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Synthesis of Bisbenzylisoquinoline Alkaloids

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Methods for the synthesis of bisbenzylisoquinoline alkaloids and also 1-benzylisoquinoline bases, which are biogenetic precursors of the dimeric alkaloids, are surveyed in the biogenetic sequence of the alkaloids. Not only total but also partial and biomimetic syntheses of bisbenzylisoquinoline bases are covered. A list of 153 references is included.

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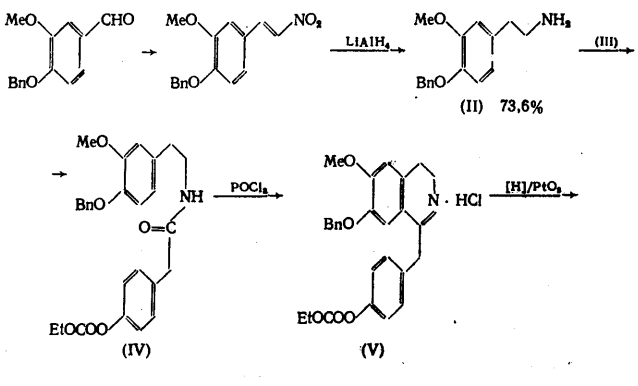
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I. INTRODUCTION

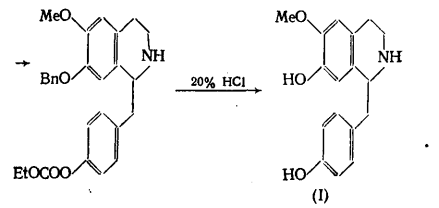
Bisbenzylisoquinoline alkaloids form a large group (>150) of naturally occurring compounds in which two benzylisoquinoline moieties are joined by one, two, or three ether links. More rarely a diphenylated carbon–carbon bond is encountered. The number and positions of the ether links are used to classify these alkaloids[1], and this classification has great value for the choice of method of synthesis. During recent years great attention has been paid to these alkaloids in connection with the discovery of their great and diverse biological activity—antitubercular, anti-inflammatory, antitumour, etc. (see reviews[2–4]).

II. SYNTHESIS OF COCLAURINE AND ITS DERIVATIVES

Since coclaurine (I) and its derivatives accompany bisbenzylisoquinoline alkaloids in plants, besides being precursors and also structural fragments, their synthesis is a necessary stage in obtaining the dimeric alkaloids. The method of synthesising coclaurine suggested originally consists in the condensation of *p*-benzyloxy-*m*-methoxyphenethylamine (II) with *p*-chloroformylphenyl ethyl oxalate (III), Bischler–Napieralski cyclisation of the resulting amide (IV) to give the dihydroisoquinoline derivative (V), reduction of the double bond over platinum dioxide, and removal of the protective groups by acid hydrolysis[5]:†



† Here and subsequently the abbreviations Me = CH_3, Et = C_2H_5, and Bn = $C_6H_5CH_2$ are employed.



This scheme has since been only slightly modified. For example, racemic coclaurine has been synthesised via the corresponding dibenzyl derivative, with the free amine (II) replaced by its *N*-formyl derivative[6]; the double bond in the dihydroisoquinoline derivative is then reduced with zinc dust in acetic acid. It has also been proposed[7] to use homovanillylamine for condensation with the acid component followed by temporary protection of the phenolic hydroxyl in the resulting amide by acetylation, which makes it possible to have fewer stages and increase the overall yield of coclaurine.

Several coclaurine derivatives—intermediates in the synthesis of bisbenzylisoquinoline alkaloids—have been synthesied similarly[8–10]. The initial amines are obtained by reducing the corresponding nitrostyrenes with lithium tetrahydroaluminate[5,11], over palladium–carbon to the oxime and then over platinum dioxide to the amine[5] or over palladium black to homovanillylamine[12]. It has been proposed[13,14] to reduce an unsubstituted or a substituted nitrostyrene with amalgamated zinc dust in acid. The reduction of *p*-benzyloxy-*m*-methoxyphenylacetonitrile with lithium tetrahydroaluminate has been described[15]. Cyclisation to dihydroisoquinoline is effected with phosphoryl chloride in various solvents, e.g. toluene[5], chloroform[6,15], or acetonitrile[16], in the last of which a good yield was obtained. Phosphorus pentachloride[15] and other phosphorus compounds, such as polyphosphoric acid and phosphorus pentoxide[17], have also been used as condensing agents.

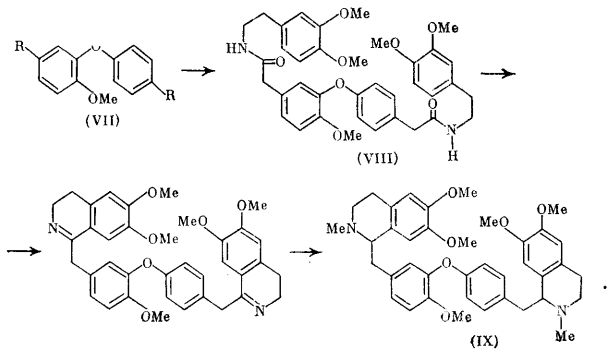
The synthesis of (±)-coclaurine has been accomplished also by Arndt–Eistert condensation of a 4-methylsulphonyloxy-ω-diazoketone with (II) to give the corresponding amide[18].

(±)-*N*-Methylcoclaurine has been obtained by the methylation of coclaurine with formaldehyde and formic acid[19], and also by reduction of the urethane derivative of dibenzylcoclaurine with lithium tetrahydroaluminate followed by hydrogenolysis[20]. Resolution of *N*-methylcoclaurine into optical antipodes was achieved by means of (+)- and (−)-di-*p*-tolyltartaric acids[21]. (±)-Armepavine and its derivatives have been resolved similarly[22,23].

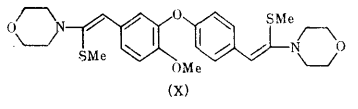
III. SYNTHESIS OF BISBENZYLISOQUINOLINE ALKALOIDS CONTAINING ONE DIPHENYL ETHER LINK

The simplest bisbenzylisoquinoline alkaloids are bases of monoether type—magnoline and dauricine—at which were aimed the first synthetic attempts. There exist two fundamental synthetic routes to such alkaloids—(*a*) from substituted diphenyl ethers by the addition of appropriate isoquinoline fragments using known methods and (*b*) by linking substituted benzylisoquinoline bases by means of ether bridges.

The first attempt to synthesise a bisbenzylisoquinoline alkaloid was made in 1935,[24] when a scheme was worked out for obtaining *O*-methyldauricine (IX)# via the intermediate 4-methoxy-3-phenoxybenzene-1,4'-dicarboxylic acid (VII: R =COOH), which was converted into the acid chloride, aldehyde, azlactone, and then the bisacetic acid (VII: R = CH_2. .COOH); the isoquinoline fragments were obtained by Bischler–Napieralski cyclisation of the corresponding bishomoveratrylamides (VIII) with subsequent conversion into the tetrahydro-*N*-methylisoquinoline derivative by the usual method:



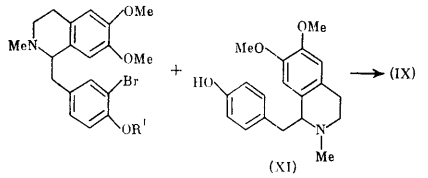
Since, however, the required compound was non-crystalline, it was converted into a methine base identical with the compound obtained from the natural alkaloid[24]. This scheme was subsequently improved by modifying the method of obtaining the initial acid (VII: R = CH_2COOH): *o*-methoxydiphenyl ether was chloromethylated, the halogen atom replaced by a cyano-group, and the latter was hydrolysed[28]; alternatively the corresponding diacetyl derivative was subjected to the Willgerodt–Kindler reaction, and the resulting bisthiomorpholide was hydrolysed[29]. The intermediate bisamide (VIII) has been obtained also by condensing homoveratrylamine with the bisenaminothioether structure[30]



Application of this scheme to the benzylated diacid gave a diastereomeric dauricine mixture[31]. Another scheme for the synthesis of (±)-dauricine was based on the Arndt–Eistert reaction of a bisdiazoketone with homoveratrylamine[32,33], which also gave a diastereomeric racemic mixture.

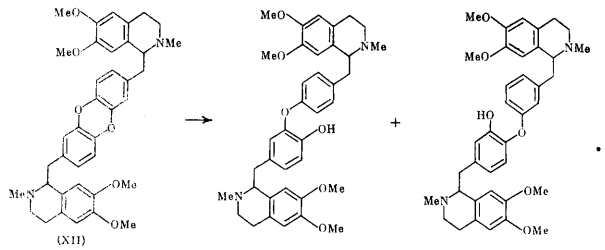
O-Methyldauricine was originally obtained by methylating natural dauricine with diazomethane. It was first detected in plant sources (*Colubrina asiatica*, etc.) only in 1970.[25–27]

Racemic magnoline was synthesised from appropriate benzyl or ethoxycarbonyl derivatives of the acid (VII).[34–36] In view of the difficulties encountered in removing the benzyl group, preference was given to the ethoxycarbonyl group. A diastereomeric mixture of (±)-cuspidaline was synthesised similarly[37,38]. A different route—condensation of (–)-armepavine with (–)-1-*m*-bromo-*p*-methoxybenzyl-1,2,3,4-tetrahydro-6,7-dimethoxy-2-methylisoquinoline, obtained by the bromination of armepavine (XI)—was used to synthesised *O*-methyldauricine in 24% yield[39]:



(±)-Dauricine[31,40,41], daurinoline[42], magnoline[43], (±)-magnoline[44], and berbamunine[45] have been obtained by the same synthetic method.

Dauricine is formed, together with an isomer differing in the position of the ether link, when the dibenzodioxin ring of compound (XII) undergoes fission in the presence of sodium in liquid ammonia[46]:

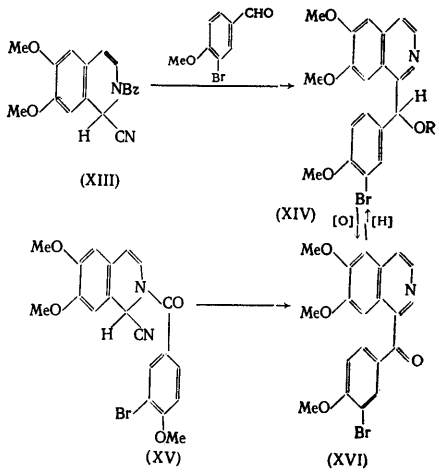


The intermediate (XII) was synthesised from the corresponding diacetyldibenzodioxin via the stages of bisthiomorpholide, diacid, diamide, bisdihydrosioquinoline derivative, and dihydric secondary base.

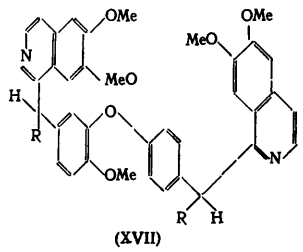
Dauricine has been obtained, in low yield, also by selective demethylation with butylmagnesium bromide of the methoxy-group in the diphenyl ether portion of *O*-methyldauricine[47].

An original sythesis of *O*-methyldauricine[48,49] consisted in reaction between 2-benzoyl-1,2-dihydro-6,7-dimethoxyisoquinolyl cyanide (Reissert's compound, XIII) and *m*-bromo-*p*-methoxybenzaldehyde, hydrolysis of the resulting *O*-benzoyl derivatives (XIV: R = C_6H_5CO) to the carbinol (XIV: R = H) in 87% yield, and reduction of this product with zinc dust in hydrobromic acid to 1-*m*-bromo-*p*-methoxybenzyl-6,7-dimethoxyisoquinoline (yield 78%), whose methiodide was reduced with sodium tetrahydroborate to 1-*m*-bromo-*p*-methoxybenzyl-1,2,3,4-tetrahydro-6,7-dimethoxy-2-methylisoquinoline and then condensed with (±)-armepavine, as mentioned above; in a modification of this synthesis 1-*m*-bromo-*p*-methoxybenzoyl-1,2-dihydro-6,7-dimethoxyisoquinolyl cyanide (XV) was converted into 1-*m*-bromo-*p*-methoxybenzoyl-6,7-dimethoxyisoquinoline (XVI) in the presence of sodium hydride in dimethylformamide (yield 49%)

and then reduced to the carbinol with sodium tetrahydroborate:

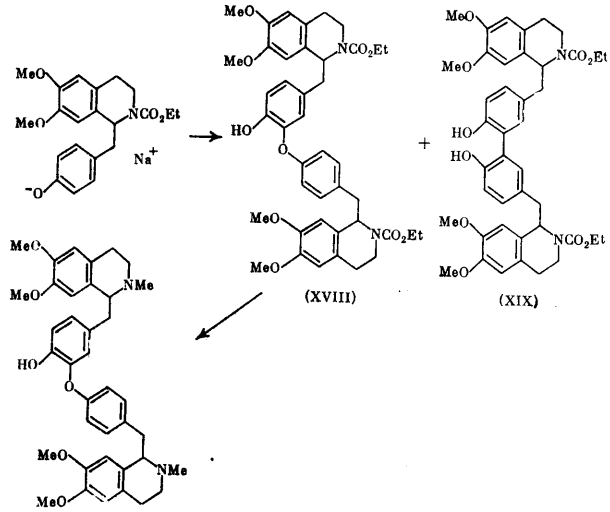


A shorter synthetic route to (±)-*O*-methyldauricine involves condensation of the diphenyl ether (VII: R = CHO) with Reissert's compound to give the bisisoquinoline base

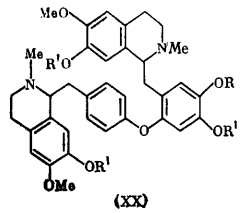


with $R = C_6H_5COO$ in 83% yield. The latter was hydrolysed with aqueous–alcoholic alkali to the diol (XVII: R = OH), which was reduced with zinc dust in a mixture of hydrobromic and acetic acids to give a 91% yield of a product from which the methiodide was obtained and further reduced with sodium tetrahydroborate to an 81% yield of *O*-methyldauricine (overall yield 52% based on Reissert's compound)[48]. Yet another alternative was to condense Reissert's compound with 5,4'-bischloromethyl-2-methoxydiphenyl ether (VII: $R = CH_2Cl$) and hydrolyse the product with aqueous–alcoholic alkali to the bisisoquinoline derivative (XVII: R = H), whose methiodide was similarly reduced to *O*-methyldauricine[50].

Theoretical interest attaches also to the biomimetic synthesis of (±)-dauricine by the electrochemical oxidation of salts of *N*-ethoxycarbonyl-*N*-norarmepavine to the compound (XVIII) followed by reduction of the ethoxycarbonyl to an *N*-methyl group; the dimer (XIX) was isolated as a by-product[51]:



Magnolamine is an alkaloid closely similar to those already discussed: it differs in the presence of an additional oxygen function and in the location of the diphenyl ether link. It was originally assumed to contain four hydroxy-groups (XX: R = R' = H) [52–55]

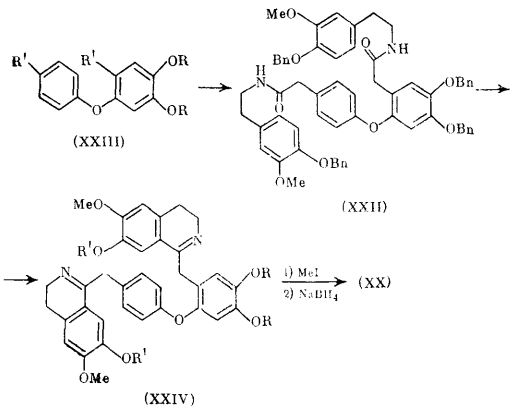


but it has now been proved that only three hydroxyls are present (XX: $R = CH_3$; R' = H).[56]

The antipode and the diastereomer of methylmagnolamine have been obtained by the condensation of (−)-6'-bromolaudanosine (XXI) with respectively (−)- and (+)-armepavine, which confirmed the *SS*-configuration of the natural alkaloid [57,58]. Similarly, condensation of the corresponding benzylated components[59] gave a stereoisomeric mixture of the tetraol having the formula originally suggested for magnolamine. Ullmann condensation in its classic form gives a very low yield (~2%). Replacement of copper powder and pyridine by pentafluorophenylcopper enables the yield of the methyl ether of magnolamine to be raised to 53%. In this case the reaction involves intermediate formation of copper phenoxide[60].

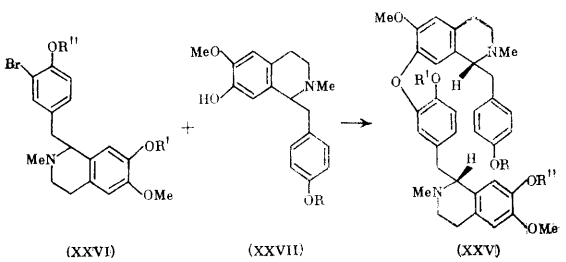
A total synthesis of a diastereomeric mixture of "magnolamine" (XX: R = R' = H) (*O*-demethylmagnolamine) was also accomplished by route (*b*) [see below], in which the bisamide (XXII) was obtained by the Arndt–Eistert method from

(II) and the bisdiazoketone (XXIII: $R = C_6H_5CH_2$; $R' = N_2CHCO$):



As in other cases, the diastereomeric mixture could not be resolved[51,62]. The tetradehydro-derivative (XXIV: $R = CH_3$: $R' = C_6H_5CH_2$) was also synthesised by a method involving formation of an intermediate bisamide[63]. Here the initial dicarboxylic acid (XXIII: $R = CH_3$; $R' = CH_2COOH$) was obtained in two ways—(*a*) chloromethylation of *mp*-dimethoxydiphenyl ether with subsequent replacement of the chlorine atoms by cyano-groups followed by hydrolysis, and (*b*) Ullmann condensation of two substituted esters of phenylacetic acids.

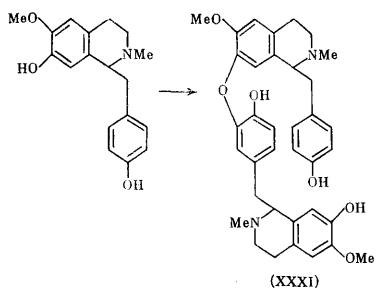
Another type of monoether base, in which benzylisoquinoline fragments are linked "head to tail", is represented by liensinine (XXV: $R = R' = H$; $R'' = CH_3$) and isoliensinine (XXV: $R = CH_3$; $R' = R'' = H$). The former was synthesised by condensation of the bromobenzylisoquinoline component (XXVI: $R' = CH_3$; $R'' = C_6H_5CH_2$) with the *p*-benzyl ether or the *p*-toluene-*p'*-sulphonic ester of *N*-methylcoclaurine (XXVII):[64,65]



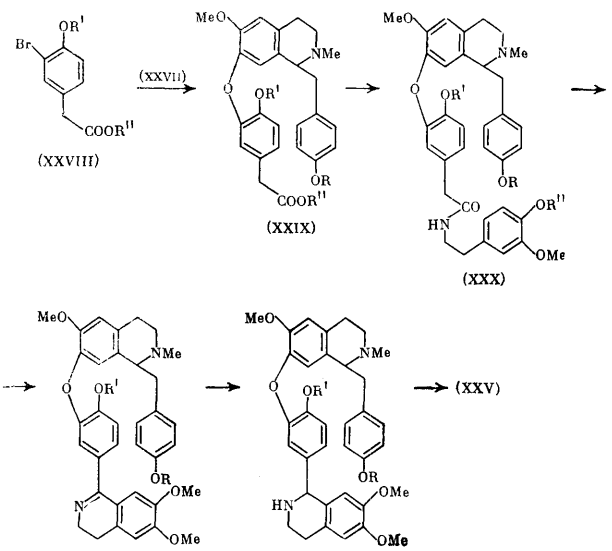
Condensation of the bases (XXVI: $R' = R'' = C_6H_5CH_2$) and (XXVII: $R = CH_3$) or their optically active forms gave (±)- and (−,−)-isoliensinine[65–69].

In another synthesis (Scheme 1) the *p*-methyl ether of *N*-methylcoclaurine (XXVII: $R = CH_3$) is condensed with the bromophenylacetic ester (XXVIII: $R' = CH_3$; $R'' = CH_3$, C_2H_5), and then the diphenyl ether (XXIX: $R = R' = CH_3$; $R'' = H$, CH_3, C_2H_5) is converted by the action of homoveratrylamine into the amide (XXX), which after cyclisation to the dihydroisoquinoline derivative, reduction, and *N*-methylation gives *OO'*-dimethyl-liensinine[70].

The enzymatic oxidative dimerisation of *N*-methylcoclaurine has been achieved, with the isolation of 7″-*O*-demethylliensinine (XXXI) together with the corresponding trimer[71]:



Scheme 1



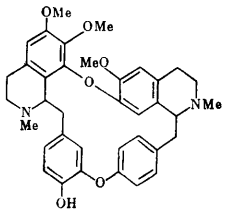
IV. SYNTHESIS OF BISBENZYLISOQUINOLINE ALKALOIDS CONTAINING TWO DIPHENYL ETHER BRIDGES

This group of alkaloids, which are formed in plants by enzymatic double dehydrogenation of two molecules of coclaurine or its derivatives, can be divided into four types of compounds differing in the location of the ether bonds.

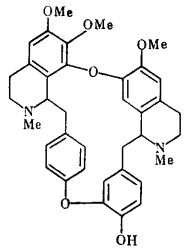
1. Oxyacanthine–Berbamine Type of Alkaloids

This group of natural bases includes the structural isomers berbamine (XXXII) (*RS*), oxyacanthine (XXXIII) (*SR*), their stereoisomers—pycnamine (XXXII) (*RR*) and repandine

(XXXII), (*SS*)—and also their derivatives.



(XXXII)



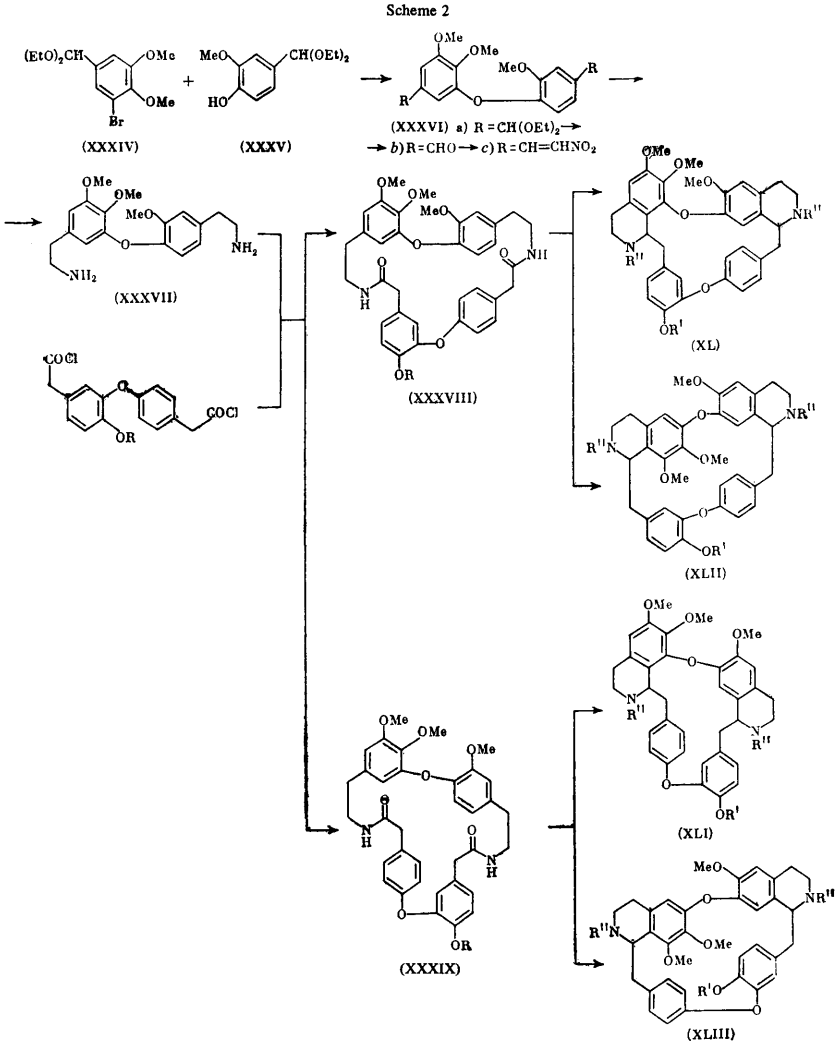
(XXXIII)

The synthesis of berbamine and oxyacanthine (Scheme 2) consists in condensation of the acetals of 5-bromoveratraldehyde and vanillin (XXXIV and XXXV) to give the diacetal (XXXVIa) of diphenyl ether (in 53% yield), which is converted by acid hydrolysis into the dialdehyde (XXXVIb) and then into the oxybisnitrostyrene (XXXVIc). The latter is reduced with lithium tetrahydroaluminate to the diamine (XXXVII).

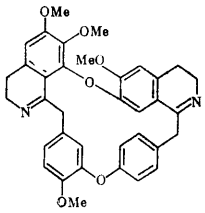
The Schotten–Baumann reaction with 2-benzyloxy-4',5-oxybisphenylacetyl chloride gives an isomeric mixture of the amides (XXXVIII) and (XXXIX), which are separated chromatographically and then subjected to Bischler–Napieralski cyclisation. Each amide forms a mixture of isomeric dihydroisoquinoline bases, which are converted without resolution into the methiodides, reduced, and then debenzylated. After cyclisation of the final products the compounds (XL)–(XLIII) were isolated, two of which were identified with berbamine and oxyacanthine[72,73].

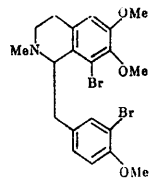
The non-phenolic alkaloids obaberine (*O*-methyloxyacanthine) and tetrandrine have been synthesised by a similar route[74]. In this case the bisamide (XXXVIII: $R = CH_3$), after cyclisation to the bisdihydroisoquinoline bases, was first reduced to the tetrahydroisoquinoline derivatives, which were separated and then methylated. One of the final compounds was identified with *O*-methyloxyacanthine. Tetrandrine was obtained (Scheme 2) from the other bisamide (XXXIX: $R = CH_3$). In the early attempts to synthesise this alkaloid by a similar scheme the dihydroisoquinoline derivatives could not be isolated[75–78]. Other schemes were also proposed, in which the initial diacid was obtained e.g. by Willgerodt rearrangement of the corresponding acetophenone

Scheme 2



[75,79]. Direct condensation of *p*-hydroxyphenylacetic and *m*-bromo-*p*-methoxyphenylacetic esters gives a low yield of the expected diphenyl ether. Obtaining the acid component by Arndt–Eistert chain lengthening has no advantages over the first method[81]. The second component for the synthesis—the diamine (XXXVII)—was also obtained by several methods, e.g. from the corresponding diacid (formed in low yield by Ullmann condensation of substituted aromatic esters) by reduction of ester to hydroxymethyl groups, replacement of the hyroxyls by chlorine and then by cyano-groups, and subsequent reduction with lithium tetrahydroaluminate[80–82]. On the other hand, the dialdehyde (XXXVIb), obtained from the corresponding acid dichloride by Rosenmund reduction, was further converted via the corresponding nitrostyrene (as described above) into the diamine (XXXVII).[75,81] This compound was synthesised from the corresponding bispropionic acid via the isopropylidene hydrazide[83].

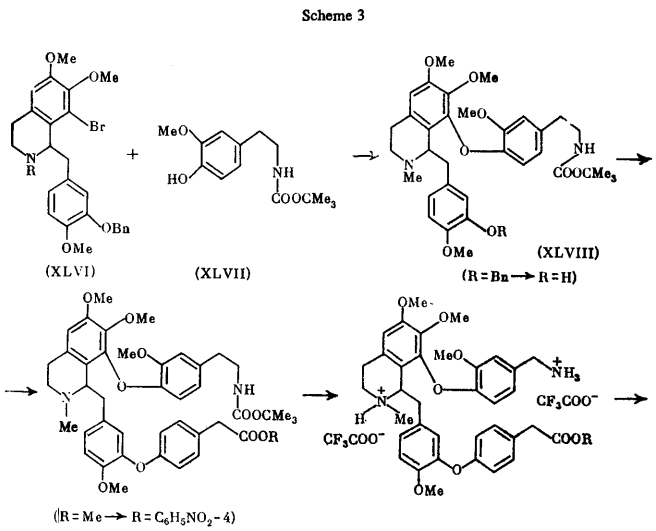

(XLIV)

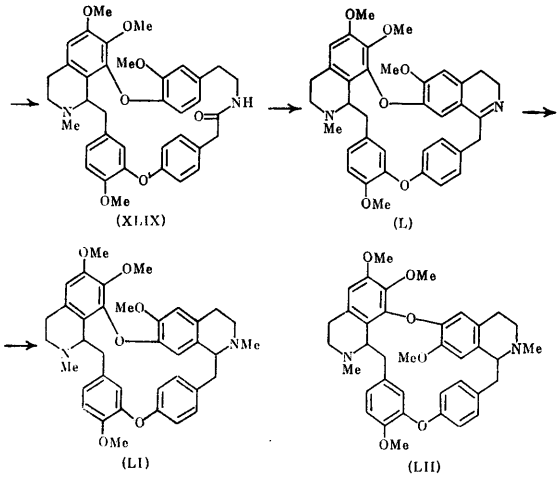

(XLV)

The alkaloid stebisimine, a bisdehydro-derivative (XLIV) isolated from *Stephania japonica*[84], was identified with an intermediate in the synthesis of obaberine[85,86].

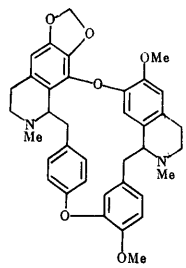
Another synthesis of tetrandrine was the condensation of *N*-methylcoclaurine with its 3′,8-dibromo-*OO*′-dimethyl derivative (XLV).[87] However, all syntheses of this type are at present merely of theoretical interest, because of the very low yields.

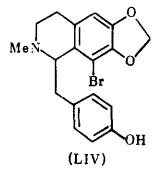
Scheme 3

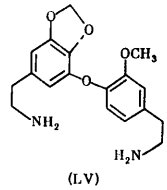

(R = Me → R = $C_6H_5NO_2$-4)


(XLIX) (L) (LI) (LII)

The first total synthesis of the optically active alkaloids—tetrandrine, isotetrandrine, and pheanthine—was accomplished in 1968 from *O*-benzyl-8-bromolaudanine (XLVI: R = H) (Scheme 3),[88,89] which was obtained from 5-bromohomoveratrylamine and *O*-benzylhomoisovanillic acid by classic methods. The tetrahydroisoquinoline derivative was resolved into its optical antipodes by means of (+)-tartaric acid, and after *N*-methylation subjected to Ullmann condensation with t-butyl *N*-*p*-hydroxy-*m*-methoxyphenethylcarbamate (XLVII) to give the diphenyl ether (XLVIII: R = $C_6H_5CH_2$) in 50% yield. After debenzylation (by hydrogenolysis) and condensation with methyl *p*-bromophenylacetate the protecting group in the diphenyl ether was removed, and the cycloamide (XLIX) isolated in 54% yield. Cyclisation to the dihydroisoquinoline (L), reduction, and *N*-methylation gave a mixture of isotetrandine and pheanthine (LI), which were separated by crystallisation of the picrates. (±)-Tetrandrine, which had previously been resolved[90], and *O*-methylthalicberine (LII) [91] were synthesised similarly. Japanese chemists have patented this synthesis of tetrandrine, isotetrandrine, and pheanthine[92].


(LIII)

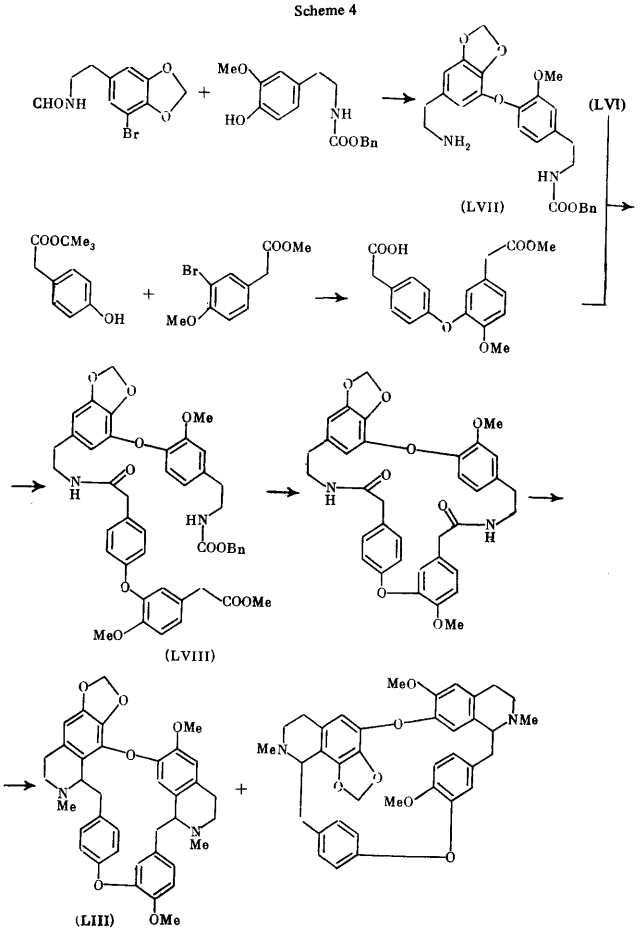

(LIV)


(LV)

The first attempts to synthesise the alkaloid cepharanthine (LIII) by double Ullmann condensation of the two tetrahydroisoquinoline fragments (LIV) and (XXVI: R′ = H; R″ = CH_3) were unsuccessful owing to difficulties in obtaining an 8-bromo-derivative with a methylenedioxy-group (LIV).[93] An attempt to synthesise this alkaloid by the scheme of double amide condensation of diacid and the diamine (LV) described

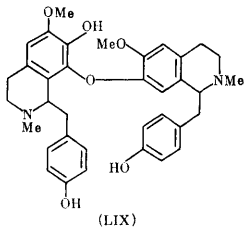
for tetrandrine gave a mixture of cyclobisamides, one of which when isolated could not be cyclised to the expected bis-dihydroisoquinoline[79,80,93–95]. Spectral results indicated that merely products of the oxidation and partial cyclisation of the bisamide had been isolated[96].

Scheme 4

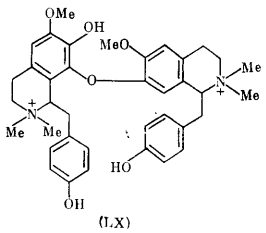


The first successful synthesis of cepharanthine was accomplished by Japanese workers, with successive formation of amide links to obtain the intermediate cyclobisamide[87,98]. Monosubstituted components—the monoether (LVI) and the benzyl *N*-aminoethylphenoxyphenethylcarbamate (LVII)—were synthesised for condensation in the presence of dicyclohexylcarbodi-imide to form initially the monoamide (LVIII) (Scheme 4). The second amide link was formed by means of activated esters. This multistage synthesis of cepharanthine has also been patented by Japanese workers[99]. As in the preceding syntheses, the Bischler–Napieralski cyclisation produces two isomeric dihydroisoquinoline bases, so that not only cepharanthine (LIII) but also its isomeric 6,7′-ether was isolated. Cepharanthine can be converted into obaberine (*O*-methylhydroxyacanthine) by removing the methylene group with a mixture of phloroglucinol and sulphuric acid and then methylating the phenolic product[100].

An attempted double oxidative coupling of *N*-methylcoclaurine units to form compounds of the oxyacanthine–tetrandrine series was unsuccessful. Use of potassium hexacyanoferrate-(III) as oxidant or enzymatic oxidation in the presence of hydrogen peroxide converts coclaurine derivatives or their quaternary ammonium salts merely into the 7′,8-dehydro-derivatives



(LIX)

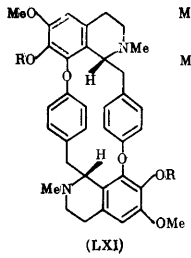


(LX)

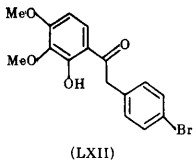
whose structures have been confirmed by synthesis[101–105].

2. Isochondrodendrine Alkaloids

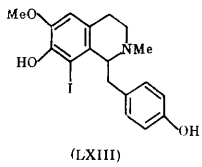
Alkaloids of this type include isochondrodendrine, its methyl ether cycleanine, insularine, etc. The *RR*-configuration has been established for the first two (LXI: R = H, CH_3), which have an axis of symmetry, in contrast to alkaloids of the berbamine–oxyacanthine series. Although alkaloids of the present type were the first to attract the attention of chemists, progress in this field has been achieved only recently. Their synthesis presented certain difficulties, since methods developed for the preceding type of bases proved relatively unsuitable. Several unsuccessful attempts were made to effect a double Ullmann condensation of (LXII) with the aim of obtaining the macrocyclic system forming the basis of isochondrodendrine[106]. An attempt to synthesise 8-iodo-*N*-methyl-coclaurine (LXIII), an intermediate in the synthesis of isochondrodendrine, was also unsuccessful[107].



(LXI)



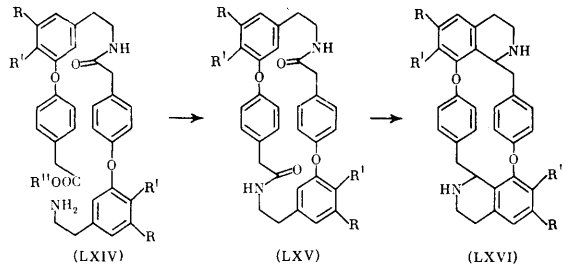
(LXII)



(LXIII)

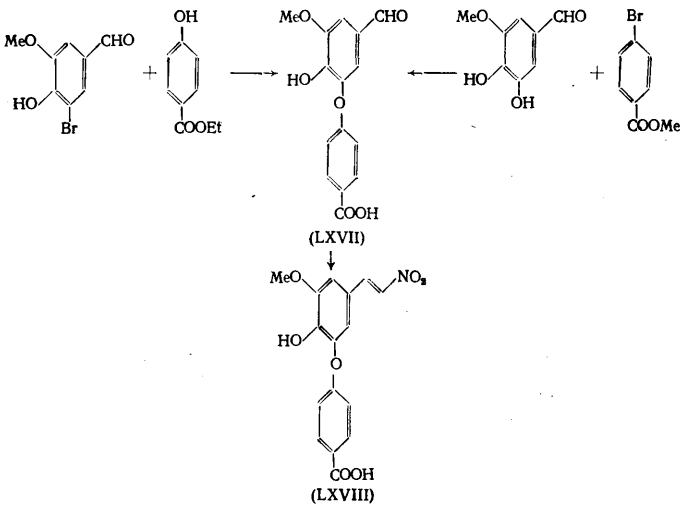
A theoretical synthesis of isochondrodendrine alkaloids was suggested by Preobrazhenskii et al.[108] and accomplished on a model compound. The main stage was intramolecular cyclisation of the monoamide (LXIV) to the macrocyclic diamide (LXV), which was converted by cyclisation followed by

reduction into (LXVI: R = R' = H):



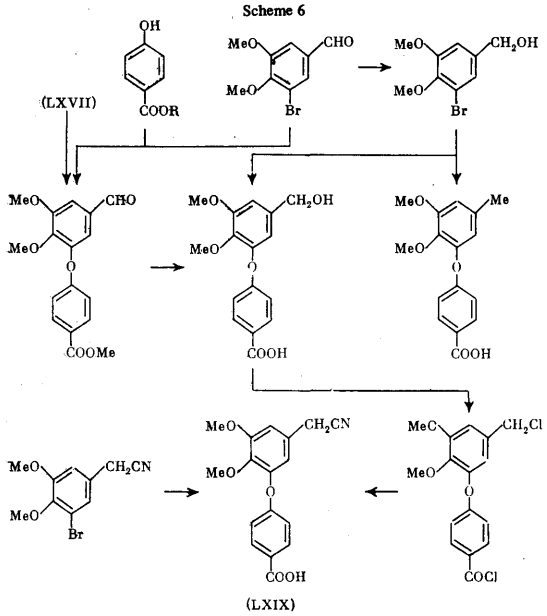
The initial diphenyl ethers were synthesised by condensing 5-bromovanillin with a *p*-hydroxybenzoic ester, or $O_{(3)}$-methylgallaldehyde with a *p*-bromobenzoic ester, to give *p*-5'-formyl-2'-hydroxy-3'-methoxyphenoxybenzoic acid (LXVII), which was converted by means of nitromethane into the corresponding nitrostyrene (LXVIII) (Scheme 5).[109] Alternatively, halogen activation was used to increase the yield of the products, by introducing a nitro-group into the halogenated component, and subsequently removing it. However, the additional operations required to eliminate the nitro-group from the nitrated diphenyl ether almost nullify the advantages of this method[109]. The nitrovinyl group can then be reduced over palladium black to an aminoethyl group[110].

Scheme 5



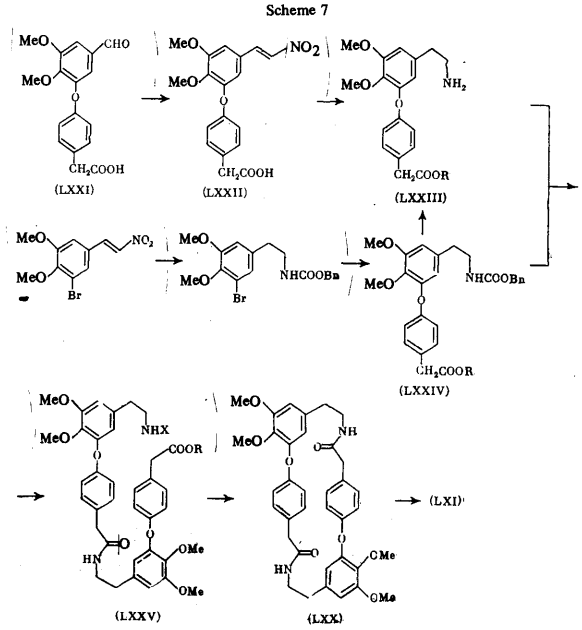
p-5'-Cyanomethyl-2',3'-dimethoxyphenoxybenzoic acid (LXIX), identical with the product of the condensation of 3'-bromo-4',5'-dimethoxyphenylacetonitrile with a *p*-hydroxybenzoic ester, was synthesised by methylating the phenolic hydroxyl in (LXVII), reducing the formyl group to a hydroxymethyl group, and then replacing the hydroxyl by a chlorine atom followed by a cyano-group (Scheme 6). Other intermediates in the synthesis have also been obtained independently, as outlined in Scheme 6.[111]

Scheme 6



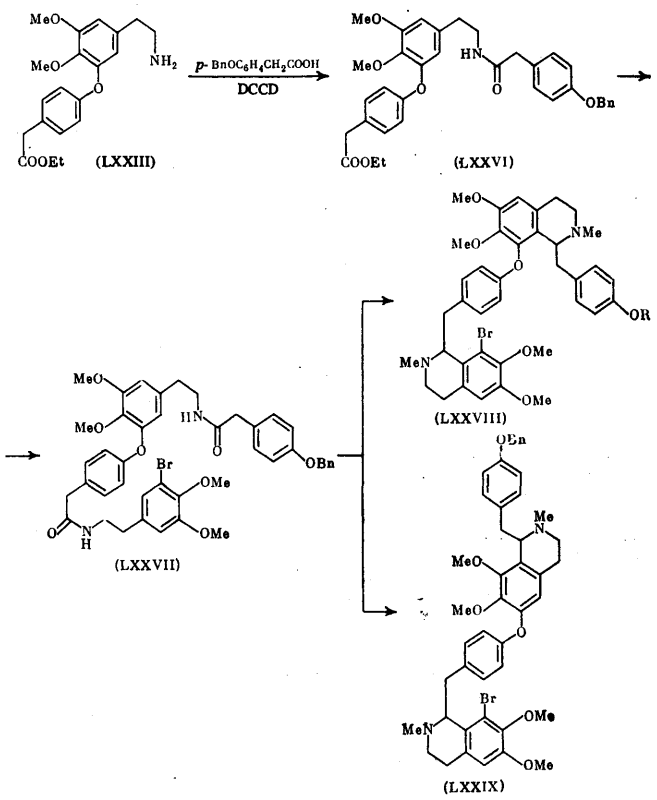
The two diphenyl ethers can be combined by Arndt–Eistert chain lengthening to give the cyclodiamide (LXV: R = R' = CH_3O). In view of the low overall yield, however, a search was made for more practicable methods of synthesis. In ticular, reduction of brominated nitrostyrenes with zinc amalgam was used to obtain 4-alkoxy-3-bromo-5-methoxyphenethylamines[13], which would yield 7-alkoxy-8-bromo-3,4-dihydro-1-*p*-hydroxybenzyl-6-methoxyisoquinolines[10], intermediates in the synthesis of these alkaloids. However, the cyclocondensation of (±)-8-bromoarmepavine was accompanied by debromination, so that only (±)-armepavine and (±)-*NOO'*-trimethylcoclaurine were isolated[112,113].

Scheme 7



In the first of two independent syntheses of (±)-cycleanine (LXI: R = CH_3) via the cyclobisamide (LXX) the acetal of 5-bromoveratraldehyde was condensed with a *p*-hydroxyphenylacetic ester, and the resulting *p*-5′-formyl-2′,3′-dimethoxyphenoxyphenylacetic acid (LXXI) was converted into the nitrostyrene (LXXII), which was reduced to the amino-acid (LXXIII) (Scheme 7). An ester of this acid was obtained by condensing benzyl *N*-5-bromohomoveratrylcarbamate with a *p*-hydroxyphenylacetic ester and then hydrogenolysing the carbamic ester (LXXIV). The two fragments (LXXIII) and (LXXIV) were condensed by means of dicyclohexylcarbodiimide in dichloromethane. The second amide link was formed by heating the *p*-nitrophenyl ester (LXXV) in the presence of pyridine and triethylamine[114–116].

Scheme 8

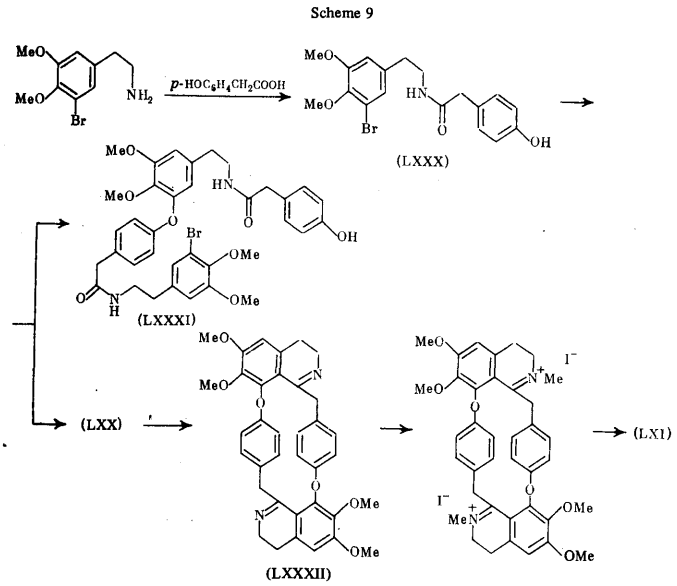


In another procedure[117] the initial amino-acid is condensed in the form of an ester [LXXIII] with *p*-benzyloxyphenylacetic acid, and the resulting amide (LXXVI) converted by reaction with 5-bromohomoveratrylamine into the diamide (LXXVII) which is cyclised, reduced, and methylated (Scheme 8). This yields a mixture of isomeric tetrahydroisoquinoline bases (LXXVIII) and (LXXIX), one of which was identified with the product of the condensation of (±)-8-bromoarmepavine with (±)-8-bromo-*NOO*′-trimethylcoclaurine in the presence of copper(II) oxide instead of metallic copper as catalyst. However, cyclocondensation of (LXXVIII: R = H) into cycleanine could not be achieved[112].

Scheme 9 outlines a successful double Ullmann cyclocondensation of the phenolic bromo-amide (LXXX), in which 5-bromohomoveratrylamine was condensed with *p*-hydroxyphenylacetic acid, and the potassium salt of the resulting bromo-amide (LXXX) was converted by an Ullmann reaction into a mixture of the cyclobisamide (LXX) and the open-chain diamide (LXXXI), which were easily separated by conversion of the latter into a salt[118]. The cyclic diamide was then subjected to Bischler–Napieralski cyclisation to give the bisdihydroisoquinoline derivative (LXXXII), whose methiodide was reduced to a mixture of tetrahydroisoquinoline bases that could be separated chromatographically. One of these showed the same chromatographic mobility as natural cycleanine.

Phenolic alkaloids—isochondrodendrine (LXI: R = H) and norcycleanine (7-*O*-demethylcycleanine)—have been obtained by the selective demethylation of cycleanine with hydrobromic acid[119].

Scheme 9



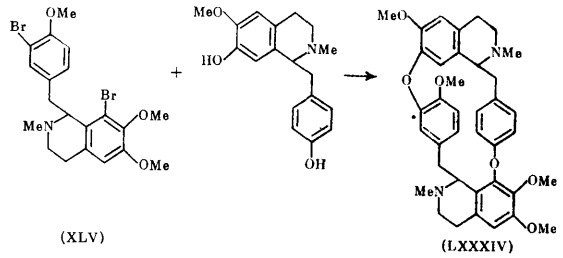
3. Curine–Tubocurarine Alkaloids

In contrast to the preceding group the present diether alkaloids are based on the unsymmetrical chondrodendrine (LXXXIII) skeleton. This group includes the alkaloids curine and the quaternary bases tubocurarine, chondrocurarine, etc. Tubocurarine chloride, the active principle of tubocurare, found application in surgical practice[120]. However, the relative inaccessability of this alkaloid and the great demand stimulated synthetic work on substitutes for curare, quaternary bisammonium salts, of which several thousands were obtained, most of them weaker than tubocurarine or having no advantages over the latter[121].

Two fundamentally different approaches have also been made to the synthesis of this group of alkaloids.

(*a*) Synthesis from benzylisoquinoline components

N-Methylcoclaurine (XI: R = H), obtained by the cleavage of isotetrandrine with sodium in liquid ammonia, was brominated at positions 3' and 8 and then diazomethylated to give 3',8-dibromo-*NOO'*-trimethylcoclaurine (XLV), which was condensed with the potassium salt of *N*-methylcoclaurine; *NOO'*-trimethylcoclaurine, isotetrandine, and dimethylcurine (LXXXIV) were found among the reaction products:

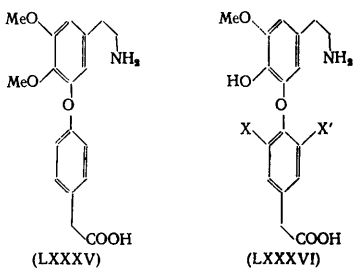


(XLV) (LXXXIV)

The use of laevorotatory components yielded (−,−)-*OO'*-dimethylcurine[122–124]. Phenolic components have also been employed for condensation, but the yield of the macroring is then very low. After methylation of the reaction products with diazomethane followed by chromatography diastereomeric racemates of *OO'*-dimethylcurine and of an acyclic base were isolated, the latter of which after debromination was identified with racemic *OO'*-dimethyl-liensinine.

(*b*) Synthesis from diphenyl ethers

The alternative synthesis of bisbenzylisoquinoline alkaloids from substituted diphenyl ethers has recently been applied to the oxyacanthine–berbamine series. However, the synthesis of amino-acid diphenyl ethers, of chondrodendrine and isochondrodendrine structural units, it made difficult by the inconvenience of obtaining them by the Ullmann reaction, because these alkaloids contain a hydroxyl next to the phenoxyphenyl link. It was shown experimentally that direct formation by the Ullmann reaction even of the simplest compounds of this type is devoid of preparative value owing to the very low yields[125]:

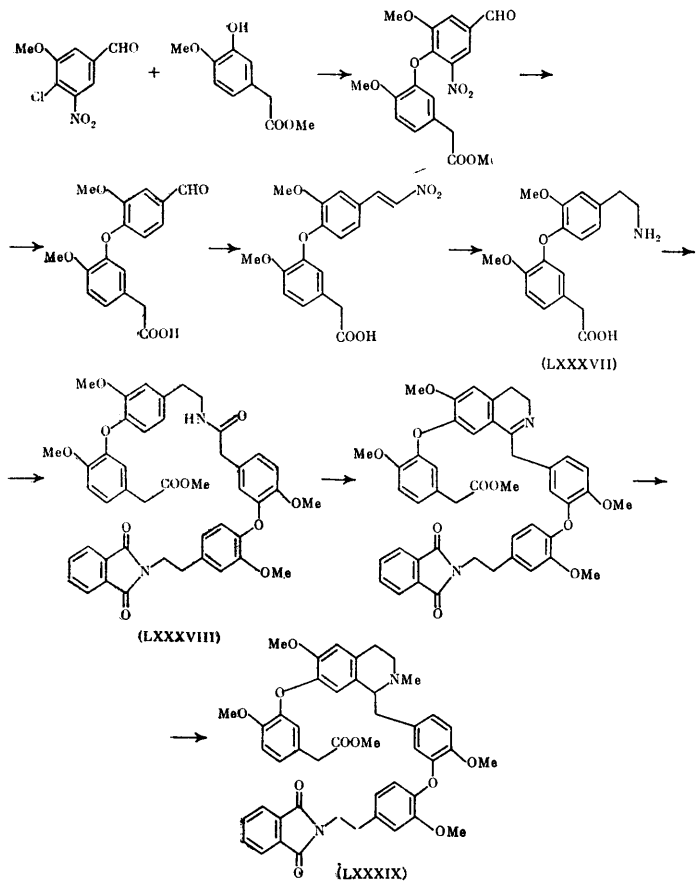


(LXXXV) (LXXXVI)

The structural formulae reveal that one diphenyl ether fragment is common to isochondrodendrine and curine, so that this moiety can be synthesised in the same way for the two alkaloids. Activation of aromatic halogen by means of groups such as nitro has been used to synthesise *p*-5'-aminoethyl-2',3'-dimethoxyphenoxyphenylacetic acid (LXXXV) [126] and several of its phenolic analogues (LXXXVI),[127,128], as well as homologous acids (see above[109–111]).

The other component, *m*-*p'*-aminoethyl-*o'*-methoxyphenoxy-*p*-methoxyphenylacetic acid (LXXXVII), was also synthesised by the method of activated ethers from 4-chloro-3-methoxy-5-nitrobenzaldehyde and isohomovanillic acid (Scheme 10).[129,130] In all cases the activating group was removed by reduction to an amino-group, diazotisation, and subsequent treatment with hypophosphoric acid. The overall yield of the amino-acid (LXXXVII) was 12%. Further condensation of the corresponding ester with a phthalimide derivative gave the amide (LXXXVIII), which after cyclisation, reduction, and *N*-methylation was converted in low yield into the non-cyclised ether (LXXXIX).[130] It was also suggested that diphenyl ethers derived from phthalimidoamino-acids could be obtained via diaryliodonium salts, but the yield of a model compound was 6%.[131]

Scheme 10

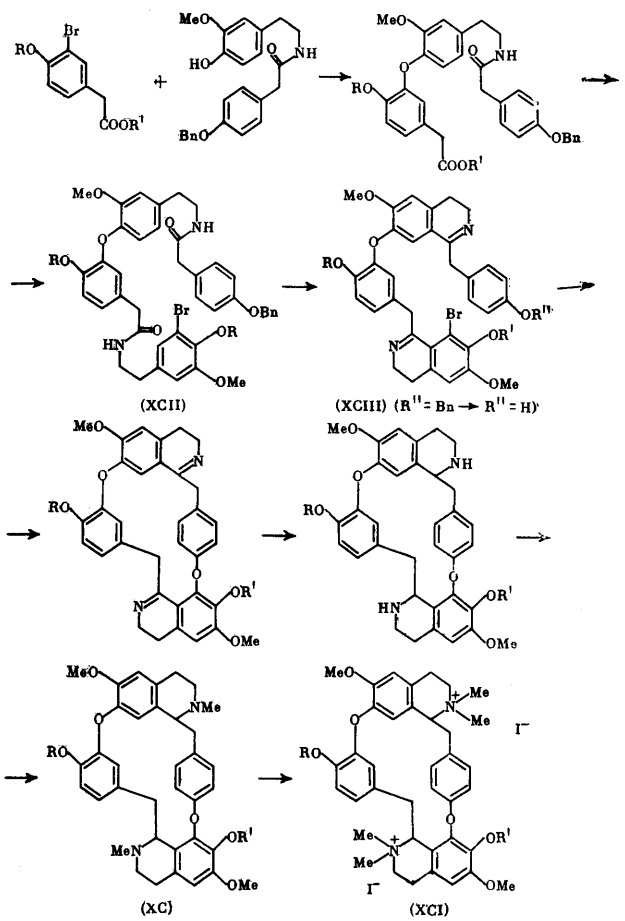


(LXXXVII) (LXXXVIII) (LXXXIX)

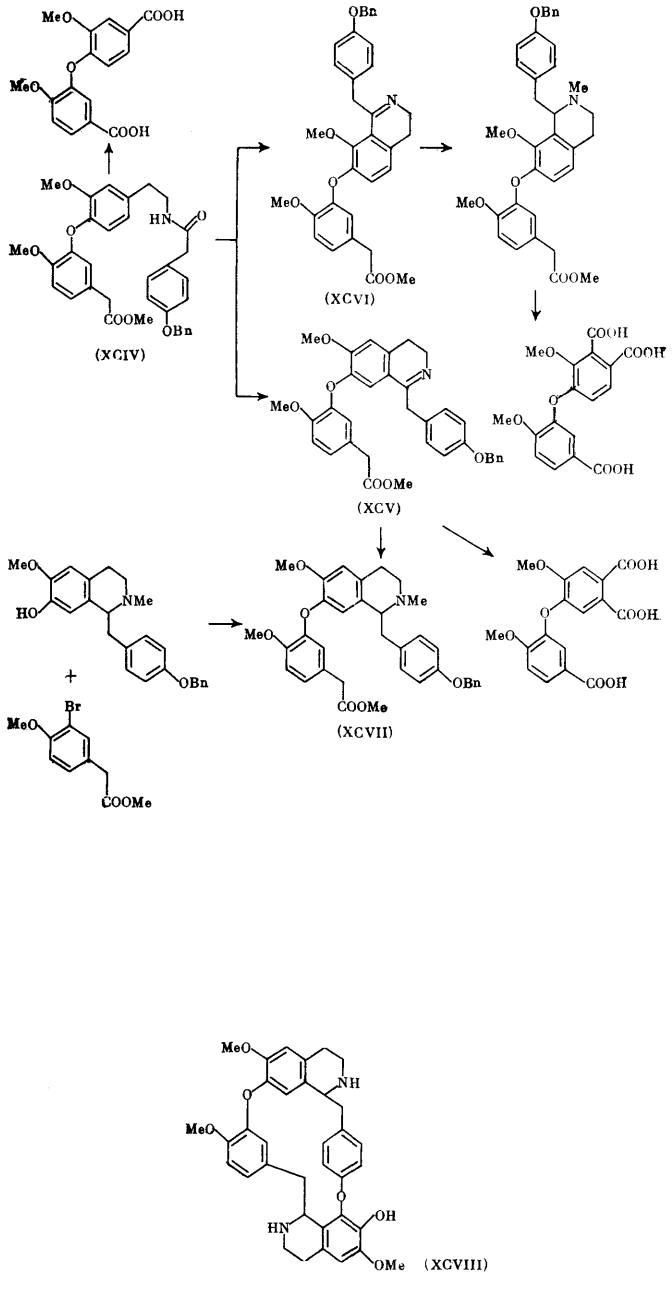
The total synthesis of racemic curine, i.e. (±)-chondrodendrine (XC: R = R' = H), its ethers, and its quaternary salts (XCI: R = R' = H, CH_3) is accomplished by successive chain extension followed by cyclisation of the diamide (XCII: R = R' = CH_3, CH_3COO) to the bisdihydroisoquinoline base (XCIII: R = R' = CH_3, CH_3COO), removal of the protecting groups, and formation of a second diphenyl ether bridge (Scheme 11).[132–137] It is noteworthy that the use of amides for Ullmann condensation enabled the required diphenyl

ethers to be obtained in good yield even when free phenolic hydroxyls were present in the compounds[138]. The amide protection of amino-groups in the Ullmann reaction later enabled Japanese workers to achieve the total synthesis of alkaloids of the oxyacanthine–tetrandrine group (see above). This scheme is simple to carry out, involves relatively few stages, and gives good yields at all stages. Diastereomeric compounds can be quite easily separated in the later stages by crystallisation of the salts. In the synthesis of (±)-chondrodendrine and its dimethiodide free hydroxy-groups must be protected by acetylation before Bischler–Napieralski cyclisation.

Scheme 11



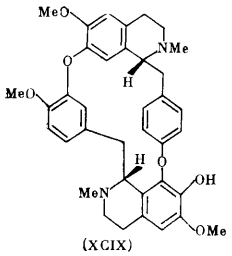
Scheme 12



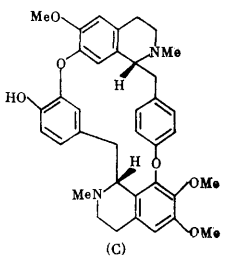
The acetamido-diphenyl ether (XCIV) was isolated in two forms, giving on cyclisation different dihydroisoquinoline derivatives (XCV) and (XCVI) (Scheme 12). The cyclisation products were identified by cross-synthesis of the compound (XCVII) and also of the oxidation products[139]. The same method was used to synthesise *NN'*-demethyl-4″-*O*-methyl chondrodendrine (*NN'*-demethylgaiatinine)[140]

The intermediate methyl *m*-l-*p'*-benzyloxybenzyl-1,2,3,4-tetrahydro-6-methoxy-2-methylisoquinolin-7-yloxy-*p*-methoxyphenylacetate (XCVII) has also been used in an alternative synthesis of *OO'*-dimethylchondrodendrine (XC: R = R' = CH_3) (Scheme 13).[141] *OO'*-Dimethyl-liensinine[70] and the non-cyclised analogue *OO'*-dimethyltubocurarine iodide[110] have been synthesised by the same route.

Demethylation of the methyl ether of curine with hydrobromic acid followed by separation of the demethylated products was reported[142], but the structures of the latter were not given. *RR*-12′-*O*-Methylcurine (4″-*O*-methylcurine) (XCIX) was obtained together with chondrofoline (C) by the partial methylation of (−)-curine with diazomethane[143].

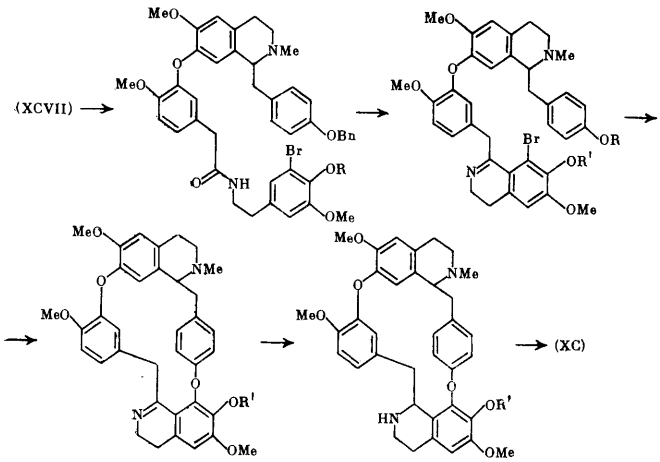


(XCIX)



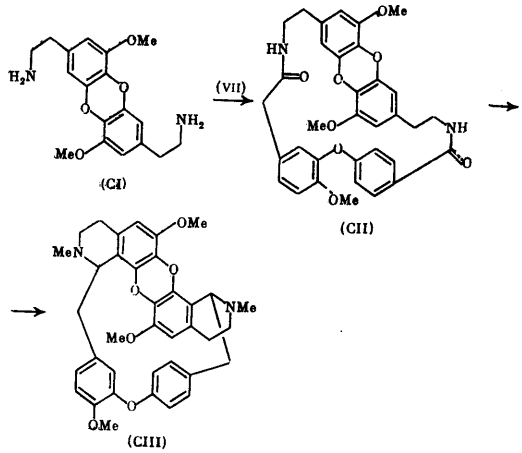
(C)

Scheme 13



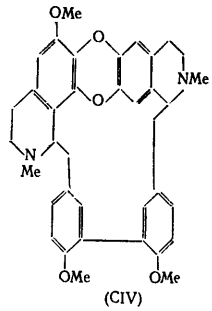
V. SYNTHESIS OF BISBENZYLISOQUINOLINE ALKALOIDS CONTAINING THREE DIPHENYL ETHER LINKS

This group of alkaloids includes micranthine, menisarine, and normenisarine, as well as trilobine and isotrilobine. The structure of menisarine has been confirmed by synthesis of a derivative[144–147]. The condensation of 2,7-bis-2′-aminoethyl-4,9-dimethoxydibenzo-5,10-dioxin (CI) with 4-methoxy-3-phenoxybenzene-1,4′-bisacetic acid at high dilution gave a macrocyclic bisamide (CII), which on cyclisation, reduction, and *N*-methylation was converted into a ditertiary base, identified with dihydro-*N*-methylmenisarine (CIII) obtained from natural menisarine:



(CI) (CII) (CIII)

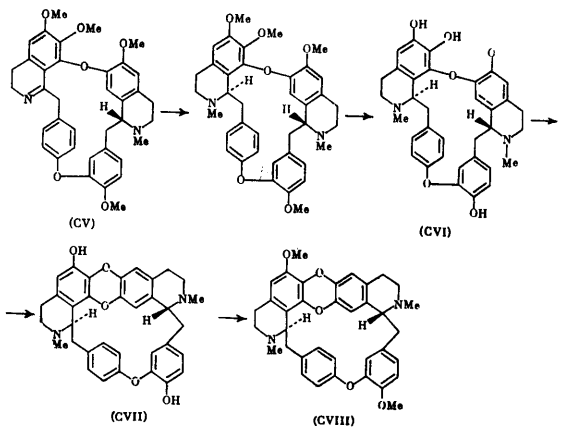
(±)-*O*-Methyltiliacorine



(CIV)

has been synthesised by an analogous scheme[148].

Scheme 14



(CV) (CVI) (CVII) (CVIII)

It is interesting to pass from the hydroxyacanthine to the trilobine group of alkaloids, which contains three diphenyl ether links. For example, (+)-epistephanine (CV), after reduction of the dihydroisoquinoline ring and *N*-methylation, was demethylated with hydrobromic acid at 100 °C to the tetraol (CVI), which when heated with this acid at 150 °C underwent dehydration to the prototrilobine derivative (CVII), diazomethylation of which gave (−)-isotrilobine (CVIII), the antipode of natural (+)-isotrilobine (Scheme 14)[149,150]. Repandine was similarly converted into isotrilobine[151,152], and dihydroepistephanine into the *N*-ethyl analogue of the antipode of trilobine[153].

---o0o---

During recent years synthetic schemes have been worked out for the chief bisbenzylisoquinoline alkaloids containing one, two, or three diphenyl ether links. The main criterion in the choice of method of synthesis is the biogenetic classification. At present most of these syntheses are merely of theoretical interest. However, the presence of high biological activity among bisbenzylisoquinoline alkaloids, e.g. antitumour and antitubercular in tetrandrine, etc., as well as their relative unavailability for practical use, makes further search desirable for practical methods of synthesis.

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