β-Phenylethylamines and the isoquinoline alkaloids

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1 β-Phenylethylamines
2 Isoquinolines
3 Naphthylisoquinolines
4 Benzylisoquinolines
5 Bis-benzylisoquinolines
6 Pavines and isopavines
7 Berberines and tetrahydoberberines
8 Secoberberines
9 Protopines
10 Phthalide-isoquinolines
11 Spirobenzylisoquinolines
12 Indanobenzazepines
13 Rhoeadines
14 Emetine and related alkaloids
15 Benzophenanthridines
16 Aporphinoid alkaloids
16.1 Propaporphines
16.2 Aporphines
16.3 Phenanthrenes
16.4 Oxoaporphines
16.5 Dioxoaporphines
16.6 Aristolochic acids and aristolactams
16.7 Azafluoranthenes
17 Alkaloids of the morphine group
18 Phenethylisoquinolines
19 Colchicine and related alkaloids
20 Erythrina alkaloids
20.1 Erythrinan alkaloids
20.2 Homoeorthylinan alkaloids
20.3 Cephalotaxine and related alkaloids
21 Other isoquinolines

A comprehensive review of the chemistry of the alkaloids within the scope of this review, other than those of the morphine group, has been published.

1 β-Phenylethylamines

N-trans-Feruloyltyramine has been isolated from Tinospora cordifolia.2 The novel bimolecular alkaloid cherinonaine, isolated from Annona cherimola, has been assigned the structure on the basis of its NMR spectra and of its fission to trans-ferulic acid and 4-hydroxy-3-methoxyamphetamine.3 The new alkaloid densine, isolated from Berberis densiflora,4 is structurally a β-phenylethylamine, but, since it is doubtless derived from dehydrosalsolidine3, it is more properly classified with the isoquinoline alkaloids.

The treatment of pseudoephedrine with (R)-α-fluoropropionamide has afforded the amide 4, α-C-alkylation of which proceeds with a high degree of stereoselectivity and hydrolysis of the products gives the corresponding chiral acids.5 The physico-chemical properties of soap solutions generated by ephedrine and pseudoephedrine myristates, which form bimolecular fibres in water,6 and the crystal structure of N-cyanomethylpseudoephedrine7 have been studied.

The pharmacological properties and physiological effects of ephedrine,8–11 of (+)- and (±)-norephedrine12 and of pseudoephedrine13 have been studied.

2 Isoquinolines

O-Methylcorypalline has been isolated from Berberis densiflora4 and from Phoebe minutiflora14 and stephaoxocanidine has been isolated from Stephania cepharantha.15 A review of the alkaloids of cacti of Gymnocalycium species has been published.16 An X-ray crystallographic study of cordycephalin has been reported.17 The iminium salt 5 has been cyclised to the (1R)-tetrahydroisoquinoline 6.18

3 Naphthylisoquinolines

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

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

Ancistrocladus guineensis
ancistrotectorine, ancistroguineine A* 10 and ancistroguineine B* 11

Ancistrocladus korupensis


367
korupensamine E* 12, michellamine D* 13, michellamine E* 14, michellamine F* 15, yaoudamine A* 16 and yaoudamine B* 17

Ancistrocladus robertsoniorum

ancistrobrevine B, ancistrocladine, ancistrorobertsonine* 18 and hamatine.

The structures of the new alkaloids have been determined by spectroscopic studies, by the correlation of 9a, 9b and 9c with 7-epi-ancistrobrevine D and by the degradation of ancistroguineine A to the amino acids 19 and 20.20

The absolute configuration of dioncophylline A 21 has been confirmed by an anomalous X-ray dispersion crystal analysis of the 5-bromo-N,O-dibenzyl derivative24 and the configurations of several of the alkaloids at the biaryl axis has been determined by studies of long range nuclear Overhauser effects.25 The Fourier transform Raman spectra of the alkaloids from Ancistrocladus heyneanus have been examined.26

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

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

N,N-Dimethyldioncophylline A iodide has been found to have enhanced antiplasmoidal activity over the free secondary base.30
activities of the naphthylisoquinoline alkaloids has been published. A series of analogues of the michellamines, in which the tetrahydroisoquinoline system has been replaced by a variety of simple aromatic systems, have been found to exhibit no activity against human immunodeficiency virus.

4 Benzylisoquinolines

1-Benzylisoquinoline alkaloids have been isolated from the following plant species, the two marked with asterisks being new alkaloids:
- *Annona cherimola*
- *Aristolochia triangularis*
- *Berberis densiflora*
- *Cocculus laurifolius*
- *Croton celtidifolius*
- *Phoebe minutiflora*
- *Papaver trinifolium*

The novel 2-benzylisoquinoline alkaloid numularine has been isolated from *Berberis numularia*. The 1H, 13C and 15N NMR spectra of (2S)-armepavine have been studied and an X-ray crystallographic study of the same alkaloid has been reported. The anion of papaverinol has been methylated to give the alkaloid setigerine. Laudanosoline hydrobromide has been oxidised by ferric chloride in aqueous ethanol buffered with sodium acetate to give an 80% yield of an aporphine that gave glaucine on O-methylation (see section 16.2).

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

In the previous review it was reported that the benzylisoquinoline 32a is not identical with the alkaloid fumarizine, to which this structure had previously been assigned. This alkaloid is also not identical with the isomeric base 32b, obtained by the asymmetric reduction of the iminium salt 31. In a similar manner the alkaloid dehassiline, to which the structure 33 has been assigned, has been shown to be different from the product of reduction of the iminium salt 34. (R)-(−)-Norroe-fractine 35 has been synthesised and shown to be a selective ligand at the dopamine D2 receptor, where it displaces raclopride.

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

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

Berberis densiflora*
oxycanthine
Stephania tetrandra59
fenfangle H* and fenfangle I* 44b.
Fastrine and jollyanine are the first head-to-tail linked bis-benzylisoquinoline alkaloids bearing an oxygen substituent at position 5 to be discovered. The structures of the new alkaloids were determined by spectroscopic methods. Fenfangjines H and I are secobis-benzylisoquinoline alkaloids clearly formed by oxidative cleavage of fenfangjine D 45, previously isolated from the same plant.60 These two alkaloids were shown to be inhibitors of the angiotensin-I converting enzyme.59
Cycleanine has been oxidised by m-chloroperbenzoic acid to a mixture of the 2α and 2β N-oxides 46a and 46b.61
The pharmacological properties and physiological effects of bebeerine,62 of berbamine,63,64 of O-benzoyl, O-ethyl, O-butyl and O-4-ethoxybutyl-berbamines65 of tetrandrine66–72 and of tubocurarine73 and the antitrypanosomal activities of curine, of

5 Bis-benzylisoquinolines

Bis-benzylisoquinoline alkaloids have been isolated from the following plant species, the four marked with asterisks being new alkaloids: Anisocyla jollyana58
cycleanine, cycleanine-2-N-oxide, dehydroapetateline, fastrine* 42, homoaromoline, isochondodendrine, jollyanine* 43, limacusine, limacusine-2'-N-oxide and O-methylcosculine
cycleanine, of isotetrandrine, of limacine and of phaeanthine have been studied.

6 Pavines and isopavines
Condensation of phenylglycinol with veratric aldehyde and with piperonal affords the imines 47a and 47b, and these have been found to react with 3,4-dimethoxybenzylmagnesium chloride with a high degree of steroespecificity to give the 1,2-diarylethylamines 48a and 48b with the (S,S) forms in 95% excess, and these were cleaved by hydrogenolysis to 49a and 49b. Alkylation of these with bromoacetaldehyde diethyl acetal afforded 50a and 50b, which were cyclised by acid through the intermediate 4-ethoxytetrahydroisoquinolines 51a and 51b to the isopavine secondary bases, which were N-methylated to (−)-O-methylthalisopavine 52a and (−)-amuresiniple 52b. Acid-catalysed cyclisation of the dihydroisoquinoline 53 has afforded the racemic isopavine, which was resolved to give (−)-thalimonine 54, confirming the assignments of the positions of the substituents in this alkaloid.

7 Berberines and tetrahydroberberines
Alkaloids of the berberine group have been isolated from the following plant species, the three marked with asterisks being new alkaloids:
Annona cherimola
Aristolochia gigantea
Aristolochia constricta
Aristolochia densiflora
Aristolochia stenophylla
Corydalis dasypterma
Papaver pseudo-orientale

A method for the estimation of berberine in body fluids has been described. The 8-oxopseudoberberine has been cleaved by sodium hydride to the olefin, which has been converted into the
The chiral carbamate 60, prepared from (15)-norlaudanosine, has been cyclised by tert-butyl lithium to 8-oxoxylopinine 61, which, on reduction with Redal, afforded (S)-(-)-xylopinine 62. In a model approach to the chiral synthesis of tetrahydroberberines the anion of the chiral α-toluamide 63 has been condensed with 3,4-dimethoxy-3,4-dihydroisoquinoline (dehydroheliamine) to give a mixture of the amide 64 and the (S)-lactam 65, the latter being the sole product under certain conditions. In a similar way the enantiomeric toluamide 66 yielded the (R)-lactam 67. Dehydroheliamine also reacts with the anion of 3-methoxyphthalide 68 giving, via 69, the 13-spiro-8-oxoberberine 70. The similar reaction with dehydroalsolidine 3 affords 71, with the opposite configuration at position 13a. Quaternary tetrahydroberberinium salts of structures 72a–i, in which n = 2 and 3, have been prepared and examined as cardiac antiarrhythmic agents. A patent claiming the use of coraline 73 and its analogues as topoisomerase inhibitors has been published.

The pharmacological properties and physiological effects of berberine, of 8-oxoberberine, of tetrahydroberberine, of berberrubine, of palmatine, of 7-chlorobenzyltetrahydrodopalmatinium salts, of 13-hydroxytetrahydrodopalmatine, of 13-alkyltetrahydrodopalmatines up to the hexyl compound and of stepholidine have been studied.

8 Secoberberines

The new secoberberine alkaloid fumaflorine 74 has been isolated from Fumaria densiflora.

9 Protopines

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

88–95 of 8-oxoberberine, of tetrahydroberberine, of berberrubine, of palmatine, of 7-chlorobenzyltetrahydrodopalmatinium salts, of 13-hydroxytetrahydrodopalmatine of 13-alkyltetrahydrodopalmatines up to the hexyl compound and of stepholidine have been studied.

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Glaucium fimbriilligerum\textsuperscript{102} protopine

Papaver fugax\textsuperscript{103} protopine.

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

10 Phthalide-isoquinolines

\(\alpha\)-Narcotine and narceine have been isolated from Papaver trinifolium.\textsuperscript{37} The alkaloid fumafurine 74, isolated from Fumaria densiflora, could also be regarded as a member of this group.

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

A method for the estimation of narcotine in body fluids has been described.\textsuperscript{107} The pharmacological properties and physiological effects of narcotine\textsuperscript{108,109} and of biceculline\textsuperscript{110} have been studied.

11 Spirobenzylisoquinolines

The chemistry of the alkaloids of this group isolated from Fumaria species has been reviewed.\textsuperscript{111} In an attempt to repeat those normally used in the extraction of alkaloids from plant material.\textsuperscript{116} The following new alkaloids have been isolated from Alangium lamarckii:\textsuperscript{115,116} 6'-O-\(\beta\)-d-glucopyranosylalangiside 95, 3'-O-\(\beta\)-d-glucopyranosylalangiside 96, 6'-O-\(\alpha\)-d-glucopyranosylalangiside 97a, 6'-O-\(\alpha\)-d-glucopyranosyl-3-O-demethyl-2-O-methylalangiside 97b, 6'-O-\(\alpha\)-d-xylopyranosylalangiside 98 and the diastereoisomeric methoxy compounds 99a and 99b. The structures of these alkaloids were determined on the basis of their NMR spectra. The methoxy compounds 99a and 99b, which have been found to be produced from alangiside on long storage of the alkaloid in methanol, are clearly products of oxidation of the alkaloid, being simple derivatives of the dialdehyde 100, which has been reasonably postulated as an intermediate in the biotransformation of alangiside into the azaberverine alkaloid alangimaridine 101. Both 99a and 99b are converted into alangimaridine under conditions identical with those normally used in the extraction of alkaloids from plant material.\textsuperscript{116}

13 Rhoeadines

Two new alkaloids of the rhoeadine group, triniifoline 94a and O-ethyltriniifoline 94b have been isolated from Papaver trinifolium.\textsuperscript{37}

14 Emetine and related alkaloids

The following new alkaloids have been isolated from Alangium lamarckii: 15 Benzophenanthridines

Benzophenanthidine alkaloids have been isolated from the following plant species: Papaver nudicaule\textsuperscript{117} chelidonium

Zanthoxylum roifolium\textsuperscript{118}

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

15 Benzophenanthridines

Benzophenanthidine alkaloids have been isolated from the following plant species:
dihydronitidine, 6-oxonitidine and zanthoxyline 102.

Zanthoxyline, which is a new alkaloid, has an unusual substitution pattern, being the first alkaloid of the group not to bear an oxygen substituent at position 8. The conformation of methyl (+)-corydalate 103 has been studied by NMR spectroscopy and the trans-stereochemistry has been confirmed.

Photo-oxidation of sanguinarine has been shown to give 6-oxosanguinarine 104.120

Sanguilutine, on treatment with potassium cyanide, gives 6-cyanodihydrosanguilutine 105a and treatment with sodium carbonate yields 6-hydroxydihydrosanguilutine 105b, which in non-polar solvents spontaneously loses water to give the bimolecular amine ether 106, the structure of which has been confirmed by X-ray crystallography. The related dimeric amine 107 is formed directly from sanguilutine and ammonia.121
A synthesis of 6-oxonitidine 109 has been achieved from the 8-oxopseudoberberine 58 by cleavage with sodium hydride to the olefin 59, followed by N-methylation and oxidation with thallium(III) nitrate in methanol to the acetal 108, which was cyclised by acid to 109.83

The pharmacological properties and physiological effects of chelerythrine have been studied.122
Phoebe formosana\textsuperscript{126}  
\textit{N}-formylanonaine, \textit{N}-formyldehydroanonaione and laurdionione\textsuperscript{*} 114

Phoebe minutiflora\textsuperscript{14}  
corytuberine, isoboldine, laurolitnine and norisocorydine

Telitoxicum glaziovii\textsuperscript{27}  
iminen.

A review of alkaloids isolated from \textit{Thalictrum} species has been published.\textsuperscript{128}

Oxidation of \textit{N}-trifluoroacetylwilsonine 115\textsuperscript{a} and of \textit{N}-trifluoroacetylnordomesticine 115\textsuperscript{b} with lead tetraacetate has afforded the 4\textsubscript{a}-acetoxy compounds 116 and 117, respectively, with no trace of the 4\textsubscript{b}-isomers.\textsuperscript{129} A kinetic study of the oxidation of boldine by singlet oxygen has been published.\textsuperscript{130}

Methods for the estimation of apomorphine, apocodeine and their glucuronides,\textsuperscript{131,132} and of boldine\textsuperscript{133} have been described.

The acid-catalysed rearrangement of thebaine in mercaptans has yielded sulfur-containing derivatives of apomorphine and apocodeine (see section 17).

In syntheses of alkaloids of the group, racemic laudanosoline has been oxidised with alcoholic ferric chloride buffered with sodium acetate to \textit{O,O}-didemethyllaurolitnine 118\textsuperscript{a}, which has been methylated to (\pm)-glaucine 118\textsuperscript{b}.\textsuperscript{41} The (\textit{S})-2\textsuperscript{-}bromolaudanosine derivative 60 has been cyclised by tributyltin hydride to (\textit{S})-\textit{N}-2-trans-(\textit{a}-cumeny)cylohexyloxy carbonylnorglaucine 119, which on reduction with lithium aluminium hydride afforded (\textit{S})-glaucine 118\textsuperscript{b}.\textsuperscript{42}

The pharmacological properties and physiological effects of acimadophine,\textsuperscript{124} of \textit{N}-methylactimadophine,\textsuperscript{124} of apomorphine,\textsuperscript{134-147} of boldine,\textsuperscript{56} of isoboldine,\textsuperscript{56} of bulbocapnine,\textsuperscript{124} of \textit{O}-methylbulbocapnine,\textsuperscript{124} of cassycichic,\textsuperscript{56} of dicentrine,\textsuperscript{124} of guatterine,\textsuperscript{56} of glaucine,\textsuperscript{148} of hernovine,\textsuperscript{124} of laumonine,\textsuperscript{124} of lauritosine,\textsuperscript{124} of \textit{N}-methylaurotetanine\textsuperscript{56} and of pachystaudine\textsuperscript{56} have been studied.

16.3 Phenanthrenes

\textit{N}-Methylsecoglaucine (glaucine methine) has been isolated from \textit{Phoebe minutiflora}\textsuperscript{14} and the new alkaloid fenfangjine F 120 has been isolated from \textit{Stephania tetrandra}.\textsuperscript{59} Fenfangjine F is the first phenanthrene alkaloid of the aporphinoid group to be discovered bearing a hydroxy group in the side-chain. The stereochemistry of the alcoholic group has not been determined.

Laurolitnine 121\textsuperscript{a} has been \textit{N}-alkylated to the tertiary bases 121\textsuperscript{b}, 121\textsuperscript{c} and 121\textsuperscript{d} and solvolysis of these with aqueous ammonium acetate has given the phenanthrenes 122\textsuperscript{a}, 122\textsuperscript{b} and 122\textsuperscript{c}. Mannich condensation of these amino phenols with formaldehyde yielded the homologues 123\textsuperscript{b}, 123\textsuperscript{c} and 123\textsuperscript{d} of the alkaloid litebamine 123\textsuperscript{a}.\textsuperscript{149}

16.4 Oxoaporphines

Oxoaporphine alkaloids have been isolated from the following plant species: \textit{Annona cherimola}\textsuperscript{33}  
\textit{liriodenine, lysicamine, oxoanolobine, oxoglaucine and o xoxylopine}

\textit{Cassysa filiformis}\textsuperscript{123}  
\textit{lysicamine}

\textit{Guatteria lehmanii}\textsuperscript{150}  
\textit{lysicamine}

\textit{Illigera luzonensis}\textsuperscript{124}  
\textit{dicentrinone and liriodenine}

\textit{Magnolia obovata}\textsuperscript{125}  
\textit{lanuginosine and liriodenine}

\textit{Telitoxicum glaziovii}\textsuperscript{127}  
\textit{O}-methylmoschatoline, splendidine and teliglazine 124

\textit{Zizyphus jujuba}\textsuperscript{151}  
\textit{lysicamine}.

The quaternary betaine teliglazine is a new alkaloid. Dicentrinone and liriodenine have been found to inhibit significantly platelet aggregation.\textsuperscript{124}

16.5 Dioxoaporphines

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

- Aristolochia triangularis\textsuperscript{34} cepharadione A, 4,5-dioxodehydroasimilobine\textsuperscript{*} 125 and triangularine I\textsuperscript{*} 126

Telitoxicum glaziovii\textsuperscript{127} dioxodehydroasimilobine 125 and ouregidione.

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

16.6 Aristolochic acids and aristolactams

Aristolochic acid D, aristolactams Ia, IIa, AIa, AII, AIIIa, BII and CII and the new 9-methoxyaristolactam Ia 6-(β-d-glucopyranosyl)-β-d-glucoside 134 have been isolated from Aristolochia triangularis.\textsuperscript{34}

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

16.6 Azafluoranthenes

Telitoxine has been isolated from Telitoxicum glaziovii.\textsuperscript{127}
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:

*Glaucium fimbrilligerum*

17 Alkaloids of the morphine group

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

*Croton chilensis* 157

*Papaver fugax* 158

Flavanidine, O-methylflavanidine and isosalutaridine

*Glaucium fimbrilligerum* 159

Salutaridine

*Papaver fugax* 158

Salutaridine and thebaine

*Papaver pseudo-orinale* 159

5,6-dihydronorsalutaridine* 143

17 Alkaloids of the morphine group

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*Glaucium fimbrilligerum* 157

Flavanidine, O-methylflavanidine and isosalutaridine

*Glaucium fimbrilligerum* 159

Salutaridine

*Papaver fugax* 158

Salutaridine and thebaine

*Papaver pseudo-orinale* 159

5,6-dihydronorsalutaridine* 143

Stephania tetrandra* 159

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

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

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

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

The preparation of northebain from nordihydrocodeinone via nordihydrothebaine has been improved. 172 Thebaine 156a is reduced to dihydrothebaine 157a by diimide. However, 6-de-methoxythebaine 156b is not converted into deoxycodeine C 157b, but into a mixture of deoxycodeine D 158 and dihydrocodeine D 159 with this reagent. 173 Thebaine has been found to react as a dieneophile with the diene 160, generated in situ by the thermal cleavage of the benzocyclobutene 161. Of the two trisubstituted double bonds in 156a that at the 8,14 position is less under the influence of the electron-donating methoxy group and the Diels–Alder reaction affords the adduct 162; in the absence of the 8,14 double bond dihydrothebaine
157a does not react. Similar addition of the diene to 6-demethoxythebaine 156b occurs at the less hindered 6,7 double bond to give 163. The reaction of deoxycodeine C 157b with the diene has not been reported.173 Acid-catalysed hydrolysis of dihydrothebaine-φ 164 under most conditions affords the kinetically controlled product, which is the ketone β-thebainone 165, but conditions have been described that afford the thermodynamically more stable C-14 epimer of 165.174 Thebaine undergoes normal Diels–Alder reaction as a diene with acynitroso compounds to give adducts 166, hydrolysable by acids to the 14-substituted codeinones 167.175

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

Details of the preparation of the following have been given: morphine 3,6-diglucuronide,179,180 the spiro compounds 172a and 172b and their naphthalene andperylen analogues,181 N-
have the effects of the alkaloid on behaviour,245–258 on immune
amphetamine, 297 of apomorphine, 298 of bicuculline, 110 of
pharmaco-dynamics 240–244 of morphine have been studied, as
proteins, 286 on the binding of DNA to proteins, 387 on apoptosis
validity of some of these must be questionable as they cover
compounds and processes well described many years ago.

A chiral synthesis of (+)-morphine, the mirror image of the
natural alkaloid, has been reported. Stobbe condensation of
isovanillin with dimethyl succinate, followed by catalytic
reduction of the resulting unsaturated ester over a chiral
rhodium catalyst afforded the diacid monoester
addition to methyl vinyl ketone to give
methyl formate yielded
removed the ketonic carbonyl group, but reduction with sodium
brominated to
oxidised to
was cyclised by rhodium acetate to the pentacyclic ketone
The oxime of this ketone, on Beckmann transformation, yielded
The effects of L-type calcium channel blockers on the
behaviour, 256,300,308,309 on responses to stress, 310 on immune
appetite, 315 on acute alcohol intoxication, 316 on cerebral blood
flow, 270 on the release of histamine 317 and on the effects of
benzodiazepines318 and of methadone.319

The pharmacological and physiological effects of the follow-
patent has been claimed covering the use of the diclofenac salt
of morphine for the relief of pain.304

The morphine antagonist actions of naloxone have been studied,306 as have the effects of this compound on
behaviour,256,300,308,309 on responses to stress,310 on immune
responses,311 on neurons,312 on opiate receptors,313,314 on appetite,315 on acute alcohol intoxication,316 on cerebral blood
flow,270 on the release of histamine317 and on the effects of
benzodiazepines318 and of methadone.319

The pharmacological and physiological effects of the following
have also been studied: morphine 3-O-glucuronide,320–322
morphine 6-O-glucuronide,321–328
methylmorphine,396
3,6-O-diacetylmorphine,296
codeine330–334
codeine glu-
18 Phenethylisoquinolines

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

![Structural formula of robustamine and colchicine](image)

19 Colchicine and related alkaloids

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

![Structural formula of colchicine intermediates](image)

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

A new synthesis of colchicine started from the aldehyde, which, with the anion of the borane complex of oxazole, afforded the racemic alcohol, when [4 + 3]-cycloaddition afforded the related compound, which was thermally cyclised to the acetylamino derivative. 395

The pharmacological properties and physiological effects of colchicine, 396–408 of 2-O-demethylcolchicine, 401 of 3-O-demethylcolchicine, 401 of isocolchicine, 398 of colchicine and of colchamine have been studied.

20 Erythrinan alkaloids

20.1 Erythrinan alkaloids

Cocculine and the new alkaloid cocculine N-oxide have been isolated from Cocculus (image). 35

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

20.2 Homoerythrinan alkaloids

Wilsonirine 217a and the new alkaloid fortune 217b have been isolated from Cephalotaxus fortunei.  

20.3 Cephalotaxine alkaloids

11-Hydroxycephalotaxine has been isolated from Cephalotaxus fortunei. A review of the alkaloids of this group has been published.  

Homoharringtonine 218 has been oxidised to a mixture of the diastereoisomeric N-oxides 219. Both of these on heating at 105 °C afforded the same products, namely 221 (formed via 220) and 224a and 224b, presumably formed from the product of Cope degradation of 222 (not isolated) via 223a and 223b. These cyclic 'N-oxide ethers', when reduced with zinc and
acetic acid, afforded homoharringtonine 218 and its isomers 225a and 225b (Scheme 2). All of these compounds showed much weaker activity than homoharringtonine against P-388 leukemia cells.409

In approaches to the synthesis of cephalotaxine the amine 226 has been cyclised to 227 and further to 228 over palladium,410 and 229a has been converted through 229b–d into 230, the carbanion of which was cyclised to 231.411 Homoveratrulamine and (α)-prolinol have afforded the amide 232, which was cyclised to 233, and reduction of this lactam and condensation of the product with pyruvic acid yielded the diketone 234, which was cyclised to the ring system 235, isomeric with that found in cephalotaxine.412

21 Other isoquinolines

Aaptamine 236, demethoxyoxyaaptamine 237 and the clearly related new base aaptosine 238, have been isolated from the Okinawan sponge Aaptos aaptos. Aaptosine does not show the potent toxicity against P-388 and A-549 tumour cells exhibited by aaptamine and demethoxyoxyaaptamine.413

22 References


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