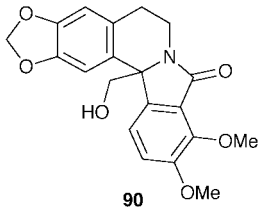
87



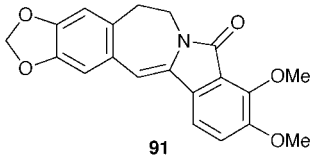
88



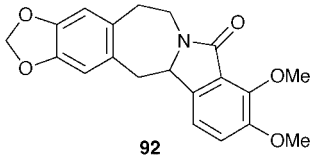
89a R = H
89b R = Me



90



91

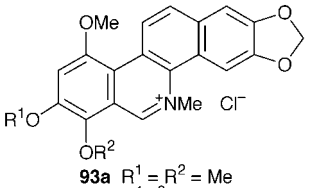


92

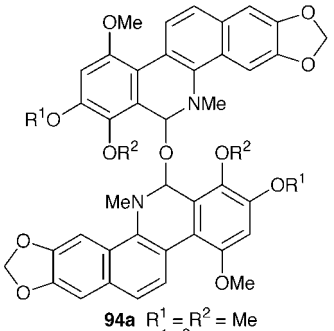
14 Benzophenanthridines

Chelilutine and chelirubine chlorides **93a** and **93b** have been converted into the bimolecular alkanolamine ethers **94a** and **94b** by aqueous sodium carbonate and into the bimolecular amines **95a** and **95b** by aqueous ammonia. The simple alkanolamines **96a** and **96b** have been detected only in solutions of the alkaloids in deuteriochloroform on shaking with aqueous sodium carbonate.[119] The NMR spectrum of 6-hydroxydihydrosanguinarine **96c**, obtained in deuteriochloroform in the same way from sanguinarine, has been studied.[120]

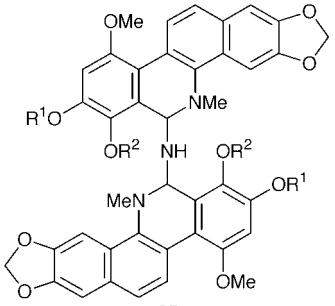
The assignment of structures **99a** and **99b** to fagaridine and isofagaridine respectively has been confirmed by detailed studies of their UV spectra[121] and by syntheses of both alkaloids by internal aryl–aryl couplings of **97a** and **97b** in the presence of tri-*n*-octyltin iodide to give **98a** and **98b**, followed by



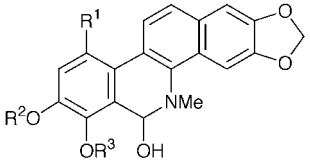
93a $R^1 = R^2 = Me$
93b $R^1R^2 = CH_2$



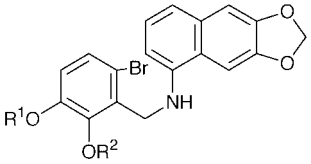
94a $R^1 = R^2 = Me$
94b $R^1R^2 = CH_2$



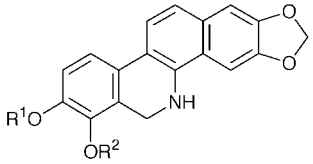
95



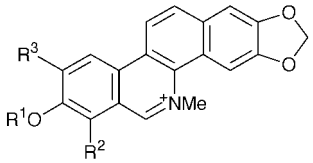
96a $R^1 = OMe,\ R^2 = R^3 = Me$
96b $R^1 = OMe,\ R^2R^3 = CH_2$
96c $R^1 = H,\ R^2R^3 = CH_2$



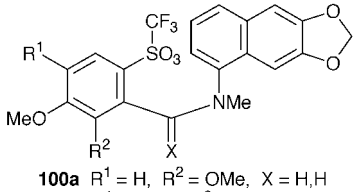
97a $R^1 = Me,\ R^2 = CH_2Ph$
97b $R^1 = CH_2Ph,\ R^2 = Me$



98a $R^1 = Me,\ R^2 = CH_2Ph$
98b $R^1 = CH_2Ph,\ R^2 = Me$



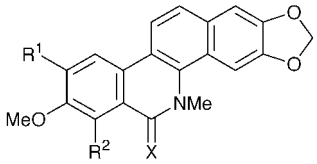
99a $R^1 = Me,\ R^2 = OH,\ R^3 = H$
99b $R^1 = R^3 = H,\ R^2 = OMe$
99c $R^1 = Me,\ R^2 = OMe,\ R^3 = H$
99d $R^1 = Me,\ R^2 = H,\ R^3 = OMe$
99e $R^1R^3 = CH_2O,\ R^2 = H$



100a $R^1 = H,\ R^2 = OMe,\ X = H,H$
100b $R^1 = OMe,\ R^2 = H,\ X = H,H$
100c $R^1 = OMe,\ R^2 = H,\ X = O$

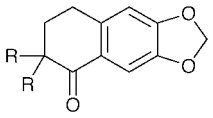
oxidation to the related isoquinolines with manganese dioxide and *N*-methylation.[121,122] Similar aryl–aryl cyclisations of the trifluoromethane sulfonates **100a**, **100b** and **100c** by palladium(II) acetate, 3-bis(diphenylphosphino)propane and tributylphosphine have afforded dihydrochelerythrine **101a**, dihydronitidine **101b** and oxonitidine **101c**, which were converted into chelerythrine **99c** and nitidine **99d**.[123,124]

An alternative approach, using the Suzuki coupling of an aryl halide with an arylboronic acid, used so successfully in the

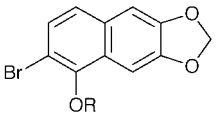


101a $R^1 = H,\ R^2 = OMe,\ X = H,H$
101b $R^1 = OMe,\ R^2 = H,\ X = H,H$
101c $R^1 = OMe,\ R^2 = H,\ X = O$

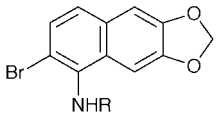
synthesis of naphthylisoquinoline alkaloids, has afforded a range of benzophenanthridine alkaloids. The required 2-bromo-1-aminonaphthalene was difficult to prepare, but was finally obtained from the 1-tetralone **102a** by bromination to **102b** and



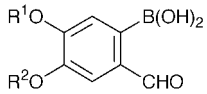
102a R = H
102b R = Br



103a R = H
103b $R = CMe_2CONH_2$



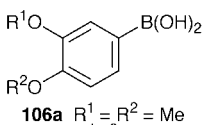
104a $R = COCMe_2OH$
104b R = H
104c R = CHO



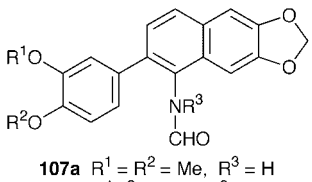
105a $R^1 = R^2 = Me$
105b $R^1R^2 = CH_2$

dehydrobromination to the 2-bromo-1-naphthol **103a**, followed by Smiles rearrangement of the ether **103b** to the amide **104a**, which was hydrolysed to the amine **104b**. This was found to react only sluggishly and inefficiently with the aldehydic boronic acids **105a** and **105b**, in attempts to generate the tetracyclic system directly, but the formamide **104c** and the simpler boronic acids **106a** and **106b** readily coupled to give good yields of **107a** and **107b**. These were then subjected to Bischler–Napieralsky ring closure to give nornitidine **108a** and noravicine **108b**. *N*-Methylation of **107a** and **107b** gave **107c** and **107d** and cyclisations of these afforded nitidine **99d** and avicine **99e**. Similar syntheses of chelerythrine **99c** and chelilutine **93b** were achieved from the boronic acids **109a** and **109b** and the amide **104c**.[125]

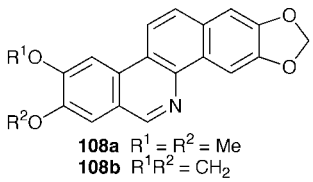
The 4-phenylisoquinoline alkaloid decumbenine B **116**,[126] which can be regarded as a degraded benzophenanthridine, has been synthesised from piperonal, the lithium salt of which **110a**, when treated with ethyl chloroformate yielded **110b**. Protection of the aldehyde group of this as the cyclic dithioketal, followed by reduction of the ester with lithium aluminium hydride and hydrolysis of the ketal, afforded **110c**, which was benzylated to give **110d**. Condensation of this with benzylamine yielded the



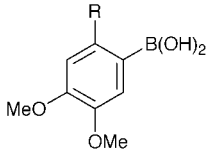
106a $R^1 = R^2 = Me$
106b $R^1R^2 = CH_2$



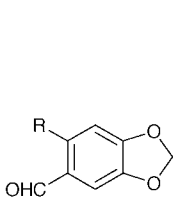
107a $R^1 = R^2 = Me,\ R^3 = H$
107b $R^1R^2 = CH_2,\ R^3 = H$
107c $R^1 = R^2 = R^3 = Me$
107d $R^1R^2 = CH_2,\ R^3 = Me$



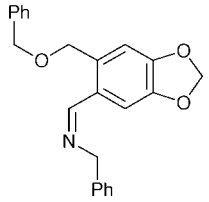
108a $R^1 = R^2 = Me$
108b $R^1R^2 = CH_2$



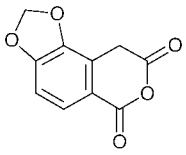
109a R = H
109b R = OMe



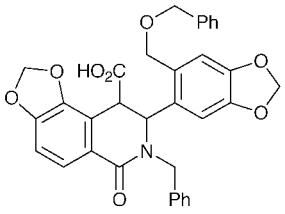
110a R = Li
110b R = CO_2Et
110c R = CH_2OH
110d R = CH_2OCH_2Ph



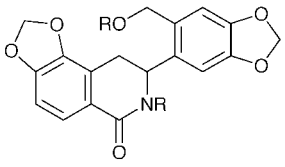
111



112

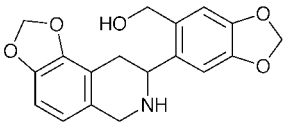


113

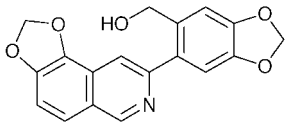


114a R = CH_2Ph
114b R = H

imine **111**, to which the anhydride **112** added to give the lactam **113**. This was decarboxylated to **114a** and the protecting groups were then removed to give **114b**, which was reduced to the amine **115**, dehydrogenation of which gave decumbenine B **116**.[127]



115



116

The pharmacological properties and physiological effects of chelerythrine[128] and the binding of fagaronine to DNA[129] have been studied

15 Aporphinoid alkaloids

15.1 Proaporphines

Proaporphine alkaloids have been isolated from the following plant species:

Annona cherimola[17]
pronuciferine

Anomianthus dulcis[1]
pronuciferine and stepharine

Orophea hexandra[39]
N-methylcrotonosine and pronuciferine.

15.2 Aporphines

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

Annona cherimola[17]
norisocorydine, norstephalgine and romucosine

Annona purpurea[130]
lirindine, *N*-methyllaurotetanine, norpurpureine, thalicmidine, 7-hydroxydehydrothalicsimidine* **117a** and *N*-formyl-7-hydroxydehydronorthalicsimidine* **117b**

Anomianthus dulcis[1]
anonaine, anolobine, asimilobine, isoboldine, *N*-methyllaurotetanine, nornuciferine and roemerine

Berberis vulgaris[19]
magnoflorine

Cassytha filiformis[131]
actinodaphnine, *N*-methylactinodaphnine, cassythicine, cathafiline, cathaformine, ocoteine, and predicentrine

Croton hemiargyreus[89]
glaucine

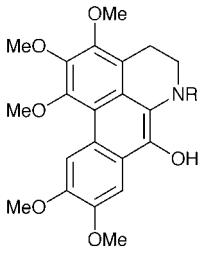
Fissistigma balansae[132]
fissilandione* **118a** and norfissilandione* **118b**

Glaucium fimbrilligerum[133]
bulbocapnine β-*N*-oxide* **119**

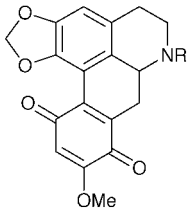
Elastostema sinuata[134]
procoteine, thalicsimidine, thaliporphine and wilsonirine

Thalictrum przewalskii[22]
magnoflorine and *N*-methylnantenine

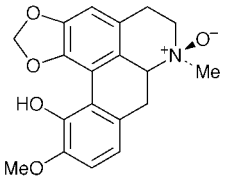
Thalictrum triternatum[111]
glaucine, thalfine and thalmine



117a R = Me
117b R = CHO

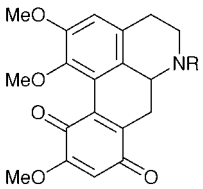


118a R = Me
118b R = H

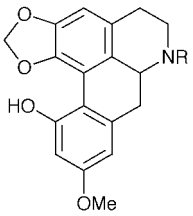


119

The new quinones **118a** and **118b** are analogues of isocorydione **120a** and norisocorydione **120b**, previously isolated from *Dehassia tetrandra*,[135] and can be prepared in a similar manner to these alkaloids, from the related phenols, *N*-methylfissolidine **121a** and fissolidine **121b**, by oxidation with Fremy's salt.[132]



120a R = Me
120b R = H

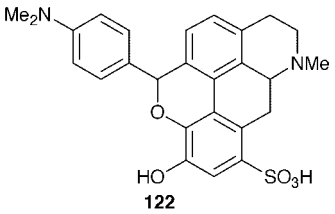


121a R = Me
121b R = H

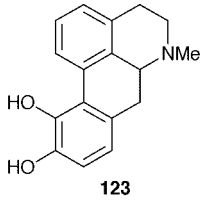
The rearrangement of morphine by concentrated sulfuric acid in the presence of 4-dimethylaminobenzaldehyde has given the apomorphine derivative **122**, available in the same way from apomorphine **123**.[136] Apomorphine and acetone afford the cyclic ketal **124**, which has been reduced by trimethylaluminium to the phenol **125a**, the trifluoroacetate of which **125b** on hydrogenation over palladium yielded **126a**, which was cleaved to 10-hydroxyaporphine **126b**.[137] The alternative cleavage of **124** to give 11-hydroxyaporphine **127** has also been accomplished.[138]

Cyclisation of the halogenated benzyldihydroisoquinolinium salts **41a**–**41c** to the aporphine dehydroroemerine is reported in section 4. The olefins **128a**–**128c** have been cyclised by Lewis acids to the tetrahydroaporphines **129a**–**129c**.[139]

The pharmacological properties and physiological effects of apomorphine[140–144] of actinodaphnine,[131] of *N*-methylactinodaphnine[131] of bulbocapnine,[145,146] of bracteoline,[147] of cassythicine[131] of cathafiline,[131] of cathaformine,[131] of dehydroglaucine,[147] of 7-acetyldehydroglaucine,[147] of 7-benzoyldehydroglaucine,[147] of 7-formyldehydroglaucine,[147] of 7-formyldehydrothalicsimidine,[130] of 7-hydroxydehydrothalicsimidine,[130] of isoboldine,[147] of ocoteine,[131] and of predicentrine[131] have been studied, and a patent claiming 9-*O*-ethylboldine **130** and its analogues as inhibhitors of metalloproteinases has been published.[148]



122



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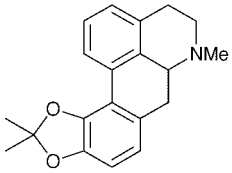
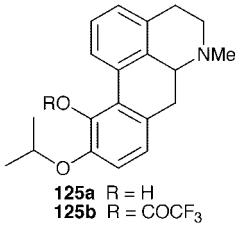
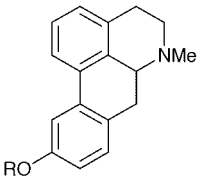


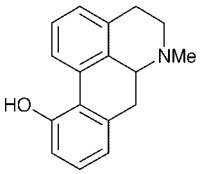
124



125a R = H
125b R = $COCF_3$



126a R = CMe_3
126b R = H



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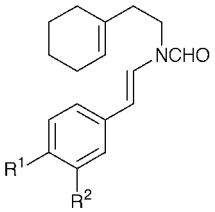
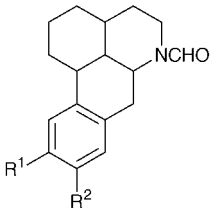
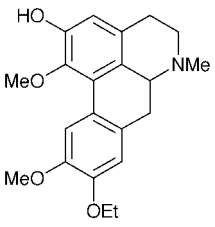


128a R^1 = H, R^2 = OMe
128b R^1 = OMe, R^2 = H
128c R^1 = Cl, R^2 = H



129a R^1 = H, R^2 = OMe
129b R^1 = OMe, R^2 = H
129c R^1 = Cl, R^2 = H



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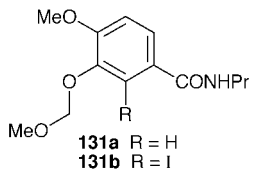
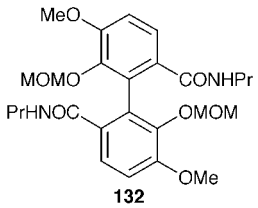


131a R = H
131b R = I



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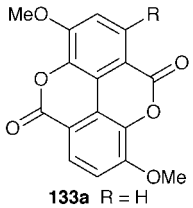
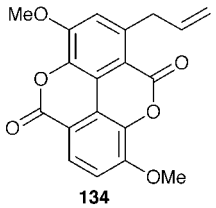


133a R = H
133b R = I



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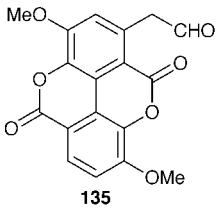

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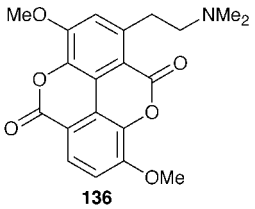
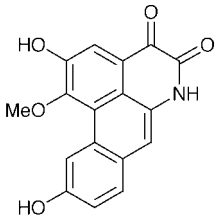
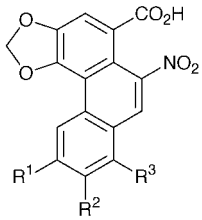


136

Aristolochia kaempferi[150] and from *Piper augustum*[151] respectively.



137



138a R^1 = R^2 = H, R^3 = OMe
138b R^1 = OH, R^2 = R^3 = H
138c R^1 = H, R^2 = OH, R^3 = OMe

15.3 Phenanthrenes

A synthesis of the alkaloid taspine which, though not itself a phenanthrene, is regarded as an oxidised member of this group, has been effected. Treatment of the substituted benzamide **131a** with butyllithium and iodine gave **131b**, which was coupled over copper powder to the biphenyl **132**, and this was hydrolysed and cyclised to the dilactone **133a**. Iodination of this yielded **133b**, which reacted with allyltributyltin and tetrakis(triphenylphosphino)palladium to give **134**, and this on ozonolysis furnished the aldehyde **135** which, on reductive amination with dimethylamine, yielded taspine **136**.[149]

15.4 Oxoaporphines

Oxoasimilobine and oxoglaucine have been isolated from *Annona cherimola*[17] and from *Croton hemiargyreus*[89] respectively. The pharmacological properties of oxoglaucine have been studied.[147]

15.5 Dioxoaporphines

The new dioxoaporphine alkaloid aristoliukine B **137** and the known alkaloid cepharadione A have been isolated from

15.6 Aristolochic acids

The aristolochic acids **138a**, **138b** and **138c** have been isolated from *Aristolochia foveolata*[152] and claimed to be new compounds, but acids of these structures have previously been reported as aristolochic acid A,[153] aristolochic acid C[154] and 7-hydroxyaristolochic acid A.[155] New esters of aristolochic acid-II and aristolochic acid A with complex alcohols have been isolated from *Aristolochia heterophylla*[156,157] as aristophyllide A **139a**, aristophyllide B **140a**, aristophyllide C **139b**, aristophyllide D **140b**, aristoterpenate-I **141a**, aristoterpenate-II **141b**, aristoterpenate-III **142a** and aristoterpenate-IV **142b**. The configurations of these at the asymmetric carbon atoms were determined from their CD spectra. The terpenoid esters **141** and **142** showed cytotoxic activity against hepatoma G cells.[157]

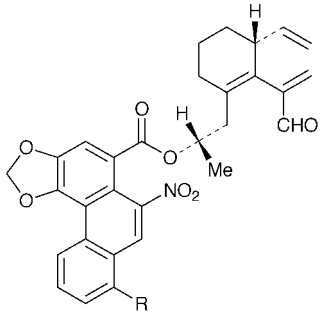
Seven phenanthrene-1-carboxylic acids, which may be degraded aristolochic acids, have been isolated from *Aristolochia curcurbitifolia*.[158]

15.7 Aristolactams

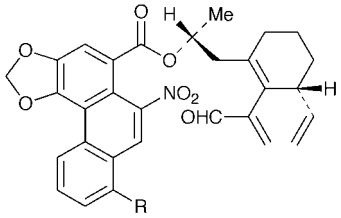
Aristolactams have been isolated from the following plant species, the six marked with asterisks being reported for the first time:

Aristolochia contricta[159]

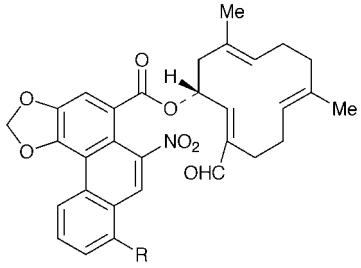
4-*O*-methylaristolactam A-IIIa *N*-β-D-glucoside* **143a**, 4-*O*-methylaristolactam A-IIIa *N*-β-D-(6-*trans*-coumaroyl)gluco-



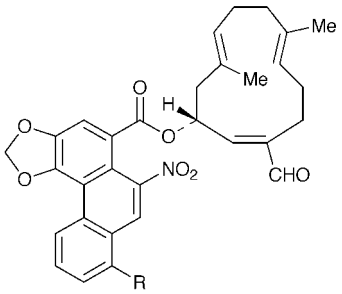
139a R = OMe
139b R = H



140a R = OMe
140b R = H



141a R = OMe
141b R = H



142a R = OMe
142b R = H

side* **144**, aristolactam B-III *N*-β-D-glucoside* **143b** and *O*-demethylaristolactam A-IIIa *N*-β-D-glucoside* **145**

Aristolochia kaempferi[150]

aristoliukine A* (3-*O*-demethylaristolactam C-II) **146**

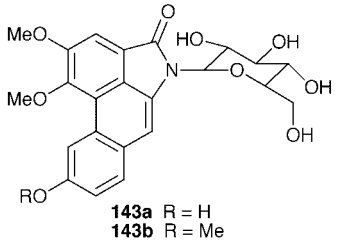
Piper augustum[151]

cepharanone B and *N*-methylpiperolactam B* **147**

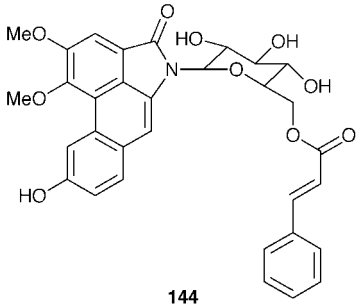
Piper tuberculatum[160]

cepharanone B

The aglycones of **143a** and **145** have not been reported as free aristolactams.



143a R = H
143b R = Me



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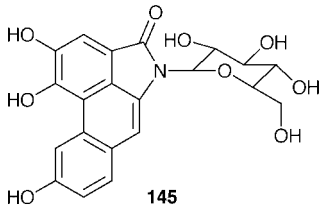

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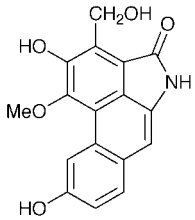

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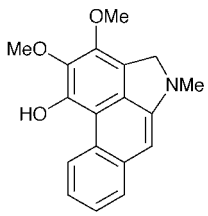


147

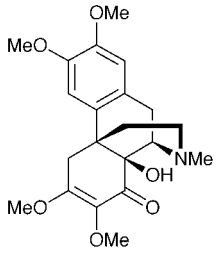
amurine

Menispermum dauricum[161]

dechloroacutumine* **149b**

Pachygone dasycarpa[162]

14-hydroxyisostephodeline* **148**



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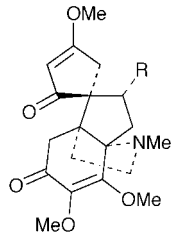


149a R = Cl
149b R = H

Dechloroacutumine **149b** was only isolated from *Menispermum dauricum* grown in chloride-free media. In the presence of chloride ion only acutumine **149a** is produced.[161]

The *O*-demethylation of codeine to morphine has been effected in 91% yield with boron tribromide and in 73% yield using L-Selectride. The latter reagent has also proved effective (30%) in the more sensitive demethylation of thebaine **151** to oripavine and in the demethylation of 14-hydroxycodeinone and of *O*-methylnaltrindole.[163] Codeine has been converted into thebaine **151** by oxidation to codeinone **150**, followed by enol methylation;[164] it has also been rearranged by butyllithium to thebainone A **152** in 74% yield, which is much superior to

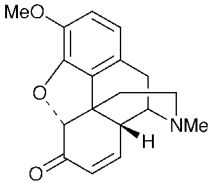
16 Alkaloids of the morphine group

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

Croton hemiargyreus[89]

salutaridine and norsalutaridine

Elastostema sinuata[134]



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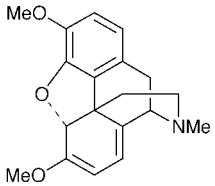

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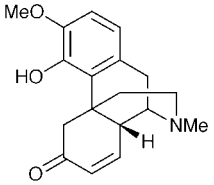
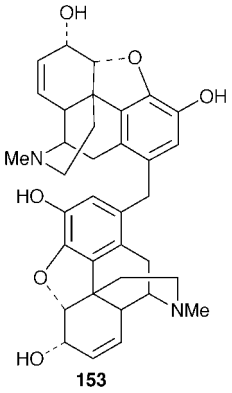


152

earlier yields by rearrangement over palladium.[165] The acid-catalysed condensation of morphine with paraformaldehyde has been shown to give a mixture of the 1,1′-methylenebis-compound **153** and the bases **154a** and **154b**.[166] Ethers of 1,2′-dimorphine and of trimorphine and tetramorphine have been obtained by the oxidation of morphine 3-ethers with potassium ferricyanide.[167]



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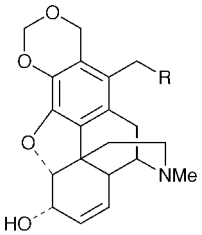
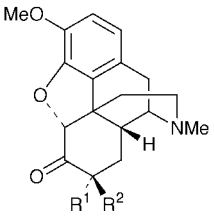
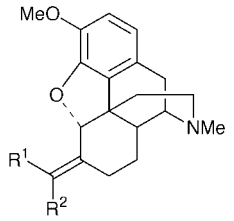


154a R = OH
154b R = H

Dihydrocodeinone **155a** on treatment with diaryliodonium iodides affords the 7α-aryl and 7,7-diaryldihydrocodeinones **155b** and **155c**,[168] and has been converted by the Wittig



155a $R^1 = R^2 = H$
155b R^1 = Ar, $R^2 = H$
155c $R^1 = R^2$ = Ar

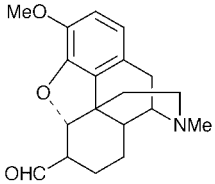


156a $R^1 = R^2 = H$
156b $R^1 = H$, R^2 = OMe
156c R^1 = OMe, $R^2 = H$
156d $R^1 = H$, $R^2 = C_6H_{11}$
156e $R^1 = C_6H_{11}$, $R^2 = H$
156f $R^1 = H$, R^2 =

156g $R^1R^2 = C_5H_{10}$

reaction into the olefins **156a**–**156e**. Of these **156b** and **156c** were hydrolysed to the aldehyde **157**, which readily suffered base-catalysed cleavage of the oxygen bridge to give the phenol **158**, and **156d** and **156e** on catalytic reduction afforded a mixture of **159** and **160**, though the non-phenolic dihydro compound **161** was obtained by reduction with diimide. Attempts to prepare the olefins **156f** and **156g** by the Wittig reaction resulted in a mixture of the dienes **162** and **163** and in production of the phenolic dimer **164** respectively, and use of the ylide from isopropyltriphenylphosphonium bromide resulted in the formation of the aldol **165**.[169]

6-Bromodihydrocodide **166** has been converted by tributyltin hydride into a mixture of deoxycodeine C **167** and dihydrodeoxycodeine D **168**,[169] and the same reagent has been used to cyclise 6-*O*-(2-bromophenyl)isocodeine **169** to the dibenzofuran **170**.[170] Morphine reacts with 4-dimethylaminobenzaldehyde in the presence of perchloric acid to give the triaryl-



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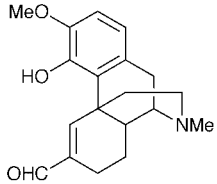

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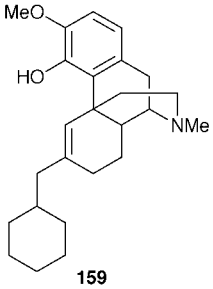

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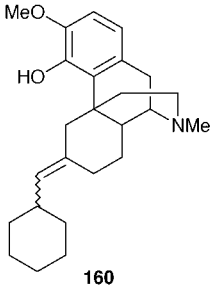

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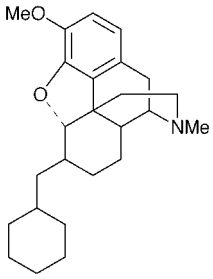

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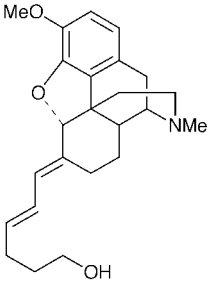

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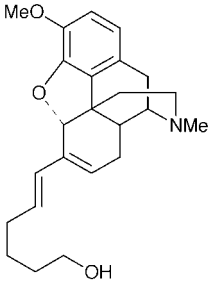

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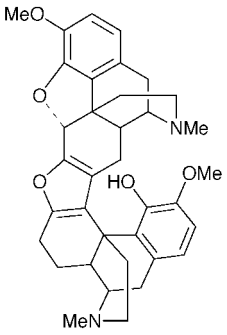

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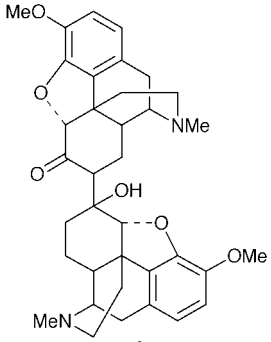
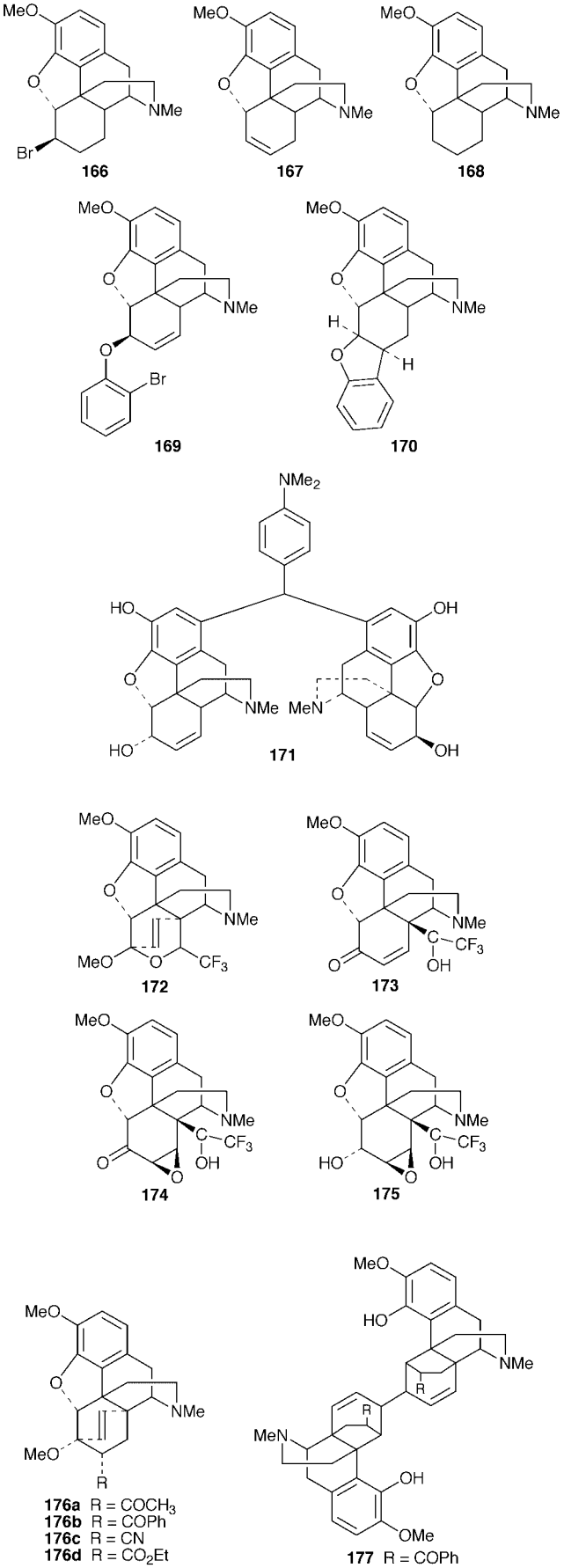


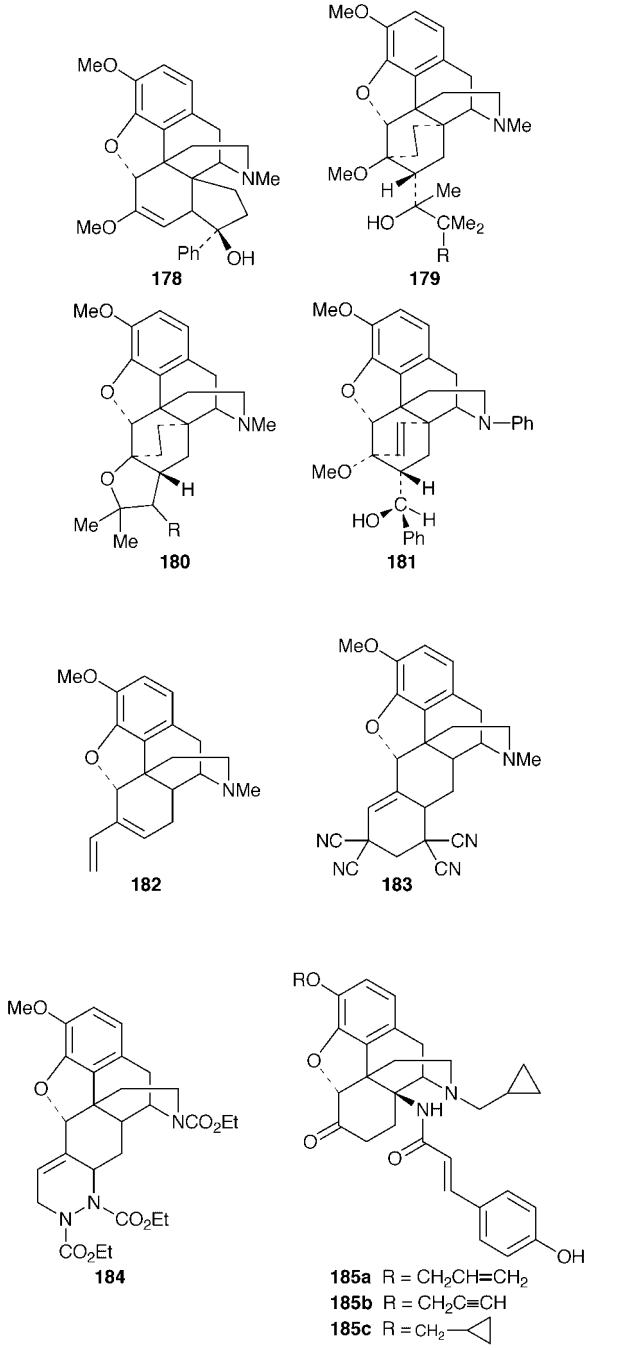
165

methane derivative **171**, but in concentrated sulfuric acid the reaction leads to the apomorphine derivative **122**.[136]

5-Methylthebaine reacts with trifluoroacetaldehyde to give the 14-substituted codeinone **173**, presumably by way of the Diels–Alder adduct **172**, and this has been epoxidised with alkaline hydrogen peroxide to **174**, which gave **175** on reduction with sodium borohydride.[171] The Diels–Alder adducts of thebaine **176a**–**176d** and their 6,14-*endo*-ethano analogues have been equilibrated with their C-7 epimers by non-nucleophilc bases in dipolar aprotic solvents, the equilibrium in all cases favouring the 7α epimers. The 7β epimer of **176c** has been reacted with phenylmagnesium bromide to give the dimeric base **177**.[172] The adduct **176b** has been rearranged by chromium iminodiacetate to the dihydro-8,14-cyclopentathebaine **178**.[173] It has been shown that the acid-catalysed rearrangement of alcohols of structure **179** to tetrahydrofurans **180** proceeds with retention of configuration at C-7.[174] This has been held to vitiate the mechanism originally proposed for this reaction[175] but nothing in that mechanism necessarily requires scrambling at this centre. X-Ray crystallographic studies of the alcohol **181** and its C-7 epimer have confirmed their structures.[176]

In Diels–Alder reactions other than those of thebaine the diene **182**, prepared from 6-*O*-trifluoroacetylcodeine and tri-

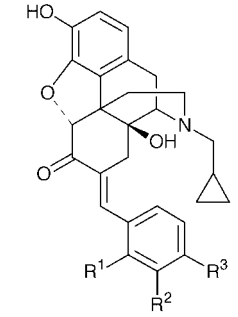




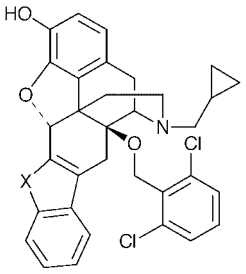
butylvinyltin, afforded poor yields of the adducts **183** and **184** with tetracyanoethylene and diethyl acetylenedicarboxylate respectively.[170]

Details of the preparation of the following have been published: the 14-aminodihydrocodeinone derivatives **185a**–**185c**,[177] *N*-benzyl-14-hydroxydihydronormorphinone,[178] 14-*O*-benzylnaltrexone,[179] 3-deoxy-14-*O*-benzylnaltrexone,[179] the 7-arylidenenaltrexones **186a**–**186k**,[180] the indole **187a**, the benzofuran **187b** and related compounds,[181–184] the quinolines **188a**–**188d** and related bases,[185] the diamine **189** and related bases,[186] the amide **190**,[187] buprenorphine,[188] 4,5-deoxythebaine **191** and its analogues,[189] ethers of morphine and of 14-hydroxymorphine,[190,191] 14-hydroxydihydromorphinone, 14-hydroxydihydrocodeinone and their derivatives,[192] ^{3}H-labelled morphine and codeine[193] and ^{18}F-labelled naltrindole.[194]

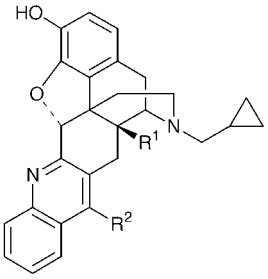
The bacterial oxidation[195] and the gluronidation[196] of morphine and of codeine and methods for the detection and estimation of morphine,[197–201] of codeine[201,202] of 6-*O*-methylcodeine,[202] of thebaine[202] and of buprenorphine[203] have been studied, and the crystal structure of the complex of morphine and (*S*)-2-phenylhydracrylic acid has been examined.[204] The hydrogenation of methyl pyruvate in the presence of dihydrocodeine or of thebaine has been found to favour the formation of an excess of the (*S*)-lactate, whereas in the



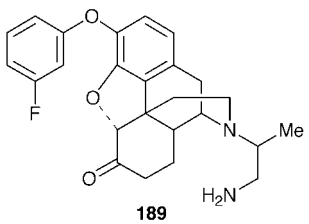
186a $R^1 = R^2 = H$, $R^3 = NO_2$
186b $R^1 = R^3 = H$, $R^2 = NO_2$
186c $R^1 = OMe$, $R^2 = R^3 = H$
186d $R^1 = R^3 = H$, $R^2 = OMe$
186e $R^1 = R^2 = H$, $R^3 = OMe$
186f $R^1 = R^2 = H$, $R^3 = Me$
186g $R^1 = F$, $R^2 = R^3 = H$
186h $R^1 = R^2 = H$, $R^3 = F$
186i $R^1 = R^3 = H$, $R^2 = F$
186j $R^1 = Cl$, $R^2 = R^3 = H$
186k $R^1 = R^2 = H$, $R^3 = CO_2Me$



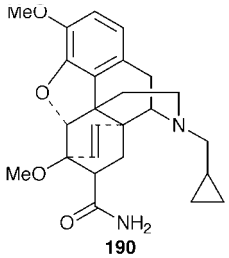
187a X = NH
187b X = O



188a $R^1 = R^2 = H$
188b $R^1 = H$, $R^2 = NH_2$
188c $R^1 = OH$, $R^2 = H$
188d $R^1 = OH$, $R^2 = NH_2$



189



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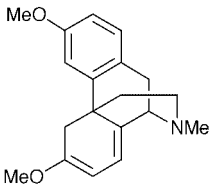
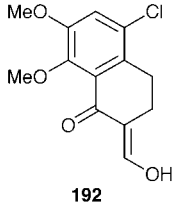


191

presence of 14-hydroxydihydrocodeinone or of naloxone an excess of the (*R*)-lactate is formed.[205]

An asymmetric synthesis of (−)-dihydrocodeinone (and hence a formal synthesis of morphine) has been achieved from 5-chloro-7,8-dimethoxy-1-tetralone. Claisen condensation of this with ethyl formate afforded **192**, which, with methyl vinyl ketone followed by retro-Claisen cleavage, yielded racemic **193**, together with 10% of the achiral **194**, which could be separately equilibrated with **193**. Racemic **193** gave **193** on resolution by chromatography on cellulose triacetate and the unwanted enantiomer was easily converted into the equilibrium mixture of racemic **193** and **194** for further use. Reaction of **193** with vinylmagnesiocuprate gave **195a** in very good yield and bromination of this gave **195b**, which was cyclised to **196** in dimethylformamide at 140 °C. The cyclic ketal of this ketone on hydroboration and oxidation afforded the alcohol **197a**, reduced to **197b** and this was converted directly into **198** by *N*-methylbenzenesulfonamide. Bromination of **198** with *N*-bromosuccinimide and dehydrobromination of the product afforded the olefin **199**, which was cyclised to **200**, and hydrolysis of this ketal yielded (−)-dihydrocodeinone **155a**.[206]

(+)-Cepharamine, the mirror image of the natural alkaloid, has been synthesised for pharmacological screening in compar-



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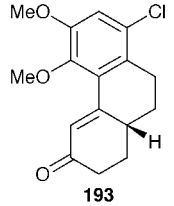

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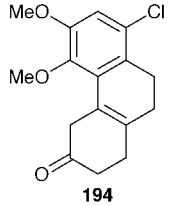

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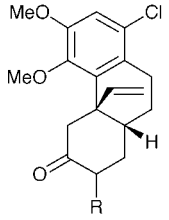
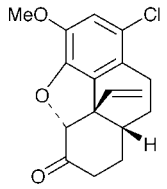


195a R = H
195b R = Br



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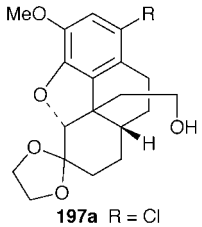
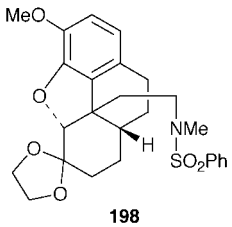
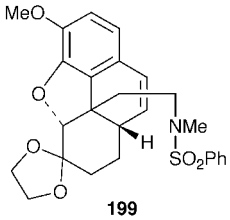


197a R = Cl
197b R = H



198



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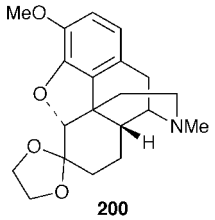
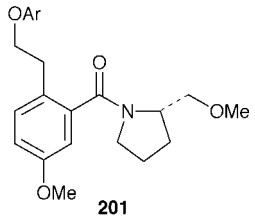
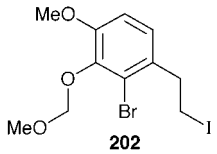


200

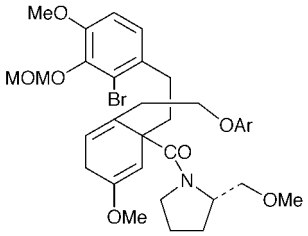
ison with morphine, which has the same absolute stereochemistry. Alkylation of the Birch reduction product of **201**



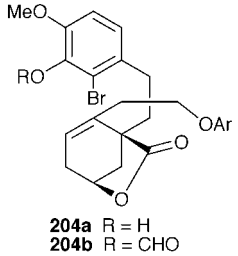
201



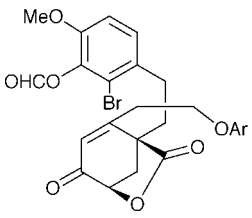
202



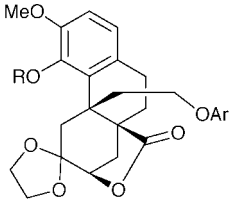
203



204a R = H
204b R = CHO



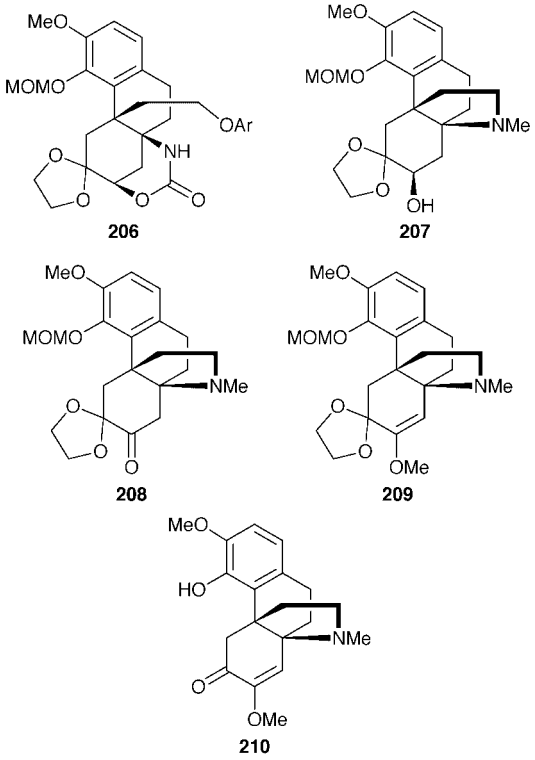
205a



205b R = H
205c $R = CH_2OMe$

with the halide **202** gave the enol ether **203**, which was hydrolysed, reduced and cyclised to the lactone **204a**. The

formyl ester of this **204b** was oxidised to the enone **205a**, which was ketalised and cyclised by tributyltin hydride to **205b**. The derived **205c** was then subjected to Hofmann rearrangement to **206** and this was reduced with lithium aluminium hydride to the cyclic amine **207**. Oxidation of this to **208** and conversion into the enol ether afforded **209**, which was hydrolysed to (+)-cepharamine **210**.[207]



206 **207** **208** **209** **210**

Approaches to the synthesis of compounds of the morphine, morphinan and hasubonine groups have been reviewed.[208]

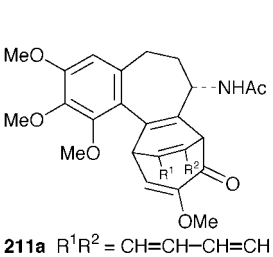
The analgesic properties,[209–260] metabolism[261] and pharmacokinetics[229,262–265] of morphine have been studied, as have the effects of the alkaloid on behaviour,[266–270] on immune responses,[271–278] on locomotor activity,[279–281] on the brain[282] on the cardiovascular system,[283,284] on the gastro-intestinal tract,[285,286] on respiration,[287,288] on neurones,[289] on spinal receptors,[290] on the jaw reflex,[291] on appetite,[279] on post-operative recovery,[292] on the hippocampus,[293,294] on the newborn,[295,296] on the progression of sepsis,[297] of inflammation[298] and of fever,[299] on the activation of neutrophils,[300] on the activity of lymphocytes,[301] on levels of cholecystokinin,[302,303] of dopamine,[304] of enkaphalins,[305] of oxytocin,[306] of adenylcyclase,[307] and of intracellular calcium[308] and on the effects of amphetamine[309] and of lignocaine.[310] The effects of diazepam on the development of tolerance to morphine have also been studied.[311]

The narcotic antagonist actions of naloxone[312–317] and the effects of this compound on behaviour,[318–323] on the cardiovascular system,[324] on immune responses,[325] on temperature,[326] on arterial gas concentrations,[327] on platelets,[328] on the effects of acute alcohol poisoning,[329,330] on levels of adrenocorticotrophin,[331] of calcitonin,[332] and of endothelin-I,[332] on the relief of testicular torsion,[333] on the gastro-intestinal tract,[334] and on the effects of (−)-clausenamide[335] have been studied.

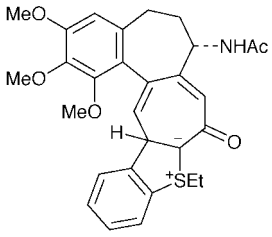
The pharmacological properties and physiological effects of the following have also been studied: 3,6-*O*,*O*-diacetylmorphine (heroin),[230,336–339] morphine 3-glucuronide,[265,340] morphine 6-glucuronide,[222,230,237,246,265,339,341,342] codeine,[247,343–347] codeine glucuronide,[348] dihydromorphinone glucuronide,[349] thebaine,[350] oripvine,[351] 14-hydroxydihydrocodeinone,[346,352–354] naloxone methiodide,[324] naltrexone,[355–366] naltrexone methiodide,[367–369] 7-benzylspiroindanylnaltrexone,[370] naltrexol,[366] naltrindole,[371,372] nalbuphine,[285,316,373–375] nalmefene,[376] β-funaltrexamine,[377–380] norbinaltorphimine,[381] 14-hydroxymorphindole,[382] buprenorphine,[233,313,357,383–393] dihydroetorphine,[394] sinomenine,[395] and stephodeline.[396]

17 Colchicine and related alkaloids

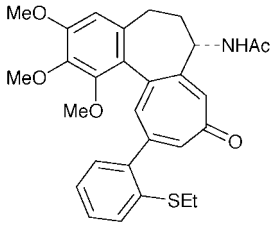
The absolute configuration of colchicine has been further confirmed.[397] A method for the hydrolysis of colchicine to *N*-deacetylcolchicine without isomerisation of the tropolone system has been described.[398] Colchicine undergoes a Diels–Alder reaction with the acetylenic dienophiles benzyne, dimethyl acetylenedicarboxylate and cyclooctyne to give the 8,12-adducts **211a**, **211b** and **211c**. In marked contrast,



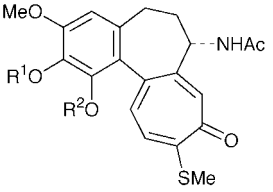
211a R^1R^2 = CH=CH–CH=CH
211b $R^1 = R^2 = CO_2Me$
211c $R^1R^2 = (CH_2)_6$



212

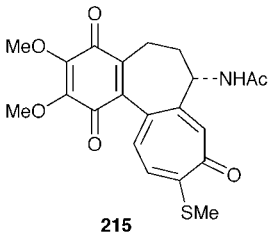


213

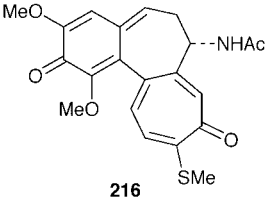


214a R^1 = Me, R^2 = H
214b R^1 =H , R^2 = Me
214c $R^1 = R^2$ = H

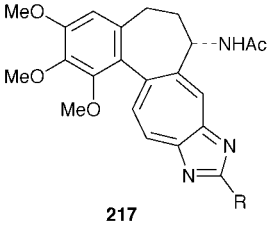
ethylthiocochicide undergoes a [3 + 2] cycloaddition of benzyne to the enol thioether system to give **212** (not isolated) which suffers hydrogen shift and cleavage of the carbon–sulfur bond to give **213**.[399] Thiocolchicine has been demethylated to **214a**, **214b** and **214c**, and of these **214a** and **214b** have been oxidised to the 1,4-quinone **215** and the quinomethane **216** respec-



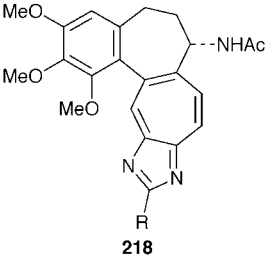
215



216



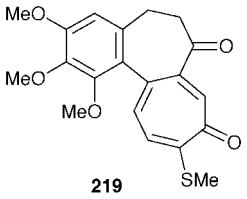
217



218

tively.[400] Colchicinoid and isocolchicinoid compounds react with amidines in dry benzene to give 1,3-diazazulenes, of type **217** from ring deactivated compounds such as colchicine and of type **218** from ring activated compounds such as 9-tolylsulfonylisocolchicine.[401]

Thiocolchicone **219** has been converted into the lactams **220a** and **220b** by heating in benzene with methylamine and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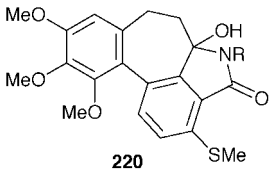
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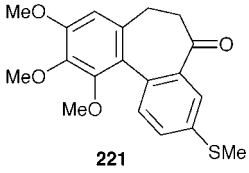
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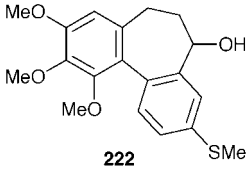
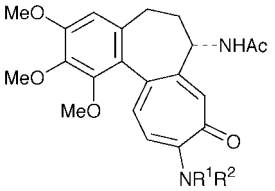
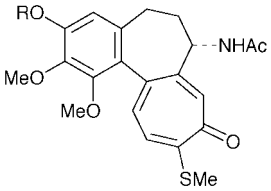

222

butylamine respectively, whereas with aniline the product was the simpler ketone **221**, which was reduced to the racemic alcohol **222**, resolved through its (−)-(1*S*)-camphamate ester.[402,403] Colchicine has been converted into the colchiceinamide **223a** by heating with piperidine[404] and phenolic colchiceinamides of general formula **223** have been prepared by the demethylation of **223b** and claimed to form a new class of topoisomerase-II inhibitors.[405] Complex ethers of 3-*O*-demethylcolchicine **224a**–**224d** have been prepared as potential pharmaceuticals.[406]


223a $R^1R^2 = (CH_2)_5$
223b R^1 = H, R^2 varies

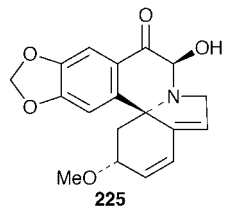

224a R = $CH_2CH(OH)CH_2OH$
224b R = $CH_2CH(OH)CH_2NH_2$
224c R = CH_2CO_2H
224d R = $CH_2CHClCH_2OH$

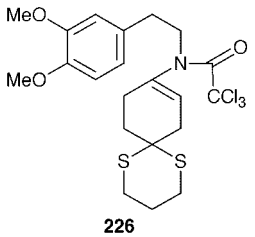
The physiological effects of colchicine,[407–412] of analogues of colchicine,[413] of colchiceine,[408] of colchemid[414] and of esters of the alcohol **222**[402] have been studied.

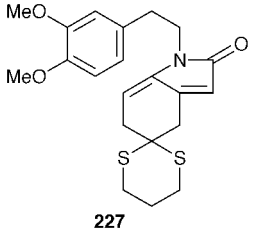
18 *Erythrina* alkaloids

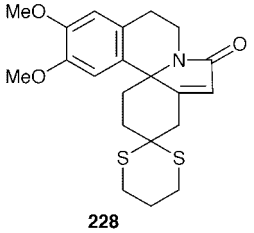
18.1 Erythrinanes

Erythraline, erythrinine, erysodine and the new alkaloid erythribidine **225** have been isolated from *Eryhrina bidwillii*.[415]

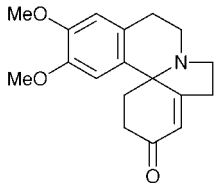

225


226


227


228

The trichloroacetamide **226** has been cyclised over nickel powder to give the lactam **227**, which was further cyclised to the erythrinane **228**. Reduction of this with lithium aluminium hydride gave the amine, which was hydrolysed to (±)-3-demethoxyerythratidinone **229**, the racemate of the natural alkaloid.[416] The sulfoxide **230** has been cyclised to the erythrinane **231**.[417] The synthetic erythrinane **232** has been oxidised by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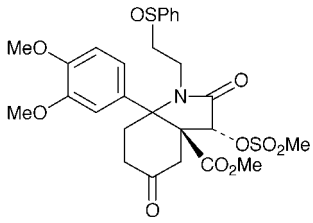
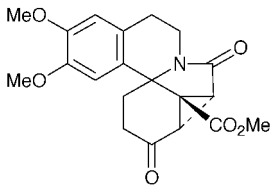
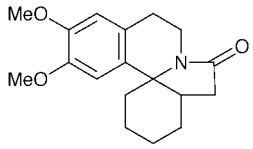
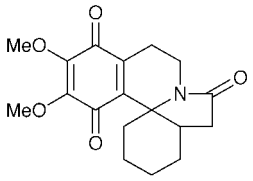

230


231


232

cerium(IV) methanesulfonate to the quinone **233**, ozonolysis of which afforded **234**, and this was reduced to the lactone **235** which has the skeleton of the alkaloid cocculolidine **236**.[418]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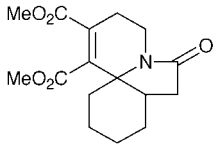
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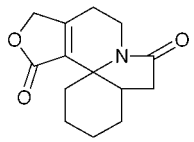
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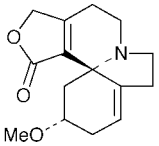

236

18.2 Homoerythrinanes

Wilsonine has been isolated from *Cephalotaxus fortunei* and its absolute configuration has been confirmed by an X-ray crystallographic study.[419]

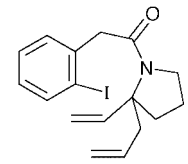
18.3 Cephalotaxine and related alkaloids

In approaches to the synthesis of cephalotaxine the amide **237** has been cyclised by palladium(II) acetate to **238**, further converted into **239**[420] and **240a**, **240b** and **240c** have been cyclised, presumably through the ylides **241** to **242a**, **242b** and **242c**.[421]

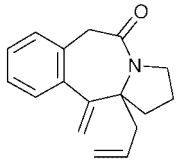
The antitumour effects of harringtonine have been studied.[422,423]

19 Other isoquinolines

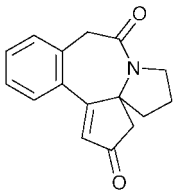
The new base aaptosamine **243**, which is not an isoquinoline but, like the similarly constituted aaptosine reported in the previous review, is probably derived from the isoquinolone aaptamine, has been isolated from the sponge *Aaptos aaptos*.[424] Syntheses of aaptamine have been reviewed.[425] The effects of



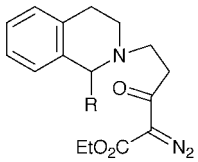
237



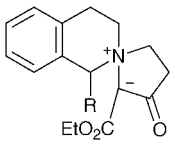
238



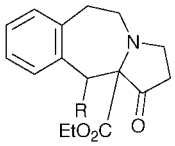
239



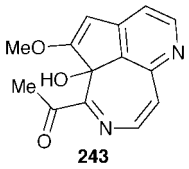
240a R = H
240b R = Me
240c R = CH=CHMe



241



242a R = H
242b R = Me
242c R = CH=CHMe



243

ecteinascidin 743 on human ovarian carcinoma xenografts have been studied.[426]

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