SYNTHESIS OF ANDROCYMBINE AND RELATED HOMOMORPHINANDIENONES

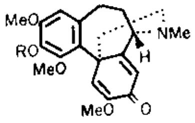
Tetsuji Kametani* and Keiichiro Fukumoto
Pharmaceutical Institute, Tohoku University, Aobayama, Sendai, Japan
Masuo Koizumi
Research Laboratories, Chugai Pharmaceutical Co. Ltd., Takada, Toshimaku, Tokyo, Japan

The synthesis of the homomorphinandienones by several methods are discussed. The total synthesis of the homomorphinandienone alkaloids androcymbine and O-methylandrocymbine by a photo-Pschorr reaction or photo-cyclodehydrohalogenation are described.

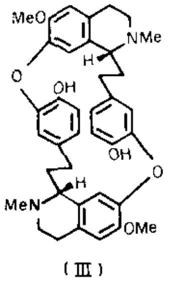
1 INTRODUCTION

Plants of the sub-family *Wurmbaeoidea* (Liliaceae) have proved to be rich sources of a large new class of alkaloids based upon the 1-phenethylisoquinoline system.[1,2] Thus, *Androcymbium melanthioides*,[3] which grows in Southern and Eastern Africa and has been used in folk medicine for the treatment of many diseases,[4] yielded androcymbine (I)[5,6] and melanthioidine (III)[7,8] as initial examples of 1-phenethylisoquinoline alkaloids while *Colchicum cornigerum* was found to contain eight such alkaloids, of which autumnaline (V) is the first unmodified 1-phenethylisoquinoline to be found in nature.[9] Further the tropolone alkaloids such as colchicine (IV) are now classified as modified 1-phenethylisoquinolines since extensive tracer studies showed that IV and related alkaloids are formed from autumnaline (V) by a novel biosynthetic pathway *via* *O*-methylandrocymbine (II) as the key intermediate.[10]

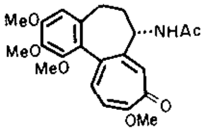
Chart 1



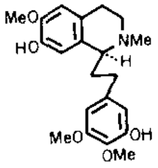
(I) R=H
(II) R=Me



(III)



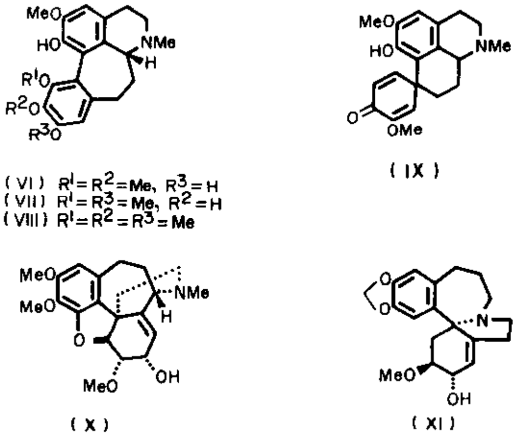
(IV)



(V)

In addition, 1-phenethylisoquinoline related alkaloids have been isolated from Kreysigia multiflora[11] such as the homoaporphines floramultine (VI), multifloramine (VII) and kreysigine (VIII), the homoproaporphine kreysiginone (IX),[12] and the homomorphine kreysiginine (X)[13] while the Schelhammera species has yielded homoerythrina type alkaloids as exemplified by schelhammerine (XI).[14]

Chart 2



(VI) $R^1=R^2=Me$, $R^3=H$
(VII) $R^1=R^3=Me$, $R^2=H$
(VIII) $R^1=R^2=R^3=Me$

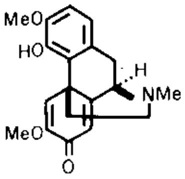
(IX)

(X)

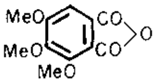
(XI)

Androcymbine (I), $C_{21}H_{25}NO_5$, was obtained as colorless prisms, m.p. 199 - 201°, $[\alpha]_D^{22}$ - 260° ± 2 (c 0.500 in $CHCl_3$). Its nmr spectrum indicated three O-methyl groups, one N-methyl group, one phenolic hydroxy group, one aromatic hydrogen, and two olefinic hydrogens while its infrared spectrum showed a characteristic cross-conjugated cyclohexadienone system similar to the corresponding absorptions of salutaridine (XII). Since oxidation of O-methylandrocymbine (II), initially derived from I and subsequently isolated[15] from Colchicum autumnale (Liliaceae), gave 3,4,5-trimethoxyphthalic anhydride (XIII) while reduction with sodium in liquid ammonia afforded the phenolic isoquinoline (XIV), Battersby and co-workers[6] proposed the structure (I). The position of the phenolic hydroxyl group is assigned by analogy with 3-demethylcolchicine (XV) and by oxidation of O-ethylandrocymbine to 3,5-diethoxy-4-methoxyphthalic anhydride.

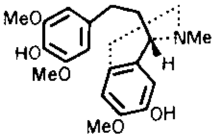
Chart 3



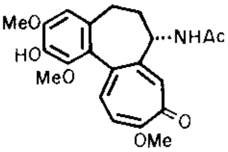
(XII)



(XIII)



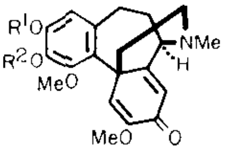
(XIV)



(XV)

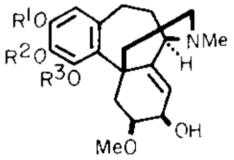
In addition to autumnaline (V), Colchicum cornigerum was found to have the homomorphinandienones CC-10 (XVI) and CC-20 (XVII) and the related alkaloids CC-2 (XVIII) and CC-3b (XIX)[9] as well as CC-21 which has been identified as an enantiomer of kreysiginine (X).[13]

Chart 4



(XVI) $R^1 = H$, $R^2 = Me$

(XVII) $R^1 + R^2 = -CH_2-$



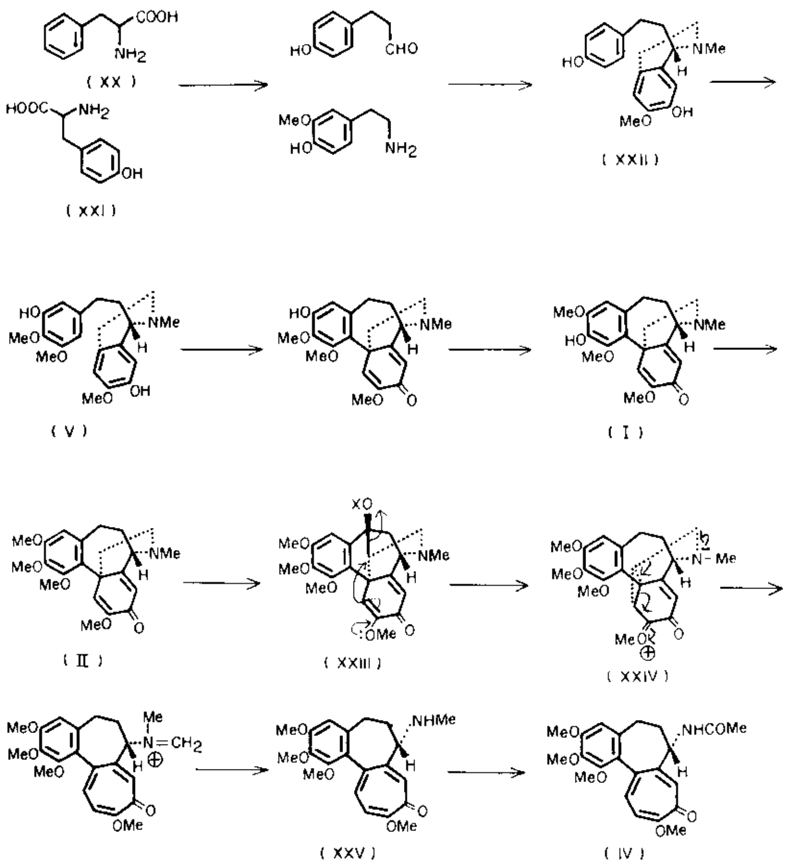
(XVIII) $R^1 + R^2 = -CH_2-$, $R^3 = Me$

(XIX) $R^1 = H$, $R^2 = R^3 = Me$ or
$R^1 = R^2 = Me$, $R^3 = H$

In view of its structural similarity with salutaridine (XII), it is reasonable to assume that the biosynthesis of androcymbine (I) involves phenol oxidation of a diphenolic 1-phenethylisoquinoline precursor. In addition, it was assumed in the structural determination of (I) that there is a close biogenetic relationship to the tropolone alkaloid since androcymbine (I) occurs together with colchicine (IV).

Supporting evidence came from the successful incorporation of phenylalanine (XX) and tyrosine (XXI) via the 1-phenethylisoquinolines (XXII and V), into colchicine (IV). Thus, a phenol oxidation of 1-phenethylisoquinolines (XXII) and (V) afforded androcymbine (I) and hydroxylation of O-methylandrocymbine (II) yielded (XXIII). The route leading to demecolcine (XXV) and colchicine (IV) has been clarified by various tracer experiments(10) and involves ring expansion reaction of XXIV by "homoallylic ionization" of

Chart 5


COOH
NH2
(XX)
HOOC
NH2
OH
(XXI)
HO
CHO
MeO
HO
NH2
HO
NMe
H
MeO
OH
(XXII)
HO
MeO
MeO
NMe
H
MeO
OH
(V)
HO
MeO
MeO
NMe
H
MeO
O
MeO
HO
MeO
NMe
H
MeO
O
(I)
MeO
MeO
MeO
NMe
H
MeO
O
(II)
XO
MeO
MeO
MeO
NMe
H
OMe
O
(XXIII)
MeO
MeO
MeO
N−Me
H
MeO
O
⊕
(XXIV)
MeO
MeO
MeO
Me
N=CH2
H
⊕
O
OMe
MeO
MeO
MeO
NHMe
H
O
OMe
(XXV)
MeO
MeO
MeO
NHCOMe
H
O
OMe
(IV)

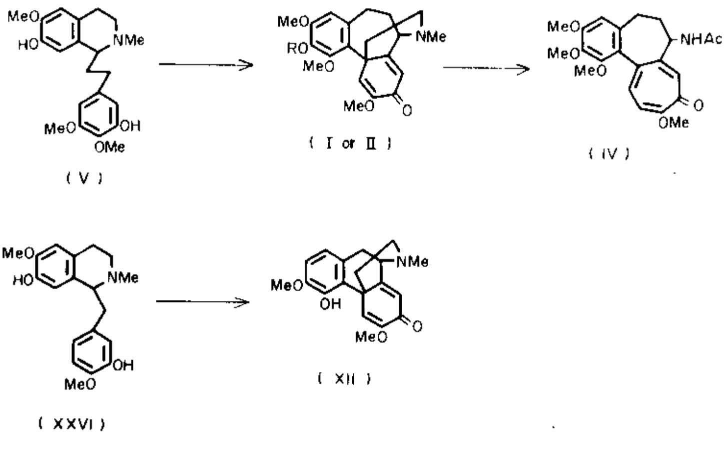
the nitrogen lone pair via (XXIV) as shown in Chart 5.

Androcymbine (I), as mentioned above, plays an important role in the biogenesis of colchicine and related tropolone alkaloids while kreysiginine (X) is structurally similar to morphine and thebaine. In view of these relationships, the synthesis of androcymbine (I) and related alkaloids were of particular interest and in this connection the several synthetic methods of the homomorphinandienone ring system will be discussed in the following chapters.

2 PHENOL OXIDATION[16,17]

The close relationship between androcymbine (I) and salutaridine (XII) which is synthesized in the poppy from reticuline (XXVI) by phenol oxidation[16] suggested a biosynthetic connection between (I) and autumnaline (V). This was confirmed by the administration of labelled O-methylandrocymbine (II) and autumnaline (V) to Colchicum autumnale plants where they were incorporated into colchicine (IV)

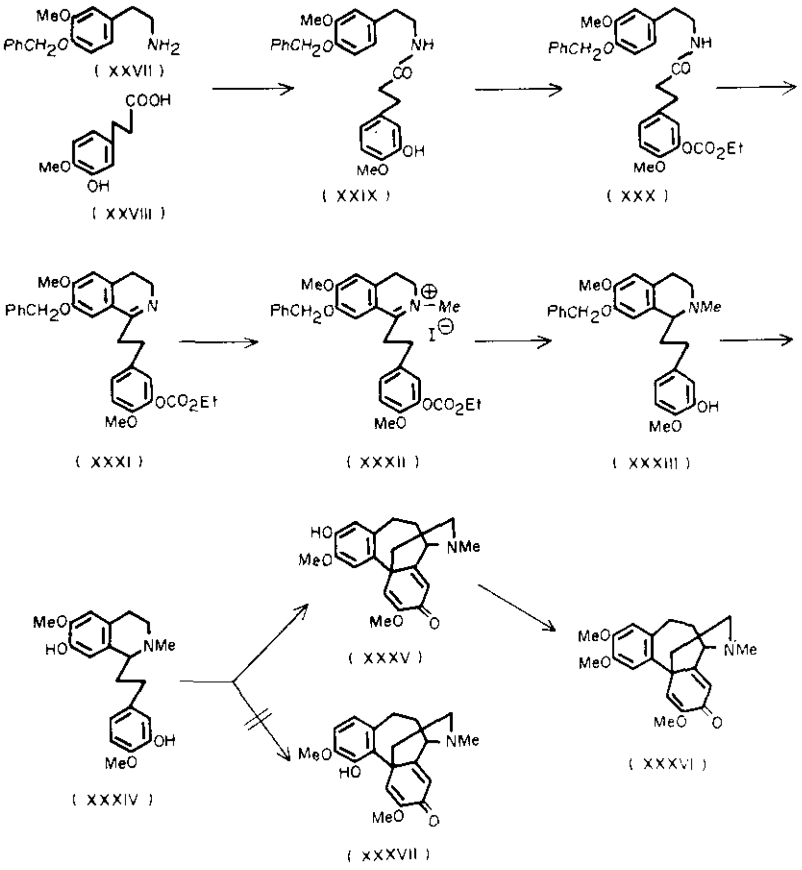
Chart 6



to the remarkably high extent of over 15 % and 9 %, respectively. These results define part of the biological pathway to colchicine as V to II (I) via oxidative coupling to produce a new carbon-carbon bond between the position para to the phenolic hydroxy groups followed by conversion to IV.[10]

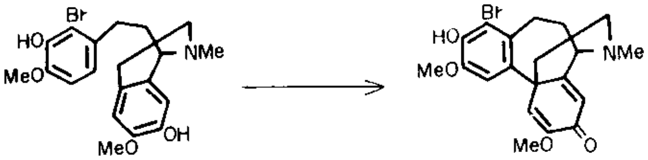
Based on this biogenesis of androcymbine and related compounds, the phenol oxidation of autumnaline (V) was examined by Kametani and Battersby, independently. The first successful synthesis was reported by Kametani and his associates[18] and involved the fusion of 4-benzyloxy-3-methoxyphenethylamine (XXVII) with 3-hydroxy-4-methoxyphenylpropionic acid (XXVIII) to furnish the amide (XXIX) whose phenolic function was protected by ethoxycarbonylation with ethyl chlorocarbonate and triethylamine. Ring closure of the amide (XXX) with phosphoryl chloride in boiling dry benzene gave the corresponding 3,4-dihydroisoquinoline (XXXI), characterized as its crystalline hydrochloride. Conversion of XXXI into the methiodide (XXXII) followed by reduction with methanolic sodium borohydride to the monophenolic 1,2,3,4-tetrahydroisoquinoline (XXXIII), which was readily purified by way of the hydrochloride and then hydrolysis with ethanolic hydrochloric acid to afford the diphenolic tetrahydroisoquinoline (XXXIV). Successful phenolic oxidative coupling of (XXXIV) was achieved with potassium ferricyanide in a mixture of 5 % sodium hydrogen carbonate and chloroform followed by chromatography on silica gel and then alumina to furnish in low yield the crystalline homomorphinandienone (XXXV). Its structure was supported by its ir spectrum which showed typical cross-conjugated α-methoxylated cyclohexadienone absorption at 1664, 1642, and 1620 cm^{-1} and by its nmr spectrum which indicated two aromatic proton singlets. The presence of the latter ruled out the alternate coupled-compound XXXVII. Further evidence for XXXV was obtained by methylation with diazomethane to give a non-phenolic base, which was spectroscopically (ir and nmr) and chromatographically identical with the demethoxy-O-methylandrocymbine (XXXVI), obtained by a modified Pschorr reaction from the aminoisoquinoline to be described later.

Chart 7



Similarly, the bromohomomorphinandienone (XXXIX) was synthesized from the diphenolic bromoisoquinoline (XXXVIII) by potassium ferricyanide oxidation in chloroform in the presence of sodium hydrogen carbonate and ammonia.[19]

Chart 8

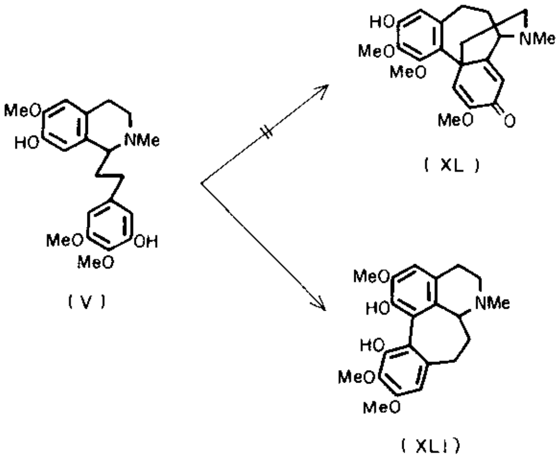


(XXXVIII)   (XXXIX)

In contrast to the above biogenetic type synthesis of homomorphinandienones the conversion of autumnaline (V) by phenol oxidations coupling to the homomorphinandienone (XL) has not been reproduced in the laboratory.[20] It is probable that steric factors were the predominant reason for failure. Instead, Battersby and co-workers[21] obtained the homoaporphine (XLI), in 25 % yield by ferricyanide oxidation of autumnaline (V), identical with the alkaloid CC-24 found in Nature.[9]

Phenol oxidation indicated that the coupling reaction between two aromatic rings in the phenethylisoquinoline system gave the homomorphinandienone structure, the fact of which suggested that the homomorphinandienone could be formed

Chart 9



by a similar type of coupling reaction.

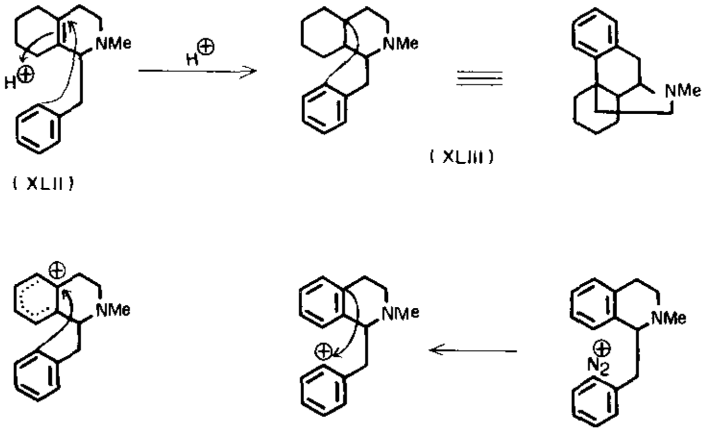
3 PSCHORR REACTION[22]

It is well known that phenol oxidation mimics one of the biogenetic pathways in Nature and provides a facile route to the synthesis of certain isoquinoline alkaloids. However, its utility is limited since intermolecular coupling also occurs to generate polymers which are formed from the starting material and/or its oxidation products. Moreover, intramolecular coupling always takes place at the ortho and para position to the phenolic hydroxy group. Thus, phenol oxidation can not be employed in the synthesis of androcymbine (I) itself where the hydroxyl is meta to the coupling site.

In view of these inherent limitations associated with phenol oxidation and in connection with the interest in a general method for the synthesis of homomorphinandienone-type compounds, the Pschorr reaction[23] was investigated as follows.

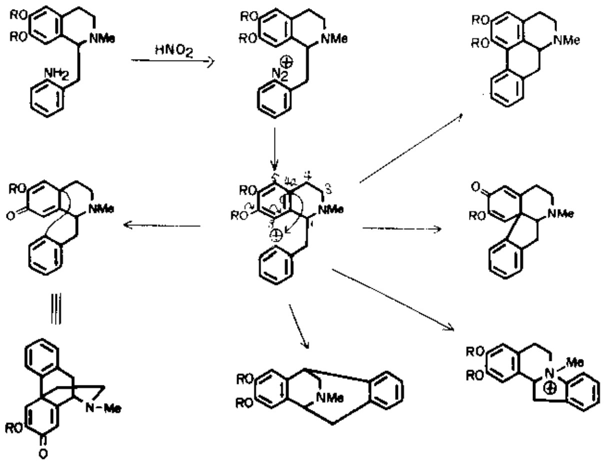
3.1 Synthesis of C-nor-Androcymbine: In the 1940's, Grewe reported the synthesis of a morphinan (XLIII) by acidic treatment of the 1-benzyloctahydroisoquinoline (XLII).[24] Since this cyclization involves a nucleophilic attack at the olefinic bond, it suggests that if the carbon atom at either C_{4a} or $C_{2'}$ in a 1-benzyltetrahydroisoquinoline was positively charged, nucleophilic attack from the other aromatic ring would also form the morphinan-type structure. This type of cyclization involving an aromatic cation is referred to as an aromatic S_N1 reaction and the generation of the cation by decomposition of an aromatic diazonium salt is known as the Pschorr reaction.

Chart 10



In connection with the synthesis of aporphines, the use of the Pschorr reaction could lead to a variety of products. Thus, the following scheme indicates the possible reaction pathways, and in the case of the formation of the morphinandienone (XLIV), the proposed mechanism indicates that nucleophilic attack of position 4a is facilitated by the E-effect of the alkoxy group.

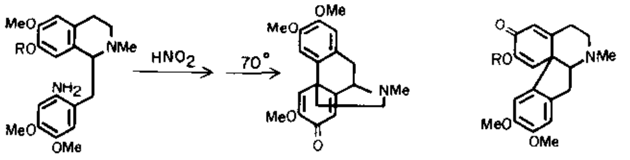
Chart II



(XLIV)

Based on the above considerations, the following preliminary experiments were carried out. Diazotization of 6'-aminolaudanosine (XLV) at 0 – 5° with a slight excess of sodium nitrite in dilute sulfuric acid followed by increasing the temperature to 70° for 1 hr, produced O-methylflavinantine (XLVII). The ethoxy analog (XLVI) was also converted to O-methylflavinantine using identical conditions. This ruled out structure (XLVIII) as that representing the dienone product.[25] Thus, by applying the Pschorr reaction which had been widely used for the synthesis of aporphines, a general synthetic method of preparing morphinandienones was developed.

Chart 12



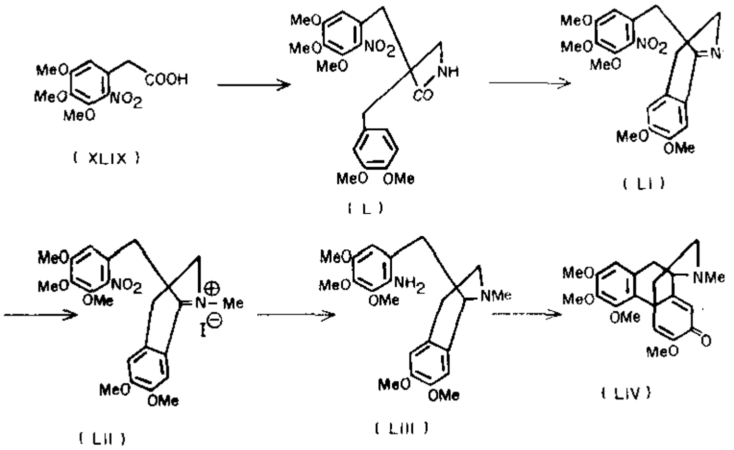
(XLV) R = Me
(XLVI) R = Et

(XLVII)

(XLVIII) R = Me or Et

This modified Pschorr reaction was applied to the synthesis of C-nor-androcymbine (LIV) as a model for the total synthesis of androcymbine (I). The starting compound, 1-(2-amino-3,4,5-trimethoxybenzyl)-1,2,3,4-tetrahydro-6,7-dimethoxy-2-methylisoquinoline (LIII), was prepared by the following standard method. Heating of homoveratrylamine with 3,4,5-trimethoxy-2-nitrophenylacetic acid (XLIX) in dry xylene afforded the amide (L) which was cyclized with phosphoryl chloride in dry chloroform to give the 3,4-dihydroisoquinoline (LI), characterized as its methiodide (LII). Reduction of (LII) with zinc and concentrated hydrochloric acid gave the key intermediate (LIII) which was unstable in air and thus used without purification. The aminoisoquinoline (LIII) was diazotized with a slight excess of sodium nitrite and 1 N sulfuric acid-acetic acid with stirring at 0° and the resulting diazonium salt decomposed and coupled at 70° for 1 hr. Careful work-up, involving silica gel and alumina chromatographies and monitoring by the ir spectroscopy, afforded many compounds from which the desired C-nor-androcymbine (LIV) was obtained and characterized by spectral data as its methiodide, mp 234 - 235°.[26]

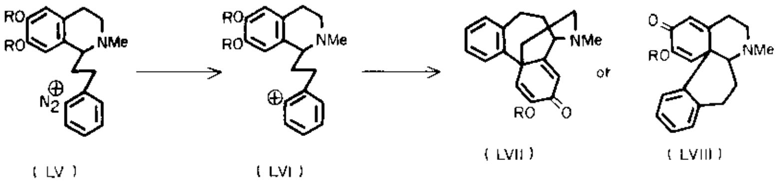
Chart 13



3.2 Synthesis of an Androcymbine-type Compound by the Pschorr Reaction[27]:

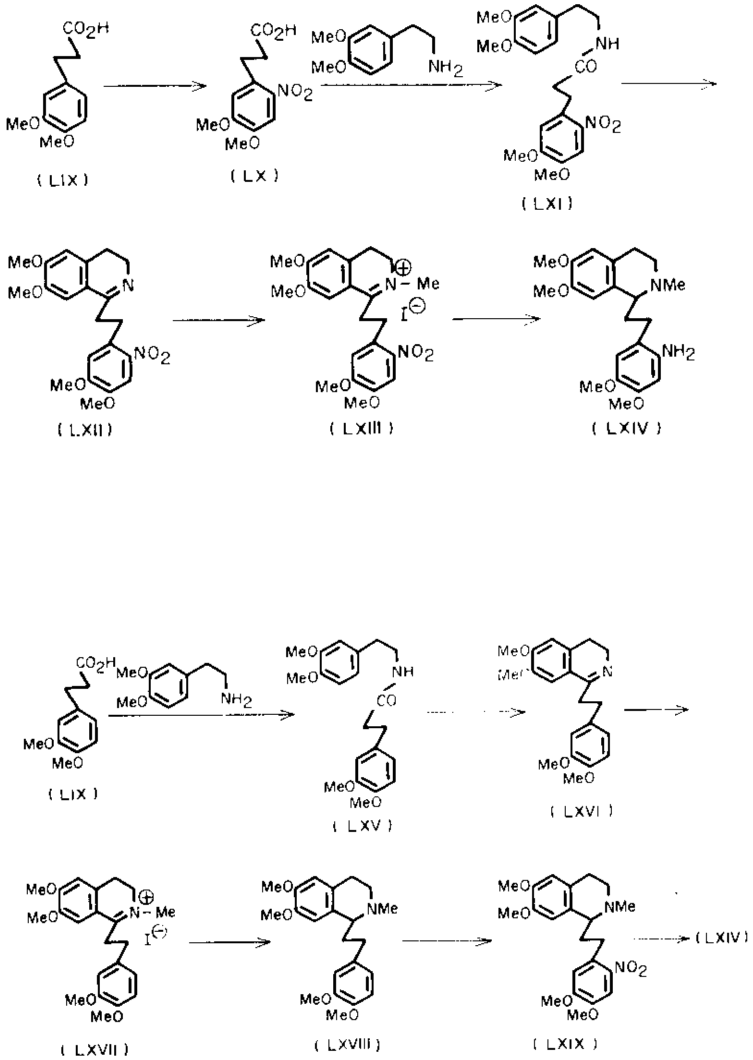
The preparation of morphinandienone-type compounds by the Pschorr reaction as described in the previous section was applied to the synthesis of the homomorphinandienone system. However, for the latter, coupling of the cation (LVI), derived from the diazotized aminophenethylisoquinoline (LV), can occur to form either the desired seven-membered ring homomorphinandienone (LVII) or by coupling between the $C_{2'}$ position and the C_{8a} carbon the thermodynamically more stable (LXIII). Bearing these two possibilities in mind, the following investigation was carried out.

Chart 14



The starting aminoisoquinoline (LXIV) was synthesized by two methods as follows. Nitration of 3,4-dimethoxyphenylpropionic acid (LIX) gave the 4,5-dimethoxy-2-nitrophenylpropionic acid (LX) which was converted into the amide (LXI) by fusion with 3,4-dimethoxyphenethylamine. Ring closure of (LXI) with phosphoryl chloride in boiling chloroform gave the 3,4-dihydroisoquinoline (LXII), characterized as its hydrochloride. The corresponding methiodide (LXIII) was then reduced with zinc powder in concentrated hydrochloric acid to afford the aminoisoquinoline (LXIV) which was readily purified as its dihydrochloride.

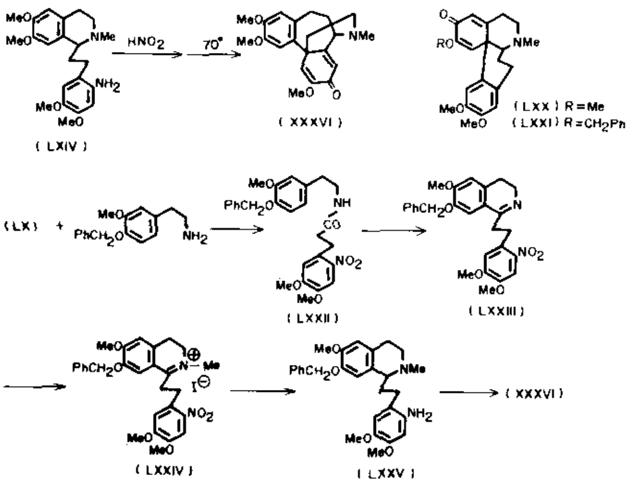
Chart 15


CO2H
MeO
MeO
(LIX)
CO2H
NO2
MeO
MeO
(LX)
MeO
MeO
NH2
MeO
MeO
NH
CO
NO2
MeO
MeO
(LXI)
MeO
MeO
N
NO2
MeO
MeO
(LXII)
MeO
MeO
⊕
N − Me
I⊖
NO2
MeO
MeO
(LXIII)
MeO
MeO
NMe
NH2
MeO
MeO
(LXIV)
CO2H
MeO
MeO
NH2
MeO
MeO
(LIX)
MeO
MeO
NH
CO
MeO
MeO
(LXV)
MeO
MeO
N
MeO
MeO
(LXVI)
MeO
MeO
⊕
N − Me
I⊖
MeO
MeO
(LXVII)
MeO
MeO
NMe
MeO
MeO
(LXVIII)
MeO
MeO
NMe
NO2
MeO
MeO
(LXIX)
(LXIV)

By the second synthesis, based on Sugasawa's method,[28] the amide (LXV), derived from 3,4-dimethoxyphenylpropionic acid (LIX) and 3,4-dimethoxyphenethylamine, was cyclized with phosphoryl chloride in boiling benzene to yield the 3,4-dihydroisoquinoline (LXVI) which was converted into its methiodide (LXVII). Borohydride reduction of LXVII, followed by nitration of the resulting 1,2,3,4-tetrahydroisoquinoline (LXVIII) with concentrated nitric acid in chloroform-acetic acid afforded the 2'-nitroisoquinoline derivative (LXIX) which was reduced by zinc and concentrated hydrochloric acid to give the starting aminoisoquinoline (LXIV).

The aminoisoquinoline (LXIV) was then diazotized with 10 % sodium nitrite in 5 % sulfuric acid at 0°, and the resulting diazonium salt decomposed at 70° to give the cyclohexadienone (XXXVI) which, after purification by silica gel chromatography, was characterized by spectral data as its methiodide,

Chart 16



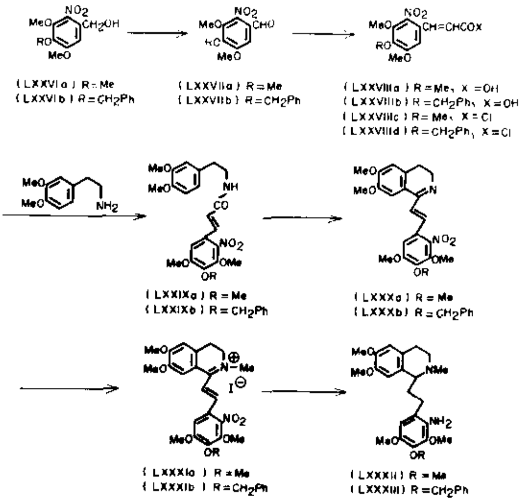
mp 251 - 252°.

The alternate structure (LXX), also consistent with above physical data, was ruled out by the following evidence. The second aminoisoquinoline (LXXV) which was synthesized by standard methods from 2-nitrophenylcarboxylic acid (LX) and 4-benzyloxy-3-methoxyphenethylamine via the amide (LXXII), the 3,4-dihydroisoquinoline (LXXIII), and its methiodide (LXXIV), gave upon diazotization the dienone (XXXVI), identical to the product obtained from (LXIV) rather than (LXXI).

3.3 Abnormal Pschorr Reaction[29]: Based on the synthesis of the homomorphinandienone system by the Pschorr reaction, the total synthesis of androcymbine (I) and O-methylandrocymbine (II) from the appropriate aminophenethylisoquinolines was investigated.

The starting aminoisoquinolines were synthesized as follows. 3,4,5-Tri-

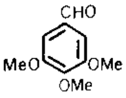
Chart 17


(LXXVIa) R=Me
(LXXVIb) R=CH_2Ph
(LXXVIIa) R=Me
(LXXVIIb) R=CH_2Ph
(LXXVIIIa) R=Me, X=OH
(LXXVIIIb) R=CH_2Ph, X=OH
(LXXVIIIc) R=Me, X=Cl
(LXXVIIId) R=CH_2Ph, X=Cl
(LXXIXa) R=Me
(LXXIXb) R=CH_2Ph
(LXXXa) R=Me
(LXXXb) R=CH_2Ph
(LXXXIa) R=Me
(LXXXIb) R=CH_2Ph
(LXXXII) R=Me
(LXXXIII) R=CH_2Ph

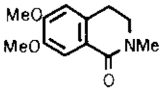
methoxy-2-nitrobenzyl alcohol (LXXVIa) and its 4-benzyloxy-analog (LXXVIb) were oxidized with active manganese dioxide and the resulting aldehydes (LXXVII) were subjected to the Knoevenagel reaction with malonic acid to give the cinnamic acids (LXXVIIIa and b). Schotten-Baumann reaction of the corresponding cinnamoyl chlorides (LXXVIIIc and d) with 3,4-dimethoxyphenethylamine afforded the amides (LXXIX), followed by Bischler-Napieralski cyclization to the 3,4-dihydroisoquinolines (LXXXa and b). The methiodides (LXXXIa and b) were then first reduced with zinc and hydrochloric acid and then with hydrogen over Adams catalyst.

The 1-(2-aminophenethyl)isoquinoline derivative (LXXXII) was then diazotized with sodium nitrite in sulfuric acid and the mixture heated to give three compounds.

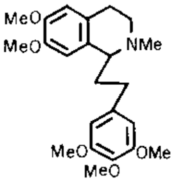
Chart 18



(LXXXIV)



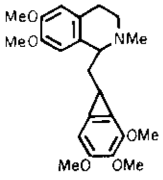
(LXXXV)



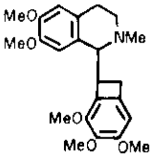
(LXXXVI)

Two of these were identified by comparison with authentic samples as 3,4,5-trimethoxybenzaldehyde (LXXXIV) and 3,4-dihydro-6,7-dimethoxy-2-methylisoquinoline-1(2H)-one (LXXXV). The third product, obtained in 36 % yield, $C_{23}H_{29}NO_5$, showed by uv spectrum the presence of a 1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline system but not of a homoaporphine system. Its nmr spectrum revealed signals for three aromatic protons and one N- and five O-methyl groups which indicated that it was not the deaminated compound (LXXXVI). The N- and O-methyl resonances were at an abnormally high field which were probably due to the existence of several groups on the same ring. Possible structures for this compound could then be limited to (LXXXVII), (LXXXVIII), (LXXXIX), (XC) and (XCI). All but (XCI) were ruled out as follows.

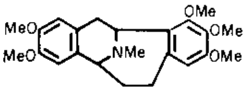
Chart 19



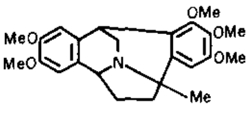
(LXXXVII)



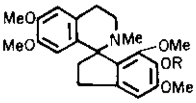
(LXXXVIII)



(LXXXIV)



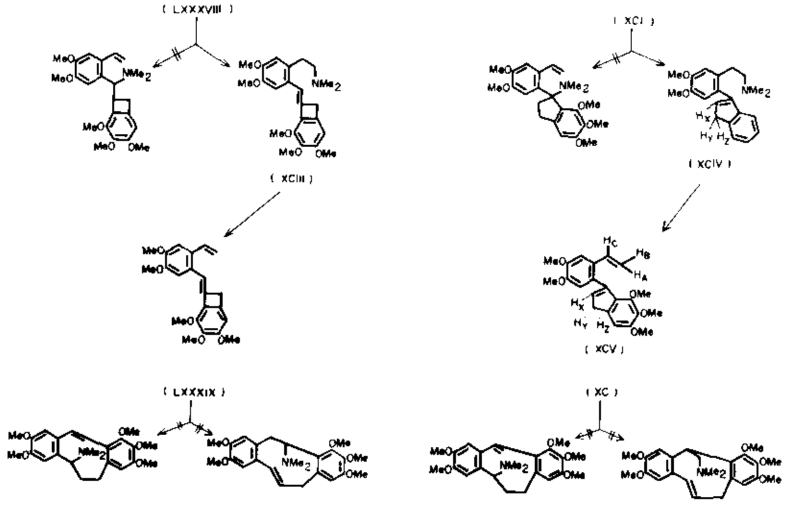
(XC)



(XCI) R = Me
(XCII) R = CH_2Ph

Since treatment of the third reaction product with cold concentrated sulfuric acid had no effect, this ruled out the cyclopropene structure (LXXXVII). Hofmann degradation gave a methine base whose nmr spectrum showed a signal for only one olefinic proton [δ 6.16 ppm (t, J 1.7 Hz)] and whose mass spectrum (M^+, m/e 413) showed a strong fragment ion [M^+ - (CH_2NMe_2)] at m/e 355 and thus consistent with either (XCIII) or (XCIV). A second Hofmann degradation caused the loss of trimethylamine and the nmr spectrum of the product showed the presence of a vinyl group as a typical ABX pattern as well as an olefinic signal at 6.16 ppm (t, *J* 1.7 Hz) coupled with a methylene doublet at 3.45 ppm (proved by decoupling). Since both chemical shifts were similar to those for indene — the coupling constant between an olefinic proton and its neighboring methylene protons in cyclopentene is known to be *J* 1.4 Hz, while that for allylic system in *cis*-benzylidenebenzocyclobutene is *J* 1.9 Hz — the product was assigned structure (XCV). This implies that the Pschorr reaction product has structure (XCI). Furthermore, oxidation of the Pschorr product with an excess of potassium permanganate did

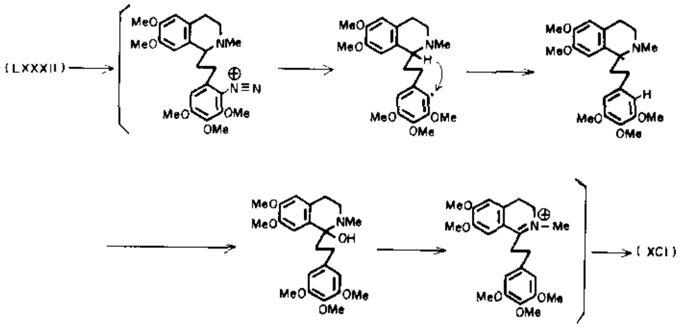
Chart 20



not furnish the isoquinoline (LXXXV), thus indicating that it was not the cyclobutane derivative (LXXXVIII).

A mechanism for the formation of compound (XCI) is shown in the following Chart.

Chart 21



Similar treatment of the 4'-benzyloxy-analog (LXXXIII) afforded the 5'-benzyloxy-analog (XCII) of the spiroisoquinoline (XCI), along with 4-benzyloxy-3,5-dimethoxybenzaldehyde and the isoquinoline (LXXXV). The spiro-compound was characterized by spectroscopic comparison with that of the spiroisoquinoline (XCI). By a slight modification of the reaction conditions aminoisoquinoline (LXXXII) gave a deaminated products (LXXXVI), identical with an authentic sample, as well as compounds (XCI), (LXXXIV) and (LXXXV). The results are summarized in Table I.

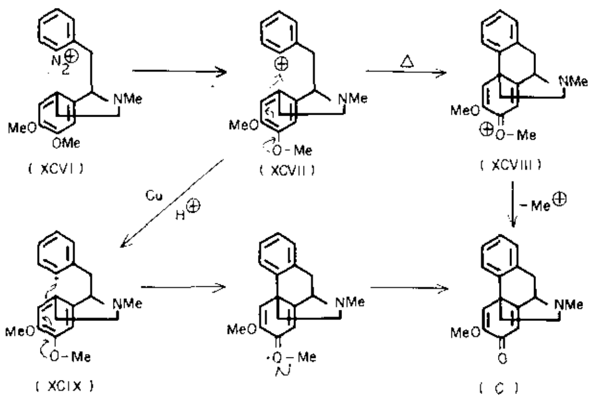
Table 1 Products of the Pschorr reaction of the (2-aminophenethyl)isoquinoline (LXXXII) under various conditions.

LXXXII (mole)	$NaNO_2$ (moles)	5% H_2SO_4 (moles)	Medium	Decomp. Temp.	Heating Time (hr.)	(XCI)	(LXXXIV)	(LXXXV)
1	6	14.5	H_2SO_4	70°	1	36	2.5	4.8
1	1.7	6	H_2SO_4	70	1	34.5		
1	1	6	AcONa	20 - 30	3			
1	6	5	H_2SO_4	70	1	9	3.4	4.0

4 PHOTO-PSCHORR REACTION[30]

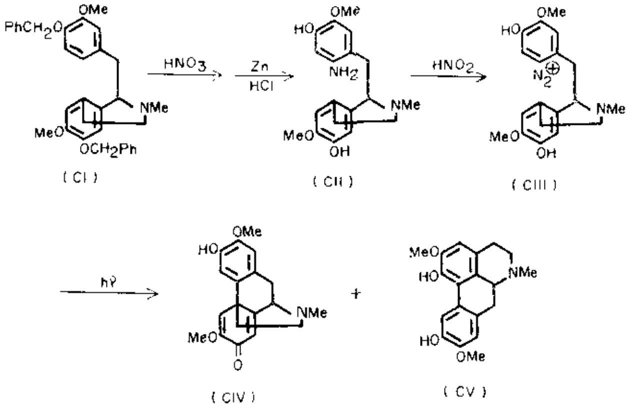
The Pschorr reactions, as utilized in the previous section for the synthesis of morphinandienones and homomorphinandienones, probably involved the ionic intermediates (XCVII and XCVIII) according to an aromatic S_N1 type mechanism. On the other hand, Osbond[31] carried out this type of reaction by decomposing a diazonium salt (XCVI) in the presence of a metal and mineral acid. Since this modification probably proceeds in a reductive manner whereby an aromatic cation, such as XCVII, generates the aromatic radical (XCIX) which then cyclizes to afford the dienone (C), it could be assumed that photolysis of a diazonium salt is a more efficient way of effecting homolysis of carbon-nitrogen bond to form the postulated radical intermediate.

Chart 22



In order to test the validity of the above assumption, a model experiment was carried out by the photolysis of the readily accessible diazotized aminoisoquinoline (CII). Nitration of *O*,*O*-dibenzylorientaline (CI) followed by reduction with zinc in hot hydrochloric acid gave 6'-aminoorientaline (CII) whose diazonium salt (CIII) was irradiated in dilute sulfuric acid at 5 - 10° for several hours to afford a separable mixture of the morphinandienone flavinantine (CIV) and the aporphine bracteoline (CV). To prevent dienone-phenol rearrangement of the resulting morphinandienone by $n \longrightarrow \pi^*$ transition, the photolytic reaction was carried out with a Hanovia 450 W mercury lamp surrounded by a pyrex filter to cut off the light below 310 nm and in the presence of a mineral acid to coordinate the nonbonding electron on the carbonyl oxygen.[32]

Chart 23

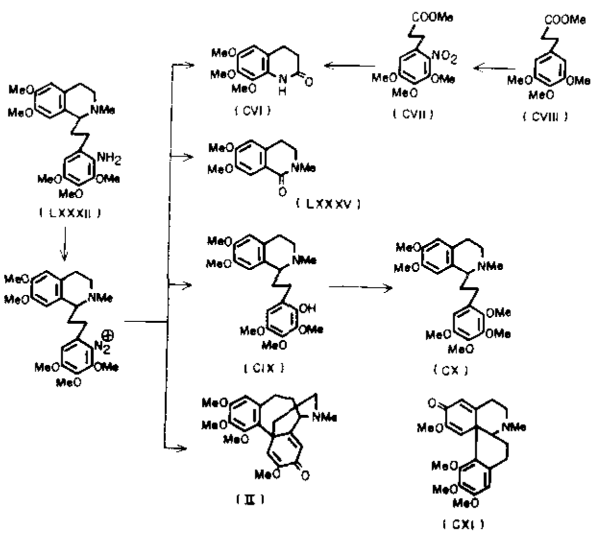


Based on this successful transformation, the photo-Pschorr reaction was used to synthesize homomorphinandienones.[23] Diazotization of the 1-(2-aminophenethyl)isoquinoline (LXXXII) followed by photolysis with a Hanovia 450 W mercury lamp using a pyrex filter at 5 - 10°, gave four compounds after chromatographical separation on silica gel.

The first compound was shown to be 3,4-dihydro-6,7,8-trimethoxycarbostyril (CVI) on the basis of its ir and nmr spectra and also by direct comparison with an authentic sample prepared by the reduction of 3,4,5-trimethoxy-2-nitrophenylpropionate (CVII), obtained from methyl 3,4,5-trimethoxyphenylpropionate (CVIII). The mechanism for the formation of (CVI) remains unclear. The second eluate afforded 3,4-dihydro-6,7-dimethoxy-2-methylisocarbostyril (LXXXV) which was identical in all repects with an authentic sample. The third compound was identified as 1,2,3,4-tetrahydro-1-(2-hydroxy-3,4,5-

trimethoxyphenethyl)-6,7-dimethoxy-2-methylisoquinoline (CIX) on the basis of the following evidence. The mass spectrum indicated the presence of a 1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline system (m/e 206) and a 2-hydroxy-3,4,5-trimethoxybenzyl moiety (m/e 197) with the expected molecular ion (m/e 417). Ir spectroscopy showed the presence of a phenolic isoquinoline; uv spectroscopy confirmed this and indicated that the compound was a 1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline. The nmr spectrum showed the presence of three aromatic protons and also the expected five O-methyl and one N-methyl resonances. O-Methylation gave a hexamethoxyisoquinoline (CX). The fourth compound of molecular formula $C_{22}H_{27}NO_5$ exhibited ir, uv, and mass spectra typical of a cross-conjugated α-methoxycyclohexadienone system. The nmr spectrum showed an N-methyl, an enolic O-methyl, three O-methyl resonances as well as singlets for two olefinic and one aromatic proton and thus data indicated

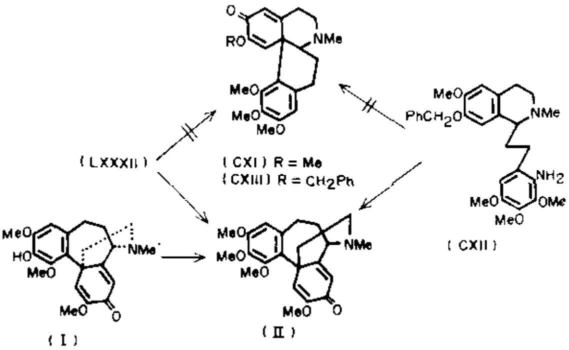
Chart 24



that the fourth compound was the desired O-methylandrocymbine (II). However, since structure (CXI), which could be formed by coupling between the 2'- and 8a-positions, was also consistent with the spectral data, the following experiments were performed in order to rule it out.

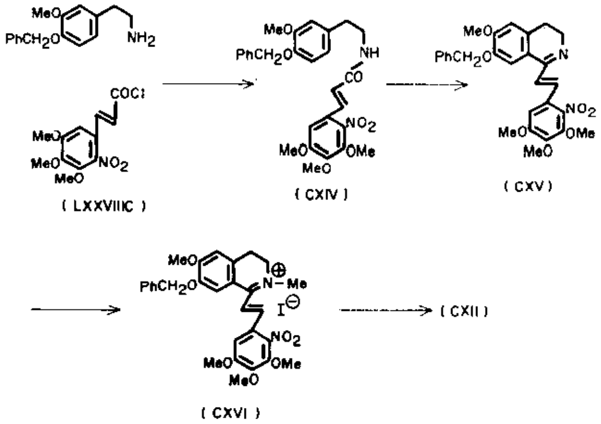
If the fourth product in the above reaction had structure (II), treatment of 1-(2-amino-3,4,5-trimethoxyphenethyl)-7-benzyloxy-1,2,3,4-tetrahydro-6-methoxy-2-methylisoquinoline (CXII) in a similar reaction would also give compound (II); if, however, the product has structure (CXI), the 2'-aminoisoquinoline (CXII) would be converted into the benzyloxy-analog (CXIII) of (CXI). Thus, the photo-Pschorr reaction of (CXII) was examined as follows.

Chart 25



Schotten-Baumann reaction of 4-benzyloxy-3'-methoxyphenethylamine with 3,4,5-trimethoxy-2-nitrocinnamoyl chloride (LXXVIIIc), followed by a Bischler-Napieralski reaction of the resulting amide (CXIV), gave the corresponding 3,4-dihydroisoquinoline (CXV), whose methiodide (CXVI) was reduced to afford the intermediate 2'-aminophenethylisoquinoline (CXII). Diazotization of (CXII) followed by photolysis of the diazonium salt, gave the dienone, spectroscopically identical with the fourth product in the reaction (II); both gave an undepressed mixed melting point. Thus, it has been demonstrated that diazotization and then photolysis of the 2'-aminophenethylisoquinolines (LXXXII) and (CXII) give the homomorphinan-dienone rather than the dienones (CXI) and (CXII).

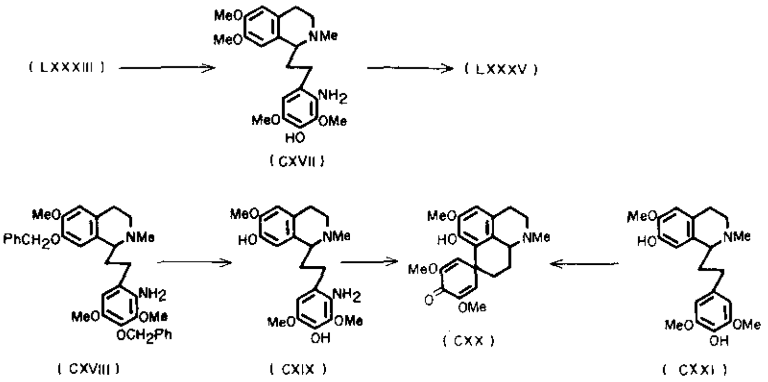
Chart 26



Further, since product (II) was identical by ir and uv with natural O-methyl-androcymbine, prepared from natural androcymbine (I), the total synthesis of O-methylandrocymbine (II) has been achieved and thus confirmed its suggested structure.[32]

The above reaction was also applied to the total synthesis of androcymbine (I). Since the most promising precursor for (I) would be phenolic aminophenethylisoquinolines (CXVII and CXIX), these were subjected to the photo-Pschorr reaction.[33] Irradiation of the diazonium salt obtained by the usual method from (CXVII) which in turn was prepared from the 4'-benzyloxy derivative (LXXXIII), gave only the isoquinolone (LXXXV). On the other hand, diazotization of the diphenolic aminoisoquinoline (CXIX), prepared from (CXVIII), gave the diazonium salt which was photolyzed with a mercury lamp under the same conditions as above to give an unexpected compound, the homoproaporphine (CXX), as the main product. The spectra of (CXX) were superimposable upon those of an authentic sample prepared from the

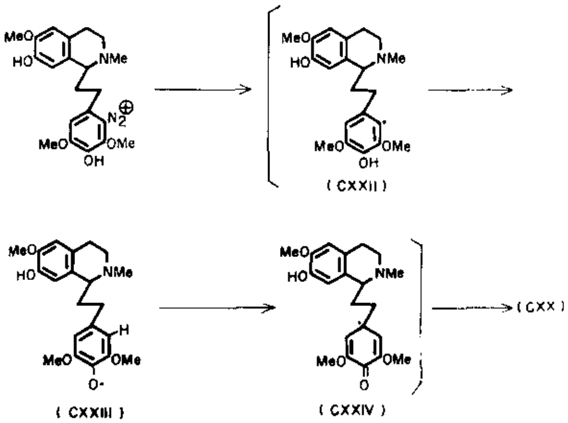
Chart 27



diphenolic isoquinoline (CXXI) by phenol oxidation.

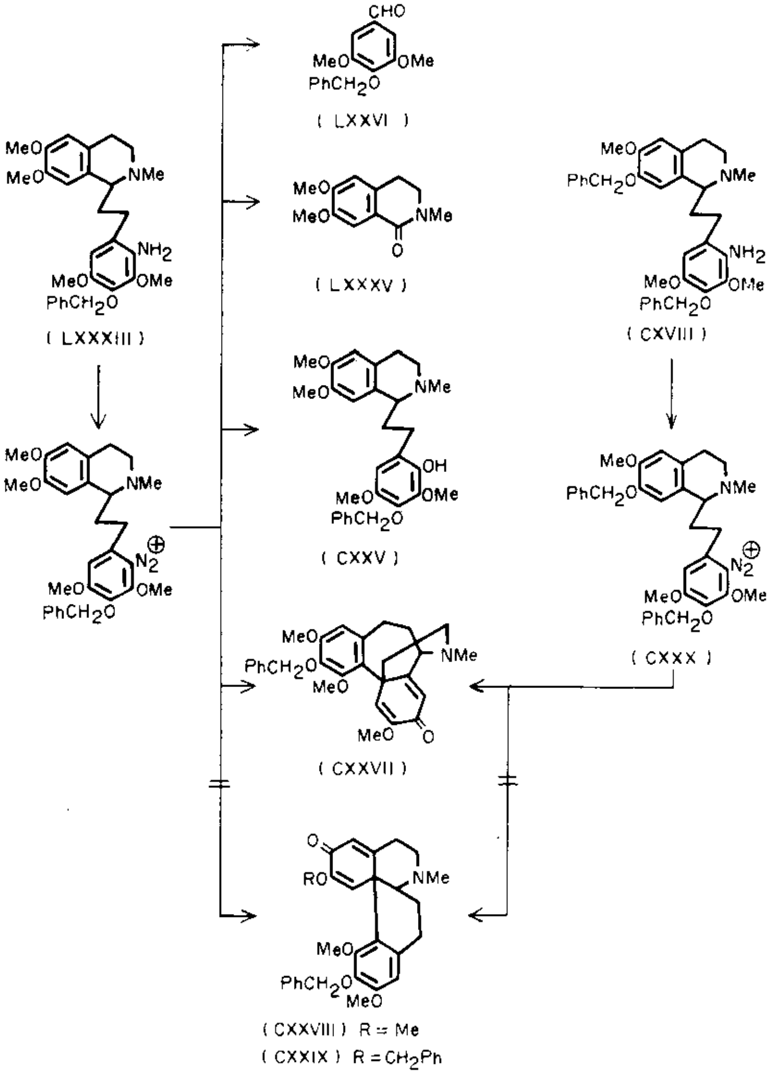
It was evident that the phenolic hydroxy group on the phenethyl residue played an important role in this abnormal reaction since the diazonium salt of the aminoisoquinoline (CXIX), when treated at 5 - 10° for 4 hr in dilute sulfuric acid without irradiation gave no homoproaporphine (CXX). Moreover, the diphenolic isoquinoline (CXIX) was inert to photolysis in the presence of nitrous acid. Therefore, it would appear that the homoproaporphine (CXX) could have been formed via the radical intermediates (CXXII), (CXXIII) and (CXXIV).[34]

Chart 28



Since the phenolic hydroxy group prevents the formation of the homomorphinan-

Chart 29

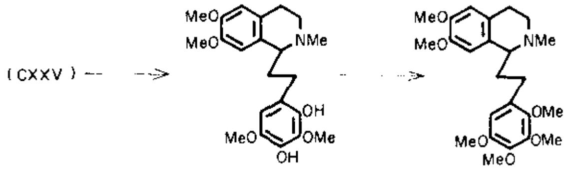


dienone, an indirect method utilizing a protected phenolic hydroxy group was examined by the photo-Pschorr reaction.

Diazotization of the 2'-aminophenethylisoquinoline (LXXXIII) in the usual manner followed by photolysis with a Hanovia 450 W mercury lamp using a pyrex filter at 5 - 10° gave four compounds after separation by silica gel column chromatography.

The first compound was identified as 4-benzyloxy-3,5-dimethoxybenzaldehyde (LXXVI) by direct comparison with an authentic sample. The second eluent afforded 3,4-dihydro-6,7-dimethoxy-2-methylisocarboxtyril (LXXXV) which was identical in all aspects with an authentic sample. The third compound was assigned as 1-(4-benzyloxy-2-hydroxy-3,5-dimethoxyphenethyl)-1,2,3,4-tetrahydro-6,7-dimethoxy-2-methylisoquinoline (CXXV) based on the following evidence. The ir spectrum indicated a phenolic isoquinoline and the uv spectrum showed

Chart 30

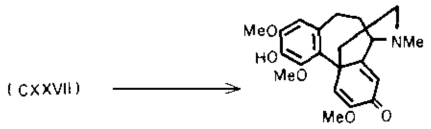


the presence of a 1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline. The nmr spectrum revealed three aromatic protons with one O-benzyl, four O-methyl, and one N-methyl resonances. Debenzylation of (CXXV) followed by O-methylation with diazomethane gave 1,2,3,4-tetrahydro-6,7-dimethoxy-1-(2,3,4,5-tetramethoxyphenethyl)-2-methylisoquinoline which was identical with an authentic sample.

The fourth compound had the molecular formula $C_{28}H_{31}NO_5$ by mass spectrometry and showed the typical cross-conjugated α-methoxycyclohexadienone system by ir and uv. The nmr spectrum showed an N-methyl, three O-methyls, and the methylene of one benzyloxy group as well as two olefinic and one aromatic protons. Accordingly, the structure could be either the desired O-benzylandrocymbine (CXXVII) or (CXVIII), however, the latter possibilities was ruled out by the following evidence.

If the structure of the dienone was (CXXVIII), the products from the amino-

Chart 31

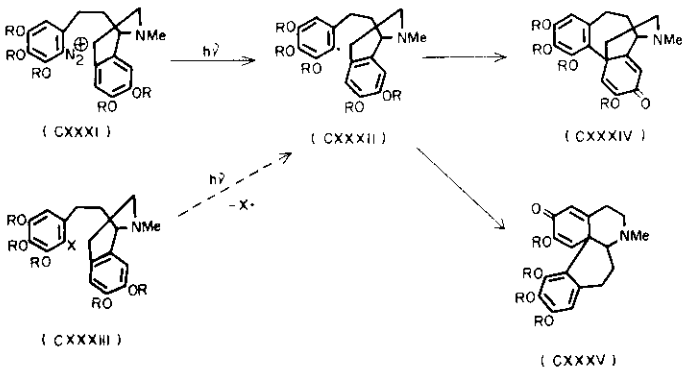


isoquinoline (LXXXIII) and (CXVIII) should be different. However, diazotization of (CXVIII), followed by photolysis of the diazonium salt (CXXX) in a manner similar to the above, gave the same dienone (CXXVII) obtained from CXXXIII. Thus, it was apparent that in both cases intramolecular reaction had occurred between the 2' and 4a position in the isoquinoline skeleton. Finally, debenzylation of (CXXVII) gave (±)-androcymbine (I) identical in ir, uv, and nmr with the natural alkaloid from Androcymbium melanthioides var. stirica.[34]

5 PHOTOLYTIC CYCLODEHYDROHALOGENATION[30]

The formation of homomorphinandienone ring system by a photo-Pschorr reaction suggested the potential utility of photolytic cyclodehydrohalogenation in the synthesis of androcymbine (I) and related compounds. Since the key intermediate in the photo-Pschorr reaction of the diazonium salt (CXXXI) is probably the aromatic radical (CXXXII), it appeared likely that the latter could be generated

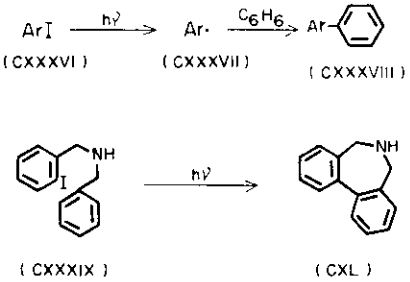
Chart 32



by radical formation at the $C_{2'}$-halo-substituted isoquinoline (CXXXIII) to also afford the homomorphinandienone (CXXXIV) although the formation of the second dienone (CXXXV), formed by coupling between $C_{2'}$ and C_{8a} is also possible.

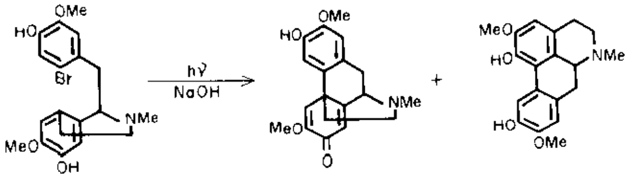
The rationale for this approach was based on the known behavior of aromatic halides on photolysis.[35] For example, photolysis of the simple aromatic halide (CXXXVI) effects homolytic cleavage of the carbon-halogen bond via the aryl radical (CXXXVII) to afford the biphenyl derivative (CXXXVIII). Similarly, since substituted aromatic halides, such as CXXXIX, are known to react by intramolecular cyclization to give the benzazepine (CXL), this model was explored as a route for the synthesis of homomorphinandienones.

Chart 33



In the initial studies, the irradiation of the readily accessible 6'-bromoorientaline (CXLI) was carried out as a model experiment with a Hanovia 450 W mercury lamp using a pyrex filter in the presence of an excess of sodium hydroxide for 7 hr at room temperature to afford the morphinandienone flavinantine (CIV) and the aporphine bracteoline (CV).[36]

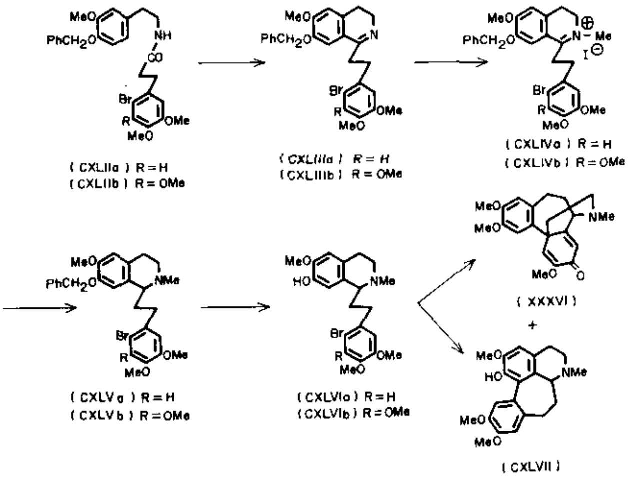
Chart 34



(CXLI) (CIV) (CV)

Based on this finding, the synthesis of homomorphinandienone was investigated as follows. Since the formation of a seven-membered ring system by a radical coupling reaction is not facile, the preliminary experiment was carried out by using easily available materials. For this purpose the phenolic 2'-bromoisoquinoline (CXLVIa) was synthesized from 2-bromo-4,5-dimethoxyphenylpropionic acid and 4-benzyloxy-3-methoxyphenethylamine in the usual manner as shown in a following chart.

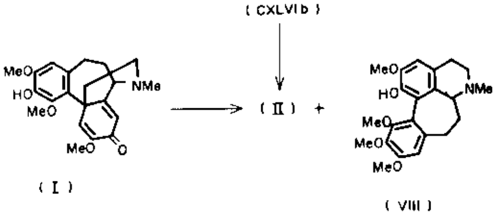
Chart 35



Irradiation of CXLVIa with a Hanovia 450-W merucry lamp surrounded by a pyrex filter in aqueous ethanolic sodium hydroxide solution at room temperature for 7 hr gave two compounds which were obtained by silica gel column chromatography. The first compound, characterized as its methiodide, was identified as the homomorphinandienone (XXXVI) by comparison of its spectroscopic data with an authentic sample. The second compound, $C_{21}H_{25}NO_4$, m/e 355 (M^+), showed a typical homoaporphine system in its uv spectrum (λ_{max} 262.5 and 290 nm), supported by an ion at m/e 388 (M^+ - OH, base peak) and also by its nmr spectrum showing three aromatic protons at δ 6.57, 6.73, and 7.18 ppm, and was therefore assigned as 1-hydroxy-2,10,11-trimethoxyhomoaporphine (CXLVII).

Thus, a new synthetic route was developed to the homomorphinandienone and homoaporphine type compounds which have the basic skeleton of the alkaloids found in *Liliaceae* species. The above synthesis of homomorphinandienones and homoaporphines should function, in principle, also with 1-(2-bromo-3,4,5-trimethoxyphenyl)-1,2,3,4-tetrahydro-7-hydroxy-6-methoxy-2-methylisoquinoline (CXLVIb), thus leading to the total synthesis of (±)-*O*-methylandrocymbine (II) and (±)-kreysigine (VIII).

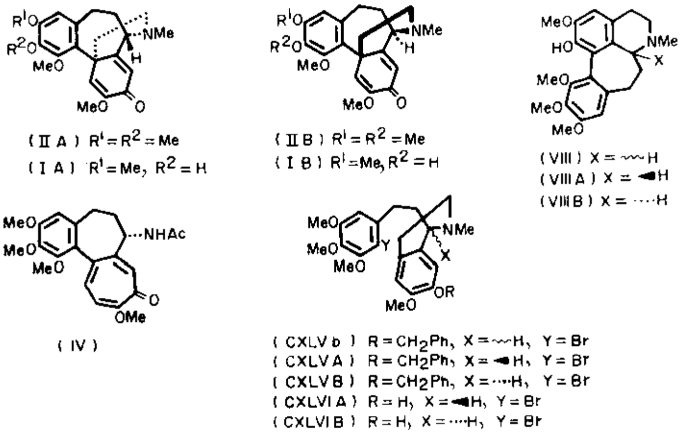
Chart 36



The precursor phenolic isoquinoline (LXLVIb) was synthesized from 2-bromo-3,4,5-trimethoxyphenylpropionic acid by standard methods. Photolysis of CXLVIb under conditions similar to the reaction of CXLVIa, yielded two compounds in addition to the starting material.[37] The first one was identical with *O*-methylandrocymbine (II) while the second compound, which showed the same molecular formula, $C_{22}H_{27}NO_5$, as *O*-methylandrocymbine, was identified as (±)-kreysigine (VIII), an alkaloid found in *Kreysigia multiflora*, by comparison of its spectroscopic data with those of an authentic sample prepared by a photo-Pschorr reaction. Moreover, the total synthesis of (-)-*O*-methylandrocymbine (IIA), (-)-

kreysigine (VIIIA), and their optical antipodes (IIB) and (VIIIB) was accomplished by applying this method[38] to the optically active 2'-bromophenethylisoquinolines (CXLVIA and B).

Chart 37



(IIA) $R^1 = R^2 = Me$
(IA) $R^1 = Me$, $R^2 = H$

(IIB) $R^1 = R^2 = Me$
(IB) $R^1 = Me$, $R^2 = H$

(VIII) X = ∼H
(VIIIA) X = ◀H
(VIIIB) X = ···H

(IV)

(CXLVb) R = CH_2Ph, X = ∼H, Y = Br
(CXLVA) R = CH_2Ph, X = ◀H, Y = Br
(CXLVB) R = CH_2Ph, X = ···H, Y = Br
(CXLVIA) R = H, X = ◀H, Y = Br
(CXLVIB) R = H, X = ···H, Y = Br

The (±)-2'-bromophenethylisoquinoline (CXLVb) was readily resolved with di-p-toluoyltartaric acid. The (-)-antipode (CXLVA), obtained from the (-)-di-p-toluoyltartrate, showed two positive Cotton effects at 290 and 250 nm and the (+)-base (CXLB), recovered from the (+)-di-p-toluoyltartrate, showed two negative Cotton effects at the same positions (Figure 1). It has been reported that in 1-phenethyltetrahydroisoquinoline derivatives, the S-series show two positive Cotton effects at 290 and 245 nm, whereas the R-series have double negative curves. It was therefore expected that the (-)-base (CXLVA) (S-configuration) would be converted into (-)-O-methylandrocymbine (IIA), whereas the (+)-isomer (CXLVB) (R-configuration) would give the optical antipode (IIB) of natural O-methylandrocymbine and (-)-kreysigine (VIIIA).

The (-)-2'-bromophenethylisoquinoline (CXLVA) was debenzylated with ethanolic hydrochloric acid and the resulting phenolic bromoisoquinoline (CXLVIA) in ethanol was irradiated with a Hanovia 450 W mercury lamp (pyrex filter) at room temperature for 7 hr to give (-)-O-methylandrocymbine (IIA) and (+)-kreysigine (VIIIB). The (+)-2'-bromophenethylisoquinoline (CXLVB) was similarly converted into (+)-O-methylandrocymbine (IIB) and (-)-kreysigine (VIIIA).

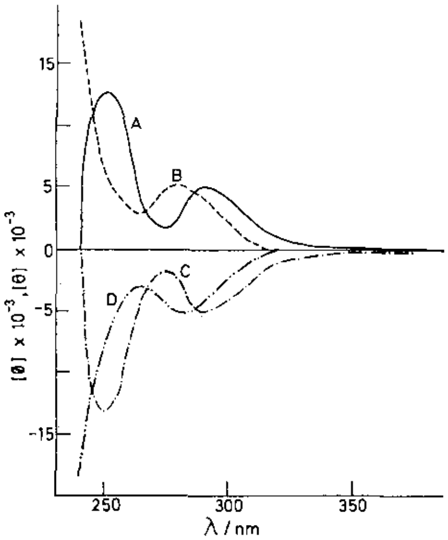


Figure 1 O.r.d. (A) and c.d. (B) curves of compound (CXLVA) and o.r.d. (C) and c.d. (D) curves of compound (CXLVB) (in methanol)

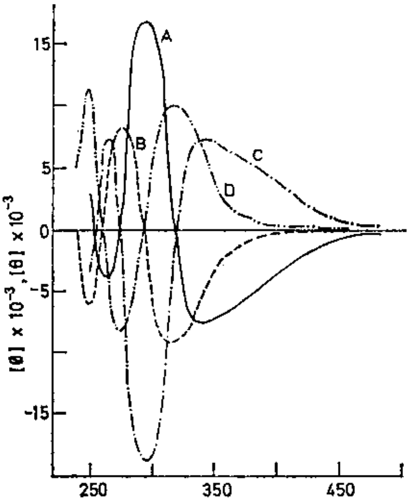


Figure 2 O.r.d. (A) and c.d. (B) curves of (–)-O-methylandrocymbine (IIA) and o.r.d. (C) and c.d. (D) curves of (+)-O-methylandrocymbine (IIB) (in methanol)

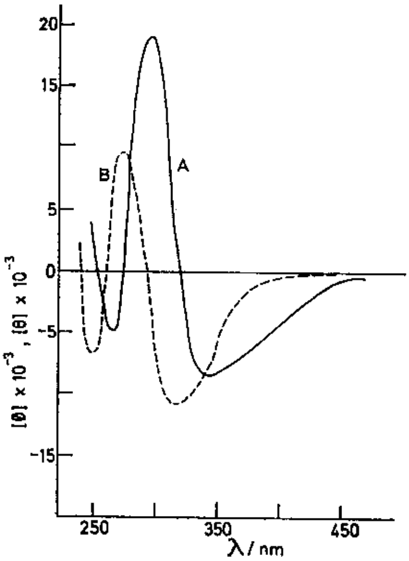


Figure 3 O.r.d. (A) and c.d. (B) curves of natural O-methylandrocymbine (in methanol)

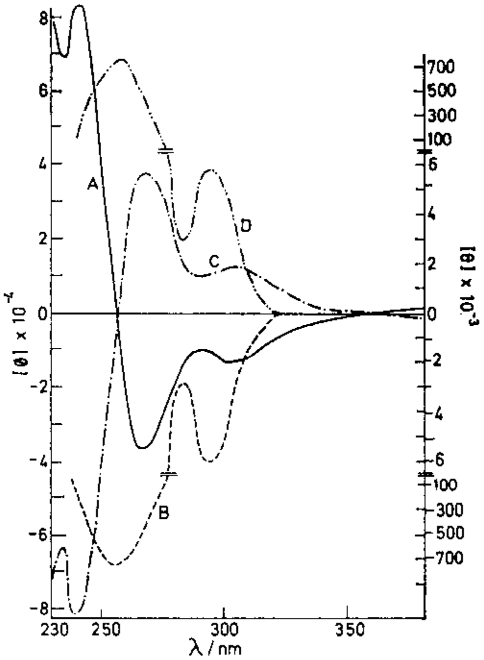
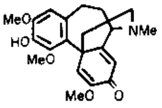


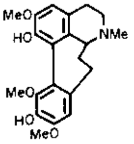
Figure 4 O.r.d. (A) and c.d. (B) curves of (+)-kreysigine (VIIIB) and o.r.d. (C) and c.d. (D) curves of (-)-kreysigine (VIIIA) (in methanol)

Both (-)-enantiomeric compounds were shown to be identical with O-methyl-

Chart 38



(I)



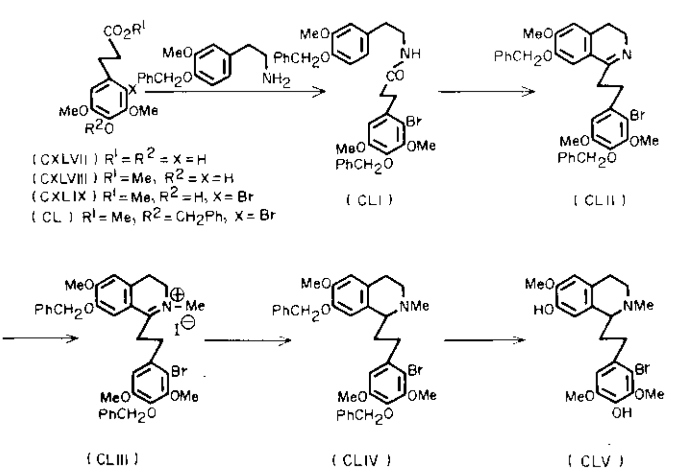
(VII)

androcymbine derived from natural androcymbine and with kreysigine prepared by photo-Pschorr reaction, respectively, by spectral comparisons.

The total syntheses of $(\pm)$-androcymbine (I) and $(\pm)$-multifloramine (VII) by photolysis of the 1-(2-bromophenethyl)isoquinoline (CLV) were also obtained as follows.[39]

The starting material (CLV) was synthesized by esterification of 4-hydroxy-3,5-dimethoxyphenylpropionic acid (CXLVII) to give the ester (CXLVII) which was brominated to furnish methyl 2-bromophenylpropionate (CXLIX). Benzylation of (CXLIX) afforded the benzyl compound (CL), which was converted into the amide (CLI) by fusion with 4-benzyloxy-3-methoxyphenethylamine. Bischler-Napieralski cyclization of (CLI) gave the 3,4-dihydroisoquinoline (CLII) whose methiodide (CLIII) was treated with sodium borohydride to afford the bromophenethyl-1,2,3,4-tetrahydro-2-methylisoquinoline (CLIV) followed by debenzylation with hydrochloric acid in boiling ethanol to give the diphenol CLV.

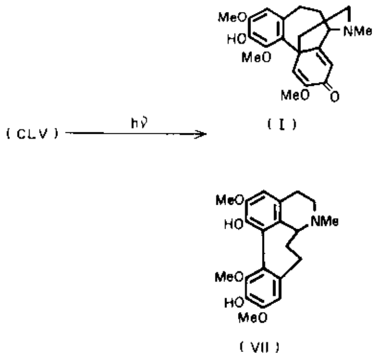
Chart 39



Irradiation of (CLV) with a Riko 400 W mercury lamp (pyrex filter) was carried out in aqueous alcoholic solution in the presence of sodium hydroxide and sodium iodide at room temperature with stirring for 8 hr to give (±)-androcymbine (I), characterized as its methiodide. The structure of this compound was confirmed by comparison (ir, uv, and nmr spectra) with natural androcymbine.

However, when the foregoing photolysis was done without sodium iodide, it afforded only (±)-multifloramine (VII).

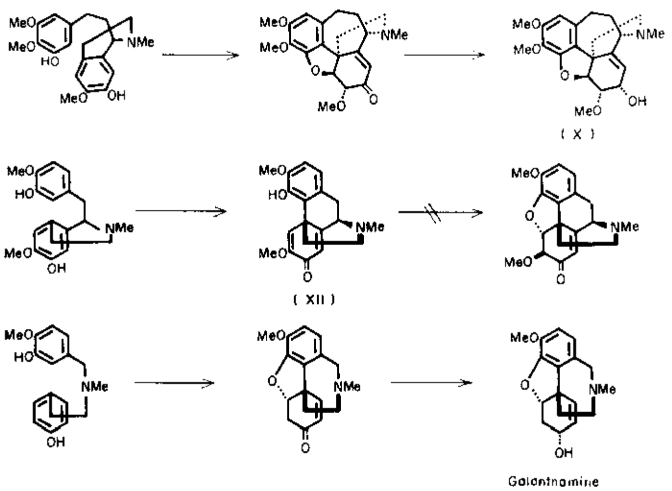
Chart 40



From a biogenetic viewpoint kreysiginine (X) is the most interesting structure in the phenethylisoquinoline series, since its synthesis would involve the reaction of an oxygenated function at the 7-position of a precursor to form an oxygen bridge. In contrast to the situation which occurs in the biogenesis of morphine where salutaridine (XII) does not undergo oxygen bridge formation, such a reaction would be similar to the biogenetic methanism for galanthamine (see following

Chart).

Chart 41

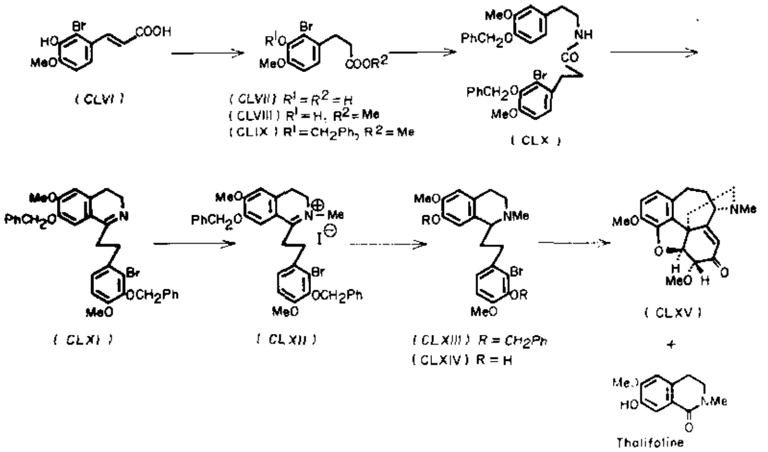


In order to investigate whether oxygen bridge formation would occur with retention of the oxygen function at the 7-position, the synthesis of a kreysiginine-type compound from 1-(2-bromo-3-hydroxy-4-methoxyphenethyl)-1,2,3,4-tetrahydro-7-hydroxy-6-methoxy-2-methylisoquinoline (CLXIV) by photolytic reaction was investigation.

The required starting bromophenol (CLXIV) was synthesized as follows. 2-Bromo-3-hydroxy-4-methoxycinnamic acid (CLVI), obtained from 2-bromoisovanilin, was hydrogenated over platinum oxide to give 2-bromo-3-hydroxy-4-methoxyphenylpriopionic acid (CLVII), which was esterified, benzylated and then condensed with 4-benzyloxy-3-methoxyphenethylamine to afford the amide (CLX). Bischler-Napieralski reaction of CLX gave the corresponding dihydroisoquinoline

(CLXI) which was converted into its methiodide (CLXII) and reduced with sodium borohydride to give the 1,2,3,4-tetrahydro-2-methylisoquinoline derivative (CLXIII) followed by debenzylation with alcoholic hydrochloric acid to yield 1-(2-bromo-3-hydroxy-4-methoxyphenethyl)-1,2,3,4-tetrahydro-7-hydroxy-6-methoxy-2-methylisoquinoline (CLXIV).

Chart 42



The bromophenolic isoquinoline (CLXIV) was irradiated for 7 hr in the presence of sodium hydroxide and sodium iodide (Riko 400 W mercury lamp using pyrex filter) to give two compounds, in addition to a major amount of starting material.[19] The first was the cleavage product thalifoline whose structure was assigned by spectral comparison with an authentic sample. The second product had a molecular formula $C_{20}H_{23}NO_4$ (by mass spectrum and methiodide microanalysis) whose ir spectrum contained bands at 1685 and 1630 cm^{-1} but no hydroxy group absorption. The enone system was also indicated by a uv band at 299 nm. Moreover, th nmr spectrum showed two coupled methine protons (revealed by decoupling experiments) at 4.63 and 4.89 in addition to an olefinic proton at 5.89, two aromatic protons at 6.70, two *O*-methyls at 3.86 and 3.62, and one *N*-methyl resonance at 2.69 ppm. The coupling constant (*J* 9.5 Hz) indicated that both protons should be located in *vicinal* and *trans* configuration. These facts indicate that ring closure to the enone has taken place so that the second product can be assigned as the kreysiginine-type structure (CLXV). Based on this finding, it would appear that this method should provide an efficient route to the synthesis of kreysiginine (X).

REFERENCES

1 T. Kametani, "The Chemistry of the Isoquinoline Alkaloids", Hirokawa Publishing Co. Inc., Tokyo and Elsevier Publishing Co., Amsterdam, 1968, pp. 222 and 258.

2 M. Shamma, "The Isoquinoline Alkaloids", Academic Press, New York, 1972, pp. 458, 465, and 469.

3 J. Herbek, Jun, and F. Šantavý, *Coll. Czech. Chem. Comm.*, 1962, **27**, 255.

4 J. M. Watt and M. G. Vreyer-Brandwijk, "Medicinal and Poisonous Plants of Southern and Eastern Africa", Levingstone, Edinburgh, 1962, 2nd Ed., p. 687.

5 A. R. Battersby, R. B. Herbert, L. Pijewska, and F. Šantavý, *Chem. Comm.*, 1965, 228.

6 A. R. Battersby, R. B. Herbert, L. Pijewska, F. Šantavý, and P. Sedmera, *J. Chem. Soc. Perkin I*, 1972, 1737.

7 A. R. Battersby, R. B. Herbert, and F. Šantavý, *Chem. Comm.*, 1965, 415.

8 A. R. Battersby, R. B. Herbert, L. Mo, and F. Šantavý, *J. Chem. Soc. (C)*, 1967, 1736.

9 A. R. Battersby, R. Ramage, A. F. Cameron, C. Hannaway, and F. Šantavý, *J. Chem. Soc. Perkin I*, 1971, 3514.

10 A. R. Battersby, R. B. Herbert, E. McDonald, R. Ramage, and J. H. Clements, *J. Chem. Soc. Perkin I*, 1972, 1741, and refs. cited therein.

11 G. M. Badger and R. B. Bradbury, *J. Chem. Soc.*, 1960, 445.

12 A. R. Battersby, R. B. Bradbury, R. B. Herbert, M. H. G. Munro, and R. Ramage, *Chem. Comm.*, 1967, 450.

13 A. R. Battersby, M. H. G. Munro, R. B. Bradbury, and F. Santavý, *Chem. Comm.*, 1968, 695; J. Friedrichson, M. F. Mackay, and A. McL. Mathieson, *Tetrahedron Lett.*, 1968, 2887; N. K. Hart, S. R. Johns, J. A. Lamberton, and J. K. Saunders, *Tetrahdron Lett.*, 1968, 2891.

14 S. R. Johns, J. A. Lamberton, and A. A. Sioumis, *Austral. J. Chem.*, 1969, **22**, 2219.

15 R. Ramage, *Ann. Reports (J. Chem. Soc.)*, 1967, **64**, 515.

16 A. R. Battersby in, "Oxidative Coupling of Phenols", ed. W. I. Taylor and A. R. Battersby, Marcel Dekker, New York, 1967.

17 T. Kametani and K. Fukumoto, "Phenol Oxidation", Gihodo, Tokyo, 1970.

18 T. Kametani, K. Fukumoto, M. Koizumi, and A. Kozuka, *Chem. Comm.*, 1968, 1605; *J. Chem. Soc. (C)*, 1969, 1295.

19 T. Kametani, T. Kohno, R. Charubala, and K. Fukumoto, *Tetrahedron*, 1972, **28**, 3227.

20 T. Kametani, H. Yagi, F. Satoh, and K. Fukumoto, *J. Chem. Soc. (C)*, 1968, 271.

21 A. R. Battersby, E. McDonald, M. H. G. Munro, and R. Ramage, *Chem. Comm.*, 1967, 934.

22 T. Kametani and K. Fukumoto, *J. Heterocyclic Chem.*, 1971, **8**, 341.

23 D. F. DeTar, *Organic Reactions*, 1957, **9**, 409; M. Shamma and W. A. Slusarchyk, *Chem. Rev.*, 1964, **64**, 59.

24 R. Grewe and A. Mondon, *Ber.*, 1948, **81**, 279.

25 T. Kametani, K. Fukumoto, F. Satoh, and H. Yagi, *Chem. Comm.*, 1968 1398; *J. Chem. Soc. (C)*, 1969, 520.

26 T. Kametani, M. Koizumi, and K. Fukumoto, *Chem. and Pharm. Bull. (Japan)*, 1969, **17**, 1809.

27 T. Kametani, K. Fukumoto, F. Satoh, and H. Yagi, *Chem. Comm.*, 1968, 1001; *J. Chem. Soc. (C)*, 1968, 3084.

28 S. Sugasawa and H. Yoshikawa, *J. Pharm. Soc. Japan*, 1934, **54**, 305.

29 T. Kametani, K. Takahashi, T. Sugahara, M. Koizumi, and K. Fukumoto, *J. Chem. Soc. (C)*, 1971, 1032.

30 T. Kametani and K. Fukumoto, *Accounts Chem. Res.*, 1972, **5**, 212.

31 B. Gregson-Allcott and J. M. Osbond, *Tetrahedron Lett.*, 1969, 1771.

32 T. Kametani, H. Sugi, S. Shibuya, and K. Fukumoto, *Chem. and Pharm. Bull. (Japan)*, 1971, **19**, 1513; *Tetrahedron*, 1971, **27**, 5376.

33 T. Kametani, M. Koizumi, and K. Fukumoto, *Chem. Comm.*, 1970, 1157; *J. Chem. Soc. (C)*, 1971, 1792; T. Kametani, M. Koizumi, K. Shishido, and K. Fukumoto, *J. Chem. Soc. (C)*, 1971, 1923.

34 T. Kametani, M. Koizumi, and K. Fukumoto, *J. Org. Chem.*, 1971, **36**, 3729.

35 R. K. Sharma and N. Kharasch , *Angew. Chem.*, 1968, **80**, 69.

36 T. Kametani, S. Shibuya, H. Sugi, O. Kusama, and K. Fukumoto, *J. Chem. Soc. (C)*, 1971, 2447.

37 T. Kametani, Y. Satoh, S. Shibuya, M. Koizumi, and K. Fukumoto, *J. Org.*

Chem., 1971, **36**, 3733.

38 T. Kametani, Y. Satoh, and K. Fukumoto, *J. Chem. Soc. Perkin I*, 1972, 2160.

39 T. Kametani and M. Koizumi, *J. Chem. Soc. (C)*, 1971, 3976.

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