ALKALOIDS FROM PLANTS OF THE SUBFAMILY WURMBAEOIDEAE

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Dedicated to Professor Tetsuji Kametani, Tohoku University, Sendai, Japan

Abstract - This review gives a survey of the most important papers on the isolation and chemistry of alkaloids (i.e. the tropolone alkaloids, their precursors, and the minor alkaloids) from plants of the subfamily Wurmbaeoideae, and of those of the biosynthesis of these compounds.

INTRODUCTION

The tropolone alkaloids from plants of the subfamily Wurmbaeoideae[1-10] form an independent group of compounds. They arise from the phenethyltetrahydroisoquinoline precursor - autumnaline (XVa). For a long time, the only known representative of this group was colchicine (Ia) which was isolated from the plant Colchicum autumnale L. This group of alkaloids also includes intermediary products (XV-XIX), leading to the formation of colchicine alkaloids with tropolone ring, and the side-products (XX-XXIX) (minor alkaloids) of this biosynthesis. The Colchicum alkaloids occur only in the plants of the sub-family Wurmbaeoideae (Family Liliaceae)[11,12] (Table A) and in Kreysigia multiflora Reichb.[13,14] whose definite classification to this sub-family has not been carried out as yet.

The colchicine alkaloids are highly toxic, in animal cell they inhibit cellular division in the metaphase (stathmokinetic or mitotic effect), and in plants they bring about polyploidy.[2,10]

The alkaloids of the Wurmbaeoideae plants are usually classified as follows:

I. Alkaloids with tropolone ring and their important derivatives

(1) Neutral and phenolic compounds (I, III, IV, V)
(2) Basic compounds (II)

} Table B

(3) Compounds without amino group or with keto group at C_7-position

(4) Compounds obtained by conversion of alkaloids with tropolone ring

(a) Lumiderivatives (VI and VII) of the compounds given sub (1) and (2) and lumicolchicone (VIII)

(b) 10,11-Oxy-10,12a-cyclo-10,11-secocolchicine (IX)

(c) 10,12a-Oxycolchicine (X)

(d) Colchicide (XI)

(e) Colchinole and its methylether (XII)

(f) Colchicinic acid (Allocolchiceine) (XIIIa) and its methyl ester (Allocolchicine) (XIIIb)

(g) Colchinale (XIV)

II. Alkaloids without tropolone ring (Tables C - H)

(1) Phenethyltetrahydroisoquinoline bases (XV)

(2) Androcymbine alkaloids (XVI)

(3) Dihydro- and tetrahydroandrocymbine alkaloids (XVII - XIX)

} Homopromorphinane group

(4) Homoproaporphine alkaloids (XX - XXVIII)

(5) Homoaporphine alkaloids (XXIX)

(6) Alkaloids without tropolone ring whose constitution is still unknown

(7) Benzyltetrahydroisoquinoline - Isocorydine (XXX)

THE ISOLATION AND THE STRUCTURES OF ALKALOIDS WITH TROPOLONE RING AND OF SOME OF THEIR DERIVATIVES

Pelletier and Caventou (1820) were the first research workers in this field. They investigated the corms of Colchicum plants contrary to Geiger (1833), Oberlin (1857), Zeisel (1883), Houdé (1884), and Merck (1916) who studied the Colchicum seeds (Summarizingly[1-7,16]). In the latter, the major alkaloid was colchicine. Therefore, for more than 60 years, it was assumed[15,16] that it was the only toxic compound contained therein. During the following years, by application of new separation methods, ca. 100 alkaloids (Tables B - H) were detected in the seeds, corms, flowers, and leaves of the Wurmbaeoideae. Recently, two new alkaloids were isolated from Colchicum latifolium, namely colchiciline (Ij) with a hydroxyl group at C_6-position in trans-configuration to the amidic group at C_7, and 10,11-oxy-10,12a-cyclo-10,11-secocolchicine (IX).[17,18]

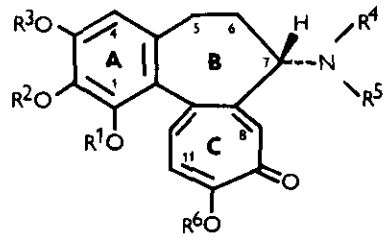
Table A. Genera of the sub-family Wurmbaeoideae[12] and their groups of alkaloids

Family: Liliaceae Subfamily: Wurmbaeoideae	Alkaloids with tropolone ring (Table B) phenolic and neutral	Alkaloids with tropolone ring (Table B) basic	Alkaloids without tropolone ring (Tables C - H)
Tribe: Glorioseae			
Genus: Gloriosa	++	-	++
Littonia	++	-	++
Sandersonia	++	-	++
Iphigenieae			
Iphigenia	++	-	++
Camptorrhiza	+	-	+++
Ornithoglossum	++	-	++
Baeometreae			
Baeometra	+	-	+++
Colchiceae			
Colchicum	+++	++ or -	+ or -
Merendera	++	++ or -	+ or -
Androcymbium	+	+	+++
Kreysigia multiflora	++	+	+++
Neodregeae			
Dipidax	+++	+	+
Neodregea	?	?	?
Wurmbaeae			
Wurmbaea	+	+ ?	+
Anguillaria	+	+ ?	+

C. autumnale gave the new alkaloids colchifoline (IVa) and 2-demethylcolchifoline (IVb) which have a radical of glycolic acid instead of an acetyl group on the nitrogen.[19-21] The leaves of this plant yielded *cornigerine* (Ib) which up till now has been isolated only from C. cornigerum growing on the Sinai peninsula.[22,23] It is of interest that, in fresh leaves and flowers of Colchicum autumnale and C. speciosum, 2- and 3-demethylderivatives of colchicine cannot be detected.[19]

The alkaloids with tropolone ring (Table B) differ only by their substituents on

Table B. Constitution of tropolone alkaloids of the subfamily Wurmbaeoideae



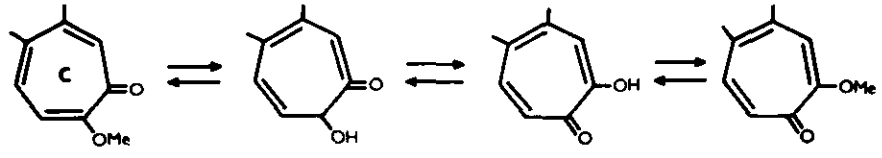
Alkaloids	Substituents					
	R^1	R^2	R^3	R^4	R^5	R^6
I						
Colchicine (Ia)	CH_3	CH_3	CH_3	H	$COCH_3$	CH_3
Cornigerine (Ib)	$-CH_2-$		CH_3	H	$COCH_3$	CH_3
3-Demethylcolchicine (Ic) (Alkaloid C)	CH_3	CH_3	H	H	$COCH_3$	CH_3
2-Demethylcolchicine (Id) (Alkaloid E_1)	CH_3	H	CH_3	H	$COCH_3$	CH_3
Colchicoside (Ie)	CH_3	CH_3	Glucose	H	$COCH_3$	CH_3
Colchiceine (If)	CH_3	CH_3	CH_3	H	$COCH_3$	H
Cornigereine (Ig)	$-CH_2-$		CH_3	H	$COCH_3$	H
3-Demethylcolchiceine (Ih)	CH_3	CH_3	H	H	$COCH_3$	H
2-Demethylcolchiceine (Ii)	CH_3	H	CH_3	H	$COCH_3$	H
Colchiciline (Alkaloid CC-12 ?) (Ij)[a]	CH_3	CH_3	CH_3	H	$COCH_3$	CH_3
N-Deacetyl-N-formylcolchicine (Ik)	CH_3	CH_3	CH_3	H	CHO	CH_3
3-Demethyl-N-deacetyl-N-formylcolchicine (I l)	CH_3	CH_3	H	H	CHO	CH_3
2-Demethyl-N-deacetyl-N-formylcolchicine (Im)	CH_3	H	CH_3	H	CHO	CH_3
N-Deacetyl-N-formylcolchiceine (In)	CH_3	CH_3	CH_3	H	CHO	H
II						
N-Deacetylcolchicine (IIa)	CH_3	CH_3	CH_3	H	H	CH_3
N-Deacetylcolchiceine (IIb)	CH_3	CH_3	CH_3	H	H	H
N-Deacetyl-3-demethylcolchicine (IIc)	CH_3	CH_3	H	H	H	CH_3
N-Deacetyl-2-demethylcolchicine (IId)	CH_3	H	CH_3	H	H	CH_3
N-Deacetyl-2,3-demethylcolchicine (IIe)	CH_3	H	H	H	H	CH_3
N-Deacetyl-N-methylcolchicine (Demecolcine, Colcemide, Colchamine) (IIf)	CH_3	CH_3	CH_3	H	CH_3	CH_3
N-Deacetyl-3-demethyl-N-methylcolchicine (Alkaloid CC-7) (IIg)	CH_3	CH_3	H	H	CH_3	CH_3
N-Deacetyl-2-demethyl-N-methylcolchicine (Alkaloid S) (IIh)	CH_3	H	CH_3	H	CH_3	CH_3
Demecolceine (IIi)	CH_3	CH_3	CH_3	H	CH_3	H
N-Deacetyl-N-dimethylcolchicine (IIj)	CH_3	CH_3	CH_3	CH_3	CH_3	CH_3
Speciosine (IIk)[45]	CH_3	CH_3	CH_3	b	CH_3	CH_3

III						
N-Methylcolchicine (N-acetyldemecolcine) (IIIa)	CH_3	CH_3	CH_3	CH_3	$COCH_3$	CH_3
N-Methyl-N-deacetyl-N-formylcolchicine (N-formyldemecolcine) (IIIb)	CH_3	CH_3	CH_3	CH_3	CHO	CH_3
IV						
Colchifoline (IVa)	CH_3	CH_3	CH_3	H	$COCH_2OH$	CH_3
2-Demethylcolchifoline (IVb)	CH_3	H	CH_3	H	$COCH_2OH$	CH_3
V						
Thiocolchicine (V)	CH_3	CH_3	CH_3	H	$COCH_3$	c

[a]) 6-Hydroxycolchicine [b]) 2-Hydroxybenzyl
[c]) Methylthiogroup instead of methoxyl group

the aromatic ring A, on the ring B, and on the amino group of this ring, and on the tropolone ring C.

In 1924, Windaus[24] assigned a phenanthrene skeleton with oxo-methoxymethylene substituents on ring C to colchicine. Cook et al.[25] and, a short time later, Dewar[26] assigned to it the correct structure with the seven-membered tropolone ring C. In 1955, the position of the substituents on this ring C was corrected[27] and this new colchicine structure was confirmed by X-ray analysis.[28] Margulis[29] as well as Lessinger and Margulis[30] studied the conformation of colchicine and isocolchicine by X-ray crystallography. Silverton[31] elucidated the structure of colchiceine (If).

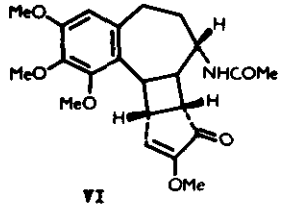


Ia If Iff Iaa

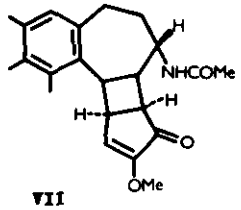
Scheme 1

The methoxyl group of the tropolone ring can be easily saponified with dilute acids or sodium hydroxide to give colchiceine (If). Its further saponification affords trimethylcolchicinic acid (= correctly deacetylcolchiceine (IIb)). Colchiceine is a mixture of colchiceine (If) and isocolchiceine (Iff). Methylation with diazomethane yields colchicine (Ia) and isomeric isocolchicine (Iaa) [32] (Scheme 1). The methoxyl group can be replaced by the amino group to give the already known colchiceinamides,[33,34] or by the thio groups (SH or SCH_3) (V).[34,35]

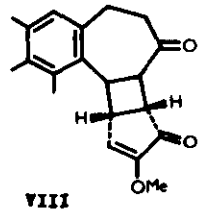
This methoxyl group of the tropolone ring can be removed by the action of hydrogen with acetone-deactivated Raney nickel to give colchicide (XI).[36] Grewe[37] converted colchicine into the α-, β-, and γ-lumiderivatives. The β- (VI) and the γ- (VII) lumiderivatives were found in all the parts of the Wurmbaeoideae.[16,38] These two lumiderivatives were prepared from the majority of the isolated tropolone alkaloids.[39-43] Mass spectrometry has revealed that α-lumicolchicine is a dimer which on thermic reaction is converted into β-lumicolchicine and then, through the effect of sunlight into γ-lumicolchicine. The last two derivatives are stereoisomers on the rings C and D.[43]



VI



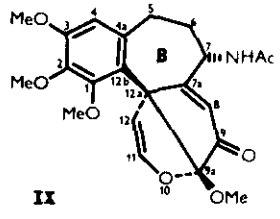
VII



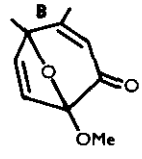
VIII

From the corms of Gloriosa superba, Canonica et al.[41] have isolated β-lumicolchicone (VIII) with a keto group instead of an acetamido group at the C_7-position.

Zeisel and Friedrich[44] prepared 10,12a-oxycolchicine (X). This substance is readily obtained from colchicine by treatment with chromium trioxide in acetic acid. Preparative experiments and physical methods have shown[45-47] that on boiling with acids, this substance is converted into colchiceine (If).

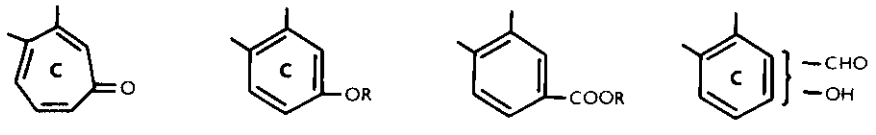


IX



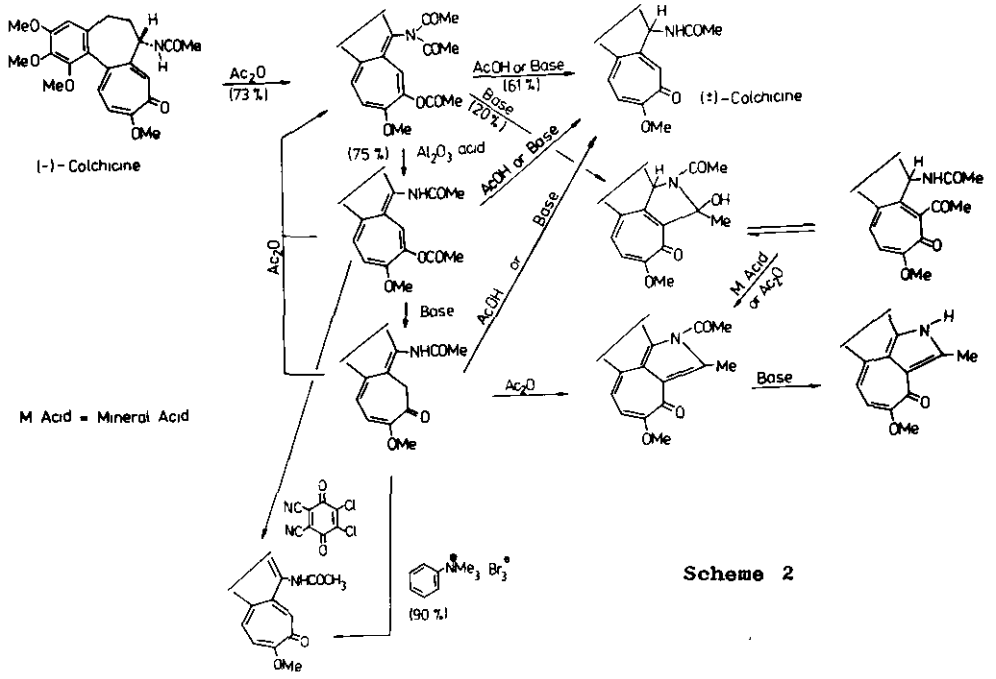
X

By treatment with potassium hypoiodide[48] or hydrogen peroxide in alkaline medium[27] the seven-membered tropolone ring of colchiceine (If) can be rearranged into colchinole (XII) with a benzene ring C. On treatment with sodium methanolate, colchicine (Ia) is converted into colchicinic acid (= allocolchiceine) (XIIIa) or its methylester (= allocolchicine) (XIIIb) in ca. 100% yield.[49-51] This reaction is often used to study the constitution and biosynthesis of alkaloids with tropolone ring. Sadykov et al. found allocolchicine and allocolchiceine derivatives in plant material.[52]



XI XII XIII XIV

While carrying out the racemization of colchicine and thiocolchicine with acetic acid anhydride, Bladé-Font prepared a new series of colchicine derivatives[53,54] (Scheme 2).



Scheme 2

Racemization of colchicine with the Schiff-base afforded racemic N-deacetyl-colchiceine, 7-oxo-deacetamidocolchicine, and 7-oxo-deacetamidoisocolchicine.[55] Biotransformation of colchicine carried out with microsomal fractions of animal liver gave colchinale (XIV).[56,57]

Battersby et al.[58] elucidated the constitution of the alkaloid speciosine (IIk) which was isolated from C. speciosum by Kiselev.[59] On heating, this alkaloid was converted into demecolcine (colchamine) (IIf).[60] Capraro and Brossi described a simple conversion of colchicine into demecolcine.[61] The French authors[62] reported the isolation of a tropolone alkaloid with glucose on the ring A (Ie) and an alkaloid containing a sulphur atom on the ring C. There was also prepared

colchicine with various substituents at C_4-position[63] and, with the help of microorganisms, 1-demethylcolchicine which has not been found in nature as yet.[64] Hufford et al.[65] screened a number of microorganisms for their ability to biotransform colchicine, and Streptomyces spectabilis and S. griseus were chosen for preparative scale fermentation. Both organisms produced C_2 and C_3 demethylcolchicine.

Corrodi and Hardegger studied the stereochemistry of the acetamido group of colchicine.[66,67] They isolated N-acetyl-L-glutamic acid after exhaustive ozonization of colchicine. Several authors studied this problem by optical rotatory dispersion and circular dichroism.[68,69] Colchicine and its natural derivatives have the S-configuration. The ^{1}H-NMR measurements have shown that the amido group of the colchicine compounds is in equatorial position.[70]

During the past three decades, the newly isolated alkaloids were identified by polarography, ultraviolet, infrared, mass spectra, ^{1}H- and ^{13}C-NMR data, and photophysical processes.[41,65,71-80,161]

In 1959 and in the following years, colchicine and some of its derivatives were synthesized by Eschenmoser et al.[81] in Switzerland, Tammelen et al.[82] and Woodward et al.[83] in the USA, by Nakamura et al.,[84] by Kotani et al.[85] and by Kato et al.[86] in Japan, and by Martel et al.[87] in France. Scott et al.[88] synthesized colchicine on the basis of the biogenetic theory postulating that the rings A and C are coupled by phenolic oxidation. Evans et al. synthesized colchicine by application of new alternatives to oxidative phenolic coupling.[89] Wallace published the synthetic approaches to morphine and colchicine alkaloid analogs.[90]

II. Alkaloids without tropolone ring

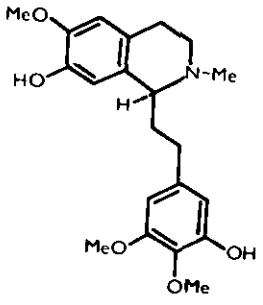
These substances form other groups of alkaloids of the plants of the sub-family Wurmbaeoideae. Androcymbine (XVIa), melanthioidine (XVc), colchicine (Ia), and demecolcine (IIf) were isolated from the leaves of the South African plant Androcymbium melanthioides.[91] The structures of androcymbine and melanthioidine were elucidated in the years between 1962 and 1968. The Tables C to G show the other isolated alkaloids without tropolone ring. All of them can be derived[91b] from phenethyltetrahydroisoquinoline - autumnaline (XVa) - on the basis of the phenolic ortho-para or para-para oxidative coupling in the same way as in the Papaver alkaloids,[92,93] which are derived from benzyltetrahydroisoquinoline.

The isolation of this new group of alkaloids has revealed how the whole group of colchicine alkaloids with tropolone ring arises. There are, however, not yet known the biological effects of any of the alkaloids of these groups of precursors or minor alkaloids since they are present in the plants only in traces.

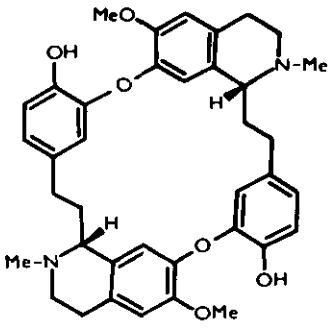
(1) Phenethyltetrahydroisoquinoline bases (XV)

Melanthioidine (XVc) was the first isolated representative of this group.[91] Its molecular weight showed it to be a dimer.[94,95] ^{1}H-NMR Spectroscopy revealed symmetry of the molecule and therefore overlapping of the signals of the protons of its two halves. Reduction with sodium in liquid ammonia gave four derivatives[95,96] which were identified as phenethyltetrahydroisoquinoline derivatives.

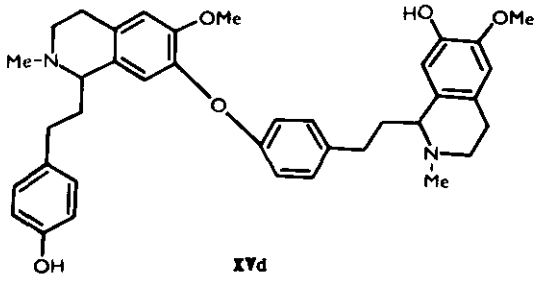
Table C. (1) Phenethyltetrahydroisoquinoline bases



XVa



XVc



XVd

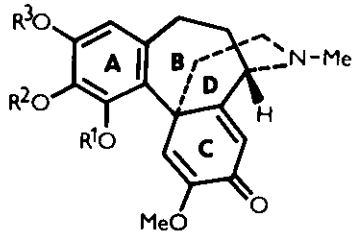
XVa S-(+)-Autumnaline (opt. antipode = Alkaloid CC-22)[14,58,102-107]

XVb Base m.p. 222° [105]

XVc R-(-)-Melanthioidine[91,94-96,107]

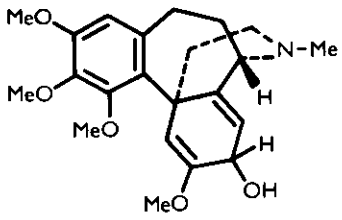
XVd Jolantinine[97,98]

Table D. (2) Homopromorphinane bases (XVI)

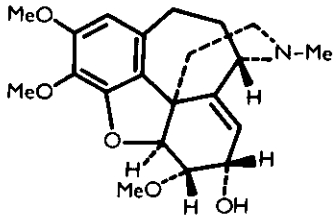


XVIa	$R^1=R^3=Me$; $R^2=H$	S-(-)-Androcymbine[91,103,108-112,115,116,124,129]
XVIb	$R^1=R^2=R^3=Me$	S-(-)-O-Methylandrocymbine[102,109,110,127b]
XVIc	$R^1=H$; $R^2=R^3=Me$	S-(-)-Collutine (= Alkaloid L-7)[113]
XVId	$R^1=R^2=R^3=Me$	R-(+)-Krokiflorine (= Alkaloid K-2)[8]
XVIe	$R^1=R^2=Me$; $R^3=H$	R-(+)-Alkaloids CC-3a and CC-10 [102,103]
XVIf	$R^1=Me$; $R^2+R^3=CH_2$	R-(+)-Alkaloid CC-20 [102,103]
XVIg	$R^1=Me$; $R^2+R^3=CH_2$	S-(-)-Alkaloid AM-3 [110,111]

Table E. (3) Dihydro- and tetrahydrohomopromorphinane bases (XVII-XIX)



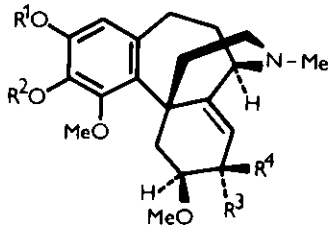
XVII S-(-)-Szovitsidine[114] (= Alkaloid OGG-2?)[111]



XVIIIa S-(-)-Kreysiginine[117-122]

XVIIIb R-(+)-Alkaloid CC-21 [102,103,109]

XVIIIc (+)-Floramultinine ?[117]



XIXa	$R^1=R^4=H$; $R^2=Me$; $R^3=OH$	R-(+)-Alkaloid CC-3b [102,103]
XIXb	$R^1+R^2=CH_2$; $R^3=H$; $R^4=OH$	R-(+)-Alkaloid CC-2 [102,103,125]

Battersby et al.[95] used Ullman's double reaction to synthesize melanthioidine from the phenolic bromophenethyltetrahydroisoquinoline compound. Consequently, the alkaloid is a bisphenethyltetrahydroisoquinoline base.
Jolantinine is another dimer alkaloid of this group.[97,98]
Kametani et al.[99-101] used Ullman's double reaction to synthesize some other derivatives in addition to melanthioidine and they decomposed racemic melanthioidine into its antipodes. Kametani's school also studied the enzymatic phenolic oxidation of this series of compounds.[100]
Battersby[14,58] and Šantavý et al.[102] isolated the phenethyltetrahydroisoquinoline alkaloid autumnaline (= alkaloid CC-22) (XVa). The synthesis and the physicochemical properties of this base and of its homologues were studied by Battersby,[14,58,95,103,104] Kametani,[99] Brossi,[105,106] and by DeAngelis.[107]

Types (2) and (3) of the homopromorphinane group

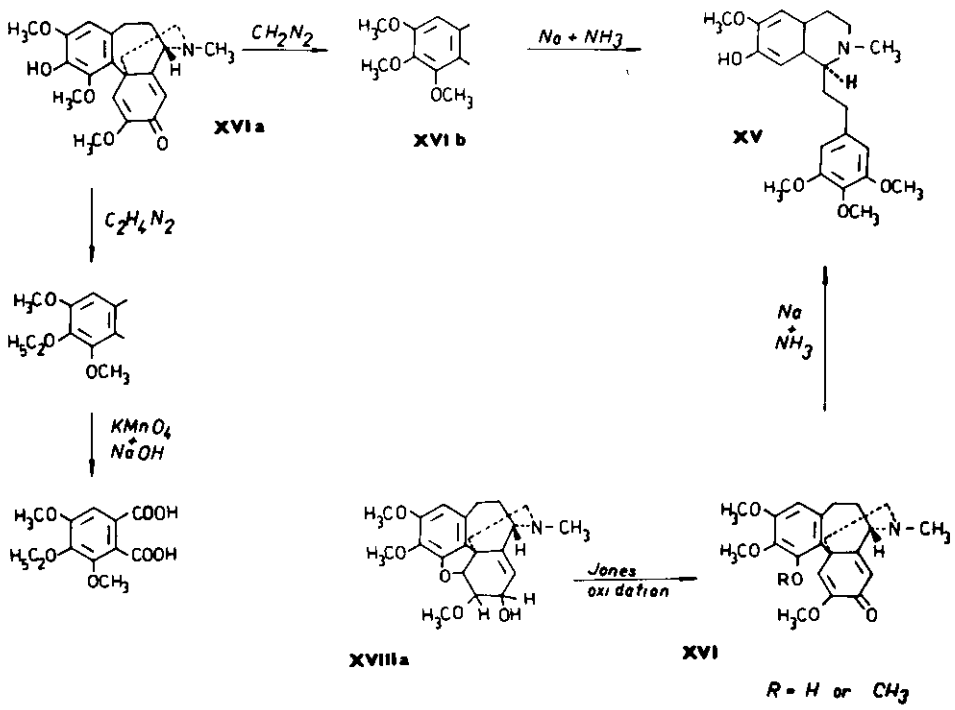
There have been isolated 13 homopromorphinane alkaloids. They differ in the number of double bonds in the ring C, in the presence or absence of the methoxyl group of this ring, and in the substituents of the ring A. This group is subdivided into two subgroups:

The substances of the androcymbine group (XVI)

The constitution of androcymbine (XVIa) (Table D), which resembles that of the promorphinane alkaloid salutaridine, was elucidated[103,108-112] by classical degradation (Scheme 3), spectroscopic and other physico-chemical methods.[112]

The substances of the dihydro- and tetrahydroandrocymbine group (XVII-XIX)

The first representative of this group is kreysiginine (XVIIIa) (Table E) which has an oxygen bridge between the rings A and C. Its constitution and the absolute configuration were elucidated by X-ray and ^{1}H-NMR analysis.[109,117-121] The dihydro- and the tetrahydrohomopromorphinane alkaloids were converted[103] into bases of the androcymbine type by Jones's oxidation. The absolute S-configuration of kreysiginine at C_7 is identical with that of androcymbine (XVIa), szovitsidine (XVII), and colchicine alkaloids with tropolone ring.
The alkaloids of this group are a twin group of promorphinane and morphinane alkaloids[92,93] with the difference that the homopromorphinane alkaloids have an additional CH_2-group in the ring B.
Kametani et al.[115,116,127] studied the biogenetical synthesis of androcymbine



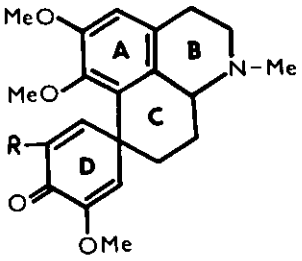
Scheme 3

and of some of its derivatives. Photolysis of 1-(2-bromo-4-hydroxy-3,5-dimethoxyphenethyl)-1,2,3,4-tetrahydro-7-hydroxy-6-methoxy-2-methylisoquinoline in the presence of sodium iodide gave racemic androcymbine (XVIa). When photolysis was carried out without sodium iodide, it afforded rac. multifloramine (XXIXc).[129]

(4) Homoproaporphine alkaloids (XX-XXVIII)

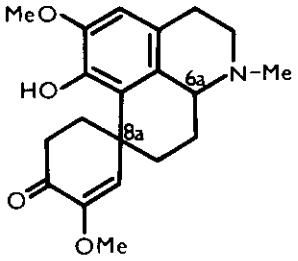
This group comprises several types of compounds (Table F). They differ in the number of double bonds in the ring D and consequently in the ultraviolet, infrared, and ^{1}H-NMR spectroscopic properties. When there is a keto group at the C_{12} or C_{13} atom of the ring D, it may form a cyclic half-acetal bridge with a phenolic group at C_1. The half-acetal hydroxyl can be free or etherified with a methyl group. Moreover, the double bond in the ring D can be in the cis- or the trans-configuration to the hydrogen at C_{6a}. The proaporphine alkaloids have similar properties.[92,93] The mass spectra of all the proaporphine and homoproaporphine alkaloids exhibit[109,126] the characteristic peaks M-1$^+$ (100%) and M-43.[161]

Table F. (4) Homoproaporphine bases (XX-XXVIII)

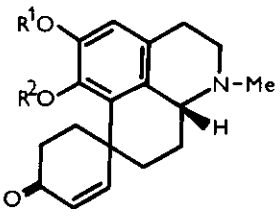


XXa R=H Kreysiginone (Dienone I, m.p. 194° and Dienone II, m.p. 202° [104,119,122-124c,176]

XXb R=OMe S-(+)-1-Hydroxy-12-methoxy-kreysiginone[105]



XXI Dihydrokreysiginone[112,123,124b,142]



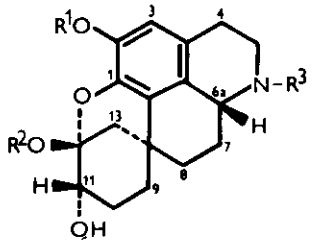
XXIIa R^1=Me; R^2=H 6aR,8aS-(+)-Bulbocodine[144] (= (+)-Jolantamine = Alkaloid K-8)[126,145]

XXIIb R^1=R^2=Me R-(+)-Krokiflorinone (= Alkaloid K-16)[146] (= Umtaline = Strumozine)[111,130]

XXIIc Jolantine = Jolantaminemethohydroxide[147]

XXIId Alkaloid OGG-3 ?[111,148]

XXIII R^1=Me; R^2=H R-(+)-Trigamine[149]



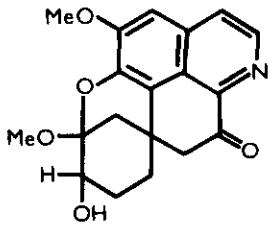
XXIVa R^1=H; R^2=R^3=Me R-(+)-Kesselringine[150,151]

XXIVb R^1=R^2=H; R^3=Me S-(-)-Kesselridine (= Alkaloid K-10)[152]

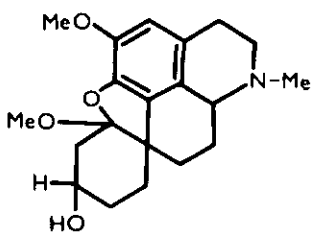
XXIVc R^1=R^2=R^3=Me R-(+)-Regeline (= Alkaloid K-15)[153]

XXIVd R^1=R^3=Me; R^2=H R-(+)-Regelamine[126,154] S-(-)-Alkaloid G-2 [111,155]

XXIVe R^1=R^3=H; R^2=Me R-(+)-Luteine (= Alkaloid L-1)[156]

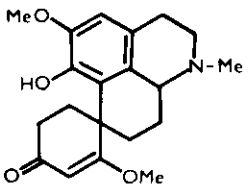


XXV Regelinone (= Alkaloid K-14)[157]



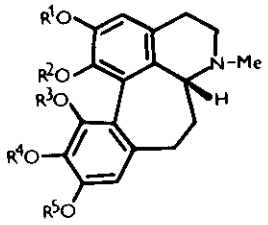
XXVI (+)-Luteicine (= Alkaloid L-3)[158]

XXVII (+)-Jolantimine (= Luteinone)[98,145]



XXVIII (-)-Luteidine (= Alkaloid L-2)[8,135,135b]

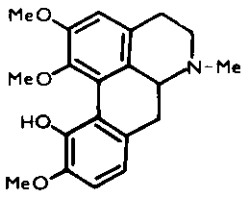
Table G. (5) Homoaporphine alkaloids (XXIX)



XXIXa	$R^1=R^3=R^4=R^5=Me$; $R^2=H$	R-(-)-Kreysigine (= Alkaloid CC-1)[14,102,117,123,124,127c,144]
XXIXb	$R^1=R^3=R^5=Me$; $R^2=R^4=H$	R-(-)-Floramultine (optical antipode S-(+)-Bechuanine=(+)-Merenderine)[14,102,117,118,122,123,130-132,159]
XXIXc	$R^1=R^3=R^4=Me$; $R^2=R^5=H$	R-(-)-Multifloramine[14,105,122-124,129]
XXIXd	$R^1=R^2=R^4=R^5=Me$; $R^3=H$	S-(+)-Szovitsamine[133]
XXIXe	$R^1=R^4=R^5=Me$; $R^2=R^3=H$	R-(-)-Alkaloid CC-24[102,103]
XXIXf	$R^1=R^3=H$; $R^2=R^4=R^5=Me$	Szovitsinine[160]
XXIXg	$R^1=R^2=R^3=R^4=R^5=Me$	R-(-)-O-Methylkreysigine[161]

(5) Homoaporphine alkaloids (XXIX)

Kreysigia multiflora[117] gave three alkaloids ((-)-kreysigine (XXIXa), (-)-floramultine (XXIXb), and O-methylkreysigine (XXIXg)), whereas Colchicum cornigerum[102] the two alkaloids (alkaloids CC-1 (XXIXa) and CC-24 (XXIXe)) which belong to this group of compounds (Table G). The alkaloid bechuanine (optical antipode of floramultine) was isolated[130] from Iphigenia bechuanica, the alkaloid merenderine from Merendera raddeana,[131,132] the alkaloid szovitsamine (XXIXd)[133] from Colchicum szovitsii, and the alkaloid isocorydine (XXX) from Camptorrhiza strumosa.[130] Isocorydine was derived from the benzyltetrahydroisoquinoline compound reticuline like the other alkaloids of the family Papaveraceae.[92,93] These alkaloids can be converted into O-methylkreysigine (XXIXg) by methylation with diazomethane. It was found that on isolation or crystallization the alkaloids without tropolone ring are very easily racemized.



XXX

For the homoaporphine alkaloids see also papers.[14,105,123,124,128,129,138-143,176]

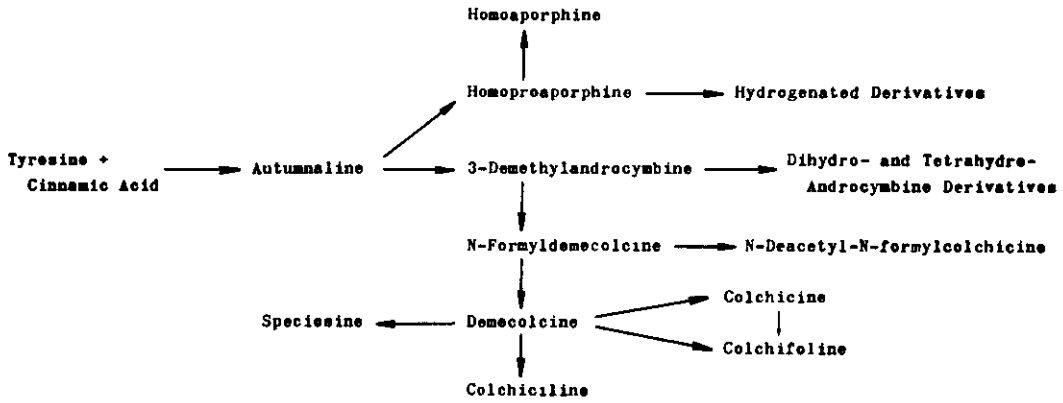
Table H. Unclassified alkaloids without tropolone ring

Floramultinine[117]	Alkaloid X-1[163]
Alkaloid O[162]	Alkaloid CL-1[164]
Alkaloid AM-4[111]	Alkaloid CL-2[164]
Alkaloid G-1[155]	Alkaloid G-4[155]

Crociflorine (Alkaloid K-2)
Regelinine (Alkaloid K-6)
Regelidine (Alkaloid K-7)
Crociflorinine (Alkaloid K-9)
Crocifloridine (Alkaloid K-11)
} 8,134-137

III. The biosynthesis of alkaloids with and without tropolone ring

Battersby et al.,[165,166] Leete et al.,[167] Hill and Unrau,[168] and also Trozyan et al.[169] studied the biosynthesis of colchicine alkaloids and its minor derivatives by using labeled phenylalanine, tyrosine, cinnamic acid, methionine, and acetic acid. According to them the ring A and the carbon atoms 5, 6, 7 and 12 of colchicine (Ia) originate from phenylalanine (or tyrosine) and cinnamic acid. Radioactive acetic acid participates only in the formation of the acetamido group.[169b] Battersby et al.[170-175] found that widening of the benzene ring A of phenethyltetrahydroisoquinoline (autumnaline (XVa)) gave rise to a tropolone ring, and phenolic oxidation to a linkage between the rings A and C of colchicine. The intermediate step of the biosynthesis of colchicine was formed by the alkaloids of androcymbine type (XVI). Consequently, autumnaline is the basic compound for the biosynthesis of homomorphinane (XVI) and tropolone alkaloids (I-V) and, moreover, for the homoproaporphines (XX-XXVIII) and homoaporphines (XXIX)[104,123] (Scheme 4).



Developmental series of phenethyltetrahydroisoquinoline (autumnaline) alkaloids

Scheme 4

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